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Absolute Configuration of Novel Marine Diterpenoid Udoteatrial Hydrate Synthesis and Cytotoxicities of *ent*-Udoteatrial Hydrate and Its Analogues

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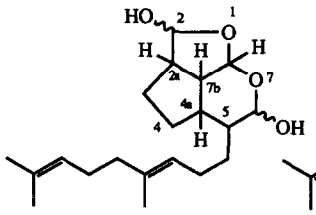
Abstract Antipode of novel marine diterpenoid udoteatrial hydrate was synthesized from (+)-genipin as a chiral building block *via* homogeranyl lactone obtained by an 1,4-addition of lithiated geranyl sulfone to the key intermediate, exomethylene lactone The stereochemistry of newly formed stereogenic center at C_5 was carefully examined by comparing ^{1}H-NMR spectra of each diastereomer of homogeranyl lactones with those of model compounds, stereochemistries of which were confirmed by single crystal X-ray determination The exomethylene lactone was successfully prepared from genipin through a catalytic hydrogenation of C_6-C_7 double bond in cyclopentene ring in genipin Our synthesis culminating the synthesis of antipode of udoteatrial hydrate could confirm the absolute configuration of udoteatrial hydrate as (*2aS, 4aS, 5S, 7bR*) The analogues of antipode of udoteatrial hydrate were also synthesized from exomethylene lactone Those analogues were subjected to the cytotoxic assay to find that diacetates of analogues involving homogeranyl side chain were cytotoxic against human carcinoma KB and A-549 cells *in vitro*

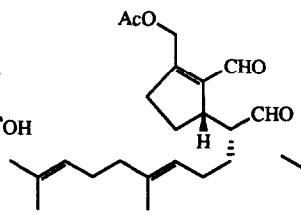
In 1981, udoteatrial hydrate (**1**)[1] was isolated by Faulkner from marine algae *Udotea flabellum* in shallow water in Florida and Belize Structural determination of **1** revealed that **1** was a hydrate form of monocyclic diterpenoid trialdehyde involving novel carbon framework named udotean skeleton with (*2aR*, 4aR*, 5S*, 7bS**) configurations Synthetic study of **1** by Whitesell *et al* [2] culminating the first total synthesis of (±)-**1**, however, concluded that the configuration at C_5 should be corrected to be (*5R**) This novel carbon framework was later found in the related marine diterpene (-)-petiodial (**2**)[3] and (-)-halimedatrial (**3**),[4] which were isolated from *Udotea petiolata* and *Halimeda* species, respectively Interestingly, the absolute configuration of **2** and **3** at carbon bearing the long side chain on cyclopentene ring was opposite to each other, while that of **1** was remained uncertain [5]

Among those novel compounds, it was reported that **2** and **3** showed significant activities against several marine bacteria, inhibition of cell division in fertilized sea urchin eggs, and cytotoxicity to herbivorous damselfish causing death within one hour Although antimicrobial activity against *Staphylococcus aureus* and *Candida albicaus* was reported, cytotoxicity as well as other biological activities of **1** have not been investigated well Because of the structural similarity of **1** to **2** and **3**, it was considered that **1** might have some biological activities comparable to those of **2** and **3**



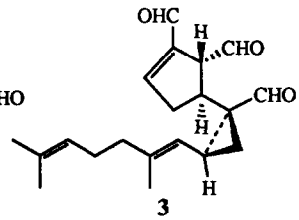
1

udoteatrial hydrate
(*2aR*, 4aR*, 5R*, 7bS**)



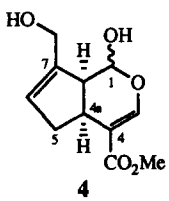
2

(-)-petiodial



3

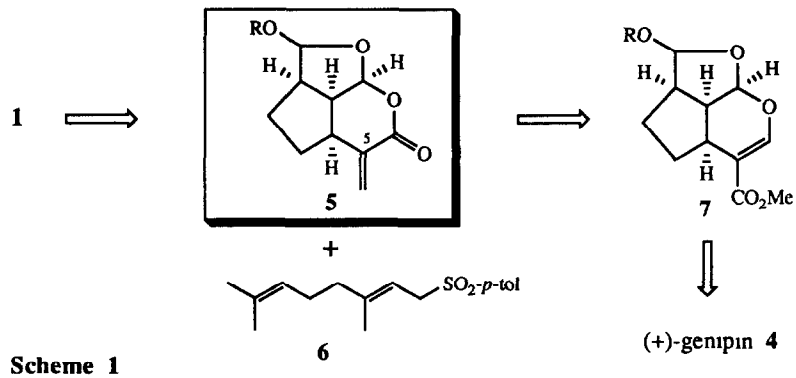
(-)-halimedatrial



4

(+)-genipin

We have studied syntheses of polyfunctional iridoids and diterpenes using monoterpene iridoid (+)-genipin (**4**) as a starting material,[5a, 6] which was available in an industry scale Since **1** could be considered to consist of the iridoid carbon framework and geranyl side chain, we decided to investigate the synthesis directed toward **1** starting from **4** to demonstrate the usefulness of **4** as a chiral building block as well as to confirm the absolute configuration of **1** Upon comparing the sign of optical rotations of the diacetates of udoteatrial hydrate with those of our synthetic compounds from **4**, the absolute configuration of **1** was determined to be (*2aS, 4aS, 5S, 7bR*) [7] Our synthetic *ent*-udoteatrial hydrate diacetates were found to be cytotoxic against human carcinoma KB and human lung carcinoma A-549 [8] We, herein, report the detail of our synthesis of antipode of **1** to determine the absolute configuration of **1** as well as brief investigations of the structure activity relationships of analogues of *ent*-udoteatrial hydrates



5

6

7

(+)-genipin **4**

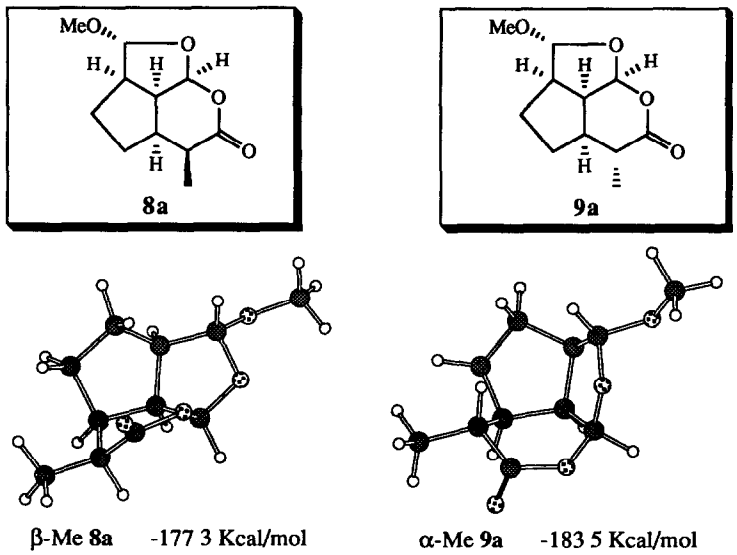
Scheme 1

Retrosynthetic analysis of udoteatrial hydrate (1)

To introduce a geranyl side chain into the iridoid framework and successive conversion into the trialdehyde effectively, the tricyclic *exo*-methylene lactone (**5**) was designed to be a key intermediate (**Scheme 1**) After introduction of geranyl side chain into **5**, **1** could be simply obtained by adjustment of oxidation state of the lactone moiety Since **5** involved all carbon required for construction of trialdehyde dihemiacetal portion, it would be useful for preparation of analogues involving variety of side chain This key intermediate **5** was expected to be derived from **4** *via* hemiacetal (**7**)

The problem upon introduction of geranyl side chain into **5** was the stereocontrol of newly formed stereogenic center at C_5 Since it seemed, however, that the side chain in **1** occupied the thermodynamically

stable α-configuration, it was considered that base catalyzed isomerization could control the stereochemistry at C_5 after introduction of the side chain into **5** To support this assumption, semiempirical calculation (MOPAC - PM3)[9] of simplified model compounds (**8a**) and α-isomer (**9a**) did show that the latter was about 6 Kcal/mol stabler than the corresponding β-isomer **8a** (**Figure 1**)

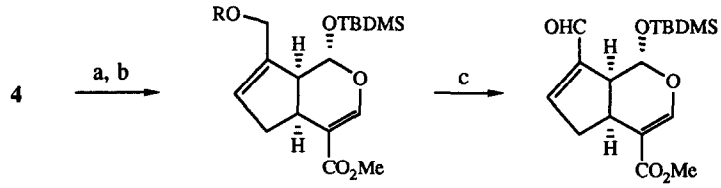


β-Me **8a** -177 3 Kcal/mol α-Me **9a** -183 5 Kcal/mol

Figure 1 calculated conformations and heats of formation of **8a** and **9a**

Preparation of key intermediate (5)

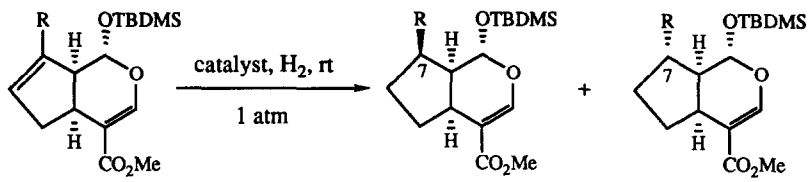
To obtain the proposed intermediate **5** from **4**, hydrogenation of C_6-C_7 double bond in **4** was first examined Three compounds (**10**) - (**12**), prepared from **4** by the sequence shown in **Scheme 2**, were hydrogenated using various catalysts and solvents to give (*7R*)- and (*7S*)-isomer as summarized in **Table 1** The hydrogenation proceeded from less hindered convex face to yield compounds involving (*7R*) configuration as expected, except entry 1 and 2 These unexpected results of hydrogenation were also found in recent reports on synthetic studies of some iridoids [10] It was probable that the steric repulsion between $TBDMSOCH_2$ group at C_7 and the TBDMS group at C_1 forced the former group to move toward a less congested side to decrease steric advantage of the convex face in these bicyclic systems Since each diastereomeric mixture of these **13**, **14** and **15** was difficult to separate in large quantities and the yield of cyclization of *7R*-**15** upon desilylation was not satisfactory because of its instability under basic conditions, we then examined the hydrogenation of aldehyde (**16**) Thus, hydrogenation of **16** prepared directly from **4** by selective oxidation of allyl alcohol moiety,[11] produced easily separable mixture of hemiacetal (**17a**) and its α-isomer (**17b**), of which stereochemistry was confirmed *via* conversion of **17a** to methyl acetal (**18a**) (**Scheme 3**)



10 R=TBDMS
11 R=H
12

Scheme 2

a) *t*-$BuMe_2SiCl$, $AgNO_3$, DMF b) cat PPTS, EtOH, rt, 90% from genipin
c) $BaMnO_4$, CH_2Cl_2, rt, 91%



10 R=CH_2OTBDMS
11 R=CH_2OH
12 R=CHO

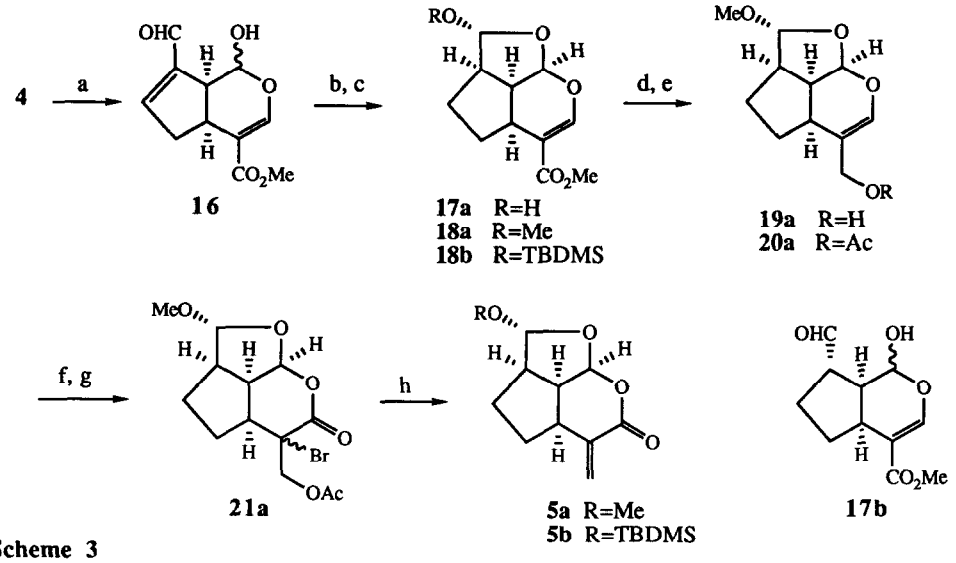
7R-**13** R=CH_2OTBDMS *7S*-**13**
7R-**14** R=CH_2OH *7S*-**14**
7R-**15** R=CHO *7S*-**15**

Table 1 hydrogenation of **10**, **11** and **12** under varoius reaction conditions

entry	substrate	catalyst [1)]	solvent	product(s) yield (%)		ratio of products [2)] *7R* *7S*
1	**10**	Pd/C	EtOH	**13**	~100	exclusively *7S*
2		Rh/Al_2O_3	AcOEt		~100	1 1
3	**11**	PtO_2	EtOH	**14**	99	8 1
4		Rh/Al_2O_3	AcOEt		80	7 3
5	**12**	Pd/C	EtOH	**15**	77	2 1
6		PtO_2	AcOEt		57	4 1
7		Rh/Al_2O_3	AcOEt		83	4 1

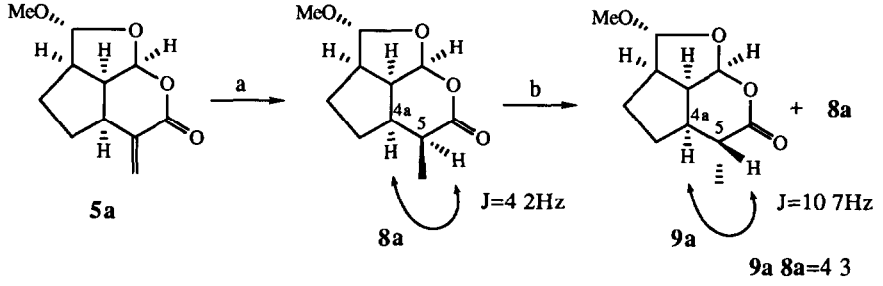
1) *ca* 1 mol% of catalysts were used
2) ratio of products was determined by ^{1}H-NMR

Reduction of the ester portion in **18a** followed by acetylation gave acetate (**20a**) Bromohydrin formation of **20a** with NBS-H_2O followed by Swern oxidation[12] afforded bromolactone (**21a**), which was successively treated with zinc in acetic acid[13] to give the key intermediate (**5a**) Similarly, **5b** (R=TBDMS) was obtained from **18b** in comparable yield to that of **5a** (see experimental section)



Scheme 3

a) $BaMnO_4$, CH_2Cl_2, rt, 71% b) cat $Rh\text{-}Al_2O_3$, H_2, AcOEt, rt, **17a** 57%, **17b** 13% c) BF_3 Et_2O, MeOH, 0 °C, 95% d) DIBAL, CH_2Cl_2, -78 °C, 90% e) Ac_2O, Et_3N, DMAP, rt, 94% f) NBS, H_2O, DMSO, rt g) $(CF_3CO)_2O$, DMSO, -65 °C, then Et_3N h) Zn, AcOH, ether, rt, **5a** 63% for 3 steps



