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Stereoelectronic and Steric Control in Chiral Cyclohexane Synthesis Toward (-)-Tetrodotoxin

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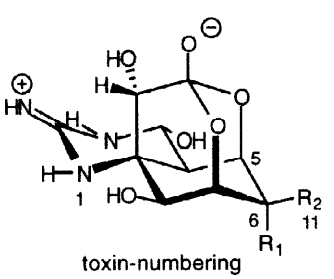
Abstract: The synthesis of important intermediates for tetrodotoxin has been explored. The chiral cyclohexane ring was constructed by electrocyclization from a triene precursor and by conversion to the highly oxygenated cyclohexane ring. In particular, the introduction of an α-hydroxy group at the 5 position (toxin-numbering) in tetrodotoxin was achieved by allylic oxidation with SeO_2.

Introduction

Tetrodotoxin[1-4] (**1**, TTX) is a highly potent neurotoxin found in the ovaries and livers of many species of *Tetraodontidae* sp. the puffer fish. A number of tetrodotoxin analogs have been found and isolated from puffers, newts, frogs and other organisms. Among them, such compounds as 6-epiTTX,[5] 11-deoxyTTX,[5] 11-oxoTTX[6] and chiriquitoxin[7] are analogs to TTX. These toxins are compact and highly functionalized molecules that bind selectively and with high affinity to voltage-dependent sodium channels on neuro cell membranes. The biological activity and unique architecture of TTX has made it a fascinating and challenging synthetic target. In spite of significant efforts,[8-15] only one total synthesis of TTX in racemic form has been accomplished that is the landmark 1972 goal of the Kishi-Goto group.[16,17] None of the papers have yet reported the synthesis of optically active TTX. We are exploring a synthetic route to TTX, and in this paper we describe some pertient developments.



Tetrodotoxin (**1**)	R_1= OH, R_2= CH_2OH
6-epiTTX[5]	R_1= CH_2OH, R_2= OH
11-deoxyTTX[5]	R_1= OH, R_2= CH_3
11-oxoTTX[6]	R_1= OH, R_2= CHO
Chiriquitoxin[7]	R_1= OH, R_2= $CH(OH)CH(NH_2)CO_2H$ (*R* *S*)

Figure 1

Retrosynthetic Analysis

Our synthetic efforts toward TTX have been based on Diels-Alder cycloaddition between a 1,3-butadiene derivative and bromo-levoglucosenone for the construction of the chiral cyclohexane ring.[18] The major disadvantage of the Diels-Alder route was difficulty of introduction of the hydroxy groups into the cyclohexane ring. Recently, we became interested in an alternative route to construct this cyclohexane ring; thus, key

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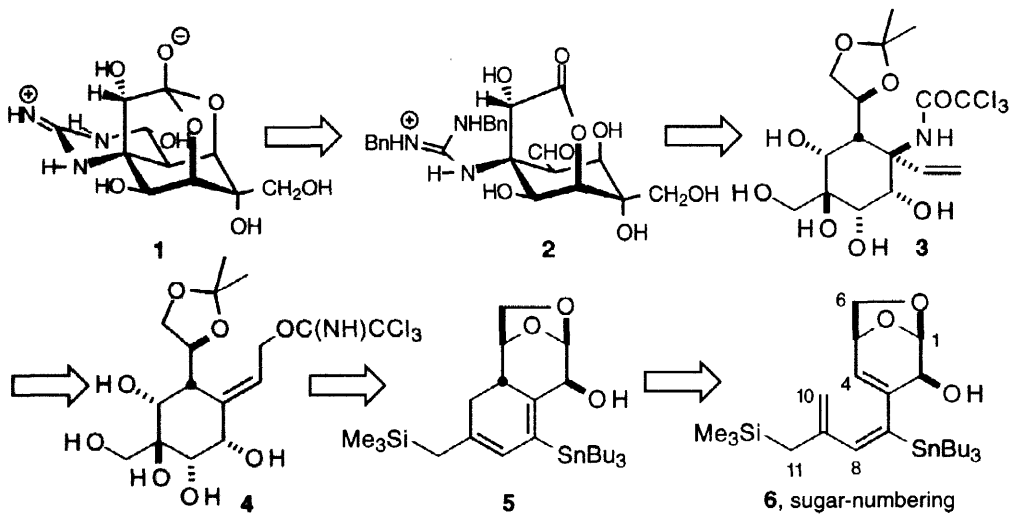
reaction for construction of the carbon framework is not a Diels-Alder cycloaddition reaction but an electrocyclic reaction.

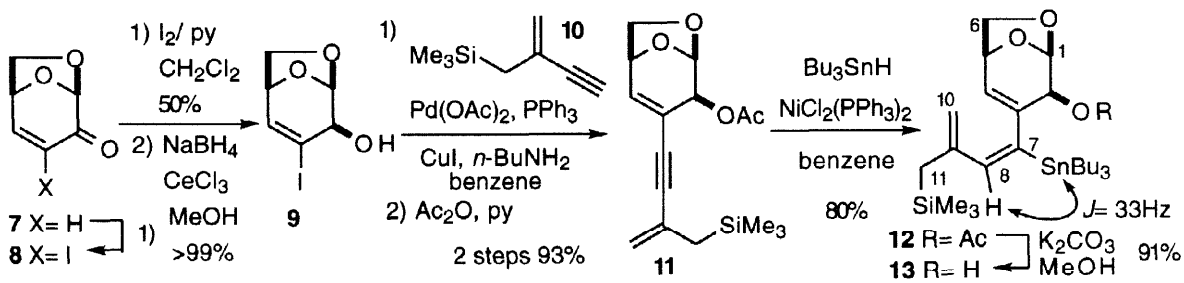
Our retrosynthetic analysis of TTX is shown in Scheme 1. The characteristic hemilactal in TTX is equivalent to the lactone in **2**. Cyclic guanidine is also equivalent to dibenzylguanidine and the aldehyde in **2**. The α-hydroxylactone in **2** is retrosynthesized to the terminal olefin in **3**.[19] The labile aldehyde in **2** is masked as acetonide in **3**. The dibenzylguanidine could be synthesized from the trichloroacetamide **3**, which was derived from a 3,3-sigmatropic rearrangement of the trichloroacetimidate **4** (so-called Overman rearrangement).[20,21] For this reason the C2-C3 double bond is indispensable and thus be well designed from the precursor **5**. The polyhydroxy allylic alcohol **4** would be functionalized from the cyclohexadiene **5**. The construction of chiral cyclohexane ring **5** is to be accomplished by electrocyclization[22] of the corresponding triene **6**.



