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Synthetic Studies on the HIJK-Ring Fragment of Ciguatoxin

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Abstract—Synthesis of the tetracyclic HIJK-ring fragment of ciguatoxin with high stereoselectivity has been achieved starting from a sugar derivative directed toward the synthesis of the right part of ciguatoxin. Sonogashira coupling of a vinyl iodide with an acetylene derivative, cobalt complex-mediated (seven- and eight-membered ring) cyclizations and a heteroconjugate addition reaction play important roles in the current research work.

Introduction

Ciguatera is one of the most widespread seafood poisonings which follows the consumption of warm water fish contaminated with sodium channel neurotoxins known as ciguatoxin.[1] These toxins are produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*[2] and transferred through the food chain among coral biota and accumulated in carnivorous fish, thus causing human intoxication. It is a major problem in the Pacific and Indian Oceans and the Caribbean Sea, where roughly 20,000 persons are affected annually. Ciguatoxin is a potent sodium channel activator that binds quasi-irreversibly to site 5 on the voltage-sensitive sodium channels (VSSC).[3] The binding site on VSSC was reported to be shared by brevetoxins or another class of structurally related marine toxins.[4]

Ciguatoxin (CTX1B),[5] one of the principal toxins causing ciguatera fish poisoning, 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.[6] The gross structure of ciguatoxin, except the absolute configuration and the relative one at C-2, was elucidated by Yasumoto and co-workers in 1989 using a purified sample of only 0.35 mg.[5b,7] In spite of structural similarity to brevetoxins, the binding affinity of ciguatoxin was shown to be some ten times more potent than that of brevetoxins. Ciguatoxin remains the most potent neurotoxin known with a mouse lethality LD_{50} of 0.25 μg/kg (i.p.).[3] Recently, the absolute configuration of ciguatoxin was successfully determined by Yasumoto and co-workers[8] as shown in Fig. 1.

Ciguatoxin possesses 33 asymmetric carbons and 12 *trans*-fused polycyclic ethers ranging from six to nine-membered, where a spiro-type five-membered oxacycle is attached at one end. The complex molecular framework of ciguatoxin arises from the folding of a single carbon chain into a web of 13 rings fused together with interesting regularity. This regularity allows each ring to include an oxygen atom and

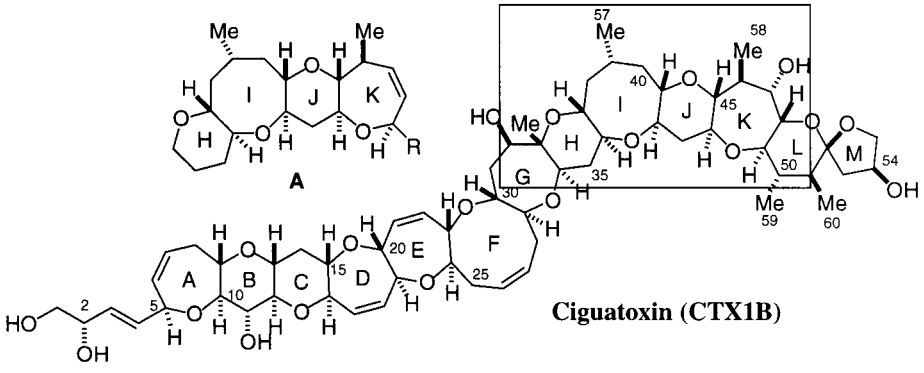

Figure 1.

Keywords: acetylene-biscobalthexacarbonyl; ciguatoxin; heteroconjugate addition; Sonogashira coupling; cyclization.
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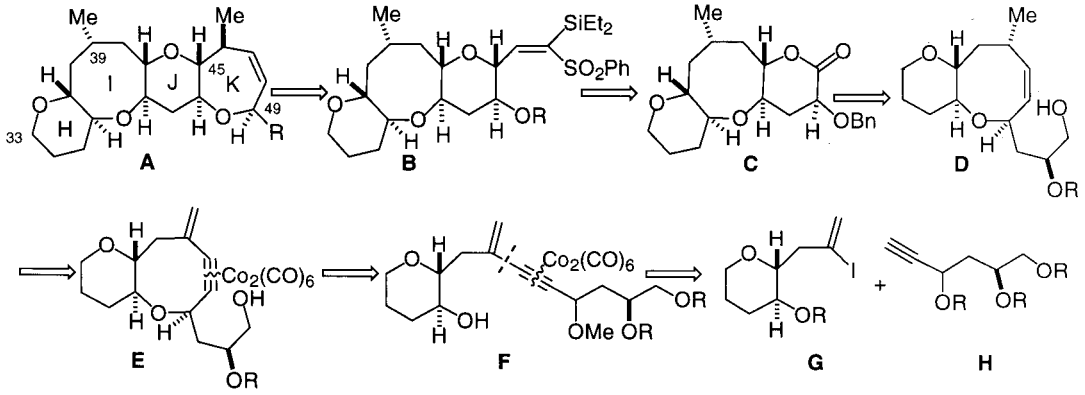


Scheme 1.

each fusion to consist of a C–C bond separating two adjacent oxygen atoms. All substituents on the ring junctions flanking the oxygens are *syn* to each other with the exception of the last one on ring M. The striking constitution of ciguatoxin presents a formidable challenge to organic synthesis. The unique and fascinating molecular architecture of ciguatoxin, its association with fish poisoning, its potent biological activity, and the prospects for expanding the arsenal of synthetic methods all contributed to our decision to pursue a total synthesis of ciguatoxin. In addition, its very limited availability from natural sources has hampered further studies on the precise conformational analysis of ring F, characterization of the interaction with sodium channels, and development of highly specific immunoassay for its detection in fish sources. The chemical synthesis of ciguatoxin appears to be a viable solution to these problems.[9]

During the course of our synthetic studies on ciguatoxin, we have developed an efficient synthetic methodology for the construction of medium-sized (seven to ten-membered) ether rings via cobalt complex-mediated cyclization.[10] We have also established a synthetic method extending a carbon–carbon bond from a pyranose ring with high stereoselectivity, and reported several examples along this line in the total syntheses of natural products.[11] This paper describes the synthesis of the HIJK-ring fragment of ciguatoxin using these methods.

Retrosynthesis

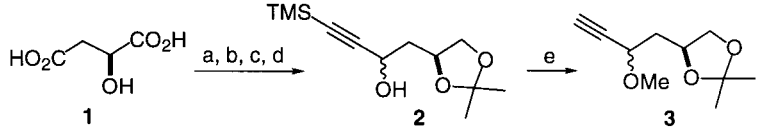
The H–I–J–K-ring fragment **A**, representing C33–C49 portion of ciguatoxin, consists of a *trans*-fused tetracyclic 6/8/6/7-membered ether ring system. Our retrosynthetic analysis for compound **A** is outlined in Scheme 1.

Retrosynthetic cleavage of ring K in compound **A** provides **B** as a potential precursor. Compound **B** could be prepared from lactone **C**. Opening of the six-membered ring J provides compound **D**, which could be derived from the corresponding cobalt complex **E**. Opening of the eight-membered ring I in **E** gives **F** as a potential precursor. Retrosynthetic removal of the dicobalthexacarbonyl group and disconnection of the indicated bond in **F** furnishes vinyl iodide **G** and acetylene **H**.

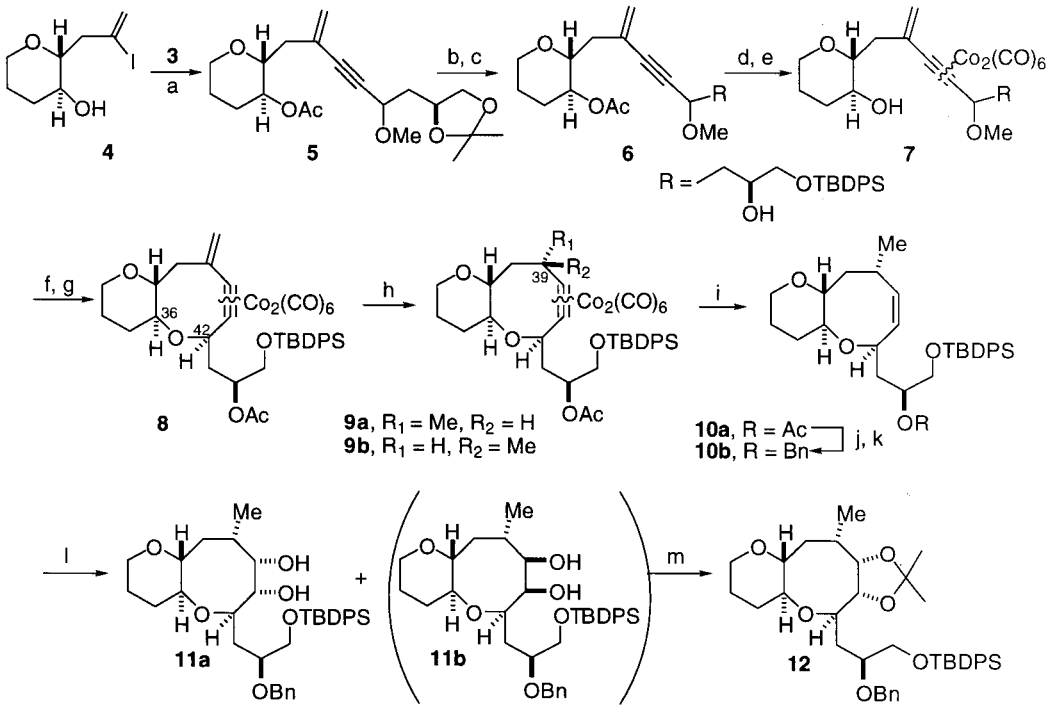
The first phase of our synthesis entailed the elaboration of acetylene derivative **3** (≡**H**) (Scheme 2). Reduction of (*S*)-malic acid **1** with borane-dimethyl sulfide (BMS) in the presence of excess trimethyl borate in THF, followed by methanol workup,[12] afforded a triol intermediate, which was converted to the corresponding acetonide with acetone in the presence of a catalytic amount of toluenesulfonic acid monohydrate. Swern oxidation[13] gave the corresponding aldehyde, which was in situ treated with lithium trimethylsilyl-acetylide to afford **2** as a 7:3 mixture of diastereomers. Protection of the hydroxyl group and removal of the trimethylsilyl group in **2** were achieved in one step by treatment of **2** with potassium hydroxide powder in dimethylsulfoxide,[14] followed by aqueous workup to provide acetylene **3** as a 7:3 mixture of diastereomers in good yield.

Synthesis of a Precursor

The second phase of our synthesis began with Sonogashira coupling reaction to establish all the requisite carbon framework for the elaboration of H–I–J-ring system; thus, coupling of the vinyl iodide **4**[15] with **3** in the presence of palladium(0) afforded compound **5** (Scheme 3). Acid catalyzed hydrolysis of the acetonide group and subsequent protection of the corresponding primary alcohol as TBDPS ether gave compound **6**. Deacetylation of **6** with potassium carbonate in methanol and cobalt complexation afforded cobalt complex **7**. The cobalt complex **7** underwent smooth

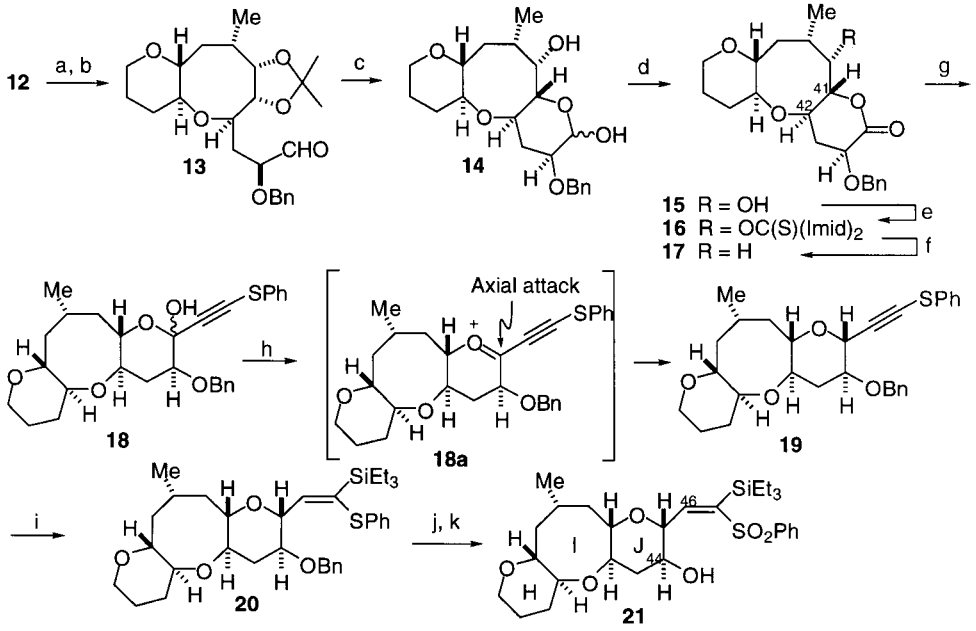


Scheme 2. Reagents, conditions and yields: (a) BH_3–SMe_2, $B(OMe)_3$, THF, 0°C, then MeOH workup; (b) acetone, TsOH (cat), rt, 91% (2 steps); (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 to 0°C; (d) trimethylsilylacetylene, *n*-BuLi, THF, −78 to 0°C, 53% (2 steps); (e) DMSO, KOH powder, CH_3I, 83%.



