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TWO LACTONE FORMATION REACTIONS FROM 1,3-DIOXIN-4-ONES HAVING HYDROXYALKYL GROUP AT THE 6-POSITION: DIFFERENCE IN RING OPENING AND CLOSURE[1]

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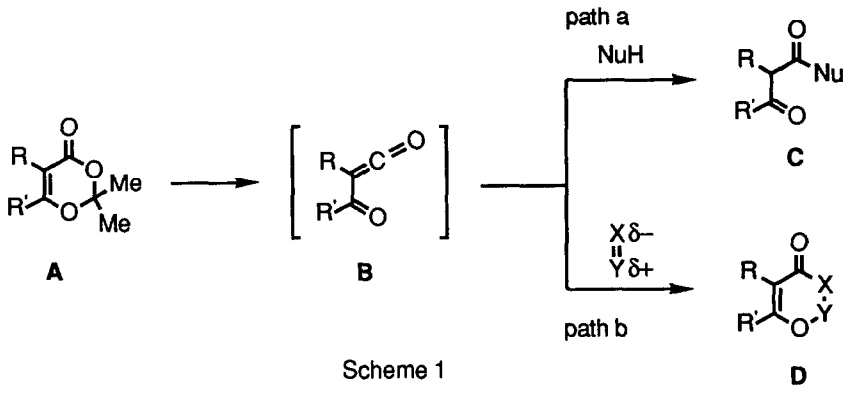
Abstract: Two methods (A: ring opening to acylketenes followed by intramolecular ketene trapping and B: methoxide-mediated ring opening followed by cyclization of the hydroxy esters thus formed) have become available for the synthesis of lactones and/or cyclic ethers from 1,3-dioxin-4-ones having 1- ∿ 4-hydroxyalkyl group at the 6-position. Mechanism and scope of both methods have been clarified.

Previously, we have shown that 1,3-dioxin-4-ones (**A**), when heated in an aprotic solvent, undergo cycloreversion to acyl ketenes (**B**), which react either with nucleophiles to give β-keto acid derivatives (**C**)[2] (path a), or with dipolar dienophiles to give six-membered heterocyclic compounds (**D**) (path b).[3] Shortly later, this ketene trapping reactions (paths a and b) have been successfully applied to the corresponding intramolecular ones.[4] In the study according to path a, it was found that, while the dioxinones having α-aminoalkyl group either at 5- or 6-position afforded β- or γ-lactams (tetramic acids),[5] these having α-hydroxyalkyl group at the 6-position gave tetronic acid and its derivatives.[6]



Scheme 1

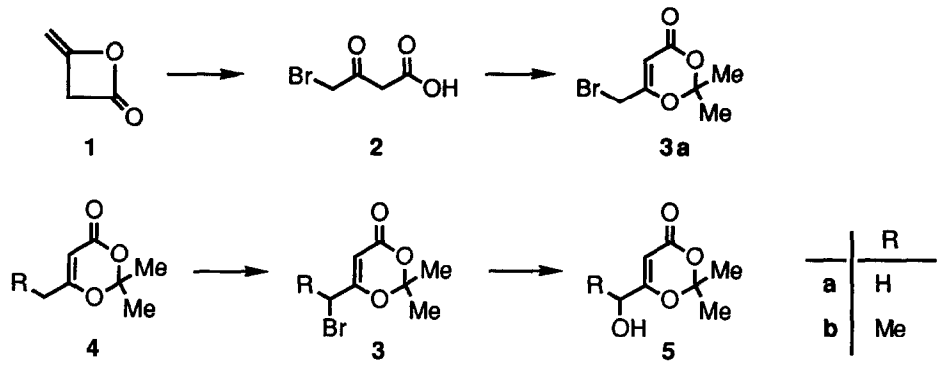
As an obvious extension of these studies, we have been interested in synthesizing β-keto-δ-lactones by heating 6-(2-hydroxyalkyl)-1,3-dioxin-4-ones in an aprotic solvent. Though this attempt was unsuccessful, the alternative method simply treating the same starting materials with methanol containing potassium carbonate has been disclosed which not only permit ready access to δ-lactones but also provides γ-lactones as well. This paper describes the results in detail and offers reasonable mechanistic explanation for the difference between the two methods.

Results and Discussion

Preparation of 1,3-dioxin-4-ones having 1-, 2-, 3-, or 4-hydroxyalkyl group at the 6-position

In this section, methods available for the preparation of dioxinones having an appropriate hydroxyalkyl group at the 6-position are described.

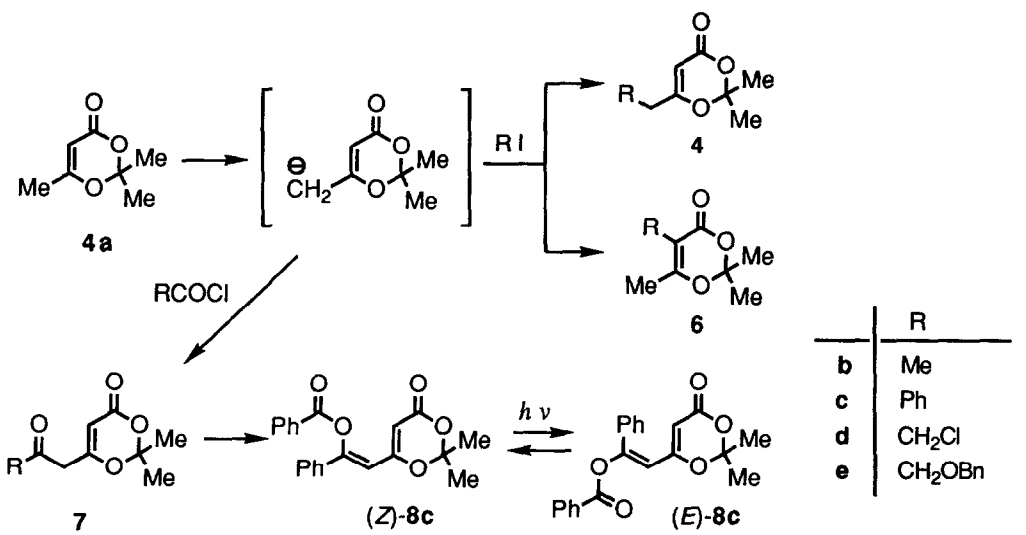
Preparation of 6-(1-hydroxyalkyl) derivatives——The parent 6-bromomethyl derivative (**3a**) can be synthesized readily from diketene (**1**).[7] Thus, treatment of **1** with bromine in CCl_4 followed by mild acid hydrolysis gave 4-bromoacetoacetic acid (**2**), which was converted into **3a** by acid-catalyzed condensation with acetone. A more general synthesis of **3a** and its derivatives, however, was achieved by direct bromination of 6-alkyldioxinones (**4**) as the key step. Replacement of the bromine atom in the resulted brominated products (**3**) by acetoxyl group followed by hydrolysis gave the corresponding alcohols (**5**).[5] By this method, two derivatives (**5a** and **5b**) were prepared and detailed experimental procedures have been already published in the previous paper.[6]



