博　士　論　文

Development of New Synthetic Reactions With Heteroatom (Ga,P,and Pb) Compounds

（ヘテロ元素(Ga,P,Pb)を用いる新合成反応の開発）

古　田　寿　昭

平　成　3　年

Doctral Dissertation

Development of New Synthetic Reactions with Heteroatom (Ga, P, and Pb) Compounds

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Contents

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Introduction

Selectivity has become a key concept in synthetic reactions. The development of new but non-selective reactions is of little or no value today. There are three types of selectivity in organic synthetic reactions; (i) **chemoselectivity**; (ii) **regioselectivity**; (iii) **stereoselectivity**. What parameters and factors should one take into consideration to obtain a high level of chemo-, regio-, and stereo-selectivity?

In general, product ratios are determined by the ratios of rate constants of simultaneously occurring reactions (kinetic control) and/or, if exist, the equilibrium constants between various products (thermodynamic control). The ratios of the rate constants (k_{exp}) may be related to the difference in the activation free energy ($\Delta G^{\ddagger}$) (equation 1-1), and the equilibrium constants (K) may be calculated from (free) enthalpies (ΔH) and entropies (ΔS) of reaction (equation 1-2).

$$k_{exp} = kT/h \cdot e^{-\Delta G^{\ddagger}/RT} = kT/h \cdot e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta H^{\ddagger}/RT}$$
$$= kT/h \cdot e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta E^{\ddagger}/RT} \cdot e^{-p\Delta V^{\ddagger}/RT} \quad (1\text{-}1)$$

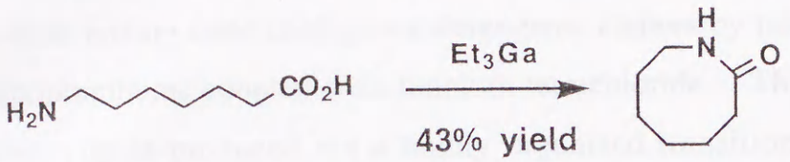
$$RT \ln K = -\Delta G = -\Delta H + T\Delta S \quad (1\text{-}2)$$

k : Boltzmann constant, h : Planck constant, R : gas constant

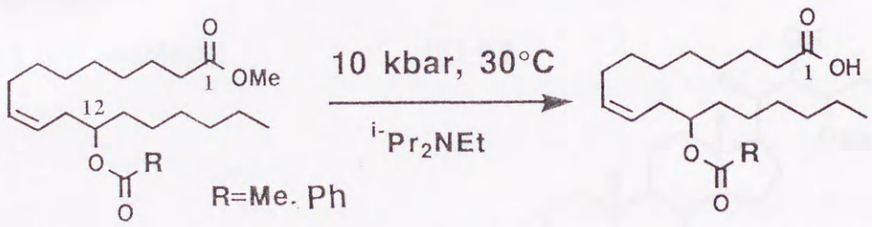
Therefore, if one wants to develop a new and selective synthetic reaction, one must consider the parameters shown in above equations.

To develop new reactions, I used heteroatom compounds as reagents and high pressure techniques as reaction condition.

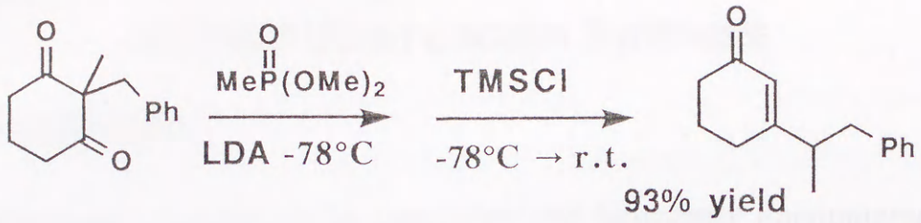
In chapter 1, I developed a new method for synthesis of medium-sized lactams by using group 13 organometalic compounds, R_3Al and R_3Ga. Those organometallic compounds can act as metal templates, and thus diminish, to some extent, unfavorable entropies ($\Delta S^{\ddagger}$) in the medium sized lactamization.



In chapter 2, highly chemo-, regio-, snd stereo-selective hydrolysis of biologically important carboxylic esters was developed by using high pressure technique. Activation volume ($\Delta V^{\ddagger}$) becomes a key to accomplish the highly selective hydrolysis which cannot be achieved by any other means.

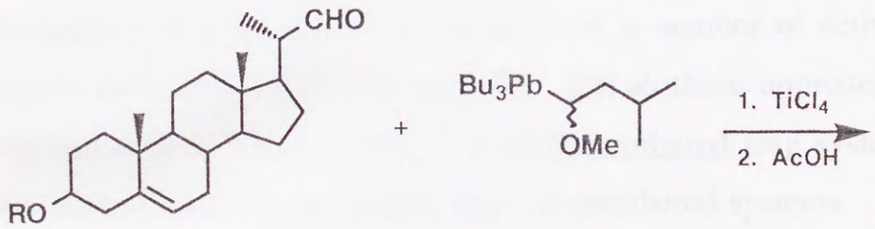


In chapter 3, I developed a new synthetic method for the synthesis of 3-substituted 2-cyclic enones from 2,2-dialkyl-1,3-cyclic diketones by using phosphonate stabilized carbanions. This unprecedented rearrangement is useful for the synthesis of 3-substituted cyclohexen-2-ones and cyclopenten-2-ones, which are not easily available with other methods. As mentioned later, the thermodynamic factors become a key in this interesting rearrangement.

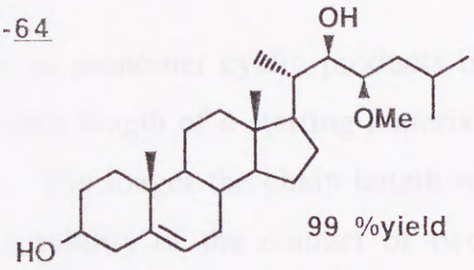


93% yield

In chapter 4, I accomplished highly stereocontrolled construction of acyclic 1,2-diols having three contiguous stereogenic centers by using α-alkoxy organoplumbums coupled with titanium tetrachloride. The high diastereoselectivity is produced via a highly organized transition state geometry created by the combination of Pb and Ti. An entropic factor ($\Delta S^{\ddagger}$) becomes a key to obtain the high diastereofacial selectivity and the kinetic resolution.



70 R=$^{t-}$ BuMe$_2$Si (±)-64



99 %yield

71 single isomer

A preliminary result has been published in the following journals as a communication.

Chapter 1. *Chem. Lett.* **1989**, 797,

Chapter 2. *J. Org. Chem.* **1990,** *55,* 3971,

Chapter 3. *J. Org. Chem.* **1991,** *56, in press.*

Chapter 1. Group13 Organometallics Mediated Medium Sized Lactam Synthesis

1-1. Introduction

Lactam macrocycles are an important and frequently encountered structure in biologically active natural products. Lactamization of simple α,ω-amino carboxylic acids has been accomplished by using catecholborane[1], dibutyltin oxide[2], titanium tetraisopropoxide[3], and alumina (or silica gel)[4].

Formation of macrocyclic lactams from α,ω-amino carboxylic acid derivatives containing chelating polar groups has been accomplished with catecholborane[5] and aminoborane[6]. *High dilution method* has been frequently used for macrolactamization of a number of activated α,ω-amino carboxylic acid derivatives[7]. But all these approaches can be applied only to the formation of 5- to 7-membered ring systems and of macrorings having rings greater than 13-membered systems.

Such a difficulty for the formation of monomer cyclic products is controlled by two entropic factors; 1) chain length of a starting material and 2) ring strain of a desired product. The longer the chain length of the starting material, the lower the probability of the contact of two reactive sites. This negative entropic effect causes low yields of large ring systems.

Since the ring strain is minimized in six membered case (i.e. chair form of cyclohexane), this entropic factor can be neglected in the case of 5-, 6-, and 7-membered rings. For example, the heats of formation for a number of cycloalkanes are tabulated in Table 1-1[8]. The total strain energies shown in the table are based upon the fact that the strain energy

of cyclohexane is zero. Three and four membered rings have a great deal of small-angle strain. Five, six and seven membered rings have almost no ring strain. Medium sized rings (8- to 11-membered) have large strain energy (Pitzer, transannular and large-angle strain)[9], while large rings (more than 12-membered) have little or no strain.

Table 1-1. ΔH_f° of Cycloalkanes, $(CH_2)_n$

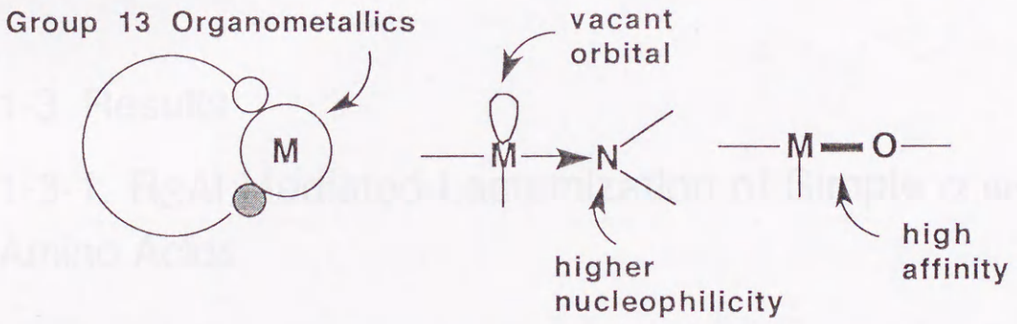
n	Cycloalkane	ΔH_f° kcal mol^{-1}	$\Delta H_f^\circ / n$ kcal mol^{-1} per CH_2 group	total strain energy kcal mol^{-1}
2	ethylene	+12.5	+6.2	22
3	cyclopropane	+12.7	+4.2	27
4	cyclobutane	+6.8	+1.7	26
5	cyclopentane	-18.4	-3.7	6
6	cyclohexane	-29.5	-4.9	(0)
7	cycloheptane	-28.2	-4.0	6
8	cyclooctane	-29.7	-3.7	10
9	cyclononane	-31.7	-3.5	13
10	cyclodecane	-36.9	-3.7	12
11	cycloundecane	-42.9	-3.9	11
12	cyclododecane	-55.0	-4.6	4
13	cyclotridecane	-58.9	-4.5	5
14	cyclotetradecane	-57.1	-4.1	12
15	cyclopentadecane	-72.0	-4.8	2
16	cyclohexadecane	-76.9	-4.8	2

The efficiency for the lactamization must be influenced by the combination of these two factors (chain length and ring strain). Normally, the lactam formation of the larger ring systems (more than 12-membered) results in low yield if the ordinary reaction condition is utilized. This is due to their longer chain length, which diminishes an opportunity for contacting the two reactive sites, and instead increases an

intermolecular coupling. High dilution method is effective to solve this problem in those cases. However, this methodology cannot be applied to formation of medium sized (8- to 11-membered) lactams, since the ring strain plays an important role. To accomplish an efficient synthesis of medium rings, it is necessary to develop a new methodology which may **release the unfavorable ring strain** in transition states.

1-2. Approach

To accomplish the medium-sized lactam synthesis without using high dilution method, I investigated group 13 organometallics mediated lactamization of simple α, ω-amino acids. I like to call "template-driven" macro-cyclization methodology. Since group 13 elements have a vacant orbital, small electronegativity, and high affinity to oxygen, these elements may bind the two reactive sites as shown in the following scheme, and facilitate the cyclization.



The metal template driven lactamization of simple α, ω-amino acids preveously reported are summarized in Table 1-2.

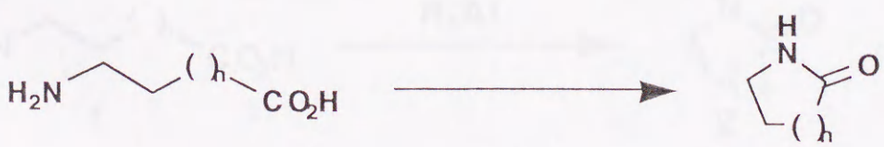
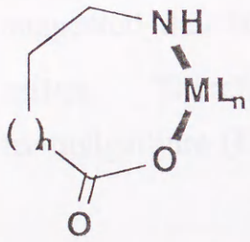


Table 1-2 Template Driven Lactamization of Simple α,ω-Amino Acids

		product yield / %			
reagents	metal	n=1	n=2	n=3	n=4
cathecol borane[1)]	B	>95		85	6
Bu_2SnO[2)]	Sn	>95	>95	>95	-
$Ti(O^i\text{-}Pr)_4$[3)]	Ti	93	75	35	-

These methods are suitable for the synthesis of 5- to 7-membered lactams, but the ring systems larger than 8-membered cannot be obtained by these methods.

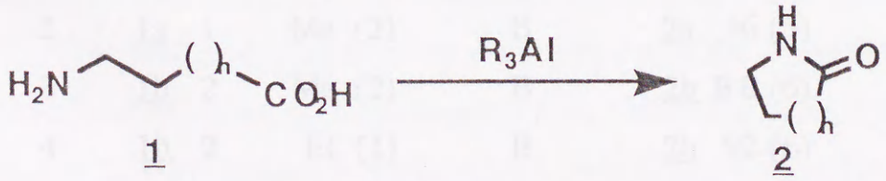


A cyclic intermediates containing metal is assumed[2)], but an unfavorable ring strain in the transition state is not released in the larger ring systems.

1-3. Results

1-3-1. R_3Al Mediated Lactamization of Simple α,ω-Amino Acids

Lactamization of simple α,ω-amino acids (1) was accomplished by using excess amounts of trialkylaluminum (R_3Al).

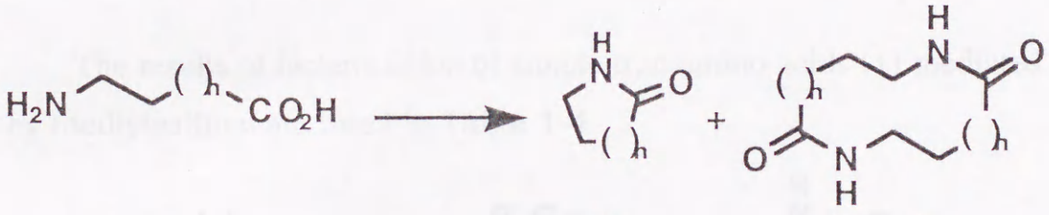


1 2 (1-1)

The results are listed in Table 1-3. Formation of 5- and 6-membered lactams proceeded with very high yield (entries 1, 3 and 4).

Seven membered lactam 2c was also produced with slightly reduced yield (entry 6). However under the same reaction conditions, no satisfactory result was obtained in the ring systems larger than 8-membered ring. Only 7% yield of the 8-membered lactam 2d was isolated (entry 9) and no 9-, 12- and 13-membered lactams were isolated (entries 10 to 14). Instead their dimeric products were obtained.

In entry 6, the reaction progress in the condensation with triethylaluminum (Et_3Al) was followed by time, and it was revealed that the reaction essentially completed after 1 hr and the starting material was recovered at this stage; 2 (69%) and 1 (30%). This observation suggested that Et_3Al would be decomposed gradually under toluene reflux. Therefore, it was anticipated that thermally more stable triethylgallium (Et_3Ga) may produce higher yield.



1 2 3

Table 1-3. R_3Al Mediated Lactamization

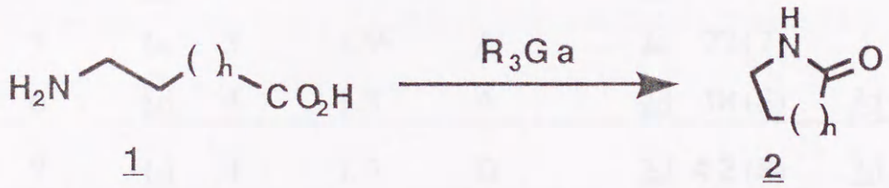
			R_3Al (equiv.)		product, yield/% (ring size)	
entry	subs.	n	R	condn.[a]	monomer	dimer
1	1a	1	Et (2)	A	2a **82** (5)	0
2	1a	1	Me (2)	B	2a 56 (5)	0
3	1b	2	Me (2)	B	2b **98** (6)	0
4	1b	2	Et (1)	B	2b 92 (6)	0
5	1b	2	Et (2)	C	2b 74 (6)	0
6	1c	3	Et (2)	A	2c **69** (7)	0
7	1c	3	Me (2)	B	2c 45 (7)	0

8	1c	3	Me (2)	D	2c	32 (7)		0
9	1d	4	Et (2)	A	2d	7 (8)	3d	2 (16)
10	1e	5	Me (2)	B		0	3e	18 (18)
11	1f	8	Et (2)	A		0	3f	4 (24)
12	1f	8	Me (2)	D		0	3f	3 (24)
13	1g	9	Me (2)	B		0	3g	9 (26)
14	1g	9	Et (2)	A		0	3g	2 (26)

a. A : substrate (1 mmol) / toluene (10 mL) / reflux
B : substrate (1 mmol) / benzene (10 mL) / reflux
C : substrate (1 mmol) / benzene (10 mL) / 45°C
D : substrate (1 mmol) / THF (10 mL) / reflux

1-3-2. Et_3Ga Mediated Lactamization of Simple α,ω-Amino Acids

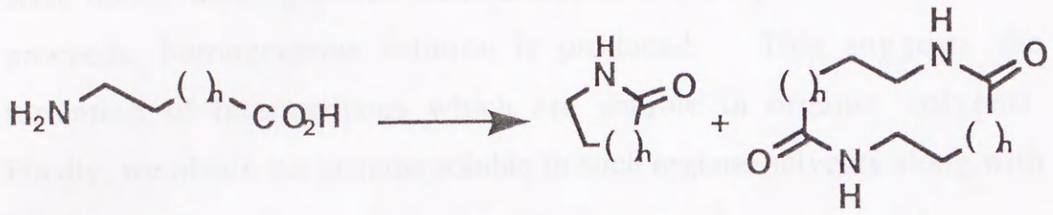
The results of lactamization of simple α,ω-amino acids (1) mediated by triethylgallium are listed in Table 1-4.



1 2 (1-2)

Formation of 5- and 6- membered lactams proceeded with very high yields (entry 1 and 2), and as expected before, the 7- membered lactam was obtained in higher yield than with triethylaluminum (entries 4 and 5). The most remarkable result was obtained in the 8-membered case. Under the condition A (same as entry 9 in Table 1-3), the 8-membered lactam 2d was obtained in 18% isolated yield (entry 6), and finally under the condition D Et_3Ga gave ***43% yield*** of the 8-membered lactam (entry 7). However even by using this procedure, the 9-membered

lactam 2e was obtained only in 7% yield (entry 9). An attempt to obtain 12-membered lactam was unsuccessful (entry 10), and the dimer 3f was obtained along with polymers.



1 2 3

Table 1-4. Et_3Ga Mediated Lactamization

entry	subs.	n	Et_3Ga (equiv.)	condn.[b]	product, yield/% (ring size) monomer	dimer
1	1a	1	1.5	A	2a **88** (5)	0
2	1b	2	2	B	2b **86** (6)	0
3	1b	2	2	C	no reaction	
4	1c	3	1.5	A	2c **81** (7)	0
5	1c	3	1.5[c]	A	2c 77 (7)	0
6	1d	4	1.5	A	2d 18 (8)	3d 4 (16)
7	1d	4	1.5	D	2d **43** (8)	3d 12 (16)
8	1e	5	1.5	A	0	3e 6 (18)
9	1e	5	1.5	D	2e 7 (9)	3e 8 (18)
10	1f	8	1.5	A	0	3f 10 (24)

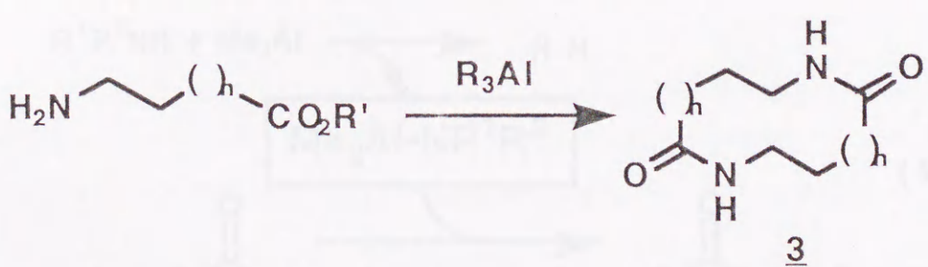
b. A : substrate (1 mmol) / toluene (10 mL) / reflux
B : substrate (1 mmol) / benzene (10 mL) / reflux
C : substrate (1 mmol) / benzene (10 mL) / 45°C
D : substrate (1 mmol) / toluene (100 mL) / reflux

c. Me_3Ga was used instead of Et_3Ga

1-3-3. Reaction of R_3Al with α, ω-Amino Acid Esters

Simple α, ω-amino acids 1 are insoluble in the common organic solvents such as toluene, benzene and THF. Therefore, the reaction must start under heterogeneous conditions, and perhaps as the reaction proceeds, homogeneous solution is produced. This suggests the formation of intermediates which are soluble in organic solvents. Finally, we obtain the lactams soluble in such organic solvents along with insoluble polymers.

Next, I investigated the reactions of R_3Al and the α,ω-amino acid esters 4 which were soluble in the aromatic hydrocarbons such as toluene and benzene. The results are listed in Table 1-5. Even though 12-membered lactam was not obtained, the yield of the dimeric 24-membered lactam was improved than the heterogeneous cases (entry 4 vs. entry 10 in Table 1-4 and entry 11 in Table 1-3).. These results suggested that large ring lactams (more than about 20-membered) can be synthesized effectively by **the R_3Al mediated cyclization of α, ω-amino acid esters**



(1-3)

3

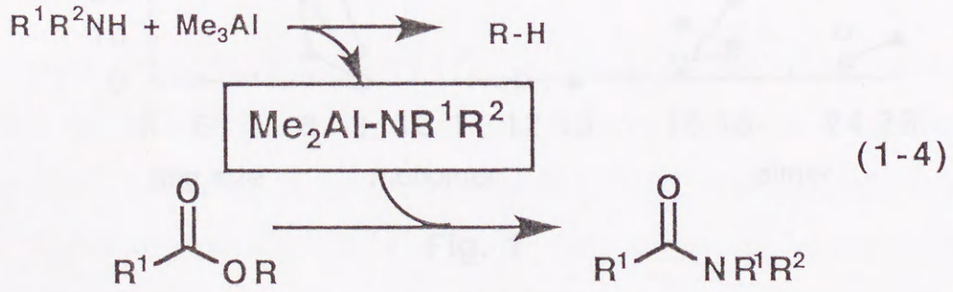
Table 1-5 R_3Al Mediated Reactions of α,ω-Amino Acid Esters

	substrate		R_3Al			
entry	n	R'	R	(equiv.)	conditions[d]	results
1	3	NBu_4	Et	2	A	no reaction
2	8	Et	Et	5	B	ethylation (65 wt%)
3	8	CH_2Ph	Me	2	A	**3f, 26% (24)**
4	8	CH_2Ph	Me	5	A	**3f, 38% (24)**
5	8	$CH_2C_6H_4NO_2$	Et	1	A	no reaction

d. A : substrate (1 mmol) / benzene (10 mL) / reflux
B : substrate (1 mmol) / toluene (10 mL) / reflux

1-4. Discussion

The intermolecular amide bond formation between carboxylic acid esters and amines is accomplished with dimethylaluminum amide (eq.1-4)[10] or with boron reagents[11]. The intramolecular β-lactam formation from β-amino acid ester is achieved by using i-Bu_3Al (eq. 1-5)[12].



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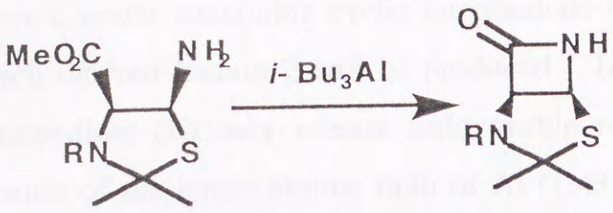


(1-5)

The present results clearly demonstrate that R_3Al mediated method can be applied to the lactam formation of the 5- to 8-membered rings from α,ω-amino acids, and more importantly that Et_3Ga is a useful reagent, more efficient than R_3Al, for macrolactamization to the 7- to 9-membered rings. Comparison between the Al and Ga procedures is made in Fig. 1.

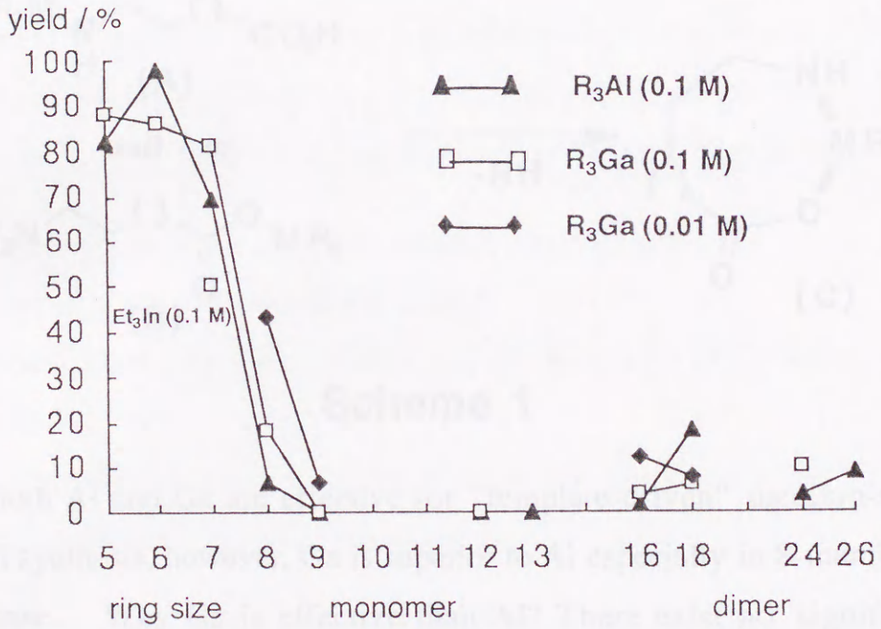
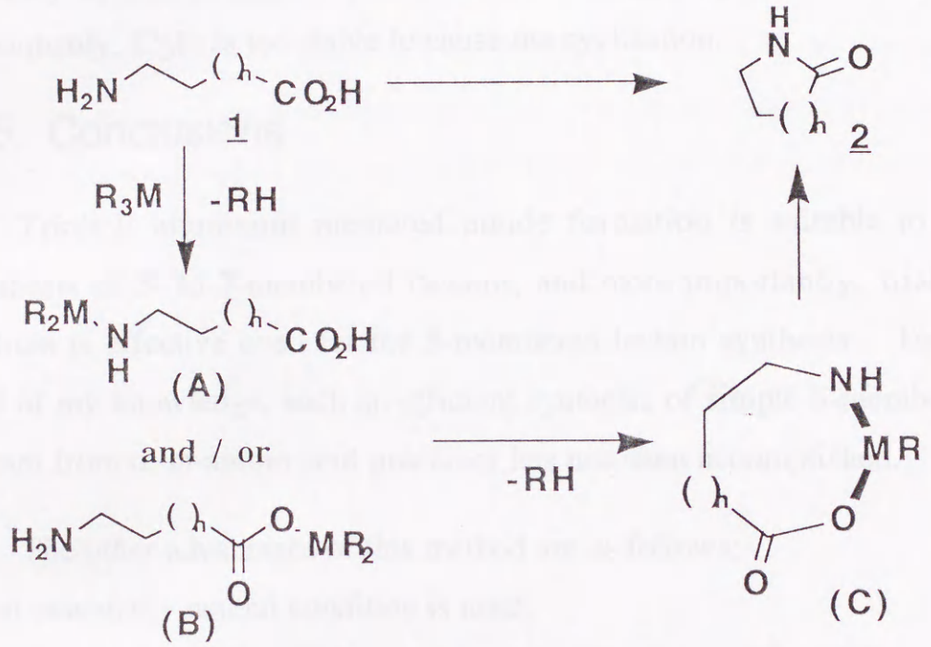


Fig. 1

A proposed mechanism of this reaction is shown in scheme 1. It is well known that trialkyl aluminums can react with both amines and carboxylic acids with evolution of alkanes. α, ω-Amino carboxylic acid 1 and R_3M (M=Al and Ga) may react with evolution of alkanes to form acyclic intermediates (A) and/or (B). Then, again with evolution of

alkanes, metal containing cyclic intermediate (C) may be produced from which desired lactam 2 will be produced. In the medium-sized case, intermediate (C) may release unfavorable ring strain to some extent because of the larger atomic radii of Al (1.43 Å, cf. C:0.77 Å) and Ga (1.22 Å), and the larger bond lengths of Al-O (ca.1.9 Å, cf. C-O:1.4 Å), Al-N (ca. 1.9 Å, cf. C-N:1.5 Å), Ga-O, and Ga-N bonds.



Scheme 1

Both Al and Ga are effective for "template-driven" medium-sized lactam synthesis, however, Ga is superior to Al especially in 8-membered ring case. Why Ga is effective than Al? There exist no significant differences between Ga and Al in their atomic radius and M-O and M-N bond lengths (M=Al or Ga). Furthermore, the comparable monomer / dimer ratios (3.5 ~ 4 : 1) were observed in both Et_3Al and Et_3Ga mediated synthesis of 8-membered lactam (entry 9 in Table 1-3, entries 6 and 7 in Table 1-4). Therefore, the reactivity difference between Et_3Al and Et_3Ga is due to the thermodynamic stability of both reagents;

Et_3Ga is thermally more stable than Et_3Al. As mentioned earlier, Et_3Al is gradually decomposed during the reaction under toluene reflux, loosing a potential as condensation reagent.

Macrolactamization with Et_3In was also attempted. Unfortunately, this reagent was less effective than Et_3Al and Et_3Ga. The thermal stability of these reagents is in an order of $Et_3In > Et_3Ga > Et_3Al$. Presumably, Et_3In is too stable to cause the cyclization.

1-5. Conclusions

Trialkyl aluminum mediated amide formation is suitable to the synthesis of 5- to 7-membered lactams, and more importantly, trialkyl gallium is effective even for the 8-membered lactam synthesis. To the best of my knowledge, such an efficient synthesis of simple 8-membered lactam from α, ω-amino acid precursor has not been accomplished.

The other advantages of this method are as follows;

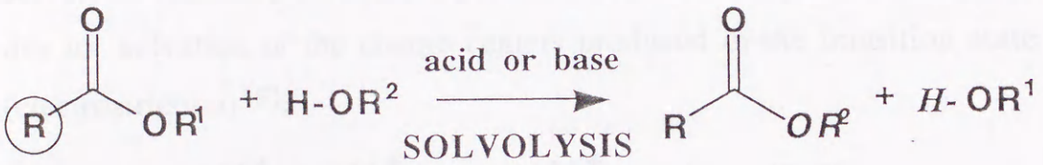
1. an essentially neutral condition is used;
2. derivatization of starting material is not necessary (free amino acids are utilized);
3. high dilution procedure is not necessarily needed (i.e. no syringe pump, considerable amount of solvent, etc....)

The mildness and simplicity of the present procedure, coupled with the good yield that can be obtained for the 5- to 8-membered lactam synthesis, should make gallium more important in organic synthesis.

Chapter 2. Mild Solvolysis of Carboxylic Acid Esters Under High Pressure

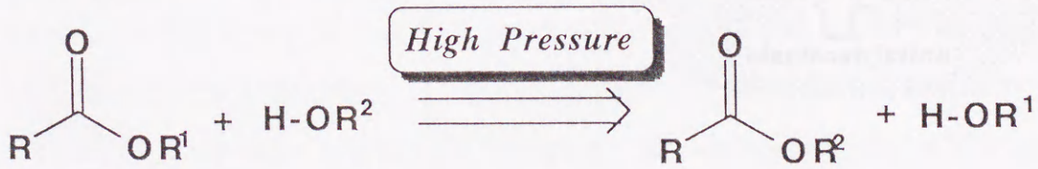
2-1. Introduction

Solvolysis of esters is one of the most essential transformations in organic synthesis. Normally, a basic or acidic aqueous solution is used for ester hydrolysis.[13] However, the hydrolysis of biologically related molecules such as amino esters, peptides,... or unsaturated fatty esters, under such conditions is accompanied more or less by side reactions, loss of chirality, or isomerization.[14]



2-2. Approach

My approach to this problem is application of high pressure. I discovered that the hydrolysis at high pressure proceeded under nearly neutral conditions, and thus the hydrolysis of the biologically related molecules was accomplished without accompanying the side reactions.



The high pressure thermodynamics of solutions are well known and the fundamental equations determining the rate in solution may be written as function of the activation volume $\Delta V^{\ddagger}$:[15]

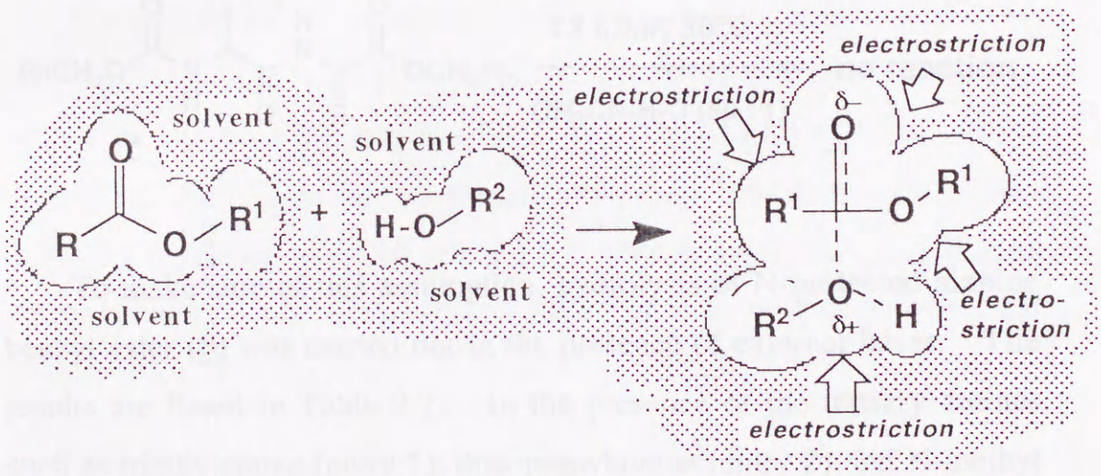
$$\left(\frac{\partial \ln k}{\partial P}\right)_T = -\frac{\Delta V^{\ddagger}}{RT} \qquad (2\text{-}1)$$

$\Delta V^{\ddagger}$: V(transition state) - V(reactant)

k : rate const. P : pressure

The activation volume is approximated to the differences in molar volume between the transition state and the initial state. It is clear from the equation (2-1) that the application of pressure accelerates reactions which have a negative volume of activation. The activation volume is divided into a structural factor and a solvent factor (2-2). In the case of solvolysis reaction, the solvent dependent factor ($\Delta V^{\ddagger}$(solv)) is negative due to solvation of the charge centers produced in the transition state (electrostriction)[16].

$$\Delta V^{\ddagger} = \Delta V^{\ddagger}(str) + \Delta V^{\ddagger}(solv) \qquad (2\text{-}2)$$

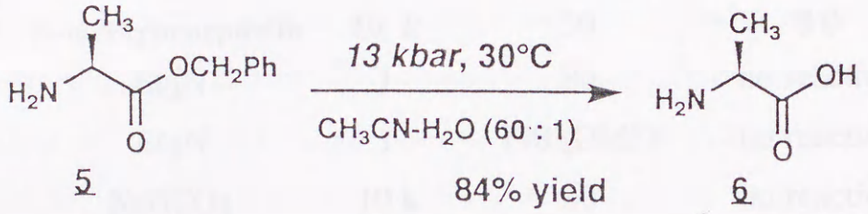


"Therefore all solvolytic displacement reactions undergo rate acceleration on application of pressure."[17]

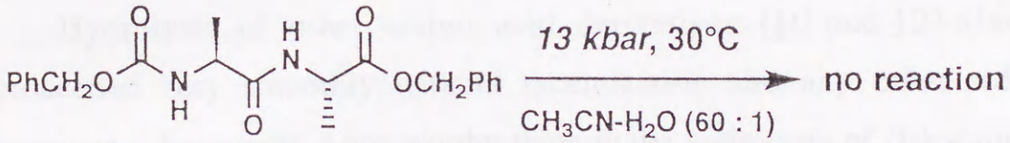
2-3. Results

2-3-1. Hydrolysis of Amino Acid Esters

At first, I tried to hydrolyze amino acid derivatives. (L)-Alanine benzyl ester (5) in acetonitrile-water (60:1) could be converted to (L)-alanine (6) in good yield at 30°C under 13 kbar. On the other hand, N-protected dipeptide ester (7) could not be hydrolyzed under the same reaction condition. It is reasonable to assume that the presence of free amino group is essential.

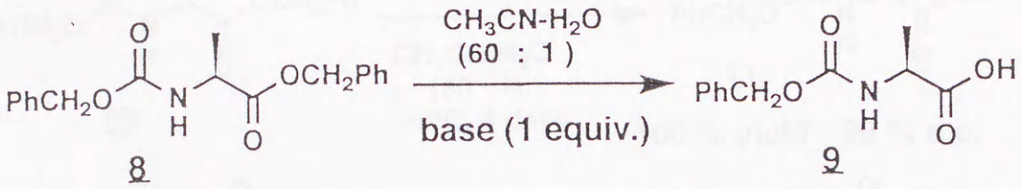


5 6



7

To make sure of this assumption, hydrolysis of N-protected alanine benzyl ester (8) was carried out in the presence of external bases. The results are listed in Table 2-1. In the presence of the tertiary amines such as triethylamine (entry 1), diisopropylamine (entry 2) and N-methyl morpholin (entry 3), the ester (8) was quantitatively hydrolyzed to acid 9 under 10 kbar. In contrast, the use of the high temperature instead of the high pressure (entries 4 and 5) and inorganic base instead of amines (entry 6) were not effective and lead to the recovery of the starting ester 8.



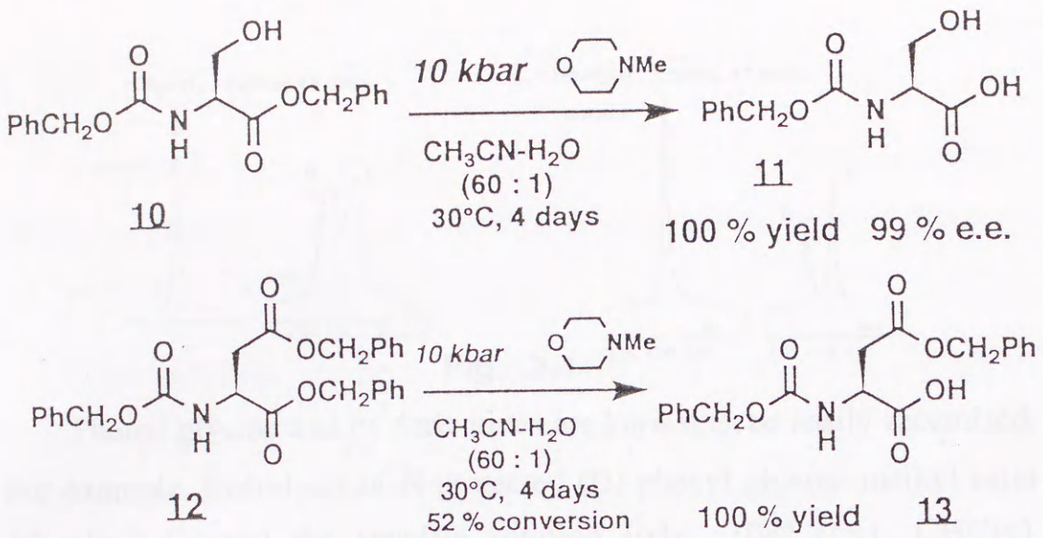
8 9

Table 2-1. Hydrolysis of Cbz-Ala-OBn

entry	base	pressure/bar	temp./°C	product, yield/%
1	**Et_3N**	**10 k**	30	**98**
2	***i*-Pr_2NEt**	**10 k**	30	**90**
3	**N-methylmorpholin**	**10 k**	30	**90**
4	Et_3N	1	80	no reaction
5	Et_3N	1	170 (DMF)	no reaction
6	$NaHCO_3$	10 k	30	no reaction

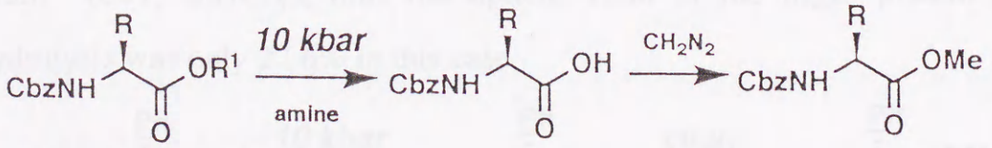
Hydrolysis of other amino acid derivatives (10 and 12) also proceeded very smoothly without racemization and any other side reactions. Especially a noteworthy thing is the hydrolysis of (L)-serine derivative 10. The usual aqueous hydrolysis produces an inherent difficulty for isolation of 11, since 11 is very water soluble. The high pressure induced hydrolysis requires normally 3~4 equivalent water, and thus isolation of water soluble products is very easy.

In a hydrolysis of aspartic acid derivative 12, high pressure method and the ordinary aqueous NaOH method[18] exhibited same chemoselectivity. Hydrolysis of the α-amino ester is faster than that of the side chain ester.



10 11 12 13

The degree of the racemization was determined by measurement of both optical rotation and ^{1}H-NMR spectrum in the presence of a chiral lanthanide shift reagent. The absolute values of optical rotation are known to be low for non-aromatic amino acid derivatives such as alanine and serine.[19] The exact degree of the racemization was determined by measurement of the ^{1}H-NMR spectrum of the product in the presence of Eu(hfc)$_3$. Lanthanide induced shift method could not be applied to the free carboxylic acid (many broad peaks were observed), thus the products were transformed to their methyl ester derivatives by treatment with diazomethane (Scheme 2-1). The ^{1}H-NMR spectra thus obtained were shown in Fig. 2-1.



Scheme 2-1

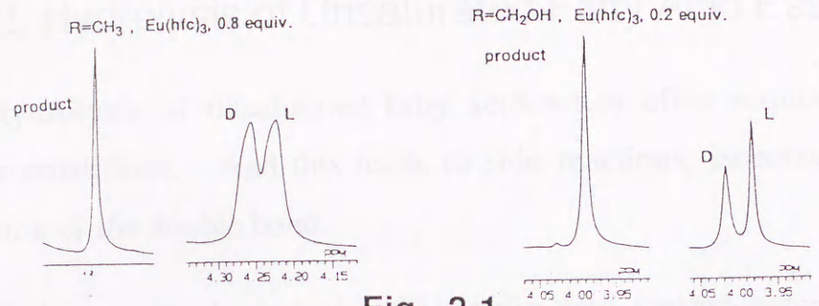
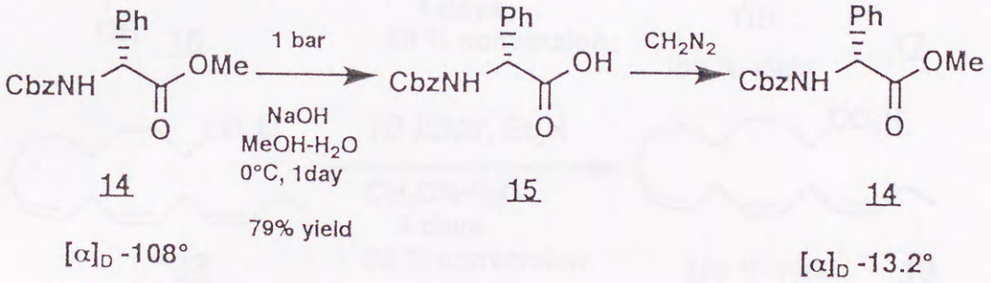
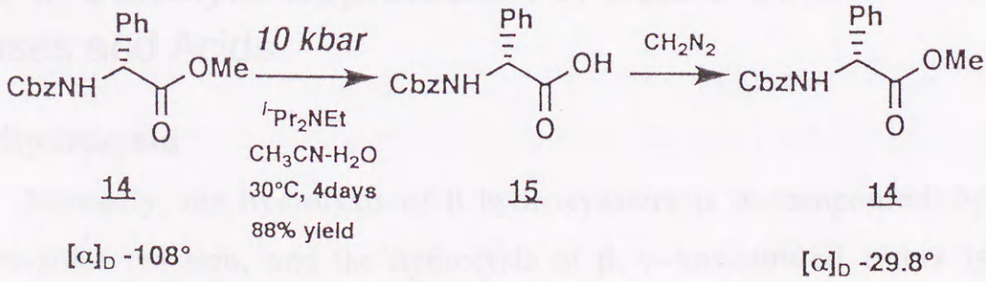


Fig. 2-1

Phenyl glycine and its derivatives are known to be easily racemized. For example, hydrolysis of N-protected (D)-phenyl glycine methyl ester 14 which showed the specific rotation $[\alpha]_D$ -108° (c=1, $CHCl_3$) proceeded at 0°C by methanolic sodium hydroxide solution and gave its carboxylic acid derivative (15) in good yield. Treatment of 15 by diazomethane reproduced methyl ester 14 and the optical rotation of this compound was only $[\alpha]_D$ -13° (c=1, $CHCl_3$).



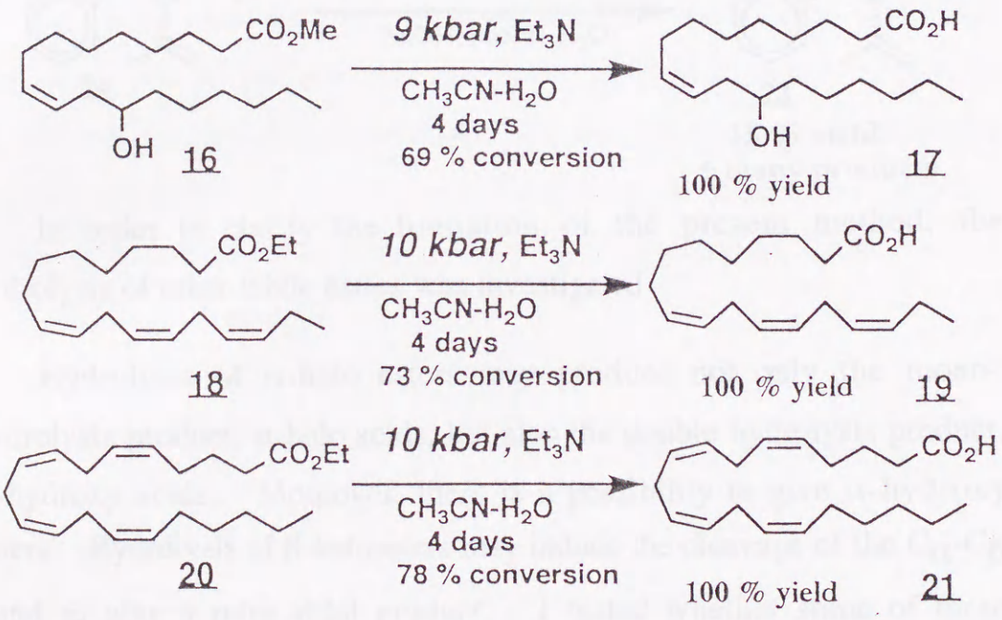
Unfortunately, the high pressure hydrolysis of 14 ($[\alpha]_D$ -108°) gave a similar result. The reproduced 14 exhibited the specific rotation $[\alpha]_D$ -29.8° (c=1, $CHCl_3$), thus the optical yield of the high pressure hydrolysis was only 27.6% in this case.



2-3-2. Hydrolysis of Unsaturated Fatty Acid Esters

Hydrolysis of unsaturated fatty acid esters often requires rather drastic conditions. And this leads to side reactions, isomerization or oxidation of the double bond.

High pressure hydrolysis of ricinolic acid methyl ester (16), γ-linolenic acid ethyl ester (18) and arachidonic acid ethyl ester (20) proceeded smoothly without side reactions. Compared with amino acid derivatives, lower reactivity of such long chain carboxylic esters is responsible for relatively low conversion of the reaction. As shown in section 2-4, application of much higher pressure will solve this problem.

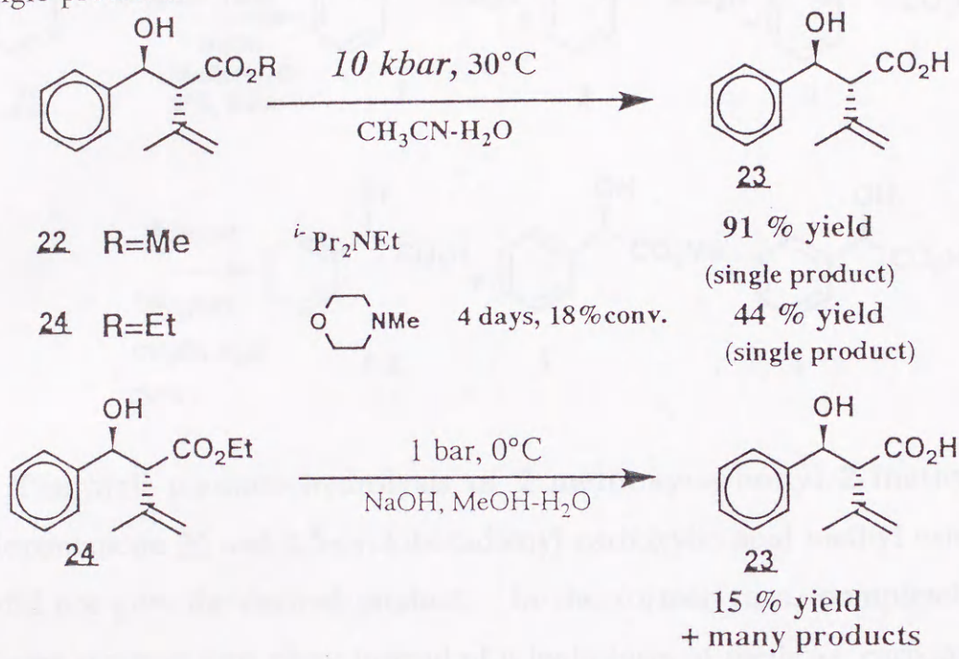


2-3-3. Solvolytic Deprotection of Esters Sensitive to Bases and Acids

a. Hydrolysis

Normally, the hydrolysis of β-hydroxyesters is accompanied by retro-aldol reaction, and the hydrolysis of β, γ–unsaturated esters is accompanied by isomerization of the double bond. The ester 22 or 24

has a β, γ–olefinic moiety in addition to a β-hydroxy group. Actually, the ordinary aqueous hydrolysis of 24 gave a number of products. The high pressure induced hydrolysis afforded the desired hydroxy acid 23 as a single products.