Scheme 1. Retrosynthetic analysis

Construction of Cyclohexane Ring by Electrocyclic Reaction

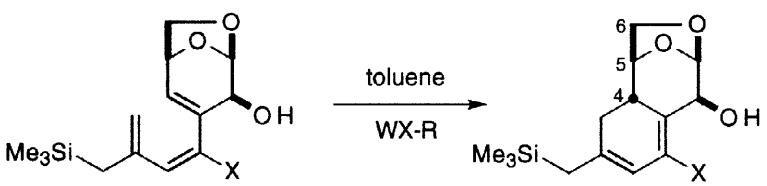
The precursor **13** for electrocyclic reaction was synthesized from levoglucosenone[23] **7** as shown in Scheme 2. The direct α-iodination of levoglucosenone **7** was achieved with a combination of iodine and pyridine.[24,25] Stereoselective reduction of iodo-levoglucosenone **8** using Luche's condition ($NaBH_4$-$CeCl_3$ in methanol)[26] gave iodo-levoglucosenol **9** in 89% yield. The vinyl iodide **9** and the acetylene **10** were subjected to Sonogashira coupling ($Pd(OAc)_2/PPh_3/CuI/n$-$BuNH_2$)[27] to provide the dienyne, which was acetylated to give **11** in 93% yield.



Scheme 2

cis-Hydrogenation of the triple bond in the dienynes **11** using Lindlar's catalyst failed to give a triene because of the competitive hydrogenation of the double bonds.[28] In order to suppress such side reactions, we examined hydrostannation of **11** under a variety of conditions. Hydrostannation of acetylene into alkenylstannane was of particular importance in synthesis, since the stannyl group of the product could be substrated to various atoms including Li and halides etc. Hydrostannation of **11** with tributyltin hydride was facilitated by nickel catalyst $NiCl_2(PPh_3)_2$[29-31] to provide the triene **12** in 80% yield as a single stereoisomer. The high regioselectively in hydrostannation of **12** was attributed to the coordinative ability of the acetyl group to the tin atom. In case of hydrostannation of deacetylated dienyne of **11**, the yield of triene was poor because of low coordinative ability of hydroxy group to the tin atom. The regiochemistry of the product was apparent from the ^{117}Sn-H coupling constant[32] in the ^{1}H-NMR spectra. Generally the proton-tin coupling constants of vinyltin compound were reported to be 30~80 Hz for *cis* and 95~120 Hz for *trans*. In case of **12** the coupling constant 33 Hz between Sn and H-8 indicated the *cis*-orientation. The NOESY showed two cross peaks between H-8 and H-10, H-8 and H-11. These results clearly showed the regio- and stereoselective addition of Sn-H to the internal acetylene as shown in Scheme 2.

After deacetylation of **12**, the triene **13a** (X= $SnBu_3$) was heated at reflux temperature in toluene to furnish the cyclization product **14** in 90% yield as a single isomer (Scheme 3). The stereochemistry of the product **14** was determined by the coupling constant between H-4 and H-5 (J = 0 Hz) and the NOESY spectrum in which a cross peak between H-4 and H-6 was observed. These results showed the stereochemistry of cyclization product as shown in Scheme 3. In our previous paper[22], **13b** (X= $SiEt_3$) gave cyclization product only 20% yield, even heated for longer than 3 hr. Difference between **13a** and **13b** was substituent group X, but reactivity changed drastically. For the successful cyclization of the triene **13a**, its conformation would be decisive so that two of the 1,6-ends of 1,3,5-hexatriene has to be close enough to overlap with their π-orbitals because of the intramolecular attractive interaction between the tin and oxygen atoms. On the other hands, allylic strain in **13b** prevented the favored conformation because of silyl group is repulsive to oxygen atoms, while compound **13c** (R= H) showed intermediate result (54%).



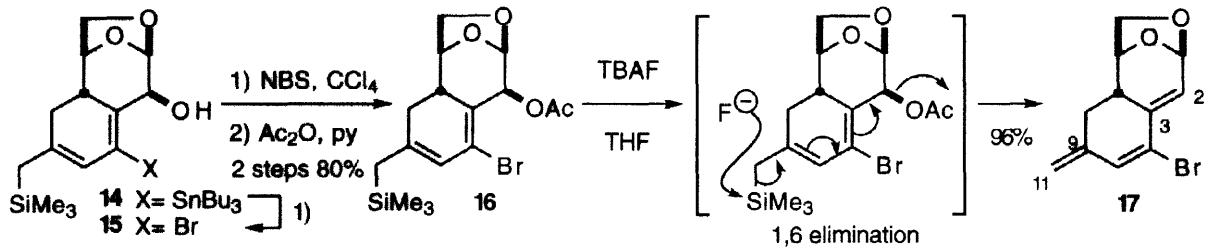
13a $SnBu_3$
13b $SiEt_3$
13c H

14a 90%
14b 20%
14c 54%

Scheme 3

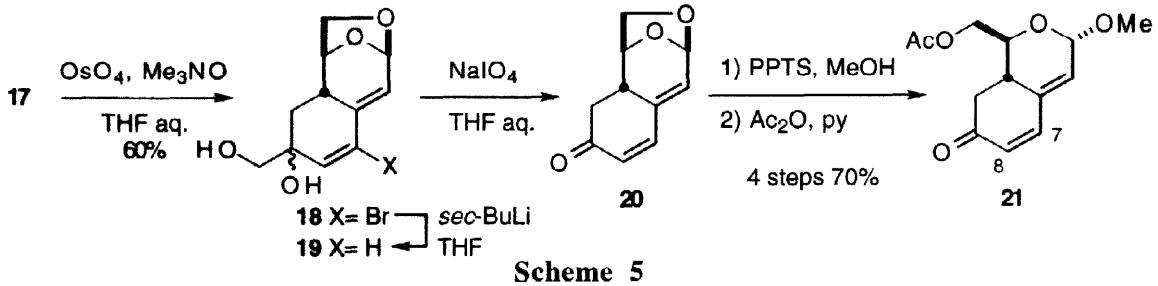
Functionalization of Cyclohexane Ring

The indispensable C2-C3 double bond for Overman rearrangement was constructed as shown in Scheme 4. We have carried out bromodestannylation of the vinyl tin **14** with *N*-bromosuccinimide to give the vinyl bromide **15**, which was transformed into the acetate **16**. Fluoride induced 1,6-elimination[33] of the diene **16** took place with TBAF in THF to give the desired triene **17** in good yield (Scheme 4).



