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Syntheses and Cytotoxicity of the AB-, C-, and BC-Ring Systems of Sesbanimides

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Preparation of some AB-ring systems **5** and **8** of sesbanimides **1** and **2**, potent antitumor alkaloids, were performed starting from the synthetic intermediates of our first total synthesis of **1** and **2**. The C-ring systems **14a—d** were synthesized by applying the previously explored novel Reformatsky reaction to various aldehydes. The optically active BC-ring systems **20** and **21** having the same absolute configurations as those of **1** and **2**, were derived from (−)-2,4-*O*-methylene-D-sorbitol (**15**) as the B-ring synthon. Since all of these compounds **5**, **8**, **14a—d**, **20**, and **21** and the previously synthesized AB-ring system **3** showed no significant in vitro cytotoxicity against P388 murine leukemia, its appeared evident that **1** and **2** exhibit their notable antitumor activity owing to cooperation of the A- and C-rings.

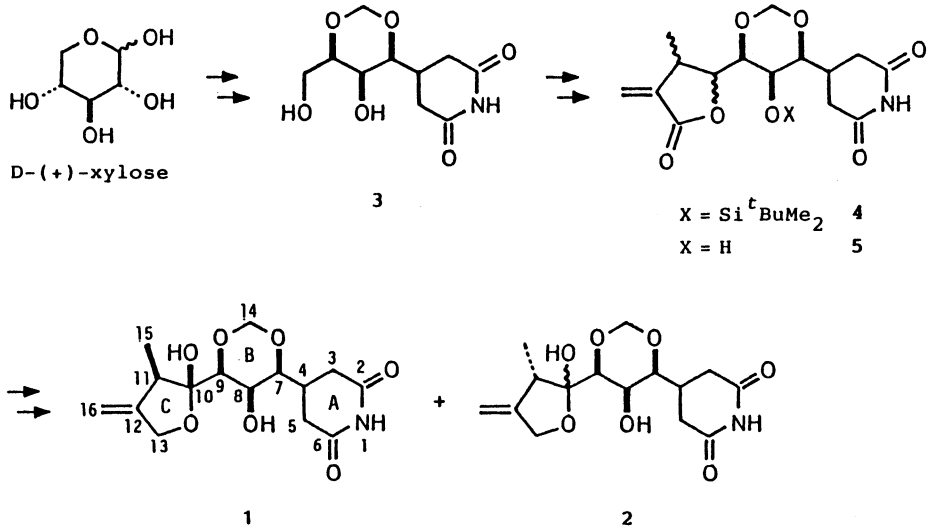
Sesbanimide A (**1**) and sesbanimide B (**2**), isolated as alkaloids from the seeds of the leguminous plants,[1,2] have been reported to exhibit notable cytotoxicity against KB cells in vitro and potent inhibitory activity against P388 murine leukemia in vivo. These compounds have unique tricyclic structures in which the three characteristic rings, glutarimide (A-ring), 1,3-dioxane (B-ring), and tetrahydrofuran (C-ring), are linked by two single bonds. Although the structure of **1** including its relative stereochemistry had been established by X-ray crystallographic analysis,[1a] its absolute configuration had not been determined.

Previously, we reported the first total synthesis of natural (+)-sesbanimide A (**1**) and (−)-sesbanimide B (**2**) from readily available D-(+)-xylose by way of the AB-ring system **3**.[3-5] Our total synthesis of these alkaloids obviously confirmed their absolute configurations.[3] With an aim to explore which parts of the structures of **1** and **2** are most responsible for their pronounced antitumor activity, the structure-activity relationships were next studied using various partial structures of **1** and **2**.

This report concerns with the syntheses of the AB-, C-, and BC-ring systems of sesbanimides achieved by employing the synthetic scheme explored in the course of our total synthesis,[3] and evaluation of cytotoxicity of these sesbanimide congeners produced in this and the previous studies.[3]

Results and Discussion

Syntheses and In Vitro Cytotoxicity of the Sesbanimide AB-Ring Systems. It was reported that **1** and **2** exhibits IC_{50} values of 7.7×10^{-3} μg ml^{-1} and 6.8×10^{-2} μg ml^{-1} against KB cells in vitro[1c] and T/C values of 140—181% in 8—12 μg kg^{-1}and 157—161% in 1.87—3.75 μg kg^{-1} dose levels against P388 murine leukemia in vivo,[1c] respectively. When the total synthesis of **1** and **2** were completed,[3] the synthetic samples of **1** and **2** were subjected to P388 murine leukemia in vitro cytotoxicity assay along with natural **1** provided by Powell. As shown in Table 1, synthetic and natural **1** were found to show the same magnitudes of cytotoxicity. Moreover, fairly intense cytotoxicity was also



Scheme 1.

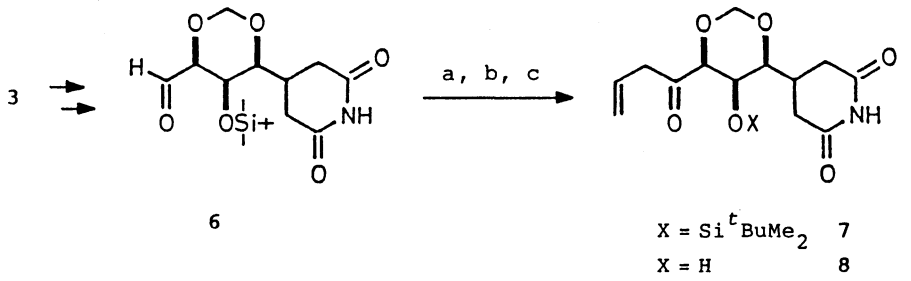
observed for synthetic **2**. These results were quite useful for identifying the synthetic samples with natural **1** and **2**, respectively.

With completion of the total synthesis of **1** and **2**, the sesbanimide congeners **3**, **5**, and **8** were first subjected to in vitro cytotoxicity assay to evaluate the roles of the AB-ring systems in prominent antitumor activity of **1** and **2**. The diol **3** had already been obtained during the course of our total synthesis. The *exo*-methylene-γ-lactone (**5**) was prepared from the synthetic intermediate **4** of **1** and **2** by simple deprotection. As shown in Scheme 2, the preparation of **8** was carried out by introducing an allyl group into the aldehyde **6** obtainable from **3**, followed by desilylation of the siloxy ketone **7**. The overall process proceeded in a moderate overall yield. Results summarized in Table 1 cleanly disclose that the AB-ring systems except for **5** carrying an *exo*-methylene-γ-lactone moiety which is well-known as a cytotoxic functionality, show no in vitro cytotoxicity against P388 murine leukemia. Although considerable in vitro cytotoxicity was recorded on **5**, it showed no significant antitumor activity against P388 murine leukemia in vivo (T/C 95% in 10 mg kg^{-1} dose level).

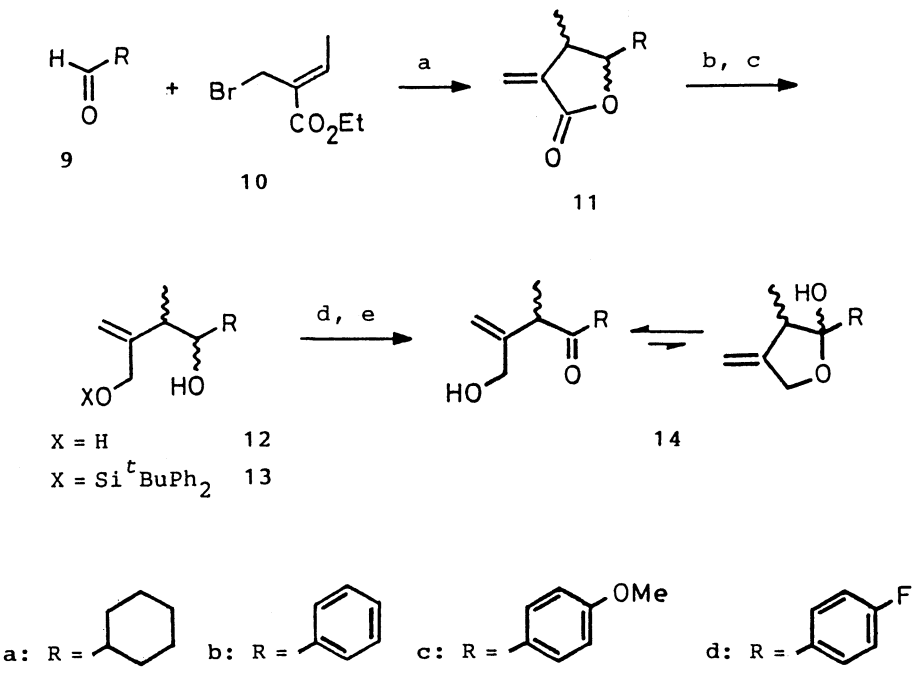
Table 1. In Vitro Cytotoxicity of Sesbanimides and Their AB-Ring Systems against P388 Murine Leukemia

Compound	$IC_{50}/\mu g\ ml^{-1}$ [a]
1	4.6×10^{-5} (3.3×10^{-5})[b]
2	3.1×10^{-2}
3	>25
5	9.0×10^{-3}
8	>30

a) Cell growth inhibition (percent) after incubation for 48 h at 37 °C. b) In vitro cytotoxicity observed on natural **1**.



