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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)

1982

KIYOMI KAKIUCHI

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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Juyomi Shakinchi

Kiyomi Kakiuchi

Suita, Osaka January, 1982

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

 Effect of Alkyl Substituents on Cyclobutyl-Cyclopropylcarbinyl 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).

- 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., <u>53</u>, 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., <u>54</u>, 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.

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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

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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:



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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 $(\underline{1})$, 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 (<u>2</u>) 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 (<u>3</u>) is well-known

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to be significant insecticide, ^{3b} and illudin S (<u>4</u>), 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 (<u>20</u>) 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 <u>in vivo</u>, moreover, is described. Also, the synthesis of oxadispiro- γ -lactone (<u>21</u>) related to the dispiro- γ -lactones is presented.



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

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

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dispiro- γ -lactones (<u>14</u>)-(<u>17</u>) 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 eightmembered 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 <u>5-13</u> were prepared by the Baeyer-Villiger oxidation (H₂O₂/AcOH or MCPBA/CHCl₃) of the corresponding ketones in good yields.



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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 <u>p</u>-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 : γ -lactone ^a					
	acid conditions		thermal	conditions		
δ -lactone	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 <u>o</u>-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.

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As shown in table 1, unsubstituted or monomethyl substituted δ -lactones <u>9-11</u> were recovered. On the other hand, dialkyl substituted δ -lactones <u>12</u> and <u>13</u> gave the corresponding γ -lactones (<u>18</u>) and (<u>19</u>) 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, <u>6</u> afforded the desired dispiro- γ -lactone (<u>15</u>) quantitatively (conversion; 81-86 %), whereas δ -lactones <u>5</u>, <u>7</u>, and <u>8</u> remained unchanged under similar conditions.

It has been well-known that the puckered geometry of cyclobutyl cation is favorable for cyclobutyl-cyclopropylcarbinyl 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



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interaction between 1,2-dialkyl substituents, the cyclobutane ring in cation <u>A</u> derived from dialkyl substituted lactones <u>12</u> and <u>13</u> may be forced to have much puckered conformation compared to those derived from unsubstituted and monomethyl substituted derivatives <u>9-11</u>. In particular, this effect of <u>6</u> 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 <u>5-13</u> 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 <u>5</u>, <u>7</u>, and <u>8</u> recovered unchanged under the acidic conditions and then thermally induced rearrangement was next examined.

An <u>o</u>-dichlorobenzene (<u>o</u>-DCB) solution of the δ -lactones was heated in a sealed tube at 240 °C for 72 h, or a hexane solution of <u>5-13</u> 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 <u>9-11</u> were recovered unchanged, whereas, as expected, dialkyl substituted ones <u>12</u> and <u>13</u> gave 16-49 % of the corresponding γ -lactones <u>18</u> and <u>19</u>, and, moreover, propella- δ -lactone <u>6</u> rearranged readily to afford 79-85 % of <u>15</u>. These results exhibited a trend similar to that observed in the acid-catalyzed reaction descrived above.

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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 <u>o</u>-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,

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0-2 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 <u>15</u>, obtained in the best yield of all dispiro- γ -lactones and related to α -methylene spiro- γ -lactone <u>2</u>, was used for the synthesis of α -alkylidene- γ lactones <u>20</u>. α -Alkylidenation of the γ -lactone <u>15</u> 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: SOC1₂, Pyridine, CH₂C1₂.

carbonyl compd	method	α-alkylidene-γ-lactone			yield(%) ^a	
			R ₁	R ₂		
Formaldehyde	A	20a	Н	Н		77 ^b
Acetaldehyde	A	20b 20c	СН _З Н	н Сн _з	(E) (Z)	54
Propionaldehyde	A	20d 20e	С ₂ Н ₅ Н	н С ₂ н ₅	(E) (Z)	30 20
Acetone	В	20f	CH ₃	CH ₃		52

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

^a Isolated yield based on 15.

^b Determined by ¹H NMR analysis.

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It was easy to establish the stereochemistry around the olefinic part of the γ -lactones <u>20b-e</u> by the comparison of the ¹H NMR chemical shifts of the vinyl protons of <u>20b-e</u> 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 (<u>20b</u>) and (<u>20c</u>). Similarly, the observed values of the olefinic protons (6.48 and 6.00 ppm) of α -propylidene- γ -lactones (<u>20b</u>) and (<u>20c</u>) and (<u>20c</u>) and (<u>20c</u>).

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} The tetrahydropyran-2-y1 (THP) ether of were synthesized. 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)-y-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 ¹H 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.

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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 <u>in vivo</u>, all of them were less active than the famous antitumor antibiotic, Mitomycin C. Interestingly, the other biological activities of these γ -lactones <u>in vivo</u>, 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 antiarrhythimia activity of α -isopropylidene- γ -lactone 20f, and the platelet aggregation inhibition activity of (Z)- α -(2-hydroxy-1-methylethylidene)- γ -lactone 20h.

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

Related to the previous section, oxadispiro- γ -lactone $(\underline{21})$, 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 <u>21</u> was synthesized in a good overall yield as shown below; (i) the cycloaddition of dichloroketene to 1,2-dimethylenecyclohexane employing the





21 77 %

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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]PROPELLAε-LACTONES

As an extention of the previous section, the acidcatalyzed 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 <u>22</u> 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.

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However, in the case of ε -lactone <u>23</u>, the corresponding propellanone was prepared by the ring enlargement¹³ 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





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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 ¹H 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, 1^{17} is due to the steric effect of the cyclohexane



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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 <u>22</u> and <u>23</u> in boiling acetic acid was undertaken. When a solution of <u>22</u> in acetic acid was heated at reflux for 3 h (after which time the starting lactone was almost consumed), interestingly, the five products <u>24-28</u> involving 1,2-disubstituted cyclopentene <u>28</u> as the major product (77 %) were obtained in 93 % combined yield.