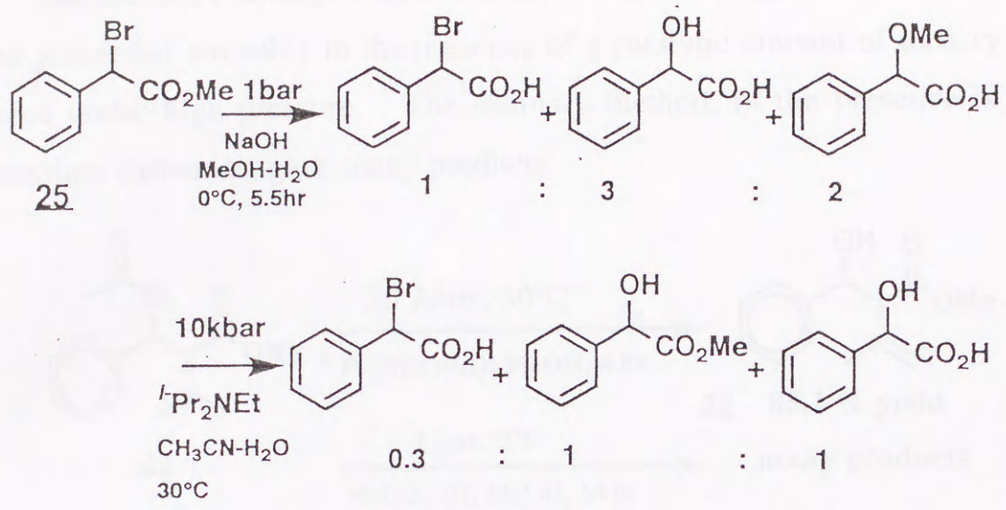


In order to clarify the limitation of the present method, the hydrolysis of other labile esters was investigated.

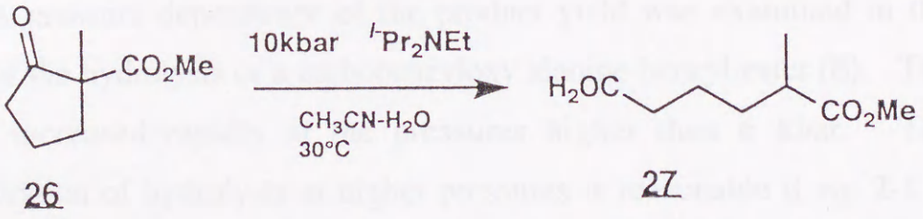
Hydrolysis of α-halo esters may produce not only the mono-hydrolysis product, α-halo acids, but also the double hydrolysis product, α-hydroxy acids. Moreover, there is a possibility to give α-hydroxy esters. Hydrolysis of β-ketoesters may induce the cleavage of the C_α-C_β bond to give a retro-aldol product. I tested whether some of these difficulties might be solved by using the high pressure technique.

Indeed, the hydrolysis of methyl 2-bromo phenylacetate 25 by methanolic NaOH solution gave four products; desired 2-bromo phenyl acetic acid, 2-hydroxy phenyl acetic acid, 2-methoxy phenyl acetic acid and unidentified carboxylic acid. Unfortunately, the high pressure method also produced a mixture of hydrolysis products. The reaction of

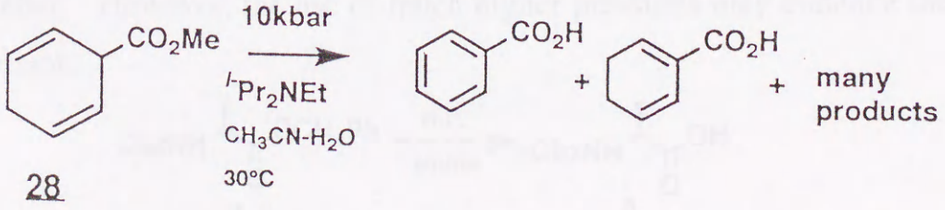
25 in the presence of ^{i}-Pr$_2$NEt under 10 kbar gave three products along with unreacted 25.



The high pressure hydrolysis of 2-methoxycarbonyl-2-methyl cyclopentanone 26 and 2,5-cyclohexadienyl carboxylic acid methyl ester 28 did not give the desired product. In the former case, completely different reaction took place instead of a hydrolysis of methoxy carbonyl group. 5-Carbomethoxy hexanoic acid was obtained as a sole product via C1-C2 bond cleavage.

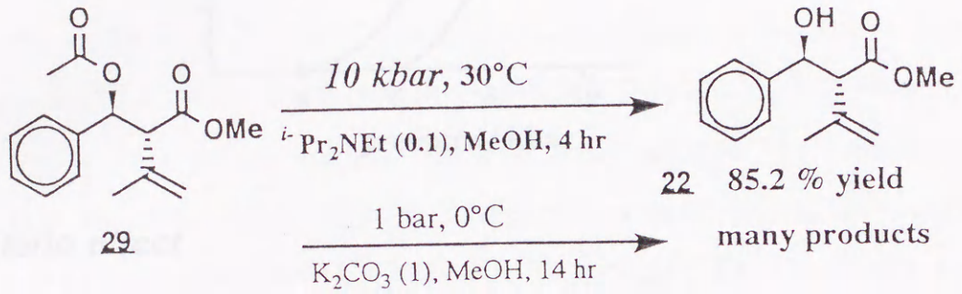


The hydrolysis of 28 resulted in the formation of complex mixtures.



b. Methanolysis

The alcohol exchange reaction of acetate group in 29 with methanol also proceeded smoothly in the presence of a catalytic amount of tertiary amine under high pressure. The ordinary method, in the presence of potassium carbonate, gave many products.



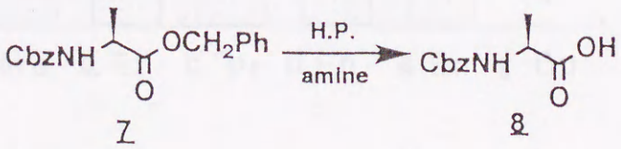
29

2-4. Discussion

The effect of pressure and structural variations upon hydrolysis was studied.

a. pressure effect

A pressure dependence of the product yield was examined in the case of the hydrolysis of a carbobenzyloxy alanine benzyl ester (8). The yield increased rapidly at the pressures higher than 6 kbar. The acceleration of hydrolysis at higher pressures is reasonable if eq. 2-1 is taken into consideration. As I mentioned earlier, relatively lower conversion was obtained in the hydrolysis of long chain fatty acid esters at 10 kbar. However, the use of much higher pressures may enhance the conversion.



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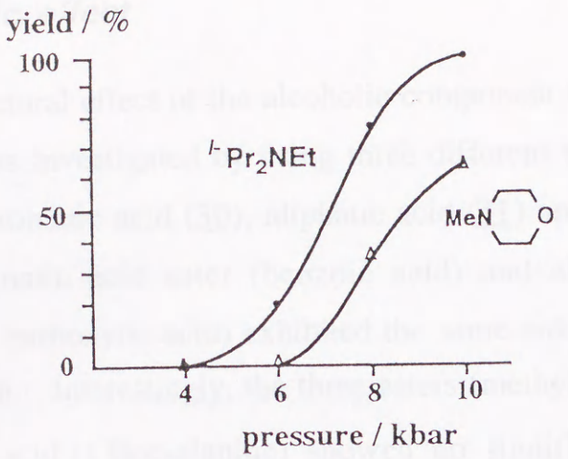
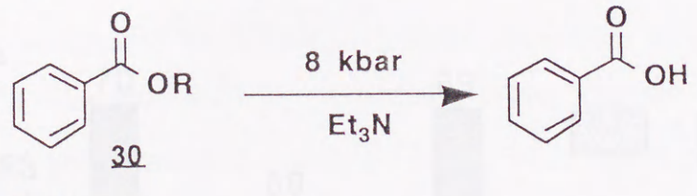
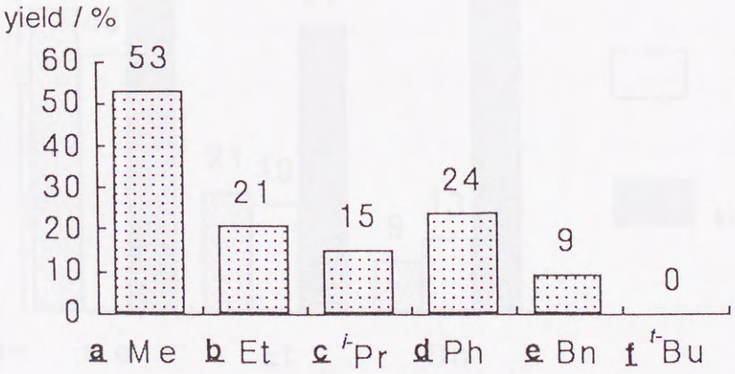


b. steric effect

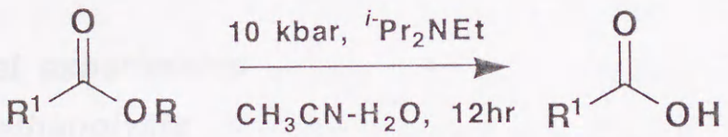
The high pressure hydrolysis of various benzoic acid esters (30a~f) was performed in the presence of triethylamine under 8 kbar in order to investigate the steric effect of the alcoholic component. An order on the ease of hydrolysis is as follows; Me » Ph> Et > ^{i}-Pr > CH_2Ph »» ^{t}-Bu. This order is identical with the order of the ordinary hydrolysis (basic hydrolysis at atmospheric pressure).

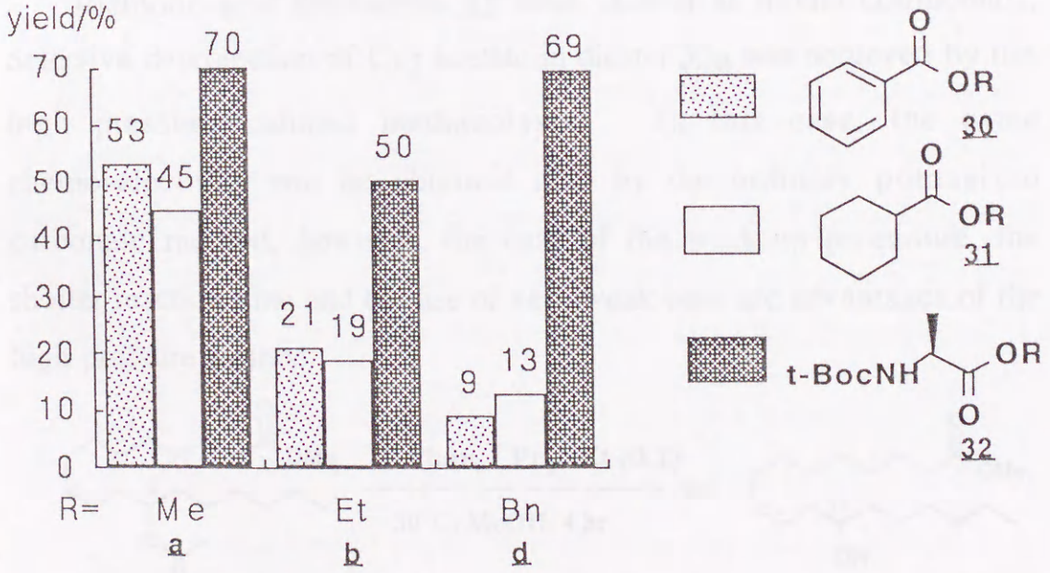




c. electronic effect

The structural effect of the alcoholic component upon high pressure hydrolysis was investigated by using three different types of carboxylic acid esters, aromatic acid (30), aliphatic acid (31) and amino acid (32). Both an aromatic acid ester (benzoic acid) and aliphatic acid ester (cyclohexane carboxylic acid) exhibited the same order of reactivity, Me » Et > CH_2Ph. Interestingly, the three esters (methyl, ethyl and benzyl) of an amino acid (t-Boc-alanine) showed no significant difference in reactivity under the high pressure condition. I don't know the exact reason for these observations, however, it is probable that the degree of the charge separation in the starting esters influences the reaction rate. In the cases of amino acid, this electronic factor was preferred rather than the steric factor observed in other cases.

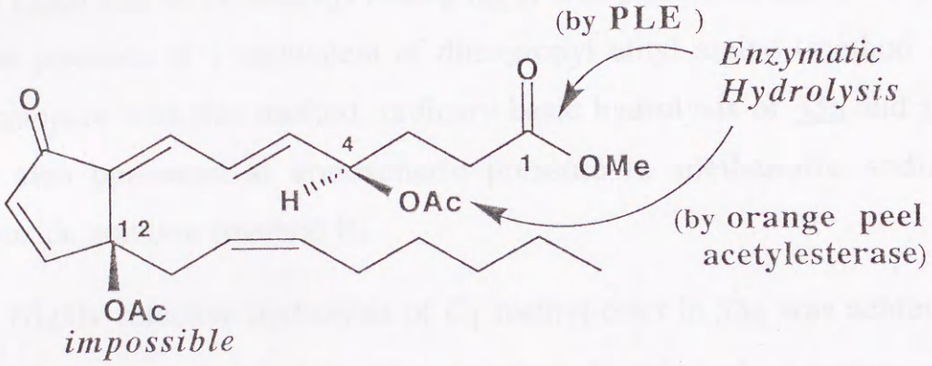




2-5. Application

Selective deprotection of an ester function in di- or tri-ester substrates is important but chemically difficult procedure. For example, selective derivatization of clavulone, a marine prostanoid, was achieved only by enzymatic hydrolysis.[20] Taking advantage of my high pressure method, I accomplished selective hydrolysis of diester substrates.

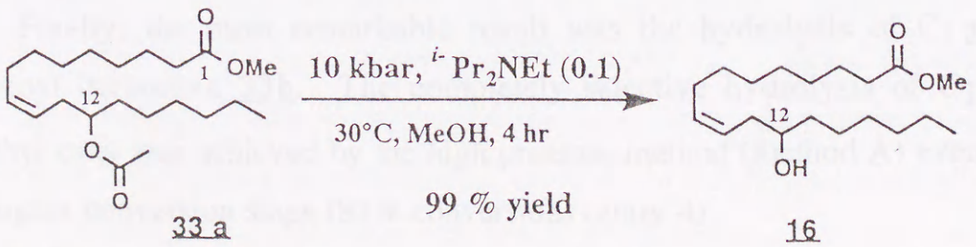
clavulone II : a marine prostanoide



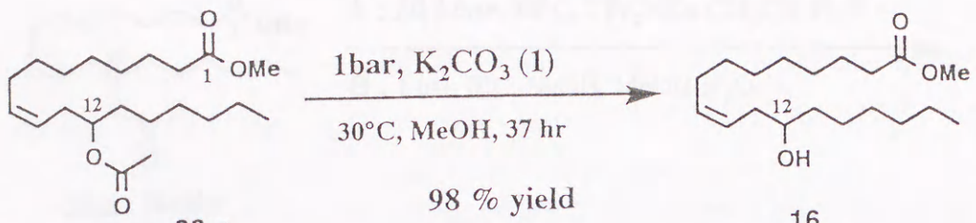
model experiments

a. methanolysis

Ricinolic acid derivatives 33 were chosen as model compounds. Selective deprotection of C_{12} acetate in diester 33a was achieved by the high pressure induced methanolysis. In this case, the same chemoselectivity can be obtained also by the ordinary potassium carbonate method, however, the ease of the work-up procedure, the shorter reaction time and the use of very weak base are advantages of the high pressure method.



33 a 16



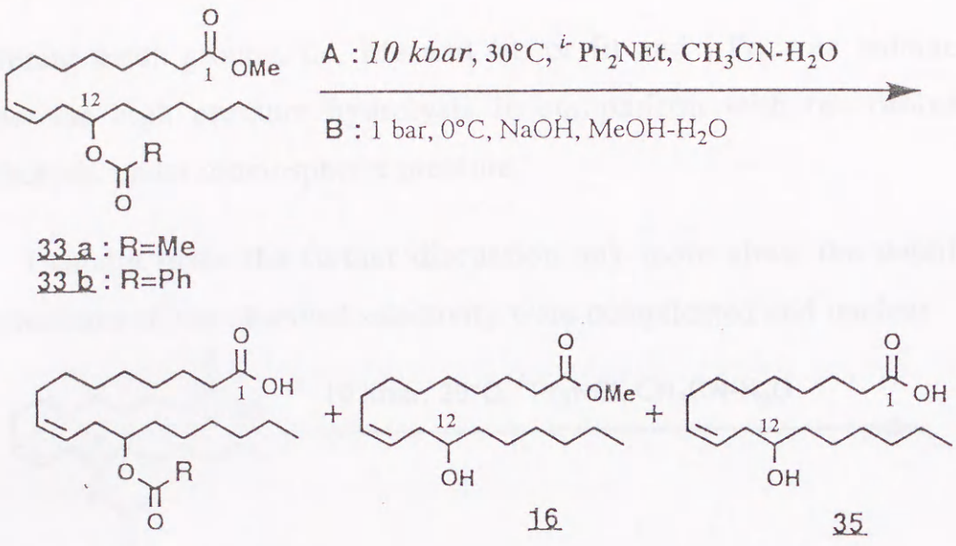
33 a 16

b. Hydrolysis

High pressure induced hydrolysis of 12-acetyl ricinolic acid methyl ester (33a) and its 12-benzoyl analog (33b) was performed under 10 kbar in the presence of 1 equivalent of diisopropyl ethyl amine (method A). To compare with this method, ordinary basic hydrolysis of 33a and 33b was also perfomed at atmospheric pressure in methanolic sodium hydroxide solution (method B).

Highly selective hydrolysis of C_1 methyl ester in 33a was achieved by high pressure induced reaction (method A) when the reaction was stopped at the low conversion stage (25% conversion). The three products were obtained in the following ratio; 34a/16/35=94.5/3.9/1.6 (entry 1). Of course, such a high chemoselectivity could not be observed in the ordinary methanolic sodium hydroxide mediated hydrolysis reaction (method B) because C_{12} acetate was also deprotected by the competing ester exchange reaction (entry 2). On the other hand, use of non-alcoholic solvents, such as DMSO, in order to avoid the ester exchange resulted in decrease of the hydrolysis rates, and thus no detectable amount of the product was obtained even after several days.

Finally, the most remarkable result was the hydrolysis of C_{12} benzoyl derivative 33b. The completely selective hydrolysis of C_1 methyl ester was achieved by the high pressure method (method A) even at higher conversion stage (81% conversion) (entry 4).

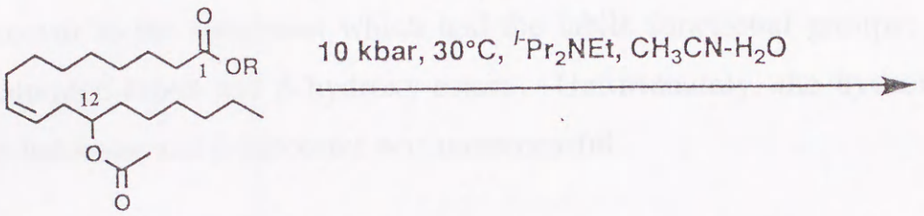


entry	substrate	method	conv./%	products ratio 34	16	35
1	33a	**A**	25	**94.5**	**3.9**	**1.6**
2	33a	B	33	20.1	64.6	15.3
3	33a	B	87	46.7	10.1	43.2
4	33b	**A**	81	**100**	**0**	**0**
5	33b	B	36	71.9	10.5	17.6

To investigate the limitation of high pressure method, the selective hydrolysis of other 12-acetyl ricinolic acid derivatives was tried. The change of C1 methyl ester to ethyl and benzyl esters resulted in decrease of the selectivity and a considerable amount of 12-hydroxy carboxylic acid 35 was produced even at lower conversion stage (entry 1 vs. entry 3 and entry 4). Finally, the hydrolysis of isopropyl ester 33e gave 12-hydroxy derivative 16e as a sole product (entry 5). These results indicated that the steric hindrance of the ester carbonyl carbon also influenced the reaction rate of the high pressure hydrolysis as observed in the ordinary case. However, the reactivity difference between two

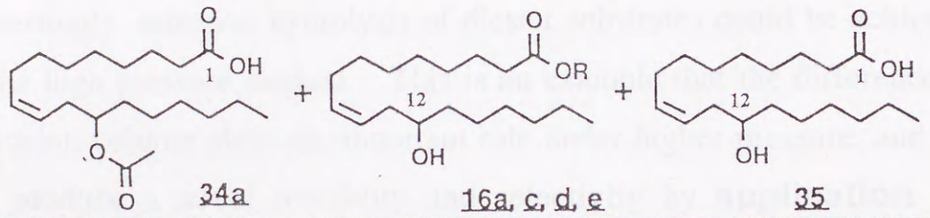
different ester groups, i.e. Me and Et, or Et and i-Pr, was enhanced under the high pressure hydrolysis in comparison with the ordinary hydrolysis under atomospheric pressure.

I cannot make the further discussion any more since the detailed mechanisms of the observed selectivity were complicated and unclear.



33a : R=Me 33c : R=Et

33d : R=CH_2Ph 33e : R=^{i}Pr



34a 16a, c, d, e 35

				products ratio		
entry	substrate	R	conv./%	34	16	35
1	33a	Me	25	94.5	3.9	1.6
2	33c	Et	10	93.8	6.2	trace
3	33c	Et	26	55	11	**34**
4	33d	CH_2Ph	16	54	6	**40**
5	33e	i-Pr	3	0	**100**	0

2-6. Conclusions

In conclusion, a mild solvolysis of carboxylic acid esters can be achieved in the presence of weakely basic amines by application of high pressure. Some advantages of this procedure are following;

1. mild (weakely basic) reaction condition,[21)]
2. hydrolysis in organic solvent containing a minimum amount of water,
3. no use of matal ions, which enables easy isolation of products.

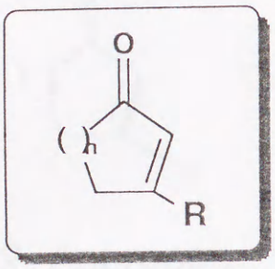
This method was successfully applied to the biologically important molecules, such as, α-amino acid esters and long chain fatty acid esters, moreover to the substrates which had the labile functional groups; β,γ-unsaturated esters and β-hydroxy esters. Unfortunately, the hydrolysis of α-haloester and β-ketoester was unsuccessful.

Pressure and structure dependences upon reaction rate were investigated and compared to the ordinary basic hydrolysis. Interestingly, selective hydrolysis of diester substrates could be achieved by the high pressure method. This is an example that the difference of activation volume plays an important role under higher pressure, and we can produce a novel reactivity and selectivity by **application of pressure**, which can not be accomplished by the previous methods.

Chapter 3. New Method for Construction of Cyclic Enones Via Phosphonate Anions

3-1. Introduction

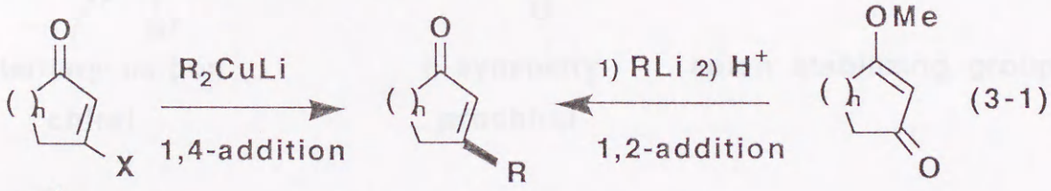
3-substituted cyclic enones



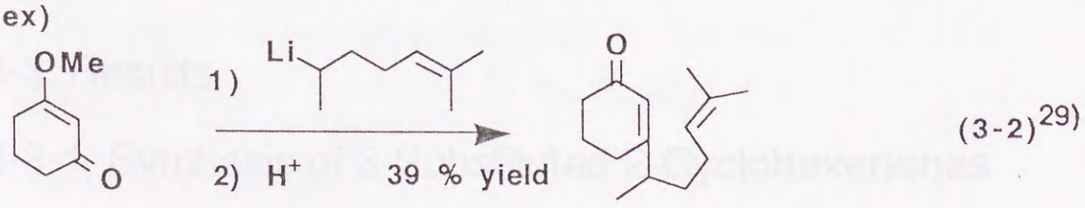
3-Substituted 2-cyclic enones are versatile building blocks for the synthesis of complex cyclic natural products such as spirocyclic and fused ring sesquiterpenes.

The synthetic method most commonly used is based either on the 1,4-addition of organocopper reagents to 3-halogenated (or acetoxy)-2-cyclic enone[22] or on the 1,2-addition of organolithium or magnesium reagents to 3-alkoxy-2-cyclic enones.[23] These organometallic-based procedures are subjected to inherent drawbacks involved in the use of organometallic reagents; introduction of secondary alkyl groups or of functional groups often causes difficulties.

1) organometallic based procedures



ex)

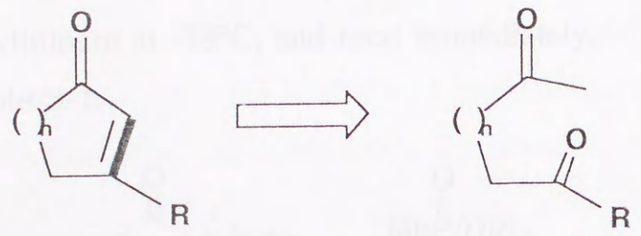


(3-2)[29]

An another method is intramolecular aldol condensation of 1,4- or 1,5-diketone substrates.[24] This method requires rather drastic

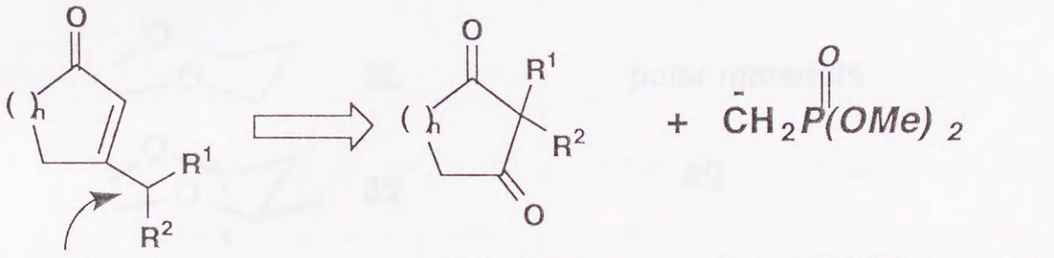
conditions and is only applicable to simple substances. Furthermore, in the case of non-symmetrical diketones selective formation of thermodynamically unstable isomer is practically impossible.

2) aldol condensation



3-2. Approach

I developed a new approach to 3-substituted-2-cyclic enones. The reaction of 2,2-disubstituted 1,3-cyclic diones with dimethyl methylphosphonate anion produces the corresponding cyclic enones in moderate to good yields.



tertiary carbon chiral | **σ–symmetry prochiral** | **anion stabilizing group**

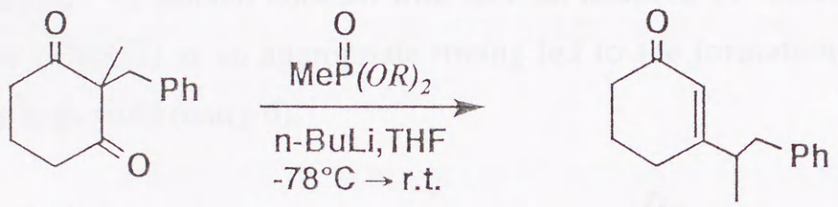
3-3. Results

3-3-1. Synthesis of 3-Substituted 2-Cyclohexenones

To optimize the reaction condition, the effects of phosphonate structures, bases and additives were investigated.

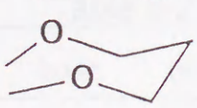
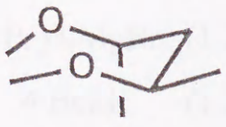
a. Phosphonate Structures

The reactions of 36a with various phosphonate stabilized anions were tried in tetrahydrofuran (THF). The phosphonate stabilized anions were generated in situ by treatment with a molar equivalent of n-butyllithium at -78°C, and used immediately. The results are listed in Table 3-1.



36a 37a

Table 3-1 Effect of the Phosphonate Structures

-$(OR)_2$		product, yield /%
-$(OMe)_2$		47
	38	polar materials
	39	49
-(O*i*-Pr)$_2$	40	18

Both methyl dimethylphosphonate and 2,4,6-trimethyl-2-oxo-1,3,2-dioxaphosphorinane were effective for this reaction.

b. Bases and Additives

The reaction of 36a with methyl dimethylphosphonate was performed under the several conditions. The results are listed in Table 3-2.

Phosphonate stabilized anion could not be generated by treatment with a magnesium diisopropylamide in THF (entry 1). Both n-butyllithium in THF and lithium diisopropylamide (LDA) in THF were suitable for the synthesis of cyclohexenone 37a (entries 2 and 3). LDA was superior to n-butyllithium. Ether was less effective than THF as a solvent (entry 4). An addition of borontrifluoride etherate resulted in failure (entry 5). In marked contrast with this, an addition of trimethyl chlorosilane (TMSCl) at an appropriate timing led to the formation of 37a in very high yield (entry 6).

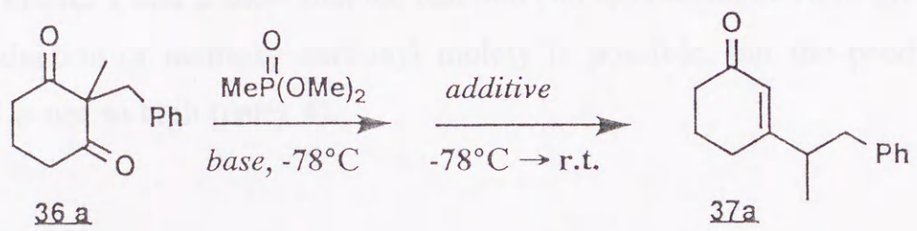


Table 3-2 Optimization of reaction conditions

entry	base	(equiv)	solvent	additive	products, yield/%
1	^{i}-Pr$_2$NMgBr	(1.2)	THF	none	no reaction
2	^{n}-BuLi	(1.2)	THF	none	47
3	LDA	(1.2)	THF	none	65
4	LDA	(1.2)	ether	none	48
5	LDA	(1.2)	THF	$BF_3 \cdot OEt_2$	polar materials
6	***LDA***	***(1.2)***	***THF***	***TMSCl***	***93***

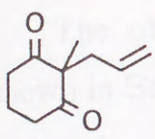
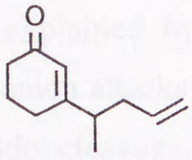
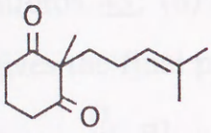
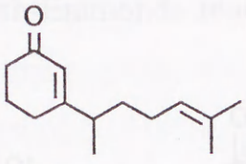
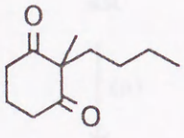
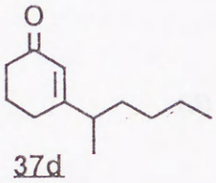
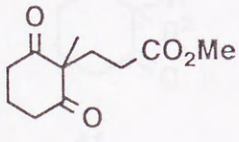
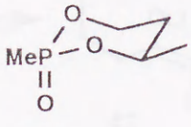
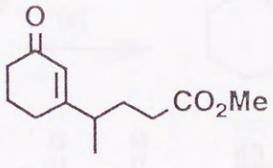
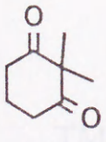
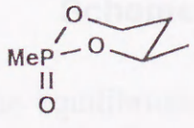
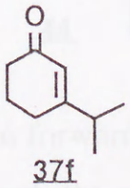
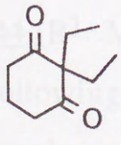
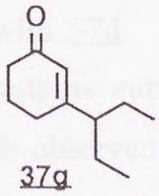
Finally, the optimal reaction condition is as follows. To a stirred cold solution of 1.2 equivalent of dimethyl methylphosphonate in dry THF at -70°C was added 1.2 equivalent of lithium diisopropyl amide under an argon atmosphere. After the mixture was stirred for 30 minutes, a solution consisting of diketone 36a in THF was added, and

stirring was then continued for 10 hr at -70°C. A solution of 1.2 equivalent of TMSCl in dry THF was then added at -70°C. The reaction mixture was allowed to warm to room temperature, and stirring was continued for an additional 36 hr. After usual work-up desired cyclohexenone 37a was obtained in 93% yield.

The results of reactions of phosphonate anions with various 1,3-cyclic diketones are summarized in Table 3-3.

Entries 1 and 2 show that the reaction can tolerate an olefinic group. Introduction of methoxy carbonyl moiety is possible, but the product yield is not so high (entry 4).

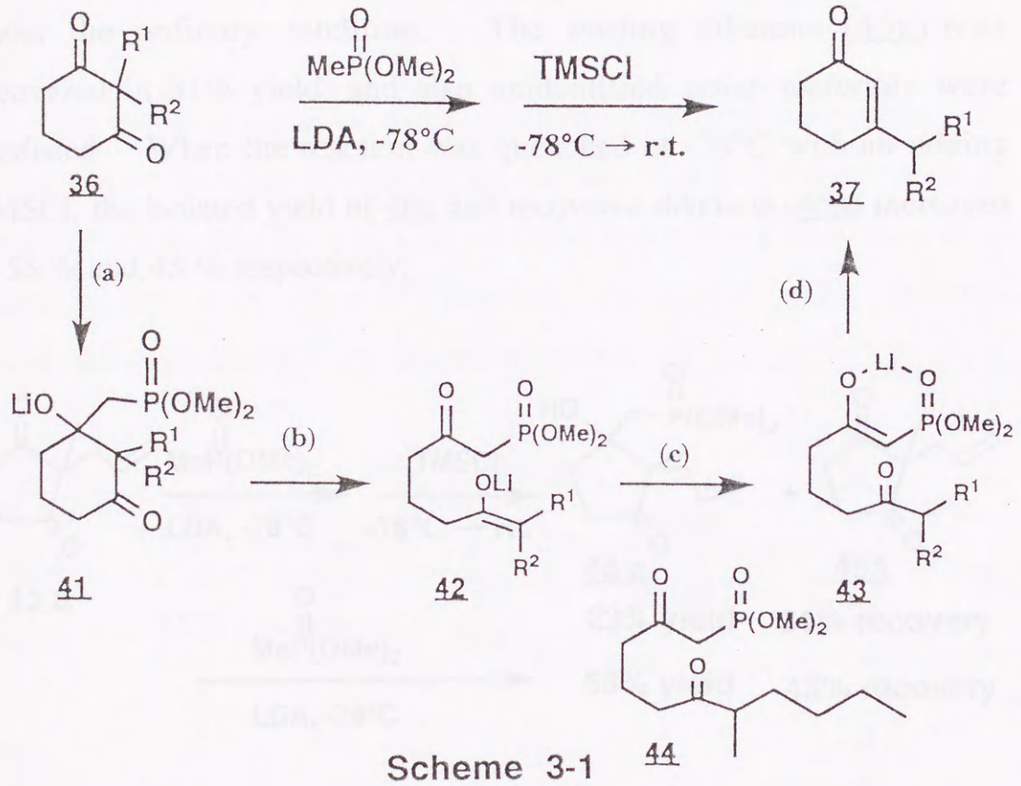
Table 3-3 Synthesis of Various 3-Substituted 2-Cyclohexenones

entry	substrate	conditions[a]	product	(yield/%)
1	 36b	$MeP(OMe)_2$	 37b	(89)
2	 36c	$MeP(OMe)_2$	 37c	(61)
3	 36d	$MeP(OMe)_2$	 37d	(65)
4	 36e		 37e	(33)
5	 36f		 37f	(58)
6	 36g	$MeP(OMe)_2$	 37g	(22)

[a]. conditions were same as entry 6 in Table 3-2 except for phosphonate

3-3-2. Reaction Mechanism

The observed rearrangement can be explained by the sequence shown in Scheme 3-1; (a) the phosphonate anion attacks one of the two carbonyl groups of 36 to give 41; (b) retro-aldol cleavage of 41 produces the keto phosphonate anion 42; (c) reorganization of the acidic proton affords 43; (d) an intramolecular Wadsworth-Emmonds reaction of 43 gives the final product 37.



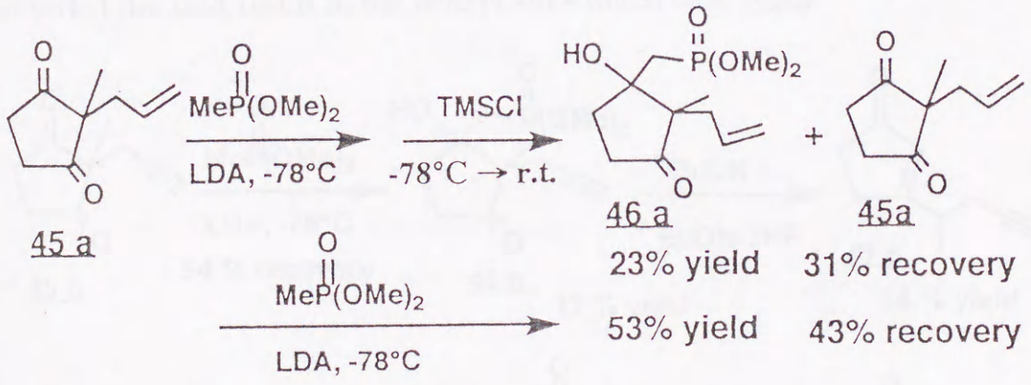
Scheme 3-1

TMSCl may shift the equilibrium in the forward direction. When the reaction was quenched after a short period, the acyclic phosphonate 44 (R^1=Me, R^2=^{n}-Bu) was isolated along with 37d. Furthermore, the following observation regarding related systems supports the above mechanism. A similar retro-aldol cleavage is observed in the reaction of 2,2-disubstituted 1,3-cyclohexanedione with alcoholic sodium

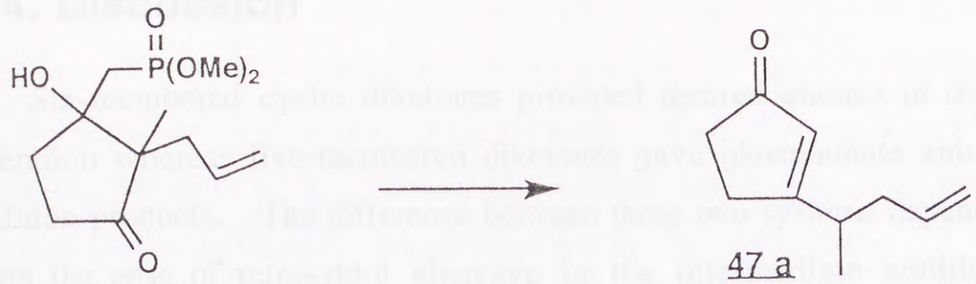
hydroxide,[25] and the bond reorganization in enol lactones has been reported previously.[26]

3-3-3. Synthesis of 3-Substituted 2-Cyclopentenones

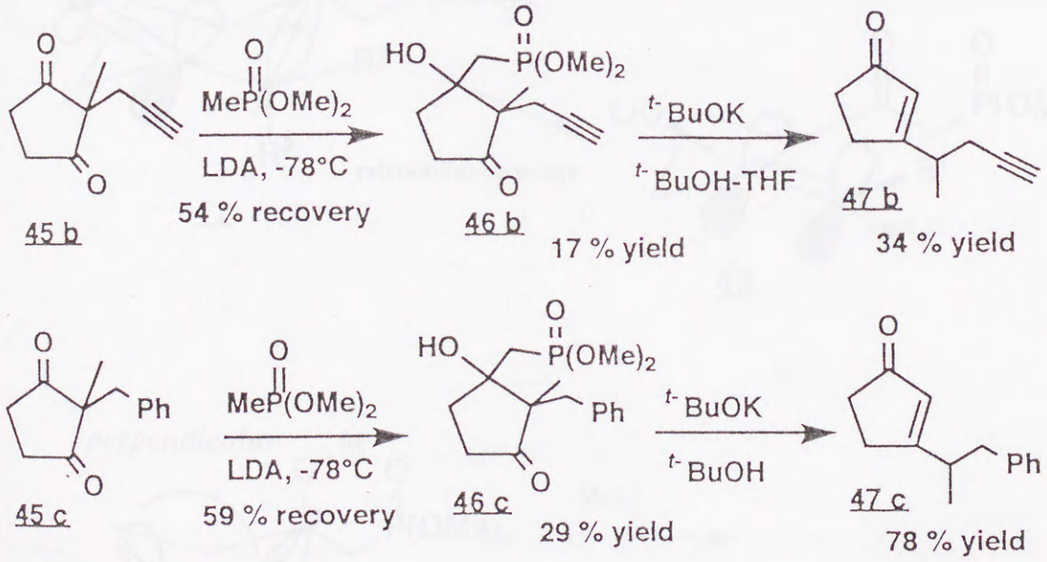
The reaction of phosphonate anion with 2,2-disubstituted 1,3-cyclopentanedione 45a was examined under the same condition. The result was quite different from six-membered ring case. Addition product 46a was isolated in 23% yield when the reaction was carried out under the ordinary condition. The starting diketone (45a) was recovered in 31% yield, and also unidentified polar materials were produced. When the reaction was quenched at -78°C without adding TMSCl, the isolated yield of 46a and recovered diketone (45a) increased to 53 % and 43 % respectively.



Base treatment of 46a gave desired cyclopentenone derivative 47a. The treatment of 46a with sodium hydride in dimethoxyethane at room temperature gave 47a in 56 % yield. Use of potassium tert-butoxide in tert-butanol was less effective and the use of potassium hydride in dimethoxyethane resulted in recovery of the starting material 46.



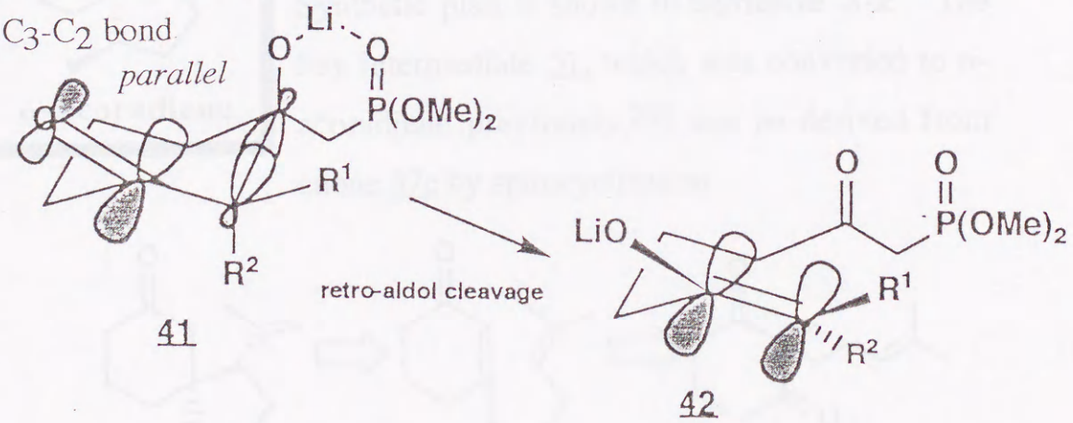
This two step sequence was also effective for other substances. In the propargyl substituted case (45b), use of potassium *tert*-butoxide in tetrahydrofuran-*tert*-butanol gave the best result in the base promoted rearrangement step. Use of potassium *tert*-butoxide in *tert*-butanol afforded the best result in the benzyl substituted case (45c).



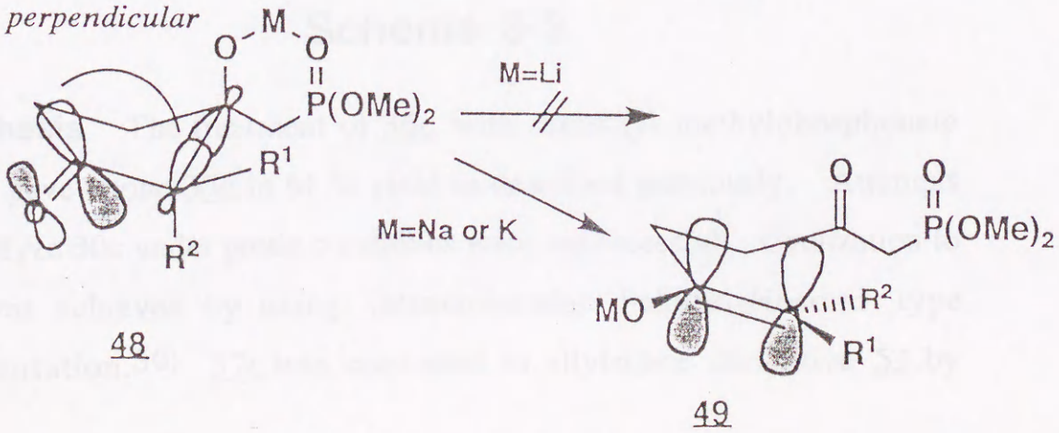
The reason for the difference in reactivity between six-membered ring system and five-membered ring system is discussed in the next section.

3-4. Discussion

Six-membered cyclic diketones provided desired enones in one operation whereas five-membered diketones gave phosphonate anion addition products. The difference between these two systems depends upon the ease of retro-aldol cleavage in the intermediate addition products. In the six-membered ring system, the C_3-C_2 bond in 41 is almost parallel to the π system of the carbonyl group. Thus, the C=O π-system assists the bond cleavage, and this is a stereoelectronically allowed process.[27] In contrast with this, the C3-C2 bond in the five-membered ring system 48 is nearly perpendicular to the π system of the carbonyl group. Since lithium-oxygen bond has a covalent character, the intermediate anion 48 (M=Li) dose not have a reactivity enough to cleave the C_3-C_2 bond.



41 42

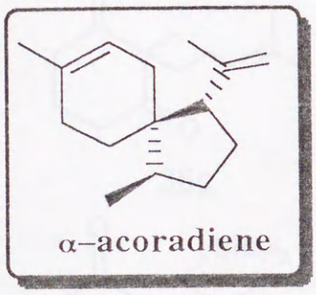


48 49

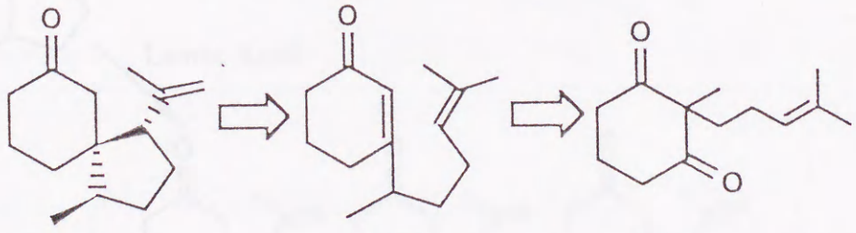
After isolating this intermediate as the protonated form (46), the treatment of 46 with bases such as NaH and KO^{t}-Bu gave rearranged cyclopentenones 47 in moderate to good yield. In this case, intermediate anion 48 (M=Na or K) has a reactivity enough to cleave the C3-C2 bond because the metal(Na or K)-oxygen bond has an ionic character.

3-5. Applications

a) Formal synthesis of (±)-α-acoradiene


α–acoradiene

The present method was applied to a short formal synthesis of (±)-α-acoradiene.[28] Synthetic plan is shown in **Scheme 3-2**. The key intermediate 51, which was converted to α-acoradiene previously,[29] can be derived from enone 37c by spirocyclization

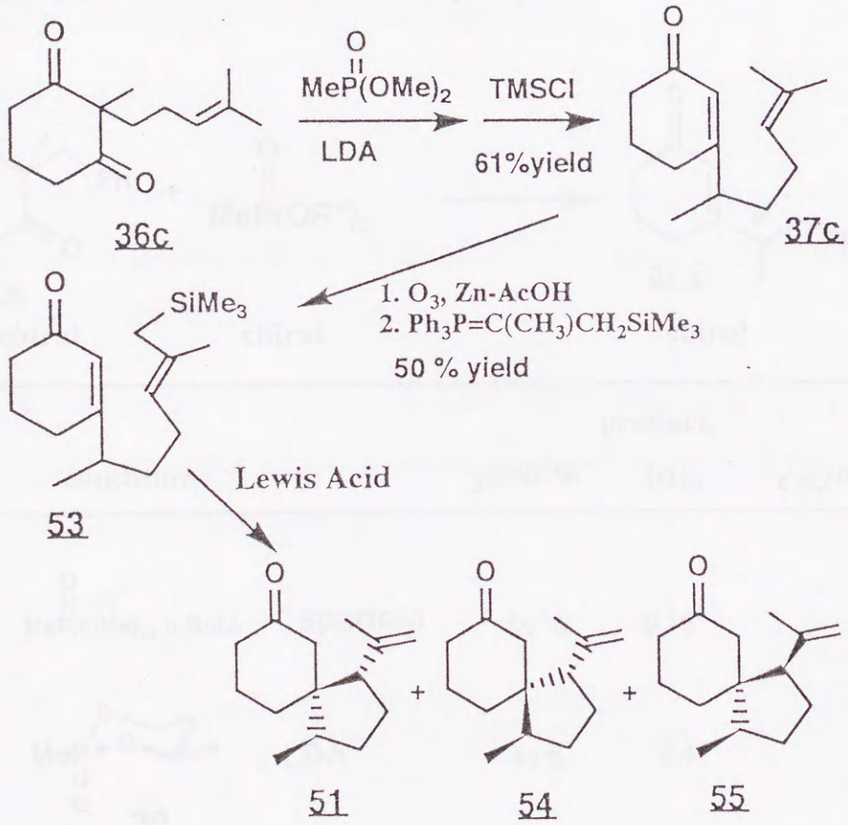


51 37c 36c

Scheme 3-2

Synthesis The treatment of 36c with dimethyl methylphosphonate anion gave enone 37c in 61 % yield as described previously. Attempts to cyclyze 30c under protic conditions were unsuccessful. Cyclization to 51 was achieved by using intramolecular Sakurai-Hosomi type condensation.[30] 37c was converted to allylsilane derivative 53 by

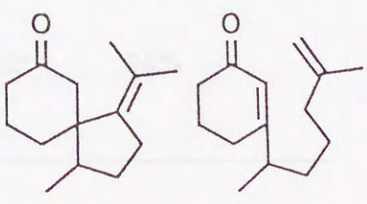
selective ozonolysis[31] followed by Wittig olefination reaction[32] in 50% yield. Allylsilane 53 was treated with various Lewis acids to perform spirocyclization. Among the Lewis acids used, only aluminum chloride derivatives gave cyclyzed products.[33] Use of $EtAlCl_2$ in CH_2Cl_2 at -78°C afforded spirocyclic ketones as a mixture of three diastereomers in 27 % yield (51:54:55=2:2:1) along with trace amounts of olefin isomerized product 56 and protodesilylation product 57. $EtAlCl_2$ in toluene gave better result concerning with chemical yield (53% yield) but slightly lower selectivity (51:54:55=1:1:1). Me_2AlCl gave similar result to $EtAlCl_2$.