Scheme 2. a) CH_2=$CHCH_2MgCl$, ether, −78 °C, 1 h. b) CrO_3·2Py, CH_2Cl_2, rt, 20 min, 42% (2 steps). c) AcOH, MeOH, rt, 5 min, 86%.



Scheme 3. a) Zn, THF, 0 °C, 2 h (for **9a**), reflux, 20 min (for **9b**), reflux, 8 min (for **9c**), reflux, 50 min (for **9d**). b) 1) ^{i}Bu$_2$AlH, CH_2Cl_2, 0 °C, 20 min; 2) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, 0 °C, 30 min. c) ^{t}BuPh$_2$SiCl, imidazole, DMF, rt, 30 min, 65% (**13a**, 3 steps). d) CrO_3·2Py, CH_2Cl_2, rt, 10 min. e) Bu_4NF, THF, rt, 1 h, 49% (**14a**, 2 steps), 30% (**14b**, 5 steps), 39% (**14c**, 5 steps), 49% (**14d**, 5 steps).

Based on these results, it was anticipated that, in place of the AB-ring systems, the C-ring systems play an important role for **1** and **2** to exhibit their antitumor activity.

Syntheses and In Vitro Cytotoxicity of the C-Ring Systems. The compounds **14a—d** were selected as representative examples of the C-ring systems of **1** and **2**. Preparation of **14a—d** were examined employing the synthetic method explored in the course of the total synthesis, to cyclohexanecarbaldehyde (**9a**) and three sorts of the aromatic aldehydes **9b—d**. As shown in Scheme 3, the regioselective Reformatsky reaction[6] of **9a** with ethyl (*E*)-2-(bromomethyl)crotonate (**10**)[7] proceeded smoothly at 0 °C to afford the *exo*-methylene-γ-lactone (**11a**) as a 1 : 1.3 mixture of the two diastereomers. The Reformatsky reaction of **9b—d** carried out in refluxing tetrahydrofuran similarly gave **11b—d** as mixtures of the two diastereomers in good yields (the ratio of diastereomers: **11b**, 1 : 6; **11c**, 1 : 5; **11d**, 1 : 6). When **9a** was subjected to the Reformatsky reaction in refluxing tetrahydrofuran, extensive decomposition of **11a** was observed. The diastereomeric mixtures of **9a—d** were immediately used for the next step without separation of the isomers. Reduction of **11a—d** to the diol **12a—d** were attempted in a similar stepwise manner to that previously reported.[3] Thus, treatments of **11a—d** with diisobutylaluminum hydride yielded the corresponding lactols, which without isolation were further reduced with sodium borohydride in the presence of cerium(III) chloride,[8] giving **12a—d**. After selective protections of the primary hydroxyl groups of **12a—d** in forms of *t*-butyldiphenylsilyl ether, Collins oxidations of the remaining secondary hydroxyl groups of the siloxy alcohols **13a—d**, followed by removal of the silyl groups with tetrabutylammonium fluoride, afforded **14a—d** in fairly good overall yields (5 steps, 30—49%). The ^{1}H NMR spectra of **14a—d** revealed that these compounds consist of equilibrated mixtures of the ketonic and hemiacetal forms in which the formers predominate (**14a**, 4 : 1; **14b**, 3 : 1; **14c**, 10 : 1; **14d**, 3 : 1). It was uncovered by the ^{1}H NMR spectra that the hemiacetal forms of **14a—d** also involve the two epimeric isomers.

With completion of the synthesis, in vitro cytotoxicity assay was carried out on **14a—d** along with the corresponding *exo*-methylene-γ-lactones (**11a—d**). Disappointingly, **14a—d** showed no significant cytotoxicity despite slight activity was observed for **11a—d**. These results are summarized in Table 2. Accordingly, it appeared that the pronounced antitumor activity of **1** and **2** do not depend merely upon their C-ring systems.

Syntheses and In Vitro Cytotoxicity of the Sesbanimide BC-Ring Systems. Since it turned out obvious that both the AB- and C-ring systems are not the origin of antitumor activity of **1** and **2**, cytotoxicity of the BC-ring systems **20** and **21** was finally studied.

The synthetic route to optically active **20** and **21** in which (−)-2,4-*O*-methylene-D-sorbitol (**15**) is employed as the B-ring synthon, are shown in Scheme 4. Thus, after oxidative cleavage of the 1,2-glycol moiety of **15** prepared from D-(−)-sorbitol according to the reported method,[9] the resulting lactol was subjected to the Reformatsky reaction with **10**, affording the *exo*-methylene-γ-lactone (**16**) in a good overall yield. Similarly to the case of previous total synthesis of **1** and **2**,[3] **16** was found to consist of a mixture of the three diastereomers concerning the C-10 and C-11 positions (sesbanimide numbering). Determination of the stereostructures of these isomers was not attempted.

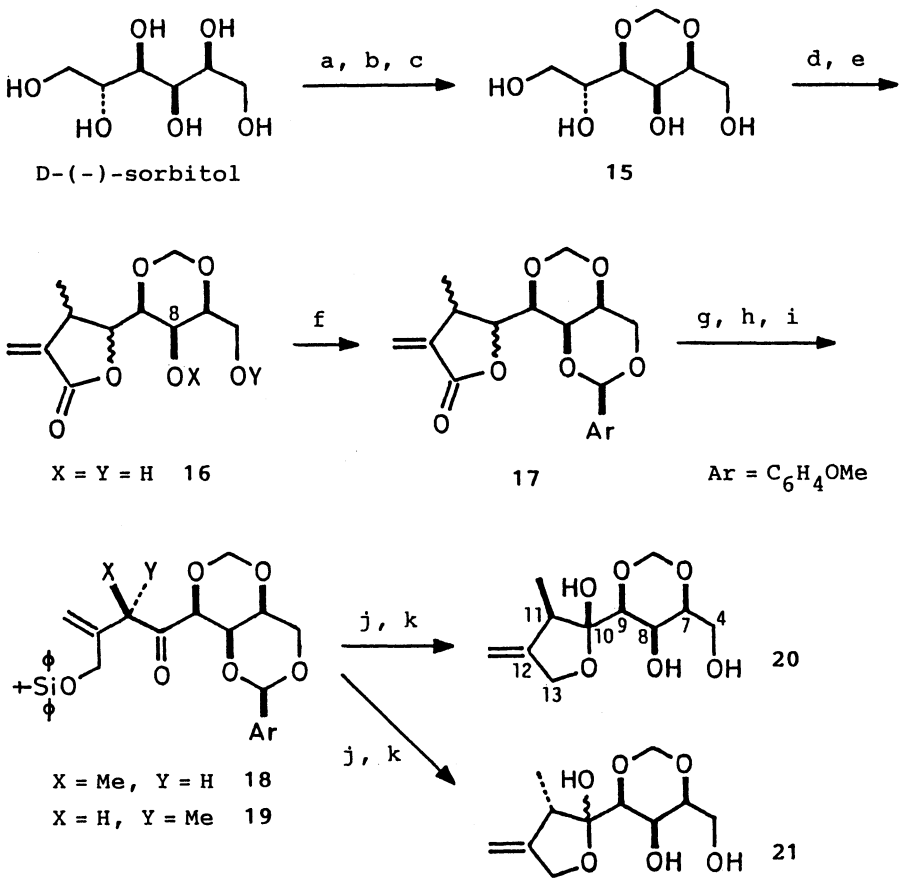
Table 2. In Vitro Cytotoxicity of the Sesbanimide C- and BC-Ring Systems and Their Corresponding *exo*-Methylene-γ-lactones against P388 Murine Leukemia

Sesbanimide C- and BC-ring system		*exo*-Methylene-γ-lactone	
Compound	IC_{50}/μg ml^{-1} [a]	Compound	IC_{50}/μg ml^{-1} [a]
14a	1.6	**11a**	0.39
14b	19	**11b**	2.6
14c	22	**11c**	1.1
14d	5.8	**11d**	0.49
20	>25	**16**	0.95
21	>25		

a) Cell growth inhibition (percent) after incubation for 48 h at 37 °C.

