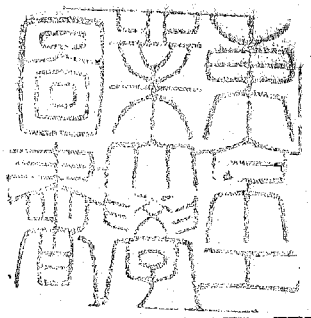
論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Application of Palladium-catalyzed Telomerization and Newly Developed Cyclization Reactions to Syntheses of Natural Products
著者(和文)	小林雄一
Author(English)	YUICHI KOBAYASHI
出典(和文)	学位:工学博士, 学位授与機関:東京工業大学, 報告番号:甲第1254号, 授与年月日:1981年3月26日, 学位の種別:課程博士, 審査員:
Citation(English)	Degree:Doctor of Engineering, Conferring organization: , Report number:甲第1254号, Conferred date:1981/3/26, Degree Type:Course doctor, Examiner:
学位種別(和文)	博士論文
Type(English)	Doctoral Thesis



APPLICATION OF PALLADIUM-CATALYZED TELOMERIZATION AND NEWLY DEVELOPED CYCLIZATION REACTIONS TO SYNTHESES OF NATURAL PRODUCTS

A thesis presented

by

Yuichi Kobayashi

to

Tokyo Institute of Technology

January 1981

Contents

Abbreviations

Ac	Acetyl
DIPHOS	Bis(diphenylphosphino)ethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
E	Electrophile
GLC	Gas chromatography
HMPA	Hexamethylphosphoramide
L	Ligand
Ms	Mesyl
Nu	Nucleophile
Py	Pyridine
R	Alkyl
$\underline{R}_f$	Rate of flow
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl

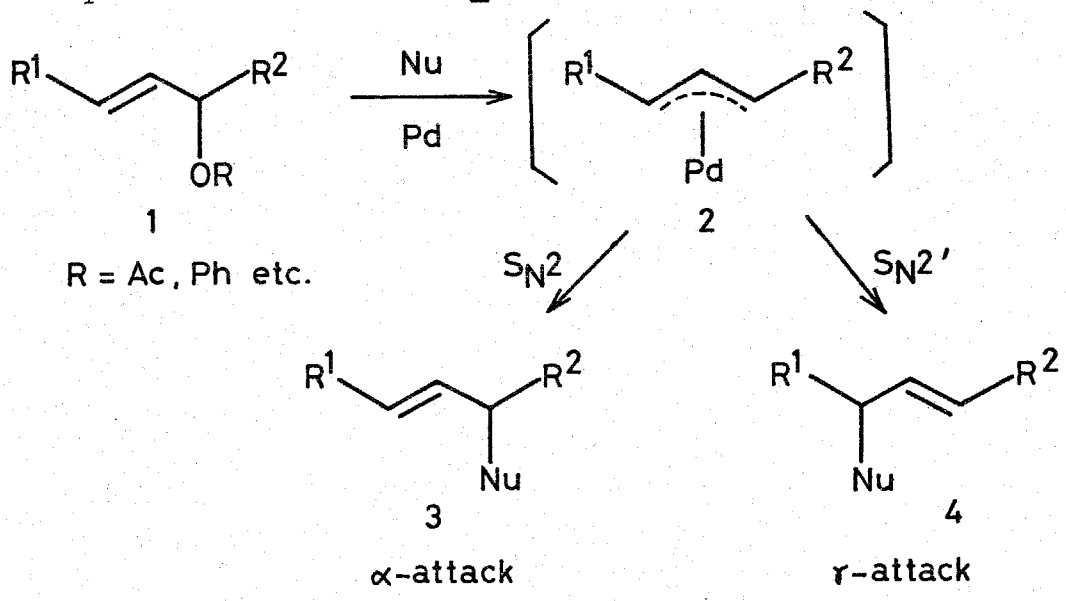
CHAPTER ONE

INTRODUCTION AND GENERAL SUMMARY

One important aspect of modern palladium chemistry is the rapid development in the ingeneous application of palladium complexes to organic synthesis, where the use of palladium compounds in a catalytic amount is the most desirable since palladium is a rather expensive metal with high atomic weight.

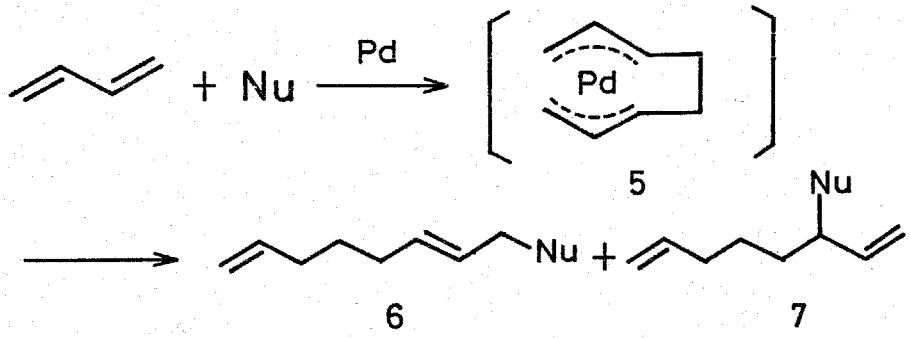
Hitherto a variety of palladium-catalyzed reactions have been disclosed and developed.[1] The followings can be referred to as representative palladium-catalyzed reactions:

(1) Substitution of allylic alcohol derivatives 1 with nucleophiles (Nu), yielding two regioisomers 3 and 4 by way of an α-attack (S_N2) and γ-attack (S_N2'), respectively, usually with a preferential attack of nucleophiles at a less hindered site of π-allylpalladium intermediates 2:



(2) Dimerization of butadiene with incorporation of certain nucleophiles (Nu) such as water, alcohols, carboxylic acids, amines,

active methylene compounds, and so on, yielding two isomeric compounds 6 and 7 by way of bis-π-allylpalladium intermediate:



Other remarkable palladium-catalyzed reactions are oxidative transformation of terminal olefins to methyl ketones,[2] acetylene carbonylation,[3] olefin insertion to aryl [4] and alkenyl halides,[5] reduction of allyl alcohol derivatives to simple olefins, [6] diene formation from allyl alcohol derivatives [7] and so on.

On the other hand, many synthetic chemists have devoted their efforts to develop useful methods for the effective syntheses of natural products and have provided many accesses to biologically active natural products. However, exploitation of highly selective and widely applicable strategies to and/or new routes to certain natural product syntheses are still necessary. The author focused his interest on this point and succeeded, in his opinion, in finding new fruitful methods and routes where palladium-catalyzed reactions play important roles.

The present thesis is consisted of the following two classes:

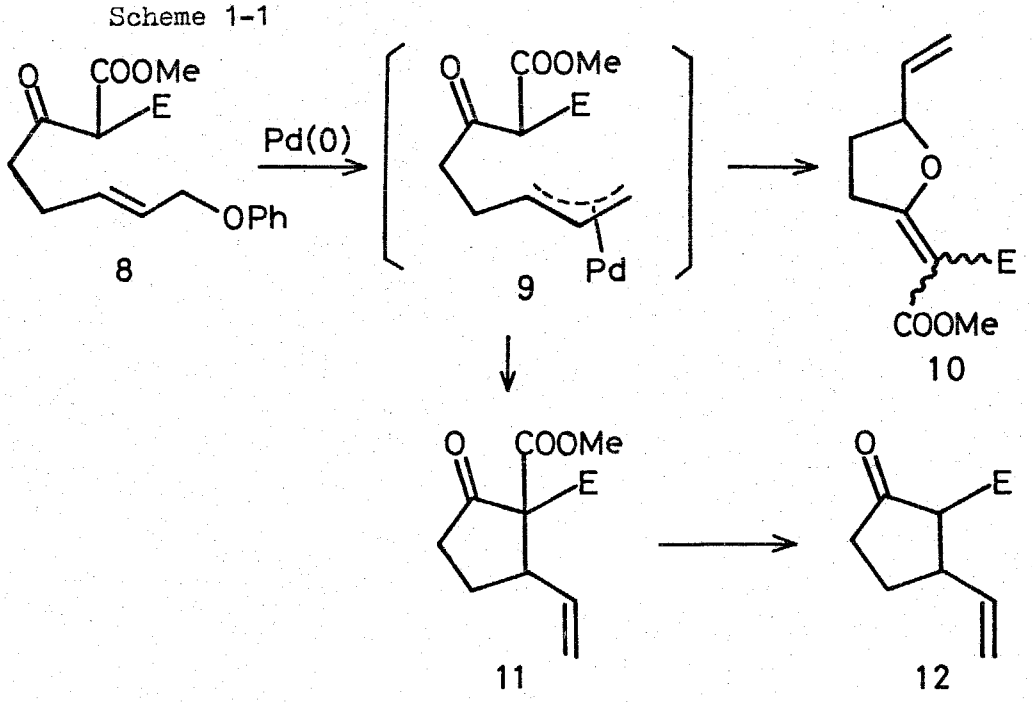
(1) Exploitation of the synthetic strategy for the synthesis of 2,3-disubstituted cyclopentanones by a palladium-catalyzed cyclization (Chapter 2) and its application to syntheses of several natural

products such as methyl jasmonate, sarkomycin, coronafacic acid, 18-functionalized steroids (Chapter 3-7).

(2) Utilization of butadiene telomers for syntheses of steroids (Chapter 8) and jasmonoids (Chapter 9).

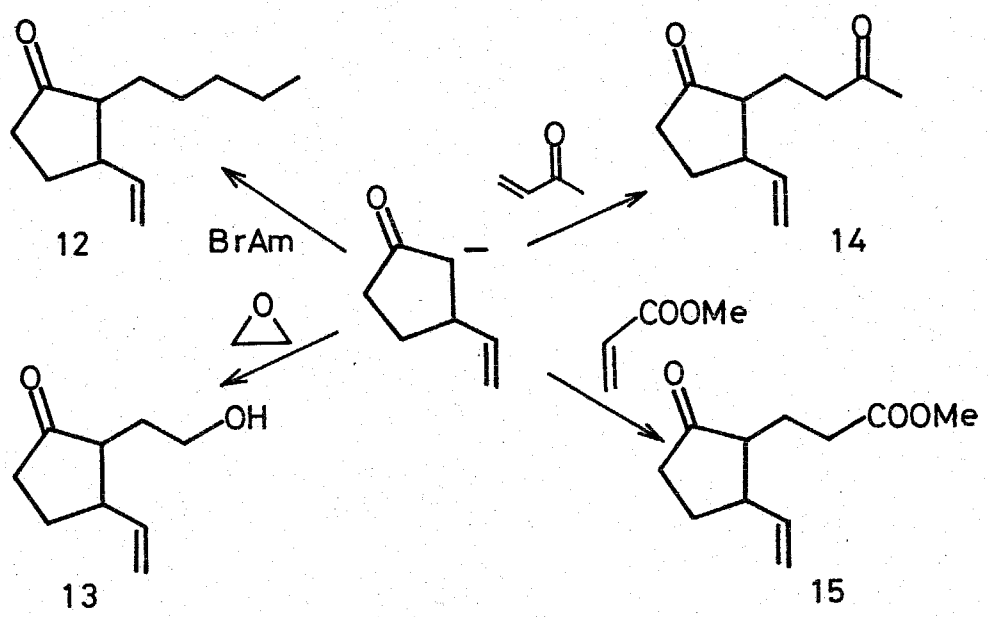
At first, new method for the synthesis of 2,3-disubstituted cyclopentanones was successfully exploited (Scheme 1-1) and are described in Chapter 2.[8] The new sequence consists of palladium-catalyzed intramolecular allylic substitution of the β-keto esters 8 possessing an appropriate side chain E to give 11 rather than 10 via π-allylpalladium-intermediates 9 and subsequent demethoxycarbonylation of 11 affording the desired 2,3-disubstituted cyclopentanones 12, where the vinyl group at C-3 position certainly provides chances for further transformations to requisite side chains.

Scheme 1-1



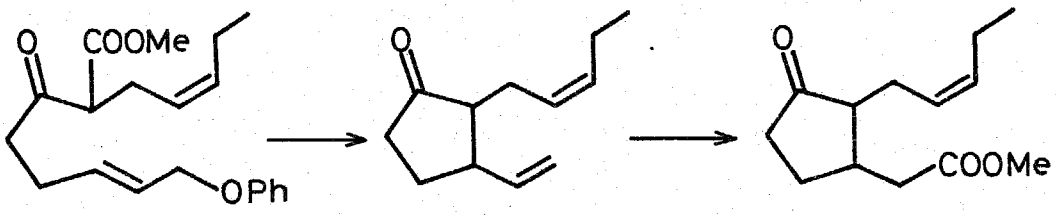
As a result, not only less reactive electrophiles but also electron deficient olefin-electrophiles such as methyl vinyl ketone and methyl acrylate could be introduced regioselectively in a proper (C-2) position of cyclopentanone ring. Some results are illustrated in Scheme 1-2 in a sence of "formal synthesis".

Scheme 1-2



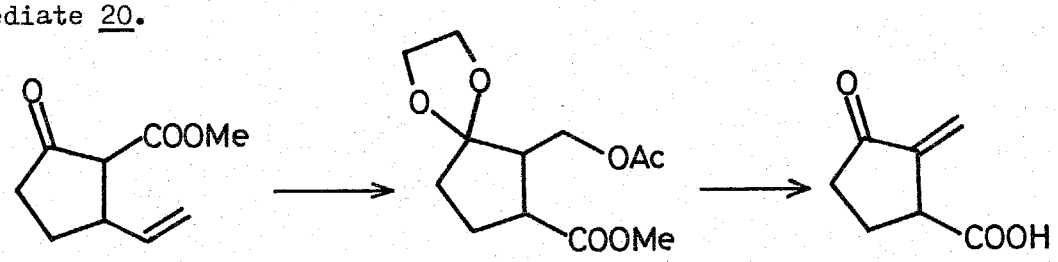
Although cyclizations of this type of five-membered rings are known to be disfavored process based on Baldwin's rule for ring closure,[9] where the O-alkylated products 10 are favored, the present palladium-mediated cyclization did afforded the desired cyclopentanones. This is the first exceptional example of the Baldwin's rule.

The cyclization provided one solution to synthesis of methyl jasmonate (19).[8] Chapter 3 discloses the synthetic pathway leading to 19 which consists of the palladium-catalyzed cyclization of the β-keto ester 17 followed by demethoxycarbonylation to give 18 and unmasking of acetic acid side chain attached at C-3 position of cyclopentanone ring.



17 18 19

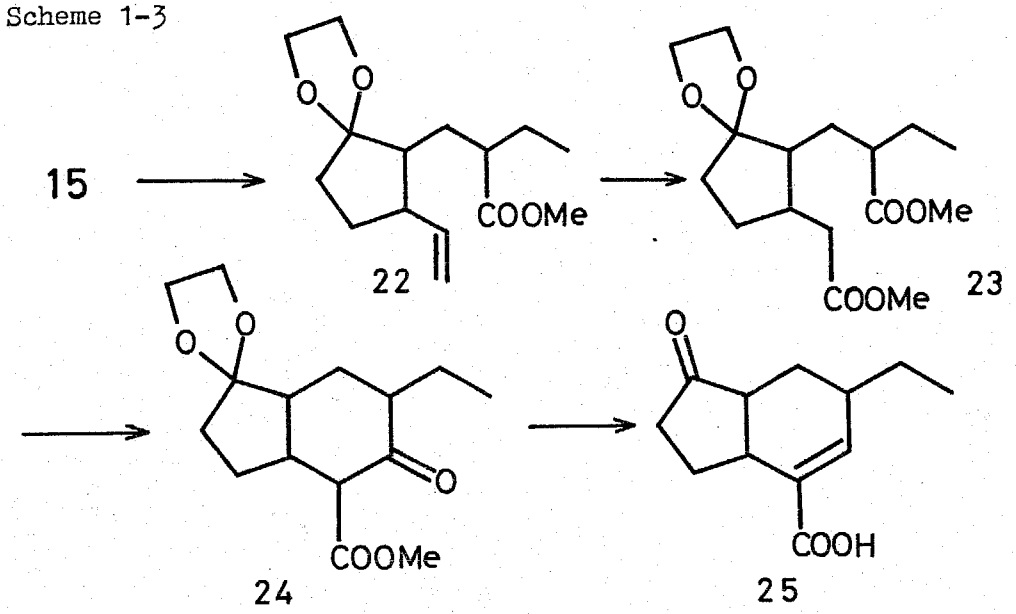
The palladium-catalyzed cyclization product 11 (E = H) is conceivably a right intermediate for the synthesis of sarkomycin (21), because 11 (E = H) already has requisite carbon atoms corresponding to 21. Chapter 4 discolses the practical transformation [10] to 21 via the intermediate 20.



11 (E = H) 20 21

The Robinson annulation and the Diels-Alder cyclization are now conventional methods for construction of indan skeletons of certain natural products. However there exist natural products with indan backbone which are not readily accessible by using these methods. Use of 2,3-disubstituted cyclopentanones offers an alternative solution, where both side chains of 2,3-disubstituted cyclopentanones take part in the construction of a cyclohexane ring of indan skeleton. A synthesis of coronafacic acid (25) is just the case.[11] Details of the synthesis of 25 are described in Chapter 5. As shown in Scheme 1-3, the ester 22 derived from 15 was further transformed to 23. The Dieckmann

Scheme 1-3

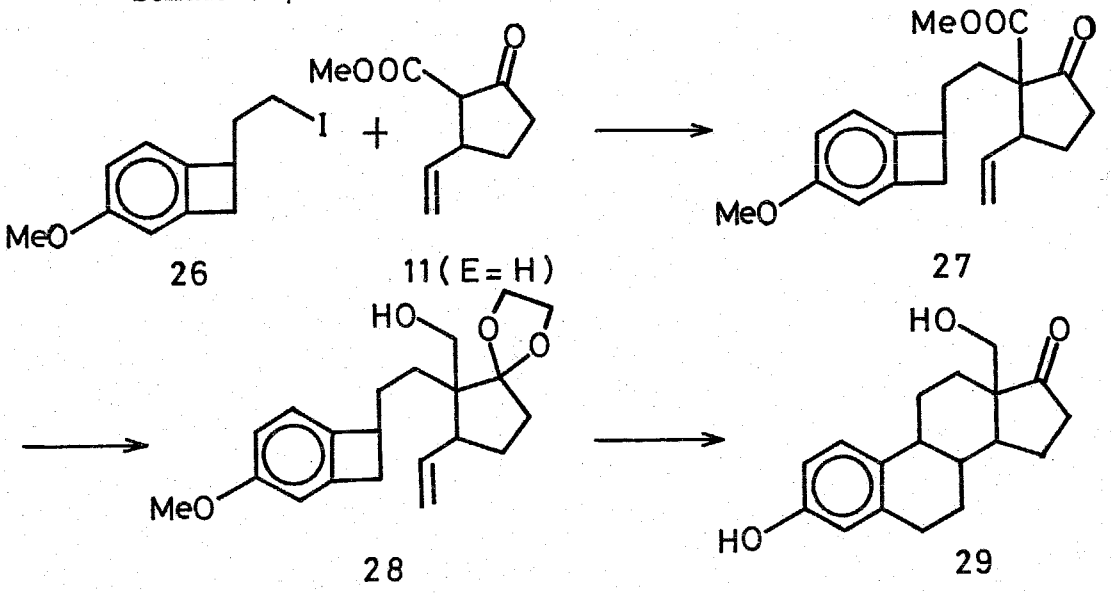


cyclization of 23 afforded the β-keto ester 24 from which coronafacic acid (25) was synthesized.

There exist many 18-functionalized steroids. Aldosterone, 18-hydroxyestrone, 18-acetoxy- and 18-hydroxypregna-1,4,20-trien-3-one, and conessine are typical examples. Because of the existence of one more functional group at C-18 position, no conventional methods such as the Robinson annulation method have been employed and as a result, there exist few total synthesis. In other word, absence of suitable starting materials refuses the success of total syntheses of this sort of functionalized steroids. With respect to this, palladium-catalyzed cyclization is promising as shown below (Chapter 6 and 7).

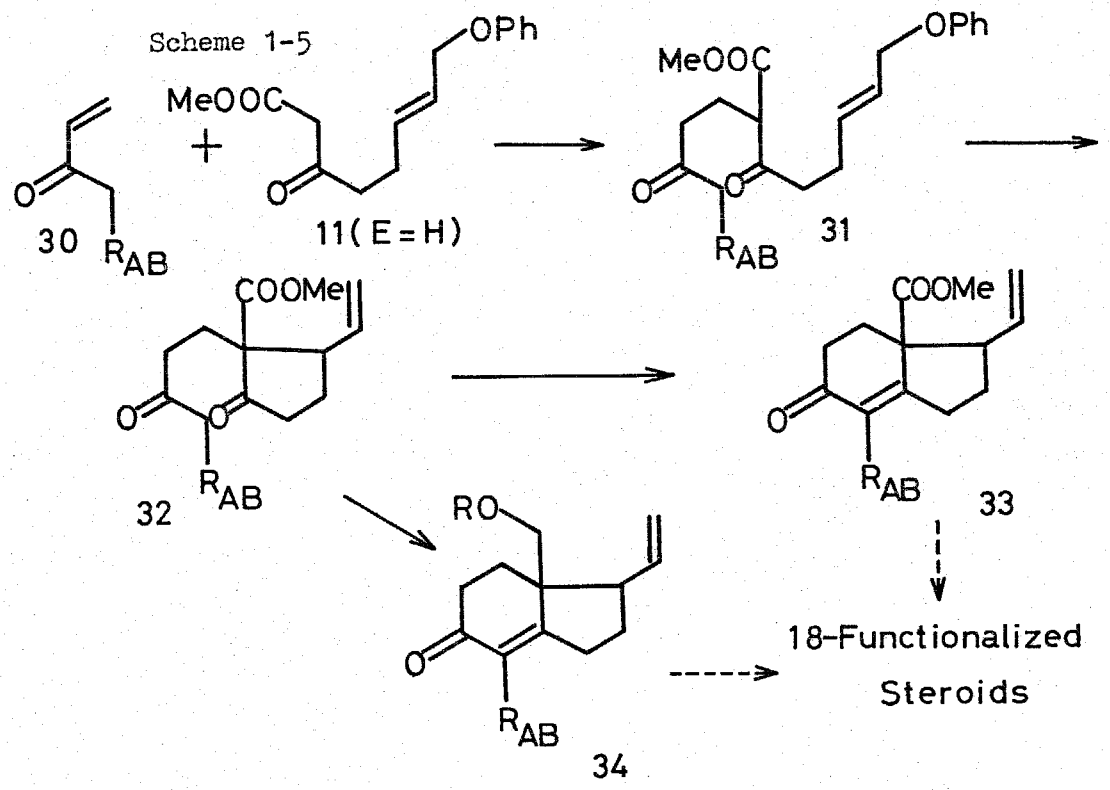
Chapter 6 deals with the synthesis of 18-hydroxyestrone (29) starting from the cyclopentanone 11 (E = H), all of whose functionalities are ideally utilized [12] (Scheme 1-4). Success of the synthesis seems to depend on the easy accessibility of 11 (E = H), which has surprisingly not been prepared yet.

Scheme 1-4



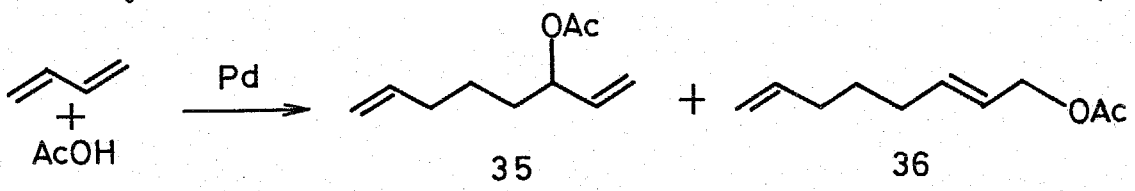
Moreover the palladium-catalyzed cyclization offered one methodology.[13] Scheme 1-5 reveals a bird's-eye view of the new methodology where the hopeful intermediates 33 and 34 are synthesized and the details are described in Chapter 7. Namely the β-keto ester

Scheme 1-5



11 (E = H) was added to the enones 30 possessing a side chain R_{AB} which is necessary to build up the A,B rings of steroids backbone. The palladium-catalyzed cyclization of the adducts 34 afforded the cyclopentanones 32 from which intermediates 33 and 34 are easily synthesized.

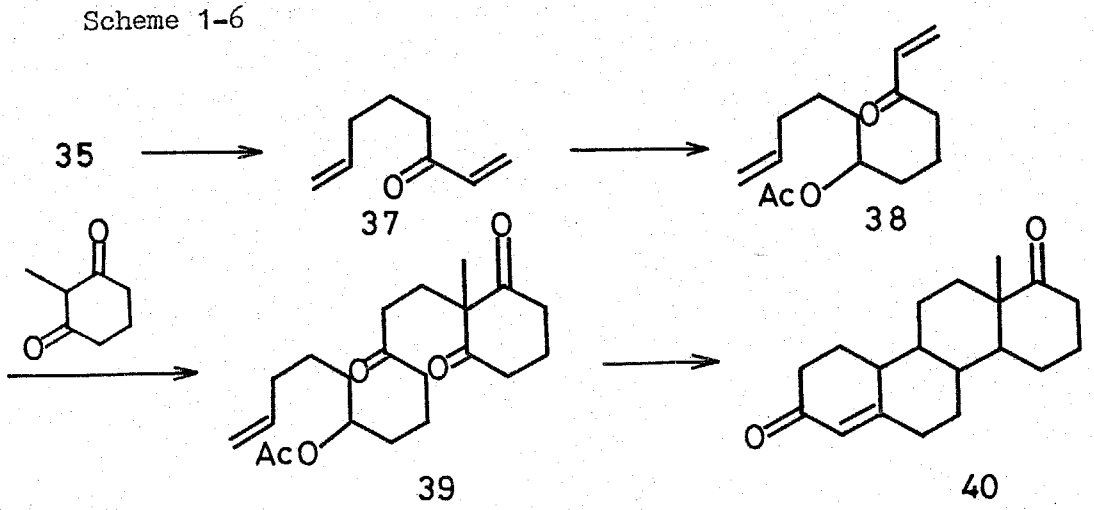
As the second subject, utilization of butadiene telomers was investigated. As one example, telomerization of butadiene with acetic acid produces a mixture of acetoxyoctadiene 35 and 36, which are easily separated by rectification.[14]



35 36

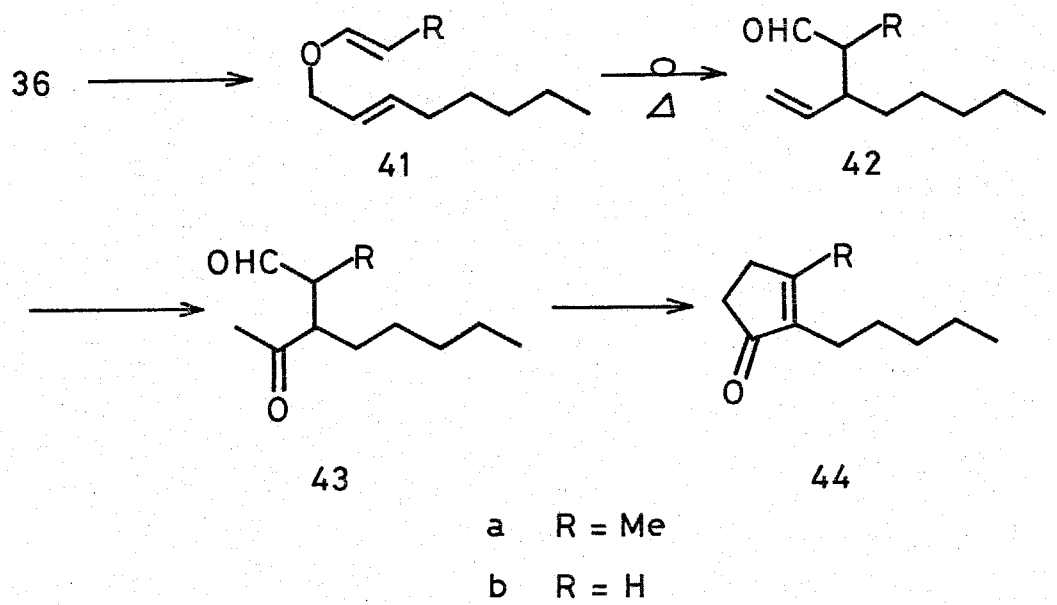
Chapter 8 deals with the convenient synthesis[15] of the new tris-annulation reagent 38 starting from the butadiene telomer 35 via the bis-annulation reagent 37[16] (Scheme 1-6). In general, the usefulness of the tris-annulation reagents is determined by easy accesibility of the

Scheme 1-6



reagent itself, stability of acids and bases, and facile procedure of the unmasking to carbonyl functions. The new tris-annulation reagent 38 fulfills these requirements and practical transformation to 19-nor-D-homoandrost-4-ene-3,17a-dione (40) is also described in Chapter 8.

On the other hand, the allylic isomer 36 is a suitable compound for the synthesis of dihydrojasmone (44a) and dihydronorjasmone (44b). Chapter 9 reaveals the synthetic pathway to 44a and 44b from 36 as shown below:[17]



a R = Me

b R = H

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CHAPTER TWO

PREPARATION OF 2,3-DISUBSTITUTED CYCLOPENTANONES BY THE PALLADIUM-CATALYZED CYCLIZATION REACTION

Summary

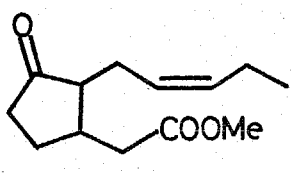
A new synthetic method for the regioselective synthesis of various 2,3-disubstituted cyclopentanones was developed. The method consists of following two steps: 1. Palladium-catalyzed cyclization, a key reaction, of methyl 2-alkyl-3-oxo-8-phenoxy-6-octenoates (33) to give methyl 1-alkyl-2-oxo-5-vinylcyclopentanecarboxylates (35); 2. Demethoxycarbonylation of 35 affording 2-alkyl-3-vinylcyclopentanones (18).

The β-keto ester 33 could be obtained easily by using conventional methods of alkylation or Michael addition of methyl 3-oxo-8-phenoxy-6-octenoate (33a) and various electrophiles such as pentyl bromide, 2-phenylethyl bromide, and 2-pentynyl chloride, or methyl vinyl ketone and methyl acrylate, respectively. The vinyl group at 3-position in cyclopentanones 18 would be converted to the requisite functional group in its own right.

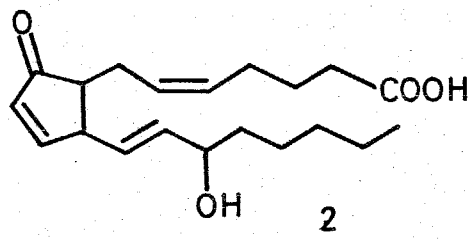
2-1 Introduction

2-1-1 Background

There are a number of natural products of cyclopentanone derivatives which possess two appropriate substituents at C-2 and C-3 positions of ring.[1] Representative are methyl jasmonate (1), an important substance in perfume industry, and prostagrandin A_2 (2).

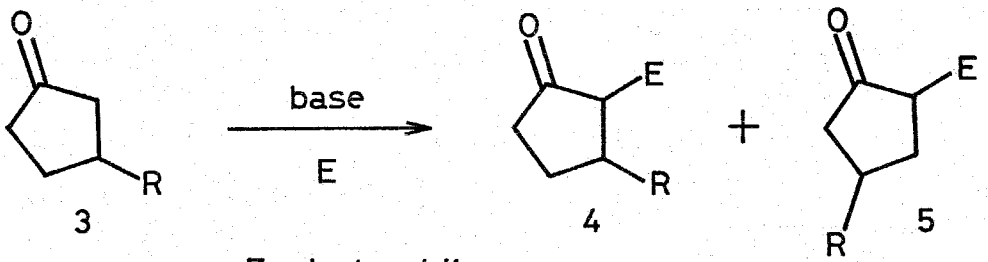


1



2

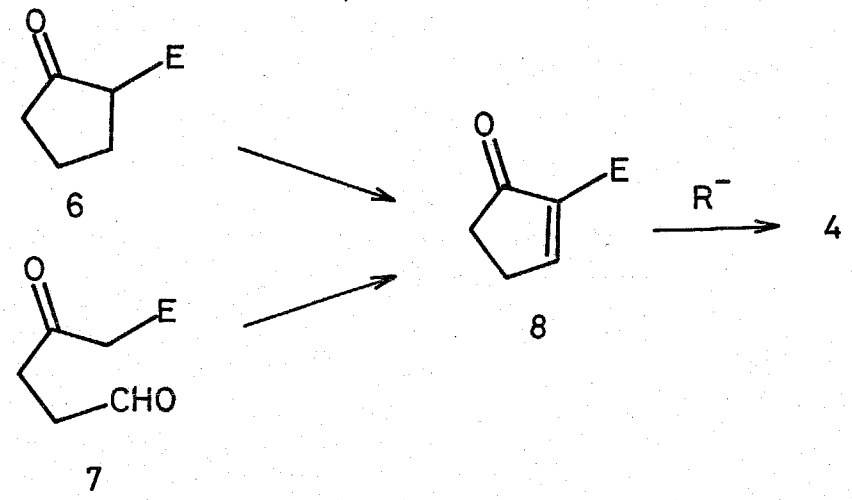
In principle, these 2,3-disubstituted cyclopentanones 4 could be synthesized from 3-substituted cyclopentanones 3 which are easily available from many starting materials. But unsymmetrical cyclopentanones 3 would lead to two regioisomeric enolates and therefore a mixture of two regioisomeric products 4 and 5 is formed.



3 4 5

E : electrophile

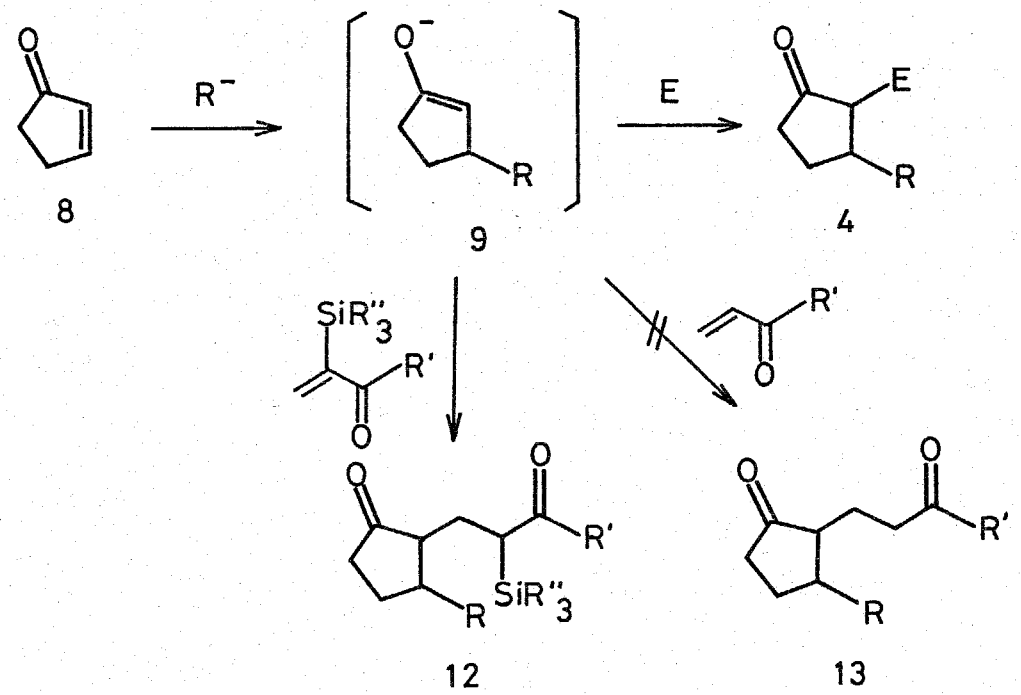
Consequently there have been an increasingly large amount of researches devoted to develop regioselective routes to these 2,3-disubstituted cyclopentanone derivatives.[2-5] One important solution to this problem is the Michael addition of an appropriate nucleophile R^- onto an enone 8



possessing a proper substituent E at C-2 position. Generally the enones 8 could be synthesized from cyclopentanones 6 by using one set of reactions of bromination at the carbon atom having a side chain E followed by dehydrobromination or from γ-leto aldehydes 7 by use of the aldol condensation. There is, however, sereous restriction that this procedure is not adaptable for the preparation of the cyclopentenones 8 which possess bromine-sensitive moieties such as olefin in the side chain E. Alternatively, the aldol condensation of γ-keto aldehydes 7 is a common method for the synthesis of 8, but the development of methods for the synthesis of 7 is one subject in modern organic syntheses as such [6,7] and generally lengthy pathways are still necessary to get the γ-keto aldehydes 7.

On the other hand, there is another methodology which consists of the 1,4-addition of an appropriate "carbanion-like species" R^- such as the Gilman reagents to 2-cyclopentenone (8) and the subsequent enolate-trapping of the regioselectively generated enolate anion with a proper electro-

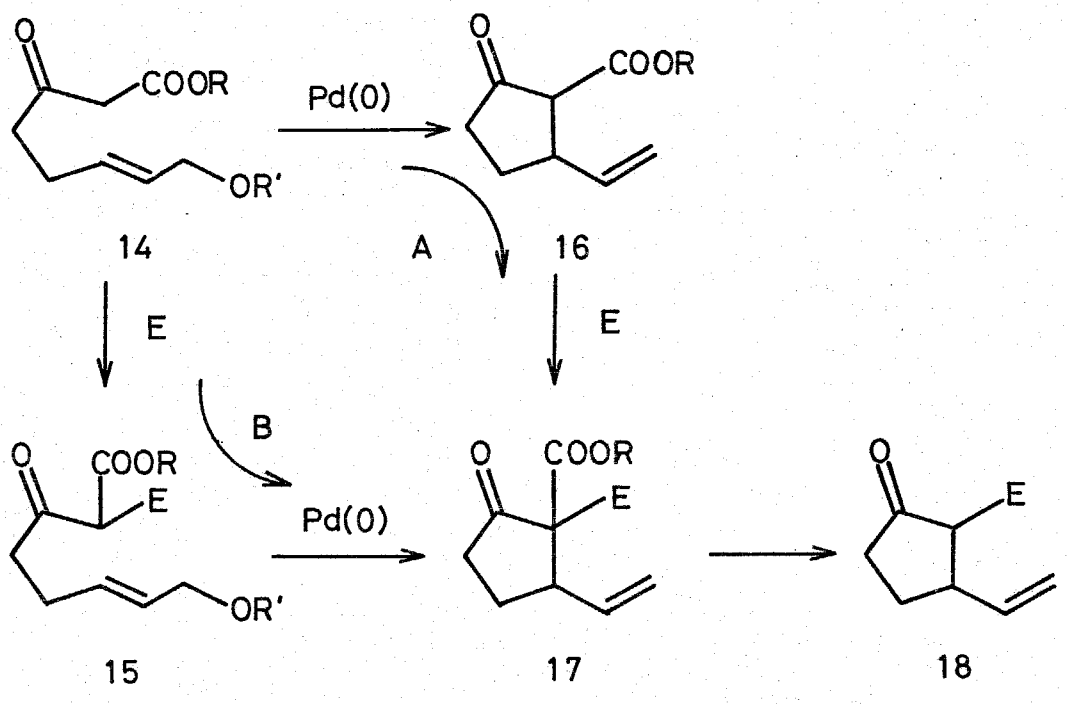
phile E.[3,10,11] This convenient method provides a direct access to the synthesis of 2,3-disubstituted cyclopentanones 4 and in fact a number of natural products have been synthesized by taking advantage of this methodology. Intrinsically this method, however, has several limitations. The electrophiles employed are restricted to the very reactive ones such as methyl iodide, ethyl iodide, some allyl iodides, formaldehyde and so on. Use of less reactive electrophiles results in forming a mixture of regioisomers and/or mono-, di-alkylated products because the integrity of the enolates 9 is not necessarily maintained due to proton transfer during the reaction.[2,3] In addition, it is known that the cuprate-generated enolates such as 9 do not condense with easily available electrophiles possessing electron deficient olefins such as methyl vinyl ketone [12] and methyl acrylate [11e] to give the desired adducts 13.



2-1-2 New Methodology for 2,3-Disubstituted Cyclopentanones

Having above backgrounds in mind, the author proposed following sequences (Scheme 2-1) to remove above mentioned restrictions and hence to provide a direct access to many natural products. The procedure involves following two routes. Route A consists of the palladium-catalyzed intramolecular S_N2' reaction of the β-keto esters 14 by way of π-allylpalladium intermediates to construct the cyclopentanones 16 and the subsequent reaction of 16 with electrophiles E to give 17, while

Scheme 2-1



R' : Ac, Ph E : elctrophile

Route B consists of, vice versa, the reaction of 14 with E and the subsequent palladium-catalyzed cyclization of 15.* Finally dealkoxycarbonylation of 17 would afford the 3-vinyl-2-alkylcyclopentanones 18, whose vinyl group could be converted to various side chains. Since many electrophiles E such as reactive halides, less reactive halides, epoxides, and vinyl ketones can react smoothly with the β-keto esters 14 and 16 to produce the substituted β-keto esters 15 and 17, respectively, the new method would provide the alternative solution for the synthesis of 2,3-disubstituted cyclopentanones.

By the way, Trost reported [14] the synthesis of the β-keto ester 20

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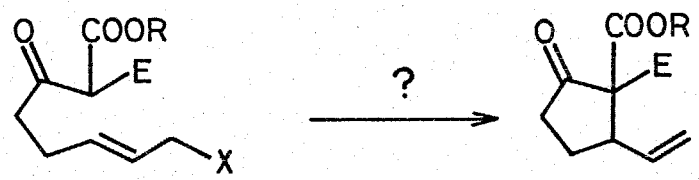
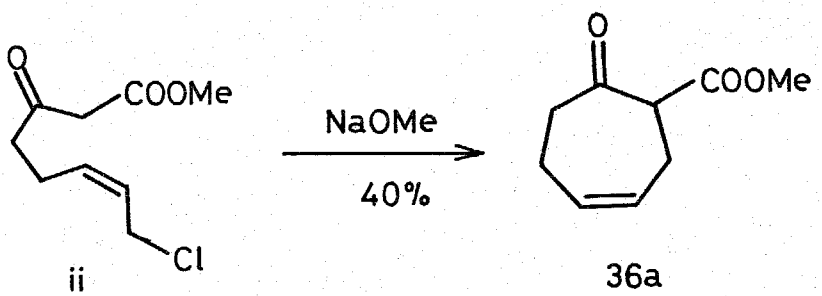
*The cyclopentanones 17 might be synthesized from the allyl halides i corresponding to the allyl phenoxide 15. However it is predictable based on Baldwin's cyclization rule (vide infra) that i would not yield 17 but the O-alkylated products and/or the cycloheptenones.



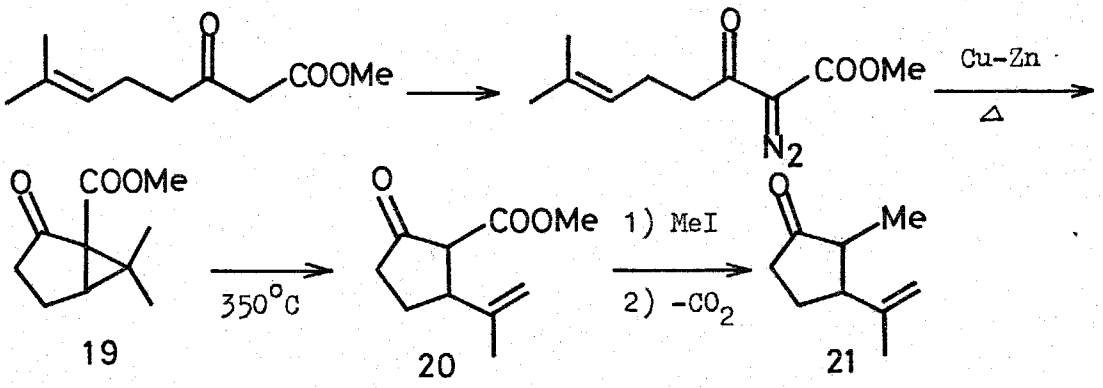
i X : halogen 17

In fact, there is one report (Ref. 19a) dealing with a similar cyclization where the halide ii of cis isomer was treated with sodium methoxide in methanol to give the cycloheptenone 36a as the only detectable product in 40% yeild.



ii 36a

by the following sequence of reactions and claimed that 19 was the intermediate for 2,3-disubstituted cyclopentanones such as 20.



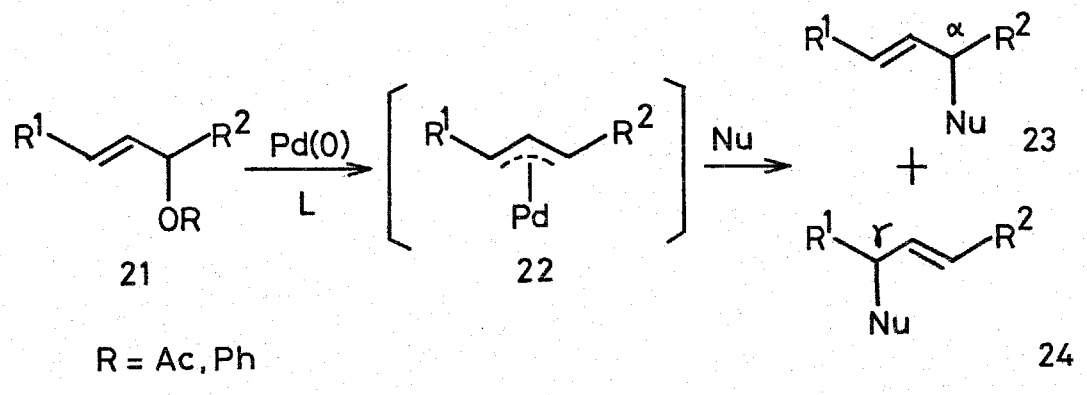
19 20 21

47% overall yield

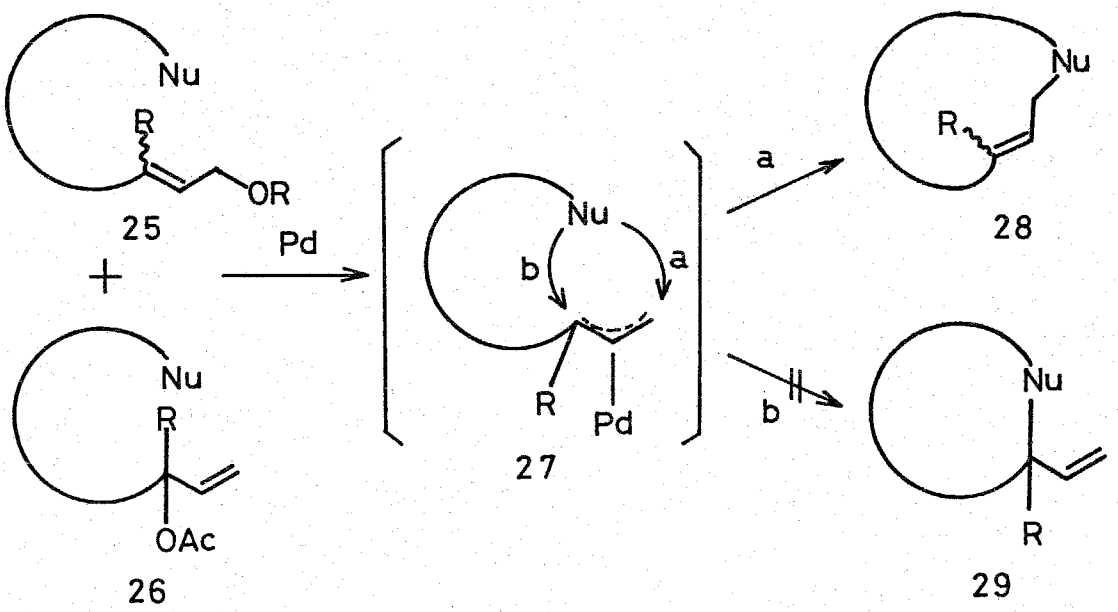
Cyclization reactions such as the present palladium-catalyzed one are claimed to be disfavored process by Baldwin,[15] who had said that all 5-Endo-Trig * ring closures are disfavored.[15d] The rule is now warranted by ample instances.[16-23] Therefore to succeed in the palladium-catalyzed cyclopentanone synthesis appears to break the Baldwin's rule.

Historically the palladium-catalyzed intermolecular alkylation of allyl acetates and of allyl phenoxides with carbon nucleophiles is well-known.[24] The reaction involves initial formation of the π-allyl-palladium intermediates 22 from allyl alcohol derivatives 21 with palladium(0) species and the subsequent attack of nucleophiles Nu on the π-allyl site of 22 provides allylic isomers 23 (α-attack, S_N2 type) and 24 (γ-attack, S_N2' type).[25] Recently Trost [26] and Nozaki [27] successfully transferred the reaction to an intramolecular process

* By his definition, 5-Endo-Trig ring closure means a five-membered ring forming process when the breaking multiple bond is endocyclic at the same time the geometry of the carbon atom undergoing the ring-closure reaction is trigonal. See Ref. 15a.

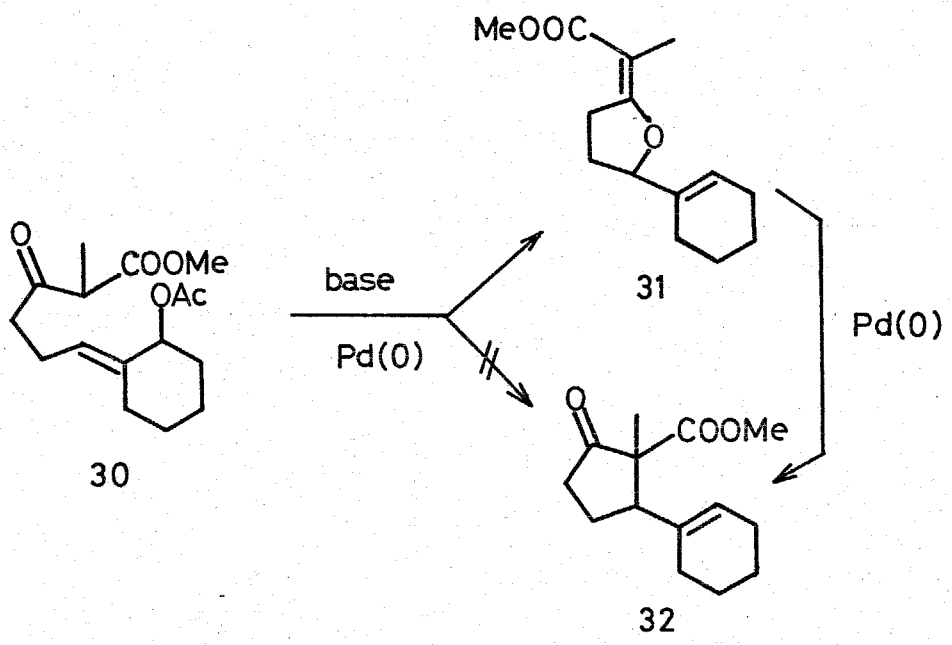


independently. Trost [26] has employed this reaction in particular for macrolide syntheses and Nozaki [27] for a synthesis of humulene, a 11-membered carbocyclic terpene. As expected, the large ring-size macrocycles 28 have been formed in all of their cases starting from 25 or 26. These results are well coincident with the reactivity of common π-allylpalladium intermediates undergoing nucleophilic attack at the less hindered end of the π-allyl system.[24]



Again, possibility of success of the proposed cyclization strongly contradicts from above precedents. However considering a number of hopeful evolutions which could be brought about from the success of the constructions of five-membered ketones, the author attempted the palladium-catalyzed cyclization.

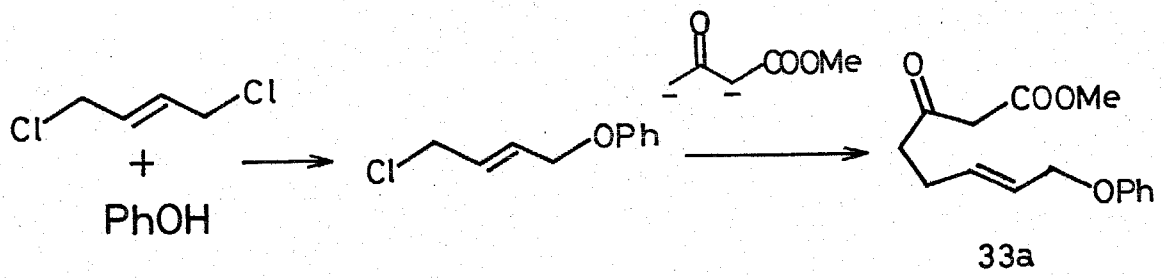
After the results of this investigation had been published, analogous cyclization was reported by Trost, who demonstrated that 31 could be converted to 32 in the presence of palladium(0) catalyst, while the allyl acetate 30 afforded only 31.[28]



2-2 Results and Discussion

2-2-1 Preparation of the Cyclization Substrates

To study the palladium-catalyzed cyclization in practice, the author selected methyl (E)-3-oxo-8-phenoxy-6-octenoate (33a) as a parent compound corresponding to 14 (See Scheme 2-1) and synthesized it according to Weiler's procedure [29] with slight modification. Dianion of methyl acetoacetate was reacted in THF-HMPA (2 equiv.) with (E)-1-chloro-4-phenoxy-2-butene, which was obtained from the displacement of (E)-1,4-dichloro-2-butene with phenol in the presence of potassium carbonate in refluxing acetone, and the desired product 33a was isolated in 84% yield after chromatography. Then the substituted β-keto esters corresponding to 15 (See Scheme 2-1) were prepared mainly from 33a (vide infra).



33a

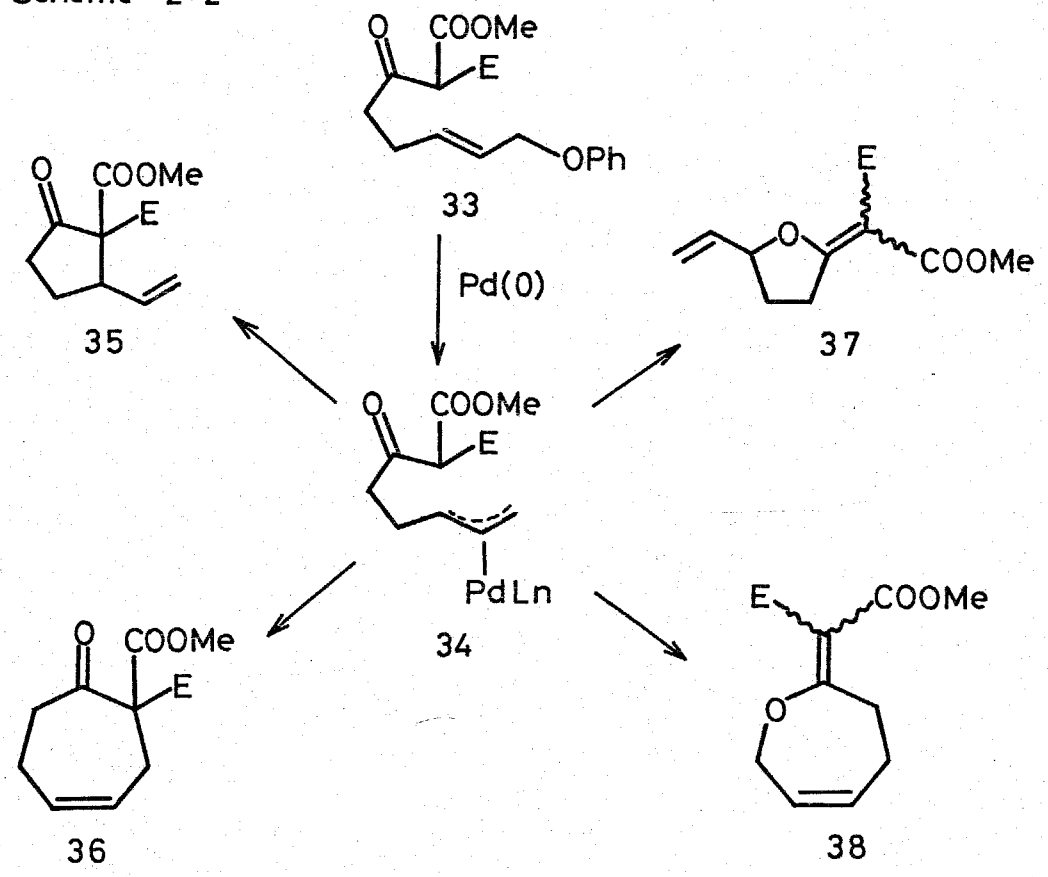
The cyclization was investigated by using at first 33a and then the substituted β-keto esters derived from 33a.

2-2-2 Preliminary Results with regard to Cyclization of the Parent β-Keto Ester 33a

From a mechanistic viewpoint as mentioned in the preceding section, the parent β-keto ester 33a forms the π-allylpalladium complex 34a

(Scheme 2-2). The complex 34a has two reaction sites on the π-allyl-moiety, while the β-keto ester function of 34a participates in the reaction as an ambident nucleophile at the oxygen atom and/or the carbon atom.[30] In a formal sense, four isomers, 35a, 36a, 37a, 38a, would arise from 34a. Among them, 35a is the desired product, being disfavored one by the Baldwin's rule,[15] while the cycloheptenone 36a and the O-alkylated product 37a are the favored products.

Scheme 2-2



a, R = H
b-j, R = H (see Table 2-4)

Keeping possibility of competitive formation of these four isomers in mind, the author carried out the reaction under nitrogen in refluxing solvents containing palladium(II) acetate (5-10 mol%), ligand (20-40 mol%), and other additives if necessary. Under these conditions, handy, stable palladium(II) acetate is said [31] to be reduced to zero-valent species to trigger off the catalytic reactions. After the reaction had been completed, the mixture was passed through a short column and the filtrate was concentrated. The residual oil was analyzed by gas chromatography to determine the ratio of products.

Preliminarily 33a was subjected to the cyclization in the presence or absence of triethylamine as a base. The results are exhibited in Table 2-1. Surprisingly all experiments produced the desired 35a accompanied with its isomer 36a.* Triethylamine exhibited no effects on reactions. The O-alkylated products 37a and 38a were not detected.

It is noteworthy that the combination of the palladium catalyst with the β-keto ester 33a broke not only the Baldwin's rule for ring

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*The authentic sample of 36a was synthesized from I along with unambiguous route as shown below.[32-35]

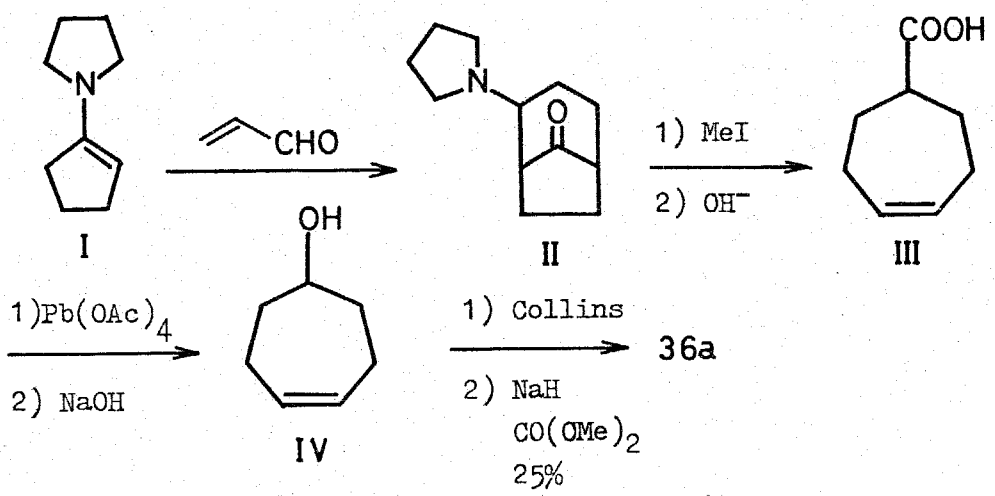


Table 2-1 Preliminary Cyclization of 33a

Run[a]	Et_3N (equiv.)	Solvent	Time (h)	Product Ratio (%)[b] 35a	36a	37a	38a and/or others
1	1	dioxane	1	47	51	0	2
2	0	dioxane	1/3	46	51	0	3
3	1	benzene	1.5	39	60	0	1
4	0	benzene	2/3	44	49	0	7

a) Reactions were carried out in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%) under reflux.

b) Determined by gas chromatography.

closure [15] but also brought about the results which are opposite to the general site-selectivity [24] in the known reaction of allyl alcohol derivatives with nucleophiles catalyzed by palladium(0) species. Unfortunately, product-selectivity for 35a was too low to be satisfied and further examination of reaction conditions had to be done.