Scheme 3. Reagents, conditions and yields: (a) *n*-$BuNH_2$, CuI, Pd(0), benzene, rt, 81%; (b) MeOH, PPTS, 60°C, 91%; (c) TBDPSCl, Et_3N, DMF, rt, 95%; (d) MeOH, K_2CO_3, rt, 89%; (e) $Co_2(CO)_8$, CH_2Cl_2, 0°C–rt, 98%; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 50 min, 81%; (g) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 97%; (h) HN=NH, MeOH, Et_3N, rt, [**9a**, 68%; **9b**, 20%]; (i) *n*-Bu_3SnH, toluene, 50°C, 67%; (j) MeOH, K_2CO_3, rt, 88%; (k) BnBr, NaH, DMF, −40–0°C, 82%; (l) OsO_4, NMO, acetone–H_2O (8:1), 0°C–rt, [**11a**, 80%; **11b**, 7%]; (m) acetone, TsOH (cat), rt, 93%.

ring closure upon treatment with boron trifluoride etherate in degassed dichloromethane at 0°C and subsequent acetylation afforded bicyclic compound **8** as a single diastereoisomer in 84% yield. The critical *syn* stereochemistry between H-36 and H-42 of **8** (ciguatoxin numbering) was proved by NOESY experiments. The observation of the cross peaks between H-36 (δ 3.08, ddd, J=11.0, 9.5, 4.8 Hz) and H-42 (δ 4.79, dd, J=10.0, 3.0 Hz) indicated a *syn* relationship between these protons. Reduction of the *exo*-cyclic olefin in **8** with diimide[16] afforded a 3:1 mixture of diastereoisomers **9a** and **9b**, epimeric at C-39, which could be separated by flash column chromatography. The



Scheme 4. Reagents, conditions and yields: (a) TBAF, THF, rt, 96%; (b) DMSO, SO_3–Py, Et_3N, 100%; (c) 80% aqueous AcOH, rt, 98%; (d) Br_2, DMF, NaOAc, 0°C–rt, 77%; (e) thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux, 67%; (f) *n*-Bu_3SnH, toluene, reflux, 88%; (g) *n*-BuLi, THF, phenylthioacetylene, −78–0°C, 84%; (h) Et_3SiH, CH_3CN, $BF_3{\cdot}OEt_2$, −15°C, 100%; (i) Et_3SiH, biscobalthexacarbonyl-2-methyl-but-3-yn-2-ol (Cat.), $ClCH_2CH_2Cl$, 60°C, 84%; (j) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0°C, 89%; (k) TMSI, $CHCl_3$, 0°C, 96%.

configuration of the newly formed methyl group was proved by NOESY experiments: thus, NOE cross peaks of protons 36/39 and 39/42 were observed in the NOESY experiments with compound **9b**. Reductive decomplexation of **9a** with tri-*n*-butyltin hydride gave *cis* olefin **10a**. Subsequent conversion of the acetyl group in **10a** to benzyl group furnished benzyl ether **10b**. Dihydroxylation[17] of **10b** with osmium tetroxide in the presence of NMO as a co-oxidant gave the diol intermediates **11a** and **11b**[18] in a ratio of 11:1. The selectivity of diastereomers **11a** and **11b** may be controlled by steric effect. Osmium attacked the double bond from the less hindered face (the opposite direction of the bulky substituent at C-42): thus, diol **11a** emerged as the major product, and **11a** were further converted to the corresponding acetonides **12**.

Removal of the TBDPS group of **12** with TBAF and oxidation of the primary alcohol afforded the corresponding aldehyde **13** (Scheme 4). Acidic hydrolysis of the acetonide group of **13** ended up with a subsequent ring J formation in one step to provide hemiacetal **14**. This hemiacetal was selectively oxidized by means of bromine into the lactone **15**. The secondary hydroxyl group on ring I was removed via Barton's protocol in two steps: thus (1) treatment of **15** with *N*,*N*′-thiocarbonyldiimidazole[19] in refluxing 1,2-dichloroethane to provide the thioester **16** and (2) deoxygenation of **16** with tri-*n*-butyltin hydride[20] in refluxing toluene to give compound **17**.[21] The lactone **17** showed the coupling constant, $J_{41,42}$=9.5 Hz, between the protons at the junctions, indicating the *trans* stereochemistry.

Tricyclic Heteroolefin

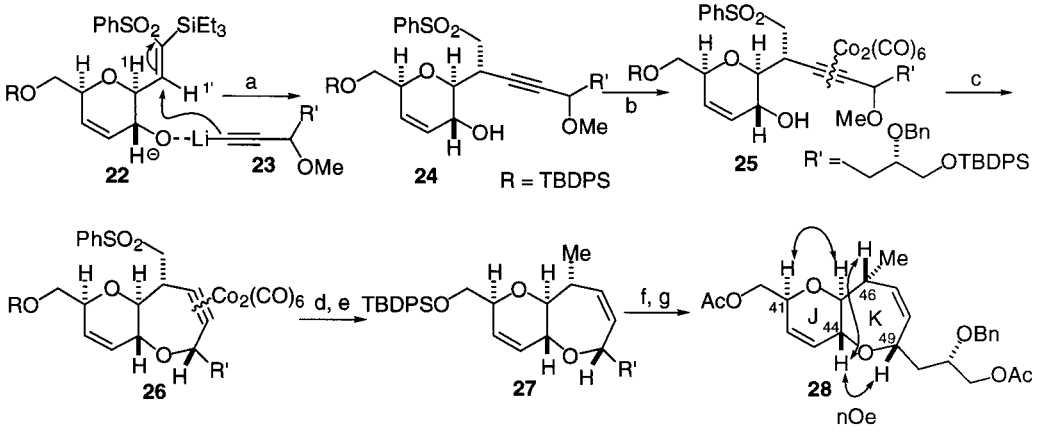
According to the retrosynthetic analysis to construct ring K, phenylthioethynyl group has to be introduced at the C-13 position of lactone **17**. Addition of lithium phenylthioacetylide afforded product **18** as a 5:1 mixture in 84% yield. Kishi reduction of **18** with $HSiEt_3$ in the presence of $BF_3{\cdot}OEt_2$ in acetonitrile provided β isomer **19** as an exclusive diastereoisomer through a process as shown in **18a**.[22] The coupling constant, $J_{44,45}$=9.5 Hz, between the protons at the juncture positions proved the *trans* stereochemistry. Hydrosilylation of phenylthioacetylene of **19** in the presence of catalytic amount of cobalt-complex[23] afforded vinylsilane **20**. Treatment of **20** with mCPBA in the presence of sodium hydrogen phosphate and subsequent debenzylation with TMSI afforded alcohol **21** ($J_{44,45}$=9 Hz, $J_{45,46}$=9 Hz) as a precursor for the elaboration of ring K.

Model Studies on Heteroconjugate Addition

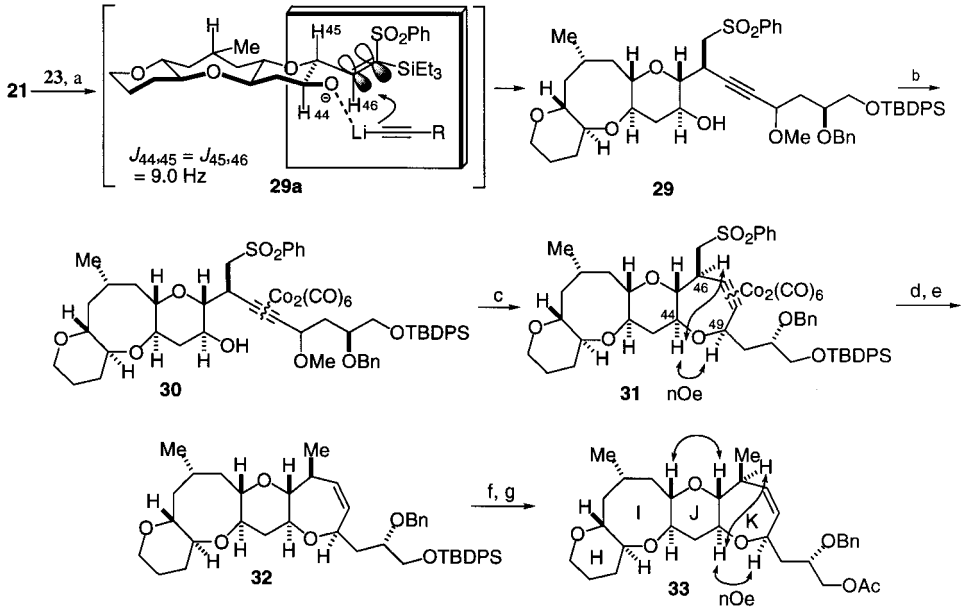
We are faced with the task of controlling the stereochemistry of the methyl group in ring K. At this phase of the project, we were mindful of the heteroconjugate addition reaction. Compound **22** was prepared from tetra-*O*-acetyl-D-glucal as a starting material for the model heteroconjugate addition reaction.[24] The orientation of this electrophilic moiety is equatorial and the coupling constant is $J_{1,1'}$=9 Hz (sugar numbering). It was expected that treatment of **22** with the lithium acetylide generated from substituted propargyl ether **23** and *n*-BuLi would provide **24** via β-chelation.[10,25] To this end, substituted propargyl ether **23** was prepared from compound **3**.[26] Thus, treatment of compound **22** with the lithium salt of **23** in THF at 0°C afforded **24** as a single adduct in 82% yield. The configuration of newly formed stereogenic center in the adduct was confirmed after seven-membered ring cyclization. Compound **24** was further converted to biscobalthexacarbonyl complex **25**. Upon treatment of **25** with boron trifluoride etherate (degassed CH_2Cl_2, 0°C, 50 min), the ring closure took place to afford bicyclic compound **26**. A prolonged reaction time was necessary to obtain the desired *syn* diastereoisomer **26** in 82% yield, because **26** is a thermodynamic product.[15,27] Reductive decomplexation of **26** with tri-*n*-butyltin hydride afforded the corresponding *cis*-olefin. Desulfonylation with sodium-amalgam in methanol gave compound **27**. Desilylation with TBAF in THF and subsequent acetylation with acetic anhydride gave diacetate **28**. The stereochemistry of **28** was demonstrated by NOESY experiments and the coupling constants ($J_{44,45}$=9.2 Hz, $J_{45,46}$=8.5 Hz) as shown in Scheme 5.

Tetracyclic Compound

Having accomplished the model study of the JK ring system, our attention turned to the synthesis of the HIJK-ring fragment of ciguatoxin. The coupling constant



Scheme 5. Reagents, conditions and yields: (a) *n*-BuLi, THF, 0°C then TBAF, THF, rt, 82%; (b) $Co_2(CO)_8$, CH_2Cl_2, 0°C–rt, 82%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 50 min, 93%; (d) *n*-Bu_3SnH, toluene, 55°C, 90%; (e) 5% Na–Hg, MeOH, rt, 91%; (f) TBAF, THF, rt, 98%; (g) Ac_2O, Py, CH_2Cl_2, rt, 100%.



Scheme 6. Reagents, conditions and yields: (a) *n*-BuLi, THF, 0°C then TBAF, THF, 0°C, 92%; (b) $Co_2(CO)_8$, CH_2Cl_2, 87%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 50 min, 81%; (d) *n*-Bu_3SnH, toluene, 55°C, 94%; (e) 5% Na–Hg, MeOH, rt, 98%; (f) TBAF, THF, rt, 97%; (g) Ac_2O, Py, CH_2Cl_2, rt, 98%.

$J_{45,46}$=8.5 Hz in compound **21** indicated an *anti* orientation of these two protons, which assisted the addition direction of the acetylide nuleophile. Thus, the heteroconjugate addition of **23** to **21** under similar conditions provided the adduct **29** as an exclusive product via a β-chelation as shown in **29a** (Scheme 6). Compound **29** was further converted to the corresponding cobalt complex **30**. Upon treatment of **30** with boron trifluoride etherate in degassed CH_2Cl_2 at 0°C for 50 min, the ring closure took place to afford compound **31** as a single diastereoisomer. The stereochemistry of **31** was confirmed from NOESY experiments as indicated and coupling constants ($J_{44,45}$=9 Hz, $J_{45,46}$=9 Hz). Reductive decomplexation of **31** with tri-*n*-butyltin hydride[28] afforded the corresponding *cis*-olefin in 94% yield. Further reduction with sodium-amalgam in methanol gave desulfonylation product **32**. Desilylation of **32** with TBAF and acetylation with acetic anhydride afforded the tetracyclic product **33**. The stereochemistry of **33** was proved by NOE experiments as shown in Scheme 6.

We have established an efficient method directed toward the synthesis of the right part of ciguatoxin and accomplished the synthesis of the HIJK-ring fragment. Further studies along this line are in progress.

Experimental

General

All melting points were recorded on a Yanaco MP-S3 hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton NMR spectra (^1H NMR) were recorded on a Varian Gemini 2000 (300 MHz) or a Bruker ARX-400 (400 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, coupling constants in Hertz, assignment). NOE experiments were performed with a Bruker ARX-400 (400 MHz). Carbon NMR spectra (^{13}C NMR) were recorded on a Varian Gemini 2000 (75.4 MHz) or a Bruker ARX-400 (100 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.