At the next stage, protection of the two hydroxyl groups of **16** was required for constructing the C-ring system according to the explored synthetic route.[3] After various protective groups were examined,[10] *p*-methoxybenzylidene group was found to be most suitable for this purpose. Benzylidenation of **16** under the usual conditions yielded the benzylidene γ-lactone (**17**) as a mixture of the three diastereomers. Separation of the mixture with column chromatography afforded a 1 : 1 mixture of the two isomers **17a** (66%) along with a small amount of the other isomer **17b** (6%). Each of the three diastereomers turned out to consist of a single isomer with regard to the benzylic position. Taking into account the difference of thermodynamic stability between the two possible isomers, the *p*-methoxyphenyl group was anticipated to take an equatorial position. Based on this speculation, stereochemistry of the benzylic position was tentatively assigned as shown in Scheme 4. Simply from practical reasons, only the main product **17a** was converted into the BC-ring systems **20** and **21**.

After reduction of the lactone part of **17a**, successive protection of the primary alcohol and Collins oxidation of the remaining secondary alcohol in a similar manner to that previously reported, gave the ketones as a mixture of the two diastereomers **18** and **19**. This mixture could be easily separated by TLC. Stepwise deprotections of the benzylidene and *t*-butyldiphenylsilyl groups transformed **18** and **19** into the optically active BC-ring systems of **1** and **2** (**20** and **21**), respec-



Scheme 4. a) 40% aq H_2CO–12M HCl, 60°C, 2 days, 52%. b) 18M H_2SO_4, AcOH–Ac_2O, 0°C, 10 min, 57%. c) NH_3 gas, MeOH, 0°C→rt, 5 h, 88%. d) $NaIO_4$, H_2O, rt, 5 min. e) **10**, Zn, THF–DMF, reflux, 1 h, 60% (2 steps). f) $MeOC_6H_4CHO$, *p*-TsOH·H_2O, PhH–CH_2Cl_2, reflux, 2 h, 66% (**17a**), 6% (**17b**). g) 1) $^iBu_2AlH$, CH_2Cl_2, −78°C, 1 h; 2) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C, 10 min, 89% (2 steps). h) $^tBuPh_2SiCl$, imidazole, DMF, rt, 5 min, 89%. i) CrO_3·2Py, CH_2Cl_2, rt, 10 min, 36% (**18**), 34% (**19**). j) 80% aq AcOH, rt, 1 h. k) Bu_4NF, THF, rt, 5 min, 70% (**20**, 2 steps), 68% (**21**, 2 steps).

tively. The 400 MHz ^1H NMR spectra of **20** and **21** showed that, similarly to **1** and **2**, these compounds completely adopt the hemiacetal structures. These phenomena may be rationalized by the formation of two intramolecular hydrogen bonds between the B- and C-rings which efficiently stabilized the hemiacetal structure.[11] Furthermore, **20** and **21** were found to consist of a single C-10 epimer and a 1 : 1.3 mixture of two equilibrated C-10 epimers, respectively. Detailed comparisons of coupling patterns of **20** and **21** with those of **1** and **2** revealed that the B- and C-rings of **20** and **21** take the same conformations as those of **1** and **2**, respectively. Based on these results, stereochemistries of the C-11 methyl groups of **18**—**21**, and that of the C-10 hydroxyl group of **20** were assigned as shown in Scheme 4.

In vitro cytotoxicity of **20** and **21** are shown in Table 2 along with that of **16**. Contrary to our expectation, no cytotoxicity was again observed for **20** and **21** although **16** showed marginal activity. These results are almost the same as those obtained for the C-ring systems **14a**—**d**. Accordingly, it became evident that the antitumor activity of **1** and **2** did not originate merely from their BC-ring systems.

Conclusion

Summing up the results accumulated by the structure-activity relationships, it appears evident that the marked antitumor activity of **1** and **2** does not originate solely from their AB-, C-, and BC-ring systems since these partial structures exhibited no significant cytotoxicity against P388 murine leukemia in vitro. Accordingly, it is anticipated that **1** and **2** show antitumor activity owing to delicate cooperation of their A- and C-rings probably including their B-rings.

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a Horiba SEPA-200 automatic digital polarimeter. IR

spectra measurements were performed with a JASCO A-200 IR spectrometer. ^{1}H NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM-400 spectrometer (400 MHz). All signals are expressed as ppm down field from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Assignments of signals are indicated according to the numbering of IUPAC nomenclature to avoid confusion. Mass spectra were taken with a Hitachi RMV-6MG mass spectrometer. Unless otherwise noted, all reactions were carried out using anhydrous solvents. Especially, tetrahydrofuran and ether freshly distilled from benzophenone ketyl were used. Wako Gel C-200 and Merck Silica Gel 60F_{254} were used as an adsorbent for column chromatography and preparative thin-layer chromatography (PTLC), respectively. The following abbreviations are used for solvents and reagents: acetic acid (AcOH), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), diisobutylaluminum hydride (DIBAL), *N*,*N*-dimethylformamide (DMF), ethanol (EtOH), ethyl acetate (AcOEt), methanol (MeOH), tetrabutylammonium fluoride (Bu_4NF), tetrahydrofuran (THF).

Syntheses of the AB-Ring Systems (5 and 8). 4-[(4*S*,5*R*,6*R*)-5-Hydroxy-6-(3-methyl-4-methylene-5-oxotetrahydrofuran-2-yl)-1,3-dioxan-4-yl]-2,6-piperidinedione (5). A solution of **4** (21 mg, 48 μmol)[3] and 10-camphorsulfonic acid (1.0 mg, 4.0 μmol) in wet CH_2Cl_2 (2.0 ml) was stirred at room temperature for 3 h. The mixture was diluted with AcOEt, washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was chromatographed (SiO_2, 50% AcOEt in $CHCl_3$) to give pure **5** (a mixture of the three diastereomers by NMR) as a colorless caramel (12 mg, 77%). ^{1}H NMR (90MHz, $CDCl_3$-D_2O) δ=1.13, 1.30, 1.32 (total 3H, each d, J=7 Hz, $C_{3''}$-Me), 2.1—3.2 (6H, m, C_3-H_2, C_4-H, C_5-H_2, $C_{3''}$-H), 3.2—4.0 (3H, m, $C_{4'}$-H, $C_{5'}$-H, $C_{6'}$-H), 4.1—4.5 (1H, m, $C_{2''}$-H), 4.74, 4.77 (total 1H, each d, J=6 Hz, $C_{2'\text{-ax}}$-H), 5.16, 5.18 (total 1H, each d, J=6 Hz, $C_{2'\text{-eq}}$-H), 5.69 (1H, m, olefinic proton), 6.32 (1H, m, olefinic proton); IR (film) 3490, 3250, 1770, 1705 cm^{-1}; MS *m*/*z* 326 (M^+H), 325 (M^+), 307 (M^+-H_2O); High-resolution MS, 325.1196, Calcd for $C_{15}H_{19}O_7N$: M, 325.1161.

