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Synthesis of the JKLM-ring fragment of ciguatoxin

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Abstract—A stereoselective synthesis of the LM-ring fragment has been achieved starting from a sugar derivative. A stereoselective synthesis of the JKLM-ring fragment has been achieved through a coupling between two segments via heteroconjugate addition, seven-membered ether ring formation mediated by an acetylene cobalt complex, and spiroketalization reaction.
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1. Introduction

Ciguatoxin (CTX) is a principal toxin of ciguatera, which is known as the most widespread seafood poisoning.[1] The causative toxins of this poisoning produced by the epiphytic dinoflagellate, *Gambierdiscus toxicus*,[2] are accumulated in carnivorous fish of many species through the food chain among coral biota, and finally causing human intoxication. The poisoning symptom does crisis to more than 20000 people annually in the world.[1] It is a serious problem especially in the societies of tropical and subtropical regions. CTX was first isolated from moray eel, *Gymnothorax javanicus*, by Scheuer and co-workers at the University of Hawaii and characterized as a polyether compound in 1980.[3] Thus far, more than 23 congeners of CTX have been identified to date.[1] Ciguatoxins (CTXs) and another structurally related marine toxin, brevetoxins (BTXs), are selective sodium channel activators, which bind quasi-irreversibly to site 5 on the voltage-sensitive sodium channels (VSSC) in nerves, heart and muscle.[4,5] In spite of structural similarity to BTXs, the binding affinity of CTX was shown to be some ten times more potent than that of BTXs.[4] CTX remains the most potent neurotoxin known with a mouse lethality LD_{50} of 0.35 μg/kg (i.p.).[4]

Since Yasumoto and co-workers determined the gross structure of CTX in 1989,[6] its complicated structure has been in the foreground of attention among the scientists. The chemical construction of CTX is a *trans*-fused polycyclic system composed of a single carbon chain that winds the length of the molecule and linking by ether oxygens into a series of five- to nine-membered oxacycles. Its absolute configuration was successfully elucidated by Yasumoto and co-workers in 1997 as shown in Figure 1.[7]

Several synthetic groups have been studying the total synthesis of CTX over last decade.[8] Recently, Hirama's group reported the first total synthesis of CTX3C, a member of the CTX family.[9] We also have endeavored to develop effective methodologies, and established valid methodologies for the construction of medium-sized ether rings via cobalt complex-mediated cyclization during the course of our studies toward the synthesis of CTX.[10] We have already achieved the syntheses of the ABC rings with the side chain,[11] the BCDE,[12] the D′EF,[13] the E′FGH[14] rings[15] using acetylene cobalt complex strategy. With regard to right part of CTX, we previously reported a model study of stereoselective synthesis of the H′IJK-ring fragment.[16] In this paper, we provide full detail of the synthesis of the LM- and the JKLM-ring fragments as the right end of CTX.

2. Synthesis of the LM-ring fragment

Firstly, we set about the synthesis of the LM-ring fragment of CTX.[17] Its retrosynthetic analysis is shown in Scheme 1. We anticipated that LM-ring system could be derived from hemiacetal **3** by asymmetric dihydroxylation reaction and then cyclization. Hemiacetal **3** could be prepared from α,β-unsaturated lactone **4** through a stereocontrolled conjugate addition and enolate trapping reaction. Lactone **4** would be synthesized starting from tri-*O*-acetyl-D-galactal **5**.

The synthesis of the initial target **1** is outlined in Scheme 2. Tri-*O*-acetyl-D-galactal **5** was deacetylated under the condition of NaOMe/MeOH to afford D-galactal **6** in 87% yield. The primary hydroxyl group of **6** was selectively silylated, and the allylic hydroxyl group was then selectively protected by benzoylation with benzoyl chloride and pyridine under −35°C. The remaining hydroxyl group was protected as the benzyl ether to afford **9**. After desilylation with TBAF and protection with TBDPS, the protected D-galactal was oxidized by PCC at 80°C to give

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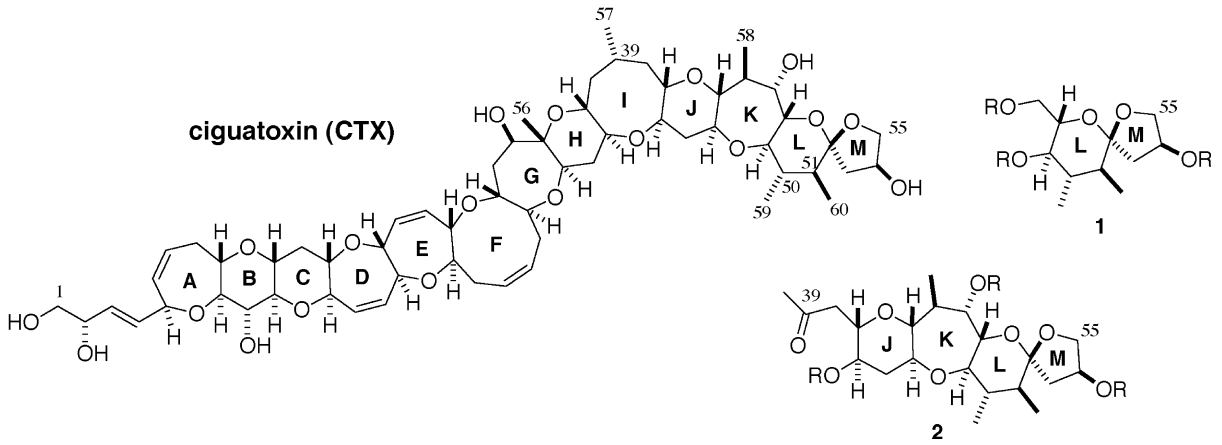
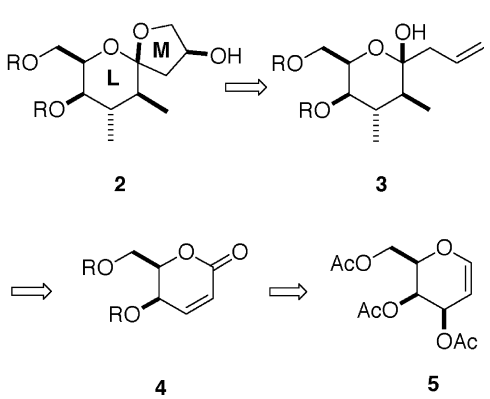


Figure 1.

lactone **12**,[18] which was treated with DBU to give the desired enlactone **13** in 98% yield.[19] With the key enlactone **13** in hand, it was treated with Me_2CuLi to give monomethylated lactone in 91% yields. After the monomethylated lactone was treated with LiHMDS for 30 min at −78°C, MeI was added to the reaction mixture at this temperature to give dimethyllactone **14** and its C51-epimer with the ratio of 7:1 in 93% combined yield. Addition of allylmagnesium bromide to dimethyllactone **14** provided hemiacetal **15**. Asymmetric dihydroxylation and spiroketalization were conducted under Sharpless condition[20] to afford a mixture of four isomers **16a–d** with the ratio of 4:4:1:1 in 75% combined yield, which were easily separated by preparative TLC.

The stereochemistry of **16a–d** was determined through careful analysis of their ^1H NMR and NOESY spectra, shown as following. The important data of compound **16a** are the coupling constants $J_{50,51}$=11.0 Hz, $J_{49,50}$=11.0 Hz, and the observation of the cross peaks between H-53α and H-54, H-53β and C60–Me on its NOESY experiment. These data indicate that the conformation of the pyranose-nucleus and the stereochemistry of C54 are as depicted in Figure 2. For **16b**, the coupling constants $J_{50,51}$=2.0 Hz, $J_{49,50}$=1.5 Hz and the observation of the cross peak between H-48 and C59–Me on its NOESY experiment suggested that C59-Me and C60-Me are axial. The observation of the cross peaks between H-53β and H-54, H-53β and C60–Me indicated that the stereochemistry of its C54 is *S* configuration.



Scheme 1. Retrosynthetic analysis of the LM-ring fragment **1**.

The stereochemistry of compounds **16c** and **d** was also determined through careful analysis of their NMR spectra, shown in Figure 2. The stereochemistry at C54 in **16c** and **d** could be easily inverted into **16b** and **1a** by Mitsunobu reaction,[21] respectively. The mixture of **16c** and **d** were treated with DEAD, PPh_3 and *p*-nitrobenzoic acid, then treated with K_2CO_3/MeOH to provide a mixture of **16c** and **b** in 95% yield (Scheme 3).

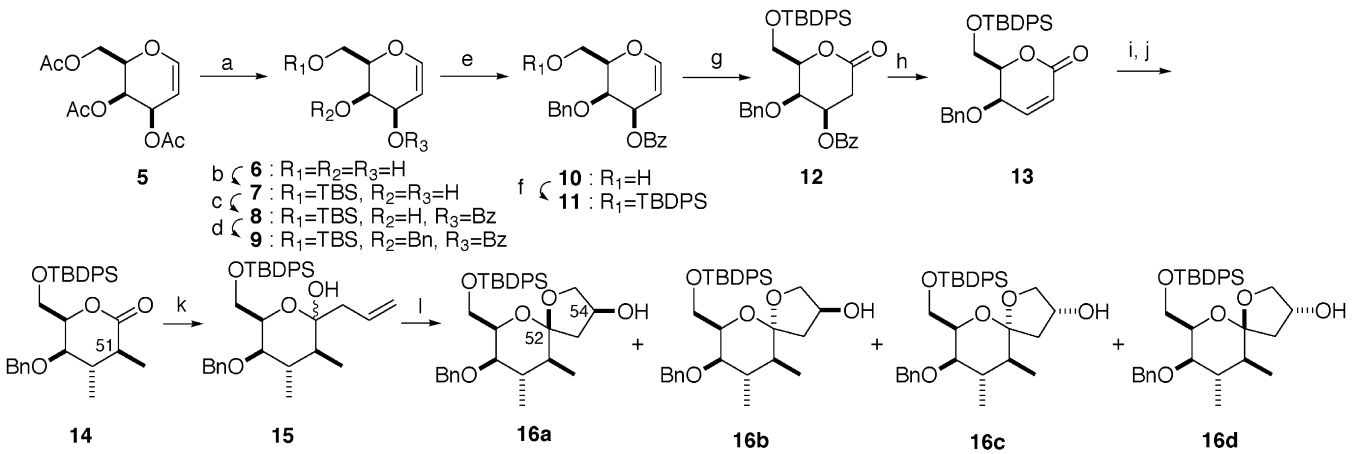
3. Synthesis of the JKLM-ring fragment

3.1. Retrosynthetic analysis

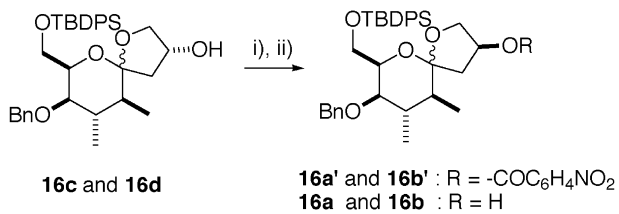
Having accomplished the synthesis of the LM-ring fragment, we now could consider the synthesis of the JKLM-ring fragment of CTX. According to our plan, the synthesis of CTX could be achieved via the coupling of two large segment, acetylene in the Segment L **17** with aldehyde in Segment R **18** (Scheme 4). This would be followed by the construction of central part (FG-ring), and finally A-ring cyclization. We have already reported the synthesis of Segment L **17**.[12b] The retrosynthetic analysis for the right part of CTX is illustrated in Scheme 5. Segment R **18** could be derived from acetylene **19**, representing C30–C38 portion of CTX, and the JKLM-ring fragment **2**. Opening of the terminal spiroketal in **2** provides **20** as a synthetic equivalent. The seven-membered ring in **20** would be constructed via acetylene cobalt complex **21**. Opening of the seven-membered ring K in **21** gives **22**, which further leads us to the two segments vinyl sulfone **23** and acetylene **24** to be coupled between the C46 and C47 positions on the basis of a heteroconjugate addition.[10j–l]

3.2. Synthesis of the acetylene subsegment

We attempted to transform the LM-ring system of **16** into acetylene **24** (Scheme 6). The C54 hydroxyl groups of **16a** and **b** were protected by benzyl group, and then treated with TBAF to afford a mixture of alcohols **25** in 92% yield. The primary alcohol of **25** was successfully converted into chloride and iodide under ordinary conditions to provide **26** and **27**. Both of the attempts for the transformation of **26** and **27** into acetylene under basic conditions were, however, unsuccessful.[22] We have also tried direct opening of



Scheme 2. *Reagents, conditions and yields*: (a) NaOMe, MeOH, 87%; (b) TBSCl, Py, DMF, room temperature, 68%; (c) BzCl, Py, DMAP, −35°C, 93%; (d) BnBr, NaH, DMF, 92%; (e) TBAF, THF, 95%; (f) TBDPSCl, imidazole, DMF, 100%; (g) PCC, $(CH_2Cl)_2$, 51%; (h) DBU, CH_2Cl_2, 98%; (i) Me_2CuLi, Et_2O 98%; (j) LiHMDS, MeI, THF, −78°C (**14**–C51-epimer=7:1); (k) $CH_2{=}CHCH_2MgBr$, Et_2O, −78°C 87%; (l) AD-mix-α, *t*-BuOH, H_2O, 75%.



Scheme 3. *Reagents, conditions and yields*: (i) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, toluene; (ii) K_2CO_3, MeOH, 95% in 2 steps.

spiroketal in **25** with 1,3-propanedithiol catalyzed with $BF_3{\cdot}OEt_2$ to afford dithiane product,[23] but it could not afford the desired product. To our regret, it would seem no other efficient way to derive the acetylene compound **24** from LM-ring system **16**, though we explored every avenue.

Faced with this impasse, we were forced to abandon this line, and seek out another way. An alternative strategy for construction of the acetylene segment **24** is shown in Scheme 7. Thus, tri-*O*-acetyl-D-glucal was converted to the enone **31** by a four-step sequence; *O*-glycosidation with

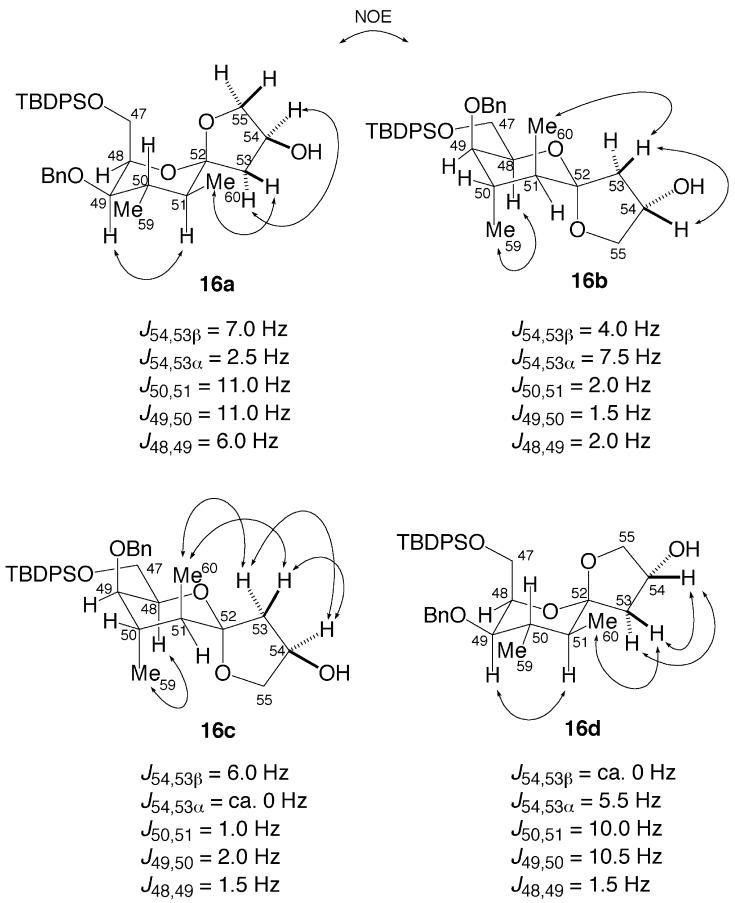
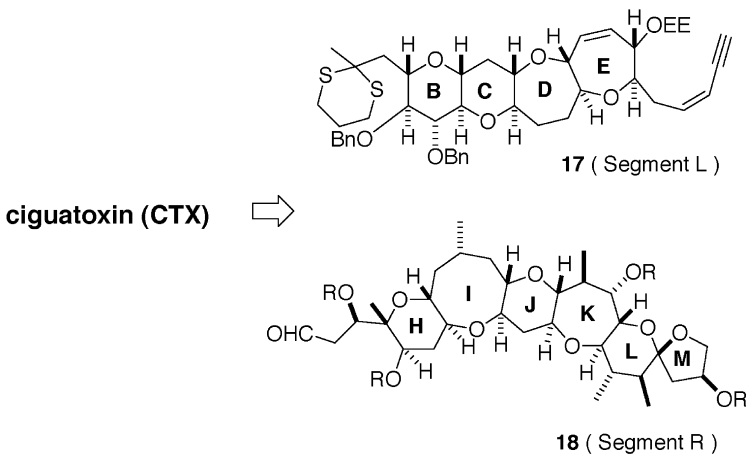
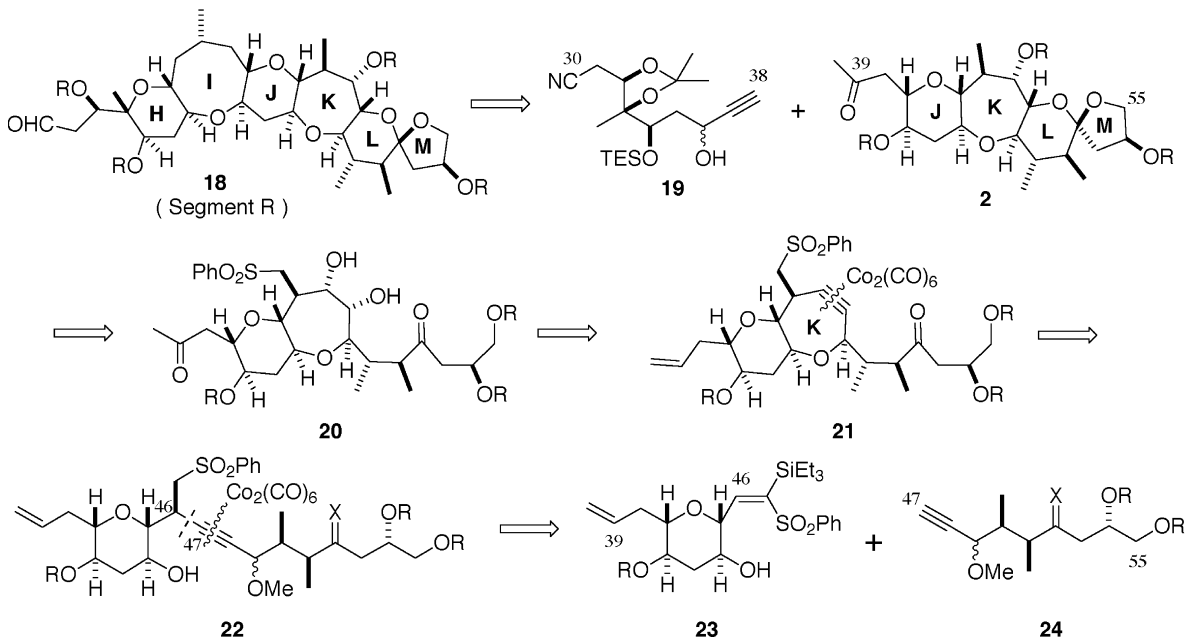


Figure 2.