$EtAlCl_2$
CH_2Cl_2, -78°C 27% (2 : 2 : 1)

$EtAlCl_2$
toluene, -74°C 53% (1 : 1 : 1)

Me_2AlCl
CH_2Cl_2, -75°C 38% (2 : 2 : 1)



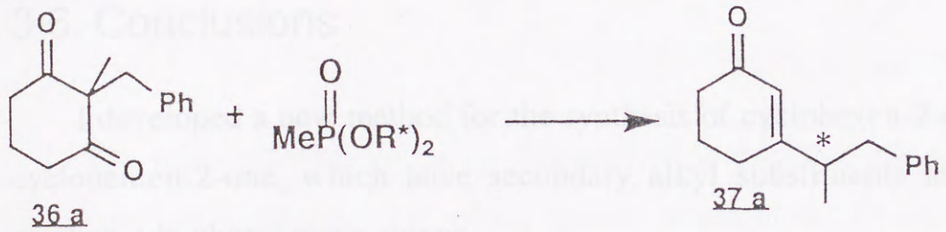
56 57

Other Lewis acids such as TMSOTf, $BF_3{\cdot}OEt_2$, $TiCl_4$ and $SnCl_4$ gave no cyclyzed product.

b) Asymmetric synthesis of 3-substituted 2-cyclohexenone

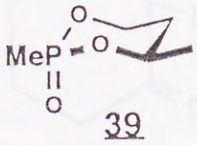
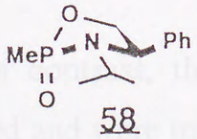
The most remarkable characteristic of the present method is that starting prochiral diketone (having σ-face symmetry) is converted into cyclic enone which has chirality at C4' position.

Asymmetric synthesis of 3-substituted 2-cyclohexenone was tried by introduction of chiral auxirialies in phosphonate anion.



36 a
prochiral chiral chiral

37 a

entry	conditions	yield/%	product, $[\alpha]_D$	e.e./%
1	$MeP(OMe)_2$, n-BuLi, spartein	46 %	-0.16°	
2	 , LDA	47%	-3.4°	
3	 , LDA	47%	12°	24%

39

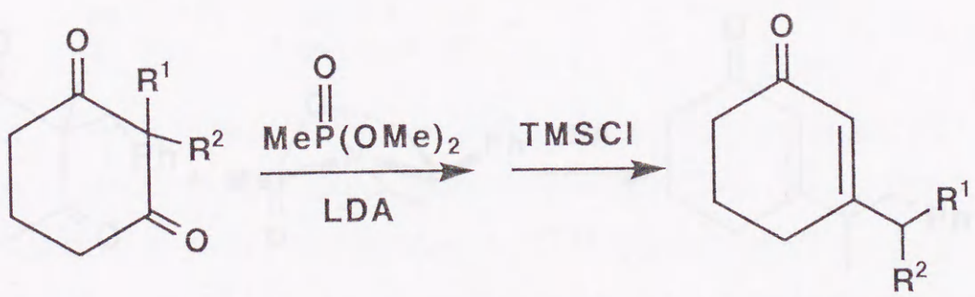
58

Use of a chiral coordinating reagent, spartein, resulted in no asymmetric induction (It showed a specific rotation of -0.16°). Slight asymmetric induction was observed when 2,4,6-trimethyl-2-oxo-1,3-dioxaphosphorinane (39), which was synthesized from (2R, 4R)-2,4-pentanediol and dichloromethylphosphate, was used as phosphonate (It showed a specific rotation of -3.4°). Finally, the homochiral phosphonate 58, which was synthesized from (2R)-2-(N-isopropylamino)-2-phenylethanol, afforded 37a in 47% chemical yield with 24% ee. ($[\alpha]_D$ +12°). Needless to say, much detailed investigation is needed to enhance the chiral induction.

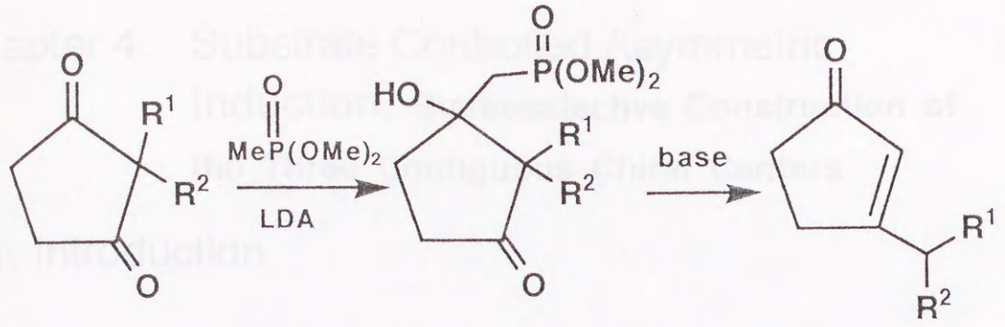
3-6. Conclusions

I developed a new method for the synthesis of cyclohexen-2-one and cyclopenten-2-one, which have secondary alkyl substituents at the 3-position, via phosphonate anions.

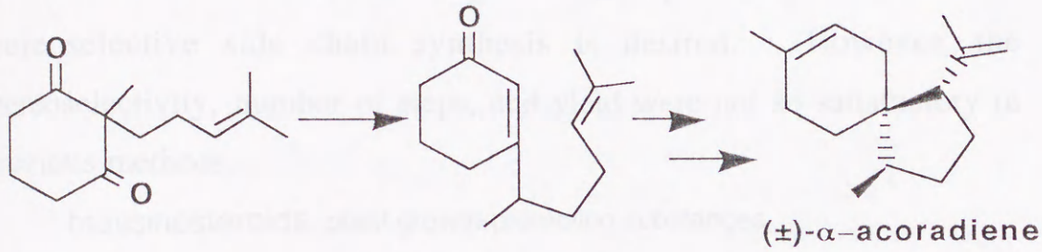
In 6-membered ring case, 1,3-diketones were directly transformed to 2-cyclohexenones in moderate to good yields by addition of methyl dimethyl phosphonate anions.



In contrast, the intermediate phosphorylated products could be isolated and were transformed to 2-cyclopentenones by the base treatment in 5-membered ring case. The difference in reactivity between 5- and 6-membered ring can be accounted for by the stereoelectronic effect.

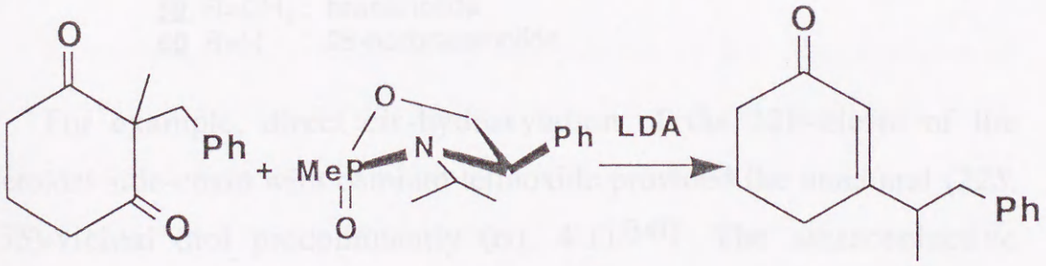


Taking advantage of the present method, a short formal synthesis of (±)-α-acoradiene was accomplished.



(±)-α-acoradiene

The most striking feature of this method is that starting prochiral diketones are converted into cyclic enones which have chirality at C4' position. This makes it possible that the asymmetric synthesis of 3-substituted 2-cyclic enones. Indeed, use of homochiral phosphonate (especially derived from homochiral phenyl glycine) gave homochiral 2-cyclohexenone derivatives in 24% ee.



24 % ee

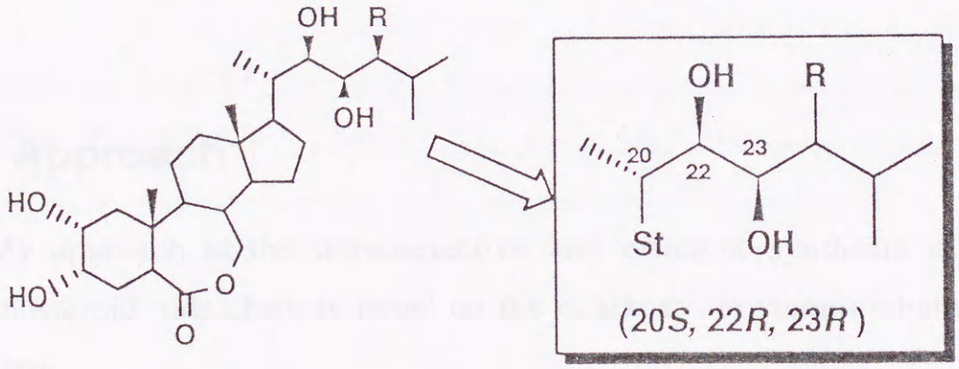
The observed enantioselectivity was not so high, however, this initial result suggests that proper choice of homochiral phosphonates may lead to high asymmetric synthesis of 3-substituted cyclohexen-2-ones.

Chapter 4. Substrate Controlled Asymmetric Induction. Stereoselective Construction of the Three Contiguous Chiral Centers

4-1. Introduction

Synthesis of brassinosteroids, new class of plant growth-promoting substances, have already been reported by several groups.[34] Because of the interest in structure-reactivity relationship, highly efficient and stereoselective side chain synthesis is desired. However, the stereoselectivity, number of steps, and yield were not so satisfactory in previous methods.

brassinosteroids, plant growth-promoting substances

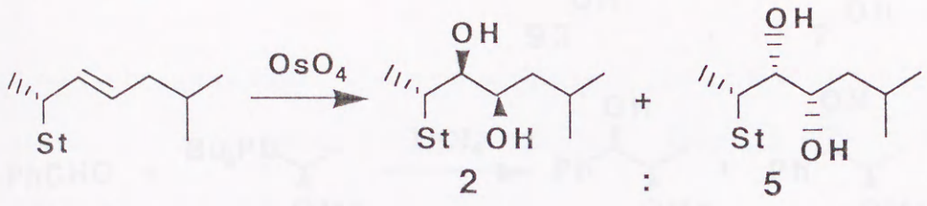


R = H, CH_3, C_2H_5

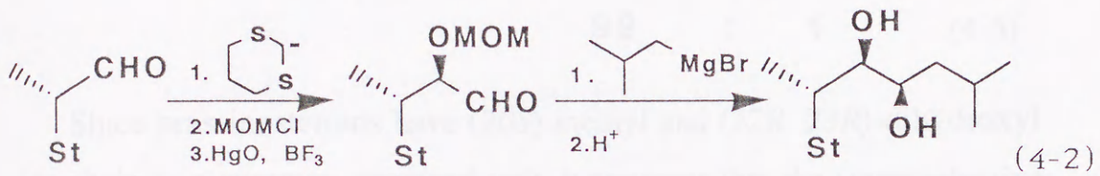
59 R=CH_3 : brassinolide
60 R=H : 28-norbrassinolide

For example, direct *cis*-hydroxylation of the 22E-olefin of the steroidal side-chain with osmium tetraoxide provided the unnatural (*22S, 23S*)-vicinal diol predominantly (eq. 4-1).[34f] The stereoselective synthesis of (*22R, 23R*)-vicinal diol derivatives was reported by Takatsuto et al[34n].(eq. 4-2) and Koreeda et al[34z].(eq. 4-3). Equation 4-2 shows stereoselective but stepwise construction of the cis-dihydroxyl group. In equation 4-3, application of allylic stannane chemistry enables

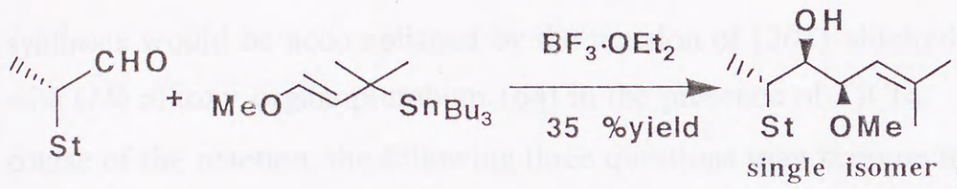
the highly stereoselective direct construction of the *cis*-dihydroxyl group in moderate yield.



(4-1)



(4-2)

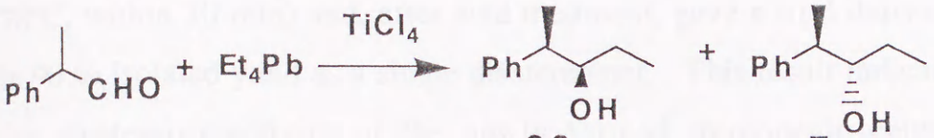


single isomer (4-3)

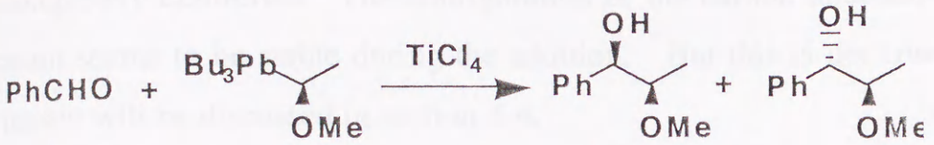
4-2. Approach

My approach to the stereoselective and efficient synthesis of brassinosteroid side-chain is based on the α-alkoxy organoplumbum chemistry.

It was previously reported in our laboratory that the reaction of tetraalkyl plumbums with aldehydes proceeded smoothly with high Cram selectivity (eq. 4-4).[35] In addition, stereodivergent synthesis of 1,2-diol derivatives was accomplished by using α-alkoxy organoplumbums.[36] In the presence of $TiCl_4$, the reaction of α-alkoxy organoplumbums with aldehydes proceeded with very high *syn* selectivity (eq. 4-5).

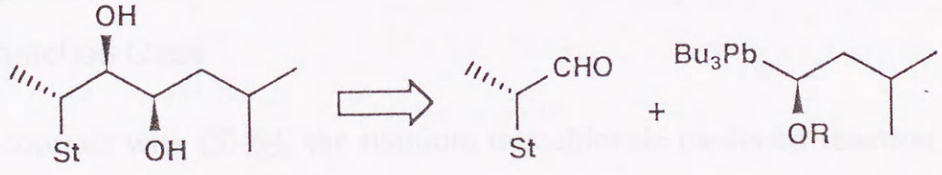


93 : 7 (4-4)



99 : 1 (4-5)

Since brassinosteroids have (*20S*)-methyl and (*22R, 23R*)-dihydroxyl side-chain as a common structural unit, it appeares that the stereoselective synthesis would be accomplished by the reaction of (*20S*)-aldehyde (70) with (*1S*)-alkoxy organoplumbum (64) in the presence of TiCl4. In the course of the reaction, the following three questions may become the key to achieve the stereoselective and efficient synthesis; (1) diastereoselectivity of the newly formed stereogenic center; (2) a possibility of the kinetic resolution when one of the reactants is racemic; (3) cofigurational stability of the carbon center attached to lead atom.



Cram-Syn 70 64

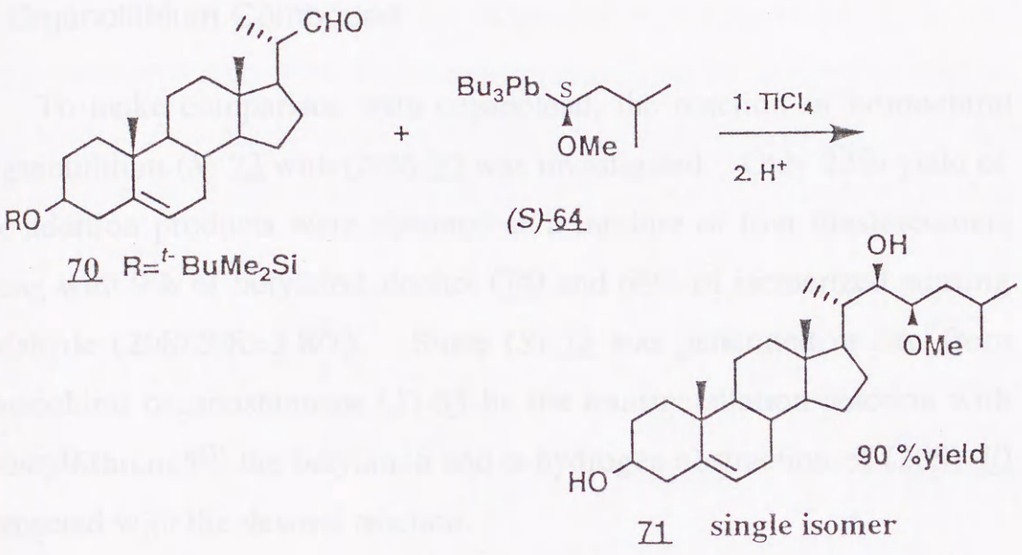
4-3. Results

4-3-1. Reaction Between Homochiral Aldehyde And Homochiral Organoplumbum

a. Matched Case

The reaction of homochiral organoplumbum (*S*)-64 with homochiral aldehyde (*20S*)-70 was investigated. This reaction proceeded rapidly (-

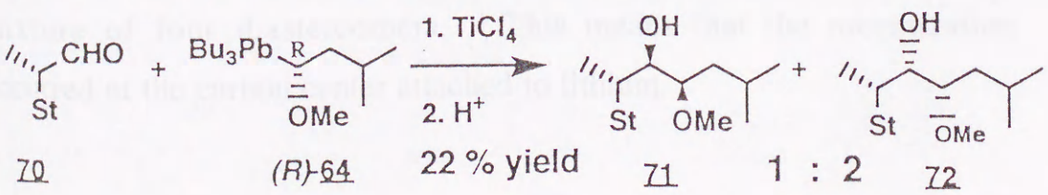
78°C, within 10 min) and, after acid treatment, gave a triol derivative 71 in 90 % isolated yield as a single diastereomer. This result indicated that the diastereoselectivity of the newly formed stereogenic center was completely controlled. The configuration of the carbon attached to lead atom seems to be stable during the addition. But this is not true. The reason will be discussed in section 4-4.



70 R=$^{t-}$BuMe$_2$Si (S)-64 71 single isomer

b. Mismatched Case

In contrast with (*S*)-64, the titanium tetrachloride mediated reaction of (*R*)-64 with (*20S*)-70 proceeded very slowly at low temperature and gave 1 to 2 mixture of triol derivatives 71 and 72 in 22 % yield. This means that partial racemization occurred in (*R*)-64 at the carbon attached to lead atom during the course of the addition. The mechanism of this racemization will be discussed later (in section 4-4).

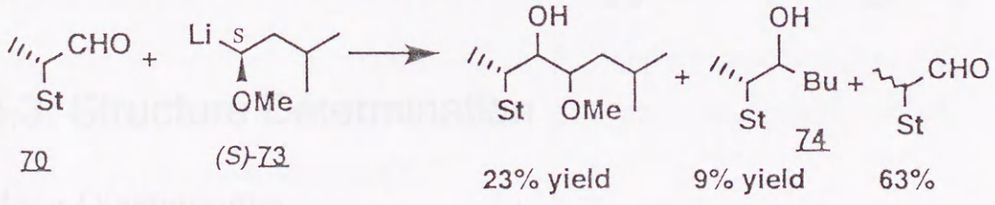


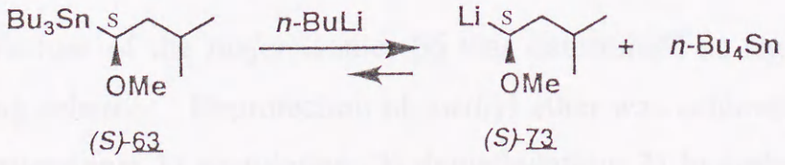
70 (R)-64 22 % yield 71 1 : 2 72

According to these results, the reactivity of the two isomeric organoplumbums (*S*)- and (*R*)-64 is quite different from each other when the homochiral aldehyde (such as 70) was used. This difference in reactivity may enable the kinetic resolution during the reaction between homochiral and racemic reactants.

c. Organolithium Compound

To make comparison with organolead, the reaction of homochiral organolithium (*S*)-73 with (*20S*)-70 was investigated. Only 23% yield of the addition products were obtained as a mixture of four diastereomers along with 9% of butylated alcohol (74) and 68% of isomerized starting aldehyde (20S/20R=3.8/1). Since (*S*)-73 was generated in situ from homochiral organostannane (*S*)-63 by the transmetallation reaction with n-butyllithium,[40] the butylation and α-hydrogen abstraction of (20S)-70 competed with the desired reaction.

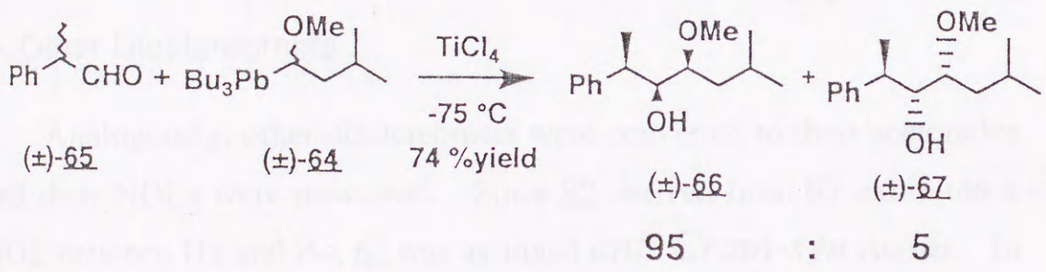




In addition to this, the desired condensation product was formed as a mixture of four diastereomers. This means that the racemization occurred at the carbon center attached to lithium.

4-3-2. Reaction Between Racemic Aldehyde And Racemic Organoplumbum.

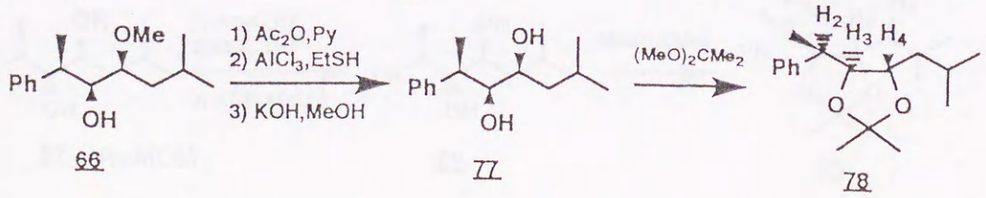
If the reaction between racemic aldehyde and racemic organoplumbum proceeds with very high diastereoselectivity, the degree of the kinetic resolution must be also high. Indeed, the reaction of 2 equivalent of (±)-65 with (±)-64 proceeded rapidly and provided two diastereomeric *syn*-diol derivatives 66 and 67 in 74 % yield (based on 64) with high diastereoselectivity (**95 : 5**). This result indicated that (*R*)-64 reacted predominantly with (*R*)-65 to give *Cram-syn* isomer 66.



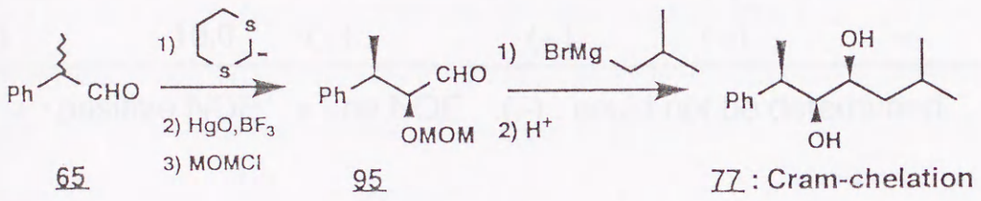
4-3-3. Structure Determination

a. Major Diastereomer

Structure of the major isomer 66 was determined as shown in the following scheme. Deprotection of methyl ether was achieved by three step conversions; 1) acetylation; 2) demethylation; 3) hydrolysis. The acetonide 78 derived from 77 exhibited a positive NOE between H_2 and H_4 and no NOE between H_2 and H_5. Therefore, the stereochemistry of the hydroxyls was determined as *syn*.



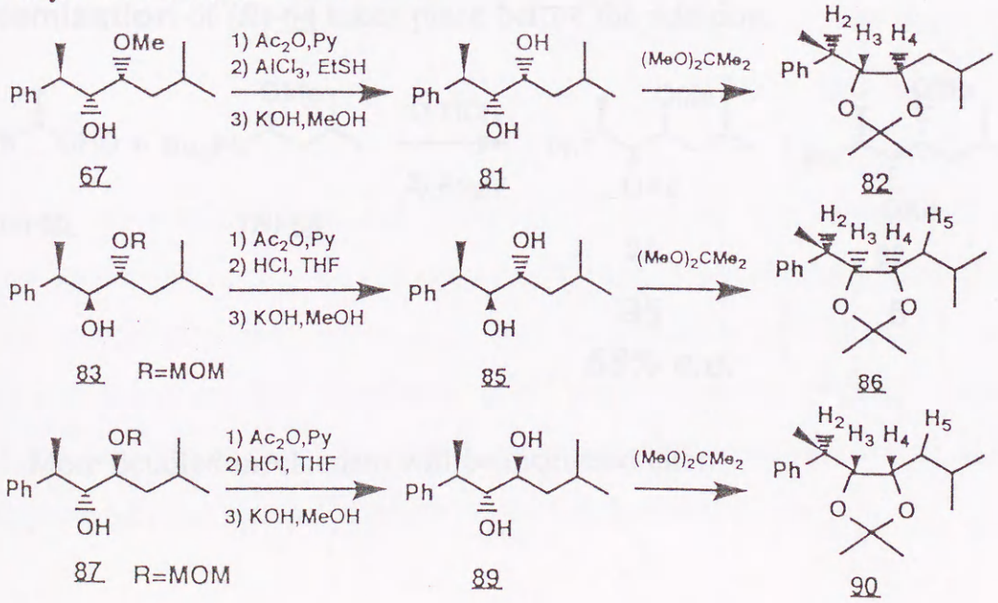
Furthermore, the addition of 1,3-dithian anion to an α-branched aldehyde such as 65 is known to provide Cram stereochemistry. The addition of the Grignard reagent to the α-alkoxymethoxyl substituted aldehyde 95 proceeds via chelation transition state to give the *syn* diol.[36] This *Cram-chelation* (*Cram-syn*) type diol was identical with 77.



65 95 77 : Cram-chelation

b. Other Diastereomers

Analogously, other diastereomers were converted to their acetonides and their NOEs were measured. Since 82 derived from 67 exhibited a NOE between H2 and H4, 67 was assinged *anti Cram-syn* isomer. In contrast with these, both 86 (derived from 83) and 90 (derived from 87) showed NOEs between H2 and H5. The stereochemistry of the hydroxyls was determined as *anti*.



67 → 81 → 82

83 R=MOM → 85 → 86

87 R=MOM → 89 → 90

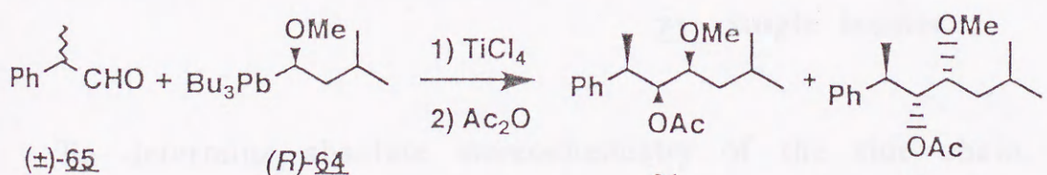
Table 4-1. Selected Coupling Constants and NOEs

	coupling costant / Hz		NOE[a]		
	H_2-H_3	H_3-H_4	H3-H4	H2-H4	H2-H5
78	7.0	7.5	×	+	×
82	4.5	8.0	×	+	×
86	9.5	5.2	+	×	+
90	10.0	(–)	(–)	(–)	+

[a] + : positive NOE × : no NOE (–) : could not be determined

4-3-4. Reaction Between Racemic Aldehyde And Homochiral Organoplumbum

The kinetic resolution of racemic aldehyde (±)-65 by 1 mole equivalent of (*R*)-64 was tested. Syn diol derivatives 91 and 92 were obtained with high level of diastereoselectivity (91 : 92 = 95 : 5) in 46% yield based on *(S)*-65. The enantiomeric excess of the major diastereomer 91 was *58 % ee*. This result indicates that a **partial racemization** of (*R*)-64 takes place before the addition.



(±)-65 (*R*)-64 91 92

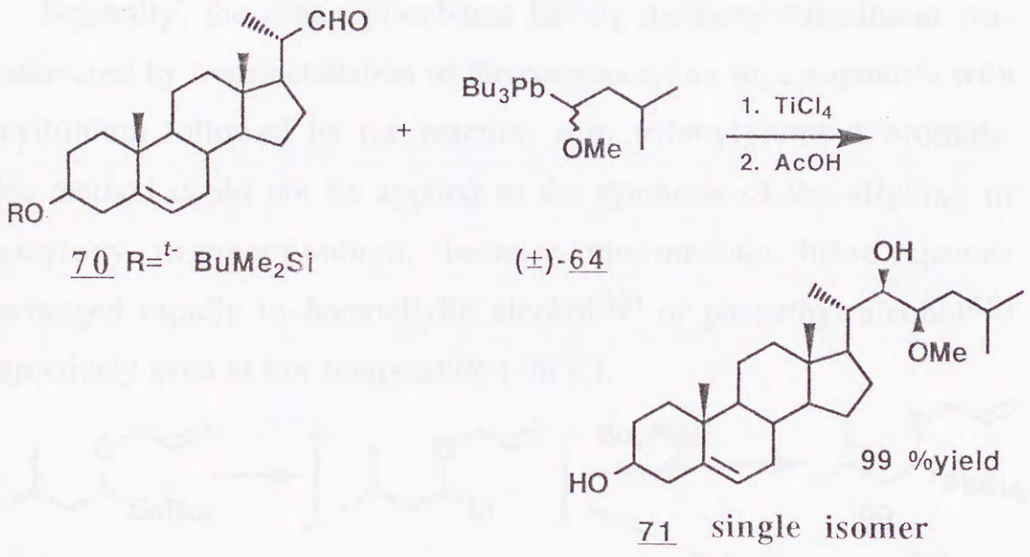
95 : 5

58% e.e.

More detailed mechanism will be diccussed later.

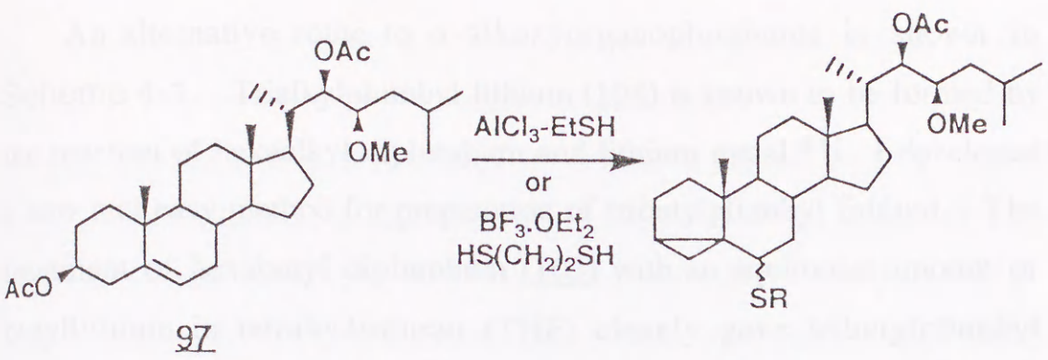
4-3-5. Reaction Between Homochiral Aldehyde And Racemic Organoplumbum. Formal Synthesis of 28-Norbrassinolide

The reaction of homochiral aldehyde 70 with 4 mole equivalents of racemic organoplumbum (±)-64 gave, after removal of silyl group, a triol derivative 71 as a single diastereomer in 99 % yield (based on 70). This result clearly indicates that the racemic organoplumbum (±)-64 was kinetically resolved by the reaction with aldehyde 70. Since the unreacted organoplumbum decomposed, the enantiomeric excess of recovered organoplumbum could not be measured.



70 R=$^{t-}$ $BuMe_2Si$ (±)-64 71 single isomer

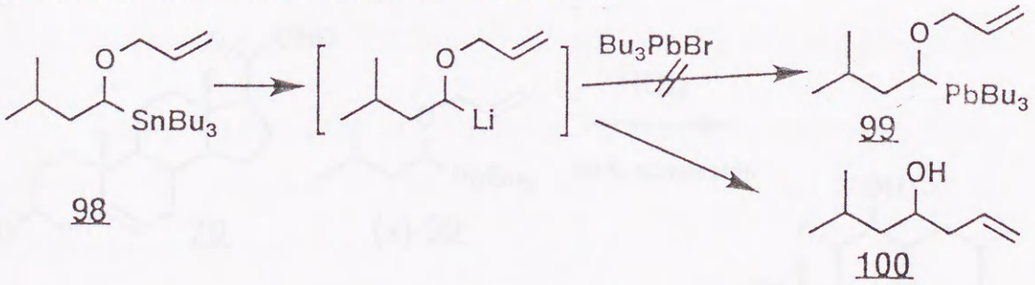
To determine absolute stereochemistry of the side chain, demethylation of 71 was tried. Although it is reported that the combination of Lewis acids and soft nucleophiles is effective for deprotection of methyl ether moiety,[38] the demethylation of 71 itself and its derivatives (such as 97) was unsuccessful. As shown in the following scheme, an undesirable deacetoxylation took place.



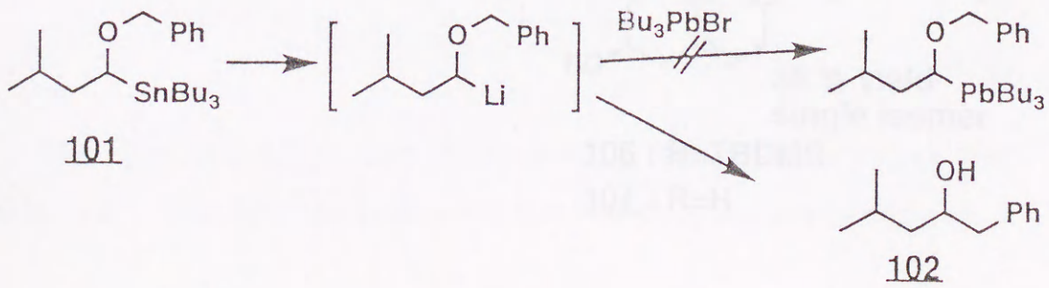
97

Then I turned my attention to the protecting group of α-hydroxyl moiety in the organoplumbum. Instead of methyl ether, allyl or benzyl ether protection may solve the difficulty because these protective groups can be easily removed.

Normally, the organoplumbums having methoxy substituent was synthesized by transmetallation of the corresponding tin compounds with butyllithium followed by the reaction with tributylplumbyl bromide. This method could not be applied to the synthesis of the allyloxy or benzyloxy organoplumbum, because intermediate lithio species rearranged rapidly to homoallylic alcohol[39] or phenethyl alcohol[40] respectively even at low temperature (-78°C).

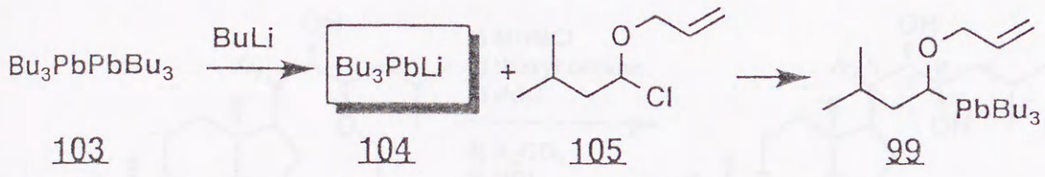


98 99 100



101 102

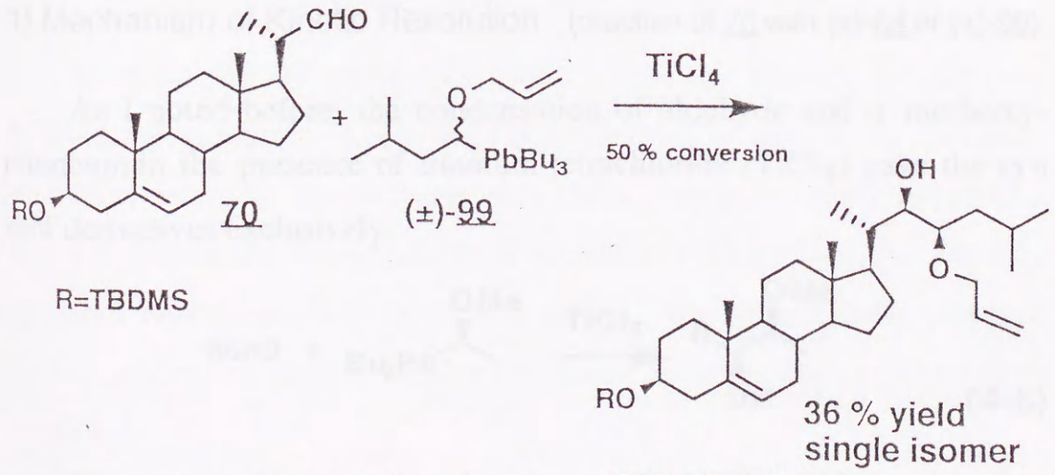
An alternative route to α-alkoxyorganoplumbums is shown in Scheme 4-1. Trialkylplumbyl lithium (104) is known to be formed by the reaction of hexaalkyl diplumbum and lithium metal.[41] I developed a new and easy method for preparation of tributylplumbyl lithium. The treatment of hexabutyl diplumbum (103) with an equimolar amount of butyllithium in tetrahydrofuran (THF) cleanly gave tributylplumbyl lithium via transmetallation. Finally, reaction of α-chloro allyl ether derivative 105 with tributylplumbyl lithium gave α-allyloxyplumbum 99.



103 104 105 99

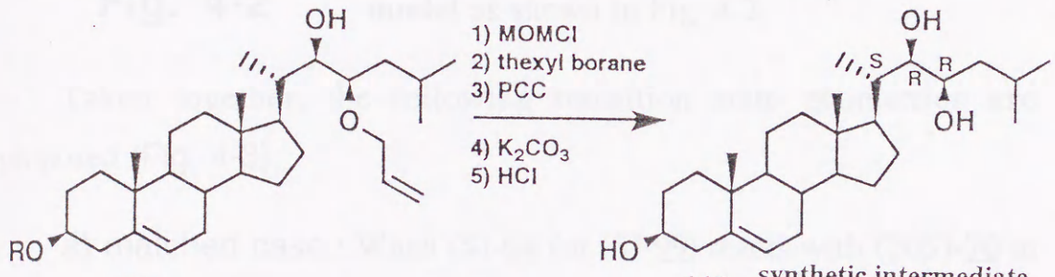
Scheme 4-1

The allyloxy reagent (±)-99 reacted with homochiral aldehyde 70 to give triol derivatives 106 (and 107) as a single diastereomer in 24 % yield (50 % conversion). The diastereoselectivity itself was comparable to that of (±)-64, but the chemical yield was lower than that of (±)-64.



106 : R=TBDMS
107 : R=H

Removal of the allyl protective group was accomplished by the following sequential steps; 1) methoxymethyl protection of C23-hydroxyl group; 2) selective hydroboration of allylic ether moiety by thexyl borane; 3) oxidation of the resulting primary alcohol by pyridinium chlorochromate (PCC); 4) base catalyzed retro-aldol cleavage of β-alkoxy aldehyde; 5) acid catalyzed deprotection of methoxymethyl ether. The triol 113 exhibits spectral data identical with those reported previously.[34f)]

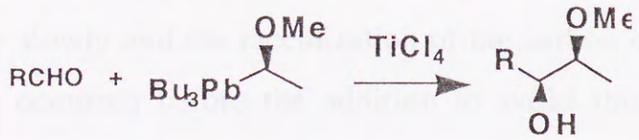


107 113 synthetic intermediate of 28-norbrassinolide

4-4. Discussion

1) Mechanism of Kinetic Resolution (reaction of 70 with (±)-64 or (±)-99)

As I noted before, the condensation of aldehyde and α-methoxy-plumbum in the presence of titanium tetrachloride ($TiCl_4$) gave the syn diol derivatives exclusively.



(4-6)

This syn selectivity can be accounted for by **intermolecular chelation**. Titanium chloride binds the two oxygen atoms, and thus a

chelated transition state is involved. Furthermore, it was established that this condensation reaction proceeded via **S_E2-retention**.[36]

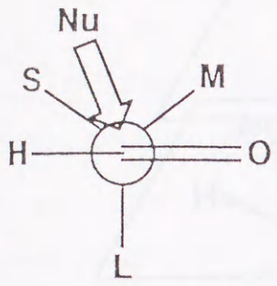


Fig. 4-2

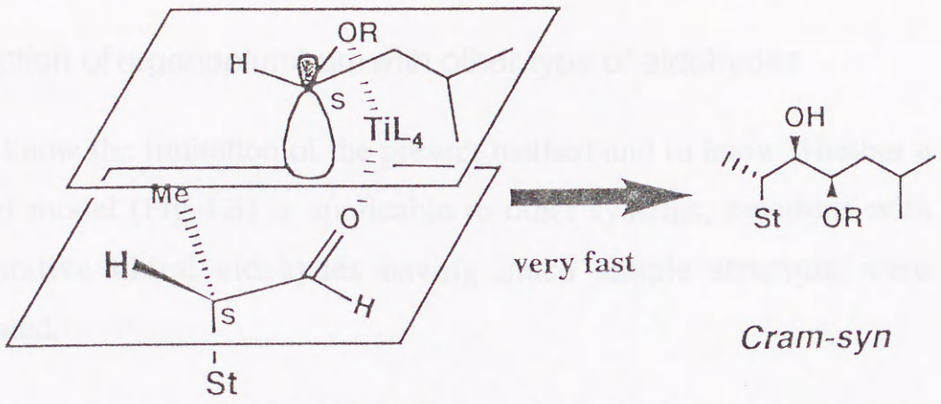
Accordingly, a similar transition state must be involved also in the reaction of the chiral aldehydes and chiral organoplumbums. It is also reasonable to assume that the aldehyde having chiral center next to the carbonyl function reacts via the **Felkin model** as shown in Fig. 4-2.

Taken together, the following transition state geometries are proposed (Fig. 4-3).

a) matched case : When (S)-64 (or (S)-99) reacts with (20S)-70 in the presence of $TiCl_4$, sterically bulky isobutyl and steroidal groups can be oriented far from each other. There exist little or no unfavorable steric interactions. Therefore, this reaction proceeds at the comparable rate to the achiral case; the use of (±)-64 or (±)-99 also produces very high stereoselectivity and the kinetic resolution takes place.

b) mismatched case : In contrast with the above case, the two bulky alkyl groups in (R)-64 and (20S)-70 must be oriented in the same direction, owing to the chelation with $TiCl_4$. A severe steric interaction exists between these two alkyl substituents. Therefore, the reaction proceeds very slowly and the racemization of the carbon center attached to lead atom occurred before the addition to avoid this severe steric repulsion.

a) matched pair



b) mismatched pair

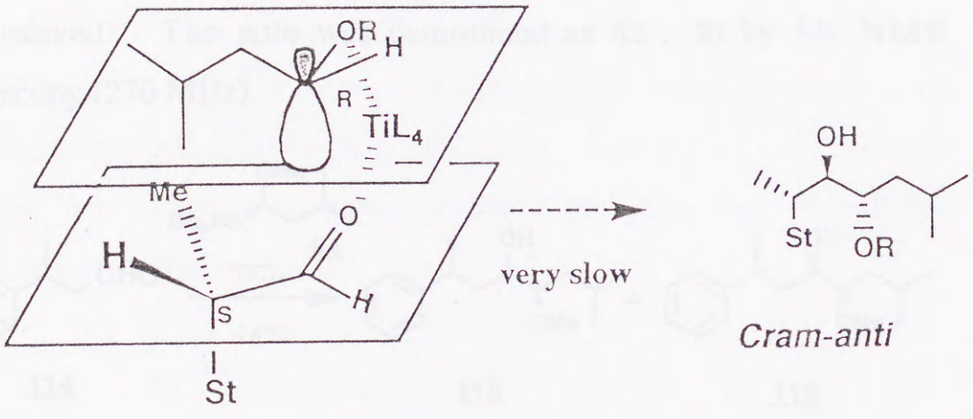


Fig. 4-3

This difference in reactivity is responsible for the observed kinetic resolution.

2) Configurational Stability at the Carbon Attached to Lead Atom

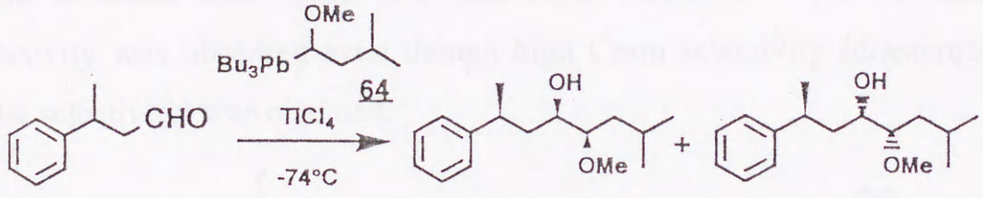
As apparent from the result of section 4-3-4, the chiral carbon center attached to lead atom was partially racemized before the addition. In section 4-3-1, perfect retention of the configuration was demonstrated for homochiral plumbum (S)-64. Partial racemization of the chiral

carbon center should also occur in this case, but resulting (R)-64 hardly reacts with (20S)-70 because these are mismatched pair.

3) Reaction of organoplumbum with other type of aldehydes

To know the limitation of the present method and to know whether a proposed model (Fig.4-3) is applicable to other systems, reactions with representative chiral aldehydes having much simple structure were investigated.

The reaction of (±)-64 with the β–branched aldehyde (±)-114 gave two diastereomeric diol derivatives 115 and 116. No stereoselectivity was observed. The ratio was determined as 52 : 48 by ^{1}H-NMR spectroscopy (270 MHz).



114 115 116

52 : 48

Even α-branched aldehydes, such as (±)-2-methylbutanal (117) and (±)-2-ethylhexanal (118), proceeded nonstereoselectively.

117 118

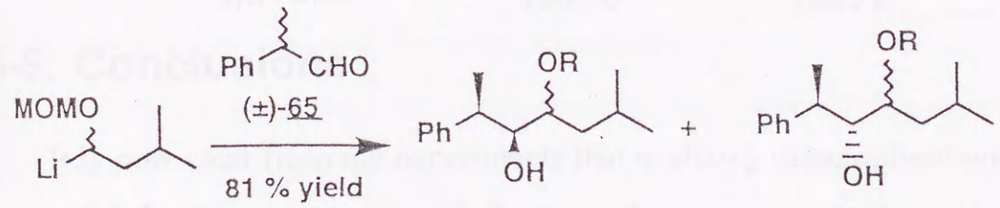
The diastereofacial preference of these aldehydes (114, 117 and 118) is generally low[42], since (i) the chiral center is in the β-position in the case of 114 and (ii) the steric demand of the two alkyl groups at the α-

position is similar in the case of 117 and 118. Therefore, it is reasonable that no diastereofacial selectivity is observed in the reaction with α-methoxy organoplumbum. Of course, kinetic resolution is not expected in these cases.

4) Other α-alkoxy organometals

Reactions of α-alkoxy organolithium 63 and organostannane 64 with (±)-65 were investigated.

The reaction of (±)-119 with (±)-65 proceeded at low temperatures, and gave diol derivatives as a mixture of four diastereomers in 81% total yield. After HPLC separation, the diastereomeric ratio was determined as 75/79/83/87=49/4/43/4; Cram/anti-Cram=92/8, syn/anti=53/47 (for Cram isomers) and 50/50 (for anti-Cram isomers). No syn/anti selectivity was observed even though high Cram selectivity (diastereo-facial selectivity) was obtained.

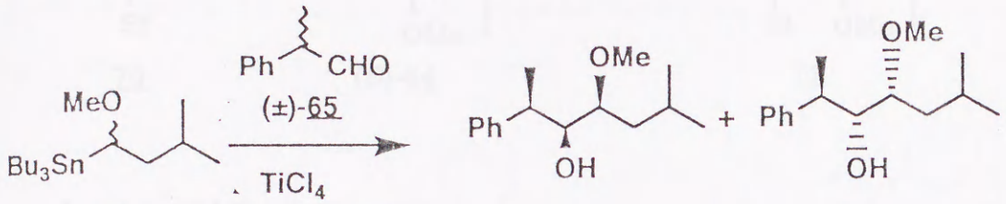


119 75 / 83 79 / 87

Cram : anti Cram	92	:	8
syn / anti	53 / 47		50 / 50

Titanium tetrachloride mediated reaction of (±)-63 and (±)-65 proceeded with diastereoselection comparable to organoplumbum (±)-64. Two diastereomeric diol derivatives 91 and 92 were obtained only in 20% total yield with diastereoselectivity 90/10. A transition state similar

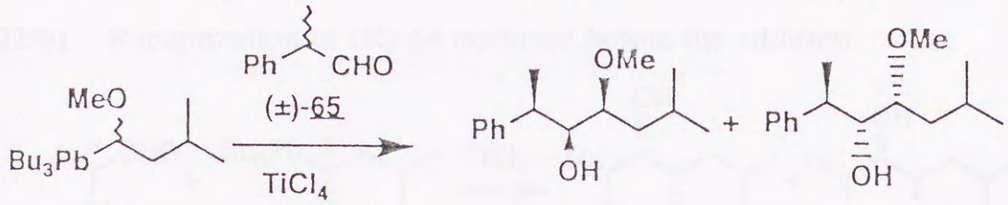
to that of organoplumbum reaction (Fig. 4-3) may be involved, and such a transition geometry can explain the observed high diastereoselectivity. Relatively lower reactivity of organostannane compared to plumbum must result in a lower yield of products.



63 19 % yield 66 : 67

Cram : anti Cram 90 : 10

syn / anti 100 / 0 100 / 0



64 74 % yield 66 : 67

Cram : anti Cram 95 : 5

syn / anti 100 / 0 100 / 0

4-5. Conclusions

It is now clear from my experiments that α-alkoxy organoplumbums are useful for the construction of three contiguous stereogenic centers containing cis-dihydroxyls on the acyclic chain.

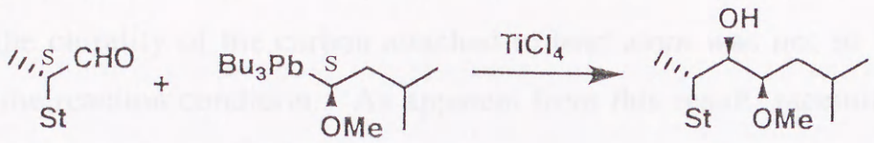
Summary on the reactions with the aldehydes having chiral center next to the carbonyl function is as follows.

1) Homochiral Aldehyde and Homochiral Organoplumbum

a. matched case

The reaction of (S)-64 and (20S)-70 afforded ***Cram-syn*** diol derivative 71 as a single diastereomer in high yield (90%). The

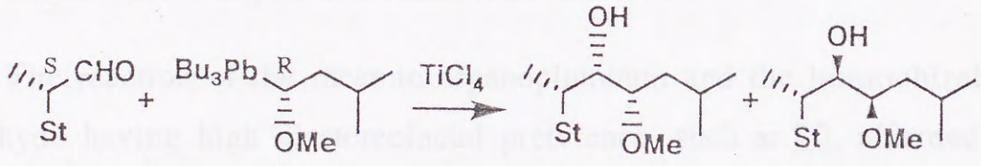
selectivity of the newly formed stereogenic center was completely controlled .



70 (S)-64 71

b. mismatched case

As opposed to the above observation, the reaction of (R)-64 with (20S)-70 gave diastereomeric mixture of diols (71/72=1/2) in low yield (22%). Racemization of (R)-64 occurred before the addition.