2-2-3 Further Investigations by using 33a

Solvent Effect

To find out the optimum conditions, the cyclization of 33a was examined in various solvents by use of palladium(II) acetate and triphenylphosphine. Table 2-2 shows the results of the solvent effect. At first THF was used (Run 1), but longer reaction time and the even worse selectivity for 35a were observed as cmopared with the use of dioxane as solvent (Table 2-1). Acetone resulted in giving somewhat better

Table 2-2 Solvent Effect

Run[a]	Solvent	Time (h)	Product Ratio (%)[b]		
			35a	36a	others
1	THF	8	37	57	6
2	acetone	2.5	60	27	13
3	CH_3CN	1	87 (59)[c]	13	0

a) Reactions were carried out in refluxing solvents by using $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%).

b) Determined by gas chromatography.

c) Isolated yield.

product ratio (Run 2). Finally, the most favorable results were obtained by use of acetonitrile, in which the reaction was completed within 1 h and 35a was easily isolated in 59% yield by column chromatography on silica gel (Run 3). None of the O-alkylated products 37a or 38a was determined throughout the experiments.

Ligand Effect

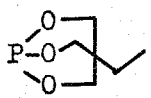
Then ligand effect was examined mainly in acetonitrile and the details are tabulated in Table 2-3. In comparison with triphenylphosphine (Run 1), monodentate ligands such as tributylphosphine (Run 2) and diphenyl-o-tolylphosphine (Run 3) gave inferior results. When the bidentate ligand, DIPHOS, was employed (Run 4), the reaction took a longer time. Subsequently the reaction was examined in the presence

Table 2-3 Ligand Effect

Run[a]	Ligand	Solvent	Time (h)	Product Ratio[b] 35a	36a	37a	others
1	PPh_3	CH_3CN	1	87	13	0	0
2	$P(n\text{-}Bu)_3$	CH_3CN	1	85	15	0	0
3	$PPh_2(o\text{-}Tol)$	CH_3CN	8	78	21	0	1
4	DIPHOS	CH_3CN	12	76	12	0	12
5	$P(OPh)_3$	CH_3CN	8	0	0	100	0
6	$P(OPh)_3$	AcOEt	8	0	0	100	0
7	c	CH_3CN	3	16	1	83	0
8	c	benzene	7	4	1	95	0
9	c	acetone	1	0	0	100 (66)[d]	0

a) Reactions were carried out in refluxing solvents by using various ligands (20 mol%) and $Pd(OAc)_2$ (5 mol%).

b) Determined by gas chromatography.

c) 

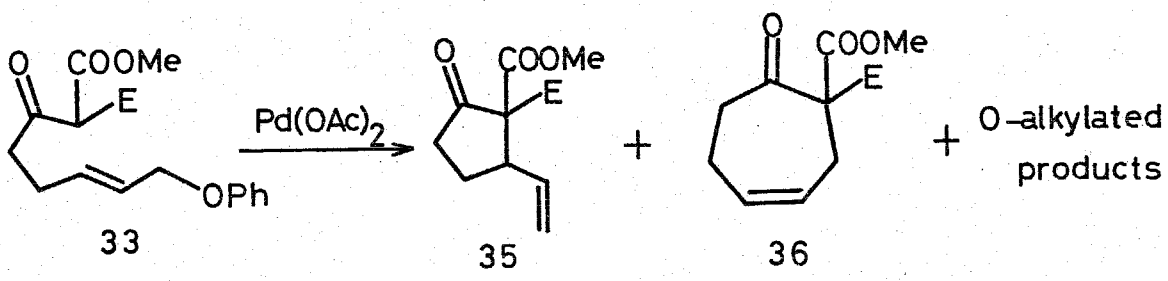
d) Isolated yield.

of phosphites as ligands (Run 5-9). Unfortunately, the O-alkylated product 37a was selectively obtained and isolated in 66% yield by silica gel chromatography. The structure of the O-alkylated product 37a was confirmed by the Claisen rearrangement to give 36a (43% yield) at 195°C. In conclusion, the selectivity for 35a could not be raised by alternating ligands. After all , the combination of $Pd(OAc)_2$-PPh_3-CH_3CN was the

best choice for cyclization of 33a affording 35a (Table 2-2, Run 3).

2-2-4 Cyclization of Substituted β-Keto Esters

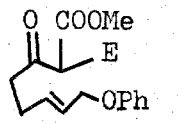
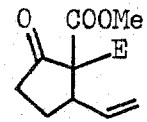
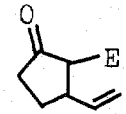
Since the investigation on cyclization of the parent β-keto ester 33a had been finished, the author turned his attention to the cyclization of the substituted β-keto esters 33, which also possess the possibility to produce four isomers, 35, 36, 37, 38 (Scheme 2-2). Reactions were carried out in the presence of palladium(II) acetate and triphenylphosphine as catalyst under refluxing acetonitrile except for Run 4,7,8 where propionitrile was used as solvent (Table 2-4).



33 35 36

At first, 33b was subjected to the cyclization and the product-ratio was analyzed by gas chromatography (Run 2). Surprisingly, the desired cyclopentanone 35b was obtained with the higher selectivity than the case of 33a (Run 1). After chromatography on silica gel, 35b was isolated in 72% yeild. A number of substituted β-keto esters 33c-33j were examined and the desired cyclopentanones 35c-35j were also isolated in high yield, respectively. Noteworthy are that various functional groups attached in substituents of β-keto esters 33 were intact during the cyclization and that no troublesome side reactions such as the retro-Dieckmann reaction took place because the cyclization conditions were almost neutral and so mild.

Table 2-4

Run	Electrophile	E	Yield (%)[a] of 33 from 33a	 33	Cyclization[b] Time (h)	Ratio 35:36	Yield[a] 35	 35	yield (%)[a] of 18 from 35	 18
1		H	-	33a	1	87:13	59	35a		18a
2		Me	c	33b	1/4	95:5	72	35b		18b
3	$Br(CH_2)_2Ph$	$(CH_2)_2Ph$	56	33c	1/4		78	35c		18c
4	$Br(CH_2)_5H$	$(CH_2)_5H$	83	33d	3		87	35d	88	18d
5		$CH_2CH=CH_2$	d	33e	1		88	35e	68	18e
6	$ClCH_2C(Me)=CH_2$	$CH_2C(Me)=CH_2$	75	33f	1		88	35f	86	18f
7		(Z)-$CH_2CH=CHEt$	e	33g	2		79	35g	67	18g
8	$ClCH_2C\equiv CEt$	$CH_2C\equiv CEt$	68	33h	1.5		74	35h	87	18h
9	$CH_2=CHCOMe$	$(CH_2)_2COMe$	74	33i	1.5		91	35i	68	18i
10	$CH_2=CHCOOMe$	$(CH_2)_2COOMe$	68	33j	1		99	35j	90	18j

a) Isolated yield.

b) Acetonitrile was used as solvent except for Run 4,7,8 where propionitrile was used.

c) Prepared from methyl 2-methyl-3-oxobutanoate and 1-chloro-4-phenoxy-2-butene in 38% yield.

d) Prepared from methyl 2-allyl-3-oxobutanoate and 1-chloro-4-phenoxy-2-butene in 38% yield.

e) Prepared from 33h by hydrogenation in 83% yield.

2-2-5 Merit of the Palladium-Catalyzed Cyclization

After the optimum conditions for the present cyclization were found out, it seems appropriate to compare briefly the new method with conventional methods with respect to the accessibility to 2,3-disubstituted cyclopentanones. As mentioned in the introduction, the most direct access to 2,3-disubstituted cyclopentanones 4 is the 1,4-addition of carbanions R^- to the enones 8 coupled with the reaction of thus generated enolate anions 9 with certain electrophiles E. Table 2-5 lists some reported results. This method, however, has some limitations. Only very reactive electrophiles can participate in the reactions successfully. Less reactive halides results in giving rise to a mixture of regioisomers 4 and 5 and vinyl ketones such as methyl vinyl

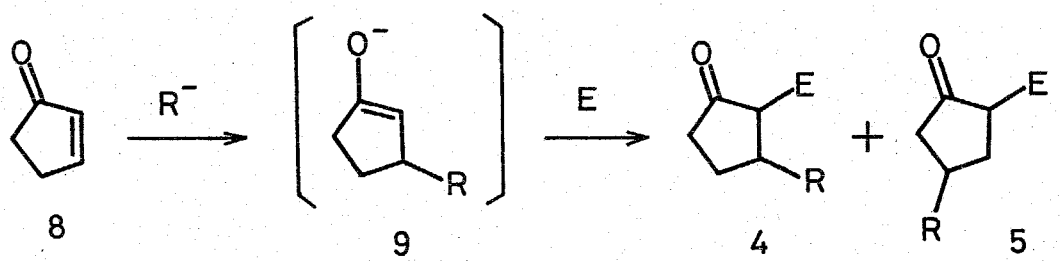


Table 2-5 Reported Results of the Synthesis of 2,3-Disubstituted Cyclopentanones 4 from 8.

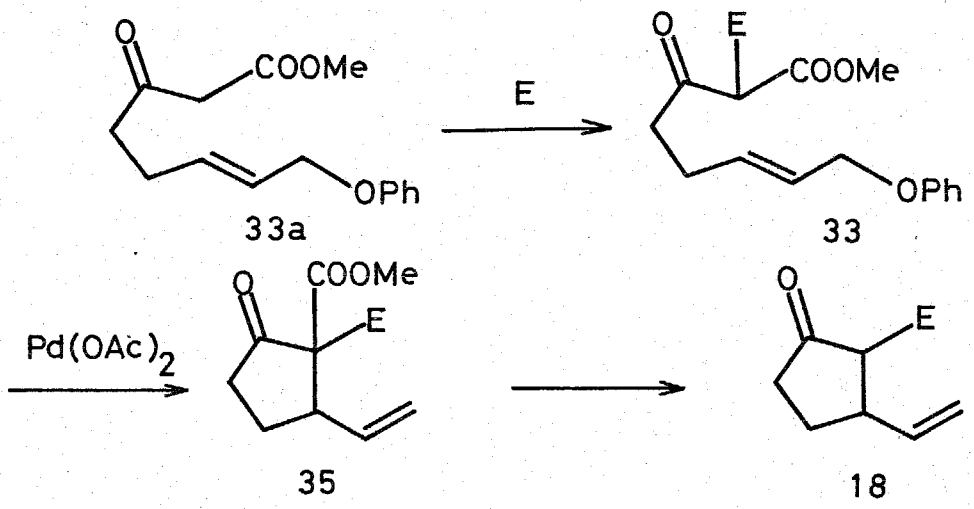
Ref.	Reagent for R^-	Electrophile	Products (Yield, %) 4	5	others
11a	$LiCu(Me)CH{=}CH_2$	$BrCH_2CH{=}CH_2$	72	0.5	
11a	$LiCu(Me)CH{=}CH_2$	$ICH_2CH{=}CHMe$	34	12	24
11a	$LiCu(Me)CH{=}CH_2$	BuI	31	8	40
11h	$LiCu(CH_2CH{=}CH_2)_2$	$ICH_2C{\equiv}CEt$	60		

ketone [12] and methyl acrylate [11e] could not afford the desired products 4. On the other hand, the new method consists of the following three steps:

(1) Preparation of the substituted β-keto esters 33 from 33a with a wide variety of electrophiles E.

(2) The new palladium-catalyzed cyclization of 33 to give 35.

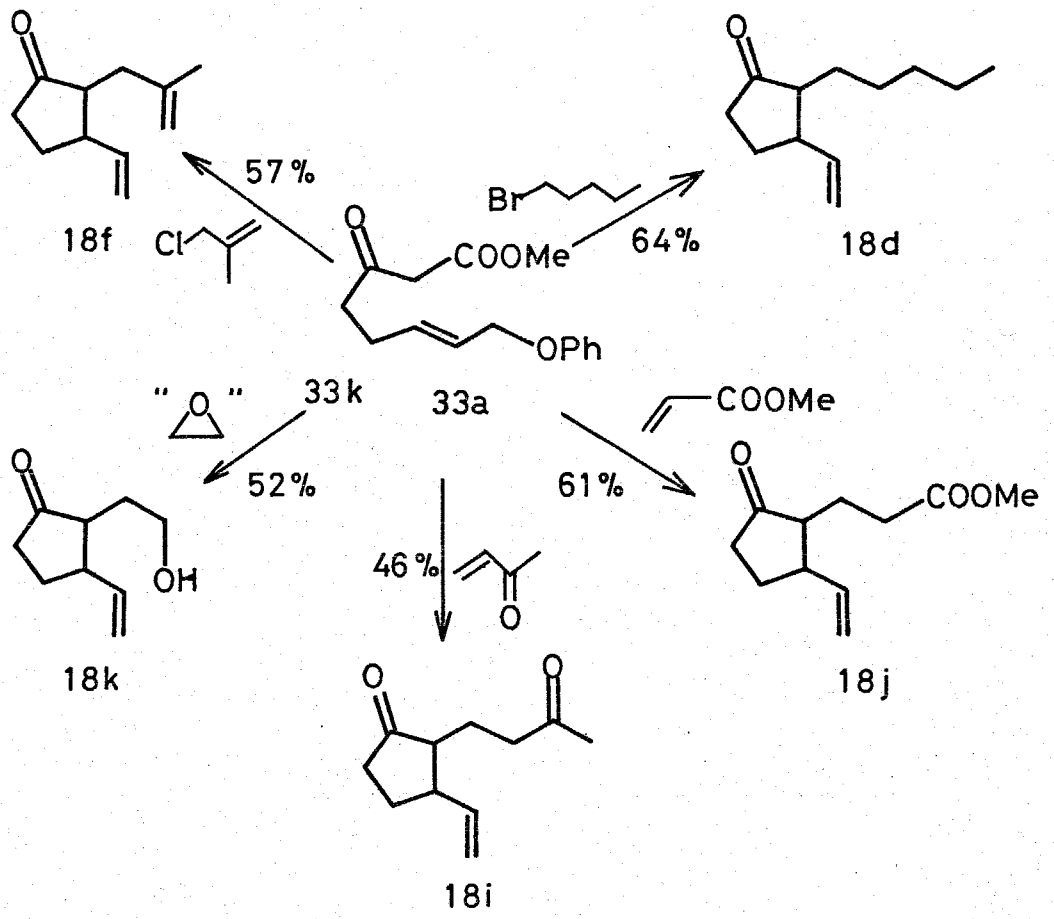
(3) Sodium iodide-mediated demethoxycarbonylation of the cyclopentanones 35 affording 18.



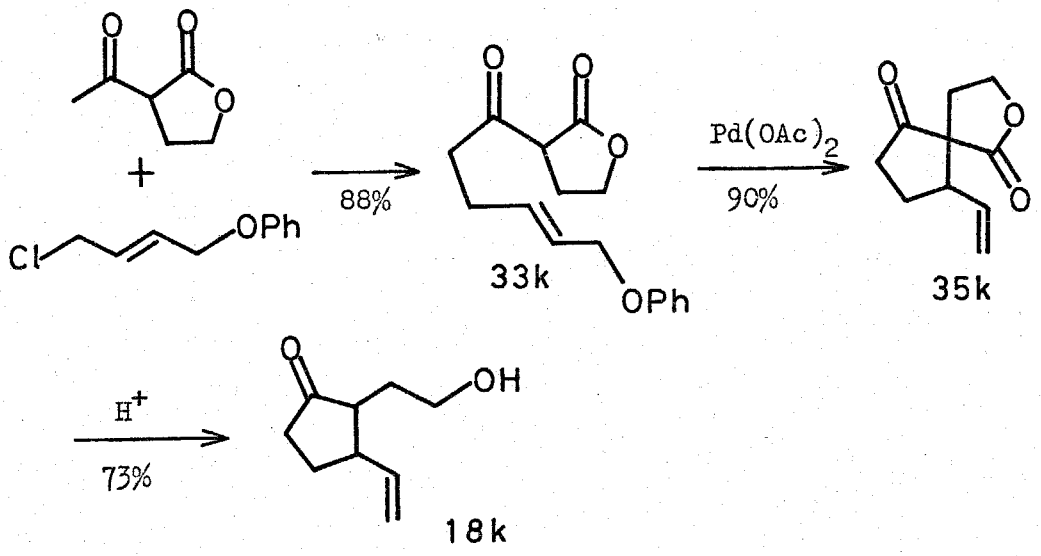
33a 33 35 18

The results are illustrated in Scheme 2-3 and the yiled of each step is recorded also in Table 2-4. When reactive halides were employed, the final products 18 such as 18e and 18f were obtained in rather low yields since the selective preparation of the mono-substituted β-keto esters was difficult. In these cases, the direct method [10,11] (8 ⟶ 9 ⟶ 4) would be of use. However, when the less reactive halide, pentyl bromide, was used, the new method recorded a better result (overall yield of 18d, 64%) (Table 2-4, Run 4). It is emphasized that the new

Scheme 2-3



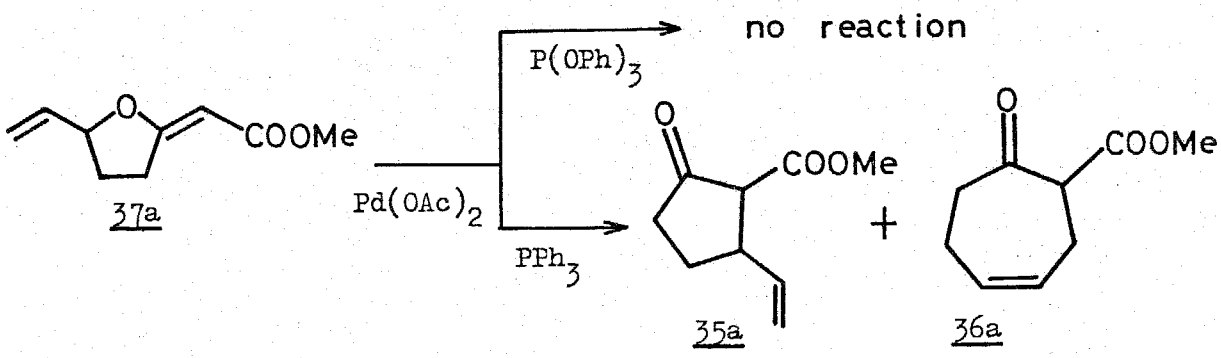
palladium-catalyzed reaction contributes to the synthesis of 18i and 18j (Table 2-4, Run 9, 10) which are hardly accessible by the direct method (8 ⟶ 4) or which may be synthesized by tedious sequences of reactions. Moreover, the epoxide-coupled product 18k could be synthesized too from the commercially available α-acetylbutyrolactone based on this methodology via 33k.



2-2-6 Consideration of the Reaction Path(s)

Further Experiments

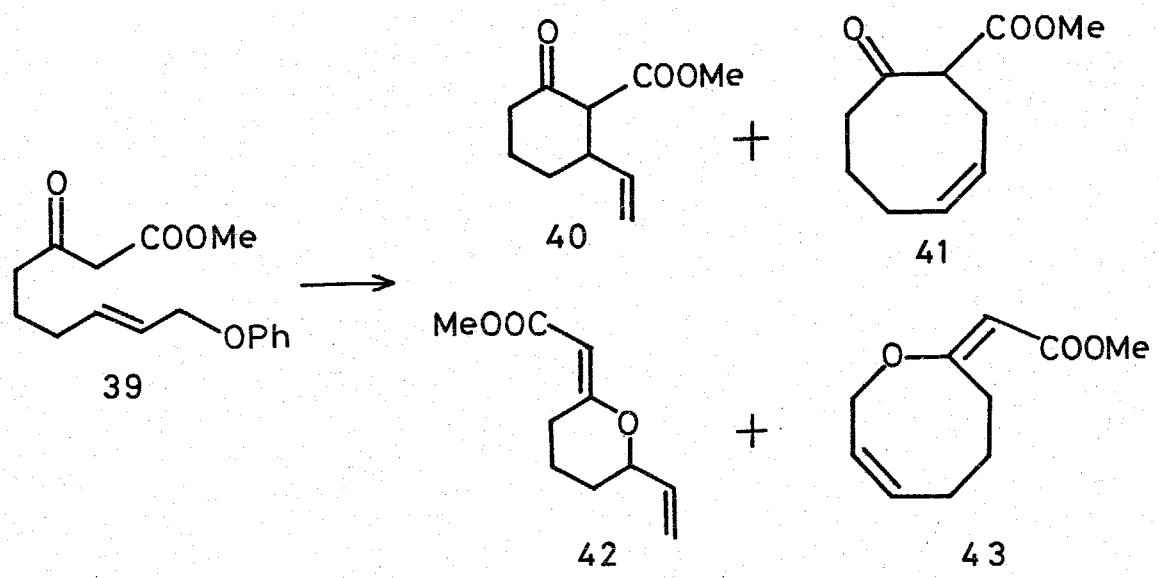
When diphenyl-o-tolylphosphine and DIPHOS were used as ligands in the cyclization of 33a (Table 2-3, Run 3,4), the O-alkylated product 37a was detected as an initial product on TLC, which was then slowly rearranged to give 35a and 36a during the reaction. To confirm this, the O-alkylated product 37a which was obtained selectively by using triphenylphosphite (Table 2-3, Run 9) was again subjected to the cyclization with palladium(II) acetate and triphenylphosphine. The rearrangement did occur and the ratios of 35a and 36a were 87:13 in acetonitrile (1 h)



CH_3CN	87	:	13
benzene	45	:	55

and 45:55 in benzene (40 min). These results suggest the presence of the rapid equilibrium between 34a and 37a.

Meanwhile, methyl 3-oxo-9-phenoxy-7-nonenoate (39) was synthesized (vide infra) to compare the reactivity of 39 with that of 33. In this case too, there is the possibility to produce four isomers, 40, 41, 42, and 43 from 39. The β-keto ester 39 was subjected to the



cyclization catalyzed by palladium(II) acetate (5 mol%) plus various ligands (20 mol%) in refluxing solvents. Some results are given in Table 2-6. It is noteworthy that the only cyclohexanone 40 was detected with high selectivity by gas chromatography even if phosphites were used as ligands. The results mean that there is another reaction path to 40 different from the path(s) to 35 and 36. Starting material 39 was synthesized from the butadiene telomer 44 [37] by way of 45.

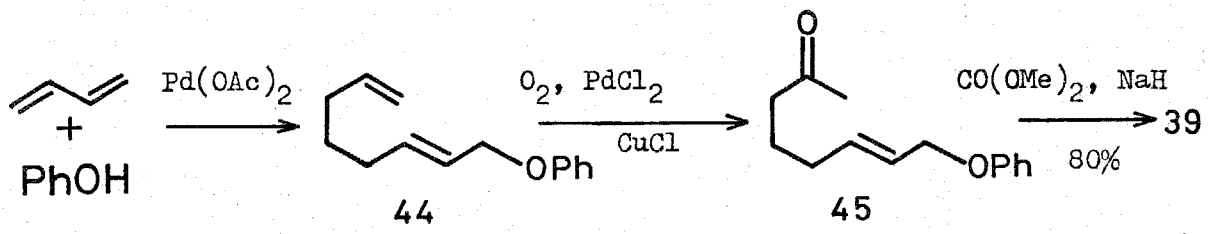
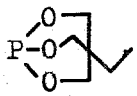


Table 2-6 Cyclization of 39

Run[a]	Ligand	Solvent	Time (h)	Product Ratio[b] 40	Others
1	PPh_3	benzene	1	88 (62)[c]	12
2	DIPHOS	benzene	1	91	9
3		benzene	1	89	11
4	PPh_3	dioxane	1.5	89	11
5	PPh_3	MeCN	1	88	12

a) Reactions were carried out by using palladium(II) acetate (5 mol%) and ligands (20 mol%) in refluxing solvents.

b) Determined by gas chromatography.

c) Isolated yield.

The new cyclization possesses following features.

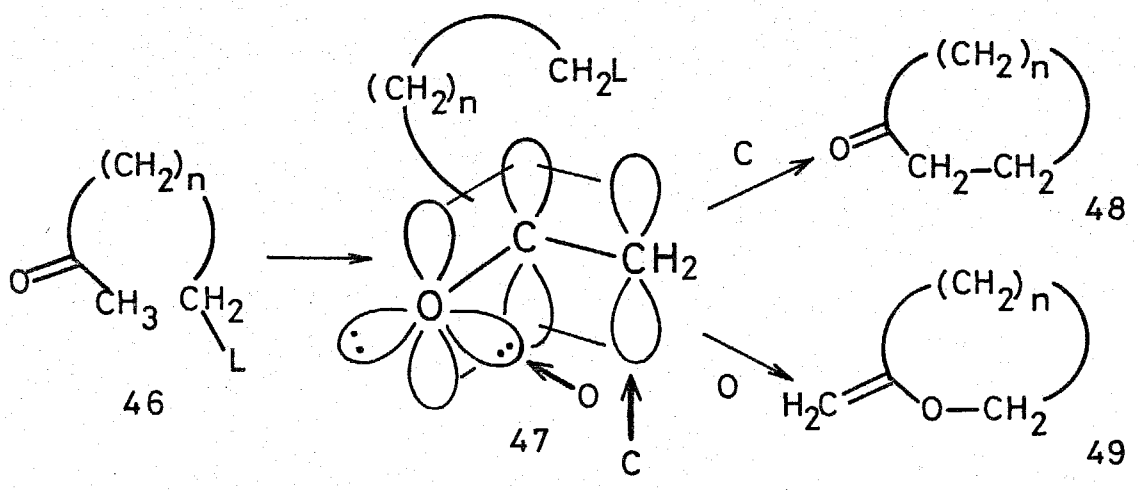
(1) The ratio of 35 and 36 was determined by solvents and substituents in 33 (Table 2-2, 2-4).

(2) Phosphine promoted the rearrangement of 37 to give a mixture of 35 and 36, the ratios of which were almost equal to those directly obtained from 33.

(3) The O-alkylated product 37 was selectively obtained by use of phosphites as ligands (Table 2-3).

(4) In the cyclohexanone synthesis, only 40 was produced independent of solvents and ligands (Table 2-5).

There is the established rule for ring closure, the Baldwin's rule,[15] where all 5-Endo-Trig reactions are "disfavored" and 6-Endo-Trig reactions are favored. This rule stems from stereoelectronic requirements. Namely, as claimed by House [16] too, the production of 48 requires approach of the electrophiles perpendicular to the plane of the enolate part of 47, whereas the oxygen-alkylation tolerates another approach in the place of the enolate. Consequently in the five-membered ring formation, the approach of the alkylating center to the carbon site of the enolate is sterically difficult, compared with its approach in the plane to the oxygen site of enolate, yielding the enol ether product 49 (n = 2). On the other hand, kinetically controlled carbon alkylation is sterically possible in the case of a six-membered ketone synthesis, affording preferentially the C-alkylated product 48 (n = 3). This stereoelectronic factors can not be ignored in the present palladium-catalyzed cyclization, which is conceivably a classical S_N2' displacement



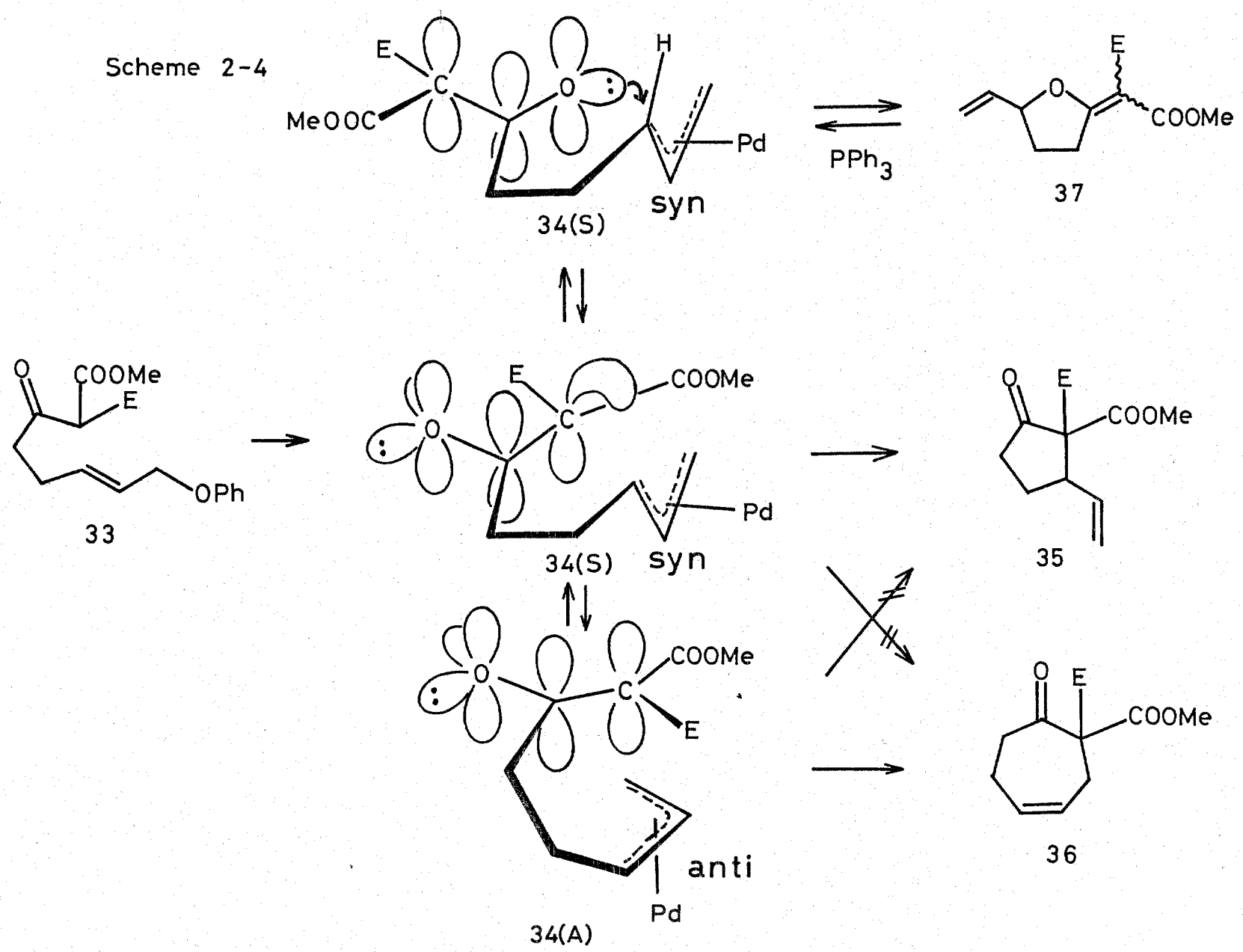
on the π-allyl moiety with the palladium species serving as a leaving group. Considering above requirements as well as the phosphine-mediated rearrangement of 37, the author reached the following conclusions (Scheme 2-4).

Initially, 33 is converted with palladium(0) species to the stable syn π-allylpalladium intermediate 34(s), which undergoes an attack of the oxygen atom of the enol (or enolate anion ?) moiety to give 37 as an initial product. There exists, however, a rapid equilibrium between 37 and the intermediate 34, where only phosphine-ligands can participate. Then 34 reacts slowly again under kinetically controlled conditions producing either 35 or 36. There is another equilibrium between the intermediate 34(s) and the less stable anti intermediate 34(a). The former affords the only desired product 35, whereas 34(A) favors the formation of the cycloheptenone 36 (cf. Ref. 19). Therefore from the results, the presence of a substituent in 33 and use of acetonitrile as solvent may well interfere with the second equilibrium, 34(S)⇌34(A), giving rise to a preferential formation of 35.

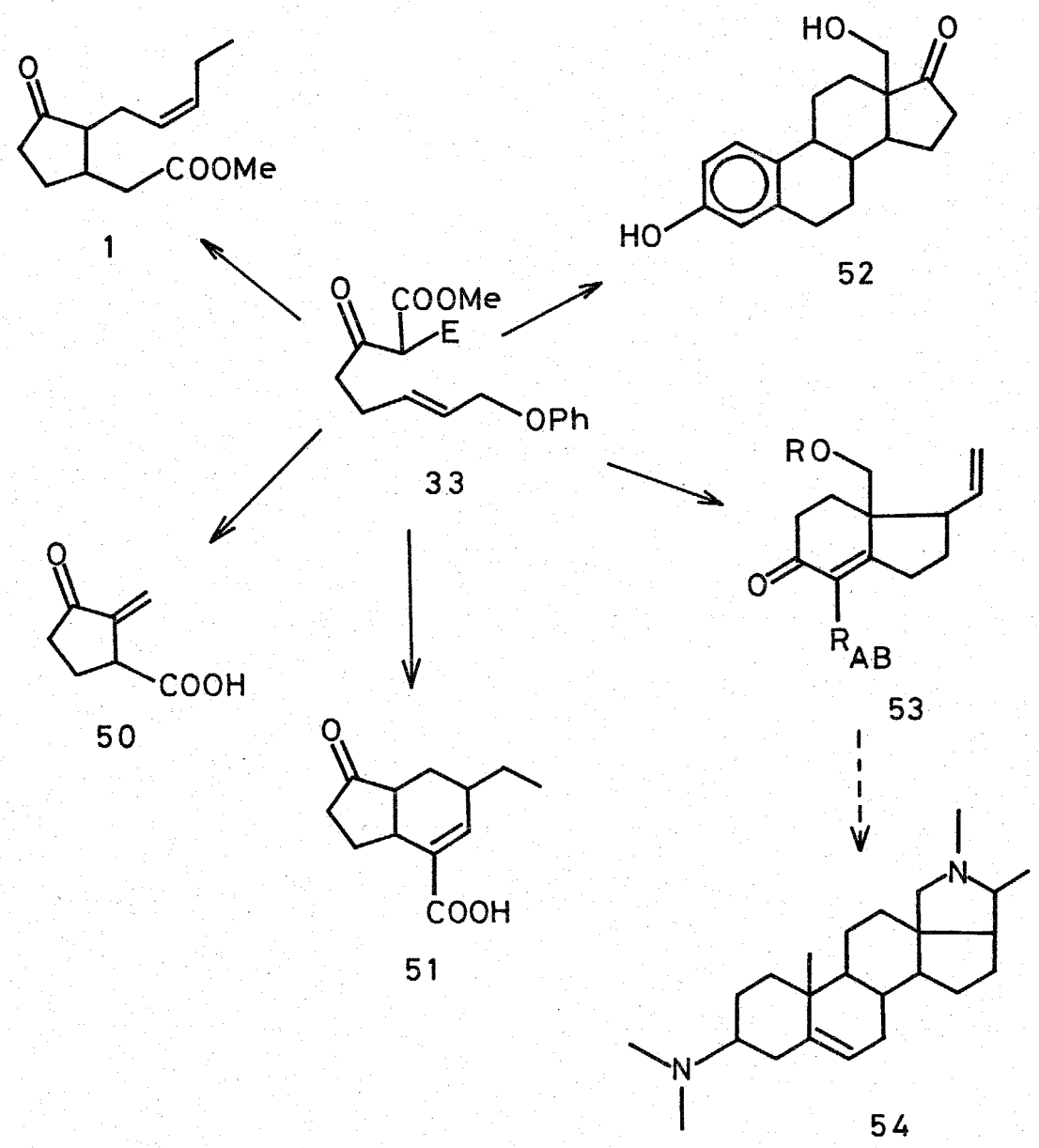
2-2-7 Conclusion and Prospect

The new methodology for the synthesis of 2,3-disubstituted cyclopentanones was successfully developed and the utility of this method was demonstrated by the synthesis of some cyclopentanones which were hitherto not selectively or easily prepared. Moreover the new cyclization could be successfully featured by the syntheses of methyl jasmonate (1),

Scheme 2-4



sarkomycin (50), coronafacic acid (51), 18-hydroxyestrone (52), and the indenones 53 which are regarded as important key intermediates for a synthesis of 18-functionalized steroids such as conessine (54).



2-3 Experimental

(E)-1-Chloro-4-phenoxy-2-butene

A mixture of potassium carbonate (45.0 g, 0.325 mol), phenol (30.6 g, 0.325 mol), and (E)-1,4-dichloro-2-butene (81.3 g, 0.650 mol) in dry acetone (300 ml) was refluxed under nitrogen for 36 h. The cooled reaction mixture was filtered free from the insoluble materials and the filtrate was concentrated in vacuo. The residue was distilled to afford (E)-1-chloro-4-phenoxy-2-butene (42.9 g, 72.3% yield).

Bp. 95-100°C (3 mmHg);

IR (neat) 1600, 1591, 1494, 1241, 755, 693 cm^{-1};

NMR (CCl_4) δ 3.38-4.05 (m, 2H, CH_2Cl), 4.31-4.50 (m, 2H, CH_2O), 5.71-5.97 (m,2H, CH=CH), 6.58-7.32 (m, 5H, aromatic).

Methyl (E)-3-Oxo-8-phenoxy-6-octenoate (33a)

Dianion of methyl acetoacetate was prepared according to Weiler's procedure from methyl acetoacetate (2.00 ml, 18.6 mmol), sodium hydride (50% mineral oil, 988 mg, 20.5 mmol), and butyllithium (1.66 M solution in hexane, 11.8 ml, 19.6 mmol) in dry THF (50 ml) at 0°C. To the solution, HMPA (6.5 ml, 37 mmol) was added and then (E)-1-chloro-4-phenoxy-2-butene (5.06 g, 27.7 mmol) dropwise. The mixture was stirred at 0°C for 0.5 h and at room temperature for 3.5 h. Then the reaction mixture was acidified by careful addition of 3N hydrochloric acid. After the evaporation of the THF, the residue was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Column chromatographic purifica-

tion of the residue on silica gel by use of benzene-hexane-ethyl acetate, 26:13:1, gave 33a (4.07 g, 83.5% yield).

Bp. 136-141°C (0.006 mmHg);

IR (neat) 1745 (C=O), 1721 (C=O), 1601, 1585, 1242, 761, 697 cm^{-1};

NMR (CCl_4) δ 2.00-2.85 (m, 4H, $(CH_2)_2CO$), 3.26 (s, 2H, $COCH_2CO$), 3.62 (s, 3H, CH_3O), 4.25-4.44 (m, 2H, CH_2O), 5.51-5.78 (m, 2H, CH=CH), 6.55-7.32 (m, 5H, aromatic).

Methyl (E)-2-Methyl-3-oxo-8-phenoxy-6-octenoate (33b)

Dianion in THF (90 ml) prepared from methyl 2-methyl-3-oxobutanoate (2.00 ml, 16.6 mmol) with sodium hydride (50% mineral oil, 1.1 g, 23 mmol) and butyllithium in hexane (1.64 M, 11.2 ml, 18 mmol) was reacted with (E)-1-chloro-4-phenoxy-2-butene at room temperature for 4.5 h. After a similar work-up as described for the preparation of 33a, 33b was obtained in 38.2% yield (1.75 g).

IR (neat) 1745 (C=O), 1716 (C=O), 1600, 1587, 1496, 1240, 756, 692 cm^{-1};

NMR (CCl_4) δ 1.23 (t, J = 7 Hz, 3H, CH_3), 1.93-2.72 (m, 4H, CH_2CH_2CO), 3.31 (q, J = 7 Hz, 1H, CH), 3.59 (s, 3H, OCH_3), 4.18-4.42 (m, 2H, CH_2OPh), 5.48-5.74 (m, 2H, CH=CH), 6.52-7.28 (m, 5H, aromatic).

Methyl (E)-3-Oxo-8-phenoxy-2-(2-phenylethyl)-6-octenoate (33c)

A mixture of the β-keto ester 33a (624 mg, 2.38 mmol), 1-bromo-2-phenylethane (354 μl, 2.62 mmol), potassium carbonate (1.32 g, 9.52 mmol), and potassium iodide (593 mg, 3.57 mmol) in acetone (20 ml) was heated under reflux for 6.5 h. The reaction mixture was filtered free from the insoluble materials and the filtrate was concentrated in vacuo.

Column chromatography of the residue on silica gel with hexane-ether, 15:1, gave 33c (491 mg, 56.4% yield).

IR (neat) 1745 (C=O), 1716 (C=O), 1600, 1585, 1241, 1033, 756, 680 cm^{-1}; NMR (CCl_4) δ 1.73-2.68 (m, 8H, CH_2CH_2CO, CH_2CH_2Ph), 3.26 (t, J = 7 Hz, 1H, CH), 3.51 (s, 3H, CH_3O), 4.13-4.36 (m, 2H, CH_2OPh), 5.43-5.79 (m, 2H, CH=CH), 6.44-7.28 (m, 5H, aromatic).

Methyl (E)-3-Oxo-2-pentyl-8-phenoxy-6-octenoate (33d)

See Chapter 3.

Methyl (E)-2-Allyl-3-oxo-8-phenoxy-6-octenoate (33e)

Dianion in THF (30 ml) prepared from methyl 2-allyl-3-oxobutanoate (1.56 g, 10 mmol) with sodium hydride (50% mineral oil, 528 mg, 11 mmol) and butyllithium in hexane (1.65 M, 6.40 ml, 10.6 mmol) was reacted with (E)-1-chloro-4-phenoxy-2-butene at room temperature for 7 h to give the product 33e (1.13 g, 37.7% yield).

Bp. 139-143°C (0.008 mmHg);

IR (neat) 1742, 1713, 1642, 1601, 1584, 1494, 1243, 1174, 753, 693 cm^{-1}; NMR (CCl_4) δ 2.06-2.78 (m, 6H, $(CH_2)_2$, CH_2), 3.42 (t, J = 7 Hz, 1H, CH), 3.63 (s, 3H, CH_3), 4.28-4.47 (m, 2H, CH_2O), 4.81-6.07 (m, 5H, CH=CH, $CH=CH_2$), 6.66-7.39 (m, 5H, aromatic).

Methyl (E)-2-(2-Methyl-2-propenyl)-3-oxo-8-phenoxy-6-octenoate (33f)

A mixture of the β-keto ester 33a (1.59 g, 6.07 mmol), methallyl chloride (770 μl, 7.9 mmol) and potassium carbonate (1.68 g, 12.1 mmol) in

acetone (23 ml) was refluxed for 46 h and cooled to room temperature. The insoluble materials were filtered and the filtrate was concentrated in vacuo to leave an oil, which was chromatographed to give 33f (1.43 g, 74.6% yield).

Bp. 145-148°C (0.03 mmHg);

IR (neat) 1741, 1711, 1644, 1598, 1583, 1492, 1239, 1172, 1030, 1010, 972, 892, 755, 691 cm^{-1};

NMR (CCl_4) δ 1.68 (br s, 3H, CH_3), 2.03-2.77 (m, 6H, $(CH_2)_2$, CH_2), 3.57 (t, J = 8 Hz, 1H, CH), 3.60 (s, 3H, CH_3O), 4.27-4.46 (m, 2H, CH_2-OPh), 4.54-4.80 (m, 2H, CH_2=C), 5.58-5.83 (m, 2H, CH=CHO, 6.62-7.39 (m, 5H, aromatic).

Methyl (E)-3-Oxo-2-((Z)-2-pentenyl)-8-phenoxy-6-octenoate (33g)

See Chapter 3.

Methyl (E)-3-Oxo-2-(2-pentynyl)-8-phenoxy-6-octenoate (33h)

As above

Dimethyl 2-((E)-2-Oxo-6-phenoxy-4-hexenyl)-1,5-pentanedioate (33i)

See Chapter 5.

Methyl (E)-3-Oxo-2-(3-oxobutyl)-8-phenoxy-6-octenoate (33j)

See Chapter 7.

Preparation of the Authentic Sample of Methyl 2-Oxo-5-cycloheptene-1-carboxylate (36a)

4-Cyclohepten-1-ol (IV) was prepared starting from cyclopentanone

pyrolidine enamine (I) according to the published procedure.[32-35] To a solution of pyridine(2.3 ml, 28 mmol) in dichloromethane (6 ml) was added chromium(VI) oxide (1.39 g, 14 mmol) in one portion at room temperature. After 15 min of stirring, the alcohol IV (262 mg, 2.34 mmol) in dichloromethane (2 ml) was added to the mixture and the resulting mixture was stirred further for 20 min. Ether was added to the mixture and the solution was decanted. The ethereal solution was washed with 3N hydrochloric acid, saturated aqueous sodium bicarbonate, and then brine, and dried over magnesium sulfate. Removal of the solvent *in vacuo* afforded 4-cyclohepten-1-one (V) (IR (neat) 1707 (C=O), 1202 cm^{-1}; NMR (CCl_4) δ 2.06-2.74 (m, 8H, $(CH_2)_2CO(CH_2)_2$), 5.57-5.73 (m, 2H, CH=CH)).

To a suspension of sodium hydride (50% mineral oil, 257 mg, 5.35 mmol) in dimethyl carbonate (4 ml) was added the above ketone V dissolved in dimethyl carbonate (2 ml). Stirring was continued at room temperature for 36 h. The reaction was quenched by careful addition of acetic acid. The mixture was poured into saturated aqueous sodium bicarbonate, and the product was extracted with ether. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel to give 36a (99 mg, 25.2% yield).

Bp. 65-70°C (2 mmHg);

IR (neat) 1736 (C=O), 1702 (C=O), 1645, 1612, 1307, 1258, 1214, 1159, 1020 cm^{-1};

NMR (CCl_4) δ 1.70-3.00 (m, 6H, $(CH_2)_2COCHCH_2$), 3.54 (s, 3H, CH_3O), 3.40-3.82 and 12.55 (m, 1H, COCHCO, keto and enol form), 5.27-5.70 (m, 2H, CH=CH).

Cyclization of the β-Keto Ester 33a

A mixrure of the β-keto ester 33a (about 1 mmol), palladium(II) acetate (5-10 mol%), ligand (20-40 mmol%) and triethylamine (1 equiv. to 33a) if necessary in a solvent (5 ml) was heated under reflux for an appropriate time under nitrogen and then cooled to room temperature. The mixture was passed through a short silica gel column with ether. The filtrate was concentrated in vacuo leaving an oil, which was injected to gas chromatography and the ratio of products was determined by calculation of peak area (Table 2-1, 2-2, 2-3). On the other hand, purification of the residual oil by silica gel column chromatography afforded the pure products 35a, 36a, and 37a.

Methyl 2-Oxo-5-vinylcyclopentanecarboxylate (35a)

Bp. 65-70°C (2 mmHg);

IR (neat) 1756 (C=O), 1722 (C=O), 1647 (C=C), 1279, 1204, 1178, 997, 922, 792, 760 cm^{-1};

NMR (CCl_4) δ 1.10-2.70 (m, 5H, $CH(CH_2)_2CO$), 2.74-3.30 (m, 1H, COCHCO), 3.62 (s, 3H, CH_3O), 4.79-5.18 (m, 2H, $\underline{CH}_2$=CH), 5.36-6.00 (m, 1H, $\underline{CH}$=CH_2).

Methyl 2-Oxo-5-cycloheptenecarboxylate (36a)

The IR and NMR spectra of 36a obtained by the palladium-catalyzed cyclization were identical in all respects with those of 36a synthesized from cyclopentanone pyrolidine enamine (vide supra).

2-Methoxycarbonylmethylidene-5-vinyltetrahydrofuran (37a):

(neat) 1701 (C=O), 1639 (enol ether C=C), 1113, 1041, 968, 937, 878, 822 cm^{-1};

NMR (CCl_4) δ 1.40-3.36 (m, 4H, $(CH_2)_2$), 3.57 (s, 3H, CH_3O), 4.53-4.97 (m, 1H, CHO), 5.01-5.45 (m, 3H, CH=C, $C\underline{H}_2$=CH), 5.58-6.20 (m, 1H, $C\underline{H}$=CH_2).

The Claisen Rearrangement of 37a

The ester 37a (83 mg, 0.49 mmol) dissolved in 1-methyl-2-pyrrolidone (1 ml) was heated at 190-195°C for 30 h and then cooled to room temperature. The mixture was poured into 3N hydrochloric acid and the product was extracted with dichloromethane. The extract was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* leaving an oil, which was chromatographed on silica gel to give the cycloheptenone 36a (36 mg, 43% yield). The IR and NMR spectra of 36a were identical in all respects with those of an authentic sample (*vide supra*).

Methyl 1-Methyl-2-oxo-5-vinylcyclopentanecarboxylate (35b)

Cyclization of 33b (285 mg, 1.03 mmol) in acetonitrile (1 ml), containing palladium(II) acetate (23 mg, 0.10 mmol) and triphenylphosphine (94 mg, 0.36 mmol) was carried out according to the procedure described for the preparation of 35a. After chromatography on silica gel,,35b was isolated in 72.4% yield (136 mg).

IR (neat) 1752 (C=O), 1730 (C=O), 1638 (C=C), 1233, 1162, 994, 921 cm^{-1};

NMR (CCl_4) δ 1.04 and 1.19 (2s, 3H, CH_3), 1.63-2.79 (m, 5H, $CH(CH_2)_2CO$), 3.52 and 3.59 (2s, 3H, CH_3O), 4.79-5.23 (m, 2H, $C\underline{H}_2$=CH), 5.34-6.07 (m, 1H, $C\underline{H}$=CH_2).

Methyl 2-Oxo-1-(2-phenylethyl)-5-vinylcyclopentanecarboxylate (35c)

The ester 33c (201 mg, 0.549 mmol) was cyclized in refluxing acetonitrile (5 ml) containing palladium(II) acetate (12 mg, 0.055mmol) and triphenylphosphine (50 mg, 0.19 mmol). After 15 min of reflux, the cyclopentanone 35c was produced in 78.4% yield (117 mg)

IR (neat) 1746 (C=O), 1729 (C=O), 1638 (C=C), 1601, 1226, 1167, 920, 752, 700 cm^{-1};

NMR (CCl_4) δ 1.53-2.93 (m, 9H,$(CH_2)_2CH$,$(CH_2)_2Ph$), 3.54 and 3.62 (2s, 3H, CH_3O), 4.83-5.28 (m, 2H, $C\underline{H}_2$ =CH), 5.40-6.04 (m, 1H , $C\underline{H}$=CH_2), 7.03 (br s, 5H, aromatic).

Methyl 2-Oxo-1-pentyl-5-vinylcyclopentanecarboxylate (35d)

See Chapter 3.

Methyl 1-Allyl-2-oxo-5-vinylcyclopentanecarboxylate (35e)

A mixture of 33e (677 mg, 2.24 mmol), palladium(II) acetate (25 mg, 0.11 mmol), and triphenylphosphine (118 mg, 0.448 mmol) in acetonitrile (10 ml) was refluxed for 1 h to give 35e (409 mg, 87.7% yield).

IR (neat) 1733, 1641, 1221, 1168, 996, 910, 680 cm^{-1};

NMR (CCl_4) δ 1.58-3.14 (m, 7H, $(CH_2)_2CH$, CH_2), 3.62 and 3.67 (2s, total 3H, CH_3O), 4.81-6.22 (m, 6H, $2CH=CH_2$).

Methyl 2-Oxo-1-(2-methyl-2-propenyl)-5-vinylcyclopentanecarboxylate (35f)

A mixture of 33f (1.05 g, 3.32 mmol), palladium(II) acetate (19 mg, 0.083 mmol), and triphenylphosphine (87 mg, 0.332 mmol) dissolved in acetonitrile (20 ml) was refluxed for 1 h to give 35f (633 mg, 85.8% yield).

IR (neat) 1727, 1640, 1214, 1172 cm^{-1};

NMR (CCl_4) δ 1.57 and 1.66 (2br s, total 3H, CH_3), 1.73-3.07 (m, 7H, $(CH_2)_2CH$, CH_2), 3.59 and 3.61 (2s, total 3H, CH_3O), 4.51-6.07 (m, 5H, $CH_2=C$, $CH=CH_2$).

Methyl 2-Oxo-1-((Z)-2-pentenyl)-5-vinylcyclopentanecarboxylate (35g)

See Chapter 3.

Methyl 2-Oxo-1-(2-pentynyl)-5-vinylcyclopentanecarboxylate (35h)

As above

Methyl 2-Oxo-1-(3-oxobutyl)-5-vinylcyclopentanecarboxylate (35i)

See Chapter 5.

Methyl 3-(1-Methoxycarbonyl-2-oxo-5-vinylcyclopentane)propionate (35j)

See Chapter 5.

2-Pentyl-3-vinylcyclopentan-1-one (18d)

See Chapter 3.

2-Allyl-3-vinylcyclopentan-1-one (18e)

A mixture of the cyclopentanone 35e (368 mg, 1.77 mmol) and sodium iodide (796 mg, 5.31 mmol) dissolved in HMPA (4 ml) containing water (7 drops) was immersed into a preheated oil bath set at 105°C. Stirring was continued at 105°C for 11 h. The cooled mixture was partitioned between ether and brine. The aqueous layer was extracted three times. Then combined extracts were washed with brine, dried over

magnesium sulfate, and concentrated *in vacuo* to leave an oil, which was subjected to silica gel chromatography to give 18e (180 mg, 67.8% yield).

IR (neat) 1736 (C=O), 1640 (C=C), 1146, 996, 914 cm^{-1};

NMR (CCl_4) δ 0.77-3.07 (m, 8H, $(CH_2)_2(CH)_2CH_2$), 4.68-6.02 (m, 6H, $2CH=CH_2$).

2-(2-Methyl-2-propenyl)-3-vinylcyclopentan-1-one (18f)

Demethoxycarbonylation of 35f (607 mg, 2.73 mmol) was carried out as above by susing sodium iodide (1.23 g, 8.19 mmol) and water (10 drops) in HMPA (5 ml) at 105°C for 12 h to give 18f (387 mg, 86.4% yield).

IR (neat) 1738 (C=O), 1640 (C=C), 1126, 886 cm^{-1};

NMR (CCl_4) δ 1.66 (br s, 3H, CH_3), 1.49-3.20 (m, 8H, $(CH_2)_2(CH)_2CH_2$), 4.56-6.13 (m, 5H, $CH_2=CH$, $CH_2=C$).

2-((Z)-2-Pentenyl)-3-vinylcyclopentan-1-one (18g)

See Chapter 3.

2-(2-Pentynyl)-3-vinylcyclopentan-1-one (18h)

As above

2-(3-Oxobutyl)-3-vinylcyclopentan-1-one (18i)

Demethoxycarbonylation of 35i (181 mg, 0.762 mmol) was carried out as above by using sodium iodide (572 mg, 3.81 mmol) and water (0.5 ml) in HMPA (5 ml) at 100-110°C for 13 h to give 18i (93 mg, 68% yield).

IR (neat) 1738 (C=O), 1713 (C=O), 1641 (C=C), 1372, 1361, 1284, 1232, 1168, 1094, 1064, 999, 921, 752 cm^{-1};

NMR (CCl_4) δ 2.04 (s, 3H,, CH_3CO), 1.07-2.90 (m, 10H, $(CH_2)_2(CH)_2$-$(CH_2)_2$), 4.88-5.26 (m, 2H, $C\underline{H}_2$=CH), 5.33-6.18 (m, 1H, $C\underline{H}$=CH_2).

Methyl 3-(2-Oxo-5-vinylcyclopentane)propionate (18j)

See Chapter 5.

2-((E)-1-Oxo-6-phenoxy-4-hexenyl)-4-butanolide (33k)

According to the procedure described for the preparation of 33a, the β-keto ester 33k was synthesized. Dianion of α-acetylbutyrolactone was prepared from it (2.15 ml, 20 mmol), sodium hydride (50% mineral oil, 1.1 g, 23 mmol), and butyllithium (1.64 M in hexane, 13.4 ml, 22.0 mmol) in THF (60 ml) and HMPA (10 ml) at 0°C. To the solution was added dropwise (E)-1-chloro-4-phenoxy-2-butene (5.0 ml, 27.4 mmol) at 0°C. Stirring was continued for 50 min between 5°C and 10°C. After work-up and chromatographic purification of silica gel, 33k was obtained in 79.9% yield (4.38 g).

IR (neat) 1762 (C=O), 1715 (C=O), 1596, 1235, 1216, 1148, 1008, 979, 757, 681 cm^{-1};

NMR (CCl_4) δ 1.64-3.01 (m, 6H, $(CH_2)_2CO$, $C\underline{H}_2CH_2O$), 3.38 (dd, J = 10 Hz, J = 7 Hz, 1H, CHCO), 3.84-4.38 (m, 4H, CH_2OCO, CH_2OPh), 5.47-5.70 (m, 2H, CH=CH), 6.42-7.24 (m, 5H, aromatic).

2-Oxa-9-vinylspiro[4.4]nonane-1,6-dion (35k)

A solution of palladium(II) acetate (63 mg, 0.28 mmol) and triphenylphosphine (296 mg, 0.564 mmol) in acetonitrile (30 ml) was refluxed under nitrogen for 15 min. The γ-lactone 33k (3.86 g, 14.1 mmol) in acetonitrile (10 ml) was slowly added to the refluxing solution over a period of 10 min. Refluxing was continued for additional 45 min with stirring. The cooled mixture was filtered through a short silica gel column and the filtrate was concentrated in vacuo to leave an oil, which was then diluted with dichloromethane (30 ml). To the solution at 0°C were added a trace amount of p-toluenesulfonic acid and 2,3-dihydropyran (1.93 ml, 21 mmol). After 30 min of stirring at 0°C, triethylamine (ca 1 ml) was added to the solution and the resulting solution was passed through a short silica gel column. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel to give 35k (2.27 g, 89.5% yield).

IR (neat) 1765, 1736, 1640 (C=C), 1374, 1175, 1028, 997, 958, 923, 682 cm^{-1}; NMR (CCl_4) δ 1.22-3.43 (m, 7H, $(CH_2)_2CH$, CH_2CH_2O), 3.93-4.38 (m, 2H, CH_2O), 4.63-5.98 (m, 3H, CH_2=CH).

2-(2-Hydroxyethyl)-3-vinylcyclopentan-1-one (18k)

To a solution of 35k (78 mg, 0.43 mmol) dissolved in ethanol (3 ml) was added 3N hydrochloric acid (1 ml) and the resulting mixture was heated under reflux for 20 h. The ethanol was evaporated in vacuo and the remaining material was partitioned between ethyl acetate and brine. The extract was dried over magnesium sulfate and concentrated in vacuo leaving an oil, which was chromatographed on silica gel.

Elution with benzene-hexane-THF, 10:5:2, gave the alcohol 18k (49 mg, 73% yield).

IR (neat) 3340 (OH), 1722 (C=O), 1036, 997, 914 cm^{-1};

NMR (CCl_4) δ 1.10-3.05 (m, 9H, $(CH_2)_2(CH)_2CH_2$, OH), 3.58 (t, J = 6 Hz, 2H, CH_2OH), 4.73-6.09 (m, 3H, $CH=CH_2$).

Palladium Catalyzed Rearrangement of the Tetrahydrofuran 37a

A mixture of 37a (86 mg, 0.51 mmol), palladium(II) acetate (11 mg, 0 0.051 mmol), triphenylphosphine (47 mg, 0.18 mmol) in acetonitrile (3 ml) was heated under reflux for 1 h and the cooled mixture was filtered through a short silica gel column with ether. The filtrate was concentrated in vacuo leaving an oil, which was analyzed by gas chromatography. The ratio of 35a and 36a was calculated to be approximately 87:13.

When benzene was used in place of acetonitrile, the ratio of 35a and 36a was about 45:55.

8-Phenoxy-6-octen-2-one (45)

A mixture of palladium(II) chloride (709 mg, 4.0 mmol), copper(I) chloride (3.96 g, 40 mmol), DMF (40 ml), and water (4 ml) was stirred at room temperature under oxygen for 1 h. Then, 1-phenoxy-2,7-octadiene (44) [37] (8.08 g, 40.0 mmol) was added and the reaction mixture was stirred for additional 8 h. The reaction was quenched with addition of 3N hydrochloric acid and the solution was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was distilled to give 8-phenoxy-

6-octen-2-one (45) (6.59 g, 76% yield).

