Pergamon

Tetrahedron 58 (2002) 1875–1888

TETRAHEDRON

Synthesis of the BCD-ring of ciguatoxin 1B using an acetylene cobalt complex and vinylsilane strategy

Kazunobu Kira, Akinari Hamajima and Minoru Isobe*

Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

Received 1 October 2001; accepted 22 November 2001

Abstract—Synthesis of the tricyclic BCD-ring segment with high stereoselectivity has been achieved starting from a sugar derivative directed toward the synthesis of the left part of ciguatoxin 1B. The central reactions in the synthesis are (i) ether ring formation mediated by an acetylene cobalt complex, (ii) decomplexation of the *endo*-acetylene cobalt complex to the vinylsilane, and (iii) ring-opening reaction of the epoxysilane into the allylic alcohol.

1. Introduction

Ciguatoxin 1B (CTX-1B, **1**, Fig. 1), one of the principal toxins causing ciguatera fish poisoning, was first isolated from the moray eel, *Gymnothorax javanicus*, by Scheuer and co-workers at the University of Hawaii and characterized as a polyether compound in 1980.[1] The gross structure of CTX-1B, except for the absolute configuration and the relative configuration at C-2, was elucidated by Yasumoto and co-workers in 1989 using a purified sample of only 0.35 mg.[2] Recently, the absolute configuration of ciguatoxin was successfully determined by Yasumoto and co-workers as shown in Fig. 1.[3] CTX-1B possesses 33 asymmetric carbons and 12 *trans*-fused polycyclic ethers ranging from six to nine-membered, where another five-membered oxacycle is spirally attached at one end. Due to the limited availability of the compound from nature, extensive studies have been made towards its synthesis.[4]

We have been studying various synthetic methodologies applicable to the **1** class of natural products, that have *syn*/*trans* stereochemistry of polycyclic oxy-ring systems. The strategy of these studies is based on the chemistry of the acetylene biscobalthexacarbonyl complex.[5] Our synthetic efforts have recently culminated in both enantiomeric forms of the left-end segment AB[6] or left-middle segment (D)EF[7] or right-middle segment including the (H)IJK segment[8] of CTX-1B. The key issues are stereoselective ether ring cyclization in *syn*/*trans* manner via the propargylic cation[9] **5** stabilized by the acetylene biscobalthexacarbonyl complex (Scheme 1).[10] The stereochemistry of cyclic products **6** is governed by the reaction conditions; the *anti* isomer being a kinetic product and the *syn* isomer being a thermodynamic product.[5b] The *endo*-acetylene cobalt complex **6** would be decomplexed to vinylsilane **7** (hydrosilylation) regioselectively.[11] Stereospecific ring-opening reaction of α,β-epoxysilane **8**, resulting in the

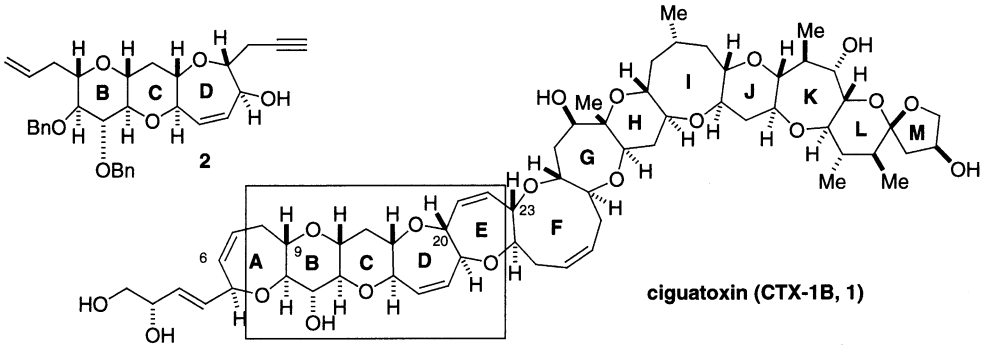
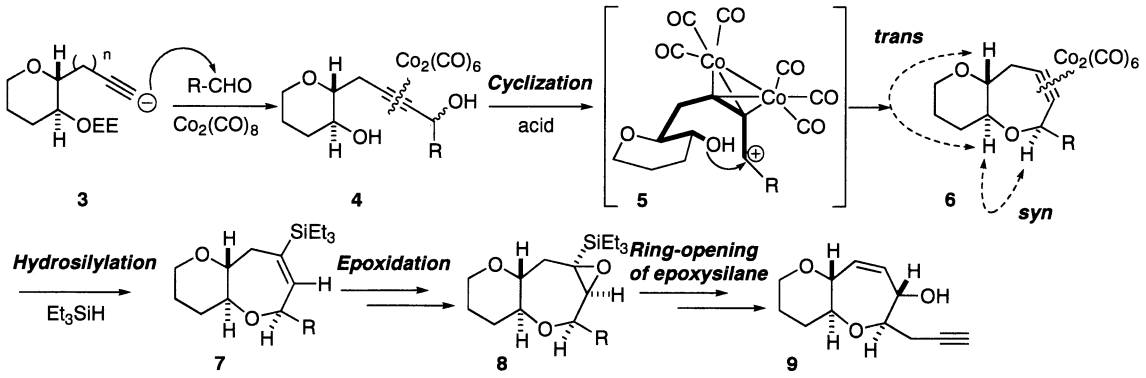


Figure 1.

Keywords: ciguatoxin; acetylene cobalt complex; hydrosilylation; vinylsilane; epoxysilane.
* Corresponding author. Tel.: +81-52-789-4109; fax: +81-52-789-4111; e-mail: isobem@agr.nagoya-u.ac.jp

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00044-3

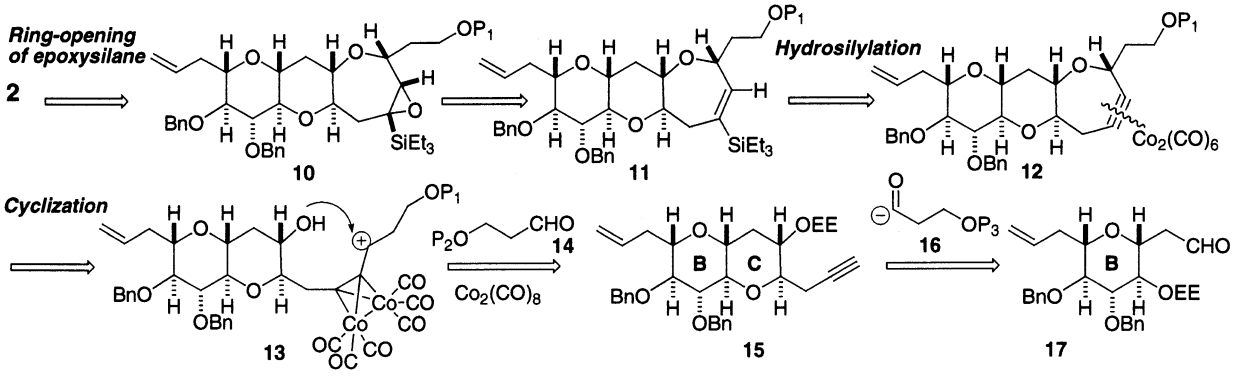


Scheme 1.

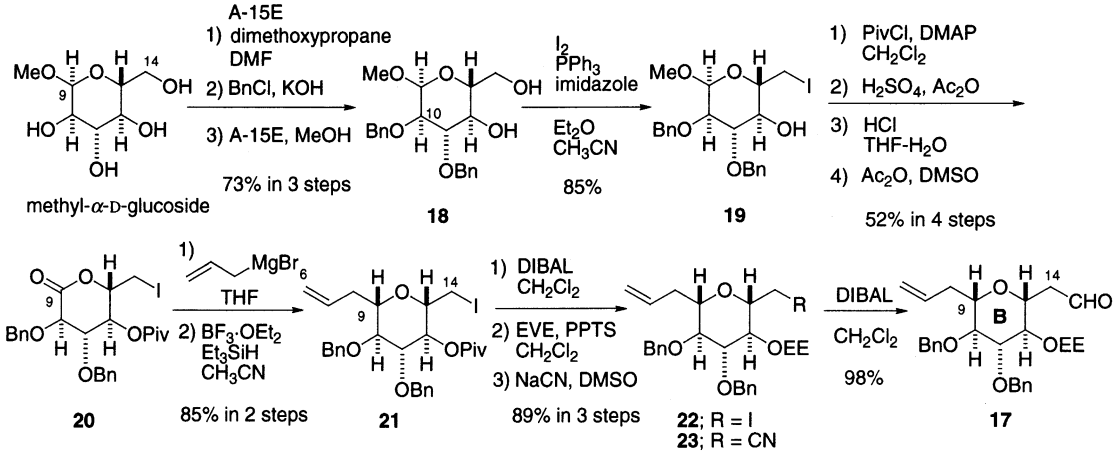
formation of allylic alcohol **9**,[7,12] has also been one of the key reactions in our synthetic studies. This paper describes the synthesis of the BCD-ring segment **2** (Fig. 1) directed toward the synthesis of the left part of CTX-1B based on this strategy.

2. Results and discussion

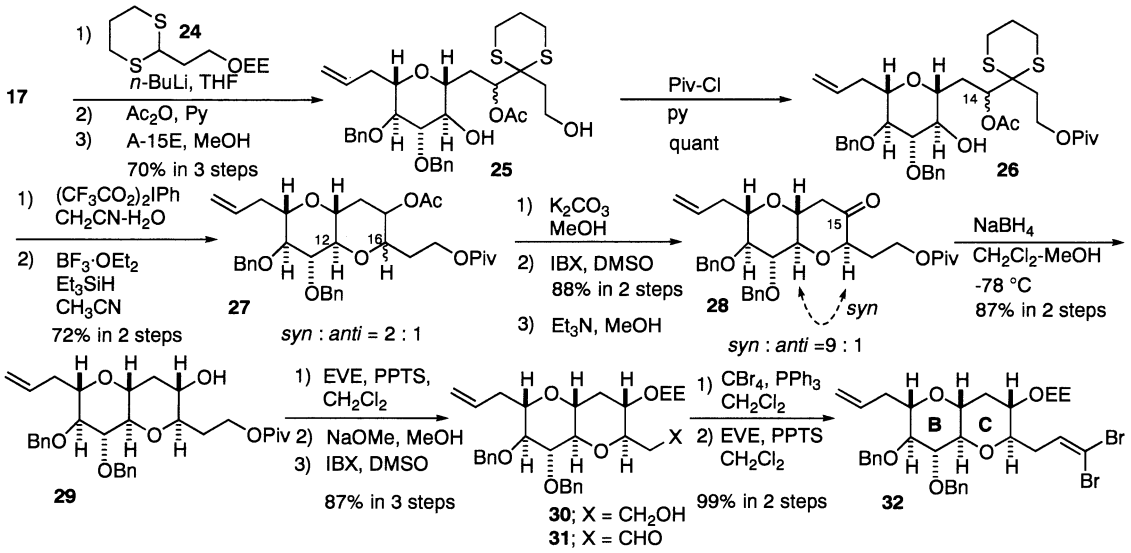
We employed the above methodology for the synthesis of **2** summarized as a retrosynthetic analysis in Scheme 2. The BCD-ring segment **2**, representing the C6–C23 portion of CTX-1B, consists of a *trans*-fused tricyclic 6/6/7-membered ether ring system. The allylic alcohol moiety on the D-ring of **2** should be transformed from the epoxysilane **10** through the ring-opening reaction of α,β-epoxysilane. Vinylsilane **11**, which would be obtained from the acetylene cobalt complex **12** through the hydrosilylation reaction, was defined as a precursor to **10**. The critical 7-membered ring cyclization would occur from the precursor propargylic cation **13** that is stabilized by the acetylene cobalt complex. This cyclization precursor should be derived from the BC-acetylene **15** and 3-oxy-propanal **14**. BC-acetylene **15** should be transformed from B-ring segment **17** and acyl anion equivalent **16**. Methyl-α-D-glucopyranoside would access to this B-ring segment **17**.



Scheme 2.



Scheme 3.