Scheme 2

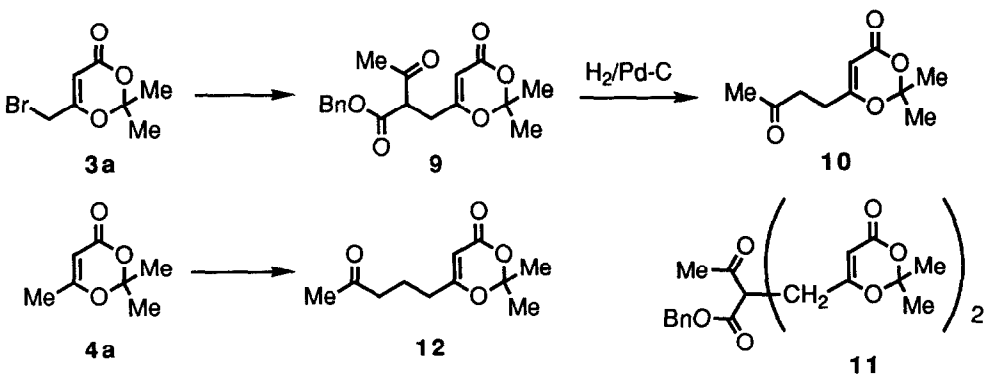
Preparation of 6-(2-hydroxyalkyl)dioxinones——Recently, Smith et al. reported a general synthetic method of 6-alkyldioxinones (**4**) from 6-methyl derivative (**4a**).[8] Thus, lithiation of **4a** with lithium diisopropylamide (LDA) followed by treatment with an appropriate alkyl iodide afforded the side-chain elongation products (**4**: R≠H) together with 5-alkylated derivatives (**6**).

We have applied this method for the synthesis of 6-(2-oxoalkyl)dioxinones (**7**) which could be nice precursors for the 6-(2-hydroxyalkyl) derivatives. Thus, treatment of **4a** with LDA followed by reaction with



Scheme 3

benzoyl chloride (1 mol equiv.) gave (Z)-**8c** in 43% yiled. Though hydrolysis of (Z)-**8c** with aq. ammonia in methanol gave desired 6-phenacyl derivative (**7c**), use of 0.5 mol equiv. of benzoyl chloride in the above reaction gave directly **7c** in 48% yield. The configuration of (Z)-**8c** obtained in the above reaction was confirmed by comparison of its NMR spectrum with that of the corresponding (E)-isomer, which was formed by irradiation (>300 nm) of the (Z)-isomer. The ^{1}H-NMR signal of the vinyl proton (δ of (Z)-isomer: 6.33 and that of (E)-isomer: 6.10) verified the assigned configurations. Essentially by the same method (using the halide in 0.6 mol equiv.), the 6-acetonyl derivative (**7b**) was obtained in 38% yield. Use of acetic anhydride instead of acetyl chloride in the above reaction resulted in lowering the yield of **7b** (14%). Though the yields are unsatisfactory, the method provides a general way to synthesize 6-(2-oxoalkyl)dioxinones (**7**). Using chloro- and benzyloxyacetyl chloride as the acylating reagent, terminally functionalized derivatives (**7d** and **7e**) were obtained in satisfactory yields.



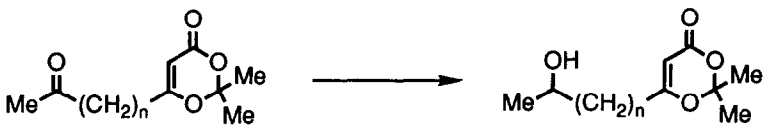
Scheme 4

Synthesis of 6-(3- and 4-oxoalkyl)dioxinones——6-(3-oxobutyl)dioxinone (**10**) was prepared by the reaction of the 6-bromomethyldioxinone (**3a**) with sodium salt of benzyl acetoacetate. The reaction afforded two products (**9** and **11**) in 49% and 22% yields, respectively. Catalytic hydrogenation of the major product (**9**) gave the 6-(3-oxobutyl)dioxinone (**10**) with spontaneous decarboxylation.

Synthesis of the 6-(4-oxopentyl)dioxinone (**12**) from 6-methyldioxinone (**4a**) by base-mediated Michael addition with methyl vinyl ketone was

reported recently in a communication form.[9] We also achieved its synthesis in essentially the same manner as described in **Experimental Section.**

By reduction with sodium borohydride, all of these oxoalkyl compounds gave the corresponding hydroxyalkyl derivatives, which could served as the substrates for the reactions to be examined in this paper.



7b n = 1 **13b** n = 1
10 n = 2 **14** n = 2
12 n = 3 **15** n = 3

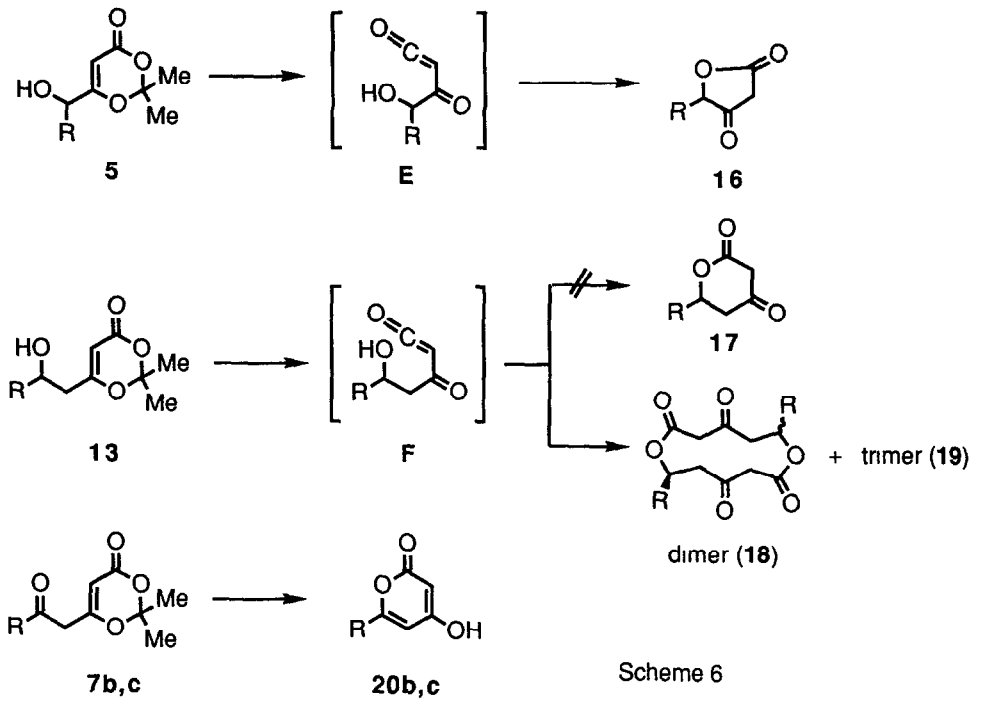
Scheme 5

Synthesis of β-keto-γ-lactones by means of intramolecular ketene trapping: Method A

As reported in our recent paper,[6] mere heating of 6-(1-hydroxyalkyl)dioxinones (**5a** and **5b**) in toluene (method A) resulted in the formation of the corresponding β-keto-γ-lactones (**16**) in satisfactory yields.

