Studies on the Synthesis of Biologically Active Compounds from [m.n.2]Propellanes

([m . n . 2] プロペランからの生理活性化合物の合成に関する研究)

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PREFACE

The work of this thesis was performed under the guidance of Professor Yoshinobu Odaira at the Department of Petroleum Chemistry, Faculty of Engineering, Osaka University.

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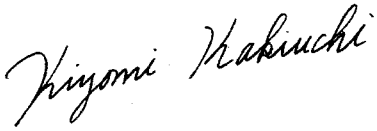


Kiyomi Kakiuchi

Suita, Osaka

January, 1982

LIST OF PAPERS

The contents of this thesis are composed of the following papers.

1) Effect of Alkyl Substituents on Cyclobutyl-Cyclopropyl-carbinyl Type Rearrangement of 2-Oxabicyclo[4.2.0]octan-3-ones
Y. Tobe, K. Kakiuchi, Y. Kawakami, Y. Sakai, K. Kimura, and Y. Odaira
Chem.Lett., 1027(1978).

2) Thermally Induced Cyclobutyl-Cyclopropylcarbinyl-Type Rearrangement of 2-Oxabicyclo[4.2.0]octan-3-ones
K. Kakiuchi, Y. Tobe, and Y. Odaira
J.Org.Chem., 45, 729(1980).

3) Synthesis of 1,6-Dioxadispiro[2.0.4.4]dodecan-7-one
K. Kakiuchi, Y. Hiramatsu, Y. Tobe, and Y. Odaira
Bull.Chem.Soc.Jpn., 53, 1779(1980).

4) Synthesis of 7-Alkylidene-5-oxadispiro[2.0.4.4]dodecan-6-ones
K. Kakiuchi, T. Yonei, Y. Tobe, and Y. Odaira
Bull.Chem.Soc.Jpn., 54, 2770(1981).

5) Acid-Catalyzed Rearrangement of [5.n.2]Propella-ε-lactones
K. Kakiuchi, T. Tsugaru, Y. Tobe, and Y. Odaira
J.Org.Chem., 46, 4204(1981).

6) Novel Acid-catalysed Rearrangement of [4.3.2]- and [5.3.2]-Propellanones
K. Kakiuchi, Y. Hato, Y. Tobe, and Y. Odaira
J.Chem.Soc., Chem.Commun., in press.

7) Alkaline Hydrolysis of Propella-δ- and ε-lactones
K. Kakiuchi, Y. Tobe, and Y. Odaira
Bull.Chem.Soc.Jpn., in press.

8) Acid-Catalyzed Rearrangement of [m.n.2]Propellanones. A Novel Approach to Tricyclo[4.3.2.$0^{1,5}$]undecane System
K. Kakiuchi, Y. Hato, T. Tsugaru, K. Itoga, Y. Tobe, and Y. Odaira
J.Am.Chem.Soc., submitted for publication.

CONTENTS

GENERAL INTRODUCTION

Up to date, a large number of natural products which possess interesting biological activities have been found out by the explosive growth of natural products chemistry owing to advances in isolation techniques, synthetic method, physico-chemical measurement, and new concepts. Furthermore, two of the most intriguing problems, structure determination and total synthesis, have in many cases become rather routine, and this enables the organic chemist to direct his effort toward new unexplored areas, for example, precisely synthetic organic chemistry concerning the relationship between the unique structure and the biological activity.

On the other hand, much attention has been foucused on the reactivity and property of propellanes, composed of three alycyclic rings conjoined the central σ bond, due to the specific structure.[1] However, many compounds involving propellane skeleton are found in nature.* Propellane, therefore, is regarded as a common compound which is able to be transformed into other polycarbocyclic ones by the skeletal rearrangement.

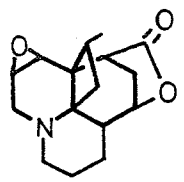
with regard to the above facts, the present investigation was carried out in order to develop high-selective process for the synthesis of the variety of biologically active compounds by use of the skeletal rearrangement of [m.n.2]propellanes triggered by the strain-release of the

cyclobutane ring. The [m.n.2]propellanones were prepared readily by photocycloaddition of ethylene to bicyclic enones and, therefore, were considered the common starting materials in this thesis.[3]

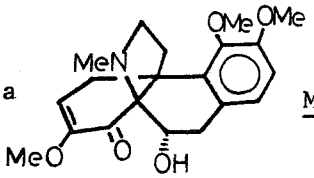
Chapter 1 deals with the synthesis of new biologically active or related compounds such as α-alkylidene dispiro-γ-lactones and 1,2-disubstituted cycloalkenes by the skeletal rearrangement of [m.n.2]propellalactones.

Chapter 2 deals with the synthesis of new tricyclic compounds, involving the basic skeleton of quadrone and its related compounds, by the acid-catalyzed rearrangement of [m.n.2]propellanones.

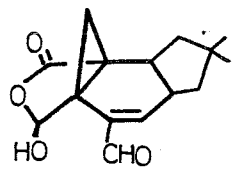
* Examples of naturally occurring propellanes:



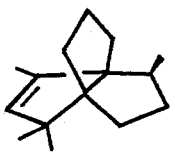
Annotinine[2a]



Prometaphanine[2b]



Marasmic Acid[2c]



Modhephene[2d]

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(c) Y. Tobe, H. Omura, A. Kunai, K. Kimura, and Y. Odaira, Bull.Chem.Soc.Jpn., 50, 319(1977).

(d) Y. Tobe, A. Doi, A. Kunai, K. Kimura, and Y. Odaira, J.Org.Chem., 42, 2523(1977).

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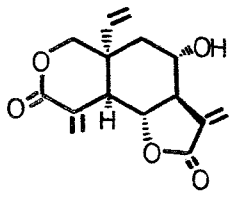
Chapter 1. TRANSFORMATION OF [m.n.2]PROPELLALACTONES INTO OTHER POLYCARBOCYCLIC RING SYSTEMS

In this chapter, the synthesis of α-alkylidene dispiro-γ-lactones by use of the cyclobutyl-cyclopropylcarbinyl rearrangement of [m.4.2]propella-δ-lactones, their related compound, and, furthermore, 1,2-disubstituted cycloalkenes by the ring-opening reaction of [5.n.2]propella-ε-lactones, is described. Also, the reactivity of these [m.n.2]-propellalactones toward the alkaline hydrolysis, related to the above rearrangement, is examined.

1-1 SYNTHESIS OF α-ALKYLIDENE DISPIRO-γ-LACTONES

Recently, sesquiterpene lactones such as vernolepin (1), mainly isolated from the Compositae, have been shown to exhibit marked antitumor, cytotoxic, and other biological activities attributed to the presence of an α-methylene-γ-lactone moiety.[1] In this connection, the synthesis of various compounds involving an α-methylene-γ-lactone and the biological activity of them have been studied productively.[2] For example, α-methylene spiro-γ-lactone (2) was found to exhibit the cytotoxic activity againist human lymphoblastic leukemia cells in culture.[2c] On the other hand, it has been well-known that some natural products, having a cyclopropane ring, display remarkable biological activities.[3] For instance, pyrethroids (3) is well-known

to be significant insecticide,[3b] and illudin S (4), containing a spiro cyclopropane ring, is well examined about antitumor activity.[3c] From the above point of view, the synthesis of α-methylene- and several α-alkylidene-γ-lactones (20) related to structure-biochemical activity relationship, containing a spiro cyclopropane ring, by use of the cyclobutyl-cyclopropylcarbinyl rearrangement of [m.4.2]propella-δ-lactones (m=3-6) easily derived from [m.3.2]propellanones, is carried out in this section. The interesting results on the screening of biological activity of the α-alkylidene-γ-lactones in vivo, moreover, is described. Also, the synthesis of oxadispiro-γ-lactone (21) related to the dispiro-γ-lactones is presented.



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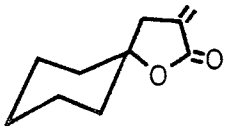

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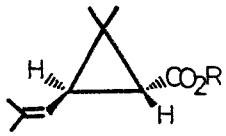

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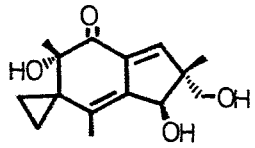

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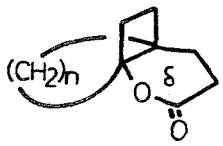
1-1-1 CYCLOBUTYL-CYCLOPROPYLCARBINYL REARRANGEMENT OF [m.4.2]PROPELLA-δ-LACTONES

In this section, the cyclobutyl-cyclopropylcarbinyl rearrangement of [m.4.2]propella-δ-lactones (5)-(8) to

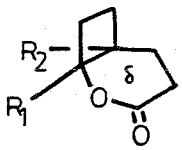
dispiro-γ-lactones (14)-(17) under acidic or thermal conditions, which is a key path for the synthesis of α-alkylidene-γ-lactones having a spiro cyclopropane ring, is examined. The propellalactones are composed of a cyclobutane ring, a δ-lactone ring, and one five- to eight-membered ring as the third ring. In order to clarify the alkyl substituent effect in the cyclobutyl-cyclopropylcarbinyl rearrangement, behavior of bicyclic δ-lactones (9)-(13) under the rearrangement conditions is also examined.

Results and Discussion

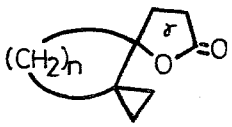
The δ-lactones 5-13 were prepared by the Baeyer-Villiger oxidation (H_2O_2/AcOH or MCPBA/$CHCl_3$) of the corresponding ketones in good yields.



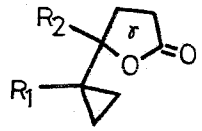
	n
5	3
6	4
7	5
8	6



	R_1	R_2
9	H	H
10	CH_3	H
11	H	CH_3
12	CH_3	CH_3
13	C_2H_5	CH_3



	n
14	3
15	4
16	5
17	6



	R_1	R_2
18	CH_3	CH_3
19	C_2H_5	CH_3

First, acid-catalyzed rearrangement was examined. An acetic acid solution of 5-13 was refluxed for 72 h, or a benzene solution of the δ-lactones with catalytic amounts of p-toluenesulfonic acid (TsOH) was refluxed for 24 h. The results are summarized in Table 1.

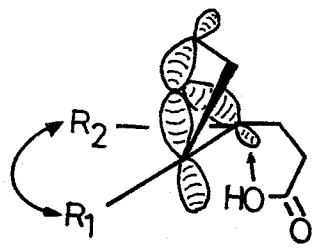
Table 1. Cyclobutyl-Cyclopropylcarbinyl Rearrangement of δ-Lactones 5-13.

δ-lactone	δ-lactone : γ-lactone[a]			
	acid conditions		thermal conditions	
	AcOH[b]	TsOH[c]	solution[d]	vapor phase[e]
5	100: 0	100: 0	89:11	88:12
6	14:86	19:81	15:85	21:79
7	100: 0	100: 0	88:12	81:19
8	100: 0	100: 0	94: 6	94: 6
9	100: 0	100: 0	100: 0	100: 0
10	100: 0	100: 0	100: 0	100: 0
11	100: 0	100: 0	100: 0	100: 0
12	80:20	57:43	74:26	51:49
13	86:14	80:20	84:16[f]	82:18[f]

[a] Yields were almost quantitative unless otherwise noted. [b] Heated at reflux in acetic acid for 72 h. [c] Heated at reflux in benzene with TsOH for 24 h. [d] Heated at 240 °C for 72 h in o-DCB solution. [e] Passed through a Pyrex column heated at 350 °C under nitrogen stream (contact time; ca. 20 sec). [f] Small amounts of unidentified products were obtained.

As shown in table 1, unsubstituted or monomethyl substituted δ-lactones 9-11 were recovered. On the other hand, dialkyl substituted δ-lactones 12 and 13 gave the corresponding γ-lactones (18) and (19) in nearly quantitative yields (conversion; 14-43 %) under similar conditions. More interestingly, in the case of propella-δ-lactones, it was found that the reactivity toward the rearrangement was greatly dependent on the size of the alicyclic ring fused to the bridgehead positions. Namely, 6 afforded the desired dispiro-γ-lactone (15) quantitatively (conversion; 81-86 %), whereas δ-lactones 5, 7, and 8 remained unchanged under similar conditions.

It has been well-known that the puckered geometry of cyclobutyl cation is favorable for cyclobutyl-cyclopropyl-carbinyl rearrangement owing to overlap of ring orbitals.[4] Accordingly, it is reasonable that the present remarkable substituent effect may be attributed to steric effect which reinforces the puckered geometry of cyclobutane ring in cation intermediate A. Namaly, because of the nonbonded



A

interaction between 1,2-dialkyl substituents, the cyclobutane ring in cation A derived from dialkyl substituted lactones 12 and 13 may be forced to have much puckered conformation compared to those derived from unsubstituted and monomethyl substituted derivatives 9-11. In particular, this effect of 6 may be larger than that of the others owing to the steric requirment of the cyclohexane ring fused to bridgehead positions to adopt chair conformation.

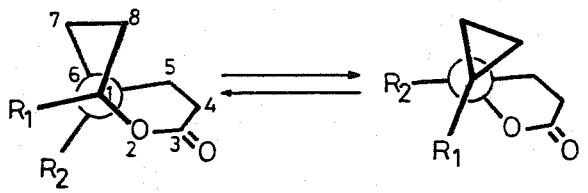
The above information about the acid-catalyzed rearrangement of δ-lactones 5-13 suggests that if the nonbonded interaction between 1,2-alkyl substituents is enhanced under thermal conditions, the present rearrangement will occur to give γ-lactones. Therefore, desired dispiro-γ-lactones may be also obtained from 5, 7, and 8 recovered unchanged under the acidic conditions and then thermally induced rearrangement was next examined.

An o-dichlorobenzene (o-DCB) solution of the δ-lactones was heated in a sealed tube at 240 °C for 72 h, or a hexane solution of 5-13 was passed through a Pyrex column heated at 350 °C (contact time; ca. 20 sec). Results are summarized in Table 1.

As shown in Table 1, unsubstituted and monomethyl substituted δ-lactones 9-11 were recovered unchanged, whereas, as expected, dialkyl substituted ones 12 and 13 gave 16-49 % of the corresponding γ-lactones 18 and 19, and, moreover, propella-δ-lactone 6 rearranged readily to afford 79-85 % of 15. These results exhibited a trend similar to that observed in the acid-catalyzed reaction descrived above.

Interestingly, the thermal rearrangement of propella-δ-lactones 5, 7, and 8 took place to afford the desired dispiro-γ-lactones (14), (16), and (17), respectively, according to expectation. Furthermore, in order to examine the possibility of reverse rearrangement of γ-lactones, an o-DCB solution of some γ-lactones such as 15 and 18 was heated at 240 °C. Significantly, the reverse rearrangement proceeded gradually with the lapse of time, and finally the quantities of both lactones became in a state of equilibrium. Namely, the ratio of 6 to 15 and that of 12 to 18 were in the ratios of 15 : 85 and 56 : 44 after about 12 and 250 h, respectively.[5,6]

The above facts infer that the present cyclobutylcyclopropylcarbinyl rearrangement may proceed by a concerted mechanism rather than by a stepwise cationic one.[7] As in the acid-catalyzed rearrangement, the remarkable substituent effect may be cosidered to be steric effect which enforces the puckered geometry of the cyclobutane ring in the δ-lactones. Such a geometry of the cyclobutane ring may permit an antiperiplanar arrangement of the two migrating bonds (C-1,



O-2 and C-6, C-7 bonds) which is desirable for concerted rearrangement to γ-lactones.

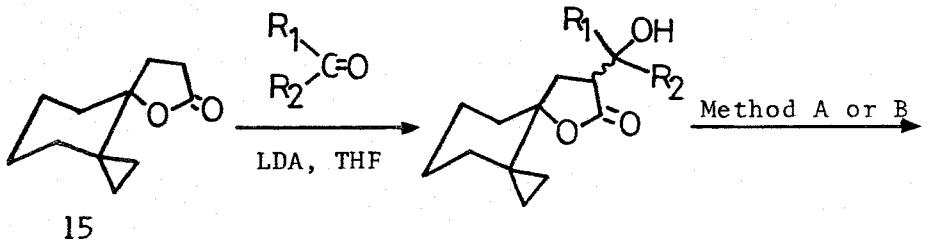
In this way, the convenient route for the synthesis of dispiro-γ-lactones having a spiro cyclopropane ring could be established by the acid-catalyzed or the novel thermally induced cyclobutyl-cyclopropylcarbinyl rearrangement.

1-1-2 SYNTHESIS OF α-ALKYLIDENE DISPIRO-γ-LACTONES AND THEIR BIOLOGICAL ACTIVITIES

In the previous section, it was found that dispiro-γ-lactones were readily derived from [m.4.2]propella-δ-lactones by the cyclobutyl-cyclopropylcarbinyl rearrangement. In this section, the synthesis of α-alkylidene dispiro-γ-lactones 20 by α-alkylidenation of dispiro-γ-lactone 15, and the interesting results about their screening of the biological activities, are presented.

Results and Discussion

The dispiro-γ-lacton 15, obtained in the best yield of all dispiro-γ-lactones and related to α-methylene spiro-γ-lactone 2, was used for the synthesis of α-alkylidene-γ-lactones 20. α-Alkylidenation of the γ-lactone 15 was carried out according to usual method comprised of α-hydroxyalkylation and subsequent dehydration as shown below.[2a,d,8] The results are summarized in Table 2.



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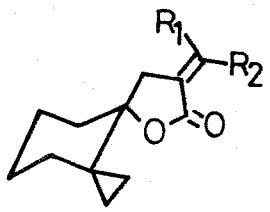


20a-20f

Method A: 1. MsCl, Pyridine,
2. DBU, PhH.