Low-resolution mass spectra (EI) were obtained on a JEOL DX-300 spectrometer. High-resolution mass spectra (HRMS) and elemental analyses were performed by the Analytical Laboratory, School of Bioagricultural Sciences, Nagoya University. Optical rotations were measured on a JASCO DIP-370 automatic digital polarimeter with a sodium lamp in 100 mm cell of 2 mL or 10 mL capacity and reported as follows: $[\alpha]_D^{t\ (°C)}$=l, [*c* (g/100 mL), solvent].

Analytical thin-layer chromatography (TLC) was conducted on 0.25 mm E. Merck silica gel 60F-254 plates. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). Flash chromatography was performed using the forced flow of indicated solvent system on Merck silica gel 60 (230–400 mesh).

Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of nitrogen or argon in glassware which had been either flame-dried or oven-dried (120°C). Operations of degassed solvent were performed on a dual bank vacuum manifold through a three-way stopcock and repeated twice before use. THF was distilled from potassium metal/benzophenone ketyl. CH_2Cl_2 and DMF were dried over activated molecular sieves 4 Å (250°C, several hours). Pyridine was dried over KOH. All other commercially available reagents were used as received.

1-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-4-trimethylsilyl-but-3-yn-2-ol (2). A dry 1 L two-necked flask equipped with a pressure-equalizing addition funnel, a magnetic stirring bar, and a reflux condenser was charged with THF (200 mL), $B(OMe)_3$ (100 mL) and (*S*)-(−)-malic acid **1** (40.20 g, 0.30 mol). To this solution was added dropwise BH_3–SMe_2 (100 mL, 1.0 mol) over 2 h in a water bath as instantaneous hydrogen elution occurred throughout addition. After stirring at 25°C for 20 h, MeOH (200 mL) was added dropwise, and the resulting solution was filtered via nitrogen pressure through a frit glass funnel charged with Super Cell to remove a minor amount of suspended solid. The clear, light-yellow filtrate was concentrated to dryness on rotary evaporator to give a yellow oil. This oil was dissolved in methanol (100 mL) and then concentrated to dryness, the residue was dissolved in methanol (100 mL), and again concentrated to dryness, and repeated once more, giving (*S*)-1,2,4-butanetriol (31.2 g) as a pale yellow oil. A solution of the triol (31.2 g) in acetone (1500 mL) was treated with *p*-toluenesulfonic acid (2.5 g) at room temperature for 1 h. To the mixture was added triethylamine (5.0 mL), the resulting solution was stirred for 10 min. The solvent was evaporated, and the residue was taken up with ethyl acetate, the solution was washed with brine, and dried over Na_2SO_4. After removal of the solvent, distillation of the residue afforded **2-(2,2-dimethyl-[1,3]dioxolan-4-yl) ethanol** (38.87 g, 91% from **1**) as a colorless oil. Small amount of the starting material (763 mg) was recovered. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, Me), 1.43 (3H, s, Me), 1.82 (1H, dt, *J*=6.0, 5.0 Hz, H-3×2), 2.32 (1H, t, *J*=5.0 Hz, OH), 3.60 (1H, d, *J*=8.0 Hz, H-1), 3.82 (2H, dd, *J*=12.0, 5.0 Hz, H-4×2), 4.09 (1H, dd, *J*=8.0, 6.0 Hz, H-1), 4.28 (1H, diffuse heptet, *J*=6.5 Hz, H-2). ^{13}C NMR (75 MHz) δ 25.6, 26.8, 35.5, 60.5, 69.4, 75.1, 109.1.

A solution of CH_2Cl_2 (800 mL) and oxalyl chloride (58.6 mL, 0.77 mmol) was placed in a 3-L flask. DMSO (110 mL, 1.54 mmol) was added dropwise to the stirred oxalyl chloride solution at −78°C. After 2 min, a solution of **2-(2,2-dimethyl-[1,3]dioxolan-4-yl) ethanol** (100 g, 0.70 mmol) in CH_2Cl_2 (100 mL) was added within 20 min, and the mixture was stirred for 15 min. Triethylamine (490 mL, 3.50 mmol) was added dropwise to the solution, and the resulting mixture was stirred for 5 min, then allowed to warm to room temperature. A solution of trimethylsilyl acetylene (126 mL, 0.98 mmol) in THF (500 mL) was treated with *n*-BuLi (1.52 M in hexane, 612 mL, 1.1 mmol) at −78°C for 5 min. After stirring at 0°C for 30 min, this solution was transferred into the stirred aldehyde solution at 0°C via stainless tubing under the nitrogen pressure, and the mixture was stirred at 0°C for 15 min. The reaction was quenched with ice-cold saturated NH_4Cl solution, the mixture was extracted with ether (×3), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (25% ether in hexane) to afford **2** (88.38 g, 52%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (9H, two s, Me_3Si), 1.37 (3H, two s, Me), 1.43 (3H, two s, Me), 1.98 (2H, m, H-4×2), 2.67 (0.7H, d, *J*=3.2 Hz, OH), 2.85 (0.3H, d, *J*=7.0 Hz, OH), 3.64 (1H, two d, *J*=8.0 Hz, H-6), 4.15 (1H, two d, *J*=8.0 Hz, H-6), 4.29 (0.7H, m, H-3), 4.49 (0.3H, m, H-3), 4.59 (1H, m, H-5).

4-(2-Methoxybut-3-ynyl)-2,2-dimethyl-[1,3]dioxolane (3). KOH powder (82.65 g, 1.48 mol) was added to DMSO (1000 mL). After stirring at room temperature for 5 min. Compound **2** (89.44 g, 0.37 mol) and CH_3I (46.25 mL, 0.74 mol) were added sequentially, and the resulting mixture was stirred for 10 min, then poured into water (2 L), and extracted with CH_2Cl_2 (1000 mL×3). The combined organic extracts were washed with water (1 L×2), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (11% ether in hexane) to afford acetylene **3** (56.70 g, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, s, Me), 1.41 (3H, s, Me), 1.80–2.20 (2H, m, H-4×2), 2.45–2.49 (total 1H, two d, *J*=2.0, 2.0 Hz, H-1), 3.42 (total 3H, two s, OMe), 3.55–3.64 (total 1H, two dd, *J*=8.2, 7.0, 8.0, 7.0 Hz, H-6), 4.05–4.15 (2H, m, H-3, H-6), 4.22–4.37 (1H, m, H-5). ^{13}C NMR (75 MHz) δ 25.6, 26.8, 39.3, 40.3, 56.4, 56.6, 67.8, 68.5, 69.4, 72.5, 72.8, 73.9, 74.7, 81.6, 108.6, 108.7. IR (KBr): 3302, 2989, 1372, 1075.

Acetic acid 2-[6-(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-methoxy-2-methylenehex-3-ynyl]-tetrahydropyran-3-yl ester (5). A slurry of $Pd(OAc)_2$ (3.72 g, 16 mmol) and CuI (2.97 g, 16 mmol) in benzene (1 L) was treated with PPh_3 (8.58 g, 32 mmol) at room temperature for 20 min. After addition of a solution of **4** (50.68 g, 0.16 mmol) and **3** (32.38 g, 0.18 mmol) in benzene (100 mL), the mixture was degassed twice with argon line, then treated with *n*-$BuNH_2$ (22.7 mL, 24 mmol), and the solution was stirred overnight under argon atmosphere. The color of the solution changed from brown to orange during this period. The reaction was quenched with saturated NH_4Cl solution, the mixture was extracted with ether (×3), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (33% ether in hexane, R_f=0.20) to afford **5** (47.36 g, 81%) as a colorless oil. $[\alpha]_D^{25}$=+0.8 (*c* 0.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (3H, s, Me), 1.42 (3H, s, Me), 1.46–1.54 (1H, m, H-35), 1.66–1.73 (2H, m, H-34×2), 1.86–2.05 (1H, m, H-43), 2.05 (3H, s, Ac), 2.07–2.19 (1H, m, H-43), 2.25 (1H, dd, *J*=14.5, 9.0 Hz, H-38), 2.46 (1H, dd, *J*=14.5, 1.5 Hz, H-38), 3.36 (1H, ddd, *J*=11.0, 2.0, 1.5 Hz, H-33), 3.52–3.61 (1H, m, H-37), 3.63 (1H, d, *J*=7.0 Hz, H-45), 3.94 (1H, dt, *J*=11.0, 2.0 Hz, H-33), 4.10 (1H, d, *J*=6.0 Hz, H-45), 4.22–4.29 (1H, m, H-42), 4.34 (1H, dd, *J*=9.0, 7.0 Hz, H-44), 4.55 (1H, dt, *J*=10.6, 5.0 Hz, H-36), 5.32 (1H, d, *J*=1.8 Hz, C=CH_2), 5.43 (1H, dd, *J*=1.8, 0.8 Hz, C=CH_2). ^{13}C NMR (75 MHz) δ 21.1, 25.0, 25.7, 26.8, 29.4, 39.4, 39.9, 40.0, 40.3, 56.4, 56.5, 67.8, 68.3, 69.0, 69.5, 69.6, 71.8, 72.7, 73.0, 85.9, 86.5, 87.0, 87.6, 108.7, 123.8, 127.3, 170.2. IR (KBr): 2940, 2859, 1737, 1373, 1241, 1101, 737. MS (EI): *m/z* 366 (M^+). HRMS (EI) calcd for $C_{20}H_{30}O_6$ M^+: 336.2042; Found, 366.2025. Anal. calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.46; H, 8.55.

Acetic acid 2-[8-(*tert*-butyldiphenylsilyl)-7-hydroxy-5-methoxy-2-methyleneoct-3-ynyl]-tetrahydropyran-3-yl ester (6). To a solution of **5** (12.63 g, 34.51 mmol) in MeOH (1500 mL) was added PPTS (2.50 g), and the mixture was heated at 60°C for 2 h. The reaction mixture was concentrated in vacuo, and the residue was subjected to silica gel

chromatography (ethyl acetate) to afford diol intermediate (10.34 g, 91%) as a colorless oil.

To a solution of the diol (10.34 g, 31.50 mmol) in DMF (300 mL) was added TBDPSCl (8.67 g, 31,50 mmol), Et_3N (13.1 mL, 94.5 mmol), and DMAP (706 mg, 6.3 mmol) at room temperature, and the mixture was stirred overnight. The reaction mixture was quenched with ice-cold 1 N HCl solution, extracted with CH_2Cl_2 (×3), and washed with saturated $NaHCO_3$ solution, and ice-water (×2). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (50% ether in hexane, R_f=0.28) to afford **6** (16.95 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s, *tert*-Bu), 1.38–1.52 (1H, m, H-35a), 1.62–1.78 (2H, m, H-34×2), 1.85–2.00 (2H, m, H-43a), 2.12–2.21 (1H, m, H-45b), 2.18–2.30 (total 1H, two dd, J=14.0, 9.0 Hz, H-38a), 2.44–2.50 (1H, br d, J=14.0 Hz, H-38b), 2.78 and 2.88 (total 1H, two d, J=3.5 Hz, OH), 3.35 (1H, dt, J=11.2, 3.0 Hz, H-33a), 3.50–3.70 (3H, m, H-37, H-45×2), 3.92 (1H, dt, J=11.2, 2.0 Hz, H-33b), 3.96–4.05 (1H, m, H-44), 4.31–4.40 (total 1H, two dd, J=12.5, 6.0 Hz, H-42), 4.56 (1H, dt, J=11.0, 4.8 Hz, H-36), 5.31, 5.33 (total 1H, two s, C=CH_2), 5.41, 5.43 (total 1H, two s, C=CH_2), 7.35–7.70 (10H, m, Ph×2). ^{13}C NMR (75 MHz) d 19.2, 21.1, 25.0, 26.8, 29.4, 39.0, 40.0, 56.5, 67.7, 68.7, 70.0 (×2), 71.8, 86.2, 87.4, 87.8, 123.7, 123.9, 127.3, 127.8, 129.8, 133.2, 135.6, 170.3. Anal. calcd for $C_{33}H_{44}O_6Si$: C, 70.18; H, 7.85. Found: C, 70.18, H, 7.94.

Dicobalthexacarbonyl-2-[8-(*tert*-butyl-diphenylsilyloxy)-7-hydroxy-5-methoxy-2-methyleneoct-3-ynyl]-tetrahydropyran-3-ol (7). A solution of **6** (16.95 g, 30.05 mmol) in MeOH (400 mL) was treated with K_2CO_3 (6.60 g, 30.05 mmol) at room temperature for 2 h. The resulting mixture was concentrated, and the residue was taken up with a mixture of ether/hexane (5:1), and filtered to remove precipitate under reduced pressure. The filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography (83% ether in hexane, R_f=0.30) to afford alcohol intermediate (13.98 mg, 89%) as a colorless oil.