Scheme 4

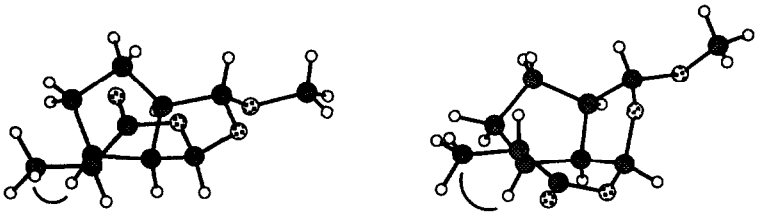
a) cat PtO_2, H_2, AcOEt, overnight, 99% b) 3eq DBU, toluene, reflux, 48 h, **9a** 42%, **8a** 31%

Determination of the stereochemistry at C_5

With the key intermediate **5a** in hand, we then examined the method to clarify the stereochemistry at C_5 upon introduction of geranyl side chain For these studies model compounds bearing methyl group at C_5 (**8a** and **9a**) were used to simplify their ^{1}H-NMR spectra Considering from the results of PM3 calculations, the α-methyl isomer **9a** would be obtained by base catalyzed isomerization of β-isomer **8a**, which was expected to be derived from **5a** by stereoselective hydrogenation We expected that their thermodynamic behavior as well as ^{1}H-NMR spectra could be efficiently used to define the stereochemistry at C_5 of the compounds bearing the homogeranyl side chain Thus, **5a** was hydrogenated with PtO_2 to give a single product, which was tentatively assigned to be **8a** bearing β-methyl group at C_5 (**Scheme 4**) Investigations of the isomerization of the C_5-β-methyl group under various conditions, however, afforded unexpected results Thus, isomerization of **8a**

proceeded in the presence of DBU at refluxing toluene but not at refluxing THF or benzene to give nearly 3 4 ratio of **8a** and **9a** Any changes of the ratio in equilibration at elevated temperature (e g xylene reflux) were not observed The isomerization of **9a** under the same conditions could confirm that two isomers were in equilibration at the above ratio In a case of **8b** and **9b**, the ratio in equilibration was found to be close to 1 1 (see experimental section)

In their 400 MHz ^{1}H-NMR spectra, the observed coupling constants between H_{4a} and H_5 ($J_{4a\text{-}5}$) of **8a** and **9a** were 4 3 and 10 7 Hz, respectively These experimental data as well as NMR informations suggested that the conformation of **8a** and **9a** especially at the 6-membered lactone ring was quite different from each other The assignment of stereochemistry at C_5 of both compounds discussed above as well as their conformations were eventually confirmed by their single crystal X-ray analysis As shown in **Figure 2**, dihedral angles of methyl group at C_5 relative to H_{4a} ($\angle CH_3\text{-}C_5\text{-}C_{4a}\text{-}H_{4a}$) in each compound were close These structural features might account for their nearly the same thermodynamic stability during the equilibration reaction



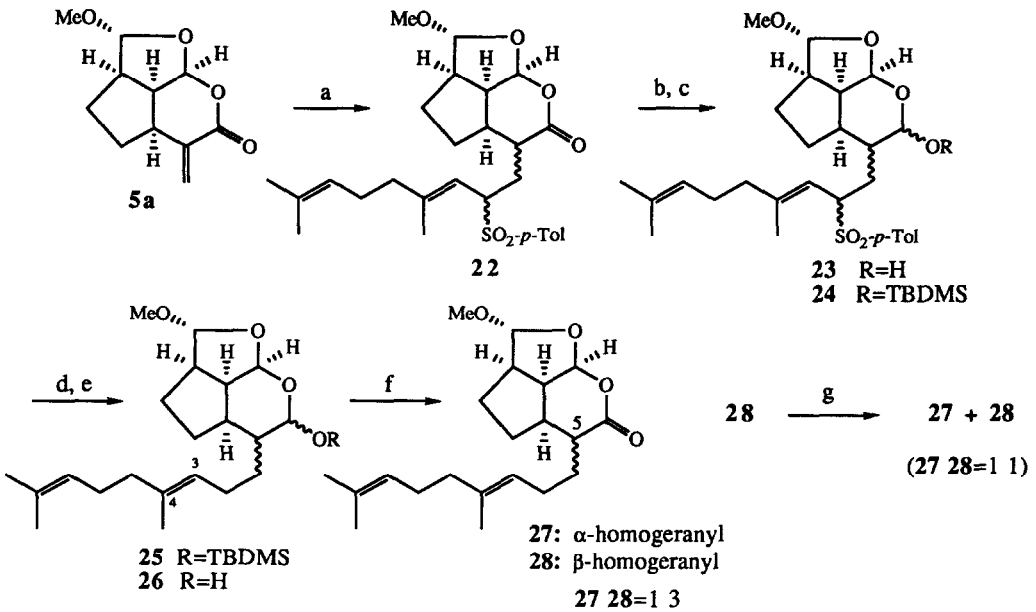
dihedral angle -59 5° dihedral angle -48 9°

8a **9a**

Figure 2 X-ray analysis of **8a** and **9a**

Synthesis of *ent*-udoteatrial hydrate and determination of its absolute configuration

Having accumulated data to assign the C_5 stereochemistry, we then examined to introduce a geranyl side chain into **5a** Thus, treatment of a lithium salt of geranyl *p*-tolylsulfone **6**[14] with **5a** afforded 1,4-addition product (**22**) (**Scheme 5**) Since removal of the sulfone group from **22** was unsuccessful because of the presence of lactone moiety, the lactone carbonyl in **22** was temporarily reduced and protected with TBDMS ether to give acetal (**24**) Birch reduction[15] of the sulfone moiety in **24** smoothly afforded homogeranyl compound (**25**) Although a small amount of the isomeric compound at $C_{3'}\text{-}C_{4'}$ double bond of **25** were observed in ^{1}H-NMR, they could be eliminated in the HPLC separation of **27** and **28** The TBDMS ether moiety in **25** was deprotected and oxidized with PCC to afford a mixture of isomeric homogeranyl lactone (**27**) and (**28**), of which ratio was found to be 1 3 in 400 MHz ^{1}H-NMR spectrum This mixture could be separated by HPLC and the major isomer **28** was isomerized into a 1 1 mixture of **27** and **28** under the influence of DBU in refluxing toluene as we experienced in model studies The chemical shifts and coupling patterns of characteristic hydrogens on the ring in **27** and **28** were in good agreement with those of **9a** and **8a**, their stereostructures were, thus, assigned to be α- and β-homogeranyl lactone, respectively (**Figure 3**) [16] These assignments were eventually confirmed by successful synthesis of *ent*-**1** from **27**



Scheme 5

a) geranyl *p*-tolyl sulphone, LDA, THF, -78 °C, then **5a**, 82% b) DIBAL, CH_2Cl_2, -78 °C, 93% c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 90% d) Li / $EtNH_2$, THF, -78 °C, 76% e) TBAF, THF, 0 °C, 90% f) PCC, CH_2Cl_2, rt, 80% (**27 28**=1 3) g) DBU, toluene, reflux, 12 h, 70% (**27 28**=1 1)

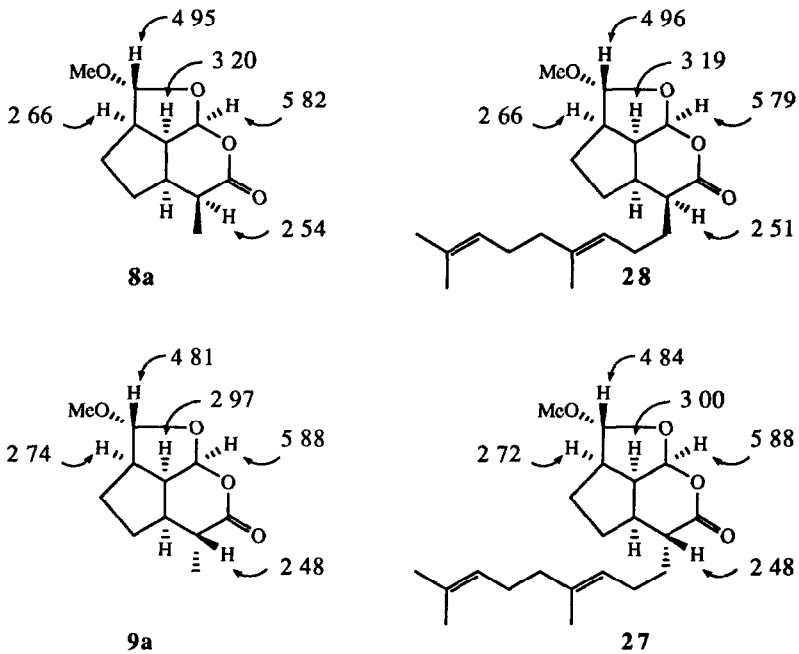
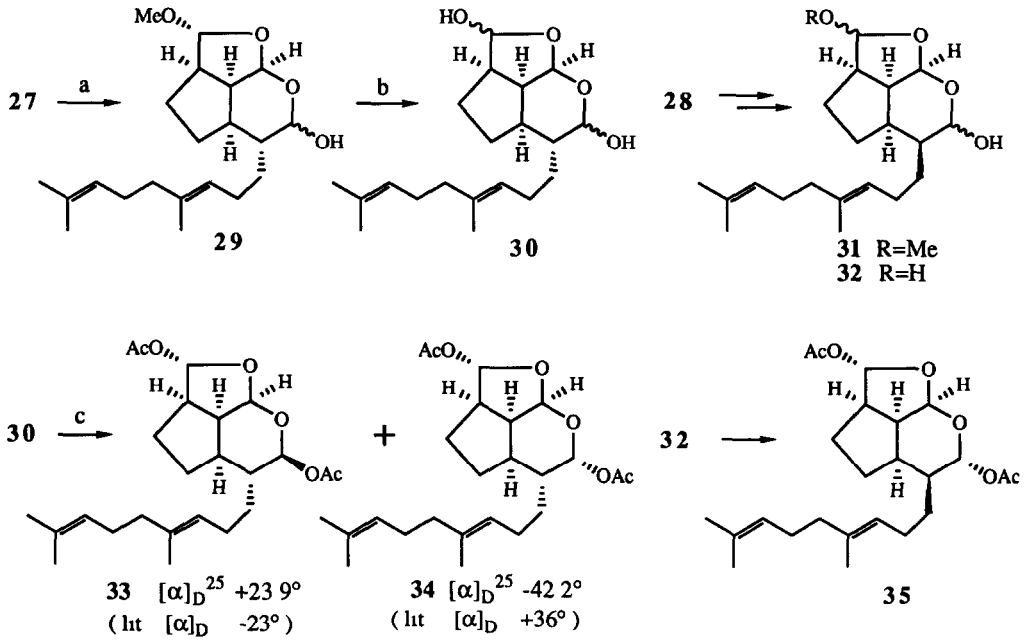


Figure 3

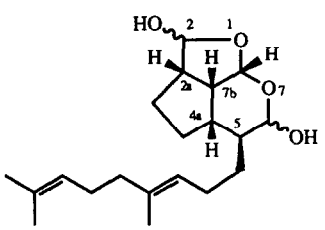


Scheme 6

a) DIBAL, CH_2Cl_2, -78 °C, 99% b) (0 1M) *p*-TsOH, THF H_2O acetone = 4 2 1, rt, 69%
c) Ac_2O, Pyr, rt, 66% for **33** and **34** (**33** **34**=2 1 1)

Reduction of the α-homogeranyl lactone **27** with DIBAL followed by acid hydrolysis[2] of the resulting hemiacetal (**29**) accomplished the synthesis of dihemiacetal (**30**) being consistent with relative structure of udoteatrial hydrate **1** (**Scheme 6**) The 5-*epi*-isomer (**32**) could be also obtained from **28** by the same procedure as for **27** (see experimental section)

In order to confirm the relative stereochemistries of **30** and **32**, they were converted into their diacetates Upon treating **30** with acetic anhydride in pyridine, two diacetates (**33**) and (**34**) were obtained in 2 1 1 ratio, which could be separated by HPLC, while acetylation of **32** produced a single diacetate (**35**) These observation were consistent with the reports of diacetylation of **1**[1] and *dl*-5-*epi*-**1**[2] Although spectral data of **33** and **34** were in good agreement with those reported,[1] the signs of optical rotations of our synthetic materials were opposite to those of natural diacetates to conclude that our synthetic **30** was the antipode of **1**, thus *ent*-**1** Therefore, the absolute structure of **1** was determined to have (***2aS***, ***4aS***, ***5S***, ***7bR***) configurations as shown



(***2aS***, ***4aS***, ***5S***, ***7bR***)
natural udoteatrial hydrate

Synthesis of analogues of *ent*-1 and their cytotoxic potency

Having achieved the synthesis of antipode of udoteatrial hydrate **30**, we then investigated the biological properties of analogues of **30** The key intermediate **5** employed in our synthesis was suitable to prepare

analogues involving a variety of side chains beside homogeranyl group To examine the effect of side chain on the biological activities, we chose the compound bearing the methyl group as a simple side chain to compare with those involving the homogeranyl group Since the monohydrate form of trialdehyde was not stable enough for storage and biological tests, their diacetates were used instead.

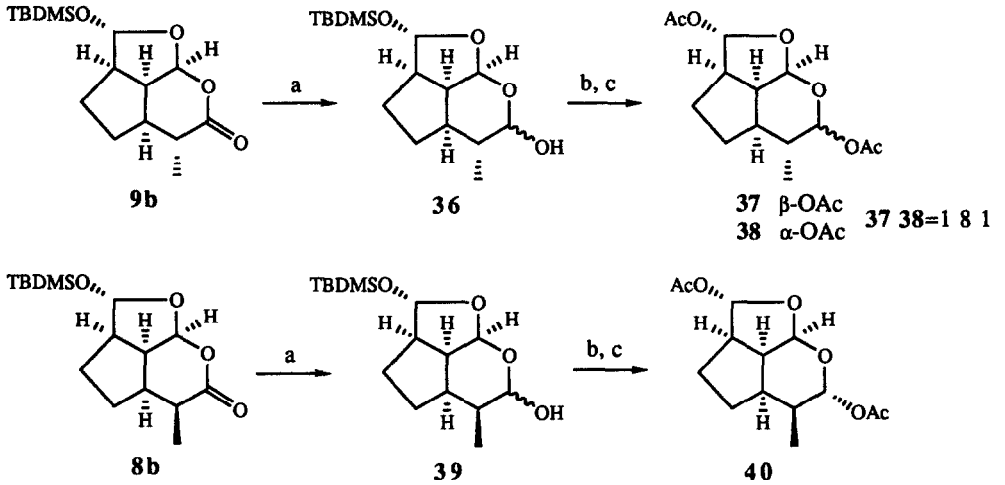
Reduction of **9b** with DIBAL gave hemiacetal (**36**), which was hydrolyzed and acetylated to afford diacetates (**37**) and (**38**) (1 8 1) in 50% yield for three steps (**Scheme 7**) Similarly, (**40**) was obtained by the same procedure as for **37** and **38** in 75% yield for three steps from **8b** Although separation of **37** and **38** was achieved by HPLC, for preliminary examination they were subjected in biological test as a form of mixture