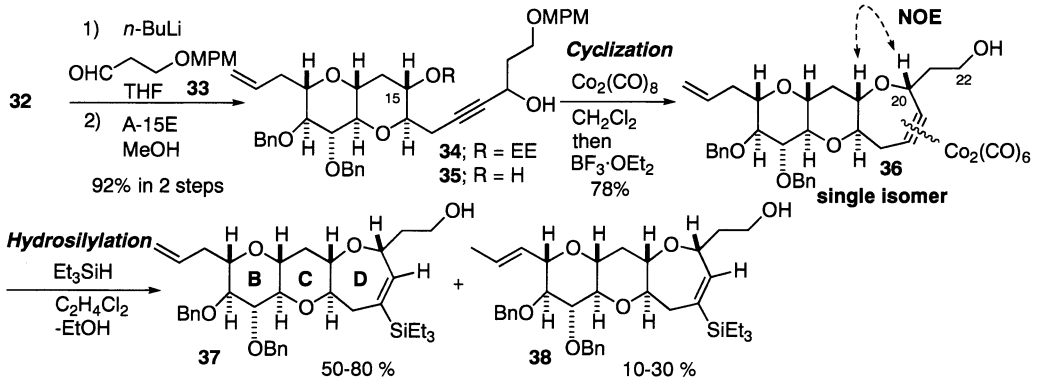


Scheme 4.

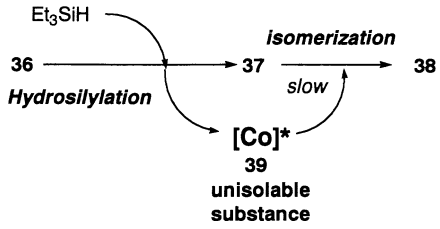
Synthesis of the B-ring **17** is summarized in Scheme 3.[13] Selective dibenzylation at C-10, 11 was performed in three steps from methyl-α-D-glucopyranoside to give **18**. This primary alcohol **18** was converted into iodide **19**. The resulting iodide **19** was transformed into lactone **20** by a four-step sequence including pivaloylation at C-12, acetolysis, hydrolysis, and oxidation.[14] Treatment of lactone **20** with allylmagnesium bromide to obtain C-9 ketal, followed by reduction of this ketal produced the α-allyl-glycoside **21**.[15] The pivaloyl protecting groups of **21** were changed into the ethoxy ethyl ether **22** in high yield. Iodine **22** was replaced with cyanide to provide nitrile **23** which was reduced with DIBAL to afford the B-ring **17**.

Synthesis of the BC-acetylene equivalent **32** is summarized in Scheme 4. Lithiation of the dithiane **24** and addition of the resulting anion to aldehyde **17** in THF at 0°C gave a coupling adduct, which has all the carbons needed to construct the BC-ring skeleton. Selective protection and deprotection provided **26**. The thioketal moiety of **26** was hydrolyzed by treatment with bis(trifluoroacetoxy)iodobenzene[16] in CH_3CN–H_2O to cyclic ketal, which was subsequently transformed into cyclic ether **27** by treatment with Et_3SiH and $BF_3{\cdot}OEt_2$ in CH_3CN at 0°C.[15] The newly generated stereogenic center in **27** at the C16 position was a mixture with ratio of 2:1. This stereochemistry was corrected by epimerization through the following 3 steps. First removal of the acetoxy group followed by oxidation[17] to the ketone at C15, and subsequent treatment of the resulting ketone with Et_3N in MeOH at room temperature gave **28** (*syn*/*anti*=9:1). Stereoselective reduction of the ketone at C15 was achieved by $NaBH_4$ in CH_2Cl_2–MeOH at −78°C[18] to give alcohol **29** which has the desired stereochemistry. At this stage, the minor isomer could be separated by silica gel column chromatography. With BC-ring **29** in hand, the side chain was required for the conversion into an acetylene equivalent for the construction of the D-ring. Removal of the pivaloyl group was followed by oxidation to aldehyde **31**, which was converted into dibromoolefin[19] as BC-acetylene equivalent **32** by Corey's protocol.

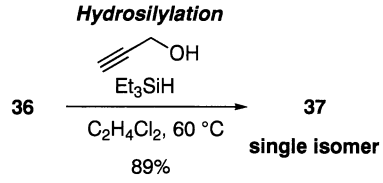
Treatment of the dibromoolefin **32** with 2.2 equiv. of *n*-BuLi generated the corresponding acetylide, which was mixed with the protected 3-oxy-propanal **33** to give the coupling product **34** (Scheme 5). After deprotection of the hydroxyl group at C15, it was successively treated with $Co_2(CO)_8$ and then $BF_3{\cdot}OEt_2$ in one-pot to afford the



Scheme 5.



Scheme 6.



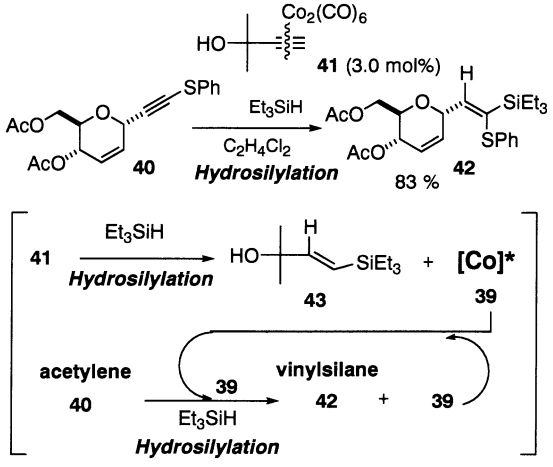
Scheme 8.

cyclization product **36** as a single stereoisomer having *syn* relationship. Hydrosilylation of **36** was conducted with Et_3SiH by heating at 60°C in dichloroethane solvent in the presence of EtOH. EtOH was added to prevent the silylation of alcohol at C-22.[11] But this hydrosilylation reaction provided a complex mixture of the desired vinylsilane **37** (50–80%) and **38** (10–30%) whose terminal olefin was isomerized into inner olefin, unexpectedly. The ratios of the position isomers **38/37** were remarkably dependent on the reaction scale; thus, as the reaction scale became large, the ratio increased.

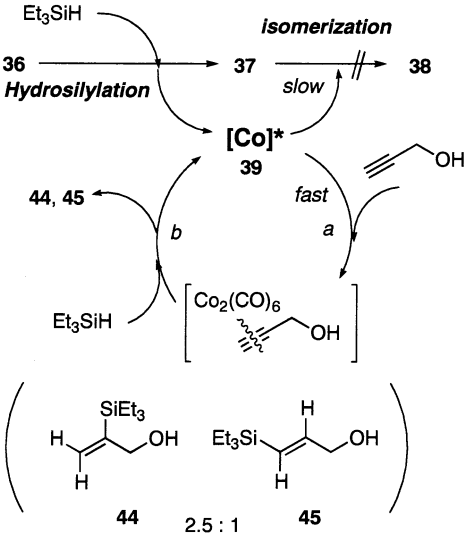
It is likely that this isomerization reaction took place by an action of 'unisolable substance [Co]* **39**' (Scheme 6). This **39** is supposed to be real active species of the catalytic hydrosilylation reaction (Scheme 7).[20] Although the **39** has not been characterized yet, it is likely to be liberated from the acetylene cobalt complex **36** when hydrosilylated. It should be assumed that it is possible to inhibit the side reactions if the 'unisolable substance **39**' can be trapped by additives.

Under these circumstances, large excess hexene was added as a dummy terminal olefin to prevent the isomerization of **37**. Although the hexene decreased the ratio of the isomer **38** (0–20%), it was not able to stop isomerization completely (the ratio of the isomer **38** was remarkably dependent on the reaction scale). Next excess 2-propene-1-ol was added in place of EtOH and hexene, but it could not completely, either (0–20%). These results show the importance of trapping the active species **39** to prevent the isomerization. In order to trap **39**, excess propargyl alcohol was added. This choice turned out to be right; adding propargyl alcohol was found to prevent the isomerization completely (Scheme 8). The vinylsilane **37** was a sole product (89%). With this dummy acetylene, it became possible to raise the reaction scale to over 1 g. It is noted that the vinylsilanes (**44**, **45**) which come from propargyl alcohol were also obtained (Scheme 9). The formation of these vinylsilanes (**44**, **45**) suggest that propargyl alcohol could trap the active species **39** (step *a*), then hydrosilylated into vinylsilane **44** or **45** (step *b*).[21]

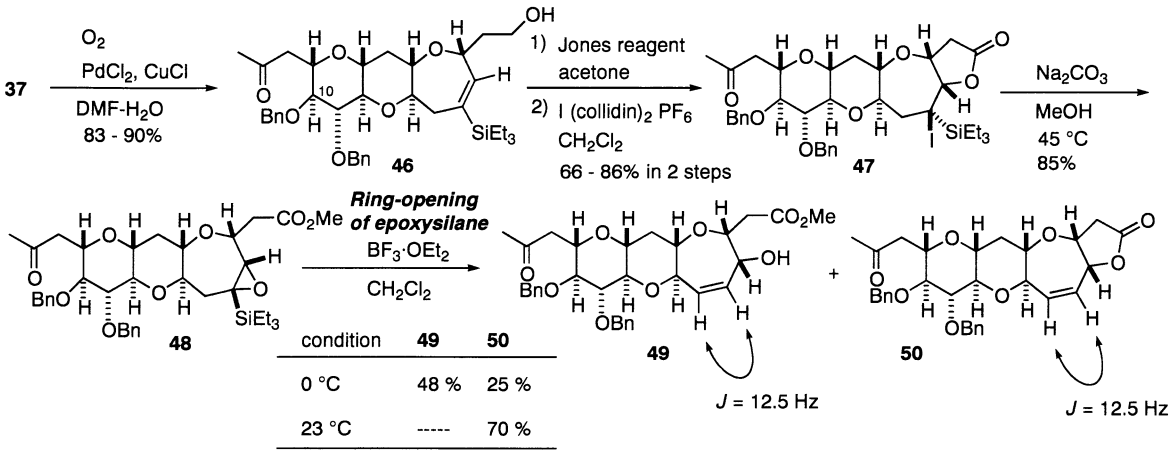
According to the route shown in Scheme 10, our attention was turned to the transformation of the vinylsilane **37** into the allylic alcohol **49**. The terminal olefin of **37** was converted into methylketone **46** through Wacker oxidation. Conversion of the terminal olefin was due to its reactive nature during the following iodo-lactonization step to provide a tetrahydrofuran by-product through an iodo-etherification[22] reaction between the terminal olefin and the C10 hydroxy group; thus Wacker oxidation was employed to protect this olefin. The terminal hydroxy group of **46** was oxidized into carboxylic acid, followed by treatment with $I(collidine)_2PF_6$[23] to give iode lactone **47** in modest yield, which was converted to epoxysilane **48** by the opening of lactone in the presence of Na_2CO_3 in MeOH.[24] With the epoxysilane **48** in hand, we tried a ring-opening reaction of epoxysilane into an allylic alcohol form. Treatment of epoxysilane **48** with $BF_3{\cdot}OEt_2$ gave a mixture of the desired allylic alcohol **49** and its lactone analog **50**, unfortunately. The methyl ester moiety of epoxysilane **48** turned out to be changed prior to this step into an inactive form to prevent lactone formation.