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

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



For the purpose of elucidating the reaction path, the change of the product distribution during the course of the rearrangement of $\underline{22}$ as well as the product distribution in the reaction of the isolated products, such as $\underline{24}$ - $\underline{26}$, and $\underline{28}$, in acetic acid (reflux, 3 h) was determined as summarized in Table 3. Judging mainly from the facts that the yield of the cyclopentene $\underline{28}$ increased with increasing reaction time and the product distribution obtained from the reaction of $\underline{25}$ after 3 h was similar to that from $\underline{22}$, 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

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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 <u>via</u> bicyclo[3.2.0]hept-1yl cation proposed in the solvolysis of bicyclo[3.2.0]hept-1-yl 3,5-dinitrobenzoate by Wiberg <u>et al</u>.¹⁹

	24-26 , an	id 28					
starting	reaction		produc	t dist	ributi	on (%)	a
material	time	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	—	<u> </u>		
2 5 ^b	3 h		6	13	3	6	72
26	3 h	<u> </u>			100		
28	3 h						100

Table 3. Acid-Catalyzed Rearrangement of 22,

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

Scheme 1.



Interestingly, the rearrangement of the ε -lactone <u>22</u> proceeds smoothly <u>via</u> lactone ring-cleavage, though the corresponding δ -lactone <u>5</u> 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 <u>23</u> under the above conditions gave a small amount of the dispiro- δ -lactone <u>31</u> and three kinds of lactone ring-cleaved acids <u>32-34</u> involving <u>34</u> as the major product (67 %).

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To elucidate the course of the reaction, the change of the product distribution during the course of the rearrangement of $\underline{24}$ and the product distribution in the reaction of isolated compounds, such as $\underline{31}$ - $\underline{34}$, were similarly determined as summarized in Table 4. From the fact that the yield of cyclohexene $\underline{34}$ increased with increasing reaction time and the reaction of $\underline{31}$ - $\underline{34}$ under similar conditions furnished the similar product distribution to that from $\underline{23}$, 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 <u>23 via</u> lactone ring-cleavage should be contrasted with the reactivity of the corresponding δ -lactone <u>6</u> which only gave the dispiro- γ -lactone <u>15</u> without any formation of lactone ring-cleavage products.¹⁷ Furthermore, the acid-catalyzed rearrangement of the dispiro- δ -lactone <u>31</u> mainly gave ring-cleavage

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	31-34.				
starting	reaction	product distribution (%)			
material	time (h)	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

Table 4. Acid-Catalyzed Rearrangement of 23 and

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 Namely, the product distribution in these (or products). 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-y-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-\deltalactone 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 <u>28</u> and cyclohexene <u>34</u>, 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.

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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 <u>et al.^{20b,d}</u> 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

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			+		
compd	<u> </u>	<u>k</u>	<u>ΔH</u> .	ΔS	k b
	°C	1 mol 'sec '	kcal/mol	eu	rel
A-Valero-	11 5	2A + 0 3			
	+1 + J 77 7	24.4 ± 0.5	7 70	20 0	100
Tactone	32.3	17.5 ± 0.0	7.30	-20.9	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			
10	43 E	0 207 + 0 002			
12	41.5	0.205 ± 0.002	0.75	70 1	
	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			
c	47 E	0 200 + 0 007			
D	41.5	0.280 ± 0.003	0 77	.	
-	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
Q	77 7	0 0200 + 0 0006			0 17
0	34.3	0.0250 ± 0.0000			0.1/

Table 5. Kinetic Data for Alkaline Hydrolysis of

δ-Lactone Series.

^a Temperatures are \pm 0.1 °C. ^b Relative rates at 32.3 °C to that of δ -valerolactone = 100.

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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 In fact, however, the rate constants were in ring size. the order of $6 > 5 > 7 \sim 8$, 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 14-17described 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

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be attributed to the puckered geometry of the cyclobutane ring reinforced by the chair conformation of the cyclohexane ring. Namely, <u>6</u> is packed closely like a compact hemisphere, in other words, <u>6</u> has a widespreading room to the direction of endo in comparison with the others, such as <u>5</u> and <u>12</u>. Therefore, the attack of the hydroxide anion upon the carbonyl carbon atom of <u>6</u> 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 propeila-e-lactones 22 and 23, which were the same, were only one-fourth as small as that of ε -caprolactone as shown This marked difference in reactivity between in Table 6. two propellalactone series can be attributed to the difference in flexibility or rigidity between δ - and ϵ -lactone Inspection of molecular models of two lactone rings 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

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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.

	T ^a	k	ΔH [‡]	_∆S [‡]	b
compd	°C	l mol ⁻¹ sec ⁻¹	kcal/mol	eu	^k rel
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

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

^a Temperatures are \pm 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

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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

<u>General.</u> 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. ¹H NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer in CCl₄ and ¹³C NMR spectra were taken on a JEOL JNM-FX-60S spectrometer in CDCl₃ with the use of Me₄Si 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.

<u>Materials.</u> [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-

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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. Calcd for C₁₁H₁₉ON₃: C, 63.12; H, 9.15; N, 20.08. Anal. Found: C, 62.86; H, 9.15; N, 20.14. Cyclopentenone, 25 2methyl,²⁴ and 3-methyl²⁶ 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 C₀H₁₅ON₃: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.65; H, 8.30; N, 23.17.

<u>Preparation of δ -Lactones.</u> δ -Lactones <u>5-13</u> 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 <u>in vacuo</u> and the residue was distilled under reduced pressure. δ -Lactones <u>5</u>-13 were obtained in 35-80 % yields and

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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 (Na₂SO₃) 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 $\underline{m}/\underline{e}$ 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 $\underline{m}/\underline{e}$ 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 C₁₂H₁₈O₂: 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 $\underline{m}/\underline{e}$ 208 (M^+), 180. Anal. Calcd for $C_{1,3}H_{2,0}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.74. <u>9</u>: IR 1720 cm⁻¹; ¹H NMR δ 1.50-2.80 (m, 9H), 4.76 (q, 1H); MS m/e 126 (M⁺), 98. <u>10</u>: IR 1720 cm⁻¹; ¹H NMR δ 1.40 (s, 3H), 1.40-2.50 (m, 9H); MS $\underline{m}/\underline{e}$ 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 C₈H₁₂O₂: C, 68.54; H, 8.63. Found: C, 68.22; H, 8.77.