With analogues **33**, **34**, **35**, **37**, **38** and **40** of diacetates of **1** in hand, we examined their biological properties Although the natural udoteatrial hydrate **1** was reported to show some antimicrobial activities, none of those analogues was active against various microorganisms At this moment it was not clear whether protection of two hemiacetal portions of **30** with acetate decrease its antimicrobial activities or the activity strictly depend on the absolute configuration of **1** On the other hand, assay of *in vitro* cytotoxicity of these analogues presented significant results Thus, the compounds involving homogeranyl side chain (**33**, **34**, **35**) were found to be cytotoxic against KB human oral epidermoid carcinoma (ATCC CLL-17) and human lung carcinoma A-549 (ATCC CLL-185) as summarized in **Table 2**

The diacetate **33** was the most toxic among analogues examined at the concentration of $4x10^{-1}$ μg/ml Although level of the cytotoxicity was sometimes observed to increase when a longer alkyl chain was substituted,[17] the effect of side chain was apparent that the methyl derivatives **37**, **38** and **40** were much less toxic relative to **33**, **34** and **35** Another significant feature was that **33** exhibited at least 4 fold more enhanced cytotoxic potency than **34** and **35** In ^{1}H-NMR the observed coupling constants between H_5 and H_6 (J_{5-6}) of **33**, **34** and **35** were 2 4, 4 9 and 9 2 Hz, respectively Considering these values as well as their stereostructures, it was realized that only the acetoxy group at C_6 in **33** occupied the axial orientation as shown in **Figure 4** From stereoelectronic point of view, it was suggested that compound with the better leaving ability of acetoxy group exhibited stronger cytotoxicity, although the mechanism of the inhibition of cell growth with these compounds was not understood at all This observation also suggested that the generation of oxonium species by elimination of acetoxy group might concern the exhibition of cytotoxicity of these compounds To support this assumption oxonium species itself could be involved in DNA alkylation of potent carcinogen aflatoxin B_1 after oxidative activation [18]

Conclusion

The antipode of novel marine diterpenoid udoteatrial hydrate **1** was synthesized from **4** *via* the key intermediate, exomethylene lactone **5a** This synthesis could demonstrate the usefulness of **4** as a chiral building block as well as could determine the absolute configuration of **1** We also found that the analogues of antipode of **1** were cytotoxic against human carcinoma *in vitro* For the exhibition of cytotoxicity, the presence of homogeranyl side chain as well as the stereochemistry of acetoxy group at C_6 were seemed to be important factors Our finding reported here may have values for the evaluation of new lead-compounds for the cancer chemotherapy. Since biological properties of natural **1**, however, have been little investigated, these cytotoxic activities observed in the diacetates of *ent*-**1** reported here were not confirmed whether it was unique to the *ent*-**1** analogues To address these issues synthesis of natural **1** is now in progress in our laboratory These results as well as their biological properties will be reported in due course



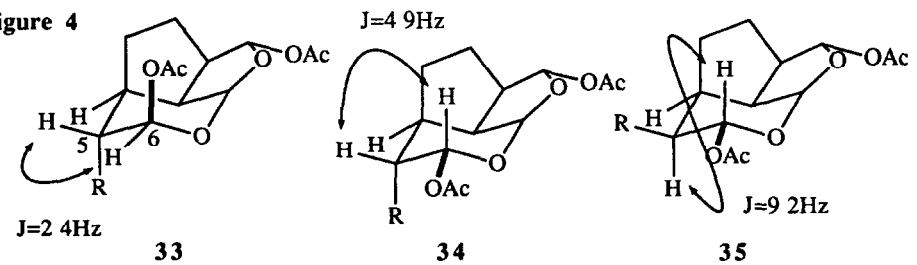
Scheme 7

a) DIBAL, toluene, -78 °C, 1h b) (0 1M) *p*-TsOH, THF H_2O acetone = 4 2 1, rt
c) Ac_2O, Pyr, rt, 50% for **37** and **38** from **9b**, 75% for **40**

Table 2 cytotoxicity of analogues of *ent*-udoteatrial hydrate against human oral epidermoid carcinoma KB and human lung carcinoma A-549

compound No	IC_{50} (μg/ml)	
	human KB cells	human A-549
33	0 4	0 5
34	1 6	1 9
35	3 4	3 9
37 and **38**	>25 0	>25 0
40	>25 0	>25 0

Figure 4



Experimental Section

^{1}H-NMR spectra were measured with Hitachi R-90H (90 MHz), JEOL FX-100 (100 MHz) or JEOL JNM GX-400 (400 MHz) spectrometers Coupling constants (*J* values) are reported in hertz ^{13}C-NMR spectra were measured with a JEOL JNM GX-400 (100 MHz) spectrometer The chemical shifts are expressed in ppm downfield from tetramethylsilane, using tetramethylsilane or residual chloroform as a internal standard IR

spectra were recorded on a JASCO A-102 spectrometer Mass spectra were recorded on a JMS D-300 or AX-500 Optical rotations were determined by JASCO MODEL DIP Fuji Davison Silica Gel BW-200 was used for silica gel flash chromatography. Pre-Coated TLC Plates Merck silica gel 60 F_{254} was used for preparative TLC HPLC was performed on μ Porasil P/N series columns with Waters Liquid Chromatography Model 510 using differential refractometer R401. Anhydrous reactions were performed under N_2 or Ar atmosphere Ether and tetrahydrofuran (THF) were distilled under N_2 from sodium/benzophenone ketyl prior to use Toluene, xylene, triethylamine (Et_3N), and diisopropylamine (i-Pr_2NH) were distilled from CaH_2 and stored over 3 or 4Å molecular sieves Dichloromethane (CH_2Cl_2) was distilled from P_2O_5 prior to use Dimethyl sulfoxide (DMSO) was distilled from CaH_2

Methyl (*1S, 4aS, 7aS*)-1-(*t*-butyldimethylsilyloxy)-7-[(*t*-butyldimethylsilyloxy)methyl]-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (10) and Methyl (*1S, 4aS, 7aS*)-1-(*t*-butyldimethylsilyloxy)-7-hydroxymethyl-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (11)

To a stirred suspension of genipin **4** (20 0 g, 88 mmol) and silver nitrate (37 6 g, 0 22 mol) in DMF (66 ml) was slowly added *t*-butyldimethylsilyl chloride (33 4 g, 0 22 mol) at 0 °C The reaction mixture was stirred vigorously at room temperature for overnight After filtration through a pad of celite, the filtrate was poured into cooled sat $NaHCO_3$ and extracted with ether for three times The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give a mixture of **10** and **11** as a brown oil This mixture could be separated to give **10** Alternatively, this mixture was added into a solution of PPTS (2 38 g, 8 8 mmol) in EtOH (200 ml) The resulting mixture was stirred at 25 °C for two days After cooling with ice bath, the reaction mixture was added to sat $NaHCO_3$ (30 ml) and concentrated *in vacuo* to remove EtOH The residue was extracted with ether for three times The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=5/1 to 1/4) gave **11** (27 3 g, 91%) as a pale yellow oil **10** $[\alpha]_D^{20}$ +34 9° (c=1 5, $CHCl_3$) MS m/e (%) 454 (M^+), 439 [(M-Me)$^+$] (1), 423 (2), 397 [(M-^{t}Bu)$^+$] (44), 365 (22), 337 (7), 265 (40), 233 (17), 221 (7), 205 (14), 191 (21), 173 (5), 147 (21), 131 (9), 89 (17), 73 (100), 59 (12) HRMS Calcd for $C_{19}H_{33}O_5Si_2$ [(M-^{t}Bu)$^+$] 397 1866, Found 397 1865 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 48, (1H, d, J=1 2 Hz, O*CH*=C), 5 80 (1H, brs, C=*CH*CH_2), 4 84 (1H, d, J=7 3 Hz, O*CH*O), 4 35 (1H, d, J=14 6 Hz, SiO*CH*$_2$C=C), 4 21 (1H, d, J=14 6 Hz, SiO*CH*$_2$C=C), 3 71 (3H, s, CO_2*Me*), 3 17 (1H, dd, J=8 6, 16 5 Hz), 2 83 (1H, m), 2 46 (1H, t, J=7 6 Hz), 2 04 (1H, m), 0 914, 0 906 (9Hx2, sx2, Si^t*Bu*x2), 0 13, 0 12 (3Hx2, sx2, Si*Me*$_2$), 0 063, 0 056 (3Hx2, sx2, Si*Me*$_2$) IR (neat) 2850, 1690, 1620, 1450, 1390, 1260 cm^{-1} **11** $[\alpha]_D^{20}$ +40 6° (c=1 2, $CHCl_3$) MS m/e (%) 340 (M^+) (6), 322 [(M-H_2O)$^+$] (43), 309 [(M-OMe)$^+$] (82), 283 [(M-^{t}Bu)$^+$] (51), 265 (49), 251 (100), 191 (63), 159 (49), 75 (49) HRMS Calcd for $C_{17}H_{26}O_4Si$ [(M-H_2O)$^+$] 322 1601, Found 322 1618 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 50 (1H, s, O*CH*=C), 5 83 (1H, brs, *CH*=C), 4 83 (1H, d, J=8 1 Hz, SiO*CH*O), 4 31 (1H, d, J=15 9 Hz, HO*CH*$_2$), 4 27 (1H, d, J=15 9 Hz, HO*CH*$_2$), 3 72 (3H, s, CO_2*Me*), 3 20 (1H, m), 2 87 (1H, m), 2 56 (1H, t, J=7 3 Hz), 2 22 (1H, brs, *OH*), 2 07 (1H, m), 0 93 (9H, s, Si^t*Bu*), 0 16, 0 14 (3Hx2, sx2, Si*Me*$_2$) ^{13}C-NMR ($CDCl_3$) δ= 167 8, 152 2, 143 6, 127 8, 110 9, 96 9, 61 2, 51 1, 48 4, 38 8, 36 2, 25 6, 17 8, 15 1, -3 7, -4 3, -5 0 IR (neat) 3450, 2900, 2850, 1690, 1620, 1440, 1380, 1280, 1150, 1130, 1100, 1040, 960, 930, 890, 830 cm^{-1}

Methyl (*1S, 4aS, 7aS*)-7-formyl-1-(*t*-butyldimethylsilyloxy)-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (12)

To a solution of **11** (12 3 g, 0 36 mol) in CH_2Cl_2 (100 ml) was added $BaMnO_4$ (91 0 g, 0 36 mol) and the mixture was stirred at room temperature for overnight The resulting mixture was filtered through a pad of celite and washed with AcOEt thoroughly The combined filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=3/2 to 1/4) gave **12** (11 1 g, 91%) as a colorless oil $[\alpha]_D^{16}$ +117° (c=1 0, $CHCl_3$) MS m/e (%) 338 (M^+), 323 [(M-Me)$^+$] (1), 307 [(M-OMe)$^+$] (6), 281 [(M-^{t}Bu)$^+$] (100), 263 (65), 249 (87), 237 (3 0), 221 (63), 207 (7), 193 (12), 179 (16), 155 (24), 119 (7), 103 (5), 89 (16), 73 (74), 63 (4), 55 (21) HRMS Calcd for $C_{17}H_{26}O_5Si$ (M^+) 338 1549, Found 338 1540 ^{1}H-NMR (90 MHz, $CDCl_3$) δ= 9 75 (1H, s, *CHO*), 7 43 (1H, s O*CH*=C), 6 93 (1H, brs, CH_2CH=C), 5 41 (1H, d, J=4 5 Hz, O*CH*OSi), 3 70 (3H, s, CO_2*Me*), 3 5-1 8 (4H), 0 90 (9H, s, Si^t*Bu*), 0 14 (3Hx2, brs, Si*Me*$_2$) IR (neat) 2920, 2840, 1700, 1685, 1630, 1435, 1290, 1170, 1110, 1075, 1015, 960, 835, 780 cm^{-1}

Methyl (*1S, 4aS, 7aS*)-1-(*t*-butyldimethylsilyloxy)-7-[(*t*-butyldimethylsilyloxy)methyl]-1,4a,5,6,7,7a-hexahydrocyclopenta[c]pyran-4-carboxylate (13)

To a solution of **10** (50 0 mg, 0 11 mmol) in AcOEt (2 ml) was added 5% Rh/Al_2O_3 (2 5 mg) The reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen for overnight The resulting mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to give colorless oil **13** (50 2 mg, quantitative yield) as an inseparable mixture of *7S*- and *7R*-isomer The ratio of two isomers was determined as 1 1 from 400 MHz ^{1}H-NMR spectrum Instead of Rh/Al_2O_3, using Pd/C in EtOH gave *7S*-**13** as an exclusive product The stereochemistry at C_7 was confirmed *via* comparing with *7S*-**13** derived from *7S*-**14** ***7S*-13 derived from *7S*-14** To a solution of *7S*-**14** (23 0 mg, 0 07 mmol) and imidazole (14 mg, 0 20 mmol) in CH_2Cl_2 (2 ml) was added *t*-butyldimethylsilylchloride (12 mg, 0 08 mmol) and the mixture was stirred at room temperature for 2 h After filtration through a pad of celite, the filtrate was concentrated *in vacuo* Preparative thin layer chromatography of the residue (SiO_2, hexane/AcOEt=10/1) gave *7S*-**13** (26 4 mg, 86%) as a colorless oil *7S*-**13** $[\alpha]_D^{24}$ -47 5° (c=1 3, $CHCl_3$) MS m/e (%) 441 [(M-Me)$^+$] (1), 425 [(M-OMe)$^+$] (25), 399 [(M-^{t}Bu)$^+$] (32), 367 (5), 324 (8), 309 (3), 267 (53), 235 (20), 223 (7), 193 (100), 187 (90), 179 (17), 161 (21), 147 (20), 133 (9), 115 (8), 105 (5), 89 (17), 73 (60), 57 (14) HRMS Calcd for $C_{19}H_{35}O_5Si_2$ [(M-^{t}Bu)$^+$] 399 2023, Found 399 2036. ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 43 (1H, d, J=1.2 Hz, O*CH*=C), 4 94 (1H, d, J=6 7 Hz, O*CH*OSi), 3 70 (3H, s, CO_2*Me*), 3 57 (2H, m, SiO*CH*$_2$CH), 2 79 (1H, m), 2 14 (1H, m), 1 88 (1H, m), 1 74 (1H, m), 1 61 (1H, m), 1 37 (2H, m), 0 90, 0 88 (9Hx2, sx2, Si^t*Bu*), 0 123, 0 120 (3Hx2, sx2, Si*Me*$_2$), 0 03 (3Hx2, s, Si*Me*$_2$) IR (neat) 2960, 2870, 1715, 1635, 1475, 1465, 1440, 1390, 1260, 1160, 1100, 1010, 845, 785 cm^{-1}

Methyl (*1S, 4aS, 7aS*)-1-(*t*-butyldimethylsilyloxy)-1,4a,5,6,7,7a-hexahydro-7-hydroxymethylcyclopenta[c]pyran-4-carboxylate (14)

