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TOTAL SYNTHESIS OF NATURAL (+)-SESBANIMIDE A AND (-)-SESBANIMIDE B[1]

Fuyuhiko Matsuda and Shiro Terashima*

Sagami Chemical Research Center,
Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

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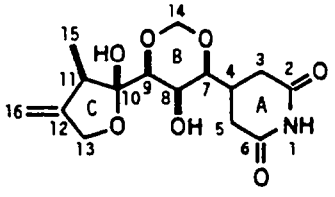
Abstract: The first total synthesis of natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2), potent antitumor alkaloids isolated from the seeds of the leguminous plant, *Sesbania drummondii*, has been accomplished starting from D-(+)-xylose. This total synthesis involves efficient construction of the optically active AB-ring system from D-(+)-xylose, introduction of the C_5-unit into the AB-ring system in a form of *exo*-methylene-γ-lactone, and elaboration of the labile C-ring system at the last stage of the synthesis. The absolute configurations of natural 1 and 2 could be obviously established by our total synthesis.

Sesbanimide A (1) and sesbanimide B (2), potent antitumor alkaloids, were isolated from *Sesbania drummondii* seeds by Powell *et al.* in 1983.[2] A number of leguminous plants, which belong to the genus *Sesbania* native to the Gulf Coastal Plain of U.S.A., are notorious for toxicity of their seeds to livestock and fowl.[3] Powell *et al.* had reported that alcoholic extracts of the seeds of *S. drummondii*, *S. vesicaria*, and *S. punicea* were markedly cytotoxic against KB cells *in vitro* and showed significant inhibitory activity against P388 murine leukemia *in vivo*.[4]



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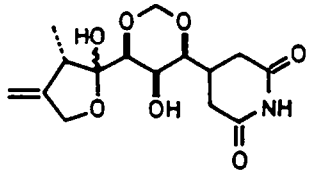


2

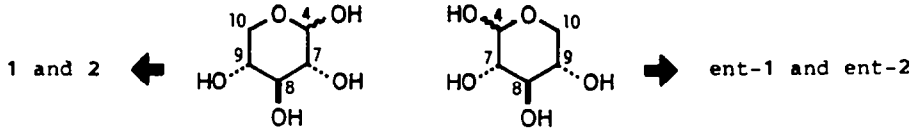
Further their investigation resulted in the isolation and structure elucidation of 1 and 2 as the antileukemic principles. Sesbanimide A (1), the major and most active component, exhibits IC_{50} values of 7.7×10^{-3} μg/ml against KB cells *in vitro* and T/C values of 140-181% in 8-12 μg/kg dose level against P388 murine leukemia *in vivo*. Sesbanimide B (2), the C-11 isomer of 1, also shows consider-

able antitumor activity, although it was inferior to that of 1.[2c] On the other hand, 1 could be also obtained from aqueous ethanolic extracts of *S. punicea* seeds native to South Africa as the toxic principle by Gorst-Allman *et al.*, monitoring the fractionation by bioassay for acute toxicity in 1 day-old chickens.[5]

Sesbanimides (1 and 2) 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 the two single bonds. Although the structure of 1 including its relative stereochemistry had been established by X-ray crystallographic analysis, its absolute configuration had not been determined.[2a] Thus, their remarkable antitumor activity and novel structures in addition to the lack of determination of their absolute stereochemistry distinguished these molecules as unusually interesting targets for total synthesis and a number of synthetic studies on sesbanimides have been reported.[6-9] We started the program directed toward the total synthesis of 1 and 2 with an aim to determine their absolute configurations and to explore the general synthetic route to these novel alkaloids applicable to preparation of various structural types of congeners. These congeners were anticipated to be useful for elucidating the structure-activity relationships of sesbanimides. Our efforts culminated in the first total synthesis of natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2) starting from readily available D-(+)-xylose, concluding the absolute configurations of 1 and 2 as shown above.[7] Other two total syntheses of the antipodes of natural 1 and 2 were also reported by Pandit *et al.*[8] and Schlessinger *et al.*[9] In both of these syntheses, the same conclusion as ours was obtained with regard to the absolute configurations of sesbanimides. This paper concerns with full details of the first total synthesis of natural 1 and 2 completed by us.[7,10]

Synthetic Strategy

From retrosynthetic perspective on 1 and 2, the most logical strategy to construct the five chiral centers involved in these novel alkaloids in an optically active form was anticipated to be introduction of the three significant asymmetric centers at the C-7, C-8, and C-9 positions, all the chiral centers present in the B-ring, from an appropriate carbohydrate. This is because both of the C-11 isomers had been isolated and the configuration at the C-10 position was expected to be governed by an equilibrium between the two possible epimers. We selected D-(+)-xylose as a starting material since the three asymmetric centers of D-xylose just correspond to the three contiguous asymmetric centers (the C-7, C-8, and C-9



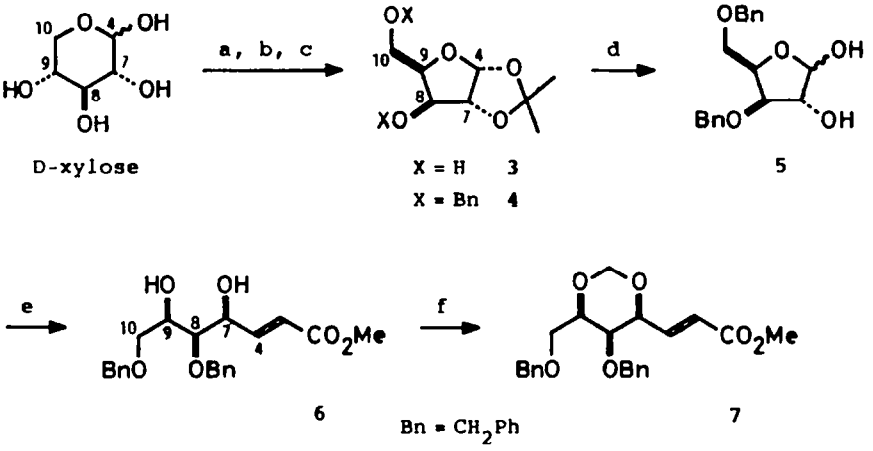
D-(+)-xylose L-(-)-xylose

positions) of sesbanimides and relatively inexpensive L-(-)-xylose can be used if the synthesis of the antipodes is required. Information obtained from the structure determination of 1 and 2 revealed that the C-ring system is very labile under the basic conditions and the B-ring system is most stable among the three rings.[2b] Therefore, it appeared reasonable to carry out the synthesis in the sequence of (1) construction of the B-ring system in an optically active form from D-xylose, (2) formation of the A-ring system, (3) introduction of the C_5-unit into the AB-ring system, and (4) formation of the C-ring system. As mentioned below, our total synthesis of 1 and 2 has been accomplished according to this synthetic plan.

Results and Discussion

Construction of the B-Ring System. Since it had been well documented that direct methylene acetalization of D-xylose did not give the desired 2,4-*O*-methylene-D-xylose but 1,2:3,5-di-*O*-methylene-α-D-xylofuranose,[11] appropriate protection of the four hydroxyl groups of D-xylose was necessary to construct the B-ring system. After several preliminary experimentions,[12] (-)-1,3-*O*-isopropylidene-α-D-xylofuranose (3), which was readily accessible from D-xylose in 2 steps and in a good overall yield,[15] was found to be quite suitable for this purpose among D-xylose derivatives so far reported. Considering the subsequent synthetic scheme, the C-3 and C-5 hydroxyl groups of 3 (the C-8 and C-10 positions of 1 and 2) were protected in forms of benzyl ethers to afford the (-)-dibenzyl ether (4). The acetonide group of 4 was removed by treating with concentrated hydrochloric acid in acetic acid.[15] Wittig reaction of the resulting hemiacetal (5) with the stabilized ylide, methoxycarbonylmethylenetriphenylphosphorane, under the strictly defined conditions (reflux, 30 sec) resulted in simultaneous opening of the furanose ring and carbon chain elongation, producing the α,β-unsaturated ester (6) in an excellent yield. Prolonged reflux caused intramolecular 1,4-addition of the C-9 hydroxyl group to the α,β-unsaturated ester moiety. Exposure of 6 to trimethylsilyl trifluoromethanesulfonate in dimethoxymethane in the presence of 2,6-lutidine as a base effected methylene acetalization to afford a high yield of the (-)-1,3-dioxane (7), corresponding to the B-ring system of 1 and 2.[16]

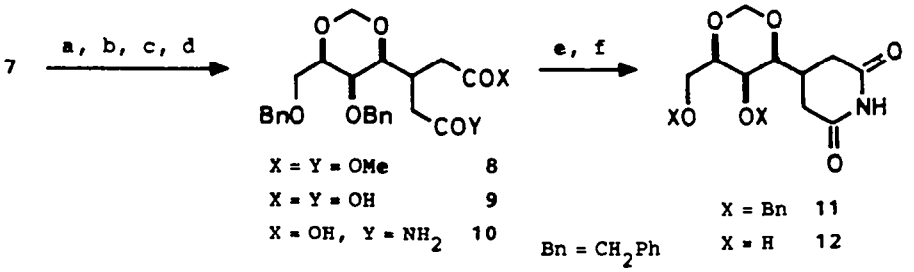
Scheme 1



a) 18M H_2SO_4, $CuSO_4$, Me_2CO, rt, 25 h, 74% b) 0.12M HCl, rt, 1 h, 96% c) 1) NaH, THF, reflux, 15 min 2) BnCl, $^nBu_4NBr$, reflux, 5 min, 92% (2 steps) d) 12M HCl, AcOH, rt, 5 min, 73% e) $Ph_3P{=}CHCO_2Me$, PhMe, reflux, 30 sec, 92% f) TMSOTf, 2,6-Lu, $(MeO)_2CH_2$, 0 °C, 15 min, 79%.