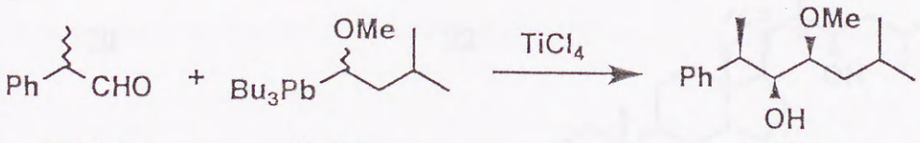


70 (R)-64 71 : 72

1 : 2

2) Racemic Aldehyde and Racemic Plumbum

The reactions of racemic plumbum ((±)-64) with α-branched aldehydes having high diastereofacial preference proceeded with high diastereoselectivity. The efficiency of the kinetic resolution in asymmetric synthesis can be predicted from this result.

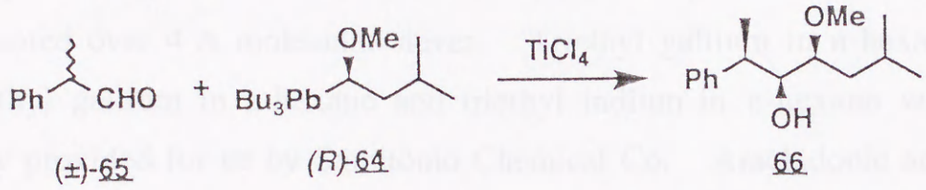


(±)-65 (±)-64 (±)-66

90% d.e.

3) Racemic Aldehyde and Homochiral Plumbum

The reaction of (±)-65 and (S)-64 proceeded with high diastereoselectivity (90% d.e.) but the enantiomeric excess of 66 was 58% ee. Thus the chirality of the carbon attached to lead atom was not so stable under the reaction condition. As apparent from this result, racemization takes place not always but in some cases.

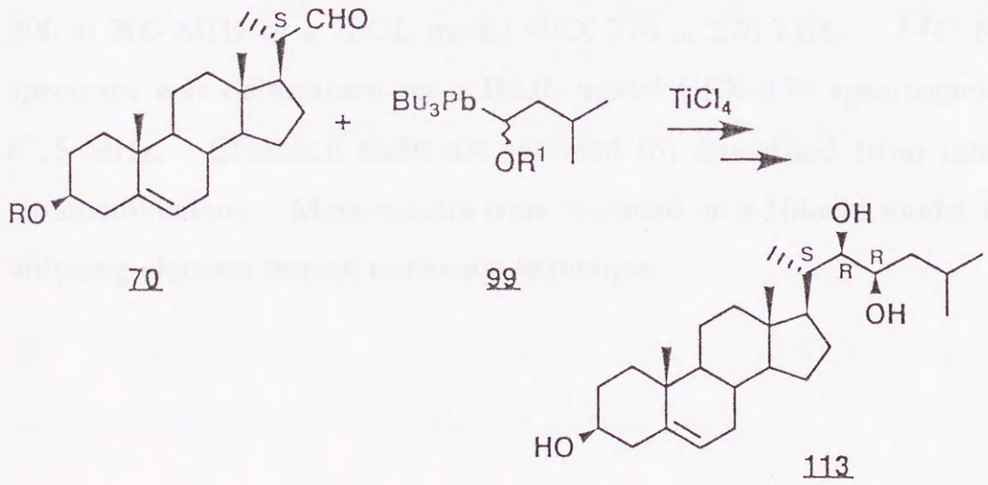


(±)-65 (R)-64 66

90% d.e. 58% e.e.

4) Homochiral Aldehyde and Racemic Plumbum

The reaction of the racemic organoplumbum and the homochiral aldehyde having high diastereofacial preference, such as 70, afforded Cram-syn 1,2-diol derivative in high yield with high diastereoselectivity. Racemic organoplumbum was kinetically resolved. This method was successfully applied to a formal synthesis of 28-norbrassinolide.



70 99 113

Experimental Section

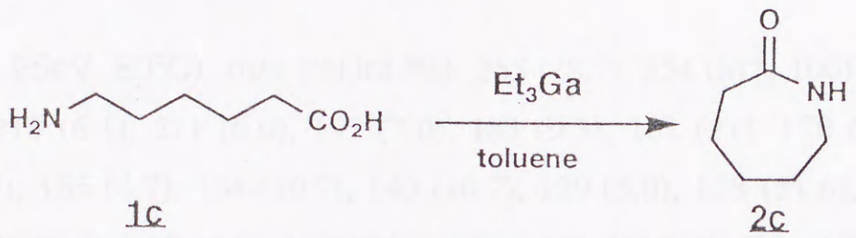
Materials. Toluene, benzen and methylene chloride were distilled over calcium hydride under innert atmosphere (argon or nitrogen) prior to use . Diethyl ether and THF were distilled over sodium-benzophenone ketyl prior to use. Methanol was distilled over magnesium methoxide and stored over 4 A molecular sieves. Triethyl gallium in n-hexane, trimethyl gallium in n-hexane and triethyl indium in n-hexane were kindly provided for us by Sumitomo Chemical Co. Arachidonic acid, ethyl ester and γ-rinolenic acid, ethyl ester were kindly provided for us by Idemitsu Chemical Co. LDA in cyclohexane was purchased from Aldrich. n-Butyllithium in n-hexane was purchased from Kanto Chemical and was analyzed by titration

Analytical. Infrared spectra were recorded on a Hitachi model 215 spectrometer. ^{1}H NMR spectra were determined on a JEOL model GSX-270 spectrometer at 270 MHz or a Varian model XL-400 at 400 MHz. The NOE experiments were performed on a Varian model XL-200 at 200 MHz or a JEOL model GSX-270 at 270 MHz. ^{13}C NMR spectrum was determined on a JEOL model GSX-270 spectrometer at 67.5 MHz. Chemical shifts are reported (δ) downfield from internal tetramethylsilane. Mass spectra were recorded on a Hitachi model M-52 utilyzing electron impact ionization tequnique.

Chapter 1

Et_3Ga Mediated Lactamization of 1c (General Procedure)

(exp.43)



1c 2c

In an oven dried, 30 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 6-aminocaproic acid (135.4 mg, 1.032 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry toluene (10 mL) and 0.73M triethylgallium in n-hexane (2.1 mL, 1.5 mmol) were added with syringes. The mixture was refluxed for 5 hr with stirring, and then cooled to room temperature. Water (0.1 mL) was added and the mixture was stirred for 1 hr. The resulting white precipitate was filtered and the filtrate was concentrated. The crude product was subjected to column chromatography (5 g of SiO_2 E. Merck No. 5554, 2% methanol / chloroform) to give pure ε-caprolactam (95.0 mg, 0.840 mmol, 81% yield).

All reactions in chapter 1 were performed as described above.

2d : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.97 (1H, brs, W1/2=28 Hz) 3.34 (2H, m) 2.42 (2H, m) 1.80 (2H, m) 1.60 (6H, m);

MS (EI, 25eV, 80°C) m/e (rel.int./%) 128 (10.6), 127 (M^+, 100), 99 (53.3), 98 (54.9), 97 (13.6), 85 (10.8), 84 (12.9), 83 (14.3), 82 (8.8), 81

(10.7), 80 (11.0), 71 (29.6), 70 (38.4), 69 (29.0), 68 (10.2), 67 (10.1), 58 (12.7), 57 (20.4), 56 (56.1), 55 (70.7), 54 (12.6).

3d : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 6.08 (2H, brs, W1/2=21 Hz) 3.29 (4H, m), 2.22 (4H, m) 1.7-1.3 (16H, m);

MS (EI, 25eV, 80°C) m/e (rel.int./%) 255 (18.7), 254 (M^+, 100), 226 (16.7), 213 (6.1), 211 (6.0), 197 (7.0), 183 (9.3), 182 (21), 170 (9.7), 156 (7.2), 155 (4.7), 154 (10.7), 140 (10.7), 129 (5.0), 128 (51.6), 127 (8.8), 126 (9.8), 112 (4.4), 110(10.2), 100 (14.0), 99 (8.0), 98 (7.0), 97 (2.7), 86 (7.0), 84 (6.1), 83 (4.4), 72 (8.2), 56 (7.4), 55 (11.6).

3e : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.5 (2H, brs) 3.30 (4H, m) 2.18 (4H, m) 1.7-1.3 (20H, m);

MS (EI, 13.5eV, 100°C) m/e (rel.int./%) 283 (54.4), 282 (M^+, 100), 254 (19.5), 237 (10,8), 211 (5.3), 210 (36.4), 198 (5.0), 197 (12.4), 196 (13.9), 184 (19.4), 156 (7.8), 155 (8.1), 142 (24.8), 141 (56.0), 129 (9.7), 127 (5.6), 126 (13), 113 (33.1), 112 (9.9), 100 (18.2), 99 (32.3), 98 (32.1), 97 (68.2), 85 (21.2), 84 (6.4), 56 (9.9).

2f : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.85 (1H, brs, W1/2=23 Hz) 3.32 (2H, m) 2.23 (2H, m) 1.7 (2H, m) 1.6 (2H, m) 1.5-1.3 (12H, m);

2g : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.58 (1H, brs, W1/2=23 Hz) 3.31 (2H, m) 2.20 (2H, m) 1.70 (2H, m) 1.50 (2H, m) 1.4-1.3 (14H, m);

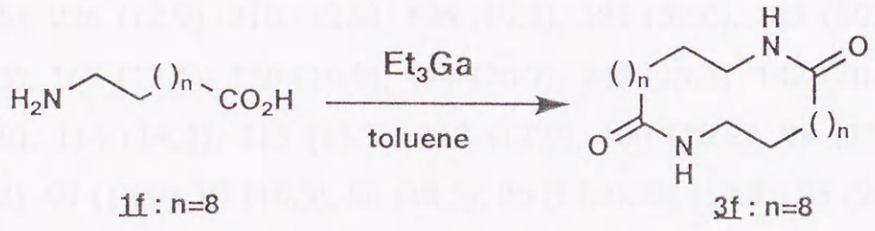
^{13}C-NMR (67.5 MHz) $\delta_{CDCl_3/ppm}$ 173.50 (s) 38.90 (t) 36.74 (t) 28.19 (t) 26.66 (t) 26.23 (t) 26.09 (t) 25.63 (t) 25.14 (t) 24.85 (t) 24.50 (t) 23.81 (t);

MS (EI, 25eV, 80°C) m/e (rel.int./%) 198 (28.1), 197 (M^+, 100), 196 (6.3), 180 (11.3), 168 (24.2), 156 (21.0), 155 (7.4), 154 (9.1), 141 (8.2),

140 (30.7), 138 (19.2), 127 (11.3), 126 (26.5), 125 (5.5), 114 (7.4), 113 (24.2), 112 (53.9), 110 (12.5), 109 (5.5) 101 (5.3) 100 (99) 99 (32.8), 98 (17.9), 97 (19.3), 96 (34.4), 88 (40.6), 86 (46.9), 84 (12.5), 82 (26.6), 74 (10.9), 73 (46.9), 71 (23.7), 70 (5.1), 60 (42.2), 58 (6.2), 56 (15.6), 45 (19.5), 43 (24.4), 30 (48.5).

3g : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.45 (2H, m) 3.28 (4H, m) 2.17 (4H, m) 1.65-1.58 (8H, m) 1.52-1.45 (4H, m) 1.35-1.25 (24H, m).

Et_3Ga Mediated Lactamization of 1f (exp.45)



1f : n=8 3f : n=8

Using general procedure, 11-aminoundecanoic acid (204.0 mg, 1.013 mmol) was converted to 24-membered lactams 3f (18.3 mg, 0.050 mmol, 10% yield) as a mixture of two rotamers. These two rotamers were separated by gel chromatography (14 g of Sephadex LH-20, 12 mmϕ x 520 mm, 100mL of 33% chloroform / methanol, flow rate 0.6 mL/min).

3f-1 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.73 (2H, brs, W1/2=12 Hz) 3.27 (4H, m) 2.18 (4H, m) 1.6 (4H, m) 1.5 (4H, m) 1.3 (24H, m);

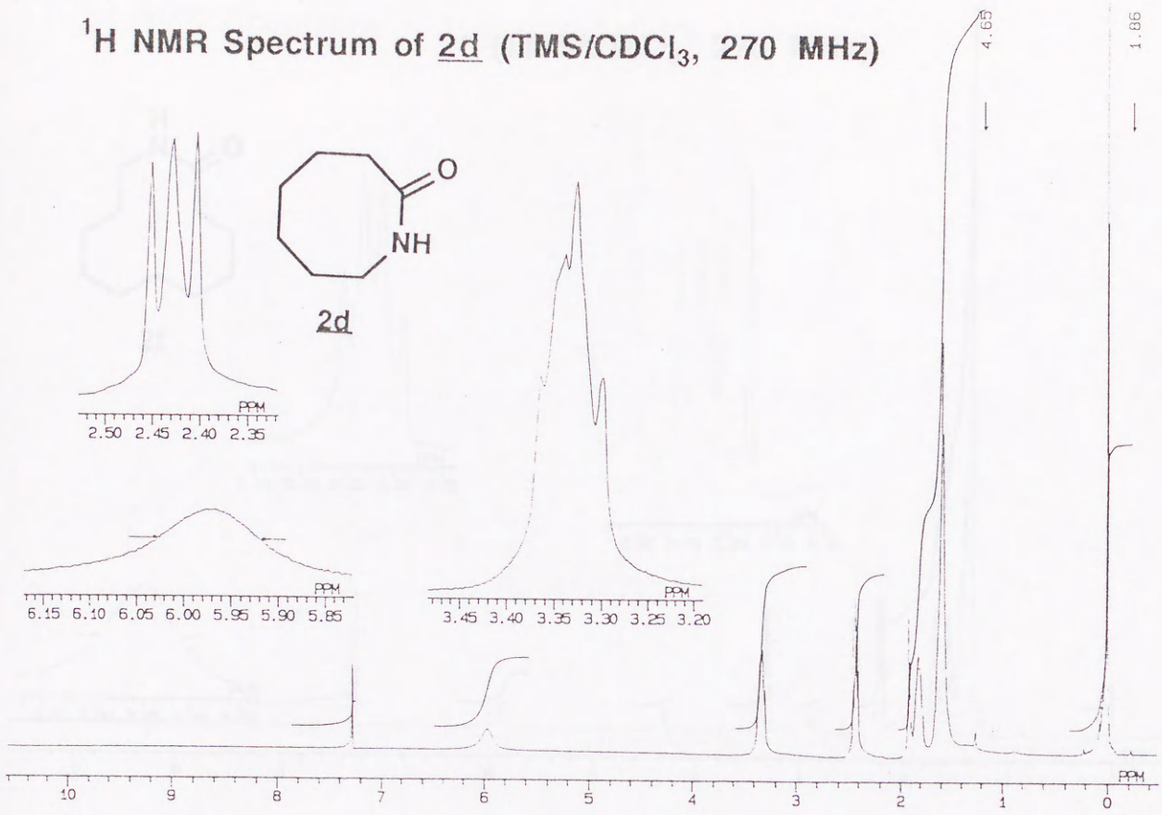
MS (EI, 56eV, 220°C) m/e (rel.int./%) 367 (11.8), 366 (M^+, 100), 338 (11.6), 337 (11.7), 325 (11.4), 323 (19.1), 295 (12.2), 294 (18.8), 180 (14.8), 263 (15.1), 249 (13.2), 238 (18.8), 226 (14.6), 225 (11.6), 224 (36.2), 210 (21.3), 196 (21.5), 185 (10.8), 184 (56.7), 183 (33.0), 182 (14.3), 171 (11.6), 170 (24.2), 156 (19.2), 152 (12.0), 144 (15.4), 142 (24.2), 129 (13.6), 128 (11.8), 126 (14.5), 114 (27.8), 113 (88.5), 112

(15.0), 111 (12.5), 101 (12.7), 100 (22.6), 99 (18.6), 98 (43.7), 97 (22.0), 95 (13.0), 91 (10.9), 87 (12.9), 86 (20.7), 85 (22.0), 84 (20.7), 83 (30.6), 82 (10.3), 81 (19.3), 73 (19.8), 72 (52.0), 71 (32.6), 70 (41.4), 69 (41.7), 67 (16.9), 57 (42.9), 56 (24.2), 55 (79.4).

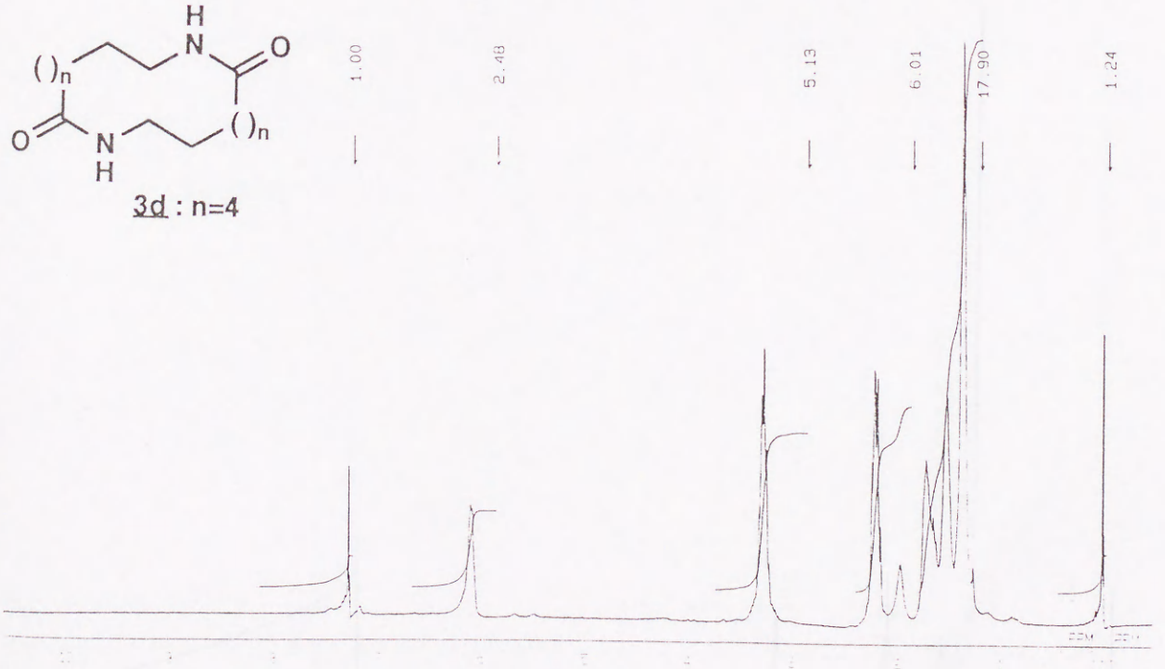
3f-2 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.50 (2H, m) 3.29 (4H, m) 2.18 (4H, m) 1.65 (4H, m) 1.50 (4H, m) 1.30 (24H, brs, W1/2=9 Hz);

MS (EI, 60eV, 220°C) m/e (rel.int./%) 367 (26.6), 366 (M^+, 100), 325 (11.6), 323 (17.4), 295 (10.6), 294 (16.2), 280 (11.3), 248 (11.0), 238 (16.5), 226 (12.9), 210 (12.9), 196 (17.8), 184 (52.0), 183 (30.9), 182 (12.5), 167 (12.6), 156 (16.9), 149 (20.7), 144 (13.5), 142 (20.0), 128 (10.8), 114 (14.2), 113 (13.3), 112 (12.0), 100 (20.2), 99 (12.8), 98 (11.2), 97 (12.0), 87 (10.5), 86 (18.5), 85 (11.3), 84 (14.4), 83 (20.7), 81 (12.1), 73 (15.6), 72 (16.4), 71 (16.2), 70 (13.1), 69 (29.6), 67 (10.7), 57 (30.4), 56 (19.6), 55 (49.0).

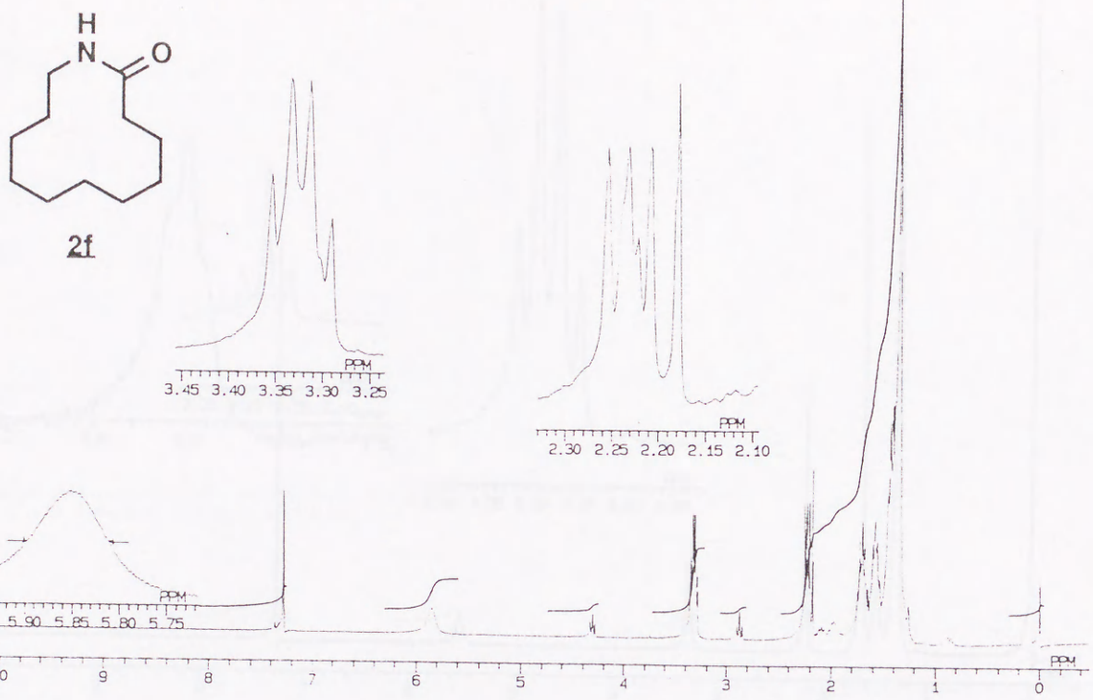
^{1}H NMR Spectrum of 2d (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 3d (TMS/$CDCl_3$, 270 MHz)

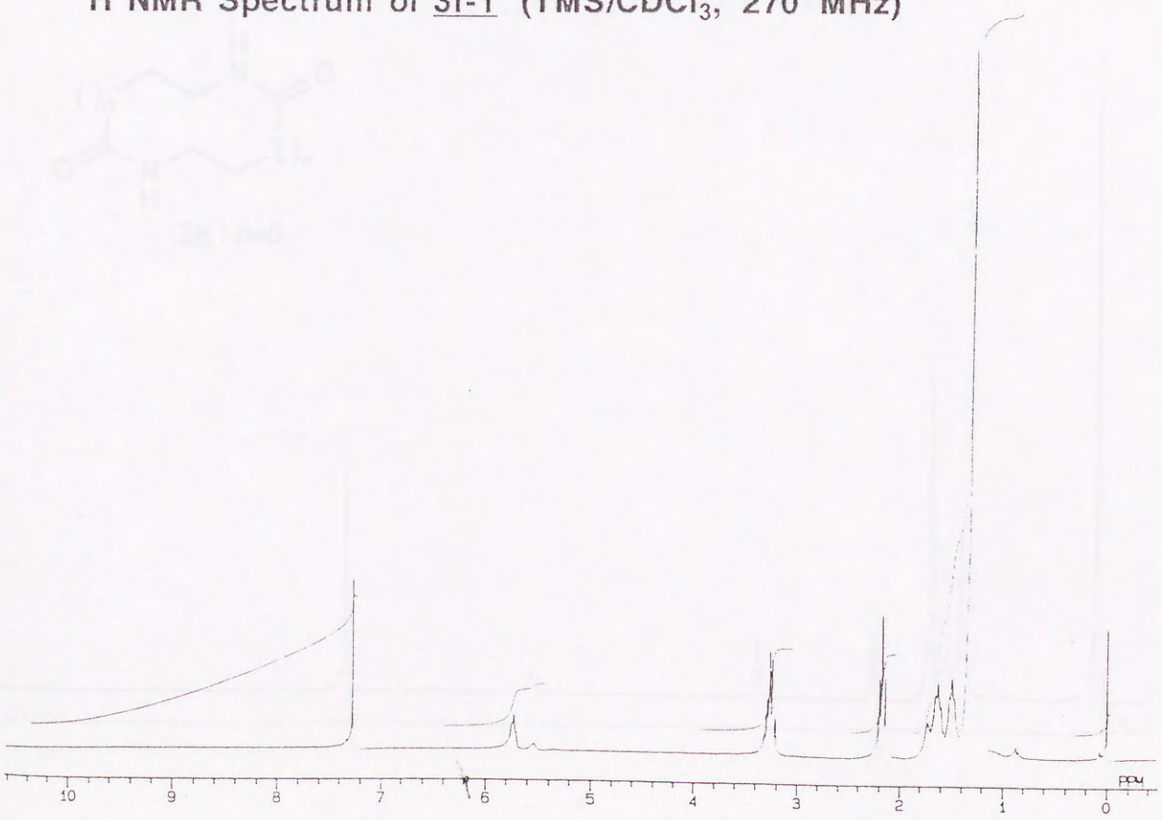


^{1}H NMR Spectrum of 2f (TMS/$CDCl_3$, 270 MHz)

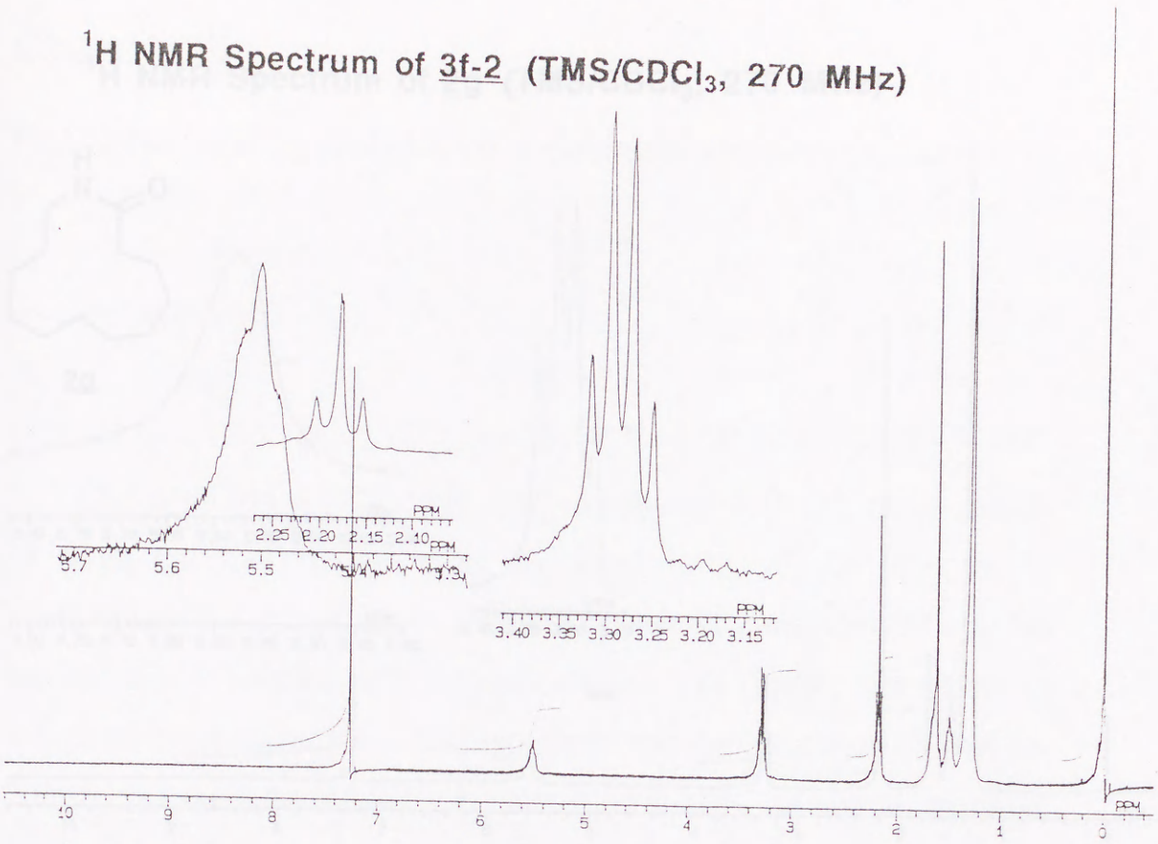


2f

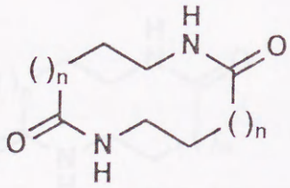
^{1}H NMR Spectrum of 3f-1 (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 3f-2 (TMS/$CDCl_3$, 270 MHz)

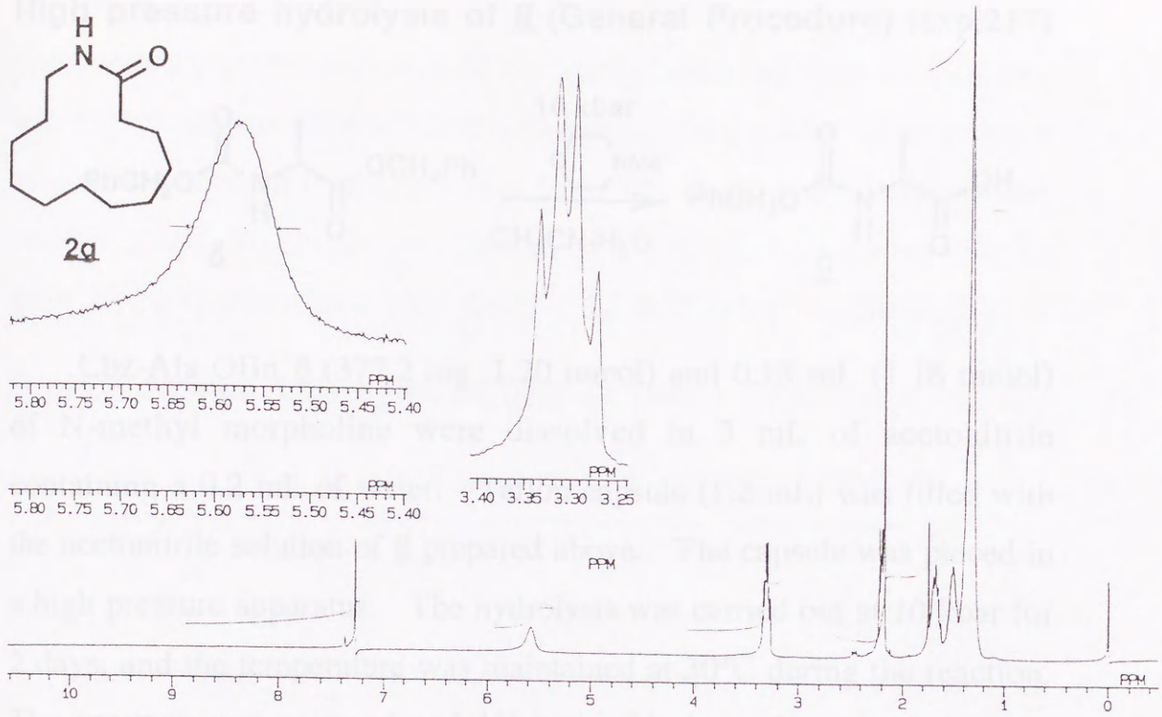


^{1}H NMR Spectrum of 3e (TMS/$CDCl_3$, 270 MHz)

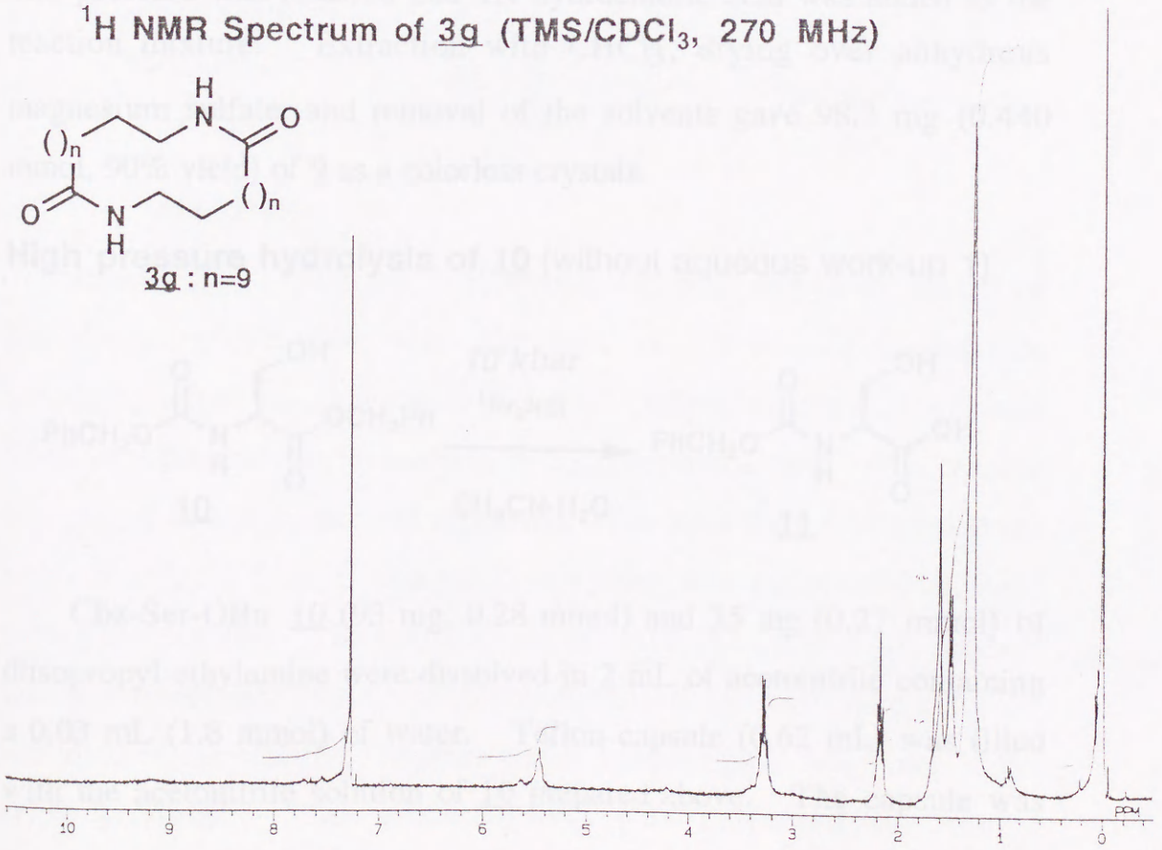


3e : n=5

^{1}H NMR Spectrum of 2g (TMS/$CDCl_3$, 270 MHz)

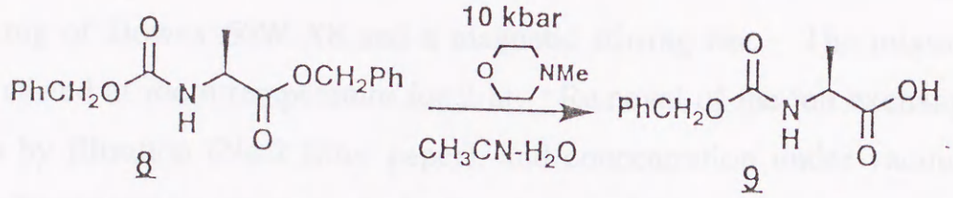


^{1}H NMR Spectrum of 3g (TMS/$CDCl_3$, 270 MHz)



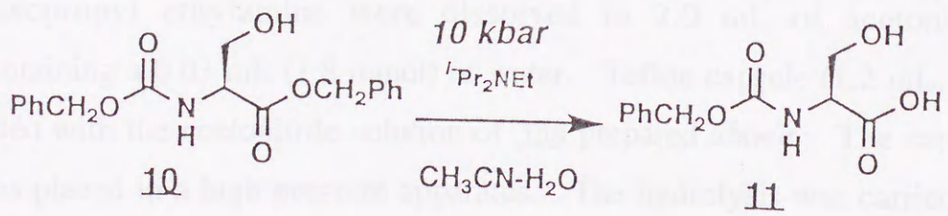
Chapter 2

High pressure hydrolysis of 8 (General Procedure) (exp.217)



Cbz-Ala-OBn 8 (377.2 mg ,1.20 mmol) and 0.13 mL (1.18 mmol) of N-methyl morpholine were dissolved in 3 mL of acetonitrile containing a 0.2 mL of water. Teflon capsule (1.2 mL) was filled with the acetonitrile solution of 8 prepared above. The capsule was placed in a high pressure apparatus. The hydrolysis was carried out at 10 kbar for 2 days, and the temperature was maintained at 30°C during the reaction. The pressure was released and 1N hydrochloric acid was added to the reaction mixture. Extraction with $CHCl_3$, drying over anhydrous magnesium sulfate, and removal of the solvents gave 98.3 mg (0.440 mmol, 90% yield) of 9 as a colorless crystals.

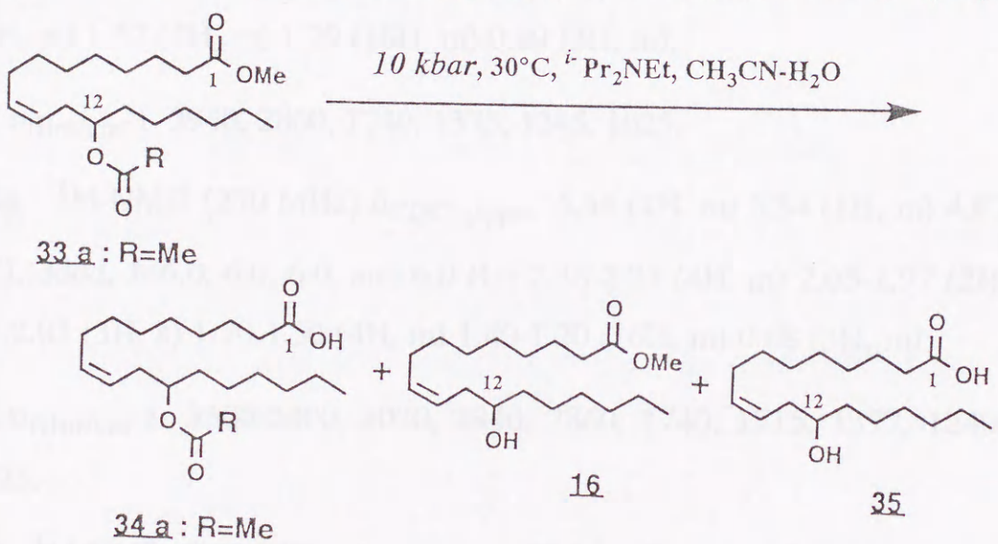
High pressure hydrolysis of 10 (without aqueous work-up 1)



Cbz-Ser-OBn 10 (93 mg, 0.28 mmol) and 35 mg (0.27 mmol) of diisopropyl ethylamine were dissolved in 2 mL of acetonitrile containing a 0.03 mL (1.8 mmol) of water. Teflon capsule (0.62 mL) was filled with the acetonitrile solution of 10 prepared above. The capsule was

placed in a high pressure apparatus. The hydrolysis was carried out at 10 kbar for 2 days, and the temperature was maintained at 30°C during the reaction. The pressure was released and the reaction mixture was transferred by methanol into a 20 mL round-bottomed flask containing a 125 mg of Dowex 50W-X8 and a magnetic stirring bar. The mixture was stirred at room temperature for 2 hr. Removal of the ion exchange resin by filtration (No.2 filter paper), and concentration under vacuum gave 20 mg (0.084 mmol, 98% yield) of 11 as colorless crystals.

High Pressure Hydrolysis of 33a (without aqueous work-up 2)



Diester 33a (177.8 mg, 0.50 mmol) and 65.7 mg (0.51 mmol) of diisopropyl ethylamine were dissolved in 2.0 mL of acetonitrile containing a 0.03 mL (1.8 mmol) of water. Teflon capsule (1.2 mL) was filled with the acetonitrile solution of 33a prepared above. The capsule was placed in a high pressure apparatus. The hydrolysis was carried out at 10 kbar for 2.5 days, and the temperature was maintained at 30°C during the reaction. The pressure was released and the reaction mixture was transferred into 20 mL round-bottomed flask by methylene chloride. Removal of the volatile materials under vacuum gave 104.7 mg of the crude products. The crude product was subjected to column

chromatography (SiO_2 60 E. Merck No.5554). The concentration of the first and second fraction, eluted with 9% ethyl acetate / n-hexane, gave 67.6 mg (0.19 mmol, 63% recovery) of 33a and 1.0 mg (0.003 mmol, 1.0% yield) of 26, respectively. The concentration of the third and fourth fraction, eluted with 3% methanol / methylene chloride, gave 24.4 mg (0.072 mmol, 24.0% yield) of 27a and 0.4 mg (0.0013 mmol, 0.4% yield) of 35, respectively.

33a : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.46 (1H, m) 5.34 (1H, m) 4.87 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 3.70 (3H, s) 2.30 (4H, m) 2.02 (5H, m) 1.57 (4H, m) 1.29 (16H, m) 0.89 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 2940, 2860, 1740, 1375, 1245, 1025.

34a : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.46 (1H, m) 5.34 (1H, m) 4.87 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 2.38-2.23 (4H, m) 2.05-1.97 (2H, m) 2.03 (3H, s) 1.70-1.50 (4H, m) 1.40-1.20 (16H, m) 0.88 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 3500-2400, 3020, 2940, 2860, 1740, 1715, 1377, 1240, 1025.

35 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.56 (1H, m) 5.40 (1H, m) 3.62 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 2.34 (2H, t, J=7.2 Hz) 2.21 (2H, t, J=6.6 Hz) 2.04 (2H, m) 1.62 (2H, m) 1.48 (2H, m) 1.40-1.20 (16H, m) 0.90 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 3600-2400, 3010, 2930, 2855, 1712, 1460, 725.

33b : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 8.04 (2H, m) 7.50-7.40 (3H, m) 5.53-5.35 (2H, m) 5.13 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 3.67 (3H, s) 2.43 (2H, m) 2.29 (2H, t, J=7.4 Hz) 2.02 (2H, m) 1.74-1.60 (4H, m) 1.4-1.2 (16H, m) 0.86 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 3020, 2945, 2860, 1745, 1722, 1452, 1275, 1115, 715.

33c : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.46 (1H, m) 5.34 (1H, m) 4.87 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 4.12 (2H, q, J=7 Hz) 2.28 (4H, m) 2.00 (5H, m) 1.7-1.5 (4H, m) 1.4-1.2 (19H, m) 0.90 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 2935, 2855, 1740, 1240.

33d : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.4-7.3 (5H, m) 5.46 (1H, m) 5.34 (1H, m) 4.87 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 2.4-2.2 (4H, m) 2.03 (3H, s) 2.05-1.97 (2H, m) 1.7-1.5 (4H, m) 1.4-1.2 (16H, m) 0.88 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 2935, 2855, 1740, 1455, 1370, 1240, 1160, 1020, 698.

33e : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.46 (1H, m) 5.34 (1H, m) 5.00 (1H, qq, J=6.0, and 6.0 Hz) 4.87 (1H, dddd, J=6.0, 6.0, 6.0, and 6.0 Hz) 2.32-2.22 (4H, m) 2.03 (3H, s) 2.05-1.97 (2H, m) 1.70-1.45 (4H, m) 1.35-1.20 (22H, m) 0.88 (3H, m);

IR $\upsilon_{film/cm^{-1}}$ 2940, 2855, 1740, 1465, 1372, 1222, 1110.

Solvolytic Deprotection of Esters Sensitive to Bases and Acids

High Pressure Hydrolysis

Hydrolysis of 22, 24, 25, 26, and 28 was performed using the general procedure.

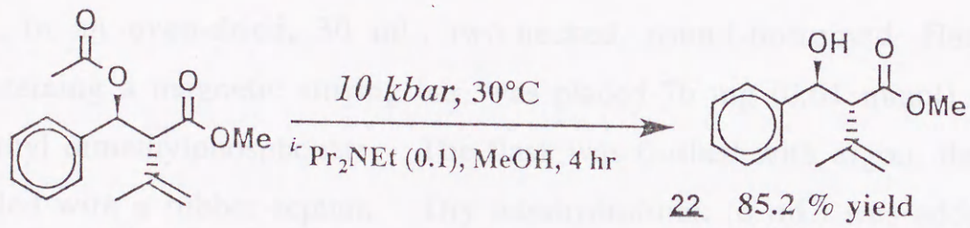
22 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.25-7.35 (5H, m) 5.04 (1H, dd, J=9.0, and 4.0 Hz) 4.84 (1H, m) 3.74 (3H, s) 3.40 (1H, d, J=9.0 Hz) 3.04 (1H, d, J=4.0 Hz) 1.55 (3H, s);

IR $\upsilon_{KBr/cm^{-1}}$ 3485, 2955, 1715, 1172, 700.

23 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.4-7.2 (5H, m) 4.96 (1H, d, J=9.0 Hz) 4.73 (1H, s) 3.36 (1H, d, J=9.0 Hz) 1.50 (3H, s);

IR $\upsilon_{KBr/cm^{-1}}$ 3300, 3150-2700, 1700, 1688, 1645, 1215, 770, 702.

High Pressure Mediated Alcohol Exchange Reaction of 29 (exp. 80 by J. M.)



29 22 85.2 % yield

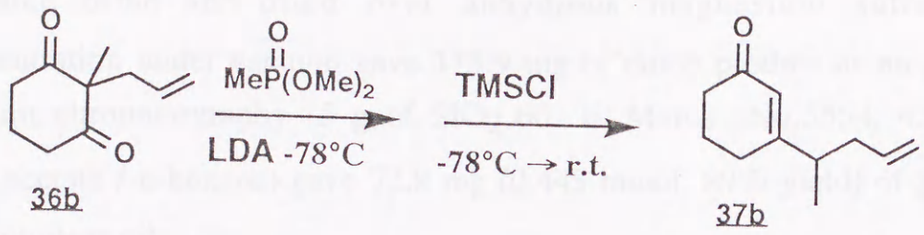
Diester 29 (131.2 mg, 0.500 mmol) and N, N-diisopropyl ethylamine (6.6 mg, 0.051 mmol) were dissolved in dry methanol (2.0 mL). Teflon capsule (1.2 mL) was filled with the methanol solution of 29 prepared above. The capsule was placed in a high pressure apparatus. The reaction was carried out at 10 kbar for 4 hr, and the temperature was maintained at 30 °C. The pressure was released and the mixture was concentrated under vacuum. The remaining solid was pure 22 (56.3 mg, 0.256 mmol, 85% yield).

29 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.4-7.25 (5H, m) 6.09 (1H, d, J=11 Hz) 4.89 (1H, s) 4.82 (1H, s) 3.74 (3H, s) 3.60 (1H, d, J=11 Hz) 2.00 (3H, s) 1.55 (3H, s);

IR $\upsilon_{KBr/cm^{-1}}$ 1740, 1240, 1160.

Chapter 3

Synthesis of 37b (General Procedure 1) (exp.453)



In an oven-dried, 30 mL, two-necked, round-bottomed flask containing a magnetic stirring bar, was placed 76 mg (0.61 mmol) of methyl dimethylphosphonate. The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (6 mL) was added with a syringe and the flask was placed in a dry ice-isopropanol bath. After 5 min., 0.30 mL (0.63 mmol) of 2.1 M lithium diisopropylamide in cyclohexane was added with a syringe and the stirring was continued for 40 min.

In an oven-dried, 20 mL, two-necked, round-bottomed flask was placed 83 mg (0.50 mmol) of 36b. The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (2 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the methyl dimethylphosphonate anion solution prepared above and the stirring was continued for 9.5 hr at -70°C.

In an oven-dried, 20 mL, two-necked, round-bottomed flask was placed 65 mg (0.60 mmol) of chloro trimethylsilane (TMSCl). The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (2 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the reaction mixture. After the addition of TMSCl, the reaction mixture was allowed to warm to room temperature and stirred for an additional 36 hr.

The reaction was quenched by adding saturated ammonium chloride solution into it, and diluted with ether. Separated aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. Concentration under vacuum gave 113.9 mg of crude product as an oil. Column chromatography (5 g of SiO_2 60 E. Merck No.5554, 4.8% ethyl acetate / n-hexane) gave 72.8 mg (0.443 mmol, 89% yield) of 37b as a colorless oil.

36b : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.58 (1H, dddd, J=17, 9.5, 7.0, and 7.0 Hz) 5.09 (1H, m) 5.04 (1H, m) 2.66 (2H, dd, J=6.0, and 2.0 Hz) 2.64 (2H, d, J=6.0 Hz) 2.53 (2H, ddd, J=7.0, 1.0, and 1.0 Hz) 2.05-1.85 (2H, m) 1.25 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 1730, 1700, 1320, 1020, 930.

37b : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 5.69 (1H, dddd, J=17, 10, 7.0, and 7.0 Hz) 5.02 (1H, dddd, J=17, 1.5, 1.5, and 1.5 Hz) 5.01 (1H, dddd, J=10, 2.0, 1.0, and 1.0 Hz) 2.36-1.95 (9H, m) 1.11 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2980, 2950, 1675, 1625, 1330, 1260, 1250, 1220, 1200, 1000, 920, 900;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 164 (M^+, 13.7), 149 (2.9), 135 (3.5), 131 (6.3), 122 (1.2), 121 (28.2), 108 (12.0), 107 (4.9), 96 (8.3), 95 (100), 94 (14.1), 93 (44.5), 91 (8.1), 81 (6.3), 80 (5.6), 79 (40.7), 68 (7.1), 67 (37.6), 55 (24.8), 53 (2.3);

HR-MS (EI) Calcd. for $C_{11}H_{16}O$ 164.1202, Found for $C_{11}H_{16}O$ 164.1201.

36d : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 2.72-2.62 (4H, m) 2.04 (1H, m) 1.87-1.74 (3H, m) 1.26 (2H, m) 1.22 (3H, s) 1.10 (2H, m) 0.87 (3H, t, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2870, 1725, 1700, 1460, 1420, 1380, 1320, 1280, 1130, 1020,

MS (EI, 25eV, 80°C) m/e (rel.int./%) 182 (M^+, 7.9), 139 (39.7), 126 (65.9), 124 (19.2), 112 (2.2), 111 (100), 100 (39.5), 98 (25.2), 97 (21.5), 96 (21.5), 93 (2.5), 84 (3.2), 81 (3.6), 72 (21.0), 70 (4.3), 69 (33.5), 67 (7.3), 55 (22.2);

HR-MS (EI) Calcd. for $C_{11}H_{18}O_2$ 182.1307, Found for $C_{11}H_{18}O_2$ 182.1304

37d : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 2.4-2.2 (5H, m) 2.05-1.95 (2H, m) 1.55-1.20 (6H, m) 1.08 (3H, d, J=7.0 Hz) 0.88 (3H, t, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2970, 2950, 2880, 1675, 1625, 1460, 1430, 1390, 1360, 1330, 1260, 1200, 900;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 180 (M^+, 4.0), 137 (13.8), 125 (3.5), 124 (82.0), 110 (2.8), 109 (16.2), 100 (67.2), 97 (27.6), 96 (100), 95 (31.2), 84 (11.7), 82 (3.0), 81 (23.0), 72 (42.7), 68 (3.5), 67 (15.6), 55 (6.9);

HR-MS (EI) Calcd. for $C_{12}H_{20}O$ (M^+) 180.1515, Found for $C_{12}H_{20}O$ (M^+) 180.1496.; Calcd. for $C_{11}H_{17}O$ (M^+-CH_3) 165.1280, Found for $C_{11}H_{17}O$ (M^+-CH_3) 165.1291.