To a solution of **11** (500 mg, 1 5 mmol) in EtOH (10 ml) was added PtO_2 (25 mg) The reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen for overnight After filtration through a pad of celite, the filtrate was concentrate *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=3/1) gave **14** (500 mg, 99%) as a colorless oil, which was an inseparable mixture of two stereoisomers (*7S*:*7R*=1 8) from 400 MHz ^{1}H-NMR spectrum Instead of PtO_2, using Rh/Al_2O_3 in AcOEt gave **14** (*7S 7R*=3 7) in 80% yield The stereochemistry at C_7 was confirmed *via* comparing with *7S*-**14** derived from *7S*-**15** ***7S*-14 derived from *7S*-15** To a solution of *7S*-**15** (36 0 mg, 0 11 mmol) in MeOH (1 ml) was added $NaBH_3CN$ (10 mg, 0 16 mmol) and two drops of acetic acid and the mixture was stirred at room temperature for 2 h After concentration *in vacuo*, the resulting residue was diluted with AcOEt, and was washed with $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Preparative thin layer chromatography of the residue (SiO_2, hexane/AcOEt=2/1) gave *7S*-**14** (26 0 mg 72%) as a colorless oil *7S*-**14** $[\alpha]_D^{23}$ -75 4° (c=1 3, $CHCl_3$) MS m/e (%) 324 [(M-H_2O)$^+$] (3), 311 [(M-MeO)$^+$] (10), 285 [(M-t-Bu)$^+$] (88), 267 (45), 253 (68), 235 (40), 223 (20), 207 (14), 193 (50), 179 (40), 161 (54), 147 (34), 135 (25), 119 (16), 105 (24), 89 (26), 75 (86), 73 (100), 59 (13) HRMS Calcd for $C_{16}H_{27}O_4Si$ [(M-OMe)$^+$] 311 1679, Found 311 1675 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 45 (1H, s, O*CH*=C), 4 74 (H, d, J=7 9 Hz, O*CH*OSi), 3 71 (3H, s, CO_2*Me*), 3 63 (1H, dd, J=5 8, 9 8 Hz, HO*CH*$_2$CH), 3 54 (1H, dd, J=7 9, 9 8 Hz, HO*CH*$_2$CH), 2 74 (1H, m), 2 27 (1H, m), 2 03 (1H, m), 1 85 (2H, m), 1 25 (2H, m), 0 91 (9H, s, Si^t*Bu*), 0.15, 0 14 (3Hx2, sx2, Si*Me*$_2$) IR (neat) 3460, 2960, 2860, 1710, 1635, 1465, 1400, 1390, 1305, 1285, 1260, 1175, 1155, 1100, 1030, 960, 845, 800, 790, 760 cm^{-1}

Methyl (*1S, 4aS, 7aS*)-1-(*t*-butyldimethylsilyloxy)-7-formyl-1,4a,5,6,7,7a-hexahydro-cyclopenta[c]pyran-4-carboxylate (15)

To a solution of **12** (10 1 g, 30 mmol) in AcOEt (200 ml) was added 5% Rh/Al_2O_3 (25 mg) The reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen for overnight After filtration through a pad of celite, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=3/1) gave **15** (8 76 g 87%) as a colorless oil, which was an inseparable mixture of two stereoisomers (*7S 7R*=1 4) Instead of Rh/Al_2O_3, using Pd/C gave **15** with a ratio of *7S 7R*=1 2 in 77% yield and PtO_2 also gave **15** with a ratio of *7S 7R*=1 4 in 57% **Isomerization of *7R-15*** To a solution of the above mixture **15** (*7S 7R*=1 4) (50 0 mg, 0 15 mmol) in CH_2Cl_2 (2 ml) was added DBU (4 µl, 0 03 mmol) and the mixture was stirred at room temperature for 1 h At this stage *7R*-isomer was disappeared and only *7S*-isomer was detected on TLC After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/ether=3/1) gave *7S*-**15** (37 4 mg, 75%) as a colorless oil *7S*-**15** $[\alpha]_D^{17}$ -43 6° (c=1 9, $CHCl_3$) MS m/e (%) 340 (M$^+$) (14), 325 [(M-Me)$^+$] (51), 283 (100), 251 (55), 223 (22), 181 (24), 155 (18), 73 (20) HRMS Calcd for $C_{17}H_{28}O_5Si$ (M$^+$) 340 1706, Found 340 1702 ^{1}H-NMR (90 MHz, $CDCl_3$) δ= 9 71 (1H, d, J=1 5 Hz, *CHO*), 7 44 (1H, d, J=1 0 Hz, O*CH*=C), 4 88 (1H, d, J=6 5 Hz, O*CH*OSi), 3 70 (3H, s, CO_2*Me*), 2 95-1 6 (7H), 0 89 (9H, s, Si^t*Bu*), 0 13 (3Hx2, s, Si*Me*$_2$) IR (neat) 2930, 2850, 1710, 1630, 1460, 1440, 1390, 1360, 1295, 1260, 1150, 1090, 950, 840, 780 cm^{-1} **Desilylation of 15 followed by acidic treatment** To a solution of **15** (*7S 7R*=1 4) (60 mg, 0 17 mmol) in THF (1 5 ml) was added AcOH

(20 ml, 0 35 mmol) and $Bu_4NF\ H_2O$ (69 mg, 0 26 mmol) at room temperature After stirred at room temperature for 2 h, to the reaction mixture was added PPTS (88 mg, 0 35 mmol) and the mixture was stirred at room temperature for another 1 h Dilution with AcOEt, the reaction mixture was washed with $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Preparative thin layer chromatography of the residue (SiO_2, hexane/AcOEt=1/1) gave a tricyclic compound **17a** (10 5 mg, 26%) as colorless needles accompanied by α-aldehyde **17b** (3 4 mg, 9%) as a colorless oil The spectroscopic data of **17a** and **17b** were reported below

Methyl (*4aS, 7aS*)-7-formyl-1-hydroxy-1,4a,5,7a-tetrahydrocyclopenta[c]pyran-4-carboxylate (16)

To a solution of **4** (5.00 g, 20 mmol) in CH_2Cl_2 (200 ml) was added $BaMnO_4$ (50 0 g, 0 20 mol) and the mixture was stirred for two days at room temperature After filtration, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=2/1 to 1/2) gave a diastereomeric mixture of **16** (3 50 g, 71%) as a colorless oil MS m/e (%) 224 (M^+) (27), 206 [$(M-H_2O)^+$] (10), 196 [$(M-CO)^+$] (35), 178 (49), 164 (100), 146 (33), 136 (63), 118 (22), 107 (42), 94 (34), 79 (53), 66 (26), 55 (12) HRMS Calcd for $C_{11}H_{12}O_5$ (M^+) 224 0684, Found 224 0688 ^{1}H-NMR (90 MHz, $CDCl_3$) δ= 9 79, 9 69 (total 1H, each s, *CHO*), 7 51, 7 45 (total 1H, each s, O*CH*=C), 7 14 (1H, m, CH_2*CH*=C), 6 57, 5 22 (total 1H, each d, J=11 and 10 5 Hz, respectively, O*CH*O), 4 71 (1H, m), 3 74, 3 72 (3H, sx2, CO_2*Me*), 3 47-2 76 (3H) IR (neat) 3425, 2950, 2850, 2725, 1730, 1710, 1675, 1630, 1440, 1375, 1285, 1240, 1160, 1100, 1065, 980, 955, 890, 800, 795, 770, 720 cm^{-1}

Methyl (*2S, 2aR, 4aS, 7aR, 7bS*)-2-hydroxy-2a,3,4,4a,7a,7b-hexahydro-*2H*-1,7-dioxacyclopent[c,d]indene-5-carboxylate (17a)

To a solution of **16** (360 mg, 1 6 mmol) in AcOEt (7 2 ml) was added 5% Rh/Al_2O_3 (20 mg, *ca* 1 mol%) The mixture was stirred under atmospheric pressure of hydrogen at room temperature for overnight After filtration, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=4/1 to 1/1) gave **17a** (184 mg, 52%) as colorless crystals and an inseparable mixture (*ca* 100 mg) containing α-aldehyde isomer **17b** and uncyclized β-aldehyde isomer After PPTS treatment in methylene chloride at room temperature to force cyclization of the latter, the resulting mixture was separated as before to give **17a** (18 mg, 5%) and **17b** (45 mg, 13%) as a colorless oil The total yield of **17a** was thus 57% **17a** was recrystallized from hexane-ethyl ether to give colorless needles **17a** m p 88 0 - 88 6 °C $[\alpha]_D^{29}$ +73 6° (c=1 2, $CHCl_3$) MS m/e (%) 226 (M^+) (65), 208 [$(M-H_2O)^+$] (12), 193 (33), 179 (29), 165 (57), 148 (100), 137 (29), 124 (50), 109 (51), 103 (55), 96 (48), 81 (41), 67 (50), 59 (19), 53 (41) HRMS Calcd for $C_{11}H_{14}O_5$ (M^+) 226 0841, Found 226 0860 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 51 (1H, s, O*CH*=C), 5 84 (1H, d, J=4 3 Hz, O*CH*O), 5 09 (1H, s, O*CH*OH), 3 74 (3H, s, CO_2*Me*), 3 51 (1H, m, *OH*), 2 85 (1H, m), 2 67 (2H, m), 2 23 (1H, m), 1 71 (1H, m), 1 14 (1H, m) IR ($CHCl_3$) 3425, 2970, 2875, 1705, 1647, 1440, 1380, 1295, 1275, 1185, 1140, 1105, 1078, 1018, 995, 960, 940, 915, 840 cm^{-1} Anal Calcd for $C_{11}H_{14}O_5$ C, 58 40, H, 6 24% Found C, 58 39, H, 6 27% **17b** MS m/e (%) 226 (M^+) (64), 208 [$(M-H_2O)^+$] (22), 194 [$(M-CH_3OH)^+$] (37), 179 (45), 165 (100), 147 (88), 137 (42), 124 (84), 119 (48), 109 (67), 103 (91), 96 (73), 91 (55), 81 (56), 67 (83), 53 (22) HRMS Calcd for $C_{11}H_{14}O_5$ (M^+) 226 0841, Found 226 0822 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 9 77, 9 75 (total 1H, each s, CHO), 7 49 (1H, m, O*CH*=C), 5 34-4 53 (2H), 3 73, 3 72 (total 3H, each s, CO_2*Me*), 3 05-2 28 (3H), 2 04-1 83 (3H), 1 34 (1H, m) IR (neat) 3400, 2950, 1700, 1630, 1440, 1390, 1300, 1190, 1150, 1100, 755, 670 cm^{-1}

Methyl (*2S, 2aR, 4aS, 7aR, 7bS*)-2a,3,4,4a,7a,7b-hexahydro-2-methoxy-*2H*-1,7-dioxacyclopent[c,d]indene-5-carboxylate (18a)

To a solution of **17a** (1 58 g, 7 0 mmol) in MeOH (36 ml) at 0 °C was added boron trifluoride etherate (1 7 ml, 14 mmol) and the reaction mixture was stirred for 1 h at 0 °C The reaction was quenched with sat $NaHCO_3$ and concentrated *in vacuo* The residue was extracted with AcOEt for three times and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=10/1 to 4/1) gave **18a** (1 60 g, 95%) as a colorless oil $[\alpha]_D^{25}$ +45 7° (c=1 3, $CHCl_3$) MS m/e (%) 240 (M^+) (17), 208 [$(M-MeOH)^+$] (35), 176 (13), 162 (3), 148 (24), 138 (100), 121 (12), 99 (4), 91 (10), 81 (7), 71 (9), 55 (4) HRMS Calcd for $C_{12}H_{16}O_5$ (M^+) 240 0998, Found 240 0999 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 52 (1H, s, O*CH*=C), 5 71 (1H, d, J=4 9 Hz, O*CH*O), 4 57 (1H, d, J=1 2 Hz, MeO*CH*O), 3 73 (3H, s, CO_2*Me*), 3 38 (3H, s, O*Me*), 2 82 (1H, dt, J=1 2, 7 3 Hz, C_{2a}-H), 2 66 (1H, dt, J=6 7, 10 4 Hz), 2 58 (1H, ddd, J=4 9, 7 3, 9 8 Hz), 2 26 (1H, m), 1 81 (1H, dd, J=6 1, 13 0 Hz), 1 70 (1H, m), 1 12 (1H, m) IR (neat) 2950, 1710, 16545, 1440, 1380, 1290, 1270, 1190, 1140, 1100, 1075, 1050, 1030, 990, 975, 940, 840, 770 cm^{-1}