Construction of the A-ring System. Introduction of a C_2-unit by Michael addition reaction to the C-4 position for constructing the carbon framework of the A-ring system was next attempted. 1,4-Addition of the sodium salt of dimethyl malonate to 7 was found to cleanly occur in tetrahydrofuran at room temperature in the presence of a catalytic amount of tetrabutylammonium bromide. In the absence of the ammonium salt, long period of heating was required to complete the addition reaction. This is probably due to decreased concentration of the malonate anion in the reaction medium. Subsequent demethoxycarbonylation of the resulting

Scheme 2



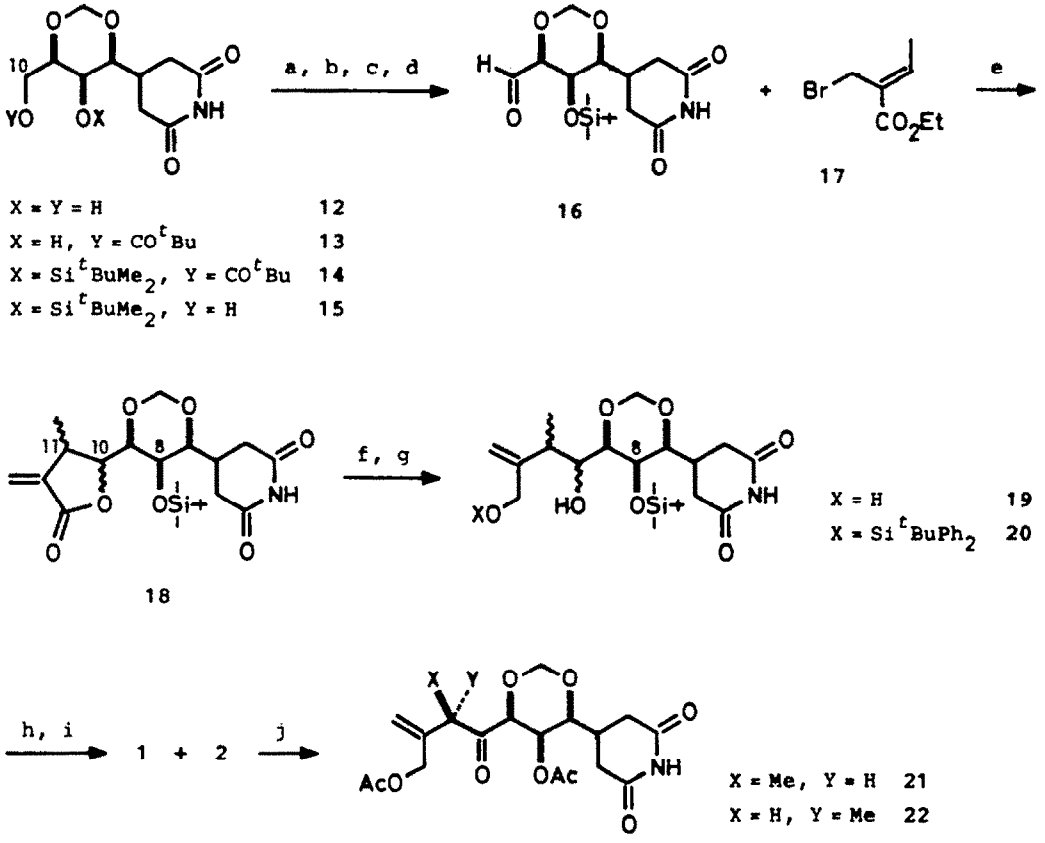
a) $NaCH(CO_2Me)_2$, $^nBu_4NBr$, THF, rt, 12 h b) NaCl, H_2O-DMSO, 160 °C, 1 h, 89% (2 steps) c) 1M KOH, rt, 48 h d) 1) MeOCOCl, Et_3N, THF, -20 °C, 3 h 2) NH_3 gas, 0 °C, 30 min e) NaOAc, Ac_2O, 100 °C, 20 min, 51% (4 steps) f) H_2 (5 atm), Pd-C, AcOH, MeOH, rt, 2 h, 95%.

Michael adduct in brine-dimethyl sulfoxide[17] gave the (-)-diester (8), which incorporated all the carbon framework found in the A-ring system. Conversion of 8 into the (-)-diol (12) was performed in a stepwise manner. After hydrolysis of the two methoxycarbonyl groups of 8, activation of the diacid (9) with methyl chloroformate in a form of the glutaric anhydride followed by ammonolysis, afforded the amide acid (10) as a mixture of two diastereomers. Dehydration of 10 with acetic anhydride in the presence of sodium acetate as a buffer smoothly produced the glutarimide ring, giving the (+)-glutarimide (11) in a good overall yield. Catalytic hydrogenation of 11 over palladium on charcoal effected removal of the two benzyl groups to produce 12 in a high yield. With 12 in hand, preparation of the AB-ring system was completed.[18]

Introduction of the C_5-Unit into the AB-Ring System. In order to construct the C-ring system, introduction of a C_5-unit into the C-10 position was required. To this end, we first examined conversion of 12 into the aldehyde (16). Thus, the primary and secondary hydroxyl groups of 12 were sequentially protected in forms of pivalate ester and *tert*-butyldimethylsilyl ether, respectively, to yield the (-)-siloxypivalate (14) by way of the (-)-pivalate (13). While other combinations of protective groups were also examined for protecting the two hydroxyl groups of 12, this combination only gave the satisfactory result. For example, methoxymethylation or 2-(trimethylsilyl)ethoxymethylation of 13 afforded a low yield of the product since 13 was unstable under the basic conditions of protection.[19] Reductive cleavage of the pivalate ester of 14 cleanly occurred with diisobutylaluminum hydride without any disruption of the glutarimide ring, affording the (-)-siloxyalcohol (15). Collins oxidation of 15 readily produced 16.

Interestingly, the glutarimide carbonyl group of 14 and 15 exhibited their absorption bands at 1670 cm^{-1} in their IR spectra (1.0 mM chloroform solution). In contrast, in the IR spectra of 11 and 13, absoptions due to the glutarimide carbonyl groups appeared at the ordinary wave numbers around 1705 cm^{-1}. Detailed comparisons of coupling patterns observed in the 400 MHz ^1H NMR spectra of 11 and 13-15 revealed that, in cases of 14 and 15, the glutarimide rings take the distorted twist-boat like conformations (B) and, in contrast, the glutarimide ring of 11 and 13 are in the stable chair like conformations (A). Comparing IR (1.0 mM chloroform solution) and 400 MHz ^1H NMR spectra of the related compounds (1, 2, 16, 18, and 19-22), it became evident that the glutarimide rings of the compounds where the C-8 hydroxyl groups are protected in forms of *tert*-butyldimethylsilyl

Scheme 3



X = Y = H 12
X = H, Y = CO^{t}Bu 13
X = Si^{t}BuMe$_2$, Y = CO^{t}Bu 14
X = Si^{t}BuMe$_2$, Y = H 15

16

17

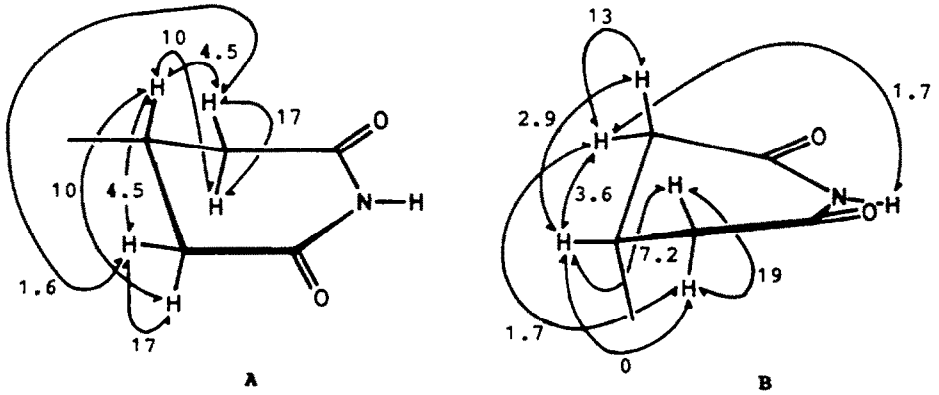
18

X = H 19
X = Si^{t}BuPh$_2$ 20

X = Me, Y = H 21
X = H, Y = Me 22

a) ^{t}BuCOCl, Py, 0 °C, 2.5 h, 91% b) ^{t}BuMe$_2$SiOTf, 2,6-Lu, CH_2Cl_2, rt, 10 min, 86% c) ^{i}Bu$_2$AlH, CH_2Cl_2, -78 °C, 1 h, 87% d) CrO_3·2Py, CH_2Cl_2, rt, 10 min, 84% e) Zn, THF, reflux, 6 min, 73% f) 1) ^{i}Bu$_2$AlH, CH_2Cl_2, -78 °C, 1 h 2) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, 0 °C, 10 min, 73% (2 steps) g) ^{t}BuPh$_2$SiCl, imidazole, DMF, rt, 40 min h) CrO_3·2Py, CH_2Cl_2, rt, 30 min i) ^{n}Bu$_4$NF, THF, rt, 10 min, 16% (1, 3 steps), 19% (2, 3 steps) j) Ac_2O, Py, rt, 12 h, 53% (21), 61% (22).