If the same method (A) was applied to the 6-(2-hydroxyalkyl)dioxinones (**13**), however, a complex mixture resulted. For example, heating of 6-(2-hydroxypropyl)dioxinone (**13b**) in toluene produced a complex mixture. Though its NMR spectrum showed almost the same signals as those of **17b** (see, **Experimental**), the separation of the products by chromatography had failed due to identical behaviors of the products. Mass spectrum of the mixture revealed the presence of dimer and trimer of the corresponding hydroxylacylketene species (**18** and **19**: R=Me).

It should be noted that, if the oxo derivatives (**7b** and **7c**) were refluxed in toluene, the corresponding 2-pyrones (**20b** and **20c**) were obtained in high yields. It is obvious that the reactions proceeded again *via* the corresponding acylketenes. We will discuss later the reason why such different reactivity exists between **5** and **13** in method A from mechanistic point of view.

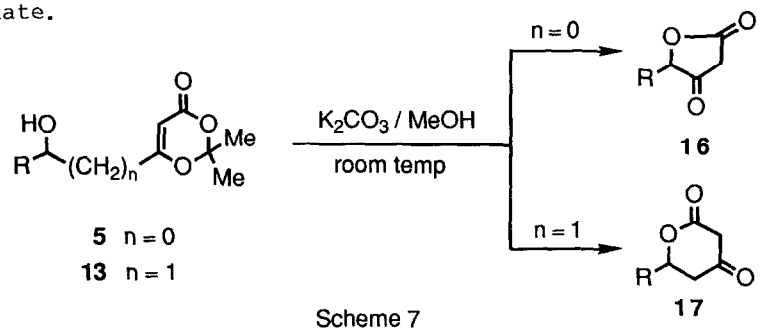


Scheme 6

Synthesis of β-ketolactones via potassium carbonate-methanol mediated ring opening: Method B

Since the intramolecular ketene trapping reaction of 5-(1-aminoalkyl)dioxinone or its 6-isomers gave the corresponding β- or γ-lactams,[5] it is obvious that this reaction, though not suitable for the formation of δ-lactones as described in the foregoing section, is fit for the formation of four- and five-membered rings.

In order to synthesize both five- and six-membered lactones from the corresponding dioxinones, the following method has been elaborated which consists of treating the latter compounds in methanol containing potassium carbonate.



Scheme 7

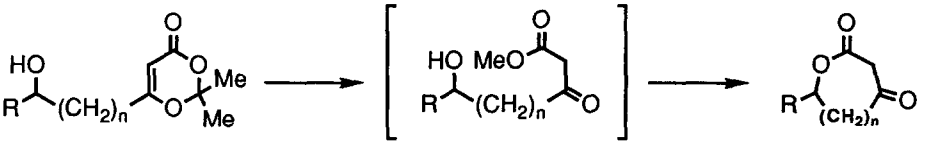
As shown in Table I, all reactions using 6-(2-hydroxyalkyl)dioxinones (13) proceeded at room temperature and the desired δ-lactones (17) were obtained all in high yields. The same method (method B), if applied to 6-(1-hydroxyalkyl)dioxinones (5), also gave γ-lactones (16) in comparable yields as those attained by the above intramolecular ketene trapping reactions.

Table I. Application of Method B to 6-(1- and 2-Hydroxyalkyl)-dioxinones (5 and 13)

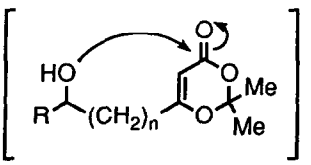
Starting Material	R	Product Compd	Yield (%)
5a	H	16a	88
5b	Me	16b	94
13b	Me	17b	78
13c	Ph	17c	99
13d	CH_2Cl	17d	84
13e	CH_2OBn	17e	84

The following mechanism is proposed for this novel lactone forming reaction (method B). In the first step (step 1), the dioxinone ring opening by methoxide ion gives rise to the β-keto esters (21 and 22), which by base-catalyzed lactone ring formation lead to the final products (16 and 17).

By treatment of the 6-methyldioxinone (4a) in methanol containing potassium carbonate, methyl acetoacetate was obtained as the sole product. This fact supports that the step 1 in method B is the dioxinone ring opening caused by methoxide ion.