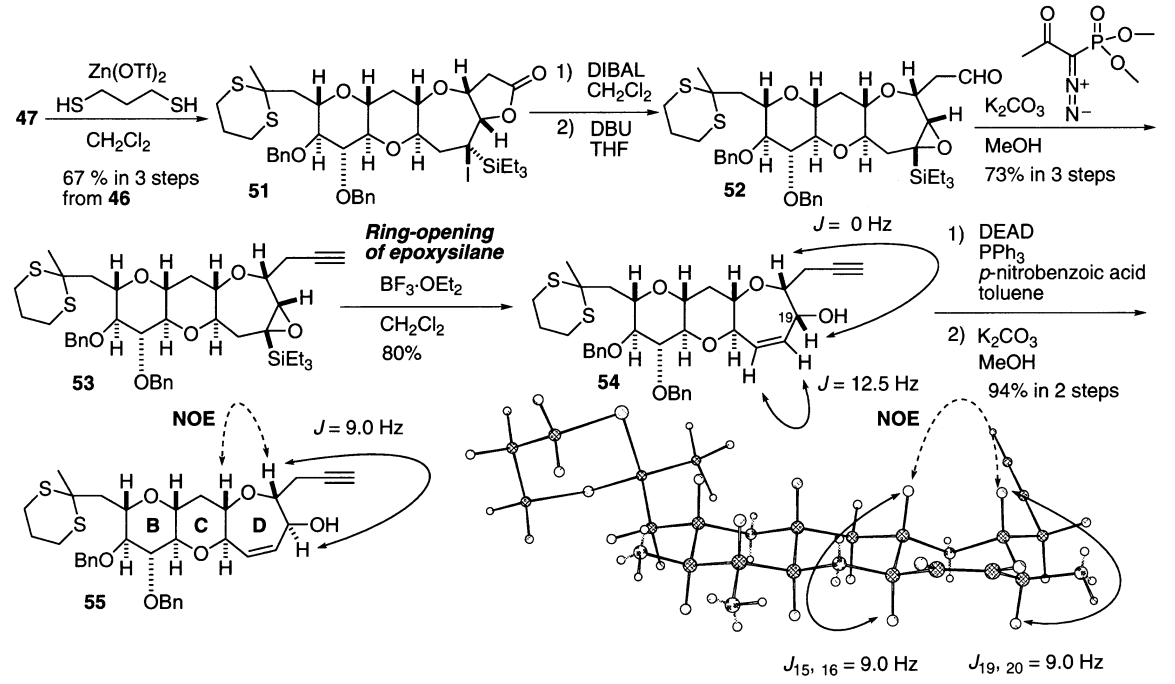
Scheme 7.



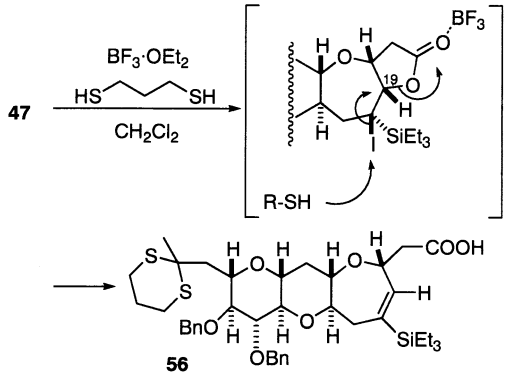
Scheme 9.



Scheme 10.



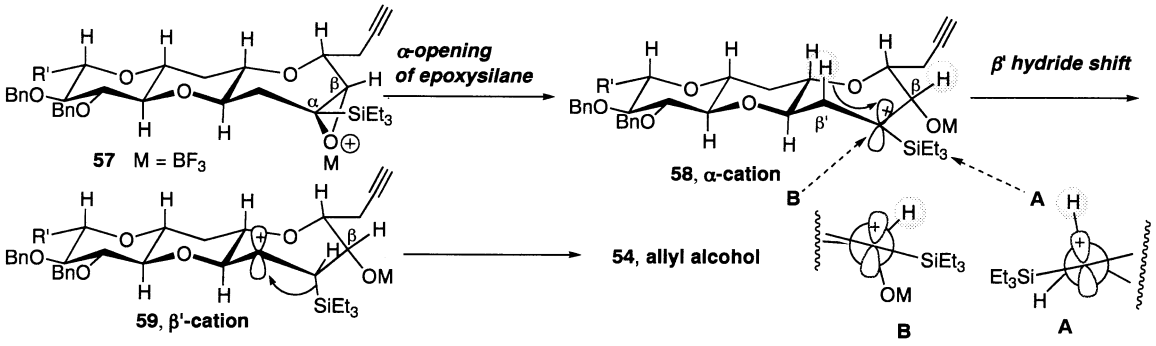
Scheme 11.



Scheme 12.

The ketone at C7 of iodo-lactone **47** was protected in the form of dithioketal **51** (Scheme 11). Originally $BF_3{\cdot}OEt_2$ was used instead of $Zn(OTf)_2$,[25] but vinylsilane **56** was reformed by a nucleophilic attack of thiol to iodide as a side reaction (Scheme 12). It can be presumed that this retro lactonization reaction took place by the effect of the silyl group that stabilizes a cation at C-19. DIBAL reduction of this lactone **51** was followed by DBU treatment in THF to yield the epoxysilane **52** having the aldehyde side chain. After converting the aldehyde **52** into the acetylene[26] **53**, the ring-opening reaction of epoxysilane **53** into the allylic alcohol **54** was achieved by treatment with $BF_3{\cdot}OEt_2$ in 80%, and its configuration was corrected under a modified Mitsunobu condition[27] using *p*-nitrobenzoic acid to afford BCD-ring **55**.[28]

A possible mechanism of the ring-opening reaction of epoxysilane **53** is shown in Scheme 13.[12] Because of the



Scheme 13.

well-known stabilization of the β cations to the silicon atom, acid-catalyzed reaction of α,β-epoxysilane might be expected to proceed with ring-opening at the β carbon. But in the case of an α,β-epoxysilane, the relative orientation of the α C–Si bond and the β C–O bond is not in the parallel alignment necessary for the stabilization of a developing positive charge by the silicon atom. Many ring-opening reactions of α,β-epoxysilanes are reported to show that these reactions proceed with strong preference for cleavage of the α C–O bond under various conditions.[29] Treatment of **53** with $BF_3{\cdot}OEt_2$ proceeded with ring-opening at the α-carbon to give α-cation intermediate **58**. Although it is assumed that the ring-opening reaction would take place in a concerted manner, the cation intermediates are expressed in Scheme 13 in stepwise form for simplification. Since hydride shift should occur to the α-cation **58** from the pseudo axial hydrogen at the β or β′-carbon that was oriented antiperiplanar to the generating empty p-orbital, the β′-hydride shift as illustrated in Newman projection A occurred predominantly in **58** to give the β′-cation **59**, which might be stabilized by the silyl group. Then the β′-cation **59** underwent a rapid loss of the silyl group to result in the formation of allylic alcohol **54**.

Thus, we have succeeded in the synthesis of the BCD-ring **55** of CTX-1B **1** using an acetylene cobalt complex-mediated cyclization and the ring-opening reaction of epoxysilane to allylic alcohol. Further efforts directed toward the total synthesis of CTX-1B are in progress in our laboratory.

3. Experimental

3.1. General

Melting points (mp) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Infrared spectra (IR) were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Brucker ARX-400 (400 MHz) and Varian Gemini-2000 (300 MHz) spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Brucker ARX-400 (100 MHz) and Varian Gemini-2000 (75 MHz) spectrometers. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass Q-TOF (ESI), 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, nonaqueous reactions were conducted in oven-dried (200°C) or flame-dried glassware under inert atmosphere of dry nitrogen or argon. Dry THF was distilled from potassium metal with benzophenone. 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 a filter aid.

3.1.1. Diol (18). To a solution of methyl-α-D-glucopyranoside (1.19 kg, 6.13 mol) in 6.0 L of DMF were added 2,2-dimethoxypropane (1.88 L, 15.3 mol) and A-15E (Amberlyst-15E, 6.0 g) at room temperature. After stirring mechanically for 3 days at room temperature, the reaction mixture was filtered and concentrated under reduced pressure to give 1.43 kg of acetonide as a crude oil, which was used directly for the next reaction without further purification.

A solution of the above acetonide (100 g) in 200 mL of CH_2Cl_2 was gradually added to a mechanically stirred solution containing 240 g (4.28 mol) of KOH in 800 mL of BnCl heated at 90°C. After stirring for 2.5 h at 115°C, the reaction mixture was cooled to room temperature and poured into an ice-cold sat. NH_4Cl solution. The resulting mixture was extracted with ether (×3). The combined extract was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a silica gel short column.

A-15E (30.0 g) was added to a solution containing the above dibenzyl ether in 2.0 L of MeOH at room temperature. After stirring mechanically for 18 h at room temperature, the reaction mixture was filtered, dried over Na_2SO_4, and concentrated in vacuo to leave a viscous oil. The residue was filtered through a silica gel short column and dissolved in ether containing a small amount of hexane and the solution was stood still for crystallization. The mother

liquors were decanted and the crystals were collected by filtration and then dried under high vacuum to afford 117 g of diol **18** in three crops (73% in 3 steps). $[\alpha]_D^{27}=+16.3°$ (*c* 1.01, $CHCl_3$). Mp 77.5°C. IR (KBr) ν_{max} 3425, 2926, 2362, 1749, 1455, 1364, 1052, 740, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (1H, br, –O*H*), 2.66 (1H, br, –O*H*), 3.36 (3H, s, –OCH_3), 3.45–3.63 (3H, m, H-10, 12, 13), 3.66–3.83 (3H, m, H-11, 14a, 14b), 4.57–4.78 (4H, m, –OCH_2Ph, –OCH_2Ph*), 5.01 (1H, d, *J*=11.5 Hz, H-9), 7.25–7.40 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.2, 62.2, 70.3, 70.7, 73.1, 75.3, 79.7, 81.3, 98.2, 127.9, 128.0, 128.1, 128.5, 128.6, 138.0, 138.7. Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.28; H, 6.93.

3.1.2. Iodide (19). To a solution of the diol **18** (63.79 g, 0.170 mol) in 1275 mL of toluene were added imidazole (29.0 g, 0.426 mol), PPh_3 (71.50 g, 0.273 mol) and I_2 (69.18 g, 0.273 mol) at room temperature. After stirring mechanically for 2 h, the reaction mixture was poured into an ice-cold sat. Na_2SO_3 solution and extracted with CH_2Cl_2 (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (ether/hexane=80:20). Recrystallization from hexane/ether gave 70.12 g (85%) of iodide **19** as white crystals. $[\alpha]_D^{26}=+22°$ (*c* 0.98, $CHCl_3$). Mp 83.5–84.0°C. IR (KBr) ν_{max} 3504, 3030, 2909, 2363, 1455, 1363, 1198, 1063, 985, 738, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (1H, s, –O*H*), 3.22–3.34 (2H, m, H-14a, 14b), 3.38–3.55 (3H, m, H-10, 12, 13), 3.44 (3H, s, –OCH_3), 3.78 (1H, t, *J*=9.0 Hz, H-11), 4.63–4.81 (4H, m, –OCH_2Ph, –OCH_2Ph*), 5.03 (1H, d, *J*=11.3 Hz, H-9), 7.25–7.45 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.9, 55.5, 69.7, 73.1, 73.6, 75.3, 79.8, 80.7, 98.1, 128.0, 128.1, 128.5, 128.7, 137.9, 138.6. Anal. Calcd for $C_{21}H_{25}IO_5$: C, 52.08; H, 5.20. Found: C, 52.08; H, 5.33.

3.1.3. Lactone (20). To a solution of the iodide **19** (100.0 g, 0.207 mol) in 2070 mL of CH_2Cl_2 were added pivaloyl chloride (38.2 mL, 0.310 mol) and DMAP (25.2 g, 0.207 mol) at 0°C. After mechanically stirring for 2 days at room temperature, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with CH_2Cl_2 (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give pivaloate as a crude oil, which was used directly in the next step without further purification.

A conc. H_2SO_4 (6.75 mL) was slowly added to a solution of above pivaloate (135.0 g) in 1350 mL of acetic anhydride at −5°C. After stirring mechanically for 15 min at −5 to 0°C, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give 146.0 g of acetate, which was used directly in the next step without further purification.

To a solution of the above acetate (146.0 g) in 2177 mL of THF and 109.0 mL of H_2O was added 109.0 mL of conc. HCl at 0°C. After stirring magnetically for 7 days at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with ether (×3). The combined extracts was dried over Na_2SO_4. Removal of the volatiles in vacuo gave acetal, which was used in next step without further purification.