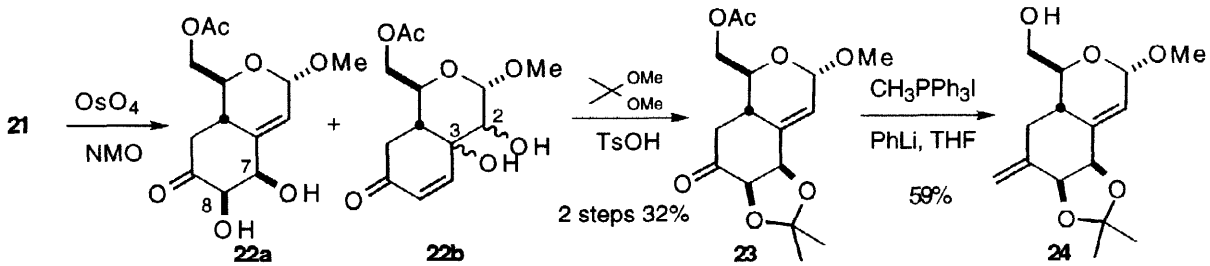
Scheme 4

Osmylation of the terminal double bond in **17** having the conformationally rigid cyclohexene backbone was, in fact, accomplished in high selectivity with a catalytic quantity of OsO_4 and trimethylamine-*N*-oxide[34] in aq THF to give **18**. The diastereomixture (4:1) **18** was not separated but directly subjected to the following reactions. Treatment of **18** with *sec*-BuLi at -78°C was followed by quenching with methanol to afford the desired diol **19**. The glycol in **19** was then cleaved with $NaIO_4$ in aqueous THF to give the dienone **20**. The 1,6-anhydro bridge of **20** was cleaved with CSA in methanol, and the resulting alcohol was protected as the acetate **21**. Thus, the acetate **21** was obtained from **18** in 4 steps with 70% overall yield (Scheme 5).



Scheme 5

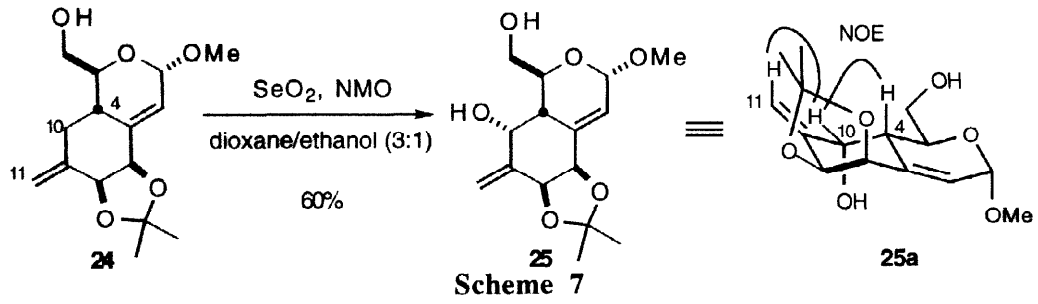
Selective hydroxylation of the α, β-enone in **21** was accomplished with a catalytic quantity of OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO)[35] in aq acetone to give the mixture **22a** and **22b** in a ratio of 6:1 in favor of **22a**. The desired diol **22a** was protected as acetonide **23** with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid in CH_2Cl_2 (Scheme 6). When the acetonide **23** was treated with Wittig reagent, exocyclic olefin **24** was obtained without the acetyl protection in 59% yield.



Scheme 6

Introduction of the hydroxy group at the C-10 position was very critical to achieve in alpha orientation as the same as that of TTX. We chose the allylic oxidation with SeO_2 for direct introduction of the hydroxy group. The cyclohexane ring of **24** would have two possible conformers **24a** and **24b**, the cyclohexane ring of the former being a chair conformer and the latter being a boat one, respectively (Figure 2). The molecular mechanics calculations suggested **24a** being 4.3 kcal/mol lower in energy than **24b** (MacroModel version 6.0

package with MM2*).[36] The coupling constant 9.9 Hz between H-4 and axial H-10 indicated that **24a** was the predominant conformer. In the usual stereoelectronic effect, opposite stereoisomer shoud be derived from conformer **24b**, but in above allylic oxidation no reaction took place at the beta face (including the beta-allylic H) because of the steric hindrance as well as the low population. Consequently the initial ene-reaction would occurred at α face of **24a** so that the allylic C-H σ-orbital can best overlap with π-orbital of the double bond during the initial ene-reaction with SeO_2[37] and the 2,3-sigmatropic rearrangement of the resulting allylic selenous acid[38,39] took place from α face having no large substituents to give the α-hydroxy group at C-10. The reaction of **24** with SeO_2 and NMO gave α-alcohol **25** as a single stereoisomer in fair yield (60%) (Scheme 7). The configuration of C-10 in **25a** was determined by the observation of NOEs between H-4 and H-10, H-10 and H-11. In this reaction, both NMO as a reoxidant[40,41] and ethanol as cosolvent were indispensable.