Bp. 120-125°C (2.5 mmHg);

IR (neat) 2950, 1715, 1600, 1240,,760, 695 cm^{-1};

NMR (CCl_4) δ 1.35-1.90 (m, 2H, CH_2), 2.00 (s, 3H, CH_3CO), 1.90-2.50 (m, 4H, CH_2CO, $CH_2C{=}C$), 4.45 (d, J = 4 Hz, 2H, CH_2O), 5.60-5.85 (m, 2H, CH=CH), 6.55-7.65 (m, 5H, aromatic).

Methyl (E)-3-Oxo-9-phenoxy-7-nonenoate (39)

To a suspension of sodium hydride (50% mineral oil, 1.51 g, 31.5 mmol) in benzene (60 ml) at room temperature under nitrogen were added the ketone 45 (5.29 g, 24.3 mmol) dissolved in benzene (40 ml) and then dimethyl carbonate (6.1 ml, 72 mmol). The mixture was heated at reflux for 6 h and then cooled to room temperature. The mixture was acidified by careful addition of 3N hydrochloric acid and the resulting mixture was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the β-keto ester 39 (5.37 g, 80.2% yield).

IR (neat) 2960, 1750, 1710, 1603, 760, 700 cm^{-1};

NMR (CCl_4) δ 1.30-2.60 (m, 6H, $(CH_2)_3$), 3.25 (s, 2H, CH_2CO), 3.60 (s, 3H, CH_3O), 4.35 (d, J = 3 Hz, 2H, CH_2O), 5.50-5.80 (m, 2H, CH=CH), 6.55-7.40 (m, 5H, aromatic).

Cyclization of Methyl (E)-3-Oxo-9-phenoxy-7-nonenoate (39)

The palladium-catalyzed cyclization was conducted according to the procedure described for the synthesis of the cyclopentanone 35 and the ratios of products were calculated by gas chromatography (Table 2-5). A sample was purified by silica gel chromatography.

Methyl 2-Oxo-6-vinylcyclohexanecarboxylate (40):

Bp. 75-80°C (2 mmHg);

IR (neat) 1748 (C=O), 1715 (C=O), 1650 (C=O enol ester), 1616 (C=C, enol), 1272, 1224, 913, 836 cm^{-1};

NMR (CCl_4) δ 1.10-2.50 (m, 7H, $CH(CH_2)_3$), 3.03-3.41 and 12.35 (m and s, total 1H, COCHCO, keto and enol form), 3.62 (s, 3H, CH_3O), 4.58-5.18 (m, 2H, $C\underline{H}_2$=CHO, 5.36-6.02 (m, 1H, $C\underline{H}$=CH_2).

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CHAPTER THREE

TOTAL SYNTHESIS OF

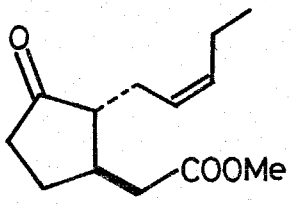
METHYL JASMONATE AND METHYL DIHYDROJASMONATE

Summary

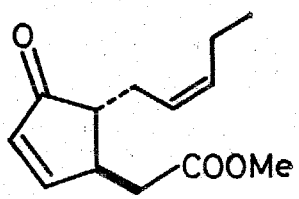
The synthesis of methyl jasmonate (1) was described. The key intermediate was 2-((Z)-2-pentenyl)-3-vinyl-1-cyclopentanone (15) which was prepared *via* the cyclopentanones obtained from the palladium-catalyzed cyclization of methyl (2-alkyl)-3-oxo-8-phenoxy-6-octenoates. Selective hydrogenation of 15 followed by Jones oxidation and then esterification completed the synthesis of 1. In a similar way, methyl dihydrojasmonate (28) was synthesized from the palladium-catalyzed cyclization product, methyl 2-oxo-1-pentyl-5-vinylcyclopentane-1-carboxylate (30).

3-1 Introduction

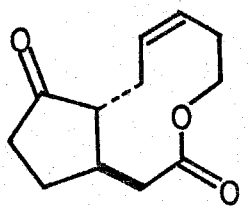
Jasmine oil extracted from jasmine flower, Jasminium Glandiflorum L., is well known as an elegant perfume[1] and has been found to contain a class of compounds which possess a five-membered cyclic ketone structure as a basic framework, being called as "Jasmonoids".[2] For example methyl jasmonate (1),[3] methyl dehydrojasmonate (2),[4] jasmine ketolactone (3),[5] and cis-jasmone (4)[2] are representatives of jasmonoids.



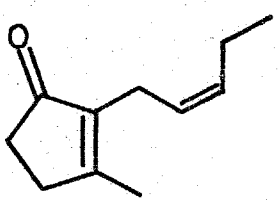
Methyl Jasmonate (1)



Methyl Dehydrojasmonate (2)



Jasmine
Ketolactone (3)

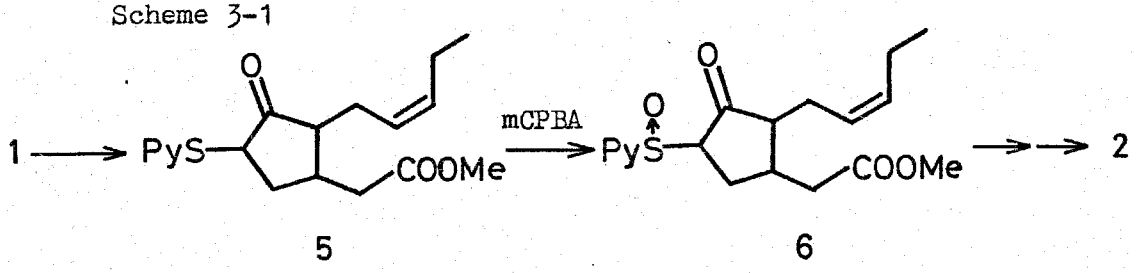


cis-Jasmone (4)

Some of jasmonoids, particularly 1 and 4, are considered to be principal ingredients responsible for the characteristic odor of the absolute oil. Although essential oil has been important material in perfume industry, it is expensive as far as one relies on the natural source. Consequently a great deal of efforts has been devoted to seek an efficient methods for the synthesis of these jasmonoids.[6-10]

It seems to be true that all possible routes to the preparation of simple cis-jasmone (4) have been reported. But as for syntheses of other jasmonoids possessing acetic acid moiety at β-position of cyclopentanone, a few reports, mainly dealing with a synthesis of 1, have been published.[11-27] In 1978, Dubs et al. reported [28] a partial synthesis of 2 from 1 as shown below:

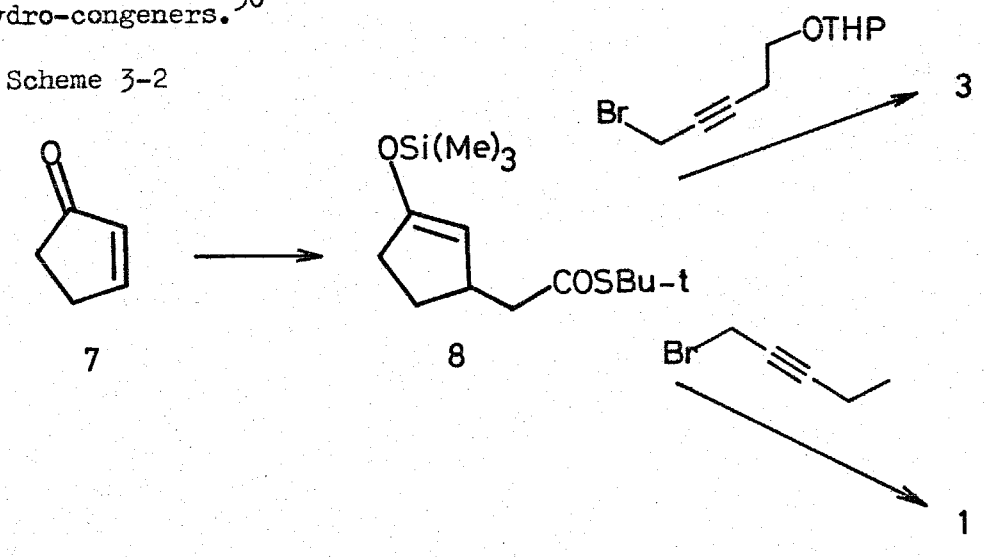
Scheme 3-1



5 6

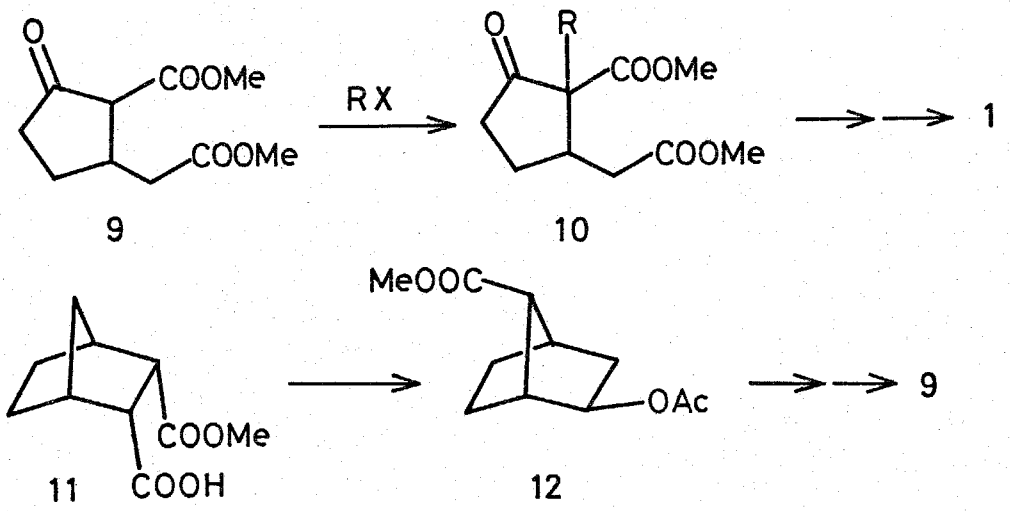
On the other hand, substituting 5-hydroxy-2-pentenyl group for 2-pentenyl group in a synthesis of 1 would provide a successful route for 3 and this idea was indeed realized by Gerlach et al. in 1978 [29](Scheme 3-2). Therefore, a synthesis of 2 and 3 would be formally achieved by finding a route to 1. Having these backgrounds, we set about developing a new synthetic pathway to methyl jasmonate (1) and its dihydro-congeners.[30]

Scheme 3-2



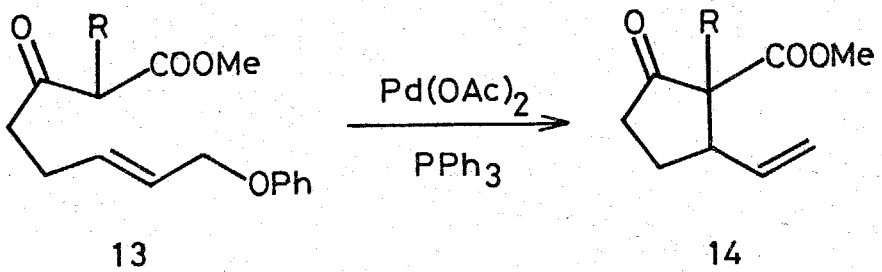
7 8

Synthetic analysis revealed that one of key intermediates [24-26,31] is the diester 9. cis-pentenyl segment (R = (Z)-$CH_2CH{=}CHCH_2CH_3$ in 10) could be easily introduced by alkylation of 9 and a synthesis of 1 would be completed. In 1975 Torii et al. prepared 9 starting from 11 using electrochemical technique as a key step (11→12) and in fact



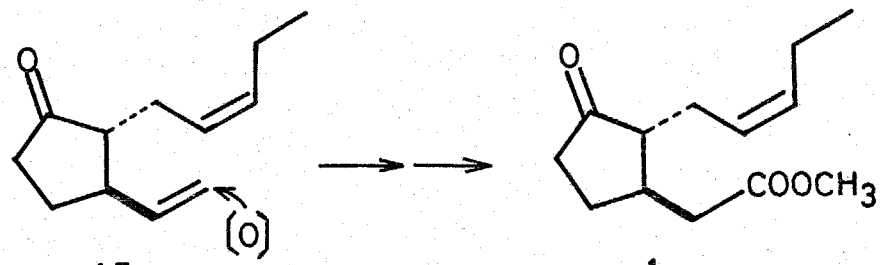
1 was synthesized from 9.[22] Later, 9, 10, and synthetic equivalents thereof have been prepared.[14,17,32,33] Much better routes, however, have to be studied as the precedent methods involve many steps of reactions.

Incidentally, palladium-catalyzed cyclopentanone synthesis (13→14) was newly found and the details are described in the preceding chapter.[30] Suppose that a vinyl group of 14 which possesses a requisite cis-2-pentenyl segment or its equivalents could be converted to an acetic acid moiety corresponding to that of 1, the cyclopentanone 14 would become a synthetic equivalent to 9 or 10 and the synthesis of 1 might be promised.



3-2 Total Synthesis of Methyl Jasmonate (1)

The cyclopentanone 15 was chosen as a subgoal of the synthesis of 1. Thus a selective oxidation of olefin attached at β-position of cyclopentanone skeleton would trigger off the completion of the synthesis. The synthetic pathway to 15 is depicted in Scheme 3-3.

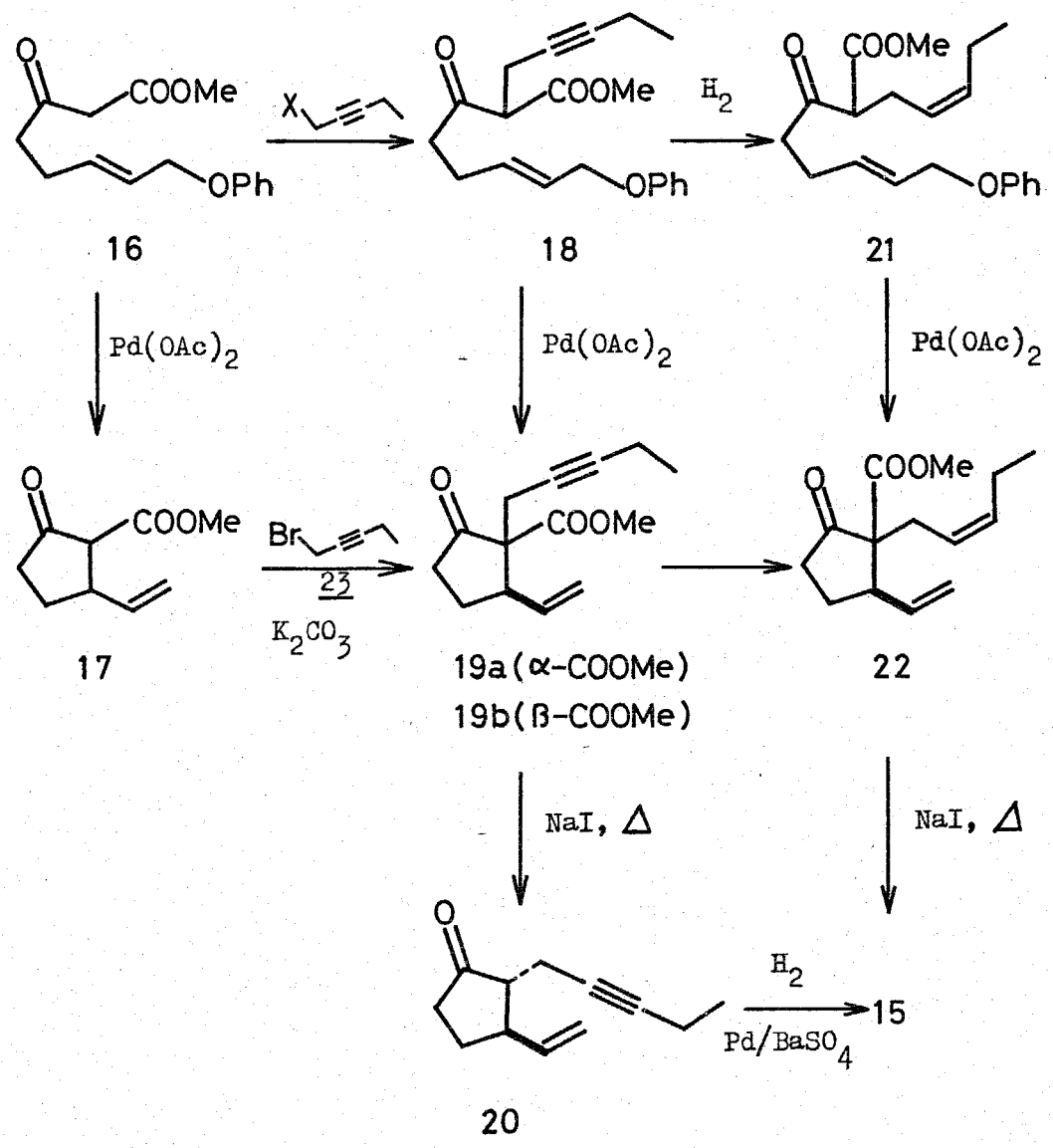


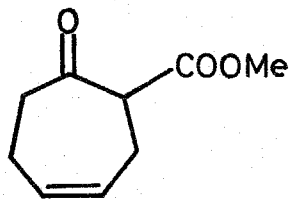
15 1

The cyclopentanone 17, now available in 59% yield by the palladium-catalyzed cyclization of 16 (See Chapter 2), was alkylated with 2-pentynyl bromide (23) [34] (See Experimental) by using potassium carbonate as a base [35] and potassium iodide [36] as a reagent preferentially promoting C-alkylation. The C-alkylated product 19b was obtained in 90% yield. Examination of the 60 MHz NMR spectrum indicated 19b was one stereoisomer and trans relationship of 2-pentynyl group to vinyl group was tentatively assigned premising a steric approach control. Demethoxycarbonylation of 19b by sodium iodide in HMPA [37] afforded 20 in 87% yield. Although the available data do not warrant a stereochemical assignment of two side chains of 20 thus synthesized, trans relationship was assigned based on thermodynamic stability of the trans isomer over the cis.

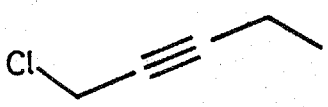
Since the cyclization of 16 gave rise to the allylic isomer 25 as a by-product besides 17 and separation of 17 from 25 was rather tedious,

Scheme 3-3


COOMe
OPh
X
H2
16
18
21
Pd(OAc)2
17
Br
23
K2CO3
19a(α-COOMe)
19b(β-COOMe)
22
NaI, Δ
20
Pd/BaSO4
15



25



24

the other sequences of reactions were carried out to avoid the drawback.

The β-keto ester 16 was alkylated prior to cyclization. At first the alkylation was carried out by using 2-pentynyl bromide (23) [34] (See Experimental)*, but the reaction was found to proceed too fast to control the formation of di-alkylated product(s) and thus 18 was obtained only in 47.5% yield by using potassium carbonate [35] in refluxing acetone or worse on 38.6% yield by using sodium methoxide in methanol. Pentynyl chloride (24)(See Experimental)* was the second choice as an alkylating agent since chlorides are about one seventies as reactive[38] as bromides and consequently might suppress the dialkylation(s). In practice, the C-alkylated product 18 could be isolated in 68% yield. As mentioned in the preceding chapter, the palladium-catalyzed cyclization of the alkylated β-keto ester 18 was highly selective to afford the

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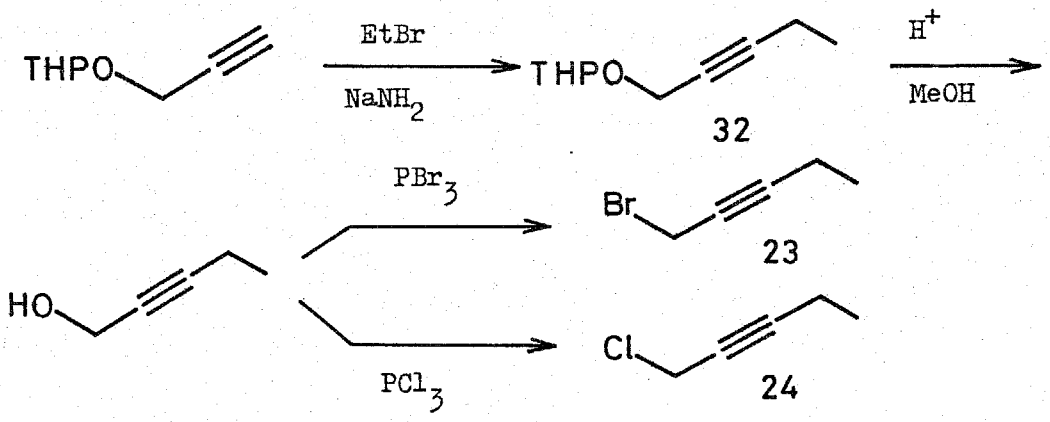
* The preparation of both halides 23 and 24 was carried out as shown below (See Experimental):



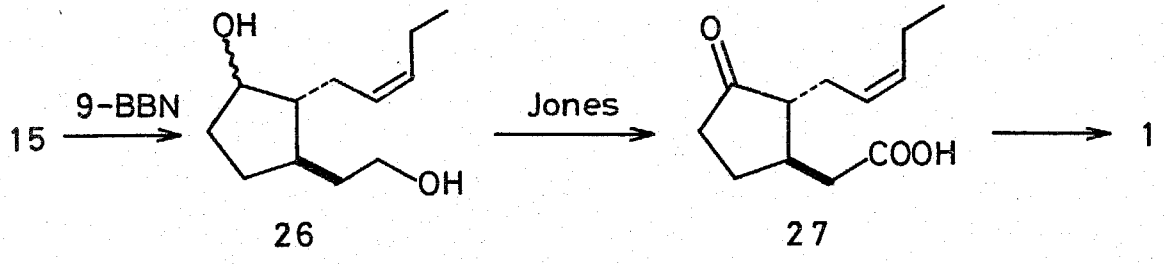
desired cyclopentanone 19 in 74% yield. NMR analysis of 19, thus obtained, indicated the presence of about a 1:1 mixture of diastereoisomers (methyl ester protons δ 3.53 and 3.61 ppm, peak area ca 1:1). Treatment of these diastereoisomers 19a and 19b with sodium iodide in HMPA [37] provided the cyclopentanone 20 as a sole product which was identical with 20 synthesized via 17.

Selective hydrogenation of 20 to 15 was carried out with 5% palladium on barium sulfate as a catalyst in hexane containing a small amount of quinoline. The olefin 15 was, however, obtained in rather moderate yield (69%), the result indicating concomitant reduction of the vinyl group. This fact implies that the partial reduction of a triple bond should be carried out before the generation of a vinyl group. Accordingly another route was investigated (Scheme 3-5). Hydrogenation of 18 proceeded selectively by using 5% palladium on barium sulfate as a catalyst and the olefin 21 was obtained in 85% yield after silica gel column chromatography. Then 21 was cyclized with palladium(II) acetate as mentioned above to give rise to in 79% yield the cyclopentanone 22 as a 1:1 mixture of diastereoisomers (NMR methyl ester resonance: δ 3.59 and 3.62 ppm, peak area ca 1:1) which were both suitable for the following transformations. Demethoxycarbonylation of 22 with sodium iodide in HMPA [37] gave the cyclopentanone 15 in 67% yield which was identical in all respects with one prepared above.

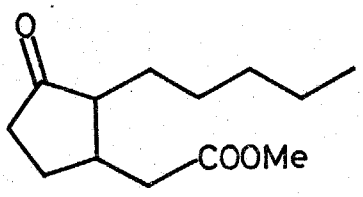
Finally the latent acetic acid side chain was unmasked as follows (Scheme 3-4). Selective hydroboration of 15 by 9-BBN,[39] followed by oxidative decomposition of the resulting boron complex with basic hydrogen peroxide yielded the crude 26. The diol 26 was then treated with

Jones reagent [40] and esterification of the resulting keto acid 27 with ethereal diazomethane provided methyl jasmonate (1). Overall yield of 1 from 15 was 41%. The spectral data (NMR and IR) of the synthetic 1 were identical in all respects with those of reported one.[20]

Scheme 3-4



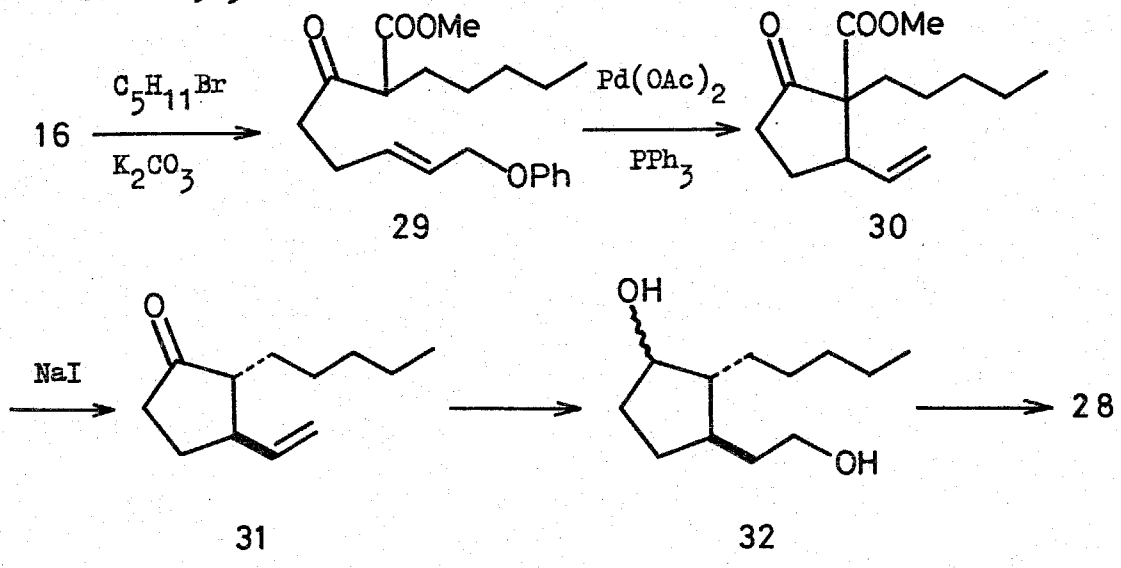
3-3 Total Synthesis of Methyl Dihydrojasmonate (28)



Methyl Dihydrojasmonate (28)

Methyl dihydrojasmonate (28) possessing pentyl side chain has quite similar odor to 1 and also has been an important material in perfume industry.[8] In this section a synthesis of 28 which parallels the synthesis of 1 is described as outlined in Scheme 3-5.

Scheme 3-5



The β-keto ester 29 prepared by alkylation of 16 with pentyl bromide in 83% yield was subjected to the palladium-catalyzed cyclization and the cyclopentanone 30 was obtained as a 1:1 mixture of diastereoisomers in 87% yield. Demethoxycarbonylation of 30 provided 31 in 88% yield. Treatment of 31 with 9-BBN [39] in THF produced the crude

diol 32 after oxidative work-up (alkaline hydrogen peroxide). By Jones oxidation [40] of 32 followed by esterification of the resulting acid by ethereal diazomethane, there was obtained methyl dihydrojasmonate (28) in 64.5% yield from 31. The synthetic 28 was identical with an authentic sample [20] by comparison of their spectral data (NMR and IR).

3-4 Experimental

Methyl 3-Oxo-8-phenoxy-6-octenoate (16)

See Chapter 2.

Methyl 2-Oxo-5-vinylcyclopentane-1-carboxylate (17)

See Chapter 2

Methyl 2-Oxo-1-(2-pentynyl)-5-vinylcyclopentane-1-carboxylate (19b)

To a solution of the cyclopentanone 17 (353 mg, 2.10 mmol) and 2-pentynyl bromide (289 µl, 402 mg, 2.73 mmol) in acetone (35 ml) were added potassium carbonate (1.16 g, 8.42 mmol) and potassium iodide (454 mg, 2.74 mmol). The mixture was heated at reflux for 12 h and cooled to room temperature. Insoluble materials were filtered and the filtrate was concentrated *in vacuo*. Chromatography of the residue on silica gel by using hexane-ether, 13:1, gave the cyclopentanone 19b (442 mg, 89.7% yield).

Bp. 110-115°C (2 mmHg);

IR (neat) 1755 (C=O), 1737 (C=O), 1639 (C=C), 1222, 1171, 921, 784 cm^{-1};

NMR (CCl_4) δ 1.07 (t, J = 7 Hz, 3H, CH_3), 1.80-3.45 (m, 9H, $CH_2C{\equiv}CH_2$, $CH(CH_2)_2CO$), 3.53 (s, 3H, CH_3O), 4.87-5.28 (m, 2H, $C\underline{H}_2{=}CH$), 5.32-6.00 (m, 1H, $C\underline{H}{=}CH_2$).

2-(2-Pentynyl)-3-vinyl-1-cyclopentanone (20)

To a solution of 19b (154 mg, 0.656 mmol) in HMPA (1 ml) were added

sodium iodide (492 mg, 2.96 mmol) and water (0.1 ml). The mixture was heated about 80-100°C for 17 h with stirring and then cooled to room temperature. The mixture was poured into ice-water and extracted three times with ether. The combined extracts were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was chromatographed on silica gel by using hexane-ether, 15:1, to afford 20 (100 mg, 87.3% yield).

IR (neat) 1750 (C=O), 1651 (C=C), 1172, 1001, 922, 799 cm^{-1};

NMR (CCl_4) δ 1.08 (t, J = 7 Hz, 3H, CH_3), 1.30-3.00 (m, 10H, $CH_2C{\equiv}CCH_2$-$CH(CH_2)_2$), 4.85-5.31 (m, 2H, $C\underline{H}_2{=}CH$), 5.40-6.11 (m, 1H, $C\underline{H}{=}CH_2$).

Methyl 3-Oxo-2-(2-pentynyl)-8-phenoxy-6-octenoate (18)

Procedure A: A mixture of the β-keto ester 16 (801 mg, 3.06 mmol), 2-pentynyl bromide (23) (0.54 g, 3.69 mmol), and potassium carbonate (1.69 g, 12.2 mmol) in acetone (40 ml) was heated at reflux for 4 h and then cooled to room temperature. After insoluble materials were filtered off, the filtrate was concentrated *in vacuo*. The remaining oil was purified by chromatography on silica gel, eluting with hexane-ether, 15:1, to give 18 (476 mg, 47.5% yield).

IR (neat) 1743 (C=O), 1719 (C=O), 1600, 1588, 1240, 1175, 1080, 1030, 1011, 972, 756, 693 cm^{-1};

NMR (CCl_4) δ 1.04 (t, J = 7 Hz, 3H, CH_3), 1.15-2.80 (m, 8H, $CH_2C{\equiv}CCH_2$, $(CH_2)_2CO$), 3.44 (t, J = 7 Hz, 1H, CH), 3.62 (s,3H, CH_3O), 4.10-4.55 (m, 2H, CH_2OPh), 5.25-5.73 (m, 2H, CH=CH), 6.40-7.27, (m, 5H, aromatic).

Procedure B: To a solution of sodium methoxide (719 mg, 11.2 mmol) in dry methanol (120 ml) under nitrogen at room temperature was added a solution of 16 (2.95 g, 11.2 mmol) in methanol (80 ml) and the reaction mixture was heated at reflux. A solution of the bromide 23 (1.65 g, 11.3 mmol) in methanol (20 ml) was added dropwise over 2.5 h. After the addition was complete, the resulting solution was refluxed for additional 1.5 h and then cooled to room temperature. Most of methanol was removed in vacuo and the remaining oil was poured into water. The aqueous phase was extracted several times with ether and the combined extracts were washed with brine, dried over magnesium sulfate and then concentrated in vacuo. Chromatography of the residue on silica gel afforded 18 (1.42 g, 38.6% yield), which was identical in all respects (IR, NMR, R_f value etc.) with one obtained above.

Procedure C: To a suspension of potassium carbonate (300 mg, 2.17 mmol) in acetone (1 ml) were added 2-pentynyl chloride (24) (72 mg, 0.70 mmol) and 16 (142 mg, 0.542 mmol) dissolved in acetone (3 ml) and the resulting mixture was heated at reflux. After 24 h, the mixture was cooled to room temperature and the insoluble materials were separated by filtration and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel to give 18 (120 mg, 67.5% yield), which was identical in all respects (IR, NMR, R_f value etc.) with one obtained in the procedures A and B.

Methyl 2-Oxo-1-(2-pentynyl)-5-vinylcyclopentane-1-carboxylate (19a, 19b)

To a solution of 18 (147 mg, 0.448 mmol) in oxygen-free propionitrile

(5 ml), which was bubbled with nitrogen for 30 min just before use, were added palladium(II) acetate (10 mg, 0.045 mmol) and triphenylphosphine (41 mg, 0.16 mmol) under nitrogen. Stirring was continued under reflux for 1.5 h. After being cooled to room temperature, the solution was filtered through a short silica gel column with ether. The filtrate was concentrated in vacuo and the residual oil was chromatographed on silica gel. Elution with hexane-ether, 15:1, gave a 1:1 mixture of 19a and 19b (78 mg, 74% yield).

IR (neat) 1755, 1737, 1639 cm^{-1};

NMR(CCl_4) δ 1.07 (t, J = 7 Hz, 3H, CH_3), 1.70-3.47 (m, 9H, $CH_2C{\equiv}CCH_2$, $(CH_2)_2CH$), 3.53 and 3.61 (2s, 3H, CH_3O), 4.87-5.28 (m, 2H, $C\underline{H}_2{=}CH$), 5.32-6.22 (m, 1H, $C\underline{H}{=}CH_2$).

2α-((Z)-2-Pentenyl)-3-vinyl-1-cyclopentanone (15)

A. From 20: A mixture of 20 (186 mg, 1.05 mmol) and 5% $Pd/BaSO_4$ (20 mg) in hexane (5 ml) containing a trace of quinoline was stirred under hydrogen atmosphere at room temperature for 12 h. The mixture was filtered to remove the catalyst through a short silica gel column and the ethereal filtrate was evaporated in vacuo. Chromatography of the residue on silica gel with ether-hexane,1:15, afforded pure 15 (129 mg, 69% yield).

IR (neat) 1750 (C=O), 1651 (C=C), 1172, 1001, 922, 799 cm^{-1};

NMR (CCl_4) δ 0.93 (t, J = 7 Hz, 3H, CH_3), 1.20-2.80 (m, 10H, $C\underline{H}_2CH_3$, $CH_2CHCH(CH_2)_2$), 4.81-6.10 (m, 5H, $CH_2{=}CH$, $CH{=}CH$).

B. From 22 : A sealed tube containing a mixture of 22 (76 mg, 0.32 mmol) (vide infra), sodium iodide (244 mg, 1.63 mmol), and water (50 µl) in HMPA (0.8 ml) was immersed in a preheated oil bath set at 100°C. Stirring was continued at the same temperature for 12 h. The mixture was cooled to room temperature, poured into ice-water, and then extracted four times with ether. The combined ethereal solutions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Chromatography of the residue on silica gel afforded the cyclopentanone 15 (39 mg, 67% yield) whose spectral data (IR, NMR) were identical with those obtained above.

Methyl 3-Oxo-2-((Z)-2-pentenyl)-8-phenoxy-6-octenoate (21)

A mixture of 18 (953 mg, 2.90 mmol) and 5% $Pd/BaSO_4$ (200 mg) in methanol (10 ml) containing a small amount of quinoline was stirred under 1 atm of hydrogen at room temperature. After 12 h, hydrogen uptake stopped and the mixture was filtered to remove the catalyst through a short silica gel column with ether. The solvents were removed off in vacuo and the residue was chromatographed on silica gel. Elution with hexane-ether, 10:1, gave 21 (811 mg, 84.7% yield).

IR (neat) 1743 (C=O), 1715 (C=O), 1600, 1585, 1241, 755, 692 cm^{-1};

NMR (CCl_4) δ 0.93 (t, J = 7 Hz, 3H, CH_3), 1.20-2.90 (m, 8H, $CH_2CH{=}CHCH_2$, $(CH_2)_2CO$), 3.29 (t, J = 7 Hz, 1H, CHCO), 3.61 (s, 3H, CH_3O), 4.25-4.45 (m, 2H, CH_2OPh), 4.75-5.80 (m, 4H, cis-CH=CH, trans-CH=CH), 6.50-7.30 (m, 5H, aromatic).

Methyl 2-Oxo-1-((Z)-2-pentenyl)-5-vinylcyclopentane-1-carboxylate (22)

To oxygen-free propionitrile (5 ml) under nitrogen were added palladium(II) acetate (9 mg, 0.04 mmol) and triphenylphosphine (38 mg, 0.145 mmol). Finally the β-keto ester 21 (136 mg, 0.413 mmol) was added. The resulting mixture was stirred under reflux under nitrogen for 2 h and then allowed to cool to room temperature. The brown solution was filtered through a short silica gel column with ether and the solvents were evaporated *in vacuo* to give a brown oil, which was chromotographed on silica gel. Elution with hexane-ether, 15:1, afforded the cyclopentanone 22 (77 mg, 79% yield).

IR (neat) 1752, 1731, 1636, 1221, 1175 cm^{-1};

NMR (CCl_4) δ 0.95 (t, J = 7 Hz, 3H, CH_3), 1.10-3.10 (m, 9H, $CH_2CH{=}CHCH_2$, $CH(CH_2)_2CO$), 3.59 and 3.62 (2s, total 3H, CH_3O), 4.72-6.25 (m, 5H, $CH{=}CH$, $CH{=}CH_2$).

Methyl Jasmonate (1)

To a soultion of the cyclopentanone 15 (35 mg, 0.20 mmol) in dry THF (10 ml) under nitrogen at 20°C was added 9-BBN (0.70 M, 0.56 ml, 0.39 mmol) in THF and the solution was stirred at 20°C. After 4 h, TLC analysis showed absence of 15. Aqueous 10% sodium hydroxide (0.5 ml) and aqueous 35% hydrogen peroxide (0.5 ml) were added to the solution, which was followed by stirring at about 50°C for 3 h and then at room temperature for 12 h. Excess hydrogen peroxide was destroyed by the addition of saturated aqueous sodium bisulfate. Brine was added to the mixture and the mixture was extracted three times with ethyl acetate. The combined organic layers were evaporated *in vacuo* to give the crude diol 26 which was used without purification for the subsequent reaction.

To a solution of the diol 26 thus obtained was added excess Jones reagent at room temperature. Stirring was continued for 1 h. The reaction was quenched by the addition of 2-propanol. The resulting mixture was poured into brine and extracted twice with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvents *in vacuo* gave crude jasmonic acid (27), which was subjected directly to esterification.

To a solution of the crude acid 27 in ether (*ca* 2 ml) was added ethereal diazomethane at room temperature until the evolution of nitrogen gas ceased. After evaporation of ether, the remaining oil was subjected to silica gel chromatography with hexane-ether, 15:1, to give pure methyl jasmonate (1) (18 mg, 41% yield from 15), whose spectral data (IR, NMR) were identical in all respects with those of an authentic sample[20]:

Bp. 97-102°C (2 mmHg) (lit.[20] 92-96°C (2.7 mmHg));

IR (neat) 1740 (C=O), 1168, 788 cm^{-1};

NMR (CCl_4) δ 0.97 (t, *J* = 7 Hz, 3H, CH_3), 1.20-2.80 (m, 12H, $CH_2CH{=}CH{-}CH_2CH$, $(CH_2)_2CHCH_2$), 3.61 (s, 3H, CH_3O), 4.95-5.60 (m, 2H, CH=CH).

Methyl 3-Oxo-2-pentyl-8-phenoxy-6-octenoate (29)

A mixture of the β-keto ester 16 (525 mg, 2.00 mmol), pentyl bromide (297 μl, 2.40 mmol), potassium carbonate (1.10 g, 8.00 mmol), and potassium iodide (365 mg, 2.20 mmol) in acetone (40 ml) was heated under nitrogen at reflux for 9 h and then allowed to cool to room temperature. Insoluble materials were filtered off and the filtrate was concentrated

in vacuo to give an oil, which was subjected to silica gel chromatograpy. Elution with hexane-ether, 15:1, afforded 29 (554 mg, 83.4% yield).

IR (neat) 1743 (C=O), 1715 (C=O), 1600, 1583, 1240, 754, 690 cm^{-1};

NMR (CCl_4) δ 0.86 (t, *J* = 7 Hz, 3H, CH_3), 1.03-2.70 (m, 12H, CH_2CH_2CO, $(CH_2)_4$), 3.23 (t, *J* = 7 Hz, 1H, COCHCO), 3.59 (s, 3H, CH_3O), 4.22-4.41 (m, 2H, CH_2O), 5.49-5.75 (m, 2H, CH=CH), 6.50-7.26 (m, 5H, aromatic).

Methyl 2-Oxo-1-pentyl-5-vinylcyclopentane-1-carboxylate (30)

To a solution of the β-keto ester 29 (80 mg, 0.24 mmol) in oxygen-free propionitrile (3 ml) under nitrogen were added palladium(II) acetate (54 mg, 0.024 mmol) and triphenylphosphine (22 mg, 0.084 mmol). The mixture was heated at reflux for 2 h. After having been cooled to room temperature, the brown solution was passed through a short silica gel column with ether. The ethereal solution was concentrated *in vacuo* to give an oil, which was chromatographed on silica gel. Elution with hexane-ether, 15:1, gave pure 30 (50 mg, 87% yield).

Bp. 107-112°C (2 mmHg);

IR (neat) 1754 (C=O), 1736 (C=O), 1228, 998, 920 cm^{-1};

NMR (CCl_4) δ 0.87 (t, *J* = 6 Hz, 3H, CH_3), 1.03-3.00 (m, 13H, $CHCH_2CH_2CO$, $(CH_2)_4$), 3.59 and 3.63 (2s, total 3H, CH_3O), 4.84-5.22 (m, 2H, $C\underline{H}_2$=CH), 5.41-6.10 (m, 1H, CH_2=C<u>H</u>).

2-Pentyl-3-vinyl-1-cyclopentanone (31)

The cyclopentanone 30 (70 mg,0.29 mmol), sodium iodide (221 mg, 1.47 mmol), and water (50 μl) were dissolved in HMPA (0.8 ml). The

mixture was heated at 100°C for 12 h and then cooled to room temperature. The mixture was transferred into brine with ether and extracted four times with ether-hexane (1:1). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Chromatographic purification of the resudue on silica gel with hexane-ether, 15:1, gave 31 (47 mg, 88% yield).

IR (neat) 1740 (C=O), 1639 (C=C), 1155, 995, 915 cm^{-1};

NMR (CCl_4) δ 0.88 (t, J = 5 Hz, 3H, CH_3), 1.05-3.00 (m, 14H, $CH(CH_2)_2$-$COCH(CH_2)_4$), 4.82-5.23 (m, 2H, CH_2=CH), 5.35-6.24 (m, 1H, CH=CH_2).

Methyl Dihydrojasmonate (28)

To a solution of 31 (78 mg, 0.43 mmol) in dry THF (10 ml) was added 9-BBN (0.70 M, 1.24 ml, 0.866 mmol) in dry THF under nitrogen at room temperature. The resulting solution was stirred at the same temperature for 4 h. Hydrogen peroxide (35%, 5 ml) and aqueous 3N sodium hydroxide (5 ml) were added to the solution at 0°C and the mixture was stirred at room temperature for 12 h. Aqueous saturated sodium bisulfite was added to decompose excess hydrogen peroxide. The mixture was extracted twice with ethyl acetate. The combined extracts were washed with 3N aqueous hydrochloric acid and brine. After having been dried over magnesium sulfate, the solvents were removed *in vacuo* to give crude diol, which was used for the next reaction without purification.

The crude diol obtained above was dissolved in acetone (5 ml) and excess Jones reagent (*ca* 2 ml) was added dropwise to the solution at

room temperature. The resulting mixture was stirred for 1 h. The reaction mixture was extracted twice with ethyl acetate and the combined extracts were washed with aqueous 1% sodium hydroxide. The aqueous layer was acidifife by the addition of 3N hydrochloric acid and re-extracted twice with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the crude dihydrojasmonic acid.

To a solution of the crude dihydrojasmonic acid in ether (*ca* 2 ml) was added excess ethereal solution of diazomethane until the evolution of nitrogen gas ceased. Ether was evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane-ether, 15:1, afforded methyl dihydrojasmonate (*28*) (64 mg, 64% yield).

Bp. 107-112°C (2 ml);

IR (neat) 1735 (C=O), 1256, 1195, 1168 cm^{-1};

NMR (CCl_4) δ 0.88 (t, *J* = 6 Hz, 3H, CH_3), 1.04-2.85 (m, 16H, CH_2CH-$(CH_2)_2COCH(CH_2)_4$), 3.60 (s, 3H, CH_3O).

2-Pentynyl 2-Tetrahydropyranyl Ether (*32*)

This substrate *32* was prepared according to Yoshida's procedure[41] with some modifications: Sodium amide was prepared from sodium (23.6 g, 1.03 mol) in anhydrous liq. ammonia (*ca* 200 ml) by the usual way. To this suspension of sodium amide was added dropwise propargyl 2-tetrahydropyranyl ether (120 g, 0.856 mol) under nitrogen at -70°C. The mixture was stirred at reflux for 1 h and then cooled to -70°C. Ethyl bromide (112 g, 1.03 mol) was added slowly to the mixture and the resulting mixture was stirred for 1 h at -70°C and subsequently for 1 h

at room temperature under evaporation of ammonia. After the reaction mixture had been kept overnight at room temperature, water was added and the mixture was extracted with ether. The ethereal solution was washed with brine, dried over magnesium sulfate, and then concentrated *in vacuo*. The residual oil was distilled under reduced presure to give 32 (140 g, 97% yield).

Bp. 105-109°C (17 mmHg) (lit.[41] 120-121°C (20 mmHg));

IR (neat) 2224, 1120, 1024 cm^{-1};

NMR (CCl_4) δ 1.17 (t, J = 12 Hz, 3H, CH_3), 1.32-1.94 (m, 6H, $(CH_2)_3$), 1.94-2.46 (m, 2H, $CH_2C{\equiv}C$), 3.20-4.00 (m, 2H, CH_2O), 4.10 (t, J = 2 Hz, 2H, $OCH_2C{\equiv}C$), 4.73 (s, 1H, OCHO).

2-Pentyn-1-ol (33)

A mixture of 36 (140 g, 0.832 mol) and a catalytic amount of p-toluenesulfonic acid in dry methanol (500 ml) was heated at 45-50°C for 12 h under nitrogen and then cooled to room temperature. The reaction was stopped by the addition of sodium bicarbonate (ca 1 g) and stirring was continued for 1 h at room temperature. The insoluble materials were separated by centrifugation and the organic components were distilled through a Widmer column to give the alcohol 33 (64.5 g, 92.3 % yield).

Bp. 70-76°C (38 mmHg) (lit.[41] 86-92°C (47 mmHg));

IR (neat) 3390, 1016 cm^{-1};

NMR (CCl_4) δ 1.15 (t, J = 10 Hz, 3H, CH_3), 1.9-2.4 (m, 2H, $CH_2C{\equiv}C$), 2.5-2.9 (m, 1H, OH), 4.13 (t, J = 1.5 Hz, 2H, CH_2O).

1-Bromo-2-pentyne (23)

To a mixture of the alcohol 33 (40.0 g, 0.476 mol) and dry pyridine (3.76 g, 47.6 mmol) under nitrogen at 0°C was added dropwise phosphorous tribromide (47.2 g, 0.174 mol). The mixture was stirred for 1 h at 0°C and then for 2 h at room temperature. Ice-water was added to the reaction mixture and the resulting mixture was extracted with ether. The extract was washed with 1% aqueous sodium hydroxide and then brine, and dried over magnesium sulfate. The solvent was removed carefully in vacuo and the residue was distilled form calcium chloride to give 23 (40.0 g, 57.2% yield).

IR (neat) 2267, 1466, 1440, 1331, 1221 cm^{-1};

NMR (CCl_4) δ 1.13 (t, J = 10 Hz, 3H, CH_3), 1.97-2.50 (m, 2H, $CH_2C{\equiv}C$), 3.92 (t, J = 1.5 Hz, 2H, CH_2Br).

1-Chloro-2-pentyne (24)

The alcohol 33 (10.9 g, 130 mmol) in dry pyridine (2.33 ml, 28.8 mmol) was added dropwise over 45 min to phosphorous trichloride (4.53 ml, 52 mmol) below 5°C. After the addition has been completed, the mixture was stirred for additional 30 min in an ice-water bath and for 7 h ar room temperature. The reaction was stopped by the addition of water. The mixture was extracted with ether and the ethereal solution was successively washed with brine, saturated aqueous sodium bicarbonate, and then brine. The solvent was removed by distillation at ordinary pressure and the residue was distilled over

calcium chloride to give the chloride 24 (6.12 g, 45.9% yield).

Bp. 119-121°C (760 mmHg);

IR (neat) 2230, 1319, 1262, 1156 cm^{-1};

NMR (CCl_4) δ 1.14 (t, J = 7 Hz, 3H, CH_3), 1.98-2.52 (m, 2H, CH_2), 3.97-4.15 (m, 2H, CH_2Cl).

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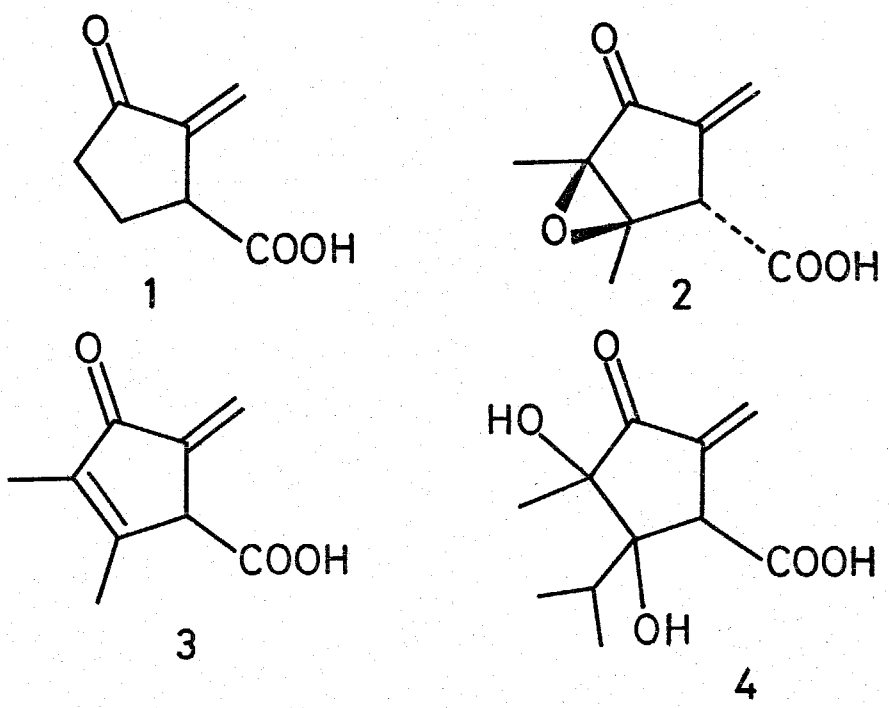
CHAPTER FOUR

TOTAL SYNTHESIS OF SARKOMYCIN

Summary

Sarkomycin (1) was synthesized starting from methyl 2-oxo-5-vinyl-cyclopentanecarboxylate (21), which was prepared from methyl 3-oxo-8-phenoxy-6-octenoate by the palladium-catalyzed cyclization. Protection of 21 with ethylene glycol followed by reduction afforded 2,2-(1,3-dioxolane)-5-vinylcyclopentanemethyl acetate (24) in total 82% yield from 21. Ozonolysis of 24 followed by Jones oxidation produced methyl 2-(acetoxymethyl)-3,3-(1,3-dioxolane)cyclopentanecarboxylate (27) in 70% yield. Treatment of 27 with 3N hydrochloric acid at room temperature gave the title compound 1 in 24% yield.

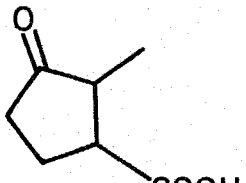
4-1 Introduction and Synthetic Strategy



In Chapter two, the author recorded the efficient synthesis of 2,3-disubstituted cyclopentanones by means of palladium catalyst.[1] For the demonstration of versatility of the cyclization-products as synthetic key intermediates, the synthesis of (±)-sarkomycin (1) was conducted. Herein, the results of the synthesis are described in detail.

In 1953, Umezawa et al. discovered [2] that *Streptomyces erthrochromogenes*, a soil microorganism found in Japan, produces an antibiotic, sarkomycin, which possesses a powerful inhibitory effect on Ehrlich ascites tumors in mice. Further pharmacological studies [3] revealed that sarkomycin caused specific destruction of tumor cells, and the preparation of this substance is marketed [4] in Japan as a prescription drug against cancer.

Hooper and his colleagues proposed [5] that the structure of this antibiotic sarkomycin, is 2-methylene-3-oxocyclopentanecarboxylic acid (1). Synthetic support was provided by showing that dihydrosarkomycin, which was obtained by catalytic hydrogenation, was identical with the known 2-metyl-3-oxocyclopentanecarboxylic acid (5).



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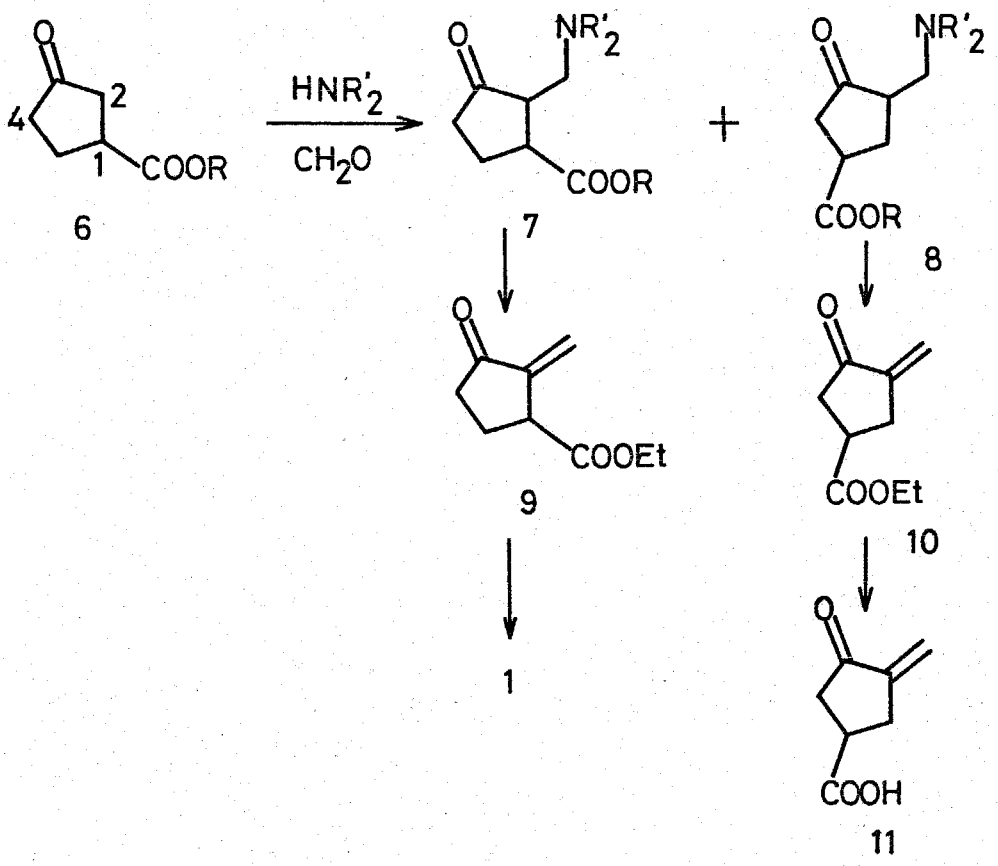
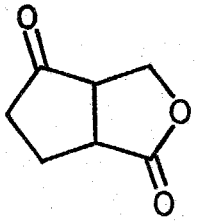
By the way, sarkomycin (1) is one of cyclopentanoid antibiotics, which were termed [6] by A. B. Smith, III for antibiotics possessing a cyclopentanone ring, and which now hold, for example, methylenomycin A (2),[7] desepoxymethylenomycin A (3),[8] and xanthocidin (4).[9] These cyclopentanoid antibiotics have a unique structural characteristic which is α-methylene-β-carboxyl functionality on cyclopentanone ring among which exo-methylene moiety is said to fulfill important functions as antitumor agents.[10]

Up to date, several total syntheses of 1 have been reported. In 1957, Toki reported [11] the first total synthesis of 1 where two suspicious steps are involved (Scheme 4-1). He claimed that the Mannich reaction on the ester 6 proceeded regioselectively to give the sole product 7 in ca 37% yield resulting from reaction at the C-2 position. This seems intrinsically unlikely because both of the α-position, C-2 and C-4, are activated by carbonyl group and therefore, would be expected to take part in the reaction. The C-4 position might be preferred because of less steric hindrance. Indeed, to settle this question

Scheme 4-1 Toki's Sarkomycin Synthesis



unambiguously, Hill et al. repeated [12] the Toki's procedure [11] exactly and carefully analyzed the products by GLC and NMR etc. They concluded that the Mannich condensation of 6 gave a 1:2 mixture of regioisomers, 7 and 8. In addition, other investigators have reported [13-15] that 8 was the sole or at least main product. Consequently the Toki's synthetic sarkomycin was badly impure. On the other hand, the last stage of Toki's synthesis [11] is acid catalyzed hydrolysis of the ester 7 affording "sarkomycin" in 29% yield. Considering the Mannich reaction to yield 7 and 8 in a ratio of 1:2 and the instability of 1 to cause



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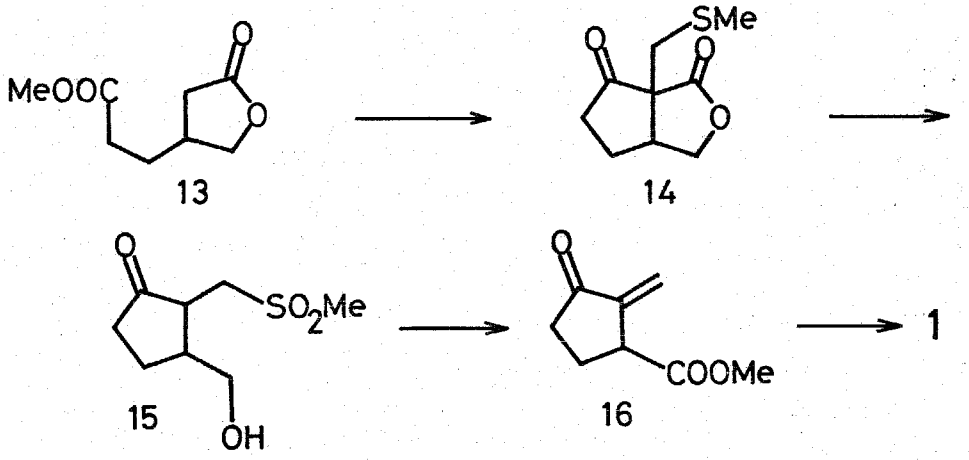
intramolecular lactonization (1→12), which is unlikely in 10, the author is suspicious that the last step might afford mainly 10 and a trace of 1 in a ratio of >2:1<.

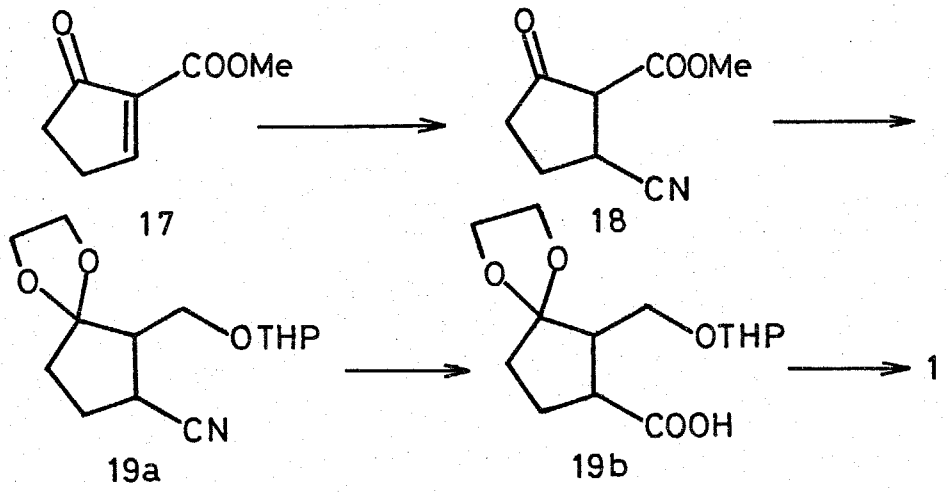
Recently Boeckmann, Jr. published [16] the regioselective synthesis of sarkomycin methyl ester (16) as shown in Scheme 4-2, but the final hydrolysis of 16 in order to produce 1 was not conducted in practice.