(−)-4-[(4*S*,5*R*,6*R*)-6-(3-Butenoyl)-5-(*t*-butyldimethylsiloxy)-1,3-dioxan-4-yl]-2,6-piperidinedione (7). The aldehyde **6** (26 mg, 73 μmol) produced from the corresponding siloxy alcohol (30 mg, 84 μmol) in 87% yield by the same Collins oxidation as that reported,[3] was dissolved in ether (2.2 ml). Allylmagnesium chloride (1.0 ml, 0.8 M (1M=1 mol dm^{-3}) ethereal solution, 0.80 mmol) was added to the ethereal solution cooled at −78 °C under an argon atmosphere. After stirring for 1 h, the mixture was diluted with saturated aqueous $NaHCO_3$, allowed to warm up to room temperature, and extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3.0 ml). The dichloromethane solution was added to a stirred mixture of Collins reagent, prepared from anhydrous CrO_3 (0.26 g, 2.6 mmol) and pyridine (0.59 g, 7.5 mmol), and dry celite (0.52 g) in CH_2Cl_2 (3.8 ml) at room temperature under an argon atmosphere. After being stirred for 20 min, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was concentrated in vacuo. The residue was dissolved in AcOEt, and the ethyl acetate solution was washed with brine, dried ($MgSO_4$), filtered, concentrated in vacuo. The residue was chromatographed (SiO_2, $CHCl_3$) to give pure **7** as a colorless caramel (12 mg, 42%), $[\alpha]_D^{20}$ −24.4° (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.10 (3H, s, SiMe), 0.22 (3H, s, SiMe), 0.86 (9H, d, Si^{t}Bu), 1.73 (1H, dd, J=2.9 and 12.5 Hz, $C_{3\text{-ax}}$-H), 2.35 (1H, brd, J=18.6 Hz, $C_{5\text{-eq}}$-H), 2.40 (1H, ddt, J=3.6, 12.5, and 1.8 Hz, $C_{3\text{-eq}}$-H), 2.52 (1H, brdq, J=7.2 and 3.6 Hz, C_4-H), 2.67 (1H, dd, J=7.2 and 18.6 Hz, $C_{5\text{-ax}}$-H), 3.34 (1H, ddt, J=6.8, 18.2, and 1.5 Hz, $C_{2''}$-H), 3.48 (1H, ddt, J=6.8, 18.2, and 1.5 Hz, $C_{2''}$-H), 3.48 (1H, brs, $C_{4'}$-H), 4.06 (1H, brs, $C_{5'}$-H), 4.14 (1H, d, J=2.2 Hz, $C_{6'}$-H), 4.78 (1H, d, J=6.3 Hz, $C_{2'\text{-ax}}$-H), 5.12 (1H, dq, J=17.2 and 1.5 Hz, $C_{4''\text{-cis}}$-H), 5.20 (1H, dq, J=10.3 and 1.5 Hz, $C_{4''\text{-trans}}$-H), 5.23 (1H, d, J=6.3 Hz, $C_{2''\text{-eq}}$-H), 5.29 (1H, ddt, J=10.3, 17.2, and 6.8 Hz, $C_{3''}$-H), 6.01 (1H, brs, NH); IR (film) 3310, 3275, 1670 cm^{-1}; MS *m*/*z* 397 (M^+), 340 ($M^+-{}^t$Bu); High-resolution MS, Found: *m*/*z* 397.1910, Calcd for $C_{19}H_{31}O_6NSi$: M, 397.1921.

4-[(4*S*,5*R*,6*R*)-6-(3-Butenoyl)-5-hydroxyl-1,3-dioxan-4-yl]-2,6-piperidinedione (8). AcOH (1.0 ml) was added to a solution of **7** (12 mg, 30 μmol) in MeOH (1.0 ml) at room temperature. After stirring for 5 min, the mixture was concentrated in vacuo. The residue was chromatographed (SiO_2, 70% AcOEt in $CHCl_3$) to afford **8** as a colorless caramel (7.5 mg, 88%). ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ=2.0—3.2 (5H, m, C_3-H_2, C_4-H, C_5-H_2), 3.42 (2H, dq, J=7 and 1 Hz, $C_{2''}$-H_2), 3.43 (1H, d, J=9 Hz, $C_{4'}$-H), 4.02 (1H, brs, $C_{5'}$-H), 4.11 (1H, d, J=1 Hz, $C_{6'}$-H), 4.80 (1H, d, J=6 Hz, $C_{2'\text{-ax}}$-H), 5.21 (1H, dq, J=17 and 1 Hz, $C_{4''\text{-cis}}$-H), 5.23 (1H, dq, J=10 and 1 Hz, $C_{4''\text{-trans}}$-H), 5.25 (1H, d, J=6 Hz, $C_{2'\text{-eq}}$-H), 5.95 (1H, ddt, J=10, 17, and 7 Hz, $C_{3''}$-H); IR (film) 3480, 3260, 1705 cm^{-1}; MS *m*/*z* 284 (M^+H), 214 ($M^+-COCH_2CH{=}CH_2$). This sample was found to readily undergo migration of the double bond on chromatographic purification. Since **8** was sufficiently pure (ca. 90% by NMR), it was directly subjected to in vitro cytotoxicity assay.

Syntheses of the C-Ring Systems 14a—d. Syntheses of the γ-Lactone 11a—d. Cyclohexanecarbaldehyde (**9a**) and three sorts of the aromatic aldehydes **9b—d** were found to show considerably different reactivity in the Reformatsky reaction. Therefore, typical experimental procedures are given for syntheses of the lactones **11a, b**. Other γ-lactones **11c, d** were prepared in a similar manner to that described for **11b**.

4-Cyclohexyl-3-methyl-2-methylene-4-butanolide (11a). A solution of **10** (0.11 g, 0.53 mmol)[7] in THF (1.5 ml) was added to a mixture of **9a** (39 mg, 0.35 mmol) and powdered Zn (0.23 g, 3.5 mmol) in THF (5.0 ml) cooled in an ice bath with stirring. After stirring for 2 h, water was added and the mixture was filtered through a pad of celite. The filtrate was extracted with ether and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (SiO_2, 5% AcOEt in hexane) of the crude product afforded pure **11a** (a 1 : 1.3 mixture of the two diastereomers by NMR) as a colorless caramel (62 mg, 92%). ^{1}H NMR (90 MHz, $CDCl_3$) δ=0.6—2.1 (11H, m, C_6H_{11}), 1.16 (1.7H, d, J=7 Hz, C_3-Me, major isomer), 1.25 (1.3H, d, J=7 Hz, C_3-Me, minor isomer), 2.87 (0.43H, m, C_3-H, minor isomer), 3.14 (0.57H, m, C_3-H, major isomer), 3.85 (0.43H, t, J=5 Hz, C_4-H, minor isomer), 4.15 (0.57H, t, J=5 Hz, C_4-H, major isomer), 5.55 (0.57H, d, J=2 Hz, olefinic proton, major isomer), 5.58 (0.43H, J=3 Hz, olefinic proton, minor isomer), 6.17 (0.57H, d, J=2 Hz, olefinic

proton, major isomer), 6.26 (0.43H, d, J=3 Hz, olefinic proton, minor isomer); IR (film) 1770, 1670 cm^{-1} MS m/z 194 (M^+), 111 ($M^+-C_6H_{11}$); High-resolution MS, Found: m/z 194.1303, Calcd for $C_{12}H_{18}O_2$: M, 194.1307.

3-Methyl-2-methylene-4-phenyl-4-butanoilde (11b). A mixture of **9b** (0.14 g, 1.3 mmol), powdered Zn (0.88 g, 13 mmol), and **10** (0.42 g, 2.0 mmol)[7] in THF (10 ml) was heated at reflux for 20 min and cooled to room temperature. The same work-up as that described for **11a**, followed by purification with column chromatography (SiO_2, 50% $CHCl_3$ in hexane), gave pure **11b** (a 1 : 6 mixture of the two diastereomers by NMR) as a colorless caramel (0.20 g, 81%). ^1H NMR (90 MHz, $CDCl_3$) δ=0.87 (2.58H, d, J=7 Hz, C_3-Me, major isomer), 1.46 (0.42H, d, J=7 Hz, C_3-Me, minor isomer), 3.25 (0.14H, m, C_3-H, minor isomer), 3.80 (0.86H, m, C_3-H, major isomer), 5.43 (0.14H, d, J=8 Hz, C_4-H, minor isomer), 6.15 (0.86H, d, J=3 Hz, olefinic proton, major isomer), 6.17 (0.14H, d, J=3 Hz, olefinic proton, minor isomer), 6.21 (0.86H, d, J=9 Hz, C_4-H, major isomer), 6.96 (0.14H, d, J=3 Hz, olefinic proton, minor isomer), 6.98 (0.86H, d, J=3 Hz, olefinic proton, major isomer), 7.7—8.2 (5H, m, aromtic protons); IR (film) 1770, 1670, 1610, 1500 cm^{-1}; MS m/z 188 (M^+); High-resolution MS, Found: m/z 188.0812, Calcd for $C_{12}H_{12}O_2$: M, 188.0837.