Methyl (*2S, 2aR, 4aS, 7aR, 7bS*)-2-(*t*-butyldimethylsilyloxy)-2a,3,4,4a,7a,7b-hexahydro-*2H*-1,7-dioxacyclopent[c,d]indene-5-carboxylate (18b)
To a solution of **17a** (50 0 mg, 0 22 mmol) and 2,6-lutidine (52 µl, 0 44 mmol) in THF (2 ml) at -78 °C was added TBDMSOTf (66 µl, 0 29 mmol) and the mixture was stirred at -78 °C for 30 min Then the reaction was quenched with sat. $NaHCO_3$ and the resulting mixture was extracted with ether for three times The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Preparative thin layer chromatography of the residue (SiO_2, hexane/ethyl ether=3/1) gave **18b** (71 0 mg, 95%) as a colorless oil $[\alpha]_D^{25}$ +22 6° (c=1 2, $CHCl_3$) MS m/e (%) 339 [(M-H)$^+$] (1), 325 [(M-Me)$^+$] (2), 309 (7), 283 [(M-tBu)$^+$] (100), 251 (35), 237 (8), 223 (25), 209 (8), 181 (39), 148 (25), 139 (7), 121 (16), 103 (11), 89 (17), 73 (69), 65 (5), 59 (17) HRMS Calcd for $C_{16}H_{25}O_5Si$ [(M-Me)$^+$] 325.1471, Found 325 1494 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 50 (1H, s, O*CH*=C), 5 76 (1H, d, J=5 0 Hz, O*CH*O), 5 00 (1H, s, SiO*CH*O), 3 71 (3H, s, CO_2*Me*), 2 79 (1H, m), 2 63 (2H, m), 2 21 (1H, m), 1 76 (1H, m), 1 68 (1H, m), 1 14 (1H, m), 0 89 (9H, s, Si*tBu*), 0 12, 0 11 (3Hx2, sx2, SiMe_2) IR (neat)· 2950, 2850, 1710, 1650, 1460, 1440, 1390, 1330, 1290, 1250, 1190, 1140, 1105, 1075, 1025, 990, 970, 850, 780 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-2a,3,4,4a,7a,7b-Hexahydro-5-hydroxymethyl-2-methoxy-*2H*-1,7-dioxacyclopent[c,d]indene (19a)
To a solution of **18a** (370 mg, 1 5 mmol) in CH_2Cl_2 (16 ml) at -78 °C was added dropwise DIBAL (0 93 M in hexane, 4 1 ml, 3 9 mmol) After 1 h at -78 °C, the reaction was quenched with AcOEt and a little of water The resulting mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=2/1 to 1/2) gave **19a** (294 mg, 90%) as a colorless oil. $[\alpha]_D^{27}$ +1 7° (c=2 3, $CHCl_3$) MS m/e (%) 212 (M$^+$) (31), 194 [(M-H_2O)$^+$] (19), 180 [(M-MeOH)$^+$] (100), 165 (44), 151 (54), 134 (92), 121 (29), 105 (48), 95 (15), 79 (30), 75 (10), 71 (40), 57 (25) HRMS Calcd for $C_{11}H_{16}O_4$ (M$^+$) 212 1049 Found· 212 1029 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 37 (1H, s, O*CH*=C), 5 65 (1H, d, J=4 3 Hz, O*CH*O), 4.53 (1H, d, J=1 2 Hz, MeO*CH*O), 4 09, 4 01 (1Hx2, each d, J=12 3 Hz, *CH*$_2$OH), 3 36 (3H, s, *Me*O), 2.78 (1H, m), 2 59 (1H, ddd, J=4.3, 7 3, 9 8 Hz, C_{7b}-H), 2 46 (1H, m), 2 11 (1H, m), 1 80 (1H, m), 1 64 (1H, m), 1 47 (1H, br, OH), 1 23 (1H, m) IR (neat) 3420, 2950, 2870, 1680, 1450, 1375, 1280, 1260, 1197, 1170, 1100, 1050, 1020, 990, 930, 900, 840, 790 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-2-(*t*-Butyldimethylsilyloxy)-2a,3,4,4a,7a,7b-hexahydro-5-hydroxymethyl-*2H*-1,7-dioxacyclopent[c,d]indene (19b)
To a solution of **18b** (1.98 g, 5 8 mmol) in CH_2Cl_2 (60 ml) at -78 °C was added dropwise DIBAL (0 93 M in hexane, 15.7 ml, 15 mmol) After 1 h at -78 °C, the reaction was quenched with AcOEt and a little of water The reaction mixture was filtered through pad of celite and the solvents were removed *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=5/1) gave **19b** (1 82 g quantitative yield) as a colorless oil $[\alpha]_D^{25}$ +2 1° (c=2.6, $CHCl_3$) MS m/e (%) 312 (M$^+$) (1), 295 [(M-OH)$^+$] (5), 279 [(M-MeOH)$^+$] (2), 265 (6), 255 [(M-tBu)$^+$] (54), 237 (23), 225 (16), 219 (5 1), 209 (14), 193 (3 0), 180 (29), 163 (9), 148 (25), 152 (18), 145 (7), 135 (27), 117 (22), 105 (26), 91 (21), 79 (26), 75 (100), 67 (12), 59 (14), 53 (9). HRMS Calcd for $C_{12}H_{16}O_5Si$ [(M-tBu)$^+$] 255 1053, Found 255 1054 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 39 (1H, s, O*CH*=C), 5 73 (1H, d, J=4 9 Hz, O*CH*O), 4 98 (1H, s, SiO*CH*O), 4 10, 4 02 (1Hx2, each d, J=12 1 Hz, *CH*$_2$OH), 2 78 (1H, m), 2 65 (2H, m), 2 46 (1H, m), 2 10 (1H, m), 1 79 (1H, m), 1 63 (1H, m), 1 25 (1H, m), 0 89 (9H, s, Si*tBu*), 0 12, 0 11 (3Hx2, sx2, SiMe_2) IR (neat) 3400, 2950, 2925, 2860, 1679, 1460, 1255, 1170, 1095, 1020, 990, 840, 780 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-5-(Acetoxymethyl)-2a,3,4,4a,7a,7b-hexahydro-2-methoxy-*2H*-1,7-dioxacyclopent[c,d]indene (20a)
To a solution of **19a** (272 mg, 1 3 mmol) and DMAP (78 0 mg, 0 64 mmol) and triethylamine (0 27 ml, 1 9 mmol) in CH_2Cl_2 (9 ml) at 0 °C was added Ac_2O (0 15 ml, 1 5 mmol) The solution was stirred at room temperature for 1 h After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/ethyl ether=5/1) gave **20a** (308 mg, 94%) as a colorless oil $[\alpha]_D^{25}$ +1 7° (c=1 7, $CHCl_3$) MS m/e (%) 254 (M$^+$) (13), 223 (21), 194 [(M-AcOH)$^+$] (100), 181 (34), 162 (57), 149 (19), 134 (79), 105 (46), 99 (14), 91 (26), 81 (37), 70 (57), 61 (62) HRMS Calcd for $C_{13}H_{18}O_5$ (M$^+$) 254 1154, Found 254 1151 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 45 (1H, s, O*CH*=C), 5 66 (1H, d, J=4 9 Hz, O*CH*O), 4 58, 4 44 (1Hx2, each d, J=11 9 Hz, *CH*$_2$OAc), 4 54 (1H, s, MeO*CH*O), 2 79 (1H, t, J=7 3 Hz), 2 61 (1H, ddd, J=4 9, 7 3, 9 8 Hz, C_{7b}-H), 2 35 (1H, m), 2 08 (1H, m), 2 04 (3H, s, *Me*CO_2), 1 82 (1H, m), 1 64 (1H, m), 1 25 (1H, m) IR (neat) 2940, 1740, 1680, 1455, 1380, 1235, 1180, 1105, 1055, 1025, 980, 960, 940, 845 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-5-(Acetoxymethyl)-2-(*t*-butyldimethylsilyloxy)-2a,3,4,4a,7a,7b-hexahydro-*2H*-1,7-dioxacyclopent[c,d]indene (20b)

To a solution of **19b** (1.82 g, 5 8 mmol) and DMAP (356 mg, 2 9 mmol) and triethylamine (1 2 ml, 8.8 mmol) in CH_2Cl_2 (40 ml) at 0 °C was added Ac_2O (0 66 ml, 7 0 mol). The solution was stirred at 0 °C for 1 h After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/ethyl ether=5/1) gave **20b** (2 02 g, 98%) as a colorless oil $[\alpha]_D^{25}$ +1.5° (c=2 8, $CHCl_3$). MS m/e (%). 354 (M^+) (1), 353 [(M-H)$^+$] (1), 297 [(M-^{t}Bu)$^+$] (68), 295 (27), 279 (5), 265 (15), 237 (100), 219 (12), 209 (26), 194 (14), 181 (11), 163 (49), 155 (15), 145 (11), 134 (32), 117 (90), 105 (15) HRMS Calcd for $C_{16}H_{27}O_3Si$ [(M-AcO)$^+$] 295 1729, Found. 295 1731 ^{1}H-NMR (90 MHz, $CDCl_3$) δ= 6 38 (1H, s, O*CH*=C), 5 67 (1H, d, J=5 Hz, O*CH*O), 4 92 (1H, s, SiO*CH*O), 4 55, 4 36 (1Hx2, each d, J=12 Hz, *CH*$_2$OAc), 2 70-2 10 (4H), 2 01 (3H, s, *Me*CO$_2$), 1 70 (3H), 0 88 (9H, s, Si*t*Bu), 0 11 (3Hx2, s, Si*Me*$_2$) IR (neat) 2950, 2860, 1740, 1680, 1465, 1380, 1250, 1175, 1100, 1020, 995, 850, 780 cm^{-1}

(*2S, 2aR, 4aS, 7aS, 7bS*)-2-Methoxy-5-methyledene-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-one (5a)

To a solution of **20a** (1.51 g, 6 0 mmol) in DMSO (56 ml) and water (1 2 ml) at 0 °C was added NBS (1.27 g, 7 1 mmol) After stirring at room temperature for 30 min, the resulting mixture was treated with sat. $NaHCO_3$, and extracted with ether for three times The combined organic phase was washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give a crude bromohydrine as a colorless oil (2 40 g) To a solution of $(CF_3CO)_2O$ (1 3 ml, 8.9 mmol) in CH_2Cl_2 (30 ml) at -60 °C, was added DMSO (0.84 ml, 12 mmol) After stirred at -65 °C for 10 min, to the resulting mixture was slowly added the crude bromohydrine in CH_2Cl_2 (20 ml) at -78 °C The reaction mixture was allowed to stir at -65 °C for 30 min Et_3N (2 5 ml, 18 mmol) was then added and the whole mixture was stirred at -65 °C for 5 min After dilution with AcOEt, the resulting mixture was washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give crude bromolactone **21a** (2 25 g) as a yellow oil To a suspension of the crude **21a** (2 25 g) and powdered zinc (1 95 g, 30 mmol) in ether (60 ml) was added AcOH (0 41 ml, 7 2 mmol) at room temperature The reaction mixture was stirred at room temperature for 1 h After filtration through a pad of celite, the reaction mixture was diluted with AcOEt and washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether= 10/1 to 4/1) gave **5a** (787 mg, 63% for 3 steps) as white solids, which was recrystallized from hexane-ethyl ether to afford colorless plates m p 61 7 - 62 3 °C $[\alpha]_D^{27}$ +1 1° (c=1 8, $CHCl_3$) MS m/e (%) 211 [(M+H)$^+$] (3), 210 (M^+) (2), 209 [(M-H)$^+$] (6), 179 [(M-CH_3O)$^+$] (86), 164 (28), 150 (71), 136 (53), 122 (82), 106 (88), 93 (100), 84 (63), 78 (72), 71 (80), 67 (40), 61 (9), 55 (23) HRMS Calcd for $C_{11}H_{15}O_4$ [(M+H)$^+$] 211 0971, Found 211 0976 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 18 (1H, s, *CH*$_2$=C), 5 82 (1H, d, J=6 1 Hz, O*CH*O), 5 56 (1H, s, *CH*$_2$=C), 4 86 (1H, d, J=3 1 Hz, MeO*CH*O), 3 42 (3H, s, *Me*O), 3 11 (1H, dt, J=6 1, 9 2 Hz, C_{7b}-H), 3 04 (1H, m), 2 77 (1H, m), 1 91 (2H, m), 1 75 (2H, m) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 165 1, 136 5, 125 3, 110 5, 102 9, 56 0, 50 7, 45 7, 42 0, 33 7, 29 2 IR (neat) 2950, 1740, 1645, 1450, 1410, 1310, 1275, 1130 (br), 1065, 1020, 990, 955, 835, 810 cm^{-1} Anal Calcd for $C_{11}H_{14}O_4$ C, 62 85, H, 6 71% Found C, 62 83, H, 6 76%

(*2S, 2aR, 4aS, 7aS, 7bS*)-2-(*t*-Butyldimethylsilyloxy)-5-methyledene-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-one (5b)

To a solution of **20b** (2 02 g, 5 7 mmol) in DMSO (54 ml) and water (1 1 ml) was added NBS (1 22 g, 6 9 mmol) at room temperature After stirring at room temperature for 30 min, the resulting mixture was extracted with ether for three times The combined organic phase was washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give bromohydrine as a crude pale yellow oil (1 76 g) To a solution of $(CF_3CO)_2O$ (0 83 ml, 5 9 mmol) in CH_2Cl_2 (15 ml) at -60 °C was added DMSO (0 55 ml, 7 8 mmol) After stirred at -65 °C for 10 min, to the resulting mixture was slowly added the crude bromohydrine in CH_2Cl_2 (17 ml) at -78 °C The reaction mixture was allowed to stir at -65 °C for 30 min Et_3N (1 63 ml, 12 mmol) was then added and the whole mixture was stirred at -65 °C for 5 min After dilution with ether, the resulting mixture was washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give crude bromolactone **21b** (1 80 g) as yellow hemicrystals To a suspension of the crude **21b** (1 80 g) and powdered zinc (1 26 g, 19 mmol) in ether (40 ml) was added AcOH (0 27 ml, 4 7 mmol) at room temperature The reaction mixture was stirred at room temperature for 1 h After filtration through a pad of celite, the filtrate was diluted with ether and washed with sat $NaHCO_3$ and brine , dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=4/1) gave **5b** (593 mg, 33% for 3 steps) as a colorless oil $[\alpha]_D^{27}$ +19 4° (c=1 3, $CHCl_3$) MS m/e (%) 309 [(M-H)$^+$] (3), 295 [(M-Me)$^+$] (2), 253 [(M-^{t}Bu)$^+$] (67), 235 (5), 225 (9), 207 (70), 191 (6 0), 181 (10), 150 (10), 133 (28), 122 (20), 105 (46), 93 (12), 75 (100), 67 (11), 57 (8) HRMS Calcd for $C_{16}H_{25}O_4Si$ [(M-H)$^+$] 309 1522, Found 309 1492 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 13 (1H, s, *CH*$_2$=C), 5 82 (1H, d, J=6 1 Hz, O*CH*O), 5 53 (1H, s, *CH*$_2$=C), 5 27 (1H, d, J=3 1 Hz, SiO*CH*O), 3 16 (1H, dt, J=6 1, 9 1 Hz, C_{7b}-H), 3 01 (1H, m), 2 73 (1H, m), 1 92 (1H, m), 1 81 (1H, m), 1 63 (2H, m),

0 89 (9H, s, Si*t*Bu), 0 13 (3Hx2, s, SiMe_2) IR (neat)· 2950, 2860, 1738, 1640, 1465, 1410, 1360, 1305, 1255, 1130, 1100, 1065, 1015, 950, 840, 785 cm^{-1}

(*2S, 2aR, 4aS, 5S, 7aS, 7bS*)-2-Methoxy-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-one (8a)

To a solution of **5a** (50 mg, 0 24 mmol) in AcOEt (5 ml) was added PtO_2 (3 mg) and the suspension was stirred at room temperature under atmospheric pressure of hydrogen for overnight The reaction mixture was then filtered through a pad of celite Concentration of the filtrate *in vacuo* gave **8a** (50 mg, quantitative yield) as white solids, which was recrystallized from hexane to give colorless needles m p 79 6 - 80 1°C $[\alpha]_D^{25}$ +23.9° (c=0.7, $CHCl_3$) MS m/e (%)· 212 (M^+) (1), 211 [(M-H)$^+$] (4), 181 [(M-OCH_3)$^+$] (32), 168 (11), 152 (19), 138 (27), 124 (13), 111 (100), 100 (51), 95 (39), 84 (67), 79 (79), 69 (89), 55 (44) HRMS Calcd for $C_{11}H_{16}O_4$ (M^+) 212 1049, Found 212 1055 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 82 (1H, d, J=6.1 Hz, O*CH*O), 4 95 (1H, d, J=3 7 Hz, MeO*CH*O), 3 46 (3H, s, *Me*O), 3 20 (1H, dt, J=6 1, 9 2 Hz, C_{7b}-H), 2 66 (1H, m), 2 54 (1H, dq, J=4.3, 6 7 Hz, Me*CH*), 2 43 (1H, m), 1 88 (1H, m), 1 75 (2H, m), 1 25 (1H, m), 1 20 (3H, d, J=6.7 Hz, CH*Me*) IR (neat) 2930, 2850, 1735, 1450, 1380, 1200, 1080, 1055, 1000, 990, 930, 750, 660 cm^{-1} Anal Calcd. for $C_{11}H_{16}O_4$ C, 62 25, H, 7 60% Found C, 62 30, H,7 68%

(*2S, 2aR, 4aS, 5S, 7aS, 7bS*)-2-(*t*-Butyldimethylsilyloxy)-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-one (8b)

To a solution of **5b** (100 mg, 0 32 mmol) in AcOEt (10 ml) was added PtO_2 (8 mg) and the reaction mixture was stirred at room temperature under atmospheric pressure of hydrogen for overnight Then the reaction mixture was filtrated through a pad of celite Concentration of the filtrate *in vacuo* gave **8b** (97 mg, 97%) as a colorless oil, which was pure enough for spectral analysis $[\alpha]_D^{27}$ +25 3° (c=1 3, $CHCl_3$) MS m/e (%) 311 [(M-H)$^+$] (2), 297 [(M-Me)$^+$] (3), 279 (1), 266 (1), 255 [(M-tBu)$^+$] (100), 237 (28), 211 (52), 199 (15), 181 (17), 171 (3), 152 (17), 135 (9), 121 (7 5), 107 (44), 95 (7), 84 (13), 79 (94), 69 (41), 56 (5) HRMS Calcd for $C_{16}H_{27}O_4Si$ [(M-H)$^+$] 311 1678, Found 311 1694 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 80 (1H, d, J=6 1 Hz, O*CH*O), 5 30 (1H, d, J=3.7 Hz, SiO*CH*O), 3 24 (1H, dt, J=6 1, 9 2 Hz, C_{7b}-H), 2 62 (1H, m), 2 54 (1H, dq, J=4 3, 6 7 Hz, *CH*Me), 2 40 (1H, m), 1 86 (1H, m), 1 73 (2H, m), 1 22 (3H, d, J=6 7 Hz, *Me*CH), 0.90 (9H, s, Si*t*Bu), 0 13 (3Hx2, s, SiMe_2) IR (neat) 2940, 2850, 1742, 1460, 1380, 1360, 1250, 1170, 1125, 1095, 1060, 1000, 975, 940, 920, 840, 780 cm^{-1}