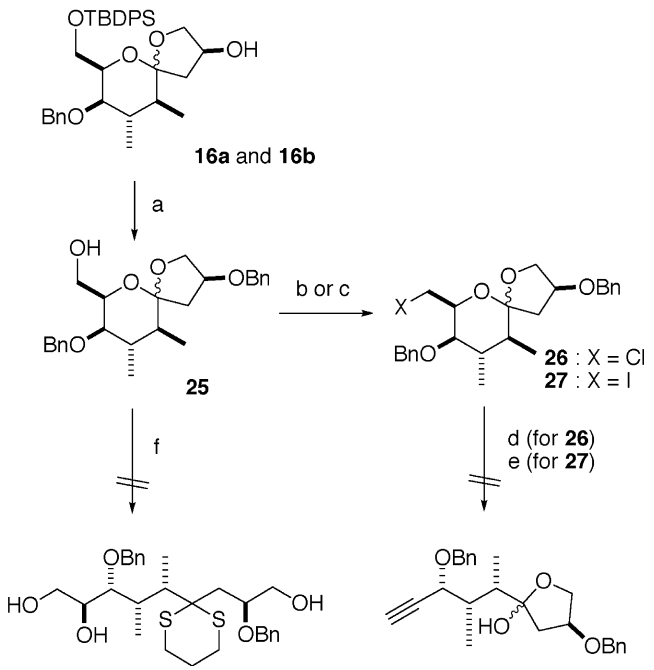


Scheme 4.

2-propanol catalyzed by $BF_3{\cdot}OEt_2$, saponification with basic MeOH, silylation under the condition of TBSCl/imidazole and oxidation by DMSO/Ac_2O. These steps were amenable to a large-scale operation. 1,4-Addition of lithium dimethyl cuprate to α,β-unsaturated carbonyl of **31**, followed by enolate trapping with MeI in the presence of *N*,*N*-dimethylacetamide as a co-solvent provided **32** as an exclusive diastereomer. The stereochemistry of **32** was confirmed by the analysis of its data of ^1H NMR and NOESY experiment (Fig. 3). The carbonyl group was stereoselectively reduced to the alcohol by $NaBH(OAc)_3$[24] after the removal of the TBS group of **32** to afford the diol **34**. Opening of the pyranose ring of **34** with 1,3-propanedithiol was unsuccessful under $BF_3{\cdot}OEt_2$ catalyzed condition. On the other hand, concentrated hydrochloric acid in chloroform provided open-chain triol compound in nearly quantitative yield, which was subsequently protected with TBS and isopropylidene group to give **37**. Coupling reaction of the lithio derivative of dithiane **37** with glycidyl methoxybenzyl ether proceeded uneventfully under mild condition[25] and afforded an alcohol, which was protected with benzyl group together with the primary alcohol after desilylation. Subsequent acidic hydrolysis of the isopropylidene group afforded **41**. Oxidative cleavage of the 1,2-diol **41** by $Pb(OAc)_4$ provided the corresponding aldehyde **42**. The aldehyde was treated with lithium TMS acetylide and MeI, and then desilylated with TBAF to give the acetylene **44**. Finally, removal of the dithiane group was performed by brief treatment of **44** with *N*-chlorosuccinimide and $AgNO_3$ in wet acetonitrile containing 2,4,6-collidine.[26] The yield of this reaction was moderate probably due to the instability of acetylene moiety under the reaction condition, though this was the most suitable method for unmasking of the ketone group of **44**. Several other procedures were also tested for this conversion (e.g. $CuCl_2$ and CuO in wet acetone,[27] [bis(trifluoroacetoxy)iodo]-benzene[28] or MeI[29] in wet acetonitrile), but they produced substantial amount of inseparable by-product. The unmasked ketone was reduced to an alcohol **46** (diastereomeric mixture at C49; ca. 2:1) which was protected by TBS group to afford the targeted compound **47**.



Scheme 5. Retrosynthetic analysis of right part of ciguatoxin.



Scheme 6. *Reagents, conditions and yields*: (a) (i) BnBr, NaH, DMF, 88%, (ii) TBAF, THF, 92%; (b) CCl_4, PPh_3, 79%; (c) I_2, imidazole, PPh_3, 82%; (d) LDA, THF, −78°C; (e) DBU, THF, reflux; (f) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, −40°C to room temperature.

3.3. Synthesis of the vinyl sulfone subsegment

The construction of the other requisite subsegment for the JKLM-ring system bearing vinyl sulfonyl group is illustrated in Scheme 8. Synthesis of the vinyl sulfone **69** began from methyl α-D-glucopyranoside derivative **48**.[12] Thus, the hydroxyl group of the C42 position in **48** was selectively protected by pivaloyl group.[30] The remaining free hydroxyl group in **49** was converted to the thiocarbamate by treating with in situ generated thiocarbonyldiimidazole, and removed under modified Barton conditions[31] to afford

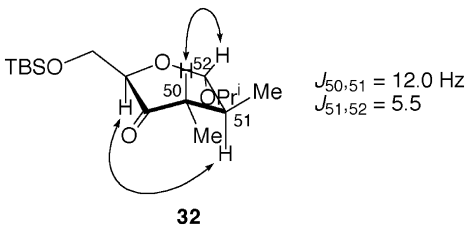
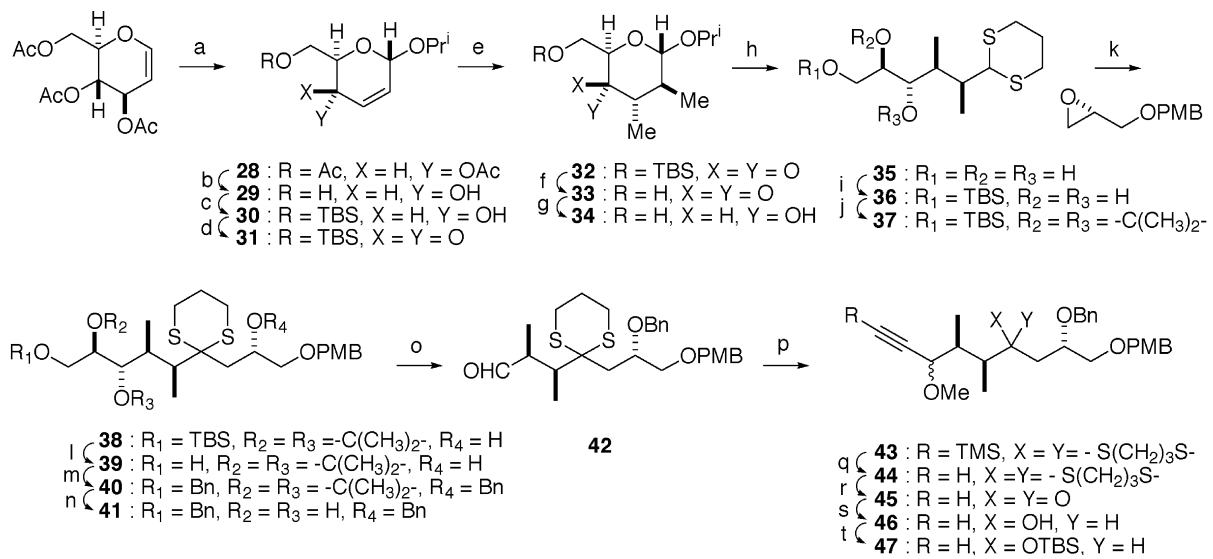
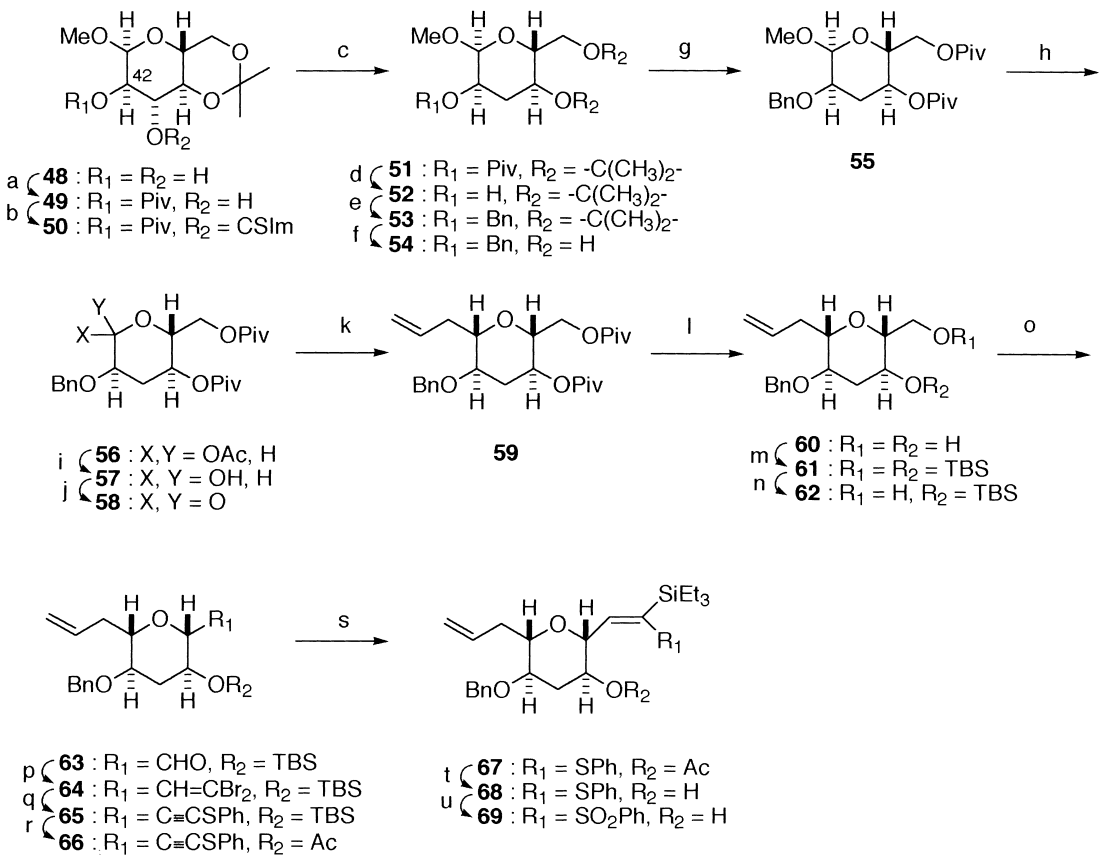


Figure 3.

compound **51**. The protective groups in **51** were manipulated to provide **55** in 4 steps under standard conditions. The acetal **55** was transformed to lactone **58** via acetolysis with sulfuric acid in acetic anhydride, hydrolysis with aqueous hydrochloric acid in ethylene glycol dimethyl ether and oxidation of the anomeric position. Addition of allylmagnesium bromide to the lactone **58**, followed by Kishi's silane reduction,[32] provided hydropyran system **59** as an exclusive diastereomer. Removal of the pivaloyl group from **59** led to diol **60** which was converted to **62** through disilylation and selective removal of the silyl group attached to the primary hydroxyl group.[33] Oxidation of the primary alcohol followed by dibromo-olefination of the resulting aldehyde **63** gave the vinyl dibromide **64**,[34] which was converted to the thiophenylacetylene **65** by further treatment with *n*-BuLi and $PhSSO_2Ph$. Then the TBS group was exchanged to acetyl group to give **66**. Concordant with our previous work, this thiophenylacetylene underwent highly regioselective hydrosilylation in the presence of a catalytic amount of cobalt complex to afford the corresponding vinylsilane **67**,[35] albeit minor amount of an inseparable isomer (later determined to be the inner olefin isomer of allyl group) could be detected by ^1H NMR. In this reaction, stoichiometric use of the cobalt complex caused increase of isomerization of terminal olefin into inner olefin. And we found that the isomerization is due to the activity of $Co_2(CO)_6$ species liberated from the catalyst. However, to our delight, the minor isomer gradually filtered out over the course of the remainder of the synthesis. Finally, removal of



Scheme 7. *Reagents, conditions and yields*: (a) *i*-PrOH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (b) Et_3N, MeOH, H_2O, 84% in 2 steps; (c) TBSCl, imidazole, DMF; (d) Ac_2O, DMSO, 97% in 2 steps; (e) CuI, MeLi, Et_2O, 0°C, then MeI, DMA, 92%; (f) TBAF, THF, 82%; (g) $NaBH(OAc)_3$, CH_3CN, AcOH, 93%; (h) 1,3-propanedithiol, HCl, $CHCl_3$; (i) TBSCl, Et_3N, DMAP, CH_2Cl_2, 89% in 2 steps; (j) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, quant.; (k) *t*-BuLi, (2*S*)-glycidylmethoxybenzyl ether, THF, HMPA, 96%; (l) TBAF, THF; (m) NaH, BnBr, DMF; (n) 80% AcOH, 70% in 3 steps; (o) $Pb(OAc)_4$, CH_2Cl_2, 99%; (p) *n*-BuLi, TMS–acetylene, THF, then MeI; (q) TBAF, THF, 86% in 2 steps; (r) NCS, $AgNO_3$, 2,4,6-collidine, CH_3CN, H_2O; (s) $NaBH_4$, MeOH; (t) TBSOTf, Py, CH_3CN, 54% in 3 steps.



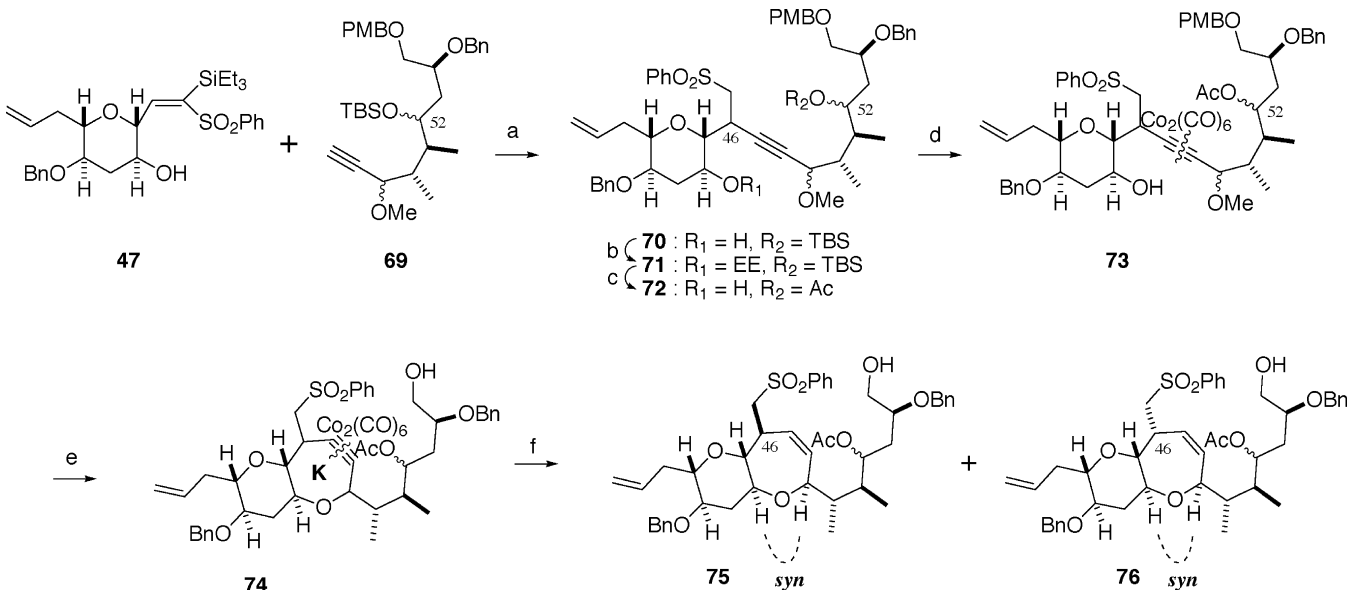
Scheme 8. *Reagents, conditions and yields*: (a) PivCl, Py, CH_2Cl_2, 68%; (b) thiophosgene, imidazole, $CHCl_3$, toluene, 90°C; (c) AIBN, NaH_2PO_2, 2-methoxyethanol, reflux, 87% in 2 steps; (d) NaOMe, MeOH, 80%; (e) KOH, BnCl; (f) Amberlyst 15E®, MeOH, 86% in 2 steps; (g) PivCl, Py, CH_2Cl_2; (h) H_2SO_4, Ac_2O, 96% in 2 steps; (i) HCl, DME, H_2O, 63%; (j) Ac_2O, DMSO, 98%; (k) (i) $CH_2{=}CHCH_2MgBr$, THF, −78°C, (ii) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_3CN, −10°C, 66% in 2 steps; (l) NaOMe, MeOH, 93%; (m) TBSCl, imidazole, DMF; (n) CSA, MeOH, 88% in 2 steps; (o) $(ClCO)_2$, DMSO, CH_2Cl_2; (p) CBr_4, PPh_3, CH_2Cl_2, 91% in 2 steps; (q) *n*-BuLi, THF, −78 to 0°C, then $PhSSO_2Ph$; (r) (i) TBAF, THF, (ii) Ac_2O, Py, 77% in 3 steps; (s) Et_3SiH, biscobalthexacarbonyl-2-methyl-but-3-yn-2-ol (cat.), 60°C, $(CH_2Cl)_2$; (t) K_2CO_3, MeOH; (u) *m*CPBA, Na_2HPO_4,CH_2Cl_2, 85% in 3 steps.

the acetyl group, followed by treatment with *m*CPBA in the presence of sodium hydrogen phosphate provided the vinyl sulfone **69**.

3.4. Heteroconjugate addition and K ring cyclization

Having accomplished the preparation of both subsegments **46** and **47** for the elaboration of the JKLM-ring system, our attention turned to the coupling of these two compounds. The coupling between **47** and **69** and subsequent K ring cyclization are depicted in Scheme 9. To our temporary delight, application of the condition employed in our previous model studies produced a coupling compound in good yield.[16a,b] Thus, generation of the lithium acetylide of **47** with *n*-BuLi in THF, followed by addition of **69**, gave diastereomeric mixture of **70** in 80% yield. However, NMR studies with **70** were ambiguous, and our empirical method for determination of the stereochemistry of adduct established through related heteroconjugate additions was not sufficiently consistent to allow us to assign with confidence the C46 configuration of **70**. While the stereochemical assignments were tentative at this point, the crucial cyclization reaction of the K ring was studied.