Scheme 7

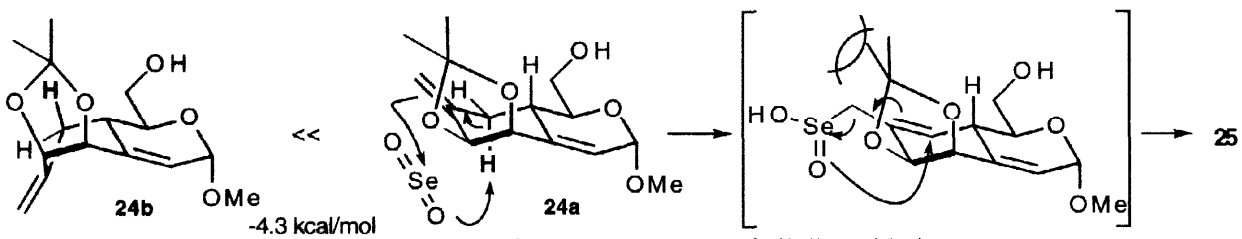
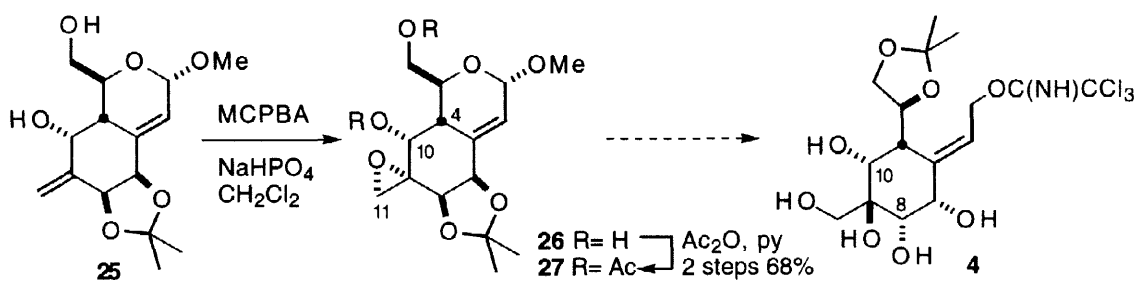


Figure 2. Reaction course of allylic oxidation

Epoxidation of the exo-olefin **25** with MCPBA gave the epoxide **26** as a single isomer, which was transformed into the acetate **27** (Scheme 8). The stereochemistry of the epoxide **27** was determined by the observation of NOEs between H-4 and H-11, H-4 and H-10. The cyclohexane ring of the product **27** was fully oxygenated for the TTX synthesis even though configurations of hydroxy groups at C-7, 8, 9 positions were necessary to invert.



Scheme 8

In summary, above new electrocyclic strategy toward TTX has shown promising way to construct the chiral cyclohexane as the carbon backbone of the target molecule. Further oxidation at each necessary carbon was achieved with high stereoselectivity. Further studies are now in progress.

Experimental

General. Melting points were determined on a Yanaco MP-S3 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 or a JEOL EX-270 instrument. Optical rotations were measured with an automatic digital polarimeter at 589 nm using a JASCO DIP-370. IR spectra were recorded on a JASCO FT/IR-8300 spectrophotometer. Elemental analyses were performed in Microanalytical Laboratory of this department.

Preparation of iodolevoglucosenoe 8

Iodine (20.0 g, 0.159 mol) dissolved in pyridine/CH_2Cl_2 (4 ml/70 ml) was added dropwise to a solution of levoglucosenone **7** (10.0 g, 0.079 mol) in CH_2Cl_2 (30 ml) at 0°C under N_2. The mixture was stirred for 24 h during which time the temperature was allowed to warm to room temperature. The mixture was diluted with ether and washed successively with 1*N* HCl (×3), sat. $Na_2S_2O_3$ (×3) and dried over anhyd. Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (ether/hexane=2/1) to give iodoenone **8** as a colorless solid:10.0 g, 50% yield. mp 85-90°C. $[\alpha]^{27}_D$ -319 (*c* 0.293, $CHCl_3$). IR (film) 1713 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, d, *J*= 6.9 Hz, H-6), 3.86 (1H, dd, *J*= 6.9, 4.9 Hz, H-6), 4.93 (1H, t, *J*= 4.9 Hz, H-5), 5.56 (1H, s, H-1), 7.96 (1H, d, *J*= 4.9 Hz, H-4). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 66.5, 74.2, 100.9, 112.2, 155.7, 183.2. Anal. Calcd for $C_6H_5IO_3$: C, 28.60; H, 2.00. Found: C, 28.60; H, 1.99.

Preparation of iodolevoglucosenol 9

Iodoenone **8** (27.0 g, 0.107 mol) was dissolved in methanol (100 ml) at 0°C. To this solution was added $CeCl_3 \cdot 7H_2O$ (48.0 g, 0.128 mol), followed by $NaBH_4$ (4.80 g, 0.128 mol). After stirring at 0 °C for 20 min, the reaction mixture was quenched by 1*N* HCl aqueous solution until the forming ceased, the mixture was diluted with ether and washed 1*N* HCl aqueous solution and dried over anhyd. Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (ether/hexane=2/1) to give iodolevoglucosenol **9** as a colorless solid: 27.0 g, >99% yield. mp 80-85°C. $[\alpha]^{27}_D$ -56.7 (*c* 0.224, $CHCl_3$). IR (film) 3553 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ 2.40 (1H, d, *J*= 11.5 Hz, OH), 3.69 (1H, dd, *J*= 6.8, 4.5 Hz, H-6), 3.86 (1H, d, *J*= 6.8 Hz, H-6), 4.22 (1H, dd, *J*= 11.5, 2.8 Hz, H-2), 4.53 (1H, t, *J*= 4.5 Hz, H-5), 5.60 (1H, d, *J*= 2.8 Hz, H-1), 6.82 (1H, d, *J*= 4.5 Hz, H-4). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 70.4, 73.5, 74.1, 100.6, 103.4, 140.4. Anal. Calcd for $C_6H_7IO_3$: C, 28.37; H, 2.78. Found: C, 28.18; H, 2.70.

Preparation of (1R, 2S, 5S)-3-(4'-trimethylsilyl-3'-methylenebut-1'-ynyl)-7,8-dioxabicyclo[3.2.1]oct-3-en-2-yl acetate 11