(*2S, 2aR, 4aS, 5R, 7aS, 7bS*)-2-Methoxy-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-one (9a)

To a solution of **8a** (46 0 mg, 0 22 mmol) in toluene (5 ml) was added DBU (0 1 ml, 0 65 mmol) The reaction solution was heated at reflux for 48 h The resulting mixture was then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=2/1 to 1/2) gave **9a** (19 2 mg, 42%) as colorless needles accompanied by recovery of **8a** (14 3 mg, 31%) m p 91 1 - 92°C (recryst from hexane) $[\alpha]_D^{27}$ - 78 7° (c=1 0, $CHCl_3$) MS m/e (%) 213 [(M+H)$^+$] (2), 212 (M^+) (1), 211 [(M-H)$^+$] (2), 181 [(M-OMe)$^+$] (57), 168 (10), 152 (22), 138 (25), 124 (13), 111 (100), 100 (28), 95 (46), 84 (61), 79 (81), 69 (89), 61 (12), 56 (29) HRMS Calcd for $C_{11}H_{17}O_4$ [(M+H)$^+$] 213 1126, Found 213 1148 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 88 (1H, d, J=6 1 Hz, O*CH*O), 4 81 (1H, s, MeO*CH*O), 3 37 (3H, s, *Me*O), 2 97 (1H, dt, J=6 1, 9 2 Hz, C_{7b}-H), 2 74 (1H, m), 2 48 (1H, dq, J=7 3, 10 7 Hz, Me*CH*), 2 21 (1H, m), 2 05 (1H, m), 1 74 (2H, m), 1 57 (1H, m), 1 20 (3H, d, J=7 3 Hz, CH*Me*) IR (neat) 2950, 1748, 1450, 1405, 1355, 1320, 1270, 1190, 1155, 1090, 1065, 1020, 1000, 980, 950, 925, 890 cm^{-1} Anal Calcd for $C_{11}H_{16}O_4$ C, 62 25, H, 7 60% Found C, 62 18, H, 7 71%

(*2S, 2aR, 4aS, 5R, 7aS, 7bS*)-2-(*t*-Butyldimethylsilyloxy)-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-one (9b)

To a solution of **8b** (57 0 mg, 0 18 mmol) in toluene (27 ml) was added DBU (68 μl, 0 55 mmol) The solution was heated at reflux for 72 h The resulting mixture was then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=10/1 to 1/1) gave **9b** (19 2 mg, 34%) as a colorless oil accompanied by recovery of **8b** (20 3 mg, 36%) $[\alpha]_D^{27}$ -44 8° (c=1 4, $CHCl_3$) MS m/e (%) 311 [(M-H)$^+$] (1), 297 [(M-Me)$^+$] (3), 266 (1), 255 [(M-tBu)$^+$] (100), 237 (22), 227 (18), 211 (22), 181 (17), 163 (8), 152 (13), 143 (3), 135 (11), 121 (5), 107 (46), 95 (7), 84 (11), 75 (71), 69 (30), 56 (5) HRMS Calcd for $C_{16}H_{27}O_4Si$ [(M-H)$^+$] 311 1678, Found 311 1657 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 95 (1H, d, J=6 1 Hz, O*CH*O), 5 23 (1H, d, J=1 2 Hz, SiO*CH*O), 3 02 (1H, dt, J=6 1, 9 3 Hz, C_{7b}-H), 2 72 (1H, m), 2 50 (1H, dq, J=6 7, 9 8 Hz, *CH*Me), 2 20 (1H, m), 2 00 (1H, m), 1 72 (3H, m), 1 21 (3H, d, J=6 7 Hz, *Me*CH), 0 89 (9H, s, Si*t*Bu), 0 12 (3Hx2, s, SiMe_2) IR (neat) 2960, 2870, 1760, 1465, 1416, 1360, 1325, 1255, 1160, 1100, 1065, 1017, 975, 925, 845, 785 cm^{-1}

(*2S, 2aR, 4aS, 7aS, 7bS*)-5-[(*3E*)-4,8-Dimethyl-2-(4-methylphenyl)sulfonyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-one (22)

To a solution of diisopropylamine (1.29 g, 9.2 mmol) in THF (10 ml) was added BuLi (1.6 M in hexane, 5 8 ml, 9 2 mmol) under argon at -78 °C After stirred at -78 °C for 10 min, the mixture was stirred at -5 °C for another 30 min. Then a solution of geranyl sulfone (6) (2 28 g, 7 8 mmol) in THF (30 ml) was added into the reaction mixture at -78 °C After stirred for 30 min at -78 °C, 5a (1 49 g, 7.1 mmol) in THF (30 ml) was added into the lithium salt of geranyl sulfone and the mixture was stirred at -78 °C for 20 min The reaction was quenched with sat. NH_4Cl and then diluted with AcOEt The resulting mixture was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. Flash chromatography of the residue (SiO_2, hexane/ether=10/1 to 1/1) gave a diastereomeric mixture of **22** (2 93 g, 82%) as a pale yellow oil MS m/e (%): 502 (M^+) (1), 471 (1), 393 (1), 361 (1), 347 (46), 329 (4), 315 (56), 297 (30), 269 (18), 247 (24), 229 (17), 201 (15), 173 (11), 135 (21), 109 (18), 93 (15), 81 (33), 69 (100), 57 (14). ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 71 (2H, m, Ar*H*), 7.30 (2H, m, Ar*H*), 5 82 (1H, m, O*CH*O), 4 95-4 75 (3H, 2xCH_2*CH*=C, MeO*CH*O), 4 19 (1H, m), 3.47-3.20 (4H including *MeO*), 2 95 (1H, m), 2.85-2 25 (6H including Ar*Me*), 2 15-1 76 (8H), 1 69 (3H, m, *Me*C=C), 1.59 (3H, m, *Me*MeC=C), 1.30-1 21 (4H including *Me*MeC=C) IR (neat) 2930, 1740, 1660, 1595, 1445, 1380, 1300, 1140, 1070, 1005, 955, 935, 920, 815, 750, 660 cm^{-1} HRMS of this and the following sample (**23**) could not be determined by ambiguous reasons

(*2S, 2aR, 4aR, 7aR, 7bS*)-5-[(*3E*)-4,8-Dimethyl-2-(4-methylphenyl)sulfonyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-ol (23)

To a solution of **22** (2 90 g, 5 8 mmol) in CH_2Cl_2 (60 ml) was slowly added DIBAL (0 93 M in hexane, 8 0 ml, 7 4 mmol) at -78 °C and the mixture was stirred at -78 °C for 2 h After addition of AcOEt and a little amount of water and dilution with ether, the reaction mixture was stirred at room temperature until white precipitates appeared. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to give a diastereomeric mixture of **23** (2 71 g, 91%) as a colorless oil This sample was pure enough for the next reaction and spectral analysis MS m/e (%) 472 [(M-CH_3OH)$^+$] (0 1), 347 (1) 317 (8), 281 (2), 231 (4), 193 (3), 109 (10), 91 (20), 69 (100), 55 (9) ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 70 (2H, m, Ar*H*), 7 27 (2H, m, Ar*H*), 5.57 (1H, m, O*CH*O), 5 09-4 86 (3H, 2xCH_2*CH*=C, HO*CH*O), 4.57 (1H, m, MeO*CH*O), 4 00 (1H, m), 3 34 (4H including *Me*O), 2 63 (2H, m), 2 43 (3H, s, Ar*Me*), 1 99-1 55 (11H), 1 69 (3H, s, *Me*C=C), 1 59 (3H, s, *Me*MeC=C), 1 41-1 19 (4H including *Me*MeC=C) IR (neat) 3460, 2930, 1660, 1600, 1500, 1450, 1380, 1300, 1185, 1140, 1095, 1050, 1015, 980, 920, 820, 732, 665 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-6-(*t*-Butyldimethylsilyloxy)-5-[(*3E*)-4,8-dimethyl-2-(4-methylphenyl)sulfonyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene (24)

To a solution of **23** (2 70 g, 5 4 mmol) and 2,6-lutidine (1 3 ml, 11 mmol) in THF (48 ml) was slowly added TBDMSOTf (1 5 ml, 6 4 mmol) at -78 °C and the mixture was stirred at -78 °C for 1 h After concentration *in vacuo*, the residue was diluted with AcOEt and was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/AcOEt=20/1 to 5/1) gave a diastereomeric mixture of **24** (3 00 g, 90%) as a colorless oil MS m/e (%) 618 (M^+) (1), 561 [(M-tBu)$^+$] (1), 529 (3), 463 (7) 431 (5), 405 (3), 373 (9), 331 (17), 313 (5), 299 (23), 281 (13), 213 (10), 185 (5), 149 (15), 123 (8), 69 (100), 57 (14) HRMS Calcd for $C_{34}H_{54}O_6Si_2S$ (M^+) 618 3410, Found 618 3414 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 7 67 (2H, m, Ar*H*), 7 28 (2H, m, Ar*H*), 5 49 (1H, d, J=5 5 Hz, O*CH*O), 5 01 (2H, m, 2xCH_2*CH*=C), 4 71 (1H, m, SiO*CH*O), 4 55 (1H, s, MeO*CH*O), 3 76 (1H, m, *CH*SO_2), 3 32 (3H, s, *Me*O), 2 58 (1H, m), 2 45 (1H, m), 2 42 (3H, s, Ar*Me*), 2 03-1 96 (4H), 1 96-1 79 (4H), 1 68 (3H, s, *Me*C=C), 1 68-1 58 (4H), 1 58, 1 41 (3Hx2, sx2, Me_2C=C), 0 84 (9H, s, Si*t-Bu*), 0 10 (3Hx2, s, SiMe_2) IR (neat) 2930, 1660, 1600, 1450, 1410, 1310, 1300, 1250, 1195, 1145, 1100, 1050, 1015, 980, 930, 865, 820, 780, 670 cm^{-1}

(*2S, 2aR, 4aS, 7aR, 7bS*)-6-(*t*-Butyldimethylsilyloxy)-5-[(*3E*)-4,8-dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene (25)

To a dark blue solution of excess amount of lithium metal in $EtNH_2$ (*ca* 5 ml) was quickly added **24** (182 mg, 0 29 mmol) in THF (3 ml) at -78 °C and the mixture was stirred vigorously at -78 °C for 15 min The reaction was then quenched with isoprene (0 1 ml) and was added solid NH_4Cl The residual metallic Li was taken away and $EtNH_2$ was removed *in vacuo* The residue was diluted with AcOEt, and was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=20/1 to 10/1) gave a diastereomeric mixture of **25** (103 mg, 76%) as a colorless oil MS

m/e (%). 464 (M^+) (3), 433 [(M-CH_3O)$^+$] (2), 407 [(M-tBu)$^+$] (8), 375 (26), 347 (5), 332 (14), 315 (3), 301 (8), 283 (21), 246 (17), 208 (13), 183 (9), 171 (30), 150 (10), 135 (13), 123 (19), 109 (26), 93 (18), 69 (100), 55 (21) HRMS Calcd for $C_{27}H_{48}O_4Si$ (M^+): 464.3322, Found 464 3337 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 53 (1H, m, O*CH*O), 5 12, 4 99 (1H, mx2, SiO*CH*O), 5 08 (2H, m, 2xCH_2*CH*=C), 4.61 (1H, m, MeO*CH*O), 3 34 (3H, s, *Me*O), 2 66-2 49 (2H), 2 25-1.86 (8H), 1.81-1 60 (3H), 1 67 (3H, s, *Me*C=C), 1 64, 1 59 (3Hx2, sx2, *Me*$_2$C=C), 1 36 (1H, m), 1.25 (1H, m), 1 15 (1H, m), 0 91 (9H, m, Si*t*Bu), 0 14 (3Hx2, Si*Me*$_2$) IR (neat) 2925, 2860, 1450, 1410, 1375, 1260, 1195, 1150, 1100, 1050, 1015, 980, 940, 920, 865, 840, 780 cm^{-1}

(2*S*, 2a*R*, 4a*R*, 7a*R*, 7b*S*)-5-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-ol (26)

To a solution of **25** (1 65 g, 3 6 mmol) in THF (20 ml) was quickly added $Bu_4NF{\cdot}H_2O$ (1 12 g, 4 3 mmol) in THF (13 ml) at -5 °C. After stirred at -5 °C for 20 minutes, the reaction was quenched with sat NH_4Cl After concentration *in vacuo*, the residue was extracted with AcOEt for three times The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=5/1 to 2/1) gave a diastereomeric mixture of **26** (0 99 g, 79%) as a colorless oil accompanied by a recovery of **25** (189 mg, 11%) MS m/e (%)· 350 (M^+) (2), 332 [(M-H_2O)$^+$] (7), 318 [(M-CH_3OH)$^+$] (9), 301 (7), 289 (5), 272 (4), 257 (7), 231 (8), 218 (4), 203 (6), 175 (7), 107 (26), 93 (21), 81 (45), 69 (100), 55 (26) HRMS Calcd for $C_{21}H_{34}O_4$ (M^+). 350 2457, Found 350 2448 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 59 (1H, m, O*CH*O), 5 09 (3H, m, 2xCH_2*CH*=C, HO*CH*O), 4 63 (1H, m, MeO*CH*O), 3 35 (3H, m, *Me*O), 2 76 (1H, m), 2 64 (2H, m), 2 27-1 68 (12H), 1 68 (3H, s, *Me*C=C), 1 60, 1.37 (3Hx2, sx2, *Me*$_2$C=C) IR (neat) 3420, 2920, 1650, 1440, 1375, 1270, 1180, 1140, 1090, 1045, 1010, 975, 905, 865, 820, 750 cm^{-1}

(2*S*, 2a*R*, 4a*S*, 5*R*, 7a*S*, 7b*S*)-5-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-one (27) and (2*S*, 2a*R*, 4a*S*, 5*S*, 7a*S*, 7b*S*)-5-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-one (28)