Scheme 4



The ^{1}H coupling constants (Hz) for the conformations A and B.

ethers always take the common distorted conformations (B). It is noteworthy that the bulky silyl group distorted the remote glutarimide ring rather than the proximate 1,3-dioxane ring.[20]

With 16 in hand, our synthetic efforts were next devoted to introduction of the C_5-unit. After several experimentions,[21] it was finally found that the regioselective Reformatsky reaction[22] employing (E)-ethyl 2-(bromomethyl)crotonate (17)[23] proceeded smoothly, giving the *exo*-methylene-γ-lactone (18) in a good yield. The ^{1}H NMR spectrum of this sample clearly disclosed that 18 consisted of the three diastereomers whose stereostructures could not be determined. The formation ratio of these diastereomers were roughly estimated as 1:1.3:1.5 by the HMR spectrum. This mixture was subjected to the final synthetic steps without separation of these isomers.

Construction of the C-Ring System: Total Synthesis of Sesbanimides. Reduction of the γ-lactone moiety of 18 was envisioned at the next stage of our synthetic scheme. However, direct reduction to the diol (19) with hydride reagents always gave unsatisfactory results in terms of the chemical yields of 19. Monitoring the reaction courses of these reductions made it clear that the conversion of 18 into the corresponding hemiacetal took place quite readily. Accordingly, transformation of 18 into 19 was attempted in a stepwise manner. Treatment of 18 with diisobutylaluminum hydride yielded the hemiacetal, which without isolation was further reduced with sodium borohydride in the presence of cerium(III) chloride,[24] affording 19 in a fairly good yield. The diol (19) was derived to an almost 1:1 mixture of 1 and 2 in a moderate overall yield by the sequence of (1) selective protection of the primary hydroxyl group of 19 as a *tert*-butyldiphenylsilyl ether, (2) Collins oxidation of the remaining secondary hydroxyl group of the resulting siloxyalcohol (20), and (3) removal of the two silyl groups with tetrabutylammonium fluoride. The three diastereomers concerning the C-10 and C-11 positions were found to exhibit considerably different reactivity in the stepwise reduction of 18 and Collins oxidation of 20. Furthermore, the labile C-8 silyl group of one isomer of 20 was partly cleaved during purification with silica gel chromatography. Due to these reasons, it was anticipated that the ratio of 1 to 2 being close to 1:1 was observed.

The mixture of 1 and 2 could be readily separated by silica gel TLC. The less polar isomer and its diacetate were identical with natural (+)-sesbanimide A (1) and the authentic (-)-diacetate (21) prepared from natural sample of 1 by our hands, respectively, in all respects (mp, mmp, optical rotation, 400 MHz ^{1}H NMR, IR, MS, and TLC mobility with several different solvent systems). Furthermore synthetic and natural 1 exhibited almost the same magnitude of activity in P388 murine leukemia *in vitro* cytotoxicity assay (IC_{50}: synthetic 1, 4.6×10^{-5} μg/ml; natural 1, 3.3×10^{-5} μg/ml). Accordingly, our synthesis of natural sesbanimide A (1) obviously confirmed its absolute configuration.

On the other hand, the more polar isomer and its diacetate were found to show the 400 MHz ^{1}H NMR spectra identical with those of natural sesbanimide B (2) and its diacetate (22), respectively. The ^{1}H NMR spectrum of synthetic 2 clearly showed that it consisted of a 1:1.8 equilibrated mixture of the two epimeric hemiacetals in a similar manner to that reported for natural 2. Other spectral data (IR and MS) of the synthetic compounds (2 and 22) further supported their structures. Since 2 has been isolated from the same plants as those giving 1, its absolute configuration can be tentatively assigned as shown. Fairly intense cytotoxicity was also observed for synthetic 2 in P388 murine leukemia *in vitro* assay (IC_{50}: synthetic 2, 3.1×10^{-2} μg/ml), although its activity was inferior to that of 1. Therefore, (-)-sesbanimide B (2) synthesized by us was anticipated to

be identical with natural 2 even if comparison of the optical rotation could not be carried out due to the lack of the reported optical rotation value.

Conclusion

The first total synthesis of natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2), potent antitumor alkaloids isolated from leguminous plant, *Sesbania drummondii*, has been accomplished starting from D-(+)-xylose and their absolute configurations have been obviously established. This total synthesis consists of the following novel aspects: (1) efficient construction of the AB-ring system in an optically active form from readily available D-(+)-xylose, (2) introduction of the C_5-unit into the AB-ring system in a form of *exo*-methylene-γ-lactone employing the regioselective Reformatsky reaction, and (3) effective elaboration of the labile C-ring system from the resulting γ-lactone. With completion of the total synthesis of 1 and 2, preparation of the partial structures of 1 and 2 such as the AB-, C-, and BC-ring systems was attempted to disclose the role of each ring of 1 and 2 in their prominent antitumor activity. This is the subject of a separate paper.[10]

Experimental Section[25]

(-)-1,2-*O*-Isopropylidene-α-D-xylofuranose (3). Acetalization of D-(+)-xylose, mp 154-156 °C, $[\alpha]_D^{20}$ +17.9° (c 10.0, H_2O), with acetone in the presence of 18M H_2SO_4 and anhydrous $CuSO_4$ (74%)[15] followed by selective hydrolysis with 0.12M HCl (96%),[15] gave 3 *via* (+)-1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose, mp 42-43 °C [lit. 44-45 °C[26a]], $[\alpha]_D^{22}$ +13.3° (c 2.00, H_2O) [lit. $[\alpha]_D^{22}$ +13.0° (c 2.00, H_2O)[26a]]. The diol (3) showed $[\alpha]_D^{22}$ -20.6° (c 2.00, H_2O) [lit. $[\alpha]_D^{22}$ -19.9° (c 2.00, H_2O)[26b]].

(-)-3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (4). A solution of 3 (25 g, 0.13 mol) in THF (340 ml) was added to a suspension of NaH (39 g, 50% dispersion in oil, 0.81 mol) in THF (170 ml) with stirring in an ice bath under an argon atmosphere. The mixture was heated at reflux for 15 min and cooled to room temperature. Benzyl bromide (88 g, 0.70 mol) and Bu_4NBr (7.4 g, 23 mmol) were added and the mixture was heated at reflux for 5 min. After cooling to 0 °C, water was added dropwise and the mixture was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10% AcOEt in hexane) to afford pure 4 as a pale yellow oil (45 g, 92%). Purification by bulb-to-bulb distillation gave an analytical sample of 4 as a colorless oil, $[\alpha]_D^{20}$ -48.4° (c 1.00, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (3H, s, Me), 1.47 (3H, s, Me), 3.76 (2H, d, J = 6 Hz, C_5-H_2), 3.97 (1H, d, J = 3 Hz, C_2-H), 4.4-4.6 (2H, m, C_3-H, C_4-H), 4.55 (2H, s, $PhCH_2$), 4.56 (1H, d, J = 12 Hz, PhCH), 4.60 (1H, d, J = 12 Hz, PhCH), 5.94 (1H, d, J = 3 Hz, C_1-H), 7.29 (5H, s, aromatic protons), 7.31 (5H, s, aromatic protons); IR (film) 1500, 1070 cm^{-1}; MS m/z 370 (M^+), 279 (M^+-$PhCH_2$). *Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.33; H, 7.14.