5 n = 0 **13** n = 1 | **21** n = 0 **22** n = 1 | **16** n = 0 **17** n = 1



G

Scheme 8

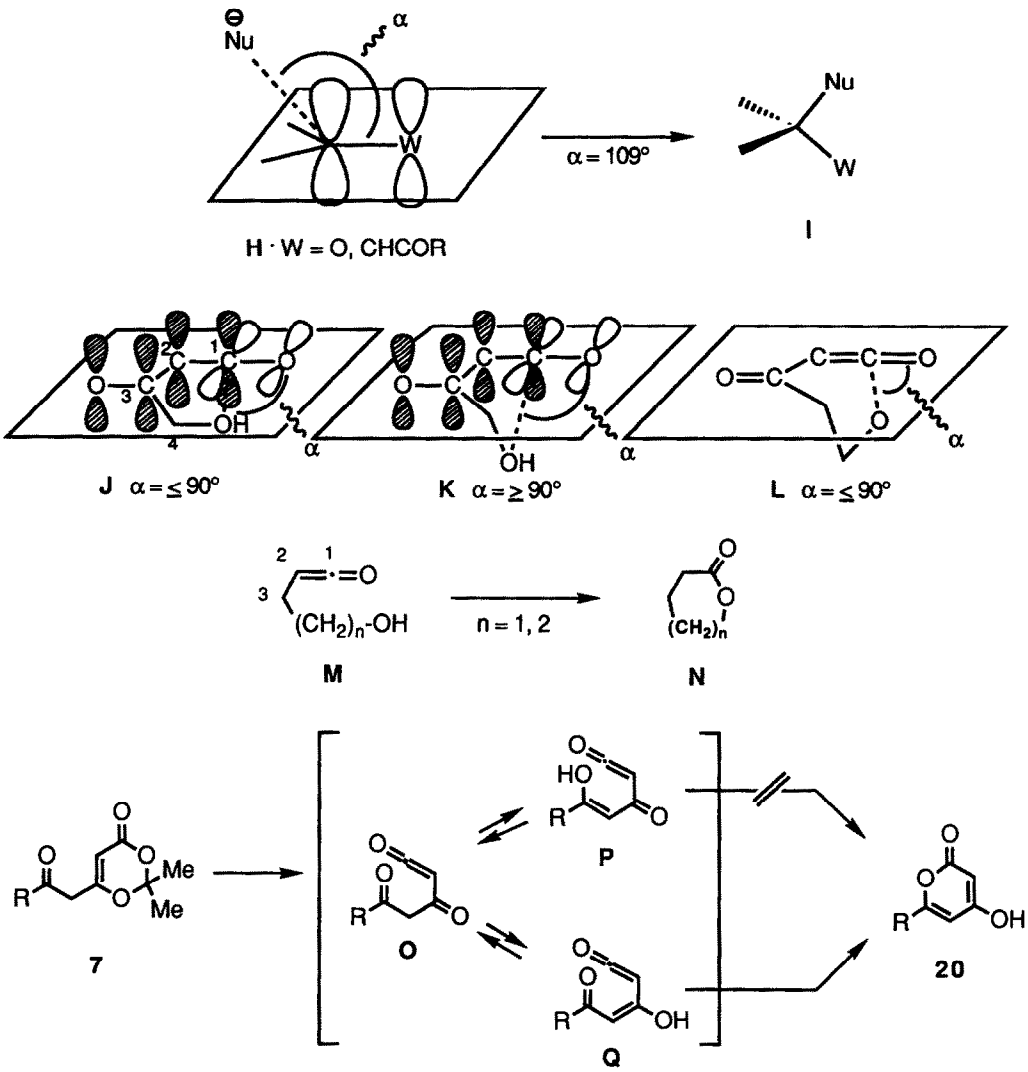
An alternative mechanism consisting from direct base-mediated intramolecular dioxinone ring opening (see **G** in Scheme 8, possible only for δ-lactone formation) is excluded by the following experiment. Thus, treatment of the dioxinones (**13b**) in tert-butanol containing potassium carbonate had ended in the complete recovery of the starting material. This fact shows that the reaction should proceed only by the intermolecular attack of methoxide ion (note that tert-butoxide ion is too bulky to act as an adequate nucleophile).

Mechanistic explanation which accounts for the difference between two types of lactone formation reaction (methods A and B)

In Baldwin rule,[10] formation of n-membered lactones from ω-hydroxy acids or esters is categorized as n-exo-trig closure reactions and predicted as an exceptionally favorable process for 5- and 6-membered lactones. In accordance, method B as described above has offered a general route to 5- and 6-membered lactones. By contrast, method A afforded only 5-membered lactones (**16**) and not 6-membered ones (**17**). In this section, we would like to propose a reasonable explanation why method A is not a feasible one to form the 6-membered lactones.

The basic concept of Baldwin rule by which the favoured exo-trigonal ring closures is predicted depends on how the required trajectory[11] (**H→I**: α=109°) is satisfied. Formally, though the intramolecular ketene trapping process (method A) belongs to 5-exo-dig mode (note that the carbon forming the final ring bond is sp hybridized, see orbital picture: **J**), the actual situation corresponds to 5-exo-trig mode (note that unshaded p-lobes correspond to those in **H**). Since $C^1=C^2$ and $C^3=O$ bonds in the acylketene species should lie in the same plane, the terminal OH group (the nucleophile) can not adopt the required trajectory so long as all of the four carbon atoms (C_1-C_4) occupy the same plane (see **J**). It is because the angle (α) must be 90° or the less. In order to aquire larger angle (α=≥90°), the oxygen atom in the hydroxymethyl group should distort out of the plane (see **K**). In this conformation (**K**), the required trajectory (α=≥90°) can be achieved.

It should be noted that the required trajectory is not readily accessible if two methylene units present in the acylketene (**L**). Within possible distortion of the terminal CH_2OH group, the length of two methylene chain is too long to adopt the required trajectory (α=<90°).



Scheme 9

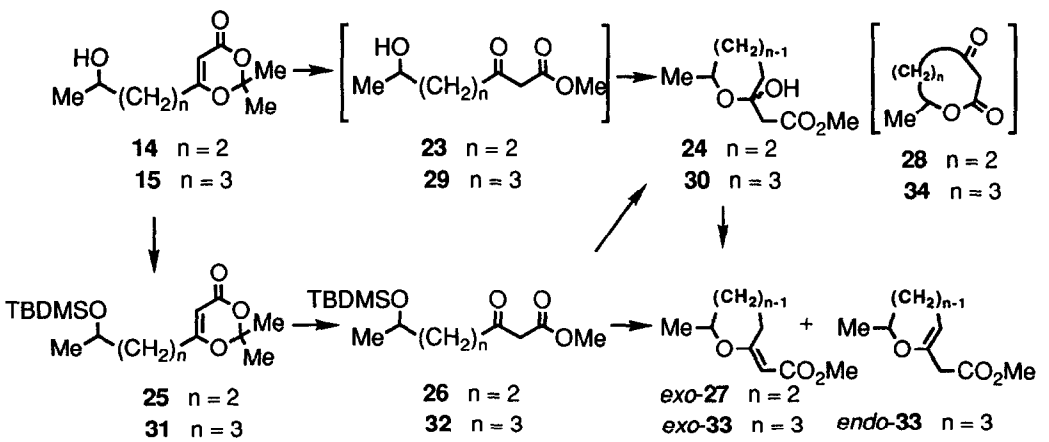
Many intramolecular ketene trapping reactions of hydroxyalkylketene (**M**) giving both 5- and 6-membered lactones (**N**) are known.[12,13] Since the requirement for planarity is restricted only to three carbon atoms (C_1-C_3) for **M** (note that the same planarity requirement for **J** and **L** is four

carbon atoms: C_1-C_4), the trajectory necessary for ring closure is readily attained even in the case of n=2.

The formation of the 2-pyrone derivatives (20) from 7 is also explainable as follows. Thus, the primarily formed ketene (O) equilibrates with either P or Q. Since the 6-exo-dig closure via P is prohibited (or at least difficult) to occur like L, the 6π-electron cyclization of Q is the only possible route to the pyrones (20). This conclusion is supported by the detailed picture of photochemistry of 2,4-cyclohexadien-1-ones obtained by Quinkert et al.[14] Thus, the dieneketenes derived from the cyclohexadienones via $^1(n,\pi^*)$ cyclize readily through thermally allowed 6π electrocyclic reaction to the starting cyclodienones (note that the former ketenes are isoelectronic with Q).