To a solution of the alcohol intermediate (13.98 g, 26.78 mmol) in degassed CH_2Cl_2 (200 mL) was added a solution of $Co_2(CO)_8$ (13.74 g,40.2 mmol) in CH_2Cl_2 (100 mL) at 0°C. After removal of the ice-bath, the mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (60% in hexane) to afford **7** (19.83 g, 92%) as a colorless oil. R_f=0.47 (ether/hexane=2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (total 9H, two s, *tert*-Bu), 1.16–1.48 (1H, m, H-35a), 1.58–1.74 (2H, m, H-34×2), 1.77–1.92 (1H, m, H-43a), 1.97–2.20 (2H, m, H-43b, H-35b), 2.30–2.43 (1H, two dd, J=9.0, 3.0; 9.0, 2.5 Hz, H-38a), 2.85–2.98 (2H, m, H-38b, OH), 3.18–3.36 (3H, m, H-33a, H-36, H-37), 3.48, 3.59 (total 3H, two s, MeO), 3.53–3.64 (1H, m, H-45a), 3.72–3.87 (2H, m, H-45b, H-33b), 3.88–4.20 (1H, m, H-44), 4.66–4.86 (total 1H, two dd, J=10.0, 7.8; 6.0, 1.5 Hz, H-42), 5.47 (1H, d, J=5.8 Hz, C=CH_2), 5.52 (1H, s, C=CH_2), 7.34–7.67 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 25.5 (d), 26.8, 33.1, 39.0, 39.2, 40.6, 42.7, 57.9, 59.3, 67.4, 67.5, 67.8, 68.1, 69.2, 70.0, 70.1, 70.3, 78.5, 80.1, 81.2, 82.0, 117.8, 119.4, 127.8, 127.9, 129.8, 133.5, 135.6, 142.9, 143.2, 199.9. HRMS (MALDI-TOF): calcd for $C_{37}H_{42}Co_2O_{11}SiNa$ $[M+Na]^+$, 831.11; found, 831.16.

Compound (8). A solution of **7** (19.83 g, 24.54 mmol) in degassed CH_2Cl_2 (1000 mL) was treated with a solution of $BF_3{\cdot}OEt_2$ (3.02 mL) in CH_2Cl_2 (200 mL) at 0°C for 50 min under argon atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (×2), and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (33% ether in hexane) to afford cobalt complex (15.44 g, 81%) as a dark-red oil.

A solution of the cobalt complex (15.24 mg, 19.24 mmol) in CH_2Cl_2 (200 mL) containing pyridine (5.0 mL) and DMAP (220 mg) was treated with acetic anhydride (7.7 mL, 38.5 mmol) at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (1000 mL), and washed with ice-cold 1 N HCl solution, saturated $NaHCO_3$ (×2) and then brine. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (25% ether in hexane, R_f=0.29) to afford **8** (15.24 g, 97%) as a colorless oil. $[\alpha]_D^{26}$=+26.0 (c 0.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 1.20–1.32 (1H, m, H-35a), 1.47–1.58 (2H, m, H-34×2), 1.79 (1H, br d, H-35b), 1.95 (1H, ddd, J=14.2, 10.0, 5.2 Hz, H-43a), 2.06 (3H, s, MeCO), 2.35–2.43 (1H, ddd, J=14.2, 10.0, 2.6 Hz, H-43b), 2.60 (1H, dd, J=14.0, 2.0 Hz, H-38a), 2.72 (1H, dd, J=14.0, 4.5 Hz, H-38b), 3.08 (1H, ddd, J=11.0, 9.5, 4.8 Hz, H-36), 3.25–3.34 (2H, m, H-33a, H-37), 3.75–3.80 (1H, dd, J=12.0, 4.0 Hz, H-45a), 3.83 (1H, dd, J=12.0, 4.0 Hz, H-45b), 3.89 (1H, br d, J=11.0 Hz, H-33b), 4.79 (1H, dd, J=10.0, 3.0 Hz, H-42), 5.24–5.31 (1H, m, H-44), 5.42 (1H, d, J=1.5 Hz, C=CH_2), 5.54 (1H, d, J=2.0 Hz, C=CH_2), 7.35–7.69 (10H, m, Ph×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.1, 21.2, 22.6, 26.6, 30.3, 31.5, 38.5, 40.3, 64.4, 7.9, 72.3, 77.2, 79.3, 80.4, 121.5, 127.8, 129.8, 133.1, 133.3, 135.6, 135.7, 141.2, 170.4. HRMS(MALDI-TOF): calcd for $C_{38}H_{41}Co_2O_{11}Si$ $[M+H]^+$, 819.11; found, 819.20.

Compound (9a, 9b). To a solution of **8** (15.24 g, 18.63 mmol) in MeOH (200 mL) was added 2,4,6-triisopropylbenzenesulfonylhydrazide (80.60 g, 0.27 mol), and triethylamine (23.9 mL, 172 mmol), and the mixture was stirred at room temperature for 2 days. The resulting mixture was filtered through a short silica gel column, and the filtrate was concentrated to afford crude (13.59 g, 89%) as a dark-red oil. The crude was separated with silica gel flash chromatography (5% ether in hexane) to afford **9a** (9.38 g, 62%) and **9b** (3.28 g, 20%). **9a**: $[\alpha]_D^{28}$=+63.7 (c 0.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 1.19–1.29 (1H, m, H-35a), 1.38 (3H, d, J=7.0 Hz, Me), 1.51–1.60 (2H, m, H-34×2), 1.80 (1H, dt, J=10.0, 7.0 Hz, H-38a), 1.85–1.97 (3H, m, H-38b, H-43a, H-35b), 2.42 (1H, ddd, J=14.0, 8.5, 3.0 Hz, H-43b), 3.02–3.10 (1H, m, H-39), 3.12–3.19 (2H, m, H-36, H-37), 3.25 (1H, dd, J=11.0, 3.0 Hz, H-33a), 3.75–3.81 (2H, m, H-45×2), 3.84–3.86 (1H, m, H-33b), 4.68 (1H, dd, J=10.8, 3.0 Hz, H-42),

5.22 (1H, dd, J=12.0, 4.0 Hz, H-43), 7.35–7.69 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) d 19.1, 21.1, 25.0, 25.7, 26.6, 29.6, 31.8, 36.9, 44.7, 64.3, 67.6, 72.1, 80.9, 83.0, 99.0, 108.5, 128.8, 129.9, 133.2, 135.7, 170.4, 199.9. HRMS(MALDI-TOF): m/z calcd for $C_{38}H_{42}Co_2O_{11}SiNa$ $[M^+Na]^+$, 843.11; found, 843.20.

Acetic acid 1-(*tert*-butyl-diphenyl-silyloxymethyl)-2-(9-methyl-2,3,4,4a,6,9,10,10a-octahydro-1,5-dioxabenzocycloocten-6-yl)-ethyl ester (10a). To a solution of **9a** (8.32 g, 10.15 mmol) in toluene (2 L, c 0.05 M) was added n-Bu_3SnH (33.3 mL, 124 mmol), the reaction mixture was heated at 55°C for 1 h. The color of solution changed from dark-red to yellow during this period. The solvent was evaporated, and the residue was purified by silica gel column chromatography (hexane→25% ether in hexane, R_f=0.24) to afford 10a (3.63 g, 67%) as a colorless oil. $[\alpha]_D^{28}=-38.2$ (c 0.94, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, d, J=7.0 Hz, Me), 1.05 (9H, s, *tert*-Bu), 1.21–1.34 (1H, m, H-35a), 1.37–1.47 (2H, m, H-34×2), 1.74 (1H, dd, J=13.0, 4.5 Hz, H-38), 1.80–2.00 (3H, m, H-43×2, H-35), 2.03 (3H, s, MeCO), 3.01–3.09 (1H, m, H-39), 3.17–3.20 (2H, m, H-36, H-37), 3.26 (1H, dd, J=11.0, 2.0 Hz, H-33a), 3.74 (2H, d, J=4.5 Hz, H-45×2), 3.79 (1H, dt, J=11.0, 2.0 Hz, H-33b), 4.00 (1H, t, J=4.5 Hz, H-42), 5.12–5.15 (1H, m, H-44), 5.20 (1H, ddd, J=11.5, 4.0, 1.0 Hz, H-41), 5.33 (1H, ddd J=11.5, 7.5, 1.0 Hz, H-40), 7.35–7.69 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.2, 21.2, 22.6, 24.3, 25.4, 26.7, 27.0, 30.7, 31.5, 36.3, 42.8, 64.6, 67.3, 72.3, 76.0, 76.4, 79.4, 127.7, 128.2, 129.7, 133.4, 133.5, 135.6, 135.7, 170.5. Anal. calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26. Found: C, 71.59; H, 8.46.

[2-Benzyloxy-3-(9-methyl-2,3,4,4a,6,9,10,10a-octahydro-1,5-dioxabenzocycloocten-6-yl)-propoxy]-*tert*-butyl-diphenyl silane (10b). A solution of **10a** (3.58 g, 6.68 mmol) in MeOH (2.0 mL) was treated with K_2CO_3 (737 mg, 5.34 mmol) at room temperature for 2 h. The resulting mixture was concentrated in vacuo, and the residue was taken up with a mixture of 25% ether in hexane, and filtered to remove the precipitate. The filtrate was concentrated to dryness, and the residue was purified by silica gel column chromatography (25% ether in hexane) to afford alcohol intermediate (2.84 g, 88%) as a colorless oil.

To a slurry of NaH (60% dispersion in mineral oil, 299 mg, 7.48 mmol, washed with hexane twice) in DMF (50 mL) was added a solution of the alcohol intermediate above (2.84 g, 5.75 mmol) in DMF (50 mL) at −40°C, and the mixture was stirred for 30 min. BnBr (0.75 mL, 11.5 mmol) was added to this solution, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with ice-cold saturated NH_4Cl solution, and the mixture was extracted with ether (×3). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography column (17% ether in hexane, R_f=0.31) to afford **10b** (2.74 g, 82%) as a colorless oil. $[\alpha]_D^{28}=-39.3$ (c 0.68, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (1H, d, J=7.0 Hz, Me), 1.07 (9H, s, *tert*-Bu), 1.18–1.30 (1H, m, H-35a), 1.35–1.48 (1H, m, H-38a), 1.49–1.57 (3H, m, H-34×2, H-43a), 1.74 (1H, dd, J=13.0, 5.0 Hz, H-38b), 1.82–1.94 (2H, m, H-43b, H-35b), 3.00–3.16 (1H, m, H-39), 3.15–3.29 (3H, m, H-37, H-36, H-33a), 3.62–3.72 (1H, m, H-45a), 3.74–3.84 (2H, m, H-45b, H-33b), 4.02–4.12 (1H, m, H-44), 4.58 (2H, OCH_2Ph), 5.12 (1H, dd, J=11.0, 4.0 Hz, H-41), 5.31 (1H, dd, J=11.0, 7.5 Hz, H-40), 7.24–7.73 (15H, m, Ph×3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 24.4, 25.5, 26.8, 27.0, 27.1, 30.7, 37.8, 42.8, 65.9, 67.3, 71.7, 76.3, 77.3, 79.5, 127.4, 127.7 (×2), 128.3 (×2), 128.6, 129.7, 133.7, 135.7, 138.3, 139.0. Anal. calcd for $C_{37}H_{48}O_4Si$: C, 75.98; H, 8.27. Found: C, 75.75; H, 8.40.

6-[2-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)-propyl]-9-methyldecahydro-1,5-dioxabenzocyclooctene-7,8-diol (11a, 11b). To a solution of **10b** (4.72 g, 8.1 mmol) in acetone (48 mL) and water (6 mL) containing NMO (2.24 g, 16.2 mmol) was added osmium tetroxide solution (4% aqueous solution, 2.91 mL, 0.4 mmol) at 0°C, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated Na_2SO_3 solution, and the mixture was stirred for 30 min. The solvent was evaporated, and the residue was taken up with ethyl acetate, and the solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography (20% ethyl acetate in hexane, R_f=0.07) to afford diols **11a** (3.99 g, 80%) and **11b** (370 mg, 7%) as colorless oils. **11a**: $[\alpha]_D^{26}=-28.5$ (c 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s, *tert*-Bu), 1.09–1.13 (1H, m, H-35a), 1.18 (3H, d, J=7.0 Hz, Me), 1.20–1.28 (1H, m, H-38a), 1.20–1.28 (1H, m, H-35b), 1.34–1.44 (1H, m, H-43a), 1.56–1.66 (2H, m, H-34×2), 1.84–1.92 (1H, m, H-38b), 1.93–2.02 (1H, m, H-43b), 2.26 (1H, d, J=1.5 Hz, OH), 2.32–2.43 (1H, m, H-39), 2.93–3.36 (2H, m, H-36, H-37), 3.28 (1H, ddd, J=9.5, 5.5, 3.0 Hz, H-33), 3.38 (1H, dt, J=9.5, 3.0 Hz, H-42), 3.68 (1H, m, dd, J=11.0, 5.5 Hz, H-45a), 3.76 (1H, dd, J=11.0, 5.0 Hz, H-45b), 3.90–3.98 (3H, m, H-40, H-41, H-33b), 4.49 (1H, d, J=11.0 Hz, OCH_2Ph), 4.69 (1H, d, J=11.0 Hz, OCH_2Ph), 7.24–7.71 (15H, m, Ph×3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.1, 26.8, 32.4, 33.6, 35.1, 66.0, 67.8, 72.3, 74.7, 75.9, 77.2, 83.8, 127.8, 128.0, 128.6, 129.9, 133.4, 135.7, 137.7. Anal. calcd for $C_{37}H_{50}O_6Si$: C, 71.81; H, 8.14. Found: C, 72.58; H, 8.81.