To a solution of the above acetal (139.0 g) in 1260 mL of DMSO was added 840 mL of acetic anhydride. After stirring magnetically for 12 h at room temperature, the reaction mixture was poured into a cold H_2O, extracted with ether (×3). The combined extract was dried over Na_2SO_4 and concentrated in vacuo to leave a viscous oil. The residue was filtered through a silica gel short column and dissolved in ether–hexane and was stood still for crystallization. The mother liquors were decanted and the crystals were collected by filtration and then dried under high vacuum to afford 61.0 g of lactone **20** in three crops (52% in four steps). $[\alpha]_D^{27}=+72°$ (*c* 0.66, $CHCl_3$). Mp 95.0–96.5°C. IR (KBr) ν_{max} 3446, 3032, 2972, 2875, 2362, 2341, 1757, 1737, 1481, 1455, 1277, 1231, 1162, 1136, 1041, 743, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (9H, s, –OPiv), 3.28 (1H, dd, *J*=11.5, 6.0 Hz, H-14a), 3.46 (1H, dd, *J*=11.5, 6.0 Hz, H-14b), 3.82 (1H, dd, *J*=5.5, 4.0 Hz, H-11), 4.16 (1H, d, *J*=5.5 Hz, H-10), 4.54 (1H, ddd, *J*=7.5, 6.0, 6.0 Hz, H-13), 4.62 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 4.66 (1H, d, *J*=12.0 Hz, –OCH_2Ph*), 4.70 (1H, d, *J*=12.0 Hz, –OCH_2Ph*), 4.91 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 5.22 (1H, dd, *J*=7.5, 4.0 Hz, H-12), 7.23–7.36 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 2.8, 26.8, 38.7, 71.1, 72.7, 73.4, 76.9, 78.9, 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 136.5, 136.9, 167.6, 177.0. Anal. Calcd for $C_{25}H_{29}IO_6$: C, 54.36; H, 5.29. Found: C, 54.36; H, 5.10.

3.1.4. Allyl glycoside (21). A solution of allylmagnesium bromide (1.0 M in ether, 50.5 mL, 0.051 mol) was slowly added to a solution of the lactone **20** (25.39 g, 0.046 mol) in 460 mL of THF at −78°C. After stirring magnetically for 1 h at −78°C, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with ether (×3). The combined extract was dried over Na_2SO_4 and concentrated in vacuo to give ketal as a crude oil, which was filtered through a silica gel short column.

To a solution of the above ketal (30.0 g) in 500 mL of CH_3CN were added 24.0 mL of Et_3SiH (0.151 mol) and 9.67 mL of $BF_3{\cdot}OEt_2$ (0.076 mol) at −10°C. After stirring magnetically for 30 min at −10 to 0°C, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with ether (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude oil, which was chromatographed on a silica gel column (ether/hexane=90:10) to give **21** (22.7 g, 85% in 2 steps). $[\alpha]_D^{27}=+23°$ (*c* 0.89, $CHCl_3$). IR (KBr) ν_{max} 3066, 3032, 2974, 2905, 2872, 2359, 2342, 1736, 1643, 1480, 1455, 1363, 1278, 1159, 1135, 1084, 996, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (9H, s, –OPiv), 2.30 (1H, dt, *J*=16.5, 7.0 Hz, H-8a), 2.60 (1H, ddt, *J*=16.5, 7.0, 1.5 Hz, H-8b), 3.06 (1H, dd, *J*=11.5, 9.0 Hz, H-14a), 3.20 (1H, dd, *J*=11.5, 2.5 Hz, H-14b), 3.35 (1H, ddd, *J*=10.0, 9.0, 2.5 Hz, H-13), 3.38–3.48 (2H, m, H-9, 10), 3.70 (1H, t, *J*=10.0 Hz, H-11), 4.62 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 4.68 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 4.79 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 4.80 (1H, d, *J*=12.0 Hz, –OCH_2Ph), 4.92 (1H, t, *J*=10.0 Hz, H-12), 5.10 (1H, dm, *J*=10.5 Hz, H-6a), 5.13 (1H, dm, *J*=18.0 Hz, H-6b), 5.98 (1H, ddt, *J*=18.0, 10.5, 7.0 Hz,

H-7), 7.23–7.36 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.3, 27.0, 35.7, 38.8, 74.0, 75.1, 75.1, 79.0, 81.4, 84.2, 117.4, 128.2, 127.7, 127.9, 128.4, 128.5, 134.4, 138.0, 138.1, 177.3. Anal. Calcd for $C_{28}H_{35}IO_5$: C, 58.14; H, 6.10. Found: C, 58.14; H, 6.14.

3.1.5. Nitrile (23). A solution of diisobutylaluminum hydride (DIBAL, 1.0 M solution in toluene, 111 mL, 0.111 mol) was slowly added to a solution of the pivaloate **21** (25.65 g, 0.044 mol) in 443 mL of CH_2Cl_2 at −78°C. After stirring magnetically for 1 h at −78°C, 60 mL of ethyl acetate and 28 mL of sat. NH_4Cl aq. were added at −78°C. Allowed to warm up to room temperature, this slurry was diluted with 280 mL of ether and stirred for further 1 h 40 min. Anhydrous sodium sulfate (98.0 g) was added to this slurry, then the mixture was filtered through the pad of Super-Cel. The filtrate was dried over Na_2SO_4, and then concentrated under reduced pressure to give alcohol (23.69 g), which was used directly in the next step without further purification.

To a solution of the above alcohol (23.69 g) in 443 mL of CH_2Cl_2 was added 8.47 mL of ethyl vinyl ether (EVE, 0.087 mol) and pyridinium *p*-toluenesulufonate (PPTS, 500 mg) at room temperature. After stirring magnetically for 12 h at room temperature, the reaction mixture was poured into a cold sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2 (×2). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give ethoxyethyl ether, which was used in the next step without further purification.

NaCN (3.26 g, 0.065 mol) was added to a solution of the above ethoxyethyl ether (26.08 g, 0.041 mol) in 443 mL of DMSO at room temperature. After raising the temperature to 65°C, the reaction mixture was stirred for 1 h. After cooling to room temperature, the reaction mixture was poured into H_2O and extracted with ether (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude oil, which was chromatographed on a silica gel column (ether/hexane=80:20) to give **23** (20.27 g, 89% in 3 steps). IR (KBr) ν_{max} 2980, 2901, 1645, 1498, 1455, 1379, 1359, 1121, 1089, 1053, 738, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09, 1.22 (total 3H, each t, J=7.0 Hz, –OCH$_2$C*H*$_3$), 1.24, 1.35 (total 3H, each d, J=5.0 Hz, –OCH(C*H*$_3$)O–), 2.30 (1H, dt, J=15.0, 8.0 Hz, H-8a), 2.58 (1H, dm, J=15.0 Hz, H-8b), 2.66, 2.75 (total 1H, each dd, J=16.5, 5.5 Hz, H-14a), 2.83, 2.90 (total 1H, each dd, J=16.5, 3.5 Hz, H-14b), 3.28–3.64 (5H, m, H-9, 10, 11, 12, 13), 3.76, 3.79 (total 2H, each q, J=7.0 Hz, –OC*H*$_2$CH$_3$), 4.63, 4.65 (total 1H, each d, J=11.0 Hz, –OC*H*$_2$Ph), 4.74–4.96 (4H, m, –OC*H*$_2$Ph, –OC*H*$_2$Ph*, –OC*H*(CH$_3$)O–), 5.09 (1H, dm, J=10.5 Hz, H-6a), 5.11 (1H, dm, J=17.0 Hz, H-6b), 5.91 (1H, m, H-7), 7.22–7.36 (10H, m, aromatic). Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58. Found: C, 72.23; H, 7.55.

3.1.6. B-ring (17). A solution of diisobutylaluminum hydride (DIBAL, 1.0 M in toluene, 14.1 mL, 14.1 mmol) was slowly added to a solution of **23** (6.25 g, 13.4 mmol) in 134 mL of CH_2Cl_2 at −78°C. After stirring for 1 h at −78 to −20°C, 10 mL of AcOEt was added at −20°C. The reaction mixture was poured into 10% AcOH aq (100 mL) and extracted with CH_2Cl_2 (×2). The combined extract was washed with sat. $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane=80:20) to afford B-ring **17** (6.17 g, 98%). IR (KBr) ν_{max} 3066, 3032, 2981, 2903, 1728, 1454, 1359, 1092, 1057, 736, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07, 1.18 (total 3H, each t, J=7.0 Hz, –OCH$_2$C*H*$_3$), 1.22, 1.30 (total 3H, each d, J=5.0 Hz, –OCH(CH$_3$)O–), 2.21 (1H, dt, J=15.0, 7.5 Hz, H-8a), 2.47–2.61 (2H, m, H-8b, 14a), 2.81, 3.01 (total 1H, each dm, J=16.0 Hz, H-14b), 3.24–3.51 (4H, m, H-9, 10, 12, 13), 3.64 (1H, t, J=9.0 Hz, H-11), 3.70–3.81 (2H, m, –OC*H*$_2$CH$_3$), 4.62, 4.64 (total 1H, each d, J=11.5 Hz, –OC*H*$_2$Ph), 4.76–4.95 (total 4H, –OC*H*$_2$Ph, –OC*H*$_2$Ph*, –OCH(CH$_3$)O–), 5.05 (1H, dm, J=10.5 Hz, H-6a), 5.11 (1H, dm, J=17.0 Hz, H-6b), 5.76–5.90 (1H, m, H-7), 7.22–7.36 (10H, m, aromatic), 9.75, 9.76 (total 1H, each t, J=2.5 Hz, –C*H*O). Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.77; H, 7.67.

3.1.7. Diol (25). To a solution of the dithiane **24** (4.35 g, 18.4 mmol) in 100 mL of dry THF was added a solution of *n*-BuLi (1.60 M in hexane, 11.5 mL, 18.4 mmol) at −78°C. After stirring for 20 min at 0°C, aldehyde **17** (7.01 g, 14.9 mmol) in 25.0 mL of THF was added and the resulting mixture was stirred for 40 min at 0°C. Then the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with ether. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, which was used in the next step without further purification.

The above coupling compound was dissolved in 100 mL of pyridine and treated with acetic anhydride (2.84 mL, 29.9 mol). After stirring at room temperature for 12 h, the reaction mixture was quenched with an ice-cold sat. NH_4Cl solution and extracted with ether (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure.

To a solution of the above acetate in 150 mL of MeOH was added A-15E (1.0 g). After stirring for 48 h at room temperature, the reaction mixture was filtered through a pad of Celite, the resin was washed thoroughly with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane=80:20) to give diol **25** (6.39 g, 70% in 3 steps). IR (KBr) ν_{max} 3422, 2900, 1741, 1713, 1642, 1498, 1454, 1426, 1372, 1237, 1089, 1043, 1028, 910, 737, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72–2.37 (9H, m, H-8a, 14a, 14b, 17a, 17b, –SC*H*$_2$C*H*$_2$CH$_2$S–), 2.08, 2.09 (total 3H, each s, –OAc), 2.45–2.80 (3H, m, 8b, –SC*H*$_2$CH$_2$CH$_2$S–), 2.97–3.50 (5H, m, H-9, 10, 11, 12, 13), 3.91 (2H, m, H-18a, 18b), 4.67, 4.68 (total 1H, each d, J=11.0 Hz, –OC*H*$_2$Ph), 4.72, 4.74 (total 1H, each d, J=11.5 Hz, –OC*H*$_2$Ph*), 4.86, 4.87 (total 1H, each d, J=11.0 Hz, –OC*H*$_2$Ph), 4.95, 4.96 (total 1H, each d, J=11.5 Hz, –OC*H*$_2$Ph*), 5.08 (1H, dm, J=10.5 Hz, H-6a), 5.10 (1H, dm, J=17.0 Hz, H-6b), 5.73, 5.84 (total 1H, dd, J=9.0, 1.5 Hz; d, J=10.0 Hz, H-15), 5.84–6.04 (1H, m, H-7), 7.26–7.38 (10H, m, aromatic). Anal. Calcd for $C_{32}H_{42}O_7S_2$: C, 63.76; H, 7.02. Found: C, 63.58; H, 7.28.