Scheme 4-2 Boeckmann, Jr.'s Synthesis of Sarkomycin

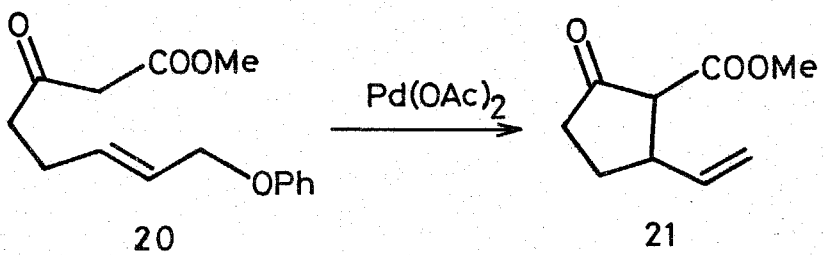


On the other hand, Marx et al. reported [17] the credible synthesis of 1 (Scheme 4-3), but regrettably the yield of each step is not wholly given and the very unstable starting material 17 had to be used in order to introduce carboxylic acid synthon in a requisite position by the 1,4-addition of cyanide ion. In addition, there are some publications with regard to the syntheses of more stable sarkomycin derivatives [18] because of its instability.[12]

Scheme 4-3 Marx's Sarkomycin Synthesis



Therefore these backgrounds necessitate the development of a different methodology. From a retrosynthetic perspective, sarkomycin is conceivable to be one of 2,3-disubstituted cyclopentanones, whose synthesis is described in Chapter two.[1] This suggestion prompted the author to take advantage of methyl 2-oxo-5-vinylcyclopentanecarboxylate (21) as a new starting material for a synthesis of 1. According to the method described in Chapter two, 21 is now available from the β-keto ester 20 by using palladium(II) acetate as a catalyst.[1] The cyclopentanone 21 possesses the requisite substitution pattern on cyclo-

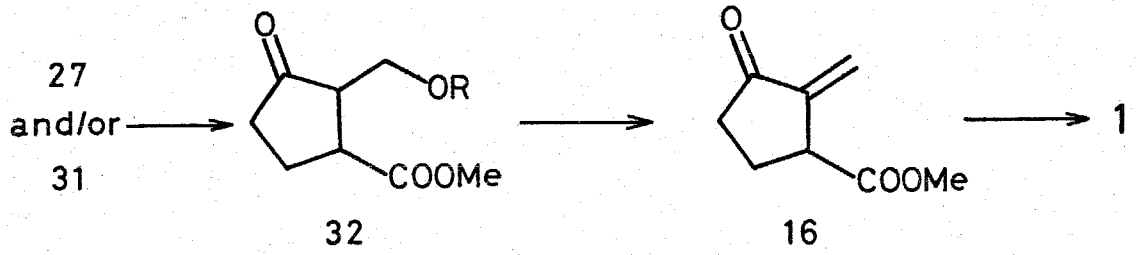


pentanone ring, where vinyl group would be unmasked to carboxylic acid easily and methoxycarbonyl group is conceivable to be a latent equivalent of exo-methylene moiety. With these considerations in mind the author set out to synthesize 1 starting from 21. As a result,

the newly developed synthetic route is particularly attractive in that it is short, regioselective, highly efficient (total 14% yield from 21). In the following section, the details of the practical sequence leading to 1 are desctibed.

4-2 Results and Discussion

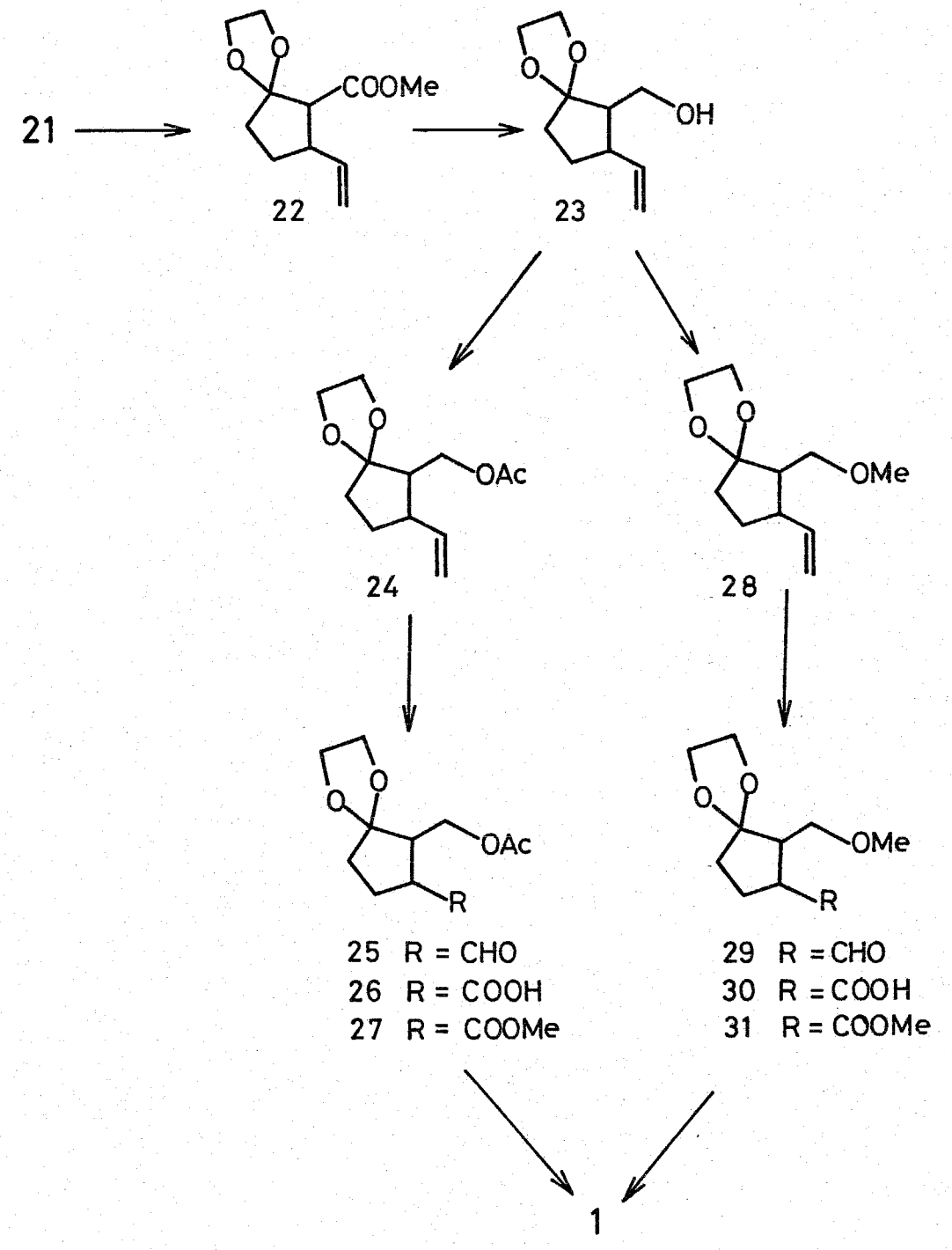
Scheme 4-4 indicates the synthetic pathway leading to 1 where the ester 27 and 31 were selected as sarkomycin precursors. The acetal ester 27 and/or 31 would be expected to change to 1 by the successive transformation of the acid catalyzed hydrolysis, the formation of the exo-methylene compound 16, and the final hydrolysis of 16 as shown below.



At the outset, the cyclopentanone 21 was converted to the acetal 22 in 87% yield by using ethylene glycol and methyl orthoformate in THF containing a trace amount of p-toluenesulfonic acid.[19] Lithium aluminum hydride reduction of 22 produced the alcohol 23 in 96% yield. Acetylation of 23 in a usual way gave the acetate 24 in 98% yield. Then the vinyl group in 24 was unmasked to the methyl ester as follows. Ozonolysis of 24 followed by the treatment with dimethyl sulfide produced the aldehyde 25, which was carefully oxidized to 26 by using Jones reagent [21] at ice-water bath temperature. Esterification of 26 with ethereal diazomethane produced the ester 27 in 70% yield from 24.

On the other hand, the alcohol 23 was converted to the methyl ether 28 with methyl iodide and sodium hydride in 96% yield. Oxidative cleavage of the vinyl group in 28 as above afforded the ester 31 in 69% yield.

Scheme 4-4 Total Synthesis of Sarkomycin



Now having set the stage for the conversion of the ester 27 or 31 to the target molecule 1, the author carried out at first the hydrolysis of 27 by treating with 3N aqueous hydrochloric acid in ether (two phase system) at 25°C for 11 h. Fortunately as expected (vide supra), sarkomycin (1) was obtained in 48% crude yield. TLC analysis of the product showed that the product 1 was almost pure and the NMR spectrum revealed two peaks centered at 5.63 and 6.17 ppm (d, J = 2.5 Hz, respectively), which was coincident thoroughly with reported value.[17] The above crude sarkomycin (1) could be chromatographed on silica gel and pure 1 was obtained in 24% yield. The low yield of the last step seems to be attributable to the instability of 1 itself. In fact, 1 was not isolated by prolonged hydrolysis (ca 26 h) and 1 was decomposed merely on standing at room temperature for ca 24 h. Alternatively, the ester 31 was subjected to hydrolysis under similar conditions described above, where 31 was hydrolyzed more slowly than 27. After 16 h, the product was purified by chromatography on silica gel and 1 was isolated in 20% yield.

4-3 Experimental

Methyl 2,2-(1,3-Dioxolane)-5-vinylcyclopentanecarboxylate (22)

To a solution of the ketone 21 (830 mg, 4.94 mmol) in dry THF (5 ml) containing a catalytic amount of p-toluenesulfonic acid under nitrogen at room temperature were injected ethylene glycol (1.38 ml, 24.7 mmol) and methyl orthoformate (812 µl, 7.41 mmol). The solution was stirred at ca 35°C for 36 h and then poured into saturated aqueous sodium bicarbonate. The mixture was extracted twice with ethyl acetate and the combined extracts were washed with brine, dried over magnesium sulfate, and finally evaporated in vacuo. The remaining oil was chromatographed on silica gel with benzene-hexane-ether, 10:5:3, to give the acetal 22 (907 mg, 86.6% yield).

IR (neat) 1734 (C=O), 1639 (C=C), 1270, 1197, 1149, 999, 946, 916 cm^{-1}; NMR (CCl_4) δ 1.12-2.08 (m, 4H, $(CH_2)_2$), 2.68 (d, J = 10 Hz, 1H, CHCO), 2.71-3.33 (m, 1H, CHC=C), 3.60 (s, 3H, CH_3O), 3.72-4.07 (m, 4H, $(CH_2)_2O$), 4.73-5.16 (m, 2H, CH_2=CH), 5.41-6.01 (m, 1H, CH=CH_2).

2,2-(1,3-Dioxolane)-5-vinylcyclopentanemethanol (23)

The ester 22 (874 mg, 4.12 mmol) was dissolved under nitrogen in dry THF (5 ml) to which was added lithium aluminum hydride (156 mg, 4.12 mmol) at 0°C. After stirring for 30 min at 0°C, the reaction was quenched by the careful addition of ethyl acetate and then water. The resulting mixture was filtered through a pad of celite under reduced pressure and the filtrate was concentrated in vacuo leaving an oil, which was chromatographed on silica gel. Elution with benzene-hexane-

THF, 10:5:2, afforded the alcohol 23 (727 mg, 95.9% yield).

IR (neat) 3450 (OH), 1642 (C=C), 1020, 950, 915 cm^{-1};

NMR ($CDCl_3$) δ 1.20-2.87 (m, 7H, $(CH_2)_2(CH)_2$, OH), 3.47-3.84 (m, 2H, $\underline{CH}_2OH$), 3.94 (br s, 4H, $(CH_2)_2O$), 4.82-5.24 (m, 2H, $\underline{CH}_2=CH$), 5.48-6.11 (m, 1H, $\underline{CH}=CH_2$).

2,2-(1,3-Dioxolane)-5-vinylcyclopentanemethyl Acetate (24)

A solution of the alcohol 23 (242 mg, 1.32 mmol) dissolved in acetic anhydride (2 ml) and pyridine (2 ml) was stirred at room temperature for 16 h and then poured into saturated aqueous sodium bicarbonate. The product was extracted twice with ether. The extracts were combined, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The remaining oil was chromatographed on silica gel with benzene-hexane-ethyl acetate, 10:5:1, gave the acetate 24 (291 mg, 98% yield).

IR (neat) 1738 (C=O), 1640 (C=C), 1235, 1031, 914 cm^{-1};

NMR (CCl_4) δ 1.90 (s, 3H, CH_3CO), 1.31-2.48 (m, 6H, $(CH_2)_2(CH)_2$), 3.81 (s, 4H, $(CH_2)_2O$), 3.98 (d, J = 6 Hz, 2H, CH_2OAc), 4.25-5.17 (m, 2H, $\underline{CH}_2=CH$), 5.45-6.04 (m, 1H, $\underline{CH}=CH_2$).

Methyl 2-(Acetoxymethyl)-3,3-(1,3-dioxolane)cyclopentanecarboxylate (27)

Ozone was passed at -70°C to a solution of the acetate 24 (352 mg, 1.56 mmol) in methanol (3 ml) at a rate of gentle bubbling. After 15 min, the cooling bath was removed and excess ozone in the solution was purged by bubbling nitrogen for 30 min. Excess dimethyl sulfide (ca 1 ml) was added to the solution and stirring was continued at room temperature for additional 3 h. Evaporation of the volatile material

in vacuo left the aldehyde 25 (IR (neat) 1732, 1235, 1024 cm^{-1}; NMR (CCl_4) δ 1.94 (s, 3H, CH_3), 3.83 (br s, 4H, $(CH_2)_2O$), 9.49-9.60 (m, 1H, CHO).

To a solution of the above aldehyde 25 in acetone (3 ml) was added excess Jones reagent at ice-water bath temperature. After 1 h, the reaction was quenched by the addition of 2-propanol. The mixture was poured onto ice-cooled brine and the product was extracted twice with ether. The combined extracts were washed twice with brine and dried over magnesium sulfate . Evaporation of the solvent *in vacuo* left the crude acid 26, which was then dissolved in ether (*ca* 3 ml) and esterified at room temperature with an ethereal solution of diazomethane. Removal of the ether provided the crude ester 27. Purification with benzene-hexane-ethyl acetate, 10:5:3, gave pure 27 (246 mg, 69.7% yield from 24).

IR (neat) 1732 (C=O), 1238, 1162, 1030, 945 cm^{-1};

NMR (CCl_4) δ 1.93 (s, 3H, CH_3CO), 1.62-2.75 (m, 6H, $(CH_2)_2(CH)_2$), 3.61 (m, 3H, CH_3O), 3.82 (s, 4H, $(CH_2)_2O$), 3.98 (d, *J* = 6 Hz, 2H, CH_2OAc).

2,2-(1,3-Dioxolane)-5-vinylcyclopentanemethoxymethane (28)

To a suspension of sodium hydride (50% oil dispersion, 138 mg, 2.88 mmol) in dry THF (2 ml) under nitrogen at room temperature was added a solution of the alcohol 23 (351 mg, 1.91 mmol) in dry THF (3 ml). After 10 min of stirring, methyl iodide (595 μl, 9.56 mmol) was added to the solution. Stirring was continued for 2 h at ambient temperature and the mixture was poured into saturated ammonium chloride. The mixture was extracted twice with ethyl acetate. The extracts were combined, washed with brine, and then dried over magnesium sulfate.

After evaporation of solvent, the remaining oil was chromatographed on silica gel by using benzene-hexane-THF, 10:5:1, to give 28 (362 mg, 95.7% yield).

IR (neat) 1640 (C=C), 1166, 1116, 1038, 909 cm^{-1};

NMR (CCl_4) δ 1.06-2.38 (m, 6H, $(CH_2)_2(CH)_2$), 3.23 (s, 3H, CH_3O), 3.00-3.47 (m, 2H, CH_2O), 3.80 (s, 4H, $(CH_2)_2O$), 4.76-5.15 (m, 2H, $\underline{CH_2}$=CH), 5.49-6.12 (m, 1H, $\underline{CH}$=CH_2).

Methyl 3,3-(1,3-Dioxolane)-2-methoxymethylcyclopentanecarboxylate (31)

The conversion of 28 to 31 was carried out according to the procedure described for the preparation of 27 from 24. Thus the methyl ether 28 (265 mg, 1.34 mmol) was dissolved in methanol (4 ml) and ozonized to give the aldehyde 29 (IR (neat) 1718 (C=O), 1117, 1022 cm^{-1}; NMR (CCl_4) δ 3.28 (s, 3H, CH_3O), 3.82 (s, 4H, $(CH_2)_2O$), 9.49-9.61 (m, 1H, CHO)). Treatment of the crude aldehyde 29 in acetone (2 ml) with Jones reagent followed by esterification afforded the ester 31 (213 mg, 69.2% yield from 28).

IR (neat) 1738 (C=O), 1161, 1118 cm^{-1};

NMR (CCl_4) δ 1.58-2.70 (m, 6H, $(CH_2)_2(CH)_2$), 3.21 (s, 3H, CH_3O), 3.59 (s, 3H, CH_3OCO), 3.80 (br s, 4H, $(CH_2)_2O$), 3.06-3.93 (m, 1H, CHCOOMe).

Sarkomycin (1)

From 27: To a solution of 27 (85 mg, 0.33 mmol) in ether (2 ml) at 25°C was added 3N hydrochloric acid (2 ml). Stirring was continued for 11 h at the same temperature and the mixture was poured onto brine. The product was extracted three times with ether and the combined ethereal

solutions were washed twice with other brine and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave sarkomycin (1) (22 mg, 48% crude yield). TLC and NMR analysis indicated that the product was almost pure. Quick purification of crude 1 by chromatography on silica gel by using benzene-hexane (2:1) to which were added ethyl acetate and methanol (10:1) little by little afforded pure 1 (11 mg, 24% yield).

IR (neat) 3350 (COOH), 1728 (C=O), 1638 cm^{-1};

NMR ($CDCl_3$) δ 1.8-2.7 (m, 5H, $(CH_2)_2CH$), 5.63 and 6.17 (d and d, J = 2.5 Hz and J = 2.5 Hz, 1H , and 1H, CH_2=CCO).

From 31 The methyl ether 31 (101 mg, 0.439 mmol) in ether (2 ml) was hydrolyzed with 3N hydrochloric acid (2 ml) at room temperature. After 16 h of stirring the crude sarkomycin (1) was isolated and purified by a similar manner described above affording pure 1 (12 mg, 20% yeild).

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CHAPTER FIVE

TOTAL SYNTHESIS OF CORONAFACIC ACID

Summary

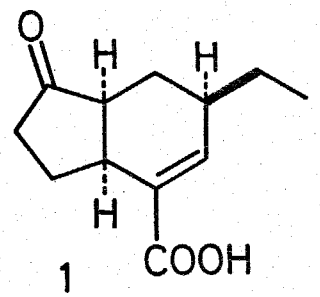
Coronafacic acid (1) was synthesized starting from methyl 3-(1-methoxycarbonyl-2-oxo-5-vinylcyclopentane)propionate (23) which was obtained by palladium catalyzed cyclization of dimethyl 2-((E) -2-oxo-6-phenoxy-4-hexenyl)-1,5-pentanedioate (22). Demethoxycarbonylation of 23 followed by acetalization and alkylation with ethyl iodide afforded methyl 3-(2,2-(1,3-dioxolane)-5-vinylcyclopentane)-2-ethylpropionate (26). Conversion of 26 to methyl 3-(2,2-(1,3-dioxolane)-5-methoxycarbonylmethyl-cyclopentane)-2-ethylpropionate (16) was effected by hydroboration with 9-BBN followed by Jones oxidation and esterification. The ester 16 was subjected to the Dieckmann cyclization with t-BuOK to give in 74% yield the key intermediate, methyl 1,1-(1,3-dioxolane)-6ξ-ethyl-3aα,4,5,6,7,7aβ-hexahydro-5-oxo-4ξ-indanecarboxylate (17), from which 1 was easily synthesized by the usual way.

5-1 Introduction

5-1-1 Background

In 1977, Sakamura et al. isolated [1] coronafacic acid (1) from the culture broth of Pseudomonas coronafacience var. atropurpurea. At the same time, coronatine (3) which is the amide of coronafacic acid (1) with coronamic acid (2) has been isolated too. The new substance 3 is a phytotoxin, which induces chlorosis on the leaves of Italian reygrass and promotes the expansion of potato cells at very low concentrations.[2]

By the way, the phytotoxin 3 has been partially synthesized [3] by the condensation of natural coronafacic acid (1) and coronamic acid (2) which was synthesized from dimethyl malonate with 1,4-dibromo-2-butene. Therefore a synthesis of 1 means formally the completion of a total synthesis of 3. Having this synthetic background for 3 in mind, the author set about the total synthesis of (±)-coronafacic acid (1). The



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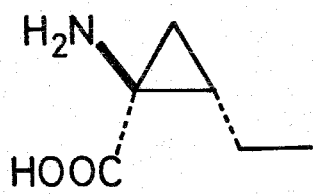

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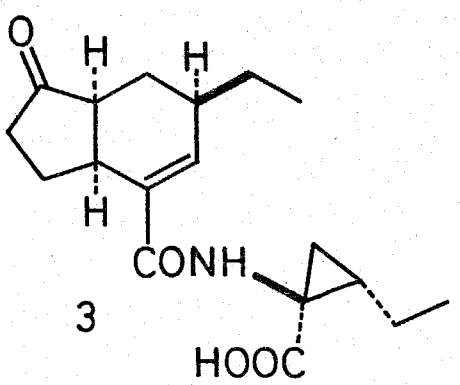

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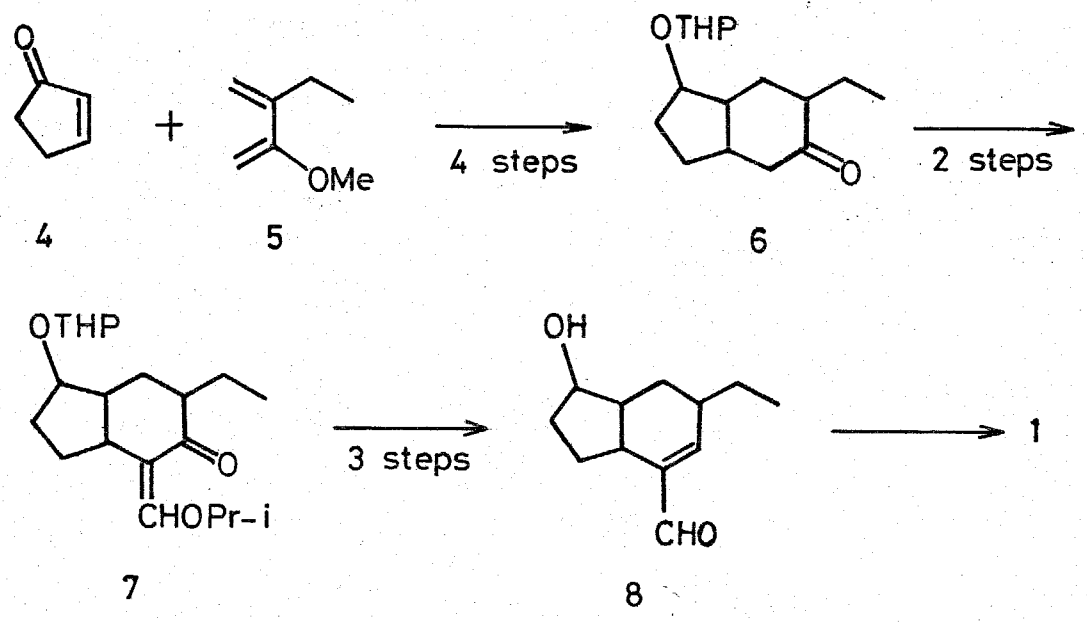
keysteps of the synthesis are the palladium-catalyzed cyclixation [4] and the Dieckmann cyclization, after which 1 was smoothly synthesized by transformation of a newly formed β-keto ester functionality, nicely disposed on cyclohexane ring.

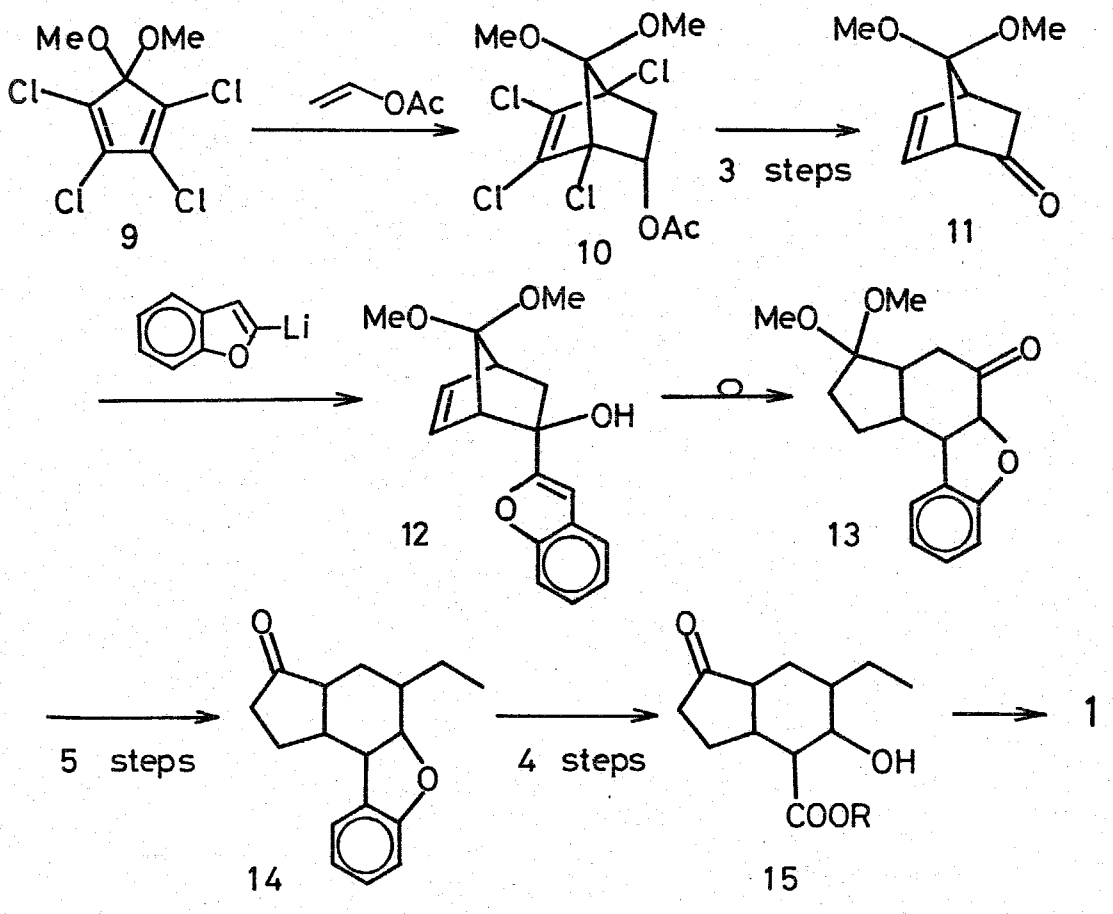
Up to date, there are two reports dealing with synthesis of 1.[5] The first one is Sakamura and Ichihara's synthesis [6] published in 1977 and shown in Scheme 5-1. In their synthesis, indane framework was constructed by the Dield-Alder reaction of the enone 4 with the diene 5 in early stage of the synthesis. But generally, the reactivity of 4 as a dienophile was so poor [7] that the yield of the key step was low (38% yield) and what is worse, the yields of each step were not given.

Scheme 5-1 The First Total Synthesis of Coronafacic Acid



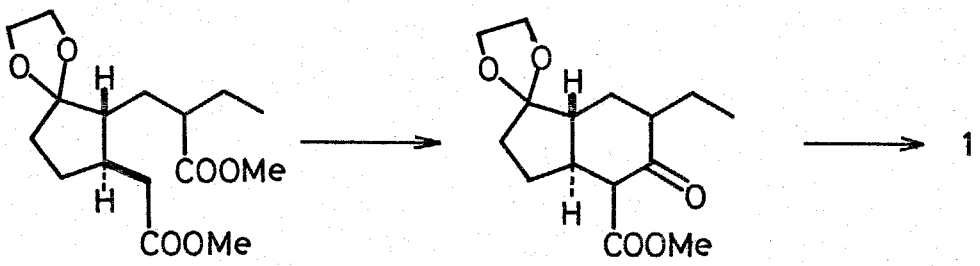
On the other hand, Jung and his co-worker have succeeded [8] in the synthesis of 1, which is briefly depicted in Scheme 5-2. One of the key steps is the anionic oxy-Cope rearrangement of an aromatic substrate 12 which was prepared from 9 in five steps, and the rearranged product 13 was further transformed to complete the synthesis as shown in Scheme 5-2. In their report, they claimed that the final product 1 could be synthesized by a nine-step process, but in practice, the synthetic pathway is somewhat too lengthy and the yields of each step were not always high.

Scheme 5-2 The Second Total Synthesis of 1 presented by Jung

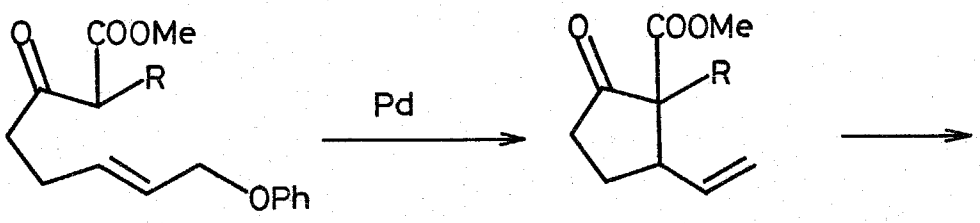


5-1-2 The New Strategy for the Synthesis of Coronafacic Acid

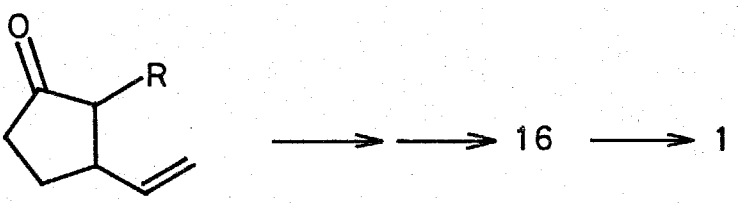
From a retro-synthetic perspective, an alternative and convenient pathway to coronafacic acid (1) could be deduced. The ester 16, which contains all carbon atoms present in 1, is conceivable to be a key intermediate and performance of the key reaction, ie., the Dieckmann cyclization of 16 in order to prepare the β-keto ester 17 would trigger off the successful conversion to the final target 1.



Meanwhile the key intermediate 16 is a 2,3-disubstituted cyclopentanone. Recently the author published [4] the general synthetic method for 2,3-disubstituted cyclopentanone derivatives by the palladium-catalyzed cyclization and its details are also described in Chapter two. By use of this method, the cyclopentanone 19 would be synthesized from the β-keto ester 18 with an appropriate side chain expressed by R which is synthetic equivalent to 2-methoxycarbonylbutyl group. Dealkoxycarbonylation of 19 followed by conversion of the vinyl group in 20 to acetic acid segment would provide the requisite intermediate 16. Having the hopeful deduction by above retro-synthetic analysis in mind, the author set about the synthesis of 1. The next section deals with the results of stage of the scenario.



18 19



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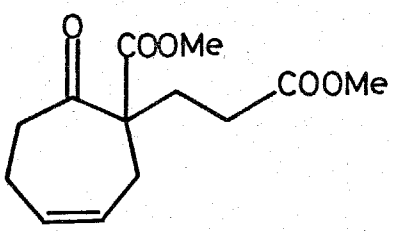
R : $CH_2CHCH_2CH_3$
$COOCH_3$

5-2 Results and Discussion

5-2-1 Construction of the Key Intermediate 16

The synthetic pathway leading to the key compound 16 is outlined in Scheme 5-3. The β-keto ester 21, available by the alkylation of dianion of methyl acetoacetate with trans 1-chloro-4-phenoxy-2-butene (see Chapter two), was converted to the substituted β-keto ester 22 in 68% yield by the Michael addition of 21 onto methyl acrylate in the presence of a catalytic amount of sodium methoxide in methanol. Then the adduct 22 was subjected to cyclization by using 1 mol% of palladium(II) acetate and 4 mol% of triphenylphosphine as catalysts in refluxing acetonitrile for 1 h. The cyclopentanone 23 was obtained in 98.8% yield. In the NMR spectrum of the product 23, four singlet resonances attributable to the methyl ester protons were observed at δ 3.53, 3.56, 3.60, and 3.65 ppm (ratio of peak height, 1:2:2:1), which indicated that 23 was a mixture of diastereoisomers. In addition, no other isomers such as the cyclpentanone 29 and/or the O-alkylated product 30 could be isolated.



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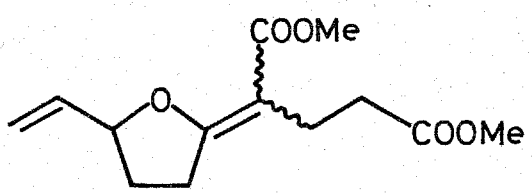

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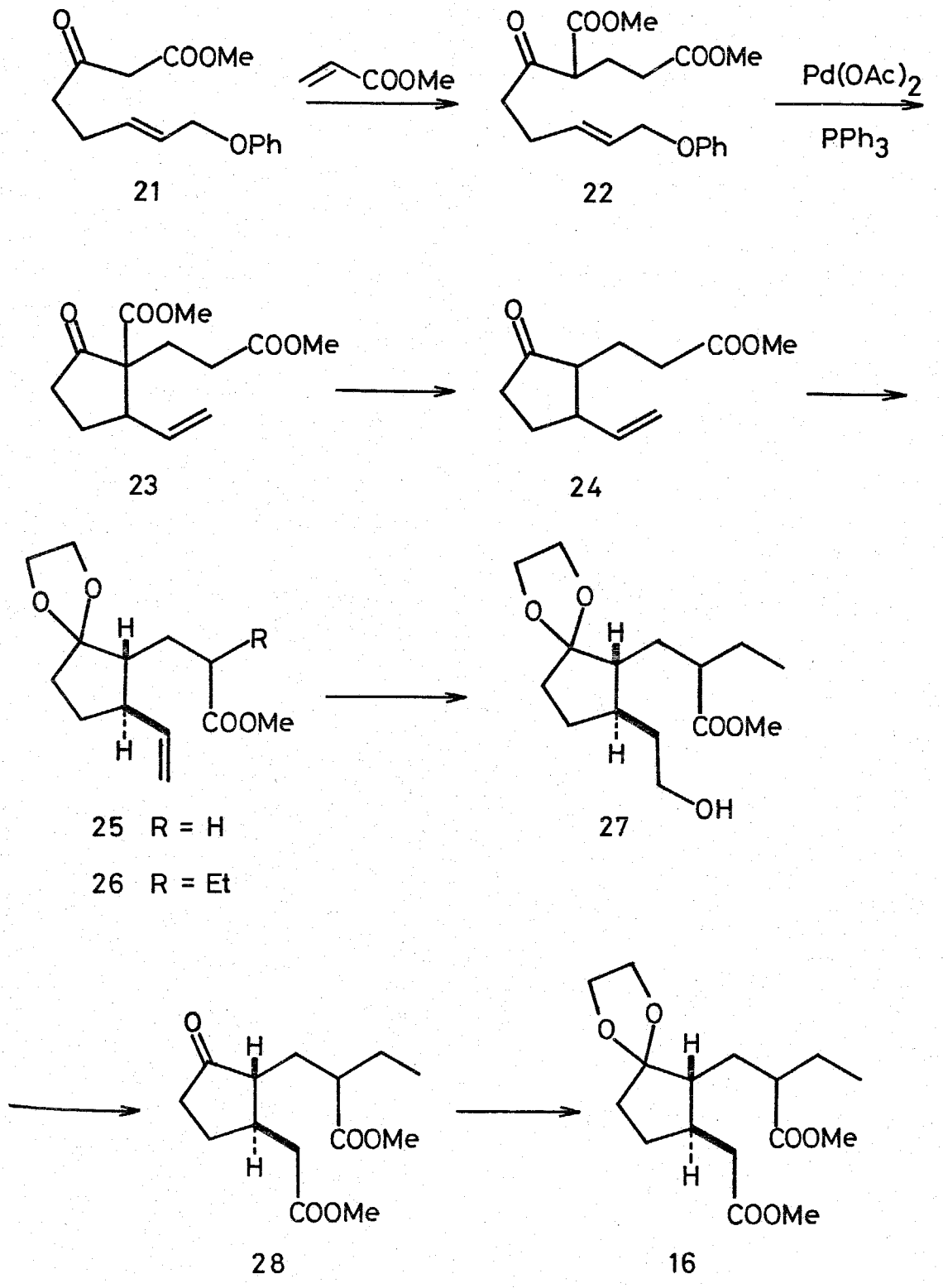
Scheme 5-3 Construction of the Key Intermediate 16



Demethoxycarbonylation [9] of 23 with sodium iodide (3 equiv.) in HMPA at 110°C for 9 h afforded in 89.7% yield the keto ester 24, which was then converted to 25 in 99% yield by using ethylene glycol (6 equiv.) and methyl orthoformate (1.5 equiv.) in THF containing a trace amount of p-toluenesulfonic acid at room tempterature.[10] To introduce the requisite side chain necessary to the target 1, the acetal 25 was alkylated according to the procedure developed by Schlessinger.[11] Treatment of 25 with lithium diisopropylamide in THF containing HMPA followed by the addition of ethyl iodide gave 26 in 88.9% yield.

Then the latent acetic acid side chain was unmasked. Hydroboration of 26 with 9-BBN[12] in THF followed by a usual work-up (alkaline hydrogen peroxide) afforded the alcohol 27 in 92% yield. Oxidation of 27 by excess Jones reagent [13] followed by esterification with ethereal diazomethane produced the crude ester 28 which was then protected with ethylene glycol in the presence of a catalytic amount of p-toluenesulfonic acid. After chromatography, the key intermediate 16 was obtained in 72% yield from the alcohol 27. In accordance with ample literatures dealing with stereochemistries of 2,3-disubstituted cyclopentanone acetals,[14] the trans stereochemistry of the acetal 16 was assigned with regard to the two side chains as denoted in the formula 16.

5-2-2 Total Synthesis of Coronafacic Acid

Now having set the stage for the Dieckmann cyclization of 16 in order to prepare the β-keto ester 17, the author set out to search for the proper conditions. Some results are shown in Table 5-1. At first the cyclization was tried by using sodium hydride as a base in refluxing THF,

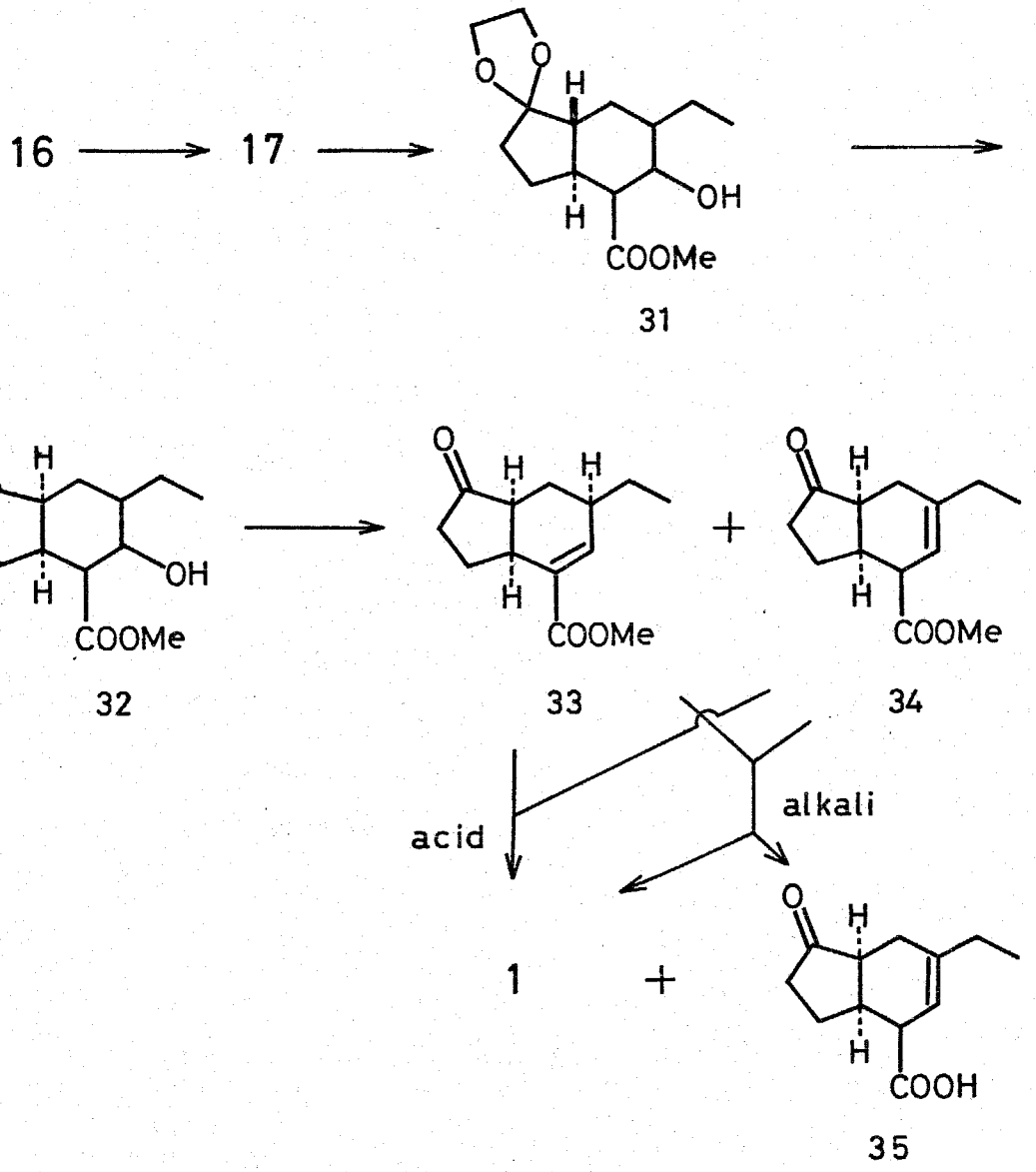
Table 5-1 The Dieckmann Cyclization of 16

Run	Base (equiv.)	Solvent	Conditions	Yield of 17 (%)
1	NaH (10)	THF	reflux, 12h	0
2	LDA (7)	THF	-70 to +20°C, 3h	45
3	t-BuOK (5)	THF	+5 to r.t. 2h	74

but no desired product 17 waa obtained (Run 1), while lithium diisopropylamide (LDA) effected the reaction unidirectionally affording 17 in 45% yield(Run 2). Finally the best conditions till now were found out: Subjection of 16 with potassium tert-butoxide in THF produced the β-keto ester 17 in 74% yield (Run 3).

The remaining transformations to coronafacic acid (1) from the intermediate 17 thus synthesized were excuted as delineated in Scheme 5-4. Thus sodium borohydride reduction of 17 followed by in situ acid-catalyzed hydrolysis of the resulting alcohol 31 gave in 95.4% yield the keto alcohol 32 which is the Jung's intermediate [8] for 1. The cis stereochemistry at ring juncture in the product 32 was tentatively assigned because the inversion of the stereochemistry of the cis-ring junction to trans-one during the conversion of 17 to 32 could be expected by considering the overwhelming stability of the latter.[15] Dehydration of 32 with phosphorous oxychloride (5 equiv.) and pyridine (7 equiv.) in refluxing toluene afforded a mixture of 33 and 34 (81%). The ratio of each products was assessed to be approximately 2:3 by calculation of NMR integration-ratio of two multiplet resonances centered at δ 6.9 and 5.4 ppm attributable to the olefin protons of 33 and 34, respectively.

Scheme 5-4 Total Synthesis of Coronafacic Acid (1)



The ratio of 33 and 34 varied roughly from 2:3 to 1:1 when the dehydration was repeated several times under conditions slightly different, one another. The results are in contrast with the Jung's outcome [8] where 33 was produced exclusively from 32 in 61% yield. Then a 1:1 mixture of 33 and 34 was hydrolyzed by use of sodium hydroxide in THF at room temperature in expectation of the concomitant olefin-isomerization to desired direction, but the products thus obtained were an about 1:1 mixture of coronafacic acid (1) and its double bond regio-isomer 35. No isomerization of 34 to 33 and/or 35 to 1 was observed since the ratio of 1 and 35, calculated by the NMR olefinic proton resonances, did not change. Whereas the pure ester 33, obtained by the treatment of 1 with ethereal diazomethane (vide infra), was hydrolyzed under the same conditions (NaOH in THF-water). In this case, the product isolated was only 1 (71% yield). On the other hand, the mixture of 33 and 34 (ratio 1:1) was subjected to hydrolysis in refluxing 3N hydrochloric acid and toluene (1:2). Surprisingly, coronafacic acid (1) could be obtained exclusively in 68% yield. Careful analysis of the NMR spectrum of the product detected no signals attributable to the olefin proton of 35 centered at δ 5.4 ppm.

From above experiments, the author concluded that the acidid conditions for 33 and/or 34 and more mildly the basic conditions for 33 only were the best choice to complete the synthesis.

5-3 Experimental

Dimethyl 2-((E)-2-Oxo-6-phenoxy-4-hexenyl)-1,5-pentanedioate (22)

To a solution of the β-keto ester 21 (1.10 g, 4.20 mmol), sodium methoxide (15 mg, 0.28 mmol), and a catalytic amount of 2,5-di-tert-butylhydroquinone in dry methanol (10 ml) was added methyl acrylate (241 mg, 2.80 mmol) nuder nitrogen at room temperature. After having been stirred at the same temperature for 36 h, the reaction mixture was poured into brine and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated *in vacuo* to give an oil. The silica gel column chromatography of the residue with benzene-hexane-ether as an eluent, 25:25:1 to 10:10:1, afforded the diester 22 (660 mg, 67.7% yield from methyl acrylate) as a colorless oil.

Bp. 173-177°C (0.04 mmHg);

IR (neat) 1737 (C=O), 1716 (C=O), 1597, 1584, 1474, 1425, 1241, 1174, 1028, 1006, 977, 744, 690 cm^{-1};

NMR (CCl_4) δ 1.83-2.78 (m, 8H, $(CH_2)_2$, $(CH_2)_2$), 3.40-3.70 (m, 1H, CH), 3.53 and 3.60 (2s, total 6H, $2CH_3O$), 4.27-4.45 (m, 2H, CH_2O), 5.58-5.79 (m, 2H, CH=CH), 6.63-7.33 (m, 5H, aromatic).

Methyl 3-(1-Methoxycarbonyl-2-oxo-5-vinylcyclopentane)propionate (23)

A solution of palladium acetate (15 mg, 0.067 mmol) and triphenylphosphine (71 mg, 0.27 mmol) in oxygen-free acetonitrile (30 ml), which was prepared by bubbling with nitrogen for 30 min before use, was refluxed under nitrogen for 15 min. Then the ester 22 (2.34 g, 6.72 mmol) dissolved in the oxygen-free acetonitrile (15 ml) was slowly added

to the solution under reflux over a period of 10 min. The resulting reddish-brown solution was refluxed for an additional 1 h. The reaction mixture was cooled to room temperature and passed through a short silica gel column. The filtrate was concentrated *in vacuo* to give an oil, which consisted of the desired product 23 and phenol as major components.

Then 2,3-dihydropyran (790 mg, 9.41 mmol) was added to a solution of the above residue and a trace of p-toluenesulfonic acid in dry dichloromethane (10 ml) at 0°C (ice-water bath) to produce tetrahydropyranyloxybenzene and to purify 23 by chromatography more easily since the R_f values of 23 and phenol were almost equal, each other (R_f: 0.34 for 23; 0.38 for phenol; 0.63 for tetrahydropyranyloxybenzene on silica gel TLC, benzene-hexane-ether, 2:2:1). The solution was slowly warmed up to room temperature over 2 h and the reaction was quenched by the addition of triethylamine (*ca* 1 ml). The volatile materials were evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with benzene-hexane-ether, 25:25:1 to 5:5:1, gave the cyclopentanone 23 (1.69 g, 98.8% yield).

Bp. 165-168°C (3 mmHg);

IR (neat) 1735 (C=O), 1637 (C=C), 1226, 1198, 1173, 1053, 992, 921 cm^{-1};

NMR (CCl_4) δ 1.68-2.87 (m, 9H, $(CH_2)_2CH$, $(CH_2)_2$), 3.53, 3.56, 3,60, and 3.65 (4s, total 6H, $2CH_3O$), 4.89-6.10 (m, 3H, CH_2=CH).

Methyl 3-(2-Oxo-5-vinylcyclopentane)propionate (24)

To a mixture of sodium iodide (2.27 g, 15.1 mmol) in HMPA (5 ml) were added the cyclopentanone 23 (1.28 g, 5.04 mmol) and water (10 drops).

The resulting mixture was immersed in an oil bath preheated at 110°C and stirring at 110°C was continued for 9 h.

The cooled reaction mixture was poured into brine and the product was extracted four times with ether. The combined solutions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residual oil was chromatographed on silica gel eluting with benzene-hexane-ether to give pure 24 (886 mg, 89.7% yield).

Bp. 115-119°C (3 mmHg);

IR (neat) 1735 (C=O), 1637 (C=C), 1197, 1172, 994, 917 cm^{-1};

NMR (CCl_4) δ 1.44-2.61 (m, 10H, $(CH_2)_2(CH)_2(CH_2)_2$), 3.56 (s, 3H, CH_3), 4.89-6.10 (m, 3H, CH_2=CH).

Methyl 3-(2,2-(1,3-Dioxolane)-5-vinylcyclopentane)propionate (25)

To a solution of the ketone 24 (264 mg, 1.35 mmol), ethylene gylcol (503 mg, 8.10 mmol), and methyl orthoformate (215 mg, 2.03 mmol) in dry THF (3 ml) was added a trace of p-toluenesulfonic acid under nitrogen atmosphere at room temperature. Stirring was continued at room temperature for 4 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and the mixture was extracted three times with ethy acetate. The combined extracts were washed with brine and dried over magnesium sulfate. The remaining material was chromatographed on silica gel. Elution with benzene-hexane-ether, 10:10:1, afforded the acetal 25 (320 mg, 99% yield).

Bp. 135-139°C (3 mmHg);

IR (neat) 1737 (C=O), 1639 (C=C), 1196, 1171, 1154, 1036, 994, 914 cm^{-1};

NMR (CCl_4) δ 1.24-2.43 (m, 10H, $(CH_2)_2(CH)_2(CH_2)_2$), 3.54 (s, 3H, CH_3),

3.82 (br s, 4H, $(CH_2)_2O$), 4.74-5.98 (m, 3H, CH_2=CH);

^{13}C NMR ($CDCl_3$) δ 23.0, 28.7, 32.4, 35.6, 48.4, 50.4, 51.4, 64.4, 114.6, 117.7, 142.2, 174.3.

Methyl 3-(2,2-(1,3-Dioxolane)-5-vinylcyclopnetane)-2-ethylpropionate (26)

To a solution of diisopropylamine (967 μl 6.90 mmol) in dry THF (4 ml) cooled to 0°C (ice-water bath) was added dropwise n-butyllithium in hexane (1.55M, 2.96 ml, 4.60 mmol) under nitrogen. After 20 min, the solution was cooled to -70°C (dry ice-acetone bath). Then a solution of the ester 25 (552 mg, 2.30 mmol) in dry THF (4 ml) and HMPA (0.8 ml, 4.6 mmol) were added dropwise to this solution successively. The reaction temperature was slowly elevated up to -15°C over 90 min and then lowered again to -70°C. Ethyl iodide (368 μl, 4.6 mmol) was injected to the solution at -70°C. The solution was stirred at -70°C for further 2.5 h and then allowed to warm to 0°C over 2 h. The reaction was quenched by addition of solid ammonium chloride (excess) and then brine was added to the mixture. The product was extracted three times with ethyl acetate and the combined extracts were washed with brine and dried over magnesium sulfate. After evaporation of the solvent *in vacuo*, the crude product was chromatographed on silica gel with benzene-hexane-ether, 25:25:1 to 5:5:1,as an eluent to give 26 (548 mg, 88.9% yield) as a colorledd oil.

Bp. 114-117°C (1 mmHg);

IR (neat) 1734 (C=O), 1641 (C=C), 1196, 1163, 1039, 995, 946, 914 cm^{-1};

NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H, CH_3), 1.16-2.76 (m, 11H, $(CH_2)_2$-$(CH)_2CH_2CHCH_2$), 3.62 (s, 3H, CH_3O), 3.89 (br s, 4H, $(CH_2)_2$), 4.79-6.08

(m, 3H, CH_2=CH).

Methyl 3-(2,2-(1,3-Dioxolane)-5-)2-hydroxyethyl)cyclopentane)-2-ethyl-propionate (27)

To a solution of the olefin (704 mg, 2.63 mmol) in dry THF (5 ml) was added 9-BBN in THF (0.70M, 4.9 ml, 3.4 mmol) at room temperature under nitrogen. After 30 min at room temperature, TLC analysis showed the reaction to complete and the reaction was quenxhed by careful addition of 3N aqueous sodium hydroxide (4 ml). Then 35% aqueous hydrogen peroxide (3 ml) was added slowly to the solution and the resulting mixture was stirred at 50°C for 1 h. After the mixture had been cooled to room temperature, excess granular sodium thiosulfate was added to quench excess hydrogen peroxide. Brine was added to the mixture and the mixture was extracted four times with ethyl acetate. The combined solutions were washed with brine, dried over magnesium slufate, and concentrated in vacuo. Silica gel column chromatography of the crude material with benzene-THF, 6:1, afforded the pure alcohol 27 (667 mg, 92.0% yield) as a colorless oil.

Bp. 111-115°C;

IR (neat) 3431 (OH), 1731 (C=O), 1197, 1167, 1039 cm^{-1};

NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 3H, CH_3), 1.14-2.71 (m, 13H, $(CH_2)_2$, $CH_2(CH)_2CH_2CHCH_2$), 2.88 (br s, 1H, OH), 3.44-3.61 (m, 2H, CH_2OH), 3.66 (s, 3H, CH_3O), 3.89 (br s, 4H, $(CH_2)_2$).

Methyl 3-(2,2-(1,3-Dioxolane)-5-methoxycarbonylmethylcyclopentane)-2-ethylpropionate (16)

To a solution of the alcohol 27 (667 mg, 2.41 mmol) in acetone (10 ml) was added dropwise the excess Jones reagent at room temperature until reddish-brown color of the mixture remained. Stirring was continued at room temperature for 30 min and the excess reagent was destroyed by addition of 2-propanol (ca 1 ml). Most of the solvent was removed in vacuo and the remaining oil was partitioned between ethyl acetate and brine. The aqueous phase was further extracted twice with ethyl acetate and the combined extracts were washed twice with brine and dried over magnesium sulfate. The solvents were removed in vacuo to give the crude carboxylic acid corresponding to the ester 10a.

The acid thus prepared was treated with excess ethereal diazomethane for 15 min at room temperature and the solution was concentrated in vacuo to afford the crude keto ester 28. Silica gel chromatography of the product which was obtained in another experiment afforded methyl 2-ethyl-3-(2-methoxycarbonylmethyl-5-oxocyclopentane)propionate (28):

Bp. 125-130°C;

IR (neat) 1736 (C=O), 1198, 1171 cm^{-1};

NMR (CCl_4) δ 0.89 (t, J = 7 Hz, 3H, CH_3), 1.18-2.92 (m, 13H, $(CH_2)_2$, $O_2CCH_2(CH)_2CH_2CH(CO_2)CH_2$), 3.60, 3.63, and 3.67 (3s, total 6H, $2CH_3O$).

The above crude keto ester 28 was then added to a benzene (ca 50 ml) solution of ethylene glycol (225 mg, 3.63 mmol) and a catalytic amount of p-toluenesulfonic acid. The solution was refluxed under nitrogen with continuous removal of generated water for 5 h and cooled to room temperature. The solution was added to saturated aqueous sodium bicarbonate and the product was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and

evaporated *in vacuo*. The residual oil was purified by chromatography on silica gel by using benzene-hexane-ethyl acetate, 20:20:1 to 5:5:1, as an eluent to give the diester 16 (547 mg, 72.0% yield from the alcohol 27) as a colorless oil.

Bp. 157-161°C (2 mmHg) ;

IR (neat) 1734 (C=O), 1194, 1163 cm^{-1};

NMR (CCl_4) δ 0.88 (t, J = 7 Hz, 3H, CH_3), 1.14-2.64 (m, 13H, $(CH_2)_2$-$(CH)_2CH_2CHCH_2$, CH_2COO), 3.58 (s, 6H, $2CH_3O$), 3.80 (br s, 4H, $(CH_2)_2$).

Methyl 1,1-(1,3-Dioxolane)-6ξ-ethyl-3aα,4,5,6,7aβ-hexahydro-5-oxo-4ξ-indanecarboxylate (17)

To a suspension of potassium tert-butoxide (191 mg, 1.71 mmol) in dry THF (2 ml) under nitrogen at 0°C (ice-water bath) was slowly added the diester 16 (107 mg, 0.341 mmol) dissolved in dry THF (2 ml). The solution was allowed to warm gradually to room temperature over 2 h. The reaction was quenched by dropwise addition of saturated aqueous aodium bicarbonate and the mixture was extracted three times with ethyl acetate. The combined solutions were washed with brine, dried over magnesium sulfate, and then evaporated *in vacuo*. Chromatography of the residue on a silica gel column by using benzene-hexane-ethyl acetate, 20:20:1 to 5:5:1,as an eluent afforded the pure β-keto ester 17 (71 mg, 74% yield).

Bp. 149-153°C (2 mmHg);

IR (neat) 1743 (C=O), 1710 (C=O), 1304, 1168, 1035, 946, 786, 760 cm^{-1};

NMR ($CDCl_3$) δ 0.89 (t, J = 7Hz, 3H, CH_3), 1.12-2.70 (m, 11H, $(CH_2)_2(CH)_2$-CH_2CHCH_2), 3.28 (dd, J = 11Hz, J = 5 Hz, 1H, CH), 3.70 (s, 3H, CH_3O),

3.87 (br s, 4H, $(CH_2)_2O$).

Methyl 6ξ-Ethyl-3aα,4,5,6,7,7aα-hexahydro-5ξ-hydroxy-1-oxo-4ξ-indanecarboxylate (32)

To a solution of the β-keto ester 17 (223 mg, 0.791 mmol) in methanol (3 ml) was added sodium borohydride (30 mg, 0.79 mmol) at 2°C. After 15 min, acetic acid (ca 0.3 ml) was added to the solution at the same temperature over 10 min and then 3N hydrochloric acid (2 ml) was added. Stirring was continued for 2 h at room temperature and the mixture was poured into brine. The product was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to leave an oil, which was chromatographed on silica gel by using benzene-hexane-THF, 20:10:1 to 10:5:1, as an eluent to give the alcohol 32 (181 mg, 95.4% yield) as white crystals.

Mp. 107-118°C (hexane containing a small amount of ether);

IR (Nujol) 3422 (OH), 1720 (C=O), 1194, 1175, 1148, 1009, 970, 828 cm^{-1};

NMR ($CDCl_3$) δ 0.68-3.18 (m, 16H, $(CH_2)_2(CH)_2CH_2CHCH_2CH_3$, $CHCO_2$,OH), 3.76 (s, 3H, CH_3O), 3.98-4.13 (m, 1H, CHOH).