Application of method B to dioxinones having (3-hydroxybutyl)- or (4-hydroxypentyl) group at the 6-position

Keeping that the dioxinone having 1- or 2-hydroxyalkyl group at the 6-position gave β-oxo-γ- and δ-lactones by method B in mind, we then applied this method to the higher methylene homologues (14 and 15). When 14 was subjected to method B, the tetrahydrofuran (24) was obtained as a mixture of epimers at the 2-position. In order to verify the formation of the ester (23) as the intermediate, the hydroxyl group of 14 was protected with tert-butyldimethylsilyl group. When the silyl ether (25) thus



Scheme 10

obtained was treated in methanol containing potassium carbonate, the expected ester (**26**) was obtained as a sole product. Treatment of **26** with aq. acetic acid then gave **24** and its dehydrated product (exo-**27**) in 68% and 28% yields, respectively. The latter product (exo-**27**) was also obtained as a sole product when **24** was treated with p-toluenesulphonic acid in benzene. It is obvious in both cases that 5-exo-trig closure to **24** is the more preferable process to 7-exo-trig closure affording the seven-membered lactone (**28**).

Similar result (6-exo-trig > 8-exo-trig) was also obtained when **15** was used as the substrate. Only difference was that the dehydrated cyclization product (**33**) was a mixture of exo- and endo-isomers (ratio of endo/exo = ca. 4).

Patasis and Patane[9] reported recently that when **15** was heated in toluene (method A), the 8-membered lactone (**34**) was obtained in high yield. In our hand, this reaction gave, in addition to **34**, significant amounts of dimer and trimer as well. Here again, the same dioxinone (**15**) afforded different products (**30** by method B and **34** by method A). The reason for the formation of **34** by method A probably reflects that the trajectory nessesary for the 8-exo-trig closure (see **H** in Scheme 9) is attained due to longer methylene chain.

Conclusion

Intramolecular ketene trapping reactions to give either lactones and amides have ample precedents[15] and, in some cases, provided novel routes to the compounds whose synthesis was difficult by other methods. The synthesis of macrocyclic lactones from 2,4-cyclohexadien-1-ones having ω-hydroxyalkyl group as one of the 2-substituents via the corresponding dieneketenes is such an example.[16] In this reaction, the configuration of C=C bond directly attacked to the ketene functions has important role in determining the products. In this paper, we have found that acylketenes derived from the dioxinones having hydroxyalkyl group at the 6-position are nice precursors for 5-membered lactones and not for the 6-membered ones (method A) and proposed an idea which accounts for this trend. Also, an alternative method (method B) which provides both 5- and 6-membered lactones has been explored. With these two methods (A and B) in hand, the products from the acylketenes from a given dioxinone has become predictable in some extent.

Our efforts are now paid to synthesize dioxinones having hydroxyalkyl

group at the 6-position as enantiomerically pure compounds (EPC) and to use them for the preparation of a variety of natural products.[17,18] The details of these studies will be reported in the subsequent paper.[19]

Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM PMX 60SI or a JEOL JNM-GX 500 spectrometer, with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a JEOL-JMS-01SG-2 spectrometer. Silica gel used for column chromatography was Wakogel C-200 and the ratios of solvent mixtures are shown as volume/volume.

2,2-Dimethyl-6-(2-oxo-2-phenylethyl)-1,3-dioxin-4-one (7c)---To a solution of lithium diisopropylamide (LDA, 22 mmol) in THF (30 ml) at -78 °C was added hexamethylphosphoric triamide (HMPA, 7.16 g, 40 mmol) and the mixture was stirred for 30 min. After the dioxinone (**4a**, 2.84 g, 20 mmol) was added dropwise, the mixture was stirred for 30 min, and then a solution of benzoyl chloride (1.40 g, 10 mmol) in THF (5 ml) was added dropwise. The whole procedure was carried out at -78°C. After the addition of benzoyl chloride, the temperature of the reaction mixture was raised gradually to room temperature. After addition of aq. HCl, the product was taken in ether and the ethereal solution was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed on silica gel. Elution with hexane-AcOEt (3:1) gave 1.17 g (48%) of **7c**.

7c: colorless flakes, mp 110-112 °C (hexane-AcOEt). High resolution MS m/z 246.0892 (M^+; calcd for $C_{14}H_{14}O_4$: 246.0891). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.70 (6H, s, 2 x CH_3), 3.90 (2H, s, CH_2), 5.43 (1H, s, C_5-H), 7.37-8.13 (5H, m, Ar).

(Z)-6-(2-Benzyloxy-2-phenylethyl)-2,2-dimethyl-1,3-dioxin-4-one [(Z)-8c]----The same reaction using an equal amount (2.81 g, 20 mmol) of benzoyl chloride afforded after chromatography over silica gel gave 1.52 g (43%) of (Z)-**8c**.

(Z)-**8c**: colorless needles, mp 118-121 °C (ether). High resolution MS m/z 350.1154 (M^+; calcd for $C_{21}H_{18}O_5$: 350.1153). IR ($CHCl_3$): 1742, 1715, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.38 (6H, s, 2 x CH_3), 5.50 (1H, s, C_5-H), 6.32 (1H, s, =CH-), 7.16-8.50 (10H, m, 2 x Ar).

A solution of (Z)-**8c** (20 mg) in $CDCl_3$ (0.4 ml) in an NMR sample tube was irradiated for 10 min by high-pressure mercury lamp (400 W) equipped with Pyrex filter. The ^{1}H-NMR spectrum of the mixture revealed approximately equal amounts of two compounds to be formed. One component was the starting (Z)-**8c**, whose olefinic proton at the side chain appeared as δ 6.32. Another component revealed the corresponding signal at δ 6.10.[20]

2,2-Dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (7b) and its Terminally Functionalyzed Derivatives---Under exactly the same conditions as used for the synthesis of **7c**, the following compounds were prepared from the corresponding acyl chlorides.

7b: yield, 38%. Colorless needles, mp 53-55 °C (CH_2Cl_2-hexane). High resolution MS m/z 184.0736 (M^+; calcd $C_9H_{12}O_4$: 184.0735. Found: 184.0735). IR ($CHCl_3$): 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.72 [6H, s, $C_2(CH_3)_2$], 2.23 (3H, s, CH_3), 3.33 (2H, s, CH_2), 5.33 (1H, s, C_6-H).

7d: yield, 69%. Colorless needles, mp 64.5-65 °C (ether-hexane). Anal. Calcd for $C_9H_{11}ClO_4$: C, 49.42; H, 5.07; Cl, 16.23. Found: C, 49.46; H, 5.11; Cl, 16.40. IR ($CHCl_3$): 1730, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.73 [6H, s, $C(CH_3)_2$], 3.59 (2H, s, =C-CH_2), 4.18 (2H, s, CH_2Cl), 5.40 (1H, s, C_5-H).