[2-Benzyloxy-3-(2,2,11-trimethyldecahydro-1,3,5,9-tetraoxabenzo[a]cyclopenta[e]cycloocten-4-yl)-propoxy]-*tert*-butyldiphenyl silane (12). A solution of **11a** (2.75 g, 4.45 mmol) in acetone (150 mL) was treated with TsOH–H_2O (73 mg) for 20 min at room temperature. The resulting mixture was treated with 5 mL of triethylamine, and stirred for 5 min. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (33% ether in hexane, R_f=0.33) to afford **12** (2.72 g, 93%) as a colorless oil. $[\alpha]_D^{26}=+17.4$ (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (9H, s, *tert*-Bu), 1.18 (3H, d, J=7.0 Hz, Me), 1.20–1.25 (1H, m, H-35a), 1.29 (3H, s, Me), 1.30 (3H, s, Me), 1.42–1.54 (3H, m, H-34×2, H-38a), 1.64–1.79 (2H, m, H-38b, H-43a), 1.98 (1H, ddd, J=14.0, 7.0, 3.0 Hz, H-43b), 2.17 (1H, br q, J=7.0 Hz, H-39), 2.26 (1H, dt, J=10.0, 6.0 Hz, H-35b), 2.93 (1H, td, J=10.0, 2.0 Hz, H-37), 3.01 (1H, td, J=10.0, 4.0 Hz, H-36), 3.36 (1H, td, J=11.5, 3.5 Hz, H-33a), 3.59 (1H, td, J=9.0, 4.0 Hz, H-42), 3.67–3.75 (4H, m, H-41,

H-44, H-45×2), 3.77–3.84 (1H, m, H-33b), 3.98 (1H, d, J=5.0, 4.0 Hz, H-40), 4.60 (1H, d, J=12.0 Hz, OCH_2Ph), 4.68 (1H, d, J=12.0 Hz, OCH_2Ph), 7.25–7.71 (15H, m, Ph×3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 25.2, 25.7, 26.1, 26.8, 28.3, 31.1, 31.6, 34.2, 36.4, 66.8, 68.0, 71.2, 77.1, 78.1, 79.2, 81.1, 84.1, 84.4, 127.3, 127.6, 127.8, 128.3, 129.7, 129.8, 133.5, 135.5, 139.1; Anal. calcd for $C_{40}H_{54}O_6Si$: C, 72.91; H, 8.26. Found: C, 72.82; H, 8.53.

2-Benzyloxy-3-(2,2,11-trimethyldecahydro-1,3,5,9-tetraoxabenzo[a]cyclopenta[e]cycloocten-4-yl)-propionaldehyde (13). A solution of **12** (2.71 g, 4.12 mmol) in THF (30 mL) was treated with TBAF (1.0 M solution in THF, 0.3 mL, 4.5 mmol) for 2 h at room temperature. The resulting mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (50% then 75% ether in hexane) to afford a white crystal (1.66 g, 96%).

A solution of the white crystal (1.65 g, 3.92 mmol) in dimethyl sulfoxide (15 mL) containing triethylamine (2.83 mL, 19.6 mmol) was treated dropwise with a solution of sulfur trioxide pyridine complex (2.60 g, 15.7 mmol) in dimethyl sulfoxide (15 mL) at room temperature for 10 min. The resulting mixture was diluted with ethyl acetate (150 mL), washed with cold water (100 mL×3), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (50% ether in hexane, R_f=0.30) to afford aldehyde **13** (1.63 g, 100%) as a colorless oil. R_f=0.73 (silica gel, 4:1, ether/hexane); $[\alpha]_D^{26}$=+10.5 (c 0.56, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, J=7.0 Hz, Me), 1.20–1.32 (2H, m, H-35, H-38a), 1.33 (3H, s, Me), 1.40 (3H, s, Me), 1.55–1.67 (2H, m, H-34×2), 1.79–1.86 (1H, m, H-38b), 1.88 (1H, dt, J=13.0, 5.0 Hz, H-43a), 2.11–2.38 (3H, m, H-39, H-43b, H-45), 2.95 (1H, td, J=10.0, 2.0 Hz, H-46), 3.14 (1H, td, J=10.0, 4.0 Hz, H-36), 3.24–3.33 (1H, m, H-37), 3.76 (1H, dd, J=9.5, 5.0 Hz, H-41), 3.80–3.88 (2H, m, H-33, H-42), 3.92 (1H, ddd, J=8.0, 5.0, 2.5 Hz, H-44), 4.02 (1H, d, J=5.0 Hz, H-40), 4.64 (2H, $PhCH_2O$), 7.30–7.40 (5H, m, Ph), 9.68 (1H, d, J=2.5 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.7, 26.1, 28.1, 31.0, 31.7, 34.1, 34.7, 68.0, 72.2, 76.0, 79.0, 80.2, 81.0, 83.7, 84.2, 107.3, 128.0, 128.1, 128.6, 137.3, 203.6. HRMS (FAB) calcd for $C_{24}H_{35}O_6$: 419.2355 (M^+H); found: 419.2342.

2-Benzyloxy-6-methyldodecahydro-4,8,12-trioxadibenzo-[a,d]cyclooctene-3,5-diol (14). Aldehyde **13** (1.62 g, 3.88 mmol) was treated with 80% aqueous acetic acid solution (30 mL) at room temperature overnight. The resulting mixture was added dropwise to ice-cold saturated aqueous $NaHCO_3$ solution (50 mL), and the solution was stirred vigorously for 10 min (pH=8), extracted with ethyl acetate (×3). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (50% ethyl acetate in hexane, R_f=0.27) to afford hemiacetal **14** (1.43 g, 98%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, J=7.0 Hz, Me), 1.36–1.57 (2H, m, H-35a, H-38a), 1.58–1.68 (2H, m, H-34×2), 1.80–1.99 (1H, m, H-43a), 1.91–2.04 (2H, m, H-38b, H-39), 2.11–2.21 (1H, m, H-43b), 2.29–2.31 (1H, m, H-35b), 2.91–3.02 (1H, m, H-36), 3.03–3.19 (2.5H, m, H-37, H-40, H-44×0.5), 3.20–3.31 (1H, m, H-33a), 3.46 (0.5H, ddd, J=8.5, 5.0, 3.0 Hz, H-44×0.5), 3.64–3.77 (2H, m, H-41, H-42), 3.82–3.85 (1H, m, H-33b), 4.59 (1H, d, J=12.0 Hz, $PhCH_2O$), 4.66 (0.5H, d, J=9.0 Hz, H-45a), 4.70 (1H, d, J=12.0 Hz, $PhCH_2O$), 5.18 (0.5H, d, J=3.0 Hz, H-45b), 7.30–7.40 (5H, m, Ph). Anal. calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.63; H, 7.98.

2-Benzyloxy-5-hydroxy-6-methyldodecahydro-4,8,12-trioxadibenzo[a,d]cycloocten-3-one (15). A solution of hemiacetal **14** (1.16 g, 3.1 mmol) in DMF (20 mL) containing sodium acetate buffer (30 mL) was treated with bromine (0.19 mL, 3.72 mmol) at 0°C. After removal of ice-bath, the mixture was stirred at room temperature for 30 min. Saturated $NaHSO_3$ solution was added to the resulting mixture until the yellow color of the solution disappeared. The mixture was extracted with CH_2Cl_2 (×3), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (33% ethyl acetate in hexane, R_f=0.27) to give lactone **15** (890 mg, 77%) as a white crystal. Mp: 163.5–164.5°C. $[\alpha]_D^{27}$=−63.0 (c 0.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, J=7.0 Hz, Me), 1.22–1.32 (1H, m, H-35a), 1.38–1.52 (1H, m, H-38a), 1.60–1.70 (2H, m, H-34×2), 1.95–2.06 (2H, m, H-38b, H-39), 2.12 (1H, dt, J=13.0, 9.0 Hz, H-43a), 2.29–2.42 (2H, m, H-43b, H-35b), 2.97 (1H, td, J=9.0, 2.0 Hz, H-36), 3.13 (1H, ddd, J=11.0, 9.0, 5.0 Hz, H-37), 3.24–3.34 (1H, m, H-33a), 3.81–3.90 (2H, m, H-33b, H-40), 3.96 (1H, dd, J=9.0, 4.8 Hz, H-44), 4.16 (1H, td, J=9.0, 6.5 Hz, H-42), 4.32 (1H, dd, J=9.0, 2.0 Hz, H-41), 4.80 (2H, d, J=12.0 Hz, $PhCH_2O$), 7.31–7.40 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.0, 32.1, 32.9, 34.2, 35.3, 67.7, 71.7, 72.5, 74.4, 83.0, 84.8, 85.5, 128.1, 128.6, 137.2, 170.4. Anal. calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.06; H, 7.61.

Imidazole-1-carbothioic acid *O*-(2-benzyloxy-6-methyl-3-oxo-dodecahydro-4,8,12-trioxadibenzo[a,d]cyclooocten-5-yl) ester (16). To a solution of **15** (845 mg, 2.25 mmol) in CH_2Cl_2 (20 mL) was added thiocarbonyldiimidazole (800 mg, 4.50 mmol), and the reaction mixture was heated at gentle reflux overnight. The resulting solution was concentrated and the residue was purified by silica gel column chromatography (50% ethyl acetate in hexane, R_f=0.27) to afford **16** (728 mg, 67%) as a white solid. Little amount of starting material (110 mg) was recovered. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, J=7.0 Hz, Me), 1.46–1.58 (2H, m, H-35a, H-38a), 1.64–1.75 (2H, m, H-34×2), 2.05–2.13 (2H, m, H-38b), 2.14–2.23 (2H, m, H-35b, H-43a), 2.31–2.42 (2H, m, H-39, H-43b), 3.04–3.10 (1H, td, J=9.0, 2.0 Hz, H-36), 3.22 (1H, td, J=9.0, 4.8 Hz, H-37), 3.28–3.35 (1H, m, H-33a), 3.85–3.91 (2H, m, H-33b, H-44), 4.09 (1H, dt, J=9.5, 7.0 Hz, H-42), 4.59 (1H, d, J=12.0 Hz, $PhCH_2O$), 4.70 (1H, dd, J=9.5, 2.5 Hz, H-41), 4.84 (1H, d, J=12.0 Hz, $PhCH_2O$), 6.25 (1H, d, J=2.5 Hz, H-40), 7.07 (1H, s, CH=C), 7.28–7.41 (5H. m, Ph), 7.63 (1H, s, C=CH), 8.35 (1H, s, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.8, 32.2, 33.5, 35.6, 36.6, 67.7, 71.8, 72.4, 73.9, 81.9, 82.8, 84.1, 85.8, 104.3, 118.1, 128.1, 128.2, 128.5, 131.2, 136.8, 168.4, 184.1. Anal. calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.42; H, 7.35, N, 6.69.

2-Benzyloxy-6-methyldodecahydro-4,8,12-trioxadibenzo-[a,d]cycloocten-3-one (17). A mixture of **16** (728 mg, 1.5 mmol) in dry toluene (20 mL) was added dropwise over 30 min to a stirred solution of refluxing toluene (50 mL) and tributyltin hydride (0.46 mL, 1.8 mmol) under N_2. After 10 min, the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (25% ethyl acetate in hexane, R_f=0.12) to afford **17** (475 mg, 88%). Mp: 127–129°C. $[\alpha]_D^{27}$=−59.2 (*c* 0.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, *J*=7.0 Hz, Me), 1.45–1.52 (1H, m, H-35a), 1.58–1.70 (4H, H-34×2, H-38a, H-40a), 1.79–1.93 (2H, m, H-38b, H-39), 2.01–2.13 (3H, m, H-35b, H-40b, H-43a), 2.39 (1H, dt, *J*=13.8, 7.8 Hz, H-43b), 3.05 (1H, td, *J*=10.0, 2.8 Hz, H-37), 3.15 (1H, td, *J*=10.0, 4.8 Hz, H-36), 3.23–3.31 (1H, m, H-33a), 3.60–3.68 (1H, td, *J*=9.5, 6.0 Hz, H-42), 3.83 (1H, br d, *J*=11.0 Hz, H-33b), 4.35 (1H, ddd, *J*=11.0, 9.5, 3.5 Hz, H-41), 4.66 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 4.89 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 7.28–7.40 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 27.8, 32.4, 36.2, 45.2, 45.6, 67.5, 72.1, 72.3, 80.1, 81.9, 82.0, 85.3, 128.1, 128.5, 137.2, 169.8. IR (KBr): 1749, 1685, 1508, 1458, 1266, 1181, 1115, 947. Anal. calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.14; H, 8.02.