To a solution of $Pd(OAc)_2$ (1.4 g, 6.5 mmol), PPh_3 (3.6 g, 13 mmol) and CuI (2.4 g, 13 mmol) in benzene (300 ml) in a three-necked flask fitted with magnetic stirrer, septum caps was added iodolevoglucosenol **9** (33 g, 0.13 mol). The resulting solution was stirred at room temperature for 10 min. Acetylene **10** (35 g, 0.26 mol) was added, followed by *n*-butylamine (26 ml, 0.26 mol) and the reaction mixture was stirred for 5 h at room temperature under N_2. The mixture was diluted with ether and washed with aqueous NH_4Cl (×3) and dried over anhyd. Na_2SO_4. After filtration and concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (200 ml) at room temperature under N_2. To this solution were added pyridine (20 ml), Ac_2O (30 ml) and a catalytic amount of DMAP (25 mg). After stirring for 2 h, the reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column

chromatography (ether/hexane=1/1) to give the acetate **11** (37 g, 93% 2 steps) as a yellow oil. $[\alpha]^{24}_D$ 28.6 (*c* 1.38, $CHCl_3$). IR (film) 2957, 2931, 2893, 2858, 2200, 1746, 1464, 1372 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.60 (2H, s, H-11×2), 2.18 (3H, s, Ac), 3.79 (1H, dd, *J*= 7.0, 4.5 Hz, H-6), 3.99 (1H, d, *J*= 7.0 Hz, H-6), 4.73 (1H, dd, *J*= 4.9, 4.5 Hz, H-5), 5.03 (1H, d, *J*= 2.0 Hz, H-10), 5.16 (1H, d, *J*= 2.0 Hz, H-10), 5.54 (1H, m, H-2), 5.64 (1H, d, *J*= 2.5 Hz, H-1), 6.39 (1H, dd, *J*= 4.9, 1.4 Hz, H-4). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 1.90, 20.8, 27.7, 71.2, 71.4, 71.6, 83.6, 94.3, 98.4, 120.0, 120.3, 128.3, 136.2, 170.6. Anal. Calcd for $C_{16}H_{22}O_4Si$: C, 62.71; H, 7.24. Found: C, 62.71; H, 7.23.

Preparation of (1Z)-(1S, 2R, 5S)-3-(1'-tributylstanyl-4'-trimethylsilyl-3'-methylenebut-1'-enyl)-7,8-dioxabicyclo[3.2.1]oct-3-en-2-yl acetate 12

The dienyne **11** (13 g, 63 mmol) and $NiCl_2(PPh_3)_2$ (1.4 g, 2.5 mmol) were dissolved in benzene (200 ml) at room temperature under N_2. To this solution was added *n*-Bu_3SnH (23 ml, 0.126 mol). After stirring for 17 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (from hexane to ether/hexane=1/5) to give the triene **12** (23 g, 80%) as a yellow oil. $[\alpha]^{25}_D$ 29 (*c* 0.065, $CHCl_3$). IR (film) 2958, 2927, 2873, 2855, 1735, 1247 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.02 (9H, s, $SiMe_3$), 0.86-1.53 (27H, m, $SnBu_3$), 1.66 (2H, AB-q, *J*= 13.0 Hz, H-11×2), 2.04 (3H, s, Ac), 3.77 (1H, dd, *J*= 6.1, 4.0 Hz, H-6), 3.91 (1H, d, *J*= 6.1 Hz, H-6), 4.67 (1H, t, *J*= 4.0 Hz, H-5), 4.73 (1H, d, *J*= 1.0 Hz, H-10), 5.10 (1H, d, *J*= 1.0 Hz, H-10), 5.60-5.65 (2H, overlapped, H-4 & H-2), 5.70 (1H, d, *J*= 2.5 Hz, H-1), 5.96 (1H, t, J_{Sn-H}= 33 Hz, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 1.60, 10.3, 13.6, 20.9, 27.2, 27.3, 28.9, 70.9, 71.5, 72.8, 98.6, 112.6, 123.2, 140.0, 142.8, 143.3, 143.4, 170.7. Anal. Calcd for $C_{28}H_{50}O_4SiSn$: C, 56.29; H, 8.43. Found: C, 56.36; H, 8.66.

Preparation of (1Z)-(1S, 2R, 5S)-3-(1'-tributylstanyl-4'-trimethylsilyl-3'-methylenebut-1'-enyl)-7,8-dioxabicyclo[3.2.1]oct-3-en-2-ol 13

A solution of acetate **12** (26 g, 43 mmol) was dissolved in methanol (100 ml) at room temperature. To this solution was added K_2CO_3 (5.9 g, 43 mmol) and stirred for 3 h. The reaction mixture was diluted with ether and washed with water and dried over anhyd. Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (ether/hexane=1/5) to give alcohol **13** (22 g, 91%) as a colorless oil. $[\alpha]^{25}_D$ 28 (*c* 0.065, $CHCl_3$). IR (film) 2958, 2927, 852, 669 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.02 (9H, s, $SiMe_3$), 0.80-1.50 (27H, m, $SnBu_3$), 1.65 (2H, s, H-11×2), 2.02 (1H, d, *J*= 11.5 Hz, OH), 3.76 (1H, dd, *J*= 6.8, 4.3 Hz, H-6), 3.84 (1H, d, *J*= 6.8 Hz, H-6), 4.38 (1H, dd, *J*= 11.5, 3.1 Hz, H-2), 4.67 (1H, dd, *J*= 4.6, 4.3 Hz, H-5), 4.71 (1H, m, H-10), 4.96 (1H, m, H-10), 5.53 (1H, d, *J*= 3.1 Hz, H-1), 5.55 (1H, d, *J*= 4.6 Hz, H-4), 6.01 (1H, t, J_{Sn-H}= 34 Hz, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 1.52, 10.3, 13.6, 27.3, 27.7, 28.9, 70.6, 70.7, 71.9, 101.0, 112.0, 121.9, 142.7, 143.6, 143.9, 144.4.

Preparation of (1S, 2R, 8S, 9R)-6-bromo-4-(trimethylsilylmethyl)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-4,6-dien-8-ol 15

A solution of the triene **13** (25 g, 45 mmol) in dry toluene (100 ml) containing 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) [WX-R] (20 mg) was heated under reflux for 4 h. The solvent was removed under reduced pressure and column chromatography (ether/hexane=1/4) of the residue gave cyclohexadiene **14** 22.5 g as yellow oil. Stannylalkene **14** (22.5 g, 41 mmol) was dissolved in CCl_4 (100 ml) and treated with *N*-bromosuccinimide (7.2 g, 41 mmol, recrystallized from water). After 3 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (ether/hexane=2/1), affording 11.3 g (2 steps, 80%) of vinylbromide **15** as yellow oil. $[\alpha]^{25}_D$ -80.0 (*c* 0.100, $CHCl_3$). IR (film) 2958, 2927 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (9H, s, $SiMe_3$), 1.64 (2H, AB-q, *J*= 13.0 Hz, H-11×2),