Methyl 6β-Ethyl-3aα,6aα,7,7aα-tetrahydro-1-oxo-4-indanecarboxylate (33) and Methyl 6-Ethyl-3aα,4,7,7 aα-tetrahydro-1-oxo-5ξ-indanecarboxylate (34)

To a solution of 32 (115 mg, 0.479 mmol) and pyridine (270 μl, 3.35 mmol) in dry toluene (3 ml) under nitrogen was added phosphorous oxychloride (223 ml, 2.40 mmol) at room temperature. The solution was

refluxed for 30 min and then cooled to room temperature. TLC analysis showed the reaction to be complete and the reaction was quenched by addition of water. The mixture was extracted three times with ether and the combined ethereal solutions were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the resulting material was chromatographed on silica gel. Elution with benzene-hexane-ether, 25:25:1 to 5:5:1, afforded a mixture of the α,β- and β,γ-unsaturated esters **33** and **34** (86 mg, 81% yield). The ratio of **33** and **34** was calculated roughly 2:3 by integration of the NMR resonances centered at δ 6.89 and 5.36 ppm corresponding to proton of α,β- and β,γ-isomers, respectively.

IR (neat) 1736, 1716 (shoulder), 1638, 1257 cm^{-1};

NMR (CCl_4) δ 0.77-3.40 (m, 14H, $(CH_2)_2CHCHCH_2$, CH, CH_2CH_3), 3.67 and 3.69 (2s, total 3H, CH_3O), 5.27-5.49 (m, 0.6H, CH=C (β,γ-isomer)), 6.84-6.97 (m, 0.4H, CH=C (α,β-isomer)).

Coronafacic Acid (1) from a Mixture of 33 and 34

To a mixture of **33** and **34** (22 mg, 0.099 mmol, α,β- : β,γ-isomer *ca* 1:1) dissolved in toluene (2 ml) was added 3N hydrochloric acid (1 ml) and the solution was refluxed for 20 h. The cooled solution was extracted three times with ethyl acetate. The combined solutions were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The remaining material was chromatographed on silica gel to give pure coronafacic acid (**1**) (14 mg, 68% yield) as white amorphous solids.

IR (Nujol) 1692 cm^{-1};

NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, CH_3), 1.12-3.01 (m, 10H, $(CH_2)_2CH$, CH_2CHCH_2), 3.02-3.47 (m, 1H, CHC=O), 7.10-7.27 (m, 1H, CH=C), 7.27-7.52 (m, 1H, OH, variable).

Methyl 6β-Ethyl-3aα,6α,7,7aα-tetrahydro-1-oxo-4-indanecarboxylate (33) from Coronafacic Acid (1)

To synthetic coronafacic acid (1) (11 mg, 0.053 mmol) in ether (3 ml) was added excess ethereal diazomethane at room temperature. After 10 min, volatile materials were removed in vacuo and the remaining oil was chromatographed on silica gel by using benzene-hexane-ether, 25:25:1 to 5:5:1, to give the pure ester 33 (11 mg, 94% yield).

Bp. 132-138°C (2 mmHg);

IR (neat) 1736 (C=O), 1711 (C=O), 1639, 1253, 748, 682 cm^{-1};

NMR (CCl_4) δ 1.00 (t, J = 6 Hz, 3H, CH_3), 1.17-2.89 (m, 10H, $(CH_2)_2CH$, CH_2CHCH_2), 3.10-3.49 (m, 1H, CHC=O), 3.69 (s, 3H, CH_3O), 6.82-6.97 (m, 1H, CH=C).

Coronafacic Acid (1) from the Ester 33

To a soultion of the ester 33 (12 mg, 0.054 mmol) in THF (0.5 ml) was added 1N aqueous sodium hydroxide (0.5 ml). Stirring was continued at room temperature for 8 h and the solution was acidified by addition of 3N hydrochloric acid. The mixture was extracted three times with ethyl acetate. The combined solutions were washed with brine, dried over magnesium sulfate, and evaporated in vacuo to leave the crude acid. The crude product was chromatographed on silica gel to give pure coronafacic acid (1) (8 mg, 71% yield), which was homogeneous by NMR

analysis and identical with that obtained from a mixture of 33 and 34 by the acid catalyzed hydrolysis (vide supra).

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CHAPTER SIX

STUDIES ON THE SYNTHESES OF FUNCTIONALIZED STEROIDS AT C-18 POSITION. PART ONE.

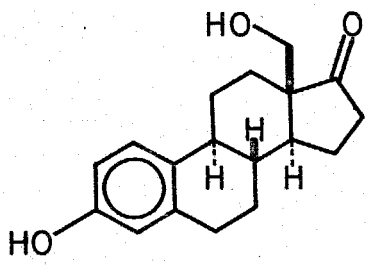
SIMPLE SYNTHESIS OF 18-HYDROXYESTRONE

Summary

The title compound, 18-hydroxyestrone (1) was synthesized [1] from 2-(4-methoxybenzocyclobutenyl)ethyl iodide (17) and methyl 2-oxo-5-vinylcyclopentane-1-carboxylate (20), which was prepared from methyl 3-oxo-8-phenoxy-6-octenoate (19) by the palladium-catalyzed cyclization. Thus methyl 1α-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5trien-7-yl)ethyl)-2-oxo-5β-vinylcyclopentane-1-carboxylate (27), prepared from the alkylation of 20 with 17 in 57% yield, was converted to 2,2-(1,3-dioxolane)-1α-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-5β-vinylmethanol (29) by protection of carbonyl group of 27 followed by lithium aluminum hydride reduction. Then 29 was heated to produce in 75% yield 17,17-(1,3-dioxolane)-3-methoxyestra-1,3,5(10)-trien-18-ol (31), which was converted to 1 easily by the usual way.

6-1 Introduction

6-1-1 Background



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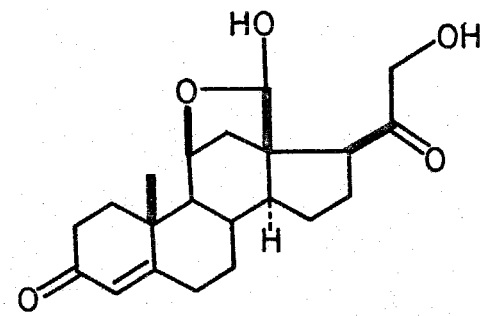

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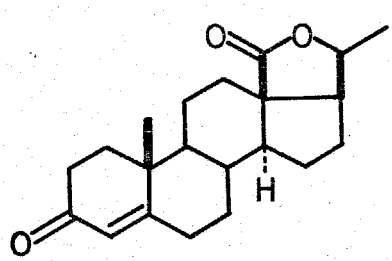

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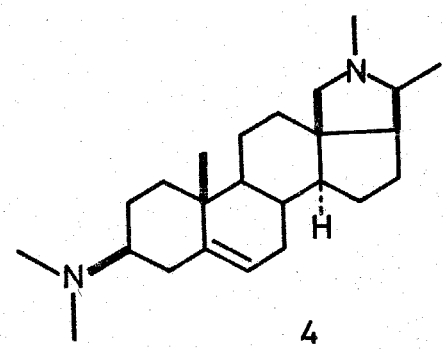
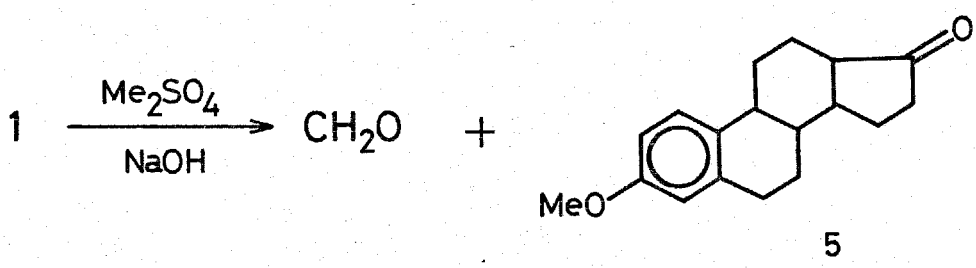


4

There are many steroids which are functionalized at C-18 position.[2,3] These include, for example, 18-hydroxyestrone (1), aldosterone (2), 20-hydroxy-3-oxopregn-4-en-18-oic acid lactone (3), and conessine (4). Until now total synthetic approaches to these compounds have been scarcely performed,[4] while partial syntheses of these steroids have been studied.[5] This fact prompted the author to explore general synthetic entries to above functionalized steroids. At first, the synthesis of 18-hydroxyestrone was undertaken and described in detail in this chapter.[1]

In 1957, Marrian and his colleagues isolated [6,7] a Kober chromogen (KC-6) from the urine of pregnant women and proposed its structure as 18-hydroxyestrone (1) by the study of its spectral and chemical properties. Confirmatory proof in favor of this structure was provided by Johnson and Marrian et al.[8] by the synthesis of 18-norestrone methyl ether (5), which was identical with a chemical degradation product of KC-6.



5

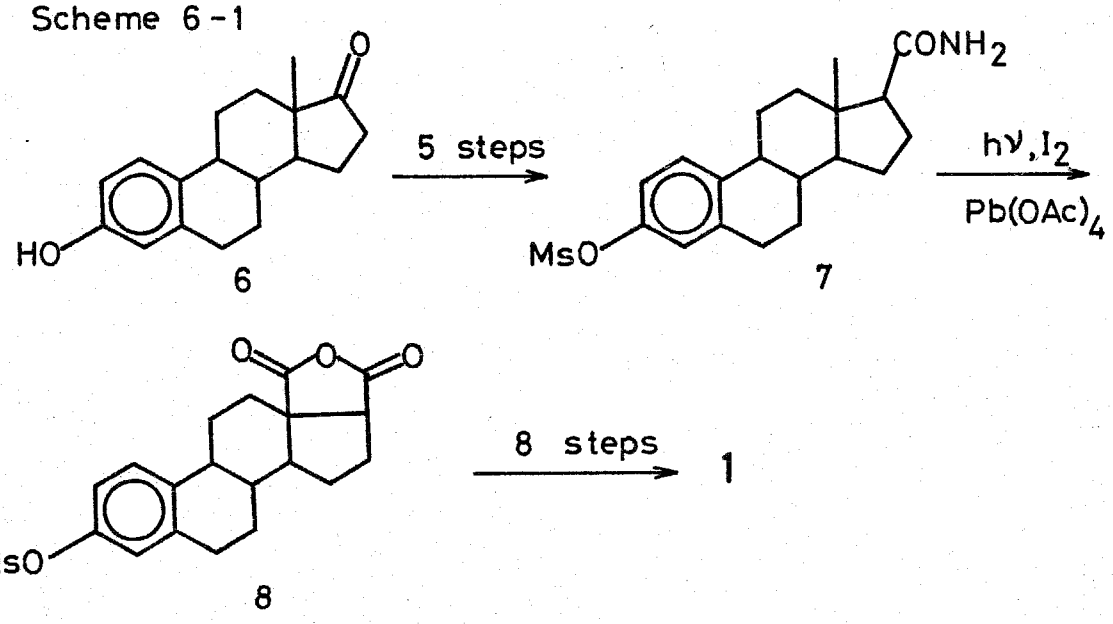
Later, 1 could be obtained by incubation of 18-hydroxyandrost-4-ene-3,17-dione with human placental tissue,[9] and also by hydroxylation of estrone with adrenal tissue preparations.[7,10-12] But its pharmacological activities, however, have been scarcely studied since very small amount of 1 could be isolated from natural source such as the urine of pregnant women.

Up to date, three syntheses of 1 have been reported. In 1968, Barton and his co-workers carried out the partial synthesis of 1 starting from estrone (6) (Scheme 6-1) and provided final crucial proof of 1 in favor of the proposed structure.[13]

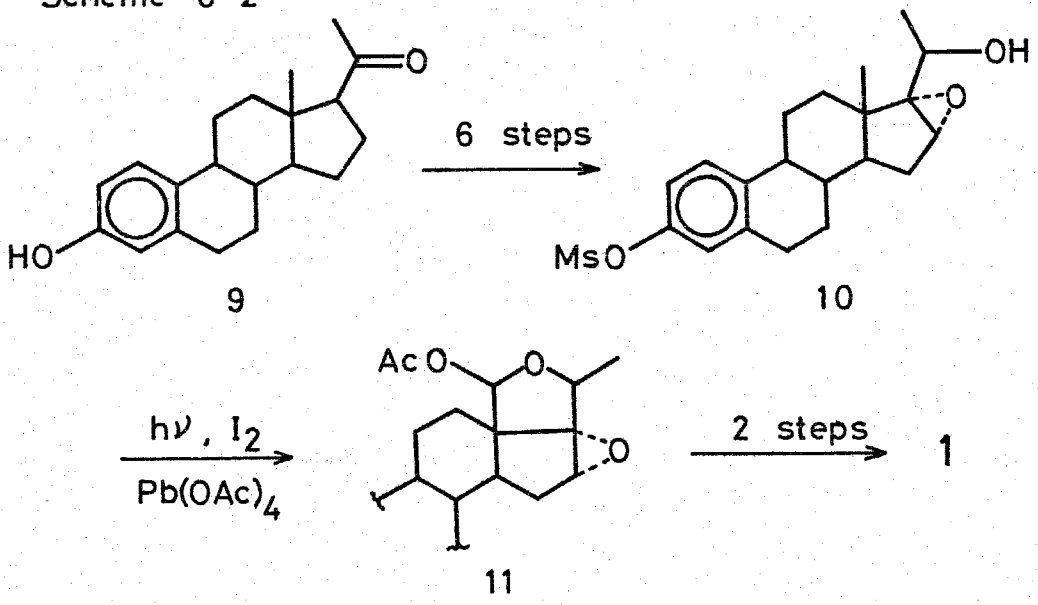
On the other hand, a shorter synthetic pathway to 1 was published by Breuer et al [14] as shown in Scheme 6-2.

However, these partial syntheses required multistep operations and the yields were low. In contrast to the above two partial

Scheme 6-1

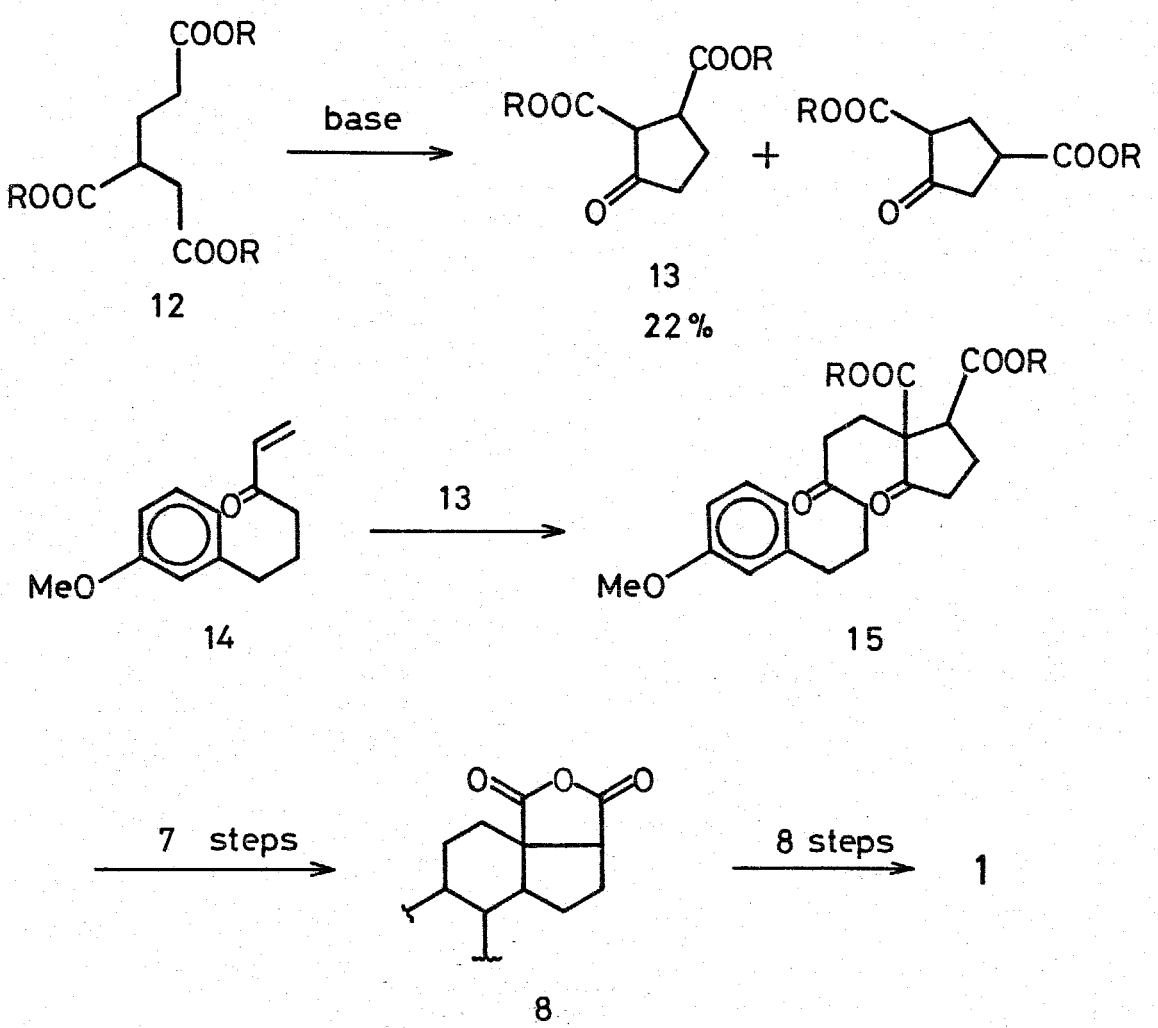


Scheme 6-2



syntheses, there is only one "non-partial" synthesis of 1 reported by Sen et al.[15] (Scheme 6-3), who claimed that their synthesis was the first formal "total" synthesis of 1. In their synthesis, the β-keto ester 13 was prepared from the triester 12 in a low yield and was added to the enone 14 to give 15 which was then converted to the Barton's intermediate 8 in 7 steps. However many steps are still required to complete the synthesis. Their synthesis implies that it seems to be

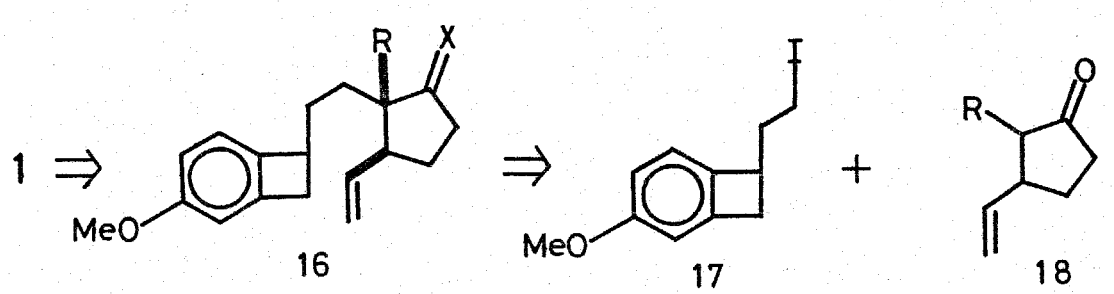
Scheme 6-3



difficulty itself to succeed in a total synthesis of this kind of steroids functionalized at C-18 with respect to absence of candidates for suitable starting materials.

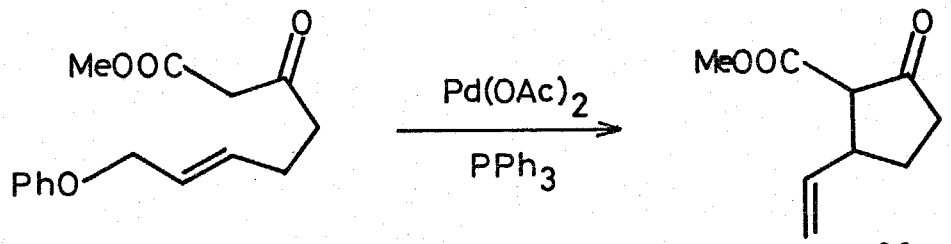
6-1-2 Synthetic Strategy

A retro-synthetic analysis of 1 led the author to adopt an alternative route to above syntheses of 1, which is based on the well-known thermal cycloaddition of an appropriate benzocyclobutene 16 developed by Kametani [16] and Oppolzer.[17] A number of common steroids have been synthesized by this methodology.[18-31] To perform the synthesis of 1 based on this methodology, the cyclopentanone 16 with trans stereochemistry between the vinyl and the functionalized 18-methyl group is an important intermediate. This compound 16 must be prepared, for example, by the alkylation of an enolate of 18 with 17. Since the synthesis of 17 have been established [23], a compound corresponding to 18 must be prepared easily and moreover must react with 17 in regio- and



R: oxidized methyl group

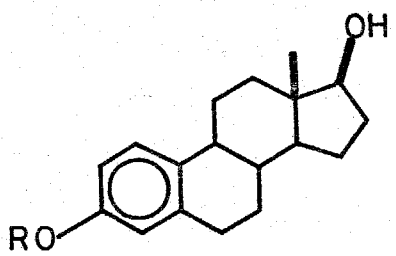
stereoselective fashion to produce 16 with the desired stereochemistry. Recently the author has developed [32] the facile preparation of 20 by the palladium-catalyzed cyclization of 19 which is described in detail in Chapter 2. The cyclopentanone 20 seems to be an ideal compound for 18 in all respects and hence it is from 20 that the successful



19 20

synthesis of 18-hydroxyestrone (1) is commenced.

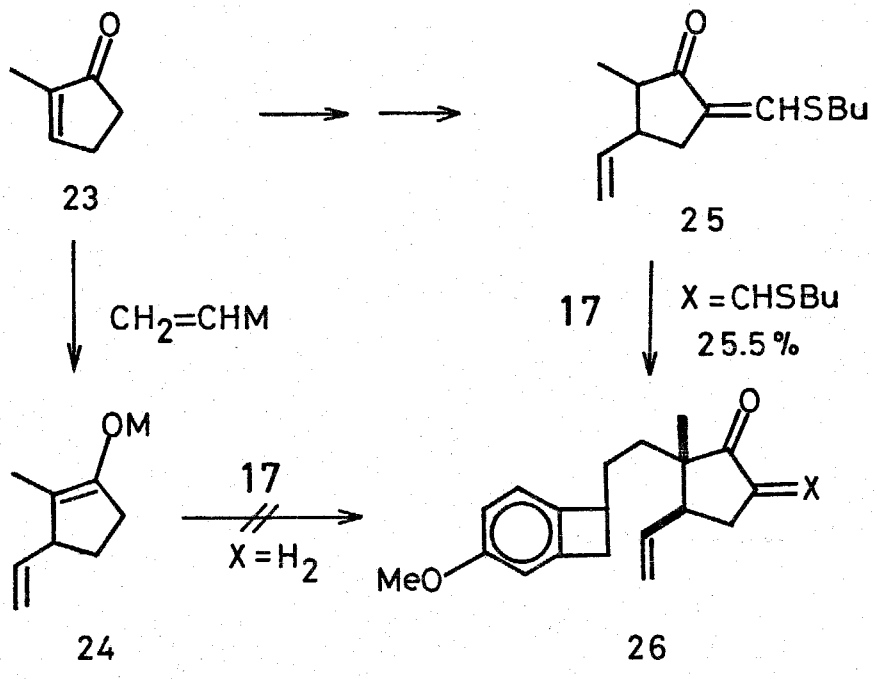
Moreover the author also met with success in the synthesis of estradiol methyl ether (21) from 16. Previously Kametani reported [23] in their estrone synthesis that 25 possessing n-butylthiomethylene group as a blocking group had been necessary to carry out the selective alkylation with 17 and, in practice, 26 (X = CHSBu) could be isolated



21 R = Me

22 R = H

from 25 only in 22.5% yield because the enolate anion 24, regioselectively derived from 23, could not afford 26 (X= H_2). It is not the modern method using alkylation of a regioselectively generated ketone enolate with an appropriate electrophiles suce as 17, but only the classical method using alkylation of an enolate derived from β-keto ester in the presence of weak base such as potassium carbonate that really can



solve the problem* of the stereoselective and , in particular, regioselective alkylation inherent in this methodology to synthesize common steroids such as estrone (6) and estradiol (22).

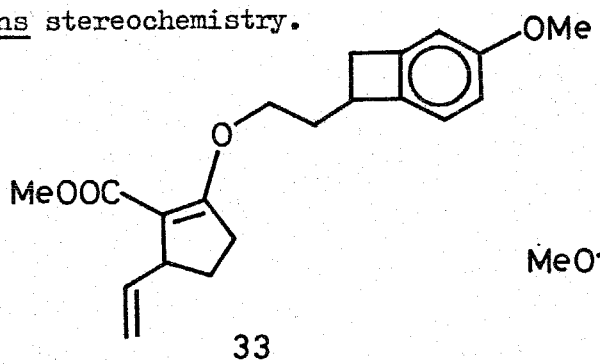
---

* Recently fruitful progresses can be seen with regard to this problem of carbon-carbon bond formation based on this methodology and as a result several estrone congeners have been synthesized [25-29,33-35] except for estrone (6) itself.

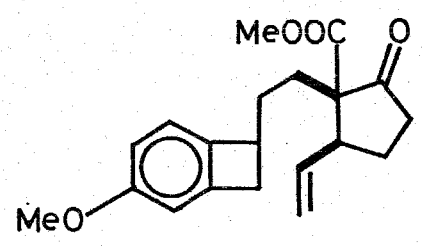
6-2 Results and Discussion

6-2-1 Total Synthesis of 18-Hydroxyestrone (1)

Synthetic pathway leading to 18-hydroxyestrone (1) is outlined in Scheme 6-4.[1] The key compound 20 was prepared according to the method described in Chapter 2,[32] while the benzocyclobutene 17 which is briefly mentioned in Appendix (vide infra) was synthesized by the method of Kametani.[23] At the outset, the cyclopentanone 20 was alkylated with 17 in the presence of potassium carbonate (10 equiv.) in refluxing acetone.[36] Careful chromatographic purification of the crude product afforded two C-alkylated compounds besides the O-alkylated one 33. Since the alkylation is expected to proceed preferetially in trans manner to the vinyl group (steric approach control), the major isomer (57% yield) was assigned to be the desired 27 and the minor one (below 4.6% yield) to be 34. This assignment was finally confirmed by the successive transformation of 27 to 18-hydroxyestrone of trans-anti-trans stereochemistry.



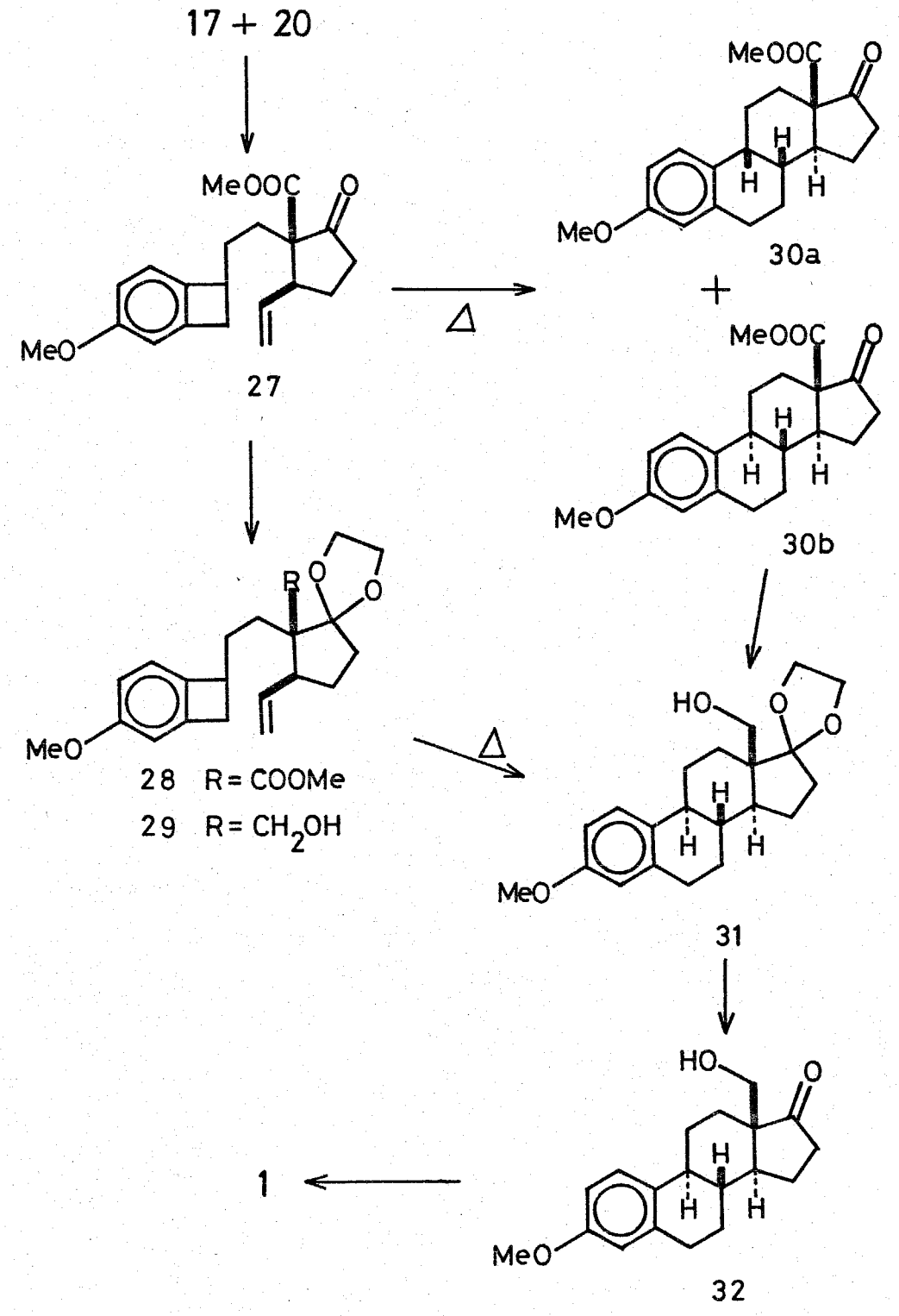
33

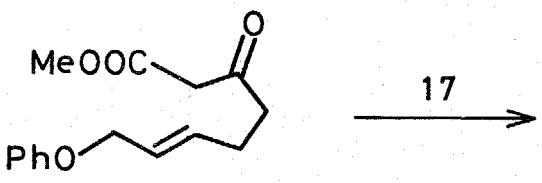


34

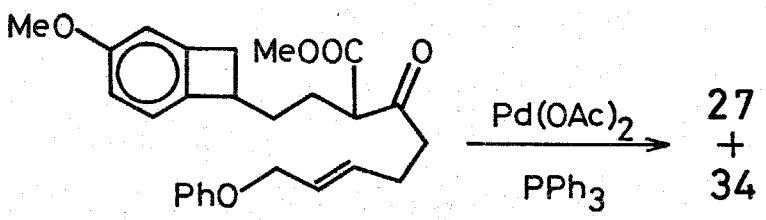
Incidentally speaking, the author attempted preliminarily another set of reactions to give 37. Thus the β-keto ester 19 was alkylated with 17 before the palladium-catalyzed cyclization to afford 35 in 87% yield. Subsequently 35 was cyclized in the presence of a catalytic

Scheme 6-4


17 + 20
MeOOC
O
MeO
27
Δ
MeOOC
O
H
H
H
MeO
30a
+
MeOOC
O
H
H
H
MeO
30b
R
O
O
MeO
28 R = COOMe
29 R = CH2OH
Δ
HO
O
O
H
H
H
MeO
31
HO
O
H
H
H
MeO
32
1



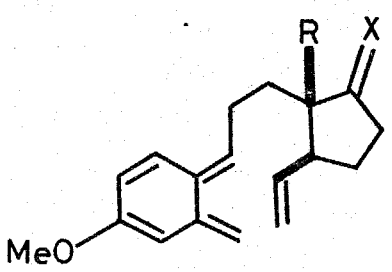
19



35

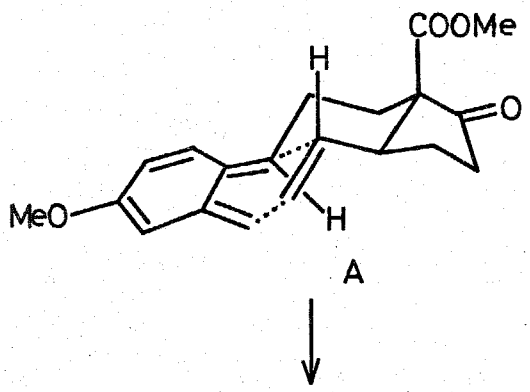
amount of palladium(II) acetate and triphenylphosphine. But 27 and 34 were obtained as a mixture in a ratio of 1:1. Therefore this preliminary route was abandoned.

Here, there are two routes leading to the intermediate 31 from which the target molecule would be synthesized easily. One is the way through the construction of steroids backbone before reduction of ester group to hydroxymethyl group and another is vice versa. At the outset, the former was examined. Thus 27 was heated in refluxing o-dichlorobenzene for 4 h to trigger off the opening of the cyclobutene ring in 27 and the subsequent intramolecular Diels-Alder reaction of the intermediate 36 (R = COOMe, X = O). Chromatography of the crude product afforded in 75% yield the mixture, whose NMR spectrum showed two singlet resonances due to methyl ester group at δ 3.58 and 3.63 ppm in a



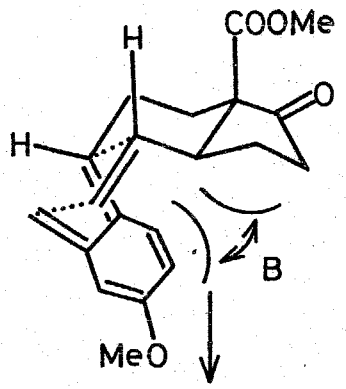
36

ratio of 4:1. Since the reaction expected to proceed through the more stable exo transition state A rather than endo state B which has steric repulsion between the aromatic and the cyclopentane ring as demonstrated by Kametani,[23] the major isomer was assigned to be 30b possessing trans B,C ring junction, whereas minor one to be cis 30a. Recrystallization of the mixture from carbon tetrachloride produced the pure trans isomer 30b, which was converted to the alcohol 31 in 71% yield by lithium aluminum hydride reduction with prior protection of the carbonyl group with ethylene glycol.



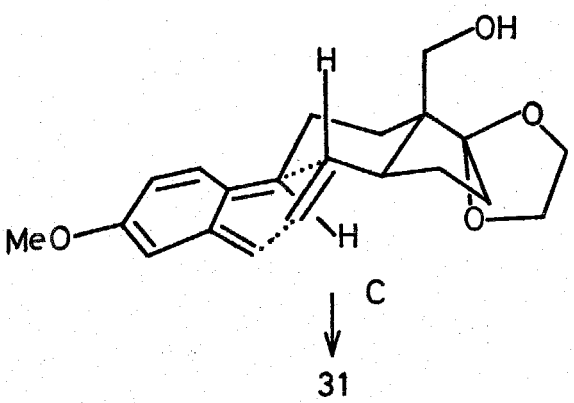
A

30b



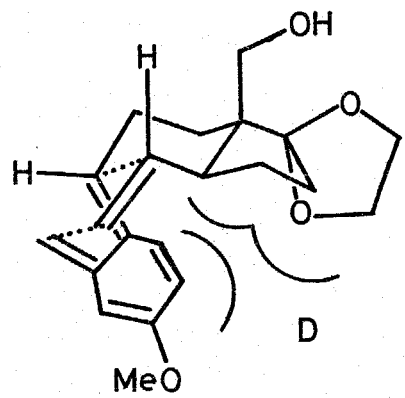
30a

On the other hand, the carbonyl group in 27 was protected with ethylene glycol affording 28 in 84% yield and subsequently 28 was reduced to the alcohol 29 in 87% yield. The cycloaddition of 29 in refluxing o-dichlorobenzene produced only 31 in 75% yield, whose homogeneity was confirmed by careful HPLC analysis and which was identified by comparison of its IR and NMR spectra with those of one derived from 30b. Compared with the results of the reaction of 27, the highly selective formation of 31 can be also explained by considering the intermediate 36 (R = CH_2OH, X = $O(CH_2)_2O$) as above. Namely, in the transition state D, the aromatic ring suffers from double steric repulsions with the cyclopentane ring and more strongly with the oxygen



C

31

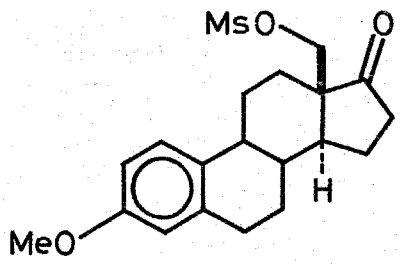


atom of the acetal group, while the transition state C leading to the desired product 31 has no such repulsions.

Then 31 was converted to 32 in 89% yield by the exposure to 3N hydrochloric acid in acetone. Finally treatment of 32 with boron tribromide in dichloromethane at -78°C for 1 h and then at 0°C for 1 h produced 18-hydroxyestrone (1) in 87% yield, which was identified by the IR (Nujol) spectrum (hydroxy group 3000-3650 cm^{-1} and carbonyl group at 1715 cm^{-1} [lit.[13] 1710 cm^{-1}]) and the NMR (pyridine) spectrum (δ 4.0, 2H, $C\underline{H}_2OH$ [lit.[14] δ 4.0 in d_5-pyridine]). The mass spectrum (m/e M^+ 286) was completely identical with the reported spectrum for the optically active one.

6-2-2 Synthesis of Estradiol Methyl Ether (21)

Having succeeded in the synthesis of 1, the author turned his attention to the second target. Thus the alcohol 32 was converted to the mesylate 37 in 83% yield with mesyl chloride in pyridine. Finally lithium aluminum hydride reduction of 37 cleanly produced estradiol methyl ether (21) in 76% yield. The IR and NMR spectra coincided to those of an authentic sample [37] which was synthesized by Dr. I. Shimizu of this laboratory from estrone methyl ether by hydride reduction.

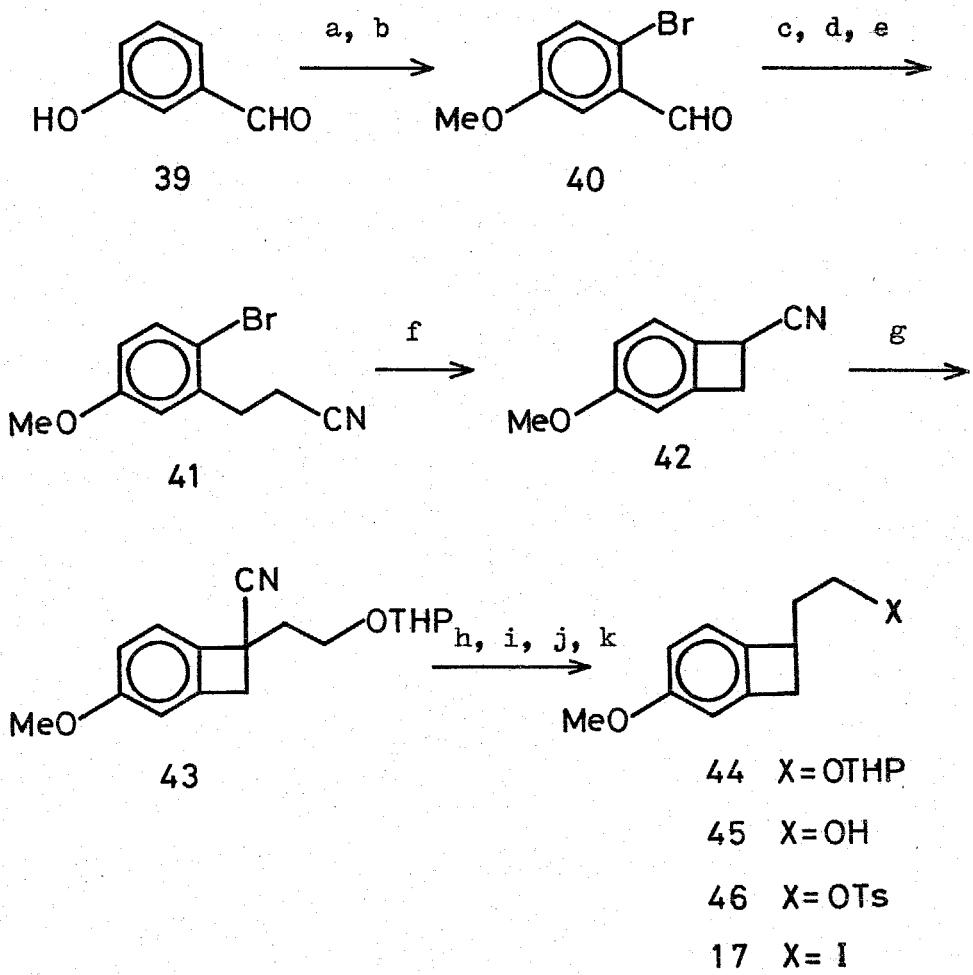


37

Appendix Preparation of the Benzocyclobutene 17

Accordingly to the method of Kametani,[23] 17 was easily prepared as shown in Scheme 6-4. Thus, methyl ether of commercially available 39 was brominated regioselectively with bromine in acetic acid to give 40 in total 84.6% yield from 39. The Knoevenagel condensation of 40 with cyanoacetic acid followed by the reduction of the latter with sodium borohydride and subsequent decarboxylation produced 41 in 78% yield from 40. The phenylpropionitrile 41 was cyclized by using sodium amide to the benzocyclobutene 42 in 81% yield. The alkylation of 42 with the tetrahydropyranyl ether derived from ethylene bromohydrin in the presence of sodium amide afforded 43 in 98% yield. Reductive decyanation of 43 by using sodium in liquid ammonia followed by cleavage of the tetrahydropyranyl group in 44 gave the alcohol 45 in 99% yield from 31. Finally 45 was tosylated to afford in 99.5% yield 46, which was converted into the desired product 17 in quantitative yield.

Scheme 6-4



a, Me_2SO_4, 2N NaOH, 93%; b, Br_2, AcONa, AcOH, r.t., 8h, 91%; c, $CH_2(CN)COOH$, $AcONH_4$, pyridine, benzene, 94%; d, $NaBH_4$, $NaHCO_3$; e, 170-180°C, 1h, 78%; f, $NaNH_2$, 81%; g, $Br(CH_2)_2OTHP$, $NaNH_2$, 98%; h, Na, t-BuOH, NH_3; i, HCl, MeOH, 88% from 43; j, TsCl, NEt_3, 99.5%; k, NaI, 100%.

6-3 Experimental

Methyl 2-Oxo-1-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-5-vinylcyclopentanecarboxylate (27) from Methyl 2-Oxo-5-vinylcyclopentane-1-carboxylate (20)

To a solution of the cyclopentanone 20 (90 mg, 0.536 mmol), the iodide 17 (154 mg, 0.536 mmol) dissolved in acetone (10 ml) was added granular potassium carbonate (740 mg, 5.36 mmol) and the mixture was refluxed for 36 h under nitrogen. After the mixture had been cooled to room temperature, the insoluble materials were filtered off and the filtrate was concentrated *in vacuo* leaving an oil, which was subjected to column chromatography on silica gel. Careful elution with hexane-ether, 5:1, gave in order of elution the desired adduct 27 (100 mg, 57% yield) and a mixture of 27 and 34 (8 mg, 4.6% yield). The ratio of 27 and 34 was approximately 1:5 from estimation of peak height of two singlet resonances due to methyl ester protons in the NMR spectrum of the mixture. The spectra of 27 are as follows:

IR (neat) 1752, 1730, 1603, 1587, 786, 758 cm^{-1};

NMR ($CDCl_3$) δ 1.05-3.65 (m, 12H, $(CH_2)_2CHCH_2$, $(CH_2)_2CH$), 3.54 (s, 3H, CH_3OCO), 3.63 (s, 3H, CH_3O), 4.77-6.06 (m, 3H, CH_2=CH), 6.39-6.92 (m, 3H, aromatic).

Methyl 2-(2-(3-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-3-oxo-8-phenoxy-6-octenoate (35)

To a solution of the β-keto ester 19 (128 mg, 0.489 mmol) and the iodide 17 (141 mg, 0.489 mmol) in acetone (5 ml) was added granular

potassium carbonate (1.3 g, 9.4 mmol) and the mixture was refluxed for 36 h with stirring. From cooled mixture insoluble materials were filtered off. The filtrate was concentrated in vacuo and the remaining oil was purified as above to give 35 (180 mg, 87% yield).

IR (neat) 1740, 1710, 1599, 1585, 752, 690, 680 cm^{-1};

NMR (CCl_4) δ 1.20-3.55 (m, 12H, $(CH_2)_2COCH(CH_2)_2CHCH_2$), 3.66 (s, 3H, CH_3OCO), 3.69 (s, 3H, CH_3O), 4.40 (d, J = 5 Hz, 2H, CH_2OPh), 5.60-5.88 (m, 2H, CH=CH), 6.54-7.35 (m, 8H, aromatic).

Methyl 2-Oxo-1-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-5-vinylcyclopentanecarboxylate (27) and (34) from 35

A mixture of the β-keto ester 35 (180 mg, 0.439 mmol), palladium(II) acetate (5 mg, 0.02 mmol), triphenylphosphine (23 mg, 0.088 mmol) dissolved in oxygen-free acetonitrile (7 ml) was refluxed under nitrogen for 6 h and then cooled to room temperature. The brown solution was passed through a short silica gel column with ether and the filtrate was concentrated in vacuo. Chromatograph on silica gel by use of hexane-ether, 5:1, afforded the C-alkylated esters 27 and 34. The NMR spectrum of the products showed three singlet resonances at δ 3.54, 3.60, 3.63 ppm, which were integrated in a ratio of 1.5:1.5:3 and assigned to methyl ester protons of 27, those of 34, and methoxy protons of 27 and 34, respectively by comparison with one obtained from 17 and 20.

Methyl 3-Methoxy-17-oxoestra-1,3,5(10)-trien-18-oate (30b) and

Methyl 9β-3-Methoxy-17-oxoestra-1,3,5(10)-trien-18-oate (30a)

A solution of 27 (106 mg, 0.323 mmol) in o-dichlorobenzene (2 ml) was heated at reflux for 4 h and then cooled to room temperature. The cooled solution was directly chromatographed on silica gel, eluting with at first hexane only and then with benzene-ethyl acetate, 5:1, to give the product as white crystals (79 mg, 75% yield) and recovered 3 (18 mg, 17% recovered). The NMR spectrum of the product revealed three singlet resonances at δ 3.58, 3.63, and 3.70 ppm, which were integrated in a ratio of 4:1:5 and assigned to methyl ester protons of the desired trans-anti-trans isomer 30b, those of the cis-anti-trans isomer 30a, and methyl ether protons of these two isomers, respectively. Recrystallization of the products from carbon tetrachloride afforded pure 30b.

Mp. 150-153°C (CCl_4)

IR ($CHCl_3$) 1753, 1723, 1610, 1501, 914 cm^{-1};

NMR ($CDCl_3$) δ 1.10-3.05 (m, 15H, methylene envelope), 3.58 (s, 3H, CH_3OCO), 3.70 (s, 3H, CH_3O), 6.44-7.16 (m, 3H, aromatic).

Methyl 2,2-(1,3-Dioxolane)-1-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-5-vinylcyclopentanecarboxylate (28)

A mixture of 27 (113 mg, 0.344 mmol) and ethylene glycol (0.2 ml, 3.6 mmol) in benzene (4 ml) containing a catalytic amount of p-toluenesulfonic acid was heated under reflux for 20 h and then cooled to room temperature. Sodium bicarbonate (50 mg) was added to the solution and the resulting mixture was stirred at room temperature for 30 min.

The insoluble materials were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene-hexane, 3:1, to give the acetal 28 (70 mg, 84% yield).

IR (neat) 1729, 1602, 1585 cm^{-1};

NMR (CCl_4) δ 1.46-3.45 (m, 12H, $CH(CH_2)_2$, $CH_2CH(CH_2)_2$), 3.58 (s, 3H, CH_3OCO), 3.67 (s, 3H, CH_3O), 3.74-3.90 (m, 4H, $(CH_2)_2O$), 4.73-6.10 (m, 3H, CH_2=CH), 6.50-7.00 (m, 3H, aromatic).

2,2-(1,3-Dioxolane)-1-(2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl)-5-vinylcyclopentanemethanol (29)

To a suspension of lithium aluminum hydride (23 mg, 0.62 mmol) in dry THF (2 ml) under nitrogen was added dropwise a solution of the ester 28 (230 mg, 0.618 mmol) dissolved in dry THF (2 ml). The mixture was stirred at room temperature for 10 min and then at reflux for 1 h. After the mixture had been cooled to room temperature, the reaction was quenched by the dropwise addition of ethyl acetate and then water. The resulting mixture was filtered through a short silica gel column and the filtrate was concentrated *in vacuo* to give an oil, which was directly chromatographed on silica gel, by using benzene-ethyl acetate, 15:1, to afford the alcohol 29 (185 mg, 87% yield).

IR (neat) 3550, 1605, 1590 cm^{-1};

NMR ($CDCl_3$) δ 1.30-2.00 (m, 8H, $2(CH_2)_2$), 2.35-3.80 (m, 7H, CH_2OH, CH_2CH, CHC=C), 3.69 (s, 3H, CH_3O), 3.86 (s, 4H, $(CH_2)_2O$), 4.70-6.20 (m, 3H, CH_2=CH), 6.53-7.04 (m, 3H, aromatic).

17,17-(1,3-Dioxolane)-3-methoxyestra-1,3,5(10)-trien-18-ol (31)

From 30b: A solution of the ester 30b (75 mg, 0.23 mmol) and ethylene glycol (0.13 ml) in benzene (5 ml) containing a trace of p-toluenesulfonic acid was refluxed overnight with continuous removal of water by use of molecular sieves and cooled to room temperature. Excess sodium bicarbonate (powder) was added to the solution and the resulting mixture was stirred at room temperature for 30 min. Filtration of the insoluble materials followed by evaporation of the filtrate left an oil, which was chromatographed on silica gel. Elution with benzene-hexane, 3:1, gave the acetal 38 (81 mg, 95% yield).

Mp. 125-129°C (hexane and ether);

IR ($CHCl_3$) 1720, 1610, 1579 cm^{-1};

NMR ($CDCl_3$) δ 1.06- 3.05 (m, 15H, methylene envelope), 3.62 (s, 3H, CH_3OCO), 3.72 (s, 3H, CH_3O), 3.93 (br s, 4H, $(CH_2)_2O$), 6.50-7.25 (m, 3H, aromatic).

To a solution of the above ester 38 (81 mg, 0.22 mmol) in dry THF (3 ml) under nitrogen at room temperature was added lithium aluminum hydride (10 mg, 0.26 mmol). The mixture was stirred at room temperature for 10 min and then under reflux for 30 min. To the cooled mixture were carefully added ethyl acetate and then water. The resulting mixture was filtered through a short silica gel column and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel by using benzene-ethyl acetate, 15:1, to give the alcohol 31 (56 mg, 75% yield).

Mp. 147-149°C (CCl_4);

IR ($CHCl_3$) 3570, 1609, 1574 cm^{-1};

NMR ($CDCl_3$) δ 0.95-3.20 (m, 16H, methylene envelope, OH) 3.40-3.85 (m, 2H, $C\underline{H}_2OH$), 3.72 (s, 3H, CH_3O), 3.90 (s, 4H, $(CH_2)_2O$), 6.50-7.30 (m, 3H, aromatic).

From 29: A solution of 29 (55 mg, 0.16 mmol) in o-dichlorobenzene (1 ml) was refluxed for 5 h and cooled to room temperature. The solution was directly subjected to column chromatography on silica gel, eluting with hexane and then benzene-ethyl acetate, 5:1. to give the pure alcohol 31 (41 mg, 75% yield). The spectra (IR, NMR) of 31 thus obtained was identical in all respects with those prepared from 30b (vide supra).

18-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (32)

To a solution of the alcohol 31 (45 mg, 0.13 mmol) dissolved in acetone (1 ml) were added 3N hydrochloric acid (0.2 ml) and water (0.1 ml) and the resulting solution was stirred at room temperature. After 5 h, the solution was poured into saturated aqueous sodium bicarbonate and the product was extracted with ethyl acetate. The extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent left an oil, which was chromatographed on silica gel by using benzene-ethyl acetate, 5:1, to give the ketone 32 (35 mg, 89% yield).

Mp. 183-185°C (benzene);

IR (Nujol) 3430, 1713, 1610, 1501 cm^{-1};

NMR ($CDCl_3$) 1.10-3.05 (m, 16H, methylene envelope, OH), 3.69-3.80 (m, 2H, $C\underline{H}_2OH$), 3.70 (s, 3H, CH_3O), 6.46-7.23 (m, 3H, aromatic).

18-Hydroxyestrone (1)

To a solution of 32 (60 mg, 0.20 mmol) in dry methylene chloride (3 ml) under nitrogen at -78°C was added boron tribromide (50 µl, 130 mg, 0.53 mmol). The mixture was stirred at -78°C for 1.5 h and then at 0°C for 1.5 h. The reaction was quenched by the addition of methanol and then water. The mixture was taken up in ethyl acetate and the solution was washed with saturated aqueous sodium bicarbonate and brine and dried over magnesium sulfate. Evaporation of the solvent left the alcohol 1 as white crystals, which were recrystallized from ethanol to give pure 1 (50 mg, 87% yield).

Mp. 205-208°C (dec. ethanol);

IR (Nujol) 300-3650 (CH), 1715, 1610, 1498 cm^{-1};

NMR (pyridine) δ 4.0 (s, 2H, CH_2O);

Mass m/e 286 (M^+).

18-Methanesulfonyloxy-3-methoxyestra-1,3,5(10)-trien-17-one (37)

A solution of the alcohol 32 (20 mg, 0.067 mmol) and mesyl chloride (50 µl, 0.65 mmol) in pyridine (1 ml) was stirred at room temperature for 10 h and then poured into ice-cooled 3N hydrochloric acid and the mixture was extracted with ethyl acetate repeatedly. The extracts were combined, washed with brine, dried over magnesium sulfate, and then concentrated in vacuo. The residue was chromatographed on silica gel. Elution with benzene-ethyl acetate, 5:1, gave the mesylate 37 (22 mg, 83% yield).

Mp. 142-144°C (hexane-CCl_4);

IR ($CHCl_3$) 1743, 1610, 1500, 1178 cm^{-1};

NMR ($CDCl_3$) δ 1.20-3.10 (m, 15H, methylene envelope), 2.96 (s, 3H, CH_3SO_3), 3.76 (s, 3H, CH_3O), 4.40 (s, 2H, CH_2O), 6.59-7.37 (m, 3H, aromatic).

Estradiol Methyl Ether (21)

To a solution of 37 (20 mg, 0.053 mmol) in dry THF (1 ml) under nitrogen was added lithium aluminum hydride (2 mg, 0.054 mmol). The mixture was heated at reflux for 1.5 h and then cooled to room temperature. The reaction was quenched by the careful addition of ethyl acetate and then water. The resulting mixture was filtered through a short silica gel column and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel to give pure 21 (12 mg, 76% yield).

Mp. 132-133°C (hexane-methanol);

IR (Nujol) 3300, 1610, 1499 cm^{-1};

NMR ($CDCl_3$) δ 0.75 (s, 3H, CH_3), 0.85-2.95 (m, 16H, methylene envelope, OH), 3.45-3.79 (m, 1H, CHOH), 3.68 (s, 3H, CH_3O), 6.43-7.20 (m, 3H, aromatic).

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CHAPTER SEVEN

STUDIES ON THE SYNTHESES OF FUNCTIONALIZED STEROIDS AT C-18 POSITION. PART TWO.

INTRODUCTION OF NEW ANNULATION METHODOLOGY

Summary

New methodology for annulation was introduced, which is of value for the synthesis of steroids possessing functionalized C-18 carbon atom. In this methodology, substrates which would be synthesized from methyl 3-oxo-8-phenoxy-6-octenoate (28) with methyl vinyl ketone, 7-octene-2,6-dione, and 11-dodecene-2,6,10-trione, respectively, or their synthetic equivalents could be conceivable to be the new bis-, tris-, and tetrakis-annulation reagents. These substrates are, in principle, subjected to the newly developed palladium-catalyzed cyclization to construct a five-membered cyclic ketone possessing a vinyl group at C-17 as well as oxidized carbon atom at C-18. The other six-membered cyclic ketone(s) for steroids framework are obtained by the conventional aldol condensation(s).

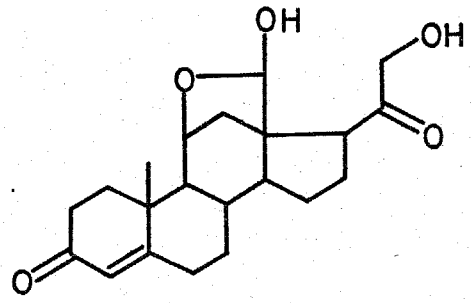
In practice various indane derivatives which are corresponding to functionalized steroids' C,D ring were synthesized. As a new bis-annulation reagent, methyl 3-oxo-2-(3-oxobutyl)-8-phenoxy-6-octenoate (34) was prepared and subjected to the cyclization in the presence of palladium(II) acetate to afford methyl 2-oxo-1-(3-oxobutyl)-5-vinyl-cyclopentanecarboxylate (40), which was then converted to both methyl 5,6,7,7a-tetrahydro-5-oxo-1ξ-vinyl-7aβ-indanecarboxylate (41) and 5,6,7,7a-tetrahydro-5-oxo-1ξ-vinylindane-7aβ-methyl acetate (45). Similarly the tris-annulation reagent, methyl 5-oxo-2-(1-oxo-6-phenoxy-4-hexenyl)-9-decenoate (37), was prepared, from which methyl 4-(3-butenyl)-5,6,

7,7a-tetrahydro-1ξ-vinyl-7aβ-indanecarboxylate (48) was synthesized by using β-alanine. Moreover, methyl 2-(7-acetoxy-3-oxododecyl)-3-oxo-8-phenoxy-6-octenoate (38), which was a model compound for the tetrakis-annulation reagent, was prepared and a variety of intermediates were also synthesized.