2-Benzyloxy-6-methyl-3-phenylsulfanylethynyldodeca-hydro-4,8,12-trioxadibenzo[a,d]cycloocten-3-ol (18). A solution of thiophenylacetylene (71 mg, 0.52 mmol) in THF (2 mL) was treated dropwise with *n*-BuLi (1.5 M in hexane, 0.35 mL, 0.52 mmol) at −78°C, and the mixture was stirred at 0°C for 30 min. To the resulting solution was added dropwise a solution of lactone **17** (95 mg, 0.26 mmol) in THF (1.5 mL) at −78°C. After 10 min, the reaction mixture was quenched with saturated NH_4Cl solution, extracted with diethyl ether (×3), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (ether/hexane=1:1, R_f=0.26) to provide a 5:1 mixture of lactol **18** (110 mg, 84%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03–1.08 (total 3H, two d, *J*=7.0 Hz, Me), 1.24–1.28 (1H, m, H-35a), 1.30–1.38 (1H, m, H-43a), 1.46 −1.57 (2H, m, H-38a, H-40a), 1.58–1.65 (2H, m, H-34×2), 1.75 (1H, br d, *J*=15.2 Hz, H-38b), 1.83–1.93 (2H, m, H-39, H-40b), 2.01 (1H, br d, *J*=12.5 Hz, H-35b), 2.10–2.15 (1H, m, H-43b), 2.62 (1H, *J*=4.0 Hz, OH), 2.98–3.16 (2H, m, H-36, H-37), 3.20–3.32 (1H, m, H-33a), 3.39–3.58 (2H, m, H-41, H-42), 3.79 (total 1H, two br d, *J*=11.5 Hz, H-33b), 4.35 (1H, dd, *J*=8.0, 4.5 Hz, H-44), 4.52 (1H, d, *J*=10.5 Hz, $PhCH_2O$), 4.72 (1H, d, *J*=10.5 Hz, $PhCH_2O$), 7.19–7.48 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.9, 28.7, 32.3, 36.7, 37.0, 45.1, 46.2, 47.0, 67.6, 72.2, 72.5, 73.0, 81.2, 81.9, 82.4, 84.1, 84.5, 89.9, 99.7, 126.4, 126.9, 127.3, 127.8, 128.0, 128.1, 128.3, 128.5, 128.7, 129.3, 129.8, 136.6, 187.0. Anal. calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.34; H, 7.02.

2-Benzyloxy-6-methyl-3-phenylsulfanylethynyldodeca-hydro-4,8,12-trioxadibenzo[a,d]cyclooctene (19). To a solution of compound **18** (110 mg, 0.22 mmol) and $HSiEt_3$ (0.15 mL, 0.88 mmol) in CH_3CN (6.0 mL) was added dropwise $BF_3{\cdot}OEt_3$ (54 mL, 0.44 mmol) at −78°C. After stirring for 5 min, the reaction mixture was diluted with ether, washed with water (×2), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel flash chromatography (ether/hexane=1: 10) to give compound **19** (95 mg, 100%) as a white solid. Mp: 161–163°C. $[\alpha]_D^{26}$=−2.6 (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, *J*=7.0 Hz, Me), 1.40–1.47 (1H, m, H-35a), 1.49–1.68 (5H, m, H-38a, H-40a, H-43a, H-34×2), 1.79–1.94 (3H, m, H-38b, H-39, H-40b), 2.02 (1H, br d, *J*=12.0 Hz, H-35b), 2.46 (1H, dt, *J*=12.8, 4.0 Hz, H-43b), 3.02–3.19 (3H, m, H-36, H-37, H-41), 3.22–3.31 (2H, m, H-42, H-33a), 3.50 (1H, ddd, *J*=11.2, 9.5, 4.0 Hz, H-44), 3.83 (1H, br d, *J*=11.0 Hz, H-33b), 4.13 (1H, d, *J*=9.5 Hz, H-45), 4.71 (2H, s, $PhCH_2O$), 7.21–7.45 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 27.6, 27.9, 32.8, 39.5, 45.5, 46.2, 67.4, 71.8, 72.1, 73.1, 76.0, 81.1, 81.7, 82.3, 84.8, 96.1, 126.7, 127.0, 127.8, 127.9, 128.5, 129.2, 132.2, 138.0. IR (KBr): 2929, 2849, 1585, 1481, 1455, 1343, 1314, 1261, 1220, 1089, 1024, 951, 805, 734, 695. Anal. calcd for $C_{29}H_{34}O_4S$: C, 72.77; H, 7.16. Found: C, 73.03; H, 7.28.

[2-(2-Benzyloxy-6-methyldodecahydro-4,8,12-trioxadi-benzo[a,d]cycloocten-3-yl)-1-phenylsulfanylvinyl]tri-ethyl silane (20). To a solution of **19** (56.0 mg, 0.12 mmol) in dichloroethane (2 mL) was added $HSiEt_3$ (82 mL, 1.17 mmol) and dicobalthexacarbonyl-2-methyl-but-3-yn-2-ol (0.1 M in $ClCH_2CH_2Cl$, 40 mL, 3 mmol %). The mixture was heated at 60°C for 30 min. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, ether/hexane=1:10) to afford compound **20** (58.5 mg, 84%) as a colorless oil. $[\alpha]_D^{27}$=−73.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (6H, q, *J*=8.0 Hz, CH_2×3), 0.86 (9H, t, *J*=8.0 Hz, Me×3), 1.03 (1H, d, *J*=7.0 Hz, Me), 1.36–1.58 (4H, m, H-35a, H-38a, H-40a, H-43a), 1.59–1.66 (2H, m, H-34×2), 1.78–1.88 (3H, m, H-38b, H-39, H-40b), 2.03 (1H, br d, *J*=11.5 Hz, H-33a), 2.47 (1H, dt, *J*=12.0, 4.5 Hz, H-43b), 3.01–3.15 (3H, m, H-36, H-37, H-41), 3.17–3.28 (2H, m, H-33a, H-42), 3.33 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H-44), 3.82 (1H, br d, *J*=11.5 Hz, H-33b), 4.48 (1H, dd, *J*=9.0, 8.0 Hz, H-45), 4.49 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 4.61 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 6.32 (1H, d, *J*=8.0 Hz, CH=C), 7.10–7.34 (10H, m, Ph×2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.3, 7.2, 25.9, 27.5, 28.0, 32.9, 38.8, 45.6, 46.2, 67.4, 70.9, 76.3, 77.3, 80.5, 81.7, 83.1, 84.6, 125.8, 127.6, 127.7, 128.3, 128.4, 129.8, 137.2, 138.4, 148.8. Anal. calcd for $C_{35}H_{50}O_4SSi$: C, 70.66; H, 8.47. Found: C, 70.71; H, 8.29.

3-[2-Benzenesulfonyl-2-(triethylsilyl)vinyl]-6-methyldo-decahydro-4,8,12-trioxadibenzo[a,d]cycloocten-2-ol (21). To a solution of **20** (75 mg, 0.13 mmol) and sodium hydrogen phosphate (129 mg, 0.91 mmol) in CH_2Cl_2 was added portionwise mCPBA (54 mg, 0.31 mmol) at 0°C. After stirring for 1 h, the reaction mixture was quenched with cold saturated $NaHCO_3$ solution and saturated sodium sulfite aqueous solution (examined with KI-starch paper). The water layer was extracted with CH_2Cl_2 (×3), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, ether/hexane=1:3, 1:1) to afford sulfone intermediate (70 mg, 89%) as a white solid.

To a solution of the sulfone intermediate (70 mg, 0.11 mmol) in $CHCl_3$ (0.1 mL) was added TMSI (0.02 mL, 0.14 mmol) at 0°C. After stirring at room temperature for 30 min, the reaction was quenched with

MeOH (1 mL) at 0°C. The mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (70 mL). The organic layer was washed sequentially with saturated $NaHCO_3$ solution, sat. $NaHSO_3$ solution, brine and concentrated. The residue was purified by silica gel chromatography (ether/hexane=1:2) to afford **21** (57 mg, 95%) as a white crystal. Mp: 42–44°C. R_f=0.29 (ether/hexane=2:1). $[\alpha]_D^{26}=-86.2$ (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (6H, q, J=7.4 Hz, CH_2×3), 0.88 (9H, t, J=7.4 Hz, Me×3), 1.04 (3H, d, J=7.2 Hz, Me), 1.43–1.54 (4H, m, H-35a, H-38a, H-40a, H-43a), 1.57–1.67 (2H, m, H-34×2), 1.75–1.95 (3H, m, H-39, H-38b, H-40b), 2.04 (1H, br d, J=12.0 Hz, H-35b), 2.50 (1H, dt, J=12.0, 4.8 Hz, H-43b), 2.99 (1H, td, J=10.0, 4.0 Hz, H-42), 3.04 (1H, td, J=9.2, 5.0 Hz, H-37), 3.12 (1H, td, J=9.2, 4.8 Hz, H-36), 3.24 (1H, td, J=10.0, 6.0 Hz, H-41), 3.28 (1H, ddd, J=11.5, 7.0, 3.0 Hz, H-33a), 3.34 (1H, td, J=9.0, 4.8 Hz, H-44), 3.83 (1H, br d, J=11.5 Hz, H-33b), 4.69 (1H, t, J=9.0 Hz, H-45), 6.36 (1H, d, J=9.0 Hz, HC=C), 7.52–7.62 (3H, m, Ph), 7.88 (2H, dt, J=7.0, 1.5 Hz, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.1, 6.9, 25.9, 27.7, 28.1, 31.5, 32.8, 43.0, 45.6, 67.5, 68.9, 78.1, 80.5, 81.9, 82.8, 84.9, 126.9, 129.1, 133.2, 142.4, 145.7, 154.2. IR (KBr): 3460, 2930, 2885, 1428, 1305, 1148, 1113, 1085. Anal. calcd for $C_{28}H_{44}O_6SSi$: C, 62.65; H, 8.26. Found: C, 62.72; H, 8.19.

2-[1-Benzenesulfonylmethyl-6-benzyloxy-7-(*tert*-butyldiphenylsilyloxy)-1-ethyl-4-methoxy-hex-2-ynyl]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,6-dihydro-2H-pyran-3-ol (24). A solution of acetylene **23** (656 mg, 1.4 mmol) in THF (5 mL) was cooled to 0°C and treated with *n*-BuLi (1.5 M in hexane, 0.75 mL, 1.1 mmol) for 15 min. A solution of compound **22** (180 mg, 0.28 mmol) in THF (1 mL) was added dropwise to the reaction mixture at 0°C, and stirring was continued for 30 min, then the mixture was poured into a cold saturated NH_4Cl solution and extracted with CH_2Cl_2 (×3), dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (1 mL) and treated with TBAF (1.0 M in THF, 0.28 mL) at 0°C for 5 min. The reaction mixture was poured into sat. NH_4Cl solution, extracted with CH_2Cl_2 (×3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (ether/hexane=4:1) to afford **24** (223 mg, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s, *tert*-Bu), 1.08 (total 9H, two s, *tert*-Bu), 1.56–2.08 (total 2H, m, H-50×2), 2.66 (total 1H, two d, J=5.0 Hz, OH), 3.23 (total 3H, two s, OMe), 3.28–3.47 (4H, m, H-46, H-54, CH_2SO_2Ph), 3.53–3.58 (1H, m, H-46), 3.62–3.76 (4H, m, H-52×2, H-40, H-51), 4.00 (total 1H, dd J=10.0, 3.0 Hz and br t, J=7.0 Hz, H-49), 4.20 (2H, m, H-41, H-44), 4.43–4.76 (total 2H, four d, J=12 Hz, OCH_2Ph), 5.79 (1H, d, J=10.5 Hz, C=CH), 5.87 (1H, d, J=10.5 Hz, CH=C), 7.30–7.90 (total 20H, m, Ph×4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 22.5, 26.7, 30.3, 30.6, 31.5, 37.6, 38.3, 56.2, 56.3, 56.9, 65.8, 66.0, 66.2, 66.6, 67.2, 68.7, 72.1, 72.7, 75.8, 76.9, 78.9, 79.0, 83.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.2, 129.3, 129.8, 133.4, 133.8, 133.9, 135.6, 135.7, 138.9, 139.5. Anal. calcd for $C_{60}H_{70}O_0SSi_2$: C, 71.53; H, 7.00. Found: C, 71.72; H, 7.19.

Dicobalthexacarbonyl-2-[1-benzenesulfonylmethyl-6-benzyloxy-7-(*tert*-butyldiphenylsilyloxy)-1-ethyl-4-methoxyhex-2-ynyl]-6-(*tert*-butyldiphenylsilyloxymethyl)-3,6-dihydro-2H-pyran-3-ol (25). To a solution of **24** (220 mg, 0.23 mmol) in degassed CH_2Cl_2 (4 mL) was added a solution of $Co_2(CO)_8$ (139 mg, 0.41 mmol) in CH_2Cl_2 (4 mL) at 0°C. After stirring at room temperature for 2 h, the solution was concentrated and the residue was purified by silica gel chromatography (ether/hexane=1:3) to afford **25** (242 mg, 82%) as a dark-red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (9H, s, *tert*-Bu), 1.08 (9H, s, *tert*-Bu), 1.80–1.86 (2H, m, H-50×2), 3.04 (1H, d, J=11.0 Hz, OH), 3.20 (3H, s, OMe), 3.25 (1H, dd, J=11.0, 4.8 Hz, H-40a), 3.42 (1H, d, J=8.8 Hz, H-45), 3.52 (1H, dd, J=10.0, 5.0 Hz, CH_2SO_2Ph), 3.60 (1H, dd, J=10.0, 5.0 Hz, CH_2SO_2Ph), 3.70–3.82 (2H, m, H-52×2), 3.90 (1H, dd, J=15.0, 4.2 Hz, H-40b), 3.89–3.95 (1H, m, H-44), 4.17–4.20 (2H, m, H-41, H-46), 4.38 (1H, dd, J=8.0, 1.5 Hz, H-49), 4.46 (1H, d, J=12.0 Hz, OCH_2Ph), 4.74 (1H, d, J=12.0 Hz, OCH_2Ph), 5.66 (1H, dt, J=10.5, 2.0 Hz, CH=C), 5.80 (1H, dt, J=10.5, 1.5 Hz, C=CH), 7.27–7.92 (25H, m, Ph×5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 31.5, 36.6, 41.1, 56.8, 58.6, 64.6, 65.8, 66.1, 72.3, 75.0, 76.4, 79.0, 82.0, 98.0, 100.6, 127.6, 127.7, 127.8, 128.0, 128.1, 128.6, 129.0, 129.5, 129.8, 130.7, 133.3, 133.7, 135.5, 135.6, 135.7, 138.0, 139.6, 200.1.