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<u>12</u>: IR 1720 cm⁻¹; ¹H NMR & 0.96 (s, 3H), 1.14 (s, 3H), 1.40-2.70 (m, 8H); MS <u>m/e</u> 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. <u>13</u>: IR 1720 cm⁻¹; ¹H NMR & 0.99 (t, 3H), 1.12 (s, 3H), 1.50-2.50 (m, 10H); MS <u>m/e</u> 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 <u>A.</u> A solution of a δ -lactone <u>5-13</u> in acetic acid was refluxed for 72 h. The solution was neutralized with saturated sodium bicarbonate (NaHCO₃) solution and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na₂SO₄), and concentrated <u>in vacuo</u>. The residue was distilled under reduced pressure. Products were analyzed by GLC and isolated by preparative GLC. The results are summarized in Table 1.

<u>Method B.</u> 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 NaHCO₃ solution and brine and then dried (Na₂SO₄). Similar workup as the above gave a mixture of δ - and γ -lactones. The results are summarized in Table 1. <u>15</u>: 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 <u>m/e</u> 180 (M⁺). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.98; H, 9.03.

<u>18</u>: 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 <u>m/e</u> 155 (M⁺+1).

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

<u>19</u>: IR 1765 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 169 (M^{+} +1). Anal. Calcd for C₁₀H₁₆O₂: 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 <u>o</u>-DCB was heated in a sealed tube at 240 °C for 72 h. After evaporation of the solvent <u>in vacuo</u>, 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.

<u>14</u>: IR 1765 cm⁻¹; ¹H NMR & 0.10-0.90 (m, 4H), 1.40-2.20 (m, 8H), 2.20-2.50 (m, 2H); MS <u>m/e</u> 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.

<u>16</u>: IR 1765 cm⁻¹; ¹H NMR & 0.10-1.00 (m, 4H), 1.10-2.20 (m, 12H), 2.30-2.60 (m, 2H); MS <u>m/e</u> 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.

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<u>17</u>: IR 1765 cm⁻¹; ¹H NMR & 0.10-1.10 (m, 4H), 1.10-2.20 (m, 14H), 2.30-2.60 (m, 2H); MS <u>m/e</u> 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.

<u>Materials.</u> 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 a-Alkylidene-y-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 (NHAC1) solution and the mixture was extracted with ether. The organic layer was washed with 5 % HCl, saturated NaHCO, solution, brine, and dried (Na₂SO₄). The solvent was removed in vacuo to give the crude alcohol product.

<u>Dehydration.</u> <u>Method A.</u> 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

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extracted with ether. The organic layer was washed with 5 % HCl, saturated NaHCO, solution, and brine. After drying (Na_2SO_4) , the solvent was evaporated <u>in vacuo</u> 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, 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 CH₂Cl₂. 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 <u>15</u> (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

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1750, 1350, 1160 cm⁻¹) gave α-methylene-γ-lactone <u>20a</u> (684 mg). Overall yield based on <u>15</u> was 77 % (determined by ¹H NMR analysis). <u>20a</u>: 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 <u>m/e</u> 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 -(1hydroxyethyl)- 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 & 0.10-1.00 (m, 4H), 1.12-2.04 (m, 11H), 2.55 (m, 2H), 6.57 (m, 1H); MS <u>m/e</u> 206 (M⁺). Anal. Calcd for C₁₃H₁₈O₂: 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).

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Dehydration of the alcohol by method A (the mesylate: IR 1740, 1350, 1160 cm⁻¹) gave the mixture of E-isomer <u>20d</u> and Z-isomer <u>20e</u> which were separated by column chromatography on silica gel (3 % ether-petroleum ether). <u>20d</u> (30 % from <u>15</u>): IR 3050, 1740, 1670 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 220 (M⁺). Anal. Calcd for $C_{14}H_{20}O_{2}$: C, 76.32; H, 9.15. Found: C,76.03; H, 9.21. <u>20e</u> (20 % from <u>15</u>): IR 3050, 1735, 1660 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 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 <u>15</u> (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 <u>20f</u> which was purified by column chromatography on silica gel (5 % ether-petroleum ether) to afford 3.2 g of <u>20f</u> (52 % from <u>15</u>): mp 70-71 °C (recrystallized from petroleum ether); IR (KBr) 3050, 1730, 1650 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 220 (M⁺). Anal. Calcd for C₁₄H₂₀O₂: C, 76.32; H, 9.15. Found: C, 76.11; H, 9.28.

<u>Tetrahydropyran-2-yl Acetonyl Ether.</u> 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-

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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 NaHCO₃ solution and the mixture was extracted with CH_2Cl_2 . The organic layer was washed with water, dried (Na₂SO₄), and concentrated <u>in vacuo</u> 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 & 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 <u>m/e</u> 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, solution and the mixture was extracted with The organic layer was washed with water, dried CH,C1,. (Na_2SO_4) , and concentrated <u>in vacuo</u> 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,

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respectively). <u>20g</u>: 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 <u>m/e</u> 236 (M⁺). Anal. Calcd for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 70.94; H, 8.58. <u>20h</u>: 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 <u>m/e</u> 236 (M⁺). Anal. Calcd for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 70.95; H, 8.57.

<u>Materials.</u> 1,2-Dimethylenecyclohexane²⁹ was prepared in a method similar to that of Davalian <u>et al.</u>,³⁰ and purified by distillation using a spinning-band distillation column.