3.1.8. Pivaloate (26). Piv-Cl (1.31 mL, 10.6 mmol) was added to a solution of the diol **25** (6.39 g, 10.6 mmol) in 200 mL of CH_2Cl_2 and 8.57 mL of pyridine at 0°C. After stirring at room temperature for 12 h, another Piv-Cl (0.39 mL, 3.18 mol) was added at 0°C. After stirring at room temperature for additional 12 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with CH_2Cl_2 (×3). The combined extract was dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=50:50) gave the pivaloate **26** (7.5 g, 100%). IR (KBr) ν_{max} 3481, 2974, 2906, 2872, 1728, 1481, 1455, 1426, 1371, 1283, 1236, 1156, 1091, 1064, 1045, 1028, 910, 736, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (9H, s, –OPiv), 1.68–2.38 (6H, m, H-14a, 14b, 17a, 17b, $-SCH_2CH_2CH_2S-$), 2.45–2.82 (4H, m, 8a, 8b, $-SCH_2CH_2CH_2S-$), 2.98–3.56 (7H, m, 9, 10, 11, 12, 13, $-SCH_2CH_2CH_2S-$), 4.30–4.38 (2H, m, H-18a, 18b), 4.64–4.97 (4H, m, $-OCH_2Ph$, $-OCH_2Ph^*$), 5.07 (1H, dm, J=10.5 Hz, H-6a), 5.09 (1H, dm, J=17.0 Hz, H-6b), 5.73, 5.85 (total 1H, each d, J=10.0 Hz, H-15), 5.85–6.05 (1H, m, H-7), 7.26–7.38 (10H, m, aromatic). Anal. Calcd for $C_{37}H_{50}O_8S_2$: C, 64.69; H, 7.34. Found: C, 64.67; H, 7.61.

3.1.9. Bicyclic ether (27). To a solution of **26** (10.84 g, 15.7 mmol) in 300 mL of CH_3CN and 30 mL of H_2O was added $(CF_3CO_2)_2IPh$ (13.57 g, 31.6 mol) at room temperature. After stirring at room temperature for 15 min, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with ether (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a silica gel short column to give the ketal.

To a solution of the above ketal in 194 mL of CH_3CN were successively added triethylsilane (6.21 mL, 38.9 mmol) and $BF_3{\cdot}OEt_2$ (2.46 mL, 19.4 mmol) at 0°C. After stirring at 0°C for 1 h, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The resulting mixture was extracted with ether (×2). The combined extract was dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=50:50) gave the **27** (6.60 g, 72% in 2 steps). IR (KBr) ν_{max} 2975, 2936, 2904, 2874, 1732, 1481, 1455, 1369, 1286, 1237, 1158, 1100, 1068, 1029, 997, 914, 751, 737, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (9H, s, –OPiv), 1.51 (1H, q, J=11.0 Hz, H-14a), 1.62–2.05 (2H, m, H-17a, 17b), 2.05, 2.12, 2.13 (total 3H, each s, –OAc), 2.17–2.64 (3H, m, H-8a, 8b, 14b), 3.12–3.76 (6H, m, H-9, 10, 11, 12, 13, 16), 4.02–4.34 (2H, m, H-18a, 18b), 4.61 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.73 (1H, d, J=11.0 Hz, $-OCH_2Ph^*$), 4.93 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.94 (1H, d, J=11.0 Hz, $-OCH_2Ph^*$), 5.02–5.12 (2H, m, H-6a, 6b), 5.76–5.94 (1H, m, H-7), 7.26–7.38 (10H, m, aromatic). Anal. Calcd for $C_{34}H_{44}O_8$: C, 70.32; H, 7.64. Found: C, 70.32; H, 7.73.

3.1.10. Bicyclic ketone (28). To a solution of **27** (4.13 g, 7.10 mmol) in 71 mL of MeOH was added K_2CO_3 (197 mg, 1.40 mmol). After stirring at room temperature for 20 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution. The resulting mixture was extracted with ether (×2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, which was used in the next step without further purification.

To the solution of above alcohol in 70 mL of DMSO was added IBX (2.88 g, 10.3 mmol). After stirring at room temperature for 12 h, the reaction was quenched with H_2O and filtered through a pad of Celite, washed thoroughly with ether. The filtrate was extracted with ether (×2). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=40:60) gave the ketone as a mixture at C-16 (3.37 g, 88% in 2 steps).

To a solution of the above ketone (2.00 g, 3.73 mmol) in 75 mL of MeOH was added Et_3N (1.04 mL, 7.45 mmol). After stirring at room temperature for 12 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution. The resulting mixture was extracted with ether (×2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a silica gel short column to give the bicyclic ketone **28** (1.99 g). IR (KBr) ν_{max} 2970, 2904, 1728, 1457, 1364, 1286, 1158, 1100, 737, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ 1.18 (9H, s, –OPiv), 1.90 (1H, ddt, J=14.5, 8.5, 5.5 Hz, H-17a), 2.25–2.34 (2H, m, H-8a, 17b), 2.50 (1H, dd, J=15.5, 11.5 Hz, H-14a), 2.57–2.63 (1H, m, H-8b), 2.97 (1H, dd, J=15.5, 5.5 Hz, H-14b), 3.37 (1H, dd, J=9.0, 8.5 Hz, H-10), 3.42–3.50 (3H, m, H-9, 12, 13), 3.72 (1H, t, J=8.5 Hz, H-11), 3.94 (1H, dd, J=8.5, 4.0 Hz, H-16), 4.18 (1H, ddd, J=11.0, 8.5, 5.5 Hz, H-18a), 4.24 (1H, ddd, J=11.0, 6.5, 5.0 Hz, H-18b), 4.64 (1H, d, J=10.5 Hz, $-OCH_2Ph$), 4.78 (1H, d, J=11.0 Hz, $-OCH_2Ph^*$), 4.95 (1H, d, J=11.0 Hz, $-OCH_2Ph^*$), 4.96 (1H, d, J=10.5 Hz, $-OCH_2Ph$), 5.08 (1H, dm, J=10.5 Hz, H-6a), 5.09 (1H, dm, J=17.0 Hz, H-6b), 5.83 (1H, dddd, J=17.0, 10.5, 8.0, 6.5 Hz, H-7), 7.26–7.38 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.2, 28.6, 35.9, 38.7, 44.9, 60.3, 73.9, 75.3, 75.4, 78.8, 79.5, 80.5, 81.9, 83.9, 117.5, 127.7, 127.8, 127.9, 128.0, 128.5, 134.1, 138.1, 138.3, 204.2. Anal. Calcd for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.70; H, 7.53.

3.1.11. Alcohol (29). A solution of the ketone **28** in 18 mL of MeOH and 18 mL of CH_2Cl_2 was cooled to −78°C and treated with $NaBH_4$ (351 mg, 9.27 mmol). After stirring at −78°C for 1 h, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with ether (×3). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=50:50) gave the alcohol **29** (1.75 g, 87% in 2 steps). $[\alpha]_D^{27}$=+28° (*c* 0.83, $CHCl_3$). IR (KBr) ν_{max} 3447, 2974, 2935, 2904, 2872, 1727, 1708, 1481, 1456, 1364, 1287, 1162, 1101, 1072, 751, 737, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (9H, s, –OPiv), 1.50 (1H, q, H-14a), 1.76 (1H, dddd, J=14.5, 9.0, 6.0, 4.5 Hz, H-17a), 2.20–2.31 (2H, m, H-8a, 17b), 2.43 (1H, ddd, J=11.5, 4.0, 4.0 Hz, H-14b), 2.58 (1H, dm, J=11.5 Hz, H-8b), 3.08–3.16 (2H, m, H-12, 13), 3.24 (1H, td, J=9.0, 3.0 Hz, H-16), 3.29 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.38 (1H, ddd, J=9.5, 7.5, 3.5 Hz, H-9), 3.44 (1H, m, H-15), 3.60 (1H, t, J=8.5 Hz, H-11), 4.18 (1H, ddd, J=11.0, 8.5, 6.0 Hz, H-18a), 4.34 (1H, ddd, J=11.0, 7.0, 4.5 Hz, H-18b), 4.61 (1H, d, J=10.5 Hz,

–OCH_2Ph), 4.73 (1H, d, J=11.0 Hz, –OCH_2Ph*), 4.94 (1H, d, J=10.5 Hz, –OCH_2Ph), 4.95 (1H, d, J=11.0 Hz, –OCH_2Ph*), 5.07 (1H, dm, J=10.0 Hz, H-6a), 5.08 (1H, dm, J=17.0 Hz, H-6b), 5.87 (1H, dddd, J=17.0, 10.0, 7.5, 6.5 Hz, H-7), 7.26–7.38 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.2, 31.2, 36.0, 38.6, 38.7, 61.0, 69.5, 73.5, 75.1, 75.3, 78.8, 78.9, 80.8, 82.6, 84.1, 117.2, 127.7, 127.8, 127.9, 128.1, 128.4, 134.5, 138.3, 138.6, 178.4. Anal. Calcd for $C_{32}H_{42}O_7$: C, 71.35; H, 7.86. Found: C, 71.35; H, 7.62.

3.1.12. Alcohol (30). To a solution of **29** (721 mg, 1.34 mmol) in 15 mL of CH_2Cl_2 were successively added ethyl vinyl ether (0.38 mL, 4.02 mmol) and pyridinium *p*-toluenesulfonate (25 mg). After stirring for 12 h at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (×2). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure, which was used in the next step without further purification.

To a solution of a above pivaloate (910 mg) in 15 mL of MeOH was added NaOMe (108 mg, 2.00 mmol). After stirring for 12 h at 45°C, the reaction mixture was poured into an ice-cold sat. NH_4Cl 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 crude residue was purified by silica gel column chromatography (ether/hexane=80:20) to give **30** (643 mg, 91% in 2 steps). IR (KBr) ν_{max} 3393, 2975, 2894, 1456, 1097, 1068, 746, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (3H, t, J=7.0 Hz, –OCH$_2$CH_3), 1.30, 1.32 (total 3H, each d, J=5.5 Hz, –OCH(O)CH_3), 1.44, 1.56 (total 1H, each q, J=11.5 Hz, H-14a), 1.68–1.84 (1H, m, H-17a), 2.05–2.62 (4H, m, H-8a, 8b, 14b, 17b), 3.06–3.86 (11H, m, H-9, 10, 11, 12, 13, 15, 16, 18a, 18b, –OCH_2CH$_3$), 4.62 (1H, d, J=11.0 Hz, –OCH$_2$Ph), 4.72, 4.81 (total 1H, each q, J=5.5 Hz, –OCH(CH$_3$)O–), 4.78 (1H, d, J=11.0 Hz, –OCH_2Ph*), 4.88 (1H, d, J=11.0 Hz, –OCH_2Ph*), 4.92 (1H, d, J=11.0 Hz, –OCH_2Ph), 5.07 (1H, dm, J=10.0 Hz, H-6a), 5.08 (1H, dm, J=17.0 Hz, H-6b), 5.80–5.95 (1H, m, H-7), 7.26–7.38 (10H, m, aromatic). Anal. Calcd for $C_{31}H_{42}O_7$: C, 70.70; H, 8.04. Found: C, 70.60; H, 7.70.

3.1.13. Aldehyde (31). The alcohol **30** (2.44 g, 4.63 mmol) was dissolved in 46 mL of DMSO. To this solution was added IBX (1.56 g, 5.56 mmol). After stirring at room temperature for 12 h, the reaction was quenched with H_2O and filtered through a pad of Celite, washed thoroughly with ether. The filtrate was extracted with ether (×2). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=30:70) gave the aldehyde **31** (2.33 g, 96%). IR (KBr) ν_{max} 2980, 2933, 2895, 1722, 1498, 1456, 1400, 1380, 1369, 1353, 1339, 1218, 1139, 1097, 1047, 1028, 751, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (3H, t, J=7.0 Hz, –OCH$_2$CH_3), 1.29 (3H, d, J=5.5 Hz, –OCH(O)CH_3), 1.49, 1.60 (total 1H, each q, J=11.5 Hz, H-14a), 2.20–2.30 (1H, m, H-8a), 2.45–2.62 (3H, m, H-8b, 14b, 17a), 2.81, 2.93 (total 1H, ddd, J=16.0, 4.0, 2.0 Hz; J=16.0, 3.5, 1.5 Hz, H-17b), 3.10 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H-13), 3.22 (1H, t, J=9.0 Hz, H-12), 3.29 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.34–3.84 (6H, m, H-9, 11, 15, 16, –OCH_2CH$_3$), 4.62 (1H, d, J=11.0 Hz, –OCH_2Ph), 4.68 (1H, d, J=11.0 Hz, –OCH_2Ph*), 4.68, 4.79 (total 1H, each q, J=5.5 Hz, –OCH(CH$_3$)O–), 4.84 (1H, d, J=11.0 Hz, –OCH_2Ph), 4.95 (1H, d, J=11.0 Hz, –OCH_2Ph*), 5.07 (1H, dm, J=10.0 Hz, H-6a), 5.08 (1H, dm, J=17.0 Hz, H-6b), 5.80–5.95 (1H, m, H-7), 7.26–7.38 (10H, m, aromatic), 9.76, 9.79 (total 1H, each q, J=1.5 Hz, –CHO). Anal. Calcd for $C_{31}H_{40}O_7$: C, 70.97; H, 7.68. Found: C, 70.95; H, 7.51.