We are aware that some attempts for the cyclization of the K ring need rather concentrated Lewis acid condition (around 10 times stronger) as compared with homologous medium sized ring formation we previously conducted using acetylene cobalt complex.[11–15] In addition, functional group at C52 turned to be a dominant factor in this reaction; attempted formation of the K ring from 1,3-dithiane derivative or TIPS ether at C52, for example, failed due to competing nucleophilic participation of the heteroatom on the functional group at C52. Therefore, the C52 TBS group, having served its role in the coupling reaction, was now replaced by an acetyl group for the purpose of diminishing the nucleophilicity at the fifth position from the cationic center. Application of the usual methods for exchange of protective groups to the above adduct **70** delivered the expected acetate **72**, which could be readily converted into corresponding acetylene cobalt complex **73** by simply mixing with $Co_2(CO)_8$ in CH_2Cl_2. Upon treatment of **73** with $BF_3{\cdot}OEt_2$, the K ring cyclization took place with attendant loss of the PMB group attached to the primary hydroxyl group to afford the bicyclic compound **74**. Reductive decomplexation of **74** was conducted with an excess amount of Bu_3SnH under heating in toluene.[36] This reaction provided the corresponding endocyclic olefin together with an inseparable mixture of the inner olefin isomers of allyl group, similar to hydrosilylation of thiophenylacetylene **66** in Scheme 8, but this time the amount of the undesired olefin isomer was considerable.



Scheme 9. *Reagents, conditions and yields*: (a) (i) *n*-BuLi, THF, (ii) TBAF, THF, 87% in 2 steps; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, quant.; (c) (i) TBAF, THF, 88%, (ii) Ac_2O, DMAP, Py, (iii) CSA, MeOH, quant. in 2 steps; (d) $Co_2(CO)_8$, CH_2Cl_2; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 93% in 2 steps; (f) bis-(trimethylsilyl)acetylene, Bu_3SnH, toluene, 87% (**75**: 68%, **76**: 19%).

Working with closely related model systems, a reliable protocol was developed for evasion from encumbering isomerization during the reductive decomplexation with hydrosilylation. By simply adding an excess amount of bis-(trimethylsilyl)acetylene in the decomplexation reaction, the formation of the side product, which stems most likely from the activity of $Co_2(CO)_6$ species liberated from the substrate, could completely suppressed.[37] Application of this procedure to the problem at hand was quite successful and cleanly afforded the desired endocyclic olefin **75** and its C46-epimer **76**, both having *syn* stereochemistry between H44 and H49, as chromatographically separable products in 87% combined yield (**75**–**76**=3.6:1). Thus, it seemed to indicate unequivocally that the stereochemical problem lay simply at C46.

On the basis of our previous work,[16a,b] it appeared that the heteroconjugate addition reaction of lithium acetylide of **47** (R=Li) toward vinyl sulfone **69** with non-protected β-hydroxyl group, which would be well-positioned to direct the addition of nucleophile to the same face of the vinyl sulfone, might proceed with extremely high stereoselectivity under adequate condition. The model studies also showed that the stereoselectivity of heteroconjugate addition is highly dependent on solvent and coordination ability of metal. What was puzzling, however, was that solvent modification had surprisingly little effect on the stereoselectivity in this particular system (Table 1).

3.5. Spiroketalization

With the requisite bicyclic compound **75** available, the only issue that remained was the crucial spiroketalization. The final stage of the synthesis of the JKLM-ring fragment is illustrated in Scheme 10. Removal of the acetyl group in **75**, followed by selective protection of the primary alcohol by TBS group and oxidation with IBX,[38] furnished ketone **79**. The terminal olefin in **79** was oxidized for the purpose of differentiation from endocyclic olefin to give methyl ketone **80**. The stereoselective dihydroxylation of the endocyclic olefin in **80** was achieved under Sharpless condition[39] to afford **81** and **82** as an equilibrium mixture, which underwent desilylation and spiroketalization in the expected sense by treatment with HF·pyridine in acetonitrile to afford the tetracyclic compound **83** as a major product with a minor spiro-isomer. Finally, reduction with sodium-amalgam in methanol gave the desulfonylation product **84**. The stereochemistry of **84** was confirmed through the NOE experiments. The results are shown in Figure 4 with arrows.

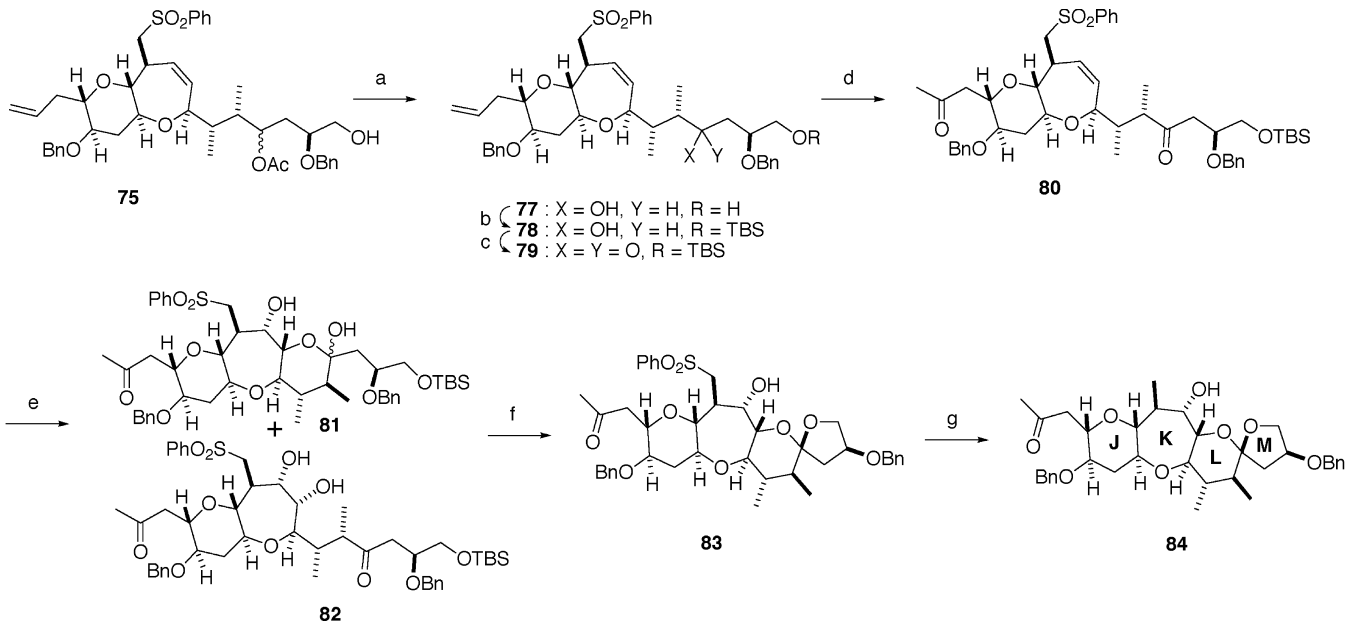
4. Conclusion

We have achieved an efficient synthesis of the JKLM ring fragment in 16 steps from acetylene **47** and vinyl sulfone **69** based on the convergent strategy. It proceeds with modest stereochemical control at C46, but virtually complete

Table 1. Stereoselectivity at C46 position in coupling between **47** and **69**

Entry	Conditions	Yield[a] (%)	Ratio[b] 75:76
1	*n*-BuLi, THF, 0°C, 30 min	80	3.6:1
2	*n*-BuLi, Et_2O/hexane, 0 to 15°C, 5 h	74	3.4:1
3	*n*-BuLi, THF/hexane (1/4), 0°C, 2 h	94	3.1:1
4	MeLi·LiBr, THF, −78 to −30°C, 2 days	74	2.0:1
5	*n*-BuLi, Et_2O, 0 to 25°C, 11 h	90	1.9:1
6	*n*-BuLi, THF, −20°C, 4 h	85	1.9:1
7	*n*-BuLi, LiBr, THF, −78 to 25°C, 3 h	D	–
8	NaH, *n*-BuLi, THF, −78 to 0°C, 30 h	D	–
9	EtMgBr, THF, −78 to 25°C, 15 h	NR	–
10	EtMgBr, Et_2O, −78 to 25°C, 15 h	NR	–

D—decomposed; NR—no reaction.
[a] Yield of adduct **70**.
[b] The ratios of the stereoisomers at C46 position were indirectly established from the ratios of **75** and **76**, which were transformed by 5 steps from the coupling product **70**.



Scheme 10. *Reagents, conditions and yields*: (a) K_2CO_3, MeOH, THF; (b) TBSCl, Et_3N, DMAP, CH_2CH_2, 95% in 2 steps; (c) IBX, DMSO, 97%; (d) $PdCl_2$, CuCl, DMF, H_2O, O_2, 85%; (e) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O; (f) HF·Py, CH_3CN, 72% in 2 steps; (g) Na–Hg, Na_2HPO_4, MeOH, 82%.

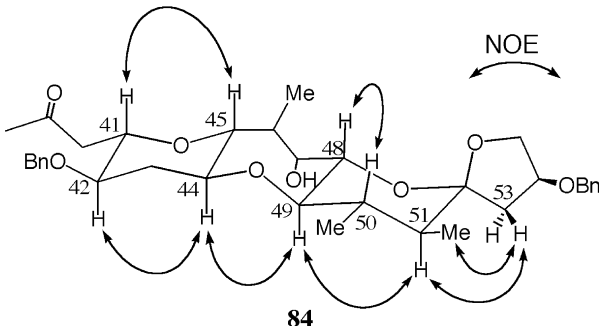


Figure 4.

control at all other positions including thermodynamically driven adjustment of *syn* selective K ring cyclization and final spiroketalization. Further studies toward the synthesis of the right part of CTX along this line are now in progress.

5. Experimental

5.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR-8300 spectrophotometer or a Paragon 1000 FT-IR spectrometer and are reported in wave number (cm^{-1}). Proton NMR spectra (^1H NMR) were recorded on a Varian Gemini 2000 (300 MHz), a Bruker ARX-400 (400 MHz) or a JEOL L500 (500 MHz). All samples were dissolved in $CDCl_3$, and chemical shift values are reported in parts per million (ppm) with tetramethylsilane (TMS, δ 0.00) as an internal standard. Data are reported as follows: chemical shift [integrated intensity, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, sep=septet, br=broadened, m=multiplet), coupling constant(s) in Hertz, assignment]. The assignment of NMR spectra was largely achieved from COSY spectra. NOESY experiments were performed with a Bruker ARX-400 (400 MHz) or a JEOL L500 (500 MHz). Carbon NMR spectra (^{13}C NMR) were recorded on a Varian Gemini 2000 (75.4 MHz), a Bruker ARX-400 (100 MHz) or a JEOL L500 (125 MHz) with proton decoupling. Chemical shift values are reported as δ in parts per million (ppm) with $CDCl_3$ (δ 77.0) as an internal standard. Optical rotations were measured on a JASCO DIP-370 digital polarimeter or a JASCO P-1010-TG polarimeter. High-resolution or low-resolution mass spectra were recorded on a Micromass Q-TOF (ESI) or a JEOL JMS-700 spectrometer (FAB and EI), and are reported in *m/z*. Elemental analyses were performed by Analytical Laboratory at School of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel coated glass plates $60F_{254}$ (Cica Merck, Art 1.05715) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution as developing agents. Cica Merck silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for open-column chromatography. Unless otherwise noted, non-aqueous reactions were conducted in oven-dried (200°C) or flame-dried glassware under inert atmosphere. Dry THF was distilled from potassium metal with benzophenone. Anhydrous Et_2O was purchased from Kanto Chemical Co., Inc. in a bottle as Ethyl Ether Anhydrous. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. $BF_3{\cdot}OEt_2$ were distilled from CaH_2. All other commercially available reagents were used as received. Hyflo-Super-Cel® (nacalai tesque) was used as filter aid.

5.1.1. D-Galactal 6. To a solution of tri-*O*-acetyl-D-galactal **5** (16.1 g, 59 mmol) in dry MeOH was added NaOMe (54 mg), the mixture was stirred for 3 days, then evaporated under reduced pressure to give a crude product (10.0 g). The residue was filtered through a silica gel column to give a syrup (9.00 g). This syrup was crystallized from AcOEt to give a white solid of D-galactal **6** (7.50 g, 87%). **6**: mp 99–100°C, $[\alpha]_D^{16}=-20.6°$ (*c* 1.350, MeOH).

5.1.2. TBS-D-galactal 7. To a mixture of D-galactal **6** (7.30 g, 50.0 mmol), pyridine (7.90 g, 100 mmol) and DMAP (0.30 g) in dry DMF (150 mL) was added TBSCl (7.90 g, 52.5 mmol) in three portions over 1 h at 0°C. After stirring for 1 h at 0°C, the mixture was stirred overnight at room temperature, then poured into 5% $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide crude oil product. The residue was purified by silica gel chromatography (AcOEt–hexane=1:1) to give TBS-D-galactal **7** (8.90 g, 68%) as colorless oil. *Compound* **7**. $[\alpha]_D^{16}=+3.94°$ (*c* 0.815, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 0.12 (6H, s, –Si(CH_3)$_2$), 0.91 (9H, s, –SiC(CH_3)$_3$), 2.73 (1H, br s, –OH), 3.18 (1H, br s, –OH), 3.88 (1H, m, H-48), 3.90–3.99 (2H, ddd, *J*=10.5, 5.0, 4.0 Hz, H-47a, 47b), 4.10 (1H, m, H-49), 4.31 (1H, m, H-50), 4.72 (1H, dt, *J*=6.5, 2.0 Hz, H-51), 6.38 (1H, dd, *J*=6.5, 1.5 Hz, H-50). ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.48, −5.46, 18.3, 25.8, 63.4, 64.2, 66.1, 75.7, 103.1, 144.5.

5.1.3. TBS-Bz-D-Galactal 8. To a solution of TBS-D-galactal **7** (6.50 g, 25.0 mmol) in dry pyridine (60.0 mL) was added dropwise benzoyl chloride (3.69 g, 26.3 mmol) over 30 min at −35°C under Ar atmosphere. After stirring for 1.5 h at this temperature, the mixture was warmed to 0°C over 15 min, then poured into saturated $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide a crude oil product (10.0 g). The residue was purified by silica gel chromatography (AcOEt–hexane=1:4) to give TBS-Bz-D-galactal **8** (8.50 g, 93%) as a colorless oil. **8**: $[\alpha]_D^{20}=63.8°$ (*c* 0.890, $CHCl_3$) ^1H NMR ($CDCl_3$, 500 MHz) δ 0.11 (6H, s, –Si(CH_3)$_2$), 0.91 (9H, s, –SiC(CH_3)$_3$), 2.94 (1H, br s, –OH), 3.92 (1H, dd, *J*=11.0, 4.0 Hz, H-47a), 4.04 (1H, dd, *J*=11.0, 6.0 Hz, H-47b), 4.06 (1H, dd, *J*=6.0, 4.0 Hz, H-48), 4.42 (1H, br s, H-49), 4.81 (1H, dt, *J*=6.5, 2.0 Hz, H-51), 5.68 (1H, dd, *J*=4.5, 2.0 Hz, H-50), 6.53 (1H, dd, *J*=6.5, 1.5 Hz, H-50), 7.40–7.60 (3H, m, aromatic), 8.10 (2H, d, *J*=7.3 Hz, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.46, 18.3, 25.8 62.9, 64.1, 68.1, 75.9, 98.6, 128.4, 129.8, 129.9, 133.2, 146.1, 166.2.

5.1.4. TBS-Bz-Bn-D-galactal 9. A slurry of 60% NaH (1.25 g) was placed in a 500 mL round bottom flask, and it was washed with hexane (×2). The residual powder was suspended in dry DMF (100 mL). To this suspension were added at 0°C a solution of TBS-Bz-D-galactal **8** (7.77 g, 21.3 mmol) in dry DMF (140 mL) and benzyl bromide (4.00 g, 23.4 mmol) at 0°C under Ar atmosphere. After stirring for 6 h, the mixture was poured into 5% $NaHCO_3$ solution, extracted with Et_2O (×3). The combined organic layer was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide the oil product (10.0 g). The residue was purified by silica gel chromatography (Et_2O–hexane=1:10) to give a colorless oil of TBS-Bz-Bn-D-galactal **9** (8.90 g, 92%). **9**: $[\alpha]_D^{16}=-98.9°$ (*c* 1.23, $CHCl_3$) ^1H NMR ($CDCl_3$, 500 MHz) δ 0.07 (6H, s, –Si(CH_3)$_2$), 0.91 (9H, s, –SiC(CH_3)$_3$), 3.89 (1H, dd, *J*=10.5, 5.0 Hz, H-47a), 4.01 (1H, dd, *J*=10.5, 7.5 Hz, H-47b), 4.16 (1H, dd, *J*=4.0, 3.5 Hz, H-49), 4.20 (1H, m, H-48), 4.60 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.78 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.86 (1H, dd, *J*=6.5, 3.5 Hz, H-51), 5.76 (1H, t, *J*=3.5 Hz, H-50), 6.46 (1H, dd, *J*=6.5, 1.0 Hz, H-50), 7.21–7.58 (8H, m, aromatic), 8.03 (2H, d, *J*=7.3 Hz, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.35, −5.26, 18.4, 25.9, 60.9, 65.7, 70.8, 73.4, 77.4, 98.5, 127.7, 127.8, 127.9, 128.3, 128.4, 129.7, 133.1, 137.9, 145.8, 166.2. FAB-MS 477 $[M^+ + Na]^+$.

5.1.5. Bz-Bn-D-galactal 10. To a solution of TBS-Bz-Bn-D-galactal **9** (3.24 g, 7.14 mmol) in dry THF (20.0 mL) was added dropwise TBAF (1 M solution in THF, 7.20 mL, 7.20 mmol) at room temperature under Ar atmosphere. After stirring for 3 h, the mixture was concentrated to dryness under reduced pressure. The residue was purified by silica gel (Et_2O–hexane=1:4) to give Bz-Bn-D-galactal **10** (2.30 g, 95%) as a colorless oil. *Compound* **10**. $[\alpha]_D^{16}=-170.2°$ (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88 (1H, br s, –OH), 3.88 (1H, dd, *J*=10.5, 5.0 Hz, H-47a), 4.04 (1H, dd, *J*=10.5, 8.0 Hz, H-47b), 4.15 (1H, t, *J*=4.0 Hz, H-49), 4.27 (1H, m, H-48), 4.55 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.79 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.93 (1H, dd, *J*=6.5, 4.0 Hz, H-51), 5.77 (1H, dt, *J*=3.5, 1.5 Hz, H-50), 6.48 (1H, dd, *J*=6.5, 1.0 Hz, H-50), 7.25–7.60 (8H, m, aromatic), 8.05 (2H, d, *J*=7.5 Hz, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 60.8, 64.8, 71.1, 72.9, 76.1, 98.3, 128.0, 128.1, 128.8 129.7, 129.9, 133.2, 137.3, 145.7, 166.2.