7e: yield, 67%. Colorless oil. High resolution MS m/z 291.1243 (M^+ + 1; calcd for $C_{16}H_{19}O_5$: 291.1231). IR ($CHCl_3$): 1735, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.76 [6H, s, $C(CH_3)_2$], 3.50 (2H, s, CH_2CO), 4.11 (2H, s, CH_2OBn), 4.73 (2H, s, OCH_2Ph), 5.33 (1H, s, C_5-H), 7.36 (5H, s, Ph).

6-(2-Benzyloxycarbonyl-3-oxobutyl)-2,2-dimethyl-1,3-dioxin-4-one (9)---Benzyl acetoacetate (5.76 g, 30 mmol) was added to a suspension of NaH (60% in oil, 1.20 g, 30 mmol) in dry N,N-dimethylformamide (30 ml) under ice cooling. To this solution was added **3a** (2.21 g, 10 mmol) dropwise (ca. 2 min). After 30 mins' stirring, ice-water was added and the product was extracted with ether and the ethereal solution was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was subjected to silica gel column chromatography (hexane-AcOEt, 5:1) to give 1.61 g (49%) of **9**. Elution with hexane-AcOEt (3:1) gave 0.574 g (12%) of **11**.

9: colorless oil. High resolution MS m/z 332.1260 (M^+; calcd for $C_{18}H_{20}O_6$: 332.1259). IR ($CHCl_3$): 1740, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.57 [6H, s, $C(CH_3)_2$], 2.23 (3H, s, CH_3), 2.83 (2H, d, J=8 Hz, CH_2), 3.83 (1H, t, J=8 Hz, C_2-H), 5.23 (3H, s, Ar-CH_2 and C_5-H), 7.40 (5H, s, Ar).

11: colorless prisms, mp 113-115 °C (CH_2Cl_2-hexane). High resolution MS m/z 414.1315 (M^+; calcd for $C_{22}H_{22}O_8$: 414.1313). IR ($CHCl_3$): 1713 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ 1.63 [12H, s, 2 x $C(CH_3)_2$], 2.07 (3H, s, CH_3), 2.93 (4H, s, 2 x CH_2), 5.17 (2H, s, $ArCH_2$), 5.23 (2H, s, 2 x C_5-H), 7.33 (5H, s, Ar).

2,2-Dimethyl-6-(3-oxobutyl)-1,3-dioxin-4-one (10)----Catalytic hydrogenation of **9** (1.61 g, 4.86 mmol) in methanol (50 ml) over 10% Pd-C (300 mg) for 40 min at atmospheric pressure gave, after usual workup, **10** in quantitative yield.

10: colorless oil. High resolution Ms m/z 198.0892 (M^+; calcd for $C_{10}H_{14}O_4$: 198.0891). IR ($CHCl_3$) 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.68 [6H, s, $C_2(CH_3)_2$], 2.18 (3H, s, CH_3), 2.28-2.95 (4H, m, 2 x CH_2), 5.23 (1H, s, C_5-H).

2,2-Dimethyl-6-(4-oxopentyl)-1,3-dioxin-4-one (12)----To a mixture of LDA [prepared from diisopropylamine (23.5 g, 0.22 mol) and n-BuLi (1.6 M solution in hexane, 137.5 ml)] and CuI (76 g, 0.4 mol) in THF (500 ml) was added dropwise, a THF solution (200 ml) of **4a** (28.4 g, 0.2 mol) at -78 °C. After 30 mins' stirring, methyl vinyl ketone (14 g, 0.2 mol) in THF (200 ml) was added and the whole was stirred at -78 °C for 1 h. After the reaction mixture was treated with saturated aqueous NH_4Cl, the product was extracted with ether and the ethereal solution was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was subjected to silica gel column chromatography (hexane-AcOEt, 3:1) to give 12.9 g (52% based on the consumed **4a**) of **12**. Elution with hexane-AcOEt (5:1) gave 12 g (42%) of the unreacted **4a**.

12: colorless oil. High resolution MS m/z 213.1130 (M^++1; calcd for $C_{11}H_{17}O_4$: 213.1126). IR ($CHCl_3$) 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.69 [6H, s, $C(CH_3)_2$], 2.16 (3H, s, CH_3), 1.55-2.73 (6H, m, 3 x CH_2), 5.24 (1H, s, C_5-H).

6-Substituted 4-Hydroxy-2-pyrones (20): General Procedure for Method A Taking 2,2-Dimethyl-6-(2-oxophenylethyl)-1,3-dioxin-4-one (7c) as the Substrate----To a refluxing toluene solution (30 ml), a toluene solution (5 ml) containing **7c** (73.8 mg, 0.3 mmol) was added dropwise in a small portion (10 min is needed for the addition). After refluxing for additional 10 min, the solvent was evaporated off. The residue was recrystallized from methanol-AcOEt to give 54 mg (71%) of **20c**. Pale yellow needles, mp 246 °C (dec.) [lit.[21] 249 °C (dec.)]

In the same manner, **20b** was synthesized from **7b** in 66% yield.

20b: colorless needles, mp 188-190 °C (MeOH-AcOEt) [lit.[22] mp 188-189 °C].

Treatment of **13b** by the above procedure (method A) gave an oily complex mixture of products, whose separation by column chromatography over silica gel failed to give pure reaction products. Mass spectroscopic measurements of several fractions thus obtained [all of the ^{1}H-NMR spectra showed almost identical signals with those of **17b** (vide infra)] showed m/z 256 and 384, corresponding to the molecular ions of dimer (**18b**) and trimer (**19b**) of the ketene (**F**: R=Me).

Sodium Borohydride Reduction of the 6-(Oxoalkyl)dioxinones (7, 10, and 12) to the Corresponding Alcohols (13-15): General procedure is described using the reduction of 7c---The oxoalkyldioxinone (**7c**) (492 mg, 2 mmmol) was dissolved in methanol (10 ml) and the solution was stirred under ice-cooling. To the above solution, finely powdered sodium borohydride (76 mg, 2 mmol) was added portionwise and the whole was stirred for 10 min. After addition of aqueous HCl to decompose the excess of reducing reagent, the product was taken up in ether and the ethereal solution was dried over anhydrous $MgSO_4$. The residue obtained by evaporation of the solvent was recrystallized from ether-hexane to give 392 mg (80%) of **13c**.

13c: colorless prisms, mp 78-80 °C. High resolution MS m/z 190.0630 (M^+-58; calcd for $C_{11}H_{10}O_3$: 190.0629). IR ($CHCl_3$): 3616, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.65 (6H, s, 2 x CH_3), 2.27 (1H, d, J=2 Hz, OH), 2.68 (2H, d, J=3.5 Hz, CH_2), 4.80-5.20 (1H, m, ArCH), 5.32 (1H, s, C_5-H), 7.37 (5H, s, Ar).