3.1.14. BC-ring (32). To a solution of CBr_4 (5.01 g, 15.0 mmol) in 30 mL of CH_2Cl_2 was added a solution of PPh_3 (7.92 g, 30.2 mmol) in 10 mL of CH_2Cl_2 at 0°C. After stirring for 10 min at 0°C, aldehyde **31** (1.98 g, 3.77 mmol) in 10 mL of CH_2Cl_2 was added and the resulting mixture was stirred for 30 min at 0°C. Then the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with ether. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, which was filtered through a silica gel short column.

To a solution of the above dibromoolefin in 50 mL of CH_2Cl_2 were successively added ethyl vinyl ether (0.72 mL, 13.1 mmol) and pyridinium *p*-toluenesulfonate (50.0 mg). After stirring for 6 h at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (×2). The combined extract was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ether/hexane=17:83) to give the BC-ring **32** (2.57 g, 99% in 2 steps). IR (KBr) ν_{max} 2979, 2889, 1456, 1376, 1098, 1069, 1029, 737, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20, 1.21 (total 3H, each t, J=7.0 Hz, –OCH$_2$CH_3), 1.30, 1.32 (total 3H, each q, J=5.5 Hz, –OCH(O)CH_3), 1.44, 1.55 (total 1H, each q, J=11.5 Hz, H-14a), 2.18–2.34 (2H, m, H-8a, 17a), 2.45–2.76 (3H, m, H-8b, 14b, 17b), 3.04–3.66 (9H, m, H-9, 10, 11, 12, 13, 15, 16, –OCH_2CH$_3$), 4.62 (1H, d, J=10.5 Hz, –OCH_2Ph), 4.72, 4.80 (total 1H, each q, J=5.5 Hz, –OCH(CH$_3$)O–), 4.74 (1H, d, J=11.0 Hz, –OCH_2Ph*), 4.95 (1H, d, J=10.5 Hz, –OCH_2Ph), 4.96 (1H, d, J=11.0 Hz, –OCH_2Ph*), 5.07 (1H, dm, J=10.0 Hz, H-6a), 5.08 (1H, dm, J=17.0 Hz, H-6b), 5.80–5.95 (1H, m, H-7), 6.55, 6.58 (total 1H, each t, J=7.0 Hz, H-18), 7.26–7.42 (10H, m, aromatic). Anal. Calcd for $C_{32}H_{40}Br_2O_6$: C, 56.48; H, 5.98. Found: C, 56.48; H, 5.85.

3.1.15. Diol (35). To a solution of the dibromoolefine **32** (3.97 g, 5.83 mmol) in 50 mL of THF was added a solution of *n*-BuLi (1.59 M in hexane, 8.81 mL, 14.0 mmol) at −78°C. After stirring for 15 min at −78°C, aldehyde **33** (1.59 g, 8.17 mmol) in 10 mL of THF was added and the resulting mixture was stirred for 60 min at −78 to 0°C. Then the reaction mixture was poured into an ice-cold sat. NH_4Cl solution and extracted with ether. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo.

To a solution of the above coupling product **34** in 50 mL of MeOH was added Amberlyst-15E (300 mg). After stirring for 2 h at room temperature, the reaction mixture was filtered through a pad of Celite, the resin was washed

thoroughly with ethyl acetate. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane=80:20) to give **35** (3.45 g, 92% in 2 steps). IR (KBr) ν_{max} 3418, 3065, 3032, 2933, 2868, 1614, 1514, 1456, 1363, 1303, 1249, 1100, 1072, 1029, 915, 823, 752, 738, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (1H, q, J=11.5 Hz, H-14a), 1.78–2.00 (2H, m, H-21a, 21b), 2.25 (1H, dt, J=14.5, 7.5 Hz, H-8a), 2.36 (1H, dt, J=11.5, 4.5 Hz, H-14b), 2.47–2.74 (3H, m, H-8b, 17a, 17b), 3.02–3.28 (2H, m, H-12, 13), 3.15 (1H, td, J=8.5, 3.5 Hz, H-16), 3.28 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.35 (1H, ddd, J=9.5, 7.5, 3.5 Hz, H-9), 3.43–3.76 (3H, m, H-15, 22a, 22b), 3.59 (1H, t, J=8.5 Hz, H-11), 3.78 (3H, s, –OMe), 4.41 (1H, d, J=2.0 Hz, $-OCH_2C_6H_4OMe$), 4.50 (1H, m, H-20), 4.60 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.75, 4.76 (total 1H, each d, J=11.5 Hz, $-OCH_2Ph^*$), 4.92 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 5.02 (1H, d, J=11.5 Hz, $-OCH_2Ph^*$), 5.06 (1H, dm, J=10.0 Hz, H-6a), 5.07 (1H, dm, J=17.0 Hz, H-6b), 5.87 (1H, dddd, J=17.5, 10.5, 7.5, 6.5 Hz, H-7), 6.86 (2H, d, J=9.0 Hz, aromatic), 7.21–7.40 (12H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 36.0, 36.9, 38.1, 55.2, 61.4, 67.3, 68.9, 72.9, 73.3, 74.6, 75.2, 78.9, 79.8, 80.7, 81.7, 82.5, 82.6, 83.5, 113.9, 117.2, 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 129.3, 129.4, 129.9, 134.6, 138.3, 138.9, 159.3. Anal. Calcd for $C_{39}H_{46}O_8$: C, 72.87; H, 7.21. Found: C, 72.80; H, 7.17.

3.1.16. Cyclic acetylene cobalt complex (36). To a solution of the diol **35** (2.45 g, 3.81 mmol) in 40 mL of CH_2Cl_2 was added a solution of $Co_2(CO)_8$ (1.96 g, 5.72 mmol) in 10 mL of CH_2Cl_2. After stirring for 20 min at room temperature, $BF_3{\cdot}OEt_2$ (0.97 mL, 7.62 mmol) was added at 0°C. After stirring for 15 min at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution and extracted with CH_2Cl_2 (×3). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane=40:60) to give **36** (2.36 g, 78%) as a dark red oil. $[\alpha]_D^{27}=-197°$ (c 0.06, $CHCl_3$). IR (KBr) ν_{max} 3066, 3032, 2935, 2876, 2094, 2053, 2025, 1456, 1433, 1095, 1071, 913, 735, 699, 519 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (1H, q, J=11.5 Hz, H-14a), 1.95 (1H, dddd, J=14.5, 10.0, 7.0, 4.5 Hz, H-21a), 2.11 (1H, tdd, J=10.5, 7.5, 4.0 Hz, H-21b), 2.26 (1H, dt, J=15.0, 7.5 Hz, H-8a), 2.45 (1H, ddd, J=11.5, 5.5, 4.0 Hz, H-14b), 2.57 (1H, dm, J=14.5 Hz, H-8b), 2.89 (1H, dd, J=16.0, 10.5 Hz, H-17a), 3.08–3.16 (2H, m, H-12, 13), 3.30 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.35 (1H, ddd, J=10.5, 8.5, 4.5 Hz, H-16), 3.38 (1H, ddd, J=9.5, 7.0, 3.0 Hz, H-9), 3.45–3.52 (1H, m, H-15), 3.51 (1H, dd, J=16.0, 4.5 Hz, H-17b), 3.58 (1H, t, J=8.5 Hz, H-11), 3.85–3.95 (2H, m, H-22a, 22b), 4.63 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.69 (1H, dd, J=10.0, 3.5 Hz, H-20), 4.80 (1H, d, J=11.5 Hz, $-OCH_2Ph^*$), 4.94 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.95 (1H, d, J=11.5 Hz, $-OCH_2Ph^*$), 5.06 (1H, dm, J=10.0 Hz, H-6a), 5.07 (1H, dm, J=17.0 Hz, H-6b), 5.85 (1H, dddd, J=17.5, 10.5, 7.5, 6.0 Hz, H-7), 7.26–7.40 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.0, 37.2, 38.7, 39.7, 60.8, 72.3, 74.9, 75.3, 77.7, 78.9, 80.8, 80.9, 81.3, 82.1, 84.2, 92.9, 101.1, 117.2, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 134.5, 138.3, 139.0, 199.0, 199.3. ESI Q-TOF MS calcd for $C_{37}H_{36}Co_2O_{12}Na$ $[M+Na]^+$ 813.077, found 813.087.

3.1.17. Vinylsilane (37). To a solution of the acetylene cobalt complex **36** (589 mg, 0.746 mmol) in 75 mL of $C_2H_4Cl_2$ were added Et_3SiH (2.38 mL, 14.9 mmol) and propargyl alcohol (2.17 mL, 37.3 mmol). After stirring for 1 h at 60°C, another Et_3SiH (1.19 mL, 7.46 mmol) was added. After stirring for additional 30 min at 60°C, the reaction mixture was filtered through Super-Cel and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ether/hexane=40:60) to give the vinylsilane **37** (407 mg, 89%). $[\alpha]_D^{24}=+21°$ (c 0.57, $CHCl_3$). IR (KBr) ν_{max} 3484, 3067, 3032, 2953, 2908, 2874, 2053, 2028, 1456, 1362, 1327, 1074, 1029, 1003, 913, 733, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.63 (6Hq, J=7.5 Hz, $-SiCH_2CH_3$), 0.95 (9H, t, J=7.5 Hz, $-SiCH_2CH_3$), 1.58 (1H, q, J=11.5 Hz, H-14a), 1.83 (1H, ddt, J=14.5, 6.5, 4.0 Hz, H-21a), 1.95 (1H, dddd, J=14.5, 9.5, 6.5, 4.5 Hz, H-21b), 2.25 (1H, dt, J=14.5, 7.5 Hz, H-8a), 2.37 (1H, dt, J=11.5, 4.0 Hz, H-14b), 2.50–2.60 (2H, m, H-8b, 17a), 2.62 (1H, dd, J=14.5, 3.0 Hz, H-17b), 2.98 (1H, ddd, J=11.5, 8.5, 3.0 Hz, H-16), 3.12 (1H, t, J=8.5 Hz, H-12), 3.12–3.16 (1H, m, H-13), 3.28 (1H, dd, J=9.5, 8.5 Hz, H-10), 3.37 (1H, ddd, J=9.5, 7.5, 3.0 Hz, H-9), 3.51 (1H, ddd, J=11.5, 8.5, 4.5 Hz, H-15), 3.60 (1H, t, J=8.5 Hz, H-11), 3.78–3.82 (2H, m, H-22a, 22b), 4.24 (1H, ddd, J=9.5, 4.5, 4.0 Hz, H-20), 4.62 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.75 (1H, d, J=11.5 Hz, $-OCH_2Ph^*$), 4.93 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.95 (1H, d, J=11.5 Hz, $-OCH_2Ph^*$), 5.05 (1H, dm, J=10.5 Hz, H-6a), 5.07 (1H, dm, J=17.5 Hz, H-6b), 5.86 (1H, dddd, J=17.5, 10.5, 7.5, 6.5 Hz, H-7), 6.02 (1H, dd, J=4.5, 2.5 Hz, H-19), 7.26–7.38 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 2.3, 7.4, 35.9, 36.5, 37.0, 37.9, 60.9, 73.9, 75.1, 75.2, 78.9, 80.9, 82.5, 82.9, 84.2, 117.1, 127.8, 128.0, 128.2, 128.4, 128.5, 134.6, 139.4, 138.8, 141.2, 145.9. Anal. Calcd for $C_{37}H_{52}O_6Si$: C, 71.57; H, 8.44. Found: C, 71.57; H, 8.58.