(E,4'S,5'R,6'R)-(-)-Methyl 3-5'-Benzyloxy-6'-benzyloxymethyl-1',3'-dioxan-4'-yl-acrylate (7). 12M HCl (300 ml) was added to a solution of 4 (15 g, 41 mmol) in AcOH (150 ml) at room temperature. After stirring for 5 min, brine was added and the mixture was extracted with AcOEt. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, 30% AcOEt in hexane), gave pure 5 (a 1:1 mixture of the two anomers by NMR) as a colorless caramel (9.7 g, 73%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ 3.6-4.8 (9H, m,

C_2-H, C_3-H, C_4-H, C_5-H_2, $PhCH_2$ x 2), 5.11 (0.5H, d, J = 12 Hz, C_1-H), 5.50 (0.5H, J = 5 Hz, C_1-H), 7.32 (10H, s, aromatic protons).

A solution of 5 (3.6 g, 11 mmol) and methoxycarbonylmethylenetriphenylphosphorane (7.5 g, 22 mmol) in toluene (70 ml) was heated at reflux for 30 sec and cooled to ambient temperature. After concentration *in vacuo*, the residue was dissolved in AcOEt. The solution was washed successively with 1M HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, 20% AcOEt in hexane) to afford pure **6** as a colorless caramel (4.0 g, 92%). ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ 3.5-3.8 (4H, m, C_5-H, C_6-H, C_7-H_2), 3.78 (3H, s, CO_2Me), 3.8-4.1 (1H, m, C_4-H), 4.55 (2H, s, $PhCH_2$), 4.65 (2H, s, $PhCH_2$), 6.20 (1H, dd, J = 2 and 16 Hz, C_2-H), 7.06 (1H, dd, J = 4 and 16 Hz, C_3-H), 7.33 (5H, s, aromatic protons), 7.35 (5H, s, aromatic protons); IR (film) 3450, 1720, 1660, 1500 cm^{-1}.

Trimethylsilyl trifluoromethanesulfonate (17 g, 78 mmol) was added to a solution of **6** (7.4 g, 19 mmol) and 2,6-lutidine (4.6 g, 43 mmol) in dimethoxymethane (150 ml) cooled at 0 °C under an argon atmosphere. After stirring for 15 min, saturated aqueous $NaHCO_3$ was added and the mixture was allowed to warm up to room temperature and extracted with AcOEt. The organic extracts were combined, washed successively with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, 20% AcOEt in hexane), gave pure **7** as a pale yellow solid (6.0 g, 79%). Further purification by recrystallization from ether-AcOEt gave an analytical sample of **7** as colorless crystals, mp 103-104 °C, $[\alpha]_D^{20}$ -38.4° (c, 1.00, $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.57 (1H, brs, C_5'-H), 3.62 (2H, d, J = 5 Hz, $PhCH_2OC\underline{H}_2$), 3.77 (1H, s, CO_2Me), 3.95 (1H, dt, J = 2 and 5 Hz, C_6'-H), 4.34 (1H, dt, J = 4 and 2 Hz, C_4'-H), 4.52 (2H, s, $PhCH_2$), 4.53 (1H, d, J = 12 Hz, PhCH), 4.56 (1H, d, J = 12 Hz, PhCH), 4.86 (1H, d, J = 6 Hz, $C_{2'-ax}$-H), 5.25 (1H, d, J = 6 Hz, $C_{2'-eq}$-H), 6.20 (1H, dd, J = 2 and 15 Hz, C_2-H), 6.75 (1H, dd, J = 4 and 15 Hz, C_3-H), 7.29 (5H, s, aromatic protons), 7.35 (5H, s, aromatic protons); IR (Nujol) 1720, 1670, 1500 cm^{-1}; MS m/z 398 (M^+), 307 (M^+-$PhCH_2$). *Anal.* Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.40; H, 6.64.

(4'S,5'R,6'R)-(-)-Dimethyl 3-5'-Benzyloxy-6'-benzyloxymethyl-1',3'-dioxan-4'-yl-glutarate (8). Dimethyl malonate (8.5 g, 64 mmol) was added to a stirred suspension of NaH (2.7 g, 50% dispersion in oil, 56 mmol) in THF (180 ml) at room temperature under an argon atmosphere. The mixture was heated at reflux for 15 min and cooled to room temperature. Bu_4NBr (0.68 g, 2.1 mmol) and a solution of **7** (1.7 g, 4.3 mmol) in THF (10 ml) were added and the resulting mixture was stirred at ambient temperature for 12 h. After addition of AcOH (3.5 g, 58 mmol), the mixture was concentrated *in vacuo*. The residue was dissolved in ether and the ethereal solution was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in DMSO (70 ml), and NaCl (0.41 g, 7.0 mmol) and water (0.31 g, 17 mmol) were added to the dimethyl sulfoxide solution. The mixture was heated at 160 °C for 1 h. After being cooled to room temperature, the mixture was diluted with brine and extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residual oil was chromatographed (SiO_2, 20% AcOEt in hexane) to give pure **8** as pale yellow crystals (1.8 g, 89%), mp 49-52 °C, $[\alpha]_D^{20}$ -7.8 °C (1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (2H, d, J = 6.2 Hz, C_2-H_2), 2.43-2.52 (1H, m, C_4-H), 2.66-2.80 (2H, m, C_3-H, C_4-H), 3.59 (1H, brs, C_5'-H), 3.63 (3H, s, CO_2Me), 3.64 (3H, s, CO_2Me), 3.64-3.70 (3H, m, C_4'-H, $PhCH_2OC\underline{H}_2$), 3.88 (1H, brt, J = 6.7 Hz, C_6'-H), 4.52 (1H, d, J = 11.8 Hz, PhCH), 4.56 (1H, d, J = 11.8 Hz, PhCH), 4.61 (1H, d, J = 11.2 Hz, PhCH), 4.68 (1H, d, J = 11.2 Hz, PhCH), 4.72 (1H, d, J = 6.2 Hz, $C_{2'-ax}$-

H), 5.13 (1H, d, J = 6.2 Hz, $C_{2'-eq}$-H), 7.24-7.38 (10H, m, aromatic protons); IR (film) 1740, 1730, 1500 cm^{-1}; MS m/z 473 (M^+H), 472 (M^+), 381 (M^+-PhCH_2); High-resolution MS 472.2078 (472.2097 calcd for $C_{26}H_{32}O_8$).

(4'S,5'R,6'R)-(+)-4-5'-Benzyloxy-6'-benzyloxymethyl-1',3'-dioxan-4'-yl-2,6-piperidinedione (11). 1M KOH (1.6 ml) was added to a solution of 8 (0.24 g, 0.51 mmol) in MeOH (1.6 ml) at room temperature. After stirring for 48 h, the mixture was acidified to pH 1 with 1M HCl, concentrated *in vacuo*, and diluted with AcOEt. The ethyl acetate solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give crude **9** as a caramel. Methyl chloroformate (87 mg, 0.80 mmol) was added to a stirred solution of crude **9** and triethylamine (0.17 g, 1.7 mmol) in THF (2.0 ml) cooled at -20 °C under an argon atmosphere. After stirring for 3 h, NH_3 gas was bubbled through the solution for 30 min. After being allowed to warm up to room temperature, the mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo* to afford crude **10** as a mixture of the two diastereomers (by TLC). A mixture of crude **10**, sodium acetate (0.33 g, 4.0 mmol), and Ac_2O (1.6 ml) was heated at 100 °C for 20 min. After being cooled to ambient temperature, the mixture was concentrated *in vacuo*, and the residue was dissolved with AcOEt. The ethyl acetate solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate *in vacuo*, followed by purification by column chromatography (SiO_2, 50% AcOEt in hexane), gave pure **11** as a pale yellow solid (0.11 g, 51%). Recrystallization from ether-AcOEt afforded an analytical sample of **11** as colorless crystals, mp 138-139 °C, $[\alpha]_D^{20}$ +54.4° (0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (1H, dd, J = 10.0 and 17.3 Hz, C_{3-ax}-H), 2.08 (1H, ddd, J = 1.6, 4.7, and 17.3 Hz, C_{3-eq}-H), 2.33-2.48 (2H, m, C_4-H, C_{5-ax}-H), 2.83 (1H, ddd, J = 1.6, 4.7, and 17.3 Hz, C_{5-eq}-H), 3.26 (1H, dd, J = 1.2 and 8.1 Hz, $C_{4'}$-H), 3.53 (1H, brs, $C_{5'}$-H), 3.67 (1H, dd, J = 5.9 and 9.2 Hz, $PhCH_2OC\underline{H}$), 3.75 (1H, t, J = 9.2 Hz, $PhCH_2OC\underline{H}$), 3.87 (1H, ddd, J = 1.1, 5.9, and 9.2 Hz, $C_{6'}$-H), 4.49 (1H, d, J = 11.7 Hz, PhCH), 4.57 (1H, d, J = 11.6 Hz, PhCH), 4.59 (1H, d, J = 11.6 Hz, PhCH), 4.73 (1H, d, J = 6.2 Hz, $C_{2'-ax}$-H), 4.81 (1H, d, J = 11.7 Hz, PhCH), 5.15 (1H, d, J = 6.2 Hz, $C_{2'-eq}$-H), 7.28-7.41 (10H, m, aromatic protons), 7.78 (1H, brs, NH); IR (Nujol) 3280, 1725, 1700, 1500 cm^{-1}; MS m/z 426 (M^+H), 425 (M^+), 334 (M^+-PhCH_2). *Anal.* Calcd for $C_{24}H_{27}O_6N$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.78; H, 6.50; N, 3.49.