4-(*p*-Methoxyphenyl)-3-methyl-2-methylene-4-butanolide (11c). The butanolide **11c** (a 1 : 6 mixture of the two diastereomers by NMR) was obtained as white crystals after purification with column chromatography. ^1H NMR (90 MHz, $CDCl_3$) δ=0.84 (2.58H, d, J=7 Hz, C_3-Me, major isomer), 1.30 (0.42H, d, J=7 Hz, C_3-Me, minor isomer), 2.29 (0.14H, m, C_3-H, minor isomer), 3.43 (0.86H, m, C_3-H, major isomer), 3.80 (3H, s, ArOMe), 4.87 (0.14H, d, J=8 Hz, C_4-H, minor isomer), 5.58 (0.86H, d, J=3 Hz, olefinic proton, major isomer), 5.60 (0.14H, J=3 Hz, olefinic proton, minor isomer), 5.61 (0.86H, J=9 Hz, C_4-H, major isomer), 6.31 (0.14H, d, J=3 Hz, olefinic proton, minor isomer), 6.33 (0.86H, d, J=3 Hz, olefinic proton, major isomer), 6.91 (2H, d, J=9 Hz, aromatic protons), 7.10 (2H, d, J=9 Hz, aromatic protons); IR (film) 1740, 1670, 1615, 1520 cm^{-1}; MS m/z 218 (M^+); High-resolution MS, Found: m/z 218.0939, Calcd for $C_{13}H_{14}O_3$: M, 218.0943.

4-(*p*-Fluorophenyl)-3-methyl-2-methylene-4-butanolide (11d). The butanolide **11d** (a 1 : 5 mixture of the two diastereomers by NMR) was obtained as a colorless caramel after purification with column chromatography. ^1H NMR (90 MHz, $CDCl_3$) δ=0.83 (2.5H, d, J=7 Hz, C_3-Me, major isomer), 1.34 (0.5H, d, J=7 Hz, C_3-Me, minor isomer), 2.98 (0.17H, m, C_3-H, minor isomer), 3.48 (0.83H, m, C_3-H, major isomer), 4.93 (0.17H, d, J=8 Hz, C_4-H, minor isomer), 5.64 (0.83H, d, J=3 Hz, olefinic proton, major isomer), 5.65 (0.83H, d, J=9 Hz, C_4-H, major isomer), 5.66 (0.17H, d, J=3 Hz, olefinic proton, minor isomer), 6.36 (0.17H, d, J=3 Hz, olefinic proton, minor isomer), 6.38 (0.83H, d, J=3 Hz, olefinic proton, major isomer), 6.9—7.5 (4H, m, aromatic protons); IR (film) 1770, 1670, 1610, 1510 cm^{-1}; MS m/z 206 (M^+); High-resolution MS, Found: m/z 206.0742, Calcd for $C_{12}H_{11}O_2F$: M, 206.0743.

Syntheses of the C-Ring Systems 14a—d from the γ-Lactones 11a—d. A typical experimental procedure is given for the synthesis of **14a**. Other C-ring systems were prepared according to the same procedure as that described for **14a**.

1-Cyclohexyl-4-hydroxy-2-methyl-3-methylene-1-butanone and 2-Cyclohexyl-2-hydroxy-3-methyl-4-methylenetetrahydrofuran (14a). DIBAL (0.56 ml, 1.0 M hexane solution, 0.56 mmol) was added to a stirred solution of **11a** (54 mg, 0.28 mmol) in CH_2Cl_2 (1.5 ml) cooled at 0 °C under an argon atmosphere. After stirring was continued for 20 min, MeOH (1.5 ml) was added, and the mixture was allowed to warm up to room temperature and concentrated in vacuo. The residue was dissolved in MeOH (3.5 ml) and the methanolic solution was cooled at 0°C. $CeCl_3 \cdot 7H_2O$ (0.11 g, 0.29 mmol) and $NaBH_4$ (11 mg, 0.29 mmol) was successively added, and the mixture was stirred for 30 min. After acidified to pH 3 with 1M HCl, the mixture was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo, to give crude **12a** as a colorless caramel. ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ=0.9—2.0 (11H, m, C_6H_{11}), 1.05, 1.15 (total 3H, each d, J=7 Hz, C_2-Me), 2.3—2.8 (1H, m, C_2-H), 3.1—3.4 (1H, m, C_1-H), 4.11 (2H, brs, C_4-H_2), 5.00 (1H, brs, olefinic proton), 5.17 (1H, brs, olefinic proton). *t*-Butyldiphenylsilyl chloride (0.11 g, 0.40 mmol) was added to a stirred solution of **12a** and imidazole (59 mg, 0.87 mmol) in DMF (0.20 ml) at room temperature under an argon atmosphere. After stirred for 30 min, the mixture was diluted with AcOEt, washed with brine, and dried ($MgSO_4$). Filtration and concentration in vacuo, followed by separation with column chromatography (SiO_2, 10% AcOEt in hexane), afforded pure **13a** as a colorless caramel (79 mg, 65%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ=0.9—1.8 (11H, m, C_6H_{11}), 0.98, 1.01 (total 3H, each d, J=7 Hz, C_2-Me), 1.07 (9H, s, Si^{t}Bu), 2.1—2.6 (1H, m, C_2-H), 3.0—3.3 (1H, m, C_1-H), 4.16 (2H, brs, C_4-H_2), 5.03, 5.10 (total 1H, each brs, olefinic proton), 5.32 (1H, brs, olefinic proton), 7.3—7.6 (6H, m, aromatic protons), 7.6—8.6 (4H, m, aromatic protons); IR (film) 3480, 1740, 1650, 1595 cm^{-1}; MS m/z 379 ($M^+-{}^t$Bu).

Pyridine (0.35 g, 4.4 mmol) was added to a stirred suspension of anhydrous CrO_3 (0.18 g, 1.8 mmol) in CH_2Cl_2 (4.5 ml) at room temperature under an argon atmosphere. After stirring was continued for 20 min, dry celite (0.36 g) and a solution of **13a** (79 mg, 0.18 mmol) in CH_2Cl_2 (1.0 ml) were successively added. After being stirred for 10 min, the mixture was diluted with ether and filtered through a pad of celite. The filtrate was washed successively with saturated aqueous $CuSO_4$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in THF (2.7 ml) and Bu_4NF (0.27 ml, 1.0 M THF solution, 0.27 mmol) was added at room temperature under an argon atmosphere. After stirring for 1 h, the mixture was diluted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed (SiO_2, 10% AcOEt in hexane) to afford pure **14a** [a 4 : 1 mixture of the equilibrated ketonic and the hemiacetal (a 4 : 1 mixture of the two diastereomeric hemiacetals) forms by NMR] as a colorless caramel (17 mg, 48%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ=1.0—2.9 (11H, m, C_6H_{11}), 1.05, 1.12 (total 0.6 H, each d, J=7 Hz, C_3-Me, hemiacetals), 1.22 (2.4H, d, J=7 Hz, C_2-Me, ketone), 3.52 (0.8H, q, J=7 Hz, C_2-H, ketone), 4.12 (1.6H, brs, C_4-H_2, ketone), 4.43 (0.4H, m, C_5-H_2, hemiacetals), 4.9—5.1 (0.4H, m, olefinic protons, hemiacetals), 5.00 (0.8H, brs, olefinic proton, ketone), 5.20 (0.8H, brs, olefinic proton, ketone); IR (film) 3480, 1710, 1650 cm^{-1}; MS m/z 196 (M^+), 129 ($M^+-C_3H_5O$); High-resolution MS, Found: m/z 196.1469, Calcd for $C_{12}H_{20}O_2$: M, 196.1463.

4-Hydroxy-2-methyl-3-methylene-1-phenyl-1-butanone and 2-Hydroxyl-3-methyl-4-methylene-2-phenyltetrahydrofuran (14b): Prepared as a colorless caramel [a 3 : 1 mixture of the equilibrated ketonic and the hemiacetal (a 4:1 mixture of the two diastereomeric hemiacetals) forms by NMR]. ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ=0.61, 1.10 (total 0.75H, each d, J=7 Hz, C_3-Me, hemiacetals), 1.40 (2.25H, d, J=7 Hz, C_2-Me, ketone), 2.5—2.8 (0.25H, m, C_3-H, hemiacetals), 4.18 (1.5H, brs, C_4-H_2, ketone), 4.32 (0.75H, q, J=7Hz, C_2-H, ketone), 4.70 (0.5H, m, C_5-H_2, hemiacetals), 4.9—5.1 (0.5H, m, olefinic protons, hemiacetals), 5.06 (0.75H, brs, olefinic proton, ketone), 5.22 (0.75H, brs, olefinic proton, ketone), 7.3—8.1 (5H, m, aromatic protons); IR (film) 3450, 1680, 1600, 1580 cm^{-1}; MS m/z 190 (M^+), 123 ($M^+-C_3H_5O$); High-resolution MS, Found: m/z 190.0969, Calcd for $C_{12}H_{14}O_2$: M, 190.0994.