1.85 (1H, dd, *J*= 15.7, 6.0 Hz, H-10), 2.45 (1H, dd, *J*= 16.0, 15.7 Hz, H-10), 2.64 (1H, dd, *J*= 16.0, 6.0 Hz, H-4), 2.64 (1H, d, *J*= 8.8 Hz, OH), 5.63 (1H, d, *J*= 2.5 Hz, H-8), 3.75 (1H, d, *J*= 7.5 Hz, H-6), 3.84 (1H, dd, *J*= 7.3, 5.0 Hz, H-6), 4.24 (1H, d, *J*= 5.0 Hz, H-5), 4.47 (1H, dd, *J*= 8.8, 5.0 Hz, H-2), 5.54 (1H, d, *J*= 5.0 Hz, H-1). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 1.60, 27.9, 36.3, 43.3, 69.4, 70.5, 75.8, 98.6, 122.4, 123.3, 124.4, 142.4. Anal. Calcd for $C_{14}H_{21}BrO_3Si$: C, 48.70; H, 6.13. Found: C, 48.70; H, 6.10.

Preparation of (1S, 2R, 8S, 9R)-6-bromo-4-(trimethylsilylmethyl)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-4,6-dien-8-yl acetate ***16***

A solution of **15** (5.2 g, 15 mmol) in pyridine (20 ml) was treated with Ac_2O and stirred at room temperature for 2 h. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was sufficiently pure to be used directly for the next step. Obtained the acetate **16** (5.8 g, >99%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (9H, s, $SiMe_3$), 1.61 (2H, AB-q, *J*= 13.0 Hz, H-11×2), 1.85 (1H, dd, *J*= 15.0, 6.0 Hz, H-10), 2.05 (3H, s, Ac), 2.46 (1H, br-t, *J*= 15.0 Hz, H-10), 2.64 (1H, dd, *J*= 15.0, 6.0 Hz, H-4), 3.66 (1H, dd, *J*= 7.5, 1.1 Hz, H-6), 3.83 (1H, dd, *J*= 7.5, 5.5 Hz, H-6), 4.19 (1H, dd, *J*= 5.5, 1.1 Hz, H-5), 5.36 (1H, dd, *J*= 5.0, 1.5 Hz, H-2), 5.59 (1H, s, H-8), 5.69 (1H, d, *J*= 5.0 Hz, H-1). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 1.63, 20.4, 28.1, 36.2, 44.0, 70.1, 71.9, 74.9, 96.6, 119.9, 122.2, 124.4, 143.3, 170.5.

Preparation of (1R, 2S, 9R)-6-bromo-4-methylene-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-5,7(8)-dien ***17***

To a solution of the acetyl derivative **16** (5.8 g, 15 mmol) in dry THF (100 ml) at room temperature, TBAF (15 ml of a ca. 1.0 M solution in THF) was added in small portions. After 10 min, the mixture was diluted with ether and washed with sat. NH_4Cl aqueous solution (×3). The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude resulted sufficiently pure to be used directly for the next step. Obtained the triene **17** (5.5 g, 96%) as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.26 (1H, dd, *J*= 14.0, 4.0 Hz, H-10), 2.53 (1H, dd, *J*= 14.0, 4.0 Hz, H-4), 2.67 (1H, br-t, *J*= 14.0 Hz, H-10), 3.69 (1H, dd, *J*= 7.0, 1.6 Hz, H-6), 3.95 (1H, dd, *J*= 7.0, 5.8 Hz, H-6), 4.45 (1H, dd, *J*= 5.8, 1.6 Hz, H-5), 4.97 (2H, br-d, *J*= 6.0 Hz, H-11), 5.64 (1H, d, *J*= 3.9 Hz, H-1), 6.24 (1H, dd, *J*= 3.9, 1.6 Hz, H-2), 6.55 (1H, s, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 34.2, 44.1, 69.4, 74.5, 95.7, 114.9, 122.4, 126.9, 133.6, 134.6, 141.7.

Preparation of (1S, 2R, 9R)-6-bromo-4-(hydroxymethyl)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-5,7(8)-dien-4-ol ***18***

A solution of **17** (4.6 g, 18 mmol) and $Me_3NO{\cdot}2H_2O$ (4.0 g, 36 mmol) in 36 ml of THF and 4 ml of H_2O at room temperature was treated with OsO_4 (4 wt % in H_2O, 5 ml). After 12 h, the mixture was treated with sat. $Na_2S_2O_3$ aqueous solution and stirred for 30 min. The aqueous layer was extracted with AcOEt (×8), and the combined extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (AcOEt), affording 3.1 g (60%) of diastereomixture **18** as form. $[\alpha]^{26}_D$ 15.2 (*c* 0.209, $CHCl_3$). IR (film) 3424 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.75 (1H, br-t, *J*= 14.0 Hz, H-10), 1.88 (1H, dd, *J*= 14.0, 4.0 Hz, H-10), 2.51 (1H, dd, *J*= 14.0, 4.0 Hz, H-4), 3.58-3.40 (2H, m, H-11×2), 3.71 (1H, dd, *J*= 6.0, 1.3 Hz, H-6), 3.94 (1H, dd, *J*= 7.0, 6.0 Hz, H-6), 4.44 (1H, dd, *J*= 6.0, 1.3 Hz, H-5), 5.62 (1H, d, *J*= 4.0 Hz, H-1), 6.19 (1H, s, H-8), 6.28 (1H, dd, *J*= 4.0, 1.8 Hz, H-2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.5, 40.4, 69.5, 69.2, 72.6, 74.6, 95.4, 125.0, 128.3, 131.6, 134.8. Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53. Found: C, 45.88; H, 4.54.