Compound (26). A solution of **25** (201 mg, 0.16 mmol) in degassed CH_2Cl_2 (50 mL) was treated with a solution of $BF_3{\cdot}OEt_2$ (0.16 mM in CH_2Cl_2, 1 mL, 0.16 mmol) at 0°C for 55 min under argon atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (×2), and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (25% ether in hexane) to afford **26** (180 mg, 93%) as a dark-red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (9H, s, *tert*-Bu), 1.05 (9H, s, *tert*-Bu), 1.76 (1H, ddd, J=15.0, 11.0, 2.0 Hz, H-50a), 2.15 (1H, ddd, J=15.0, 11.0, 2.0 Hz, H-50b), 2.96 (1H, dd, J=10.0, 8.0 Hz, H-40), 3.24 (1H, dd, J=10.0, 7.0 Hz, CH_2SO_2Ph), 3.31 (1H, dd, J=9.0, 4.0 Hz, H-45), 3.38 (1H, dd, J=10.0, 5.5 Hz, H-40), 3.44 (1H, dd, J=10.0, 6.0 Hz, H-CH_2SO_2Ph), 3.62 (1H, ddd, J=8.0, 5.0, 2.5 Hz, H-41), 3.74–3.78 (2H, m, H-52×2), 3.81–3.86 (1H, m, H-51), 3.94–4.23 (2H, m, H-44, H-46), 4.43 (1H, d, J=12.0 Hz, OCH_2Ph), 4.65 (1H, dd, J=10.5, 2.0 Hz, H-49), 4.73 (1H, d, J=12.0 Hz, OCH_2Ph), 7.24–7.82 (25H, m, Ph×5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 39.7, 42.6, 59.7, 65.7, 66.0, 72.3, 75.3, 75.5, 77.2, 78.3, 78.4, 96.9, 103.3, 127.7, 127.8, 127.9, 127.9, 128.1, 128.3, 128.5, 129.1, 129.7, 129.9, 133.3, 133.4, 133.6, 135.6, 135.7, 138.9, 140.0, 198.8. HRMS (FAB) calcd for $C_{65}H_{66}O_{13}Co_2SSi_2$: 1260.2430 ($M^+$); found: 1260.2419.

Acetic acid 2-benzyloxy-3-[2-(*tert*-butyldiphenylsilyloxymethyl)-9-methyl-4a,6,9,9a-tetrahydro-2H-1,5-dioxabenzocyclohepten-6-yl]-propyl ester (27). To a solution of **26** (70 mg, 0.057 mmol) in toluene (3 mL) was added *n*-Bu_3SnH (0.15 mL, 0.57 mmol), and the reaction mixture was heated at 55°C for 2 h. The color of solution changed from dark-red to yellow during this period. The solvent was evaporated, and the residue was purified by silica gel flash chromatography (hexane→25% ether in hexane) to afford a olefin intermediate (50 mg, 90%) as a colorless oil.

To a solution of the olefin intermediate (30 mg, 0.024 mmol) in MeOH (0.5 mL) was added 5% sodium amalgam (110 mg, 0.24 mmol). The mixture was stirred at room temperature overnight. The resulting mixture was filtered through Supper Cell and concentrated. The residue was purified by silica gel chromatography (ether/hexane=1:10) to afford **27** (20 mg, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 1.07 (9H, s, *tert*-Bu), 1.20 (3H, d, J=7.0 Hz, Me), 1.71 (2H, dt, J=9.5, 3.5 Hz, H-50×2), 2.45 (1H, m, H-46), 2.88 (1H, dd, J=8.5, 8.0 Hz, H-45), 3.61 (1H, dd, J=10.0, 5.2 Hz, H-40a), 3.69–3.76 (4H, m, H-44, H-52×2, H-40b), 3.84 (1H, m, H-51), 4.15–4.21 (2H, m, H-41, H-49), 4.50 (1H, d, J=11.5 Hz, $PhCH_2O$), 4.78 (1H, d, J=11.5 Hz, $PhCH_2O$), 5.43 (1H, dt, J=12.0, 2.5 Hz, H-47), 5.52 (1H, dt, J=12.0, 2.5 Hz, H-48), 5.59 (1H, dt, J=10.2, 2.0 Hz, H-43), 5.82 (1H, dt, J=10.2, 1.5 Hz, H-42), 7.30–7.72 (25H, m, Ph×5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 19.1, 26.7, 26.8, 38.9, 66.5, 66.9, 72.8, 74.4, 75.6, 76.2, 78.0, 79.6, 127.7, 128.1, 128.5, 129.7, 133.6, 133.7, 134.2, 134.8, 135.7, 138.9. Anal. calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.43; H, 7.28.

Acetic acid 6-(3-acetoxy-2-benzyloxypropyl)-9-methyl-4a,6,9,9a-tetrahydro-2H-1,5-dioxabenzocyclohepten-2-ylmethyl ester (28). A solution of **27** (15 mg, 0.02 mmol) in THF (0.5 mL) was treated with TBAF (1.0 M in THF, 0.02 mL) at room temperature for 1 h. The mixture was concentrated and the residue was purified by silica gel (ether/hexane=10:1, R_f=0.19) to afford diol intermediate (6.6 mg, 98%). The diol was dissolved in CH_2Cl_2 (0.3 mL) and treated with Ac_2O (0.1 mL), and pyridine (0.15 mL) at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with 1 N HCl, saturated $NaHCO_3$ (×3) and brine. Concentration of the solvent and the residue was purified by silica gel chromatography (ether/hexane=1:1, R_f=0.15) to afford **28** (8.1 mg, 100%) as a colorless oil. $[\alpha]_D^{25}=-103.7$ (c 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J=7.0 Hz, Me), 1.75 (2H, dt, J=9.8, 4.0 Hz, H-50×2), 2.08 (3H, s, MeCO), 2.10 (3H, s, MeCO), 2.49 (1H, m, H-46), 2.89 (1H, dd, J=9.2, 8.5 Hz, H-45), 3.74 (1H, ddd, J=9.2, 3.5, 1.5 Hz, H-44), 3.92 (1H, J=12.5, 4.8 Hz, H-51), 4.05–4.13 (3H, m, H-52a, H-40×2), 4.21 (1H, ddd, J=10, 5, 3 Hz, H-49), 4.28 (1H, m, H-41), 4.31 (1H, dd, J=12.0, 4.2 Hz, H-52b), 4.51 (1H, d, J=11.8 Hz, $PhCH_2O$), 4.73 (1H, d, J=11.8 Hz, $PhCH_2O$), 5.45 (1H, dt, J=12.0, 2.4 Hz, H-47), 5.55 (1H, dt, J=12.0, 3.0 Hz, H-48), 5.64 (1H, d, J=10 Hz, CH=CH), 5.68 (1H, d, J=10 Hz, CH=CH), 7.28–7.36 (5H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 20.9, 29.7, 38.9, 39.3, 65.9, 66.1, 72.4, 73.1, 74.3, 77.6, 79.7, 126.9, 127.9, 128.1, 128.5, 130.8, 133.7, 134.9, 138.2, 170.8, 170.9. HRMS (EI): calcd for $C_{25}H_{33}O_7$: m/z 445.2148 (M+H), found: 445.2131.

3-[1-Benzenesulfonylmethyl-6-benzyloxy-7-(*tert*-butyldiphenylsilyloxy)-4-methoxyhept-2-ynyl]-6-methyldodecahydro-4,8,12-trioxadibenzo[a,d]cycloocten-2-ol (29). A solution of acetylene **23** (128 mg, 0.27 mmol) in THF (1 mL) was cooled to 0°C and treated with *n*-BuLi (1.5 M in hexane, 0.15 mL, 0.22 mmol) for 15 min. A solution of compound **21** (34 mg, 0.054 mmol) in THF (0.7 mL) was added dropwise to the reaction mixture at 0°C. After stirring for 20 min, the mixture was poured into a cold saturated NH_4Cl solution, and extracted with CH_2Cl_2 (×3), dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (0.5 mL) and treated with TBAF (1.0 M in THF, 0.05 mL) at 0°C for 5 min. The reaction mixture was poured into sat. $NaHCO_3$ solution, extracted with CH_2Cl_2 (×3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (ether/hexane=3:1) to afford **29** (47 mg, 92%) as a white solid. Mp: 131–133°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, d, J=7.0 Hz, Me), 1.07 (9H, s, *tert*-Bu), 1.38–1.47 (5H, m, H-35, H-38, H-40a, H-43, H-50a), 1.57–1.64 (2H, m, H-34×2), 1.72–1.83 (4H, m, H-38, H-39, H-40b, H-50b), 1.95–2.01 (1H, m, H-35), 2.29 (1H, m, H-43), 2.41 (1H, d, J=6.0 Hz, OH), 2.91 (1H, dt, J=10, 3 Hz, H-37), 3.01–3.08 (2H, m, H-36, H-41), 3.10–3.14 (3H, m, H-42, H-44, H-51), 3.19 (total 3H, two s, OMe), 3.26 (1H, m, H-33), 3.39 (1H, dd, J=10.2, 4.0 Hz, CH_2SO_2Ph), 3.49 (1H, dd, J=10.2, 6.8 Hz, CH_2SO_2Ph), 3.63–3.75 (3H, m, H-45, H-52×2), 3.81 (1H, br d, J=11.8 Hz, H-33), 3.96 (1H, dd, J=9.8, 3.5 Hz, H-49), 4.45 (1H, d, J=12.0 Hz, $PhCH_2O$), 4.71 (1H, d, J=12.0 Hz, $PhCH_2O$), 7.30–7.92 (20H, m, Ph×4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.3, 25.9, 26.9, 27.7, 28.8, 29.7, 32.8, 38.6, 41.7, 45.2, 46.2, 56.1, 57.4, 66.6, 67.2, 67.3, 67.5, 72.7, 75.9, 80.4, 81.0, 81.5, 81.7, 82.4, 83.6, 84.6, 127.6, 127.7, 127.9, 128.1, 128.4, 129.3, 129.7, 133.5, 135.7, 138.8, 139.7. Anal. calcd for $C_{52}H_{66}O_8SSi$: C, 71.03; H, 7.57. Found: C 69.96; H, 7.64.

Compound (30). To a solution of **29** (42 mg, 0.048 mmol) in degassed CH_2Cl_2 (2 mL) was added a solution of biscobaltoctacarbonyl (30 mg, 0.086 mmol) in degassed CH_2Cl_2 (0.5 mL) at 0°C. After stirring at room temperature for 1 h, the mixture was concentrated and the residue was purified by silica gel chromatography (ether/hexane=1:2) to afford cobalt complex **30** (49 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, J=7.0 Hz, Me), 1.26–1.35 (3H, m, H-35a, H-38a, H-40a), 1.36–1.44 (1H, m, H-50a), 1.45–1.55 (2H, m, H-43a, H-50b), 1.56–1.62 (2H, m, H-34×2), 1.69–1.84 (3H, m, H-38b, H-40b, H-39), 1.95–2.03 (2H, m, H-35b, H-43b), 2.80 (1H, td, J=10.0, 2.6 Hz, H-37), 2.91 (1H, td, J=10.0, 4.5 Hz, H-36), 2.98 (1H, m, H-45), 3.05 (1H, td, J=10.0, 5.0 Hz, H-42), 3.29 (2H, m, H-41, CH_2SO_2Ph), 3.37 (1H, dd, J=9, 3 Hz, H-33a), 3.44 (3H, s, OMe), 3.68 (1H, dd, J=11, 5 Hz, H-52a), 3.76 (1H, dd, J=11, 3 Hz, H-52b), 3.81–3.86 (4H, m, H-33b, H-44, H-46, H-51), 4.04 (1H, dd, J=15, 10 Hz, CH_2SO_2Ph), 4.40 (1H, d, J=11.2 Hz, OCH_2Ph), 4.55 (1H, d, J=10 Hz, H-49), 4.86 (1H, d, J=11.2 Hz, OCH_2Ph), 7.36–7.91 (20H, m, Ph×4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.1, 22.6, 26.1, 26.7, 27.4, 28.1, 31.5, 32.7, 37.0, 41.3, 42.5, 45.4, 45.9, 59.1, 59.8, 65.1, 67.5, 73.3, 77.6, 79.0, 80.5, 81.2, 82.2, 84.8, 95.1, 98.5, 128.0, 128.2, 128.5, 128.8, 129.1, 129.4, 129.9, 133.2, 135.7, 137.7, 139.3, 199.5, 200.5.