4-Hydroxy-1-(*p*-methoxyphenyl)-2-methyl-3-methylene-1-butanone and 2-Hydroxy-3-methyl-4-methylene-2-(*p*-methoxyphenyl)tetrahydrofuran (14c): Prepared as a colorless caramel (a 10 : 1 mixture of the equilibrated ketonic and hemiacetal forms by NMR). The ^{1}H NMR spectrum of the ketonic form is as follows. ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ=1.40 (3H, d, J=7 Hz, C_2-Me), 3.89 (3H, s, ArOMe), 4.22 (2H, brs, C_4-H_2), 4.32 (1H, q, J=7 Hz, C_2-H), 5.06 (1H, brs, olefinic proton), 5.22 (1H, brs, olefinic proton), 7.66 (2H, d, J=9 Hz, aromatic protons), 8.02 (2H, d, J=9 Hz, aromtic protons); IR (film) 3460, 1675, 1600, 1575, 1510 cm^{-1}; MS m/z 220 (M^+), 153 ($M^+-C_3H_5O$); High-resolution MS, Found: m/z 220.1080, Calcd for $C_{13}H_{16}O_3$: M, 220.1099. The ratio of the two diasteromeric hemiacetals could not be determined.

1-(*p*-Fluorophenyl)-4-hydroxy-2-methyl-3-methylene-1-butanone and 2-(*p*-Fluorophenyl)-2-hydroxy-3-methyl-4-methylenetetrahydrofuran (14d): Prepared as a colorless caramel [a 3 : 1 mixture of the eqilibrated ketonic and the hemiacetal (a 1 : 4 mixture of the two diastereomeric hemiacetals) forms by NMR]. ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ=0.67, 1.10 (total 0.75H, each d, J=7 Hz, C_3-Me, hemiacetals), 1.37 (2.25H, d, J=7 Hz, C_2-Me, ketone), 2.4—2.7 (0.25H, m, C_3-H, hemiacetals), 4.19 (1.5H, brs, C_4-H_2, ketone), 4.28 (0.75H, q, J=7 Hz, C_2-H, ketone), 4.66 (0.5H, m, C_5-H_2, hemiacetals), 4.9—5.1 (0.5H, m, olefinic protons, hemiacetals), 5.02 (0.75H, brs, olefinic proton, ketone), 5.22 (0.75H, brs, olefinic proton, ketone), 7.06 (0.5H, t, J=9 Hz, aromatic protons, hemiacetals), 7.13 (1.5H, t, J=9 Hz, aromatic protons, ketone), 7.61 (0.5H, dd, J=6 and 9 Hz, aromatic protons, hemiacetals), 8.05 (1.5H, dd, J=6 and 9 Hz, aromatic protons, ketone); IR (film) 1685, 1600, 1510 cm^{-1}; MS m/z 208 (M^+), 141 ($M^+-C_3H_5O$); High-resolution MS, Found: m/z 208.0885, Calcd for $C_{12}H_{13}O_2F$: M, 208.0899.

Syntheses of the BC-Ring Systems (20 and 21). (−)-2,4-*O*-Methylene-D-sorbitol (15). Methylene acetalization of D-(−)-sorbitol, mp 92—95°C [α]$_D^{20}$ −2.2° (*c* 10.0, H_2O), with 40% aqueous formaldehyde and 12 M HCl (52%),[9] followed by sequential selective acetolysis with AcOH and Ac_2O (57%),[9] and deacetylation with NH_3 gas in MeOH (89%), afforded **15** via (−)-1,3 : 2,4 : 5,6-tri-*O*-methylene-D-sorbitol, mp 214—216°C (recrystallized from EtOH) [lit, 212—216°C (recrystallized from EtOH)[9]], [α]$_D^{20}$ −31.3° (*c* 1.20, $CHCl_3$) [lit, [α]$_D^{20}$ −30.8° (*c* 1.20, $CHCl_3$)[9]] and (+)-3,5-bis(*O*-acetoxymethyl)-1,6-di-*O*-acetyl-2,4-*O*-methylene-D-sorbitol, mp 110—112°C (recrystallized from EtOH) [lit, mp 111—112°C (recrystallized from EtOH)[9]], [α]$_D^{20}$ +29.5° (*c* 1.20, $CHCl_3$) [lit, [α]$_D^{20}$ +29.8° (*c* 1.20, $CHCl_3$)[9]]. The product **15** showed mp 165—166°C (recrystallized from EtOH) [lit, mp 163—164°C (recrystallized from EtOH)[9]] and [α]$_D^{20}$ −9.8° (*c* 1.30, H_2O) [lit, [α]$_D^{20}$ −9.8° (*c* 1.30, H_2O)[9]].

4-[(4*R*,5*R*,6*S*)-5-Hydroxy-6-hydroxymethyl-1,3-dioxan-4-yl]-3-methyl-2-methylene-4-butanolide (16). $NaIO_4$ (2.2 g, 10 mmol) was added to a solution of **15** (2.0 g, 10 mmol) in water (40 ml) at room temperature. After stirring for 5 min, the mixture was concentrated in vacuo. The residue was diluted with MeOH, and filtered through a pad of celite. The filtrate was concentrated in vacuo. A mixture of the residual oil, **10** (3.2 g, 15 mmol),[7] and powdered Zn (6.8 g, 0.10 mol) in a mixture of THF (80 ml) and DMF (5.0 ml) was heated at reflux for 1 h. After cooling to ambient temperature, the mixture was concentrated in vacuo. The residue was diluted with AcOEt, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed (SiO_2, AcOEt) to give pure **16** (a mixture of the three diastereomers by NMR) as a colorless caramel (1.5 g, 60%). ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ=1.13, 1.32, 1.38 (total 3H, each d, J=7 Hz, C_3-Me), 2.7—3.4 (1H, m, C_3-H), 3.5—4.1 (5H, m, $C_{4'}$-H, $C_{5'}$-H, $C_{6'}$-H, $C_{4'}$-CH_2OH), 4.2—4.8 (1H, m, C_4-H), 4.82, 4.83, 4.85 (total 1H, each d, J=6 Hz, $C_{2'\text{-ax}}$-H), 5.18, 5.20, 5.35 (total 1H, each d, J=6 Hz, $C_{2'\text{-eq}}$-H), 5.68 (1H, m, olefinic proton), 6.29 (1H, m, olefinic proton); IR (film) 3450, 1765, 1665 cm^{-1}; MS m/z 245 (M^+H), 244 (M^+); High-resolution MS, Found: m/z 244.0956, Calcd for $C_{11}H_{16}O_6$: M, 244.0947.

4-[(1*R*,2*R*,6*S*,9*R*)-9-(*p*-Methoxyphenyl)-3,5,8,10-tetraoxabicyclo[4.4.0]dec-2-yl]-3-methyl-2-methylene-4-butanolide (17). A solution of **16** (0.82 g, 3.4 mmol), *p*-anisaldehyde (2.3 g, 17 mmol), and *p*-toluenesulfonic acid monohydrate (0.20 g, 1.1 mmol) in a mixture of benzene (100 ml) and CH_2Cl_2 (20 ml) was heated at reflux for 3 h. After being cooled to room temperature, the mixture was concentrated in vacuo. The residue was diluted with AcOEt and the ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated in vacuo. The crude product was separated with column chromatography (SiO_2, 30% AcOEt in hexane) to yield pure **17a** (a 1 : 1 mixture of the two diastereomers by NMR) as a colorless caramel (0.80 g, 66%) and pure **17b** as a colorless caramel (68 mg, 6%).

17a (the mixture of two less polar diastereomers): ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.25 (1.5H, d, J=7 Hz, C_3-Me), 1.28 (1.5H, d, J=7 Hz, C_3-Me), 3.20 (1H, m, C_3-H), 3.63 (1H, brs, $C_{6'}$-H), 3.77 (1H, dd, J=2 and 9 Hz, $C_{2'}$-H), 3.82 (1.5H, s, ArOMe), 3.84 (1.5H, s, ArOMe), 4.11 (1H, brs, $C_{1'}$-H), 4.15 (1H, dd, J=2 and 12 Hz, $C_{7'}$-H), 4.35 (1H, dd, J=1 and 12 Hz, $C_{7'}$-H), 4.45 (0.5H, dd, J=5 and 9 Hz, C_4-H), 4.84 (0.5H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 4.85 (0.5H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 4.87 (0.5H, dd, J=7 and 9 Hz, C_4-H), 5.29 (1H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 5.65 (2H, m, $C_{9'}$-H, olefinic proton), 6.29 (0.5H, d, J=2 Hz, olefinic proton), 6.32 (0.5H, d, J=3 Hz, olefinic proton), 6.95 (2H, d, J=9 Hz, aromatic protons), 7.50 (2H, d, J=9 Hz, aromatic protons); IR (film) 1760, 1665, 1615, 1590, 1515 cm^{-1}; MS m/z 362 (M^+), 361 (M^+−H); High-resolution MS, Found: m/z 362.1359, Calcd for $C_{19}H_{22}O_7$: M, 362.1365.