1,1-Dichloro-5-methylene-spiro[3.5]nonan-2-one. А 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 The excess zinc was filtered and washed with ether. h. 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 NaHCO₂ solution and brine, and dried (Na₂SO₄). The solvent was removed <u>in vacuo</u> and the residue was distilled under reduced pressure. After

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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 <u>m/e</u> 222 (M⁺+4), 220 (M⁺+2), 218 (M⁺). Anal. Calcd for C₁₀H₁₂OCl₂: C, 54.82; H, 5.52. Found: C, 54.91; H, 5.56.

<u>5-Methylene-spiro[3.5]nonan-2-one.</u> 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 NaHCO₃ solution, brine, and dried (Na₂SO₄). The solvent was removed <u>in vacuo</u> 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 & 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 <u>m/e</u> 150 (M⁺). Anal. Calcd for C₁₀H₁₄O: C, 79.95; H, 9.39. Found: C, 79.84; H, 9.54.

<u>1,6-Dioxadispiro[2.0.4.4]dodecan-7-one (21).</u> 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 NaHCO₃ solution, brine, and dried (Na_2SO_4) . The solvent was evaporated <u>in vacuo</u> and the residue was chromatographed on silica gel (20 %

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ether-petroleum ether) to give 471 mg of 21^{12} (77 %): IR 1765 cm⁻¹; ¹H NMR & 1.20-2.00 (m, 8H), 2.04-2.72 (m, 4H), 3.60-4.20 (m, 2H); MS <u>m/e</u> 182 (M⁺). Anal. Calcd for C₁₀H₁₄O₃: C, 65.91; H, 7.74. Found: C, 65.72; H, 7.75.

<u>Materials.</u> 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 & 1.18-2.60 (m); MS <u>m/e</u> 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 dimethylformamide 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.

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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_z 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 $_3$ After drying (Na_2SO_A) , the solvent was evaporated solution. 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 C₁₄H₂₄OSi: 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, Cl solution and the solution was washed with saturated NaHCO₃ solution, water, and dried After removal of the solvent in vacuo, the (Na₂SO₄). 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 C₁₅H₂₆OSi: 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

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(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 C₁₂H₁₆0: 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 Na₂SO₃ solution,

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saturated NaHCO₃ solution, and water. After drying (Na_2SO_4) , the solvent was removed <u>in vacuo</u> and the residue was chromatographed on silica gel (20 % ether-petroleum ether) to give 8.6 g of the ε -lactone <u>22</u> 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 <u>m/e</u> 180 (M⁺). Anal. Calcd for C₁₁H₁₆O₂: 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 % etherpetroleum 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 <u>m/e</u> 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 <u>m/e</u> 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 <u>in vacuo</u>, 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]heptyl)butyric acid (24) (6 %), 4-(4-spiro[2.4]hept-4-enyl)butyric

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acid (25) (5 %), 8-methylene-l-oxaspiro[5.5]undecan-2-one (26) (2 %), m-tolylbutyric acid (27) (3 %), and 4-[2-(2acetoxyethyl)cyclopent-l-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.

<u>24</u>: 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 <u>m/e</u> 180 (M⁺-60). The methyl ester of <u>24</u> 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 <u>m/e</u> 194 (M⁺-60). Anal. Calcd for C₁₄H₂₂O₄: C, 66.11; H, 8.72. Found: C, 66.11; H, 8.62.

<u>25</u>: IR 3500-2500, 1690, 1650, 870 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 180 (M⁺). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.29; H, 8.97. <u>26</u>: IR 3050, 1720, 1645, 890 cm⁻¹; ¹H NMR & 1.98-2.60 (m, 14H), 4.67 (s, 1H), 4.73 (s, 1H); MS <u>m/e</u> 180 (M⁺). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.23; H, 9.00.

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

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ture.³⁷

<u>28</u>: IR 3500-2500, 1720, 1690, 1230 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 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 <u>28</u> was prepared by the treatment with ethereal diazomethane: IR 1725, 1230, 1160 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 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

The reaction of 236 mg (1.22 m mol) of 23 or 237 mg 31. (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-eny1)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 The products were purified by prepara-31 was recovered. The product distribution was recorded as tive GLC. 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.

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Calcd for C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.84; H, 9.38.

<u>33</u>: mp 41.5-42.5 °C (recrystallized from pentane); IR 3500-2500, 1670, 1630, 1250, 870 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 194 (M⁺). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.35. <u>34</u>: IR 3500-2500, 1720, 1690, 1220 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 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 <u>34</u> was prepared by the treatment with ethereal diazomethane: IR 1725, 1220, 1150 cm⁻¹; ¹H NMR & 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 <u>m/e</u> 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 (NaHSO₃), 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-petro-leum ether) to give 181 mg of the corresponding diol (63 %):

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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 <u>in vacuo</u> 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 <u>m/e</u> 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 (Na₂SO₄), and concentrated <u>in vacuo</u> to yield 297 mg of the crude diethylene thicketal (IR 1720, 670 cm⁻¹) which was used directly in the next reaction.

The above thicketal 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

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

<u>Methyl 11-Acetoxyundecanoate (30).</u> 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 (Na₂SO₄), and concentrated <u>in vacuo</u>. 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 icewater and the mixture was extracted with ether. The organic layer was washed successively with dilute HCl, saturated NaHCO₃ solution, and brine, and then dried (Na₂SO₄). After removal of the solvent <u>in vacuo</u>, 162 mg of <u>30</u> 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),

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2.21 (t, 2H), 3.60 (s, 3H), 3.96 (t, 2H); MS <u>m/e</u> 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.

<u>Materials.</u> 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 <u>9</u> and <u>12</u> and propellalactones <u>5-8</u> and <u>22-23</u> 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.

<u>Kinetic Measurement.</u> 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 °C³⁹ and the activation parameters were evaluated from the slope of the least-square Arrhenius plots.

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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 6 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 C₁₀H₁₃OC1: C, 65.04; H, 7.10. Found: C, 64.90; H, 7.13.