Method B: $SOCl_2$, Pyridine,
CH_2Cl_2.

Table 2. Synthesis of α-Alkylidene-γ-lactones.

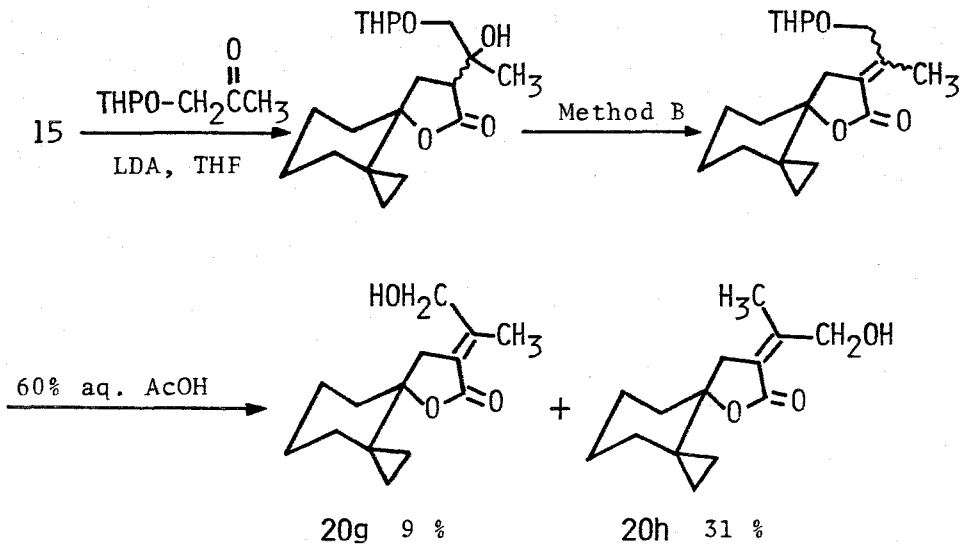
carbonyl compd	method	α-alkylidene-γ-lactone	R_1	R_2		yield(%)[a]
Formaldehyde	A	20a	H	H		77[b]
Acetaldehyde	A	20b	CH_3	H	(E)	54
		20c	H	CH_3	(Z)	7
Propionaldehyde	A	20d	C_2H_5	H	(E)	30
		20e	H	C_2H_5	(Z)	20
Acetone	B	20f	CH_3	CH_3		52

[a] Isolated yield based on 15.

[b] Determined by ^1H NMR analysis.

It was easy to establish the stereochemistry around the olefinic part of the γ-lactones 20b-e by the comparison of the ^{1}H NMR chemical shifts of the vinyl protons of 20b-e with those of α-alkylidene-γ-lactones described in literature.[9] The chemical shifts of the olefinic protons (6.57 and 6.11 ppm for E and Z isomers, respectively) were the most remarkable point to descriminate between the geometrical isomers of α-ethylidene-γ-lactones (20b) and (20c). Similarly, the observed values of the olefinic protons (6.48 and 6.00 ppm) of α-propylidene-γ-lactones (20d) and (20e) distinguished one from the other.

Furthermore, the α-alkylidene-γ-lactones having a hydroxyl group which was expected to enhance the reactivity of the conjugated lactone toward biological nucleophiles[1a] were synthesized. The tetrahydropyran-2-yl (THP) ether of hydroxyacetone was used for α-hydroxyalkylation of the γ-lactone 15. Dehydration by the method B gave the mixture of E/Z isomers of the THP-ether, which was treated with 60 % aqueous acetic acid to give (E)- and (Z)-α-(2-hydroxy-1-methylethylidene)-γ-lactones (20g) and (20h) in 9 % and 31 % overall yields from 15, respectively (see below). The distinction in stereochemistry between two isomers was accomplished by the comparison of the chemical shifts of the methyl groups in ^{1}H NMR spectra (2.16 and 1.90 ppm for E and Z isomers, respectively) with those of α-isopropylidene-γ-lactone (20f), since the methyl groups of 20f located in syn- and anti-positions toward the carbonyl group show resonances at 2.20 and 1.84 ppm, respectively.



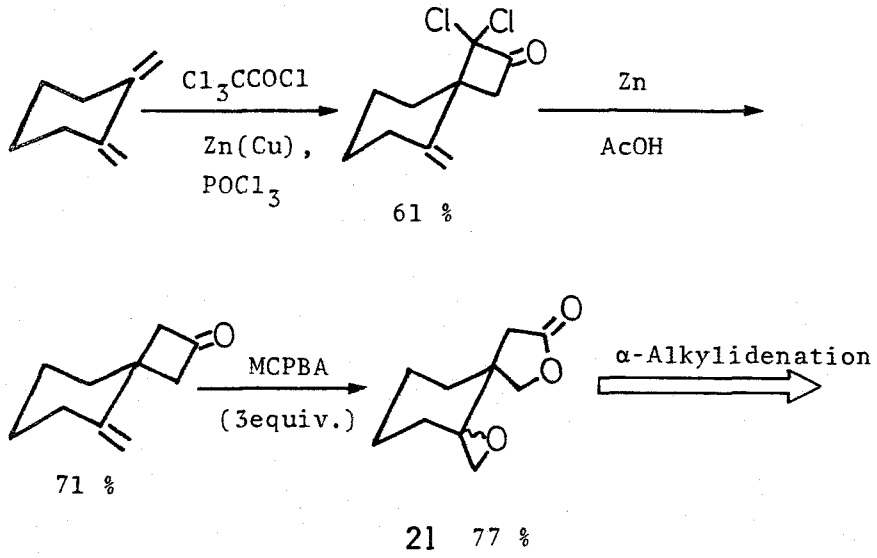
The screening of biological activities of a series of the present α-alkylidene-γ-lactones 20a, 20b, 20d-f, and 20h gave attractive results. Concerning the antitumor activity of these γ-lactones against Sarcoma 180 A in vivo, all of them were less active than the famous antitumor antibiotic, Mitomycin C. Interestingly, the other biological activities of these γ-lactones in vivo, however, were founf out: the antihistamine activity of (E)-α-propylidene-γ-lactone 20d, the antihistamine and the anticholine activities of (Z)-α-propylidene-γ-lactone 20e, the anti-arrhythimia activity of α-isopropylidene-γ-lactone 20f, and the platelet aggregation inhibition activity of (Z)-α-(2-hydroxy-1-methylethylidene)-γ-lactone 20h.

1-1-3 SYNTHESIS OF DISPIRO-γ-LACTONE INVOLVING AN EPOXIDE RING

Related to the previous section, oxadispiro-γ-lactone (21), a useful intermediate of α-alkylidene-γ-lactones involving an epoxide ring which is expected to enhance the reactivity of the conjugated lactone toward biological nucleophiles,[1a] is synthesized in this section.

Results and Discussion

Oxadispiro-γ-lactone 21 was synthesized in a good overall yield as shown below; (i) the cycloaddition of dichloroketene to 1,2-dimethylenecyclohexane employing the



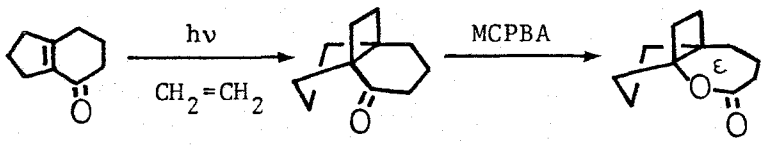
higher-dilution method,[10] (ii) the reductive removal of the chlorine atoms with zinc dust-acetic acid,[11] (iii) the oxidation with MCPBA.[12]

1-2 ACID-CATALYZED REARRANGEMENT OF [5,n,2]PROPELLA-ε-LACTONES

As an extention of the previous section, the acid-catalyzed rearrangement involving the lactone cleavage of [5.n.2]propella-ε-lactones (22) and (23), higher homologues of the propella-δ-lactones 5 and 6, leading to the interesting 1,2-disubstituted cycloalkenes (28) and (34), is described in this section. Since 28 and 34 are considered to be useful intermediates for the synthesis of prostagrandin and thromboxane derivatives, in particular, the rearrangement is investigated in detail. Furthermore, the two factors governing the skeletal rearrangement of these propellalactones, the steric effect of the third ring and the effect of lactone ring size toward the acid-catalyzed cleavage, are presented.

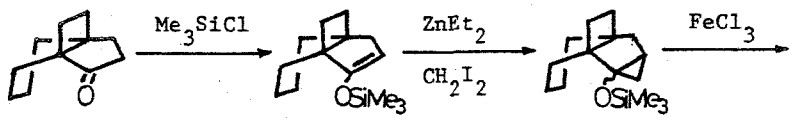
Results and Discussion

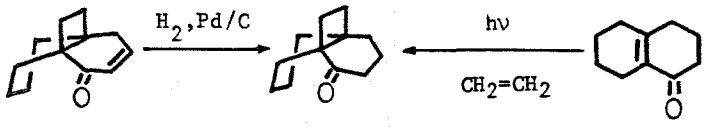
The ε-lactone 22 was prepared in a manner similar to the δ-lactones: photocycloaddition of bicyclo[4.3.0]non-1(6)-en-2-one to ethylene (91 %), followed by the Baeyer-Villiger oxidation of the propellanone with MCPBA in chloroform.



22

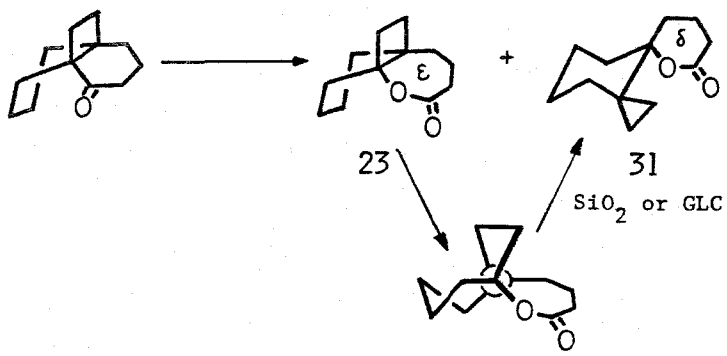
However, in the case of ε-lactone 23, the corresponding propellanone was prepared by the ring enlargement[13] of readily available [4.3.2]propellanone (tricyclo[4.3.2.$0^{1,6}$]-undecan-7-one) because of the inefficiency of the photocycloaddition of bicyclo[4.4.0]dec-1(6)-en-2-one to ethylene (29 %). The process leading to the [4.4.2]propellanone is the following : (i) preparation of the trimethylsilyl enol ether of the ketone (79 %), (ii) cyclopropanation of the enol ether by the Furukawa method (69 %),[14] (iii) oxidative





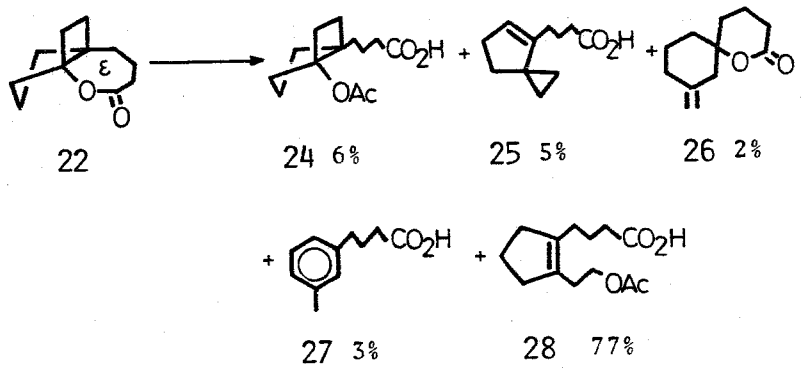
cleavage of the siloxycyclopropane with iron (III) chloride (82 %),[15] and (iv) catalytic hydrogenation of the [4.4.2]-propellaenone (84 %).

Significantly, the subsequent Baeyer-Villiger oxidation of the ketone with MCPBA in chloroform, followed by purification by column chromatography on silica gel,[16] led to the formation of two products, the expected ε-lactone 23 (32 %) and the dispiro-δ-lactone (31) (52 %) which was formed via the cyclobutyl-cyclopropylcarbinyl rearrangement of 23 with silica gel catalysis. Moreover, it has been ascertained that 23, having a cyclohexane ring, rearranges readily under GLC conditions (10 % FFAP on Uniport B, 180 °C) or on standing for a long time at room temperature (traced by ^{1}H NMR analysis). It should be contrasted with the fact that the ε-lactone 22, having a cyclopentane ring, was quite stable under the above conditions. Evidently, the facility of the rearrangement of the ε-lactone 23, in analogy with the δ-lactone 6,[17] is due to the steric effect of the cyclohexane



ring enforcing the more puckered comformation of the cyclobutane ring which is favorable for the rearrangement.

In order to obtain information on the acid-catalyzed rearrangement of the propella-ε-lactones under conditions similar to the case of the propella-δ-lactones, the reaction of 22 and 23 in boiling acetic acid was undertaken. When a solution of 22 in acetic acid was heated at reflux for 3 h (after which time the starting lactone was almost consumed), interestingly, the five products 24-28 involving 1,2-disubstituted cyclopentene 28 as the major product (77 %) were obtained in 93 % combined yield.

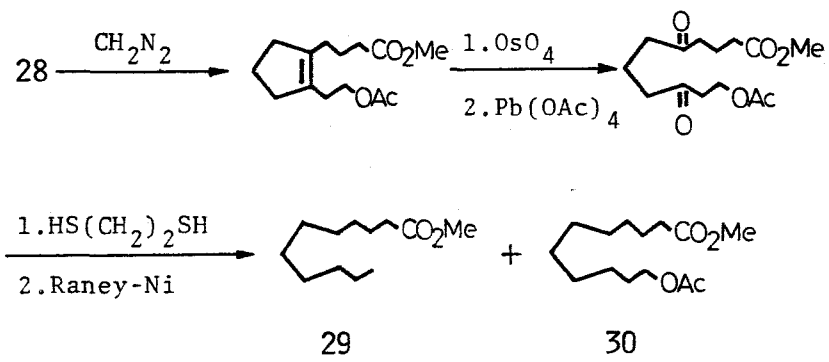


22 24 6% 25 5% 26 2%

27 3% 28 77%

The structures of these compounds were determined by spectral and analytical data (for 24-26, and 28) or comparison with the authentic sample (for 27). The structure of the major product 28 was further confirmed by degradation of 28 to methyl undecanoate (29) and methyl 11-acetoxyundecanoate (30) as shown below. Osmium tetra-

oxide oxidation followed by lead tetraacetate oxidation of the methyl ester of 28 and subsequent thio-ketal reduction of the 1,5-diketone gave two kinds of esters in a ratio 85 : 15 which were identical with 29 and 30, respectively.[18]



For the purpose of elucidating the reaction path, the change of the product distribution during the course of the rearrangement of 22 as well as the product distribution in the reaction of the isolated products, such as 24-26, and 28, in acetic acid (reflux, 3 h) was determined as summarized in Table 3. Judging mainly from the facts that the yield of the cyclopentene 28 increased with increasing reaction time and the product distribution obtained from the reaction of 25 after 3 h was similar to that from 22, it is reasonable to consider that the reaction proceeds according to Scheme 1. Namely, the bicyclo[3.2.0]hept-1-yl cation initially formed by ring-opening of the ε-lactone with acid

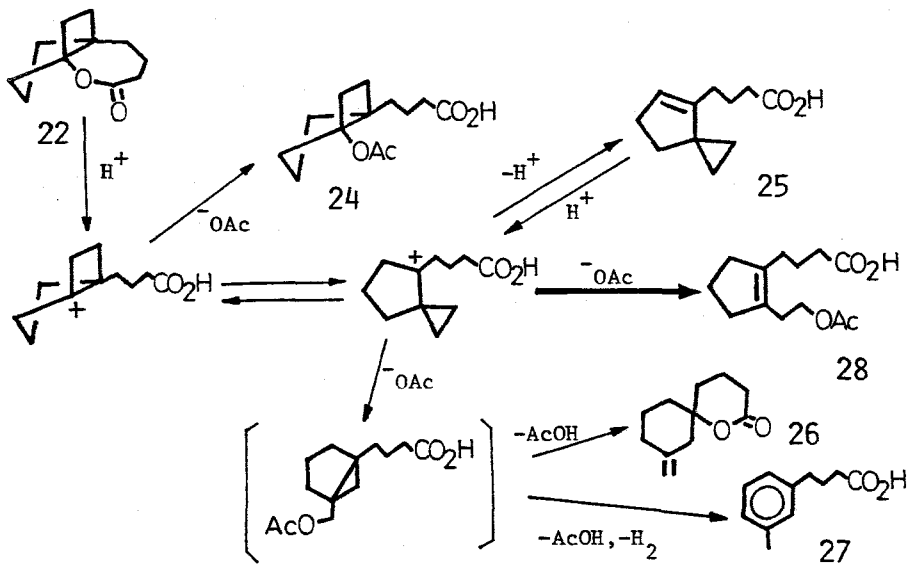
rearranges to cyclopropylcarbinyl cation, followed by attack of acetic acid (or acetate anion) on the cyclopropane ring, concerted with ring-cleavage and/or rearrangement. Then the major product 28, which is the most thermodynamically stable one, may be finally formed. The other products, such as 24-27, may be derived from the respective cations or arisen by elimination of acetic acid from the intermediate as shown in Scheme 1. The present scheme bears a striking resemblance to the reaction scheme via bicyclo[3.2.0]hept-1-yl cation proposed in the solvolysis of bicyclo[3.2.0]hept-1-yl 3,5-dinitrobenzoate by Wiberg et al.[19]

Table 3. Acid-Catalyzed Rearrangement of 22, 24-26, and 28

starting material	reaction time	product distribution (%)[a] 22	24	25	26	27	28
22[b]	10 min	85	2	8	—	—	5
	30 min	54	4	15	3	3	21
	1 h	40	6	13	3	3	35
	3 h	8	6	5	2	3	76
24	3 h	—	100	—	—	—	—
25[b]	3 h	—	6	13	3	6	72
26	3 h	—	—	—	100	—	—
28	3 h	—	—	—	—	—	100

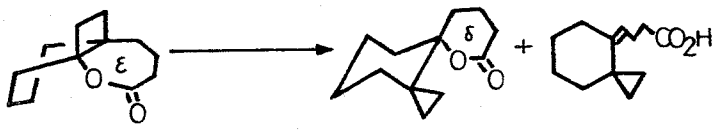
[a] Mole percent of identified products. [b] Small amounts of unidentified products were obtained (<4%).