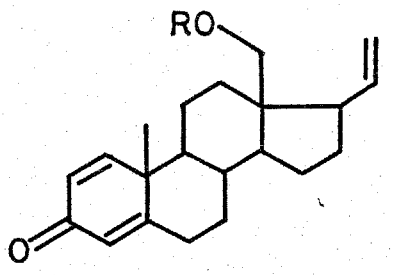
7-1 Introduction

As mentioned briefly in the preceding chapter, there are many steroids which possess functionalized 18-methyl groups of various oxidation states.[2] Aldosterone (1),[3] 18-acetoxy- and 18-hydroxy-1,

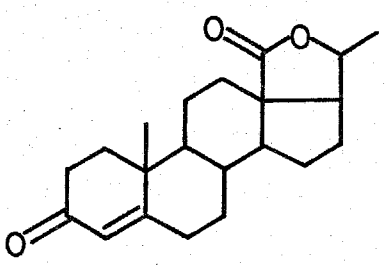
Fig. 7-1 18-Methyl Functionalized Steroids



1



2 R = Ac
3 R = H



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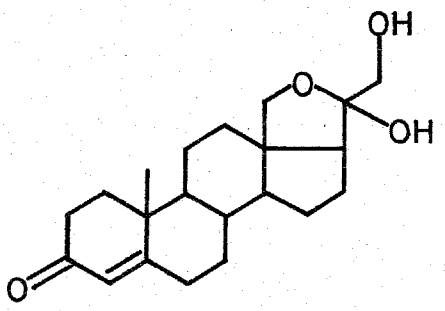

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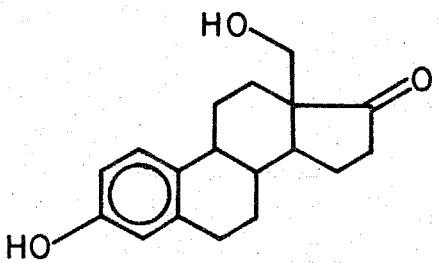

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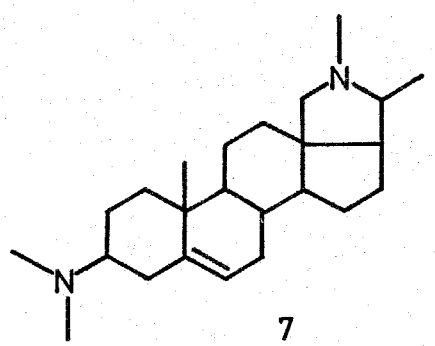

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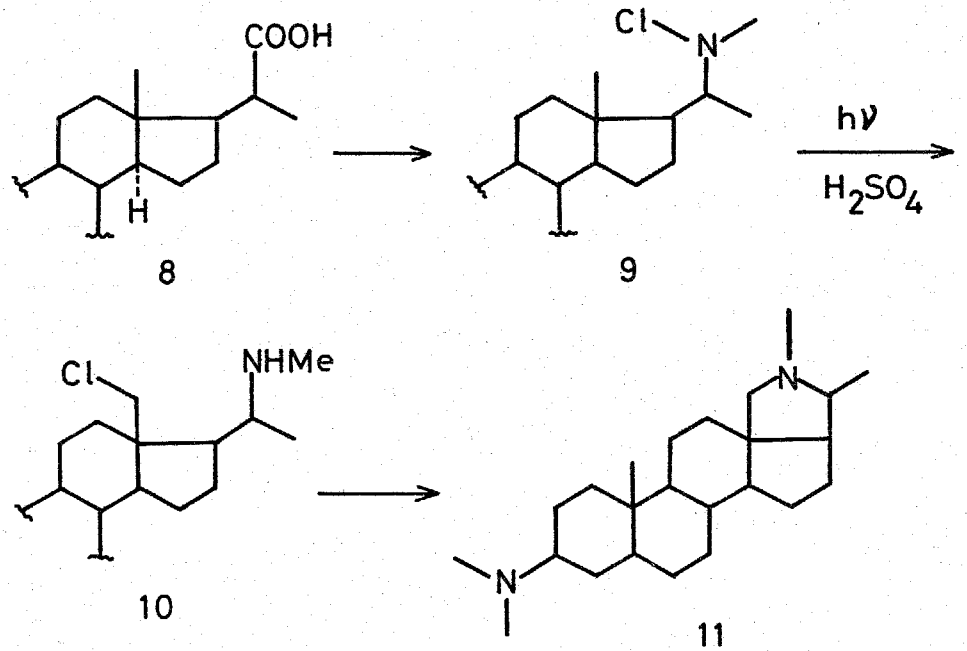
4,20-trien-3-one (2 and 3),[4] 20-hydroxypregn-4-en-3-on-18-oic acid 18 → 20 lactone (4),[5] 11-deoxy-18-hydroxycorticosterone (5),[6] 18-hydroxyestrone (6),[7] and conessine (7) are representative. The existence of various kind of functionalities at C-18 carbon atom may generate pharmacologically important properties which differ from those of common steroids. For example, aldosterone (1), first isolated in a pure state in 1953,[3] is famous as powerful adrenal cortical hormone. On the other hand, 11-deoxy-18-hydroxycorticosterone (5), which is produced by the adrenal cortex and has been proposed as an intermediate in aldosterone (1) biosynthesis,[6] is considered important in hypertension.[8]

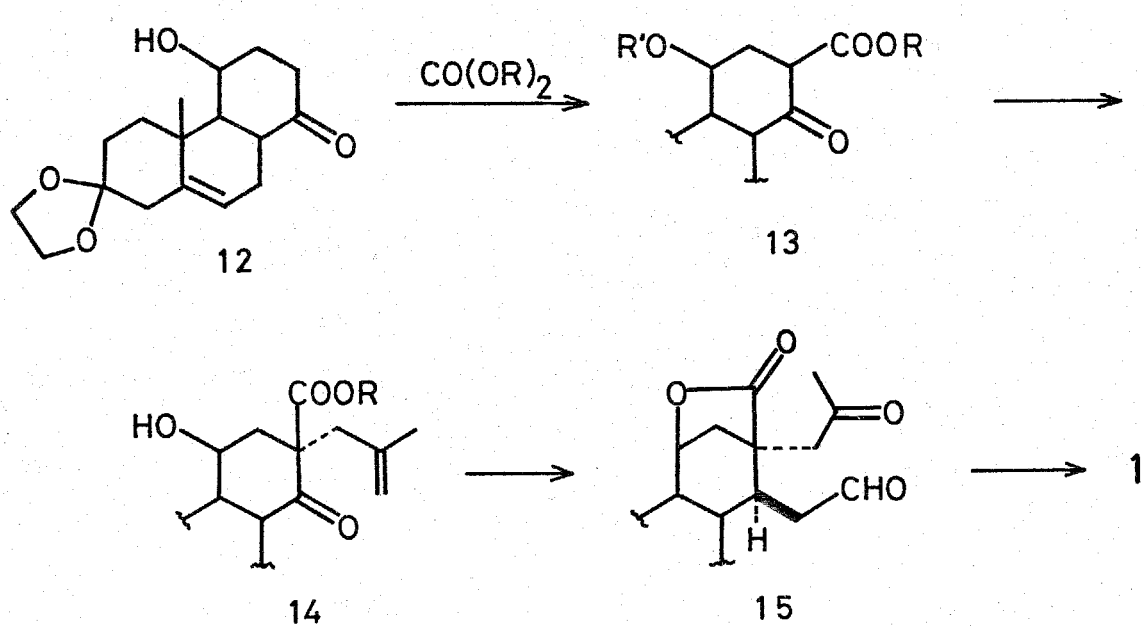
The synthesis of such structures poses a unique problem concerning the method of introducing a functionalized methyl group corresponding to C-18 carbon. As one solution for this problem, many partial synthetic approaches to these steroids have been reported. For example, Corey



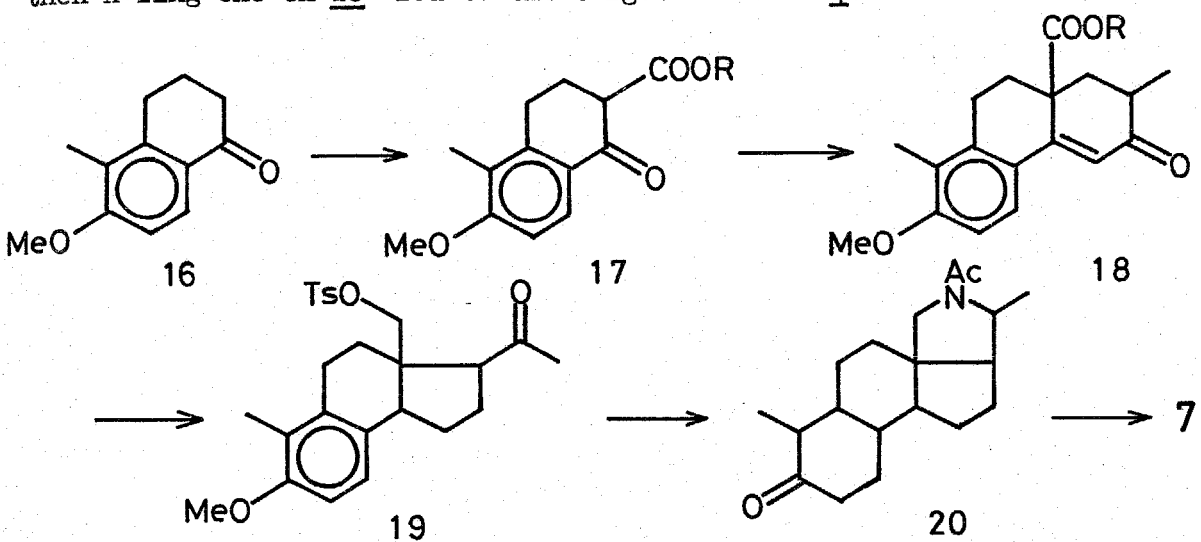
et al. reported [9] the synthesis of dihydroconessine (11), where the photo-assisted free radical chain decomposition of N-chloro-20-amino-steroid (9) in acid solution affording 18-chlorosteroid (10) was one of key steps, but this method failed to synthesize conessine (7) itself.

In addition many investigators have devoted to explore more efficient syntheses of the functionalized steroids along with the methodology of this kind of partial synthesis, which includes photolysis of, for example, the 20-nitrile to the 18-nitrate [10] and photo-assisted lead tetraacetate oxidation of 18-methyl group [11] and so on.[12]

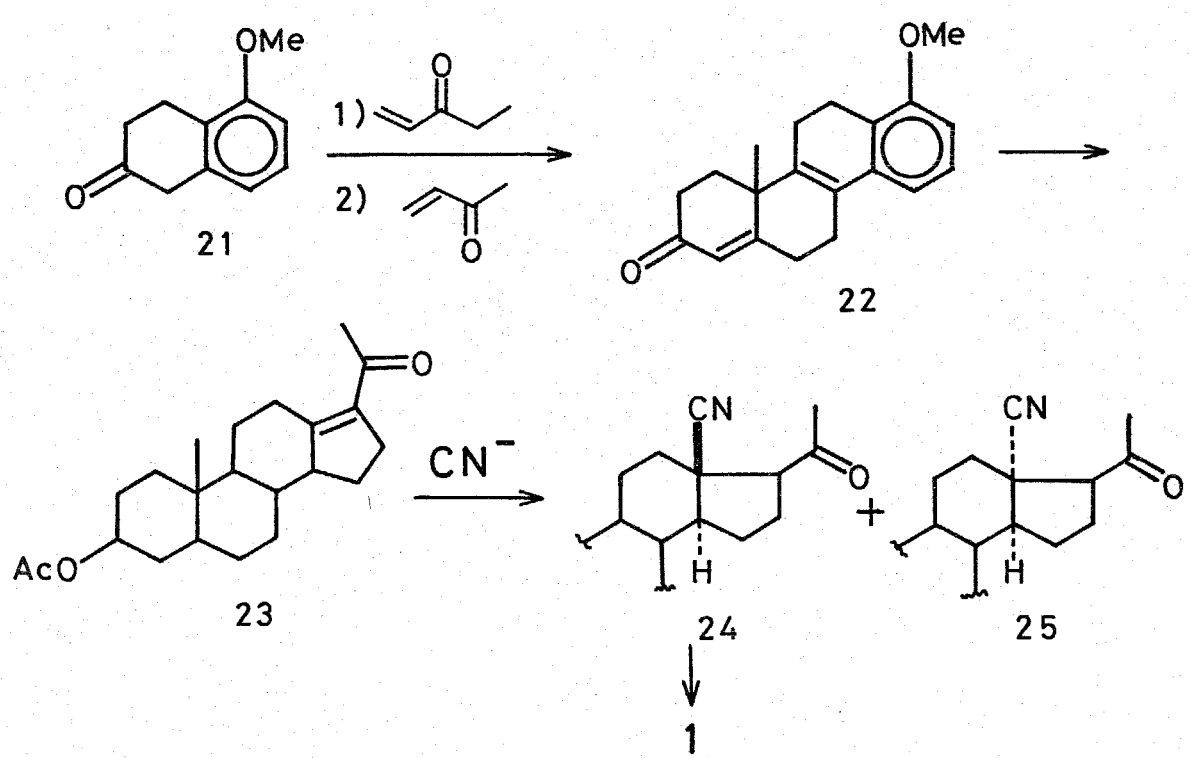
On the other hand, there are several total synthetic approaches to these functionalized steroids. J. Schmidlin's aldosterone (1) synthesis [13] consists of the introduction of the alkoxycarbonyl group as C-18 aldehyde synthon on the Sarett's ketone 12, an A, B, and C ring synthon, followed by the introduction of D ring component and of a side chain attached at C-17.



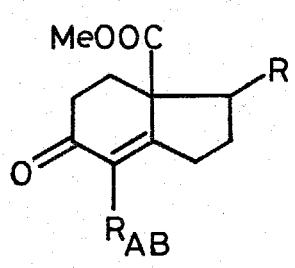
Stork reported [14] the total synthesis of conessine (7). In this synthesis too, alkoxycarbonyl group was introduced on the B,C ring synthon 16 and successive introduction of D ring component on 17 and then A ring one on 20 led to the target molecule 7.



Conessine was also synthesized from 21,[15] where the key step was 1,4-addition of cyanide ion onto the enone 23 but this reaction afforded 24 and 25 as a 1:1 mixture.



In several syntheses reported before including above three examples reactions are not selective and overall yields were very low. These results seem to stem from the absence of effective general synthetic approaches to these steroids, while synthetic methodology for common steroids is almost established which employs basically the Robinson annulative method starting from an appropriate mono-cyclic ketone corresponding to D ring or a bi-cyclic ketone corresponding to C,D rings.[16-18] Therefore, adaptation of the methodology for the common steroids syntheses might provide with a general route to the synthesis of the functionalized steroids. With this idea in mind, the author proposes that the suitable intermediates for synthesis of these functionalized steroids are such compounds as formulated by 26 and/or 27, which possess appropriate substituents R in the cyclopentane ring at C-17 and proper side chains R_{AB} necessary to build A,B ring by the conventional Robinson annulative cyclization.



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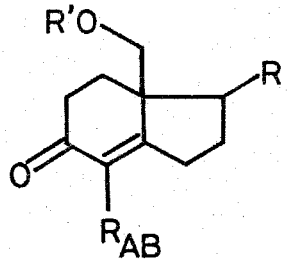
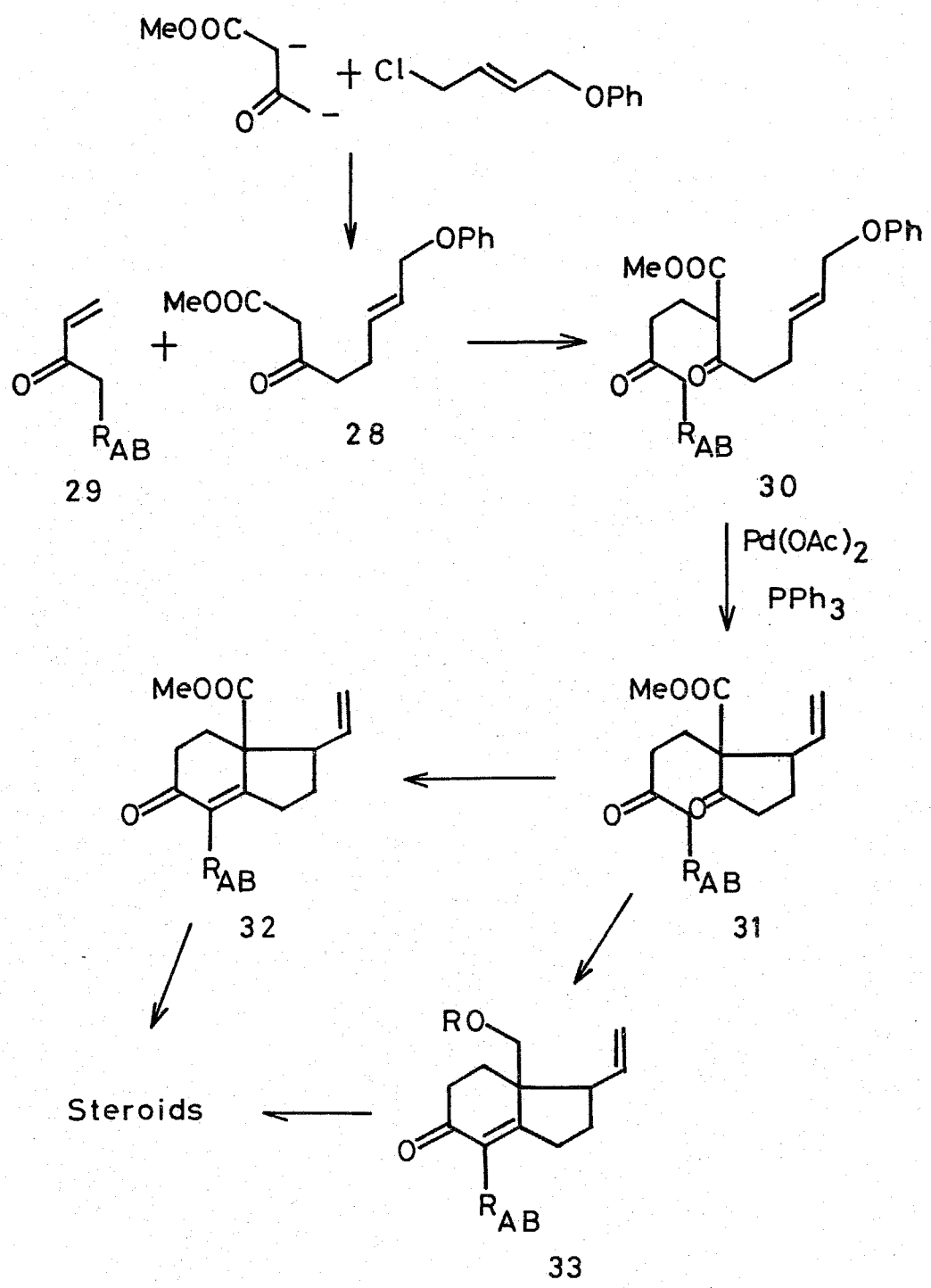


27

Incidentally the new cyclopentanone synthesis has been established and the detail of the results is described in Chapter 2.[19] Combining this new reaction and proposed intermediates 26 and 27 , the author drew a synthetic route outlined in Scheme 7-1. The palladium-catalyzed cyclization of the β-keto ester which could be obtained by the Michael addition of 28 to the enone 29 would provide the cyclopentanone 31,

Scheme 7-1


MeOOC
Cl
OPh
MeOOC
OPh
28
29
MeOOC
OPh
30
R_{AB}
$Pd(OAc)_2$
PPh_3
MeOOC
MeOOC
32
31
RO
Steroids
33

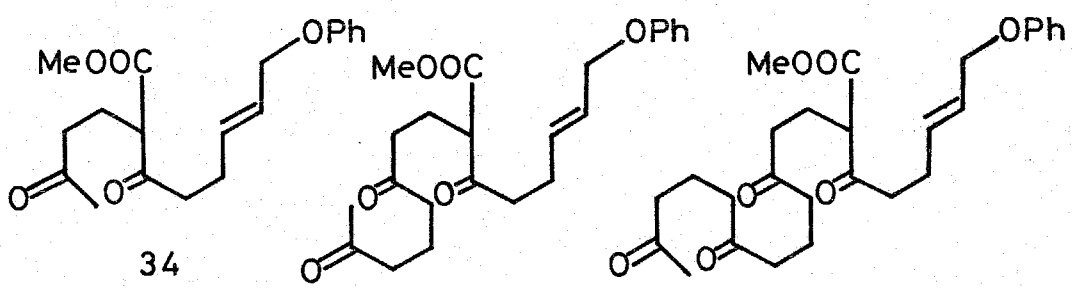
from which the intermediate 32 and 33 corresponding to 26 and 27 might be prepared and the vinyl group in 32 and 33 would be transformed to functionalized groups required in the functionalized steroids.

Herein, a linear compounds 30 can be classified as new bis-, tris-, and tetrakis-annulation reagents according to the substituents R_{AB} in 30 as shown below.

(1) R_{AB} = H in the formula 30: The compound 34 or its equivalent is the bis-annulation reagent, which itself can construct one five-membered ketone by the palladium-catalyzed cyclization and another six-membered ketone by the conventional aldol condensation.

(2) $R_{AB} = (CH_2)_2COCH_3$ in the formula 30: The compound 35 or its equivalent is the tris-annulation reagent, which can construct one five- and two six-membered cyclic ketones via 32 or 33 by a similar reaction mentioned above.

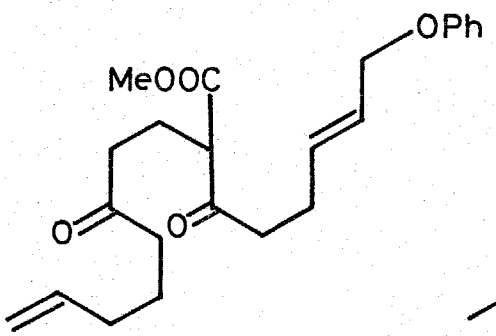
(3) $R_{AB} = (CH_2)_2CO(CH_2)_3COCH_3$ in the formula 30: The compound 36 or its equivalent is the tetrakis-annulation reagent, which can construct one five- and all three six-membered cyclic ketone via 32 or 33.



34 35 36

It is noteworthy that this classification differs from the classical bis-, tris-, and tetrakis-annunation reagents which construct two, three, and four fused six-membered cyclic ketones from one reagent, respectively, by repeating merely intramolecular aldol condensations.[18,19]

The β-keto ester 34 itself was picked up for the bis-annulation reagent. For the tris-annulation reagent, was chosen 37, whose terminal olefin would be easily converted to methyl ketone by palladium(II)-catalyzed oxidation,[20] while 38 was prepared as a model compound for the tetrakis-annulation reagent.[21] In the following section, the preparations of these reagents and the detail of their transformations to the intermediate 32 and 33 are presented.



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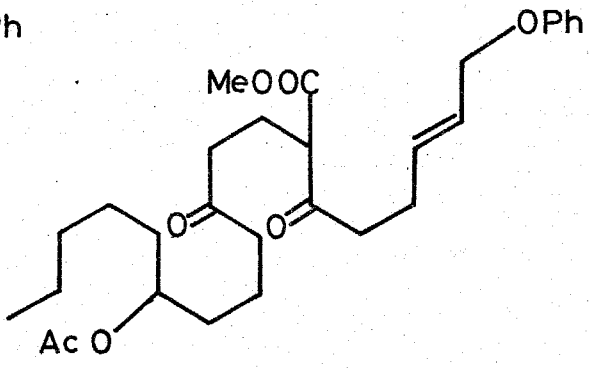

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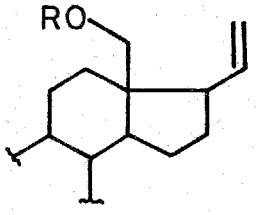
7-2 Results and Discussion

7-2-1 New Bis-annulation Reagent 34

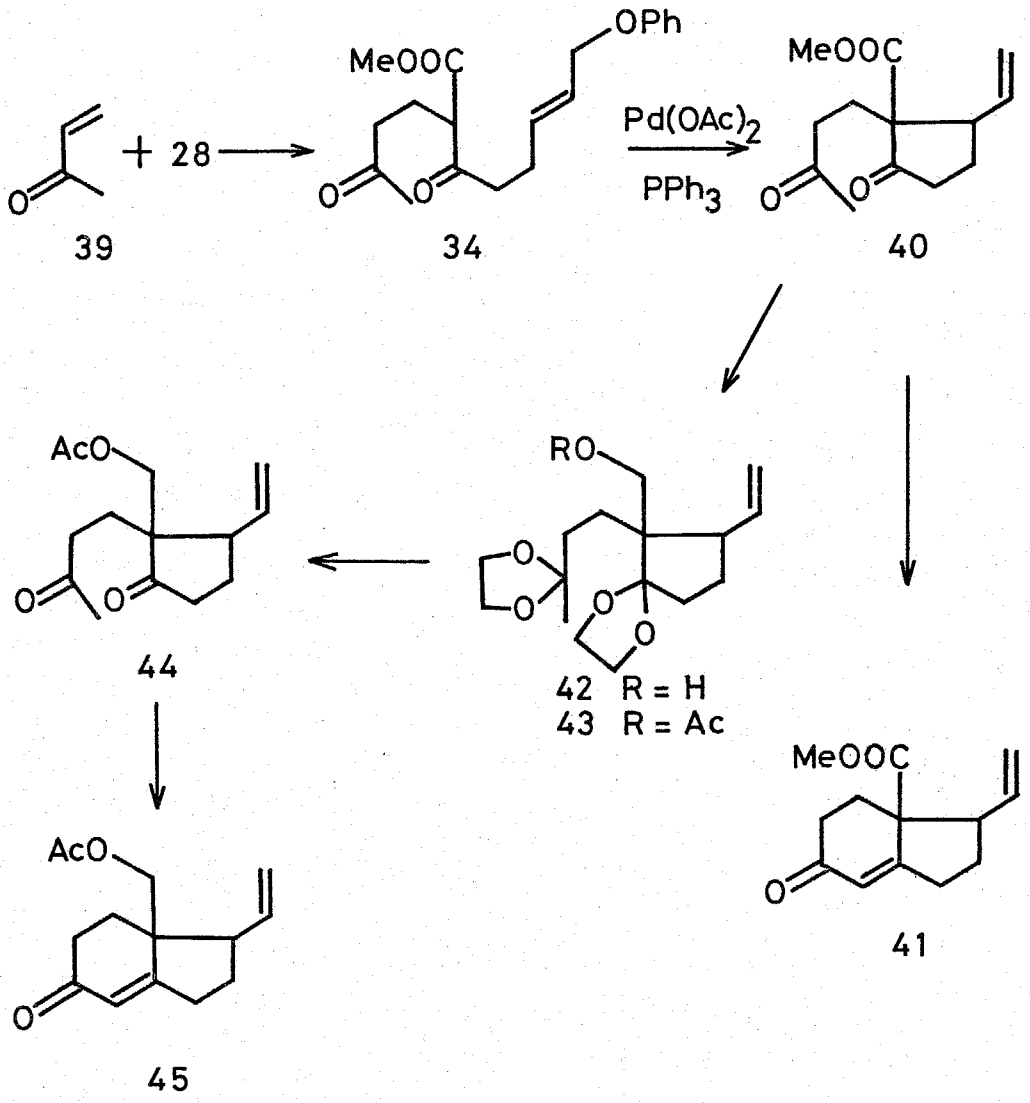
As shown in Scheme 7-2, the new bis-annulation reagent 34 was prepared in 74% yield by the Michael addition of the β-keto ester 28 onto methyl vinyl ketone (39) in the presence of a catalytic amount of sodium methoxide in methanol. Then palladium-catalyzed cyclization of 34 was carried out under optimum conditions described in Chapter 2.[19] Thus, 34 was added to refluxing acetonitrile containing palladium(II) acetate (5 mol%) and triphenylphosphine (20 mmol%) and the desired cyclopentanone 40 was obtained selectively in 91% yield. It is noteworthy that competitive reactions such as the retro-Dieckmann reaction which is sometimes troublesome in alkylation of a β-keto ester with a halide under basic conditions were not observed since the conditions of the cyclization were almost neutral and so mild. In the NMR spectrum of 40, besides the signals attributable to vinylprotons in the region of δ 4.92-6.05 ppm (integration, total 3H), however, the signal of methyl ester protons were observed indicated that 40 consisted of diastereoisomers in a ratio of 2:1. Finally 40 was cyclized in a refluxing solution of toluene and acetic acid (2:1) containing β-alanine[21] to give 41 in 74% yield.

Then keeping the structures of 2 and 3 in mind, the author carried



2 R = Ac
3 R = H

Scheme 7-2



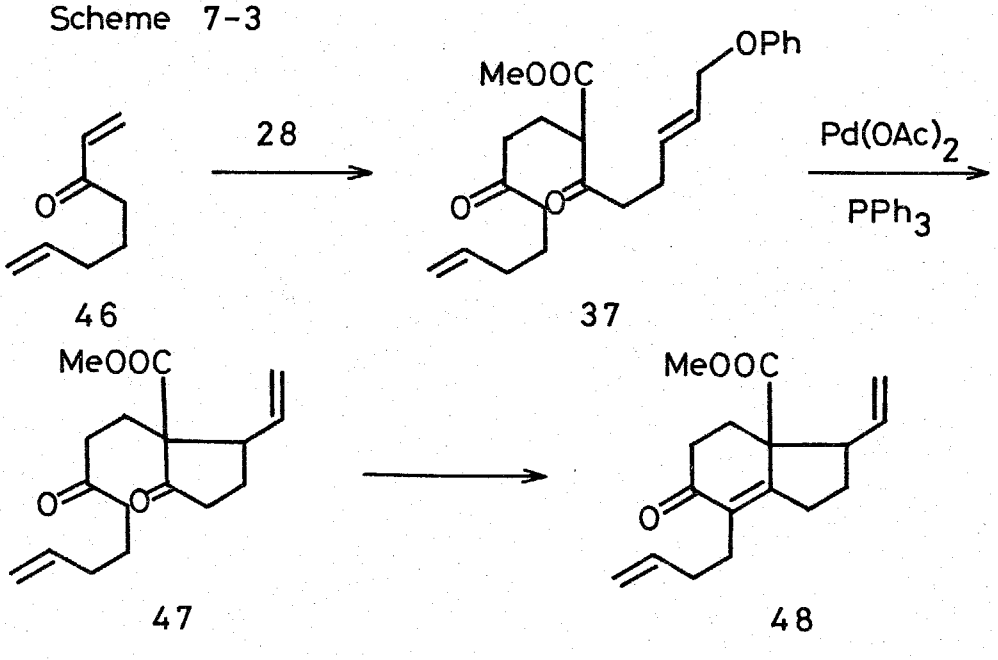
out the following transformations in order to synthesize the enone 45 which has proper functionalities to 2 and 3 (Scheme 7-1). The acetalization of 40, which was a 2:1 mixture of its diastereoisomers, with ethylene glycol and a trace amount of p-toluenesulfonic acid followed by lithium aluminum hydride reduction afforded the alcohol 42 in 32% yield (not optimized). The acetate 43 obtained in 94% yield from 42 by the usual way was converted to the diketone 44 in 96% yield. Finally

β-alanine-assisted aldol condensation [21] of 44 in refluxing benzene and acetic acid (2:1) afforded the desired product 45 in 59% yield, which was conceivably a 2:1 mixture of diastereoisomers which stems from those of 40.

7-2-2 New Tris-annulation Reagent 37

The classical bis-annulation reagent 46, easily available from butadiene telomer,[22] and the β-keto ester 28 were reacted in a similar way described above and the new tris-annulation reagent 37 was obtained in 81% yield (Scheme 7-3). Then 37 was subjected to the cyclization [19] in the presence of 5 mol% of palladium(II) acetate and 20 mol% of triphenylphosphine in refluxing acetonitrile for 1 h and the cyclopentanone 47 was obtained in 66% yield. From the NMR spectrum of 47, the ratio of diastereoisomers of 47 was calculated to be about 1:1. Finally the intramolecular aldol condensation of 47 with β-alanine

Scheme 7-3

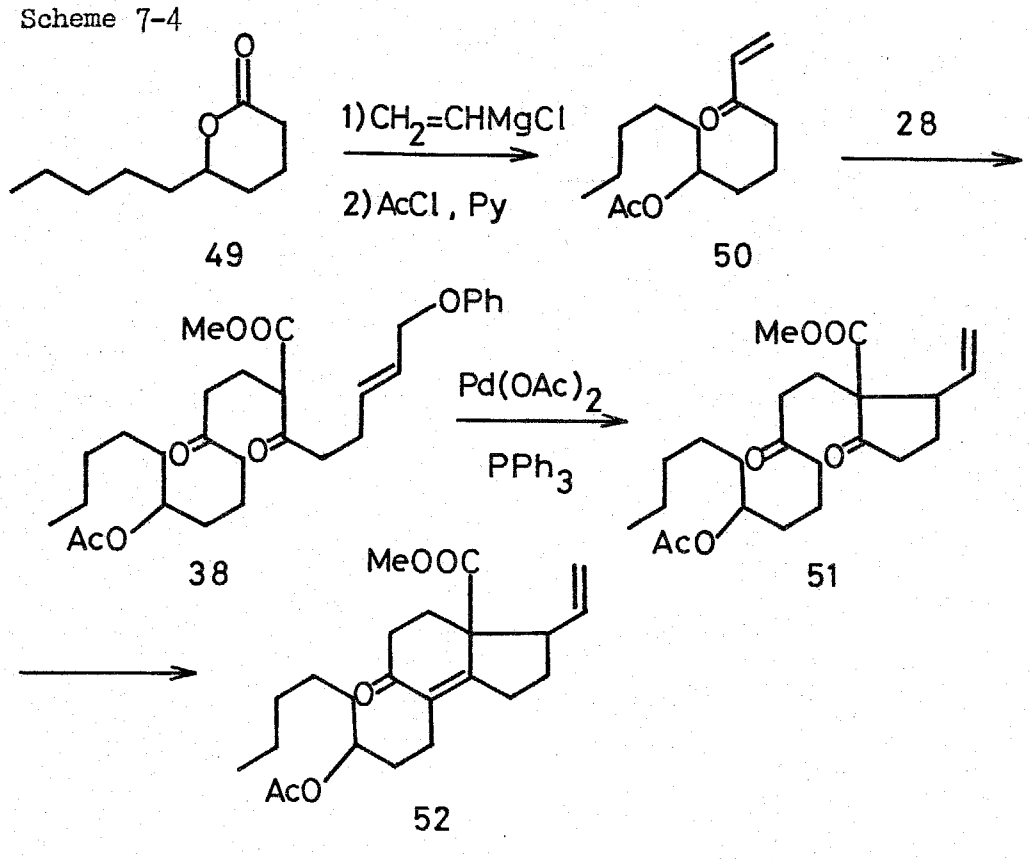


in a mixed solvent of toluene and acetic acid produced the enone 48 in 50% yield. The NMR spectrum of 48 showed singlet resonances at δ 3.68 and 3.72 ppm, attributable to methyl ester protons, whose peak height indicated a ratio of approximately 1:1.

7-2-3 The Model Compound for New Tetrakis-annulation Reagent

As a model compound for new tetrakis-annulation reagent was chosen the acetate 38 [21] which was prepared as follows (Scheme 7-4). The addition of vinylmagnesium chloride 23 to the δ-lactone 49 in THF at -70°C followed by acetylation with acetyl chloride afforded the enone 50 in 75% yield from 49. The Michael addition of the β-keto ester 28 to the enone 50 in the presence of sodium methoxide in methanol at ice-water temperature for 6 h produced the desired reagent 38 in 85% yield.

Scheme 7-4

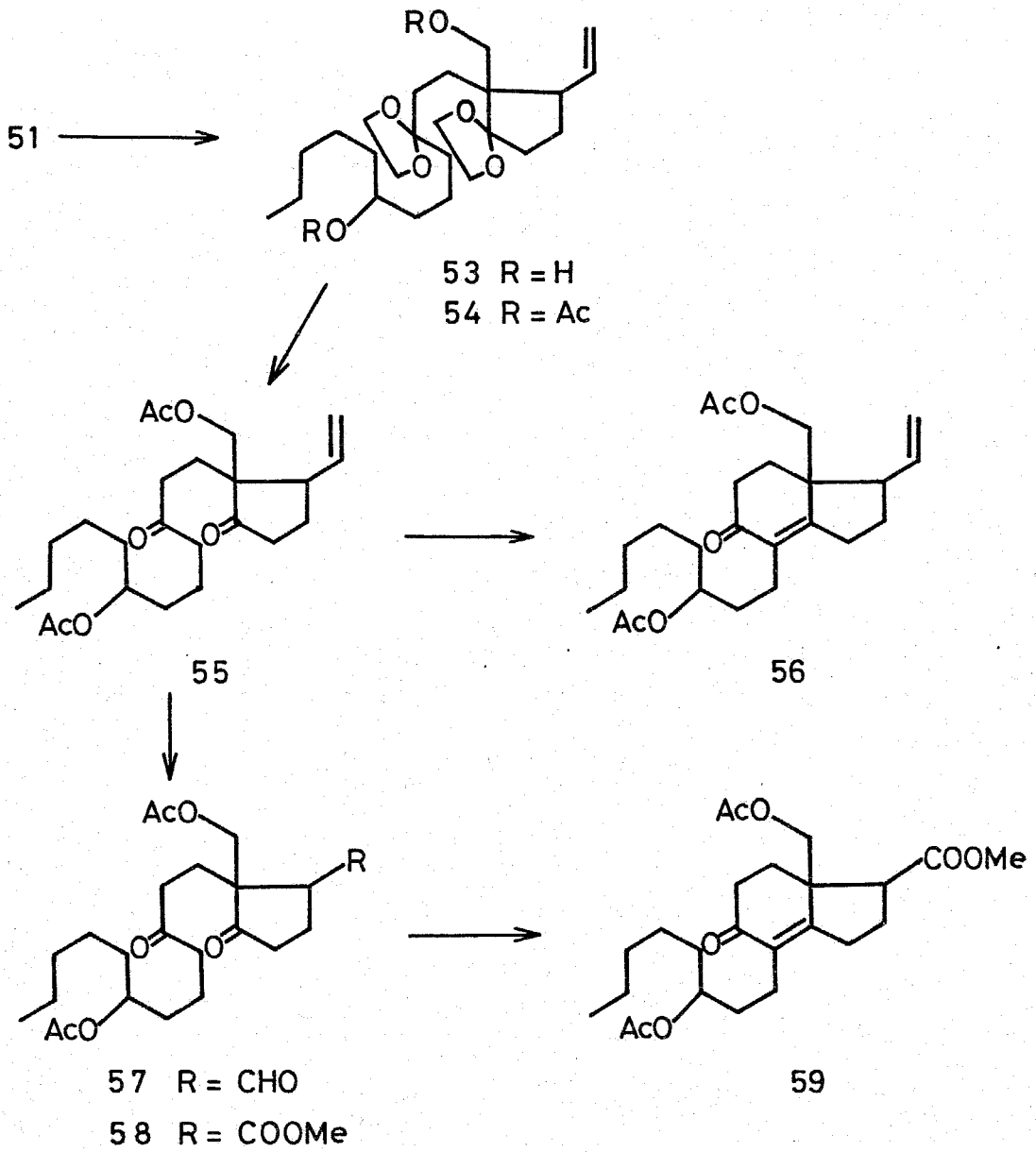


A similar palladium-catalyzed cyclization [19] of 38 in refluxing acetonitrile for 90 min produced the cyclopentanone 51 in 91% yield. In this experiment, 51 was found to be a 3:2 mixture of diastereoisomers, which was based on the peak height at δ 3.58 and 3.63 ppm corresponding to methyl ester protons in the NMR spectrum of 51. Then the enone 52 was obtained in 62% yield by the aldol condensation of 51 with β-alanine (Scheme 7-4).

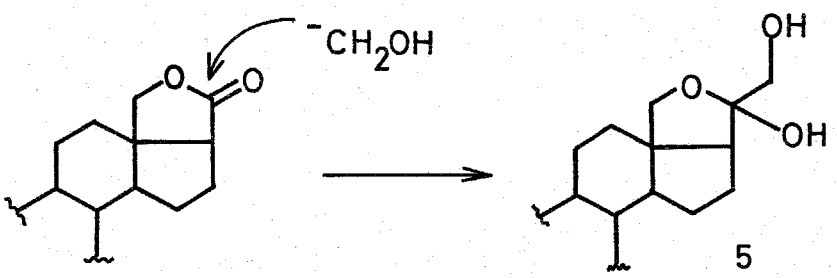
The next subgoals are the acetate 56 and 59, which could be smoothly synthesized from 51. The synthetic sequence is depicted in Scheme 7-5. Initially, two carbonyl groups in 51 (diastereoisomeric ratio, ca 3:2) were protected with ethylene glycol and the resulting protected ester was reduced with lithium aluminum hydride. After chromatography, the alcohol 53 was isolated in 58% overall yield from 38 and acetylation of 53 by the usual way gave the diacetate 54 in 64% yield. Heating 54 with a catalytic amount of pyridinium p-toluenesulfonate [24] in refluxing aqueous acetone produced the diketone 55 in 95% yield. The cyclization of 55 with β-alanine in refluxing toluene and acetic acid [21] finally afforded the enone 56 in 61% yeild.

On the other hand, the enone 59 was synthesized as follows. Ozonolysis of 55 in methanol at -66°C followed by in situ reduction with excess dimethyl sulfide [25] gave the crude aldehyde 57. Jones oxidation [26] of 57 and the subsequent esterification of the resulting acid with diazomethane afforded 58 in 98% yeild. The last stage was the aldol cyclization of 58 by heating with β-alanine in refluxing toluene and acetic acid (3:1) [21] to give the enone 59 in 77% yield.

Scheme 7-5


51
RO
RO
O
O
O
O
O
53 R = H
54 R = Ac
AcO
AcO
O
O
55
AcO
AcO
O
56
AcO
AcO
R
O
O
57 R = CHO
58 R = COOMe
AcO
AcO
COOMe
O
59

Finally the author attempted to synthesize the enone 65 (Scheme 7-6). From a γ-lactone moiety attached to D ring such as those in 64, hydroxyacetyl part of the corticosterone 5 would be able to introduced.



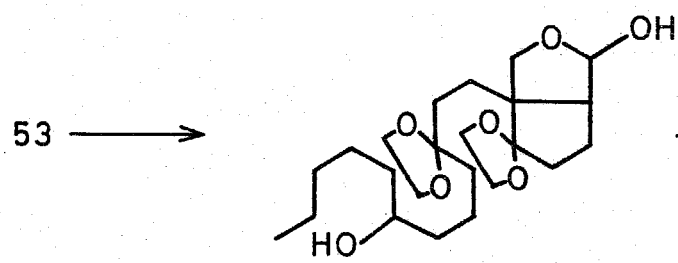
5

Initially the alcohol 53 was converted to the corresponding hemiacetal 60 by ozonolysis followed by in situ reduction [25] (excess dimethyl sulfide). Careful oxidation of crude 60 by Jones reagent [26] in acetone at 0°C for 30 min preferentially afforded the requisite the γ-lactone 61 in 42% yield form 53 without the cleavage of the acetal group. Sodium borohydride reduction of the γ-lactone 61 gave in 92% yield the alcohol 62, from which the acetate 63 was easily prepared in 85% yield (acetic anhydride and pyridine). Acid catalyzed cleavage of the acetal moiety in 63 resulted in the formation of the diketone 64 in 71% yield. Then an attempt to effect the aldol condensation of 64 was tried in the presence of β-alanine (3.2 equiv.) under reflux for 3 h, but unfortunately no desired product 65 could be isolated. Other trials under varieties of conditions have been unsuccessful.

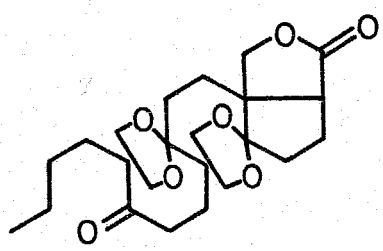
7-2-4 Conclusion

In this chapter, the new annulation methodology for the synthesis of 18-functionalized steroids with appropriate side chain attached at C-17 position was demonstrated by the successful synthesis of C,D ring moieties

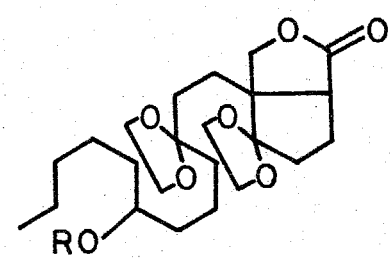
Scheme 7-6



60

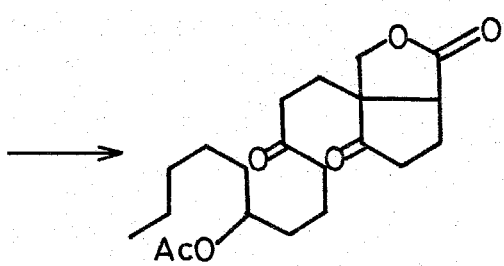


61

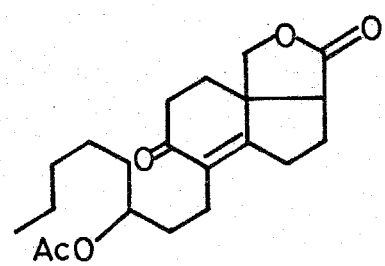


62 R = H

63 R = Ac



64



65

possessing various functionalities. Although the synthesis is not co completed and further elaboration is still necessary, this methodology is conceivably promising in this field.

7-3 Experimental

Methyl 3-Oxo-8-phenoxy-6-octenoate (28)

See Chapter 2.

Methyl 3-Oxo-2-(3-oxybutyl)-8-phenoxy-6-octenoate (34)

A solution of the β-keto ester 28 (1.80 g, 6.87 mmol), sodium methoxide (37 mg, 0.687 mmol), and a catalytic amount of 2,5-di-tert-butylhydroquinone in dry methanol (20 ml) was immersed in an ice-water bath and then methyl vinyl ketone (39) (279 µl, 241 mg, 3.44 mmol) was added to the solution under nitrogen. After stirring between 4°C an and 6°C for 6 h, the mixture was quenched by the addition of aqueous 3N hydrochloric acid. The resulting mixture was extracted twice with ethyl acetate and the combined extracts were washed twice with brine and dried over magensium sulfate. The solvent was removed *in vacuo* to give an oil, which was chromatographed on silica gel. Elution with benzene-hexane-ether, 2:2:1, afforded the bis-annulation reagent 34 (845 mg, 74.0% yield from 39).

IR (neat) 1740 (C=O), 1710 (C=O), 1598, 1237, 1171, 1030, 1011, 977, 958, 693 cm^{-1};

NMR (CCl_4) δ 2.02 (s, 3H, CH_3CO), 1.70-2.75 (m, 8H, $(CH_2)_2CCO(CH_2)_2$), 3.37 (t, J = 7 Hz, 1H, CHCO), 3.59 (s, 3H, CH_3O), 4.21-4.47 (m, 2H, CH_2OPh), 5.47-5.78 (m, 2H, CH=CH), 6.53-7.28 (m, 5H, aromatic).

Methyl 2-Oxo-1-(3-oxobutyl)-5-vinylcyclopentanecarboxylate (40)

Oxygen-free acetonitrile (5 ml), prepared by bubbling nitrogen for

30 min before use, was added under nitrogen to the flask containing palladium(II) acetate (20 mg, 0.089 mmol) and triphenylphosphine (117 mg, 0.446 mmol). After the mixture had been refluxed for 15 min, the β-keto ester 34 (595 mg, 1.79 mmol) dissolved in the oxygen-free acetonitrile (5 ml) was added slowly to the refluxing solution and heating was continued for additional 90 min. Then the cooled solution was filtered through a short silica gel column with ether and the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed on silica gel with benzene-hexane-ether, 4:4:1, to give the cyclopentanone 40 (387 mg, 90.7% yield). The NMR spectrum of 40 showed two singlet resonances due to the methyl ester protons at δ 3.66 and 3.70 ppm which were integrated in a ratio of approximately 2:1, respectively.

IR (neat) 1725 (C=O), 1713 (C=O), 1227, 1168 cm^{-1};

NMR ($CDCl_3$) δ 2.08 and 2.12 (2s, total 3H, CH_3CO), 1.58-2.96 (m, 9H, $CH(CH_2)_2CO$, $(CH_2)_2CO$), 3.66 and 3.70 (2s, total 3H, CH_3O), 4.92-6.05 (m, 3H, CH_2=CH).

Methyl 5,6,7,7a-Tetrahydro-5-oxo-1ξ-vinyl-7aβ-indanecarboxylate (41)

To a solution of 40 (32 mg, 0.13 mmol) in acetic acid (1 ml) and toluene (2 ml) was added β-alanine (23 mg, 0.27 mmol) under nitrogen. The mixture was stirred under reflux for 2 h and then cooled to room temperature. After evaporation of most of the solvent *in vacuo*, excess granular potassium carbonate was added to remove a trace of re remaining acetic acid and the meixture was filtered through a short alumina column with ether. The ethereal solution was concentrated *in vacuo* to give an oil, which was chromatographed on silica gel. Elution

with benzene-hezane-ether afforede the enone 41 (22 mg, 74%). The ratio of diastereoisomers of 41 was calculated to be about 2:1 from the NMR methyl eater proton resonances appeared at δ 3.59 and 3.62 ppm.

IR (neat) 1721 (C=O), 1665 (C=O), 1231, 1167 cm^{-1};

NMR ($CDCl_3$) δ 1.52-3.28 (m, 9H, $(CH_2)_2CO$, $(CH_2)_2CH$), 3.59 and 3.62 (2s, total 3H, CH_3O), 4.83-6.06 (m, 4H, CH_2=CH, C=CHCO).

2,2-(1,3-Dioxolane)-1-(3,3-(1,3-dioxolane)butyl)-5-vinylcyclopentane-methanol (42)

To a solution of 40 (798 mg, 3.31 mmol, diastereoisomeric ratio, 2:1) in benzene(ca 50 ml) were added ethylene glycol (3.7 ml, 66.2 mmol) and a catalytic amount of p-toluenesulfonic acid. The mixture was refluxed for 2 days with continuous removal of water and then cooled to room temperature. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The extract was removed in vacuo leaving the crude acetal, which was used in the subsequent reduction without purification.

To a suspension of lithium aluminum hydride (126 mg, 3.31 mmol) in dry THF (5 ml) was added the above acetal dissolved in dry THF (10 ml). The mixture was refluxed for 1 h and then cooled to room temperature. Excess lithium aluminum hydride was destroyed by careful addition of ethyl acetate and then water. The resulting mixture was filtered through a pad of celite with ethyl acetate under reduced presssure and filtrate was concentrated in vacuo to give the crude alcohol 42, which was purified by chromatography over silica gel. Elution with benzene-hexane-THF (10:5:1) as eluent afforded pure 42 (324 mg, 32.8%).

IR (neat) 3460 (OH), 1041 cm^{-1};

NMR ($CDCl_3$) δ 1.29 (br s, 3H, CH_3), 1.02-3.06 (m, 9H, $(CH_2)_2$, $(CH_2)_2CH$), 3.26-3.70 (m, 3H,CH_2OH), 3.82 (br s, 8H, $2(CH_2)_2O$), 4.72-6.21 (m,3H,CH_2=CH).

2,2-(1,3-Dioxolane)-1-(3,3-dioxolane)butyl)-5-vinylcyclopentanemethyl Acetate (43)

To a solution of 42 (58 mg, 0.19 mmol) in pyridine (1 ml) was added acetic anhydride (1 ml) and the resulting solution was stirred at room temperature for 12 h. Most of the solvent was removed in vacuo and the remaining oil was directly chromatographed on silica gel. Elution with benzene-hexane-ethyl acetate, 10:5:2, afforded the pure acetate 43 (62 mg, 94% yield).

IR (neat) 1737 (C=O), 1237, 1037 cm^{-1};

NMR ($CDCl_3$) δ 1.29 (s, 3H,CH_3), 2.00 (s,3H, CH_3CO), 1.38-2.73 (m, 9H, $(CH_2)_2$, $(CH_2)_2CH$), 3.85 (br s, 8H, $2(CH_2)_2O$), 3.94-4.15 (m, 2H, CH_2OAc), 4,68-5.10 (m, 2H, CH_2=CH), 5.44-6.17 (m, 1H, CH=CH_2).

2-Oxo-1-(3-oxobutyl)-5-vinylcyclopentanemethyl Acetate (44)

A mixture of the acetate 43 (49 mg, 0.14 mmol), water (4 drops), and a catalytic amount of p-toluenesulfonic acid dissolved in acetone was refluxed for 2 h. The cooled solution was concentrated in vacuo and the residue was chromatographed on silica gel with benzene-hexane-ethyl acetate, 10:5:2, as an eluent to give 44 (35 mg, 96% yield).

IR (neat) 1735 (C=O),1715 (C=O), 1233, 1037 cm^{-1};

NMR ($CDCl_3$) δ 1.98, 2.07, and 2.10 (3s,total 6H, $2CH_3CO$), 1.10-3.13 (m, 9H, $(CH_2)_2CO$, $CH(CH_2)_2CO$), 3.73-4.32 (m, 2H, CH_2OAc), 4.89-6.23 (m, 3H, CH_2=CH).

5,6,7,7a-Tetrahydro-5-oxo-1ξ-vinylindane-7aβ-methyl Acetate (45)

To a solution of 44 (22 mg, 0.087 mmol) dissloved in benzene (2 ml) and acetic acid (1 ml) was added β-alanine (16 mg, 0.17 mmol) and the mixture was refluxed for 90 min. Most of the cooled solvent was removed in vacuo and excess granular potassium carbonate and ether were added to the residue. The resulting mixture was filtered through a short alumina cloumn with ether and the filtrate was concentrated in vacuo. Then the residue was subjected to chromatography over silica gel with benzene-hexane-ether, 10:5:3, to give the pure enone 45 (12 mg, 59% yield).

IR (neat) 1732 (C=O), 1655 (C=O), 1218, 1037, 912 cm^{-1};

NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3CO), 1.47-3.03 (m, 9H, $(CH_2)_2$, $CH(CH_2)_2$), 3.80-4.22 (m, 2H, CH_2OAc), 4.80-6.14 (m, 4H, CH_2=CH, C=CHCO).

Methyl 5-oxo-2-(1-oxo-6-phenoxy-4-hexenyl)-9-decenoate (37)

To a solution of the β-keto ester 28 (1.44 g, 5.50 mmol) and sodium methoxide (59 mg, 1.1 mmol) in dry methanol (15 ml) cooled to ice-water temperature under nitrogen was added the enone 46 (1.36 g, 11.0 mmol) dissolved in dry methanol (5 ml). Stirring was continued at same temperature for 1 h. Then benzene was added to the solution and the resulting solution was filtered through a short silica gel column with benzen-ether (1:1). The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography to give the tris-annulation reagent 37 (1.72 g, 81.1% yield).

IR (neat) 1741 (C=O), 1712 (C=O), 1600,1239, 1009, 758, 694 cm^{-1};

NMR (CCl_4) δ 1.06-2.77 (m, 14H, $(CH_2)_3CO(CH_2)_2$, $(CH_2)_2CO$), 3.37 (t, J = 7 Hz, 1H, CHCO), 3.58 (s, 3H, CH_3O), 4.17-4.43 (m, 2H, CH_2OPh),

4.64-5.08 (m, 2H, CH_2=CH), 5.24-6.08 (m, 3H, HC=CH, CH=CH_2), 6.50-7.31 (m, 5H, aromatic).

Methyl 2-Oxo-1-(3-oxo-7-octenyl)-5-vinylcyclopentanecarboxylate (47)

After a mixture of palladium(II) acetate (5 mg, 0.02 mmol) and triphenylphosphine (23 mg, 0.088 mmol) in oxygen-free acetonitrile (3 ml) had been refluxed under nitrogen for 15 min, the β-keto ester 37 (166 mg, 0.430 mmol) dissolved in the oxygen-free acetonitrile (5 ml) was added slowly under reflux and refluxing was continued for an additional 1 h. The cooled brown solution was filtered through a short silica gen column with ether and the filtrate was concentrated in vacuo leaving an oil, which was chromatographed over silica gel. Elution with benzene-hexane-ether, 2:4:1, gave the cyclopentanone 47 (83 mg, 66% yield), whose NMR spectrum showed two singlet resonances attributable to methyl ester protons at δ 3.60 and 3.66 ppm, whose peak height indicated a ratio of about 1:1, respectively.

IR (neat) 1730 (C=O), 1714 (C=O), 1640, 1598, 1222, 1170, 998, 918 cm^{-1};
NMR ($CDCl_3$) δ 1.13-2.96 (m, 15H, $(CH_2)_3CO(CH_2)_2$, $CH(CH_2)_2CO$), 3.60 and 3.66 (2s, 3H, CH_3O), 4.72-6.13 (m, 6H, $2CH_2$=CH).

Methyl 4-(3-Butenyl)-5,6,7,7a-tetrahydro-1§-vinyl-7aβ-indanecarboxylate (48)

The crude cyclopentanone 47, prepared from the β-keto ester 37 (420 mg, 1.09 mmol), palladium acetate (24 mg, 0.11 mmol), and triphenylphosphine (100 mg, 0.38 mmol), was dissolved in acetic acid (1 ml) and toluene (3 ml) and β-alanine (194 mg, 2.18 mmol) was added to the solution. The resulting mixture was refluxed for 2 h and then cooled to room

temperature. After evaporation of solvent, 10% aqueous sodium hydroxide was added to the residue and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and then evaporated *in vacuo*. The residue was chromatographed over silica gel to give the enone 48 (126 mg, 50.1% yield from the β-keto ester 37). NMR analysis indicated that 48 consisted of its diastereoisomers in a ratio of 1:1.

IR (neat) 1722 (C=O), 1660 (C=O), 1230, 1160, 995, 913 cm^{-1};

NMR ($CDCl_3$) δ 1.10-3.04 (m, 13H, $(CH_2)_2$, $(CH_2)_2CO$, $CH(CH_2)_2$), 3.68 and 3.72 (2s, total 3H, CH_3O), 4.77-6.08 (m, 6H, $2CH_2=CH$).

5-Oxo-1-pentyl-6-heptenyl Acetate (50)

To a solution of the δ-lactone 49 (8.60 g, 50.6 mmol) dissolved in dry THF solution (80 ml) at -70°C under nitrogen was added slowly vinylmagnesium chloride in THF (2.08M, 27 ml, 56.2 mmol). Stirring was continued at the same temperature for 45 min. The reaction was quenched by careful addition of 10% aqueous ammonium chloride and the mixture was gradually warmed up to room temperature and extracted twice with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* left an oil.

The crude material obtained above and pyridine (12.3 ml, 152 mmol) were dissolved in dry ether under nitrogen. The solution was cooled to -50°C and acetyl chloride (7.2 ml, 101 mmol) was added slowly to the solution. The mixture was stirred at -50°C for 1 h and then the

cooling bath was removed. After being stirred overnight, the mixture was poured into 3N aqueous hydrochloric acid and extracted twice with ethyl acetate, which was then washed with saturated aqueous sodium bicarbonate and brine. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel with benzene-hexane-ethyl acetate, 10:5:1, to give the pure enone 50 (9.05 g, 74.5% yield).

IR (neat) 1729 (C=O), 1682 (C=O), 1612 (C=C), 1239, 1016, 962, 674 cm^{-1}; NMR (CCl_4) δ 0.65-1.80 (m, 15H, $CH_3(CH_2)_4COAc(CH_2)_2$), 1.91 (s, 3H, CH_3CO), 2.22-2.66 (m, 2H, CH_2CO), 4.52-4.99 (m, 1H, CHOAc), 5.49-6.32 (m, 3H, CH_2=CH).

Methyl 2-(7-Acetoxy-3-oxododecyl)-3-oxo-8-phenoxy-6-octenoate (38)

A solution of 28 (2.58 g, 9.85 mmol) and sodium methoxide (35 mg, 0.66 mmol) dissolved in dry methanol (15 ml) was cooled to ice-water temperature under nitrogen and the enone 50 (1.58 g, 6.56 mmol) dissolved in dry methanol (7 ml) was slowly added to the mixture at the same temperature. After being stirred for additional 6 h at 2°C-4°C, the solution was poured into 10% aqueous ammonium chloride and the mixture was extracted with ethyl acetate twice. The combined extracts were successively washed with brine, dried over magnesium sulfate, and then evaporated *in vacuo* leaving an oil, which was chromatographed over silica gel. Elution with benzene-hexane-ether, 10:5:2, gave the adduct 38 (2.06 g, 85.3% yield).

IR (neat) 1730 (C=O), 1718)C=O), 1600, 1588, 1241, 1028, 772, 689 cm^{-1}; NMR (CCl_4) δ 1.93 (s, 3H, CH_3CO), 0.62-2.77 (m, 25H, $CH_3(CH_2)_4COAc$-

$(CH_2)_3CO(CH_2)_2CCO(CH_2)_2$), 3.39 (t, J = 6 Hz, 1H, CHCO), 3.60 (s, 3H, CH_3O), 4.14-4.95 (m, 3H, CHOAc, CH_2OPh), 5.45-5.83 (m, 2H, CH=CH), 6.55-7.39 (m, 5H, aromatic).

Methyl 1-(7-Acetoxy-3-oxododecyl)-2-oxo-5-vinylcyclopentane-carboxylate (51)

Oxygen-free propionitrile (5 ml) was added under nitrogen to a flask containing palladium(II) acetate (6 mg, 0.03 mmol) and triphenylphosphine (24 mg, 0.091 mmol) and the mixture was allowed to reflux. After 15 min, a solution of the β-keto ester 38 (262 mg, 0.522 mmol) dissolved in the oxygen-free propionitrile (3 ml) was added slowly and refluxing was continued under nitrogen for additional 90 min. The cooled brown solution was filtered through a short silica gel column with ether and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography to give the cyclopentanone 51 (194 mg, 91.1% yield). The NMR spectrum of 51 revealed two singlet resonances at δ 3.58 and 3.63 ppm evidently due to methyl ester protons. Relative ratio of these peak heights was approximately 2:3.

IR (neat) 1730 (C=O), 1718 (C=O), 1236, 1018 cm^{-1};

NMR ($CDCl_3$) δ 1.97 (s, 3H, CH_3CO), 0.62-2.84 (m, 26H, $CH_3(CH_2)_4COAc$-$(CH_2)_3CO(CH_2)_2$, $(CH_2)_2CH$), 3.58 and 3.63 (2s, total 3H, CH_3O), 4.58-6.07 (m, 4H, CHOAc, CH_2=CH).