(4'S,5'R,6'R)-(-)-4-5'-Hydroxy-6'-hydroxymethyl-1',3'-dioxan-4'-yl-2,6-piperidinedione (12). A mixture of **11** (1.0 g, 2.4 mmol) and 10% Pd-C (0.50 g) in a mixture of MeOH (20 ml) and AcOH (2.0 ml) was stirred for 2 h at room temperature under a hydrogen atmosphere (5 atm). The catalyst was filtered off and washed with hot water. The combined filtrates were concentrated *in vacuo* to give pure **12** as a colorless solid (0.55 g, 95%). Recrystallization from butanol gave an analytical sample of **12** as colorless crystals, mp 214-216 °C, $[\alpha]_D^{20}$ -6.0° (c 0.50, DMSO). ^1H NMR (400 MHz, DMSO-d_6-D_2O) δ 2.29-2.67 (5H, m, C_3-H_2, C_4-H, C_5-H_2), 3.35 (1H, brd, J = 6.9 Hz, $C_{4'}$-H), 3.42 (1H, brs, $C_{5'}$-H), 3.43-3.57 (3H, m, $C_{6'}$-H, $HOC\underline{H}_2$), 4.65 (1H, d, J = 6.1 Hz, $C_{2'-ax}$-H), 4.97 (1H, d, J = 6.1 Hz, $C_{2'-eq}$-H); IR (Nujol) 3320, 1705 cm^{-1}; MS m/z 246 (M^+H). *Anal.* Calcd for $C_{10}H_{15}O_6N$: C, 48.98; H, 6.17; N, 5.71. Found: C, 49.17; H, 6.22; N, 5.69.

(4'S,5'R,6'R)-(-)-4-5'-Hydroxy-6'-pivalyloxymethyl-1',3'-dioxan-4'-yl-2,6-piperidinedione (13). Pivalyl chloride (0.31 g, 2.6 mmol) was added to a stirred suspension of **12** (0.64 g, 2.6 mmol) in pyridine (13 ml) cooled in an ice bath under an argon atmosphere. After stirring for 30 min, another portion of pivalyl chloride (0.63 g, 5.2 mmol) was added to the reaction mixture and the stirring was further continued for 2 h. After addition of MeOH (3.2 ml), the mixture was allowed to warm up to room temperature, concentrated *in vacuo*, and diluted with

AcOEt. The ethyl acetate solution was washed successively with saturated aqueous $CuSO_4$ and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield pure 13 as a colorless solid (0.78 g, 91%). This was recrystallized from ether-MeOH to give an analytical sample of 13 as colorless crystals, mp 189-191 °C, $[\alpha]_D^{20}$ -3.6° (c 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (9H, s, CO^tBu), 2.36 (1H, dd, J = 10.0 and 16.9 Hz, C_{3-ax}-H), 2.47 (1H, dd, J = 10.0 and 17.3 Hz, C_{5-ax}-H), 2.52 (1H, d, J = 11.4 Hz, OH), 2.64 (1H, dtt, J = 8.5, 4.5, and 10.0 Hz, C_4-H), 2.75 (1H, ddd, J = 1.6, 4.5, and 16.9 Hz, C_{3-eq}-H), 2.93 (1H, ddd, J = 1.6, 4.5, and 17.3 Hz, C_{5-eq}-H), 3.38 (1H, dd, J = 1.0 and 8.5 Hz, $C_{4'}$-H), 3.39 (1H, brd, J = 11.4 Hz, $C_{5'}$-H), 3.83 (1H, ddd, J = 1.0, 5.9, and 6.7 Hz, $C_{6'}$-H), 4.21 (1H, dd, J = 6.7 and 11.7 Hz, CO_2CH), 4.29 (1H, dd, J = 5.9 and 11.7 Hz, CO_2CH), 4.73 (1H, d, J = 6.4 Hz, $C_{2'-ax}$-H), 5.12 (1H, d, J = 6.4 Hz, $C_{2'-eq}$-H), 7.91 (1H, brs, NH); IR (Nujol) 3530, 1730, 1695 cm^{-1}; MS m/z 328 (M^+-H), 314 (M^+-Me). *Anal.* Calcd for $C_{15}H_{23}O_7N$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.56; H, 7.05; N, 4.21.

(4'S,5'R,6'R)-(-)-4-5'-*tert*-Butyldimethylsiloxy-6'-hydroxy-methyl-1',3'-dioxan-4'-yl-2,6-piperidinedione (15). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.24 g, 0.91 mmol) was added to a stirred mixture of 13 (85 mg, 0.26 mmol) and 2,6-lutidine (0.24 g, 2.2 mmol) in CH_2Cl_2 (1.7 ml) at room temperature under an argon atmosphere. After stirring was continued for 10 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 residue was chromatographed (SiO_2, 20% AcOEt in hexane) to give pure 14 as a colorless caramel (98 mg, 86%), $[\alpha]_D^{20}$ -13.6° (0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (3H, s, SiMe), 0.26 (3H, s, SiMe), 0.89 (9H, s, Si^tBu), 1.20 (9H, s, CO^tBu), 1.76 (1H, dd, J = 2.9 and 12.5 Hz, C_{3-ax}-H), 2.23 (1H, brd, J = 18.6 Hz, C_{5-eq}-H), 2.42 (1H, ddt, J = 3.6, 12.5, and 1.8 Hz, C_{3-eq}-H), 2.52 (1H, brdq, J = 7.2 and 3.6 Hz, C_4-H), 2.68 (1H, dd, J = 7.2 and 18.6 Hz, C_{5-ax}-H), 3.44 (1H, brs, $C_{4'}$-H), 3.59 (1H, brs, $C_{5'}$-H), 3.92 (1H, ddd, J = 2.0, 5.4, and 7.3 Hz, $C_{6'}$-H), 4.15 (1H, dd, J = 5.4 and 12.5 Hz, CO_2CH), 4.27 (1H, dd, J = 7.3 and 12.5 Hz, CO_2CH), 4.77 (1H, d, J = 6.3 Hz, $C_{2'-ax}$-H), 5.13 (1H, d, J = 6.3 Hz, $C_{2'-eq}$-H), 5.92 (1H, brs, NH); IR (film) 3340, 3220, 1730, 1680 cm^{-1}; MS m/z 444 (M^+H), 443 (M^+), 428 (M^+-Me), 386 (M^+-^{t}Bu), 342 (M^+-OCO^tBu).

DIBAL (0.91 ml, 1.0 M hexane solution, 0.91 mmol) was added to a solution of 14 (98 mg, 0.22 mmol) in CH_2Cl_2 (2.0 ml) cooled at -78 °C under an argon atmosphere. After stirring was continued for 1 h, the reaction was quenched by the addition of MeOH (0.37 ml). The mixture was warmed up to ambient temperature, diluted with 20% MeOH in AcOEt, and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue was chromatographed (SiO_2, 5% MeOH in $CHCl_3$) to afford pure 15 as a colorless solid (69 mg, 87%). Recrystallization from ether-$CHCl_3$ yielded an analytical sample of 15 as colorless crystals, mp 176-178 °C, $[\alpha]_D^{20}$ -10.4° (c 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 0.19 (3H, s, SiMe), 0.26 (3H, s, SiMe), 0.89 (9H, s, Si^tBu), 1.75 (1H, dd, J = 2.9 and 12.5 Hz, C_{3-ax}-H), 2.33 (1H, brd, J = 18.6 Hz, C_{5-eq}-H), 2.41 (1H, ddt, J = 3.6, 12.5, and 1.7 Hz, C_{3-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-ax}-H), 3.42 (1H, brs, $C_{4'}$-H), 3.59 (1H, brs, $C_{5'}$-H), 3.63 (1H, dd, J = 4.0 and 11.4 Hz, HOCH), 3.78 (1H, ddd, J = 1.9, 4.0, and 7.7 Hz, $C_{6'}$-H), 3.89 (1H, dd, J = 7.7 and 11.4 Hz, HOCH), 4.80 (1H, d, J = 6.3 Hz, $C_{2'-ax}$-H), 5.16 (1H, d, J = 6.3 Hz, $C_{2'-eq}$-H); IR (Nujol) 3450, 3310, 1665 cm^{-1}; MS m/z 359 (M^+), 344 (M^+-Me), 302 (M^+-^{t}Bu). *Anal.* Calcd for $C_{16}H_{29}O_6NSi$: C, 53.46; H, 8.13; N, 3.90. Found: C, 53.20; H, 8.18; N, 3.64.