Scheme 1.

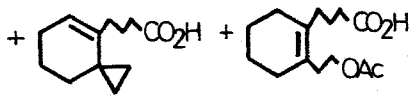


Interestingly, the rearrangement of the ε-lactone 22 proceeds smoothly via lactone ring-cleavage, though the corresponding δ-lactone 5 was recovered unchanged under similar conditions.[17] From the above fact, it is obvious that the reactivity of the propellalactones for the rearrangement is governed by the effect of lactone ring size rather than the steric effect of the third ring described above.

Moreover, the treatment of the ε-lactone 23 under the above conditions gave a small amount of the dispiro-δ-lactone 31 and three kinds of lactone ring-cleaved acids 32-34 involving 34 as the major product (67 %).



23 31 8% 32 6%



33 19% 34 67%

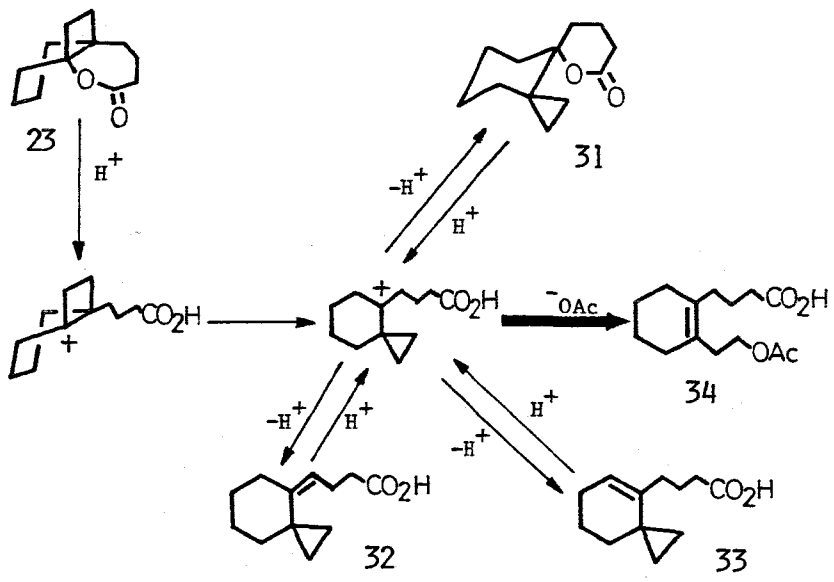
To elucidate the course of the reaction, the change of the product distribution during the course of the rearrangement of 24 and the product distribution in the reaction of isolated compounds, such as 31-34, were similarly determined as summarized in Table 4. From the fact that the yield of cyclohexene 34 increased with increasing reaction time and the reaction of 31-34 under similar conditions furnished the similar product distribution to that from 23, the observed products are considered to be derived from the rearrangement through cyclopropylcarbinyl type cation as shown in Scheme 2.

The facility of the rearrangement of 23 via lactone ring-cleavage should be contrasted with the reactivity of the corresponding δ-lactone 6 which only gave the dispiro-γ-lactone 15 without any formation of lactone ring-cleavage products.[17] Furthermore, the acid-catalyzed rearrangement of the dispiro-δ-lactone 31 mainly gave ring-cleavage

Table 4. Acid-Catalyzed Rearrangement of 23 and 31-34.

starting material	reaction time (h)	product distribution (%) 31	32	33	34
23	3	8	6	19	67
	72	4	2	2	92
31	3	10	5	15	70
32	3	6	12	24	58
33	3	8	8	24	60
34	3	—	—	—	100

Scheme 2.



products, while that of the dispiro-γ-lactone 15 gave only 6 but a little.[6] These results show an additional factor related to lactone ring size in spirolactone intermediates (or products). Namely, the product distribution in these propellalactones is presumably governed by the stability (and/or rate of formation from the intermediate carbonium ion) of the rearranged dispiro lactones. For example, in the δ-lactone 6, the lactone ring cleaves to give a carbonium ion, which rearranges and then recloses to give the stable dispiro-γ-lactone 15 (five-membered ring formation). On the other hand, in the ε-lactone 23 or 22, the reclosing from the cyclopropylcarbinyl cation intermediates to the dispiro-δ-lactone 31 or the hypothetical dispiro-δ-lactone may be less favorable (six-membered ring formation), and the recyclization from them to 23 or 22 seems unlikely to occur (seven-membered ring formation). As a result, further ring-cleavage of the carbonium ion intermediates takes place predominantly.

In conclusion, the two factors governing the skeletal rearrangement of the propellalactones have been elucidated. One is the steric effect of the third ring on the geometry of the cyclobutane ring, and the other is the effect of lactone ring size toward acid-catalyzed cleavage. But the latter is the dominant factor. Finally, the synthetic route of the 1,2-disubstituted cyclopentene 28 and cyclohexene 34, useful intermediates for the synthesis of prostagrandin and thromboxane derivatives, could be established by the lactone ring-cleavage of [5.n.2]propella-ε-lactones 22 and 23.

1-3 ALKALINE HYDROLYSIS OF PROPELLA-δ- AND ε-LACTONES

It has been well-known that the transition state of alkaline hydrolysis of lactones is the formation of the tetrahedral intermediate and that the hydroxide anion attacks perpendicularly to the plane of the carbonyl group.[20] Also, it becomes apparent that the substituent effect which affects the rate of the hydrolysis is primarily due to the steric factor in the transition state.[20c,f] Accordingly, in order to clarify the steric effect of the third ring governing the reactivity of the skeletal rearrangement of propellalactones described in the previous sections, the rates for the alkaline hydrolysis of a series of propella-δ- and ε-lactones are measured in this section.

Results and Discussion

The rates of the alkaline hydrolysis of various lactones were measured in 25 % (v/v) ethanol-water by the pH method of Hall *et al.*[20b,d] and the kinetic data are summarized in Table 5 and 6.

Firstly, the effect of alicyclic rings or two methyl groups substituted at 4- and 5-positions of δ-valerolactone on the alkaline hydrolysis was taken up. As shown in Table 5, the rate constants of a series of δ-lactones obviously decreased with going on from δ-valerolactone to tricyclic propella-δ-lactones through bicyclic ones. The striking aspect of the present data is that the rate constant of

Table 5. Kinetic Data for Alkaline Hydrolysis of δ-Lactone Series.

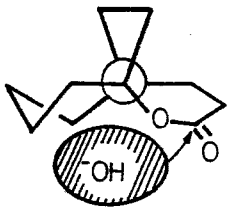
compd	T[a] °C	k 1 $mol^{-1} sec^{-1}$	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ eu	k_{rel}[b]
δ-Valero-	41.5	24.4 ± 0.3			
lactone	32.3	17.3 ± 0.0	7.38	-28.9	100
	25.0	11.4 ± 0.1			
9	41.5	1.36 ± 0.03			
	32.3	0.854 ± 0.013	8.79	-30.1	4.8
	25.0	0.561 ± 0.006			
12	41.5	0.203 ± 0.002			
	32.3	0.124 ± 0.002	9.35	-32.1	0.72
	25.0	0.0794 ± 0.0005			
5	41.5	0.145 ± 0.002			
	32.3	0.0934 ± 0.0026	9.78	-31.4	0.54
	25.0	0.0544 ± 0.0014			
6	41.5	0.280 ± 0.003			
	32.3	0.179 ± 0.001	9.33	-31.5	1.0
	25.0	0.110 ± 0.002			
7	41.5	0.0309 ± 0.0008			
	32.3	0.0241 ± 0.0008	7.69	-40.8	0.14
8	32.3	0.0290 ± 0.0006			0.17

[a] Temperatures are ± 0.1 °C. [b] Relative rates at 32.3 °C to that of δ-valerolactone = 100.

bicyclic δ-lactone 9 compared with that of δ-valerolactone decreased by a factor of about one-twentyth by the fusion of such a small cyclobutane ring. Moreover, the further deceleration was naturally observed in the cases of propella-δ-lactones 5-8, or bicyclic δ-lactone 12, being substituted by two methyl groups at the both angular bridgehead positions of 9. For example, the rate constant of 8 is less than that of 9 by a factor of about twenty eighth by the additional fusion of a eight-membered ring to the bicyclo[4.2.0] ring system. The effect of the third ring on the present alkaline hydrolysis may be regarded as the steric hindrance toward the attack of the hydroxide anion to the carbonyl group which is situated in position β to a bridgehead carbon atom, and, accordingly, it would be expected that the degree of the deceleration of the rate might be consistent with that of enlargement of the third ring size. In fact, however, the rate constants were in the order of 6 > 5 > 7 ~ 8, and that of 6, having a cyclohexane ring, was twice of that of 5, having a cyclopentane ring, and was even one and half times larger than that of 12.

These results are of very significance in connection with those of the cyclobutyl-cyclopropylcarbinyl rearrangement of 5-8 to the corresponding dispiro-γ-lactones 14-17 described in the previous section. The two reactions exhibited very similar feature of the ring size effect of the third ring. As borne out by the inspection of molecular model as well as by the reasoning for the previous rearrangement, this unique feature of 6 in reactivity may

be attributed to the puckered geometry of the cyclobutane ring reinforced by the chair conformation of the cyclohexane ring. Namely, 6 is packed closely like a compact hemisphere, in other words, 6 has a widespreading room to the direction of endo in comparison with the others, such as 5 and 12. Therefore, the attack of the hydroxide anion upon the carbonyl carbon atom of 6 may take place more smoothly.



In the case of ε-lactone series, on the other hand, the steric effect of two alicyclic rings fused to ε-caprolactone on the alkaline hydrolysis was much less than in the case of δ-lactone series. Namely, the rate constants of two propella-ε-lactones 22 and 23, which were the same, were only one-fourth as small as that of ε-caprolactone as shown in Table 6. This marked difference in reactivity between two propellalactone series can be attributed to the difference in flexibility or rigidity between δ- and ε-lactone rings. Inspection of molecular models of two lactone rings clearly indicates that the ε-lactone ring is more flexible than the δ-lactone one. It may be reasonable that the rate of more flexible ε-lactone for the hydrolysis is much slower

than that of more rigid δ-lactone.[21] This consideration implies that the flexibility of the ε-lactone makes it possible to depress the hydrolytic rate by the steric effect of adjacent methylene groups to the carbonyl one in the lactone ring itself. In addition, it is deduced from the kinetic data that the steric effect based on the flexibility of the ε-lactone ring plays more important role than that of the third ring.

Table 6. Kinetic Data for Alkaline Hydrolysis of ε-Lactone Series.

compd	T^a / °C	k / $l\ mol^{-1} sec^{-1}$	$\Delta H^{\ddagger}$ / kcal/mol	$\Delta S^{\ddagger}$ / eu	k_{rel} [b]
ε-Capro-	41.5	1.58 ± 0.03			
lactone	32.3	1.04 ± 0.02			
	25.0	0.678 ± 0.009	8.33	-31.3	100
22	41.5	0.458 ± 0.006			
	32.3	0.279 ± 0.010			
	25.0	0.194 ± 0.002	8.41	-33.5	29
23	25.0	0.193 ± 0.002			29

[a] Temperatures are ± 0.1 °C. [b] Relative rates at 25.0 °C to that of ε-caprolactone = 100.

In conclusion, from the kinetic study of the alkaline hydrolysis of a series of propella-δ- and ε-lactones, the steric effect of the third ring toward the attack of the

hydroxide anion has been elucidated. In particular, in the case of propella-δ-lactones, this effect played as important role as in the case of cyclobutyl-cyclopropylcarbinyl rearrangement of them. In the case of propella-ε-lactones, on the other hand, the alkaline hydrolysis was dominantly governed by the steric effect attributable to the flexibility of the ε-lactone ring, and, that of the third ring was of no great consequence.

EXPERIMENTAL

General. All melting and boiling points are uncorrected. Infrared spectra were recorded on a JASCO IR-G or a Hitachi 260-10 spectrometer as liquid films unless otherwise stated. ^{1}H NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer in CCl_4 and ^{13}C NMR spectra were taken on a JEOL JNM-FX-60S spectrometer in $CDCl_3$ with the use of Me_4Si as an internal standard. Mass spectra were measured with a Hitachi RMU-6E spectrometer. Analytical GLC was carried out on a Hitachi 163 gas chromatograph and preparative GLC separation was conducted on a Varian Aerograph 90-P or a Varian Aerograph 920 gas chromatograph with the use of a 10 % FFAP column.

Materials. [m.3.2]Propellanones (m=3-6) and 1,5-dimethylbicyclo[3.2.0]heptan-2-one were prepared in 51-73 % yields by photocycloaddition of the corresponding enones to ethylene in ether at -70 °C.[22] Bicyclo[3.2.0]heptan-2-one,[23] 1-

methyl,[24] 5-methyl,[24] and 1-ethyl-5-methyl substituted derivatives were prepared in 30-71 % yields as the above ketones. 1-Ethyl-5-methylbicyclo[3.2.0]heptan-2-one: IR 1710 cm^{-1}; ^1H NMR δ 0.75 (t, 3H), 1.22 (s, 3H), 1.40-2.08 (m, 10H); MS m/e 152 (M^+). Semicarbazone, mp 198-199.5 °C. Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 62.86; H, 9.15; N, 20.14. Cyclopentenone,[25] 2-methyl,[24] and 3-methyl[26] substituted ones were prepared according to the literature procedures and 2-ethyl-3-methyl derivative was prepared by a method similar to that for the 2,3-dimethyl one.[27] 2-Ethyl-3-methylcyclopentenone: IR 1680, 1640 cm^{-1}; ^1H NMR δ 0.90 (t, 3H), 2.00-2.50 (m, 9H); MS m/e 124 (M^+). Semicarbazone, mp 216-217 °C. Anal. Calcd for $C_9H_{15}ON_3$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.65; H, 8.30; N, 23.17.

Preparation of δ-Lactones. δ-Lactones 5-13 were prepared by the Baeyer-Villiger oxidation of the corresponding ketones in two methods.

A solution of the ketone and 20-fold excess of 30 % aqueous hydrogen peroxide in acetic acid was stirred at room temperature and the progress of the reaction was monitored by GLC. The solution was poured into water and extracted with ether, and the organic layer was washed with saturated sodium carbonate (Na_2CO_3) solution and brine, and dried over anhydrous sodium sulfate (Na_2SO_4). The solvent was removed in vacuo and the residue was distilled under reduced pressure. δ-Lactones 5-13 were obtained in 35-80 % yields and

purified by preparative GLC.[28]

A solution of the ketone and 2.5-fold excess of 85 % m-chloroperbenzoic acid (MCPBA) in chloroform was stirred at room temperature. The solution was washed with saturated sodium sulfite (Na_2SO_3) solution and water, and dried (Na_2SO_4). Products were isolated as described above (40-90 %).

5: IR 1720 cm^{-1}; ^1H NMR δ 1.30-2.20 (m, 12H), 2.30-2.50 (m, 2H); MS m/e 166 (M^+), 138. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.90; H, 8.78.

6: IR 1720 cm^{-1}; ^1H NMR δ 1.00-2.15 (m, 14H), 2.20-2.50 (m, 2H); MS m/e 180 (M^+), 152. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 9.13.

7: mp 34-36 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR δ 1.20-2.20 (m, 16H), 2.50-2.70 (m, 2H); MS m/e 194 (M^+), 166. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.92; H, 9.44.

8: IR 1720 cm^{-1}; ^1H NMR δ 1.00-2.20 (m, 18H), 2.50-2.70 (m, 2H); MS m/e 208 (M^+), 180. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.74.

9: IR 1720 cm^{-1}; ^1H NMR δ 1.50-2.80 (m, 9H), 4.76 (q, 1H); MS m/e 126 (M^+), 98.

10: IR 1720 cm^{-1}; ^1H NMR δ 1.40 (s, 3H), 1.40-2.50 (m, 9H); MS m/e 141 (M^++1), 43. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.31; H, 8.72.

11: IR 1720 cm^{-1}; ^1H NMR δ 1.24 (s, 3H), 1.40-2.60 (m, 8H); 4.32 (t, 1H); MS m/e 141 (M^++1), 99. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.22; H, 8.77.

12: IR 1720 cm^{-1}; ^1H NMR δ 0.96 (s, 3H), 1.14 (s, 3H), 1.40-2.70 (m, 8H); MS m/e 155 (M^++1), 140. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.05; H, 9.25.
13: IR 1720 cm^{-1}; ^1H NMR δ 0.99 (t, 3H), 1.12 (s, 3H), 1.50-2.50 (m, 10H); MS m/e 169 (M^++1), 140. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.06; H, 9.98.

Acid-Catalyzed Rearrangement of δ-Lactones 5-13. Method A. A solution of a δ-lactone 5-13 in acetic acid was refluxed for 72 h. The solution was neutralized with saturated sodium bicarbonate ($NaHCO_3$) solution and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled under reduced pressure. Products were analyzed by GLC and isolated by preparative GLC. The results are summarized in Table 1.