Preparation of (1S, 2R, 9R)-4-(hydroxymethyl)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-5,7(8)-dien-4-ol ***19***

To a solution of vinylbromide **18** (297 mg, 1.03 mmol) in dry THF (20 ml) under N_2 at -78 °C, 5 eq. of *sec*-butyllithium (5 ml of a 1.08 M solution in cyclohexane) was added slowly and the solution was stirred for 5 min, the mixture was quenched by MeOH and then warmed to room temperature. To this mixture were added sat. NH_4Cl aqueous solution and the aqueous layer was extracted with AcOEt (×10). The extracts were dried over anhyd. Na_2SO_4 and after evaporation of the solvent, the crude resulted sufficiently pure to be used directly for the next step. Obtained 200 mg of crude product **19**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.78 (1H, br-t, *J*= 13.0 Hz, H-10), 1.96 (1H, dd, *J*= 13.0, 1.5 Hz, H-10), 2.06 (1H, br, OH), 2.27 (1H, br, OH), 2.43 (1H, dd, *J*= 13.0 Hz, H-4), 3.52 (2H, AB-q, H-11×2), 3.76 (1H, dd, *J*= 6.8, 1.8 Hz, H-6), 3.97 (1H, dd, *J*= 6.8, 5.7 Hz, H-6), 4.45 (1H, dd, *J*= 5.7, 1.8 Hz, H-5), 5.57 (1H, d, *J*= 4.0 Hz, H-1), 5.77 (1H, d, *J*= 9.5 Hz, H-7), 5.93 (1H, d, *J*= 4.0 Hz, H-2), 6.26 (1H, d, *J*= 9.5 Hz, H-8).
Elemental analyses was assigned by carbonated compound of **19**. $[\alpha]^{27}_D$ -169 (*c* 0.293, $CHCl_3$). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.94; H, 5.39.

Preparation of (1S, 2R, 9R)-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodeca-5,7(8)-dien-4-one ***20***

Diol **19** (200 mg, 0.961 mmol) was dissolved in 3 ml of THF/H_2O=3/1 solution and treated with $NaIO_4$ (334 mg, 1.44 mmol) in one portion at room temperature. After 30 min, the colorless solid was precipitated. Water was added to the mixture and diluted with ether. The organic layer was separated and water layer was extracted with ether. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (ether/hexane=2/1) to give the α, β-enone **20** 166 mg (97%). $[\alpha]^{27}_D$ -67 (*c* 0.090, $CHCl_3$). IR (film) 1672 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.60-2.84 (3H, overlapped, H-4, H-10×2), 3.79 (1H, dd, *J*= 7.1, 1.8 Hz, H-6), 4.00 (1H, dd, *J*= 7.1, 5.7 Hz, H-6), 4.44 (1H, dd, *J*= 5.7, 1.8 Hz, H-5), 5.64 (1H, d, *J*= 3.7 Hz, H-1), 5.94 (1H, d, *J*= 9.6 Hz, H-7), 6.26 (1H, br-d, *J*= 3.7 Hz, H-2), 7.11 (1H, d, *J*= 9.6 Hz, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 42.1, 44.5, 69.8, 74.0, 95.2, 128.5, 130.3, 133.5, 145.8, 197.3. Anal Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.26; H, 5.94.

Preparation of (1S, 3R)-1-(acetoxymethyl)-3-methoxy-8,8a-dihydroisochroman-7-one ***21***

To a solution of enone **20** (166 mg, 0.932 mmol) in 3 ml of methanol was added 10 mg of CSA at room temperature and was stirred for 20 min. The acid was neutralized with pyridine, the solution was evaporated to dryness. The crude alcohol in pyridine (3 ml) was treated with Ac_2O (1 ml) and stirred at room temperature for 1 h. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column chromatography (ether) to give the acetate **21** (164 mg, 4 steps 70 % from **18**) as a yellow oil. $[\alpha]^{26}_D$ -79.3 (*c* 3.748, $CHCl_3$). IR (film) 1735, 1671 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.11 (3H, s, Ac), 2.17 (1H, dd, *J*= 15.0, 13.5 Hz, H-10), 2.62 (1H, dd, *J*= 15.0, 5.4 Hz, H-10), 2.82 (1H, br, H-4), 3.46 (3H, s, OMe), 3.96 (1H, m, H-5), 4.27 (2H, m, H-6), 5.11 (1H, br-d, *J*= 2.8 Hz, H-1), 6.07 (1H, d, *J*= 9.6 Hz, H-7), 6.08 (1H, overlapped, H-2), 7.07 (1H, d, *J*= 9.6 Hz, H-8). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.5, 33.0, 38.5, 55.2, 63.3, 69.2, 95.1, 128.9, 135.1, 144.6, 170.4, 196.6. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.89; H, 6.58.

Preparation of (1S, 3R, 5R, 6S)-1-(acetoxymethyl)-3-methoxy-5,6,8,8a-tetrahydroisochroman-7-one-5,6-acetonide ***23***

The enone **21** (694 mg, 2.75 mmol) was dissolved in 10 ml of acetone/water=9/1 solution at room temperature under N_2. To this solution was added NMO (1.60 g, 13.8 mmol) and 4 mol% solution of OsO_4 (0.5 ml, in H_2O solution). After stirring for 8 h, the reaction mixture was diluted with AcOEt and $Na_2S_2O_3$ solution was added. After separation of organic layer, water layer was extracted by AcOEt (×10). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The crude mixture was to

be used directly for the next step. ^{1}H-NMR spectrum of the crude reaction product showed a **22a** and **22b** ratio of 6:1.

To a solution of crude mixture in 2 ml of acetone was added 1 ml of 2,2-dimethoxypropane and 10 mg of $TsOH{\cdot}H_2O$ at room temperature for 3 h. The acid was neutralized with pyridine, the solution was evaporated to dryness. Purification of column chromatography (ether/hexane=2/1) gave the acetonide **23** (286.8 mg, 32% 2 steps) as colorless powder. $[\alpha]^{26}_D$ 26 (*c* 0.064, $CHCl_3$). IR (film) 1738 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, Me), 1.49 (3H, s, Me), 2.08 (3H, s, Ac), 2.16 (1H, br-t, *J*= 12.7 Hz, H-10), 2.61 (1H, dd, *J*= 12.7, 4.5 Hz, H-10), 2.77 (1H, br, H-4), 3.50 (3H, s, OMe), 3.86 (1H, m, H-5), 4.15 (1H, dd, *J*= 11.9, 5.5 Hz H-6), 4.29 (1H, dd, *J*= 11.9, 2.5 Hz, H-6), 4.41 (1H, d, *J*= 5.4 Hz, H-7), 4.78 (1H, d, *J*= 5.4 Hz, H-8), 4.99 (1H, d, *J*= 2.7 Hz, H-1), 6.14 (1H, d, *J*= 2.7 Hz, H-2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.7, 26.1, 27.0, 33.5, 40.6, 55.5, 63.7, 69.6, 79.2, 80.9, 94.9, 110.7, 129.2, 134.4, 170.8, 205.2. Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.75; H, 6.96.