44 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 3.79 (6H, d, J=11 Hz) 3.09 (2H, d, J=22.5 Hz) 2.65 (2H, t, J=6.5 Hz) 2.47 (2H, m) 1.9-1.2 (9H, m) 1.05 (3H d, J=6.5 Hz) 0.89 (3H, t, J=6.5 Hz).

36e : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 3.64 (3H, s) 2.71 (2H, dd, J=2.0, and 6.5 Hz) 2.68 (2H, d, J=6.5 Hz) 2.22 (2H, m) 2.14 (2H, m) 1.98 (2H, m) 1.27 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 1740, 1735, 1700, 1440, 1380, 1320, 1300, 1270, 1220, 1200, 1180, 1030, 905;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{11}H_{16}O_4$ 212.1048, Found for $C_{11}H_{16}O_4$ 212.1048.

37e : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 3.67 (3H, s) 2.4-2.22 (7H, m) 2.02-1.7 (4H, m) 1.12 (3H, d, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2950, 1740, 1670, 1620, 1460, 1440, 1370, 1320, 1260, 1190, 1170, 895;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{12}H_{18}O_3$ 210.1256, Found for $C_{12}H_{18}O_3$ 210.1257.

37f : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.89 (1H, m) 2.44-2.30 (5H, m) 1.99 (2H, m) 1.11 (6H, d, J=7.0 Hz).

36g : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 2.61 (4H, t, J=6.5 Hz) 2.39 (2H, t, J=7.0 Hz) 1.79 (4H, q, J=7.3 Hz) 0.76 (6H, t, J=7.3 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2880, 1730, 1695, 1460 ,1435, 1380, 1320, 1220, 1020, 905;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{10}H_{16}O2$ (M^+) 168.1151, Found for $C_{10}H_{16}O2$ (M^+) 168.1139, Calcd. for $C_8H_{11}O_2$ (M^+-C_2H_5) 139.0759, Found for $C_8H_{11}O_2$ (M^+-C_2H_5) 139.0759.

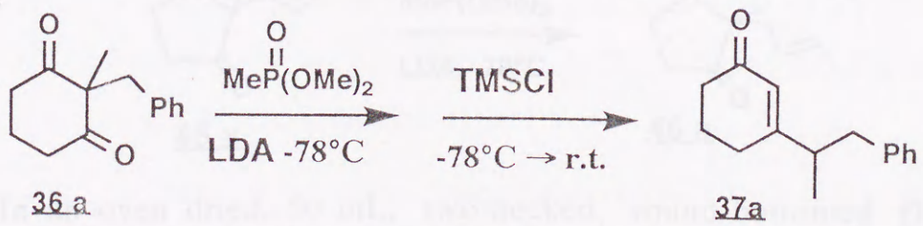
37g : ^{1}H-NMR (60 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 2.5-1.2 (11H, m) 0.83 (6H, t, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2870, 1670;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 166 (M^+, 18.4), 151 (1.6), 137 (3.1), 129 (33.0), 128 (3.6), 123 (2.3), 110 (85.5), 109 (8.9), 101 (38.9), 100 (40.5), 96 (8.2), 95 (46.7), 87 (2.7), 84 (40.9), 83 (4.6), 82 (16.4), 81 (14.3), 79 (2.7), 71 (19.5), 67 (19.5), 59 (100), 58 (2.4), 55 (65.6);

HR-MS (EI) Calcd. for $C_{11}H_{18}O$ 166.1358, Found for $C_{11}H_{18}O$ 166.1358.

Synthesis of 37a (without aqueous work-up) (exp.447)



This reaction was performed as described in the general procedure except that 115 mg (0.532 mmol) of 36a and 73 mg (0.67 mmol) of TMSCl were used. The reaction mixture was concentrated under vacuum without aqueous work-up, and subjected to column

chromatography (5 g of SiO_2 60 E. Merck No.5554, 4.8% ethyl acetate / n-hexane) directly. Cyclohexenone 37a (106.1 mg, 0.495 mmol, 93% yield) was obtained as a colorless oil.

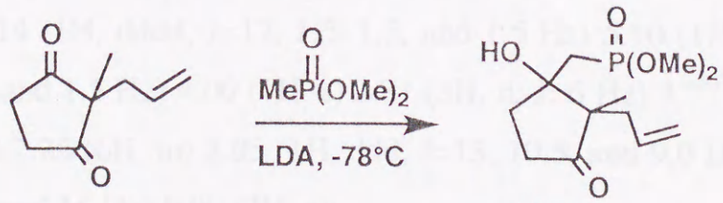
37a : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.30-7.10 (5H, m) 5.86 (1H, brs) 2.80 (1H, m) 2.64-2.58 (2H, m) 2.35-2.25 (4H, m) 1.98-1.90 (2H, m) 1.09 (3H, d, J=6.6 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2980, 2950, 2890, 1675, 1620, 1460, 895, 700;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 214 (M^+, 4.5), 182 (6.2), 139 (39.7), 126 (56.9), 124 (20.3), 112 (4.3), 111 (85.7), 109 (3.1), 100 (59.7), 98 (12.7), 97 (22.0), 96 (39.5), 95 (10.6), 93 (5.1), 92 (9.3), 91 (100), 84 (4.7), 81 (5.3), 72 (17.9), 69 (21.0), 68 (1.1), 67 (6.4), 56 (2.6), 55 (10.8);

HR-MS (EI) Calcd. for $C_{15}H_{18}O$ 214.1358, Found for $C_{15}H_{18}O$ 214.1356.

Reaction of 45a with methyl dimethylphosphonate anion (General Procedure 2) (exp. 29 by E. O.)



45 a 46 a

In an oven dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar was placed methyl dimethyl phosphonate (541 mg, 4.36 mmol). The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (THF) (30 mL) was added with a syringe and the flask was placed in a dry ice-IPA bath.

After 5 min, 2.1 M lithium diisopropylamide (LDA) in cyclohexane (1.9 mL, 4.0 mmol) was added dropwise with a syringe and the stirring was continued for 1 hr.

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum was placed 45a (553 mg, 3.63 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry THF (6 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the methyl dimethylphosphonate anion solution prepared above over 10 min. After 4 hr, the reaction was quenched by adding diluted ammonium chloride solution into it, and the cooling bath was removed immediately. Extraction with methylene chloride, washing with saturated brine, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude product (1.065 g) as a yellow oil. The crude product was subjected to column chromatography (45 g of SiO2 60 E. Merck No.5554, 1% methanol / methylene chloride) to give 46a (520 mg, 1.88 mmol, 52% yield) as a yellow oil and recovered 45a (231 mg, 1.52 mmol, 42 %).

46a : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 6.00 (1H, dddd, J=17, 10, 8.0, and 7.0 Hz) 5.14 (1H, dddd, J=17, 1.5, 1.5, and 1.5 Hz) 5.10 (1H, dddd, J=10, 1.5, 1.5, and 1.5 Hz) 4.00 (1H, s) 3.81 (3H, d, J=6 Hz) 3.77 (3H, d, J=6.0 Hz) 2.50-2.25 (6H, m) 2.05 (1H, ddd, J=13, 10.5, and 9.0 Hz) 1.96 (1H, dd, J=20, and 15 Hz) 0.90 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3450, 2850, 1740, 1640, 1460, 1405, 1240, 1180, 1060, 1040, 920, 850;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

Anal Calcd. C : 52.17%, H : 7.66%; Found C : 52.35%, H : 7.58%

Using the General Procedure 2, the reaction of 45b (150 mg, 1.00 mmol) with methyl dimethylphosphonate gave 46b (47.5 mg, 0.17 mmol, 17% yield) along with recovered 45b (81 mg, 0.54 mmol, 54%).

46b : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.10 (1H, s) 3.82 (3H, d, J=5.0 Hz) 3.78 (3H, d, J=5.0 Hz) 2.86 (1H, dd, J=17, and 15.5 Hz) 2.68 (1H, ddd, J=17, 2.5, and 0.5 Hz) 2.12-2.04 (3H, m) 1.08 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3550-3200, 3300 (s), 3000, 1740, 1220, 1040, 980, 920, 860, 830;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{12}H_{19}O_5P$ 274.0970 (M^+) Found for $C_{12}H_{19}O_5P$ 274.0971 (M^+).

Using the General Procedure 2, the reaction of 45c (104 mg, 0.51 mmol) with methyl dimethylphosphonate gave 46c (49 mg, 0.15 mmol, 29% yield) along with recovered 45c (61 mg, 0.30 mmol, 59%).

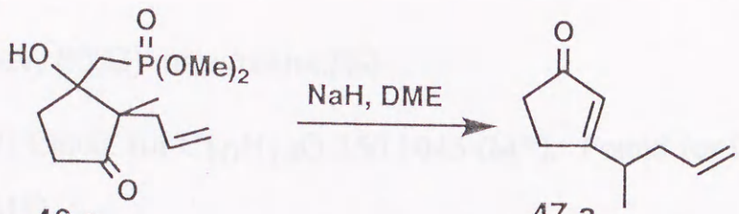
46c : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.40-7.15 (5H, m) 4.30 (1H, s) 3.85 (3H, d, J=11 Hz) 3.73 (3H, d, J=11 Hz) 3.30 (1H, d, J=13.5 Hz) 2.88 (1H, d, J=13.5 Hz) 2.70 (1H, ddd, J=19, 10.5, and 9.0 Hz) 2.48 (1H, ddd, J=14, 9.0, and 1.0 Hz) 2.37 (1H, brdd, J=13, and 9.0 Hz) 2.12 (1H, ddd, J=13, 10.5, and 9.0 Hz) 1.80-1.65 (2H, m) 0.90 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3550-3300, 3000, 1740, 1495, 1465, 1460, 1400, 1370, 1220, 1070, 1040, 990, 960, 930, 860, 710;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{16}H_{23}O_5P$ 326.1283 (M^+), Found for $C_{16}H_{23}O_5P$ 326.1283 (M^+).

Base Promoted Rearrangement of 46a (exp. 31 by E. O.)



46 a 47 a

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed sodium hydride (60% disp. in mineral oil, 25 mg, 0.63 mmol). The flask was evacuated under vacuum, then flushed with argon. Sodium hydride was washed with three portions of dry dimethoxyethane (DME), then 3 mL of dry DME was added with a syringe. The flask was placed in an ice-water bath.

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum was placed 46a (59 mg, 0.214 mmol). Dry DME (2 mL) was added with a syringe, and the solution was transferred dropwise, via a cannula, into the suspension of sodium hydride prepared above over 10 min. The mixture was stirred at 0°C for 1.5 hr, and then at room temperature for 18 hr. The reaction was quenched by adding diluted ammonium chloride solution into it. Extraction with methylene chloride, washing with saturated brine, dried over anhydrous magnesium sulfate, and concentration under vacuum gave pure 47a (18 mg, 0.12 mmol, 56% yield) as a colorless oil.

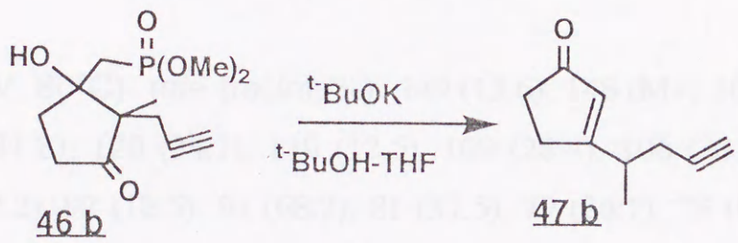
47a : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.95 (1H, m) 5.72 (1H, dddd, J=16.5, 10.5, 7.0, and 7.0 Hz) 5.06 (1H, dddd, J=16.5, 1.5, 1.5, and 1.5 Hz) 5.04 (1H, dddd, J=10.5, 1.5, 1.5, and 1.5 Hz) 2.65-2.58 (3H, m) 2.42-2.23 (4H, m) 1.17 (3H, d, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3100, 2970, 2920, 1710, 1640, 1610, 1440, 1180, 1170, 990, 920, 860;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{10}H_{14}O$ 150.1045 (M^+), Found for $C_{10}H_{14}O$ 150.1046 (M^+).

Base Promoted Rearrangement of 46b (General Procedure 3) (exp. 67 by E. O.)



46 b 47 b

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed potassium tert-butoxide (KOt-Bu) (21 mg, 0.19 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry THF (3 mL) and tert-butanol (0.03 mL) were added with syringes. The mixture was placed in an ice-water bath.

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum was placed 46b (34 mg, 0.12 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry THF (2 mL) was added with a syringe, and the solution was transferred dropwise, via a cannula, into the KO^t-Bu solution prepared above over 5 min. The mixture was stirred at room temperature for 19 hr, then quenched by adding diluted ammonium chloride solution into it. Extraction with methylene chloride, washing with saturated brine, dried

over anhydrous magnesium sulfate, and concentration under vacuum gave crude products (22 mg). The crude products were subjected to column chromatography to give pure 47b (6 mg, 0.04 mmoi, 34% yield) along with recovered 46b (5 mg, 0.02 mmol, 17%).

47b : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 6.03 (1H, dd, J=2.5, and 1.5 Hz) 2.77 (1H, brdq, J=6.5, and 6.5 Hz) 2.66-2.63 (2H, m) 2.44-2.41 (4H, m) 2.01 (1H, t, J=2.5 Hz) 1.28 (3H, d, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3300 (s), 2970, 2920, 1715, 1615, 1460, 1440, 1250, 1180, 980;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 149 (13.6), 148 (M+, 100), 147 (13.2), 133 (31.8), 120 (34.1), 119 (12.5), 109 (28.4), 106 (33.0), 105 (79.5), 94 (18.2), 92 (18.5), 91 (68.2), 81 (37.5), 79 (26.1), 78 (9.1), 77 (14.8), 67 (13.6), 65 (9.1), 53 (29.5).

The KO^{t}-Bu promoted rearrangement of 46c (69 mg, 0.21 mmol) was performed using general procedure 3 except that tert-butanol was used as solvent. After column chromatography (2.5 g of SiO2 60 E. Merck No. 5554, 9% ethyl acetate / n-hexane), 33 mg (0.16 mmol, 78% yield) of 47c was isolated as a colorless oil.

47c : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.35-7.10 (5H, m) 5.94 (1H, m) 2.90-2.85 (2H, m) 2.68 (1H, m) 2.59-2.55 (2H, m) 2.38 (2H, dd, J=4.5, and 4.5 Hz) 1.15 (3H, d, J=6.5 Hz);

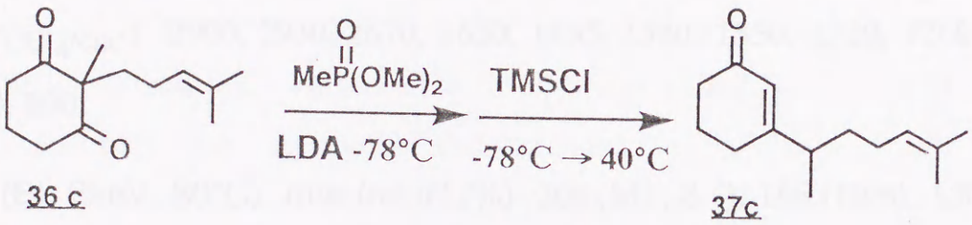
IR $\upsilon_{CCl_4/cm^{-1}}$ 3020, 2970, 2920, 1715, 1610, 1490, 1450, 1440, 1180, 700;

MS (EI, 25eV, 80°C) m/e (rel.int./%)

HR-MS (EI) Calcd. for $C_{14}H_{16}O$ 200.1202 (M^+), Found for $C_{14}H_{16}O$ 200.1215 (M^+).

Formal Synthesis of (±)-α-acoradiene

Synthesis of 37c (exp.481)



36 c 37c

This reaction was performed as described in the general procedure except that 109 mg (0.499 mmol) of 36c was used and the reaction mixture was stirred for 12.5 hr at 40°C after warming to room temperature. Column chromatography (7 g of SiO_2 60 E. Merck No.5554, 4.8% ethyl acetate / n-hexane) gave 62.6 mg (0.303 mmol, 61% yield) of 37c and 5.4 mg (0.026 mmol, 5.2% recovery) of 36c in n-hexane fraction followed by 15.4 mg of unidentified polar material (maybe 80c) in methylene chloride fraction.

36c : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.00 (1H, m) 2.75-2.58 (4H, m) 2.03-1.80 (6H, m) 1.65 (3H, s) 1.56 (3H, s) 1.24 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2980, 2945, 1730, 1700, 1460, 1425, 1380, 1320, 1025;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 206 (M^+-2, 13.1), 150 (14.3), 148 (2.0), 137 (70.2), 128 (30.3), 127 (100), 124 (66.0), 111 (11.7), 110 (19.3), 109 (22.5), 98 (27.6), 97 (7.1), 96 (12.2), 95 (37.4), 93 (2.1), 84 (3.9), 83 (51.6), 82 (99), 81 (40.6),

HR-MS (EI) Calcd. for $C_{13}H_{19}O_2$ (M^+-H) 207.1385, Found for $C_{13}H_{19}O_2$ 207.1370.

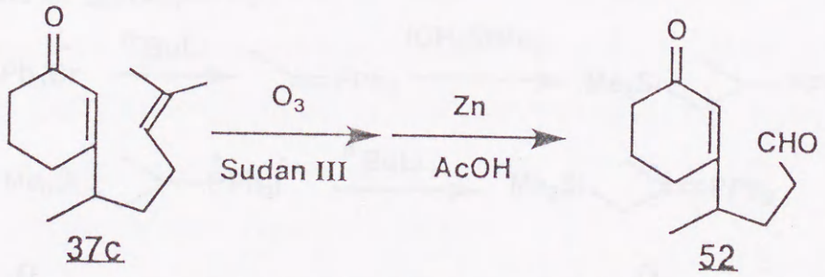
37c : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 5.06 (1H, m) 2.38-2.25 (5H, m) 2.02-1.90 (4H, m) 1.68 (3H, brs) 1.58 (3H, brs) 1.54-1.36 (2H, m) 1.09 (3H, d, J=7.0 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2930, 2670, 1620, 1455, 1380, 1350, 1320, 1260, 1190, 890;

MS (EI, 25eV, 80°C) m/e (rel.int./%) 206 (M^+, 8.4), 166 (12.6), 150 (9.1), 148 (7.0), 137 (66.7), 129 (4.4), 124 (66.1), 123 (9.2), 110 (50.6), 109 (32.5), 97 (15.3), 96 (36.1), 95 (51.1), 93 (16.0), 84 (23.5), 83 (6.8), 82 (100), 81 (33.3), 79 (5.3), 71 (24.8), 69 (13.7), 68 (2.2), 67 (43.9), 55 (41.5);

HR-MS (EI) Calcd. for $C_{14}H_{22}O$ 206.1671, Found for $C_{14}H_{22}O$ 206.1670.

Ozonolysis of 37c (exp.546)



37c 52

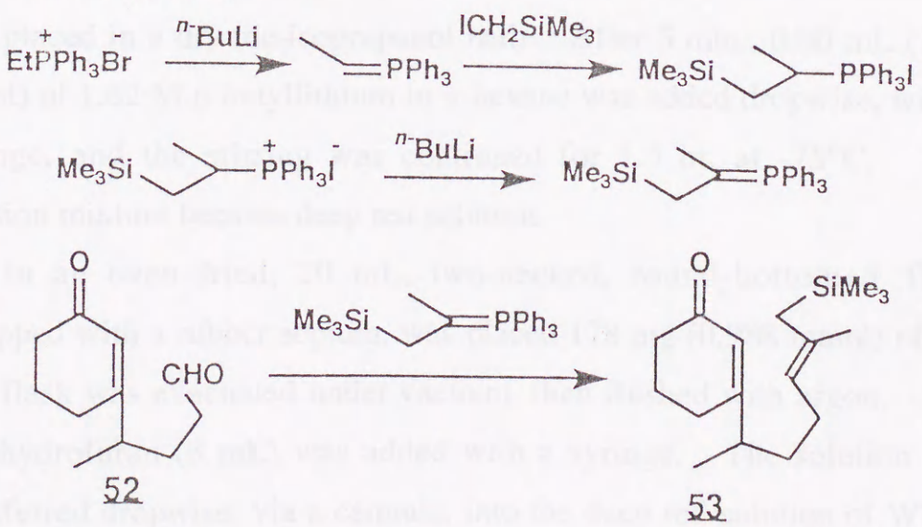
A 200mL, round-bottomed flask equipped with a magnetic stirring bar, and a Claisen adapter with a gas inlet and a drying tube ($CaCl_2$), was charged with 1.031 g (4.997 mmol) of 37c and 100 mL of dry methylene chloride containing 0.45 mL (5.6 mmol) of pyridine. A small amount of Sudan III was added as an indicater. The flask was placed in a dry ice-

isopropanol bath and a stream of ozone was bubbled through the light red solution.

After 30 min, the light red color of the solution disappeared. After this point TLC showed that the reaction was essentially complete, then a stream of oxygen was passed for 5 min. to displace the ozone. The cold (-75°C) reaction mixture was immediately poured into 200 mL Erlenmeyer flask containing 2.55 g (39.0 mmol) of powdered zinc and a magnetic stirring bar. Acetic acid (5 mL) was added and the mixture was vigorously stirred in a water bath for 2 hr.

The reaction mixture was filtered through Celite pad and the filtrate was washed with water (10 mL×2), 5% sodium hydroxide solution (10 mL×2), water (10 mL×3), and saturated brine, then dried over anhydrous magnesium sulfate. Concentration under vacuum gave 1.2 g of crude aldehyde. ^{1}H-NMR (60 MHz) showed that the crude product contained enone-aldehyde 52, and a small amount of solvents. Unpurified 52 was used in a next reaction to avoid decomposition through the purification steps.

Synthesis of 53 (exp.547)



In an oven-dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed 416 mg (1.12 mmol) of ethyl triphenylphosphonium bromide. The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (10 mL) was added with a syringe and the flask was placed in an ice-water bath. n-Butyllithium in n-hexane (1.62 M, 0.80 mL, 1.30 mmol) was added dropwise, with a syringe, to the stirring white suspension and the stirring was continued for 55 min. at room temperature. The reaciton mixture became a red solution with the formation of ethylidene triphenylphosphorane. The flask was placed in an ice-water bath.

In an oven-dried, 20 mL, two-necked, round-bottomed flask was placed 240 mg (1.12 mmol) of iodomethyl trimethylsilane (note 1). The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (2 mL) was added with a syringe. The solution was transferred, via a cannula, into the ethylidene triphenylphosphorane solution prepared above, and the stirring was continued for 4 hr at room temperature. The reaction mixture became yellow suspension. The flask was placed in a dry ice-isopropanol bath. After 5 min., 0.80 mL (1.30 mmol) of 1.62 M n-butyllithium in n-hexane was added dropwise, with a syringe, and the stirring was continued for 1.5 hr. at -75°C. The reaction mixture became deep red solution.

In an oven-dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum, was placed 178 mg (0.988 mmol) of 52. The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (3 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the deep red solution of Wittig reagent prepared above, and the stirring was continued for 0.5 hr. at -

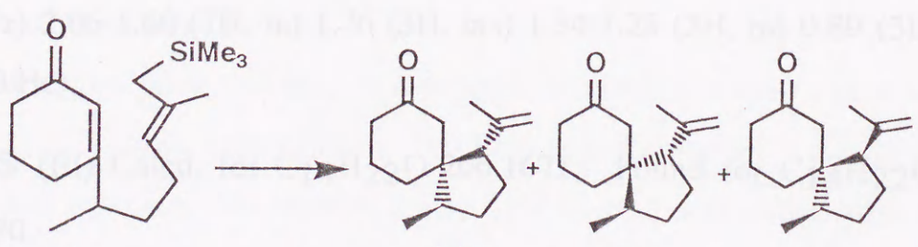
75°C. The light red reaction mixture was allowed to warm to room temperature and stirred for additional 3 hr..

The reaction was quenched by adding saturated ammonium chloride solution into it, and the mixture was diluted with ether. The separated aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, then concentrated under vacuum to give 694.9 mg of crude products. Column chromatography (30 g of SiO_2 60 E. Merck No.5554, 4.8% ethyl acetate / n-hexane) gave 135.4 mg (0.486 mmol, 49% yield) of 53 as a colorless oil. ^{1}H-NMR (270 MHz) examination indicated that the geometric isomer of 53 was not produced. After 1 year storage in a refragerator, the E/Z isomerization occurred.

53 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.87 (1H, brs) 4.90 (1H, m) 2.37 2.27 (5H, m) 2.00-1.85 (4H, m) 1.66-1.40 (4H, m) 1.45 (3H, brd, J=3.5 Hz) 1.08 (3H, d, J=7.0 Hz) -0.01 (9H, s);

HR-MS (EI) Calcd. for $C_{17}H_{30}OSi$ 278.2066, Found for $C_{17}H_{30}OSi$ 278.2065.

Synthesis of (±)-α-acoradiene (Lewis acid mediated spiro-cyclization of 53)



53 51 54 55

In an oven-dried, 20 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed 26.6 mg (0.0955 mmol) of 53. The flask was evacuated under vacuum, then flushed with argon. Dry toluene (10 mL) was added with a syringe and the flask was placed in a dry ice-isopropanol bath. After 5 min., 0.14mL (0.14 mmol) of 1 M ethyl aluminum dichloride in n-hexane was added dropwise, with a syringe, and the stirring was continued for 25 min. The reaction was quenched by adding 10 mL of water into it and diluted with ether. The separated aqueous layer was extracted with ether and the combined organic layer was dried over anhydrous magnesium sulfate. Concentration and column chromatography (3.5 g of SiO_2 60 E.Merck No.5554, 4.8% ethyl acetate / n-hexane) gave 10.4 mg (0.0504 mmol, 53% yield) of spirocyclic ketone as a mixture of three diastereomers. The diastereomeric ratio was determined as 51/54/55=1/1/1 by ^{1}H-NMR spectroscopy(270 MHz).

These diastereomers were further separated by preparative HPLC (YMC SIL-5-06 S-5 60A SIL, 3.2% ethyl acetate / n-hexane, flow rate 18 mL/min., retention time 51 : 22 min. 54 : 20 min. 55 : 24 min.)

51 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.96 (1H, m) 4.72 (1H, m) 2.51 (1H, t, J=9.0 Hz) 2.30-2.26 (2H, m) 2.16 (1H, d, J=13 Hz) 2.12 (1H, d, J=13 Hz) 2.06-1.60 (7H, m) 1.76 (3H, brs) 1.34-1.23 (2H, m) 0.89 (3H, d, J=7.0 Hz);

HR-MS (EI) Calcd. for $C_{14}H_{22}O$ 206.1671, Found for $C_{14}H_{22}O$ 206.1670.

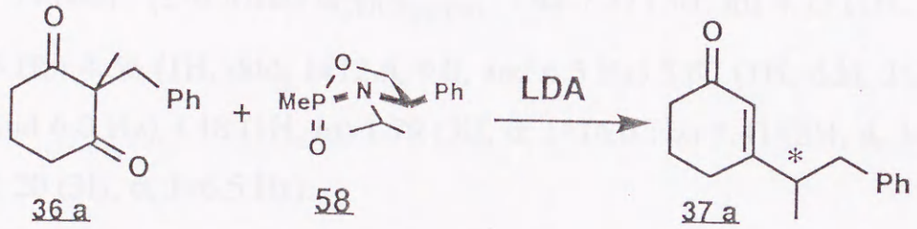
54 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.88 (1H, m) 4.68 (1H, m) 2.35-2.16 (5H, m) 2.0-1.44 (7H, m) 1.76 (3H, dd, J=0.6, and 0.6 Hz) 1.30-1.16 (4H, m) 0.91 (3H, d, J=6.5 Hz);

HR-MS (EI) Calcd. for $C_{14}H_{22}O$ 206.1671, Found for $C_{14}H_{22}O$ 206.1670.

55 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.94 (1H, m) 4.77 (1H, m) 2.41 (1H, d, J=14 Hz) 2.26-2.17 (4H, m) 1.92-1.52 (7H, m) 1.77 (3H, brs) 1.41-1.26 (2H, m) 0.94 (3H, d, J=7.0 Hz);

HR-MS (EI) Calcd. for $C_{14}H_{22}O$ 206.1671 (M^+), Found for $C_{14}H_{22}O$ 206.1670 (M^+).

Asymmetric Synthesis of 37a (exp. 3 by E. O.)



In an oven-dried, 30 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 58 (289 mg, 1.21 mmol). The flask was evacuated under vacuum, then flushed with nitrogen. Dry THF (10 mL) was added with a syringe and the flask was placed in a dry ice-IPA bath. After 5 min., 2.1 M LDA in cyclohexane (0.52 mL, 1.1 mmol) was added with a syringe and the stirring was continued for 1 hr.

In an oven-dried, 20 mL, two-necked, round-bottomed flask was placed 36a (218 mg, 1.01 mmol). The flask was flushed with nitrogen, then sealed with a rubber septum. Dry THF (2 mL) was added with a syringe. The solution was transferred dropwise , via a cannula, into the anion solution of 58 prepared above and the stirring was continued at -78°C for 6 hr.. The reaction mixture was gradually warmed to room temperature over 19 hr, and then quenched by adding diluted ammonium

chloride solution into it. Extraction with methylene chloride and ether, washed with saturated brine, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude products (349 mg). The crude product was subjected to column chromatography to give pure 37a (101 mg, 0.471 mmol, 47% yield). $[\alpha]_D^{28}$ +12.2° (c 1.1, $CHCl_3$)

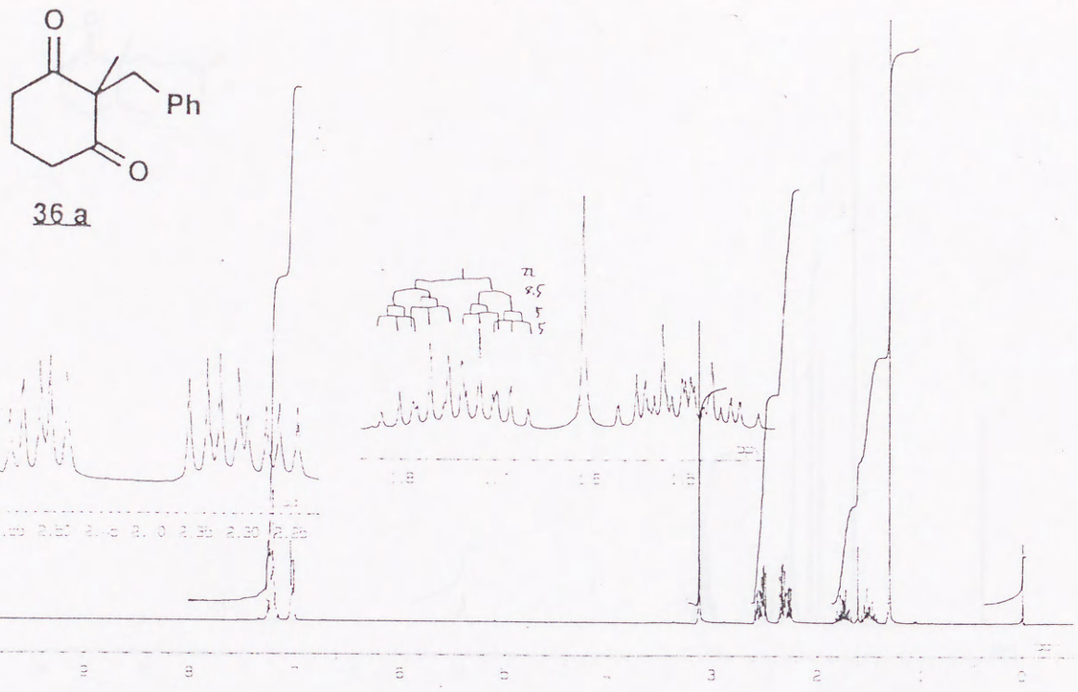
The enantiomeric excess of 37a was determined by HPLC using chiral column (CHIRAL CELL OC, 20 mmϕ x 500 mm, 9% IPA / n-hexane, flow rate 4.0 mL / min). After recycling 15 times, two peakes were separated, and the ratio was determined as (+)-37a/(-)-37a = 62/38.

58 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.42-7.27 (5H, m) 4.73 (1H, brt, J=7.5 Hz) 4.56 (1H, ddd, J=12.5, 9.0, and 6.5 Hz) 3.87 (1H, ddd, J=9.0, 8.0, and 6.0 Hz) 3.18 (1H, m) 1.79 (3H, d, J=16.0 Hz) 1.41 (3H, d, J=7.0 Hz) 1.20 (3H, d, J=6.5 Hz).

39 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.82 (1H, m) 4.55 (1H, m) 1.96-1.91 (2H, m) 1.54 (3H, d, J=17 Hz) 1.51 (3H, d, J=6.5 Hz) 1.39 (3H, dd, J=6.5, and 1.2 Hz);

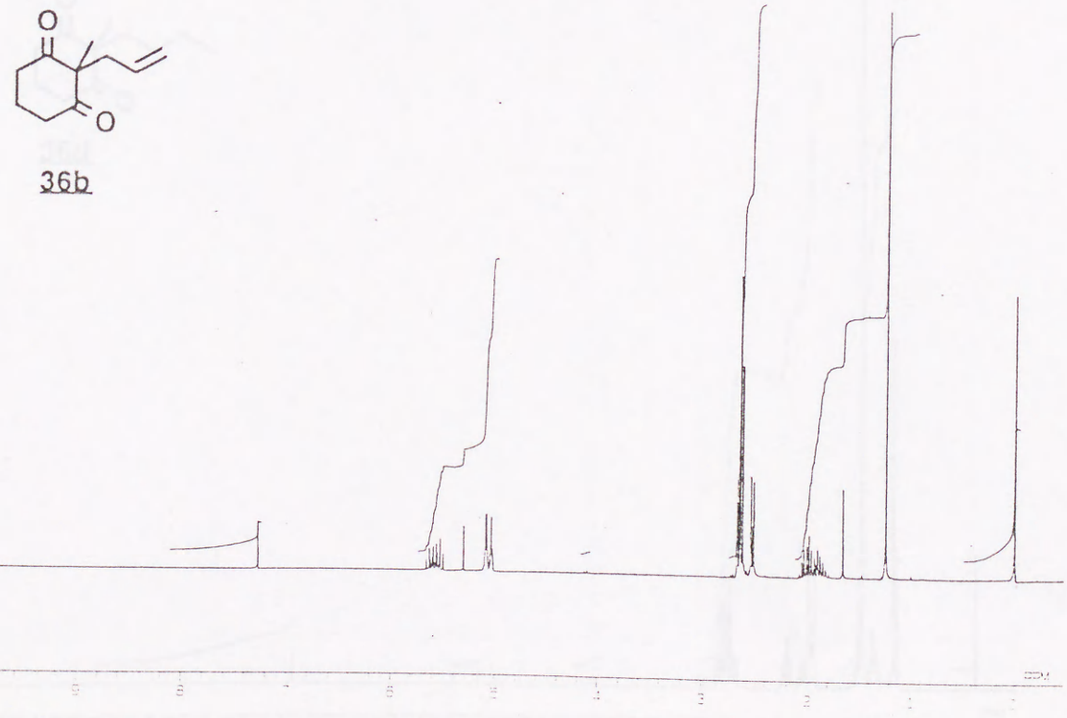
MS (EI) m/e (rel.int./%) 164 (M+, 1.5), 149 (9.4), 124 (2.3), 123 (50.7), 119 (3.2), 105 (2.1), 97 (100), 94 (2.0), 92 (2.7), 80 (3.1), 79 (22.5), 71 (8.4)., 69 (4.5), 68 (11.4), 65 (1.3), 62 (1.6), 58 (2.0), 53 (1.3).

^{1}H NMR Spectrum of 36a (TMS/$CDCl_3$, 270 MHz)



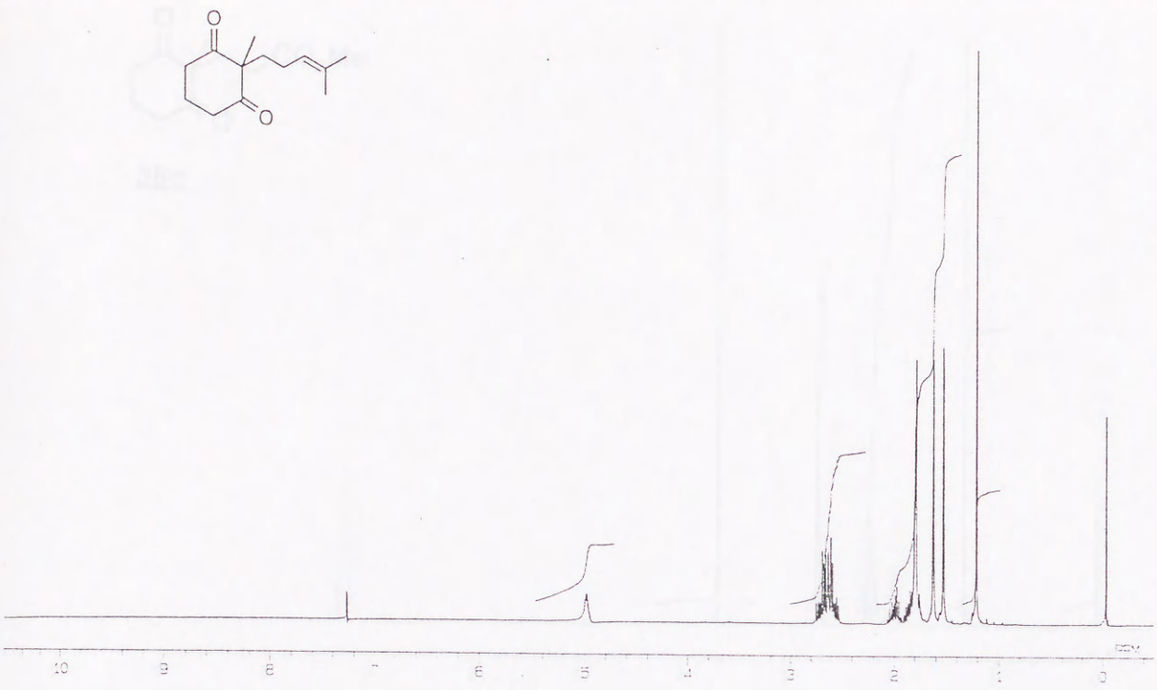
36 a

^{1}H NMR Spectrum of 36b (TMS/$CDCl_3$, 270 MHz)



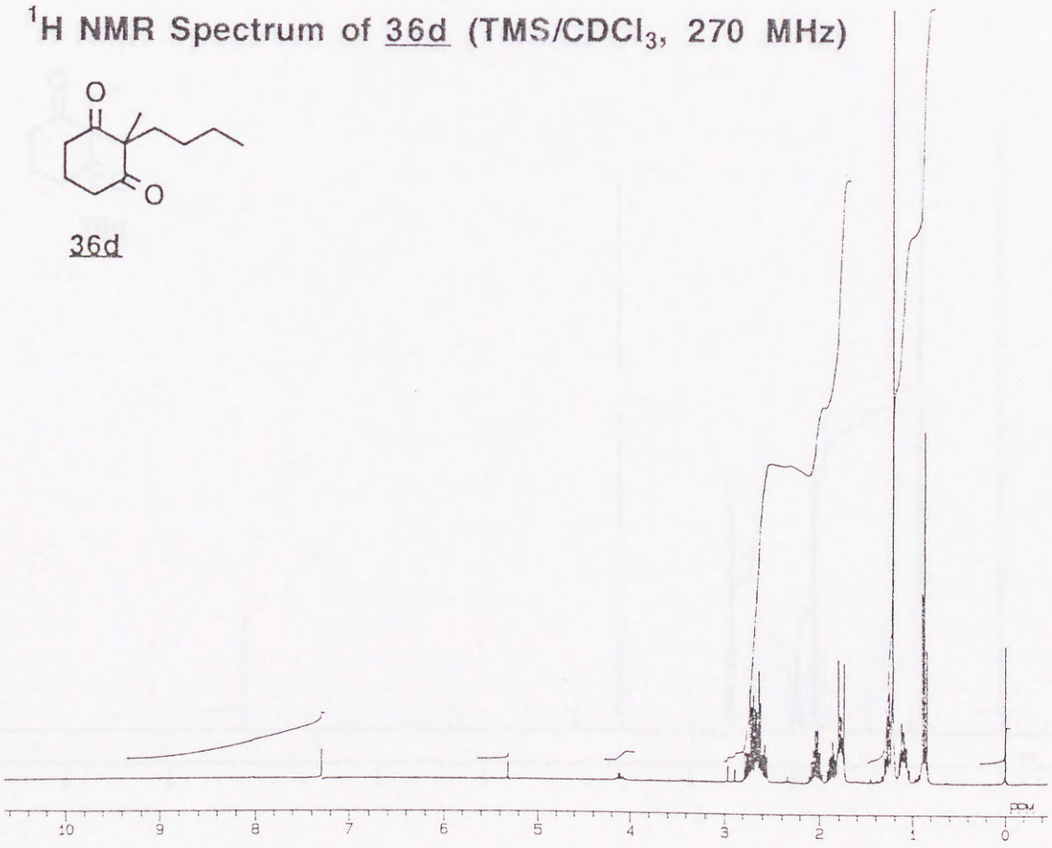
36b

^{1}H NMR Spectrum of 36c (TMS/$CDCl_3$, 270 MHz)

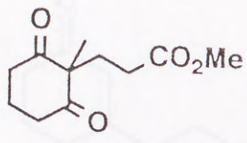


^{1}H NMR Spectrum of 36d (TMS/$CDCl_3$, 270 MHz)

36d

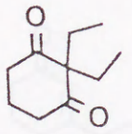


^{1}H NMR Spectrum of 36e (TMS/$CDCl_3$, 270 MHz)



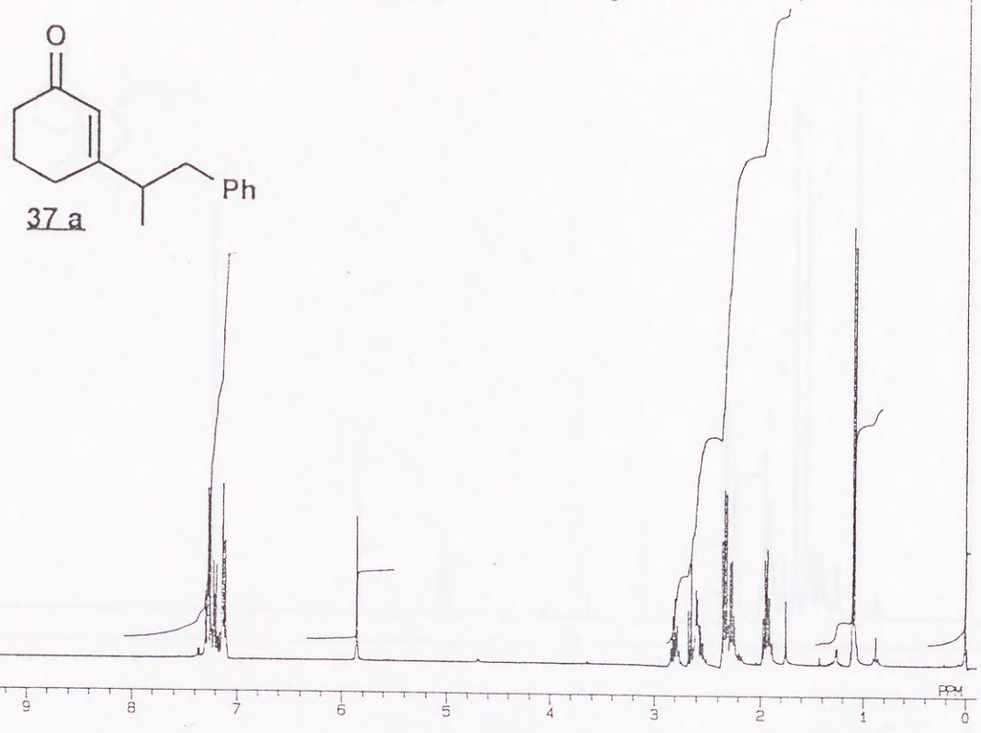
36e

^{1}H NMR Spectrum of 36g (TMS/$CDCl_3$, 270 MHz)

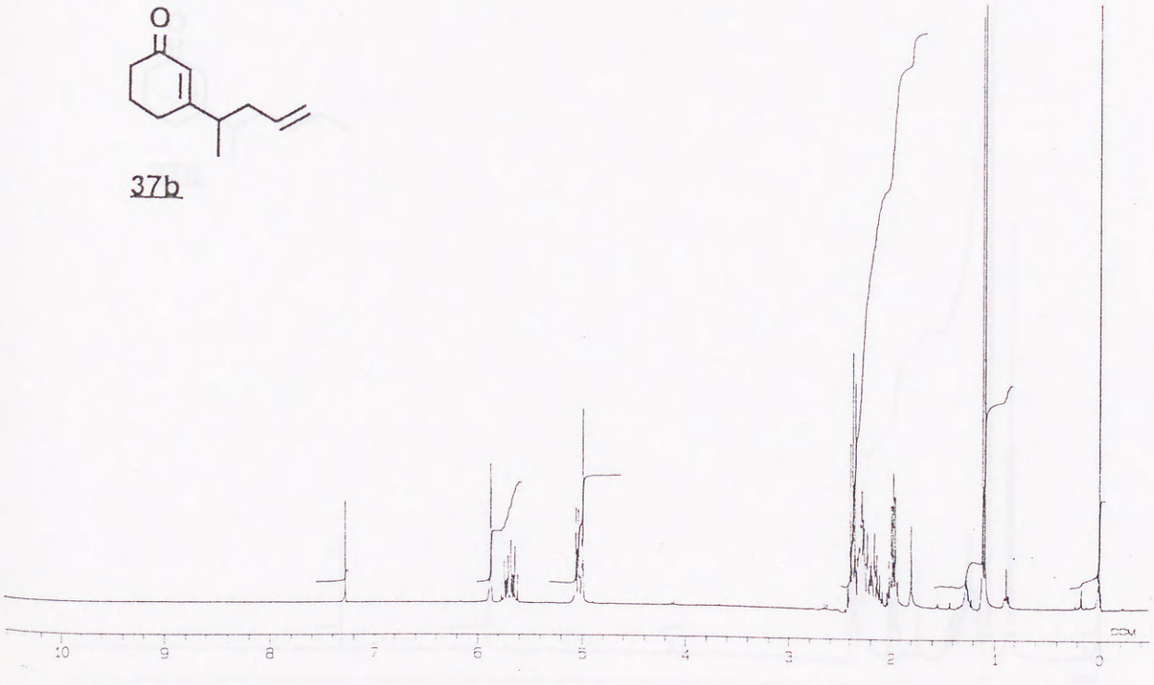


36g

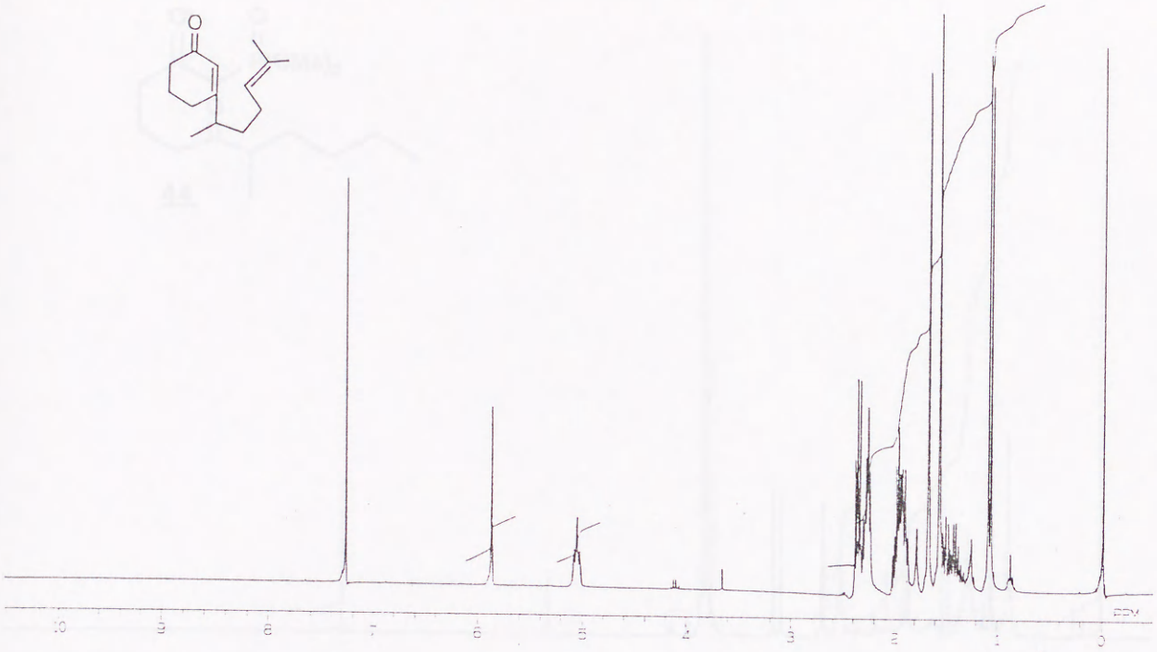
^{1}H NMR Spectrum of 37a (TMS/$CDCl_3$, 270 MHz)



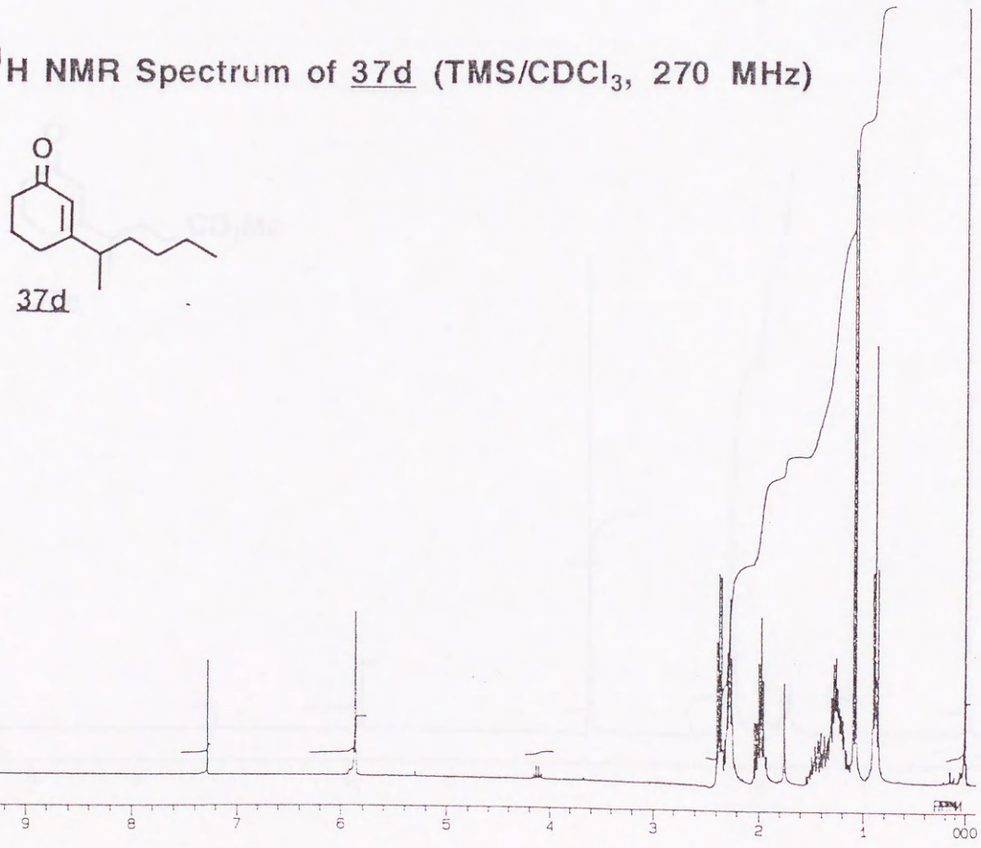
^{1}H NMR Spectrum of 37b (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 37c (TMS/$CDCl_3$, 270 MHz)