(4'S,5'R,6'R)-4-5'-*tert*-Butyldimethylsiloxy-6'-3"-methyl-4"-methylene-5"-oxo-tetrahydrofuran-2"-yl-1',3'-dioxan-4'-yl-2,6-piperidinedione (16). Pyridine (1.6

g, 20 mmol) was added to a stirred suspension of anhydrous CrO_3 (0.75 g, 7.5 mmol) in CH_2Cl_2 (11 ml) at room temperature under an argon atmosphere. After stirring for 20 min, dry celite (1.5 g) and a solution of **15** (0.17 g, 0.47 mmol) in CH_2Cl_2 (3.4 ml) were added and stirring was further continued for 15 min. The mixture was diluted with ether, filtered through a pad of celite, and concentrated *in vacuo*. The residue was dissolved in AcOEt. The ethyl acetate solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **16** (*ca.* 95% pure by NMR) as a colorless foam (0.15 g, 84%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.10 (3H, s, SiMe), 0.21 (3H, s, SiMe), 0.86 (9H, s, Si^{t}Bu), 1.6-3.0 (5H, m, C_3-H_2, C_4-H, C_5-H_2), 3.51 (1H, brs, C_4'-H), 4.07 (1H, brs, C_5'-H), 4.17 (1H, d, J = 2 Hz, C_6'-H), 4.75 (1H, d, J = 6 Hz, $C_{2'-ax}$-H), 5.29 (1H, d, J = 6 Hz, $C_{2'-eq}$-H), 6.03 (1H, brs, NH), 9.59 (1H, s, COH); IR (Nujol) 3320, 1725, 1680 cm^{-1}. This compound (**16**) was unstable to chromatographic purification. Thus, it was directly used for the next step without further purification.

A mixture of **16** (0.15 g, 0.42 mmol), powdered Zn (0.27 g, 4.1 mmol), and **17** (0.13 g, 0.63 mmol)[23] in THF (6.0 ml) was heated at reflux for 6 min. After being cooled to ambient temperature, the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt and filtered through a pad of celite. The filtrate was washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the crude product yielded pure **18** (a 1:1.3:1.5 mixture of the three diastereomers by NMR) as a colorless caramel (0.13 g, 73%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.20, 0.24, 0.29 (total 6H, each s, $SiMe_2$), 0.90 (9H, s, Si^{t}Bu), 1.22, 1.32, 1.34 (total 3H, each d, J = 7 Hz, $C_{3''}$-Me), 1.6-3.4 (6H, m, C_3-H_2, C_4-H, C_5-H_2, $C_{3''}$-H), 3.4-3.9 (3H, m, C_4'-H, C_5'-H, C_6'-H), 4.2-4.7 (1H, m, $C_{2''}$-H), 4.80, 4.82 (total 1H, each d, J = 6 Hz, $C_{2'-ax}$-H), 5.16, 5.18, 5.25 (total 1H, each d, J = 6 Hz, $C_{2'-eq}$-H), 5.65 (1H, m, olefinic proton), 6.10 (1H, brs, NH), 6.32 (1H, m, olefinic proton); IR (film) 3210, 1770, 1675 cm^{-1}; MS m/z 439 (M^+), 382 (M^+-^{t}Bu); High-resolution MS 439.2012 (439.2026 calcd for $C_{21}H_{33}O_7NSi$).

(4'S,5'R,6'R)-4-6'-1",4"-Dihydroxy-2"-methyl-3"-methylene-butyryl-5'-*tert*-butyldimethylsiloxy-1',3'-dioxan-4'-yl-2,6-piperidinedione (19). DIBAL (0.64 ml, 1.0 M hexane solution, 0.64 mmol) was added to a solution of **18** (80 mg, 0.18 mmol) in CH_2Cl_2 (1.9 ml) cooled at -78 °C. After stirring for 1 h, the mixture was diluted with MeOH (1.9 ml), allowed to warm up to room temperature, and concentrated *in vacuo*. The residue was dissolved in MeOH (3.8 ml). A solution of $CeCl_3 \cdot 7H_2O$ (0.16 g, 0.43 mmol) in MeOH (0.30 ml) and a solution of $NaBH_4$ (17 mg, 0.45 mmol) in MeOH (0.5 ml) were successively added to the methanolic solution, and the mixture was stirred for 10 min. After addition of 5% aqueous NH_4Cl, the mixture was diluted with AcOEt, dried ($MgSO_4$), filtered through a pad of celite, and concentrated *in vacuo*. The crude product was separated by column chromatography (SiO_2, 10% MeOH in AcOEt) to afford pure **19** (a mixture of the three diastereomers by NMR) as a colorless caramel (59 mg, 73%). ^{1}H NMR (90 MHz, $CDCl_3$-D_2O) δ 0.20, 0.22. 0.27 (total 6H, each s, $SiMe_2$), 0.90 (9H, s, Si^{t}Bu), 1.07, 1.21, 1.23 (total 3H, each d, J = 7 Hz, $C_{2''}$-Me), 1.5-3.2 (6H, m, C_3-H_2, C_4-H, C_5-H_2, $C_{3''}$-H), 3.2-4.5 (6H, m, C_4'-H, C_5'-H, C_6'-H, $C_{1''}$-H, $C_{4''}$-H_2), 4.67, 4.78, 4.81 (total 1H, each d, J = 6 Hz, $C_{2'-ax}$-H), 4.9-5.4 (3H, m, $C_{2'-eq}$-H, olefinic protons); IR (film) 3350, 1660 cm^{-1}; MS m/z 443 (M^+), 386 (M^+-^{t}Bu); High-resolution MS 443.2314 (443.2339 calcd for $C_{21}H_{37}O_7NSi$).

(4'S,5'R,6'S,3"R)-(+)-4-5'-Hydroxy-6'-2"-hydroxy-3"-methyl-4"-methylene-tetrahydrofuran-2"-yl-1',3'-dioxan-4'-yl-2,6-piperidine-dione [(+)-Sesbanimide A] (1) and (4'S,5'R,6'S)-(-)-4-5'-Hydroxy-6'-2"-hydroxy-3"-methyl-4"-methylene-tetrahydrofuran-2"-yl-1',3'-dioxan-4'-yl-2,6-piperidinedione [(-)-Sesbanimide B] (2).

tert-Butyldiphenylsilyl chloride (95 mg, 0.35 mmol) was added to a stirred solution of **19** (94 mg, 0.21 mmol) and imidazole (53 mg, 78 mmol) in DMF (0.18 ml) at room temperature under an argon atmosphere. After being stirred for 40 min, the mixture was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, 50% AcOEt in hexane), afforded **20** (*ca.* 90% pure by NMR) as a colorless caramel (0.13 g, 90%). ^1H NMR (90 MHz, $CDCl_3$-D_2O) δ 0.17, 0.20, 0.24 (total 6H, each s, $SiMe_2$), 0.86, 0.88 (total 9H, each s, Si^tBu), 1.05 (9H, s, Si^tBu), 1.12, 1.17, 1.25 (total 3H, each d, J = 7 Hz, $C_{2''}$-Me), 1.6-3.0 (6H, m, C_3-H_2, C_4-H, C_5-H_2, $C_{2''}$-H), 3.0-5.4 (8H, m, $C_{4'}$-H, $C_{5'}$-H, $C_{6'}$-H, $C_{1''}$-H, $C_{4''}$-H_2, olefinic protons), 7.3-7.6 (6H, m, aromatic protons), 7.6-8.0 (4H, m, aromatic protons); IR (film) 3330, 1680 cm^{-1}.

Pyridine (1.3 g, 16 mmol) was added to a stirred suspension of anhydrous CrO_3 (0.59 g, 5.9 mmol) in CH_2Cl_2 (11 ml) at room temperature under an argon atmosphere. After stirring was continued for 20 min, dry celite (1.2 g) and a solution of **20** (0.13 g, 0.19 mmol) in CH_2Cl_2 (7.2 ml) were successively added to the reaction mixture. The mixture was stirred for 30 min, diluted with ether, filtered through a pad of celite, and concentrated *in vacuo*. The residue was dissolved in THF (4.0 ml) and Bu_4NF (0.40 ml, 1.0 m THF solution, 0.40 mmol) was added at room temperature under an argon atmosphere. After being stirred for 10 min, the mixture was diluted with AcOEt, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, 1% MeOH in AcOEt) of the crude product gave an almost 1:1 mixture of **1** and **2**, which was separated by PTLC (SiO_2, 10% MeOH in AcOEt) to yield pure **1** as a colorless solid (11 mg, 18%) and pure **2** (a 1:1.8 equilibrated mixture of the epimeric hemiacetals by NMR) as a colorless caramel (13 mg, 21%).