Method B. A solution of the δ-lactone and catalytic amounts of TsOH in benzene was heated at reflux for 24 h. The benzene solution was washed with saturated $NaHCO_3$ solution and brine and then dried (Na_2SO_4). Similar work-up as the above gave a mixture of δ- and γ-lactones. The results are summarized in Table 1.
15: mp 32-34 °C; IR 1765 cm^{-1}; ^1H NMR δ 0.15-1.00 (m, 4H), 1.20-2.20 (m, 10H), 2.30-2.50 (m, 2H); MS m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.98; H, 9.03.
18: IR 1765 cm^{-1}; ^1H NMR δ 0.49 (m, 2H), 0.67 (t, 2H), 1.10 (s, 3H), 1.40 (s, 3H), 1.80-2.60 (m, 4H); MS m/e 155 (M^++1).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.87; H, 9.27.

19: IR 1765 cm^{-1}; ^1H NMR δ 0.25-0.68 (m, 4H), 0.80 (t, 3H), 1.40 (s, 3H), 1.50 (q, 2H), 1.80-2.60 (m, 4H); MS m/e 169 (M^++1). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.69.

Thermal Rearrangement of δ-Lactones 5-13. (a) In Solution. A solution of the δ-lactone in o-DCB was heated in a sealed tube at 240 °C for 72 h. After evaporation of the solvent in vacuo, the residue was analyzed by GLC and the γ-lactones were separated by column chromatography on silica gel (10 % ether-petroleum ether), and purified by preparative GLC. The results are summarized in Table 1.

(b) In Vapor Phase. A hexane solution of the δ-lactone was passed through a Pyrex column (80 cm) heated at 350 °C in nitrogen stream (contact time; ca. 20 sec), and collected in dry-ice acetone trap. Similar work-up as the above gave a mixture of δ- and γ-lactones. The results are summarized in Table 1.

14: IR 1765 cm^{-1}; ^1H NMR δ 0.10-0.90 (m, 4H), 1.40-2.20 (m, 8H), 2.20-2.50 (m, 2H); MS m/e 166 (M^+), 111. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.88; H, 8.56.

16: IR 1765 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.10-2.20 (m, 12H), 2.30-2.60 (m, 2H); MS m/e 194 (M^+), 166. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.33; H, 9.59.

17: IR 1765 cm^{-1}; ^1H NMR δ 0.10-1.10 (m, 4H), 1.10-2.20 (m, 14H), 2.30-2.60 (m, 2H); MS m/e 208 (M^+), 180. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.13; H, 9.56.

Materials. Acetaldehyde, propionaldehyde, and hydroxyacetone were distilled prior to use. Acetone was distilled from potassium carbonate (K_2CO_3) before use.

General Procedure for Synthesis of α-Alkylidene-γ-lactones (20a-f). α-Hydroxyalkylation. A solution of diisopropylamine (2 m mol) in dry tetrahydrofuran (THF) (1.5 mL) cooled to -78 °C was treated dropwise with butyllithium (1.5 m mol) in hexane under nitrogen atmosphere. After stirring at -78 °C for 1 h, a solution of the γ-lactone 15 (1 m mol) in dry THF (0.2 mL) and dry hexamethylphosphoric triamide (HMPT) (0.1 mL) was added dropwise via a syringe. After addition was complete, stirring was continued at -78 °C for 30 min, then a carbonyl compound (1 m mol) was added via a syringe and the mixture was stirred for 2 h. The reaction was quenched by saturated ammonium chloride (NH_4Cl) solution and the mixture was extracted with ether. The organic layer was washed with 5 % HCl, saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). The solvent was removed in vacuo to give the crude alcohol product.

Dehydration. Method A. The above alcohol (1 m mol) was dissolved in dry pyridine (2 mL) and treated at 0-5 °C with methanesulfonyl chloride (3 m mol). After stirring at 5 °C for 9 h, an ice-water was added and the mixture was

extracted with ether. The organic layer was washed with 5 % HCl, saturated $NaHCO_3$ solution, and brine. After drying (Na_2SO_4), the solvent was evaporated in vacuo to give the crude mesylate. The crude mesylate (1 m mol) was dissolved in dry benzene (2.0 mL) containing 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (1.4 m mol) and the mixture was stirred at room temperature for 6 h. Water was added and the mixture was extracted with ether. The organic layer was washed with 5 % HCl, saturated $NaHCO_3$ solution, and brine. After drying (Na_2SO_4), the solvent was removed in vacuo leaving the crude α-alkylidene-γ-lactones. Method B. Thionyl chloride (1.2 m mol) was added dropwise to a solution of the crude alcohol (1 m mol) in dry pyridine (0.5 mL) and dry methylene chloride (CH_2Cl_2) (1.5 mL). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. After addition of a few pieces of ice, the mixture was extracted with CH_2Cl_2. The organic layer was washed with 5 % HCl, water, and dried (Na_2SO_4). The solvent was removed in vacuo to give the crude α-alkylidene-γ-lactones. Analytical samples of the γ-lactones were obtained by preparative GLC.

7-Methylene-5-oxadispiro[2.0.4.4]dodecan-6-one (20a).
The reaction of 15 (829 mg, 4.6 m mol) and formaldehyde, generated by depolymerization of paraformaldehyde (3.5 g) at 160 °C (bath temperature) and passed into the reaction mixture at -20 °C under nitrogen stream, gave the crude α-hydroxymethyl-γ-lactone (873 mg, 90 %: IR 3450, 1750 cm^{-1}). Dehydration of the alcohol by method A (the mesylate: IR

1750, 1350, 1160 cm^{-1}) gave α-methylene-γ-lactone 20a (684 mg). Overall yield based on 15 was 77 % (determined by ^1H NMR analysis). 20a: IR 3050, 1750, 1660 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.23-2.00 (m, 8H), 2.68 (t, J=2.8 Hz, 2H), 5.50 (t, J=2.6 Hz, 1H), 6.10 (t, J=2.6 Hz, 1H); MS m/e 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.59; H, 8.56.

(E)- and (Z)-7-Ethylidene-5-oxadispiro[2.0.4.4]dodecan-6-one (20b) and (20c). The reaction of 15 (5.7 g, 31.6 m mol) and acetaldehyde (1.4 g, 31.6 m mol) gave the crude α-(1-hydroxyethyl)-γ-lactone (7.3 g, quantitatively: IR 3450, 1740 cm^{-1}). Dehydration of the alcohol by method A (the mesylate : IR 1750, 1350, 1160 cm^{-1}) gave the mixture of E-isomer 20b and Z-isomer 20c which were separated by column chromatography on silica gel (3 % ether-petroleum ether). 20b (54 % from 15): IR 3050, 1750, 1670 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.12-2.04 (m, 11H), 2.55 (m, 2H), 6.57 (m, 1H); MS m/e 206 (M^+). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.76. 20c (7 % from 15) IR 3050, 1740, 1660 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.12-2.00 (m, 8H), 2.10 (m, 3H), 2.62 (m, 2H), 6.11 (m, 1H); MS m/e 206 (M^+). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.37; H, 8.89.

(E)- and (Z)-7-Propylidene-5-oxadispiro[2.0.4.4]dodecan-6-one (20d) and (20e). The reaction of 15 (6.0 g, 33.3 m mol) and propionaldehyde (2.3 g, 33.3 m mol) gave the crude α-(1-hydroxypropyl)-γ-lactone (6.4 g, 80 %: IR 3450, 1740 cm^{-1}).

Dehydration of the alcohol by method A (the mesylate: IR 1740, 1350, 1160 cm^{-1}) gave the mixture of E-isomer 20d and Z-isomer 20e which were separated by column chromatography on silica gel (3 % ether-petroleum ether). 20d (30 % from 15): IR 3050, 1740, 1670 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.10 (t, 3H), 1.28-2.00 (m, 8H), 2.18 (m, 2H), 2.56 (m, 2H), 6.48 (m, 1H); MS m/e 220 (M^+). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C,76.03; H, 9.21. 20e (20 % from 15): IR 3050, 1735, 1660 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.03 (t, 3H), 1.16-2.00 (m, 8H), 2.64 (m, 4H), 6.00 (m, 1H); MS m/e 220 (M^+). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.14; H, 9.24.

7-Isopropylidene-5-oxadispiro[2.0.4.4]dodecan-6-one (20f). The reaction of 15 (5.0 g, 27.8 m mol) and acetone (1.6 g, 27.8 m mol) gave the crude α-(1-hydroxy-1-methylethyl)-γ-lactone (6.4 g, 97 %: IR 3450, 1735 cm^{-1}). Dehydration of the alcohol by method B gave the crude α-isopropylidene-γ-lactone 20f which was purified by column chromatography on silica gel (5 % ether-petroleum ether) to afford 3.2 g of 20f (52 % from 15): mp 70-71 °C (recrystallized from petroleum ether); IR (KBr) 3050, 1730, 1650 cm^{-1}; ^1H NMR δ 0.10-1.00 (m, 4H), 1.15-1.80 (m, 8H), 1.84 (m, 3H), 2.20 (m, 3H), 2.58 (m, 2H); MS m/e 220 (M^+). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.11; H, 9.28.

Tetrahydropyran-2-yl Acetonyl Ether. A solution of hydroxyacetone (10 g, 0.135 mol) in 200 mL of dry CH_2Cl_2 containing 1.0 g of TsOH was treated at 0 °C with 3,4-di-

hydro-2H-pyran (13.6 g, 0.162 mol). After stirring at 0 °C for 3.5 h, the reaction was quenched by the addition of saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* leaving the crude THP-ether. Column chromatography on silica gel (20 % ether-petroleum ether) followed by distillation gave 12 g of the pure ether in 57 % yield: bp 64-66 °C (2 mm); IR 1710, 1110, 1060, 1010 cm^{-1}; ^1H NMR δ 1.36-2.00 (m, 6H), 2.10 (s, 3H), 3.52 (m, 1H), 3.80 (m, 1H), 4.00 (m, 2H), 4.58 (t, 1H); MS *m/e* 156 (M^+-2). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.56; H, 8.99.

(E)- and (Z)-7-(2-hydroxy-1-methylethylidene)-5-oxadispiro-[2.0.4.4]dodecan-6-one (20g) and (20h). The reaction of *15* (6.0 g, 33.3 m mol) and the above ether (5.3 g, 33.3 m mol) gave the crude alcohol (11.2 g, quantitatively: IR 3450, 1750, 1010 cm^{-1}). Dehydration of the alcohol by method B afforded the crude THP-lactone (10.1 g, 95 % from *15*: IR 3050, 1720, 1650, 1010 cm^{-1}). The above lactone was dissolved in 100 mL of 60 % aqueous acetic acid and the solution was stirred at 45 °C for 3 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* leaving the mixture of E-isomer *20g* and Z-isomer *20h*. Separation by column chromatography on silica gel (20 % ether-petroleum ether) gave 0.7 g of *20g* and 2.4 g of *20h* (9 % and 31 % from *15*,

respectively). 20g: IR 3400, 3050, 1730, 1650 cm^{-1}; ^1H NMR δ 0.10-0.90 (m, 4H), 1.08-2.04 (m, 8H), 2.16 (m, 3H), 2.64 (m, 2H), 2.74 (broad s, 1H), 4.10 (s, 2H); MS m/e 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.94; H, 8.58. 20h: IR 3400, 3050, 1720, 1650 cm^{-1}; ^1H NMR δ 0.10-0.95 (m, 4H), 1.08-1.85 (m, 8H), 1.90 (m, 3H), 2.62 (m, 2H), 3.48 (broad s, 1H), 4.36 (s, 2H); MS m/e 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.95; H, 8.57.

Materials. 1,2-Dimethylenecyclohexane[29] was prepared in a method similar to that of Davalian et al.,[30] and purified by distillation using a spinning-band distillation column.

1,1-Dichloro-5-methylene-spiro[3.5]nonan-2-one. A solution of 8.1 mL (0.078 mol) of freshly distilled trichloroacetyl chloride and 6.8 mL (0.078 mol) of phosphoryl chloride (distilled from K_2CO_3) in 440 mL of dry ether was added dropwise over 5 h to a mixture of 8.4 g (0.078 mol) of 1,2-dimethylenecyclohexane and 7.6 g (0.114 mol) of activated zinc in 600 mL of dry ether under a nitrogen atmosphere. The reaction mixture was stirred at reflux for additional 30 h. The excess zinc was filtered and washed with ether. The filtrate was concentrated in vacuo to ca. 25 % of its original volume, an equal volume of pentane added, and the solution was decanted from the residue, washed successively with water, a cold saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was distilled under reduced pressure. After

recovery of 2.6 g of the hexane (bp 60 °C (90 mm)), 7.1 g of the dichloro ketone was obtained as pale yellow oil (61 %): bp 86-88 °C (0.8 mm); IR 1800, 1635 cm^{-1}; ^1H NMR δ 1.16-2.50 (m, 8H), 2.66 (d, J=17 Hz, 1H), 3.62 (d, J=17 Hz, 1H), 4.80 (s, 1H), 5.08 (s, 1H); MS m/e 222 (M^++4), 220 (M^++2), 218 (M^+). Anal. Calcd for $C_{10}H_{12}OCl_2$: C, 54.82; H, 5.52. Found: C, 54.91; H, 5.56.

5-Methylene-spiro[3.5]nonan-2-one. A mixture of 7.0 g (0.032 mol) of the above adduct, 10 g of zinc, and 10 mL of acetic acid in 150 mL of dry ether was stirred at room temperature for 30 h.[31] The reaction mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was distilled under reduced pressure to give 3.4 g of the cyclobutanone (71 %): bp 68-69 °C (3 mm); IR 1775, 1635 cm^{-1}; ^1H NMR δ 1.45-1.82 (m, 6H), 2.02-2.28 (m, 2H), 2.45-2.80 (m, 2H), 2.88-3.24 (m, 2H), 4.68 (s, 1H), 4.78 (s, 1H); MS m/e 150 (M^+). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.84; H, 9.54.

1,6-Dioxadispiro[2.0.4.4]dodecan-7-one (21). A solution of 500 mg (3.3 m mol) of the above ketone and 2.2 g (9.9 m mol) of 80 % MCPBA in 27 mL of chloroform was stirred at room temperature and the progress of the reaction was monitored by GLC. After 6 days, the solution was washed saturated Na_2SO_3 solution, saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (20 %

ether-petroleum ether) to give 471 mg of 21[12] (77 %): IR 1765 cm^{-1}; ^1H NMR δ 1.20-2.00 (m, 8H), 2.04-2.72 (m, 4H), 3.60-4.20 (m, 2H); MS m/e 182 (M^+). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.72; H, 7.75.

Materials. Bicyclo[4.3.0]non-1(6)-en-2-one and bicyclo-[4.4.0]dec-1(6)-en-2-one were prepared according to the method of Hill and Conley.[32]

[4.3.2]Propellanone (Tricyclo[4.3.2.$0^{1,6}$]undecan-2-one). A solution of 14.8 g (0.11 mol) of the enone in 270 mL of CH_2Cl_2 was irradiated (Pyrex filter) at -70 °C for 25 h while ethylene was bubbled into the solution. After removal of the solvent, the residue was distilled under reduced pressure to give 16.2 g of the propellanone (91 %): bp 67-70 °C (3 mm); IR 1680 cm^{-1}; ^1H NMR δ 1.18-2.60 (m); MS m/e 164 (M^+). Semicarbazone, mp 220-221 °C. Anal. Calcd for $C_{12}H_{19}ON_3$: C, 65.12; H, 8.65; N, 18.99. Found: C, 64.88; H, 8.61; N, 19.01.

[4.4.2]Propellanone (Tricyclo[4.4.2.$0^{1,6}$]dodecan-2-one).[33]

(1) By Photocycloaddition. A solution of 6.4 g (0.043 mol) of the enone was irradiated for 11 h as described above. Distillation gave 2.2 g of the propellanone (29 %).

(2) By Ring Enlargement. Trimethylsilyl Enol Ether.[34] To a solution of 25.5 g (0.24 mol) of chlorotrimethylsilane and 45.4 g (0.45 mol) of triethylamine in 100 mL of dimethyl-formamide was added 31.8 g (0.19 mol) of tricyclo[4.3.2.$0^{1,6}$]-undecan-7-one (described 1-1-1) under nitrogen atmosphere.