Methyl 4-(3-Acetoxyoctyl)-5,6,7,7a-tetrahydro-1ξ-vinyl-7aβ-indane-carboxylate (52)

To a solution of 51 (72 mg, 0.81 mmol) dissolved in acetic acid (1 ml) and toluene (2 ml) was added β-alanine (31 mg, 0.35 mmol) and the mixture was refluxed for 2 h. After cooling to room temperature, the solution was concentrated in vacuo and excess granular potassium carbonate and ether were added. The resulting mixture was filtered through a short silica gel column with ether and the filtrate was concentrated in vacuo leaving an oil, which was chromatographed on silica gle to give the enone 52 (44 mg, 62% yeild). The ratio of the peak-integration appeared at δ 3.63 and 3.68 ppm in the NMR spectrum of 52 was about 2:3.

IR (neat) 1724 (C=O), 1661 (C=O), 1233, 1171, 1019, 919, 731, cm^{-1};
NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3CO), 0.64-2.98 (m, 24H, $CH_3(CH_2)_4COAc$-$(CH_2)_2$, $(CH_2)_2CO$, $(CH_2)_2CH$), 3.63 and 3.68 (2s, total 3H, CH_3O), 4.62-6.07 (m, 4H, CHOAc, CH_2=CH).

1-(3,3-(1,3-Dioxolane)-7-hydroxydodecyl)-2-oxo-5-vinylcyclopentane-methanol (53)

The cyclopentanone 51,prepared from 38 (2.51 g, 5.00 mmol), palladium(II) acetate (56 mg, 0.25 mmol), and triphenylphosphine (230 mg, 0.877 mmol), was dissolved in benzene (ca 50 ml) to which were added a catalytic amount of p-toluenesulfonic acid and ethylene glycol (1 ml). The resulting mixture was refluxed with continuous removal of water overnight. The cooled solution was poured into 10% aqueous sodium hydroxide and the mixture was extracted with ethyl acetate. The extract was washed again with another 10% aqueous sodium hydroxide and

then brine. After being contacted with magnesium sulfate, the solution was concentrated in vacuo leaving the crude diacetal, which was subjected without purification to the nest reaction.

To the above material dissolved in dry THF (20 ml) was added lithium aluminum hydroxide (285 mg, 7.51 mmol) under nitrogen at room temperature. The mixture was heated under reflux for 1 h and then cooled to room temperature. Excess lithium aluminum hydride was destroyed by the careful a dition of water and the resulting mixture was filtered through a celite pad with ethyl acetate under reduced pressure. The filtrate was then concentrated in vacuo and the residue was directly chromatographyed on silica gel. Elution with benzene-THF, 4:1, afforded the pure dialcohol 53 (1224 mg, total 57.5% yield from 38).

IR (neat) 3436 (OH), 1634 (C=C), 1040, 946, 13, 679 cm^{-1};

NMR ($CDCl_3$) δ 0.67-3.03 (m, 28H, $CH_3(CH_2)_4COH(CH_2)_3C(CH_2)_2$, $(CH_2)_2CH$, OH), 3.26-3.74 (m,3H, CHOH, CH_2OH), 3.74-4.03 (br s, 8H, $2(CH_2)_2O$), 4.73-6.28 (m,3H, CH_2=CH).

1-(7-Acetoxy-3,3-(1,3-dioxolane)dodecyl)-2-oxo-5-vinylcyclopentane-methyl Acetate (54)

To a solution of the alcohol 53 (982 mg, 2.31 mmol) and pyridine (1.12 ml, 13.8 mmol) in dry ether (30 ml) at -40°C under nitrogen was added slowly acetyl chloride (656 μl, 9.23 mmol). The resulting mixture was gradually warmed up to room temperature with stirring. After 20 h, the mixture was poured onto 3N aqueous hydrochloric acid and the resulting mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate and then brine.

The extract was dried over magnesium sulfate, and evaporated *in vacuo* to give the crude acetate 54. Purification by chromatography on silica gel with benzene-hexane-ethyl acetate, 10:5:2, gave pure 54 (750 mg, 63.7% yield).

IR (neat) 1732 (C=O), 1638 (C=C), 1235, 1033, 949, 912, 681 cm^{-1};

NMR ($CDCl_3$) δ 2.02 (s, 6H, $2CH_3CO$), 0.68-2.84 (m, 26H, $CH_3(CH_2)_4COAc$-$(CH_2)_3C(CH_2)_2$, $CH(CH_2)_2$), 3.89 (br s, 8H, $2(CH_2)_2O$), 4.08 (br s,2H, CH_2OAc), 4.71-6.26 (m, 4H, CHOAc, CH_2=CH).

1-(7-Acetoxy-3-oxododecyl)-2-oxo-5-vinylcyclopentanemethyl Acetate (55)

A solution of 54 (227 mg, 0.445 mmol), pyridinium p-toluenesulfonate (11 mg, 0.045 mmol), and water (5 drops) in acetone (3 ml) was refluxed for 8 h and then cooled to room temperature. After evaporation of the solvent, the residue was directly chromatographed on silica gel, eluting with benzene-hexane-ether, 2:1:1, to give the diketone 55 (198 mg, 94.8% yield).

IR (neat) 1731 (C=O), 1722 (C=O), 1236, 1035, 919, 691 cm^{-1};

NMR ($CDCl_3$) δ 1.98 and 2.00 (2s, 6H, $2CH_3CO$), 0.64-2.93 (m, 26H, CH_3-$(CH_2)_4COAc(CH_2)_3CO(CH_2)_2$, $(CH_2)_2CH$), 3.70-4.29 (m, 2H, CH_2OAc), 4.52-6.18 (m, 4H, CHOAc, CH =CH).

4-(3-Acetoxyoctyl)-5,6,7,7a-tetrahydro-5-oxo-1ξ-vinylindane-7aβ-methyl Acetate (56)

To a solution of the diketone 55 (55 mg, 0.13 mmol) dissolved in acetic acid (1 ml) and toluene (2 ml) was added β-alanine (23 mg, 0.26 mmol) and the mixture was heated at reflux for 2 h. The mixture was cooled

to room temperature and most of solvent was removed *in vacuo*. Excess granular potassium carbonate and ether were added to the resulting mixture and then the mixture was filtered through a short alumina column with ether. The filtrate was concentrated *in vacuo* leaving an oil. Purification of the oil by silica gel chromatography with benzene-hexane-ether, 10:5:2, gave the enone 56 (32 mg, 61% yield).

IR (neat) 1736 (C=O), 1658 (C=O), 1232, 1034, 911, 676 cm^{-1};

NMR ($CDCl_3$) 0.63-2.97 (m, 24H, $CH_3(CH_2)_4COAc(CH_2)_2$, $(CH_2)_2$, $(CH_2)_2CH$), 3.74-4.29 (m, 2H, CH_2OAc), 4.68-6.13 (m, 4H, CHOAc, CH_2=CH).

Methyl 2-(7-Acetoxy-3-oxododecyl)-2-acetoxymethyl-3-oxocyclopentane-carboxylate (58)

A solution of 55 (71 mg, 0.17 mmol) in methanol (3 ml) was cooled to -66°C and ozone was bubbled through the solution gently. After 5 min, absence of the starting material 55 was indicated by TLC. Then excess ozone in the soultion was purged by gentle bubbling of nitrogen for about 30 min with gradual warming up to room temperature. Then excess dimethyll sulfide (*ca* 1 ml) was added to the solution and stitring was continued at room temperature for 12 h. The volatile materials were removed *in vacuo* to give the crude aldehyde 57.

NMR ($CDCl_3$) δ 9.78-10.01 (m, 1H, CHO).

The above aldehyde 57 was dissolved in acetone (5 ml) and then cooled to ice-water bath temperature. To the solution was added excess Jones reagent [26] and the mixture was stirred at the same temperature for 20 min. The oxidation was stopped by addition of excess 2-propanol

and the solvent was removed *in vacuo* to give an oil, which was poured in into brine and the resulting mixture was extracted four times with ethyl acetate. The combined solutions were washed with brine and dried over magnesium sulfate. Evaporation of the solcent *in vacuo* left the intermediate carboxylic acid.

The crude acid thus obtained was dissolved in methylene chloride (*ca* 3 ml) and ethereal diazomethane was added to the solution at room remperature. After 5 min, the solution was concentrated *in vacuo* leaving an oil, which was chromatographed on silica gel. Elution with benzene-hexane-ethyl acetate, 10:5:2, gave pure 58 (75 mg, 98% yield from 55). In the NMR spectrum of the ester 58, two singlet resonances attributable to methyl ester protons were obsereved at δ 3.63 and 3.69 ppm, whose integrations were a ratio of about 1:1.

IR (neat) 1737 (C=O), 1238, 1040, 684 cm^{-1};

NMR ($CDCl_3$) δ 1.96, 1.98, and 2.00 (3s, total 6H, $2CH_3CO$), 0.66-2.65 (m, 26H, $CH_3(CH_2)_4COAc(CH_2)_3CO(CH_2)_2,(CH_2)_2CH$), 3.65 and 3.69 (2s, total 3H, CH_3O), 3.79-4.40 (m, 2H, CH_2OAc), 4.56-5.12 (m, 1H, CHOAc)

Methyl 4-(3-Acetoxyoctyl)-7aβ-acetoxymethyl-5,6,7,7a-tetrahydro-5-oxo-1ξ-indanecarboxylate (59)

To a mixture of the ester 58 (101 mg, 0.22 mmol) and β-alanine (40 mg, 0.45 mmol) in toluene (3 ml) was added acetic acid (1 ml) and the mixture was refluxed for 90 min. After having been cooled to room temperature, the solution was concentrated *in vacuo* and then excess granular potassium carbonate and ether were added to the remaining oil. The resulting

mixture was filtered through a short alumina column with ether and the filtrate was concentrated *in vacuo* leaving an oil, which was chromatographed over silica gel with benzene-hexane-ether, 2:1:1, to give the enone 59 (75 mg, 77% yield). NMR spectrum of 59 showed two singlet resonances of methyl ester protons at δ 3.62 and 3.69 ppm (the ratio of each peak-heights, 2:3).

IR (neat) 1730 (C=O), 1663 (C=O), 1237, 1032, 683 cm^{-1};

NMR ($CDCl_3$) δ 1.97, 2.02, and 2.07 (3s, total 6H, $2CH_3CO$), 0.57-3.34 (m, 24H, $CH_3(CH_2)_4COAc(CH_2)_2$, $(CH_2)_2CO$, $(CH_2)_2CH$, 3.63 and 3.69 (2s, total 3H, CH_3O), 3.78-4.4- (m, 2H, CH_2OAc), 4.58-5.03 (m, 1H, CHOAc).

4,4-(1,3-Dioxolane)-3a-(3,3-(1,3-dioxolane)-7-oxododecyl)-1,2,3,3a,4,5,6,6a-octahydro-2-oxapentalen-1-one (61)

A solution of the alcohol 53 (91 mg, 0.214 mmol) dissolved in methanol (3 ml) was cooled to -62°C and then gently bubbled with ozone. After 5 min, bubbling was stoped and TLC analysis showed the absence of 53. The cooling bath was removed and the solution was slowly warmed up to room temperature with continuous bubbling of nitrogne. After 30 min, excess dimethyl sulfide (*ca* 0.5 ml) was added to the solution and stirring was continued at room temperature for additional 90 min. The volatile materials were removed *in vacuo* and the crude hemiacetal 60 was obtained.

The above hemiacetal 60 was dissloved in acetone (3 ml) and cooled to ice-water bath temperature. Jones reagent (excess) was added to the solution and stirring was continued at the same temperature for 30 min. The mixture was partitioned between brine and ethyl acetate.

The organic layer was washed with saturated aqueous sodium bicarbonate and then brine. This extract was dried over magnesium sulfate and evaporated *in vacuo*. The remaining oil was purified by chromatography on silica gel to afford the γ-lactone 61 (38 mg, 42% yield from 53).

IR (neat) 1772 (C=O), 1711 (C=O), 1152, 1022, 950 cm^{-1};

NMR ($CDCl_3$) δ 0.67-2.84 (m, 26H, $CH_3(CH_2)_4CO(CH_2)_3C(CH_2)_2$, $(CH_2)_2CH$), 3.94 (br s, 8H, $2(CH_2)_2O$), 4.09 and 4.43 (d and d, J = 10Hz, and J = 10 Hz, 2H, CH_2OCO).

4,4-(1,3-Dioxolane)-3a-(3,3-(1,3-dioxolane)-7-hydroxydodecyl)-1,2,3,3a,4,5,6,6a-octahydro-2-oxapentalen-1-one (62)

To a solution of 61 (50 mg, 0.12 mmol) in methanol (2 ml) was added sodium borohydride (5 mg, 0.13 mmol) at room temperature. After 10 min, acetic acid (2 drops) was added to the solution. Stirring was continued for 50 min and the mixture was concentrated *in vacuo* leaving an oil, which was directly subjected to chromatography on silica gel, eluting with benzene-hexane-THF, 10:5:2, to give the alcohol 62 (46 mg, 92% yield).

IR (neat) 3486 (OH), 1775 (C=O), 1146, 1023, 732 cm^{-1};

NMR ($CDCl_3$) δ 0.67-2.83 (m, 27H, $CH_3(CH_2)_4COH(CH_2)_3C(CH_2)_2$, $(CH_2)_2CH$), 3.43-3.70 (m, 1H, CHOH), 3.89 (s, 8H, $2(CH_2)_2O$), 4.06 and 4.40 (d and d, J = 10 Hz and J = 10 Hz, 2H, CH_2OCO).

5,5-Dioxolane-7-(4,4-(1,3-dioxolane)-1,2,3,3a,4,5,6,6a-octahydro-2-oxa-1-oxo-3a-pentalene)-1-pentylheptyl Acetate (63)

A solution of 62 (46 mg, 0.11 mmol), acetic anhydride (1 ml), and

pyridine (1 ml) was stirred at ambient temperature for 3 days and then concentrated *in vacuo*. The residue was directly chromatographed on silica gel. Elution with benzene-hexane-ethyl acetate, 10:5:3, afforded the acetate 63 (43 mg, 85% yield).

IR (neat) 1772 (C=O), 1732 (C=O), 1238, 1151, 1020, 949, 753 cm^{-1};
NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3CO), 0.64-2.78 (m, 26H, $CH_3(CH_2)_4COAc$-$(CH_2)_3C(CH_2)_2$, $(CH_2)_2CH$), 3.85 (br s, 8H, $2(CH_2)_2O$), 4.02 and 4.34 (d and d, J = 10Hz and J = 10 Hz, 2H, CH_2OCO), 4.63-5.02 (m, 1H, CHOAc).

7-(1,2,3,3a,4,5,6,6a-Octahydro-2-oxa-1,4-dioxo-3a-pentalene)-1-pentylheptyl Acetate (64)

The acetate 63 (43 mg, 0.092 mmol), p-toluenesulfonic acid (4 mg), and water (0.3 ml) were added to acetone (3 ml) and the mixture was refluxed for 3 h. The cooled solution was concentrated *in vacuo* and the residual oil was directly subjected to chromatography on silica gel to give the diketone 64 (25 mg, 71% yield).

IR (neat) 1777 (C=O), 1735 (C=O), 1719 (C=O), 1242, 1019, 735 cm^{-1};
NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3CO), 0.73-3.11 (m, 26H, $CH_3(CH_2)_4COAc$-$(CH_2)_3CO(CH_2)_2$, $(CH_2)_2CH$), 4.02 and 4.34 (d, and d, J = 10Hz and J = 10 Hz, 2H, CH_2OCO), 4.66-4.97 (m, 1H, CHOAc).

An Attempted Cyclization of 64

Ror example, the diketone 64 (13 mg, 0.034 mmol) and β-alanine (10 mg, 0.11 mmol) were added to toluene (1.5 ml) and acetic acid (0.5 ml) and the mixture was heated under reflux ofor 3 h. After having been

cooled to room temperature, the reaction mixture was analyzed by TLC, which indicated the presence of only 64 and a spot attributable to the desired product 65 could not be detected.

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CHAPTER EIGHT

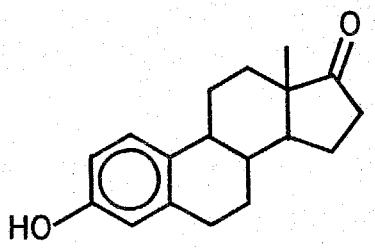
A NEW TRIS-ANNULATION REAGENT PREPARED FROM A BUTADIENE TELOMER, AND ITS APPLICATION TO STEROIDS SYNTHESIS

Summary

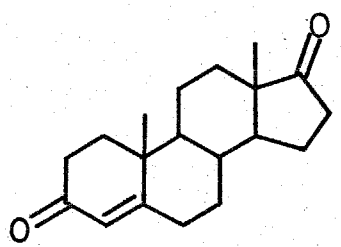
The new tris-annulation reagent, 5-oxo-1-(4-pentenyl)-6-heptenyl acetate (19) was prepared starting from 1-vinyl-5-hexenyl acetate (20), which is available by the palladium-catalyzed dimerization of butadiene with acetic acid, by way of the bis-annulation reagent, 1,7-octadien-3-one (13). The usefulness of the reagent 19 for the construction of steroid skeleton was demonstrated by the synthesis of 19-nor-D-homo-androst-4-ene-3,17a-dione (21).

8-1 Introduction and Strategy

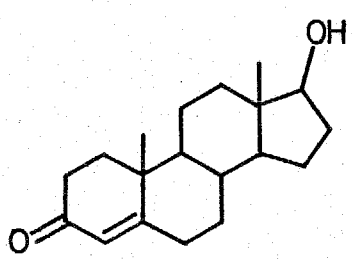
Some steroids have contraceptive activity.[2-4] In addition to this property, many steroids exhibit pharmacologically important activities.[5-7] Estrone (1), which is synthesized from 2 *in vivo*, possesses ability to produce heat in female mammalian species. Teststerone (3) is famous as a male sex hormone. Progesterone (4) is a human pregnancy hormone. Since steroids are involved in normal regulation of many physiological functions as described above, much attention of synthetic chemists has been paid to find out highly efficient syntheses of these steroids.[8-15]



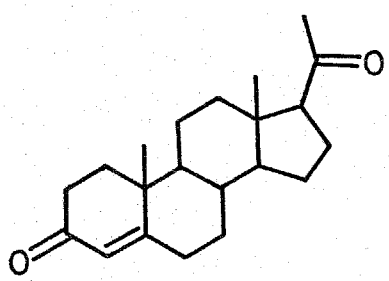
estrone (1)



androst-4-ene-3,17-dione (2)

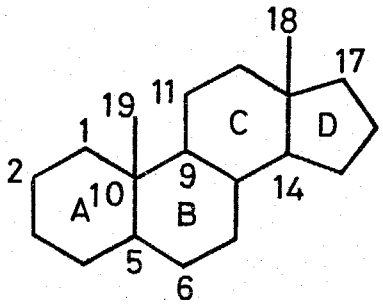


testosterone (3)

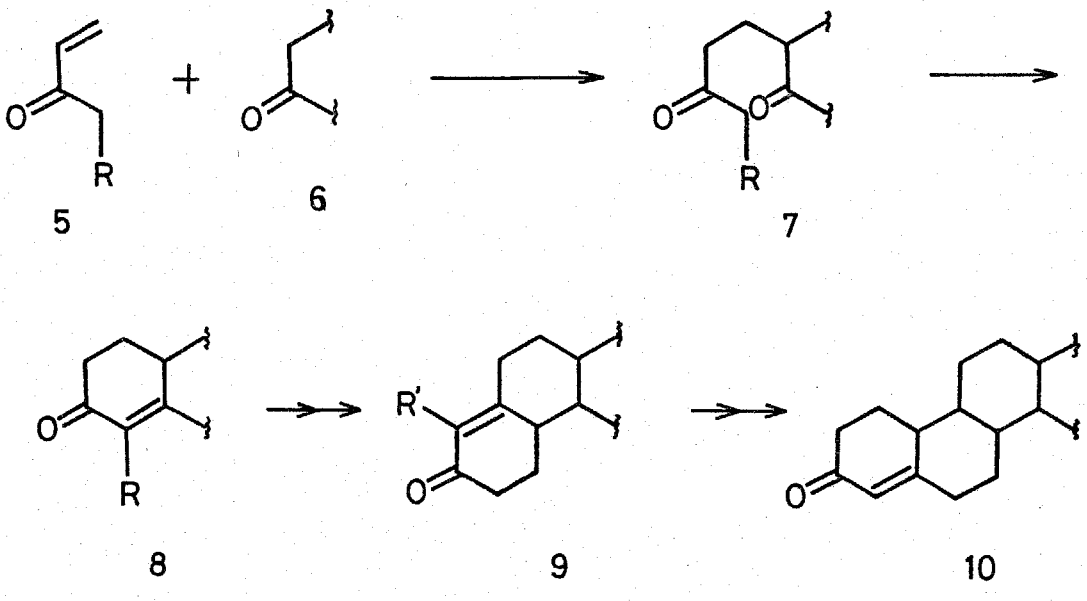


progesterone (4)

Steroids are compounds containing four or more fused rings having the same basic skeleton as shown below:

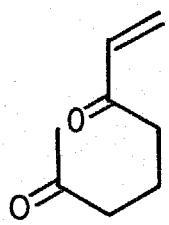


Among possible stereoisomers, most of naturally occurring steroids are one isomer of trans-anti-trans-anti-trans stereochemistry, which means that the backbone is thermodynamically stable and is relatively flat. The three trans terms refer to AB, BC, and CD ring fusions, while the anti terms refer to the geometries at C-9,10 and C-8, 14. Therefore highly stereoselective reactions must be employed to create new asymmetric centers in desired directions. With regard to this stereochemestry, CD ring trans junction is, inter alia, of great importance in total syntheses of steroids starting from one compound corresponding to D ring by successive employments of "Robinson type" ring construction (ie., aldol condensation) methods (vide infra), because the CD ring trans fusion may control stereochemistry of other asymmetric centers in desired directions.[15]



Meanwhile for the purpose of constructing steroid backbone starting from a mono- or bi-cyclic ketone, a chain which is capable of being cyclized must be introduced regioselectively onto a pre-existing ring.[17-19] One method[20,21] is the Michael addition of an enolate of a cyclic or an acyclic ketone 6 onto a vinyl ketone 5 to yield 7, followed by cyclization and dehydration to a cyclohexenone 8. When R in 5 is hydrogen, the reaction is called "the Robinson annulation" or systematically "mono-annulation". When the enone 5 is a synthetic equivalent of oct-7-ene-2,6-dione (11), 5 is called a "bis-annulation reagent",[22] with which two fused six-membered cyclic ketones can be constructed from one reagent (5 ⟶ 9), instead of repeating the original Robinson annulation twice. Moreover there exists a concept of "tris-annulation" (5 ⟶ 10), which means the construction of three fused six-membered cyclic ketones from one reagent, namely a "tris-annulation reagent", which is a synthetic

equivalent to 11-dodecene-2,6,10-trione (12). In other words, tris-annulation reagents are linear 12-carbon compounds having a terminal enone or its equivalent in one side, a masked methyl ketone in another end, and an oxygen function at the position 6.



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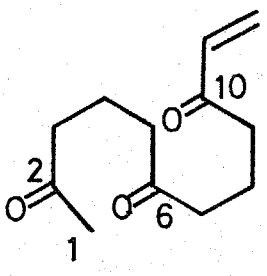

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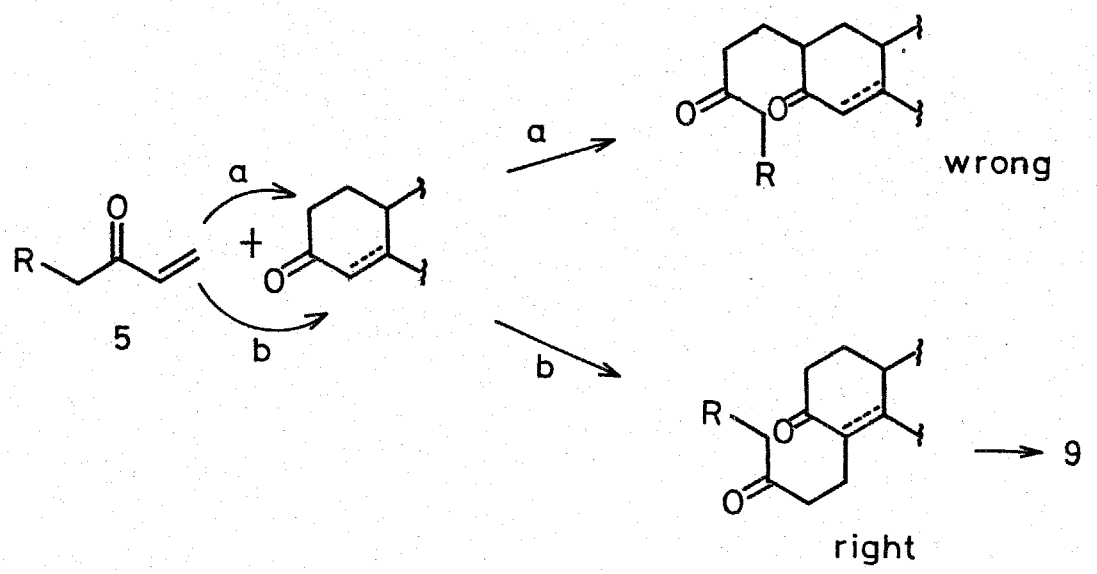
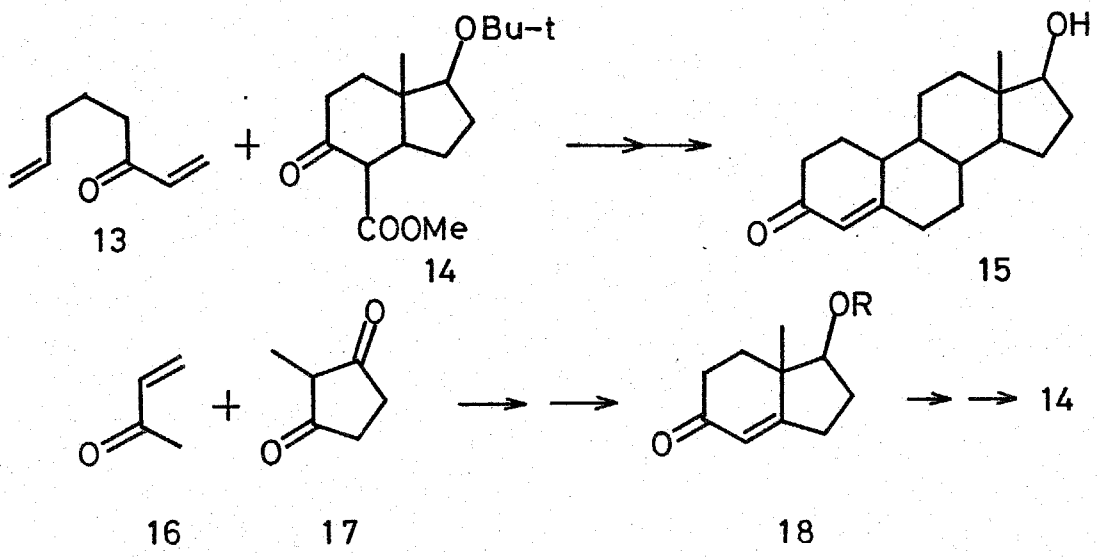
To construct steroids skeleton from mono cyclic ketone corresponding to D ring, the Robinson annulation must be repeated three times in regio-selective manner at a desired site before or after reduction of 8 (R = H) to build up the enone 9 or 10. But in general the requisite regio-selective carbon-carbon bond formation is not warranted as such;

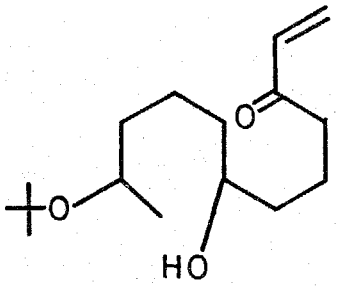


This problem has been partially solved by use of bis-annulation reagents, with which two rings of three requisite rings of steroid skeleton can be constructed. There still remain problems of regioselective carbon-carbon bond construction. For example, Tsuji et al.[23] prepared 1,7-octadien-3-one (13) as a bis-annulation reagent and synthesized 19-nortestosterone (15) from 13 with the β-keto ester 14, which had been prepared from 2-methylcyclopentane-1,3-dione (17) with methyl vinyl ketone (16) via the enone 18 according to the method developed by Hajos et al.[24] In their synthesis, methoxycarbonyl group is necessarily introduced on the enone 18 in order to carry out the regioselective carbon-carbon bond formation with the bis-annulation reagent 13. Consequently it is

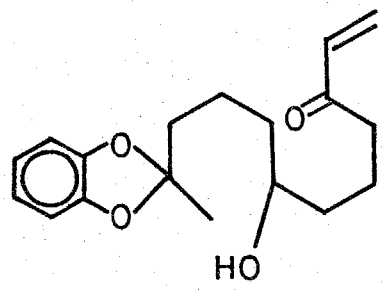


preferable to introduce the tris-annulation concept to avoid such a crucial carbon-carbon construction. Under this concept, several groups have succeeded in synthesis of steroids by using various tris-annulation reagents, most of which are listed in Figure 8-1.

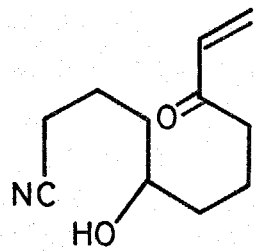
Figure 8-1



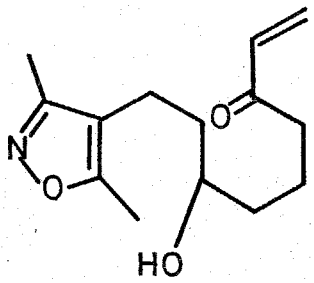
Ref. 25



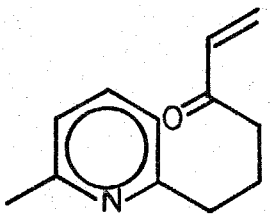
Ref. 26



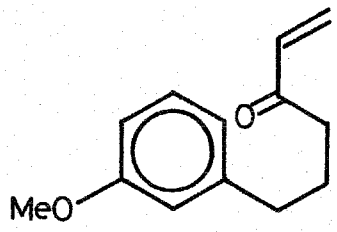
Ref. 27



Ref. 28

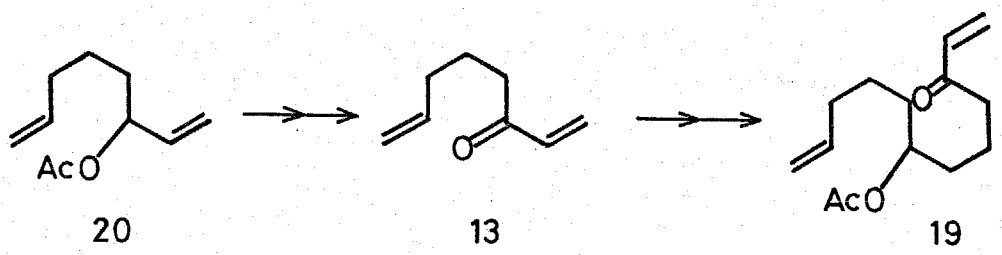


Ref. 29



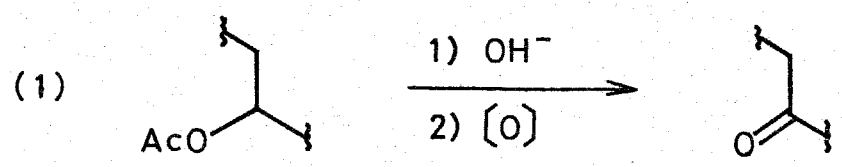
Ref. 30

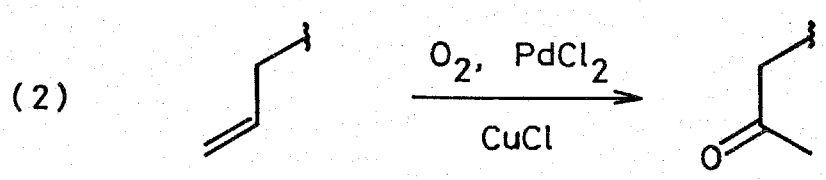
The usefulness of a tris-annulation reagent is assessed by easy accessibility of the reagent itself, stability to acids and bases, and facile procedure and high efficiency of unmasking, but the reported reagents do not always satisfy these requirements. With these backgrounds, the author has synthesized the tris-annulation reagent 19 from the bis-annulation reagent 13 [23] which could be prepared easily from the



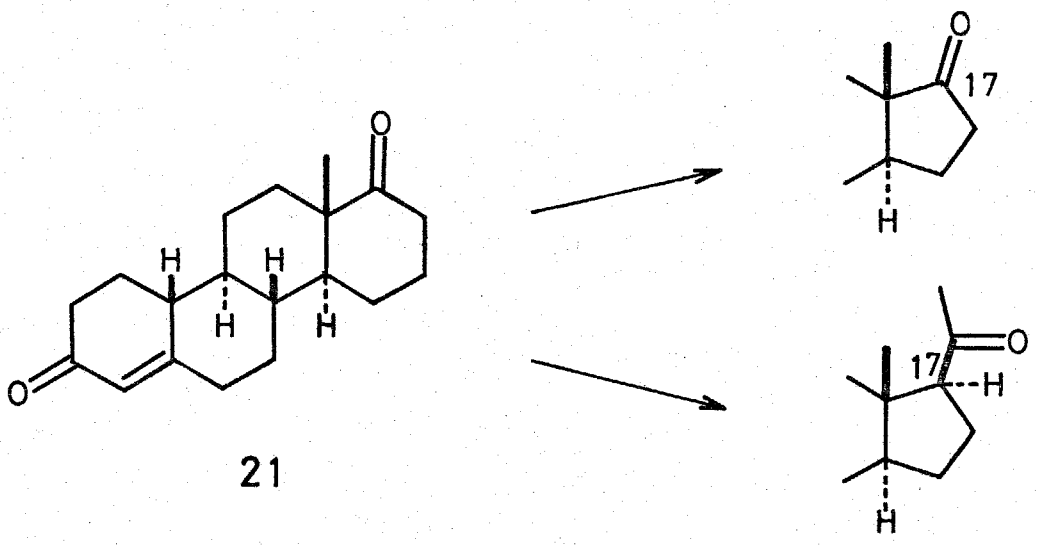
20 13 19

butadiene telomer 20.[31] This reagent 19 undergoes the Michael addition and then the acetoxy group is converted to ketone by hydrolysis and subsequent oxidation. Finally the terminal olefin is converted to methy ketone by palladium-catalyzed oxidation.[32]





In the next section the synthesis of 19 and the results of its application to the construction of steroid backbones including 19-nor-D-homoandrost-4-ene-1,17a-dione (21) are described in detail.[1] Although 21 possesses six-membered cyclic ketone as D ring, it is not a serious matter because there are ample examples to convert it into a five-membered ring with carbonyl function [33] or acetyl group [34] at C-17 as shown below.

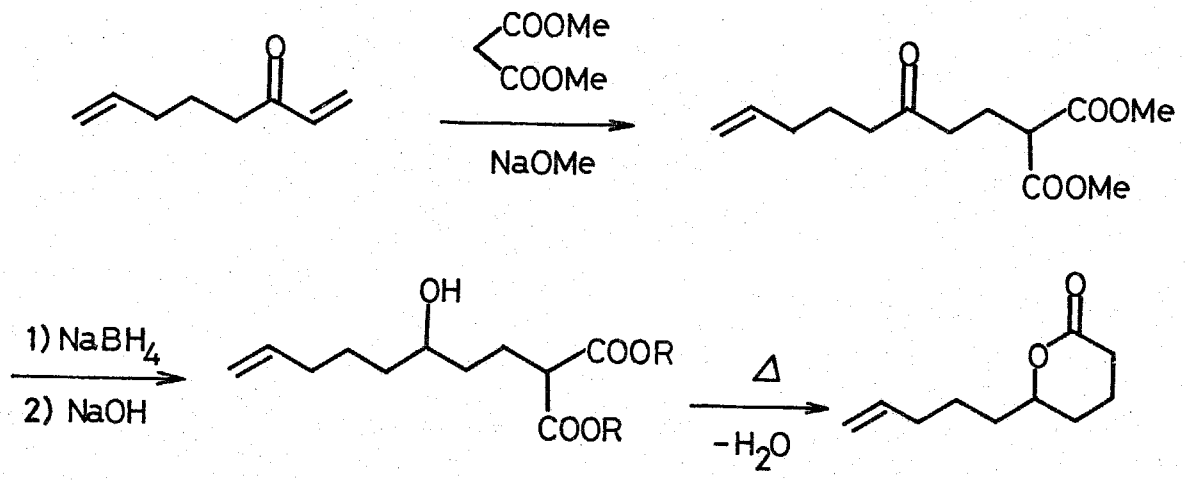


8-2 Results and Discussion

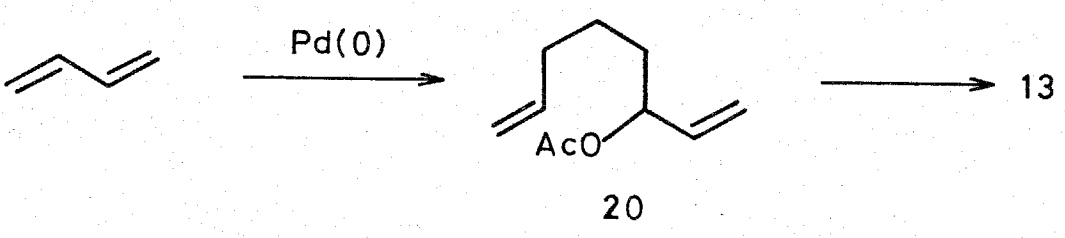
8-2-1 Preparation of the tris-Annulation Reagent 19

The reagent 19 was prepared in good yield as outlined in Scheme 8-1.

Scheme 8-1



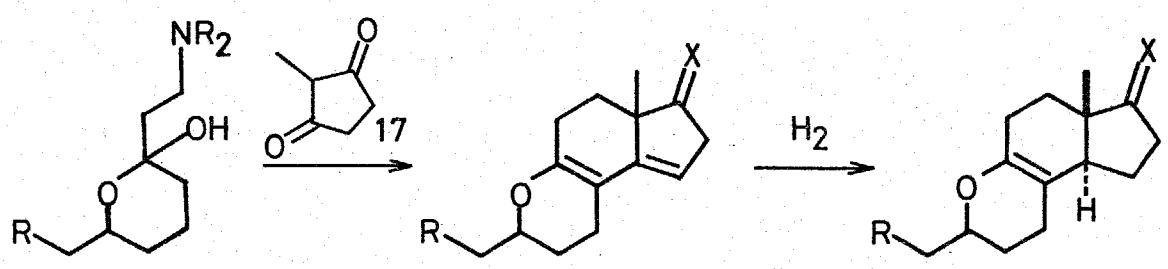
The starting material was the enone 13 which was easily prepared from the acetate 20 [31] according to the method of Tsuji and Shimizu et al.[23]



The Michael addition of dimethyl malonate to 13 was carried out in the presence of sodium methoxide in methanol. After TLC analysis had indicated the absence of 13 and the formation of the adduct 22, sodium borohydride was added directly to the solution and the alcohol 23a was isolated in 65% yield from 13. Saponification of the diester 23a in a usual way gave the diacid 23a, which was then subjected to decarboxylation and simultaneous dehydration by heating under reduced pressure (ca 115°C (20 mmHg)) to give the δ-lactone 24 in 77% yield from 23a. Reaction of 24 with vinylmagnesium chloride [35] below -60°C afforded 25 in a quantitative yield. Finally acetylation of 25 with acetic anhydride and pyridine gave the tris-annulation reagent 19 in 61% yield from 24.

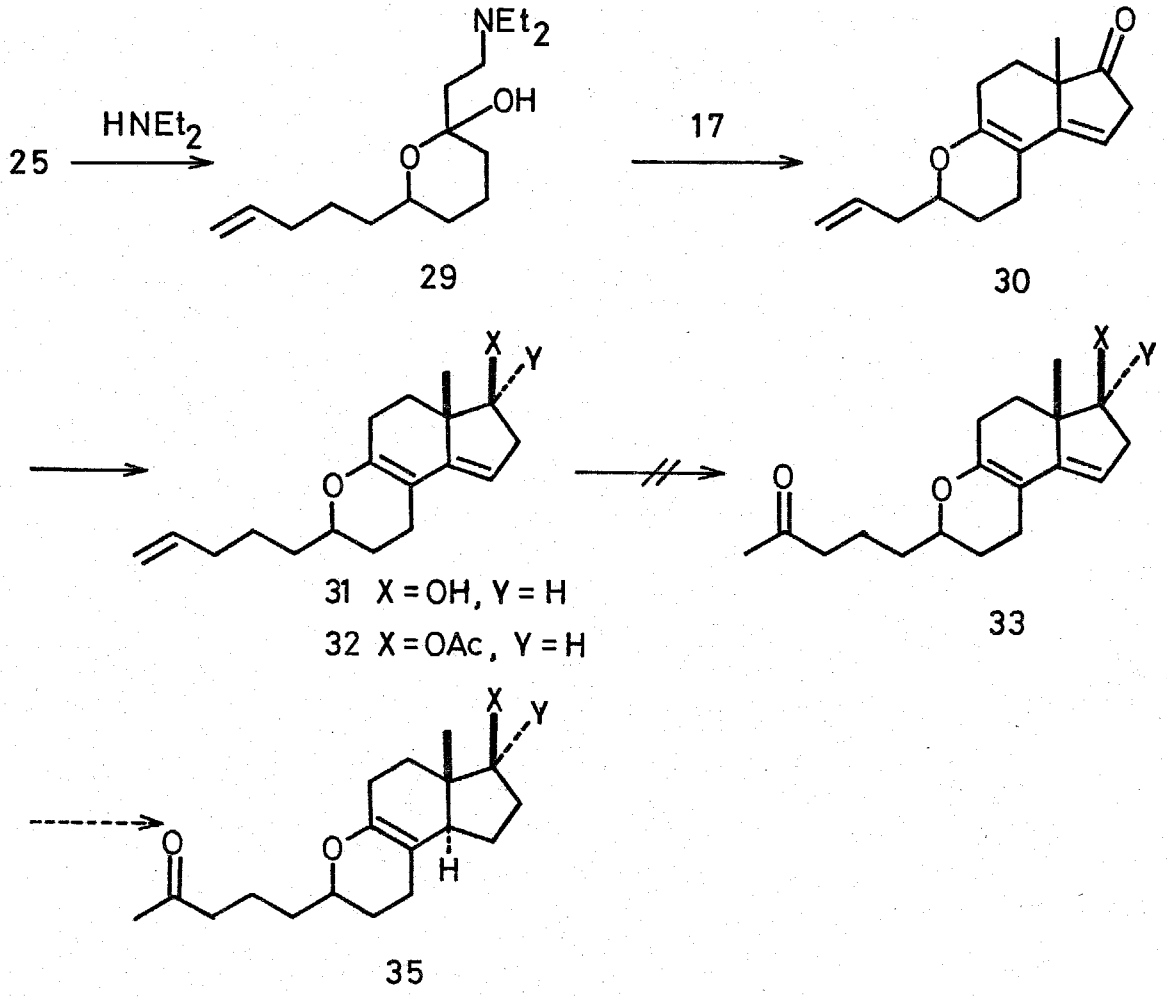
8-2-2 Preliminary Results

It is well known that steroids have always trans-fused C,D rings. As mentioned in the introduction, this trans stereochemistry is a keystone since it may control the stereochemistry of other asymmetric centers in desired directions.[16] Saucy et al. [25-28, 36-38] prepared the dienol ether 27 and succeeded in its hydrogenation to give the enol ether 28 possessing the correct trans C,D ring junction. Preliminarily the author applied their method. Scheme 8-2 shows the results. It is



26 27 28

Scheme 8-2



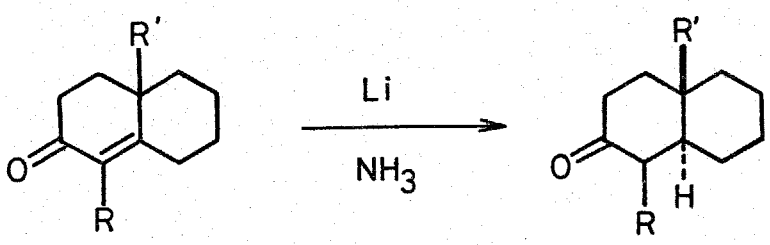
the alcohol 25 instead of 19 that was necessary to prepare a dienol ether corresponding to 27. Treatment of 25 with excess diethylamine afforded in a quantitative yield the Mannich base 29, which was then condensed with 17 in toluene and acetic acid under reflux to produce the dienol ether 30 in 81% yield from 25. Reduction of 30 with lithium aluminum hydride gave the alcohol 31. Next, the transformation of the terminal olefin moiety of 31 to the methyl ketone by the palladium(II)-catalyzed oxidation[32] was tried. Unfortunately no desired product 33 could be isolated. The failure may simply be ascribable to the presence

of the hydroxy function of 31. Subsequently the palladium-catalyzed oxidation of 32 which had been prepared from 31 in a usual way was carried out. No desired product, however, could be obtained.

There is the dienol ether moiety in both 31 and 32. Namely it seems to be likely that this common moiety prevented palladium(II) species from coordinating the isolated olefin to trigger off the normal oxidation because favorable coordination of the dienol ether moiety to palladium(II) species stems from a higher π-electrone density of the dienol ether moiety than that of simple double bond.[39] Therefore other synthetic pathway to steroid backbone was exploited as follows.

8-2-3 Total Synthesis of 19-Nor-D-homoandrost-4-ene-1,17a-dione (21)

As mentioned above, since C,D ring trans fusion may control the stereochemistry of other asymmetric centers in desired directions,[16] stereoselective reactions must be employed in a total synthesis of steroids even using the tris-annulation reagent 19. In 1960's, Stork et al. published[40] the elegant work, in which lithium-ammonia reduction of 36 gives the trans decalone 37 and this method have been applied to the syntheses of many natural products possessing this stereochemistry including steroids. Scheme 8-3 illustrates the synthetic pathway



36 37

starting from 19 to the title compound 21, including the lithium ammonia reduction (41 → 42).

The Michael addition of 2-methylcyclohexane-1,3-dione (38) to the tris-annulation reagent 19 was easily performed in a mixed solvent of ethyl acetate and triethylamine at room temperature and the adduct 39 was obtained in 91.3% yield. Then the aldol condensation of 39 was examined under various conditions. Some results are picked up in Table 8-1. Preliminarily, the conditions which have been sometimes used in similar cases [29, 30] were applied (Run 1,2,3) and the desired product 40 was obtained only in 20% yield when β-alanine had been used under the conditions presented in Run 3 of Table 8-1. After many trials the yield of the condensation was raised up to 73-83% yield when the solution of 39 in ethyl acetate and toluene (1:4) or acetic acid only had been refluxed in the presence of β-alanine alone (Run 4,5). Finally the best conditions were found out: Refluxing a solution of 39 in toluene and acetic acid (4:1) in the presence of 2 equiv. of β-alanine for 2 h resulted in the formation of 40 in 94.4% yield (Run 6).

Next the enone 40 had been reduced selectively to the alcohol 41 with sodium borohydride in methanol at -7°C before the lithium ammonia reduction was carried out. A solution of 41 was added to a solution of lithium (ca 6 equiv.) in liquid ammonia at -72°C. After 20 min the reaction was stopped by the addition of excess ammonium chloride to the solution and 42 was isolated in a moderate crude yield. In this case, proton source such as tert-butyl alcohol to quench the anion generated at C-14 was not necessary since the substrate 41 as such is a good quencher:

Scheme 8-3

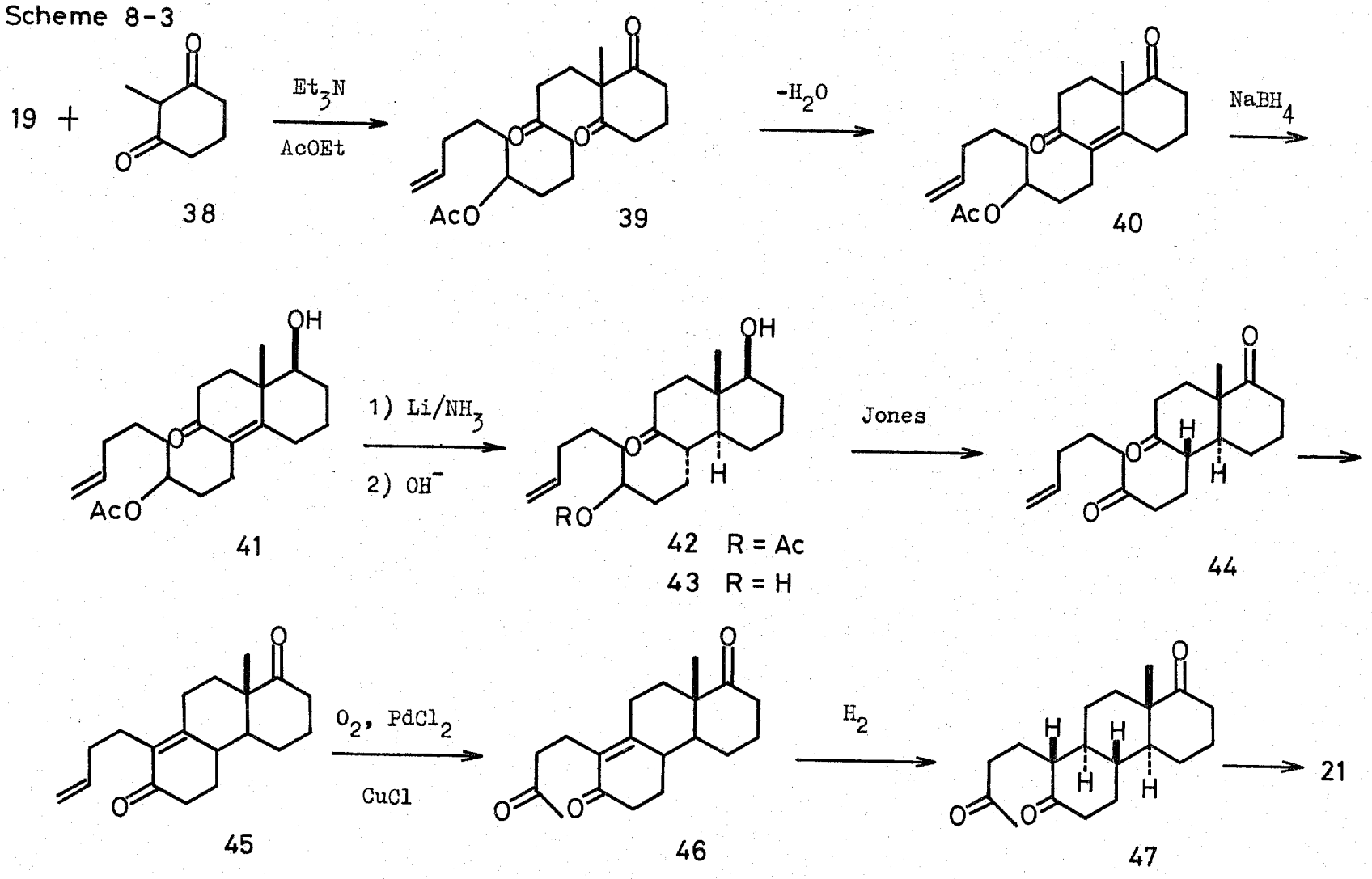
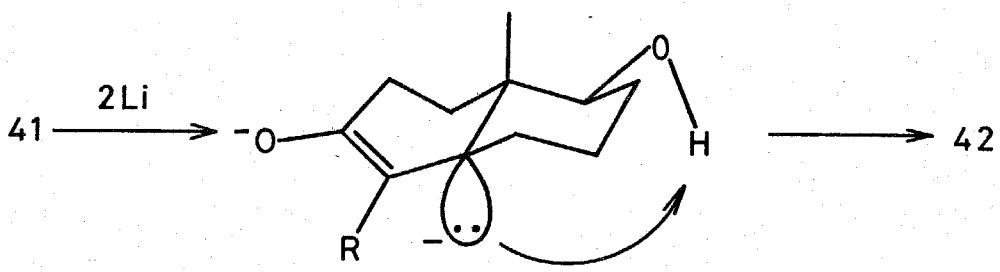

19 +
38
Et3N
AcOEt
AcO
39
-H2O
40
NaBH4
OH
AcO
41
1) Li/NH3
2) OH-
RO
42 R = Ac
43 R = H
Jones
44
O2, PdCl2
CuCl
45
46
H2
47
21

Table 8-1 The Aldol Condensation of 39

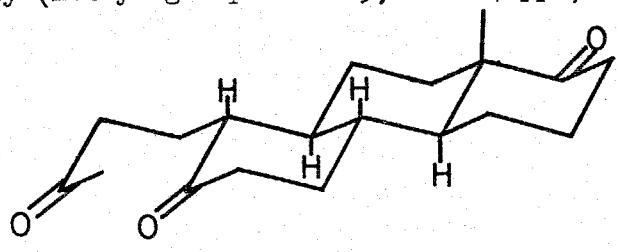
Run	Base (equiv.)	Solvent	Temp.	Time (h)	Yield of 40 (%)
1	PhCOOH (6) Et_3N (4)	xylene	reflux	72	0
2	aq. 1N $HClO_4$ (2)	CH_3CN	reflux	24	0
3	aq. 1N $HClO_4$ (0.5) β-alanine (1)	CH_3CN	reflux	72	20
4	β-alanine (2)	toluene AcOEt (4:1)	reflux	3	73.3
5	β-alanine (2)	AcOH	reflux	3	83.2
6	β-alanine (2)	toluene AcOH (4:1)	reflux	2	94.4



The crude reduction product 42 was subsequently hydrolyzed and the diol 43 was produced in 67% yield from the enone 41. Jones oxidation [41] of 43 afforded the trione 44 in 58% yield.

The 60 MHz spectrum of 44 showed one singlet peak attributable to methyl group at δ 1.31 ppm which demonstrates that 44 was single stereoisomer having trans octalone framework. Furthermore this trans relationship was attested by the synthesis of 21 (vide infra).

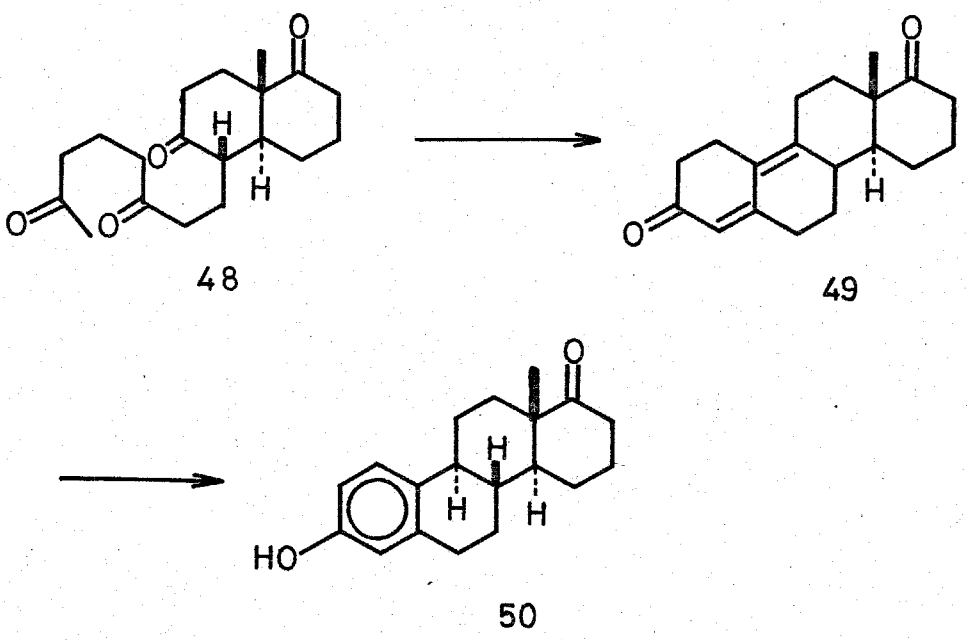
The aldol condensation of 44 was carried out in refluxing benzene containing a small amount of p-toluenesulfonic acid to give 76% yield of the enone 45, which was then transformed to 46 in 84% yield by the palladium-catalyzed oxidation [32] under oxygen. The enone 46 was hydrogenated over a palladium catalyst in THF and ethanol in the presence of a small amount of triethylamine to produce 47 in quantitative yield. The homogeneity of 47 with equatorial 3-oxobutyl group was confirmed by NMR spectroscopy (methyl group at C-13, δ 1.17 ppm).



thermodynamically stable conformer of 47

Finally treatment of 47 with aq. 4N hydrochloric acid in refluxing methanol gave in 92% yield 19-nor-D-homoandrost-4-ene-3,17a-dione (21), which was identified by comparison of its IR and NMR spectra with those of an authentic sample.[42]

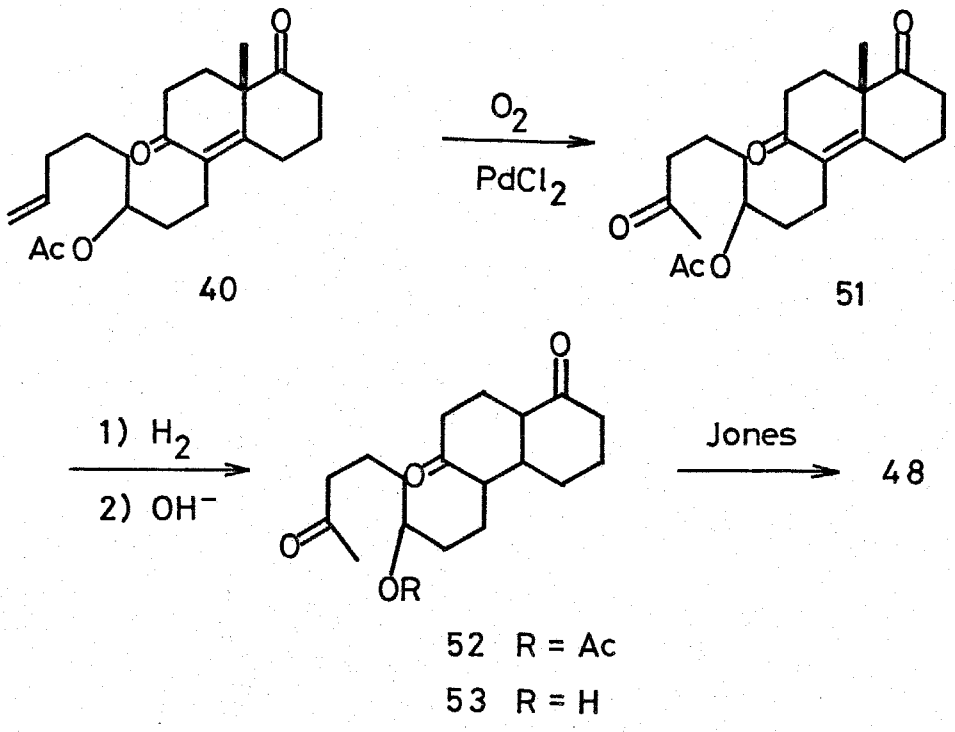
8-2-4 Attempted Approach to D-Homoestrone



To test further possibility of the method using the tris-annulation reagent 19, the synthesis of D-homoestrone (50) was attempted. As a suitable precursor of 50, was chosen the dienone 49, from which 50 was readily synthesized by Danishefsky et al.[43] and other groups.[30, 44]

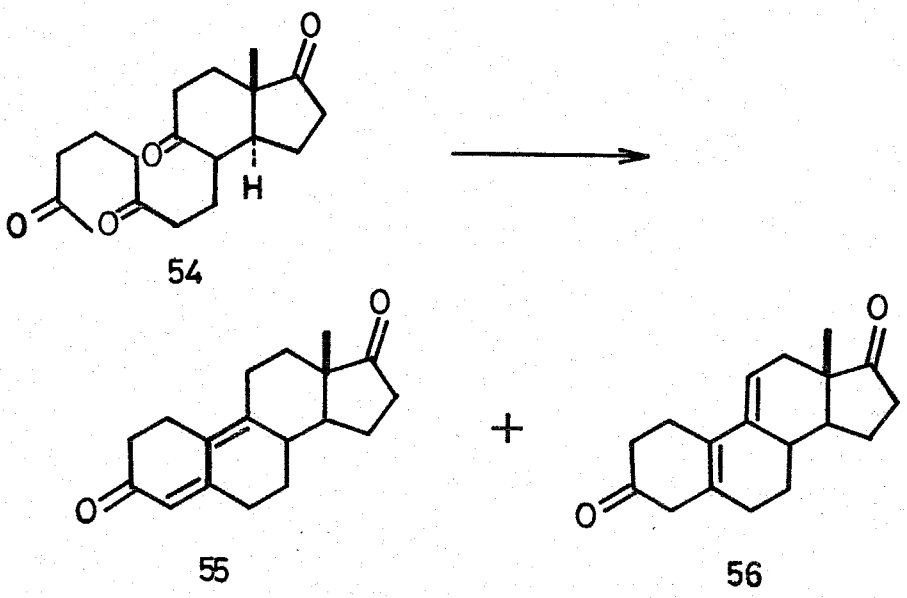
Synthetic analysis revealed that the dienone 49 might be synthesized from 48 by repeating the "aldol type" cyclization twice in one flask. With above assumption, the synthesis of 48 was commenced from the enone 40 as depicted in Scheme 8-4.