Sesbanimide A (1): Recrystallization of pure **1** from ether-CH_2Cl_2 gave colorless crystals, mp 156-157 °C [lit. mp 158-159 °C,[2b] 155-156 °C[5]], $[\alpha]_D^{20}$ +55.3 ° (c 0.17, $CHCl_3$) [lit. $[\alpha]_D^{20}$ +54.7° (c 0.17, $CHCl_3$)[5]]. ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.21 (3H, d, J = 6.8 Hz, $C_{3''}$-Me), 2.40 (1H, dd, J = 9.6 and 16.9 Hz, $C_{3\text{-}ax}$-H), 2.49 (1H, dd, J = 9.6 and 17.2 Hz, $C_{5\text{-}ax}$-H), 2.62 (1H, m, $C_{3''}$-H), 2.65 (1H, dtt, J = 8.7, 4.5, and 9.6 Hz, C_4-H), 2.78 (1H, ddd, J = 1.5, 4.5, and 16.9 Hz, $C_{3\text{-}eq}$-H), 2.92 (1H, ddd, J = 1.5, 4.5, and 17.2 Hz, $C_{5\text{-}eq}$-H), 3.36 (1H, dd, J = 1.2 and 8.7 Hz, $C_{4'}$-H), 3.60 (1H, d, J = 0.8 Hz, $C_{6'}$-H), 4.02 (1H, brs, $C_{5'}$-H), 4.49 (1H, 12.9 and 2.2 Hz, $C_{5''}$-H), 4.56 (1H, dq, J = 12.9 and 2.2 Hz, $C_{5''}$-H), 4.79 (1H, d, J = 6.2 Hz, $C_{2'\text{-}ax}$-H), 4.97 (1H, q, J = 2.2 Hz, olefinic proton), 5.03 (1H, dt, J = 3.0 and 2.2 Hz, olefinic proton), 5.24 (1H, d, J = 6.2 Hz, $C_{2'\text{-}eq}$-H); IR (Nujol) 3370, 3330, 3230, 1750, 1670 cm^{-1}; MS m/z 327 (M^+), 309 (M^+-H_2O). This sample showed no depression on mixed melting point measurement with authentic **1**, mmp 155-157 °C. The spectral (400 ^1H NMR, IR, MS) and chromatographic (TLC) behavior of this sample were identical with those of authentic **1**. The authentic sample of **1**, mp 157-158 °C, $[\alpha]_D^{20}$ +56.5° (c 0.17, $CHCl_3$), was prepared by recrystallization of natural **1**, provided by Dr. R.G. Powell (U.S. Department of Agriculture), from ether-CH_2Cl_2.

Sesbanimide B (2): $[\alpha]_D^{20}$ -22.4° (c 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.08 (1.08H, d, J = 7.3 Hz, $C_{3''}$-Me, minor epimer), 1.14 (1.92H, d, J = 6.8 Hz, $C_{3''}$-Me, major epimer), 2.37 (0.36H, dd, J = 10.0 and 16.9 Hz, $C_{3\text{-}ax}$-H, minor epimer), 2.43 (0.64H, dd, J = 9.9 and 16.8 Hz, $C_{3\text{-}ax}$-H, major epimer), 2.46 (0.36H, dd, J = 10.0 and 17.2 Hz, $C_{5\text{-}ax}$-H, minor epimer), 2.51 (0.64H, dd, J = 9.9 and 17.4 Hz, $C_{5\text{-}ax}$-H, major epimer), 2.61 (0.36H, dtt, J = 4.3, 8.0, and 10.0 Hz, C_4-H, minor epimer), 2.73 (0.64H, dtt, J = 4.5, 8.3, and 9.9 Hz, C_4-H, major epimer), 2.75 (0.36H, m, $C_{3''}$-H, minor epimer), 2.76 (0.36H, ddd, J = 1.6, 4.3, and

16.9 Hz, C_{3-eq}-H, minor epimer), 2.78 (0.64H, ddd, J = 1.6, 4.5, and 16.8 Hz, C_{3-eq}-H, major epimer), 2.91 (0.36H, ddd, J = 1.6, 4.3, and 17.2 Hz, C_{5-eq}-H, minor epimer), 2.95 (0.64H, ddd, J = 1.6, 4.5, and 17.4 Hz, C_{5-eq}-H, major epimer), 2.96 (0.64H, m, $C_{3''}$-H, major epimer), 3.34 (0.64H, dd, J = 1.2 and 8.3 Hz, $C_{4'}$-H, major epimer), 3.40 (0.36H, dd, J = 1.1 and 8.0 Hz, $C_{4'}$-H, minor epimer), 3.59 (0.36H, d, J = 1.0 Hz, $C_{6'}$-H, minor epimer), 3.61 (0.64H, d, J = 1.2 Hz, $C_{6'}$-H, major epimer), 3.96 (0.64H, brs, $C_{5'}$-H, major epimer), 4.08 (0.36H, brs, $C_{5'}$-H, minor epimer), 4.48 (0.36H, dq, J = 12.8 and 2.2 Hz, $C_{5''}$-H, minor epimer), 4.51 (0.64H, dq, J = 12.8 and 2.2 Hz, $C_{5''}$-H, major epimer), 4.56 (0.64H, dq, J = 12.8 and 2.2 Hz, $C_{5''}$-H, major epimer), 4.58 (0.36H, ddt, J = 1.2, 12.8, and 2.2 Hz, $C_{5''}$-H, minor epimer), 4.77 (0.36H, d, J = 6.2 Hz, $C_{2'-ax}$-H, minor epimer), 4.79 (0.64H, d, J = 6.2 Hz, $C_{2'-ax}$-H, major epimer), 4.98 (0.34H, q, J = 2.2 Hz, olefinic proton, minor epimer), 5.01 (0.64H, q, J = 2.2 Hz, olefinic proton, major epimer), 5.05 (0.34H, dt, J = 2.2 and 4.1 Hz, olefinic proton, minor epimer), 5.08 (0.64H, dt, J = 3.0 and 2.2 Hz, olefinic proton, major epimer), 5.19 (0.34H, d, J = 6.2 Hz, $C_{2'-eq}$-H, minor epimer), 5.22 (0.64H, d, J = 6.2 Hz, $C_{2'-eq}$-H, major epimer); IR (film) 3470, 3250, 1700 cm^{-1}; MS m/z 327 (M^+), 309 (M^+-H_2O). The 400 MHz ^1H NMR spectrum of this sample was identical with that of natural sesbanimide B (2) reported by Powell *et al.*[2b]

(4'S,5'R,6'S,3"R)-(-)-4-5'-Acetoxy-6'-4"-acetoxy-2"-methyl-3"-methylenebutyryl-1',3'-dioxan-4'-yl-2,6-piperidinedione (21).

a) Preparation from Synthetic 1. A solution of synthetic 1 (9.0 mg, 28 µmol) and Ac_2O (0.10 ml) in pyridine (0.20 ml) was stirred at room temperature for 12 h. The mixture was diluted with AcOEt, washed successively with saturated aqueous $CuSO_4$ and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by PTLC (SiO_2, 80% AcOEt in hexane) to give pure 21 as a colorless solid (6.0 mg, 53%). Recrystallization of 21 from ether afforded colorless crystals, mp 120-121 °C [lit. mp 128-129 °C[2b]], $[\alpha]_D^{20}$ -89.2° (c 0.13, $CHCl_3$) [lit. $[\alpha]_D^{20}$ -86° (c 0.38, $CHCl_3$)[1b]]. ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, J = 6.9 Hz, $C_{3''}$-Me), 2.09 (3H, s, OAc), 2.10 (3H, s, OAc), 2.29 (1H, dtt, J = 8.6, 4.6, and 9.3 Hz, C_4-H), 2.46 (1H, dd, J = 9.3 and 17.3 Hz, C_{3-ax}-H), 2.53 (1H, dd, J = 9.3 and 17.3 Hz, C_{5-ax}-H), 2.79 (1H, ddd, J = 1.3, 4.6, and 17.3 Hz, C_{3-eq}-H), 2.89 (1H, ddd, J = 1.3, 4.6, and 17.3 Hz, C_{5-eq}-H), 3.51 (1H, dd, J = 1.1 and 8.6 Hz, $C_{4'}$-H), 3.71 (1H, q, J = 6.9 Hz, $C_{2''}$-H), 4.31 (1H, d, J = 1.8 Hz, $C_{6'}$-H), 4.61 (2H, brs, $C_{4''}$-H_2), 4.81 (1H, d, J = 6.4 Hz, $C_{2'-ax}$-H), 4.96 (1H, brs, olefinic proton), 5.17 (1H, brs, olefinic proton), 5.28 (1H, d, J = 6.4 Hz, $C_{2'-eq}$-H), 5.43 (1H, brs, $C_{5'}$-H), 7.91 (1H, brs, NH); IR (Nujol) 3200, 3100, 1755, 1705 cm^{-1}; MS m/z 352 (M^+-OAc). This sample was identical with authentic 21 prepared from natural 1 [see b)], on the basis of spectral (400 MHz ^1H NMR, IR, and MS) and chromatographic (TLC) comparisons and mixed melting point measurement, mmp 121-122 °C.

b) Preparation of Authentic 21 from Natural 1. The same acetylation of natural 1 (11 mg, 34 µmol) as that described for synthetic 1 gave pure 21 as a colorless solid (6.0 mg, 43%) after purification by PTLC (SiO_2, 80% AcOEt in hexane). Recrystallization of this sample from ether afforded an authentic sample of 23 as colorless crystals, mp 121-122 °C, $[\alpha]_D^{20}$ -87.7° (c 0.13, $CHCl_3$).