17b (the more polar diastereomer): ^{1}H NMR (90 MHz, $CDCl_3$) δ=1.24 (3H, d, J=7 Hz, C_3-Me), 3.25 (1H, m, C_3-H), 3.60 (1H, brs, $C_{6'}$-H), 3.82 (3H, s, ArOMe), 3.88 (1H, dd, J=1 and 13 Hz, $C_{7'}$-H), 4.23 (1H, dd, J=1 and 13 Hz, $C_{7'}$-H), 4.48 (1H, dd, J=5 and 8 Hz, C_4-H), 4.85 (1H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 5.32 (1H, d, J=6 Hz, $C_{4'\text{-eq}}$-H), 5.48 (1H, d, J=3 Hz, olefinic proton), 5.50 (1H, s, C9′-H), 6.19 (1H, d, J=3 Hz, olefinic

proton), 6.90 (2H, d, J=9 Hz, aromatic protons), 7.40 (2H, d, J=9 Hz, aromatic protons); IR (film) 1770, 1670, 1615, 1590, 1515 cm^{-1}; MS m/z 362 (M^+), 361 (M^+−H); High-resolution MS, Found: m/z 362.1354, Calcd for $C_{19}H_{22}O_7$: M, 362.1365.

(−)-(2*R*)-4-(*t*-Butyldiphenylsiloxy)-1-[(1*R*,2*S*,6*R*,9*R*)-9-(*p*-methoxyphenyl)-3,5,8,10-tetraoxabicyclo[4.4.0]dec-2-yl]-2-methyl-3-methylene-1-butanone (18) and (−)-(2*S*)-4-(*t*-Butyldiphenylsiloxy)-1-[(1*R*,2*S*,6*R*,9*R*)-9-(*p*-methoxyphenyl)-3,5,8,10-tetraoxabicyclo[4.4.0]dec-2-yl]-2-methyl-3-methylene-1-butanone (19). DIBAL (6.7 ml, 1.0 M hexane solution, 6.7 mmol) was added to a solution of **17a** (0.78 g, 2.2 mmol) in CH_2Cl_2 (40 ml) cooled at −78°C under an argon atmosphere. After stirring for 1 h, the reaction was quenched by the addition of MeOH (40 ml). The mixture was allowed to warm up to room temperature, and concentrated in vacuo. The residue was diluted with MeOH. $CeCl_3 \cdot 7H_2O$ (2.0 g, 5.4 mmol) and $NaBH_4$ (90 mg, 2.4 mmol) were successively added to the methanolic solution cooled at 0 °C. After stirring for 10 min, AcOH was added to the mixture to destroy excess $NaBH_4$. The mixture was concentrated in vacuo. The residue was diluted with AcOEt, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue with column chromatography (SiO_2, 10% AcOEt in $CHCl_3$) afforded the corresponding diol (a 1 : 1 mixture of the two diastereomers by NMR) as a colorless caramel (0.60 g, 86%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ=1.11, 1.21 (total 3H, each d, J=7 Hz, $C_{2''}$-Me), 2.5—3.2 (1H, m, $C_{2'}$-H), 3.5—4.5 (6H, C_1-H, C_2-H, C_6-H, C_7-H_2, $C_{1'}$-H), 3.83 (3H, s, ArOMe), 4.15 (2H, brs, $C_{4'}$-H_2), 4.75, 4.83 (total 1H, each d, J=6 Hz, $C_{4\text{-ax}}$-H), 5.09 (1H, brs, olefinic proton), 5.20 (1H, brs, olefinic proton), 5.26, 5.29 (total 1H, each d, J=6 Hz, $C_{4\text{-eq}}$-H), 5.60 (1H, s, C_9-H), 6.94 (2H, d, J=9 Hz, aromatic protons), 7.51 (2H, d, J=9 Hz, aromatic protons).

t-Butyldiphenylsilyl chloride (1.6 g, 5.8 mmol) was added to a solution of the resulting diol (0.68 g, 1.9 mmol) and imidazole (0.89 g, 13 mmol) in DMF (1.5 ml) at room temperature under an argon atmosphere. After stirring for 5 min, the mixture was diluted with AcOEt. The ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was chromatographed (SiO_2, 20% AcOEt in hexane) to give the siloxy alcohol (a 1 : 1 mixture of the two diastereomers by NMR) as a colorless caramel (1.0 g, 89%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ=1.04, 1.08 (total 9H, each s, Si^{t}Bu), 1.09, 1.18 (total 3H, each d, J=7 Hz, $C_{2'}$-Me), 2.5—2.9 (1H, m, $C_{2'}$-H), 3.2—4.5 (8H, m, C_1-H, C_2-H, C_6-H, C_7-H_2, $C_{1'}$-H, $C_{4'}$-H_2), 4.50, 4.80 (total 1H, each d, J=6 Hz, $C_{4\text{-ax}}$-H), 5.0—5.2 (2H, m, olefinic protons), 5.25 (1H, d, J=6 Hz, $C_{4\text{-eq}}$-H), 5.58 (1H, s, C_9-H), 6.86, 6.90 (total 2H, each d, J=9 Hz, C_9-aromatic protons), 7.2—7.9 (12H, C_9-aromatic protons, $SiPh_2$).

Pyridine (2.5 g, 32 mmol) was added to a stirred suspension of anhydrous CrO_3 (1.1 g, 11 mmol) in CH_2Cl_2 (20 ml) at room temperature under an argon atmosphere. After stirring for 20 min, dry celite (4.4 g) and a solution of the obtained siloxy alcohol (0.21 g, 0.35 mmol) in CH_2Cl_2 (5.0 ml) were successively added, and the mixture was stirred for 10 min. The mixture was diluted with ether and filtered through a pad of celite. The filtrate was washed successively with water, saturated aqueous $CuSO_4$, and brine, and dried ($MgSO_4$). Filtration and concentration in vacuo followed by separation with PTLC (SiO_2, 20% AcOEt in hexane), yielded pure **18** as a colorless caramel (76 mg, 36%) and pure **19** as colorless solid (72 mg, 34%). The latter solid (**19**) was recrystallized from ether-hexane to give colorless crystals.

18 (the less polar diastereomer): $[\alpha]_D^{20}$ −104° (*c* 1.00, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ=1.07 (9H, s, Si^{t}Bu), 1.10 (3H, d, J=7 Hz, C_2-Me), 3.57 (1H, brs, $C_{6'}$-H), 3.62 (1H, q, J=7 Hz, C_2-H), 3.79 (3H, s, ArOMe), 4.06 (1H, dd, J=2 and 12 Hz, $C_{7'}$-H), 4.15 (1H, d, J=2 Hz, $C_{2'}$-H), 4.26 (3H, m, C_4-H_2, $C_{1'}$-H), 4.32 (1H, dd, J=1 and 12 Hz, $C_{7'}$-H), 4.63 (1H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 4.88 (1H, brs, olefinic proton), 5.05 (1H, d, J=6 Hz, $C_{4'\text{-eq}}$-H), 5.36 (1H, brs, olefinic proton), 5.50 (1H, s, $C_{9'}$-H), 6.85 (2H, d, J=9 Hz, $C_{9'}$-aromatic protons), 7.3—7.8 (10H, m, $SiPh_2$), 7.35 (2H, d, J=9 Hz, $C_{9'}$-aromatic protons); IR (film) 1725, 1650, 1620, 1590, 1520 cm^{-1}; MS m/z 545 (M^+−^{t}Bu). Found: C, 69.46; 7.14%. Calcd for $C_{35}H_{42}O_7Si$: C, 69.74; H, 7.02%.