Scheme 8-4



The enone 40 was oxidized [32] to the methyl ketone 51 in 80.7% yield under oxygen in the presence of a catalytic amount of palladium(II) chloride. Catalytic hydrogenation of 51 under hydrogen by using a palladium catalyst in triethylamine and ethyl acetate (1:3) gave the expected trans decalone 52 in a nearly quantitative yield and subsequent hydrolysis of 52 produced the alcohol 53 in 90% yield from 51. Treatment of 53 with excess Jones reagent [41] afforded 55.6% yield of the tetraone 48. The homogeneity of 48 was confirmed by one singlet peak (δ 1.35 ppm) of the 60 MHz NMR spectrum of 48 due to methyl group attached at C-13.

Then the conditions of the aldol cyclization of 48 was studied. Timely Hoffmann-LaLoche group reported [45] that 54 cyclized into 55 and 56 (1:1) in 70% yield when heated in refluxing toluene with piperidinium acetate. By use of their condition, the aldol condensation of 48 was



attempted but no desired product could be isolated. Then many other conditions were tried. For example;

(a) β-alanine in refluxing toluene and acetic acid;

(b) aq. 5% potassium hydroxide in THF and ether;

(c) p-toluenesulfonic acid in refluxing acetic acid, benzene, or hexane;

(d) piperidinium p-toluenesulfonate in refluxing benzene

and so on,

Unfortunately under above conditions no desired product 49 was produced.

8-3 Experimental

Dimethyl 3-Hydroxy-7-octenylmalonate (23a)

To a solution of dimethyl malonate (8.6 ml, 75 mmol) and sodium methoxide (135 mg, 2.5 mmol) in dry methanol was added the enone 13 (4.58 g, 36.9 mmol) dissolved in methanol (50 ml) over 30 min at 0°C. The reaction mixture was stirred for 1 h at 0°C and then at room temperature. After 36 h, TLC analysis showed the complete absence of the enone 13 and the formation of the adduct 22. The solution was again cooled in an ice-water bath and sodium borohydride (946 mg, 25 mmol) was added to the solution. After stirring had been continued at 0°C for an additional 1 h, acetic acid (ca 0.3 ml) was added and then most of the solvent was removed in vacuo. The residue was poured onto aqueous saturated sodium bicarbonate and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give the crude alcohol 23a, which was purified by chromatography on silica gel. Elution with benzene-hexane-THF, 10:5:2, afforded pure 23a (6.20 g, 65.1% from 13).

TLC, R_f 0.27 (benznen-hexane-ethyl acetate, 8:4:3);

Bp. 128-131°C (2 mmHg);

IR (neat) 3436 (OH), 1758 and 1736 (C=O), 1645 (C=C), 1254, 1226, 1154, 1014, 911 cm^{-1};

NMR ($CDCl_3$) δ 1.20-2.27 (m, 10H, $(CH_2)_3CH(CH_2)_2$), 2.57 (s, 1H, OH), 3.31-3.68 (m, 1H, C<u>H</u>OH), 3.37 (t, <u>J</u> = 7 Hz, 1H, $CH(COO)_2$, 3.68 (s, 6H, $2CH_3O$), 4.73-5.15 (m, 2H, CH_2=C), 5.42-6.12 (m, 1H, C<u>H</u>=CH_2).

In a similar experiment, the above reaction was quenched before the addition of sodium borohydride and the analytically pure sample of the adduct 22 was obtained. Physical data of dimethyl 3-oxo-7-octenylmalonate (22) are as follows:

TLC, R_f 0.26 (benzene-hexane-ether, 20:10:3);

Bp. 110-113°C (2 mmHg);

IR (neat) 1754, 1733, 1712, 1642 (C=C), 1261, 1233, 1202, 1158, 1031, 918 cm^{-1};

NMR ($CDCl_3$) δ 1.44-2.68 (m, 10H, $(CH_2)_3CO(CH_2)_2$), 3.43 (t, J = 7 Hz, 1H, CH), 3.72 (s, 6H, $2CH_3O$), 4.74-5.17 (m, 2H, CH_2=C), 5.42-6.13 (m, 1H, CH=CH_2).

9-Decen-5-olide (24)

To a solution of the alcohol 23a (1.71 g, 6.63 mmol) dissolved in methanol (15 ml) were added water (5 ml) and sodium hydroxide (1.06 g, 26.5 mmol). The mixture was heated under reflux for 1 h and cooled to room temperature. Most of the solvent was evaporated in vacuo and water (ca 100 ml) was added to the residue. After neutral components has been extracted twice with dichloromethane, the aqueous layer was acidified to ca pH 3 by the addition of 3N hydrochloric acid and granular sodium chloride was added to the mixture. The crude acid 23b thus obtained was extracted four times with ethyl acetate. The combined extracts were rinsed with brine, dried over magnesium sulfate, and concentrated in vacuo. The diacid 23b was heated under reduced pressure (ca 114°C (20 mmHg) for 2 h) to cause decarboxylation and dehydration. Finally the lactone 24 was obtained (862 mg, 77.4% yield) by distillation under reduced pressure (108-111°C (2 mmHg)).

IR (neat) 1733 (C=O), 1640 (C=C), 1245, 1182, 1047, 929, 910 cm^{-1};
NMR ($CDCl_3$) δ 1.08-2.71 (m, 12H, $(CH_2)_3C(CH_2)_3$), 4.03-4.56 (m, 1H, CH), 4.75-5.22 (m, 2H, CH_2=C), 5.43-6.18 (m, 1H, C<u>H</u>=CH_2).

3,4,5,6-Tetrahydro-6-(4-pentenyl)-2-vinyl-2H-pyran-2-ol (25)

To a solution of 24 (135 mg, 0.804 mmol) in dry THF (5 ml) under nitrogen cooled to -70°C was added vinylmagnesium chloride [35] (0.94M, 1.7 ml, 1.6 mmol) by syringe. The solution was stirred for 50 min between -60 and -70°C and the reaction was quenched by dropwise addition of methanol (ca 100 μl) and then aqueous 10% ammonium chloride was added. The mixture was allowed to warm gradually up to room temperature. The solvent was removed in vacuo and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude 25, which was purified by silica gel chromatography. Elution with benzene-hexane-ethyl acetate, 10:5:3, afforded pure 25 (157 mg, 100% yield).

TLC, R_f 0.25 (benzene-hexane-THF, 10:5:3);
IR (neat) 3451 (OH), 1723, 1673, 1641, 1613, 1185, 1083, 995, 907, 788 cm^{-1};
NMR ($CDCl_3$) δ 1.04-2.80 (m, 13H, $(CH_2)_3C(OH)(CH_2)_3$), 3.36-3.87 (m, 1H, CH), 4.78-6.48 (m, 6H, $2CH_2$=CH).

5-Oxo-1-(4-pentenyl)-6-heptenyl Acetate (19)

Acetic anhydride (3.6 ml, 38 mmol) and the crude 25 (2.59 g) obtained from 24 (2.13 g, 12.7 mmol) by similar procedure described above were

dissolved in pyridine (6 ml) and the mixture was stirred for 20 h at ambient temperature. After having been concentrated (ca 3 ml) in vacuo, the mixture was poured into 3N hydrochloric acid and then extracted three times with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bicarbonate, and brine and dried over magnesium sulfate. The residue obtained by evaporation of solvents in vacuo was chromatographed on silica gel by use of benzene-hexane-ether,10:5:2, as an eluent to give 19 (1.84 g, 61% yield from 24).

TLC, R_f 0.41 (benzene-hexane-ether, 10:5:3);

IR (neat) 3090, 1748 (C=O), 1701 (C=O), 1681, 1641, 1619, 1247, 1027, 997, 967, 906 cm^{-1};

NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 1.03-2.78 (m, 12H), 4.66-6.40 (m, 7H, $2CH_2$=CH, CHOAc).

3a,4,5,7,8,9-Hexahydro-3aβ-methyl-7-(4-pentenyl)cyclopenta[f]-2H-1-benzopyran-3-one (30)

The alcohol 25 (175 mg, 0.804 mmol) dissolved in benzene (3 ml) was treated with diethylamine (250 μl, 177 mg, 2.4 mmol) at room temperature. After 1 h, the solvent was removed in vacuo to give the crude Mannich base 29: NMR ($CDCl_3$) δ 1.00 (t, J = 7 Hz, 6H, $2CH_3$), 4.72-6.36 (m, 3H, $CH=CH_2$).

The above Mannich base 29 and 2-methylcyclopentane-1,3-dione (17) (135 mg, 1.21 mmol) were added to toluene (3 ml) and acetic acid (1 ml). The solution was refluxed under nitrogen for 1 h. The cooled solvent was removed in vacuo. The residue was chromatographed on alumina with benzene-hexane-ethyl acetate, 30:10:3, as an eluent to give the dienol ether 30 (178 mg, 80.5% yield from 25).

TLC, R_f 0.62 (benzene-hexane-ethyl acetate, 10:5:1);
IR (neat) 3055, 1743 (C=O), 1638 (C=C), 1228, 1161, 911, 778 cm^{-1};
NMR ($CDCl_3$) δ 1.07 (s, 3H, CH_3), 1.18-2.50 (m, 14H, $(CH_2)_3C(CH_2)_2$, $(CH_2)_2$), 2.71-3.07 (m, 2H, CH_2CO), 3.44-4.00 (m, 1H, CH), 4.70-6.13 (m, 4H, CH=C, CH_2=CH).

3a,4,5,7,8,9-Hexahydro-3aβ-methyl-7-(4-pentenyl)cyclopenta[f]-2H-1-benzopyran-3β-ol (31)

To the dienol ether 30 (62 mg, 0.23 mmol) dissolved in THF (3 ml) under nitrogen was added lithium aluminum hydride (29 mg, 0.76 mmol) below 5°C. After having been stirred for 1 h, the reaction mixture was quenched by addition of wet ether followed by addition of aqueous 10% ammonium chloride. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over potassium carbonate. The solvent was removed in vacuo to give crude 31 (73 mg).
TLC, R_f 0.20 (benzene-hexane-ethyl acetate, 20:10:3); NMR ($CDCl_3$
NMR ($CDCl_3$) δ 0.89 (s, 3H, CH_3), 4.70-6.18 (m, 4H, CH_2=CH, CH=C).

This alcohol 31 was not purified further, but used directly in the next oxidation reaction.

Attempted Oxidation of 31 to 33 : Palladium(II) chloride (4 mg, 0.02 mmol) and copper(I) chloride (23 mg, 0.23 mmol) was added to DMF-water (10:1, 0.5 ml) and the mixture was stirred under oxygen at room temperature for 2 h. Then the alcohol 31 dissolved in DMF-water (10:1, 1 ml) was added in one portion and stirring was continued under oxygen at room

temperature for 12 h. The mixture was acidified to ca pH 3 by addition of 3N hydrochloric acid and extracted three times with ether. The combined organic solutions were rinsed with brine and dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was analyzed by NMR spectroscopy, but no signal attributable to methyl ketone of the desired product 33 at ca δ 2.1 ppm could be detected.

3β-(3a,4,5,7,8,9-Hexahydro-3aβ-methyl-7-(4-pentenyl)cyclopenta[f]-2H-1-benzopyranyl) Acetate (32)

The crude alcohol 31, which was obtained from 30 (178 mg, 0.645 mmol) by the reduction with lithium aluminum hydride as described above, was dissolved in acetic anhydride (0.5 ml) and pyridine (6 ml) and the mixture was stirred at room temperature for 38 h. Then the solvent was removed in vacuo and the residue was directly chromatographed on silica gel with benzene-hexane-ethyl acetate, 15:5:2, to give the pure acetate 32 (147 mg, 72.1% yield from 30).

TLC, R_f 0.55 (benzene-hexane-ethyl acetate, 10:5:3);

NMR ($CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.03-2.88 (m, 16H), 3.36-3.88 (m, 1H, CHO), 4.63-6.08 (m, 5H, CH_2=CH, CH=C, CHOAc).

Attempted Oxidation of 32 to 34: The acetate 32 (147 mg, 0.465 mmol) was subjected to the palladium-catalyzed oxidation as described above. But no desired product 34 could be isolated.

7-(1-Ethyl-2,6-dioxocyclohexyl)-5-oxo-1-(4-pentenyl) Acetate (39)

To a solution of the enone 19 (1.84 g, 7.73 mmol) in ethyl acetate (30 ml) and triethylamine (15 ml) was added 2-methylcyclohexane-1,3-dione (38) (1.46 g, 11.6 mmol) and the mixture was stirred for 20 h at about 30°C. The solvent was removed in vacuo and the remaining material was directly chromatographed on silica gel with benzene-hexane-ethyl acetate, 10:5:3 to 4:2:3, as an eluent to give the trione 39 (2.57 g, 91.3% yield).

TLC, R_f 0.27 (benzene-hexane-ethyl acetate, 10:5:3);

IR (neat) 3070 (C-H olefinic), 1728 (C=O), 1693 (C=O), 1640 (C=C), 1243, 1023, 910, 685 cm^{-1};

NMR ($CDCl_3$) δ 1.20 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.07-2.86 (m, 22H), 4.63-5.23 (m, 3H, CH_2=C, CHOAc), 5.40-6.24 (m, 1H, C<u>H</u>=CH_2).

1-(2-(2,3,4,4a,5,6,7,8-Octahydro-4aβ-methyl-2,5-dioxo-1-naphthalenyl)-ethyl)-5-hexenyl Acetate (40)

The trione 39 (458 mg, 1.26 mmol) and β-alanine (224 mg, 2.51 mmol) were added to a solution of toluene (4 ml) and acetic acid (1 ml) under nitrogen at room temperature. The mixture was heated under reflux for 2 h and cooled to room temperature. Most of the solvent was evaporated in vacuo and the residue was diluted with ethyl acetate. Excess potassium carbonate was added to the solution to remove a small amount of remaining acetic acid and the resulting mixture was filtered through a silica gel column. Removal of the solvent in vacuo gave crude 40, which was chromatographed on silica gel. Elution with benzene-hexane-ethyl acetate, 10:5:3, as an eluent afforded the desired enone 40 (411 mg, 94.4% yield).

TLC, R_f 0.44 (benzene-hexane-ethyl acetate, 8:4:3);

IR (neat) 3076 (C-H olefinic), 1730 (C=O), 1715 (C=O), 1665 (C=O), 1609 (C=C), 1244, 1118, 1021, 915, 792, 763 cm^{-1};

NMR ($CDCl_3$) δ 1.43 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.05-3.15 (m, 20H, methylene envelope), 4.57-5.20 (m, 3H, CH_2=C, CHOAc), 5.45-6.18 (m, 1H, C<u>H</u>=CH_2).

1-(2-(2,3,4,4a,5,6,7,8-Octahydro-5β-hydroxy-4aβ-methyl-2-oxo-1-naphthalenyl)ethyl)-5-hexenyl Acetate (41)

To a solution of 40 (140 mg, 0.405 mmol) in methanol cooled at -7°C was added sodium borohydride (4 mg, 0.11 mmol) and the mixture was stirred at -7°C for 20 min. The reaction was stopped by addition of acetic acid (two drops). After removal of the solvent in vacuo, the residue was poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate several times. The combined solutions were rinsed with brine, dried over magnesium sulfate and evaporated in vacuo. The crude product was subjected to chromatography on silica gel with benzene-hexane-THF, 10:5:2, as an eluent to give the alcohol 41 (141 mg, 100% yield).

TLC, R_f 0.21 (benzene-hexane-THF, 10:5:3);

IR (neat) 3470 (OH), 3080 (C-H olefinic), 1718 (C=O), 1669 (C=O), 1607 (C=C), 1245, 788, 762 cm^{-1};

NMR ($CDCl_3$) δ 1.17 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.04-2.87 (m, 20H, methylene envelope), 3.10 (br s, 1H, OH) 3.20-3.68 (m, 1H, CHOH), 4.57-5.73 (m, 3H, CH_2=C<u>H</u>, CHOAc), 4.54-6.18 (m, 1H, C<u>H</u>=CH_2).

1β,2,3,4,4a,5,6,7,8,8aα-Decahydro-5β-hydroxy-1α-(3-hydroxy-7-octenyl)-4aβ-methyl-2-naphthalenone (43)

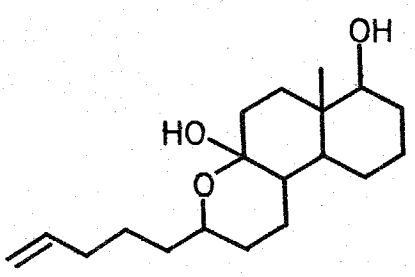
Lithium (15 mg, 2.2 mmol) was added to liquid ammonia (distilled from sodium) under nitrogen at -72°C. After 10 min, a solution of the alcohol 41 (125 mg, 0.359 mmol) in dry THF (2 ml) was added in one portion to the lithium ammonia solution at -72°C and the solution was stirred for additional 20 min. Excess granular ammonium chloride had been added to the solution until the deep blue color disappeared. After evaporation of ammonia on standing at room temperature, the remaining material was filtered through a silica gel column with ethyl acetate to remove white precipitates. The filtrate was concentrated *in vacuo* to give 42, which was subjected to the next reaction.

The above crude 42 and sodium hydroxide (165 mg, 4.13 mmol) were dissolved in methanol (7 ml) and water (1 ml) and stirring was continued at room temperature for 24 h. The mixture was poured into water and extracted three times with ethyl acetate. The combined solutions were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The remaining oil was chromatographed on silica gel with benzene-hexane-ethyl acetate, 4:2:1, to provide 43 (74.6 mg, 67.5% yield).

TLC, R_f 0.48 (benzene-hexane-THF, 4:2:3);

IR (neat) 3425 (OH), 3100 (C-H olefinic), 1717 (C=O)*, 1643 (C=C), 1112,

*The resonance due to the carbonyl moiety of 43 is very weak which indicates most of 43 exists as its hemiacetal form 43a as shown below;



43a

1026, 976, 969, 941, 903, 831 cm^{-1};

NMR ($CDCl_3$) δ 0.87 (s, 3H, CH_3), 0.68-2.43 (m, 24H, 2XOH, methylene envelope), 3.04-3.48 (m, 1H, CH), 3.72-4.18 (m, 1H, CH), 4.80-5.23 (m, 2H, CH_2=C), 5.50-6.28 (m, 1H, C<u>H</u>=CH_2).

1β,2,3,4,4a,5,6,7,8,8α-Decahydro-1α-(3-oxo-7-octenyl)-4β-methyl-naphthalene-2,5-dione (<u>44</u>)

Jones reagent was added (seven drops) to a solution of <u>43</u> (52 mg, 0.17 mmol) dissolved in acetone (2 ml) and the mixture was stirred for 4.5 h at room temperature. Then isopropyl alcohol was added until the color of the solution changed from red to green. After most of the solvent has been removed <u>in vacuo</u>, the remaining material was poured into water and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated <u>in vacuo</u> to give the crude <u>44</u>, which was purifird by chromatography on silica gel. Elution with benzene-hexane-ethyl acetate, 10:5:2, gave <u>44</u> (30 mg, 58% yield).

TLC, R_f 0.35 (benzene-hexane-ethyl acetate, 10:5:3);

IR (neat) 3070 (C-H olefinic), 1702 (C=O), 1638 (C=C), 1112, 997, 902 cm^{-1};

NMR ($CDCl_3$) δ 1.31 (s, 3H, CH_3), 1.02-3.02 (m, 22H, methylene envelope), 4.72-5.18 (m,2H, CH_2=C), 5.40-6.12 (m, 1H, C<u>H</u>=CH_2);

^{13}C NMR ($CDCl_3$) δ 16.4,20.0, 22.8, 24.6, 25.7, 33.0, 33.1, 37.0, 37.6, 39.7, 42.0, 48.7, 49.4, 115.1, 137.9, 210.7, 210.8, 213.7.

8-(3-Buthyl)-1,2,3,4,4aα,4bβ,5,6,7,9,10,10a-dodecahydro-10aβ-methyl-phenanthrene-1,7-dione (45)

To a solution of the trione 44 (81 mg, 0.23 mmol) dissolved in benzene (5 ml) was added a catalytic amount of p-toluenesulfonic acid. The mixture was heated under reflux for 3 h and then cooled to room temperature. After addition of triethylamine (ca 0.5 ml), the solution was passed through an alumina column with THF as an eluent. The filtrate was concentrated in vacuo and the residue was directly chromatographed on silica gel to give the pure enone 45 (58 mg, 76% yield).

TLC, R_f 0.43 (benzene-hexane-ethyl acetate, 10:5:3);

IR (neat) 1709 (C=O), 1667 (C=O), 1609 (C=C), 1155, 1118, 993, 940, 912 cm^{-1};

NMR ($CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.10-3.06 (m, 20H, methylene envelope), 4.75-5.08 (m, 2H, CH_2=C), 5.42-6.15 (m, 1H, C<u>H</u>=CH_2).

1,2,3,4,4aα,4bβ,5,6,7,9,10,10a-Dodecahydro-10aβ-methyl-8-(3-oxobutyl)-phenanthrene-1,7-dione (46)

Palladium(II) chloride (6.2 mg, 0.035 mmol) and copper(I) chloride (35 mg, 0.35 mmol) were added to 10:1 DMF-water (1 ml) and the mixture was stirred under oxygen atmosphere at room temperature for 2 h. Then the enone 45 (101 mg, 0.353 mmol) dissolved in 10:1 DMF-water (1 ml) was added and stirring was continued under oxygen at room temperature for additional 24 h. This solution was acidified with 3N hydrochloric acid and the resulting black-brown solution was extracted five times with ethyl acetate. The combined solution were washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give an oil, from which excess DMF was removed in vacuo (ca 100°C (35 mmHg)). The remaining oil was

chromatographed on silica gel by using benzene-hexane-ethyl acetate, 10:5:2, to afford 46 as white crystals (89 mg, 84% yield).

TLC, R_f 0.31 (benzene-hexane-THF, 10:5:3);

Mp. 121-122°C (hexane-ethanol);

IR (KBr) 1711 (C=O), 1692 (C=O), 1659 (C=O), 1603 (C=C), 1273, 1175 cm^{-1};

NMR ($CDCl_3$) δ 1.23 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.07-3.08 (m, 20H, methylene envelope).

1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10a-Tetradecahydro-10aβ-methyl-8α-(3-oxobutyl)phenanthrene-1,7-dione (47)

A solution of the enone 46 (111 mg, 0.334 mmol) in triethylamine-THF-ethanol (1:100:100, 4 ml) containing 5% palladium on carbon (10 mg) was hydrogenated under hydrogen atmosphere at ambient temperature. After 36 h, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the crude 34, which was subjected to chromatography on silica gel to afford the trione 47 as white crystals (109 mg, 97.6% yield).

TLC, R_f 0.26 (benzene-hexane-THF, 10:5:3);

Mp. 98-99°C (hexane-ethanol);

IR (KBr) 1720 (C=O), 1698 (C=O), 1165, 1077, 957, 934, 720, 557 cm^{-1};

NMR ($CDCl_3$) δ 1.17 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 0.93-2.89 (m, 22H, methylene envelope).

19-Nor-D-homoandrost-4-ene-1,17a-dione (21)

To a solution of 47 (98 mg, 0.32 mmol) dissolved in methanol (4 ml) was added 4N hydrochloric acid (1 ml) and the resulting mixture was heated

under reflux for 2 h. After the cooled solution had been concentrated *in vacuo* to approximately 2 ml, brine was added to the residue. The mixture was extracted three times with ethyl acetate-benzene(2:1) and the extracts were dried over magnesium sulfate to give the crude 21, which was subjected to chromatography on silica gel. Elution with benzene-ether, 10:1 to 4:1, as an eluent afforded 21 as white crystals (85 mg, 92% yield).

TLC, R_f 0.27 (benzene-ether, 3:1);

Mp. 171-172°C (hexane-ethyl acetate)

IR (KBr) 1700 (C=O), 1660 (C=O), 1612 (C=C), 1257, 1201, 1108, 1090, 968, 878 cm^{-1};

NMR ($CDCl_3$) δ 1.13 (s, 3H, CH_3), 0.53-2.98 (m, 22H, methylene envelope), 5.66-5.81 (m, 1H, CH=C).

1-(2-(2,3,4,4a,5,6,7,8-Octahydro-4aβ-methyl-2,5-dioxo-1-naphtalenyl)-ethyl)-5-oxohexyl Acetate (51)

Palladium(II) chloride (27 mg, 0.15 mmol) and copper (I) chloride (150 mg, 1.52 mmol) were added to 10:1 DMF-water (2 ml) and the resulting mixture was stirred under oxygen at ambient temperature for 2 h. Then the enone 40 (525 mg, 1.52 mmol) dissolved in 10:1 DMF-water (2 ml) was added to the mixture and stirring was continued for further 24 h. This mixture was acidified with 3N hydrochloric acid and the resulting black-brown mixture was extracted five times with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Excess DMF remained in the residue was removed *in vacuo* (*ca* 100-105°C (35-40 mmHg)) to afford an oil, which was subjected to chromatography on silica gel. Elution with benzene-hexane-THF,

10:5:1, gave 51 (443 mg, 80.7% yield).

TLC, R_f 0.28 (hexane-benzene-THF, 5:10:3);

IR (neat) 1735 (C=O), 1718 (C=O), 1670 (C=O), 1609 (C=C), 1245, 1021, 920, 735 cm^{-1};

NMR ($CDCl_3$) δ 1.41 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.04-3.07 (m, 20H, methylene envelope), 4.54-4.97 (m,1H, CHOAc).

1β,2,3,4,4a,5,6,7,8,8aα-Decahydro-1α-(3-hydroxy-7-oxooctyl)-4aβ-methylnaphthalene-2,5-dione (53)

A solution of the enone 51 (622 mg, 1.72 mmol) in ethyl acetate (6 ml) and triethylamine (2 ml) containing 5% palladium on carbon (183 mg,) was stirred under 1 atm of hydrogen at room temperature. After 12 h, the catalyst was removed by filtration and the solvent was evaporated *in vacuo* affording 52. A pure sample of 52 was obtained by chromatography on silica gel.

TLC, R_f 0.37 (benzene-hexane-methanol, 10:5:3);

IR (neat) 1735 (C=O), 1710 (C=O), 1241, 1164, 1012 cm^{-1};

NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 1.16-2.93 (m, 22H, methylene envelope), 4.55-5.06 (m, 1H, CH).

To a solution of the crude 52 dissolved in methanol (10 ml) and water (2 ml) was added sodium hydroxide (137 mg, 3.43 mmol) and the mixture was stirred for 7 h at ambient temperature. Methanol was evaporated *in vacuo* and the residue was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude oil was purified on silica gel

(benzene-hexane-methanol, 20:10:1) providing the pure 53 (496 mg, 90.0% yield from the enone 51).

TLC, R_f 0.31 (benzene-hexane-methanol, 10:5:3);

IR (neat) 3480 (OH), 1705 (C=O), 1083, 784, 759 cm^{-1};

NMR ($CDCl_3$) δ 1.13 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 0.88-3.02 (m, 23H, methylene envelope), 3.52-4.13 (m, 1H, CHO).

1β,2,3,4,4a,5,6,7,8,8aα-Decahydro-4aβ-methyl-1α-(3,7-dioxooctyl)-naphthalene-2,5-dione (48)

To a solution of the alcohol 53 (496 mg, 1.54 mmol) in acetone (10 ml) was added dropwise Jones reagent (excess) and the reaction mixture was stirred at room temperature for 2 h. Then isopropyl alcohol was added until the red solution turned to green. After removal of the solvent *in vacuo*, the residue was poured into water and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give crude 48, which was chromatographed on silica gel. Elution with benzene-hexane-THF, 20:10:3 to 10:5:3) gave the tetraone 48 (276 mg, 55.6% yield).

TLC, R_f 0.25 (benzene-hexane-THF, 10:5:3);

IR (neat) 1708 (C=O), 1160, 1114 cm^{-1};

NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.04-3.05 (m, 22H, methylene envelope).

Attempted Cyclization of 48

Many conditions for the cyclozation were examined, but no desired product 49 could be obtained. For example, 48 (37 mg, 0.116 mmol) and

piperidinium acetate (12 mg, 0.083 mmol) were added to toluene (2 ml) and the solution was refluxed overnight. The reaction mixture was cooled and diluted with ethyl acetate. The solution was washed successively with 3N hydrochloric acid, aqueous saturated sodium bicarbonate, and brine, and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the resulting crude material was analyzed. TLC (benzene-hexane-THF, 10:5:3) detected no desired product 49. Other conditions are briefly mentioned in the text (*vide supra*).

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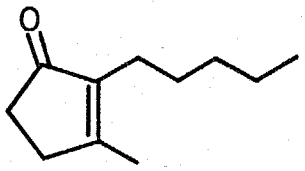
CHAPTER NINE

A CONVENIENT SYNTHETIC METHOD OF DIHYDROJASMONE AND DIHYDRO-NORJASMONE FROM A BUTADIENE TELOMER

Summary

Dihydronorjasmone (3), which is one of the precursors of dihydrojasmone (1) and methyl dihydrojasmonate (2), was synthesized from 1,7-octadienyl acetate (4) obtained by the palladium-catalyzed dimerization of butadiene with acetic acid. Key steps of the synthesis are the Claisen rearrangement of 2-octenyl vinyl ether (7) to 3-pentyl-4-pentenal (8), the subsequent oxidation of 8 to 3-pentyl-4-oxopentanal (9) by using palladium(II) chloride as a catalyst, and then the cyclization of 9. Ruthenium-catalyzed selective isomerization of allyl 2-octenyl ether (12), which was prepared from 4, followed by the Claisen rearrangement produced 2-methyl-3-pentyl-4-pentenal (13), from which 1 was synthesized easily.

9-1 Introduction



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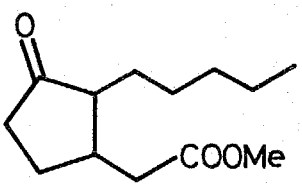

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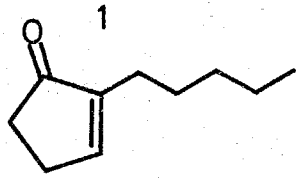

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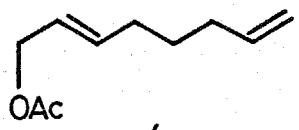

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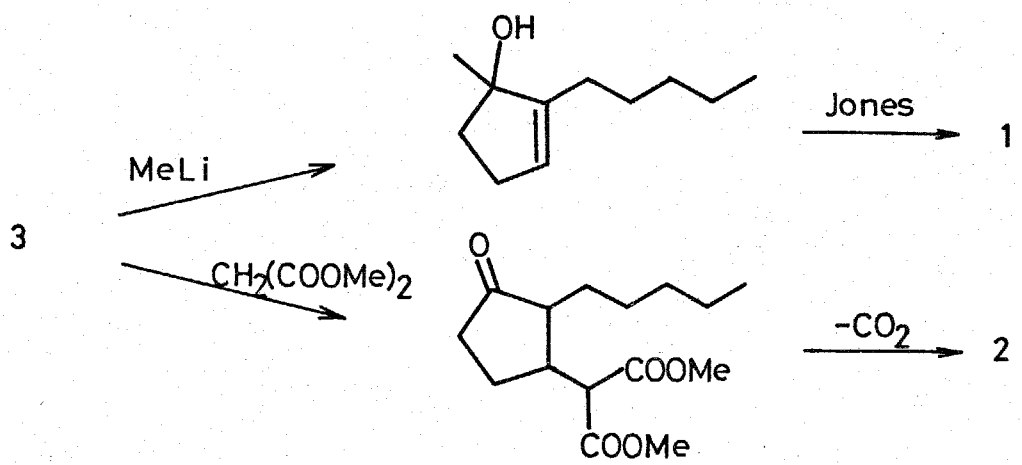
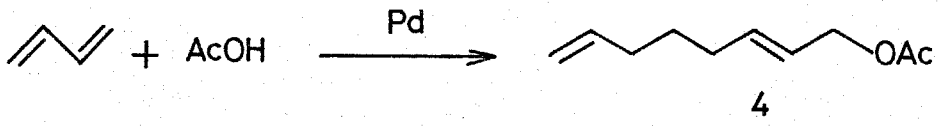
Dihydrojasmone (1) and methyl dihydrojasmonate (2) are commercially important compounds since they are employed as basic odorous components of jasmine-like fragrance.[2,3] Although there are few commercially satisfactory methods, many works have been devoted to achieve the preparation of 1 and 2 in the last decade and now are going on.[4-7] From synthetic view of these compounds simple methods must be exploited. 2-Pentyl-2-cyclopentenone (3), so called dihydronorjasmone, has sometimes been used as a proper precursor to 1 and 2. Thus dihydrojasmone (1) is prepared by the addition of methyllithium to 3 followed by Jones oxidation,[8,9] while the Michael addition of methyl malonate, for instance, onto 3 followed by demethoxycarbonylation of the adduct completes[10-12] the



synthesis of methyl dihydrojasmonate (2).[13-15] This means that one of the key precursors for the synthesis of both 1 and 2 is the cyclopentenone 3.

Meanwhile, it is well-known that 1-acetoxy-2,7-octadiene (4) is easily available in large quantity from butadiene and acetic acid by palladium-catalyzed reaction.[16,17]



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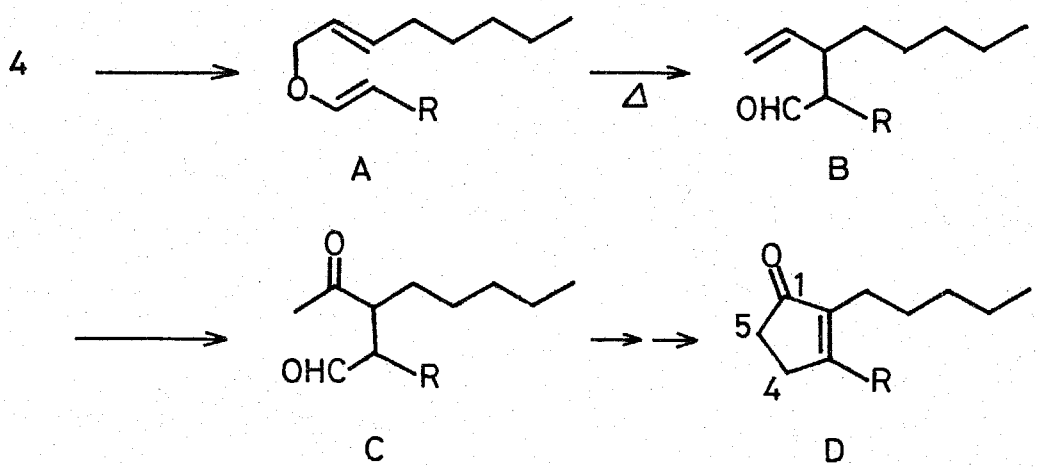
In view of synthetic utility of this butadiene telomer 4, especially for commercial purpose, it appears to be important to design a synthetic routes to 1 and/or 3 starting from this acetate 4. In this chapter a convenient synthesis of 1 and 3 is described, featuring a series of reactions which involve the construction of requisite cyclopentenone framework by way of C-4 and C-5 bond formation of D.[1]



The following reactions are key steps:

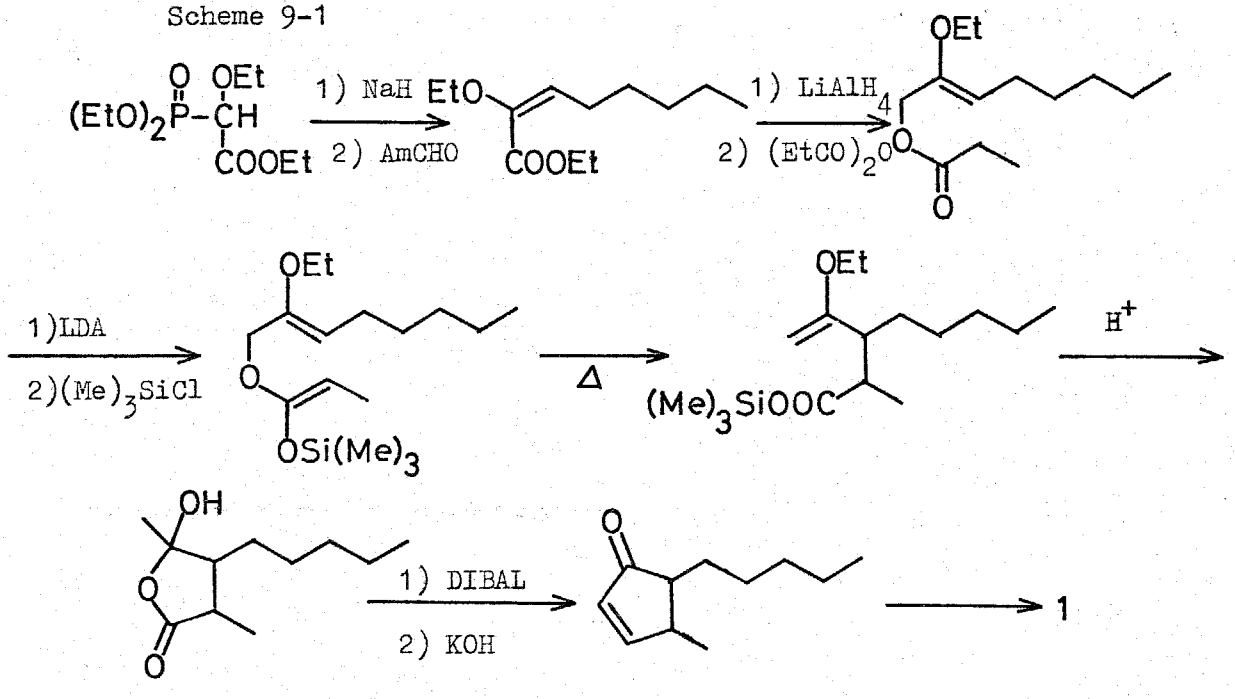
(1) Thermal rearrangement of the vinyl ether A, where $RuCl_2(PPh_3)_3$ catalyzed isomerization of the allyl ether to the vinyl ether is adopted in a case of R = CH_3.

(2) Palladium-catalyzed conversion of olefin moiety of B to methyl ketone.

(3) Intramolecular aldol condensation which makes the cyclopentenone framework.

Recently Ireland reported a synthesis of dihydrojasmone (1) closely similar to this synthesis (Scheme 9-1).[18] Being compared with his synthesis, this synthesis is straightforward because basic starting materials were easily available and the reaction involved could be easily carried out.

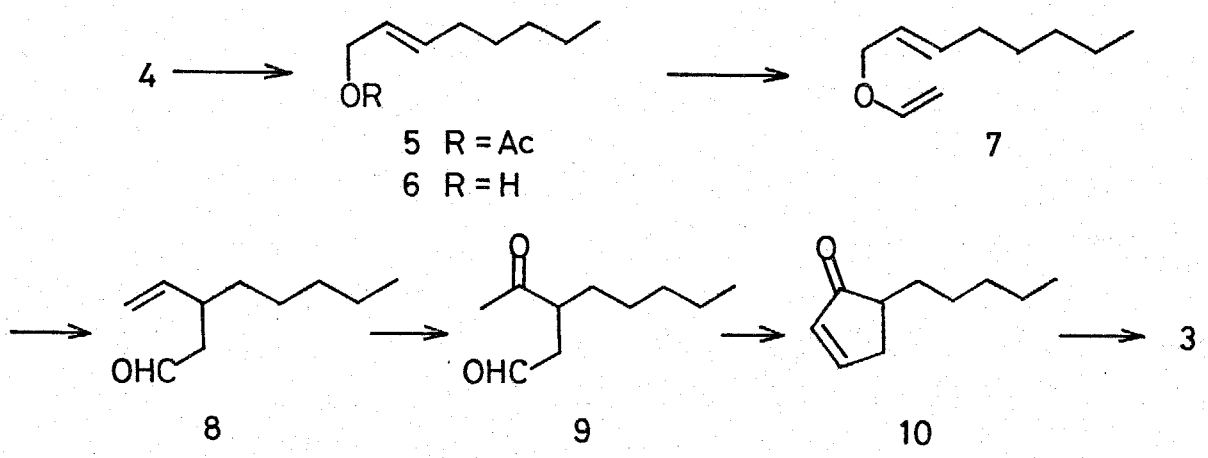
Scheme 9-1



9-2 Synthesis of Dihydronorjasmone (3)

The synthetic pathway leading to dihydronorjasmone (3) from 1-acetoxy-2,7-octadiene (4) is outlined in Scheme 9-2. One of the key steps of this synthesis is the Claisen rearrangement of the vinyl ether 7 to the aldehyde 8 from which 3 was synthesized via 9 and 10.

Scheme 9-2

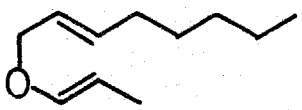


The acetate 5, obtained by chemoselective hydrogenation of 4 [16,17] by using $RuCl_2(PPh_3)_3$ [19] as a catalyst under hydrogen atmosphere, was hydrolyzed to give the alcohol 6 quantitatively. The transformation of 6 to the vinyl ether 7 was performed in 71% yield in the presence of mercury(II) acetate in refluxing ethyl vinyl ether. The Claisen rearrangement of 7 was carried out in a sealed glass tube heated at 180-190°C for 2 h and the aldehyde 8 was isolated in 79% yield. The aldehyde 8 was converted to the γ-keto aldehyde 9 in 90% yield by using palladium(II) chloride (10 mol%) and copper(I) chloride (100 mol%) under oxygen atmosphere.[20] Next 9 was subjected to the aldol cyclization by Ireland's method by using aqueous sodium hydroxide and methanol at room temperature. TLC analysis showed that 9 was completely consumed

but many components were produced. From the mixture no desirable product could be isolated. Therefore effort was directed toward finding optimum conditions. After many trials, best conditions were found: Refluxing a solution of 9 in a mixed solution of ether, THF, and 5% aqueous potassium hydroxide (2:2:1) for 4 h afforded the cyclopentenone 10 in 68% yield from 8. Under these conditions, double bond did not migrate to the more substituted one. The absence of 3 was indicated by NMR analysis. In the olefinic resonances of the NMR spectrum of the crude 10, only two signals attributable to olefin protons of 10 were observed (δ 6.01, dd, J = 6 Hz, J = 1.5 Hz and δ 7.53, dd, J = 6 Hz, J = 2 Hz) and the signal due to olefin proton of 3 (δ 7.01-7.29, m) could not be detected. The double bond isomerization [18,21] of 10 by aqueous potassium hydroxide completed the synthesis of 3.[22-27] Though 3 and 10 could not be differentiating on silica gel TLC, NMR analysis showed that 3 was homogeneous and not contaminated by the isomer 10.

9-3 Synthesis of Dihydrojasmone (1)

Similar to the synthesis of dihydronorjasmone (3), the synthesis of dihydrojasmone (1) was carried out. In this dihydrojasmone synthesis, the vinyl ether 11 [28] must be synthesized to carry out the Claisen rearrangement.



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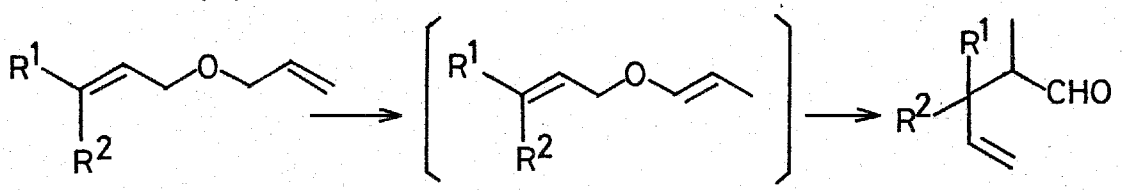
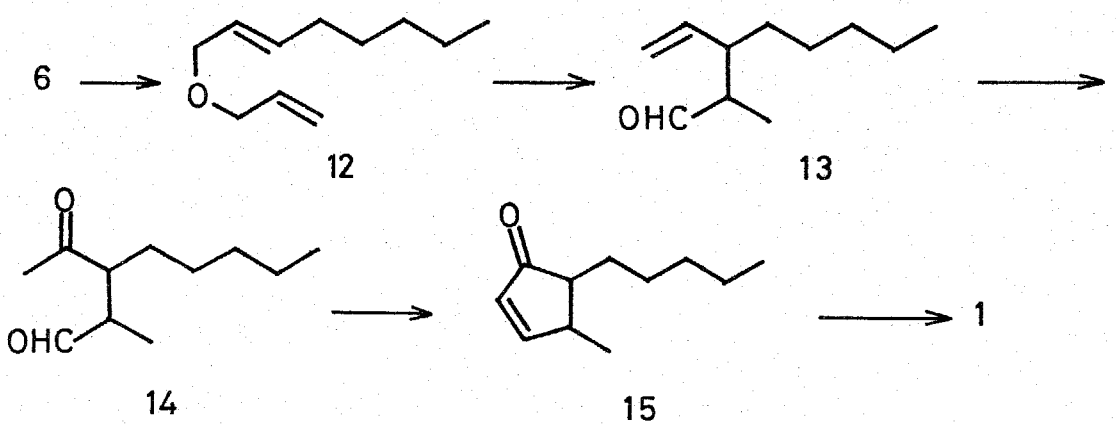
Recently, Salomon et al. reported selective $RuCl_2(PPh_3)_3$ catalyzed rearrangement of unsymmetrical diallyl ethers to γ,δ-unsaturated aldehydes which was found to proceed via the initial rearrangement to vinyl ether, followed by the Claisen rearrangement as shown in Scheme 9-3.

Scheme 9-3

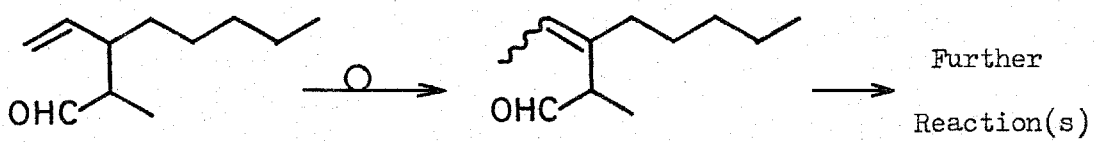


This conversion seems to be suitable for the dihydrojasmone synthesis which is depicted in Scheme 9-4.

Scheme 9-4



Sodium salt of 6, prepared from sodium hydride and the alcohol 6, was reacted with allyl bromide to give 12 in 82.8% yield. To the allyl ether 12 was added $RuCl_2(PPh_3)_3$ and the mixture was heated at 200°C for 1 h. As expected, the rearrangement proceeded selectively and the aldehyde 13 was isolated as a sole product in 61% yield. In contrast to the rearrangement of the vinyl ether 7, that of 12 to 13 resulted in lower yield. This seems to be ascribable to undesired isomerization of the terminal olefin of the rearrangement product 13 in the presence of ruthenium species to yield 16 followed by further reaction(s). Then 13 was subjected to the oxidation reaction promoted by palladium(II) chloride (0.1 equiv.) and copper (I) chloride (1 equiv.) under oxygen atmosphere.[20] The crude 14, thus obtained, was cyclized to the cyclopentenone 15 in 36% yield from 13 in a mixture of ether, THF, and aqueous 4% sodium hydroxide. The gaschromatography indicated that the product 15 was not contaminated by 1. Finally 15 was isomerized to dihydrojasmone (1) by use of aqueous potassium hydroxide.



13 16

9-4 Experimental

2-Octenyl Acetate (5)

In a 100-ml steel reaction vessel containing $RuCl_2(PPh_3)_3$ (200 mg, 0.21 mmol) were placed the acetate 4 (7.00 g, 41.7 mmol), desulfurized benzene (23 ml), and dry ethanol (10 ml). The vessel was flushed three times with hydrogen. Under the initial hydrogen pressure of 23 atm., the solution was stirred at room temperature until theoretical hydrogen uptake (ca 17 atm) was attained (ca 3 h). The solvent was removed in vacuo and the residue was distilled to yield the allyl acetate 5 (6.84 g, 96.5% yield).

Bp. ca 110°C (11 mmHg);

IR (neat) 1742 (C=O), 1230, 1026, 968 cm^{-1};

NMR (CCl_4) δ 0.65-1.68 (m, 9H, $CH_3(CH_2)_3$), 1.97 (s, 3H, CH_3CO), 1.76-2.26 (m, 2H, $CH_2CH=CH$), 4.27-4.99 (m, 2H, CH_2O), 5.35-5.70 (m, 2H, CH=CH).

2-Octenol (6)

To a solution of sodium hydroxide (363 mg, 9.08 mmol) in water (5 ml) was added the allyl acetate 5 (707 mg, 4.59 mmol) dissolved in methanol (5 ml). The mixture was stirred at room temperature for 6 h and volatile materials were removed in vacuo. The residue was poured into brine and extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated in vacuo. The chromatography of the residue on silica gel afforded the alcohol 6 (507 mg, 95.3% yield).

IR (neat) 3350 cm-1;

NMR (CCl_4) δ 0.68-2.24 (m, 11H, $CH_3(CH_2)_4$), 3.77 (s, 1H, OH), 3.86-4.05 (m, 2H, CH_2O), 5.46-5.68 (m, 2H, CH=CH).

2-Octenyl Vinyl Ether (7)

To a solution of the allyl alcohol 6 (580 mg, 4.53 mmol) in ethyl vinyl ether (7 ml) was added mercury(II) acetate (144 mg, 0.453 mmol). The solution was stirred under reflux for 19 h and then cooled to room temperature. Potassium carbonate (ca 100 mg) was added to the flask and the mixture was stirred for 30 min at room temperature. After inorganic salts were removed by filtration, the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel with hexane-ether, 30:1 to 3:1, to afford the vinyl ether 7 (498 mg, 71.3% yield) and the recovered 6 (155 mg, 26.7% yield).

IR (neat) 1632, 1610, 1318, 1198, 967, 809 cm^{-1};

NMR (CCl_4) δ 0.62-2.33 (m, 11H, $CH_3(CH_2)_4$), 3.89 (dd, J = 7 Hz, J = 2 Hz, 2H, CH_2O), 3.94-4.24 (m, 2H, CH_2=C), 5.38-5.70 (m, 2H, CH=CH), 6.32 (dd, J = 15 Hz, J = 7 Hz, 1H, CH=CH_2).

3-Pentyl-4-pentenal (8)

A sealed glass tube containing the vinyl ether 7 (353 mg, 2.29 mmol) was immersed in an oil bath set at 183-190°C for 2 h and cooled to room temperature. The crude product was directly chromatographed over a silica gel column with hexane-ether, 30:1 to give the aldehyde 8 (279 mg, 79% yield).

IR (neat) 3066 (C=C), 2706 (CHO), 1727 (C=O), 1638 (C=C), 992, 916 cm^{-1};

NMR (CCl_4) δ 0.87 (t, J = 6 Hz, 3H, CH_3), 1.07-1.57 (m, 8H, $(CH_2)_4$), 2.17-2.55 (m, 3H, $CHCH_2CO$), 4.72-5.90 (m, 3H, CH_2=CH), 9.53 (t, J =

2 Hz, 1H, CHO).

3-Pentyl-4-oxopentanal (9)

A mixture of Palladium(II) chloride (12 mg, 0.067 mmol) and copper(I) chloride (70 mg, 0.70 mmol) in DMF-water (10:1, 1 ml) was stirred at room temperature under oxygen atmosphere for 2 h. To this falsk was then added the aldehyde 8 (103 mg, 0.669 mmol) in DMF-water (10:1, 1 ml) and the mixture was stirred under oxygen atmosphere for additional 6 h. To the resulting green mixture was added 1N hydrochloric acid and the black mixture was extracted with ether (four 5-ml portions). The combined ethereal solutions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give the crude products which were chromatographed over a silica gel column with benzene-hexane-ethyl acetate, 10:5:1, to yield the keto aldehyde 9 (102 mg, 90.9% yield).

IR (neat) 2720 (CHO), 1720 (shoulder, C=O), 1712 (C=O) cm^{-1};

NMR (CCl_4) δ 0.87 (t, J = 7 Hz, 3H, CH_3), 1.04-1.24 (m, 8H, $(CH_2)_4$), 2.15 (s, 3H, CH_3CO), 2.23-3.07 (m, 3H, CH_2CHCO), 9.53 (s, 1H, CHO).

5-Pentyl-2-cyclopenten-1-one (10)

To THF (2 ml) solution of the crude 9 which was prepared from the aldehyde 8 (133 mg, 0.868 mmol) was added 5% aqueous potassium hydroxide (2 ml). The mixture was stirred at reflux for 4 h and then extracted with ether (three 10-ml portions). The combined ethereal solutions were washed with brine and dried over magnesium sulfate. Removal of the solvents left the raw product which was chromatographed on silica gel with benzene-hexane-ether, 10:5:1, to give the cyclopentenone 10 (90 mg, 68%

yield from 8).

IR (neat) 1710 (C=O), 1588 (C=C), 1344, 1174, 771 cm^{-1};

NMR (CCl_4) δ 0.88 (t, J = 6 Hz, 3H, CH_3), 1.06-3.10 (m, 11H, $(CH_2)_4CHCH_2$), 6.01 (dd, J = 6 Hz, J = 1.5 Hz, 1H, CH=CHCO), 7.53 (dd, J = 6 Hz, J = 2 Hz, 1H, CH=CHCO).

Dihydronorjasmone (3)

To 5% aqueous potassium hydroxide (4 ml) was added the cyclopentenone 8 (54 mg, 0.36 mmol) in methanol (2 ml). The mixture was refluxed for 40 min and cooled to room temperature. The product was extracted with ether (three 5-ml portions). The combined ethereal solutions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Chromatography of the residue on silica gel gave dihydronorjasmone (3) (44 mg, 81% yield).

Bp. 128-131°C (24 mmHg);

IR (neat) 1706 (C=O), 1633 (C=C), 1004, 792 cm^{-1};

NMR (CCl_4) δ 0.88 (t, J = 6 Hz, 3H, CH_3), 1.07-2.78 (m, 12H, $(CH_2)_4$, $(CH_2)_2CO$), 7.01-7.29 (m, 1H, CH=C).

Allyl 2-Octenyl Ether (12)

To a suspension of sodium hydride (885 mg, 18.5 mmol, 50% oil dispersion) in dry THF (30 ml) was injected the allyl alcohol 6 (2.06 g, 2.50 ml, 16.1 mmol) and the resulting mixture was stirred for 30 min. Allyl bromide (2.53 g, 1.81 ml, 20.9 mmol) was added and the mixture was stirred at room temperature for additional 3.5 h. Aqueous ammonium chloride (10%) was added and volatile materials were removed under reduced pressure.

The residue was extracted with ether (two 20-ml portions). The combined ethereal solutions were washed with brine and dried over magnesium sulfate. The solvent was removed by a rotary evaporator and the residue was chromatographed over a silica gel column with hexane-ether, 30:1, to give the allyl ether 12 (2.50 g, 92.4% yield).

IR (neat) 1098, 1073, 968, 919 cm^{-1};

NMR (CCl_4) δ 0.90 (t, J = 5 Hz, 3H, CH_3), 1.08-1.73 (m, 6H, $(CH_2)_3$), 1.80-2.26 (m, 2H, $CH_2C{=}C$), 3.67-3.99 (m, 4H, CH_2OCH_2), 4.87-6.18 (m, 5H, $CH_2{=}CH$, $CH{=}CH$).

2-Methyl-3-pentyl-4-pentenal (13)

The allyl ether 12 (100 mg, 0.595 mmol) and $RuCl_2(PPh_3)_3$ (0.9 mg, 0.0009 mmol) were placed in a glass tube. The tube was heated in an air bath at 200-205°C for 1 h and then cooled to room temperature. The reaction mixture was directly chromatographed over a silica gel column with hexane-ether, 30:1, to give 13 (61 mg, 61% yield).

IR (neat) 2690 (CHO), 1728 (C=O) cm^{-1};

NMR (CCl_4) δ 0.55-2.63 (m, 18H, $CH_3(CH_2)_4CHCHCH_3$), 4.70-5.97 (m, 3H, $CH_2{=}CH$), 9.42-9.61 (m, 1H, CHO).

4-Methyl-5-pentyl-2-cyclopenten-1-one (15)

A mixed solvent of DMF-water (10:1, 2 ml) containing palladium(II) chloride (31.7 mg, 0.179 mmol) and copper(I) chloride (177 mg, 1.79 mmol) was stirred at room temperature under oxygen for 2 h. The aldehyde 13 (248 mg, 1.48 mmol) in DMF-water (10:1, 1 ml) was added and the solution was further stirred under oxygen for additional 7 h. After the

addition of 1N hydrochloric acid, the mixture was extracted with ether (four 10-ml portions). The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of solvents left the crude aldehyde 14 (NMR (CCl_4) δ 2.09 (d, J = 4 Hz, 3H, CH_3CO), 9.50 (s, 1H, CHO)), which was used in the next reaction without further purification.

To a solution of THF (3 ml) and 4% aqueous hydroxide (2 ml) was added the ethereal (4 ml) solution of the aldehyde 14 thus obtained and the resulting mixture was vigorously stirred at 30-38°C for 5 h. The products were extracted several times with ether and the combined ethereal solutions were washed with brine, dried over magnesium sulfate, and then concentrated *in vacuo*. The cyclopentenone 15 (89 mg, 36% yield from 13) was isolated from the remaining materials by silica gel column chromatography with benzene-hexane-ether (10:5:1).

IR (neat) 1709 (C=O), 1588 (C=C), 1174 cm^{-1};

NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3H, CH_3), 1.24 (d, J = 7 Hz, 3H, CH_3), 1.10-2.90 (m, 10H, $(CH_2)_4$, CHCHCO), 6.09 (dd, J = 6 Hz, J = 1 Hz, 1H, CH=CHCO), 7.48 (dd, J = 6 Hz, J = 2 Hz, 1H, CH=CHCO).

Dihydrojasmone (1)

A mixture of 15 (180 mg, 1.08 mmol), methanol (3 ml), and aqueous 5% potassium hydroxide (6 ml) was refluxed for 40 min and cooled to room temperature. The products were extracted with ether and the extract was washed with brine, dried over magnesium sulfate. Removal of solvents afforded the crude products which were purified by silica gel chromatography to give dihydrojasmone (1) (168 mg, 93.2% yield).

IR (neat) 1699 (C=O), 1644 (C=C), 1178, 1071, 681 cm^{-1};

NMR (CCl_4) δ 0.87 (t, $\underline{J}$ = 6 Hz, 3H, CH_3), 1.07-2.59 (m, 12H, $(CH_2)_2CO$, $(CH_2)_4$), 1.99 (s, 3H, CH_3).

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Acknowledgment

The author expresses his deep gratitude and sincere appreciation to Professor Jiro Tsuji of this Department for his warm and continuous instruction and encouragement throughout the course of the present work.

He is also indebted to Dr. Keiji Yamamoto for his kind guidance and helpful suggestions during this work and for reading the entire manuscript.

He wishes to thank Dr. Takashi Takahashi for his numerous discussions and Dr. Isao Shimizu for his helpful suggestions, in particular, about the synthesis of dihydrojasmone.

The author feels very fortunate to have had the opportunity to collaborate with Mr. Hiroshi Okumoto in the synthesis of 18-hydroxyestrone and Mr. Hideaki Kataoka in the cyclization study and the synthesis of methyl jasmonate.

Furthermore, he gratefully acknowledges the other members of Professor Jiro Tsuji's group and Mme. Michiko Date for their technical assistance.

He would like to record his profound appreciation to Noriko, his wife, for her understanding and for sparing him the time, which truly belonged to her, that went into the completion of this work.

Yuichi Kobayashi

January 1981