Preparation of (1S, 3R, 5R, 6S)-1-(hydroxymethyl)-3-methoxy-7-methylene-5,6,8,8a-tetrahydroisochroman-5,6-acetonide ***24***

Phenyllithium (2.4 ml, 1.08 M) was added dropwise at room temperature to a suspension of methyltriphenylphosphonium iodide (1.07 g, 2.65 mmol) in THF. The resultant bright orange solution was stirred at room temperature for 1.5 h. The ylide solution was then cooled to 0°C, and a solution of ketone **23** (287 mg, 0.885 mmol) in THF was added slowly by syringe. After stirring for additional 30 min at room temperature, the reaction mixture was quenched with CH_3OH, diluted with ether. The mixture was washed with aqueous NH_4Cl, dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography to give the olefin **24** (147.3 mg, 59%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, Me), 1.49 (3H, s, Me), 1.74 (1H, dd, *J*= 12.0, 11.0 Hz, H-10), 2.55 (2H, m, H-4 & H-10), 3.43 (3H, s, OMe), 3.63 (1H, m, H-5), 3.71 (1H, dd, *J*= 11.5, 6.0 Hz, H-6), 3.86 (1H, dd, *J*= 11.5, 2.5 Hz, H-6), 4.53 (2H, overlapped, H-7 & H-8), 4.93 (1H, br-d, *J*= 2.8 Hz, H-10), 5.00 (1H, br-s, H-10), 5.19 (1H, br-s, H-1), 5.94 (1H, d, *J*= 2.5 Hz, H-2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.9, 27.4, 32.5, 32.9, 55.4, 62.9, 71.7, 78.7, 95.0, 109.6, 113.3, 126.8, 137.5, 142.8.
Elemental analyses was assigned by acetylated compound of **24**. $[\alpha]^{26}_D$ 4.6 (*c* 0.070, $CHCl_3$), IR (film) 1740 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.94; H, 7.62.

Preparation of (1S, 3R, 5R, 6S, 8R, 9R)-8-hydroxy-1-(hydroxymethyl)-3-methoxy-7-methylene-5,6,8,8a-tetrahydroisochromane-5,6-acetonide ***25***

A stirred mixture of 24.1 mg (85.5 μmol) of **24**, 200 mg (1.71 mmol) of NMO and 10 mg (0.09 mmol) of SeO_2 in 3 ml of dioxane/EtOH (3/1) was heated at reflux temperature under N_2 for 4 h. After the mixture was concentrated to one third of its volume, it was diluted with AcOEt, washed with brine, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (AcOEt) to give the diol **25** (17 mg, 60%) as a yellow oil. $[\alpha]^{26}_D$ -5.28 (*c* 0.275, $CHCl_3$). IR (film) 3448, 1654 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, Me), 1.49 (3H, s, Me), 2.69 (1H, br-dd, *J*= 10.0, 2.7 Hz, H-4), 3.43 (3H, s, OMe), 3.76 (1H, dd, *J*= 12.0, 5.0 Hz, H-6), 3.90 (1H, dd, *J*= 12.0, 2.2 Hz, H-6), 4.18 (1H, ddd, *J*= 10.0, 5.0, 2.2 Hz, H-5), 4.38 (1H, d, *J*= 2.7 Hz, H-10), 4.58 (1H, d, *J*= 5.2 Hz, H-7), 4.83 (1H, m, H-8), 4.94 (1H, d, *J*= 2.5 Hz, H-1), 5.22 (1H, br, H-11), 5.33 (1H, br-d, *J*= 1.5 Hz, H-11), 6.13 (1H, d, *J*= 2.5 Hz, H-2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 26.6, 27.9, 38.7, 55.4, 63.0, 67.1, 72.5, 74.9, 78.0, 95.1, 109.8, 113.7, 129.9, 134.6, 146.7. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.39; H, 7.23.

Preparation of (1S, 3R, 5R, 6S, 8R, 9R)-8-acetoxy-1-(acetoxymethyl)-3-methoxyspiro[5,6,7,8,8a-pentahydroisochromane-7,3'-oxirane]-5,6-acetonide 27

A solution of **25** (17.6 mg, 59.1 μmol) and Na_2HPO_4 (16.8 mg, 0.118 mmol) in CH_2Cl_2 (1 ml) were treated with *m*-chloroperbenzoic acid (MCPBA, 80% purity, 13.2 mg, 0.077 mmol) and stirred at room temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 and then washed with sat. $NaHCO_3$ aqueous solution (×2). The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. A solution of crude alcohol **26** in pyridine (1 ml) was treated with Ac_2O (0.5 ml) and stirred at room temperature for 1 h. The reaction mixture was diluted with toluene, and concentrated under reduced pressure. The crude product was purified by column chromatography (ether/hexane=2/1) to give the acetate **27** (16 mg, 68%) as a yellow oil. $[\alpha]^{27}_D$ -44 (*c* 0.080, $CHCl_3$). IR (film) 3448, 1740, 1373, 1067 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, Me), 1.49 (3H, s, Me), 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 2.78 (1H, d, *J*= 5.2 Hz, H-11), 2.82 (1H, br-d, *J*= 11.0 Hz, H-4), 3.26 (1H, d, *J*= 5.2 Hz, H-11), 3.42 (3H, s, CH_3), 3.78 (1H, m, H-5), 4.21 (1H, dd, *J*= 12.0, 2.7 Hz, H-6), 4.52 (1H, dd, *J*= 12.0, 4.5 Hz, H-6), 4.53 (1H, d, *J*= 6.0 Hz, H-7), 4.84 (1H, d, *J*= 6.0 Hz, H-8), 4.95 (1H, br, H-10), 4.95 (1H, br, H-1), 6.18 (1H, d, *J*= 2.2 Hz, H-2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.8, 20.9, 25.8, 26.7, 37.8, 50.2, 55.7, 60.2, 63.8, 64.9, 72.5, 72.9, 95.1, 109.8, 130.7, 132.8, 170.1, 170.9. Anal. Calcd for $C_{19}H_{26}O_9$: C, 57.28; H, 6.58. Found: C, 57.17; H, 6.80.

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