5.1.6. TBDPS-Bz-Bn-D-galactal 11. To a mixture of Bz-Bn-D-galactal **10** (1.44 g, 4.24 mmol) and TBDPSCl (1.40 g, 5.09 mmol) imidazole (634 mg, 9.32 mmol) in dry DMF (20.0 mL) was added dropwise at room temperature. After stirring for 2 h, the mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt (×3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a crude oil. The residue was purified by silica gel chromatography (Et_2O–hexane=1:10) to provide TBDPS-Bz-Bn-D-galactal **11** (2.44 g, 100%). *Compound* **11**: $[\alpha]_D^{16}=-55.3°$ (*c* 0.560, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (9H, s, –SiC(CH_3)$_3$), 4.01 (1H, dd, *J*=11.0, 5.0 Hz, H-47a), 4.12 (1H, dd, *J*=11.0, 7.5 Hz, H-47b), 4.18 (1H, t, *J*=3.5 Hz, H-49), 4.31 (1H, m, H-48), 4.56 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.74 (1H, d, *J*=12.0 Hz, –CH_2Ph), 4.81 (1H, dd, *J*=6.0, 3.5 Hz, H-51), 5.73 (1H, t, *J*=4.0 Hz, H-50), 6.34 (1H, d, *J*=6.0 Hz, H-50), 7.22–7.74 (18H, m, aromatic), 8.03 (2H, d, *J*=7.5 Hz, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 26.5, 26.9, 61.4, 65.5, 7.0, 73.2, 77.2, 98.4, 127.66, 127.68, 127.71, 128.3, 128.4, 129.6, 129.68, 129.69, 129.98, 132.9, 133.4, 133.5, 134.8, 135.59, 135.65, 137.8, 145.7, 166.2.

5.1.7. Lactone 12. The mixture of TBDPS-Bz-Bn-D-galactal **11** (2.17 g, 3.75 mmol) and PCC (2.82 g) in 30 mL 1,2-dichloroethane was heated at 80°C for 6 h under Ar atmosphere. After the reaction was completed, the mixture was poured onto a silica gel column and eluted with hexane–Et_2O=4:1 to provide lactone **12** (1.13 g, 51%) as colorless oil. **12**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (9H, s, –SiC(CH_3)$_3$), 3.05 (2H, ddd, *J*=17.5, 11.0, 8.0 Hz, H-51), 3.86 (1H, dd, *J*=10.5, 5.5 Hz, H-47a), 3.96 (1H, dd, *J*=10.5, 9.0 Hz, H-47b), 4.40 (1H, m, H-48), 4.42 (1H, m, H-49),

4.73 (1H, d, J=11.0 Hz, –CH_2Ph), 4.80 (1H, d, J=11.0 Hz, –CH_2Ph), 5.42 (1H, ddd, J=11.0, 8.0, 2.0 Hz, H-50), 7.22–7.62 (18H, m, aromatic), 7.98 (2H, dd, J=7.8, 1.0 Hz, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 26.9, 32.2, 61.2, 65.8, 69.7, 71.3, 75.1, 79.0, 127.6, 127.8, 127.9, 128.4, 128.6, 129.2, 129.8, 129.9, 130.1, 132.6, 132.7, 133.6, 135.4, 135.5, 137.5, 165.6, 167.8. FAB-MS 617 $[M+Na]^+$, 578 $[M+H]^+$.

5.1.8. Enlactone 13. To a solution of lactone **12** (1.13 g, 1.9 mmol) in dry CH_2Cl_2 (20.0 mL) was added DBU (380 mg, 2.47 mmol) at room temperature under Ar atmosphere. After stirring for 2 h, the mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography (Et_2O–hexane=1:2) to give enlactone **13** (889 mg, 98%) as a colorless oil. *Compound* **13**: $[\alpha]_D^{16}=-93.1°$ (c 1.030, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (9H, s, –SiC(CH_3)$_3$), 3.91 (1H, dd, J=10.5, 5.5 Hz, H-47a), 4.12 (1H, dd, J=10.3, 8.5 Hz, H-47b), 4.19 (1H, dd, J=5.5, 3.5 Hz, H-49), 4.44 (1H, ddd, J=8.5, 5.5, 3.5 Hz, H-48), 4.60 (2H, s, –CH_2Ph), 6.09 (1H, d, J=10.0 Hz, H-51), 6.88 (1H, dd, J=10.0, 5.5 Hz, H-50), 7.22–7.63 (15H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 26.8, 61.0, 65.8, 71.9, 79.7, 123.9, 127.7, 127.81, 127.83, 128.0, 128.5, 129.8, 129.9, 132.7, 132.9, 135.4, 135.5, 137.5, 142.8, 162.6. FAB-MS 495 $[M+Na]^+$, 473 $[M+H]^+$.

5.1.9. Dimethyllactone 14. A solution of MeLi (1.14 M in Et_2O, 11.8 mL, 13.5 mmol) was added dropwise to a slurry solution of CuI (1.28 g, 6.75 mmol) in dry Et_2O (20 mL) at 0°C under Ar atmosphere. After the mixture was stirred for 10 min, the copper reagent was treated with TMSCl (2.2 mL, 16.9 mmol). After the mixture was cooled at −20°C, a solution of enlactone **13** (795 mg, 1.69 mmol) in dry Et_2O (10 mL) was added, the mixture was stirred overnight at this temperature. After the reaction was completed, the mixture was poured into NH_3/NH_4Cl solution (pH=8) and extracted with Et_2O. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide crude oil product. The residue was purified by silica gel chromatography (Et_2O–hexane=1:2) to give a colorless oil (748 mg, 91%). To a solution of LiHMDS (1 M in THF, 4.00 mL, 4.00 mmol) in dry THF (20 mL) was added dropwise a solution of the oil (1.48 g, 3.03 mmol) in dry THF (25 mL) at −78°C under Ar atmosphere. After stirring for 30 min, methyl iodide (1 mL, 15.16 mmol) was added dropwise. After stirring for 30 min, the mixture was quenched by saturated NH_4Cl, then warmed to room temperature and extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide the crude oil. This crude oil was purified by silica gel chromatography (Et_2O–hexane=1:5) to give dimethyllactone **14** (1.25 g) and its C51-epimer **14′** (170 mg) in 93% combined yield. *Compound* **14**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (9H, s, –SiC(CH_3)$_3$), 1.08 (3H, d, J=7.0 Hz, CH_3-59), 1.21 (3H, d, J=6.5 Hz, CH_3-60), 1.83 (1H, m, H-50), 2.02 (1H, dq, J=9.0, 7.0 Hz, H-51), 3.53 (1H, dt, J=2.0, 2.0 Hz, H-49), 3.88–3.97 (2H, ddd, J=10.5, 7.5, 5.5 Hz, H-47a), 4.42 (1H, td, J=7.5, 2.0 Hz, H-48), 4.39 (1H, d, J=12.0 Hz, –CH_2Ph), 4.57 (1H, d, J=12.0 Hz, –CH_2Ph), 7.18–7.60 (15H, m, aromatic). ^{13}C NMR ($CDCl_3$ 125 MHz) δ 14.7, 19.2, 19.3, 26.8, 38.6, 40.1, 61.5, 71.1, 77.1, 77.2, 127.5, 127.7, 127.8, 127.8, 128.4, 129.8, 129.9, 132.9, 135.5, 135.5, 137.8, 174.4. FAB-MS 525 $[M+Na]^+$, 503 $[M+H]^+$, **14′** (C51-epimer of **14**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (3H, d, J=7.5 Hz, CH_3-60), 1.04 (9H, s, –SiC(CH_3)$_3$), 1.18 (3H, d, J=7.0 Hz, CH_3-59), 2.37 (1H, m, H-50), 3.05 (1H, dq, J=7.5, 5.0 Hz, H-51), 3.73 (1H, t, J=3.0 Hz, H-49), 3.82 (1H, dd, J=10.0, 5.5 Hz, H-47a), 4.03 (1H, dd, J=10.0, 8.5 Hz, H-47b), 4.47 (1H, ddd, J=8.5, 5.5, 3.0 Hz, H-48), 4.57 (1H, d, J=11.4 Hz, –CH_2Ph), 4.68 (1H, d, J=11.4 Hz, –CH_2Ph), 7.24–7.62 (15H, m aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0, 13.1, 19.2, 26.8, 34.2, 34.7, 61.7, 71.7, 75.3, 78.6, 127.4, 127.7, 127.8, 128.4, 129.8, 129.9, 132.9, 133.1, 135.5, 135.6, 137.9, 173.5. FAB-MS 525 $[M+Na]^+$, 503 $[M+H]^+$.

5.1.10. LM-Ring fragment 16a–d. To a solution of dimethyllactone **14** (330 mg, 0.66 mmol) in dry Et_2O (10 mL) was added allylmagnesium bromide (1 M in THF, 1.00 mL) at −78°C under Ar atmosphere. After stirring for 3 h, the mixture was added saturated NH_4Cl solution, then warmed to room temperature, extracted with Et_2O (×3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a crude oil. The residue was purified by silica gel chromatography (Et_2O–hexane=1:10) to give hemiacetal **15** as a colorless oil mixture (270 mg, 87% based on recovering starting material) and recover starting material (42 mg).

To a mixture of AD-mix-α (280 mg) in 50% aqueous *t*-BuOH (5.00 mL) was added hemiacetal **15** (90 mg) at 0°C, then the mixture was stirred for 2 days at this temperature. After starting material disappeared, the reaction was quenched by Na_2SO_3 (100 mg), then the mixture was stirred for 30 min, extracted with AcOEt (×3). The combined organic layer was washed by brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide a crude oil. The residue was purified by preparative TLC (Et_2O–hexane=1:1) to give LM-ring fragment **16a** (R_f=0.38, 28 mg), **16b** (R_f=0.0.38, 27 mg), **16c** (R_f=0.0.66, 7 mg) and **16d** (R_f=0.0.66, 8 mg) in 75% combined yield. *Compound* **16a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (3H, d, J=6.0 Hz, CH_3-59), 0.97 (3H, d, J=6.5 Hz, CH_3-60), 1.05 (9H, s, –SiC(CH_3)$_3$), 1.49 (1H, dq, J=11.0, 6.5 Hz, H-51), 1.54 (1H, br s, OH-54), 1.72 (1H, m, H-50), 1.94 (1H, ddd, J=14.0, 2.5, 1.0 Hz, H-53a), 2.21 (1H, dd, J=14.0, 7.0 Hz, H-53b), 3.22 (1H, dd, J=11.0, 6.0 Hz, H-49), 3.70 (1H, d, J=10.0 Hz, H-55a), 3.88 (1H, dd, J=11.0, 4.0 Hz, H-47a), 4.10 (1H, d, J=11.5 Hz, –CH_2Ph), 4.11 (1H, ddd, J=8.0, 6.0, 4.0 Hz, H-48), 4.25 (1H, dd, J=10.0, 4.0 Hz, H-55b), 4.26 (1H, d, J=11.5 Hz, –CH_2Ph), 4.31 (1H, dd, J=11.0, 8.5 Hz, H-47b), 7.05–7.70 (15H, m aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 15.5, 19.2, 26.9, 34.4, 42.5, 47.0, 63.2, 71.4, 71.9, 75.2, 79.7, 109.0, 127.5, 127.59, 127.61, 127.9, 128.2, 129.5, 129.6, 133.9, 134.1, 135.7, 135.7. FAB-MS 583 $[M+Na]^+$, 561 $[M+H]^+$. *Compound* **16b**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (9H, s, –SiC(CH_3)$_3$), 1.18 (3H, d, J=7.5 Hz, CH_3-59), 1.21 (3H, d, J=7.5 Hz, CH_3-60), 1.52 (1H, br s, OH-54), 1.73 (1H, m, H-51), 1.73 (1H, dd, J=13.5, 4.0 Hz, H-53), 2.09 (1H, qt, J=7.5, 2.0 Hz, H-50), 2.39 (1H, dd,

J=13.5, 7.5 Hz, H-53), 3.21 (1H, t, J=1.5 Hz, H-49), 3.73 (1H, dd, J=10.0, 2.0 Hz, H-55), 3.76 (1H, dd, J=10.0, 6.5 Hz, H-47), 3.84 (1H, dd, J=10.0, 6.5 Hz, H-47), 4.00 (1H, td, J=6.5, 2.0 Hz, H-48), 4.37 (1H, d, J=11.5 Hz, –CH_2Ph), 4.53 (1H, m, H-2), 4.65 (1H, d, J=11.5 Hz, –CH_2Ph), 7.23–7.69 (15H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9, 19.2, 19.8, 26.9, 35.6, 39.2, 46.9, 63.8, 69.0, 70.1, 71.0, 74.1, 110.3, 127.3, 127.6, 127.6, 127.6, 127.9, 128.2, 129.6, 133.7, 135.5, 135.6, 138.8. FAB-MS 583 $[M+Na]^+$, 561 $[M+H]^+$. *Compound* **16c**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (9H, s, –SiC(CH_3)$_3$), 1.12 (3H, d, J=7.5 Hz, CH_3-59), 1.20 (3H, d, J=7.5 Hz, CH_3-60), 1.53 (br s, 1H, OH-55), 1.59 (1H, qd, J=7.5, 1.0 Hz, H-51), 1.78 (1H, dd, J=13.5, 6.0 Hz, H-53a), 2.05 (1H, qt, J=7.5, 2.0 Hz, H-50), 2.17 (1H, d, J=13.5, 2.0 Hz, H-48), 3.05 (1H, dd, J=2.0, 1.5 Hz, H-49), 3.62 (1H, dd, J=10.5, 4.5 Hz, H-47), 3.87 (1H, dd, J=10.5, 8.0 Hz, H-47), 3.89 (1H, dd, J=10.0, 1.0 Hz, H-55a), 4.12 (1H, ddd, J=8.0, 4.5, 2.0 Hz, H-48), 4.16 (1H, dd, J=10.0, 5.5 Hz, H-55b), 4.24 (1H, m, H-54), 4.26 (1H, d, J=12.0 Hz, –CH_2Ph), 4.58 (1H, d, J=12.0 Hz, –CH_2Ph), 7.14–7.64 (15H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0, 19.1, 19.8, 26.8, 35.1, 38.9, 45.0, 64.3, 69.2, 70.9, 71.0, 76.7, 77.5, 110.4, 127.4, 127.7, 127.7, 127.9, 128.2, 129.6, 129.7, 133.4, 133.5, 135.6, 135.6, 135.8, 138.4. FAB-MS 583 (M^++Na, 5), 561 (M^++H, 14), 543 (M^+−OH, 6). *Compound* **16d**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80 (3H, d, J=6.5 Hz, CH_3-60), 0.88 (3H, d, J=6.5 Hz, CH_3-59), 1.01 (9H, s, –SiC(CH_3)$_3$), 1.45 (1H, br s, OH-54), 1.52 (1H, dq, J=10.0, 6.5 Hz, H-51), 1.68 (1H, m, H-50), 1.86 (1H, d, J=13.5 Hz, H-53a), 2.02 (1H, dd, J=13.5, 5.5 Hz, H-53b), 3.14 (1H, dd, J=10.5, 6.0 Hz, H-49), 3.71 (1H, dd, J=11.5, 4.0 Hz, H-47), 3.94 (1H, d, J=11.5 Hz, –CH_2Ph), 3.98 (1H, dd, J=10.0, 5.0 Hz, H-55a), 4.03 (1H, d, J=11.5 Hz, –CH_2Ph), 4.10 (1H, ddd, J=10.0, 6.0, 4.0 Hz, H-48), 4.22 (1H, d, J=10.0 Hz, H-55b), 4.26 (1H, m, H-54), 4.27 (1H, dd, J=11.5, 10.0 Hz, H-47), 6.70–7.66 (15H, m, aromatic) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.3, 15.4, 19.1, 26.9, 34.2, 41.8, 43.6, 62.9, 71.4, 72.2, 74.9, 78.2, 79.4, 109.7, 127.6, 127.7, 127.9, 128.2, 129.6, 129.7, 133.6, 133.9, 135.7, 135.8, 137.8. FAB-MS 583 $[M+Na]^+$, 561 $[M+H]^+$.

5.1.11. Inversion of stereogenic center at C54 of 16c and d. To a mixture of spiroketal **16c** and **d** (67.4 mg, 0.120 mmol), *p*-nitrobenzoic acid (90.0 mg, 0.602 mmol) and PPh_3 (158 mg, 0.602 mmol) in dry toluene (5.00 mL) was added DEAD (0.100 mL, 0.602 mmol) at room temperature under Ar atmosphere, then the mixture was stirred for 1 h. After the reaction was completed, the mixture was evaporated under reduced pressure and purified by preparative TLC (Et_2O–hexane=1:1) to give *p*-nitrobenzoate **16a**′ (R_f=0.0.68, 26.0 mg) and **16b**′ (R_f=0.0.74, 35 mg) in 95% combined yield. *Compound* **16a**′ (*p*-nitrobenzoate of **16a**) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (3H, d, J=7.5 Hz, CH_3), 1.07 (3H, d, J=6.5 Hz, CH_3), 1.07 (9H, s, –SiC(CH_3)$_3$), 1.55 (1H, m, H-51), 1.75 (1H, dq, J=11.0, 6.5 Hz, H-51), 2.18 (1H, d, J=15.0 Hz, H-53a), 2.45 (1H, dd, J=15.0, 7.5 Hz, H-53b), 3.24 (1H, dd, J=11.0, 6.0 Hz, H-49), 3.88 (1H, dd, J=11.0, 4.0 Hz, H-47), 4.0 (1H, d, J=11.0 Hz, H-55a), 4.09 (1H, d, J=11.5 Hz, –CH_2Ph), 4.14 (1H, m, H-48), 4.23 (1H, d, J=11.5 Hz, –CH_2Ph), 4.48 (1H, dd, J=11.0, 4.5 Hz, H-55b), 5.59 (1H, br s, H-54), 7.04–8.28 (19H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5, 15.4, 19.3, 27.0, 34.5, 42.6, 44.2, 63.2, 71.5, 72.1, 75.3, 76.6, 79.6, 108.9, 123.6, 127.6, 127.7, 127.7, 128.2, 129.6, 129.7, 130.6, 133.8, 134.1, 135.5, 135.7, 135.7, 137.9, 150.7, 164.4. *Compound* **16b**′ (*p*-nitrobenzoate of **16b**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (9H, s, –SiC(CH_3)$_3$), 1.16 (3H, d, J=7.5 Hz, CH_3), 1.21 (3H, d, J=7.5 Hz, CH_3), 1.74 (1H, qd, J=7.5, 1.5 Hz, H-51), 1.95 (1H, dd, J=14.0, 4.5 Hz, H-53a), 2.09 (1H, qt J=7.5, 2.0 Hz, H-50), 2.57 (1H, dd, J=14.0, 7.5 Hz, H-53b), 3.21 (1H, br s., H-49), 3.78 (1H, dd, J=10.5, 6.5 Hz, H-47), 3.84 (1H, dd, J=10.5, 6.0 Hz, H-47), 3.96–4.0 (2H, m, H-48, 55a), 4.09 (1H, dd, J=10.5, 5.5 Hz, H-55b), 4.36 (1H, d, J=12.0 Hz, –CH_2Ph), 4.63 (1H, d, J=12.0 Hz, –CH_2Ph), 5.50 (1H, m, H-54), 7.21–8.28 (19H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.8, 19.2, 19.7, 26.9, 35.6, 38.9, 43.6, 63.8, 69.3, 71.1, 71.2, 75.7, 76.6, 110.1, 123.5, 127.4, 127.6, 128.2, 129.6, 129.7, 130.6, 130.7, 133.7, 133.8, 135.5, 135.7, 138.7, 150.6, 164.6.