The resulting mixture was refluxed with stirring for 42 h (monitored by GLC) and then cooled, diluted with 200 mL of pentane, and washed with three portions of cold saturated $NaHCO_3$ solution. The aqueous washes were extracted with pentane and the combined organic layer was washed rapidly in succession with cold 1.5 N HCl and cold saturated $NaHCO_3$ solution. After drying (Na_2SO_4), the solvent was evaporated *in vacuo* and the residue was distilled under reduced pressure to yield 36.4 g of the trimethylsilyl enol ether (79 %): bp 79 °C (3 mm); IR 1615, 1230 cm^{-1}; ^1H NMR δ 0.18 (s, 9H), 0.80-2.16 (m, 14H), 4.43 (t, 1H); MS *m/e* 236 (M^+). Anal. Calcd for $C_{14}H_{24}OSi$: C, 71.12; H, 10.23. Found: C, 71.17; H, 10.54. *Siloxycyclopropane.*[14] To a stirred solution of 36.0 g (0.15 mol) of the above enol ether in 400 mL of hexane was added 37.1 g (30.7 mL, 0.30 mol) of diethylzinc by the use of a syringe under nitrogen atmosphere. Then 56.3 g (0.21 mol) of methylene iodide was added dropwise during about 30 min and the resulting solution was stirred for 38 h at room temperature. The reaction was quenched by addition of cold NH_4Cl solution and the solution was washed with saturated $NaHCO_3$ solution, water, and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was distilled under reduced pressure to yield 26.4 g of the siloxycyclopropane (69 %): 93 °C (3.5 mm); IR 3050, 1220 cm^{-1}; ^1H NMR δ 0.12 (s, 9H), 0.40-0.96 (m, 2H), 1.00-2.40 (m, 15H); MS *m/e* 250 (M^+). Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 72.00; H, 10.76. *[4.4.2]Propellaenone.*[15] To a stirred solution of 48.7 g

(0.30 mol) of anhydrous iron (III) chloride in 200 mL of dimethylformamide was added dropwise a solution of 26.0 g (0.10 mol) of the above siloxycyclopropane and 8.1 mL (0.10 mol) of pyridine in 200 mL of dimethylformamide over 3.5 h at 0-10 °C under nitrogen atmosphere. The resulting brown solution was stirred at room temperature for 1 h and then poured into cold 1 N HCl and the mixture was extracted with chloroform. The organic layer was washed with 1 N HCl, water, and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was distilled under reduced pressure to yield 15.2 g of the [4.4.2]propellaenone (82 %): bp 109 °C (5 mm); IR 3050, 1640, 770 cm^{-1}; ^1H NMR δ 0.90-2.60 (m, 14H), 6.00 (d×t, 1H), 6.72 (m, 1H); MS m/e 176 (M^+). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.41; H, 9.00. [4.4.2]Propellanone. 15.0 g (0.085 mol) of the above propellaenone was hydrogenated in 150 mL of methanol in the presence of 5 % palladised carbon (catalytic amount) at room temperature under atmospheric pressure of hydrogen. Filtration and concentration of the filtrate in vacuo, subsequently, chromatography of the residue on silica gel gave 12.8 g of the ketone (84 %). The GLC retention time and IR spectra were identical with those of the ketone which was prepared by photocycloaddition.

[5.3.2]Propella-ε-lactone (22). A solution of 8.2 g (0.05 mol) of the ketone and 2.5-fold excess of MCPBA in 350 mL of chloroform was stirred at room temperature for 6 days. The solution was washed with saturated Na_2SO_3 solution,

saturated $NaHCO_3$ solution, and water. After drying (Na_2SO_4), the solvent was removed in vacuo and the residue was chromatographed on silica gel (20 % ether-petroleum ether) to give 8.6 g of the ε-lactone 22 as a white solid (96 %): mp 60-61 °C (recrystallized from petroleum ether); IR (KBr) 1700 cm^{-1}; ^1H NMR δ 1.24-2.16 (m, 14H), 2.24-2.60 (m, 2H); MS m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.33; H, 9.17.

[5.4.2]Propella-ε-lactone (23) and 5-Oxadispiro[2.0.5.4]-tridecan-6-one (31). 5.8 g (0.033 mol) of the ketone was oxidized as described for 22. After usual work-up, the crude product was chromatographed on silica gel (20 % ether-petroleum ether) to yield 2.0 g (32 %) of the ε-lactone 23 and 3.3 g (52 %) of the δ-lactone 31. 23: mp 34.5-35.5 °C; IR (KBr) 1700 cm^{-1}; ^1H NMR δ 0.90-2.54 (m); MS m/e 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.21; H, 9.42. 31: IR 3050, 1720 cm^{-1}; ^1H NMR δ 0.15-0.60 (m, 3H), 0.90-1.20 (m, 2H), 1.30-2.12 (m, 11H), 2.18-2.60 (m, 2H); MS m/e 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.41.

Acid-Catalyzed Rearrangement of ε-Lactone 22. A solution of 135 mg (0.75 m mol) of the ε-lactone 22 in 5 mL of acetic acid was heated at reflux for 3 h. After removal of the solvent in vacuo, the residue was analyzed by GLC (3 mm × 1 m column: 10 % FFAP) using octacosane as an internal standard. Five products, 4-(5-acetoxybicyclo[3.2.0]hepty1)-butyric acid (24) (6 %), 4-(4-spiro[2.4]hept-4-enyl)butyric

acid (25) (5 %), 8-methylene-1-oxaspiro[5.5]undecan-2-one (26) (2 %), m-tolylbutyric acid (27) (3 %), and 4-[2-(2-acetoxyethyl)cyclopent-1-enyl]butyric acid (28) (77 %) were obtained (conversion 93 %). The product distribution was recorded at appropriate intervals and the results are summarized in Table 3. The products were separated by column chromatography on silica gel and purified by preparative GLC.

24: IR 3500-2500, 1720, 1690, 1230 cm^{-1}; ^1H NMR δ 1.12-1.90 (m, 10H), 1.92 (s, 3H), 1.96-2.60 (m, 6H), 11.50 (broad s, 1H); MS m/e 180 (M^+-60). The methyl ester of 24 was prepared by the treatment with ethereal diazomethane: IR 1720, 1240, 1160 cm^{-1}; ^1H NMR δ 1.00-1.88 (m, 9H), 1.92 (s, 3H), 1.94-2.64 (m, 7H), 3.64 (s, 3H); MS m/e 194 (M^+-60). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.11; H, 8.62.

25: IR 3500-2500, 1690, 1650, 870 cm^{-1}; ^1H NMR δ 0.32-0.76 (m, 4H), 1.40-2.00 (m, 6H), 2.20-2.56 (m, 4H), 5.36 (m, 1H),[35] 11.84 (broad s, 1H); MS m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.29; H, 8.97.

26: IR 3050, 1720, 1645, 890 cm^{-1}; ^1H NMR δ 1.98-2.60 (m, 14H), 4.67 (s, 1H), 4.73 (s, 1H); MS m/e 180 (M^+). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.23; H, 9.00.

27: IR 3500-2500, 1690, 1600, 770, 690 cm^{-1}; ^1H NMR δ 1.60-2.76 (m, 9H), 6.78-7.20 (m, 4H), 11.56 (broad s, 1H); MS m/e 178 (M^+). The spectral data were identical with those of authentic sample which was prepared according to the litera-

ture.[37]

28: IR 3500-2500, 1720, 1690, 1230 cm^{-1}; ^1H NMR δ 1.50-1.88 (m, 4H), 1.96 (s, 3H), 2.00-2.48 (m, 10H), 4.00 (t, 2H), 10.30 (broad s, 1H); MS m/e 240 (M^+). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.71; H, 8.59. The methyl ester of 28 was prepared by the treatment with ethereal diazomethane: IR 1725, 1230, 1160 cm^{-1}; ^1H NMR δ 1.50-1.88 (m, 4H), 1.96 (s, 3H), 2.00-2.48 (m, 10H), 3.60 (s, 3H), 4.00 (t, 2H); MS m/e 254 (M^+). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.86; H, 8.96.

Acid-Catalyzed Rearrangement of ε-Lactone 23 and δ-Lactone 31. The reaction of 236 mg (1.22 m mol) of 23 or 237 mg (1.22 m mol) of 31 in 5 mL of acetic acid was carried out in the manner similar to that of 22. After removal of the solvent in vacuo, the residue was chromatographed on silica gel to give the following products. 23 gave, 19 mg of 31 (8 %), 16 mg of 4-(4-spiro[2.5]octylidene)butyric acid (32) (6 %), 45 mg of 4-(4-spiro[2.5]oct-4-enyl)butyric acid (33) (19 %), and 215 mg of 4-[2-(2-acetoxyethyl)cyclohex-1-enyl)-butyric acid (34) (67 %). 31 gave, 10 mg of 32 (4 %), 45 mg of 33 (14 %), and 214 mg of 34 (69 %) and 23 mg (10 %) of 31 was recovered. The products were purified by preparative GLC. The product distribution was recorded as described above and the results were summarized in Table 4. 32: IR 3500-2500, 1680, 1630, 1250, 890 cm^{-1}; ^1H NMR δ 0.28 (t, 2H), 0.48 (t, 2H), 1.20-1.88 (m, 6H), 1.96-2.50 (m, 6H), 4.98 (t, 1H), 11.20 (broad s, 1H); MS m/e 194 (M^+). Anal.

Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.84; H, 9.38.

33: mp 41.5-42.5 °C (recrystallized from pentane); IR 3500-2500, 1670, 1630, 1250, 870 cm^{-1}; ^1H NMR δ 0.35 (t, 2H), 0.72 (t, 2H), 1.30-1.84 (m, 8H), 1.98-2.36 (m, 4H), 5.36 (t, 1H), 11.64 (broad s, 1H); MS m/e 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.35.

34: IR 3500-2500, 1720, 1690, 1220 cm^{-1}; ^1H NMR δ 1.40-1.90 (m, 6H), 1.94 (s, 3H), 1.96-2.40 (m, 10H), 3.96 (t, 2H), 10.36 (broad s, 1H); MS m/e 254 (M^+). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.08; H, 8.91.

The methyl ester of 34 was prepared by the treatment with ethereal diazomethane: IR 1725, 1220, 1150 cm^{-1}; ^1H NMR δ 1.42-1.90 (m, 6H), 1.94 (s, 3H), 1.98-2.36 (m, 10H), 3.60 (s, 3H), 3.96 (t, 2H); MS m/e 268 (M^+). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.09; H, 9.22.

Degradation of the Methyl Ester of 28. A solution of 254 mg (1.00 m mol) of the methyl ester of 28, 256 mg (1.01 m mol) of osumium tetraoxide in 3.9 mL of pyridine was stirred in the dark at room temperature for 67 h. To this solution was added a mixture of 0.46 g of sodium hydrogensulfite ($NaHSO_3$), 7.7 mL of water, and 5.1 mL of pyridine. The resulting solution was stirred for additional 6 h and extracted with chloroform. The organic layer was washed with water, dried (K_2CO_3), and concentrated in vacuo. The residue was chromatographed on silica gel (50 % ether-petroleum ether) to give 181 mg of the corresponding diol (63 %):

IR 3450, 1720, 1220 cm^{-1}; ^1H NMR δ 1.10-1.92 (m, 12H), 1.99 (s, 3H), 2.31 (t, 2H), 3.00 (broad s, 2H), 3.63 (s, 3H), 4.20 (t, 2H); MS m/e 256 (M^+-32).

To a rapidly stirred solution of 113 mg (0.39 m mol) of the above diol in 8 mL of benzene was added 200 mg (0.45 m mol) of lead tetraacetate in 8 mL of benzene. The mixture was stirred for 1 h at room temperature and filtered. The filtrate was dried (K_2CO_3) and concentrated in vacuo to yield a light brown solid. Recrystallization from petroleum ether-acetone gave 83 mg of the corresponding diketone (83 %): mp 57 °C; IR (KBr) 1710, 1690 cm^{-1}; ^1H NMR δ 1.20-1.96 (m, 4H), 1.96 (s, 3H), 2.12-2.72 (m, 10H), 3.61 (s, 3H), 4.22 (t, 2H); MS m/e 226 (M^+-60). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.50; H, 7.76.

A solution of 139 mg (0.49 m mol) of the above diketone and a small amount of hydroquinone in 0.4 mL of ethylene dithioglycol was added dropwise into 0.3 mL of the cooled boron trifluoride etherate. The resulting solution was stirred at room temperature for 34 h. The reaction was quenched by 10 % K_2CO_3 solution and the mixture was extracted with benzene. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield 297 mg of the crude diethylene thioketal (IR 1720, 670 cm^{-1}) which was used directly in the next reaction.

The above thioketal was dissolved in 100 mL of ethanol and heated at reflux for 4 h with about 7 g of Raney nickel (W-4). The mixture was filtered and the filtrate was concentrated in vacuo to yield 61 mg of the mixture of

methyl undecanoate (29) (46 %) and methyl 11-acetoxyundecanoate (30) (8 %). Spectral data and GLC retention times of two products were identical with those of the authentic samples prepared as described below.

Methyl 11-Acetoxyundecanoate (30). To a suspention of 12.0 g (0.061 mol) of methyl undec-10-enoate and 0.69 g (0.020 mol) of sodium borohydride in 30 mL of dry THF was added 3.1 mL (0.024 mol) of boron trifluoride etherate under nitrogen atmosphere. The mixture was stirred at room temperature for 1.5 h and then water, 6.5 mL of 3 N sodium hydroxide solution, and 6.5 mL of 30 % hydrogen peroxide were added successively and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled under reduced pressure to give 9.4 g of methyl 11-hydroxyundecanoate (72 %): bp 131-134 °C (2 mm); IR 3400, 1725, 1230 cm^{-1}.

To an ice-cold solution of 134 mg (0.62 m mol) of the above ester in 0.5 mL of pyridine was added 0.1 mL (3.1 m mol) of acetic anhydride. The resulting solution was stirred at room temperature for 1 day and poured into ice-water and the mixture was extracted with ether. The organic layer was washed successively with dilute HCl, saturated $NaHCO_3$ solution, and brine, and then dried (Na_2SO_4). After removal of the solvent in vacuo, 162 mg of 30 was obtained (quantitative) which was purified by preparative GLC: IR 1725, 1220 cm^{-1}; ^1H NMR δ 1.14-1.86 (m, 16H), 1.96 (s, 3H),

2.21 (t, 2H), 3.60 (s, 3H), 3.96 (t, 2H); MS m/e 237 (M^+-31). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.85; H, 10.24.

Materials. δ-Valero- and ε-caprolactones are commercial samples (Wako Pure Chemical Ind. or Tokyo Kasei) and were purified by distillation before use. Bicyclic δ-lactones 9 and 12 and propellalactones 5-8 and 22-23 were prepared as described above and were purified by silica gel column chromatography or distillation. Water was prepared by distillation of deionized water under nitrogen atmosphere and was used throughout. Commercially available ethanol (Wako, super special grade) was used without further purification.

Kinetic Measurement. Hitachi-Horiba pH meter H-7 SD and Horiba combination electrode # 6326 were used for pH measurement. Water containing 25 % ethanol was used as the solvent to form a homogeneous solution.[38] The second-order rate constants were calculated from the pseudo first-order rate constants and were the average of at the least three runs of the same lactone concentration. The rate measurement were made at three different temperatures in the range of 25.0 °C -41.5 °C[39] and the activation parameters were evaluated from the slope of the least-square Arrhenius plots.

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(5) Thermolysis of the δ-lactone 6 and 12 under similar conditions gave the same results.

(6) In addition, when an acetic acid solution of the γ-lactone 15 was refluxed, the equilibrium mixture of both lactones was also obtained (6 : 11 = 14 : 86) after about 72 h.

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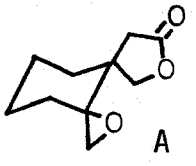
(12) Though 21 consisted of two isomers (A) and (B) they could not be separated completely by GLC or column chromatography; therefore they were characterized as a mixture. Attempt on separation and structure assignment of them is in prosress.



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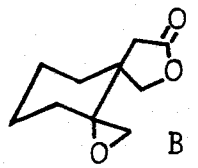

B

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(17) Described in the previous section (1-1-1).

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(31) After 2 h, the monochlorocyclobutanone was obtained as a main product which was purified by preparative GLC: bp 107-108 °C (5 mm); IR 1785, 1635 cm^{-1}; ^1H NMR δ 1.16-2.20 (m, 8H), 2.85 (s, 2H), 4.82 (s, 1H), 4.86 (s, 1H) 4.95 (s, 1H); MS m/e 186 (M^++2), 184 (M^+). Anal. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.10. Found: C, 64.90; H, 7.13.

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(38) In the case of 8, the satisfactory data were not obtained at 25.0 °C and 41.5 °C because the solubility was limited at 25.0 °C and ethanol evaporated at 41.5 °C during the long reaction time. Also, the rate constant of 7 at 25.0 °C did not give reliable data.

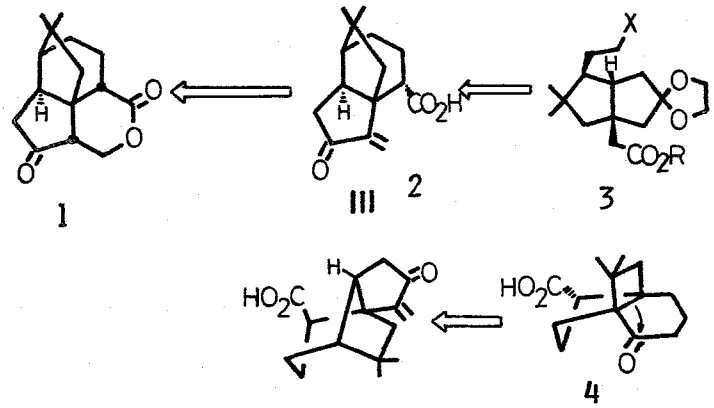
(39) Since 23 was more reactive and rearranged easily to 31 at 32.3 °C and 41.5 °C, the rate could not be measured under the above conditions.

Chapter 2. SYNTHESIS OF NOVEL TRICYCLIC COMPOUNDS BY ACID-CATALYZED REARRANGEMENT OF [m,n,2]-PROPELLANONES

Since quadrone (1) was isolated from a fermentation broth of a strain of Aspergillus terreus and was found to display significant in vitro activity against KB human epidermoid carcinoma of the nasopharynx (ED_{50} 1.3 μg) and in vivo activity against P388 lymphocytic leukemia in mice in 1978 by Ranieri and co-workers,[1] much attention has been paid to the sesquiterpene lactone 1 as an attractive synthetic target because of its biological activities and the intriguing nature of its tetracyclic ring system.[2-5]

However, the structure of quadrone, per se, offers no apparent rationale for its antitumor properties. It is seen on inspection that the α-methylene keto acid 2 having

Scheme 1.