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- (39) Since <u>23</u> was more reactive and rearranged easily to <u>31</u> 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 (<u>1</u>) was isolated from a fermentation broth of a strain of <u>Aspergillus terreus</u> and was found to display significant <u>in vitro</u> activity against KB human epidermoid carcinoma of the nasopharynx (ED_{50} 1.3 µg) and <u>in vivo</u> activity against P388 lymphocytic leukemia in mice in 1978 by Ranieri and co-workers,¹ much attention has been paid to the sesquiterpene lactone <u>1</u> 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, <u>per se</u>, offers no apparent rationale for its antitumor properties. It is seen on inspection that the α -methylene keto acid $\frac{2}{2}$ having

Scheme 1.



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 $(1\underline{S}^*, 5\underline{R}^*, 6\underline{S}^*)$ -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 $\underline{2}$ has been regarded as an attractive subgoal, and the total synthesis of quadrone <u>via 2</u> was accomplished very recently by two groups, Danishefsky² and Helquist³ and their colleagues. However, the key compound $\underline{2}$ was obtained by multiple-step reactions with careful regioand stereochemical control, for example, by the intramolecular cyclization of iodo ester such as $\underline{3}$ having <u>cis</u>-bicyclo-[3.3.0]octane skeleton (Scheme 1). Therefore, a new synthetic route to the compound $\underline{2}$, such as a novel rearrangement approach from a [4.3.2]propellanone derivative $\underline{4}$ 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 acidcatalyzed 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 $(m \ge 3, n \ge 2)$ 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 <u>6</u> (path a). The cation <u>6</u> under-

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goes another 1.2-alkyl shift to give $[m-1.n.\overline{3}]$ propellanone⁶ (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-l.n.2.1]paddlanone (10) by further 1,2shift (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 $[4.\overline{3}.2]$ -, $[\overline{4}.3.2]$ and [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 $[\overline{4},2,2]$ 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 $(\underline{13}) - (\underline{18})$ 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 $\underline{13}$ - $\underline{18}$ are constituted of a cyclobutane, a five-

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to seven-membered cycloalkanone, and a five- to sevenmembered 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.



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 sevenmembered ring as the third ring, [$\overline{4}$.3.2]propellanone ($\underline{15}$),¹⁰ [$\overline{4}$.4.2]propellanone ($\underline{16}$),¹¹ and [$5.\overline{4}$.2]propellanone ($\underline{17}$),¹² were carried out. Treatment of $\underline{15}$ or $\underline{16}$ with TsOH in benzene at reflux gave [$\overline{3}$.3.3]propellanone ($\underline{19a}$) or [$4.\overline{3}$.3]propellanone ($\underline{20}$) as a sole product (80 % or 90 %) in accord with the result of Cargill <u>et al.</u>.¹¹ Moreover, treatment

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of <u>17</u> under similar conditions gave $[5.\overline{3}.3]$ propellanone (<u>21</u>) quantitatively (99 %). The structual assignment of <u>19a</u>, <u>20</u>, and <u>21</u> 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 <u>19a</u> was confirmed by the ¹³C NMR spectra (δ 60.44 (s), 40.35 (t), 24.62 (t))¹³ of the hydrocarbon <u>19b</u> derived by the Wolff-Kishner reduction of <u>19a</u>. Thus, it is obvious that the rearrangement of the propellanones <u>15-17</u> in nonnucleophilic media takes place <u>via</u> 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) <u>19a</u>, <u>20</u>, and <u>21</u> regardless of the ring size of the third ring.



On the other hand, in the presence of a nucleophile, the propellanones <u>15-17</u> behave in a quite different way depending on the ring size of the third ring. The reaction of [$\overline{4}$.3.2]propellanone (<u>15</u>) with sulfuric acid (H₂SO₄) in aqueous THF afforded (1<u>S</u>^{*}, 5<u>R</u>^{*}, 6<u>S</u>^{*})-tricyclo[4.3.2.0^{1,5}]un-

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decane-5,6-diol (22a) in 83 % yield along with a trace amount of [$\overline{3}$.3.3]propellanone ($\underline{19a}$). Similarly, treatment of $\underline{15}$ with TsOH in acetic acid gave the hydroxy acetate 22b (68 %) together with $\underline{19a}$ (15 %). The structures of 22a and 22b were elucidated on the basis of the spectroscopic data and were confirmed by the following chemical transformations.



22b X = 0Ac

Lead tetraacetate oxidation of the diol $\underline{22a}$ to spiro[4.6]undecane-1,8-dione ($\underline{24a}$) and the subsequent thioketal reduction of $\underline{24a}$ gave spiro[4.6]undecane ($\underline{24b}$) which was entirely identical with the authentic sample prepared independently. Since LiAlH₄ reduction of the hydroxy acetate $\underline{22b}$ afforded the diol $\underline{22a}$, the gross structure, i.e., 5,6disubstituted tricyclo[4.3.2.0^{1,5}]undecane, of $\underline{22a}$ and $\underline{22b}$ was established. In order to differentiate the position of the acetoxyl functionality ($\underline{22b}$ or $\underline{23}$), $\underline{22b}$ was subjected to dehydration with thionyl chloride-pyridine followed by the oxidative degradations ((i) oxidation of the olefin $\underline{25}$

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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 <u>26</u> 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 (<u>22b</u>) not at C-5 (<u>23</u>). Finally, ($1S^*$, $5R^*$, $6S^*$) stereochemistry of <u>22a</u> and <u>22b</u> 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 <u>22a</u> and <u>22b</u>

Scheme 3.