To a solution of *p*-nitrobenzoate **16a**′ and **16b**′ (1.00 g, 1.41 mmol) in MeOH (20 mL) was added K_2CO_3 (195 mg, 1.41 mmol) at room temperature under Ar atmosphere. After stirring for 2 h, the mixture was evaporated under reduced pressure. The residue was dissolved in distilled water and extracted with AcOEt (×3). The combined organic layer was dried over Na_2SO_4 and filtered, evaporated under reduced pressure. The residue was purified by silica gel chromatography (Et_2O–hexane=1:5) to give the mixture of **16a** and **b** (785 mg, 99%).

5.1.12. Alcohol 25. To a solution of spiroketals **16a** and **b** (292 mg, 0.521 mmol) in DMF (3.00 mL) was added 47.1 mg of 60% NaH (47.1 mg) at 0°C under Ar atmosphere. After stirring for 30 min, the mixture was added BnBr (269 mg, 1.56 mmol), then stirred for 5 h. The mixture was added ice-water (0.50 mL), subsequently added saturated $NaHCO_3$ solution, and extracted with AcOEt (×3). The combined organic layer was washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated to give a crude oil. The residue was purified by silica gel column (Et_2O–hexane=1:20) to give a mixture of benzyl ether (227 mg, 88% based on recovered starting material) and recovered starting material (70 mg). To a solution of the mixture of benzyl ether (200 mg, 0.308 mmol) in THF (5.00 mL) was added TBAF (1.20 mL, 1 M in THF, 1.20 mmol) at room temperature under Ar atmosphere, then the mixture was stirred for 6 h. The mixture was evaporated under reduced pressure to give a crude oil. The residue was purified by silica gel chromatography (Et_2O–hexane=1:2) to give alcohol **25** (117 mg, 92%) as colorless oil. *Compound* **25**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (3H, d, J=6.5 Hz, CH_3), 0.96 (3H, d, J=6.5 Hz, CH_3), 1.43 (1H, m, H-51), 1.92 (1H, m, H-50), 2.06 (2H, ddd, J=14.0, 7.0, 4.0 Hz, H-53a), 3.76 (1H, m, H-49), 3.93 (4H, m, H-47, 48, 55a, 55b), 4.21 (1H, m, H-54), 4.38 (2H, d, J=12.0 Hz, –CH_2Ph), 4.47 (1H, d, J=12.0 Hz, –CH_2Ph), 4.56 (1H, d, J=12.0 Hz, –CH_2Ph), 7.24–7.34 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 15.5, 26.5, 34.6, 42.8, 43.7, 63.1, 71.1, 72.4, 73.2, 78.2, 80.8, 109.2, 127.5, 127.7, 127.7, 128.0, 128.1, 128.4, 128.5, 134.8.

5.1.13. Chloride 26. A solution of alcohol **25** (44.2 mg,

0.107 mmol) and PPh_3 (113 mg, 0.429 mmol) in CCl_4 (10 mL) was refluxed overnight under Ar atmosphere. After the reaction was completed, the mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (Et_2O–hexane=1:3) to give chloride **26** (36.6 mg, 79%). *Compound* **26**. ^1H NMR ($CDCl_3$, 125 MHz) δ 1.17 (3H, d, J=7.5 Hz, CH_3), 1.20 (3H, d, J=7.0 Hz, CH_3), 1.72 (1H, dq, J=7.5, 2.0 Hz, H-51), 1.85 (1H, dd, J=13.0, 5.0 Hz, H-53a), 2.13 (1H, tq, J=7.5, 2.0 Hz, H-50), 2.38 (1H, dd, J=13.0, 7.5 Hz, H-53b), 3.20 (1H, br s, H-49), 3.58 (2H, ddd, J=11.0, 7.5, 6.0 Hz, H-47a, 47b), 3.92 (1H, dd, J=10.0, 2.5 Hz, H-55a), 4.01 (1H, dd, J=10.0, 6.0 Hz, H-55b), 4.04 (1H, ddd, J=7.5, 6.0, 2.0 Hz, H-48), 4.33, (1H, m, H-53), 4.36 (1H, d, J=11.5 Hz, –CH_2Ph), 4.44 (1H, d, J=11.5 Hz, –CH_2Ph), 4.67 (2H, d, J=11.5 Hz, –CH_2Ph), 7.24–7.34 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.8, 19.7, 35.4, 38.8, 43.9, 44.3, 69.1, 71.1, 71.5, 71.6, 77.6, 110.5, 127.6, 127.6, 127.7, 127.8, 128.3, 128.4, 138.1, 138.3. FAB-MS 431 $[M+H]^+$.

5.1.14. Iodide 27. To a mixture of alcohol **25** (54 mg, 0.129 mmol), PPh_3 (67.5 mg, 0.257 mmol) and imidazole (18 mg, 0.257 mmol) in dry toluene (5.00 mL) was added iodine (65.3 mg, 0.257 mmol) at room temperature under Ar atmosphere, then the mixture was stirred for 6 h. After the reaction was quenched by adding saturated $NaHCO_3$ solution, the mixture was extracted with Et_2O. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a crude oil. The crude oil was purified by preparative TLC to give a mixture of iodide **27** (55 mg, 82%). *Compound* **27**. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (3H, d, J=7.0 Hz, CH_3), 0.97 (3H, d, J=7.5 Hz, CH_3), 2.02 (2H, m, H-51a, 53a), 2.16 (1H, dd, J=13.5, 7.5 Hz, H-53b), 2.23 (1H, m, H-50), 3.06 (1H, dd, J=10.0, 5.5 Hz, H-47a), 3.19 (1H, dd, J=10.0, 8.5 Hz, H-47b), 3.89 (2H, m, H-48, 55a), 4.00 (1H, dd, J=9.5, 5.0 Hz, H-55b), 4.22 (1H, m H-54), 4.35 (1H, d, J=12.0 Hz, –CH_2Ph), 4.38 (2H, dd, J=12.0 Hz, –CH_2Ph), 4.61 (1H, d, J=12.0 Hz, –CH_2Ph), 7.18–7.28 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.3, 13.2, 13.3, 32.2, 34.6, 42.8, 68.9, 71.2, 71.3, 72.1, 78.1, 78.4, 110.5, 127.6, 127.6, 127.9, 128.1, 128.4, 128.4, 138.3. FAB-MS 523 $[M+H]^+$, 395. *Compound* **27′** (anomeric isomer of iodide **27**): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (3H, d, J=7.5 Hz, CH_3), 1.22 (3H, d, J=7.5 Hz, CH_3), 1.71 (1H, qd, J=7.5, 1.5 Hz, H-51), 1.84 (1H, dd, J=13.0, 5.5 Hz, H-53a), 2.12 (1H, qt, J=7.5, 2.0 Hz, H-50), 2.40 (1H, dd, J=13.0, 7.5 Hz, H-53b), 3.27 (1H, t, J=2.0 Hz, H-49), 3.35 (1H, dd, J=10.0, 9.0 Hz, H-47a), 3.94 (1H, dd, J=9.5, 2.5 Hz, H-55a), 4.06 (1H, ddd, J=9.0, 5.0, 2.0 Hz, H-48), 4.17 (1H, dd, J=9.5, 6.0 Hz, H-55b), 4.34 (1H, d, J=11.5 Hz, –CH_2Ph), 4.41 (1H, m, H-55b), 4.47 (1H, dd, J=11.5 Hz, –CH_2Ph), 4.70 (1H, d, J=11.5 Hz, –CH_2Ph), 7.24–7.34 (10H, m, aromatic). FAB-MS 523 $[M+H]^+$.

5.1.15. Diol 29. To a solution of tri-*O*-acetyl-D-glucal (200 g, 0.735 mol) and 2-propanol (112 mL, 1.47 mol, 2 equiv.) in dry CH_2Cl_2 (2.00 L) was added dropwise $BF_3{\cdot}OEt_2$ (46.4 mL, 0.367 mol, 0.5 equiv.) at 0°C. After stirring for 50 min at room temperature, the reaction mixture was poured into cold saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_2, and concentrated under reduced pressure to give acetal **28** as a crude oil, which was used in the next step without further purification.

To a solution of the crude oil of acetal **28** in MeOH (1.50 L) were added H_2O (300 mL) and Et_3N (300 mL) at room temperature. After stirring for 5.5 h at room temperature, the reaction mixture was concentrated under reduced pressure, and recrystallized (hexane/ether) to give diol **29** (117 g, 84% in 2 steps). *Compound* **29**. Mp 98–100°C. IR (KBr) ν_{max} 3392, 2970, 2937, 2900, 1439, 1386, 1326, 1096, 1029, 947, 819, 794 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 1.24 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 2.23 (1H, br s, –OH), 2.40 (1H, br s, –OH), 3.75 (1H, dt, J=9.0, 4.5 Hz, H-48′), 3.86 (2H, m, H-47′a, 47′b), 3.98 (1H, sep, J=6.0 Hz, –CH(CH$_3$)$_2$), 4.21 (1H, t, J=4.5 Hz, H-49), 5.09 (1H, br s, H-52), 5.73 (1H, dt, J=10, 2.5 Hz, H-50), 5.96 (1H, br-d, J=10 Hz, H-51). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 23.6, 62.8, 64.3, 70.4, 71.2, 92.5, 127.0, 133.2. Anal. calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.26; H, 8.48.

5.1.16. Alcohol 30. To a solution of diol **29** (20.4 g, 0.108 mol) and imidazole (22.1 g, 0.324 mol, 3 equiv.) in DMF (1.00 L) was added TBSCl (19.6 g, 0.13 mol) at 0°C. After stirring for 30 min at 0°C, the reaction mixture was poured into cold saturated $NaHCO_3$ solution and extracted with Et_2O (×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt–hexane=1:9) to give alcohol **30** (32.8 g, 100%). *Compound* **30**. IR (KBr) ν_{max} 3448, 2959, 2931, 2887, 2859, 1473, 1385, 1256, 1131, 1087, 1031, 837, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (6H, s, –Si(CH_3)$_2$), 0.90 (9H, s, –SiC(CH_3)$_3$), 1.16 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 1.23 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 2.80 (1H, d, J=4.0 Hz, –OH), 3.77 (2H, m, H-47′a, 47′b), 3.88 (1H, m, H-48′), 3.95 (1H, sep, J=6.0 Hz, –CH(CH$_3$)$_2$), 4.16 (1H, m, H-49), 5.04 (1H, m, H-52), 5.73 (1H, dt, J=10.5, 2.5 Hz, H-50), 5.96 (1H, dt, J=10.5, 1.0 Hz, H-51). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.7, −5.6, 18.2, 21.9, 23.7, 25.8, 65.5, 67.2, 69.9, 70.1, 92.4, 126.5, 132.6. Anal. calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.57; H, 9.98.

5.1.17. Enone 31. The alcohol **30** (32.8 g, 0.108 mol) was dissolved in DMSO (600 mL) and acetic anhydride (400 mL). After stirring for 12 h at room temperature, the reaction mixture was poured into cold H_2O and extracted with Et_2O (×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt–hexane=1:19) to give enone **31** (31.6 g, 97%). *Compound* **31**. IR (KBr) ν_{max} 2958, 2931, 2885, 2859, 1698, 1473, 1384, 1319, 1255, 1135, 1091, 1065, 1035, 917, 837, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (3H, s, –Si(CH_3)$_2$), 0.07 (3H, s, –Si(CH_3)$_2$), 0.87 (9H, s, –SiC(CH_3)$_3$), 1.21 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 1.26 (3H, d, J=6.0 Hz, –CH(CH_3)$_2$), 3.98 (1H, dd, J=11.5, 5.5 Hz, H-47′a), 4.07 (1H, sep, J=6.0 Hz, –CH(CH$_3$)$_2$), 4.08 (1H, dd, J=11.5, 2.5 Hz, H-47′b), 4.49 (1H, dd, J=5.5, 2.5 Hz, H-48′), 5.40 (1H, d, J=3.5 Hz, H-36), 6.08 (1H, d, J=10.5 Hz, H-50), 6.84 (1H, dt, J=10.5, 3.5 Hz, H-51). ^{13}C

NMR ($CDCl_3$, 75 MHz) δ −5.5, −5.5, 18.2, 21.8, 23.2, 25.7, 62.5, 71.0, 76.0, 91.4, 127.9, 144.7, 195.2. $[\alpha]_D^{29}=-10.32°$ (*c* 0.990, $CHCl_3$). Anal. calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 59.96; H, 9.53.

5.1.18. Dimethylketol 33. To a stirred solution containing CuI (6.82 g, 35.8 mmol) in dry Et_2O (236 mL) was added methyl lithium (1.14 M solution in Et_2O, 62.8 mL, 71.6 mmol) at 0°C. After stirring for 15 min, the reaction mixture was mixed with enone **31** (10.7 g, 35.4 mmol) with dry Et_2O (118 mL). After stirring for further 30 min, to the reaction mixture were slowly added iodomethane (11.1 mL, 177 mmol) and *N*,*N*-dimethylacetamide (138 mL). The resulting mixture was gradually warmed to room temperature. After stirring 2.5 h the reaction mixture was poured into a cold 1.2N HCl solution. The resulting mixture was filtered through a Hyflo-Super-Cel® and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:19) to give dimethylketone **32** (11.5 g, 98%).

To a solution of dimethylketone **32** (10.8 g, 32.8 mmol) in THF (164 mL) was added TBAF (1.0 M solution in THF, 164 mL, 164 mmol) at 0°C. After stirring for 40 min at room temperature, the reaction mixture was pouring into cold saturated NH_4Cl solution, and extracted with Et_2O (×3), the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide dimethylketol **33** (6.31 g, 89%). *Compound* **33**. IR (KBr) ν_{max} 3436, 2974, 2367, 1729, 1637, 1457, 1381, 1071, 1011 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.03 (3H, d, *J*=6.5 Hz, CH_3-59), 1.11 (3H, d, *J*=6.5 Hz, CH_3), 1.15 (3H, d, *J*=6.0 Hz, –CH(CH_3)$_2$), 1.18 (3H, d, *J*=6.0 Hz, –CH(CH_3)$_2$), 1.58 (1H, dq, *J*=12.5, 6.5 Hz, H-51), 2.25 (1H, br, –O*H*), 2.32 (1H, dq, *J*=12.5, 6.5 Hz, H-50), 3.82 (1H, dd, *J*=12.0, 4.0 Hz, H-47′a), 3.91 (1H, dd, *J*=12.0, 4.0 Hz, H-47′b), 3.93 (1H, sep, *J*=6.0 Hz, –C*H*(CH_3)$_2$), 4.17 (1H, t, *J*=4.0 Hz, H-48′), 4.73 (1H, d, *J*=6.0 Hz, H-52). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 10.2, 16.4, 21.4, 23.4, 39.9, 44.3, 62.0, 69.3, 74.5, 102.2. HRMS (FAB) calcd for $C_{11}H_{21}O_4$ $[M+H]^+$ 217.1440, found 217.1463.

5.1.19. Diol 34. To a solution of dimethylketol **33** (4.89 g, 22.6 mmol) in CH_3CN (113 mL) and AcOH (113 mL) was added $NaBH(OAc)_3$ (16.8 g, 67.8 mmol) at −10°C. After stirring for 30 min, the reaction mixture was pouring into cold NaOH and $NaHCO_3$ solution, and extracted with Et_2O (×3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:1) to provide diol **34** (4.75 g, 96%). *Compound* **34**. IR (KBr) ν_{max} 3405, 2971, 2932, 1457, 1381, 1340, 1101, 1073, 1045, 1013. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.00 (3H, d, *J*=7.0 Hz, CH_3), 1.07 (3H, d, *J*=7.0 Hz, CH_3), 1.13 (3H, d, *J*=6.0 Hz, –CH(CH_3)$_2$), 1.20 (3H, d, *J*=6.0 Hz, –CH(CH_3)$_2$), 1.51–1.69 (2H, m, *H*-51, 50), 2.19 (1H, br, –OH), 2.44 (1H, br, –OH), 3.67–3.83 (4H, m, H-49, 48′, 47′a, 47′b), 3.88 (1H, sep, *J*=6.0 Hz, –C*H*(CH_3)$_2$), 4.50 (1H, d, *J*=3.5 Hz, H-52). $[\alpha]_D^{29}=+110.3°$ (*c* 1.030, $CHCl_3$). Anal. calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.41; H, 10.35.

5.1.20. Dithiane 37. To a solution of diol **34** (9.01 g, 41.3 mmol) and 1,3-propanedithiol (8.59 mL, 82.6 mmol) in $CHCl_3$ (30.6 mL) was slowly added 12N HCl (183 mL) at 0°C. After stirring for 10 min at 0°C, the reaction mixture was poured into a cold saturated NaOH and $NaHCO_3$ solution slowly and extracted with AcOEt (×10). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel short column (100% AcOEt) to provide triol **35** as a dark green crude oil (15.3 g) that was used directly without further purification.

To a solution of the crude oil (15.3 g) in CH_2Cl_2 (413 mL) were added Et_3N (17.3 mL, 124 mmol), DMAP (5.04 g, 41.3 mmol) and TBSCl (7.47 g, 49.5 mmol) at room temperature. After stirring for 4 h at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with AcOEt (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide a crude oil containing diol **36** (21.5 g) that was used directly without further purification.