3.1.18. Methylketone (46). To a solution of the alcohol **37** (3.35 g, 5.40 mmol) in 50 mL of DMF and 10 mL of H_2O were added $PdCl_2$ (48 mg, 0.27 mmol) and CuCl (7.6 mg, 0.54 mmol). After stirring under O_2 atmosphere for 48 h at room temperature, the reaction mixture was poured into an ice-cold H_2O and extracted with CH_2Cl_2 (×3). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ether/hexane=80:20) to give the methylketone **46** (2.85 g, 83%). $[\alpha]_D^{24}=+7.7°$ (c 1.15, $CHCl_3$). IR (KBr) ν_{max} 3489, 2953, 2874, 1718, 1455, 1418, 1357, 1330, 1086, 733, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (6H, q, J=8.0 Hz, $-SiCH_2CH_3$), 0.95 (9H, t, J=8.0 Hz, $-SiCH_2CH_3$), 1.52 (1H, q, J=11.5 Hz, H-14a), 1.78–2.00 (2H, m, H-21a, 21b), 2.11 (3H, s, H-6), 2.34 (1H, dt, J=11.5, 4.0 Hz, H-14b), 2.48 (1H, dd, J=16.0, 8.5 Hz, H-8a), 2.54–2.61 (2H, m, H-17a, 17b), 2.69 (1H, dd, J=16.0, 3.0 Hz, H-8b), 2.97 (1H, dt, J=3.0, 9.0 Hz, H-16), 3.12 (1H, t, J=9.0 Hz, H-12), 3.16–3.24 (1H, m, H-13), 3.24 (1H, t, J=9.0 Hz, H-10), 3.51 (1H, ddd, J=11.5, 9.0, 4.0 Hz, H-15), 3.63 (1H, t, J=8.5 Hz, H-11), 3.74–3.83 (3H, m, H-9, 22a, 22b), 4.24 (1H, dt, J=9.5, 4.0 Hz, H-20), 4.59 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.75 (1H, d, J=10.5 Hz, $-OCH_2Ph^*$), 4.93 (1H, d, J=11.0 Hz, $-OCH_2Ph$), 4.96 (1H, d, J=10.5 Hz, $-OCH_2Ph^*$), 6.02 (1H, dd, J=4.0, 1.5 Hz, H-19), 7.25–7.40 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 75 MHz)

δ 2.3, 7.3, 30.6, 36.5, 36.8, 37.9, 46.0, 60.7, 74.0, 75.1, 75.1, 75.2, 75.6, 80.7, 82.4, 82.7, 83.9, 127.8, 127.9, 128.1, 128.2, 128.4, 128.5, 138.1, 138.6, 141.1, 146.0, 206.5. Anal. Calcd for $C_{37}H_{52}O_7Si$: C, 69.78; H, 8.23. Found: C, 69.77; H, 8.23.

3.1.19. Iodolactone (51). To a solution of the methylketone **46** (433 mg, 0.68 mmol) in 34 mL of acetone was added Jones' reagent at 0°C over 30 min until the color of reaction mixture became to orange. The reaction mixture was treated with 2-propanol and extracted with CH_2Cl_2 (×3). The combined extract was concentrated under reduced pressure. The residue was filtered through a silica gel short column to give the carboxylic acid.

The above carboxylic acid was dissolved in 66 mL of CH_2Cl_2. To this solution was added $I(collidine)_2PF_6$ (514 mg, 1.00 mmol). After stirring at room temperature for 2 h, the reaction was quenched with 1N HCl aq. and extracted with CH_2Cl_2 (×2). The combined extract was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a silica gel short column to give the iodolactone.

To a solution of the above ketone in 12 mL of CH_2Cl_2 were added ethanedithiol (161 μL, 1.61 mmol) and $Zn(OTf)_2$ (389 mg, 1.07 mmol). After stirring for 2 h at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_3$ solution. The resulting mixture was extracted with CH_2Cl_2 (×2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ether/hexane=50:50) to give **51** (392 mg, 67% in 3 steps). $[\alpha]_D^{24}=+5.8°$ (*c* 0.11, $CHCl_3$). IR (KBr) ν_{max} 3447, 2953, 2911, 2876, 1793, 1456, 1418, 1374, 1340, 1209, 1159, 1144, 1097, 1074, 1010, 904, 733, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (6H, q, *J*=7.5 Hz, $-SiCH_2CH_3$), 1.08 (9H, t, *J*=8.0 Hz, $-SiCH_2CH_3$), 1.50 (1H, q, *J*=11.0 Hz, H-14a), 1.51 (3H, s, H-6), 1.72–1.88 (2H, m, $-SCH_2CH_2CH_2S-$), 1.79 (1H, dd, *J*=15.0, 8.5 Hz, H-8a), 2.35 (1H, dt, *J*=11.0, 4.5 Hz, H-14b), 2.41 (1H, dd, *J*=16.0, 2.5 Hz, H-17a), 2.46 (1H, ddd, *J*=14.5, 5.5, 3.5 Hz, $-SCH_2CH_2CH_2S-$), 2.54 (1H, d, *J*=15.0 Hz, H-8b), 2.56 (1H, d, *J*=17.5 Hz, H-21a), 2.58 (1H, ddd, *J*=14.5, 5.5, 3.5 Hz, $-SCH_2CH_2CH_2S-$), 2.67 (1H, ddd, *J*=14.5, 11.5, 3.0 Hz, $-SCH_2CH_2CH_2S-$), 2.73 (1H, dd, *J*=17.5, 5.0 Hz, H-21b), 2.78 (1H, ddd, *J*=14.5, 11.0, 3.0 Hz, $-SCH_2CH_2CH_2S-$), 2.97 (1H, dd, *J*=16.0, 7.5 Hz, H-17b), 3.10 (1H, t, *J*=8.5 Hz, H-12), 3.15 (1H, ddd, *J*=11.0, 9.0, 4.0 Hz, H-13), 3.23 (1H, dd, *J*=9.5, 8.5 Hz, H-10), 3.55–3.60 (1H, m, H-9, 16), 3.67 (1H, t, *J*=8.5 Hz, H-11), 4.49 (1H, ddd, *J*=11.5, 9.5, 4.0 Hz, H-15), 4.63 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 4.69 (1H, d, *J*=2.5 Hz, H-19), 4.71 (1H, dd, *J*=5.0, 2.5 Hz, H-20), 4.81 (1H, d, *J*=11.5 Hz, $-OCH_2Ph^*$), 4.98 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 5.03 (1H, d, *J*=11.5 Hz, $-OCH_2Ph^*$), 7.26–7.39 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.8, 8.3, 24.8, 26.0, 26.7, 28.8, 35.8, 35.9, 37.1, 38.6, 41.6, 48.4, 73.9, 74.5, 74.9, 75.6, 78.2, 79.2, 81.1, 81.5, 83.2, 84.1, 89.7, 127.6, 127.8, 128.1, 128.4, 128.4, 138.4, 138.7, 174.2. Anal. Calcd for $C_{40}H_{55}O_7S_2Si$: C, 55.41; H, 6.39. Found: C, 55.42; H, 6.52.

3.1.20. Epoxysilane-aldehyde (52). To a solution of the lactone **51** (85 mg, 98.0 μmol) in 3.0 mL of CH_2Cl_2 was added 0.12 mL of DIBAL (1.0 M in toluene, 0.118 mmol) at −78°C. After stirring for 1 h at −78°C, AcOEt was added to the reaction mixture at −78°C, then poured into ice-cold sat. NH_4Cl solution and extracted with CH_2Cl_2 (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure, which was used directly in the next step without further purification.

To a solution of the above lactol in 3.0 mL of THF was added DBU (0.044 mL, 0.30 mmol) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was poured into ice-cold sat. NH_4Cl solution and extracted with ether (×3). The combined extract was dried over Na_2SO_4 and concentrated under reduced pressure to give 64.0 mg of aldehyde **52**, which was directly used in the next step without further purification. IR (KBr) ν_{max} 3567, 3446, 2956, 2876, 1792, 1725, 1559, 1497, 1456, 1419, 1363, 1333, 1103, 1074, 1028, 735, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (6H, q, *J*=7.5 Hz, $-SiCH_2CH_3$), 1.00 (9H, t, *J*=7.5 Hz, $-SiCH_2CH_3$), 1.50 (1H, q, *J*=11.0 Hz, H-14a), 1.51 (3H, s, H-6), 1.72–1.88 (2H, m, $-SCH_2CH_2CH_2S-$), 1.80 (1H, dd, *J*=15.0, 8.5 Hz, H-8a), 1.89 (1H, dd, *J*=15.0, 10.5 Hz, H-17a), 2.26 (1H, dt, *J*=11.5, 4.5 Hz, H-14b), 2.60–2.90 (4H, m, $-SCH_2CH_2CH_2S-$), 2.54 (1H, d, *J*=15.0 Hz, H-8b), 2.61 (1H, dd, *J*=15.0, 3.5 Hz, H-17b), 2.68 (1H, ddd, *J*=16.0, 4.0, 1.5 Hz, H-21a), 2.71 (1H, S, H-19), 2.91 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-15), 3.00 (1H, ddd, *J*=16.0, 9.0, 1.5 Hz, H-21b), 3.02–3.10 (2H, m, H-12, 13), 3.23 (1H, dd, *J*=9.5, 8.5 Hz, H-10), 3.32 (1H, ddd, *J*=10.5, 9.5, 3.5 Hz, H-16), 3.54 (1H, t, *J*=8.5 Hz, H-9), 3.58 (1H, t, *J*=8.5 Hz, H-11), 4.26 (1H, dd, *J*=9.0, 4.0 Hz, H-20), 4.63 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 4.76 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 4.94 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 5.00 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 7.26–7.39 (10H, m, aromatic), 9.82 (1H, t, *J*=1.5 Hz, –CHO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 1.3, 7.2, 24.7, 26.0, 26.6, 28.6, 35.4, 36.3, 41.5, 48.3, 49.2, 53.5, 59.8, 71.9, 73.2, 75.0, 75.7, 76.9, 77.8, 79.9, 81.1, 81.7, 84.6, 127.7, 127.9, 128.1, 128.3, 128.4, 128.5, 138.3, 138.9, 200.3.

3.1.21. Epoxysilane–acetylene (53). To a solution of the aldehyde **52** (37 mg, 50.0 μmol) and K_2CO_3 (28 mg, 0.199 mmol) in 2.5 mL of dry MeOH was added dimethyl-1-diazo-2-oxopropyl phosphonate (29 mg, 0.15 mmol) in 0.5 mL of MeOH at room temperature. After stirring for 9 h at room temperature, the reaction mixture was diluted with ether and poured into an ice-cold sat. $NaHCO_3$ solution and extracted with ether (×3). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=30:70) gave the acetylene **53** (27.5 mg, 73% in 3 steps). $[\alpha]_D^{27}=-31°$ (*c* 0.21, $CHCl_3$). IR (KBr) ν_{max} 2952, 2911, 2876, 1734, 1456, 1418, 1335, 1103, 1073, 1014, 913, 736, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.63 (6H, q, *J*=8.0 Hz, $-SiCH_2CH_3$), 1.00 (9H, t, *J*=8.0 Hz, $-SiCH_2CH_3$), 1.51 (3H, s, H-6), 1.52 (1H, q, *J*=11.0 Hz, H-14a), 1.72–1.88 (2H, m, $-SCH_2CH_2CH_2S-$), 1.81 (1H, dd, *J*=14.5, 8.5 Hz, H-8a), 1.87 (1H, dd, *J*=15.0, 10.5 Hz, H-17a), 2.05 (1H, t, *J*=2.5 Hz, H-23), 2.31 (1H, ddd, *J*=11.0, 4.5, 4.0 Hz, H-14b), 2.44–2.68 (2H, m, $-SCH_2CH_2CH_2S-$), 2.54 (1H, d, *J*=14.5 Hz, H-8b), 2.59

(1H, dd, *J*=15.0, 3.5 Hz, H-17b), 2.59 (1H, ddd, *J*=16.5, 8.5, 2.5 Hz, H-21a), 2.66 (1H, ddd, *J*=16.5, 6.5, 2.5 Hz, H-21b), 2.69 (1H, ddd, *J*=14.5, 11.5, 3.0 Hz, $-SCH_2CH_2CH_2S-$), 2.80 (1H, ddd, *J*=14.5, 11.5, 3.0 Hz, $-SCH_2CH_2CH_2S-$), 2.87 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-15), 3.03 (1H, ddd, *J*=11.0, 9.0, 4.0 Hz, H-13), 3.05 (1H, S, H-19), 3.07 (1H, t, *J*=9.0 Hz, H-12), 3.23 (1H, dd, *J*=9.5, 8.5 Hz, H-10), 3.33 (1H, ddd, *J*=10.5, 9.0, 3.5 Hz, H-16), 3.54 (1H, dd, *J*=9.5, 8.5 Hz, H-9), 3.58 (1H, t, *J*=8.5 Hz, H-11), 3.80 (1H, dd, *J*=8.5, 6.5 Hz, H-20), 4.63 (1H, d, *J*=11.0 Hz, $-OCH_2Ph$), 4.76 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 4.94 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 5.00 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 7.26–7.39 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.4, 7.4, 24.8, 25.9, 26.1, 26.7, 28.7, 35.5, 36.4, 41.6, 48.4, 53.0, 58.5, 70.4, 73.4, 75.0, 75.3, 75.7, 77.2, 77.8, 80.0, 80.6, 81.2, 81.8, 84.7, 127.7, 127.8, 128.1, 128.2, 128.4, 128.5, 138.4, 138.9. Anal. Calcd for $C_{41}H_{56}O_6S_2Si$: C, 66.81; H, 7.66. Found: C, 66.71; H, 7.87.