19 (the more polar diastereomer): mp 210—211 °C, $[\alpha]_D^{20}$ −5.4° (*c* 1.00, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ=1.06 (9H, s, Si^{t}Bu), 1.18 (3H, d, J=7 Hz, C_2-Me), 3.50 (1H, brs, $C_{6'}$-H), 3.60 (1H, q, J=7 Hz, C_2-H), 3.75 (3H, s, ArOMe), 4.00 (1H, dd, J=2 and 12 Hz, $C_{7'}$-H), 4.21 (2H, m, $C_{1'}$-H, $C_{2'}$-H), 4.26 (1H, dd, J=1 and 12 Hz, $C_{7'}$-H), 4.28 (2H, s, C_4-H_2), 4.72 (1H, d, J=6 Hz, $C_{4'\text{-ax}}$-H), 4.95 (1H, brs, olefinic proton), 5.24 (1H, d, J=6 Hz, $C_{4'\text{-eq}}$-H), 5.28 (1H, brs, olefinic proton), 5.52 (1H, s, $C_{9'}$-H), 6.80 (2H, d, J=9 Hz, $C_{9'}$-aromatic protons), 7.34 (2H, d, J=9 Hz, $C_{9'}$-aromatic protons), 7.3—7.8 (10H, m, $SiPh_2$); IR (Nujol) 1725, 1650, 1615, 1590, 1520 cm^{-1}; MS m/z 524 (M^+−^{t}Bu). Found: C, 69.73; H, 7.10%. Calcd for $C_{35}H_{42}O_7Si$: C, 69.74; H, 7.20%.

(+)-(4*S*,5*R*,6*S*)-5-Hydroxy-6-hydroxymethyl-4-[(2*R*,3*R*)-2-hydroxy-3-methyl-4-methylenetetrahydrofuran-2-yl]-1,3-dioxane (20). A solution of **18** (73 mg, 0.12 mmol) in 80% aqueous AcOH (6.0 ml) was stirred at room temperature for 1 h and concentrated in vacuo. Bu_4NF (0.25 ml, 1.0 M THF solution, 0.25 mmol) was added to a solution of the concentration residue in THF (1.5 ml) at room temperature under an argon atmosphere. After being stirred for 5 min, the mixture was concentrated in vacuo. The residue was diluted with AcOEt, washed with brine, dried ($MgSO_2$), and filtered. Concentration of the filtrate in vacuo followed by purification with column chromatography (SiO_2, 10% AcOEt in $CHCl_3$), gave pure **20** as a colorless caramel (21 mg, 70%), $[\alpha]_D^{20}$ +68.2° (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ=1.22 (3H, d, J=6.8 Hz, $C_{3'}$-Me), 2.61 (1H, m, $C_{3'}$-H), 3.61 (1H, d, J=1.1 Hz, C_4-H), 3.70 (1H, ddd, 1.3, 4.4, and 5.7 Hz, C_6-H), 3.85 (1H, dd, J=4.4 and 12.0 Hz, C_6-C*H*OH), 3.91 (1H, dd, J=5.7 and 12.0 Hz, C_6-C*H*OH), 4.17 (1H, brs, C_5-H), 4.47 (1H, dq, J=13.0 and 2.2 Hz, $C_{5'}$-H), 4.57 (1H, dq, J=13.0 and 2.2 Hz, $C_{5'}$-H), 4.87 (1H, d, J=6.2 Hz, $C_{2\text{-ax}}$-H), 4.95 (1H, q, J=2.2 Hz, olefinic proton), 5.01 (1H, dt, J=3.0 and 2.2 Hz, olefinic proton), 5.27 (1H, d, J=6.2 Hz, $C_{2\text{-eq}}$-H); IR (film) 3420, 1720 cm^{-1}; MS m/z 246 (M^+), 228 (M^++H_2O); High-resolution MS, Found: m/z 246.1079, Calcd for $C_{11}H_{18}O_6$: M, 246.1103.

(−)-(4*R*,5*R*,6*S*)-5-Hydroxy-6-hydroxymethyl-4-[(3*S*)-2-hydroxy-3-methyl-4-methylenetetrahydrofuran-2-yl]-1,3-dioxane (21). The same sequential deprotections of **19** (72 mg, 0.12 mmol) as that described for **20**, followed by purification with column chromatography (SiO_2, 30% AcOEt in $CHCl_3$) yielded pure **21** (a 1 : 1.3 mixture of the two equilibrated epimers at the $C_{2'}$-position by NMR) as a colorless caramel (20 mg, 68%), $[\alpha]_D^{20}$ −21.2° (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ=1.09 (1.3H, d, J=7.3 Hz, $C_{3'}$-Me, minor epimer), 1.17 (1.7H, d, J=6.8 Hz, $C_{3'}$-Me, major epi-

mer), 2.76 (0.43H, brq, J=7.3 Hz, $C_{3'}$-H, minor epimer), 2.92 (0.57H, m, $C_{3'}$-H, major epimer), 3.60 (0.43H, d, J=1.2 Hz, C_4-H, minor epimer), 3.66 (0.57H, d, J=1.2 Hz, C_4-H, major epimer), 3.69 (0.57H, ddd, J=1.2, 4.6, and 6.2 Hz, C_6-H, major epimer), 3.72 (0.43H, ddd, J=1.0, 4.4, and 5.4 Hz, C_6-H, minor epimer), 3.83 (0.57H, dd, 4.6 and 11.9 Hz, C_6-C*H*OH, major epimer), 3.87 (0.43H, dd, J=4.4 and 12.0 Hz, C_6-C*H*OH, minor epimer), 3.90 (0.43H, dd, J=5.4 and 12.0 Hz, C_6-C*H*OH, minor epimer), 3.95 (0.57H, dd, J=6.2 and 11.9 Hz, C_6-C*H*OH, major epimer), 4.05 (0.57H, brs, C_5-H, major epimer), 4.22 (0.43H, brs, C_5-H, minor epimer), 4.46 (0.43H, dq, J=12.9 and 2.2 Hz, $C_{5'}$-H, minor epimer), 4.52 (0.57H, dq, J=12.8 and 2.2 Hz, $C_{5'}$-H, major epimer), 4.56 (0.57H, dq, J=12.8 and 2.2 Hz, $C_{5'}$-H, major epimer), 4.59 (0.43H, ddt, J=1.2, 12.9, and 2.2 Hz, $C_{5'}$-H, minor epimer), 4.85 (0.43H, d, J=6.2 Hz, $C_{2'\text{-ax}}$-H, minor epimer), 4.87 (0.57H, d, J=6.2 Hz, $C_{2'\text{-ax}}$-H, major epimer), 4.96 (0.43H, q, J=2.2 Hz, olefinic proton, minor epimer), 5.00 (0.57H, q, J=2.2 Hz, olefinic proton, major epimer), 5.04 (0.43H, dt, J=1.5 and 2.2 Hz, olefinic proton, minor epimer), 5.07 (0.57H, dt, J=3.0 and 2.2 Hz, olefinic proton, major epimer), 5.24 (0.43H, J=6.2 Hz, $C_{2\text{-eq}}$-H, minor epimer), 5.26 (0.57H, J=6.2 Hz, $C_{2\text{-eq}}$-H, major epimer); IR (film) 3420, 1725 cm^{-1}; MS m/z 246 (M^+), 228 (M^+-H_2O); High-resolution MS, Found: m/z 246.1089, Calcd for $C_{11}H_{18}O_6$: M, 246.1103.

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10) Initially, protection of **16** in a form of the bis(*t*-butyldimethylsilyl) ether was examined by treating with *t*-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine as a base. However, the C-8 silyl group (sesbanimide numbering) of the produced bissilyl ether (**16**: X=Y=Si^{t}BuMe$_2$) was found to be so labile that most of this silyl ether cleaved during purification with silica-gel column chromatography to give the monosilyl ether (**16**: X=H, Y=Si^{t}BuMe$_2$) as the main product. Comparisons of the ^{1}H NMR spectra of **16** and its bis- and monosilyl ethers made it clear that unexpected lability of the C-8 silyl group can be explained by remote distortion of the γ-lactone moiety brought about by the C-8 bulky silyl group. Thus, in the NMR spectrum of **16** (X=Y=Si^{t}BuMe$_2$), the signals of olefinic protons appeared at δ 5.07 and 5.33. In contrast, the olefinic protons of **16** (X=Y=H) and **16** (X=H, Y=Si^{t}BuMe$_2$) show the ordinary chemical shifts at δ 5.68 and 6.29 and δ 5.65 and 6.28, respectively. Similar remote distortion of the glutarimide ring by the C-8 bulky silyl group has been observed in the course of the total synthesis of **1** and **2**.[3]

11) The similar two intramolecular hydrogen bonds may stabilize the structures of **1** and **2** which solely take the hemiacetal forms.