13b (from **7b**): yield, 87%. Colorless oil. High resolution MS m/z 186.0892 (M^+; calcd for $C_9H_{14}O_4$: 186.0891). IR ($CHCl_3$): 3616, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, d, J=3 Hz, -CH(OH)C$\underline{H}_3$), 1.68 [6H, s, $C_2(CH_3)_2$], 2.37 (2H, d, J=3 Hz, CH_2), 2.60-3.0 (1H, m, OH), 3.87-4.37 (1H, m, C$\underline{H}$OH), 5.33 (1H, s, C_5-H).

13d (from **7d**): yield, 98%. Colorless oil. High resolution MS m/z 222.0500 (M^+; calcd for $C_9H_{11}{}^{35}ClO_4$: 222.0472). IR ($CHCl_3$): 3160, 1725, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.87 [6H, s, $C(CH_3)_2$], 2.52 (2H, d, J=6.0 Hz, =C-CH_2), 2.87-3.29 (1H, br s, OH), 3.62 (2H, d, J=5.6 Hz, CH_2Cl), 3.83-4.43 (1H, m, C$\underline{H}$OH), 5.40 (1H, s, C_5-H).

13e (from **7e**): yield, 93%. Colorless oil. High resolution MS m/z 293.1380 (M^+ + 1; calcd for $C_{16}H_{21}O_5$: 293.1388). IR ($CHCl_3$): 3450, 1730, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.66 [6H, s, $C(CH_3)_2$], 2.40 (2H, d, J=6.8 Hz, -C-CH_2), 3.35-3.83 (2H, m, C$\underline{H}$2OBn), 3.50 (1H, br s, OH), 3.95-4.24 (1H, m, C$\underline{H}$OH), 4.56 (2H, s, C$\underline{H}_2$Ph), 5.33 (1H, s, C_5-H), 7.33 (5H, s, Ph).

14 (from **10**): yield, 92%. Colorless oil. High resolution MS m/z

201.1130 (M^+ + 1; calcd for $C_{10}H_{17}O_4$: 201.1126). IR ($CHCl_3$): 3630, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.25 [3H, d, J=6 Hz, CH(OH)C<u>H</u>$_3$], 1.70 [7H, s, C(CH_3)$_2$ and OH], 1.90 (1H, s, C_2-H), 2.10-2.60 (3H, m, C_2-H and C_1H_2), 3.88 (1H, q, J=6 Hz, C<u>H</u>OH), 5.30 (1H, s, C_5-H).

15 (from **12**), yield 88%. Colorless oil. High resolution MS m/z 215.1264 (M^+ + 1; calcd for $C_{11}H_{19}O_4$: 215.1282). IR ($CHCl_3$): 3500, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.18 [3H, d, J=6.2 Hz, CH(OH)C<u>H</u>$_3$], 1.20-1.90 (4H, m, 2 x CH_2), 1.68 [6H, s, C(CH_3)$_2$], 1.90-2.50 (3H, m, =C-CH_2 and OH), 3.52-4.06 (1H, m, C<u>H</u>OH), 5.24 (1H, s, C_5-H).

Synthesis of γ- and δ-Lactones (16 and 17) from 6-(Hydroxyalkyl)-1,3-dioxin-4-ones (5 and 13)---As shown in Table I, the following lactones were prepared according to method B.

17b (from **13b**): colorless powder, mp 124-126 °C (EtOH) [lit.[23] mp 123-125 °C]. ^{1}H-NMR ($CDCl_3$) δ 1.53 (3H, d, J=6.4 Hz, CH_3), 2.47 (1H, dd, J=18.6, 11.6 Hz), 2.73 (1H, dd, J=18.6, 2.6 Hz), 3.44 (1H, d, J=18.8 Hz), 3.51 (1H, d, J=18.8 Hz), 4.76-4.84 (1H, m, OCH).

17c (from **13c**): colorless prisms, mp 132-133 °C (AcOEt-hexane). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.66; H, 5.44. ^{1}H-NMR ($CDCl_3$) δ 2.90 (1H, dd, J=18.3, 10.4 Hz), 2.97 (1H, dd, J=18.3, 3.7 Hz), 3.50 (1H, d, J=19.2 Hz), 3.69 (1H, d, J=19.2 Hz), 5.71 (1H, dd, J=10.4, 3.7 Hz, OCH), 7.38-7.48 (5H, m, Ph).

17d (from **13d**): colorless needles, mp 85-86 °C (AcOEt-ether). Anal. Calcd for $C_6H_7ClO_3$: C, 44.44; H, 4.35; Cl, 21.58. Found: C, 44.54; H, 4.27; Cl, 21.57. IR ($CHCl_3$): 1775, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.72 (1H, dd, J=18.3, 11.0 Hz), 2.87 (1H, dd, J=18.3, 3.1 Hz), 3.50 (1H, d, J=18.9 Hz), 3.59 (1H, d, J=18.9 Hz), 3.80 (2H, d, J=4.9 Hz, CH_2Cl), 4.86-4.92 (1H, m, O-CH).

17e (from **13e**): colorless needles, mp 77-78 °C (AcOEt-ether). Anal. Calcd for $C_{13}H_{14}O_6$: C, 66.41; H, 6.03. Found: C, 66.61; H, 5.80. IR ($CHCl_3$): 1760, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.68 (1H, dd, J=17.4, 6.4 Hz), 2.79 (1H, dd, J=17.4, 5.2 Hz), 3.42 (1H, d, J=19.5 Hz), 3.51 (1H, d, J=19.5 Hz), 3.64 (1H, dd, J=10.7, 3.4 Hz), 3.83 (1H, dd, J=10.7, 3.4 Hz), 4.53 (1H, d, J=11.9 Hz), 4.58 (1H, d, J=11.9 Hz), 4.80-4.85 (1H, m, OCH), 7.25-7.40 (5H, m, Ph).

The γ-lactones (**16a** and **16b**) were obtained from the same starting materials in comparable yields by the application of method A.[6] As noted in the text, however, δ-lactones (**17b-17e**) could be synthesized only by method B and application of method A to **13** resulted in the formation of

dimers and trimers (see **18** and **19** in Scheme 6) as the major products.

Application of Method B to the Dioxinones Having Hydroxyalkyl Group at the 6-Position Giving the Tetrahydrofuran Derivatives: General procedure for method B is described using 14 as the substrate----A solution of **14** (200 mg, 1 mmol) and potassium carbonate (207 mg, 1.5 mmol) in MeOH (3 ml) was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was neutralized by the addition of diluted HCl and extracted by ether. After drying over $MgSO_4$, the solvent was evaporated. The residue thus obtained was subjected to silica gel column chromatography (hexane-AcOEt, 5:1) to give 139 mg (80%) of **24**.

24, colorless oil. High resolution MS m/z 157.0843 (M^+ - OH; calcd for $C_8H_{13}O_3$: 157.0864). IR ($CHCl_3$): 3500, 1720 cm^{-1}.