To a mixture of **26** (975 mg, 2 8 mmol) and 4Å molecular sieves in CH_2Cl_2 (27 ml) was added PCC (3 67 g, 17 mmol) at room temperature The reaction was stirred at room temperature for 19 h After dilution with ether, the reaction mixture was filtered through a pad of celite The filtrate was washed with water and diluted HCl and extracted with AcOEt for three times The combined organic phase was washed with sat $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ AcOEt=20/1 to 5/1) gave **27** and **28** (777 mg, 80%) as a colorless oil The ratio of **27.28** was 1 3 from ^{1}H-NMR and GC **27** and **28** were separated by HPLC through a μ Porasil P/N 27477 column (hexane/AcOEt=10/1) **27** $[\alpha]_D^{24}$ -15 0° (c=1 1, $CHCl_3$) MS m/e (%). 348 (M^+) (38), 334 (38), 316 [(M-CH_3OH)$^+$] (49), 299 (19), 288 (12), 273 (43), 261 (18), 247 (45), 237 (25), 224 (46), 211 (18), 192 (28), 173 (42), 166 (74), 149 (24), 138 (29), 123 (53), 109 (80), 95 (24), 82 (100), 69 (85), 57 (11) HRMS Calcd. for $C_{21}H_{32}O_4$ (M^+) 348 2300, Found 348 2313 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 88 (1H, d, J=6 1 Hz, O*CH*O), 5 08 (2H, m, 2xCH_2*CH*=C), 4 84 (1H, d, J=2.4 Hz, MeO*CH*O), 3 41 (3H, s, *Me*O), 3.00 (1H, dt, J=6 7, 9 2 Hz), 2 72 (1H, m), 2 48 (1H, dt, J=4 3, 7 8 Hz, *C*$_5$*H*), 2 34 (1H, m), 2 17-1 90 (6H), 1 82 (1H, m), 1 78-1 5 (5H), 1 67 (3H, s, *Me*C=C), 1 60 (3Hx2, s, *Me*$_2$C=C) IR (neat) 2925, 2875, 1750, 1450, 1400, 1280, 1192, 1150, 1115, 1070, 1010, 980, 955, 930, 835, 750 cm^{-1} **28** $[\alpha]_D^{24}$ +25 2° (c=1 9, $CHCl_3$). MS m/e (%) 348 (M^+) (47), 334 [(M-CH_3)$^+$] (63), 316 [(M-CH_3OH)$^+$] (23), 273 (31), 260 (17), 247 (29), 224 (56), 213 (15), 201 (23), 192 (19), 173 (41), 151 (18), 137 (20), 123 (45), 109 (60), 95 (23), 82 (86), 69 (100), 61 (18), 55 (12) HRMS Calcd for $C_{21}H_{32}O_4$ (M^+) 348 2300, Found 348 2283 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 79 (1H, d, J=6.1 Hz, O*CH*O), 5 09 (2H, m, 2xCH_2*CH*=C), 4 96 (1H, d, J=3 7 Hz, MeO*CH*O), 3 47 (3H, s, *Me*O), 3 19 (1H, dt, J=6 1, 9.2 Hz), 2 66 (1H, m), 2 51 (1H, ddd, J=4 3, 9 2, 13 4 Hz, *C*$_5$*H*), 2 35 (1H, dt, J=4 3, 9 2 Hz), 2 18-1 95 (7H), 1 9-1 7 (3H), 1 68 (3H, s, *Me*C=C), 1 60 (3Hx2, s, *Me*$_2$C=C), 1 4-1 2 (2H) IR (neat) 2950, 2875, 1740, 1450, 1380, 1275, 1155, 1130, 1070, 1010, 990, 954, 908, 835, 755 cm^{-1}

Isomerization of 28 to 27 To a solution of **28** (202 mg, 0 58 mmol) in toluene (15 ml) was added DBU (0 27 ml, 1 8 mmol) The mixture was heated at refluxing for 35 h The reaction mixture was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ether=20/1 to 5/1) gave a mixture of **27** and **28** (140 mg, 70%) in 1 1 ratio

(2*S*, 2a*R*, 4a*R*, 5*R*, 7a*R*, 7b*S*)-5-[(3*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-ol (29)

To a solution of **27** (86.0 mg, 0.25 mmol) in CH_2Cl_2 (2.6 ml) was added DIBAL (0.93 M in hexane, 0 35 ml, 0.32 mmol) at -78 °C and the mixture was stirred at -78 °C for 1 h After dilution with AcOEt and ether, a little of water was added to the mixture, which was then warmed up to room temperature, and was stirred until white precipitate appeared After filtration through a pad of celite, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/AcOEt=5/1 to 2/1) gave a diastereomeric mixture of **29** (86 mg, 99%) as a colorless oil The ratio of two diastereomer was 4 1 by ^{1}H-NMR spectrum MS m/e (%) 351 [(M+H)$^+$] (6), 332 [(M-H_2O)$^+$] (4), 318 [(M-CH_3OH)$^+$] (11), 300 (68), 289 (3), 277 (5), 257 (6), 231 (10), 219 (8), 203 (6), 175 (7), 135 (16), 107 (32), 93 (25), 81 (43), 69 (100), 55 (23). HRMS Calcd for $C_{21}H_{32}O_3$ [(M-H_2O)$^+$]. 332 2351, Found 332 2334 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 57 (1H, d, J=4 9 Hz, O*CH*O), 5 35 (4/5H, s, HO*CH*O), 5 07 (2H, m, 2xCH_2*CH*=C), 4.88 (1/5H, d, J=6 4 Hz, HO*CH*O), 4 63, 4 55 (1H, sx2, MeO*CH*O), 3 50 (1H, br, *OH*), 3 32 (3H, s, *Me*O), 2 66-2 54 (2H), 2 12-1 71 (12H), 1 66 (3H, s, *Me*C=C), 1 58 (3Hx2, s, *Me*$_2$C=C), 1.45 (1H, m), 1 32 (1H, m) IR (neat) 3440, 2930, 1450, 1380, 1275, 1200, 1142, 1100, 1065, 1050, 1020, 980, 850 cm^{-1}

(*2aR*, *4aR*, *5R*, *7aR*, *7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-2,6-diol, *ent*-udoteatrial hydrate (30)
To a solution of **29** (70 mg, 0 20 mmol) was added a solution of *p*-TsOH (0 1 M in THF·H_2O acetone =4 2 1, 5 ml) and the reaction mixture was stirred at room temperature for 10 h. After dilution with AcOEt, the resulting mixture was washed with sat $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/AcOEt=2/1) gave **30** (43 mg, 69%) as a colorless oil MS m/e (%) 336 (M$^+$) (1), 318 [(M-H_2O)$^+$] (9), 300 [(M-2H_2O)$^+$] (6), 275 (3), 257 (6), 217 (6), 193 (6), 175 (7), 150 (18), 135 (19), 107 (36), 95 (24), 82 (56), 69 (100), 55 (21) HRMS Calcd for $C_{20}H_{30}O_3$ [(M-H_2O)$^+$] 318 2196, Found 318 2198 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 57 (1H, d, J=4 9 Hz, O*CH*O), 5 35 (4/5H, s, HO*CH*O), 5 07 (2H, m, 2xCH_2*CH*=C), 4 88 (1/5H, d, J=6 4 Hz, HO*CH*O), 4 63, 4 55 (1H, sx2, MeO*CH*O), 3 50 (1H, br, *OH*), 3 32 (3H, s, *Me*O), 2 74-2 60 (2H), 2 14-1 72 (12H), 1 66 (3H, s, *Me*C=C), 1 58 (3Hx2, s, *Me*$_2$C=C), 1 45 (1H, m), 1 32 (1H, m) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 135 4, 131 3, 124 7, 124 3, 102 3, 102 0, 89 7, 51 1, 39 7, 39 3, 39 0, 37 2, 36 4, 31 4, 30 2, 26 7, 25 7, 17 7, 16 1 IR (neat) 3400, 2950, 1715 (br), 1650 (br), 1450, 1380, 1240, 1140, 1070, 995, 900, 755 cm^{-1}

(*2S*, *2aR*, *4aR*, *5S*, *7aR*, *7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2-methoxy-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-ol (31)
To a solution of **28** (38 mg, 0 11 mmol) in CH_2Cl_2 (1 2 ml) was added DIBAL (0 93 M in hexane, 0 15 ml, 0 14 mmol) at -78 °C and the mixture was stirred at -78 °C for 1 h After dilution with AcOEt and ether, a little of water was added to the mixture, which was warmed up to room temperature, and was stirred until white precipitate appeared After filtration through a pad of celite, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane /AcOEt=5/1) gave a diastereomeric mixture of **31** (37 mg, 97%) as a colorless oil MS m/e (%) 350 (M$^+$) (1), 332 [(M-H_2O)$^+$] (2), 318 [(M-CH_3OH)$^+$] (4), 300 (10), 289 (2), 275 (4), 257 (7), 231 (4), 203 (3), 175 (4), 150 (9), 123 (14), 107 (21), 95 (14), 81 (34), 69 (100), 55 (18) HRMS Calcd for $C_{21}H_{34}O_4$ (M$^+$) 350 2457, Found 350 2445 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 60 (1H, d, J=5 5 Hz, O*CH*O), 5 08 (3H, m, HO*CH*O, 2xCH_2*CH*=C), 4 62 (1H, s, MeO*CH*O), 3 34 (3H, s, *Me*O), 3 08 (1H, br, *OH*), 2 71-2 52 (2H), 2 22 (1H, m), 2 14-1 92 (8H), 1 84 (1H, m), 1 79-1 69 (2H), 1 70 (3H, s, *Me*C=C), 1 59 (3Hx2, s, *Me*$_2$C=C), 1 41 (1H, m), 1 25 (1H, m) IR (neat) 3440, 2925, 1450, 1142, 1100, 1050, 1015, 980, 940, 910, 820 cm^{-1}

(*2aR*, *4aR*, *5S*, *7aR*, *7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-2,6-diol, *ent*-5-*epi*-udoteatrial hydrate (32)
To a solution of **31** (35 mg, 0 10 mmol) was added a solution of *p*-TsOH (0 1 M in THF H_2O acetone=4 2 1, 2 5 ml) and the reaction mixture was then stirred at room temperature for overnight After dilution with AcOEt, the resulting mixture was washed with sat $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/AcOEt=3/1 to 1/1) gave **32** (26 mg, 79%) as a colorless oil MS m/e (%) 318 [(M-H_2O)$^+$] (3), 300 [(M-2H_2O)$^+$] (5), 275 (4), 257 (7), 239 (2), 229 (3), 207 (3), 175 (7), 150 (3), 123 (22), 107 (34), 95 (25), 81 (41), 69 (100), 55 (27) ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 73-4 84 (5H, 2xHO*CH*O, O*CH*O, 2xCH_2*CH*=C), 2 98 (1H, m), 2 66 (2H, m), 2 24 (1H, m), 2 04-0 88 (14H), 1 68 (3H, s, *Me*C=C), 1 60, 1 58 (3Hx2, sx2, *Me*$_2$C=C) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 138 6, 135 6, 124 3, 124 0, 103 7, 101 4, 92 6, 50 3, 42 8, 40 8, 39 9, 39 7, 30 4, 30 3, 26 7, 26 3, 25 7, 25 1, 17 7, 16 1 IR (neat) 3400, 2925, 1735-1650 (br), 1450, 1375, 1145, 1105, 1075, 1000, 760 cm^{-1}

(*2S, 2aR, 4aR, 5R, 6S, 7aR, 7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-2,6-diol diacetate (33) and (*2S, 2aR, 4aR, 5R, 6R, 7aR, 7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d] indene-2,6-diol diacetate (34)

To a solution of **30** (44 0 mg, 0 13 mmol) in pyridine (1 ml) was added Ac_2O (43 µl, 0 46 mmol) at room temperature and the mixture was stirred at room temperature for 18 h After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/AcOEt=20/1 to 10/1) gave a mixture of **33** and **34** (36 mg, 66%) as a colorless oil. HPLC separation with µ Porasil P/N 27477 column (hexane/AcOEt=10/1) gave **33** (23 5 mg, 43%) and **34** (11.0 mg, 20%) respectively. **33:** $[\alpha]_D^{25}$ +23.9° (c=1.2, $CHCl_3$) MS m/e (%): 360 [(M-AcOH)$^+$] (4), 300 [(M-2AcOH)$^+$] (15), 257 (5), 231 (7), 203 (7), 175 (9), 161 (4), 150 (37), 135 (21), 121 (14), 107 (47), 94 (18), 81 (30), 69 (100), 55 (15). HRMS Calcd for $C_{22}H_{32}O_4$ [(M-AcOH)$^+$]· 360.2301, Found 360 2328 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 21 (1H, d, J=2.4 Hz, AcO*CH*O), 5 85 (1H, s, AcO*CH*O), 5.66 (1H, d, J=4 9 Hz, O*CH*O), 5 07 (2H, m, 2xCH_2*CH*=C), 2 74 (2H, m), 2 08 (3H, s, *Me*CO), 2 03 (3H, s, *Me*CO), 2 00-1.62 (12H), 1.67 (3H, s, *Me*C=C), 1 59, 1.58 (3Hx2, sx2, Me_2C=C), 1 42 (2H, m) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 170 1, 169.6, 136 0, 131 4, 124 3, 123 6, 102 3, 101 0, 89.9, 50 9, 40.6, 39 7, 38.9, 37 7, 32 1, 29.99, 29 95, 26.7, 25 7, 25.5, 21 2, 21 1, 17 7, 16 0 IR ($CHCl_3$) 2920, 2850, 1735, 1450, 1142, 1375, 1200, 1155, 1070, 1000, 970, 930, 885, 850, 820 cm^{-1} **34:** $[\alpha]_D^{23}$ -42.2° (c=0 6, $CHCl_3$). MS m/e (%): 360 [(M-AcOH)$^+$] (7), 318 (4), 301 [(M-2AcOH)$^+$] (12), 257 (4), 233 (8), 203 (6), 175 (8), 150 (27), 135 (19), 121 (13), 107 (39), 93 (16), 81 (31), 69 (100), 55 (15) HRMS Calcd for $C_{22}H_{32}O_4$ [(M-AcOH)$^+$]: 360 2301 Found. 360 2320 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 97 (1H, s, AcO*CH*O), 5 91 (1H, d, J=4.9 Hz, AcO*CH*O), 5 66 (1H, d, J=5 5 Hz, O*CH*O), 5 08 (2H, m, 2xCH_2*CH*=C), 2.75 (2H, m), 2 08 (3H, s, *Me*CO), 2 03 (3H, s, *Me*CO), 2 13-1 95 (12H), 1 68 (3H, s, *Me*C=C), 1 60, 1 59 (3Hx2, sx2, Me_2C=C), 1 45 (2H, m) ^{13}C-NMR (C_6D_6) δ= 169.4, 169.3, 135 9, 131 3, 124 8, 124 2, 101 7, 101.6, 92 9, 50 1, 40 3, 40 1, 38.3, 35 6, 32 1, 31 3, 30 0, 27 1, 25.8, 25 5, 21 0, 20.8, 17 7, 16.1. IR ($CHCl_3$). 2920, 2850, 1733, 1450, 1370, 1200, 1080, 1000, 970, 905, 870, 835 cm^{-1}.