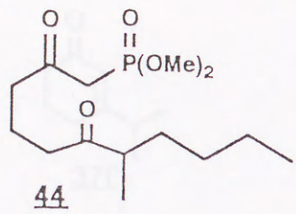


^{1}H NMR Spectrum of 37d (TMS/$CDCl_3$, 270 MHz)



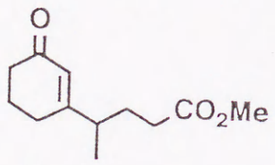
37d

^{1}H NMR Spectrum of 44 (TMS/$CDCl_3$, 270 MHz)



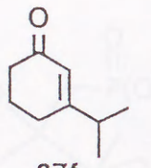
44

^{1}H NMR Spectrum of 37e (TMS/$CDCl_3$, 270 MHz)



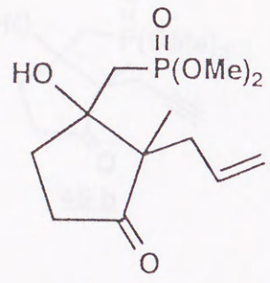
37e

^{1}H NMR Spectrum of 37f (TMS/$CDCl_3$, 270 MHz)



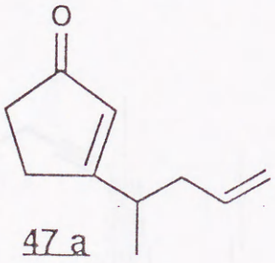
37f

^{1}H NMR Spectrum of 46a (TMS/$CDCl_3$, 270 MHz)



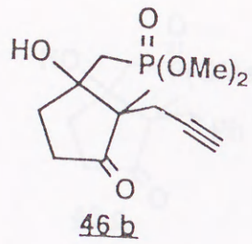
46 a

^{1}H NMR Spectrum of 47a (TMS/$CDCl_3$, 270 MHz)



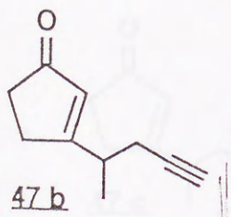
47 a

^{1}H NMR Spectrum of 46b (TMS/$CDCl_3$, 270 MHz)



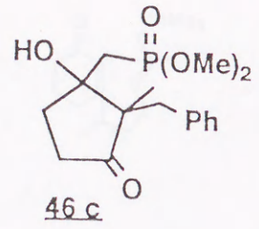
46 b

^{1}H NMR Spectrum of 47b (TMS/$CDCl_3$, 270 MHz)



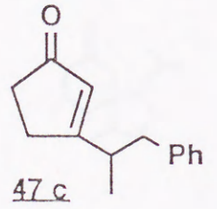
47 b

^{1}H NMR Spectrum of 46c (TMS/$CDCl_3$, 270 MHz)



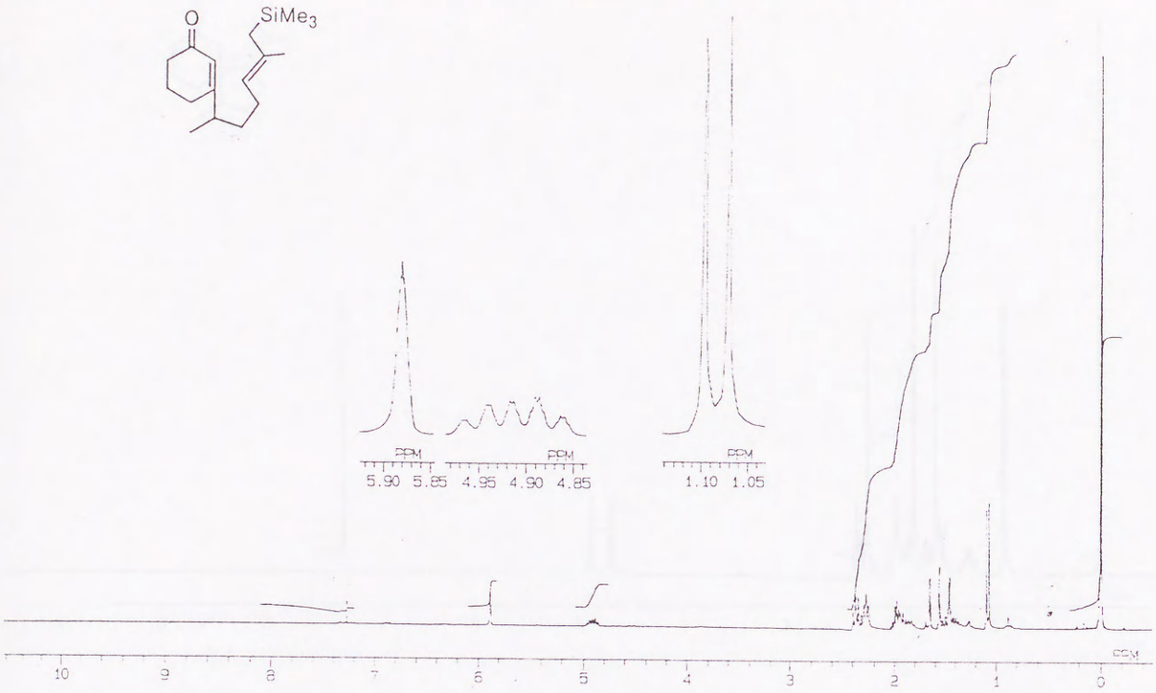
46 c

^{1}H NMR Spectrum of 47c (TMS/$CDCl_3$, 270 MHz)

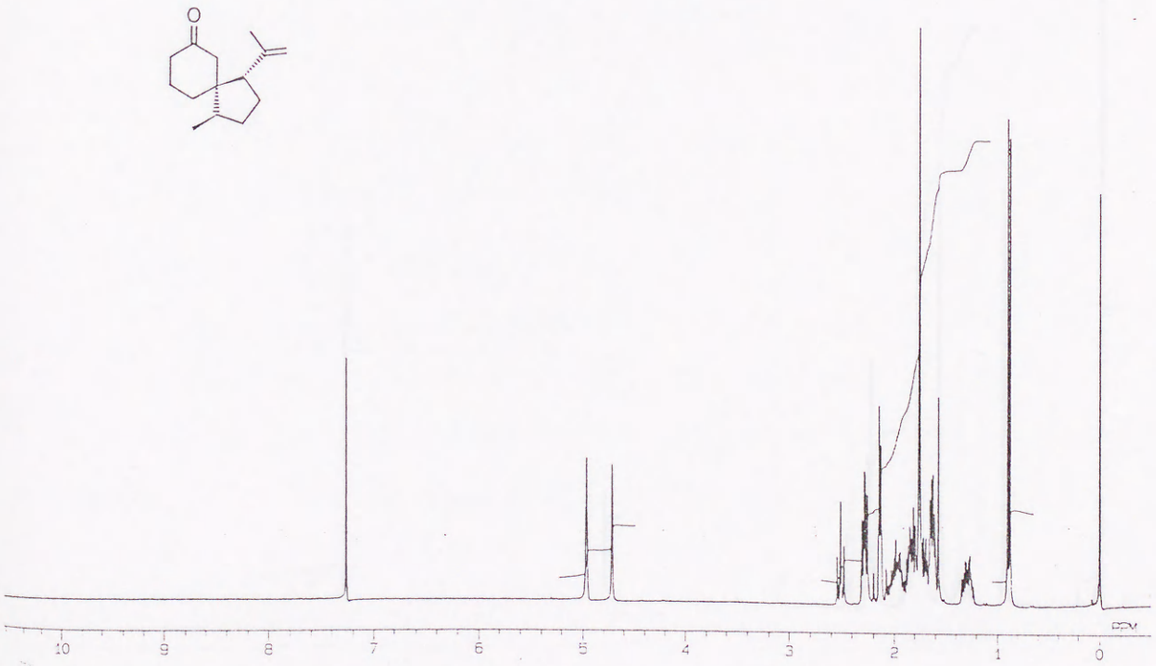


47 c

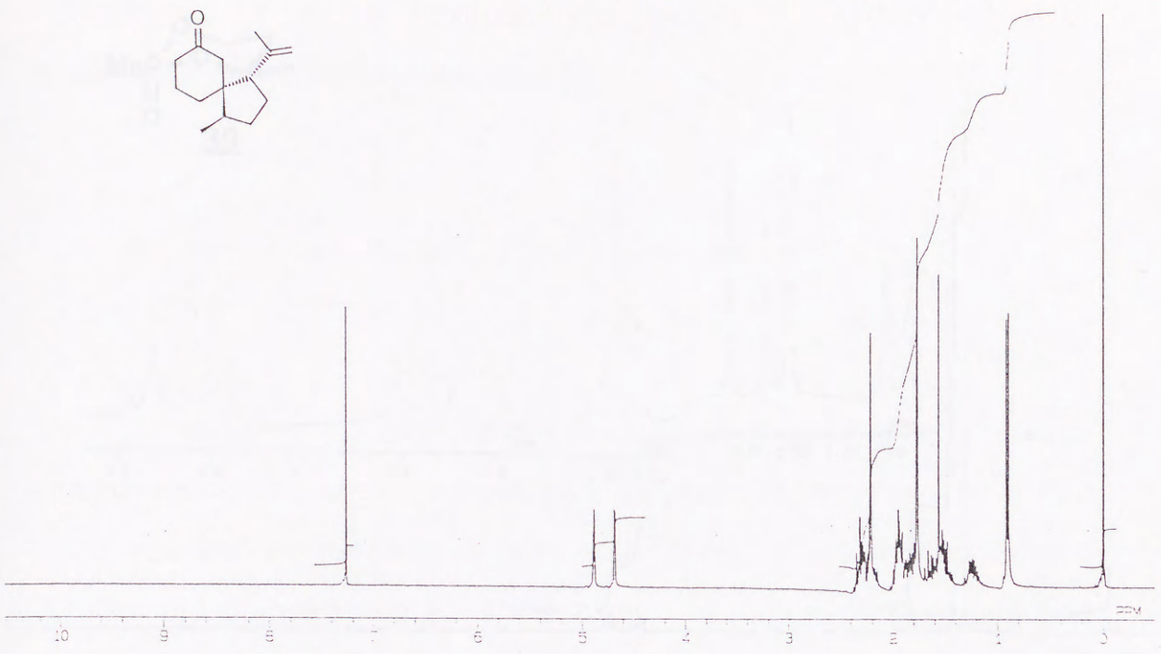
^{1}H NMR Spectrum of 53 (TMS/$CDCl_3$, 270 MHz)



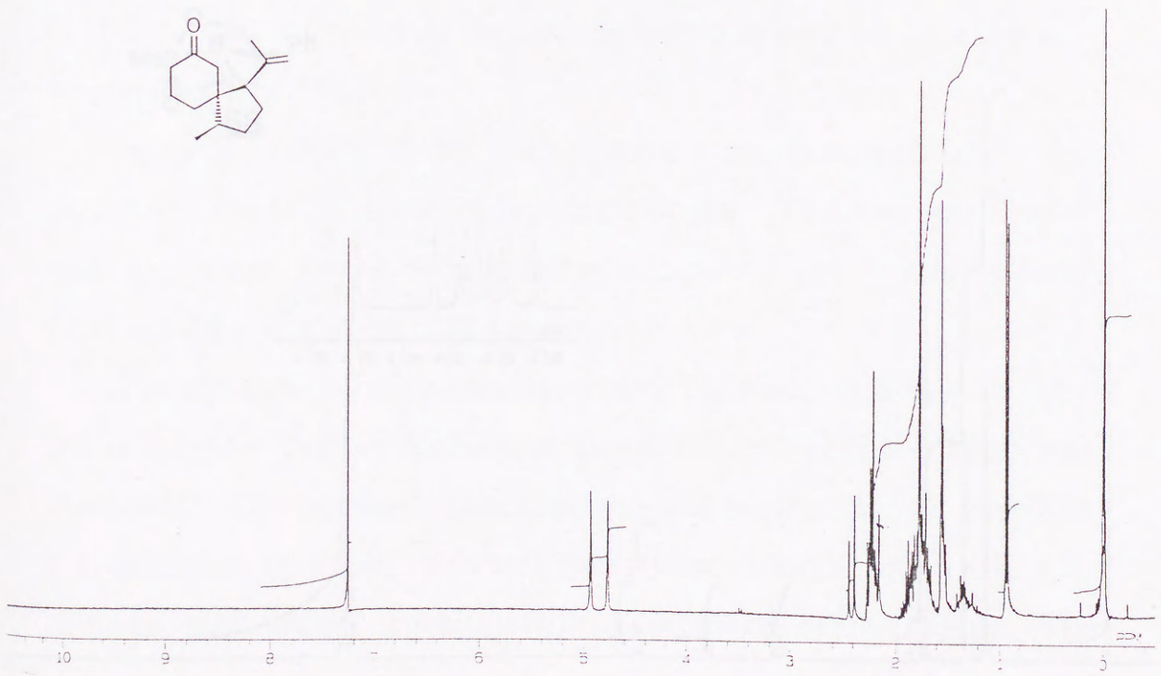
^{1}H NMR Spectrum of 51 (TMS/$CDCl_3$, 270 MHz)



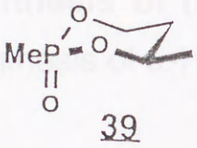
^{1}H NMR Spectrum of 54 (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 55 (TMS/$CDCl_3$, 270 MHz)

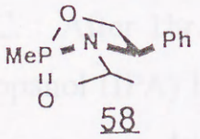


^{1}H NMR Spectrum of 39 (TMS/$CDCl_3$, 270 MHz)

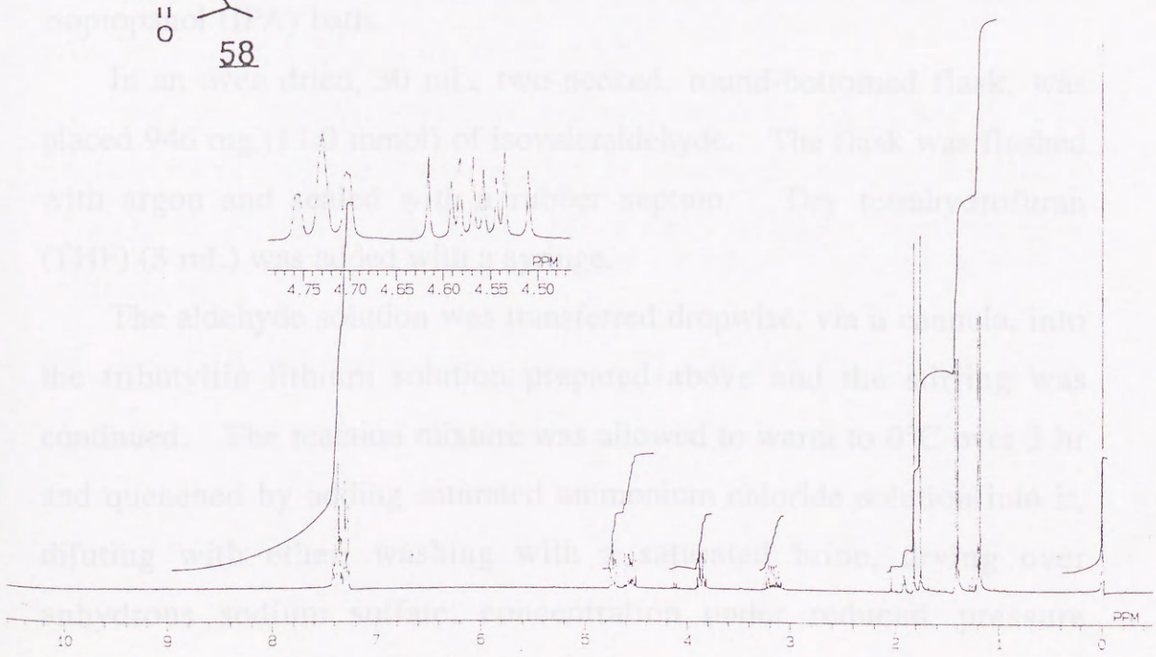


39

^{1}H NMR Spectrum of 58 (TMS/$CDCl_3$, 270 MHz)

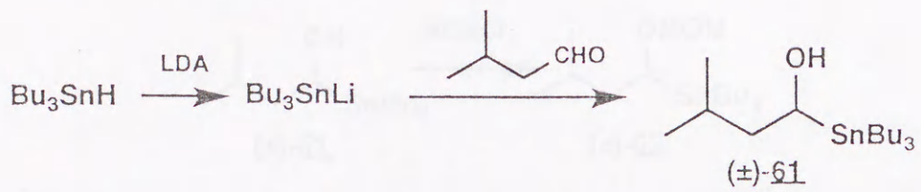


58



Chapter 4

Synthesis of (±)-64 (General Procedure 1) (exp.765 and 761)
Synthesis of α-Hydroxystannane 61



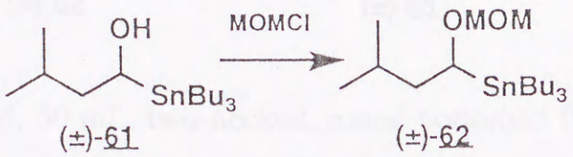
An oven dried, 100 mL, two-necked, round-bottomed flask maintained under argon, containing a magnetic stirring bar and sealed with a rubber septum, was charged with 10 mL of dry tetrahydrofuran (THF) and placed in an ice-water bath. Lithium diisopropylamide (LDA) in cyclohexane (2.1 M, 4.8 mL, 10.1 mmol) was added to the flask with a syringe. Tributyltin hydride (2.7 mL, 10.0 mmol) was added dropwise ,with a syringe, to the lithium diisopropylamide solution at 0°C. After 1hr. stirring, the cooling bath was replaced by a dry ice-isopropanol (IPA) bath.

In an oven dried, 30 mL, two-necked, round-bottomed flask, was placed 946 mg (11.0 mmol) of isovaleraldehyde. The flask was flushed with argon and sealed with a rubber septum. Dry tetrahydrofuran (THF) (3 mL) was added with a syringe.

The aldehyde solution was transferred dropwise, via a cannula, into the tributyltin lithium solution prepared above and the stirring was continued. The reaction mixture was allowed to warm to 0°C over 3 hr and quenched by adding saturated ammonium chloride solution into it, diluting with ether, washing with a saturated brine, drying over anhydrous sodium sulfate, concentration under reduced pressure (temperature < 30°C). The crude α-hydroxystannane 61 was obtained as

an oil. The product was immediately converted to the O-methoxymethyl derivatives as described below.

MOM Protection of 61



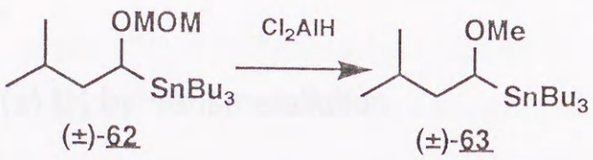
(±)-61 (±)-62

In an 50 mL, round-bottomed flask fitted with an anhydrous calcium chloride tube, was placed the unpurified 61. The flask was filled with 15 mL of dry methylene chloride and cooled in an ice-water bath. Chloromethyl methyl ether (1.15 mL, 15.1 mmol) and 3.5 mL (20.1 mmol) of diisopropyl ethylamine in 5 mL of methylene chloride were added to the stannane solution with stirring. After 37 hr., the reaction mixture was diluted with methylene chloride and washed with water (10 mL×2) and saturated brine (10 mL). The methylene chloride layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 5.75 g of the crude product.

Methoxy methyl protected α-alkoxystannane 62 (1.883 g, 4.47 mmol, 45% overall yield) was isolated by column chromatography (100 g of SiO_2 60 E. Merck No.5554, 1% of ethyl acetate / ^{n}-hexane) as a colorless oil.

62 : ^{1}H-NMR (60 MHz) $\delta_{CDCl_3/ppm}$ 4.50 (2H, s) 4.10 (1H, dd, J=9.0, and 5.0 Hz) 3.30 (3H, s) 1.9-0.8 (36H, m)

Cl_2AlH Reduction of 62 (exp. 671)



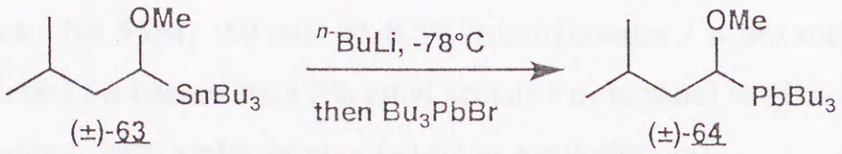
(±)-62 (±)-63

An oven dried, 50 mL, two-necked, round-bottomed flask containing a magnetic stirring bar, was placed 2.85 g (21.4 mmol) of aluminum chloride. One neck was connected to a three-way stopcock with a balloon filled with argon, and the other neck was equipped with a rubber septum. The flask was evacuated under vacuum , then flushed with argon. This process was repeated three times. Dry ether (18 mL) was added with a syringe at 0°C. To the resulting clear colorless solution was added 275 mg (7.25 mmol) of lithium aluminum hydride and the stirring was continued for 1 hr in an ice-water bath. The reaction mixture became white slurry.

An oven dried, 20 mL, two-necked, round-bottomed flask, was placed 1.501g (3.561 mmol) of 62, and evacuated under vacuum, then flushed with argon. Dry ether (6 mL) was added. To the previously prepared white slurry of Cl_2AlH was added the ether solution of 62 via a cannula at 0°C, and the stirring was continued for 30 min at 0°C then 12 hr at room temperature. The unreacted aluminum hydride species was cautiously hydrolyzed by dropwise addition of water (10 mL) at 0°C. The organic layer was diluted with ether (20 mL), then separated and dried over anhydrous sodium sulfate. Filtration and concentration gave 63 (1.297 g, 3.32 mmol, 93% yield) as a colorless oil.

63 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 3.82 (1H, dd, J=10.3, and 4.4 Hz) 3.28 (3H, s) 1.91 (1H, ddd, J=13.5, 10.3, and 5.0 Hz) 1.74 (1H, m) 1.6-0.87 (34H, m).

Synthesis of (±)-64 by transmetallation



In an oven dried, 30 mL, two-necked, round-bottomed flask, containing a magnetic stirring bar, was placed 119 mg (0.304 mmol) of α-methoxy stannane 63. One neck was connected to a three-way stopcock equipped with a balloon filled with argon and the other neck was capped with a rubber septum. The flask was evacuated under vacuum, then flushed with argon. This process was repeated three times. Dry tetrahydrofuran (2 mL) was added with a syringe, and the flask was cooled in a dry ice-isopropanol (IPA) bath. After 5 min., 0.18 mL (0.30 mmol) of 1.64 M n-butyllithium in n-hexane was added with a syringe and the stirring was continued for 20 min. toward the completion of the transmetallation.

In an oven dried, 20 mL, two-necked, round-bottomed flask, was placed 156 mg (0.34 mmol) of tributylplumbyl bromide. The flask was sealed with rubber septum and evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (1 mL) was added with a syringe.

The tributylplumbyl bromide solution was transferred dropwise, via a cannula, into the α-methoxy lithium solution prepared above and the stirring was continued for 40 min. After the addition of 2 mL of water,

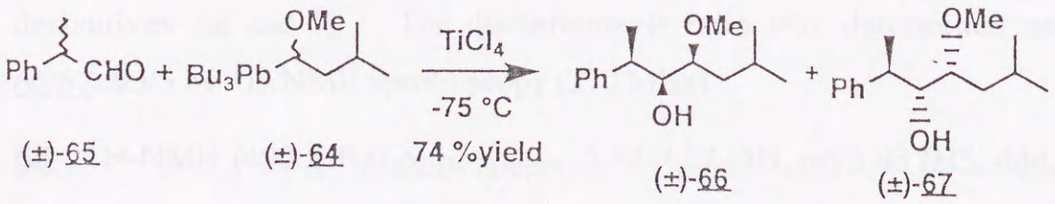
the reaction mixture was allowed to warm to room temperature and diluted with ether. Aqueous layer was picked up using Pasteur pipette and remaining organic layer was dried over anhydrous sodium sulfate. Filtration and concentration under vacuum (temperature < 30°C) gave crude α-methoxyplumbum and tetrabutylstannane. The crude product was immediately subjected to column chromatography (10 g of SiO_2 60 E. Merck No.5554, 50 mL of 0.5% triethylamine / n-hexane, 1.4% ethyl acetate / n-hexane then 2% ethyl acetate / n- hexane) to give 107 mg (0.223 mmol, 73% yield) of pure (±)-64 as a colorless oil.

Since 64 was gradually decomposed in open air, it was immediately used in a next condensation reaction.

64 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.48 (1H, dd, J=10.6, and 4.4 Hz, ^{207}Pb satellites gave $J_{H,\ Pb}$=80 Hz) 3.31 (3H, s) 2.10 (1H, ddd, J=13.9, 10.3, and 4.8 Hz) 1.90-1.68 (6H, m) 1.58-1.45 (8H, m) 1.37-1.25 (6H, m) 0.90 (15H, m);

IR $\upsilon_{film/cm^{-1}}$ 2960, 2930, 2890, 1465, 1380, 1200, 1160, 1120, 1080.

Reaction of (±)-65 and (±)-64 in the presence of $TiCl_4$ (General Procedure 2) (exp.673)



(±)-65 (±)-64 (±)-66 (±)-67

In an oven dried, 30 mL, two-necked, round-bottomed flask, containing a magnetic stirring bar, was placed 127 mg (0.947 mmol) of aldehyde (65). One neck was connected to a three-way stopcock equipped with a balloon filled with argon. The flask was flushed with

methelene chloride. The flask was placed in a dry ice-isopropanol bath. After 5 min., 1.0 mL (1.0 mmol) of 1.0 M titanium tetrachloride was added with a syringe and the stirring was continued for 10 min. The reaction mixture became yellow slurry.

In an oven dried, 20 mL, two-necked, round-bottomed flask, was placed 227 mg (0.473 mmol) of α-methoxyplumbum (64). The flask was evacuated under vacuum, then flushed with argon. Dry methylene chloride (2 mL) was added.

The α-methoxyplumbum solution prepared above was transferred dropwise, via a cannula, into the stirring yellow slurry of $TiCl_4$-65 complex.

The reaction mixture turned black green in color and was allowed to warm to room temperature over 13.5 hr. with stirring. The reaction was terminated by addition of diluted sodium bicarbonate solution and the stirring was continued for additional 10 min. The organic layer was separated and washed with 1 M hydrogen chloride solution, then dried over anhydrous magnesium sulfate. Filtration and concentration gave crude product as solid. The crude product was subjected to column chromatography (6.5 g of SiO_2 60 E. Merck No.5554, 4.8% ethyl acetate / n-hexane) to give 82.4 mg (0.349 mmol, 74% yield) of diol derivatives 66 and 67. The diastereomeric ratio was determined as 66/67=95/5 by ^{1}H-NMR spectroscopy (270 MHz)

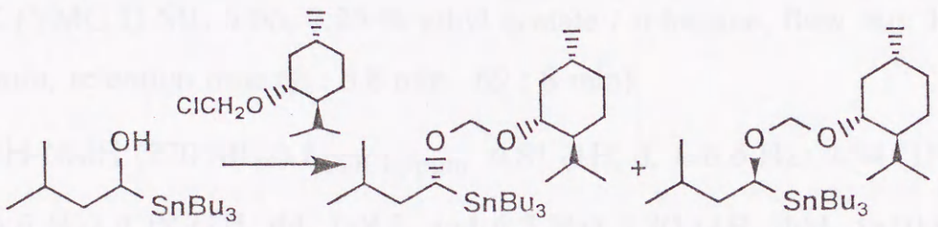
66 : ^{1}H-NMR (400 MHz) $\delta_{CDCl_3/ppm}$ 7.32-7.17 (5H, m) 3.48 (H_3, ddd, J=9.0, 9.0, and 2.0 Hz) 3.29 (3H, s) 2.90 (H_4, ddd, J=9.0, 8.0, and 5.5 Hz) 2.89 (H_2, dq, J=2.0, and 7.0 Hz) 2.11 (1H, d, J=9.0 Hz) 1.53 (1H, m) 1.44 (H_{5a}, ddd, J=13.5, 8.0, and 5.5 Hz) 1.37 (3H, d, J=7.0 Hz) 1.31 (H_{5b}, ddd, J=13.5, 8.0, and 5.5 Hz) 0.85 (3H, d, J=6.5 Hz) 0.64 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3560-3300, 2955, 2930, 1450, 1095, 1050, 700;

HR-MS (EI) Calcd. for $C_{15}H_{24}O_2$ 236.1776 (M^+), Found for $C_{15}H_{24}O_2$ 236.1777 (M^+).

Synthesis of (S)-64 (exp.639 and 642)

Synthesis and Separation of (-)-Menthyloxymethyl protected Stannanes 68 and 69



(±)-61 68 69

Using the general procedure 1, 61 was synthesized from 431 mg (5.0 mmol) of isovaleraldehyde.

The unpurified 61 was immediately converted to the O-menthyloxy methyl derivatives as described below. The crude 61 was dissolved in 20 mL of dry methylene chloride containing 0.96 mL (5.5 mmol) of diisopropyl ethylamine (Hunig's base) and cooled to 0°C under a drying tube ($CaCl_2$). Chloromethyl (-)-menthyl ether (1.06 g, 5.2 mmol) in 4 mL of dry methylene chloride was added to the stirring solution of the crude stannane. After 2 hr, very small amount of 4-(N, N-dimethyl)amino pyridine was added and the stirring was continued for additional 19 hr at room temperature.

The reaction mixture was poured into 30 mL of n-hexane and washed successively with ice-cold saturated ammonium chloride solution (2 × 20 mL), water (20 mL) and saturated brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated

under reduced pressure (temperature < 30°C) to give 2.48 g of crude product as an oil.

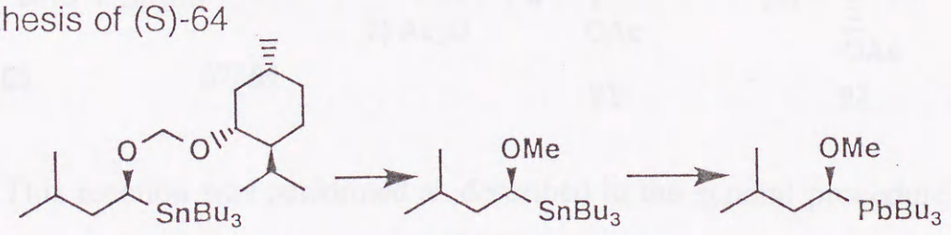
α-Alkoxy organostannanes (1.71 g, 3.1 mmol, 63 % overall yield) were isolated by column chromatography (50 g of SiO_2 60 E.Merck No.5554, 500 mL of n-hexane then 330 mL of 9 % ethyl acetate / n-hexane) as a mixture of diastereomers.

This diastereomeric mixture was further separated by preparative HPLC (YMC D-SIL-5-06, 0.25 % ethyl acetate / n-hexane, flow rate 18 mL / min, retention time 68 : 6.8 min 69 : 8 min).

68 : 1H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.81 (1H, d, J=6.6 Hz) 4.54 (1H, d, J=6.6 Hz) 4.18 (1H, dd, J=8.5, and 6.5 Hz) 3.30 (1H, ddd, J=10.6, 10.6, and 6.5 Hz) 2.23 (1H, m) 2.09 (1H, m) 1.83 (1H, m) 1.64-0.86 (48H, m) 0.78 (3H, d, J=7.0 Hz)

69 : 1H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 4.68 (1H, d, J=6 Hz) 4.65 (1H, d, J=6 Hz) 4.19 (1H, dd, J=9, and 6 Hz) 3.24 (1H, ddd, J=10.6, 10.6, and 4.0 Hz) 2.20-2.12 (2H, m) 1.88 (1H, ddd, J=13.5, 9.0, and 5.5 Hz) 1.7-0.88 (48H, m) 0.77 (3H, d, J=7.0 Hz)

Synthesis of (S)-64



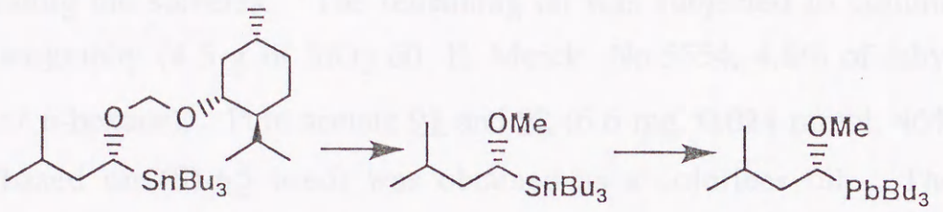
69 (S)-63 (S)-64

Using general procedure 1, the reduction of 69 (174.9 mg, 0.32 mmol) by Cl_2AlH gave 182.7 mg of the crude products and 106.6 mg (0.27 mmol, 85% yield) of (S)-63 was isolated by column chromatography (15 g of SiO_2 60 E. Merck No.5554, 400 mL of 0.5%

ethyl acetate / n-hexane then 300 mL of 1% ethyl acetate / n-hexane) as a colorless oil. $[\alpha]_D^{27}$ 36.6° (c=1.1, $CHCl_3$).

(S)-63 was transmetallated to (S)-64 by using the general procedure 1, and (S)-64 was immediately used in a next reaction.

Synthesis of (R)-64 (exp. 645)

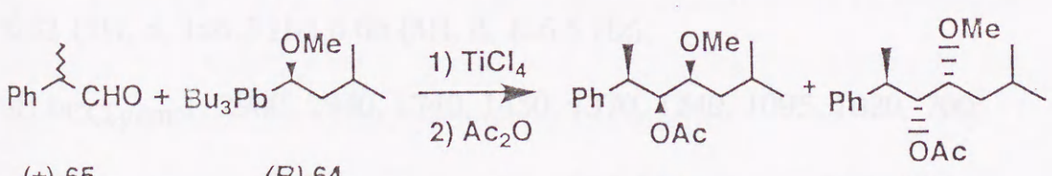


68 (R)-63 (R)-64

In the same manner, 405.5 mg (0.7434 mmol) of 68 was reduced to give 231.1 mg (0.591 mmol, 80% yield) of (R)-63 as a colorless oil. $[\alpha]_D^{27}$ -41.3° (c=1.1, $CHCl_3$).

(R)-63 was transmetallated to (R)-64 by using the general procedure 1, and (R)-64 was immediately used in a next reaction

Reaction of (±)-65 and (R)-64 (exp.665)



(±)-65 (R)-64 91 92

This reaction was performed as described in the general procedure 2 except that 14 mg (0.10 mmol) of (±)-2-phenyl propanal (65), 0.1 mL(0.1 mmol) of 1M titanium tetrachloride in methylene chloride, and 49.1 mg (0.102 mmol) of (R)-64 was used.

The crude diol derivatives were acetylated as follows because of ease of the purification step.

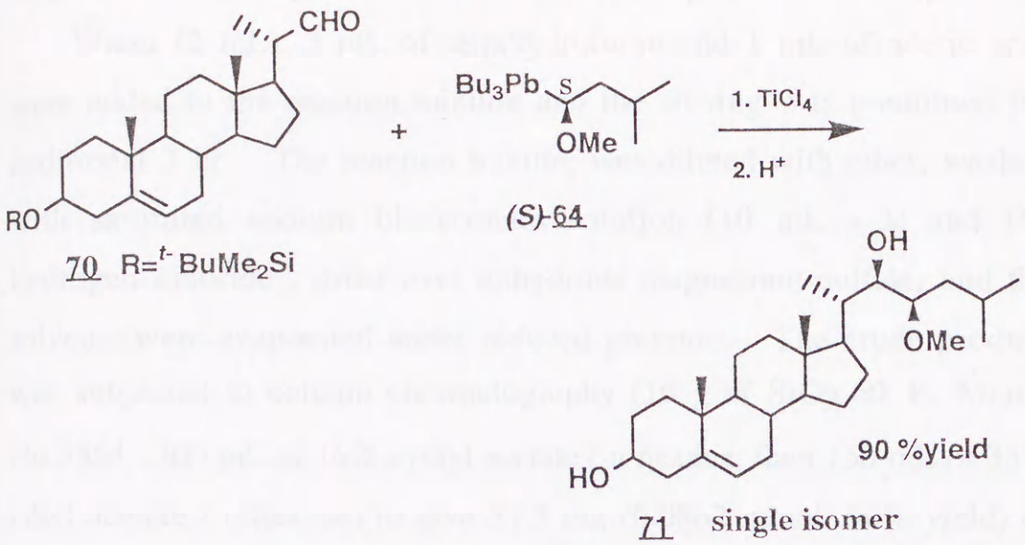
The crude yellow oil was dissolved in 2 mL of dry pyridine containing 0.5 mL of acetic anhydride and the mixture was stirred at room temperature. After 12 hr, the reaction mixture was diluted with ether, washed with 1M hydrogen chloride and saturated sodium bicarbonate solution, drying over anhydrous magnesium sulfate, and evaporating the solvents. The remaining oil was subjected to column chromatography (4.5 g of SiO_2 60 E. Merck No.5554, 4.8% of ethyl acetate / n-hexane). Pure acetate 91 and 92 (6.6 mg, 0.024 mmol, 46% yield based on (S)-65 used) was obtained as a colorlees oil. The diastereomeric ratio was determined as 91/92(=66/67)=***95/5*** by ^{1}H-NMR spectroscopy (270 MHz). The enantiomeric excess of 91 (=66) was determined as ***58%ee*** by measurement of ^{1}H-NMR spectroscopy in the presence of 0.1 equivalent of a chiral lantanide shift reagent Eu(hfc)$_3$.

91 : ^{1}H-NMR (400 MHz) $\delta_{CDCl_3/ppm}$ 5.17 (H3, dd, J=10.5, and 2.0 Hz) 3.27 (H2, dq, J=10.5, and 7.0 Hz) 3.21 (3H, s) 2.90 (H4, ddd, J=8.5, 5.5, and 2.0 Hz) 2.18 (3H, s) 1.58 (H6, m) 1.30 (H5a, ddd, J=14.0, 8.5, and 5.5 Hz) 1.18 (H5b, ddd, J=14.0, 8.5, and 5.5 Hz) 1.22 (3H, d, J=7.0 Hz) 0.81 (3H, d, J=6.5 Hz) 0.66 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2940, 1740, 1450, 1370, 1240, 1095, 1020, 700;

HR-MS (EI) Calcd. for $C_{14}H_{22}O$ 206.1671 (M^+), Found for $C_{14}H_{22}O$ 206.1670 (M^+).

Reaction of 70 and (S)-64 (General Procedure 3) (exp.657)



70 R=$^{t-}$BuMe$_2$Si

(S)-64

71 single isomer

In an oven dried, 30 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed 42.8 mg (0.0962 mmol) of 70 (ca. 12.5/1 epimeric mixture). The flask was evacuated under vacuum, then flushed with argon. This process was repeated three times. Dry methylene chloride (2 mL) was added with a syringe and the flask was placed in a dry ice-isopropanol bath. After 5 min., 0.10 mL (0.10 mmol) of 1M titanium tetrachloride in methylene chloride was added with a syringe and the stirring was continued for 5 min. The reaction mixture became yellow slurry.

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum, was placed 98 mg (0.20 mmol) of (S)-64. The flask was evacuated under vacuum and flushed with argon. Dry methylene chloride (2 mL) was added with a syringe.

The α-methoxyplumbum solution prepared above was transferred dropwise, via a cannula, into the stirring yellow slurry of 70-TiCl4 complex and the stirring was continued for 1.5 hr at -75°C. The reaction mixture was allowed to warm to room temperature over 12 hr.

Although silyl and methyl protected triol product can be isolated at this stage, removal of silyl ether makes the isolation process more easy.

Water (2 mL), 3 mL of tetrahydrofuran and 1 mL of acetic acid were added to the reaction mixture and the stirring was continued for additional 2 hr. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate solution (10 mL × 3) and 1M hydrogen chloride , dried over anhydrous magnesium sulfate, and the solvents were evaporated under reduced pressure. The crude product was subjected to column chromatography (10 g of SiO_2 60 E. Merck No.5554, 300 mL of 16% eythyl acetate / n-hexane, then 150 mL of 33% ethyl acetate / n-hexane) to give 37.3 mg (0.0862 mmol, 90% yield) of desilylated triol derivative71 as a colorless crystal.

71 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.35 (1H, brd, J=5 Hz) 3.58-3.46 (2H, m) 3.44 (3H, s) 3.20 (1H, ddd, J=8, 8, and 4.5 Hz) 2.44 (1H, brs) 2.3-0.9 (25H, m) 1.01 (3H, s) 0.96 (3H, d, J=6.5 Hz) 0.95 (3H, d, J=6.5 Hz) 0.92 (3H, d, J=6.5 Hz) 0.69 (3H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2950, 1460, 1090, 1060;

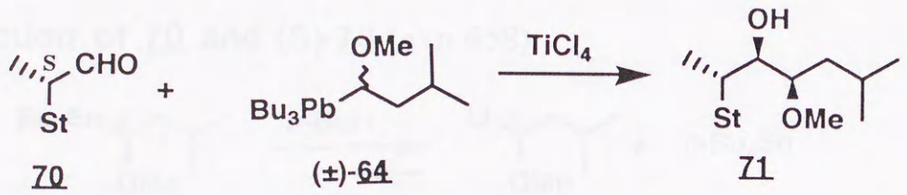
HR-MS (EI) Calcd. for C28H48O3 432.3604, Found for C28H48O3 432.3605.

97 (diacetate of 71) : ^{1}H-NMR (400 MHz) $\delta_{CDCl_3/ppm}$ 5.37 (1H, brd, J=5 Hz) 4.98 (H_{22}, dd, $J_{22,23}$=8.0, and $J_{20,\ 22}$=1.2 Hz) 4.60 (1H, m) 3.37 (3H, s) 3.31 (H_{23}, ddd, $J_{22,23}$=8.0, $J_{23,24a}$=9.8, and $J_{23,24b}$=3.2 Hz) 2.33-2.30 (2H, m) 2.10 (3H, s) 2.07 (3H, s) 2.0-1.8 (5H, m) 1.6-1.4 (7H, m) 1.25-1.0 (16H, m) 1.02 (3H, s) 0.97 (3H, d, J=7.0 Hz) 0.69 (3H s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3550-3200, 2955, 2940, 2870, 1740, 1465, 1370, 1240.

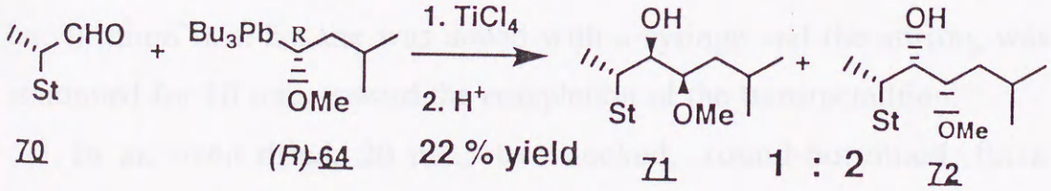
Anal. Calcd. for C : 74.38%, H : 10.14%; Found for C : 73.82%, H : 10.16%.

Reaction of 70 and (±)-64 (exp.676)



This reaction was performed as described in the general procedure 3 except that 62 mg (0.14 mmol) of 70, 0.16 mL (0.16 mmol) of 1 M titanium tetrachloride in methylene chloride and 266 mg (0.554 mmol) of (±)-64 were used. After column chromatography (20 g of SiO_2 60 E. Merck No. 5554, 33% ethyl acetate/ n-hexane), 59.7 mg (0.138 mmol, 99% yield) of desilylated triol derivative 71 was obtained. The isomeric purity of 71 was determined by the measurement of ^{1}H-NMR spectroscopy (270 MHz).

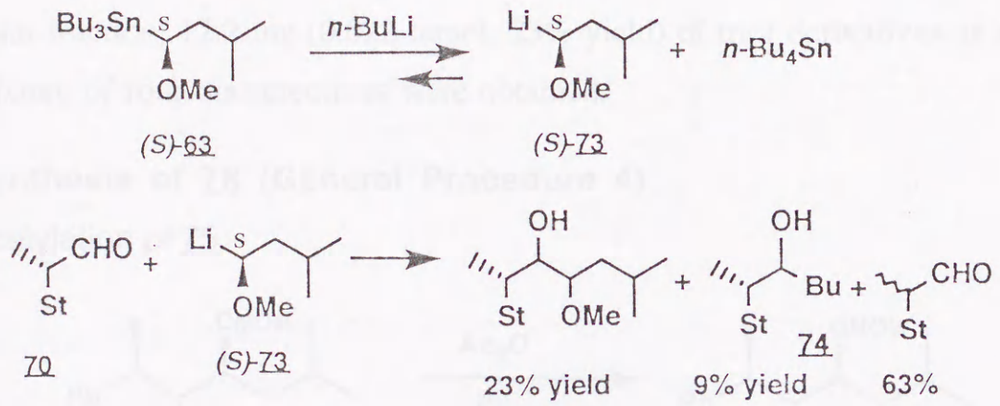
Reaction of 70 and (R)-64 (exp.655)



This reaction was performed as described in the general procedure 3 except that 40 mg (0.090 mmol) of 70, 0.10 mL (0.10 mmol) of 1 M titanium tetrachloride in methylene chloride, and 84 mg (0.18 mmol) of (R)-64 were used.

After column chlomatography (5 g of SiO_2 60 E. Merck No.5554, 17% ethyl acetate / n-hexane), 8.8 mg (0.020 mmol, 23% yiel) of triol derivatives 71 and 72 were obtained. The ratio was determined as 71/72=1/2 by ^{1}H-NMR spectroscopy (270 MHz).

Reaction of 70 and (S)-73 (exp.658)



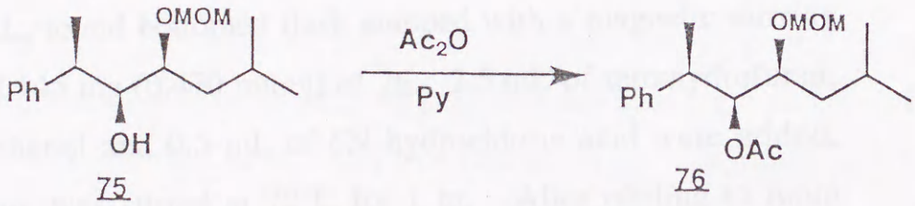
In an oven dried, 30 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed a 41.9 mg (0.107 mmol) of α-methoxystannane (S)-63. The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (3 mL) was added with a syringe and the flask was placed in a dry ice-isopropanol bath. After 5 min., 0.065 mL (0.0103 mmol) of 1.58 M n-butyllithium in n-hexane was added with a syringe and the stirring was continued for 10 min. toward the completion of the transmetalltion.

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum, was placed 43.2 mg (0.097 mmol) of 70. The flask was evacuated under vacuum, then flushed with argon. Dry methylene chloride (2 mL) was added with a syringe and the solution was transferred dropwise, via a cannula, into the α–methoxy lithium solution prepared above. The reaction mixture was allowed to warm to room temperature with stirring over 15 hr, then quenched by adding water into

it. Separated organic layer was dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue (84 mg) was subjected to column chromatography (8 g of SiO_2 60 E. Merck No.5554, 4.8% of ethyl acetate / n-hexane). In less polar fraction, 29.7 mg (0.0668 mmol, 69% recovery) of epimerized starting aldehyde was recovered. In the next fraction, 9.8 mg of butylated alcohol 74 was obtained. In more polar fraction, 12.2 mg (0.022 mmol, 23% yield) of triol derivatives as a mixture of four diastereomers were obtained.

Synthesis of 78 (General Procedure 4)

Acetylation of 75

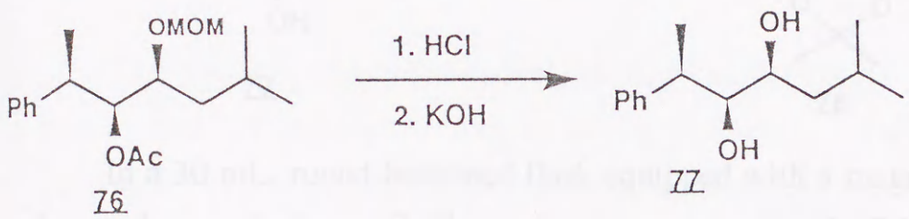


In a 50 mL, round-bottomed flask equipped with a magnetic stirring bar and anhydrous calcium chloride ($CaCl_2$) drying tube was placed 148.3 mg (0.557 mmol) of 75. Dry pyridine (2 mL) and 2 mL of acetic anhydride were added and the mixture was stirred at room temperature for 14 hr. The mixture was diluted with ether, then washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. Drying over anhydrous magnesium sulfate and concentration under vacuum gave 145 mg (0.470 mmol, 84% yield) of acetate 76 as a colorless oil.

76 : ^{1}H-NMR (270 MHz) 7.34-7.20 (5H, m) 5.24 (H3, dd, J=9.9, and 2.2 Hz) 4.61 (1H, d, J=7.0 Hz) 4.38 (1H, d, J=7.0 Hz) 3.38 (H4, m) 3.36 (3H, s) 3.20 (H2, dq, J=9.5, and 7.0 Hz) 2.17 (3H, s) 1.62 (1H, m) 1.34 (1H, m) 1.22 (3H, d, J=7.0 Hz) 0.81 (3H, d, J=6.2 Hz) 0.69 (3H, d, J=6.6 Hz);

IR υ_{CCl_4}/cm^{-1} 2960, 1740, 1500, 1470, 1455, 1370, 1240, 1150, 1055, 1030.