2,2-Dimethyl-6(3-tert-Butyldimethylsilyloxybutyl)-1,3-dioxin-4-one (25)----tert-Butyldimethylchlorosilane (1.28 g, 8.48 mmol) and imidazole (576 mg, 8.48 mmol) were added to a solution of **14b** (1.13 g, 5.65 mmol) in dry DMF (10 ml) under ice-cooling and the whole was stirred at room temperature for 2 h. After dilution with water, the product was extracted by ether and the ethereal solution was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was separated by silica gel column chromatography (hexane-AcOEt, 20:1) to give 1.77 g (qunat.) of **25**.

25, colorless oil. High resolution MS m/z 257.1200 (M^+ - ^tBu; calcd for $C_{12}H_{21}O_4Si$: 257.1208). IR ($CHCl_3$): 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 0.05 [6H, s, $Si(CH_3)_2$], 0.91 (9H, s, ^tBu), 1.15 (3H, d, J = 6 Hz, $OCHCH_3$), 1.40-1.90 (2H, m, CH_2), 1.68 [6H, s, $C(CH_3)_2$], 2.10-2.55 (2H, m, $=C-CH_2$), 3.60-4.10 [1H, m, CH(OSi)], 5.23 (1H, s, C_5-H).

Application of Method A to 25 Giving 26---Compound **26** was prepared by the application of method A to **25**. Thus, refluxing of **25** in toluene for 2 h afforded **26** in 98% yield.

26: colorless oil. High resolution MS m/z: 231.1078 (M^+ - ^tBu; calcd for $C_{10}H_{19}O_4Si$: 231.1051). IR ($CHCl_3$): 1745, 1715 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 0.05 [6H, s, $Si(CH_3)_2$], 0.89 (9H, s, ^tBu), 1.13 (3H, d, J=6H z, $OCHCH_3$), 1.50-1.96 (2H, m, CH_2), 2.63 (2H, t, J=7.6 Hz, $COCH_2$), 3.45 (2H x 5/6, s, CH_2), 3.66-4.16 (1H, m, CH-OSi), 3.73 (3H, s, OCH_3), 4.99 (1H x 1/6, s, O-C=CH), 12.08 (1H x 1/6, s, OH).

Formation of Tetrahydrofuran Derivatives (24 and exo-27) from Methyl (3-Oxo-6-tert-butyldimethylsilyloxy)heptanoate (26)---A solution of **26** (864 mg, 3 mmol) in AcOH-THF-H_2O (2:1:1, 6 ml) was stirred overnight at room temperature. After the solvent was evaporated under reduced pres-

sure, water was added to the residue. After drying the ether extract over $MgSO_4$, the solvent was evaporated. The residue thus obtained was subjected to silica gel column chromatography (hexane-AcOEt, 20:1) to give 117 mg (25%) of exo-**27**. Elution with hexane-AcOEt (5:1) afforded 355 mg (68%) of **24**.

exo-**27**: colorless oil. High resolution MS m/z 156.0782 (M^+; calcd for $C_8H_{12}O_3$; 156.0786). IR ($CHCl_3$): 1700, 1640, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, d, J=6 Hz, $OCHCH_3$), 1.55-2.28 (2H, m, CH_2), 2.90-3.40 (2H, m, $=C-CH_2$), 3.66 (3H, s, OCH_3), 4.48-4.58 (1H, m, O-CH), 5.27 (1H, s, =C-H).

Dehydration of 24 to exo-27----To a solution of **24** (261 mg, 1.5 mmol) in benzene (3 ml) was added p-TsOH (26 mg, 0.15 mmol) and molecular sieves 4A (activated powder, 500 mg) and the whole mixture was stirred overnight at room temperature. After filtration to remove the molecular sieve, the filtrate was evaporated *in vacuo* and subjected to silica gel column chromatography (hexane-AcOEt, 20:1) to give 196 mg (84%) of exo-**27**.

Formation of the Tetrahydropyran Derivative (30) from 15---Compound **30** was synthesized in 75% yield from **15** by the same procedure as described for the conversion of **14** to **24**.

30: yield, 75%. Colorless oil. High resolution MS m/z 188.1058 (M^+; calcd for $C_9H_{16}O_4$: 188.1048). IR ($CHCl_3$): 3500, 1720 cm^{-1}.

Synthesis of 31 from 15----The silylation of **15** with tert-butyldimethylchlorosilane afforded **31** as the sole product.

31: yield, 96%. Colorless oil. High resolution MS m/z 271.1347 (M^+ - ^{t}Bu; calcd for $C_{13}H_{23}O_4Si$: 271.1364). IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.05 [6H, s, $Si(CH_3)_2$], 0.91 (9H, s, ^{t}Bu), 1.13 [3H, d, J=6 Hz, $CH(OH)CH_3$], 1.0-1.8 (4H, m, 2 x CH_2), 1.68 [6H, s, $C(CH_3)_2$], 1.90-2.40 (2H, m, =CH), 3.55-4.15 (1H, m, CHOSi), 5.23 (1H, s, C_5-H).

Preparation of 32 from 31 by Method A---Refluxing of **31** in toluene as described for the conversion of **25** to **26** gave **32** in 98% yield.

32: colorless oil. High resolution MS m/z 245.1219 (M^+ - ^{t}Bu; calcd for $C_{11}H_{21}O_4Si$: 245.1208). IR ($CHCl_3$): 1745, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.05 [6H, s, $Si(CH_3)_2$], 0.89 (9H, s, ^{t}Bu), 1.13 (3H, d, J=6 Hz, $OCHCH_3$), 1.20-1.98 (4H, m, 2 x CH_2), 2.33-2.80 (2H, m, CH_2CO), 3.45 (2H x 5/6, s, CH_2), 3.50-4.0 (1H, m, CHOSi), 5.0 (1H x 1/6, s, OC=CH), 12.04 (1H x 1/6, s, OH).

Conversion of 32 to 30, exo-33, and endo-33---Treatment of **32** in AcOH-THF-water as described for the conversion of **26** to **24** and exo-**27** gave **30**

and **33** (a mixture of endo- and exo-isomers).

30: yield, 76%.

endo-**33** and exo-**33** (ca. 4:1 mixture): yield, 6%. Colorless oil. High resolution MS m/z 170.0957 (M^+; calcd for $C_9H_{14}O_3$: 170.0942). IR ($CHCl_3$): 1740, 1720 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ chemical shifts of olefinic protons 4.52-4.80 (1H x 3/4, m) for endo-isomer and 5.29 (1H x 1/4, br s) for the exo-isomer.

Dehydration of 30 to exo- and endo-33---Compound exo- and endo-**33** (a mixture of 4:1) was obtained from **30** in 76% yield by the same procedure as described in the dehydration of **24** to exo-**27**.

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