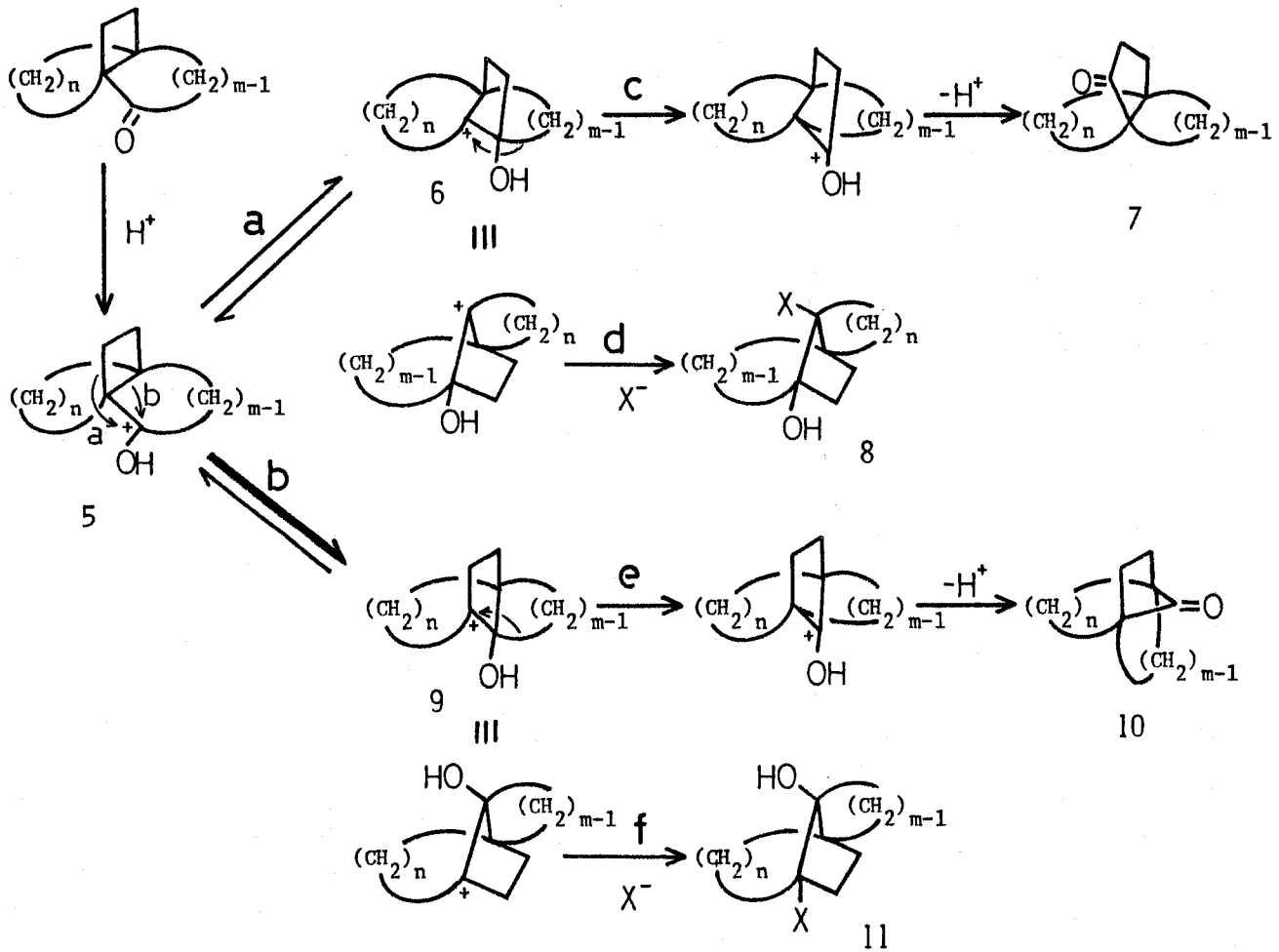
(1S*, 5R*, 6S*)-tricyclo[4.3.2.$0^{1,5}$]undecane skeleton, nominally related to quadrone in a retro-Michael sense, might well be the carrier of biological activities.[2c]

On such grounds, as well as an obvious retrosynthetic methodology, compound 2 has been regarded as an attractive subgoal, and the total synthesis of quadrone *via* 2 was accomplished very recently by two groups, Danishefsky[2] and Helquist[3] and their colleagues. However, the key compound 2 was obtained by multiple-step reactions with careful regio- and stereochemical control, for example, by the intramolecular cyclization of iodo ester such as 3 having *cis*-bicyclo-[3.3.0]octane skeleton (Scheme 1). Therefore, a new synthetic route to the compoumd 2, such as a novel rearrangement approach from a [4.3.2]propellanone derivative 4 by the 1,2-alkyl shift of the central propellane bond, emerges.

In this chapter, in order to obtain the basic information about this skeletal rearrangement utilized for the synthesis of quadrone and related compounds, the acid-catalyzed rearrangement of [m.n.2]propellanones to novel tricyclic compounds is described. Furthermore, the factors governing the migratory modes or the reactivity associated with the constituent ring size of propellanones are presented.

In general, two migratory modes are available for the acid-catalyzed rearrangement of [m.n.2]propellanones ($m \geq 3$, $n \geq 2$) containing a cyclobutane ring as shown in Scheme 2. One is well-known 1,2-alkyl shift of the external cyclobutane bond to afford the cation 6 (path a). The cation 6 under-

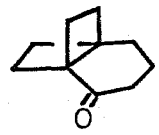
Scheme 2.



goes another 1,2-alkyl shift to give [m-1.n.$\bar{3}$]propellanone[6] (7) (path c)[7] or may be trapped by a nucleophile to furnish the tricyclic alcohol 8 (path d).[8] The other is rare but significant 1,2-alkyl shift of the central propellane bond (path b) giving [m-1.n.2.1]paddlanone (10) by further 1,2-shift (path e) or the desired tricyclic alcohol 11 by trapping with a nucleophile (path f). There are ample precedents of the former mode of migration (path a), especially, in the acid-catalyzed rearrangement of [4.$\bar{3}$.2]-, [$\bar{4}$.3.2]- and [$\bar{4}$.4.2]propellanone derivatives in nonnucleophilic media, which was extensively studied by Cargill and coworkers,[7a-c] and was utilized for the total synthesis of modhephene by Smith and Jerris.[7d] On the other hand, until recently, the latter mode of migration (path b) had been unknown. Eaton and collaborators presented, very recently, an example of this mode in the acid-catalyzed rearrangement of highly strained [$\bar{4}$.2.2]propellanone (12)[9] in the presence of a variety of nucleophiles. The above findings suggest that the migratory modes of [m.n.2]propellanones may be greatly affected by the constituent ring size of the propellanones as well as reaction conditions (in the presence or absence of a nucleophile).

Hence, the acid-catalyzed rearrangement of [m.n.2]-propellanones (13)-(18) is investigated systematically, in order to elucidate the generality of the novel rearrangement (path b) affording the interesting tricyclic ring systems related to quadrone and related compounds. Since the propellanones 13-18 are constituted of a cyclobutane, a five-

to seven-membered cycloalkanone, and a five- to seven-membered cycloalkane moiety (the third ring), the effect of the ring size of both cycloalkanone and cycloalkane (the third ring) moieties on the migratory modes will be clarified.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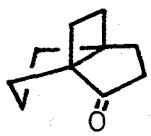
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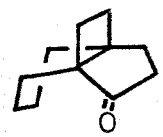
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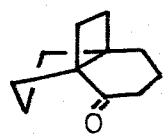
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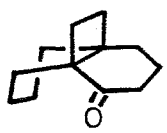
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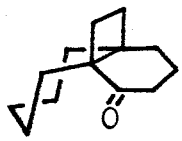
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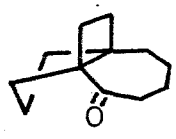
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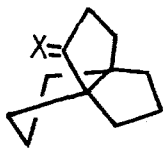
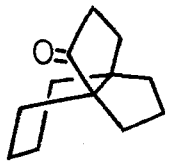
Results

Firstly, for the purpose of elucidation of the third ring size effect, the acid-catalyzed reactions of the cyclohexanone derivatives, having a five-, six-, and seven-membered ring as the third ring, [$\overline{4}$.3.2]propellanone (15),[10] [$\overline{4}$.4.2]propellanone (16),[11] and [5.$\overline{4}$.2]propellanone (17),[12] were carried out. Treatment of 15 or 16 with TsOH in benzene at reflux gave [$\overline{3}$.3.3]propellanone (19a) or [4.$\overline{3}$.3]-propellanone (20) as a sole product (80 % or 90 %) in accord with the result of Cargill et al..[11] Moreover, treatment

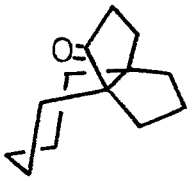
of 17 under similar conditions gave [5.$\overline{3}$.3]propellanone (21) quantitatively (99 %). The structual assignment of 19a, 20, and 21 was based on the spectroscopic data, particularly, the carbonyl absorption in the IR spectra appeared at 1730-1735 cm^{-1} due to cyclopentanone. Specifically, the structure of 19a was confirmed by the ^{13}C NMR spectra (δ 60.44 (s), 40.35 (t), 24.62 (t))[13] of the hydrocarbon 19b derived by the Wolff-Kishner reduction of 19a. Thus, it is obvious that the rearrangement of the propellanones 15-17 in non-nucleophilic media takes place via 1,2-alkyl shift of the external bond (path a) followed by another Wagner-Meerwein shift and the subsequent deprotonation (path c) to afford [m.3.3]propellanones (m=3-5) 19a, 20, and 21 regardless of the ring size of the third ring.



19a X = O
19b X = H_2



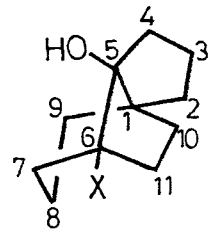
20



21

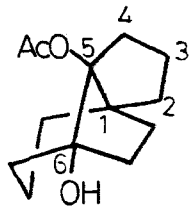
On the other hand, in the presence of a nucleophile, the propellanones 15-17 behave in a quite different way depending on the ring size of the third ring. The reaction of [$\overline{4}$.3.2]propellanone (15) with sulfuric acid (H_2SO_4) in aqueous THF afforded (1S*, 5R*, 6S*)-tricyclo[4.3.2.$0^{1,5}$]un-

decane-5,6-diol (22a) in 83 % yield along with a trace amount of [3.3.3]propellanone (19a). Similarly, treatment of 15 with TsOH in acetic acid gave the hydroxy acetate 22b (68 %) together with 19a (15 %). The structures of 22a and 22b were elucidated on the basis of the spectroscopic data and were confirmed by the following chemical transformations.



22a X = OH

22b X = OAc

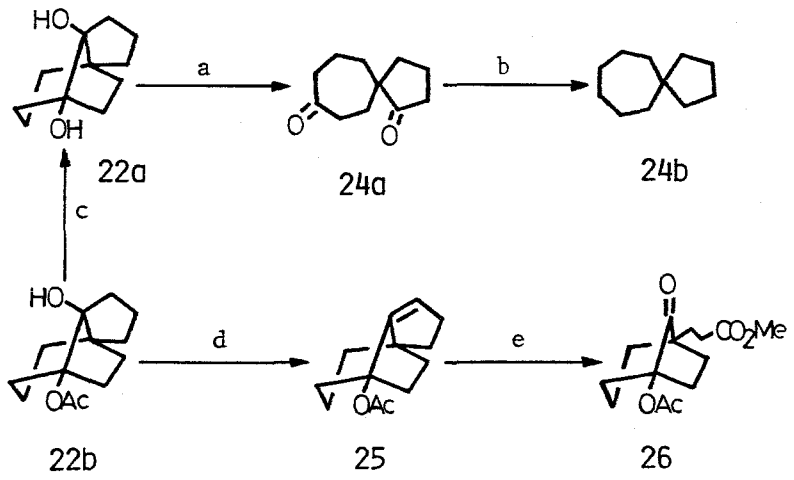


23

Lead tetraacetate oxidation of the diol 22a to spiro[4.6]-undecane-1,8-dione (24a) and the subsequent thioketal reduction of 24a gave spiro[4.6]undecane (24b) which was entirely identical with the authentic sample prepared independently. Since $LiAlH_4$ reduction of the hydroxy acetate 22b afforded the diol 22a, the gross structure, i.e., 5,6-disubstituted tricyclo[4.3.2.$0^{1,5}$]undecane, of 22a and 22b was established. In order to differentiate the position of the acetoxyl functionality (22b or 23), 22b was subjected to dehydration with thionyl chloride-pyridine followed by the oxidative degradations ((i) oxidation of the olefin 25

with osmium tetraoxide, (ii) oxidative cleavage of the vicinal diol by lead tetraacetate, (iii) oxidation with bromine-water, and (iv) treatment with ethereal diazomethane) as shown in Scheme 3. From the fact that the obtainable keto ester 26 showed an IR absorption at 1760 cm^{-1} being characteristic of bicyclo[3.2.1]octan-8-one,[14] it is deduced that the acetoxyl group is located at C-6 (22b) not at C-5 (23). Finally, (1S*, 5R*, 6S*) stereochemistry of 22a and 22b was presumed on the basis of the greater thermodynamic stability (5~6 kcal/mol) of (1S*, 5R*, 6S*)-tricyclo-[4.3.2.$0^{1,5}$]undecane than that of (1S*, 5S*, 6S*) isomer.[15] It is, therefore, deduced that the formation of 22a and 22b

Scheme 3.

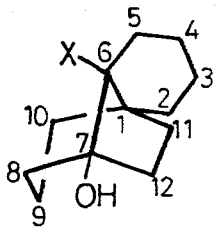


a. $Pb(OAc)_4$, 72 %; b. (i) $HS(CH_2)_2SH$, (ii) Raney-Ni, 31 %; c. $LiAlH_4$, quantit.; d. $SOCl_2$/Pyridine, 83 %; e. (i) OsO_4, (ii) $Pb(OAc)_4$, (iii) Br_2/H_2O, (iv) CH_2N_2, 89 %.

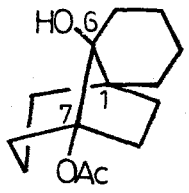
involves novel 1,2-alkyl shift of the central bond (path b) followed by the attack of the nucleophile to the bridgehead cation 9 (path f).[16]

Treatment of [$\bar{4}$.4.2]propellanone (16) with H_2SO_4 in aqueous THF furnished [4.$\bar{3}$.3]propellanone (20) as the major product (71 %) along with a small amount (9 %) of (1S*, 6R*, 7S*)-tricyclo[5.3.2.$0^{1,6}$]dodecane-6,7-diol (27a) and a trace amount of two unidentified products A and B. Similarly, reaction of 16 with TsOH in acetic acid afforded 20 (61 %) mainly together with the hydroxy acetate 27b (6 %) and the unidentified A and B (~20 %).[17] The structure of the diol 27a was established by the identity with the diol obtained from the acid-catalyzed rearrangement of [$\bar{5}$.3.2]-propellanone (18) with H_2SO_4 in aqueous THF (vide infra). Since the hydroxy acetate 27b gave the diol 27a by $LiAlH_4$ reduction but was distinct from the 6-hydroxy-7-acetate 28 derived by treatment of 18 with TsOH in acetic acid (vide infra), the structure of 27b was revealed to be 7-hydroxy-tricyclo[5.3.2.$0^{1,6}$]dodecan-6-yl acetate. The stereochemistry of C-6 in 27a and 27b is assumed to be 1S*, 6R*, 7S* on the basis of mechanistic considerations, i.e., back side attack of a nucleophile to the developing p orbital.[7c] It is evident that 27a and 27b as well as 20 are formed through 1,2-alkyl shift of the external cyclobutane bond (path a). Moreover, even in the presence of a nucleophile, [5.$\bar{4}$.2]propellanone (17) afforded only [5.$\bar{3}$.3]propellanone (21) (72 % with H_2SO_4 in aqueous THF and 94 % with TsOH in acetic acid), which is also formed via path a $\longrightarrow$ c, without

any formation of diol or hydroxy acetate corresponding 22a, b, 23, 27a, b, and 28.