a. $Pb(OAc)_4$, 72 %; b. (i) $HS(CH_2)_2SH$, (ii) Raney-Ni, 31 %; c. $LiA1H_4$, quantit.; d. $SOC1_2/Pyridine$, 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 $[\overline{4}.4.2]$ propellanone $(\underline{16})$ with H_2SO_4 in aqueous THF furnished $[4.\overline{3}.3]$ propellanone (20) as the major product (71 %) along with a small amount (9 %) of $(1\underline{S}^{*}, 6\underline{R}^{*}, 7\underline{S}^{*})$ -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 $[\overline{5}, 3, 2]$ propellanone (18) with H_2SO_4 in aqueous THF (vide infra). Since the hydroxy acetate 27b gave the diol 27a by LiAlH, 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-hydroxytricyclo[5.3.2.0^{1,6}]dodecan-6-yl acetate. The stereochemistry of C-6 in 27a and 27b is assumed to be $1\underline{S}^*$, $6\underline{R}^*$, $7\underline{S}^{*}$ 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, [5.4.2]propellanone (17) afforded only [5.3.3]propellanone $(\underline{21})$ (72 % with H_2SO_4 in aqueous THF and 94 % with TsOH in acetic acid), which is also formed via path a \rightarrow c, without

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any formation of diol or hydroxy acetate corresponding $\underline{22a}$, <u>b</u>, $\underline{23}$, $\underline{27a}$, <u>b</u>, and $\underline{28}$.



Next, in order to clarify the ring size effect of cycloalkanone moiety, the acid-catalyzed reactions of the cyclopentanone derivatives, $[\overline{3}.3.2]$ propellanone $(\underline{13})^{18}$ and $[4.\overline{3}.2]$ propellanone $(\underline{14})^{19}$, and the cycloheptanone derivative, $[\overline{5}.3.2]$ propellanone $(\underline{18})^{20}$, 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 $\underline{13}$ and $\underline{14}$ 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 $[\overline{5}.3.2]$ propellanone (<u>18</u>) occurs very smoothly. In the absence of a nucleophile (TsOH in boiling benzene), $[4.\overline{3}.3]$ propellanone (20)

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formed by 1,2-alkyl shift of the external bond (path a \rightarrow path c) was obtained as a sole volatile product (21 % yield). Reaction of <u>18</u> with H₂SO₄ in aqueous THF, however, afforded $(1\underline{S}^*, 6\underline{R}^*, 7\underline{S}^*)$ -tricyclo[5.3.2.0^{1,6}]dodecane-6,7-diol (<u>27a</u>) as the major product (88 %) along with a trace amount of <u>20</u>. Moreover, treatment of <u>18</u> with TsOH in acetic acid gave 6-hydroxy-($1\underline{S}^*, 6\underline{R}^*, 7\underline{S}^*$)-tricyclo[5.3.2.0^{1,6}]dodecan-7-yl acetate (<u>28</u>) predominantly (80 %) together with a small amount (2 %) of <u>20</u>. The structures of <u>27a</u> and <u>28</u> were confirmed by the way similar to that for <u>22a</u> and <u>22b</u> (Scheme 4). Lead tetraacetate oxidation of the diol <u>27a</u> 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 %.

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by thicketal reduction of the dione 29a gave spiro[5.6]dodecane (29b) which was identical with the authentic material prepared independently.²¹ Since LiAlH, 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 $(1\underline{S}^*, 6\underline{R}^*, 7\underline{S}^*)$ -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 $\underline{13}$ - $\underline{18}$ 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 $(\underline{12})$ and $(\underline{15})$, having a cyclobutane or cyclopentane ring as

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entry	[m.n.2]propellanone				product (%)				
	compd	ring size of cycloalkanone	ring size of the third ring	nucleophile	external bond shift		central bond shift		unidenti-
					path c	path d	path e	path f	fied
1	[3.3.2]	5	5	H ₂ 0 ^a					
2	$[4.\overline{3},2]$	5	6	H ₂ O ^a					
3	[4.2.2] ^b	6	4	none ^a				-	·
	14			H ₂ O				100	
4	[ā.3.2] 15	6	5	none	80				
			·	H ₂ O	trace			83	
				АсОН	15			68	
5	[4.4.2]	6	6	none ^C	90				
	10			H ₂ O	71	9			trace
				AcOH	61	6			~ 20

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

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	[m.n.2]propellanone				product (%)				
entry	compd	ring size of cycloalkanone	ring size of the third rin	nucleophile	external bond shift		central bond shift		unidenti-
					path c	path d	path e	path f	fied
б	[5.4.2]	6	7	none	99				
	17			H ₂ O	72				
				АсОН	94		 		
7	[5 .3.2] 18	7	5	none	21				
				H ₂ 0	trace			88	
				АсОН	2			80	

Table 1. (Continued)

^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 $[\overline{4}, 4, 2]$ - and $[5, \overline{4}, 2]$ 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 wellknown 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 $[\overline{3}, 3, 3]$ propellanone (19a) via path a \rightarrow path c under thermodynamic control. since the formation of a paddlanone 10 is unlikely.

It is noted that, in contrast to <u>12</u> and <u>15</u>, <u>16</u> gives only a small amount of the products <u>27a</u> and <u>27b</u> formed by the trap with the nucleophile (path d) and that <u>17</u> 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 <u>6</u> 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

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products, the propellanones $\underline{7}$ (m=4, n=3-5) and the tricyclic compounds $\underline{8}$, 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

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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 <u>15</u> and <u>18</u>, 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 (<u>1</u>). The total synthesis of <u>1</u> as well as the synthesis of the related compounds by use of the present rearrangement approach are now being undertaken.