To a solution of the crude oil (21.5 g) in CH_2Cl_2 (413 mL) were added 2,2-dimethoxypropane (101 mL, 825 mmol) and *p*-toluenesulfonic acid monohydrate (3.53 g, 18.6 mmol). After stirring 5 days at room temperature, the reaction mixture was poured into a cold saturated $NaHCO_3$ solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:9) to provide dithiane **37** (15.7 g, 90% in 3 steps) as a colorless oil. *Compound* **37**. IR (KBr) ν_{max} 2934, 2360, 1464, 1380, 1250, 1220, 1102, 1073, 838, 777, 669, 517 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (6H, s, –Si(CH_3)$_2$), 0.87 (3H, d, *J*=6.5 Hz, CH_3), 0.89 (9H, s, –SiC(CH_3)$_3$), 1.03 (3H, d, *J*=6.5 Hz, CH_3), 1.31 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.80–1.95 (1H, m, –$SCH_2CH_2CH_2S$–), 2.04–2.15 (1H, m, –$SCH_2CH_2CH_2S$–), 2.29–2.46 (2H, m, H-50, 51), 2.77–2.92 (4H, m, –$SCH_2CH_2CH_2S$–), 3.48 (1H, dd, *J*=10.5, 4.5 Hz, H-47′a), 3.73 (1H, dd, *J*=10.5, 7.5 Hz, H-47′b), 3.91 (1H, dd, *J*=10.5, 4.5 Hz, H-49), 3.94 (1H, d, *J*=9.5 Hz, H-52), 4.07 (1H, dt, *J*=7.5, 4.5 Hz, H-48′). ^{13}C NMR ($CDCl_3$, 75 MHz), δ −5.6, −5.5, 10.7, 10.9, 18.2, 25.5, 25.9, 26.1, 28.4, 30.2, 30.3, 31.9, 37.2, 52.9, 62.4, 78.2, 79.5, 107.3. $[\alpha]_D^{29}=+13.76°$ (*c* 1.015, $CHCl_3$). Anal. calcd for $C_{20}H_{40}O_3S_2Si$: C, 57.09; H, 9.58. Found: C, 56.98; H, 9.82.

5.1.21. Dibenzyl ether 40. A solution of dithiane **37** (1.22 g, 2.90 mmol) in 10% HMPA/THF (19.0 mL) was treated with *t*-BuLi (1.48 M in pentane, 2.35 mL, 3.48 mmol) at −78°C. Immediately thereafter a precooled (−78°C) solution of (2*S*)-glycidylmethoxybenzyl ether (676 mg, 3.48 mmol) in 10 % HMPA/THF (9.51 mL) was added. The reaction mixture was rapidly warmed to −45°C and then quenched with saturated aqueous NH_4Cl. At ambient temperature the mixture was partitioned between Et_2O and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide alcohol **38** (1.71 g, 96%).

To a solution of the alcohol **38** (1.71 g, 2.78 mmol) in THF (23.6 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 4.17 mL, 4.17 mmol) at 0°C. After stirring for 10 min at room temperature, the reaction mixture was poured into cold saturated NH_4Cl solution and extracted with Et_2O (×3). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was used directly without further purification. A one-necked flask was charged with NaH (60% dispersed in mineral oil, 455 mg, 11.4 mmol). After most of the mineral oil has been removed by washing with hexane, DMF (9.11 mL) was added to the flask, followed by a solution of the crude oil in DMF at 0°C. After stirring 1 h at room temperature, the reaction mixture was cooled to 0°C again. Benzyl bromide (0.81 mL, 6.83 mmol) and a solution of tetrabutylammonium iodide (84.0 mg, 0.278 mmol) in DMF (4.55 mL) were added to the mixture. After the addition has been complete, the mixture was allowed to room temperature and stirred for 4 h. The reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:9) to provide dibenzyl ether **40** (1.67 g, 88% in 2 steps). *Compound* **40**. IR (KBr) ν_{max} 2933, 2361, 1616, 1514, 1457, 1379, 1248, 1074, 909, 821, 735, 698, 576, 516 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 0.98 (3H, d, J=6.5 Hz, –CH_3), 1.10 (3H, d, J=6.5 Hz, CH_3), 1.24 (3H, s, –OC(CH_3)$_2$O–), 1.31 (3H, s, –OC(CH_3)$_2$O–), 1.89 (2H, m, –$SCH_2CH_2CH_2S$–), 2.15–2.30 (2H, m, H-53a, 53b), 2.58–2.89 (6H, m, H-50, 51, –$SCH_2CH_2CH_2S$–), 3.47 (1H, dd, J=9.5, 6.5 Hz, H-47′a), 3.50 (1H, dd, J=9.5, 5.5 Hz, H-55a), 3.55 (1H, dd, J=9.5, 5.0 Hz, H-55b), 3.64 (1H, dd, J=9.5, 5.5 Hz, H-47′b), 3.79 (3H, s, –$C_6H_4OCH_3$), 3.90 (1H, dd, J=10.5, 5.0 Hz, H-49), 4.04 (1H, m, H-54), 4.24 (1H, ddd, J=6.5, 5.5, 5.0 Hz, H-48′), 4.47 (1H, d, J=11.5 Hz, –$CH_2C_6H_4OCH_3$), 4.51 (1H, d, J=11.5 Hz, –$CH_2C_6H_4OCH_3$), 4.54 (1H, d, J=11.0 Hz, –OCH_2Ph), 4.60 (2H, d, J=11.0 Hz, –OCH_2Ph), 4.69 (1H, d, J=11.0 Hz, –OCH_2Ph), 6.83–6.89 (2H, m, aromatic), 7.21–7.40 (12H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 8.5, 13.3, 25.2, 25.8, 25.9, 28.4, 31.8, 37.3, 39.2, 55.3, 59.2, 69.8, 72.0, 72.3, 72.9, 73.5, 76.3, 76.6, 80.0, 107.6, 113.8, 127.3, 127.5, 127.8, 127.9, 128.2, 128.3, 129.2, 130.5, 138.3, 139.0, 159.2. $[\alpha]_D^{29}=-4.00°$ (c 0.580, $CHCl_3$). Anal. calcd for $C_{39}H_{52}O_6S_2$: C, 68.79; H, 7.70. Found: C, 68.67; H, 7.82.

5.1.22. Aldehyde 42. A solution of dibenzyl ether **40** (11.4 g, 16.7 mmol) in 80% acetic acid (167 mL) was stirred at 40°C for 1 day. The reaction mixture was poured into a cold NaOH and $NaHCO_3$ solution and extracted with AcOEt (×4). The resulting extract was dried over Na_2SO_4, and concentrated under reduced pressure to give a crude oil that was chromatographed on a silica gel column (AcOEt–hexane=1:2) to provide diol **41** (9.89 g, 81%).

To a solution of diol **41** (9.89 g, 15.4 mmol) in dry CH_2Cl_2 (51.4 mL) was slowly added lead(IV) acetate (8.21 g, 18.5 mmol) with dry CH_2Cl_2 (103 mL) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was poured into a cold saturated $NaHCO_3$ and Na_2SO_3 solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide aldehyde **42** (7.43 g, 99%) as a colorless oil. *Compound* **42**. IR (KBr) ν_{max} 2907, 2860, 2712, 2367, 1721, 1613, 1513, 1455, 1364, 1302, 1302, 1248, 1174, 1090, 1035, 909, 821, 738, 699, 581, 522, 460 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.03 (3H, d, J=7.0 Hz, CH_3), 1.14 (3H, d, J=7.0 Hz, CH_3), 1.90 (2H, br m, –$SCH_2CH_2CH_2S$–), 2.13 (1H, dd, J=15.5, 6.0 Hz, H-53a), 2.19 (1H, dd, J=15.5, 3.0 Hz, H-53b), 2.71–2.76 (4H, m, –$SCH_2CH_2CH_2S$–), 2.90 (1H, qd, 7.0, 4.0 Hz, H-51), 3.05 (1H, qdd, J=7.0, 4.0, 1.0 Hz, H-50), 3.51 (1H, dd, J=10.0, 6.0 Hz, H-55a), 3.58 (1H, dd, J=10.0, 4.5 Hz, H-55b), 3.80 (3H, s, –$C_6H_4OCH_3$), 4.03–4.09 (1H, m, H-54), 4.49 (1H, d, J=12.0 Hz, –$CH_2C_6H_4OCH_3$), 4.52 (1H, d, J=12.0 Hz, –$CH_2C_6H_4OCH_3$), 4.63 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.66 (1H, d, J=11.5 Hz, –CH_2Ph), 6.85–6.90 (2H, m, aromatic), 7.23–7.38 (7H, m, aromatic), 9.56 (1H, d, J=1.0 Hz, H-49). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 11.2, 11.6, 24.6, 25.6, 26.0, 37.3, 38.6, 47.1, 55.2, 58.4, 71.7, 71.9, 72.8, 76.0, 113.8, 127.5, 128.1, 128.3, 129.3, 130.4, 138.7, 159.3, 203.4. $[\alpha]_D^{28}=-33.87°$ (c 0.555, $CHCl_3$). HRMS (FAB) calcd for $C_{27}H_{37}O_4S_2$ $[M+H]^+$ 489.2133, found 489.2133.

5.1.23. Acetylene 47. To a solution of (trimethylsilyl)acetylene (3.22 mL, 22.8 mmol) in dry THF (76.0 mL) was slowly added *t*-BuLi (1.59 M in *n*-hexane, 13.4 mL, 21.3 mmol) at −78°C. After stirring for 15 min at 0°C, the reaction mixture was added the solution of aldehyde **42** (7.43 g, 15.2 mmol) in dry THF (76.0 mL). After stirring for 20 min at 0°C, the reaction mixture was added iodomethane (9.46 mL, 152 mmol). After stirring for 2.5 h at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×4). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:9) to provide a colorless oil (8.14 g, 89%) containing the propargyl ether **43**.

To a solution of the propargyl ether **43** (8.01 g, 13.3 mmol) in THF (119 mL) was added TBAF (1.0 M solution in THF, 14.7 mL, 14.7 mmol) at 0°C. After stirring for 10 min at room temperature, the reaction mixture was poured into cold saturated NH_4Cl solution and extracted with Et_2O (×3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide the acetylene **44** (6.99 g, 99%).

To a solution of *N*-chlorosuccinimide (2.70 g, 20.2 mmol), silver nitrate (3.86 g, 22.7 mmol), and 2,4,6-collidine (8.01 mL, 60.7 mmol) in CH_3CN (20.2 mL) and H_2O (10.1 mL) was added a solution of the acetylene **44** (2.54 g, 4.80 mmol), in CH_3CN (20.2 mL) at −10°C. After stirring for 5 min, the reaction mixture was treated successively at 1 min intervals with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and brine (10 mL each). The mixture was filtered through Hyflo-Super-Cel®. After the filter cake was washed thoroughly with 1:1 hexane–CH_2Cl_2, the organic layer of the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The

remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide the a colorless oil (4.39 g) containing ketone **45** and 2,4,6-collidine.

To a solution of ketone **45** (4.39 g) in MeOH (48.0 mL) was added $NaBH_4$ (728 mg, 19.2 mmol) at 0°C. After stirring for 30 min at 0°C, the reaction mixture was poured into cold 1.2N HCl and extracted with AcOEt (×5). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:9) to provide alcohol **46** (1.78 g, 51% in 2 steps).

To a solution of the alcohol **46** (525 mg, 1.19 mmol) in CH_3CN (11.9 mL) were added pyridine (0.96 mL, 11.9 mmol) and TBSOTf (0.55 mL, 2.38 mmol) at 0°C. After stirring for 5 h at room temperature, the reaction mixture was poured into cold saturated aqueous NH_4Cl and extracted with Et_2O (×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=1:19) to provide acetylene **47** (648 mg, 98%). *Compound* **47**. IR (KBr) ν_{max} 3307, 2930, 2361, 1614, 1514, 1464, 1362, 1250, 1096, 836, 774, 697, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 0.00–0.08 (6H, m, –Si(CH_3)$_2$), 0.86–1.03 (15H, m, –SiC(CH_3)$_3$, CH_3-59, CH_3-60), 1.62–1.99 (4H, m, H-50, 51, 53a, 53b), 2.36–2.45 (1H, m, H-47), 3.32–3.40 (3H, m, –OCH_3), 3.48–4.06 (5H, m, H-49, 52, 54, 55a, 55b), 3.83 (3H, s, –O$CH_2C_6H_4OCH_3$), 4.49–4.76 (4H, m, –OCH_2Ar), 6.90 (2H, br-d, J=8.0 Hz, aromatic), 7.27–7.39 (7H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ −4.5, −4.4, −4.3, −4.0, −3.9, 10.7, 10.9, 11.1, 11.5, 12.1, 12.4, 12.7, 18.0, 25.9, 34.6, 34.7, 37.5, 37.7, 38.1, 38.5, 38.6, 38.8, 38.9, 55.3, 56.5, 56.7, 71.4, 71.6, 71.9, 72.0, 72.4, 73.0, 74.1, 74.6, 74.7, 75.6, 75.8, 76.1, 81.7, 82.2, 113.8, 127.3, 127.4, 127.5, 127.7, 128.2, 129.2, 130.5, 130.6, 139.0, 139.1, 159.2. Anal. calcd for $C_{33}H_{50}O_5Si$: C, 71.44; H, 9.08. Found: C, 71.30; H, 9.11.

5.1.24. Pivalate 49. To a solution of methyl-α-D-glucopyranoside (1.19 kg, 6.13 mol) in *N*,*N*-dimethylformamide (6.00 L) were added 2,2-dimethoxypropane (1.88 L, 15.3 mol) and Amberlyst 15E® (6.00 g) at room temperature. After stirring for 3 days at room temperature, the reaction mixture was filtered and concentrated under reduced pressure to give the diol as gummy paste (1.43 kg). To the solution of the paste (100.0 g, ca. 0.42 mol) in CH_2Cl_2 (2.00 L) and pyridine (200 mL) at 0°C under N_2 atmosphere was added pivaloyl chloride (52.6 mL, 0.427 mol) dropwise. After stirring for 2 days at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The resulting extract was dried over Na_2SO_4 and concentrated in vacuo to leave a viscous oil. The oil was dissolved in Et_2O containing small amount of hexane and stand still for crystallization. The mother liquors were decanted and the crystals were collected by filtration and then dried at high vacuum. The recrystallization procedure was repeated twice. A total of 92.0 g of pivaloate **49** (68%) was obtained in three crops. *Compound* **49**. IR (KBr) ν_{max} 3476, 2990, 2917, 2880, 2840, 2361, 1736, 1482, 1374, 1270, 1198, 1167, 1042, 990, 945, 850, 750, 666, 521 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (9H, s, –COC(CH_3)$_3$), 1.43 (3H, s, –CCH_3), 1.52 (3H, s, –CCH_3), 2.92 (1H, br-d, –OH), 3.43 (3H, s, –OCH_3), 3.46–3.92 (6H, m, H-42, 43, 44, 45, 46a, 46b), 4.77 (1H, d, J=4.0 Hz, H-41). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 26.8, 28.9, 38.6, 55.2, 62.1, 62.7, 68.7, 73.3, 74.1, 97.5, 99.7, 178.1. $[\alpha]_D^{25}$=+124.1° (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.59; H, 8.46.

5.1.25. Diol 54. To a solution of imidazole (17.1 g, 0.251 mol) in $CHCl_3$ (170 mL) was gradually added thiophosgene (4.80 mL, 62.8 mmol) as a solution of toluene (60.0 mL) while cooling so that temperature may not go up too much by the exothermic reaction. After the reaction mixture was stirred for 1 h at room temperature, a solution of pivaloate **49** (10.0 g) in toluene (86 mL) and CH_3Cl (20 mL) was added, and stirring the resulting mixture was continued for further 2 days at refluxing temperature. The resulting mixture was concentrated under reduced pressure to give a crude oil. The remaining oil was chromatographed on a silica gel short column (Et_2O–hexane=3:7) to provide a yellow oil containing the thiocarbamate **50** (13.1 g). $NaH_2PO_2{\cdot}H_2O$ (18.0 g, 170 mmol) and small amount of toluene were placed in a flask. After the azeotropic operation with toluene was repeated 3 times, the flask was charged with 2-methoxyethanol. (212 mL). The flask was maintained under a dry Ar atmosphere and heated at 105°C in an oil bath. The mixture was stirred vigorously and AIBN (4.18 g, 25.0 mmol) was added as a solution of 2-methoxyethanol (63.8 mL) by portions. Immediately after adding the solution of AIBN, the thiocarbamate **50** (7.28 g, 17.0 mmol) was added as a solution of 2-methoxyethanol (63.8 mL) slowly. After stirring for 10 min, the solution was poured into iced water, and the mixture was extracted with AcOEt (×3). The extracts were combined and dried over Na_2SO_4, and the solvent was removed by evaporation on a rotary evaporator to give a yellow crude oil. The oil was chromatographed on a silica gel column (Et_2O–hexane=2:1) to provide colorless oil containing the deoxygenated compound **51** (5.32 g).

To a solution of the colorless oil of **51** (32.6 g, 108 mmol) in MeOH and THF (720 mL, MeOH–THF=1:1) was added NaOMe (17.5 g, 323 mmol) at room temperature. After stirring for 45 min, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure to give a crude oil that was chromatographed on a silica gel column (Et_2O–hexane=1:1) to provide the alcohol **52** (21.8 g, 93%).

To a solution of alcohol **52** (15.1 g, 69.2 mmol) in benzyl chloride (553 mL) was added potassium hydroxide (166 g) at room temperature. After stirring for 1 h at 110°C, the reaction mixture was cooled to room temperature and poured into a cooled saturated ammonium chloride solution. The resulting mixture was extracted with Et_2O (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel short column to remove the large quantities of non-volatile benzyl alcohol generated from benzyl chloride by the aqueous work up. A yellow oil

containing the benzyl ether **53** (22.4 g) was obtained in the end, and that was used in the next step without further purification.

To a solution of the benzyl ether **53** (37.1 g, 0.12 mol) in MeOH (1150 mL) was added Amberlyst 15E® (11.5 g) at room temperature. After stirring for 40 min at room temperature, the reaction mixture was filtered and concentrated under reduced pressure to leave a viscous oil. The remaining oil was chromatographed on a silica gel short column (Et_2O–hexane=4:1) to provide diol **54** (32.0 g, 99% in 2 steps). *Compound* **54**. IR (KBr) ν_{max} 3324, 2907, 2361, 1734, 1456, 1378, 1330, 1237, 1182, 1106, 1052, 909, 842, 739, 697, 600, 520 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.84 (1H, q, J=11.5 Hz, H-43a), 2.16 (1H, dt, J=11.5, 4.5 Hz, H-43b), 3.06 (2H, br s, –O*H*), 3.39 (3H, s, –OCH_3), 3.42–3.63 (3H, m, H-42, 44, 45), 3.72 (1H, d, J=15.0 Hz, H-46a), 3.78 (1H, d, J=15.0 Hz, H-46b), 4.54 (1H, d, J=12.0 Hz, –OCH_2Ph), 4.62 (1H, d, J=12.0 Hz, –OCH_2Ph), 7.24–7.38 (5H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 32.9, 54.8, 62.2, 65.6, 70.9, 72.0, 73.6, 97.0, 127.8, 127.8, 128.4, 137.9. $[\alpha]_D^{28}$=+65.7° (*c* 0.99, $CHCl_3$). Anal. calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.67; H, 7.53.