Sequential removal of MOM group and acetyl group



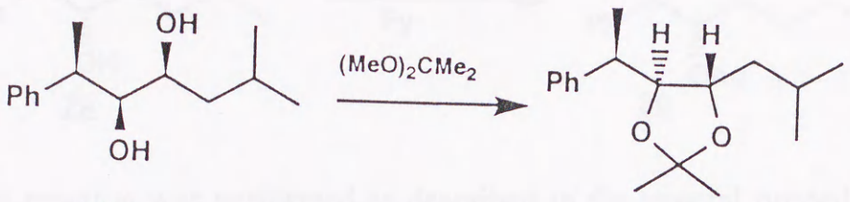
76 77

In a 50 mL, round-bottomed flask euipped with a magnetic stirring bar was placed 145 mg (0.470 mmol) of 76. 2.5 mL of tetrahydrofuran, 2.5 mL of methanol and 0.5 mL of 6N hydrochloric acid were added, then the mixture was stirred at 70°C for 1 hr. After cooling to room temperature, 10 mL of 5% potassium hydroxide in methanol was added and the mixture was stirred at 70°C for 1 hr. The reaction mixture was cooled to room temperature, evaporated under vacuum, extracted with ethyl acetate, washed with saturated brine, dryed over anhydrous magnesium sulfate and concentrated under vacuum. The remaining oil (106 mg) was subjected to column chromatography (10 g of SiO_2 60 E. Merck No. 5554, 17% ethyl acetate / n-hexane) to give more than 90 mg (0.40 mmol, 86% yield) of 77 as a colorless crystal.

77 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.33-7.20 (5H, m) 3.49-3.45 (2H, m) 2.96 (H2, dq, J=7.0, and 7.0 Hz) 1.95 (2H, brs, W1/2=16 Hz) 1.70 (1H, m) 1.42-1.27 (2H, m) 1.35 (3H, J=7.0 Hz) 0.83 (3H, d, J=6.6 Hz) 0.82 (3H, d, J=6.6 Hz);

HR-MS (EI) Calcd. for C14H22O2 222.1620, Found for C14H22O2 222.1620.

Acetonide formation



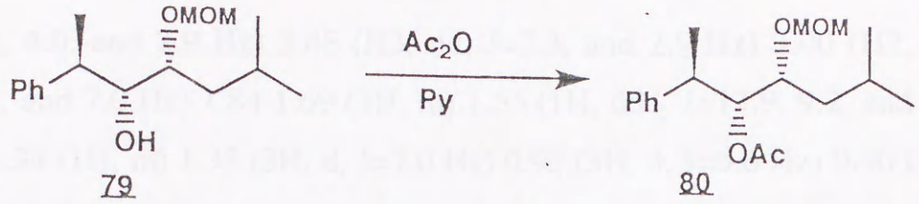
77 78

In a 30 mL, round-bottomed flask equipped with a magnetic stirring bar and an anhydrous $CaCl_2$ drying tube was placed 47.9 mg (0.215 mmol) of 77. Dry ether (1 mL), 1 mL of dimethoxypropane and very small amount of p-toluene sulfonic acid monohydrate were added. The reaction mixture was stirred at room temperature for 3 hr, then quenched by adding diluted sodium bicarbonate solution into it. Extraction with ether, drying over anhydrous magnesium sulfate and concentration under vacuum gave 47.4 mg (0.179 mmol, 83% yield) of pure 78.

78 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.32-7.18 (5H, m) 3.77 (H4, ddd, J=9.5, 7.5. and 2.5 Hz) 3.64 (H3, dd, J=7.5, and 7.5 Hz) 2.78 (H2, dq, J=7.0, and 7.0 Hz) 1.57 (H6, m) 1.40 (3H, d, J=7.0 Hz) 1.40 (6H, s) 1.16 (H5a, ddd, J=14, 9.5, and 4.5 Hz) 0.71 (3H, d, J=6.5 Hz) 0.66 (3H, d, J=6.5 Hz) 0.42 (H5b, ddd, J=14, 9.5, and 4.5 Hz);

Synthesis of 82

Acetylation of 79



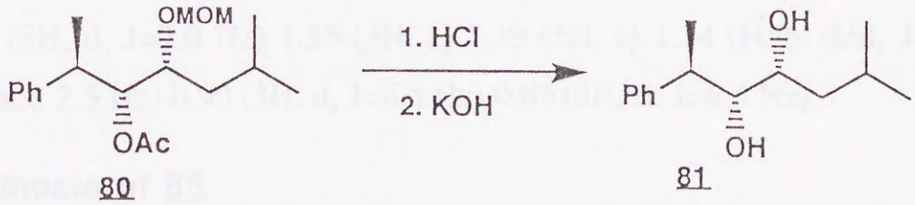
79 80

This reaction was performed as described in the general procedure 4 except that 14 mg (0.053 mmol) of 79 was used. After work up procedure, 16.2 mg (0.0525 mmol, 99% yield) of acetate 80 was obtained.

80 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.29-7.16 (5H, m) 5.09 (H3, dd, J=9.2, and 3.3 Hz) 4.73 (1H, d, J=7.0 Hz) 4.70 (1H, d, J=7.0 Hz) 3.81 (H4, ddd, J=7.0, 7.0, and 3.3 Hz) 3.44 (3H, s) 3.18 (H2, dq, J=9.2, and 7.0 Hz) 1.78 (3H, s) 1.48-1.26 (3H, m) 1.33 (3H, d, J=7.0 Hz) 0.93 (3H, d, J=6.6 Hz) 0.86 (3H, d, J=6.6 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2955, 1740, 1470, 1455, 1370, 1240, 1150, 1100, 1040.

Removal of both MOM and acetyl groups



80 81

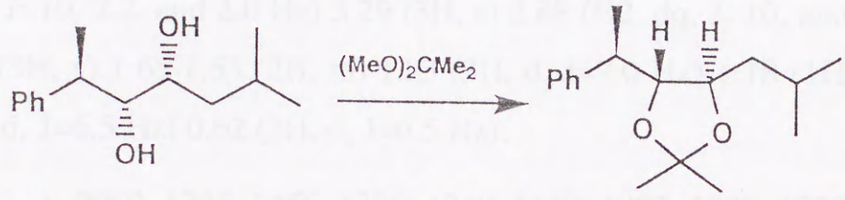
This reaction was performed as described in the general procedure 4 except that 16.2 mg (0.0525 mmol) of 80 was used. After column chromatography (3 g of SiO_2 60 E. Merck No. 5554, 33% ethyl acetate /

n-hexane), 9.9 mg (0.045 mmol, 85% yield) of 81 was isolated as a colorless crystal.

81 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.37-7.22 (5H, m) 3.69 (H4, ddd, J=9.2, 4.0, and 2.9 Hz) 3.48 (H3, dd, J=7.3, and 2.9 Hz) 3.00 (H2, dq, J=7.3, and 7.0 Hz) 1.84-1.69 (3H, m) 1.55 (1H, ddd, J=13.9, 9.2, and 5.5 Hz) 1.34 (1H, m) 1.33 (3H, d, J=7.0 Hz) 0.95 (3H, d, J=6.6 Hz) 0.90 (3H, d, J=6.6 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3600-3200, 2950, 1495, 1450, 1380.

Acetonide Formation

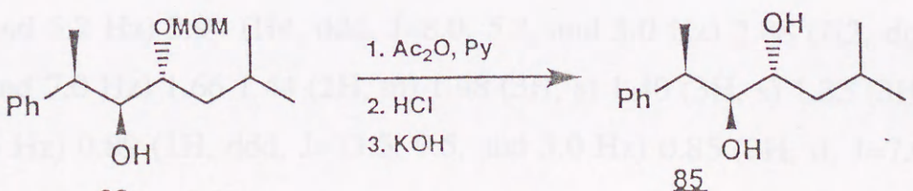


81 82

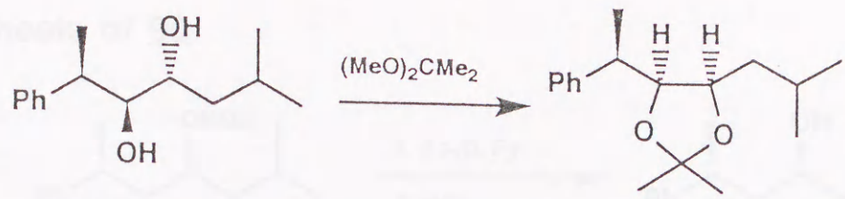
Diol 81 (9.9 mg, 0.045 mmol) was transformed to 7.9 mg (0.030 mmol, 67% yield) of pure 82 using the general procedure 4.

82 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.33-7.18 (5H, m) 3.74 (H3, dd, J=8.0, and 4.8 Hz) 3.63 (H4, ddd, J=9.5, 8.0, and 2.5 Hz) 2.91 (H2, dq, J=4.5, and 7.0 Hz) 1.75 (H6, m) 1.44 (H5a, ddd, J=14, 9.0, and 4.5 Hz) 1.37 (3H, d, J=7.0 Hz) 1.35 (3H, s) 1.19 (3H, s) 1.14 (H5b, ddd, J=14, 9.0, and 2.5 Hz) 0.90 (3H, d, J=6.5 Hz) 0.85 (3H, d, J=6.5 Hz).

Synthesis of 86



83 85



85 86

Using the general procedure 4, 83 was transformed to diol 85 in good yield, then 61.3 mg (0.276 mmol) of 85 was transformed to 60.4 mg (0.228 mmol, 83% yield) of pure acetonide 86.

84 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.34-7.21 (5H, m) 5.42 (H3, dd, J=10, and, 2.0 Hz) 4.60 (1H, d, J=7.0 Hz) 4.40 (1H, d, J=7.0 Hz) 3.38 (H4, ddd, J=10, 2.2, and 2.0 Hz) 3.29 (3H, s) 2.88 (H2, dq, J=10, and 7.0 Hz) 2.14 (3H, s) 1.65-1.53 (2H, m) 1.23 (3H, d, J=7.0 Hz) 1.18 (1H, m) 0.91 (3H, d, J=6.5 Hz) 0.62 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 1745, 1455, 1370, 1240, 1140, 1095, 1040, 1020.

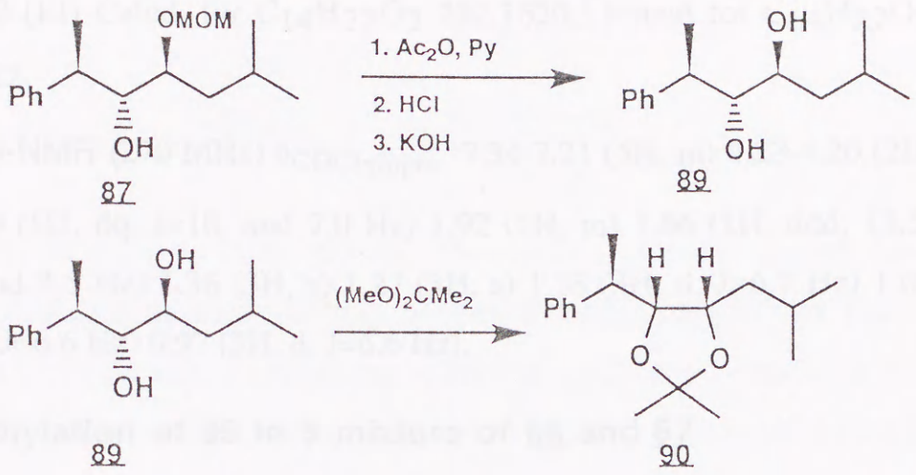
85 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.32-7.18 (5H, m) 3.77 (H3, dd, J=8.5, and 4.0 Hz) 3.43 (H4, m) 2.85 (H2, ddq, J=7.0, 1.0, and 7.0 Hz) 1.68 (1H, m) 1.50-1.26 (4H, m) 1.38 (3H, d, J=7.0 Hz) 0.92 (3H, d, J=6.5 Hz) 0.69 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3600-3200, 2955, 1500, 1470, 1460, 1060, 1010, 705.

HR-MS (EI) Calcd. for $C_{14}H_{22}O_2$ 222.1620, Found for $C_{14}H_{22}O_2$ 222.1622.

86 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.32-7.16 (5H, m) 4.32 (H3, dd, J=9.5, and 5.2 Hz) 3.94 (H4, ddd, J=8.0, 5.2, and 3.0 Hz) 2.88 (H2, dq, J=9.5, and 7.0 Hz) 1.66-1.44 (2H, m) 1.48 (3H, s) 1.40 (3H, s) 1.35 (3H, d, J=6.5 Hz) 0.89 (1H, ddd, J=13.5, 9.5, and 3.0 Hz) 0.85 (3H, d, J=7.0 Hz) 0.65 (3H, d, J=6.5 Hz);

Synthesis of 90



Using the general procedure 4, 11.1 mg (0.042 mmol) of 87 was transformed to 11 mg (0.036 mmol, 86% yield) of acetate 88, then 7.5 mg (0.034 mmol, 94% yield) of diol 89. Diol 89 (7.5 mg, 0.034 mmol) was transformed to 5.4 mg (0.020 mmol, 60% yield) of pure acetonide 90.

88 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.30-7.16 (5H, m) 5.31 (H3, dd, J=9.9, and 2.6 Hz) 4.82 (1H, d, J=7.3 Hz) 4.49 (1H, d, J=7.3 Hz) 3.92 (H4, ddd, J=10.6, 2.6, and 2.2 Hz) 3.40 (3H, s) 2.93 (H2, dq, J=9.9, and 7.0 Hz) 1.85 (H6, m) 1.76 (3H, s) 1.67 (H5, ddd, J=14.3, 10.6 and 3.7 Hz) 1.80 (H5, m) 1.27 (3H, d, J=7.0 Hz) 0.98 (3H, d, J=9.9 Hz) 0.96 (3H, d, J=9.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2920, 1745, 1370, 1240, 1140, 1090, 1045, 1030.

89 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.37-7.22 (5H, m) 3.80-3.73 (2H, m) 2.85 (H2, dq, J=7.0, and 7.0 Hz) 1.87 (1H, m) 1.76 (1H, d, J= Hz) 1.60 (1H, d, J= Hz) 1.57 (1H, m) 1.29 (1H, m) 1.24 (3H, d, J=7.0 Hz) 1.00 (3H, d, J=7.0 Hz) 0.94 (3H., d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3600-3300, 2970, 1500, 1460, 1385, 1040, 705.

HR-MS (EI) Calcd. for $C_{14}H_{22}O_2$ 222.1620, Found for $C_{14}H_{22}O_2$ 222.1622.

90 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.34-7.21 (5H, m) 4.28-4.20 (2H, m) 2.90 (H2, dq, J=10, and 7.0 Hz) 1.92 (1H, m) 1.66 (1H, ddd, 13.5, 11.0, and 3.5 Hz) 1.36 (3H, s) 1.27 (3H, s) 1.18 (3H, d, J=6.7 Hz) 1.00 (3H, d, J=6.6 Hz) 0.97 (3H, d, J=6.6 Hz).

Demethylation of 95 to 5 mixture of 66 and 67

Acetylation

66 67 91 92

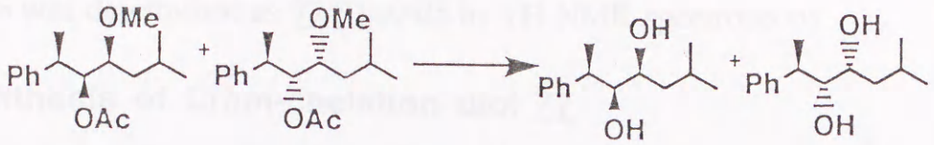
95 : 5

Acetylation of 66 and 67 was performed using the genreral procedure 4 in good yield.

91 : ^{1}H-NMR (400 MHz) $\delta_{CDCl_3/ppm}$ 5.17 (H3, dd, J=10.5, and 2.0 Hz) 3.27 (H2, dq, J=10.5, and7.0 Hz) 2.90 (H4, ddd, J=8.5, 5.5, and 2.0 Hz) 3.21 (3H, s) 2.18 (3H, s) 1.58 (H6, m) 1.30(H5a, ddd, J=14, 8.5, and 5.5 Hz) 1.22 (3H, d, J=7.0 Hz) 1.18 (H5b, ddd, J=14, 8.5and 5.5 Hz) 0.81 (3H, d, J=6.5 Hz) 0.66 (3H, d, J=6.5 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2960, 2940, 1740, 1450, 1370, 1240, 1095, 1020, 700.

Demethylation of acetates followed by hydrolysis



91 92 77 81

95 : 5

[Hood] In an oven dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 105 mg (0.79 mmol) of anhydrous aluminum chloride. The flask was evacuated under vacuum, then flushed with argon. Ethane thiol (2 mL) was added with a syringe and the flask was placed in an ice-water bath.

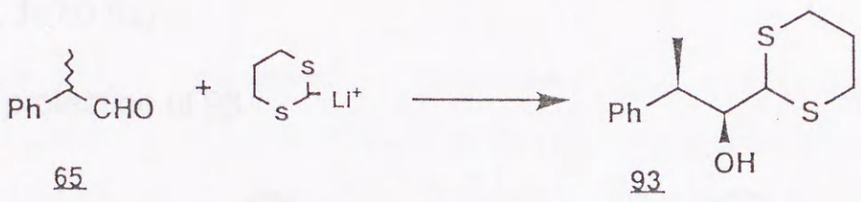
In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum was placed 44.2 mg (0.159 mmol) of acetates 91 and 92. The flask was evacuated under vacuum, then flushed with argon. Dry methylene chloride (2 mL) was added with a syringe and the solution was transferred, via a cannula, into the $AlCl_3$-EtSH solution prepared above. The mixture was stirred at room temperature for 2.5 hr. The reaction was quenched by adding 5 mL of water into it. Ether extraction and removal of volatile materials gave crude demethylated alcohols as an oil. Alkalin hydrolysis of acetate groups was performed without further purification.

In an 30 mL, round-bottomed flask were placed the crude products. Methanol (5 mL) and 3 pelets of sodium hydroxide were added, and the mixture was stirred at room temperature for 1 hr. After removal of methanol, 5 mL of water was added. Extraction with ether, drying over anhydrous magnesium sulfate, and concentration under vacuum gave 29.2 mg of crude diols. After column chromatography (8 g of SiO_2 60 E. Merck No. 5554, 17% of ethyl acetate / n-hexane), 17.9 mg (0.081

mmol, 51% yield) of diols 77 and 81 were obtained. The diastereomeric ratio was determined as 77/81=95/5 by 1H-NMR spectroscopy.

Synthesis of Cram-chelation diol 77

Reaction of 65 and 1,3-dithian anion



65 93

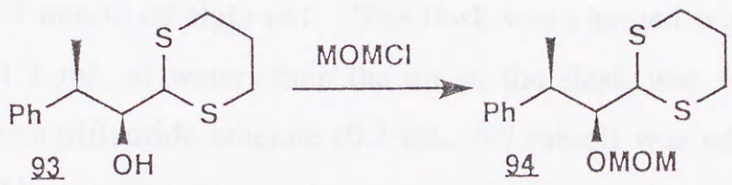
In an oven dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was placed 1.201 g (9.988 mmol) of 1,3-dithiane. The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (20 mL) was added with a syringe, and the flask was placed in a dry ice-IPA bath. After 5 min, 6.7 mL (11 mmol) of 1.64 M n-butyllithium in n-hexane was added dropwise with a syringe and the stirring was continued at -78°C for 25 min, then at -35°C for 1.5 hr.

An oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum was charged with argon. Aldehyde 65 (1.32 mL, 9.95 mmol) and 3 mL of dry THF were added with syringes. The resulting solution was transfered dropwise, via a cannula, into the yellow solution of 1,3-dithian anion prepared above and the reaction mixture was allowed to warm to room temperature over 8.5 hr. The reaction was terminated by adding saturated ammonium chloride solution into it, then extracted with ether, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. The remaining solid (3.034 g) was subjected to column chromatography (90 g of SiO_2 60 E. Merck No. 5554, 9% ethyl acetate / n-hexane, 13% ethyl acetate / n-

hexane, then 17% ethyl acetate / n-hexane). Thioacetal-alcohol 93 (1.978 g, 7.775 mmol, 78% yield) was obtained.

93 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.38-7.20 (5H, m) 3.91 (1H, m) 3.82 (1H, d, J=5.0 Hz) 3.27 (1H, dq, J=7.0, and 7.0 Hz) 2.91-2.85 (2H, m) 2.75-2.65 (2H, m) 2.34 (1H, brd, J=4.0 Hz) 2.06-1.88 (2H, m) 1.34 (3H, d, J=7.0 Hz).

MOM protection of 93



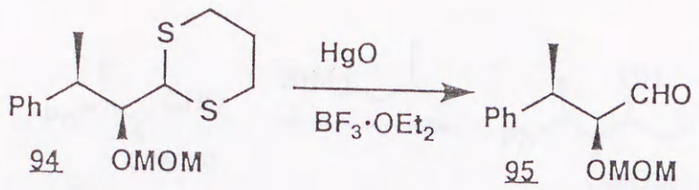
93 94

In a 50 mL, round-bottomed flask equipped with a magnetic stirring bar and anhydrous $CaCl_2$ drying tube was placed 1.016 g (3.993 mmol) of 93. Dry methylene chloride (5 mL) containing 1.4 mL (8.0 mmol) of diisopropyl ethylamine and 0.46 mL (6.1 mmol) of chloromethyl methyl ether (MOMCl) was added and the stirring was continued at room temperature for 31 hr.

The reaction was terminated by adding a diluted sodium bicarbonate solution into it, then extracted with ether, dried over anhydrous magnesium sulfate and concentrated under vacuum. MOM protected thioacetal 94 (1.06 g, 3.75 mmol, 94% yield) was obtained.

94 : ^{1}H-NMR (60 MHz) $\delta_{CDCl_3/ppm}$ 7.45-7.30 (5H, m) 4.87 (1H, d, J=6.0 Hz) 4.67 (1H, d, J=6.0 Hz) 4.05-3.87 (2H, m) 3.47 (3H, s) 3.30 (1H, m) 2.9-2.7 (4H, m) 2.1-1.9 (2H, m) 1.40 (3H, d, J=7.0 Hz).

Removal of thioacetal

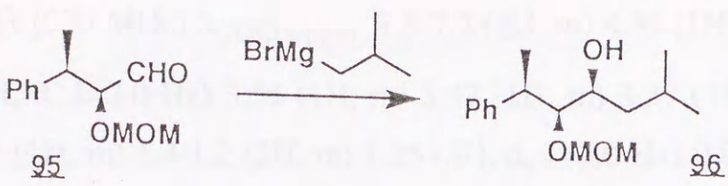


In a 50 mL, two-necked, round-bottomed flask equipped with a dropping funnel, a magnetic stirring bar and a rubber septum was placed 1.25 g (5.77 mmol) of HgO red. The flask was charged with 7 mL of THF and 1.2 mL of water, then the air in the flask was replaced by argon. Borontrifluoride etherate (0.7 mL, 5.7 mmol) was added with a syringe. The reaction mixture became orange suspension. Thioacetal 94 (815 mg, 2.89 mmol) in 0.5 mL of THF was added dropwise, through the dropping funnel, into the flask over 15 min and the stirring was continued at room temperature. After 1 hr, yellow solid was dissolved and the stirring was continued for additional 3 hr.

The reaction was terminated by pouring it into ether and the resulting white precipitates were filtered off through filter paper. The filtrate was washed with saturated bicarbonate solution and saturated brine, then dried over anhydrous magnesium sulfate and concentrated under vacuum. The remaining oil (490 mg) was subjected to column chromatography (20 g of SiO_2 60 E. Merck No.5554, 5% ethyl acetate / n-hexane) to give 384 mg (1.84 mmol, 64% yield) of MOM protected aldehydes 95-syn and 95-anti as a colorless oil (syn : anti = 19 : 1).

95-syn : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 9.59 (1H, d, J=1.8 Hz) 7.4-7.2 (5H, m) 4.66 (1H, d, J=6.9 Hz) 4.50 (1H, d, J=6.9 Hz) 4.04 (1H, dd, J=5.5, and 1.8 Hz) 3.24 (3H, s) 3.27 (1H, dq, J=5.5, and 7.3 Hz) 1.37 (3H, d, J=7.3 Hz);

Addition of isobutyl Grignard reagent to 95



95 96

An oven dried, 50mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was charged with magnesium turnings (60 mg, 2.5 mmol). The flask was evacuated and dried under vacuum with a heat gun, then flushed with dry argon. Dry ether(1 mL) and a small amount of iodine were added. After 5 min, the mixture was stirred at room temperature untill the brown color of iodine was disappeared, then dry ether (5 mL) was added with a syringe. Isobutyl bromide (0.23 mL, 2.1 mmol) was added dropwise, with a syringe, over 10 min.

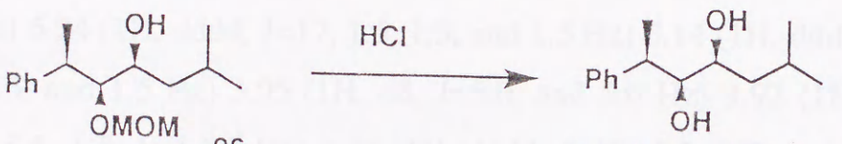
An oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum, was placed 95 (-syn and -anti) (309.7 mg, 1.49 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry ether (2 mL) was added with a syringe and the flask was placed in an ice-water bath.

The isobutyl magesium bromide solution prepared above was transferred dropwise, via a cannula, into the aldehyde solution and the mixture was allowed to warm to room temperature over 4.5 hr. The reaction mixture was cooled again with an ice-water bath, then hydrolyzed by adding 1N hydrochloric acid solution into it. Extraction with ether, drying over anhydrous magnesium sulfate, and concentration under vacuum gave 346 mg of crude products as an oil. Acid catalyzed

hydrolysis of MOM protecting group in 96 was performed without further purification.

96 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.3-7.2 (5H, m) 4.53 (1H, d, J=7.0 Hz) 4.18 (1H, d, J=7.0 Hz) 3.55 (1H, m) 3.37 (1H, m) 3.37 (3H, s) 3.08 (1H, m) 1.80 (1H, m) 1.4-1.2 (3H, m) 1.25 (3H, d, J=7.0 Hz) 0.87 (6H, d, J=6.5 Hz).

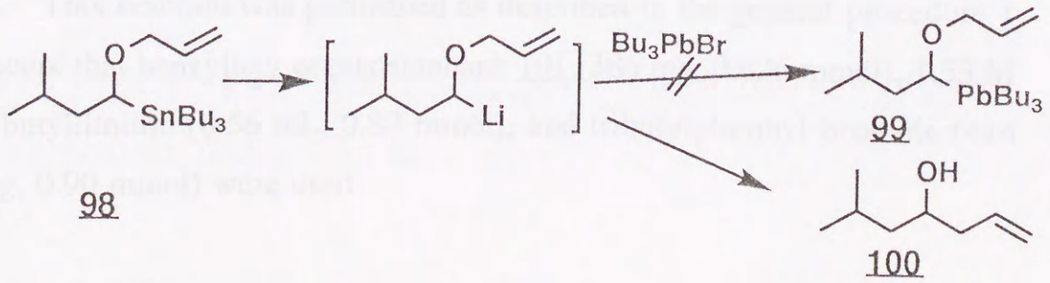
Removal of MOM Protective Group



96 77 : Cram-chelation

In a 50 mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser, was placed the unpurified 96 (346 mg) . Methanol (5 mL), tetrahydrofuran (5 mL), and 6M hydrochloric acid (1 mL) were added, then the mixture was stirred at 70°C for 2 hr. After cooling to room temperature, solvents were evaporated under vacuum (20 mmHg). Extraction with ether, drying over anhydrous magnesium sulfate, concentration under vacuum gave 251 mg (1.13 mmol, 76% yield based on 95) of diols as colorless crystals. A major isomer has the identical spectral data to 77.

Transmetallation of Allyloxy Organostannane With n-Butyllithium (exp.697)



98 99 100

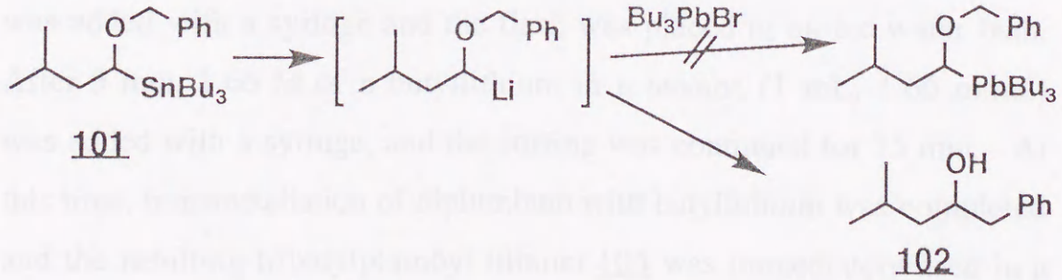
This reaction was performed as described in the general procedure 1 except that allyloxy organostannane 98 (210 mg, 0.503 mmol), 1.66 M n-butyllithium (0.32 mL, 0.53 mmol), and tributylplumbyl bromide (255 mg, 0.56 mmol) were used.

Unfortunately, the desired allyloxy organoplumbum 99 was not obtained and the crude product may contain homoallyl alcohol 100 which can be produced via [2. 3]-Wittig rearrangement.

98 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.90 (1H, dddd, J=17, 10, 5.5, and 5.5 Hz) 5.24 (1H, dddd, J=17, 1.5, 1.5, and 1.5 Hz) 5.14 (1H, dddd, J=10, 1.5, 1.5, and 1.5 Hz) 3.95 (1H, dd, J=5.0, and 5.0 Hz) 3.92 (1H, dddd, J=12, 5.5, 1.5, and 1.5 Hz) 3.82 (1H, dddd, J=12, 5.5, 1.5, and 1.5 Hz) 1.92 (1H, ddd, J=13.5, 10, and 5.0 Hz) 1.74 (1H, m) 1.55-1.25 (14H, m) 0.90-0.80 (20H, m).

100 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.82 (1H, dddd, J=) 5.1 (2H, m) 3.74 (2H, m).

Transmetallation of Benzyloxy Organostannane With n-Butyl-lithium (exp.691)



101 102

This reaction was performed as described in the general procedure 1 except that benzyloxy organostannane 101 (386 mg, 0.826 mmol), 1.55 M n-butyllithium (0.56 mL, 0.87 mmol), and tributylplumbyl bromide (414 mg, 0.90 mmol) were used.

After column chromatography (5 g of SiO_2 60 E. Merck No.5554, 0.5% of triethylamine / n-hexane, 1.4% ethyl acetate / n-hexane), 194 mg of oily product which did not contain α-alkoxy plumbum was obtained. The structure of the product may be 102 which can be produced via [1,2]-Wittig rearrangement.

101 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.34-7.17 (5H, m) 4.47 (1H, d, J=11 Hz) 4.34 (1H, d, J=11 Hz) 4.03 (1H, dd, J=10, and 4.5 Hz) 1.95 (1H, m) 1.77 (1H, m) 1.55-1.25 (14H, m) 0.93-0.85 (20H, m).

Synthesis of 99 (exp. 733)

Preparation of Tributylplumbyl Lithium

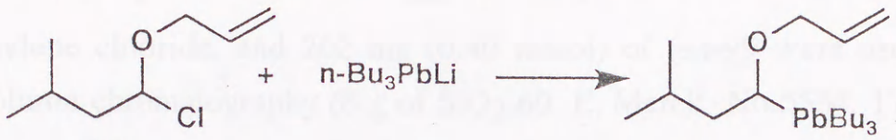
$$(n\text{-}Bu_3Pb)_2 \xrightarrow{n\text{-BuLi}} n\text{-}Bu_3PbLi + n\text{-}Bu_4Pb$$

103 → 104

In an oven dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed hexabutyl diplumbum 103 (2.1 g, 2.8 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (10 mL) was added with a syringe and the flask was placed in an ice-water bath. After 5 min, 1.66 M of n-butyllithium in n-hexane (1 mL, 1.66 mmol) was added with a syringe, and the stirring was continued for 15 min. At this time, transmetallation of diplumbum with butyllithium was completed and the resulting tributylplumbyl lithium 104 was immediately used in a next reaction. The flask was placed in a dry ice-water bath.

103 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 1.8-1.65 (24H, m) 1.35-1.25 (12H, m) 0.90 (18H, t, J=7.2 Hz).

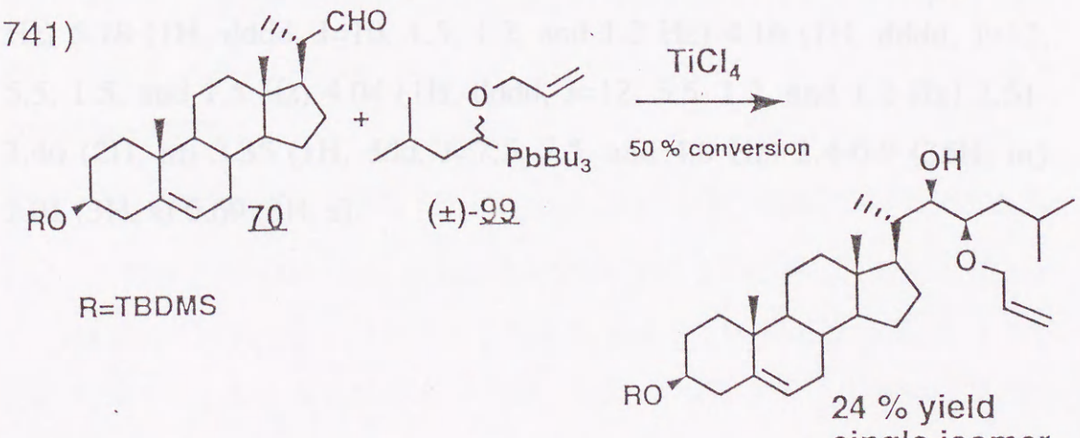
Synthesis of 99



105 104 99

In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum, was placed α-allyloxy chloride (260 mg, 1.60 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (3 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the tributylplumbyl lithium solution prepared above. The reaction mixture was allowed to warm to 0°C over 3 hr, then quenched by adding water into it. Separated organic layer was dried over anhydrous magnesium sulfate, and concentrated under vacuum. After column chromatography (15 g of SiO_2 E. Merck No.5554, 0.5% of triethylamine / n-hexane, n-hexane, and 2% of ethyl acetate / n-hexane), 495 mg (0.98 mmol, 61% yield) of 99 was isolated as a slightly yellow oil.

Reaction of 70 with (±)-99 in the Presence of $TiCl_4$ (exp. 741)



70 (±)-99

R=TBDMS

24 % yield
single isomer

106 : R=TBDMS
107 : R=H

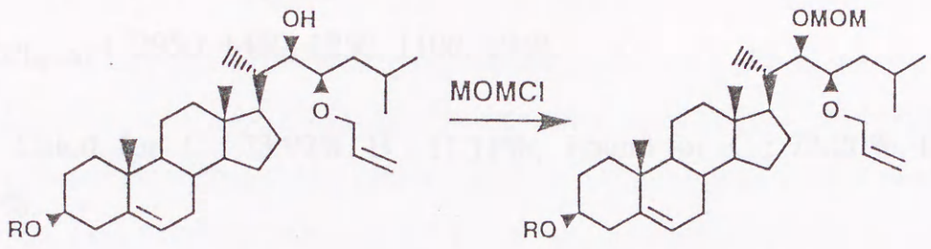
This reaction was performed as described in the general procedure 3 except that 38 mg (0.085 mmol) of 70, 0.1 mL (0.1 mmol) of 1M $TiCl_4$ in methylene chloride, and 202 mg (0.40 mmol) of (±)-99 were used. After column chromatography (8 g of SiO_2 60 E. Merck No.5554, 17% of ethyl acetate / n-hexane, then 33% ethyl acetate / n-hexane), 12 mg (0.021 mmol, 25% yield) of 106 (R=TBDMS) and 4 mg (0.0094 mmol, 11% yield) of 107 (R=H) were obtained.

106 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.94 (1H, dddd, J=17, 10, 5.5, and 5.5 Hz) 5.32 (1H, brd, J=2 Hz) 5.28 (1H, dddd, J=17, 1.5, 1.2, and 1.2 Hz) 5.18 (1H, dddd, J=10, 1.5, 1.2, and 1.2 Hz) 4.16 (1H, dddd, J=12, 5.5, 1.2, and 1.2 Hz) 4.04 (1H, dddd, J=12, 5.5, 1.2, and 1.2 Hz) 3.52-3.44 (2H, m) 3.35 (1H, ddd, J=8.0, 8.0, and 4.0 Hz) 2.41 (1H, brd, J=1.5 Hz) 2.35-0.95 (33H, m) 1.00 (3H, s) 0.89 (9H, s) 0.69 (3H, s) 0.06 (6H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3600-3200, 2970, 2950, 2880, 1470, 1390, 1260, 1095, 895, 880, 845.

107 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.94 (1H, dddd, J=17, 10, 5.5, and 5.5 Hz) 5.35 (1H, brd, J=5 Hz) 5.29 (1H, dddd, J=17, 1.5, 1.5, 1.5 Hz) 5.18 (1H, dddd, J=10, 1.5, 1.2, and 1.2 Hz) 4.16 (1H, dddd, J=12, 5.5, 1.5, and 1.5 Hz) 4.04 (1H, dddd, J=12, 5.5, 1.2, and 1.2 Hz) 3.51-3.46 (2H, m) 3.35 (1H, ddd, J=7.5, 7.5, and 4.0 Hz) 2.4-0.9 (35H, m) 1.01 (3H, s) 0.69 (3H, s).

MOM Protection of 106 (exp.762)



106 : R=TBDMS 108 : R=TBDMS

An 100 mL, round-bottomed flask equipped with a magnetic stirring bar and a $CaCl_2$ drying tube, was charged with 19 mg (0.033 mmol) of 106 and 2 mL of dry methylene chloride. The flask was placed in an ice-water bath. After 5 min, 0.3 mL of diisopropyl ethylamine, 0.1 mL of chloromethyl methyl ether, and 2 mg of 4-(N,N-dimethylamino) pyridine were added and the mixture was allowed to warm to room temperature. After 8 hr, the reaction was quenched by adding diluted sodium bicarbonate solution into it. Extraction with ether, drying over anhydrous magnesium sulfate, and concentration under vacuum gave 32 mg of crude product.

The crude product was subjected to column chromatography (5 g of SiO_2 60 E. Merck No.5554, 2% of ethyl acetate / n-hexane) to give 18.2 mg (0.030 mmol, 89% yield) of MOM protected product 108 as a colorless crystal.

108 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.92 (1H, dddd, J=17, 10, 5.5, and 5.5 Hz) 5.32 (1H, brd, J=5.0 Hz) 5.25 (1H, dddd, J=17, 1.5, 1.5, and 1.5 Hz) 5.14 (1H, dddd, J=10.5, 1.5, 1.5, and 1.5 Hz) 4.84 (1H, d, J=6.5 Hz) 4.70 (1H, d, J=6.5 Hz) 4.17 (1H, dddd, J=12, 5.5, 1.2, and 1.2 Hz) 4.03 (1H, dddd, J=12, 5.5, 1.2, and 1.2 Hz) 3.52-3.35 (3H, m) 3.41 (3H,

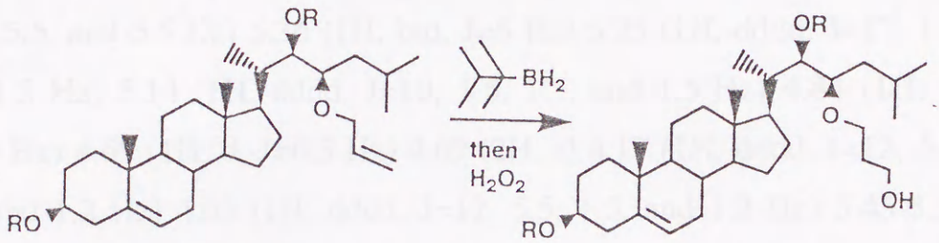
s) 1.00 (3H, s) 0.93 (3H, d, J=6.5 Hz) 0.91 (3H, d, J=6.5 Hz) 0.89 (9H, s) 0.70 (3H, s) 0.06 (6H, s);

IR $\upsilon_{CCl_4/cm^{-1}}$ 2950, 1460, 1250, 1100, 1040.

Anal. Calcd. for C : 73.97%, H : 11.11%; Found for C : 73.20%, H : 10.97%.

Removal of Allyl Protective Group in 109 (exp.747)

Hydroboration of Bis(MOM) Protected allyl ether 109



109 : R=MOM　　110 : R=MOM

An oven dried, 20 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was charged with argon. Dry tetrahydrofuran (1 mL) and 10M borane-dimethylsulfide complex (0.1 mL, 1 mmol) were added with syringes, and the flask was placed in an ice-water bath. Freshly distilled isobutylene (0.12 mL, 1.0 mmol) was added with a syringe and the stirring was continued for 1 hr.

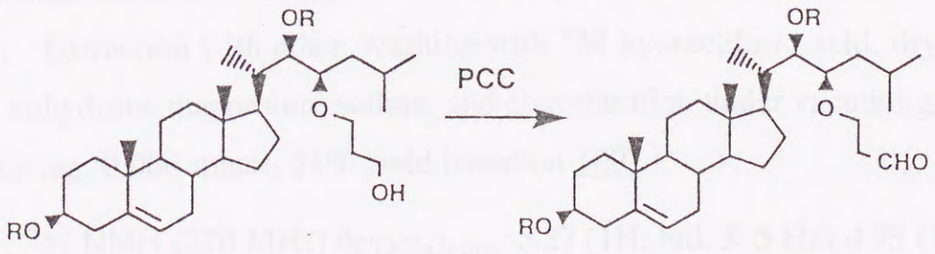
In an oven dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septam, was placed 109 (10.6 mg, 0.019 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry tetrahydrofuran (1 mL) was added with a syringe, and the flask was placed in an ice-water bath. After 5 min, 0.1 mL of thexylborane solution prepared above was added, with a syringe, to the flask, and the stirring was continued for 1 hr.

The reaction was carefully quenched by adding ethanol (3 mL) dropwise into it. After the addition of 3M sodium hydroxide (0.06 mL, 0.18 mmol) and 30% hydrogen peroxide (0.09 mL), the mixture was stirred at 0°C for 1.5 hr. Evaporation of solvents, extraction with ether, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude product 110 (14 mg). After short column chromatography (SiO_2), 110 was subjected to a next reaction.

109 (R=MOM): ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.92 (1H, dddd, J=17, 10.5, 5.5, and 5.5 Hz) 5.36 (1H, brd, J=5 Hz) 5.25 (1H, dddd, J=17, 1.5, 1.5, 1.5 Hz) 5.14 (1H, dddd, J=10, 1.5, 1.5, and 1.5 Hz) 4.84 (1H, d, J=6.5 Hz) 4.69 (1H, d, J=6.5 Hz) 4.69 (2H, s) 4.17 (1H, dddd, J=12, 5.5, 1.5, and 1.2 Hz) 4.03 (1H, dddd, J=12, 5.5, 1.5, and 1.2 Hz) 3.45-3.38 (2H, m) 3.41 (3H, s) 3.37 (3H, s) 2.4-0.9 (34H, m) 1.02 (3H, s) 0.70 (3H, s).

110 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.36 (1H, brd, J=5 Hz) 4.81 (1H, d, J=6.5 Hz) 4.71 (1H, d, J=6.5 Hz) 4.69 (2H, s) 3.87 (1H, m) 3.77-3.72 (4H, m) 3.64 (1H, m) 3.39 (3H, s) 3.34 (3H, s) 2.3-0.9 (37H, m) 1.01 (3H, s) 0.70 (3H, s).

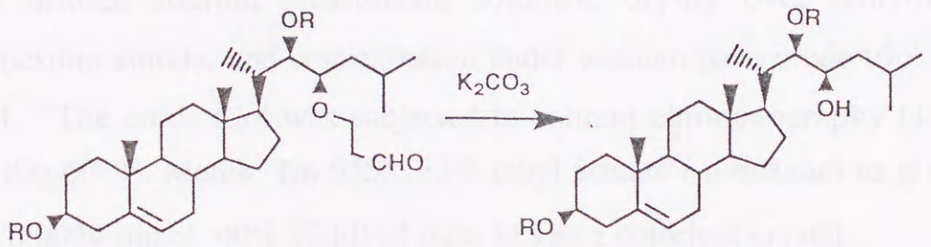
Oxidation of Primary Alcohol in 110 Using PCC (exp.750)



110 : R=MOM　　111 : R=MOM

In a 50 mL, round-bottomed flask equipped with a magnetic stirring bar and a $CaCl_2$ drying tube, were placed pyridinium chloro chromate (8 mg, 0.04 mmol) and dry methylene chloride (1 mL). The methylene chloride solution (1.5 mL) of 110 prepared above was added to the flask in one portion, and the stirring was continued for 3.5 hr. The reaction was quenched by adding ether into it. The resulting brown suspension was directly filtered through silica gel (SiO_2 60 E. Merck No.5554, ether). The filtrate was concentrated under vacuum and the resulting crude aldehyde 111 was subjected to the next reaction without further purification.

Base Promoted Retro-aldol Cleavage of 111 (exp.750)

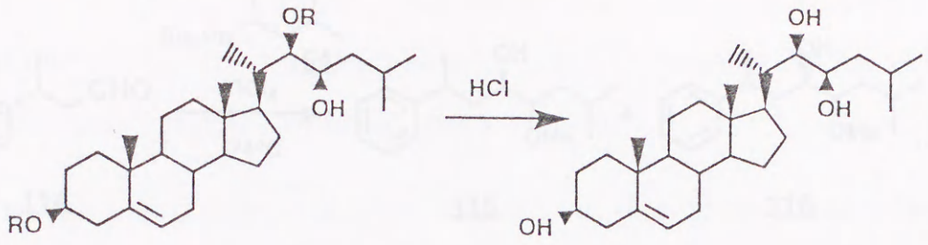


111 : R=MOM　　112 : R=MOM

A 30 mL, round-bottomed flask equipped with a magnetic stirring bar, was charged with the unpurified aldehyde 111, methanol (4 mL), and potassium carbonate (2 mg). The reaction mixture was stirred for 2 days. Extraction with ether, washing with 1M hydrochloric acid, drying over anhydrous magnesium sulfate, and concentration under vacuum gave 112 (3 mg, 0.006 mmol, 31% yield based on 109).

112 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.27 (1H, brd, J=5 Hz) 4.73 (1H, d, J=7.0 Hz) 4.63 (2H, s) 4.60 (1H, d, J=7.0 Hz) 3.63 (1H, m) 3.4-3.3 (2H, m) 3.40 (3H, s) 3.34 (3H, s) 2.3-0.8 (34H, m) 1.00 (3H, s) 0.70 (3H, s).

Synthesis of 113 (exp.753)



112 : R=MOM　　113

A 50 mL, round-bottomed flask equipped with a magnetic stirring bar and a Liebig condenser, was chaged with 112 (3 mg, 0.006 mmol), methanol (3 mL), and 12M hydrochloric acid (0.03 mL). The reaction mixture was stirred at 60°C for 15 hr. Extraction with ether, washing with diluted sodium bicarbonate solution, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude triol as a solid. The crude triol was subjected to column chromatography (1.4 g of SiO_2 60 E. Merck No.5554, 33% ethyl acetate / n-hexane) to give 1 mg (0.0024 mmol, 40% yield) of pure 113 as a colorless crystal.

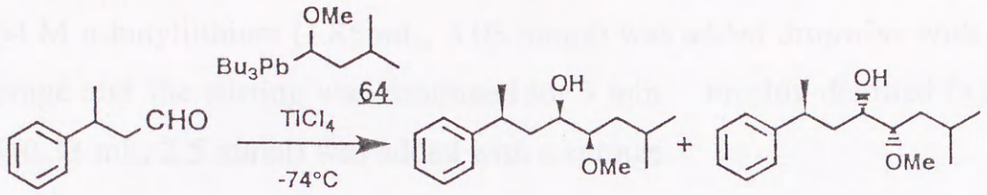
113 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 5.36 (1H, brd, J=5 Hz) 3.65-3.50 (2H, m) 3.37 (1H, brd, J=8 Hz) 2.27 (1H, m) 2.00-1.82 (4H, m) 1.7-1.1 (22H, m) 1.01 (3H, s) 0.96 (3H, d, J=7 Hz) 0.94 (3H, d, J=7 Hz) 0.91 (3H, d, J=7 Hz) 0.71 (3H, s);

IR $\upsilon_{KBr/cm^{-1}}$ 3400, 2930, 1480, 1381, 1058;

HR-MS (EI) Calcd. for $C_{27}H_{46}O_3$ 418.3447, Found for $C_{27}H_{46}O_3$ 418.3448.

mp 154-156°C

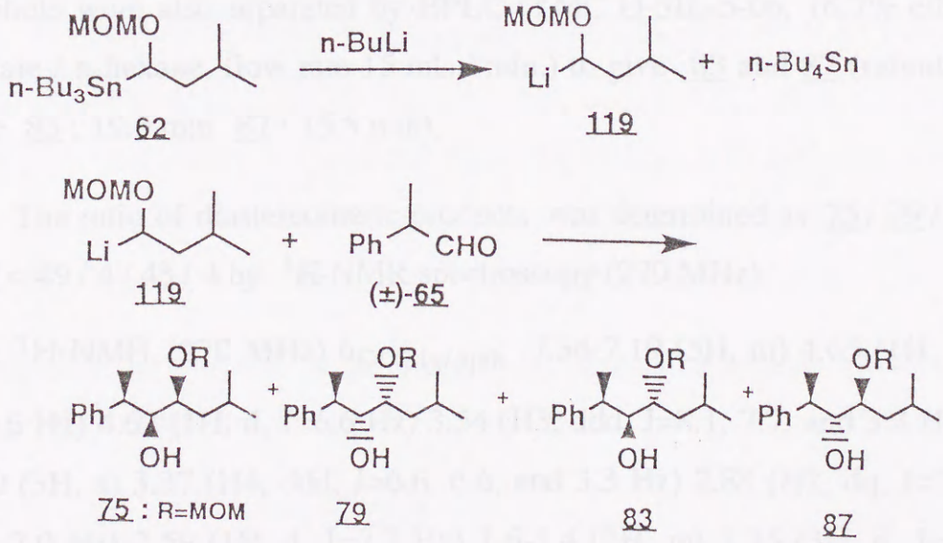
Reaction of (±)-114 with (±)-64 (exp.757)



114 115 116

This reaction was performed by using the general procedure 2 except that (±)-114 (87 mg, 0.59 mmol), (±)-64 (138 mg, 0.288 mmol), and 1 M $TiCl_4$ (0.6 mL, 0.6 mmol) were used. After acetylation (Ac_2O, pyridine), column chromatography (10 g of SiO_2, 5% ethyl acetate / n-hexane) gave 115 and 116 (total 52 mg, 0.21 mmol, 72% yield) . The diastereomeric ratio was determined as 116/117=52/48 by ^{1}H-NMR spectroscopy (270 MHz). The stereochemistry of the products was not determined.

Reaction of (±)-65 with (±)-119 (exp.767)



In an oven dried, 50 mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a rubber septum, was placed 62 (1.311 g, 3.112 mmol). The flask was evacuated under vacuum, then

flushed with argon. Dry tetrahydrofuran (10 mL) was added with a syringe and the flask was placed in a dry ice-IPA bath. After 5 min, 1.64 M n-butyllithium (1.85 mL, 3.03 mmol) was added dropwise with a syringe and the stirring was continued for 3 min. Freshly distilled (±) - 65 (0.33 mL, 2.5 mmol) was added with a syringe.