EXPERIMENTAL

<u>Materials</u>. $[\overline{3}.3.2]$ Propellanone $(\underline{13})$, ¹⁸ $[4.\overline{3}.2]$ propellanone one $(\underline{14})$, ¹⁹ $[\overline{4}.3.2]$ propellanone $(\underline{15})$, ²⁶ $[\overline{4}.4.2]$ propellanone $(\underline{16})$, ²⁶ and $[\overline{5}.3.2]$ propellanone $(\underline{18})^{20}$ were prepared as described previously. $[5.\overline{4}.2]$ Propellanone $(\underline{17})$ was prepared by the ring enlargement of $[5.\overline{3}.2]$ propellanone¹⁸

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according to our previous method for the preparation of <u>16</u> ((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 $[5.\overline{4}.2]$ propellaenone (92 %)). <u>17</u>: IR 1690 cm⁻¹; MS <u>m/e</u> (relative intensity) 192 (M⁺, 25), 164 (100); ¹H NMR & 0.90-2.60 (m). Semicarbazone, mp 225-227 °C. Anal. Calcd for C₁₄H₂₃ON₃: 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

<u>13-18.</u> In Nonnucleophilic Media. A solution of the ketone and a equal or small excess amount of <u>p</u>-toluenesulfonic acid monohydrate (TsOH·H₂O) in benzene was heated at reflux. Progress of the reaction was monitored by GLC. The cooled reaction solution was washed with saturated NaHCO₃ solution and the aqueous solution was extracted with ether. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate (MgSO₄), and concentrated <u>in</u> 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 <u>in vacuo</u>, the reaction mixture was diluted with water and was extracted with chloroform. The organic layer was washed with water, dried (MgSO₄), and concentrated

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<u>in vacuo</u> to leave the crude products. <u>B.</u> 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 NaHCO₃ solution and the mixture was extracted with CH_2Cl_2 . The organic layer was washed with water, dried (MgSO₄), and concentrated <u>in vacuo</u> to leave the crude products. The products were separated by column chromatography on silica gel and purified by preparative GLC.

 $[\overline{3.3.3}] Propellanone (19a).^{13a}$ The reaction of 239 mg (1.46 m mol) of <u>15</u> and TsOH·H₂O (264 mg) in 10 mL of benzene for 2 h gave 192 mg of <u>19a</u> (80 %): mp 54-55 °C; IR (KBr) 1735 cm⁻¹; MS <u>m/e</u> (relative intensity) 164 (M⁺, 58), 136 (61), 108 (89), 107 (100), 80 (92), 79 (80); ¹H NMR & 1.12-2.00 (m, 14H), 2.23 (t, 2H).

[4.3.3]Propellanone (20).¹¹ The reaction of 290 mg (1.63 m mol) of <u>16</u> and TsOH·H₂O (571 mg) in 20 mL of benzene for 1 h gave 262 mg of <u>20</u> (90 %): IR (KBr) 1735 cm⁻¹; MS <u>m/e</u> (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 <u>18</u> and TsOH·H₂O (1.14 g) in 50 mL of benzene for 4 h gave 225 mg of <u>20</u> (21 %) as a sole volatile product along with polymeric materials.

[5.3.3]Propellanone (21). The reaction of 157 mg (0.82 m mol) of $\underline{17}$ and TsOH·H₂O (181 mg) in 25 mL of benzene for 2 h

gave 155 mg of <u>21</u> (99 %): IR 1730 cm⁻¹; MS <u>m/e</u> (relative intensity) 192 (M⁺, 33), 135 (57), 123 (100), 104 (35); ¹H NMR & 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 <u>17</u> 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); ¹³C 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 C₁₁H₁₈O₂: C, 72.49; H, 9.96. Found: C, 72.13; H, 9.92. 5-Hydroxy-(15^{*}, 5R^{*}, 6S^{*})-tricyclo[4.3.2.0^{1,5}]undecan-6-yl The reaction of 397 mg (2.42 m mol) of Acetate (22b). 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 & 1.06-2.16 (m, 18H contains s at 1.96), 2.28-2.60 (m, 1H), 4.08 (s, 1H); ¹³C NMR & 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 C₁₃H₂₀O₃: C, 69.61; H, 8.99. Found: C, 69.68; H, 9.28.

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(15^{*}, 68^{*}, 75^{*})-Tricyclo[5.3.2.0^{1,6}]dodecane-6,7-diol (27a). The reaction of 527 mg (2.96 m mol) of <u>18</u> by the method A at room temperature for 20 h gave a trace amount of <u>20</u> and 510 mg of the diol <u>27a</u> (88 %): mp 85-86 °C; IR (KBr) 3330, 1180, 1115 cm⁻¹; MS <u>m/e</u> (relative intensity) 196 (M⁺, 56), 178 (100, M⁺-H₂O), 149 (45), 109 (76); ¹H NMR & 0.72-2.28 (m, 18H), 2.39 (s, 2H); ¹³C NMR & 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 <u>16</u> by the method A gave 164 mg of <u>20</u> (71 %), unidentified products <u>A</u> and <u>B</u> (<1 %), and 22 mg of the diol 27a (9 %).

<u>7-Hydroxy-(15^{*}, 68^{*}, 75^{*})-tricyclo[5.3.2.0^{1,6}]dodecan-6-y1</u> <u>Acetate (27b).</u> The reaction of 226 mg (1.27 m mol) of <u>16</u> by the method B for 48 h gave 137 mg of <u>20</u> (61 %), the two unidentified products A (17 %) and B (~3 %), and 18 mg of the hydroxy acetate <u>27b</u> (6 %): mp 96-97 °C; IR (KBr) 3450, 1710,²⁷ 1290, 1255 cm⁻¹; MS <u>m/e</u> (relative intensity) 238 (M⁺, 7), 178 (100, M⁺-AcOH), 149 (39), 136 (49); ¹H NMR & 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.

<u>Unidentified Product A.</u>¹⁸: IR 3400, 3030, 1060 cm⁻¹; MS <u>m/e</u> (relative intensity) 178 (M⁺, 60), 149 (100), 135 (33), 107 (34); ¹H NMR & 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.