3.1.22. Allylic alcohol (54). To a solution of the epoxysilane **53** (20 mg, 27.1 μmol) in 2.7 mL of CH_2Cl_2 was added $BF_3{\cdot}OEt_2$ (0.20 M in $C_2H_4Cl_2$, 0.069 mL, 54.3 μmol). After stirring for 30 min at room temperature, the reaction mixture was poured into an ice-cold sat. $NaHCO_2$ solution. The resulting mixture was extracted with CH_2Cl_2 (×2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (ether/hexane=50:50) to give the allyl alcohol **54** (13.5 mg, 80%). $[\alpha]_D^{26}=-32°$ (*c* 0.12, $CHCl_3$). IR (KBr) ν_{max} 3444, 3292, 3029, 2924, 1457, 1375, 1101, 1086, 1074, 1060, 1028, 737, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, s, H-6), 1.61 (1H, q, *J*=11.5 Hz, H-14a), 1.81 (1H, dd, *J*=15.0, 8.5 Hz, H-8a), 1.72–1.90 (2H, m, $-SCH_2CH_2CH_2S-$), 2.02 (1H, t, *J*=2.5 Hz, H-23), 2.38 (1H, dt, *J*=11.5, 4.5 Hz, H-14b), 2.53 (2H, dd, *J*=7.0, 2.5 Hz, H-21a, 21b), 2.56 (1H, d, *J*=15.0 Hz, H-8b), 2.45–2.83 (4H, m, $-SCH_2CH_2CH_2S-$), 3.10 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-13), 3.15 (1H, t, *J*=9.0 Hz, H-12), 3.26 (1H, dd, *J*=9.5, 8.5 Hz, H-10), 3.40 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-15), 3.58 (1H, ddbr, *J*=9.5, 8.5 Hz, H-9), 3.65 (1H, t, *J*=8.5 Hz, H-11), 3.77 (1H, t, *J*=7.0 Hz, H-20), 4.02 (1H, ddd, *J*=9.5, 2.5, 1.5 Hz, H-16), 4.10 (1H, dbr, *J*=7.5 Hz, H-19), 4.63 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 4.77 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 4.98 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 5.02 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 5.81 (1H, dd, *J*=12.5, 1.5 Hz, H-17), 5.71 (1H, ddd, *J*=12.5, 7.5, 2.5 Hz, H-18), 7.26–7.38 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 24.7, 25.9, 26.6, 28.7, 36.7, 41.5, 48.3, 68.2, 70.0, 73.0, 75.1, 75.7, 77.9, 79.0, 80.2, 80.8, 81.1, 82.2, 82.3, 84.4, 127.7, 127.9, 128.0, 128.3, 128.4, 128.5, 129.0, 135.8, 138.3, 138.7. Anal. Calcd for $C_{35}H_{42}O_6S_2$: C, 67.49; H, 6.80. Found: C, 67.22; H, 6.90.

3.1.23. BCD-ring (55). To a solution of **54** (20.0 mg, 32.0 μmol) in 1.6 mL of toluene were added *p*-nitrobenzoic acid (27.0 mg 0.16 mmol), triphenylphosphine (51.0 mg, 0.19 mmol) and diethyl azodicarboxylate (31 μL, 0.19 mmol) at 0°C. After stirring for 40 min at room temperature, the reaction was poured into ice-cold sat. NH_4Cl solution and extracted with ether (×3). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was filtered through a silica gel short column to give the *p*-nitrobenzoate.

To a solution of the above *p*-nitrobenzoate in 1.6 mL of MeOH was added K_2CO_3 (4.4 mg, 32.0 μmol). After stirring for 30 min at room temperature, the reaction mixture was poured into an ice-cold sat. NH_4Cl solution. The resulting mixture was extracted with CH_2Cl_2 (×2). The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue with silica gel column chromatography (ether/hexane=20:80) gave the BCD-ring **55** (18.7 mg, 94% in 2 steps). $[\alpha]_D^{23}=-34°$ (*c* 0.17, $CHCl_3$). IR (KBr) ν_{max} 3449, 3297, 3031, 2883, 1455, 1423, 1368, 1333, 1276, 1101, 1064, 911, 737, 699, 645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (3H, s, H-6), 1.59 (1H, q, *J*=11.5 Hz, H-14a), 1.81 (1H, dd, *J*=15.0, 8.5 Hz, H-8a), 1.72–1.90 (2H, m, $-SCH_2CH_2CH_2S-$), 2.04 (1H, t, *J*=3.0 Hz, H-23), 2.35 (1H, dt, *J*=11.5, 4.5 Hz, H-14b), 2.53 (1H, ddd, *J*=17.0, 6.5, 3.0 Hz, H-21a), 2.55 (1H, d, *J*=15.0 Hz, H-8b), 2.65 (1H, ddd, *J*=17.0, 3.5, 3.0 Hz, H-21b), 2.45–2.83 (4H, m, $-SCH_2CH_2CH_2S-$), 3.10 (1H, ddd, *J*=11.5, 9.0, 4.5 Hz, H-13), 3.13 (1H, dd, *J*=9.0, 8.5 Hz, H-12), 3.25 (1H, dd, *J*=9.5, 8.5 Hz, H-10), 3.34 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-15), 3.48 (1H, ddd, *J*=9.0, 6.5, 3.5 Hz, H-20), 3.57 (1H, ddm, *J*=9.5, 8.5 Hz, H-9), 3.64 (1H, t, *J*=8.5 Hz, H-11), 3.88 (1H, ddd, *J*=9.0, 3.0, 1.5 Hz, H-16), 4.32 (1H, dbr, *J*=9.0 Hz, H-19), 4.61 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 4.77 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 4.99 (1H, d, *J*=11.0 Hz, $-OCH_2Ph^*$), 5.00 (1H, d, *J*=11.5 Hz, $-OCH_2Ph$), 5.67 (1H, dd, *J*=12.5, 1.5 Hz, H-18), 5.71 (1H, dd, *J*=12.5, 1.5 Hz, H-17), 7.26–7.38 (10H, m, aromatic). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 24.8, 26.1, 26.7, 28.8, 36.7, 41.7, 48.3, 70.3, 73.1, 73.2, 75.1, 75.7, 77.9, 78.8, 80.3, 80.8, 81.2, 82.2, 82.6, 84.4, 127.6, 127.8, 128.0, 128.2, 128.4, 128.4, 131.5, 133.9, 138.3, 138.8. Anal. Calcd for $C_{35}H_{42}O_6S_2$: C, 67.49; H, 6.80. Found: C, 67.52; H, 6.64.

Acknowledgements

We are grateful to Mr Kitamura (analytical laboratory in this school) for elemental analyses. This work was supported by JSPS-RFTF, Grant-In-Aid for Scientific Research, and JSPS-DC fellowship.

References

1. (a) Scheuer, P. J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. *Science* **1967**, *155*, 1267. (b) Tachibana, K. PhD Thesis, University of Hawaii, 1980. (c) Nukina, M.; Koyanagi, L. M.; Scheuer, P. J. *Toxicon* **1984**, *22*, 169.
2. (a) Murata, M.; Lebrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929. (b) Murata, M.; Lebrand, A.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380.
3. Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325.
4. (a) Oishi, T.; Tanaka, S.; Ogasawara, Y.; Maeda, K.; Oguri, H.; Hirama, M. *Synlett* **2001**, 952. (b) Oishi, T.; Uehara, H.;

Nagumo, Y.; Shoji, M.; Brazidec, J.-Y. L.; Kosaka, M.; Hirama, M. *Chem. Commun.* **2001**, 381 and references therein. (c) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425. (d) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1090 and references therein. (e) Fujiwara, K.; Tanaka, H.; Murai, A. *Chem. Lett.* **2000**, 610. (f) Fujiwara, K.; Takaoka, D.; Kusumi, K.; Kawai, K.; Murai, A. *Synlett* **2001**, 691 and references therein. (g) Leeuwenburgh, M. A.; Kulker, C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1999**, *12*, 1945.

5. (a) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665. (b) Isobe, M.; Kira, K. *Journal of Synthetic Organic Chemistry Japan* **2000**, *58*, 23. (c) *idem, ibid* **2000**, *58*, 99.
6. (a) Hosokawa, S.; Isobe, M. *Synlett* **1995**, *64*, 1179. (b) Hosokawa, S.; Isobe, M. *Synlett* **1996**, *40*, 351. (c) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37. (d) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911. (e) Saeeng, R.; Isobe, M. *Heterocycles* **2001**, *54*, 789.
7. Kira, K.; Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951.
8. (a) Liu, T.-Z.; Isobe, M. *Synlett* **2000**, *125*, 587. (b) Liu, T.-Z.; Isobe, M. *Tetrahedron* **2000**, *56*, 5391. (c) Liu, T.-Z.; Isobe, M. *Tetrahedron* **2000**, *56*, 10209.
9. Connor, R. E.; Nicholas, K. M. *J. Organomet. Chem.* **1977**, *125*, C45.
10. Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, *39*, 473.
11. Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609.
12. Kira, K.; Isobe, M. *Chem. Lett.* **2001**, *89*, 432.
13. Preparation of this material having a different protective group was previously reported. See Ref. 6c.
14. (a) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416. (b) Kuzuhara, H.; Fletcher, H. G. *J. Org. Chem.* **1967**, *32*, 2531. (c) Kuzuhara, H.; Fletcher, H. G. *J. Org. Chem.* **1967**, *32*, 2534.
15. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
16. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
17. Frigeiro, M.; Santagostiono, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.
18. Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200.
19. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *40*, 3769.
20. Isobe, M.; Nishizawa, R.; Nishikawa, T.; Yoza, K. *Tetrahedron Lett.* **1999**, *40*, 6927.
21. The detail of the propargyl alcohol effect and 'unisolable substance [Co]* **39**' are to be discussed in another paper.
22. (a) Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075.
23. (a) Simonot, B.; Rousseau, G. *J. Org. Chem.* **1994**, *59*, 5912. (b) Simonot, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 4527. (c) Homsi, F.; Rousseau, G. *J. Org. Chem.* **1998**, *63*, 5255.
24. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
25. Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662.
26. (a) Callant, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (c) Müller, S.; Liepllld, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *26*, 521.
27. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *26*, 3017.
28. Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821.
29. (a) Cuadrado, P.; Gonzalez-Nogal, A. M. *Tetrahedron Lett.* **2000**, *41*, 1111. (b) Hudrlik, P. F.; Tafesse, L.; Hudrlik, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 11689. (c) Kobayashi, Y.; Shimizu, K.; Sato, F. *Chem. Commun.* **1997**, *5*, 493. (d) Raubo, P.; Wicha, J. *Tetrahedron: Asymmetry* **1996**, *7*, 763. (e) Bassindale, A. R.; Taylor, P. G.; Xu, Y. *Tetrahedron Lett.* **1996**, *37*, 555. (f) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1989**, *30*, 5693. (g) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967. (h) Zhang, Y.; Miller, J. A.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2043. (i) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1988**, *53*, 414.