The reaction mixture was stirred for 2.5 hr, then poured into water. Extraction with ether, drying over anhydrous magnesium sulfate, concentration under vacuum gave crude products (1.724 g) as an oil. The crude products were subjected to column chromatography (100 g of SiO_2 60 E. Merck No.5554, 9% ethyl acetate / n-hexane) to give 325.4 mg (1.22 mmol, 49% yield) of less polar alcohols and 213.9 mg (0.803 mmol, 32% yield) of more polar alcohols.

The less polar alcohols were further separated by HPLC (YMC D-SIL-5-06, 16.7% ethyl acetate / n-hexane, flow rate 15 mL / min.) to give 75 and 79 (retention time 75 : 12 min 79 : 10 min). The more polar alcohols were also separated by HPLC (YMC D-SIL-5-06, 16.7% ethyl acetate / n-hexane, flow rate 15 mL / min.) to give 83 and 87 (retention time 83 : 19.5 min 87 : 15.5 min).

The ratio of diastereomeric products was determined as 75 / 79 / 83 / 87 = 49 / 4 / 43 / 4 by ^{1}H-NMR spectroscopy (270 MHz).

75 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.34-7.19 (5H, m) 4.65 (1H, d, J=6.6 Hz) 4.62 (1H, d, J=6.6 Hz) 3.54 (H3, ddd, J=8.1, 7.7, and 3.3 Hz) 3.40 (3H, s) 3.37 (H4, ddd, J=6.6, 6.6, and 3.3 Hz) 2.88 (H2, dq, J=7.0, and 7.0 Hz) 2.59 (1H, d, J=7.7 Hz) 1.6-1.4 (2H, m) 1.35 (3H, d, J=7.0 Hz) 0.86 (3H, d, J=6.6 Hz) 0.69 (3H, d, J=6.6 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3560-3250, 2950, 1495, 1470, 1455, 1390, 1370, 1150, 1100, 1040, 700.

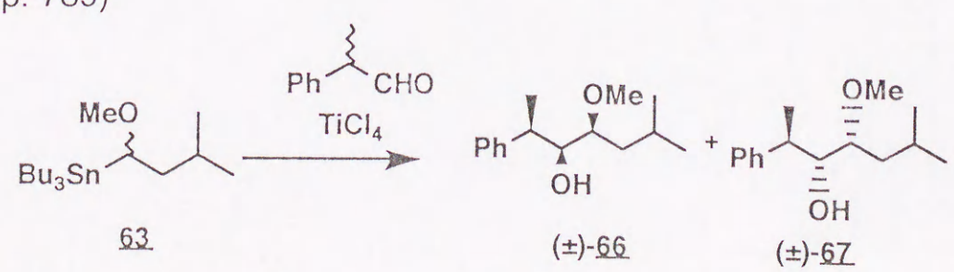
79 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.31-7.20 (5H, m) 4.67 (1H, d, J=6.6 Hz) 4.63 (1H , d, J=6.6 Hz) 3.60-3.50 (2H, m) 3.42 (3H, s) 2.93 (H2, dq, J=7.0, and 7.0 Hz) 2.57 (1H, brs, W1/2=11 Hz) 1.68 (1H, m) 1.58-1.45 (2H, m) 1.34 (3H, d, J=7.0 Hz) 0.92 (3H, d, J=6.6 Hz) 0.82 (3H, d, J=6.2 Hz);

IR $\upsilon_{CCl_4/cm^{-1}}$ 3600-3300, 2960, 1495, 1465, 1450, 1100, 1040, 910, 700.

83 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.32-7.16 (5H, m) 4.63 (1H, d, J=6.8 Hz) 4.51 (1H, d, J=6.8 Hz) 3.94 (H3, ddd, J=9.0, 3.0, and 2.5 Hz) 3.37 (3H, s) 3.31 (H4, ddd, J=10, 2.5, and 2.5 Hz) 2.75 (H2, dq, J=9.0, and 6.5 Hz) 2.52 (1H, d, J=3.0 Hz) 1.65-1.52 (2H, m) 1.39 (3H, d, J=7.0 Hz) 1.13 (1H, m) 0.89 (3H, d, J=6.5 Hz) 0.59 (3H, d, J=6.5 Hz).

87 : ^{1}H-NMR (270 MHz) $\delta_{CDCl_3/ppm}$ 7.35-7.21 (5H, m) 4.78 (1H, d, J=7.0 Hz) 4.65 (1H, d, J=7.0 Hz) 3.91 (H3, ddd, J=9.0, 2.5, and 2.5 Hz) 3.86 (H4, ddd, J=10, 2.5, and 2.5 Hz) 3.39 (3H, s) 2.77 (H2, dq, J=9.0, and 7.0 Hz) 2.06 (1H, d, J=2.5 Hz) 1.89-1.74 (2H, m) 1.22 (1H, m) 1.21 (3H, d, J=7.0 Hz) 0.99 (3H, d, J=6.5 Hz) 0.96 (3H, d, J=6.5 Hz).

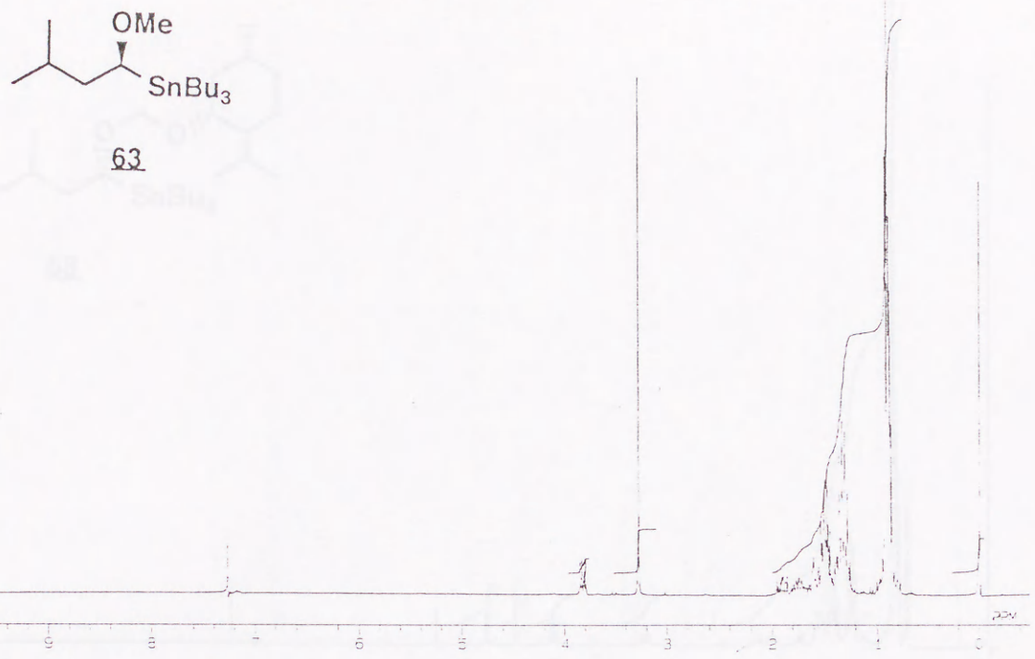
Reaction of (±)-65 with (±)-63 in the Presence of TiCl4 (exp. 789)



63 (±)-66 (±)-67

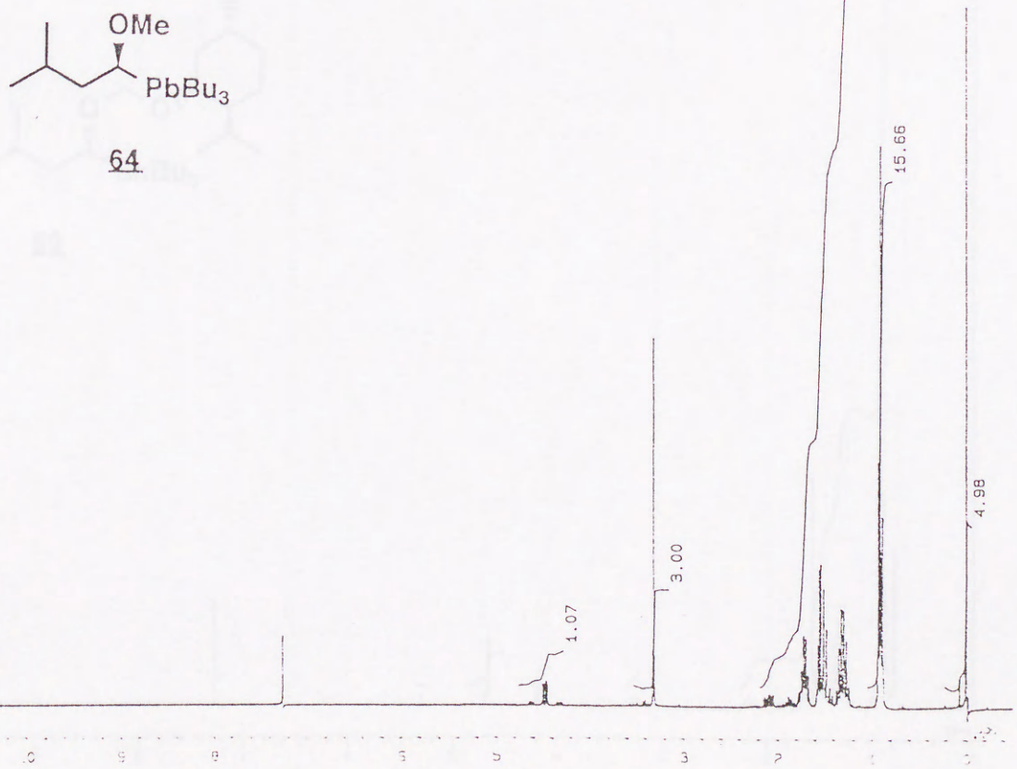
This reaction was performed by using the general procedure 2 except that (±)-63 (384 mg, 0.982 mmol), (±)-65 (0.2 mL, 1.5 mmol), and 1 M $TiCl_4$ (1.5 mL, 1.5 mmol) were used. Column chromatography (20 g of SiO_2, 6% ethyl acetate / n-hexane) gave 66 and 67 (total 46 mg, 0.19 mmol, 20% yield) along with recovered 65 (163 mg, 1.22 mmol) . The diastereomeric ratio was determined as 66/67=90/10 by ^{1}H-NMR spectroscopy (270 MHz).

^{1}H NMR Spectrum of 63 (TMS/$CDCl_3$, 270 MHz)



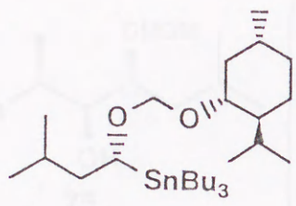
63

^{1}H NMR Spectrum of 64 (TMS/$CDCl_3$, 270 MHz)



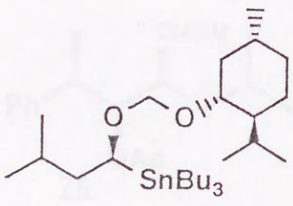
64

^{1}H NMR Spectrum of 68 (TMS/$CDCl_3$, 270 MHz)



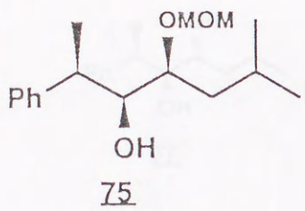
68

^{1}H NMR Spectrum of 69 (TMS/$CDCl_3$, 270 MHz)



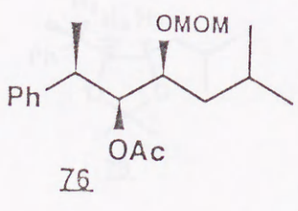
69

^{1}H NMR Spectrum of 75 (TMS/$CDCl_3$, 270 MHz)



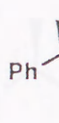
75

^{1}H NMR Spectrum of 76 (TMS/$CDCl_3$, 270 MHz)



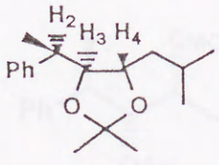
76

^{1}H NMR Spectrum of 77 (TMS/$CDCl_3$, 270 MHz)



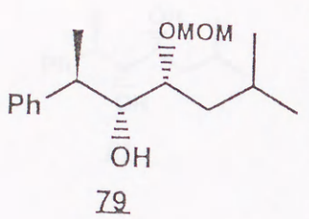
77

^{1}H NMR Spectrum of 78 (TMS/$CDCl_3$, 270 MHz)



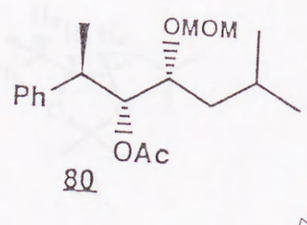
78

^{1}H NMR Spectrum of 79 (TMS/$CDCl_3$, 270 MHz)



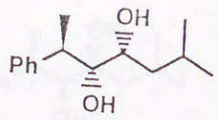
79

^{1}H NMR Spectrum of 80 (TMS/$CDCl_3$, 270 MHz)



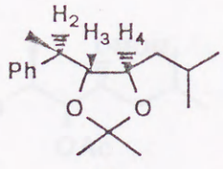
80

^{1}H NMR Spectrum of 81 (TMS/$CDCl_3$, 270 MHz)



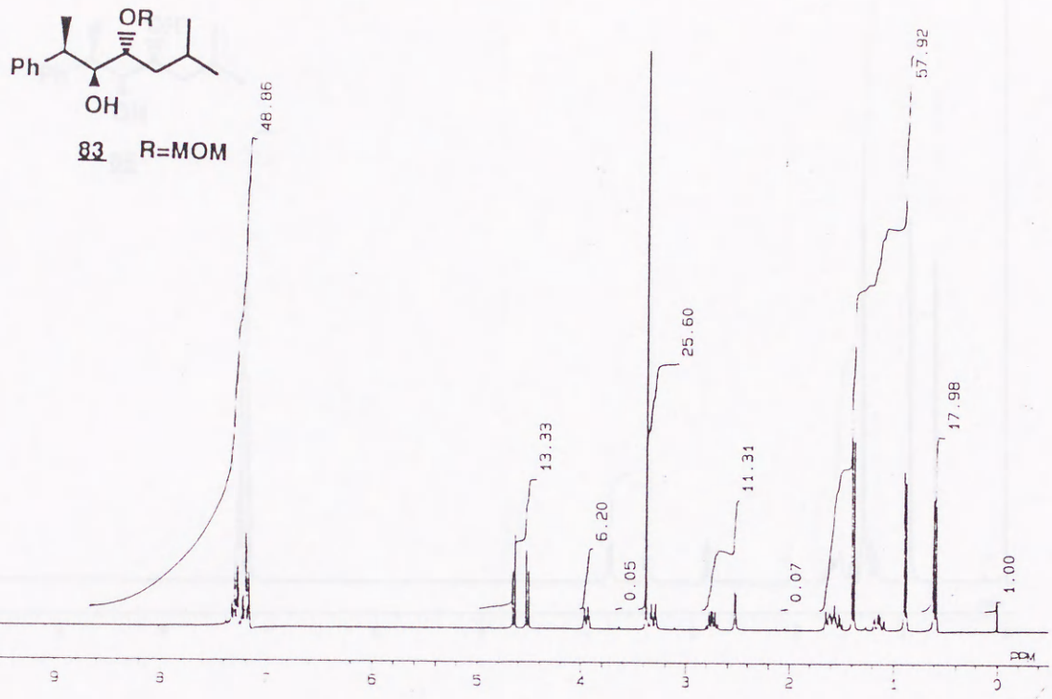
81

^{1}H NMR Spectrum of 82 (TMS/$CDCl_3$, 270 MHz)

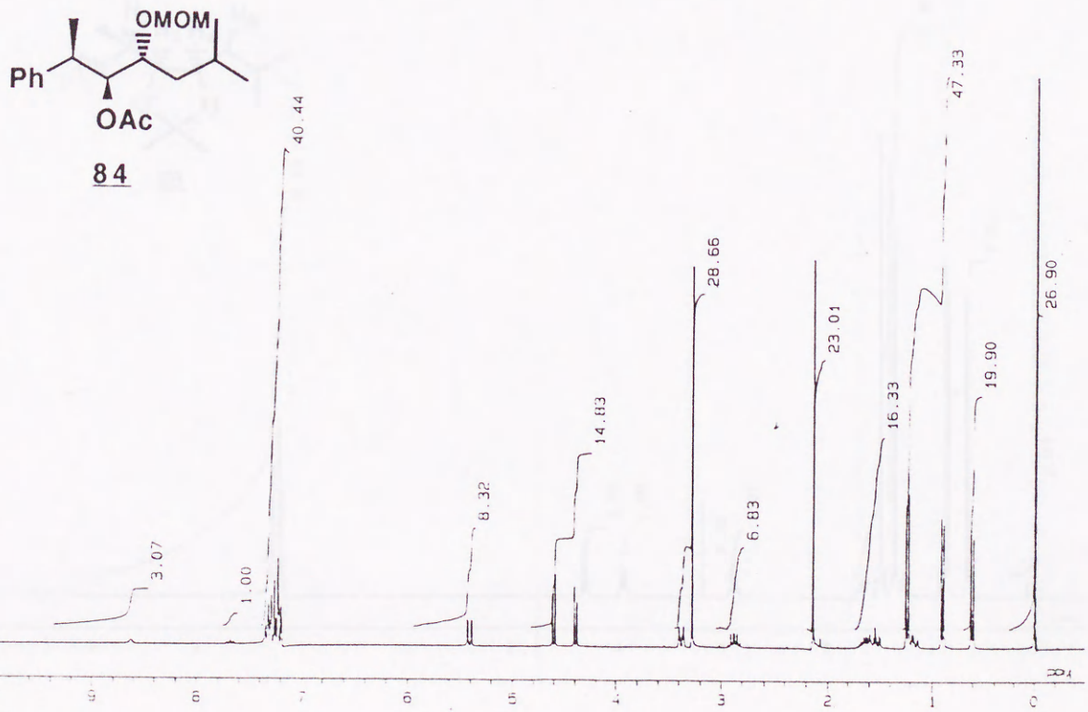


82

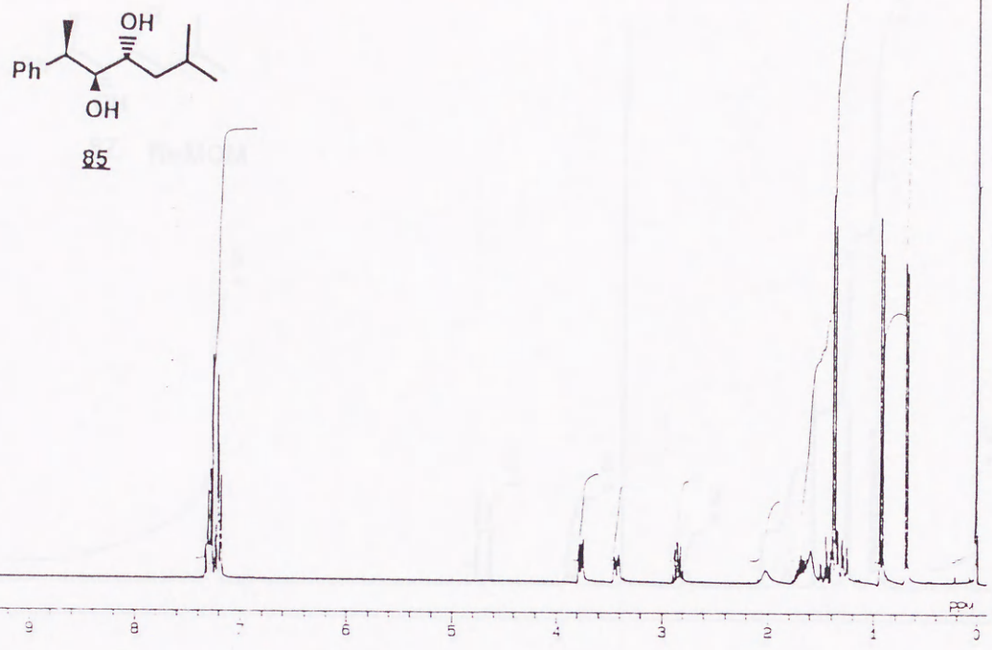
^{1}H NMR Spectrum of 83 (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 84 (TMS/$CDCl_3$, 270 MHz)

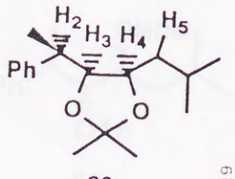


^{1}H NMR Spectrum of 85 (TMS/$CDCl_3$, 270 MHz)



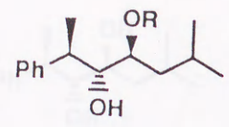
85

^{1}H NMR Spectrum of 86 (TMS/$CDCl_3$, 270 MHz)



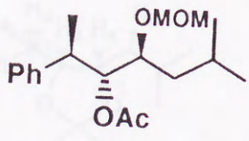
86

^{1}H NMR Spectrum of 87 (TMS/$CDCl_3$, 270 MHz)



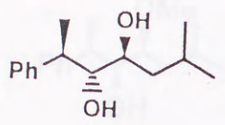
87 R=MOM

^{1}H NMR Spectrum of 88 (TMS/$CDCl_3$, 270 MHz)



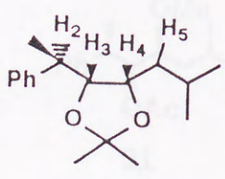
88

^{1}H NMR Spectrum of 89 (TMS/$CDCl_3$, 270 MHz)



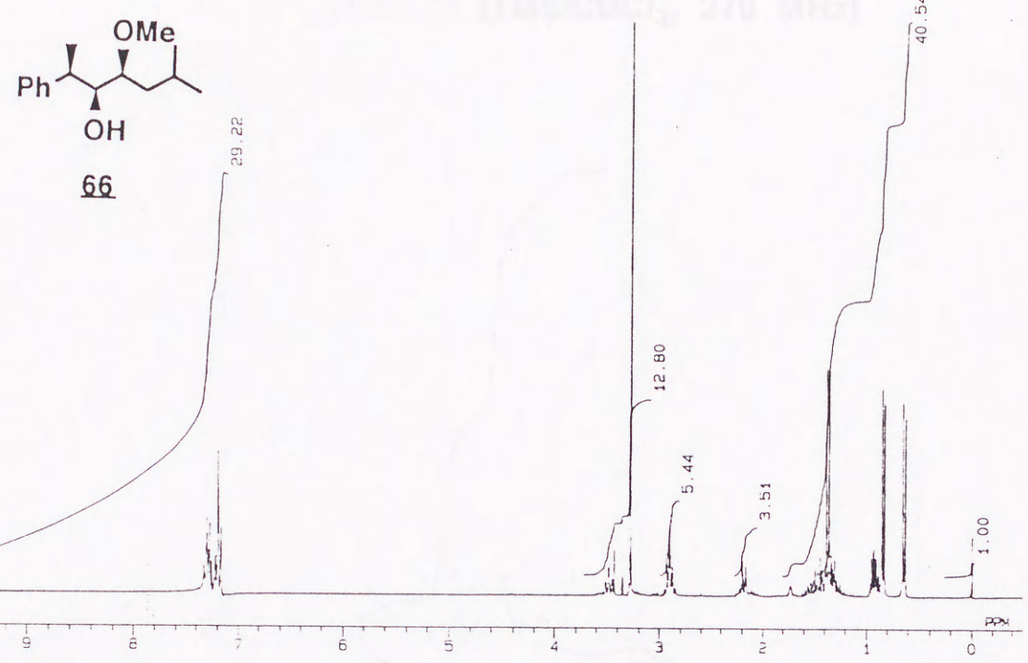
89

^{1}H NMR Spectrum of 90 (TMS/$CDCl_3$, 270 MHz)

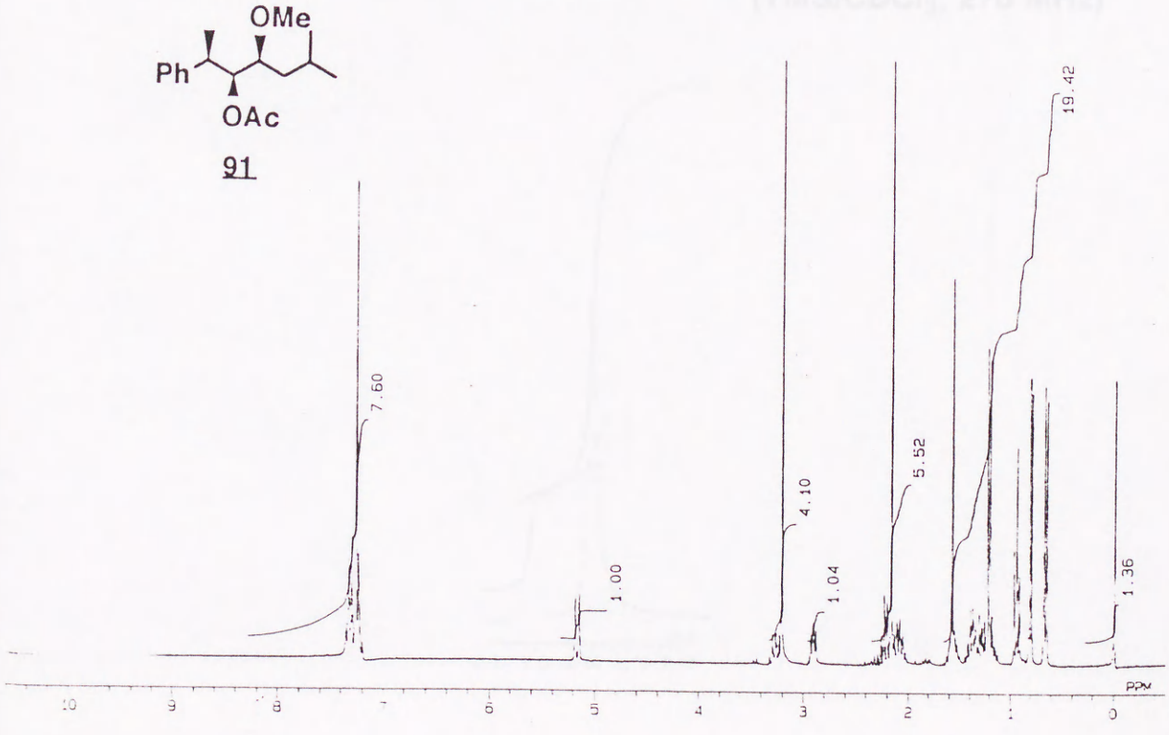


90

^{1}H NMR Spectrum of 66 (TMS/$CDCl_3$, 270 MHz)



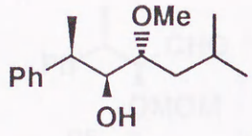
^{1}H NMR Spectrum of 91 (TMS/$CDCl_3$, 270 MHz)



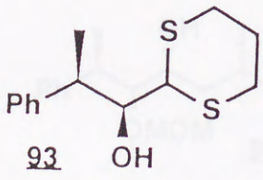
^{1}H NMR Spectrum of (±)-91 + Eu(hfc)$_3$ (0.2 equiv.)
(TMS/$CDCl_3$, 270 MHz)

^{1}H NMR Spectrum of 91 (58%ee) + Eu(hfc)$_3$ (0.2 equiv.)
(TMS/$CDCl_3$, 270 MHz)

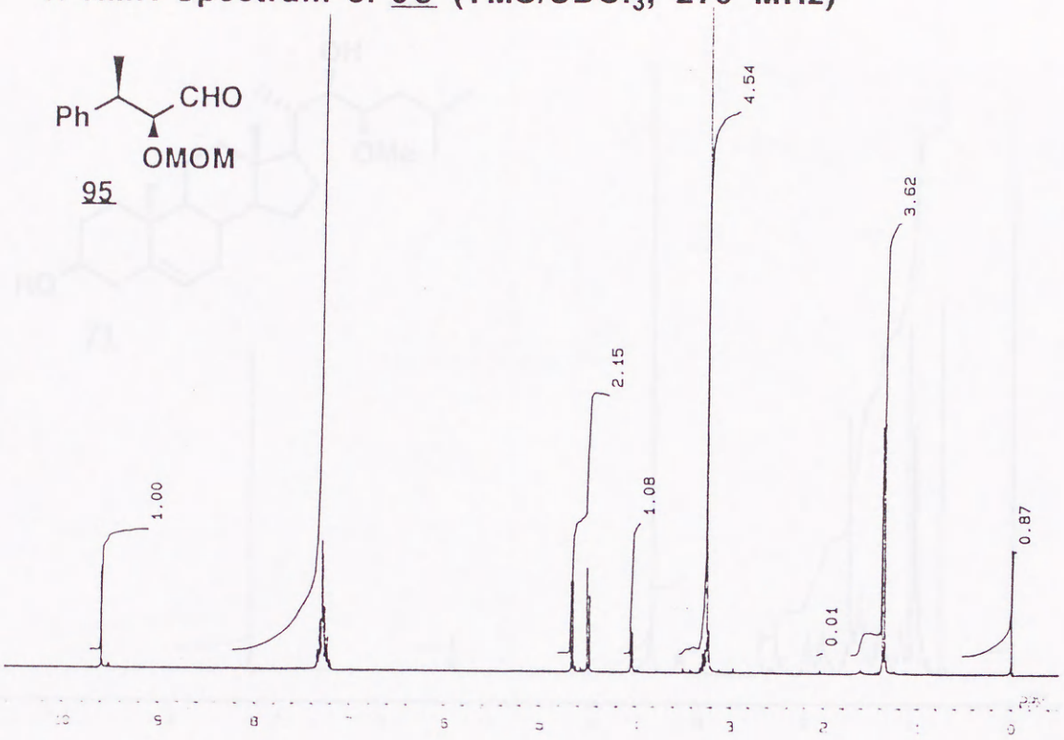
^{1}H NMR Spectrum of Cram-anti isomer
(TMS/$CDCl_3$, 270 MHz)



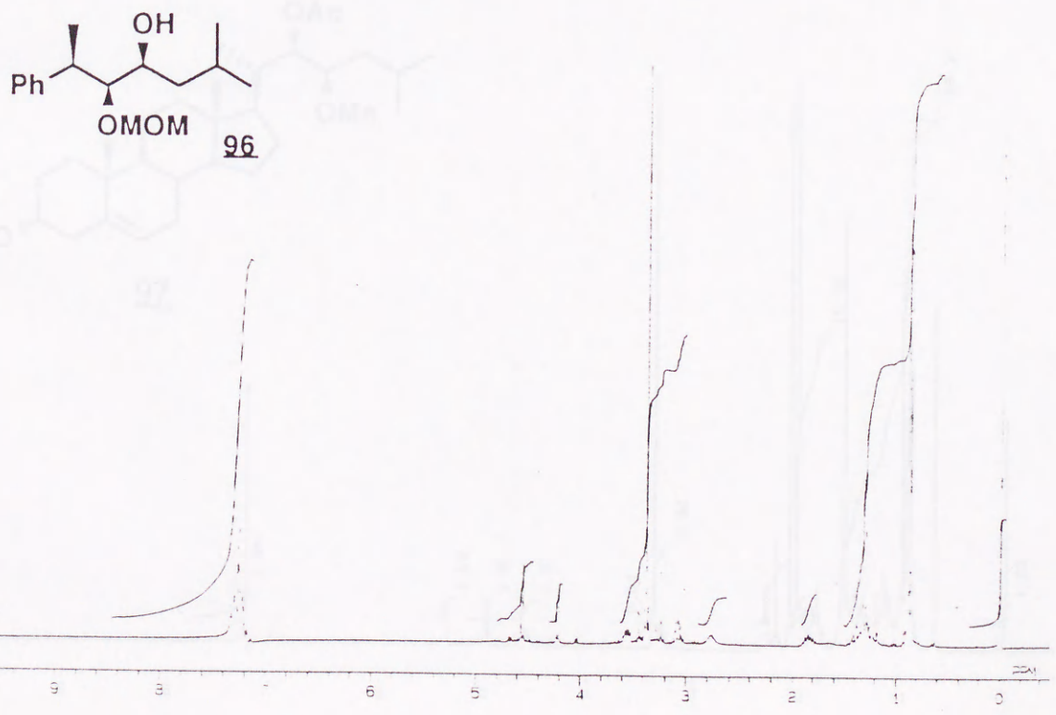
^{1}H NMR Spectrum of 93 (TMS/$CDCl_3$, 270 MHz)



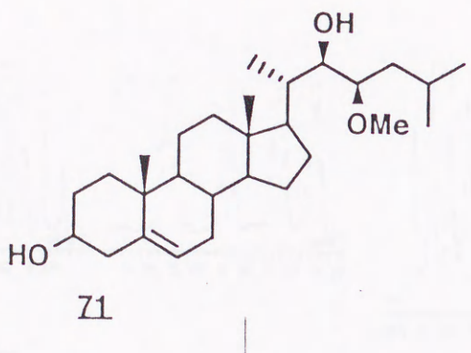
^{1}H NMR Spectrum of 95 (TMS/$CDCl_3$, 270 MHz)



^{1}H NMR Spectrum of 96 (TMS/$CDCl_3$, 270 MHz)

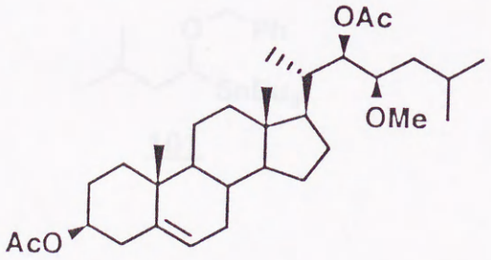


^{1}H NMR Spectrum of 71 (TMS/$CDCl_3$, 270 MHz)



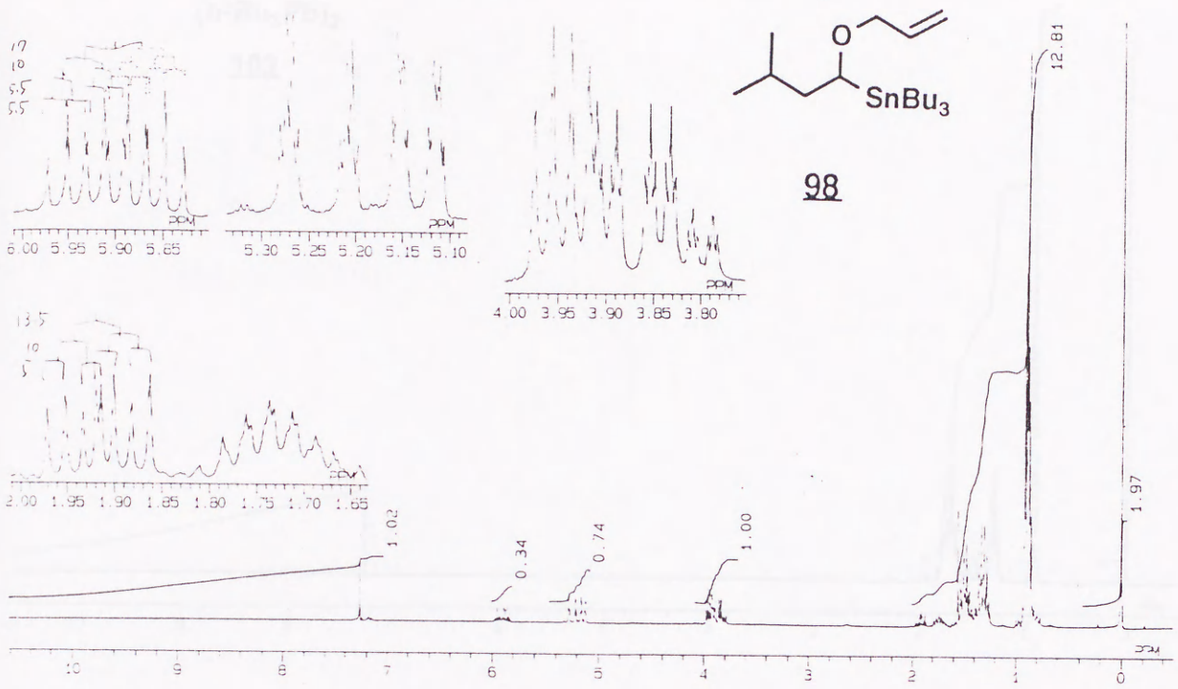
71

^{1}H NMR Spectrum of 97 (TMS/$CDCl_3$, 270 MHz)



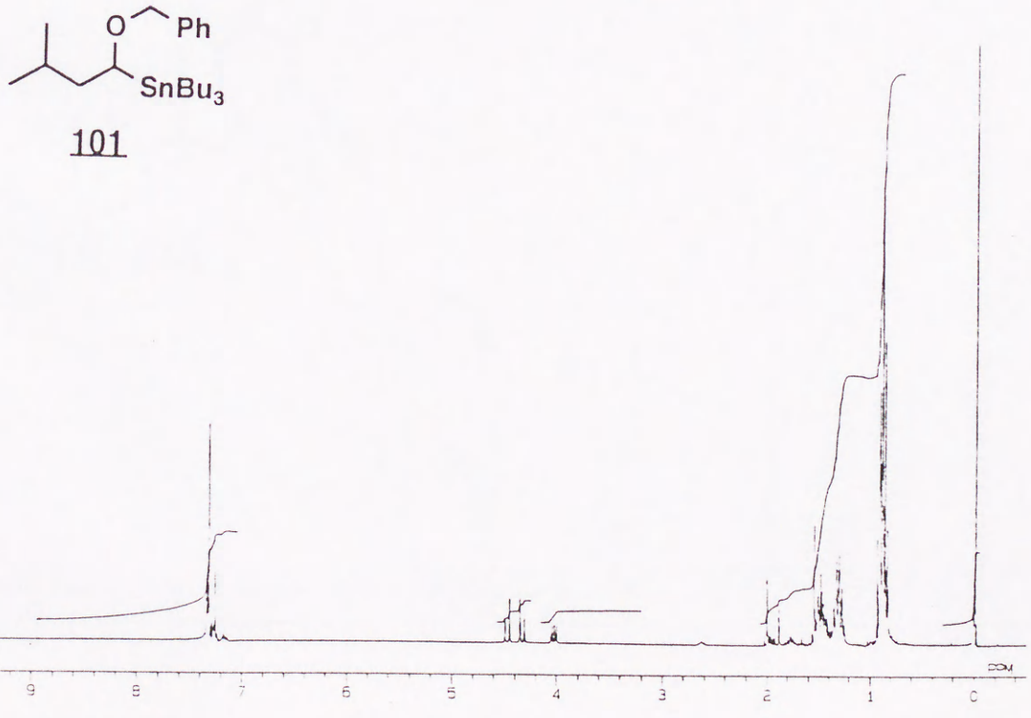
97

^{1}H NMR Spectrum of 98 (TMS/$CDCl_3$, 270 MHz)



98

^{1}H NMR Spectrum of 101 (TMS/$CDCl_3$, 270 MHz)

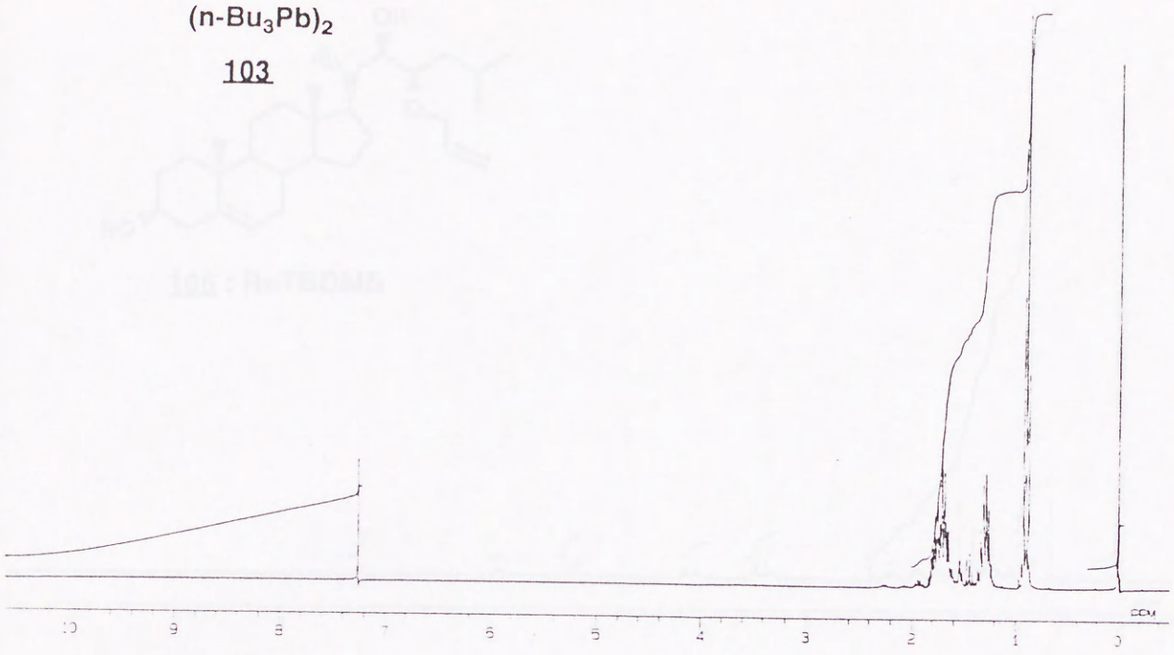


101

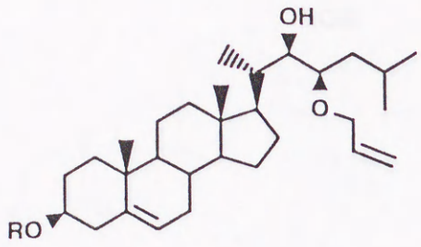
^{1}H NMR Spectrum of 103 (TMS/$CDCl_3$, 270 MHz)

$(n\text{-}Bu_3Pb)_2$

103

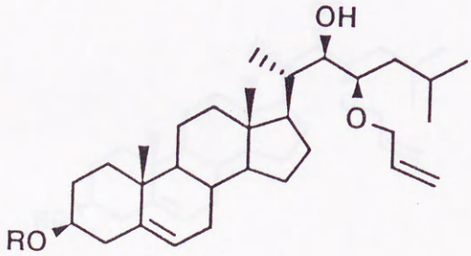


^{1}H NMR Spectrum of 106 (TMS/$CDCl_3$, 270 MHz)



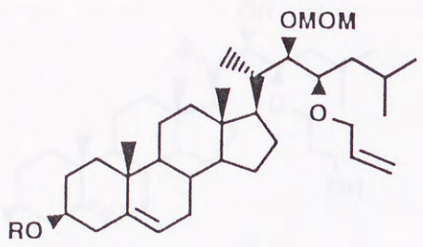
106 : R=TBDMS

^{1}H NMR Spectrum of 107 (TMS/$CDCl_3$, 270 MHz)



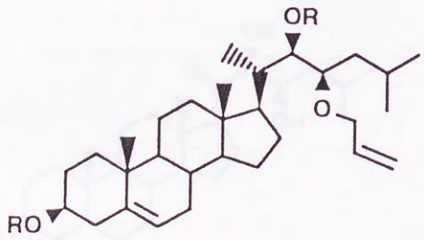
107 : R=H

^{1}H NMR Spectrum of 108 (TMS/$CDCl_3$, 270 MHz)



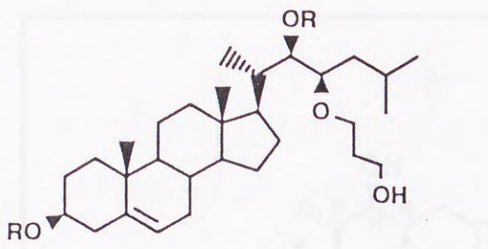
108 : R=TBDMS

^{1}H NMR Spectrum of 109 (TMS/$CDCl_3$, 270 MHz)



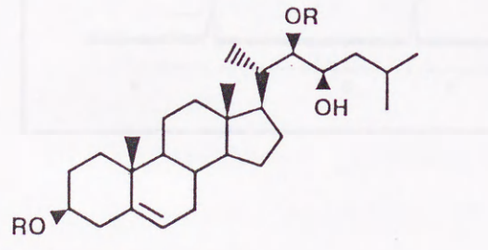
109 : R=MOM

^{1}H NMR Spectrum of 110 (TMS/$CDCl_3$, 270 MHz)



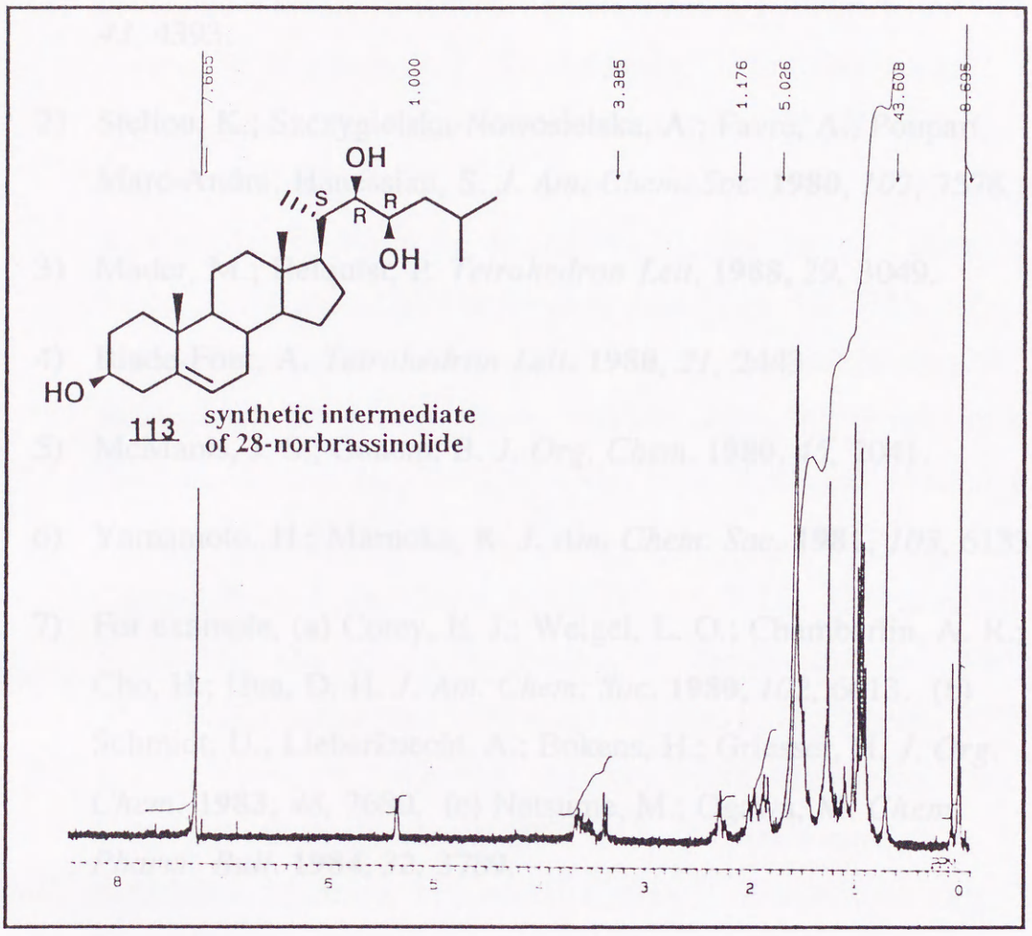
110 : R=MOM

^{1}H NMR Spectrum of 112 (TMS/$CDCl_3$, 270 MHz)



112 : R=MOM

^{1}H NMR Spectrum of 113 (TMS/$CDCl_3$, 270 MHz)



113 synthetic intermediate of 28-norbrassinolide

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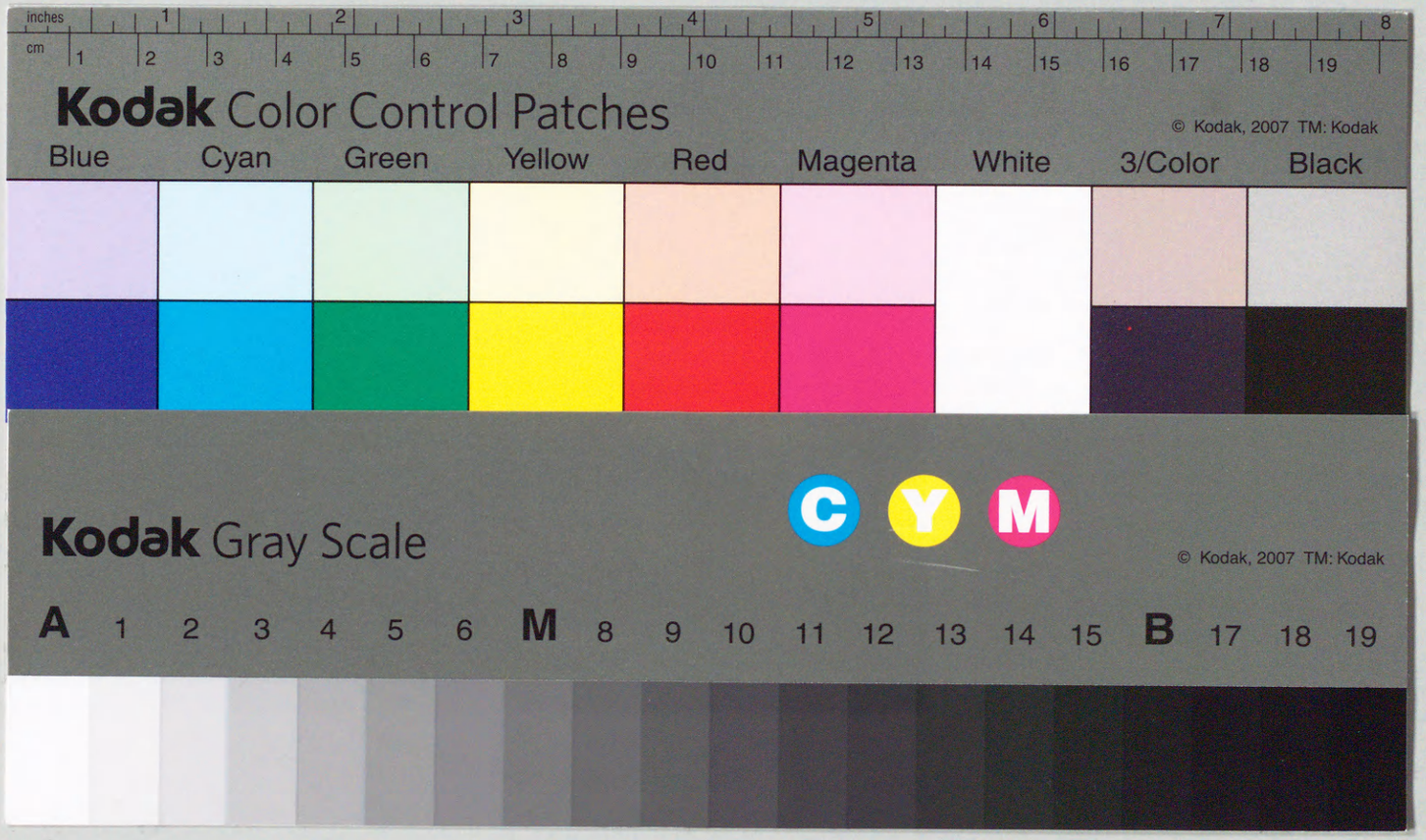
Heteroatomkgaf, and Pb7 Compounds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