<u>6-Hydroxy-(1S^{*}, 6R^{*}, 7S^{*})-tricyclo[5.3.2.0^{1,6}]dodecan-7-y1</u> <u>Acetate (28).</u> The reaction of 825 mg (4.63 m mol) of <u>18</u> by the method B for 15 h gave 17 mg of <u>20</u> (2 %) and 880 mg of the hydroxy acetate <u>28</u> (80 %): IR 3450, 1735, 1710,²⁷ 1280, 1260 cm⁻¹; MS <u>m/e</u> (relative intensity) 238 (M⁺, 9), 178 (100, M⁺-AcOH), 149 (72); ¹H NMR & 0.68-1.86 (m, 17H), 1.94 (s, 3H), 2.40-2.60 (m, 1H), 3.88 (s, 1H); ¹³C NMR & 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 $[\overline{3}.3.2]$ Propellanone (13) and $[4.\overline{3}.2]$ 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 $\underline{14}$ 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

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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 <u>in vacuo</u> 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. LiAlH₄ 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 LiAlH₄ 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 (MgSO₄). After evaporation of the solvent <u>in vacuo</u>, the crude product was chromatographed on silica gel to give

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200 mg of <u>19b</u> (35 %): mp 110-112 °C (lit.^{13b} 116-117 °C); IR 2930, 2850, 1460, 1440 cm⁻¹; MS <u>m/e</u> (relative intensity) 150 (M⁺, 60), 107 (100), 79 (30); ¹³C NMR & 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 $\underline{22a}$ 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 <u>in vacuo</u> followed by column chromatography on silica gel to yield 457 mg of spiro[4.6]undecane-1,8-dione (<u>24a</u>) (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 (MgSO₄), and concentrated <u>in vacuo</u> to yield the crude diethylene thioketal (IR 1450, 1420, 1270, 1200 cm⁻¹).

The above thicketal 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 <u>in vacuo</u> to yield the crude hydrocarbon <u>24b</u>. Chromatography on silica gel afforded 163

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mg of <u>24b</u> (22 % from <u>22a</u>): IR 2920, 2850, 1455 cm⁻¹; MS <u>m/e</u> (relative intensity) 152 (M⁺, 32), 96 (73), 95 (83), 82 (100), 67 (88); ¹H NMR δ 1.16-1.80 (m); ¹³C 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 C₁₁H₂₀: C, 86.76; H, 13.24. Found: C, 86.57; H, 13.14.

<u>Preparation of an Authentic Sample of 24b.</u> 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 <u>19b</u> to give 1.74 g of the hydrocarbon (63 %) which was identical (IR, MS, ¹³C NMR) with 24b obtained by the degradation of <u>22a</u>.

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 CH₂Cl₂ 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 CH₂Cl₂. The organic layer was washed with water, dried $(MgSO_A)$, 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 & 1.20-2.12 (m, 13H contains s at 1.96), 2.16-2.76 (m, 4H), 5.04 (t, 1H); ¹³C NMR & 169.97 (s), 154.83 (s), 110.91 (d), 83.69 (s), 55.68 (s), 38.07 (t), 36.06 (t),

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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 NaHSO₃ 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 (K₂CO₃). Evaporation of the solvent <u>in vacuo</u> 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. NaHSO₃ solution was added and the mixture was extracted with ether. The organic layer was washed with brine and dried (MgSO₄). Evaporation of the solvent <u>in vacuo</u> 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 <u>26</u> (89 % from <u>25</u>) which was purified by preparative GLC: IR 1760, 1735, 1720, 1240, 1050 cm^{-1} ; MS <u>m/e</u> (relative intensity) 268 (M⁺, 17), 208 (38), 170 (53), 125 (51), 43 (100); ¹H NMR & 0.80-2.56 (m, 17H contains s at 2.00), 3.57 (s, 3H). Anal. Calcd for

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C₁₄H₂₀O₅: 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 <u>m/e</u> (relative intensity) 166 (M⁺, 56), 96 (100), 81 (71), 67 (66); ¹³C NMR & 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).

<u>Preparation of an Authentic Sample of 29b.</u> The authentic sample of <u>29b</u> was prepared by the literature method.²⁹ Condensation of 20 g (0.18 mol) of cycloheptanone with 1,5dibromopentane 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, ¹³C NMR) with <u>29b</u> obtained by the degradation of <u>27a</u>.

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

Dehydration of 640 mg (3.51 m mol) of <u>28</u> with thionyl chloride-pyridine gave 457 mg of tricyclo[$5.3.2.0^{1,6}$]dodec-5-en-7-y1 acetate (<u>30a</u>) (72 %): IR 3050, 1740, 1250 cm⁻¹;

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MS <u>m/e</u> (relative intensity) 220 (M⁺, 21), 178 (44), 160 (100, M⁺-AcOH), 136 (68); ¹H NMR & 1.16-2.12 (m, 17H contains s at 1.96), 2.20-2.64 (m, 2H), 5.60 (t, 1H); ¹³C NMR & 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 <u>30a</u> 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 <u>31</u> (62 % from <u>30a</u>): IR 1760, 1735, 1720, 1240 cm⁻¹; MS <u>m/e</u> (relative intensity) 282 (M⁺, 7), 184 (43), 55 (30), 43 (100); ¹H NMR & 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 LiAlH₄ 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 <u>m/e</u> (relative intensity) 178 (M⁺, 41), 149 (61), 136 (100), 135 (62); ¹H NMR & 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.

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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-one³⁰ afforded 314 mg of <u>33</u> (10 %): IR 2910, 2860, 1465, 1440 cm⁻¹; MS <u>m/e</u> (relative intensity) 166 (M⁺, 17), 95 (64), 82 (100), 67 (94), 41 (66); ¹H NMR & 1.20-1.80 (m); ¹³C NMR & 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 C₁₂H₂₂: 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 <u>A</u> 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 <u>A</u> is distinct from the unsaturated alcohol <u>30b</u>, which may be formed from <u>16</u> by the migration of the external bond (path a) followed by the deprotonation, derived from <u>30a</u> by LiAlH₄ reduction.
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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 $[\overline{3}.3.3]$ -

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propellane (<u>19b</u>) (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

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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 <u>in vivo</u>.

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-

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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.