Compound (31). A solution of **30** (46 mg, 0.039 mmol) in degassed CH_2Cl_2 (4 mL) was treated with a solution of 0.16 M $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0°C for 50 min under argon atmosphere. The reaction mixture was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (×2), and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (33% ether in hexane) to afford

31 (36 mg, 81%) as a dark-red solid. Mp: 136–138°C. $[\alpha]_D^{25}=-209.9$ (*c* 0.19, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, *J*=7 Hz, Me), 1.06 (9H, s, *tert*-Bu), 1.21 (2H, m, H-35a, H-38a), 1.37 (2H, m, H-40a, H-43a), 1.55 (1H, dd, *J*=14, 4 Hz, H-38b), 1.64 (2H, m, H-34×2), 1.78 (2H, m, H-35b, H-39), 1.92 (2H, m, H-40b, H-50a), 2.00 (1H, td, *J*=10, 5 Hz, H-43b), 2.24 (1H, ddd, *J*=15, 7.5, 4 Hz, H-50b), 2.69 (1H, t, *J*=9 Hz, H-45), 2.89 (1H, td, *J*=10, 5.5 Hz, H-37), 2.98 (2H, m, H-41, H-42), 3.03 (1H, td, *J*=10, 5 Hz, H-36), 3.13 (1H, ddd, *J*=11, 9, 5 Hz, H-44), 3.25 (1H, ddd, *J*=14, 7, 5 Hz, H-33a), 3.29 (1H, td, *J*=9, 1.5 Hz, H-46), 3.38 (1H, dd, *J*=14, 8 Hz, CH_2SO_2Ph), 3.83 (4H, m, H-33b, H-51, H-52×2), 3.91 (1H, dd, *J*=14, 1.8 Hz, CH_2SO_2Ph), 4.56 (1H, dd, *J*=9.5, 4.5 Hz, H-49), 4.59 (1H, d, *J*=12 Hz, $PhCH_2O$), 4.64 (1H, d, *J*=12 Hz, $PhCH_2O$), 7.30–7.68 (20H, m, Ph×4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 22.7, 26.0, 26.9, 27.5. 28.1, 31.6, 32.8, 38.9, 40.4, 42.9, 45.4, 46.1, 60.7, 66.0, 67.5, 71.6, 78.0, 80.5, 80.7, 82.0, 82.2, 84.7, 97.5, 103.4, 127.5, 127.6, 127.7, 128.1, 128.3, 129.2, 129.7, 133.4, 133.7, 135.7, 138.8, 140.4, 198.7, 199.4. HRMS (FAB) calcd for $C_{57}H_{62}Co_2O_{13}SSi$ (M^+): *m/z* 1132.2344; found: 1132.2329.

Compound (32). To a solution of **31** (30 mg, 0.027 mmol) in toluene (1.5 mL) was added *n*-Bu_3SnH (0.075 mL, 0.27 mmol), and the reaction mixture was heated at 55°C for 2 h. The color of solution changed from dark-red to yellow during this period. The solvent was evaporated and the residue was purified by silica gel flash chromatography (hexane then 33% ether in hexane) to afford an olefin intermediate (21 mg, 94%) as a colorless oil.

To a solution of the olefin intermediate (15 mg, 0.018 mmol) in MeOH (0.3 mL) was added 5% sodium amalgam (61 mg, 0.18 mmol as sodium). The mixture was stirred at room temperature for 2 h. The resulting mixture was filtered through a short silica gel pad, washed with ether, and the combined filtrate was concentrated. The residue was purified by silica gel chromatography (ether/hexane=1:3) to afford **32** (12.2 mg, 98%) as white solid. Mp: 149–151°C. $[\alpha]_D^{23}=+11.4$ (*c* 0.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, *J*=7.0 Hz, Me), 1.06 (9H, s, *tert*-Bu), 1.15 (3H, d, *J*=7.0 Hz, Me), 1.43–1.54 (4H, m, H-35a, H-38a, H-40a, H-43a), 1.60–1.64 (3H, m, H-34×2, H-50a), 1.78–1.91 (4H, m, H-50b, H-38b, H-40b, H-39), 1.98 (1H, br d, *J*=12.5 Hz, H-35b), 2.11 (1H, dt, *J*=12.0, 4.8 Hz, H-43b), 2.41 (1H, m, H-46), 2.59 (1H, t, *J*=9.0 Hz, H-45), 3.00–3.08 (3H, m, H-36, H-37, H-41), 3.17 (1H, dt, *J*=9.0, 5.0 Hz, H-42), 3.22 (1H, dt, *J*=9.0, 5.0 Hz, H-44), 3.29 (1H, dt, *J*=11.0, 4.0 Hz, H-33a), 3.62 (1H, td, *J*=6.0, 4.0 Hz, H-41), 3.72 (1H, dd, *J*=10.5, 4.0 Hz, H-52a), 3.80 (1H, dd, *J*=10.5, 6.0 Hz, H-52b), 3.84 (1H, br d, *J*=11 Hz, H-33b), 4.04 (1H, m, H-49), 4.49 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 4.62 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 5.42 (1H, ddd, *J*=11.0, 3.5, 2.0 Hz, H-47), 5.66 (1H, ddd, *J*=11.0, 7.0, 2.5 Hz, H-48), 7.28–7.71 (15H, m, Ph×3). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.7, 19.1, 25.9, 26.8, 27.6, 28.1, 32.7, 38.0, 40.7, 45.7, 46.3, 66.2, 67.5, 71.8, 73.8, 80.6, 80.9, 81.5, 82.0, 83.6, 84.8, 127.5, 127.7, 127.9, 128.3, 129.7, 133.6, 135.3, 135.7, 136.8, 138.9. HRMS (FAB) calcd for $C_{45}H_{60}Co_2O_6Si$ (M^+): *m/z* 724.4159; found: 724.4145.

Compound (33). A solution of **32** (12 mg, 16.9 mmol) in THF (0.2 mL) was treated with TBAF (1.0 M in THF, 17 mL, 17 mmol) at room temperature for 30 min. The resulting mixture was concentrated and the residue was purified by silica gel chromatography (ether/hexane=4:1) to afford 7.9 mg of the corresponding alcohol (97%). The alcohol was dissolved in CH_2Cl_2 (0.3 mL), to this solution was added acetic anhydride (0.05 mL), pyridine (0.07 mL) and DMAP (1 mg), and the mixture was stirred at room temperature for 10 min. The resulting mixture was diluted with CH_2Cl_2 (10 mL), washed with 1 N HCl aqueous solution and saturated $NaHCO_3$ solution (×3), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (ether/hexane=2:3) to afford **33** (8.6 mg, 98%) as a colorless oil. $[\alpha]_D^{23}=+33.5$ (*c* 0.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, d, *J*=7.0 Hz, Me), 1.16 (3H, d, *J*=7.0 Hz, Me), 1.49 (1H, m, H-35a), 1.52–1.61 (3H, m, H-40a, H-38a, H-43a), 1.64 (2H, m, H-34×2), 1.74 (1H, ddd, *J*=12.0, 6.5, 5.0 Hz, H-50a), 1.85 (2H, m, H-40b, H-38b), 1.91 (1H, m, H-39), 1.98 (1H, dt, *J*=12, 6 Hz, H-50b), 2.02 (1H, m, H-35b), 2.07 (3H, s, Ac), 2.23 (1H, dt, *J*=12.5, 5.0 Hz, H-43b), 2.44 (1H, ddd, *J*=9, 7, 4 Hz, H-46), 2.63 (1H, t, *J*=9.2 Hz, H-45), 3.03 (1H, ddd, *J*=9.0, 3.5, 2.0 Hz, H-41), 3.08 (1H, m, H-37), 3.13 (1H, dt, *J*=9.5, 4.8 Hz, H-36), 3.22 (1H, ddd, *J*=9.0, 7.0, 4.8 Hz, H-42), 3.28 (1H, m, H-33a), 3.33 (1H, dt, *J*=9.0, 4.8 Hz, H-45), 3.75 (1H, ddd, *J*=12.0, 5.8, 3.5 Hz, H-51), 3.83 (1H, br d, *J*=11.5 Hz, H-33b), 4.07 (1H, m, H-51), 4.12 (1H, dd, *J*=12.0, 6.0 Hz, H-52a), 4.26 (1H, dd, *J*=12.0, 3.5 Hz, H-52b), 4.54 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 4.59 (1H, d, *J*=12.0 Hz, $PhCH_2O$), 5.45 (1H, ddd, *J*=11.0, 3.2, 2.2 Hz, H-47), 5.65 (1H, ddd, *J*=11.0, 4.0, 2.8 Hz, H-48), 7.33 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 21.0, 26.0, 27.7, 28.2, 32.9, 37.6, 38.3, 40.8, 45.7, 46.4, 65.9, 67.5, 71.6, 73.5, 80.7, 81.0, 81.4, 81.9, 83.6, 84.8, 127.7, 128.0, 128.4, 134.6, 136.9, 138.2, 171.0. HRMS (FAB) calcd for $C_{31}H_{45}O_7$: 529.3087 (M+H); found: 529.3076.

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References

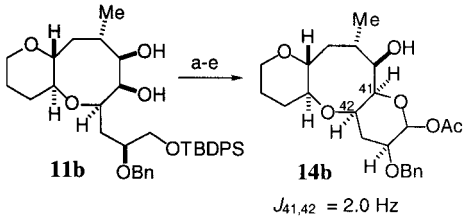
1. Gillespie, N. C.; Lewis, R. J.; Pearn, J.; Bourke, A. T. C.; Helms, M. J.; Bourke, J. B.; Shields, W. J. *Med. J. Aust.* **1986**, *145*, 584–590.

2. Yasumoto, Y.; Nakajima, R.; Bagnis, R.; Adachi, R. *Nippon Suisan Gakkaishi* **1977**, *43*, 1021–1023.

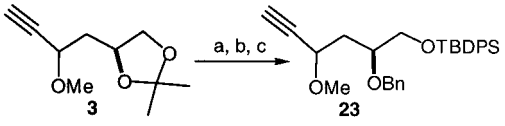
3. (a) Lombert, A.; Bidard, J.-N.; Lazdunski, M. *FEBS Lett.* **1987**, *219*, 355–359. (b) Lewis, R. J.; Sellin, M.; Poli, M. A.; Norton, R. S.; Macleod, J. K.; Sheil, M. M. *Toxicon* **1991**, *29*, 1115–1127.

4. (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Ergon D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*,

6773–6776; (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514–518.
5. (a) For recent reviews on ciguatoxin and related marine toxins, see: (i) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909; (ii) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3–18. (b) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929–8931. (c) Oguri, H.; Hishayama, S.; Sato. O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* **1997**, *53*, 3057–3072.
6. (a) Scheuer, P. J.; Takahashi, W; Tsutsumi, J.; Yoshida, T. *Science* **1967**, *155*, 1267–1268. (b) Tachibana, K. PhD thesis, University of Hawaii, 1980.
7. (a) Murata, M.; Legrand, A. M.; Yasumoto, T. *Tetrahedron Lett.* **1989**, *30*, 3793–3794. (b) Murata, M.; Legrand, A. M.; Scheuer, P. J.; Yasumoto, T. *Tetrahedron Lett.* **1992**, *33*, 525–526.
8. Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *111*, 11325–11326.
9. For recent synthetic studies from other groups, see: (a) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337–1340. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075–1077. (c) Sasaki, M.; Noguchi, T.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425–1428. (d) Oguri, H.; Sakaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405–5408. (e) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063–1064. (f) Oishi, T.; Nagumo, Y.; Shoji, M.; Brazidec, J.-Y. L.; Uehara, H.; Hirama, M. *Chem. Commun.* **1999**, 2035–2036. (g) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1–20. (h) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21–44.
10. (a) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, *11*, 916–918. (b) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509–2520. (c) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, 473–474. (d) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37–48. (e) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911–1914. (f) For a review, see: Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665–2676.
11. (a) Isobe, M.; Jiang, Y. *Tetrahedron Lett.* **1995**, *36*, 567–570. (b) Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767–4776. (c) Tsuboi, K.; Ichikawa, Y.; Isobe, M. *Synlett* **1997**, *6*, 713–715.
12. (a) Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052–3054. (b) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749–8757.
13. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2483.
14. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169–2173.
15. Liu, T.-Z.; Li, J.-M.; Isobe, M. *Tetrahedron* **2000**, Submitted for publication.
16. (a) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *37*, 3475–3478. (b) Cusack, N. J.; Reese, C. B.; Roozpeikar, B. *Chem. Commun.* **1972**, 1132–1133. (c) Cusack, N. J.; Reese, C. B.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157–2162.
17. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2447–2455. (b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
18. Diol **11b** was converted to **14b** through the following steps:



Reagents, conditions and yields: (a) Acetone, TsOH (Cat.), rt, 93%; (b) TBAF, THF, rt, 89%; (c) DMSO, SO_3·Py, Et_3N, 89%; (d) 80% aqueous AcOH, rt, 91%; (e) Ac_2O, Et_3N, CH_2Cl_2, 100%.
19. Rasmussen, J. R. *J. Org. Chem.* **1980**, *45*, 2725–2727.
20. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.
21. Liu, T.-Z.; Isobe, M. *Synlett* **2000**, *2*, 266–268.
22. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
23. (a) Jiang, Y.; Isobe, M. *Tetrahedron* **1996**, *52*, 2877–2892. (b) Isobe, M.; Nishizawa, R.; Nishikawa, T.; Yoza, K. *Tetrahedron Lett.* **1999**, *40*, 6927–6932.
24. Kirschbaum, B.; Isobe, M. Unpublished results.
25. Isobe, M.; Funabashi, Y.; Ichikawa, Y.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 2021–2024.
26. Compound **23** was synthesized as follows:



Reagents, conditions and yields: (a) MeOH, TsOH, rt, 93%; (b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 85%; (c) NaH, BnBr, DMF, 0°C, 89%.
27. (a) See ref. 10(c). (b) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609–2612. (c) See ref. 10(b).
28. Hosokawa, S.; Isobe, M. *Synlett* **1995**, *12*, 1179–1180.