5.1.26. Lactone 58. To a solution of diol **54** (30.7 g, 0.11 mol) in CH_2Cl_2 (1150 mL) were added pivaloyl chloride (42.3 mL, 0.34 mol) and DMAP (41.9 g, 0.34 mol) at 0°C. After stirring for 1 h at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining oil was chromatographed on a silica gel short column (Et_2O–hexane=1:4) to provide the dipivaloate **55** (48.2 g, 97% in 2 steps) that was used directly in the next step without further purification.

To a solution of dipivaloate **55** (24.5 g, 56.1 mmol) in acetic anhydride (561 mL) was slowly added conc. H_2SO_4 (1.12 mL) at 0°C. After stirring for 15 min at 0°C, the reaction mixture was poured into a cold saturated $NaHCO_3$ solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining oil was chromatographed on a silica gel column (AcOEt–hexane=1:9) to provide the acetate **56** (22.7 g, 87%). The acetate **56** existed as a mixture of anomers.

A mixture of the acetate **56** (21.2 g, 45.6 mmol) in 1,2-dimethoxyethane (414 mL), H_2O (20.7 mL) and conc. HCl (20.7 mL) was stirred vigorously and heated to 55°C for 14 h. After the reaction mixture was cooled to room temperature, it was poured into a cold saturated $NaHCO_3$ solution and extracted with Et_2O (×3). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to give the hemiacetal **57** (12.6 g, 66%) as a mixture of anomers.

The oil of the hemiacetal **57** (8.40 g, 19.9 mmol) was dissolved in DMSO (119 mL) and acetic anhydride (79.5 mL). After magnetically stirring for 14 h at room temperature, the reaction mixture was added Et_2O and washed with saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining oil was chromatographed on a short silica gel column (AcOEt–hexane=1:9) to give lactone **58** (7.75 g, 93%). *Compound* **58**. IR (KBr) ν_{max} 2976, 2875, 2361, 1735, 1457, 1364, 1282, 1150, 1040, 742, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.20 (18H, s, –COC(CH_3)$_3$), 2.03 (1H, ddd, J=14.5, 7.0, 6.5 Hz, H-43a), 2.60 (1H, ddd, J=14.5, 7.0, 6.0 Hz, H-43b), 4.10 (1H, dd, J=6.0, 6.5 Hz, H-42), 4.23 (1H, dd, J=12.5, 4.0 Hz, H-46a), 4.28 (1H, dd, J=12.5, 2.5 Hz, H-46b), 4.65 (1H, d, J=12.0 Hz, –OCH_2Ph), 4.83 (1H, ddd, J=9.0, 4.0, 2.5 Hz, H-45), 4.87 (1H, d, J=12.0 Hz, –OCH_2Ph), 5.04 (1H, dt, J=9.0, 7.0 Hz, H-44), 7.25–7.38 (5H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 26.8, 27.0, 32.7, 38.7, 38.8, 61.9, 64.0, 71.9, 72.6, 77.5, 128.1, 128.3, 128.6, 136.8, 168.8, 177.3, 178.0. $[\alpha]_D^{28}$=+77.9° (*c* 1.005, $CHCl_3$). Anal. calcd for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.84; H, 7.80.

5.1.27. Allylhydropyrane 59. To a solution of lactone **58** (14.1 g, 0.33 mmol) in THF (334 mL) was added allylmagnesium bromide (1.0 M solution in Et_2O, 38.5 mL, 0.38 mmol) at −78°C. After stirring for 30 min, the reaction mixture was quenched by addition of AcOEt and poured into a cold saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×3) and dried over Na_2SO_4. Removal of the volatiles in vacuo gave crude product that was chromatographed on silica gel (AcOEt–hexane=3:17) to give hemiacetal (15.2 g) as a mixture of anomers. It was used directly in the next step without further purification. To a solution of the crude product (15.2 g, 32.9 mmol) in CH_3CN (334 mL) were added Et_3SiH (16.1 mL, 98.6 mmol) and $BF_3{\cdot}OEt_2$ (6.37 mL, 49.3 mmol) at −10°C. After stirring for 20 min, the reaction mixture was poured into a cold saturated $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O (×3) and dried over Na_2SO_4. Removal of the volatiles in vacuo gave crude product that was chromatographed on silica gel (AcOEt–hexane=1:19) to give allylhydropyrane **59** (8.02 g, 54% in 2 steps). *Compound* **59**. IR (KBr) ν_{max} 3448, 3068, 2976, 2874, 2362, 1732, 1644, 1481, 1364, 1285, 1150, 1110, 1035, 990, 914, 838, 739, 699, 596 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.20 (18H, s, –COC(CH_3)$_3$), 1.44 (1H, q, J=11.5 Hz, H-43a), 2.24 (1H, m, H-40a), 2.61 (1H, m, H-40b), 2.72 (1H, ddd, J=11.5, 5.0, 4.0 Hz, H-43b), 3.24–3.38 (total 2H, m, H-41, 42), 3.57 (1H, ddd, J=10.0, 6.0, 2.0 Hz, H-45), 4.06 (1H, dd, J=12.0, 6.0 Hz, H-46a), 4.21 (1H, dd, J=12.0, 2.0 Hz, H-46b), 4.43 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.62 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.66 (1H, ddd, J=11.5, 10.0, 5.0 Hz, H-44), 4.98–5.13 (2H, m, H-57), 5.79–5.95 (1H, m, H-39), 7.25–7.38 (5H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 26.9, 27.0, 34.6, 35.7, 38.6, 38.7, 62.9, 66.8, 71.0, 75.0, 77.2, 80.1, 116.8, 127.8, 127.8, 128.4, 134.6, 137.9, 177.3, 178.2. $[\alpha]_D^{30}$=+7.24° (*c* 0.990, $CHCl_3$). Anal. calcd for C26H38O6: C, 69.93; H, 8.58. Found: C, 69.98; H, 8.60.

5.1.28. Alcohol 62. To a solution of allylhydropyrane **59** (8.02 g, 18.0 mmol) in MeOH (180 mL) was added NaOMe (5.82 g, 108 mmol) at room temperature. After stirring for 4 h, the reaction mixture was poured into a cold saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×7) and dried over Na_2SO_4. Removal of the volatiles in vacuo gave crude product that was chromatographed on

silica gel column (AcOEt–hexane=2:1) to give diol **60** (4.65 g, 93%).

To a solution of diol **60** (6.24 g, 22.4 mmol) in DMF (149 mL) were added imidazole (7.63 g, 112 mmol) and TBSCl (10.1 g, 67.3 mmol) at 0°C. After stirring for 8 h at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The resulting extracts were washed with H_2O (×2), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude oil that was chromatographed on a silica gel short column (AcOEt–hexane=1:19) to provide colorless oil containing disilylether **61** (13.0 g).

The oil of disilylether **61** was dissolved in 257 mL of methanol and treated with CSA (1.04 g, 4.48 mmol) at −10°C for 1 h. The reaction mixture was poured into a cold saturated $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O (×3) and dried over Na_2SO_4. Removal of the volatiles in vacuo gave a crude product that was chromatographed on silica gel column (AcOEt–hexane=1:9) to give alcohol **62** (7.72 g, 88% in 2 steps). *Compound* **62**. IR (KBr) ν_{max} 3496, 3074, 3032, 2930, 2859, 1642, 1473, 1456, 1362, 1253, 1096, 1005, 912, 861, 837, 777, 737, 698, 670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 0.06 (6H, s, –Si(CH_3)$_2$), 0.88 (9H, s, –SiC(CH_3)$_3$), 1.46 (1H, q, J=11.5 Hz, H-43a), 2.00 (1H, br, –OH), 2.22 (1H, m, H-40a), 2.39 (1H, dt, J=11.5, 4.5 Hz, H-43b), 2.63 (1H, m, H-40b), 3.13–3.23 (2H, m, H-42, 45), 3.31 (1H, ddd, J=9.0, 7.5, 3.0 Hz, H-41), 3.58 (1H, ddd, J=11.0, 9.0, 4.5 Hz, H-44), 3.58 (1H, br, H-46a), 3.80 (1H, br, H-46b), 4.48 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.61 (1H, d, J=11.5 Hz, –OCH_2Ph), 5.00–5.13 (2H, m, H-57), 5.79–5.93 (1H, m, H-39), 7.24–7.39 (5H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ −5.1, −4.3, 17.8, 25.6, 36.0, 38.9, 62.7, 66.8, 71.1, 75.5, 79.5, 81.6, 117.0, 127.9, 127.9, 128.5, 134.8, 138.2. $[\alpha]_D^{29}$=+1.59° (*c* 1.015, $CHCl_3$). Anal. calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.26; H, 9.35.

5.1.29. Thiophenylacetylene 65. To a magnetically stirred solution containing oxalyl chloride (3.06 mL, 35.0 mmol) in CH_2Cl_2 (250 mL) was added a mixture of DMSO (4.97 mL, 70.1 mmol) and CH_2Cl_2 (16.7 mL) at −78°C. After stirring for 20 min, to the reaction mixture was added alcohol **62** (6.88 g, 17.5 mmol) with CH_2Cl_2 (83.5 mL). After stirring for 1 h, to the reaction mixture was slowly added Et_3N (14.7 mL, 105 mmol), which was gradually warmed to −30°C. After stirring 1 h, the reaction mixture was poured into a cooled saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×3). The extracts were concentrated under reduced pressure. The remaining residue was passed through a silica gel and Na_2SO_4 short column (100% AcOEt) to provide a colorless oil containing the aldehyde **63**.

To a magnetically stirred solution containing carbon tetrabromide (23.2 g, 70.1 mmol) in CH_2Cl_2 (58.4 mL) was added a solution of Ph_3P (4.46 g, 140 mmol) in CH_2Cl_2 (58.4 mL) at 0°C. After stirring for 10 min at 0°C, the reaction mixture was added the oil of aldehyde **63** with CH_2Cl_2 (58.4 mL). After stirring for 20 min, the reaction mixture was poured into a cooled saturated $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:19) to give the dibromo-olefin **64** (8.76 g, 91%).

To a stirred solution containing the dibromo-olefin **64** (8.26 g, 15.1 mmol) in THF (158 mL) was added a solution of *n*-BuLi (21.2 mL, 33.2 mmol, 1.57 M in *n*-hexane) at −78°C. The reaction mixture was gradually warmed to 0°C for 1.5 h. After that, the reaction mixture was added $PhSSO_2Ph$ (7.92 g, 31.6 mmol) with THF (63.2 mL). After stirring for 1 h, the reaction mixture was poured into cold saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:19) to give thiophenylacetylene **65** (6.71 g, 98%). *Compound* **65**. IR (KBr) ν_{max} 3228, 3065, 2929, 2857, 2366, 2175, 1642, 1584, 1473, 1328, 1252, 1087, 1025, 915, 838, 778, 739, 688, 595, 538 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 0.06 (6H, s, –Si(CH_3)$_2$), 0.86 (9H, s, –SiC(CH_3)$_3$), 1.48 (1H, dt, J=12.0, 10.5 Hz, H-43a), 2.30 (1H, br-dt, J=14.0, 7.0 Hz, H-40a), 2.44 (1H, dt, J=12.0, 4.0 Hz, H-43b), 2.63 (1H, m, H-40b), 3.21–3.35 (2H, m, H-41, 42), 3.64 (1H, ddd, J=11.0, 9.0, 4.5 Hz, H-44), 4.05 (1H, d, J=9.0 Hz, H-45), 4.48 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.61 (1H, d, J=11.5 Hz, –OCH_2Ph), 5.04–5.15 (2H, m, H-57), 5.86–6.01 (1H, m, H-39), 7.18–7.44 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ −4.7, 4.6, 17.9, 25.6, 35.9, 39.4, 70.0, 71.1, 72.6, 74.1, 74.9, 80.2, 96.9, 117.1, 126.6, 127.9, 128.5, 129.2, 132.2, 134.7, 138.1. $[\alpha]_D^{29}$=+0.63° (*c* 1.050, $CHCl_3$). Anal. calcd for $C_{29}H_{38}O_3SSi$: C, 70.40; H, 7.74./ Found: C, 70.41; H, 7.47.

5.1.30. Vinyl sulfone 69. To a solution of thiophenylacetylene **65** (6.71 g, 14.8 mmol) in THF (103 mL) was added TBAF (1.0 M solution in THF, 30.9 mL, 44.4 mmol) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was poured into cold saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to give an alcohol (4.66 g, 83%).

To a solution of the alcohol (3.43 g, 9.01 mmol) in 90.1 mL of CH_2Cl_2 were added acetic anhydride (1.27 mL, 13.5 mmol) and DMAP (1.21 g, 9.92 mmol) at 0°C. After stirring for 10 min at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The resulting extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:9) to give acetate **66** (3.66 g, 96%).

To a stirred solution containing the acetate **66** (3.66 g, 8.66 mmol) in 1,2-dichloroethane (86.6 mL) were added Et_3SiH (13.8, 86.6 mmol) and biscobalthexacarbonyl-2-methyl-but-3-yn-2-ol (467 mg, 1.30 mmol) at room temperature. After stirring for 1.5 h at 60°C, the reaction mixture was concentrated under reduced pressure. The

remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:9) to give the vinyl sulfide **67** (4.30 g, 100%).

To a solution of vinyl sulfide **67** (4.30 g, 8.66 mmol) in MeOH (86.6 mL) was added K_2CO_3 (1.20 g, 8.66 mmol) at 0°C. After stirring for 1.5 h at room temperature, the reaction mixture was poured into a cold saturated NH_4Cl solution and extracted with Et_2O (×3). The resulting extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=3:17) to give alcohol **68** (4.17 g, 97%).

To a solution of alcohol **68** (3.77 g, 7.59 mmol) and Na_2HPO_4 (7.54 g, 53.1 mmol) in CH_2Cl_2 (75.8 mL) was added *m*CPBA (70%, 4.12 g, 167 mmol) at 0°C. After stirring for 1 h, the reaction mixture was poured into a cold $NaHCO_3$ and Na_2SO_3 solution. The resulting mixture was extracted with Et_2O and dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to give vinyl sulfone **69** (3.68 g, 85%). *Compound* **69**. IR (KBr) ν_{max} 3484, 3067, 2956, 2876, 1603, 1447, 1298, 1237, 1140, 1082, 1004, 912, 843, 742, 699, 575 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 0.58–0.88 (15H, m, Si(CH_2CH_3)$_3$), 1.47 (1H, q, J=11.5 Hz, H-43a), 2.16 (1H, m, H-40a), 2.55 (1H, m, H-40b), 2.73 (1H, dt, J=12.0, 4.5 Hz, H-43b), 3.01 (1H, d, J=9.0 Hz, –OH), 3.11–3.27 (2H, m, H-41, 42), 3.34 (1H, m, H-44), 4.45 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.63 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.76 (1H, t, J=9.0 Hz, H-45), 4.97–5.05 (2H, m, H-57), 5.68–5.83 (1H, m, H-39), 6.40 (1H, d, J=9.0 Hz, H-46), 7.26–7.40 (5H, m, aromatic), 7.48–7.63 (3H, m, aromatic), 7.83–7.90 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 3.1, 6.9, 35.6, 39.4, 68.8, 70.8, 75.2, 78.5, 79.8, 116.7, 126.7, 127.9, 128.0, 128.5, 129.2, 133.2, 134.7, 138.1, 145.8, 154.3. $[\alpha]_D^{29}=-116°$ (c 0.355, $CHCl_3$). Anal. calcd for $C_{29}H_{40}O_5SSi$: C, 65.87; H, 7.62. Found: C, 65.87; H, 7.73.

5.1.31. Heteroconjugate adduct 70. To a stirred solution containing acetylene **47** (2.40 g, 4.32 mmol) in dry THF (43.2 mL) was added *n*-BuLi (1.59 M solution in hexane, 2.72 mL, 4.32 mmol) at 0°C. After stirring for 30 min, the reaction mixture was added vinyl sulfone **69** (722 mg, 1.37 mmol) with dry THF (14.4 mL). After stirring 2.5 h the reaction mixture was poured into a cooled saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude oil (3.28 g). To a solution of the crude oil (3.28 g) in THF (14.4 mL) was added TBAF fluoride (1.0 M solution in THF, 2.73 mL, 2.73 mmol) at 0°C. After stirring for 5 min at 0°C, the reaction mixture was quenched by pouring into cold saturated NH_4Cl solution, and extracted with Et_2O (×3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil that was chromatographed on a silica gel column (AcOEt–hexane=1:3) to provide heteroconjugate adduct **70** (1.05 g, 80% in 2 steps) and excess acetylene **47** (1.56 g, 65%). *Compound* **70**. IR (KBr) ν_{max} 3448, 2930, 1613, 1514, 1455, 1306, 1250, 1087, 836, 775, 748, 698, 527 cm^{-1}. Anal. calcd for $C_{56}H_{76}O_{10}SSi$: C, 69.39 H, 7.90. Found: C, 69.39; H, 7.97.

5.1.32. Alcohol 72. To a solution of heteroconjugate adduct **70** (169 mg, 0.174 mmol) in CH_2Cl_2 (1.43 mL) was added ethyl vinyl ether (0.27 mL) and PPTS (3.0 mg) at room temperature. After stirring for 1.5 h, the reaction mixture was poured into a cold saturated $NaHCO_3$ solution and extracted with Et_2O (×3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to give the ethoxyethyl ether **71** (181 mg, 100%).

To the solution of the ethoxyethyl ether **71** (127 mg, 0.122 mmol) in THF (1.22 mL) was added TBAF (1.0 M solution in THF, 1.22 mL, 1.22 mmol) at room temperature. After magnetically stirring for 6 days at 50°C, the reaction mixture was pouring into cold saturated NH_4Cl solution, and extracted with Et_2O (×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:3) to provide an alcohol (99.7 mg, 88%).