27a X = OH
27b X = OAc



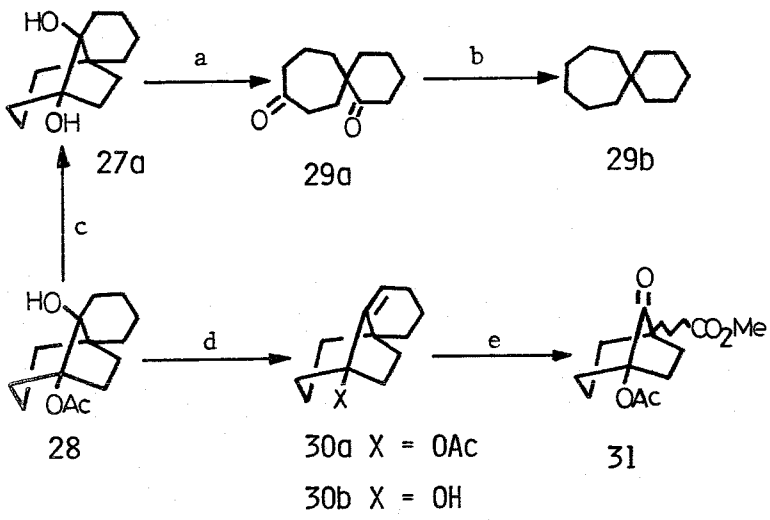
28

Next, in order to clarify the ring size effect of cycloalkanone moiety, the acid-catalyzed reactions of the cyclopentanone derivatives, [$\bar{3}$.3.2]propellanone (13)[18] and [4.$\bar{3}$.2]propellanone (14)[19], and the cycloheptanone derivative, [$\bar{5}$.3.2]propellanone (18)[20], having a five- or six-membered ring as the third ring, were examined. It was found, unfortunately, that the acid-catalyzed rearrangement of the propellanones 13 and 14 having a cyclopentanone moiety did not take place in the presence of a nucleophile (H_2O-H_2SO_4-THF), despite the fact that the corresponding tosylates readily undergo rearrangement of the external bond in the buffered solvolyses.[8]

On the contrary, the rearrangement of [$\bar{5}$.3.2]propellanone (18) occurs very smoothly. In the absence of a nucleophile (TsOH in boiling benzene), [4.$\bar{3}$.3]propellanone (20)

formed by 1,2-alkyl shift of the external bond (path a ⟶ path c) was obtained as a sole volatile product (21 % yield). Reaction of 18 with H_2SO_4 in aqueous THF, however, afforded (1S*, 6R*, 7S*)-tricyclo[5.3.2.$0^{1,6}$]dodecane-6,7-diol (27a) as the major product (88 %) along with a trace amount of 20. Moreover, treatment of 18 with TsOH in acetic acid gave 6-hydroxy-(1S*, 6R*, 7S*)-tricyclo[5.3.2.$0^{1,6}$]dodecan-7-yl acetate (28) predominantly (80 %) together with a small amount (2 %) of 20. The structures of 27a and 28 were confirmed by the way similar to that for 22a and 22b (Scheme 4). Lead tetraacetate oxidation of the diol 27a followed

Scheme 4.



a. $Pb(OAc)_4$, 76 %; b. (i) $HS(CH_2)_2SH$, (ii) Raney-Ni, 47 %; c. $LiAlH_4$, quantit.; d. $SOCl_2$/Pyridine, 72 %; e. (i) OsO_4, (ii) $Pb(OAc)_4$, (iii) Br_2/H_2O, (iv) CH_2N_2, 62 %.

by thioketal reduction of the dione 29a gave spiro[5.6]-dodecane (29b) which was identical with the authentic material prepared independently.[21] Since $LiAlH_4$ reduction of the hydroxy acetate 28 gave the diol 27a, which was identified with the diol obtained by the acid-catalyzed rearrangement of [$\overline{4}$.4.2]propellanone (16) in H_2SO_4-aqueous THF (vide supra), 6,7-disubstituted (1S*, 6R*, 7S*)-tricyclo[5.3.2.$0^{1,6}$]dodecane skeleton of 27a and 28 was established. Moreover, from the fact that the dehydration of the hydroxy acetate 28 and the subsequent oxidative degradation of the olefin 30a (Scheme 4) furnished the keto ester 31 having bicyclo[3.2.1]octan-8-one skeleton (IR 1760 cm^{-1}), it is indicated that the acetoxyl functionality of 28 is located at C-7. The above results clearly indicate that the formation of 27a and 28 involves novel 1,2-alkyl shift of the central bond (path b) followed by the attack of a nucleophile (path f) in analogy with the case of [$\overline{4}$.3.2]propellanone (15).

The results on the acid-catalyzed rearrangement of the propellanones 13-18 as well as that of [$\overline{4}$.2.2]propellanone (12) are summarized in Table 1.

Discussion

As shown in Table 1 (entries 3-6), the ring size of the third ring critically affects the migratory modes of the acid-catalyzed rearrangement of [m.n.2]propellanones. Namely, in the cases of [$\overline{4}$.2.2]- and [$\overline{4}$.3.2]propellanones (12) and (15), having a cyclobutane or cyclopentane ring as

Table 1. Acid-Catalyzed Rearrangement of [m.n.2]Propellanones.

entry	[m.n.2]propellanone			nucleophile	product (%)				
	compd	ring size of cycloalkanone	ring size of the third ring		external bond shift		central bond shift		unidentified
					path c	path d	path e	path f	
1	[$\bar{3}$.3.2] 13	5	5	H_2O[a]	—	—	—	—	—
2	[4.$\bar{3}$.2] 14	5	6	H_2O[a]	—	—	—	—	—
3	[4.2.2][b] 12	6	4	none[a]	—	—	—	—	—
				H_2O	—	—	—	100	—
4	[$\bar{4}$.3.2] 15	6	5	none	80	—	—	—	—
				H_2O	trace	—	—	83	—
				AcOH	15	—	—	68	—
5	[$\bar{4}$.4.2] 16	6	6	none[c]	90	—	—	—	—
				H_2O	71	9	—	—	trace
				AcOH	61	6	—	—	~ 20

Table 1. *(Continued)*

entry	[m.n.2]propellanone compd	ring size of cycloalkanone	ring size of the third ring	nucleophile	product (%) external bond shift path c	external bond shift path d	central bond shift path e	central bond shift path f	unidentified
6	[5.$\bar{4}$.2] 17	6	7	none	99	—	—	—	—
				H_2O	72	—	—	—	—
				AcOH	94	—	—	—	—
7	[$\bar{5}$.3.2] 18	7	5	none	21	—	—	—	—
				H_2O	trace	—	—	88	—
				AcOH	2	—	—	80	—

[a] No reaction. [b] Reference 9. [c] See also reference 11.

the third ring, the novel central bond shift (path b) occurs predominantly in the presence of a nucleophile. On the other hand, in the cases of [$\bar{4}$.4.2]- and [5.$\bar{4}$.2]propellanones (16) and (17), having a cyclohexane or cyclopentane ring as the third ring, only the products derived from the external bond shift (path a) were obtained. It is, therefore, deduced that the migratory modes of the acid-catalyzed rearrangement of [m.n.2]propellanones may depend on the strain of the central propellane bond. In the case of highly strained propellanone 12 and moderately strained one 15, the migration of the central bond may be kinetically more favored than that of the external bond, because it is well-known that the central bond of highly strained small ring propellanes have extensive p orbital character[22] and consequently, the participation of the central bond to the adjacent carbonium ion center is expected.[22a,23] In the absence of a nucleophile, however, 15 gave [$\bar{3}$.3.3]propellanone (19a) *via* path a $\longrightarrow$ path c under thermodynamic control, since the formation of a paddlanone 10 is unlikely.

It is noted that, in contrast to 12 and 15, 16 gives only a small amount of the products 27a and 27b formed by the trap with the nucleophile (path d) and that 17 does none of such products even in the presence of a nucleophile. The above fact suggests that the second Wagner-Meerwein shift (path c) in the cation intermediate 6 is faster than the attack by a nucleophile (path d). Though the real reason is not clear at present, it will be reasonable to consider that the thermodynamic stabilities of two kinds of

products, the propellanones 7 (m=4, n=3-5) and the tricyclic compounds 8, may at least contribute to the above difference in the product distribution.[24]

From the results in Table 1 (entries 1, 2, 4, 5, and 7), it is demonstrated that the ring size of the cycloalkanone moiety greatly affects the reactivity of the [m.n.2]-propellanones toward acid-catalyzed rearrangement. While, in the case of the cyclopentanone derivatives 13 and 14, the acid-catalyzed rearrangement was not observed regardless of the ring size of the third ring, the cyclohexanone derivatives 15 and 16 underwent rearrangement quite readily. Moreover, since the reaction time required for consumption of the cycloheptanone derivative 18 was much shorter than that of the corresponding cyclohexanone derivative 15 (see Experimental Section), it is indicated that the rearrangement of 18 takes place more easily than that of 15. It has been pointed out by Fetizon et al. that the dihedral angle between the carbonyl axis and the migratory bond is an important factor governing the reactivity in the acid-catalyzed rearrangement of cyclobutylcarbinyl ketones.[25] It is, therefore, infered that the ring size effect of the cycloalkanone moiety may be attributed to the conformational flexibility of this moiety which is desirable for achievement of the maximum interaction of p orbital of the cycloalkyl cation with the central or external cyclobutane bond. Thus, while the cyclohexanone and cycloheptanone derivatives 15, 16, and 18 undergo the rearrangement readily because of flexibility of the cycloalkanone moiety, 13 and 14 may be

unreactive owing to the rigidity of the cyclopentanone moiety.

In conclusion, the two factors governing critically the reactivity and selectivity in the acid-catalyzed rearrangemnt of the [m.n.2]propellanones are found out. One is the ring size effect of the cycloalkane moiety (the third ring) which governs the migratory modes of the rearrangement, and the other is the ring size effect of the cycloalkanone moiety which affects the reactivity toward the rearrangement.

Finally, it should be pointed out that the present rearrangement of the propellanones such as 15 and 18, which are readily available by the photocycloaddition of bicyclic α,β-unsaturated ketones to ethylene, offers an efficient route to the synthesis of the novel tricyclic ring systems related to the tumor inhibitor quadrone (1). The total synthesis of 1 as well as the synthesis of the related compounds by use of the present rearrangement approach are now being undertaken.

EXPERIMENTAL

Materials. [$\bar{3}$.3.2]Propellanone (13),[18] [4.$\bar{3}$.2]propellanone (14),[19] [$\bar{4}$.3.2]propellanone (15),[26] [$\bar{4}$.4.2]propellanone (16),[26] and [$\bar{5}$.3.2]propellanone (18)[20] were prepared as described previously. [5.$\bar{4}$.2]Propellanone (17) was prepared by the ring enlargement of [5.$\bar{3}$.2]propellanone[18]

according to our previous method for the preparation of 16 ((i) preparation of trimethylsilyl enol ether of the ketone (90 %), (ii) cyclopropanation of the enol ether by the Furukawa method (59 %), (iii) oxidative cleavage of the siloxycyclopropane with iron (III) chloride (63 %), and (iv) catalytic hydrogenation of [5.$\bar{4}$.2]propellaenone (92 %)). 17: IR 1690 cm^{-1}; MS m/e (relative intensity) 192 (M^+, 25), 164 (100); ^1H NMR δ 0.90-2.60 (m). Semicarbazone, mp 225-227 °C. Anal. Calcd for $C_{14}H_{23}ON_3$: C, 67.44; H, 9.23; N, 16.86. Found: C, 67.43; H, 9.30; N, 16.85.

General Procedure of Acid-Catalyzed Reaction of Propellanones 13-18. In Nonnucleophilic Media. A solution of the ketone and a equal or small excess amount of p-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$) in benzene was heated at reflux. Progress of the reaction was monitored by GLC. The cooled reaction solution was washed with saturated $NaHCO_3$ solution and the aqueous solution was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate ($MgSO_4$), and concentrated in vacuo to leave the crude product.

In Nucleophilic Media. A. A solution of 500 mg of the ketone, 0.5 mL of concentrated H_2SO_4, and 0.5 mL of water in 5 mL of THF was heated at 50 °C unless otherwise stated. Progress of the reaction was monitored by GLC. After evaporation of THF in vacuo, the reaction mixture was diluted with water and was extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and concentrated

in vacuo to leave the crude products. B. A solution of 500 mg of the ketone and a catalytic amount of $TsOH \cdot H_2O$ in 10 mL of acetic acid was heated at 50 °C. Progress of the reaction was monitored by GLC. The cooled reaction solution was neutralized with saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo to leave the crude products. The products were separated by column chromatography on silica gel and purified by preparative GLC.

[$\bar{3}$.3.3]Propellanone (19a).[13a] The reaction of 239 mg (1.46 m mol) of 15 and $TsOH \cdot H_2O$ (264 mg) in 10 mL of benzene for 2 h gave 192 mg of 19a (80 %): mp 54-55 °C; IR (KBr) 1735 cm^{-1}; MS m/e (relative intensity) 164 (M^+, 58), 136 (61), 108 (89), 107 (100), 80 (92), 79 (80); ^1H NMR δ 1.12-2.00 (m, 14H), 2.23 (t, 2H).

[4.$\bar{3}$.3]Propellanone (20).[11] The reaction of 290 mg (1.63 m mol) of 16 and $TsOH \cdot H_2O$ (571 mg) in 20 mL of benzene for 1 h gave 262 mg of 20 (90 %): IR (KBr) 1735 cm^{-1}; MS m/e (relative intensity) 178 (M^+, 84), 136 (57), 123 (69), 122 (90), 121 (100), 79 (58). The reaction of 1.08 g (6.08 m mol) of 18 and $TsOH \cdot H_2O$ (1.14 g) in 50 mL of benzene for 4 h gave 225 mg of 20 (21 %) as a sole volatile product along with polymeric materials.

[5.$\bar{3}$.3]Propellanone (21). The reaction of 157 mg (0.82 m mol) of 17 and $TsOH \cdot H_2O$ (181 mg) in 25 mL of benzene for 2 h

gave 155 mg of 21 (99 %): IR 1730 cm^{-1}; MS m/e (relative intensity) 192 (M^+, 33), 135 (57), 123 (100), 104 (35); ^1H NMR δ 0.92-2.04 (m, 18H), 2.24 (t, 2H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.85; H, 10.48. The reaction of 97 mg (0.51 m mol) or 224 mg (1.17 m mol) of 17 by the method A or B for 12-24 h gave 70 mg (72 %) or 211 mg (94 %) of 21.

(1S*, 5R*, 6S*)-Tricyclo[4.3.2.$0^{1,5}$]undecane-5,6-diol (22a). The reaction of 965 mg (5.88 m mol) of 15 by the method A for 96 h gave a trace amount of 9 and 727 mg of the diol 22a (83 %): mp 120-122 °C; IR (KBr) 3380, 1150, 1090 cm^{-1}; MS m/e (relative intensity) 182 (M^+, 34), 164 (56), 97 (100); ^1H NMR δ 1.12-2.48 (m); ^{13}C NMR δ 87.87 (s), 81.09 (s), 52.03 (s), 34.52 (t), 34.13 (t), 33.77 (t), 31.82 (t), 29.87 (t), 28.96 (t), 20.46 (t), 19.87 (t). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.13; H, 9.92.

5-Hydroxy-(1S*, 5R*, 6S*)-tricyclo[4.3.2.$0^{1,5}$]undecan-6-yl Acetate (22b). The reaction of 397 mg (2.42 m mol) of 15 by the method B for 144 h gave 60 mg of 19a (15 %) and 364 mg of the hydroxy acetate 22b (68 %): IR 3450, 1735, 1710,[27] 1280, 1250 cm^{-1}; MS m/e (relative intensity) 224 (M^+, trace), 164 (98), 136 (100), 118 (58); ^1H NMR δ 1.06-2.16 (m, 18H contains s at 1.96), 2.28-2.60 (m, 1H), 4.08 (s, 1H); ^{13}C NMR δ 172.22 (s), 92.81 (s), 85.96 (s), 53.82 (s), 34.54 (t), 34.25 (t), 31.90 (t), 30.14 (t), 29.26 (t), 21.87 (q), 20.65 (t), 20.30 (t). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.68; H, 9.28.

(1S*, 6R*, 7S*)-Tricyclo[5.3.2.0^{1,6}]dodecane-6,7-diol (27a). The reaction of 527 mg (2.96 m mol) of 18 by the method A at room temperature for 20 h gave a trace amount of 20 and 510 mg of the diol 27a (88 %): mp 85-86 °C; IR (KBr) 3330, 1180, 1115 cm^{-1}; MS m/e (relative intensity) 196 (M^+, 56), 178 (100, M^+-H_2O), 149 (45), 109 (76); ^{1}H NMR δ 0.72-2.28 (m, 18H), 2.39 (s, 2H); ^{13}C NMR δ 80.90 (s), 77.90 (s), 42.74 (s), 34.21 (t), 34.04 (t), 31.77 (t), 30.92 (t), 29.18 (t), 25.80 (t), 21.43 (t), 21.02, 19.16. Anal. Calcd for $C_{12}H_{18}O_2$: C, 73.43; H, 10.17. Found: C, 73.39; H, 10.35. The reaction of 231 mg (1.30 m mol) of 16 by the method A gave 164 mg of 20 (71 %), unidentified products A and B (<1 %), and 22 mg of the diol 27a (9 %).

7-Hydroxy-(1S*, 6R*, 7S*)-tricyclo[5.3.2.0^{1,6}]dodecan-6-yl Acetate (27b). The reaction of 226 mg (1.27 m mol) of 16 by the method B for 48 h gave 137 mg of 20 (61 %), the two unidentified products A (17 %) and B (~3 %), and 18 mg of the hydroxy acetate 27b (6 %): mp 96-97 °C; IR (KBr) 3450, 1710,[27] 1290, 1255 cm^{-1}; MS m/e (relative intensity) 238 (M^+, 7), 178 (100, M^+-AcOH), 149 (39), 136 (49); ^{1}H NMR δ 0.80-2.56 (m, 21H contains s at 2.08), 4.37 (s, 1H). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.51; H, 9.28.

Unidentified Product A.[18]: IR 3400, 3030, 1060 cm^{-1}; MS m/e (relative intensity) 178 (M^+, 60), 149 (100), 135 (33), 107 (34); ^{1}H NMR δ 0.92-2.80 (m, 17H), 4.96 (t, 1H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.49; H,

10.31.

6-Hydroxy-(1S*, 6R*, 7S*)-tricyclo[5.3.2.$0^{1,6}$]dodecan-7-yl Acetate (28). The reaction of 825 mg (4.63 m mol) of 18 by the method B for 15 h gave 17 mg of 20 (2 %) and 880 mg of the hydroxy acetate 28 (80 %): IR 3450, 1735, 1710,[27] 1280, 1260 cm^{-1}; MS m/e (relative intensity) 238 (M^+, 9), 178 (100, M^+-AcOH), 149 (72); ^1H NMR δ 0.68-1.86 (m, 17H), 1.94 (s, 3H), 2.40-2.60 (m, 1H), 3.88 (s, 1H); ^{13}C NMR δ 172.41 (s), 93.59 (s), 76.72 (s), 44.33 (s), 34.00 (t), 31.70 (t), 30.73 (t), 29.84 (t, 2C), 25.98 (t), 21.72 (q) 21.23 (t), 20.65 (t), 19.47 (t). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.75; H, 9.48.