(*2S, 2aR, 4aR, 5S, 6R, 7aR, 7bS*)-5-[(*3E*)-4,8-Dimethyl-3,7-nonadienyl]-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-2,6-diol diacetate (35)

To a solution of **32** (26.0 mg, 0.08 mmol) in pyridine (1 ml) was added Ac_2O (30 µl, 0.52 mmol) at room temperature and the mixture was stirred at room temperature for 18 h After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/AcOEt=4/1) gave **35** (16 9 mg, 52%) as a colorless oil $[\alpha]_D^{26}$ +30 2° (c=0.8, $CHCl_3$) MS m/e (%)· 360 [(M-AcOH)$^+$] (3), 317 (3), 300 [(M-2AcOH)$^+$] (14), 283 (4), 257 (7), 223 (8), 203 (6), 181 (15), 150 (31), 135 (19), 107 (34), 93 (16), 81 (33), 69 (100), 55 (18) HRMS Calcd. for $C_{22}H_{32}O_4$ [(M-AcOH)$^+$]· 360 2301, Found. 360 2302 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 99 (1H, d, J=9 2 Hz, AcO*CH*O), 5 98 (1H, s, AcO*CH*O), 5.64 (1H, d, J=4 9 Hz, O*CH*O), 5 08 (2H, m, CH_2*CH*=C), 2 72 (2H, m), 2 35 (1H, m), 2 10 (3H, s, *Me*CO), 2 03 (3H, s, *Me*CO), 2 01-1 70 (9H), 1 68 (3H, s, *Me*C=C), 1 60, 1 59 (3Hx2, sx2, Me_2C=C), 1.74-1 50 (3H), 1 26 (1H, m) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 169.8, 169.6, 135.9, 131.4, 124.2, 123.5, 102 8, 102.7, 91 1, 49 3, 42 5, 39 74, 39 68, 37 5, 30 2, 29 2, 26.7, 26.0, 25.7, 24.9, 21 2, 21 1, 17 7, 16.1 IR (neat)· 2920, 1750, 1440, 1365, 1230, 1180, 1145, 1075, 980, 920, 825, 750 cm^{-1}

(*2S, 2aR, 4aR, 5R, 7aR, 7bS*)-2-(*t*-Butyldimethylsilyloxy)-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-*2H*-1,7-dioxacyclopent[c,d]indene-6-ol (36)

To a solution of **9b** (28 0 mg, 0.09 mmol) in toluene (1.5 ml) was added DIBAL (0 93 M in hexane, 0 11 ml, 0 10 mmol) at -78 °C and the mixture was stirred at -78 °C for 1 h After dilution with ether, a little of water was added to the mixture, which was warmed up to room temperature, and was stirred until white precipitate appeared After filtration through a pad of celite, the filtrate was concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=10/1 to 5/1) gave a diastereomeric mixture of **36** (27 7 mg, 98%) as a colorless oil The ratio of diastereomer was 2 1 by ^{1}H-NMR spectrum MS m/e (%) 281 [(M-OMe)$^+$] (1), 257 [(M-tBu)$^+$] (11), 239 (23), 211 (38), 183 (24), 172 (6), 165 (42), 145 (5), 137 (14), 109 (20), 97 (15), 75 (100), 67 (22), 58 (15) HRMS Calcd. for $C_{12}H_{21}O_4Si$ [(M-tBu)$^+$]. 257 1209, Found 257 1231 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5.68 (1H, m, O*CH*O), 5 30 (2/3H, br, O*CH*OH), 5 12 (1/3H, s, SiO*CH*O), 5 01 (2/3H, s, SiO*CH*O), 4 66 (1/3H, br, O*CH*OH), 3 17-3 09 (1H), 2 64 (2H, m), 2 06 (1H, m), 1 88 (2H, m), 1 69 (2H, m), 1 49 (1H, m), 1 03 (3H, d, J=6 7 Hz, *Me*CH), 0 87 (9H, s, Si^t*Bu*), 0 09 (3Hx2, s, SiMe_2) IR (neat) 3440, 2930, 2850, 1460, 1390, 1360, 1250, 1140, 1090, 1010, 990, 910, 835, 775, 750 cm^{-1}

(2*S*, 2*aR*, 4*aR*, 5*R*, 6*S*, 7*aR*, 7*bS*)-5-Methyl-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene -2,6-diol diacetate (37) and (2*S*, 2*aR*, 4*aR*, 5*R*, 6*R*, 7*aR*, 7*bS*)-5-Methyl-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-2,6-diol diacetate (38)

To a solution of **36** (26.0 mg, 0 08 mmol) was added a solution of *p*-TsOH (0 1 M in THF H_2O acetone =4·2 1, 2 ml) and the reaction mixture was stirred at room temperature for overnight. After dilution with AcOEt, the resulting mixture was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/AcOEt=1/1 to 1/5) gave monohydrate (16 mg, 93%) as a colorless oil, to which was added pyridine (1 ml), and Ac_2O (28 μl, 0 29 mmol) and the mixture was stirred at room temperature for 18 h. After concentration *in vacuo*, preparative thin layer chromatography of the residue (SiO_2, hexane/AcOEt=2/1) gave a mixture of **37** and **38** (12 5 mg, 55%) as a colorless oil HPLC separation with μ Porasil P/N 27477 column (hexane/AcOEt=10/1) gave **37** (6.6 mg) and **38** (3 6 mg) respectively. **37:** $[\alpha]_D^{28}$ +29 1° (c=0 3, $CHCl_3$) MS m/e (%) 283 [(M-H)$^+$] (1), 225 [(M-AcO)$^+$] (25), 224 [(M-AcOH)$^+$] (2), 196 (15), 165 (48), 153 (10), 136 (100), 125 (11), 107 (19), 100 (46), 79 (38), 67 (19), 58 (17) HRMS Calcd for $C_{12}H_{16}O_4$ [(M-AcOH)$^+$]· 224.1048, Found· 224 1055 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 13 (1H, d, J=1.8 Hz, AcO*CH*O), 5.88 (1H, s, AcO*CH*O), 5.69 (1H, d, J=4 9 Hz, O*CH*O), 2 74 (2H, m), 2 08 (3H, s, *Me*CO), 2 03 (3H, s, *Me*CO), 2 10-1 75 (5H), 1 48 (1H, m), 1 00 (3H, d, J=6 7 Hz, *Me*CH) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 170 1, 169 7, 102 5, 101 0, 90.9, 50 8, 40 1, 39 7, 33 3, 31 4, 29 9, 21 2, 21 1, 14 7 IR (neat) 2970, 2880, 1740, 1370, 1235, 1078, 978, 927, 825 cm^{-1} **38:** $[\alpha]_D^{28}$ -86 1° (c=0 2, $CHCl_3$) MS m/e (%)· 256 (1), 225 [(M-AcO)$^+$] (37), 224 [(M-AcOH)$^+$] (1), 210 (7), 196 (14), 183 (26), 165 (78), 153 (11), 136 (100), 121 (11), 107 (22), 100 (59), 79 (47), 67 (23), 58 (22) HRMS Calcd for $C_{12}H_{17}O_4$ [(M-AcO)$^+$] 225 1127, Found 225 1143 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6 01 (1H, s, AcO*CH*O), 5 718 (1H, d, J=8 6 Hz, AcO*CH*O), 5 716 (1H, d, J=4 3 Hz, O*CH*O), 2 78 (2H, m), 2 10 (3H, s, *Me*CO), 2 03 (3H, s, *Me*CO), 2 04 (1H, m), 1 97-1 82 (3H), 1 72-1 62 (2H), 0 99 (3H, d, J=6 1 Hz, *Me*CH) ^{13}C-NMR (100 MHz, C_6D_6) δ= 169 7, 169 2, 101 9, 101 3, 94 6, 49 9, 42 8, 40 2, 31 2, 30 7, 29 4, 20 8, 20 7, 16 0 IR (neat) 2975, 2900, 1742, 1455, 1421, 1370, 1240, 1170, 1090, 1060, 1020, 997, 970, 930, 868, 830, 752 cm^{-1}

(2*S*, 2*aR*, 4*aR*, 5*S*, 7*aR*, 7*bS*)-2-(*t*-Butyldimethylsilyloxy)-5-methyl-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-6-ol (39)

To a solution of **8b** (36 0 mg, 0 12 mmol) in toluene (2 ml) was added DIBAL (0 93 M in hexane, 0 14 ml, 0 13 mmol) at -78 °C and the mixture was stirred at -78 °C for 1 h After dilution with ether, the mixture was washed with 10% aq H_3PO_4, sat $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash chromatography of the residue (SiO_2, hexane/ethyl ether=10/1 to 2/1) gave **39** (36 0 mg, 99%) as a yellow oil $[\alpha]_D^{28}$ +9 6° (c=1 5, $CHCl_3$) MS m/e (%) 313 [(M-H)$^+$], 295 [(M-CH_3)$^+$] (1), 281 (1), 268 (1), 239 (7), 227 (2), 211 (31), 199 (2), 183 (18), 172 (6), 165 (29), 145 (4), 137 (15), 119 (17), 109 (17), 97 (13), 75 (100), 67 (15), 58 (13) HRMS Calcd for $C_{16}H_{29}O_4Si$ [(M-H)$^+$] 313 1835, Found 313 1862 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 66 (1H, d, J=4 9 Hz, O*CH*O), 5 03 (1H, s, SiO*CH*O), 4 99 (1H, d, J=8 5 Hz, O*CH*OH), 3 17 (1H, br, *OH*), 2 60 (2H, m), 2 10 (1H, m), 1 78 (2H, m), 1 61 (2H, m), 1 30 (1H, m), 1 01 (3H, d, J=6 7 Hz, *Me*CH), 0 87 (9H, s, Si*t-Bu*), 0 10, 0 09 (3Hx2, sx2, Si*Me*$_2$) IR (neat) 3425, 2940, 2850, 1460, 1255, 1120, 1100, 1000, 980, 910, 855, 840, 780 cm^{-1}

(2*S*, 2*aR*, 4*aR*, 5*S*, 6*R*, 7*aR*, 7*bS*)-5-Methyl-2a,3,4,4a,5,6,7a,7b-octahydro-2*H*-1,7-dioxacyclopent[c,d]indene-2,6-diol diacetate (40)

To a solution of **39** (29 0 mg, 0 08 mmol) was added a solution of *p*-TsOH (0 1 M THF H_2O acetone =4 2 1, 2 ml) and the reaction mixture was stirred at room temperature for overnight After dilution with AcOEt, the resulting mixture was washed with sat $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* Flash column chromatography of the residue (SiO_2, hexane/AcOEt=1/1 to 1/5) gave monohydrate (14.0 mg, 84%) as a white solid, to which was added pyridine (1 ml), and Ac_2O (27 μl, 0 27 mmol) and the mixture was stirred at room temperature for 18 h After concentration *in vacuo*, flash chromatography of the residue (SiO_2, hexane/AcOEt=5/1 to 2/1) gave **40** (17 7 mg, 89%) as a colorless oil $[\alpha]_D^{26}$ +29 9° (c=0 9, $CHCl_3$) MS m/e (%) 225 [(M-AcO)$^+$] (26), 224 [(M-AcOH)$^+$] (4), 196 (17), 183 (25), 165 (25), 153 (12), 136 (100), 125 (11), 107 (22), 100 (70), 79 (47), 67 (23), 58 (21) HRMS Calcd for $C_{12}H_{16}O_4$ [(M-AcOH)$^+$] 224 1048, Found 224 1046 ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 5 96 (1H, d, J=9 2 Hz, AcO*CH*O), 5 95 (1H, AcO*CH*O), 5 67 (1H, d, J=5 5 Hz, O*CH*O), 2 73 (1H, m), 2 66 (1H, m), 2 23 (1H, m), 2 10 (3H, s, *Me*CO), 2 02 (3H, s, *Me*CO), 1 91 (1H, m), 1 70 (3H, m), 1 50 (1H, m), 0 95 (3H, d, J=7 3 Hz, *Me*CH) ^{13}C-NMR (100 MHz, $CDCl_3$) δ= 169 9, 169 6, 103 9, 102 5, 90 9, 49 4, 42 6,

41 4, 32 9, 30.5, 26.1, 21 2, 21 0, 14 6 IR (neat) 2950, 1750, 1375, 1230, 1180, 1140, 1085, 1070, 1040, 1010, 980, 930, 825 cm^{-1}.

General procedure for cytotoxic assay

Cytotoxic assay was conducted by using suspensions of human lung carcinoma, A-549 (ATCC CCL-185) in Ham's F12K medium with 10% fetal bovine serum (FBS) and human oral epidermoid carcinoma, KB (ATCC CCL-17) in Eagle's MEM with no-essential amino acids and 10% FBS These suspensions were distributed in a 96-well microtiter plate, which were cultivated at 37°C in an atmosphere of 5% carbon dioxide, 7% oxygen, and 88% nitrogen. After 24 hours, human recombinant basic FGF (endothelial cell growth factor) was added thereto in the final concentration of 2 ng/ml and DMF solution of a test compound was further added, followed by cultivation for 3 days After cultivation, growth rate of these cells were measured by MTT method (Cancer Treatment Reports, Vol. 71, page 1141-1149, 1987) IC_{50} value of the test compound was determined from a graph of growth curve of these cells

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References and Notes

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1 Nakatsu, T., Ravi, B N , Faulkner, D. J. *J Org Chem* **1981**, *46*, 2435

2 Whitesell, J K , Fisher, M , Jardine, P. D. S. *J Org Chem* **1983**, *48*, 1557

3 a) Fattorousso, E., Magno, S , Novellino, E *Experientia* **1983**, *39*, 1275 b) Paul, V J , Fenical, W *Tetrahedron* **1984**, *39*, 2913

4 Paul, V. J , and Fenical, W *Tetrahedron* **1984**, *40*, 3053

5 The absolute configurations of closely related diterpene petiodial and halimedatrial have been confirmed by their syntheses a) petiodial Isoe, S , Ge, Y , Yamamoto, K , Katsumura, S *Tetrahedron Lett* **1988**, *29*, 4591 b) halimedatrial Nagaoka, H , Miyaoka, H , Yamada, Y *Tetrahedron Lett* **1990**, *31*, 1573

6 a) Nakatani, K , Hiraishi, A , Han, Q , Isoe, S *Chem Lett* **1992**, 1851 b) Ge, Y , Isoe, S. *Chem Lett* **1992**, 139 c) Isoe, S , Katsumura, S , Okada, T , Yamamoto, K , Takemoto, T , Inaba, H , Han, Q ; Nakatani, K *Tetrahedron Lett* **1987**, *28*, 5865 d) Nakatani, K , Hiraishi, A , Han, Q , Isoe, S *Bull Chem Soc Jpn in press* and see also ref 5a, 7 and 8

7 Ge, Y , Kondo, S , Odagaki, Y , Katsumura, S , Nakatani, K ; and Isoe, S *Tetrahedron Lett* **1993**, *34*, 2621

8 Ge, Y , Nakatani, K , Isoe, S *BioMed Chem Lett* **1993**, *3*, 1085

9 MOPAC Ver 5 01, J J P Stewart, Seiler RES , LAB , U S , AIR FORCE ACADEMY, COLO SPGS , CO 80840

10 a) Kigawa, Y , Tanaka, M , Katsuhara, T , Mitsuhashi, H , Maruno, M , Wakamatsu, T *The 36th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics*, **1992**, 312 b) Bonini, C , and Fabio, R D *Tetrahedron Lett* **1982**, *23*, 5199

11 Firouzabadi, H., Ghaderi, E *Tetrahedron Lett* **1978**, *19*, 839

12 Mancuso, A J , Huang, S , Swern, D *J Org Chem* **1978**, *43*, 2480

13 Ireland, R E , Thaisrivongs, S , Vanier, N., Wilcox, C S *J Org Chem* **1980**, *48*, 48

14 a) Sato, K , Inoue, S , Onishi, A , Uchida, N , Minowa, N *J Chem Soc , Perkin I*, **1981**, 761 b) Grieco, P A , Masaki, Y *J Org Chem* **1974**, *39*, 2135 c) Altman, L J , Ash, L , Marson, S *Synth Commun* **1974**, 129

15 A. J Birch, G S R Subba Rao in "Advances in Organic Chemistry, Methods and Results," ed by E C Taylor, Wiley-Interscience, New York, Vol 8, pp 1 - 65 (1972)

16 In our preliminary communication (ref 7), the coupling constant of $J_{4a,5}$ in **27** was erroneously assigned as 11 6 Hz This coupling constants could not be unambiguously obtained in order to the coupling with $C_{1'}$ methylene moiety in homogeranyl side chain The signal assigned C_5H was observed at 2 48 ppm as doublet of triplet, but it could be read as doublet of doublet of doublet The estimated coupling constant beside the smallest one which was certainly 4 3 Hz were 7 3 and 8 5 Hz In experimental section, the mean value (7 8 Hz) was reported

17 For a recent example, see Herscovici, J , Bennani-Baiti, M I , Montserret, R , Frayssinet, C , Antonakis, K *BioMed Chem Lett* **1991**, *1*, 721

18 For a synthesis of activated form of aflatoxin B_1 and its reaction with calf thymus DNA to afford guanine adduct, see Baertschi, S W , Raney, K D , Stone, M P , Harris, T M *J Am Chem Soc* **1988**, *110*, 7929