To the solution of the alcohol (246 mg, 0.265 mmol) in CH_2Cl_2 (2.65 mL) were added pyridine (107 μL, 1.33 mmol), acetic anhydride (75 μL, 0.796 mmol) and DMAP (32.0 mg, 0.265 mmol) at room temperature. After stirring for 1 h, the reaction mixture was poured into cold saturated NH_4Cl solution, extracted with Et_2O (×3) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide the acetate (257 mg, 100%). To the solution of the acetate (257 mg, 0.265 mmol) in MeOH (2.65 mL) was added camphorsulfonic acid (6 mg, 0.027 mmol) at room temperature. After stirring for 5 min, the reaction mixture was pouring into cold saturated $NaHCO_3$ solution, extracted with Et_2O (×3) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:3) to provide alcohol **72** (218 mg, 91%). *Compound* **72**. IR (KBr) ν_{max} 3447, 2935, 2361, 1732, 1613, 1514, 1455, 1373, 1306, 1247, 1087, 820, 749, 699, 560 cm^{-1}. Anal. calcd for $C_{52}H_{64}O_{11}S$: C, 69.62 H, 7.19. Found: C, 69.49; H, 7.29.

5.1.33. Endocyclic olefin 75 and 76. To the solution of alcohol **72** (167 mg, 0.172 mmol) in CH_2Cl_2 (0.86 mL) was added di-cobaltoctacarbonyl (295 mg, 0.862 mmol) with CH_2Cl_2 (0.86 mL) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel short column (AcOEt–hexane=1:1) to provide a crude oil (218 mg) that was used directly in the next step without further purification. To the solution of the crude oil (218 mg,) in CH_2Cl_2 (17.2 mL) was added $BF_3{\cdot}OEt_2$ (0.22 mL, 1.72 mmol) at 0°C. After stirring for 30 min at 0°C, the reaction mixture was poured into a cold saturated $NaHCO_3$ solution, extracted with Et_2O (×3), and washed with brine. The extracts were dried over Na_2SO_4

and concentrated under reduced pressure. The remaining oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to give the bicyclic product **74** (165 mg, 93%).

To the solution of **74** (165 mg, 0.160 mmol) in toluene (7.99 mL) was added bis(trimethylsilyl)acetylene (1.09 mL, 4.79 mmol) and *n*-Bu_3SnH (0.43 mL, 1.60 mmol). After stirring 30 min at 60°C, the reaction mixture was concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=9:41) to provide the endocyclic olefin **75** (81.0 mg, 68%) and its C46-epimer **76** (22.0 mg, 19%). *Compound* **75**. IR (KBr) ν_{max} 3447, 2929, 2876, 2343, 1729, 1455, 1373, 1306, 1245, 1147, 1086, 1028, 915, 748, 699, 607, 532 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ 0.87 (3H, d, J=7.0 Hz, CH_3), 0.88 (3H, d, J=7.0 Hz, CH_3), 1.43 (1H, ddd, J=12.0, 11.5, 11.0 Hz, H-43a), 1.55–1.60 (1H, m, H-50), 1.79–1.93 (4H, m, –OH, H-51, 53a, 53b), 1.98 (3H, s, $-OCOCH_3$), 2.00–2.08 (1H, m, H-40a), 2.53–2.56 (1H, m, H-40b), 2.59 (1H, dt, J=12.0, 4.0 Hz, H-43b), 2.75 (1H, dd, J=9.0, 8.5 Hz, H-45), 3.05 (1H, m, H-41), 3.08 (1H, td, J=9.0, 2.5 Hz, H-46), 3.10 (1H, dd, J=13.5, 10.5 Hz, H-58a), 3.18 (1H, ddd, J=11.0, 9.0, 4.5 Hz, H-42), 3.34 (1H, ddd, J=11.5, 8.5, 4.5 Hz, H-44), 3.54 (1H, m, H-54), 3.59 (1H, ddd, J=11.5, 6.5, 4.5 Hz, H-55a), 3.79 (1H, ddd, J=11.5, 6.5, 4.5 Hz, H-55b), 3.84 (1H, dd, J=13.5, 1.5 Hz, H-58b), 3.90 (1H, br, H-49), 4.42 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.54 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.58 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.62 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.92–5.04 (3H, m, H-52, 57), 5.62–5.73 (1H, m, H-39), 5.83 (1H, ddd, J=11.5, 4.5, 3.5 Hz, H-48), 5.93 (1H, ddd, J=11.5, 3.5, 2.0 Hz, H-47), 7.20–7.38 (10H, m, aromatic), 7.52–7.56 (2H, m, aromatic), 7.62–7.66 (1H, m, aromatic), 7.88–7.91 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 36.7, 37.0, 37.6, 37.9, 38.4, 38.5, 39.1, 39.4, 39.6, 39.7, 57.0, 57.2, 63.3, 64.2, 70.7, 70.8, 70.9, 70.9, 71.2, 72.3, 72.9, 73.0, 75.8, 75.8, 76.8, 77.1, 77.2, 77.5, 77.8, 78.9, 79.1, 79.4, 79.5, 79.6, 80.5, 81.3, 116.8, 116.9, 127.7, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.9, 129.1, 131.0, 131.9, 133.6, 135.1, 135.6, 135.8, 138.1, 138.1, 138.1, 138.2, 140.1, 170.4, 170.8. Anal. calcd for $C_{43}H_{54}O_9S$: C, 69.14 H, 7.29. Found: C, 69.11; H, 7.25. *Compound* **76**. ^1H NMR ($CDCl_3$, 400 MHz), δ 0.89 (3H, d, J=7.0 Hz, CH_3), 0.90 (3H, d, J=6.5 Hz, CH_3), 1.38 (1H, q, J=11.0 Hz, H-43a), 1.43–1.51 (1H, m, H-50), 1.77–2.00 (4H, m, –OH, H-51, 53a, 53b), 2.00 (3H, s, $-OCOCH_3$), 2.03–2.12 (1H, m, H-40a), 2.43 (1H, m, H-40b), 2.66 (1H, dt, J=11.5, 4.0 Hz, H-43b), 3.05 (1H, dddd, J=11.0, 8.0, 4.5, 2.0 Hz, H-46), 3.09–3.16 (2H, m, H-41, 42), 3.16 (1H, dd, J=9.5, 4.5 Hz, H-45), 3.34 (1H, ddd, J=11.5, 9.0, 4.5 Hz, H-44), 3.40 (1H, dd, J=14.0, 11.0 Hz, H-58a), 3.48 (1H, dq, J=8.0, 4.0 Hz, H-54), 3.60 (1H, dd, J=14.0, 2.0 Hz, H-58b), 3.62 (1H, ddd, J=12.0, 7.5, 4.0 Hz, H-55a), 3.81 (1H, ddd, J=12.0, 5.0, 4.0 Hz, H-55b), 4.04 (1H, td, J=4.0, 2.5 Hz, H-49), 4.42 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.55 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.58 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.62 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.92–4.98 (2H, m, H-57), 5.08 (1H, ddd, J=10..0, 5.5, 2.5 Hz, H-52), 5.54–5.64 (1H, m, H-39), 5.70 (1H, dd, J=11.5, 4.0 Hz, H-48), 5.91 (1H, ddd, J=11.5, 8.0, 2.0 Hz, H-47), 7.25–7.38 (10H, m, aromatic), 7.51–7.58 (2H, m, aromatic), 7.61–7.65 (1H, m, aromatic), 7.88–7.91 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 11.0, 11.6, 21.2, 30.3, 35.9, 36.1, 37.3, 38.2, 39.5, 56.4, 62.8, 70.6, 71.1, 72.5, 75.1, 75.8, 78.3, 79.5, 116.8, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 129.2, 130.5, 133.5, 134.5, 136.0, 138.1, 138.2, 139.4, 170.4. Anal. calcd for $C_{43}H_{54}O_9S$: C, 69.14 H, 7.29. Found: C, 69.11; H, 7.25.

5.1.34. Ketone 79. To a solution of endocyclic olefin **75** (118 mg, 0.16 mmol) in THF (1.58 mL) and MeOH (1.58 mL) was treated with K_2CO_3 (39 mg, 0.28 mmol) overnight at room temperature. The reaction mixture was poured into saturated NH_4Cl solution and extracted with AcOEt (×3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was chromatographed on a silica gel column (AcOEt–hexane=2:3) to provide diol **77** (104 mg, 93%).

To a solution of the diol **77** (104 mg, 0.15 mmol) in CH_2Cl_2 (1.48 mL) were added Et_3N (206 μL, 1.48 mmol), DMAP (18 mg, 0.15 mmol), and TBSCl (111 mg, 0.74 mmol) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was poured into cold saturated NH_4Cl solution, extracted with Et_2O (×3), and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide silyl ether **78** (114 mg, 94%).

To a solution of silyl ether **78** (114 mg, 0.14 mmol) in DMSO (1.39 mL) was added IBX (78 mg, 0.28 mmol) at room temperature. After stirring for 4 h, the reaction mixture was added H_2O and filtered through Hyflo-Super-Cel®. After the filter cake was washed with Et_2O, the organic phase of the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=1:4) to provide ketone **79** (111 mg, 98%). *Compound* **79**. IR (KBr) ν_{max} 3066, 2929, 2858, 1712, 1455, 1307, 1252, 1087, 837, 748, 698, 565, 533 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ 0.05 (3H, s, $-Si(CH_3)_2$), 0.06 (3H, s, $-Si(CH_3)_2$), 0.86 (3H, d, J=7.0 Hz, CH_3-59), 0.89 (9H, s, $-SiC(CH_3)_3$), 1.02 (3H, d, J=7.0 Hz, CH_3-60), 1.38 (1H, dt, J=12.0, 11.0 Hz, H-43a), 1.92–2.05 (2H, m, H-40a, 50), 2.45 (1H, dt, J=12.0, 4.5 Hz, H-43b), 2.49–2.56 (1H, m, H-40b), 2.63–2.81 (5H, m, H-45, 46, 51, 53a, 53b), 2.96–3.09 (3H, m, H-41, 42, 44), 3.10 (1H, dd, J=14.0, 10.0 Hz, H-58a), 3.59 (1H, dd, J=10.5, 5.5 Hz, H-55a), 3.70 (1H, dd, J=10.5, 5.0 Hz, H-55b), 3.76 (1H, dd, J=14.0, 2.0 Hz, H-58b), 3.81 (1H, ddd, J=6.0, 4.0, 2.0 Hz, H-49), 4.06 (1H, dt, J=7.5, 4.5 Hz, H-54), 4.34 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.55 (1H, d, J=11.5 Hz, $-OCH_2Ph$), 4.56 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.65 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.94–5.03 (2H, m, H-57), 5.61–5.74 (2H, m, H-39, 47), 5.90 (1H, ddd, J=11.5, 3.0, 2.5 Hz, H-48), 7.20–7.36 (10H, m, aromatic), 7.52–7.57 (2H, m, aromatic), 7.61–7.66 (1H, m, aromatic), 7.84–7.91 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 10.9, 13.7, 18.3, 25.9, 36.1, 36.8, 39.6, 44.6, 48.5, 57.3, 64.7, 70.9, 72.9, 75.0, 76.0, 78.0, 78.7, 79.3, 79.7, 116.8, 127.6, 127.7, 128.0, 128.3, 129.1, 130.6, 133.5, 134.9, 135.1, 138.1, 138.7, 140.0. Anal. calcd for $C_{47}H_{64}O_8SSi$: C, 69.08 H, 7.89. Found: C, 69.07; H, 7.87.

5.1.35. Diketone 80. To a solution of ketone **79** (71 mg, 0.087 mmol) in DMF (1.58 mL) and H_2O (158 μL) was

added $PdCl_2$ (1.5 mg, 8.7 μmol) and CuCl (4.3 mg, 0.043 mmol) at room temperature. After stirring overnight under O_2 atmosphere, the reaction mixture was filtered through Hyflo-Super-Cel®. After the filter cake was washed with Et_2O, the organic layer of the filtrate was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel column (AcOEt–hexane=3:17) to provide diketone **80** (62 mg, 85%). *Compound* **80**. IR (KBr) ν_{max} 2929, 2858, 2359, 1714, 1456, 1362, 1307, 1252, 1087, 837, 749, 699, 535, 419 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ 0.05 (3H, s, –Si(CH_3)$_2$), 0.06 (3H, s, –Si(CH_3)$_2$), 0.85 (3H, d, J=7.0 Hz, CH_3-59), 0.89 (9H, s, –Si(CH_3)$_3$), 1.03 (3H, d, J=7.0 Hz, CH_3-60), 1.40 (1H, dt, J=12.0, 11.0 Hz, H-43a), 1.96 (1H, qnd, J=7.0, 4.0 Hz, H-50), 2.10 (3H, s, –COCH_3), 2.32 (1H, dd, J=16.0, 9.5 Hz, H-40a), 2.48 (1H, dt, J=12.0, 4.5 Hz, H-43b), 2.66 (1H, q, J=7.0 Hz, H-51), 2.67 (1H, dd, J=17.0, 8.0 Hz, H-53a), 2.68 (1H, t, J=8.0 Hz, H-45), 2.76 (1H, dd, J=16.0, 3.0 Hz, H-40b), 2.78 (1H, dd, J=17.0, 4.0 Hz, H-53b), 2.80–2.83 (1H, m, H-46), 2.97 (1H, ddd, J=11.0, 9.0, 4.5 Hz, H-42), 3.05 (1H, ddd, J=11.0, 8.5, 4.5 Hz, H-44), 3.09 (1H, dd, J=14.0, 9.5 Hz, –C$H_2$$SO_2$Ph), 3.51 (1H, dt, J=9.5, 3.0 Hz, H-41), 3.57 (1H, dd, J=14.0, 1.5 Hz, –C$H_2$$SO_2$Ph), 3.59 (1H, dd, J=10.5, 5.5 Hz, H-55a), 3.71 (1H, dd, J=10.5, 5.0 Hz, H-55b), 3.82 (1H, ddd, J=5.5, 3.5, 1.5 Hz, H-49), 4.07 (1H, dtd, J=7.5, 5.5, 4.5 Hz, H-54), 4.30 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.56 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.57 (1H, d, J=11.0 Hz, –OCH_2Ph), 4.66 (1H, d, J=11.0 Hz, –OCH_2Ph), 5.67 (1H, ddd, J=12.0, 3.5, 2.0 Hz, H-55a), 5.81 (1H, dt, J=12.0, 2.5 Hz, H-47), 7.20–7.36 (10H, m, aromatic), 7.52–7.57 (2H, m, aromatic), 7.61–7.66 (1H, m, aromatic), 7.85–7.89 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz), δ −5.4, 10.9, 13.9, 18.2, 25.9, 30.8, 36.7, 39.5, 39.7, 44.7, 45.8, 48.5, 57.5, 64.7, 70.6, 72.9, 75.5, 76.0, 76.2, 78.6, 78.7, 79.0, 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 129.1, 130.2, 133.5, 134.6, 137.9, 138.7, 140.1, 206.3, 212.8. HRMS (FAB) calcd for $C_{47}H_{65}O_9SSi$ $[M+H]^+$ 833.4119, found 833.4105.

5.1.36. JKLM-ring fragment 84. To the oil of diketone **80** (8.9 mg, 0.011 mmol) were added a mixture of AD-mix-α (299 mg) and methylsulfonamide (1.0 mg, 0.011 mmol) in 50% aqueous *t*-BuOH (2.14 mL) in 0°C. After stirring overnight, the reaction mixture was quenched by adding Na_2SO_3 (320 mg), extracted with AcOEt (×3) and washed with saturated $NaHCO_3$ solution. The organic layer was concentrated under reduced pressure. The remaining crude oil was chromatographed on a silica gel short column (100% AcOEt) to provide an equilibrium mixture of **81** and **82** (7.7 mg, 83%).

To a solution of the equilibrium mixture of **81** and **82** (2.9 mg, 3.3 μmol) in CH_3CN (0.68 mL) was added two drops of HF·pyridine at room temperature. After stirring for 30 min, the reaction mixture was quenched by adding $NaHCO_3$ solution, extracted with Et_2O (×3) and washed with brine. The organic layer was concentrated under reduced pressure. The remaining crude oil was purified by preparative TLC (AcOEt–hexane=1:1) to give tetracyclic product **83** (1.8 mg, 73%).

To a solution of **83** (3.4 mg, 4.73 μmol) in MeOH (2.36 mL) was added large excess amount of Na_2HPO_4 (ca. 100 mg) and Hg-Na (*c*a. 100 mg). After stirring for 4.5 h, the reaction mixture was filtered through Hyflo-Super-Cel®. After the filter cake was washed with Et_2O, the organic phase of the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The remaining crude oil was purified by preparative TLC (AcOEt–hexane=1:1) to give JKLM-ring fragment **84** (2.3 mg, 82%). *Compound* **84**. IR (KBr) ν_{max} 3447, 2926, 1717, 1636, 1456, 1355, 1077, 1025, 938, 739, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (3H, d, J=6.5 Hz, CH_3-60), 1.06 (3H, d, J=6.5 Hz, CH_3-59), 1.01 (3H, d, J=7.5 Hz, CH_3-58), 1.40 (1H, q, J=11.5 Hz, H-43a), 1.48 (1H, dq, J=11.0, 6.5 Hz, H-51), 1.61 (1H, ddq, J=11.0, 10.0, 6.5 Hz, H-50), 2.00 (1H, qdd, J=7.5, 5.0, 3.5 Hz, H-46), 2.08 (1H, dd, J=14.0, 4.0 Hz, H-53a), 2.13 (1H, dd, J=14.0, 6.5 Hz, H-53b), 2.14 (3H, s, –COCH_3), 2.45 (1H, dd, J=15.5, 9.0 Hz, H-40a), 2.54 (1H, dt, J=12.0, 4.5 Hz, H-43), 2.79 (1H, dd, J=15.5, 3.5 Hz, H-40b), 2.95 (1H, dd, J=9.5, 5.0 Hz, H-45), 3.15 (1H, ddd, J=11.5, 9.0, 4.5 Hz, H-42), 3.26 (1H, t, J=9.5 Hz, H-49), 3.59 (1H, td, J=9.0, 3.5 Hz, H-41), 3.62 (1H, dd, J=9.5, 2.0 Hz, H-48), 3.65 (1H, dd, J=3.5, 2.0 Hz, H-47), 3.69 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H-44), 3.85 (1H, dd, J=9.5, 5.0 Hz, H-55a), 3.96 (1H, dd, J=9.5, 2.0 Hz, H-55b), 4.26 (1H, dddd, J=6.5, 5.0, 4.0, 2.0 Hz, H-54), 4.39 (1H, d, J=11.5 Hz, –OCH_2Ph), 4.45 (1H, d, J=12.0 Hz, –OCH_2Ph), 4.47 (1H, d, J=12.0 Hz, –OCH_2Ph), 4.63 (1H, d, J=11.5 Hz, –OCH_2Ph), 7.20–7.37 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 15.8, 19.7, 29.7, 30.6, 36.8, 38.4, 42.0, 42.5, 46.5, 70.6, 71.1, 71.6, 71.9, 75.1, 75.8, 78.1, 78.4, 86.6, 109.3, 127.6, 127.7, 127.8, 127.8, 128.4, 138.0, 138.1, 207.2. HRMS (FAB) calcd for $C_{35}H_{47}O_8$ $[M+H]^+$ 595.3271, found 595.3262.

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