Attempted Acid-Catalyzed Rearrangement of [$\bar{3}$.3.2]Propellanone (13) and [4.$\bar{3}$.2]Propellanone (14). The reaction of 666 mg (4.44 m mol) of 13 by the method A for 180 h gave only polymeric materials and about 200 mg (30 %) of 13 was recovered.

The reaction of 705 mg (4.30 m mol) of 14 by the method A for 195 h gave only polymeric materials and about 200 mg (30 %) of 14 was recovered.

Lithium Aluminum Hydride Reduction of 22b to 22a. To a stirred suspension of 38 mg (1.00 m mol) of $LiAlH_4$ in 7 mL of dry ether was added dropwise a solution of 186 mg (0.83 m mol) of 22b in 7 mL of dry ether and the mixture was stirred at room temperature for 1 h. Water was added carefully and 10 % HCl was subsequently added to dissolve the

white precipitate. The organic layer was separated and the aqueous solution was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution, brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give 151 mg of a diol (quantitative) which was purified by preparative GLC. Melting point, IR spectra, and GLC retention time of the diol were identical with those of *22a*.

Lithium Aluminum Hydride Reduction of 27b to 27a. $LiAlH_4$ reduction of 87 mg (0.37 m mol) of *27b* was carried out as described above to give 70 mg of a diol (98 %) whose melting point, IR and Mass spectra, and GLC retention time were identical with those of *27a*.

Lithium Aluminum Hydride Reduction of 28 to 27a. 87 mg (0.37 m mol) of *28* was reduced by $LiAlH_4$ as described above to afford 72 mg of a diol (quantitative) whose melting point, IR spectra, and GLC retention time were identical with those of *27a*.

[3.3.3]Propellane (19b). A solution of 624 mg (3.80 m mol) of *19a*, 0.8 g of KOH, and 0.7 mL of 80 % hydrazine hydrate in 7 mL of diethylene glycol was refluxed at 150 °C for 3 h. Excess hydrazine was distilled off and the mixture was heated at 210 °C for 4 h. The cooled reaction mixture was neutralized with 5 % HCl and the mixture was extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). After evaporation of the solvent *in vacuo*, the crude product was chromatographed on silica gel to give

200 mg of 19b (35 %): mp 110-112 °C (lit.[13b] 116-117 °C); IR 2930, 2850, 1460, 1440 cm^{-1}; MS m/e (relative intensity) 150 (M^+, 60), 107 (100), 79 (30); ^{13}C NMR δ 60.44 (s, 2C), 40.35 (t, 6C), 24.62 (t, 3C).

Oxidative Degradation of 22a to Spiro[4.6]undecane (24b). To a rapidly stirred solution of 640 mg (3.51 m mol) of 22a in 60 mL of benzene was added a solution of 1.87 mg (4.22 m mol) of lead tetraacetate in 60 mL of benzene. The mixture was stirred at room temperature for 1 h and filtered. The filtrate was dried (K_2CO_3) and concentrated in vacuo followed by column chromatography on silica gel to yield 457 mg of spiro[4.6]undecane-1,8-dione (24a) (IR 1730, 1695 cm^{-1}).

A solution of the above diketone and a small amount of hydroquinone in 2.1 mL of ethylene dithioglycol was added dropwise into 1.5 mL of boron trifluoride etherate cooled in an ice bath. The resulting solution was stirred at room temperature for 69 h. The reaction was quenched by 10 % K_2CO_3 solution and the mixture was extracted with benzene. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield the crude diethylene thioketal (IR 1450, 1420, 1270, 1200 cm^{-1}).

The above thioketal was dissolved in 100 mL of ethanol and refluxed for 4 h with about 15 g of Raney nickel (W-4). The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to yield the crude hydrocarbon 24b. Chromatography on silica gel afforded 163

mg of 24b (22 % from 22a): IR 2920, 2850, 1455 cm^{-1}; MS m/e (relative intensity) 152 (M^+, 32), 96 (73), 95 (83), 82 (100), 67 (88); ^1H NMR δ 1.16-1.80 (m); ^{13}C NMR δ 46.08 (s), 41.33 (t, 2C), 40.45 (t, 2C), 29.89 (t, 2C), 24.53 (t, 2C), 24.38 (t, 2C). Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.57; H, 13.14.

Preparation of an Authentic Sample of 24b. Spiro[4.6]-undecan-6-one was prepared by the literature method.[28] The Wolff-Kishner reduction of 3.03 g (18.2 m mol) of the ketone was carried out as described for 19b to give 1.74 g of the hydrocarbon (63 %) which was identical (IR, MS, ^{13}C NMR) with 24b obtained by the degradation of 22a.

Oxidative Degradation of 22b to the Keto Ester 26. To a solution of 675 mg (3.01 m mol) of 22b in 1.4 mL of pyridine and 5 mL of CH_2Cl_2 cooled at 0 °C was added dropwise 0.33 mL (4.52 m mol) of thionyl chloride via a syringe. The resulting solution was stirred at 0 °C for 30 min and then at room temperature for 4 h. The reaction was quenched by ice-water and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel to give 513 mg of tricyclo[4.3.2.$0^{1,5}$]undec-4-en-6-yl acetate (25) (83 %): IR 3060, 1740, 1250 cm^{-1}; MS m/e (relative intensity) 206 (M^+, 28), 146 (76), 136 (100), 135 (91); ^1H NMR δ 1.20-2.12 (m, 13H contains s at 1.96), 2.16-2.76 (m, 4H), 5.04 (t, 1H); ^{13}C NMR δ 169.97 (s), 154.83 (s), 110.91 (d), 83.69 (s), 55.68 (s), 38.07 (t), 36.06 (t),

35.87 (t), 35.48, 33.53 (t), 21.77 (q), 21.25 (t). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.81; H, 9.18.

A solution of 73 mg (0.36 m mol) of 25 and 103 mg (0.40 m mol) of osmium tetraoxide in 2.4 mL of pyridine was stirred in the dark at room temperature for 44 h. To the resulting brown solution was added a solution of 148 mg (1.44 m mol) of $NaHSO_3$ in 3.6 mL of water and 1.8 mL of pyridine, and the mixture was stirred for 18 h and extracted with chloroform. The organic layer was washed with 1N HCl, water, and dried (K_2CO_3). Evaporation of the solvent in vacuo gave the diol (IR 3450, 1735, 1710,[27] 1280, 1080 cm^{-1}).

The crude diol was oxidized by lead tetraacetate as described for the oxidation of 22a to give the crude keto aldehyde (IR 1760, 1735, 1710, 1240 cm^{-1}).

To the above aldehyde was added a large excess of saturated bromine-water and the mixture was stirred at room temperature for 30 min. $NaHSO_3$ solution was added and the mixture was extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave the keto acid which showed carbonyl absorptions at 1760, 1735, 1710 cm^{-1}.

The crude keto acid was treated with ethereal diazomethane to give the keto ester 26 (89 % from 25) which was purified by preparative GLC: IR 1760, 1735, 1720, 1240, 1050 cm^{-1}; MS m/e (relative intensity) 268 (M^+, 17), 208 (38), 170 (53), 125 (51), 43 (100); ^1H NMR δ 0.80-2.56 (m, 17H contains s at 2.00), 3.57 (s, 3H). Anal. Calcd for

$C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.59; H, 7.55.

Oxidative Degradation of 27a to Spiro[5.6]dodecane (29b). The degradation of 27a to 29b was carried out as described for 22a. Lead tetraacetate oxidation of 1.00 g (5.10 m mol) of 27a gave 751 mg of spiro[5.6]dodecane-1,9-dione (29a) (76 %: IR 1710, 1690, 1125 cm^{-1}). The subsequent thioketal reduction of 326 mg (1.68 m mol) of 29a afforded 130 mg of the spiro hydrocarbon 29b (47 %): IR 2920, 2850, 1425 cm^{-1}; MS m/e (relative intensity) 166 (M^+, 56), 96 (100), 81 (71), 67 (66); ^{13}C NMR δ 39.72 (t, 2C), 38.79 (t, 2C), 35.58 (s), 30.82 (t, 2C), 26.70 (t), 22.75 (t, 2C), 22.09 (t, 2C).

Preparation of an Authentic Sample of 29b. The authentic sample of 29b was prepared by the literature method.[29] Condensation of 20 g (0.18 mol) of cycloheptanone with 1,5-dibromopentane gave 12.5 g of spiro[5.6]dodecan-7-one (39 %; IR 1690 cm^{-1}). The Wolff-Kishner reduction of 5.0 g (27.8 m mol) of the above ketone afforded 1.8 g of the spiro hydrocarbon (39 %) which was identical (IR, MS, ^{13}C NMR) with 29b obtained by the degradation of 27a.

Oxidative Degradation of 28 to the Keto Ester 31. The degradation of 28 was carried out in a manner similar to that of 22b.

Dehydration of 640 mg (3.51 m mol) of 28 with thionyl chloride-pyridine gave 457 mg of tricyclo[5.3.2.$0^{1,6}$]dodec-5-en-7-yl acetate (30a) (72 %): IR 3050, 1740, 1250 cm^{-1};

MS m/e (relative intensity) 220 (M^+, 21), 178 (44), 160 (100, M^+-AcOH), 136 (68); ^{1}H NMR δ 1.16-2.12 (m, 17H contains s at 1.96), 2.20-2.64 (m, 2H), 5.60 (t, 1H); ^{13}C NMR δ 170.01 (s), 148.39 (s), 110.67 (d), 86.30 (s), 40.07 (s), 38.99 (t), 37.04, 35.13 (t), 33.27, 24.36 (t), 21.87 (q), 20.40, 20.11. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.18; H, 9.33.

The oxidation of 235 mg (1.07 m mol) of 30a by osmium tetraoxide gave the diol (IR 3500-3430, 1735, 1710,[27] 1255, 1075 cm^{-1}) which was subjected to lead tetraacetate oxidation to afford the keto aldehyde (IR 1760, 1735, 1720, 1250 cm^{-1}). Treatment of the crude aldehyde with saturated bromine-water gave the keto carboxylic acid (IR 1760, 1735, 1720, 1060 cm^{-1}) and the subsequent esterification with ethereal diazomethane afforded 172 mg of the keto ester 31 (62 % from 30a): IR 1760, 1735, 1720, 1240 cm^{-1}; MS m/e (relative intensity) 282 (M^+, 7), 184 (43), 55 (30), 43 (100); ^{1}H NMR δ 1.14-2.60 (m, 19H contains s at 2.00), 3.60 (s, 3H). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.85; H, 8.13.

Lithium Aluminum Hydride Reduction of 30a to 30b.[17] 122 mg of 30a (0.55 m mol) was reduced by $LiAlH_4$ as described above to afford 98 mg of the unsaturated alcohol 30b (quantitative) which was purified by preparative GLC. 30b: IR 3370, 1170, 1140, 1060, 920 cm^{-1}; MS m/e (relative intensity) 178 (M^+, 41), 149 (61), 136 (100), 135 (62); ^{1}H NMR δ 0.84-2.16 (m, 17H), 5.32 (t, 1H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.47; H, 10.25.

Preparation of Spiro[4.7]dodecane (33).[21] The Wolff-Kishner reduction of 3.5 g (19. 4 m mol) of spiro[4.7]-dodecan-6-one[30] afforded 314 mg of 33 (10 %): IR 2910, 2860, 1465, 1440 cm^{-1}; MS m/e (relative intensity) 166 (M^+, 17), 95 (64), 82 (100), 67 (94), 41 (66); ^1H NMR δ 1.20-1.80 (m); ^{13}C NMR δ 45.97 (s), 39.39 (t, 2C), 36.02 (t, 2C), 28.87 (t, 2C), 25.14 (t), 24.45 (t, 2C), 24.00 (t, 2C). Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.55; H, 13.54.

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(16) 1,2-Alkyl shift of the external bond (path a) and the subsequent attack of acetate anion (path d) would lead to 23.

(17) Though the structure of the unidentified A is not clarified as yet, it is indicated that it is a tricyclic tertiary alcohol having a trisubstituted double bond on the basis of the spectral and analytical properties. Moreover, it should be pointed out that A is distinct from the unsaturated alcohol 30b, which may be formed from 16 by the migration of the external bond (path a) followed by the deprotonation, derived from 30a by $LiAlH_4$ reduction.

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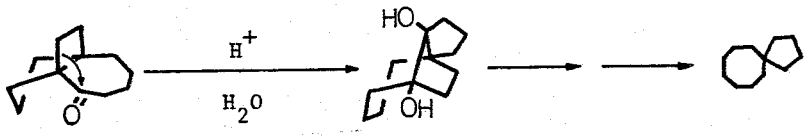
(21) Spiro[4.7]dodecane (33) would be obtained by the similar degradation of tricyclo[4.4.2.$0^{1,5}$]dodecane-5,6-diol (32) which might be formed by 1,2-alkyl shift of the external bond (path a $\longrightarrow$ path d) of 18. It was, however, unambiguously shown that the hydrocarbon derived from the diol 27a was entirely different in

spectroscopic properties from the authentic sample of spiro[4.7]dodecane which was prepared independently (see Experimental Section).



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(24) Obviously, the attack of a nucleophile to the carbonium ion intermediate 9 (path f; formation of a tricyclic compound 11) is highly favored compared with the second Wagner-Meerwein shift (path e; formation of a paddlanone 10). On the other hand, the propellanones 7 (m=4, n=4,5) may be thermodynamically more stable than the corresponding tricyclic compounds 8 (m=4, n=4,5) in view of the greater thermodynamic stability of [$\bar{3}$.3.3]-

propellane (19b) (m=4, n=3) over tricyclo[4.3.2.$0^{1,5}$]-undecanes (m=4, n=3).[15]

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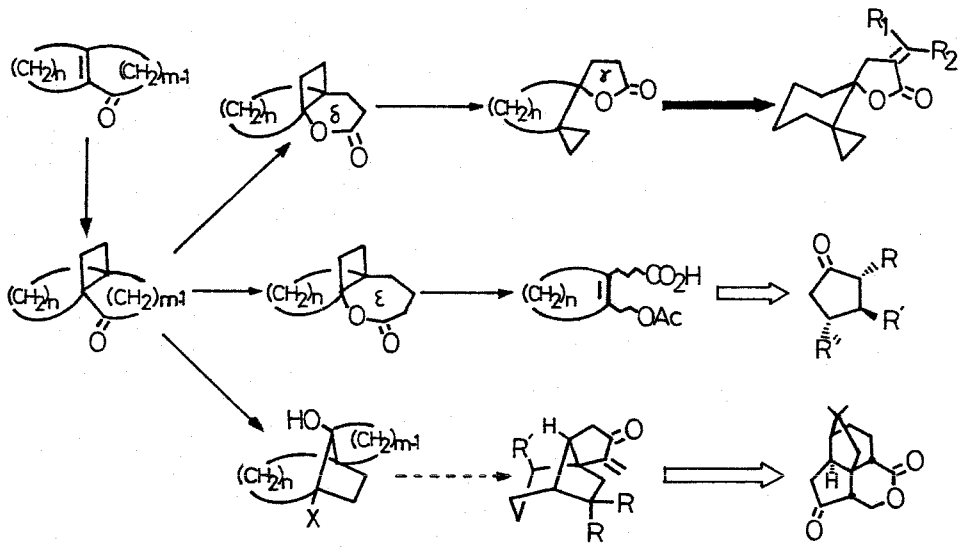
CONCLUSION

The principal purpose of this thesis is to develop high-selective process for the synthesis of biologically active compounds by use of the skeletal transformation of [m.n.2]propellanes.

The results obtained in the present work can be summarized as following.



In chapter 1, various α-alkylidene dispiro-γ-lactones, constituted of α-alkylidene spiro-γ-lactone which was expected as the compound possessing antitumor or other

biological activities, and a spiro cyclopropane ring, were synthesized efficiently by use of the cyclobutyl-cyclopropylcarbinyl rearrangement of [m.4.2]propella-δ-lactones, easily obtained from [m.3.2]propellanones. It was, furthermore, found out that these α-alkylidene-γ-lactones exhibited the interesting biological activities in vivo.

Moreover, 1,2-disubstituted cycloalkenes, advantageously taken as useful intermediates for the synthesis of prostagrandin and thromboxane derivatives, were synthesized by the lactone ring-cleavage of [5.n.2]propella-ε-lactones readily derived from [4.n.2]propellanones. Also, two factors governing the skeletal transformation of these propellalactones, which were the steric effect of the third ring on the geometry of cyclobutane ring, and the effect of the lactone ring size toward acid-catalyzed cleavage, were elucidated.

In the last part of this chapter, the rates of the alkaline hydrolysis of a series of propella-δ- and ε-lactones were measured and the steric effect of the third ring toward the attack of the hydroxide anion was clarified. In particular, it was found out that, in the propella-δ-lactones, this effect played as important role as in the case of the cyclobutyl-cyclopropylcarbinyl rearrangement of them.

In chapter 2, from the systematic investigation about the acid-catalyzed rearrangement of easily obtainable [m.n.2]propellanones, a new synthetic method of novel tricyclic compounds, being the basic skeleton of quadrone which was well-known to exhibit strong antitumor or other bio-

logical activities, was established. The route of the total synthesis of quadrone as well as the synthesis of the related compounds by use of the present rearrangement approach would be opened. Furthermore, the ring size effect of the third ring governing the migratory modes of the rearrangement, and the ring size effect of the cycloalkanone moiety which affected the reactivity toward the rearrangement, were found out.

The auther hopes that this thesis contributes to the establishment of the synthetic route of biologically active compounds.