(4'S,5'R,6'S,3"S)-(+)-4-5'-Acetoxy-6'-4"-acetoxy-2"-methyl-3"-methylenebutyryl-1',3'-dioxan-4'-yl-2,6-piperidinedione (22). The same acetylation of 2 (13 mg, 40 µmol) as that described for 1 followed by purification by PTLC (SiO_2, 80% AcOEt in hexane), yielded pure 22 as a colorless caramel (10 mg, 61%), $[\alpha]_D^{20}$ +55.6° (c 5.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 7.0 Hz, $C_{2''}$-Me), 2.08 (3H, s, OAc), 2.09 (3H, s, OAc), 2.37 (1H, dtt, J = 8.5, 4.4, and 9.3 Hz, C_4-H),

2.43 (1H, dd, J = 9.3 and 17.3 Hz, C_{3-ax}-H), 2.53 (1H, dd, J = 9.3 and 17.3 Hz, C_{5-ax}-H), 2.77 (1H, ddd, J = 1.4, 4.4, and 17.3 Hz, C_{3-eq}-H), 2.83 (1H, ddd, J = 1.4, 4.4, and 17.3 Hz, C_{5-eq}-H), 3.54 (1H, dd, J = 1.2 and 8.5 Hz, $C_{4'}$-H), 3.63 (1H, q, J = 7.0 Hz, $C_{2''}$-H), 4.42 (1H, d, J = 1.7 Hz, $C_{6'}$-H), 4.57 (1H, d, J = 13.6 Hz, $C_{4''}$-H), 4.62 (1H, d, J = 13.6 Hz, $C_{4''}$-H), 4.81 (1H, d, J = 6.4 Hz, $C_{2'-ax}$-H), 5.05 (1H, brs, olefinic proton), 5.24 (1H, brs, olefinic proton), 5.30 (1H, d, J = 6.4 Hz, $C_{2'-eq}$-H), 5.37 (1H, brs, $C_{5'}$-H), 7.88 (1H, brs, NH); IR (film) 3230, 1735, 1795 cm^{-1}; MS m/z 372 (M^+-OAc). The 400 MHz ^1H NMR spectrum of this sample was identical with that provided by Dr. R.G. Powell (U.S. Department of Agriculture).

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References and Notes

(1) This paper is dedicated to Professor E.J. Corey on the occasion of his 60th birthday.

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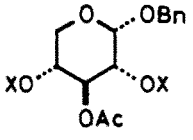
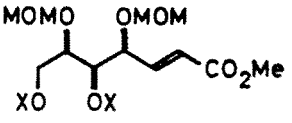
(12) Construction of the B-ring system from benzyl 3-*O*-acetyl-α-D-xylopyranoside (i) obtainable from D-xylose according to the known procedure[13,14] was first examined. Both direct methylene acetalization of i (CSA, $CH_2(OMe)_2$, reflux) and acidic treatment of the dimethoxymethyl ether (ii) of i (CSA, CH_2Cl_2, reflux) were found to afford no desired 1,3-dioxane derivatives. Accordingly, ii was converted into the acyclic α,β-unsaturated ester (iii) by succes-

sive reductive cleavage of the acetoxy group ($LiAlH_4$, ether, 0 °C, 10 min, 99%), hydrogenolysis of the benzyloxy group (H_2, EtOH-AcOH, rt, 12 h, 84%), and simultaneous pyranose ring opening and carbon chain elongation by Wittig reaction ($Ph_3P{=}CHCO_2Me$, PhMe, reflux, 1.5 h, 53%). The two hydroxyl groups of **iii** were protected as benzoate esters (**iv**) (PhCOCl, DMAP, Py, rt, 10 min, 67%). Attempted protection of **iii** by other protective groups such as benzyl group, which may be more stable than benzoyl group under acidic conditions, met failure due to lability of **iii** under the conditions for protection. All attempts to elaborate the 1,3-dioxane ring by treating **iv** with protic acids (CSA, CH_2Cl_2, reflux), Lewis acids ($BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C), or trimethylsilyl trifluoromethanesulfonate (CH_2Cl_2, 0 °C) were turned out to be fruitless and the preferential removal of the two benzoyl groups was always observed. These preliminary experiments disclosed that the C-3 and C-5 hydroxyl groups of D-xylose should be selectively protected at the early stage of the synthesis by the protective groups which may be stable during formation of the 1,3-dioxane ring.



X = H i
X = MOM ii



X = H iii
X = COPh iv

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(16) The acetalization proceeded only sluggishly when protic acids such as 10-camphorsulfonic acid (CH_2Cl_2, reflux) were employed in place of trimethylsilyl trifluoromethanesulfonate.
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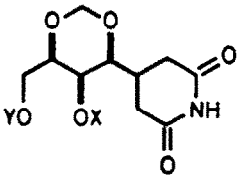
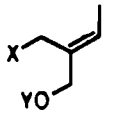
(18) Since the absolute configurations of **1** and **2** had not been determined at the outset of this work, the antipode of **12** (ent-**12**) was prepared from L-(-)-xylose according to the same synthetic route as that employed for preparation of **12**. Following data were collected for ent-**3**, ent-**4**, ent-**7**, ent-**8**, ent-**11**, and ent-**12**: ent-**3**, colorless caramel, $[\alpha]_D^{20}$ +19.8° (c 2.00, H_2O); ent-**4**, colorless caramel, $[\alpha]_D^{20}$ +50.4° (c 1.00, $CHCl_3$); ent-**7**, colorless crystals, mp 103-104 °C, $[\alpha]_D^{20}$ +33.6° (c 1.00, $CHCl_3$); ent-**8**, pale yellow crystals, mp 49-52 °C, $[\alpha]_D^{20}$ +9.4° (c 1.00, $CHCl_3$); ent-**11**, colorless crystals, mp 134-135 °C, $[\alpha]_D^{20}$ -53.2° (c 0.50, $CHCl_3$); ent-**12**, colorless crystals, mp 214-216 °C, $[\alpha]_D^{20}$ +5.6° (c 0.50, DMSO). The ^1H NMR spectra of these compounds belonging to ent-series were identical with those of their antipodes (the natural series) reported in the experimental part.
(19) Similarly, methoxymethylation or 2-(trimethylsilyl)ethoxymethylation of the trityl ether (**v**) produced from **12** by selective tritylation of the primary hydroxyl group, did not give the desired product and only *tert*-butyldimethylsilylation afforded the siloxytrityl ether (**vi**). However, reductive removal of the trityl group of **vi** accompanied simultaneous cleavage of the labile C-8 silyl group under hydrogenation conditions. Increased instability of the C-8 silyl group is probably due to unusual distortion of the glutarimide ring induced by this silyl group as described in the text.



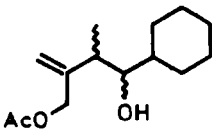
X = H, Y = CPh_3 v
X = Si^tBuMe_2, Y = CPh_3 vi

(20) Similar remote distortion by a bulky silyl group was also observed in the course of synthesis of the BC-ring systems of **1** and **2**.[10]
(21) Various types of addition reactions were attempted using cyclohexanecarbaldehyde (**vii**) as a model aldehyde. Thus, reactions of the bromide (**viii**) with **vii** in the presence of zinc metal, tin metal, or chromium(III) chloride,

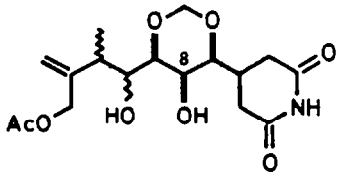
were found to produce no addition products. On the other hand, Lewis acid catalyzed addition of the allylstannane (ix) to vii proceeded smoothly in a regioselective manner to give the desired alcohol (xi), although the same reaction carried out using the allylsilane (x) in place of ix did not afford xi. However, addition reaction of ix to 16 accompanied desilylation, only giving the diol (xii) as the addition product. Lability of the *tert*-butyldimethylsilyl ether at the C-8 position may be accounted for by unusual distortion of the glutarimide ring described in the text.



X = Br, Y = Si^tBuPh_2 viii
X = Sn^nBu_3, Y = Ac ix
X = $SiMe_3$, Y = Ac x



xi



xii

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(25) All m.ps were determined with a Yamato melting point apparatus and are uncorrected. A Sibata GTO-250R apparatus was used for bulb-to-bulb distillation. 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. ^1H 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 downfield 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 peaks are indicated according to the numbering of IUPAC nomenclature to avoid confusion. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Unless otherwise noted, all reactions were performed using anhydrous solvents. Especially, tetrahydrofuran and ether freshly distilled from sodium 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), acetic anhydride (Ac_2O), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), diisobutylaluminum hydride (DIBAL), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate (AcOEt), methanol (MeOH), tetrabutylammonium bromide (Bu_4NBr), tetrabutylammonium fluoride (Bu_4NF), tetrahydrofuran (THF).

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