Tetrahedron xxx (2015) 1–15

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Concise synthesis of the C15–C38 fragment of okadaic acid, a specific inhibitor of protein phosphatases 1 and 2A

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ARTICLE INFO

Article history:
Received 25 February 2015
Received in revised form 31 March 2015
Accepted 1 April 2015
Available online xxx

This paper is dedicated to Professor Jiro Tsuji on the occasion of his receiving the 2014 Tetrahedron Prize for Creativity in Organic Chemistry

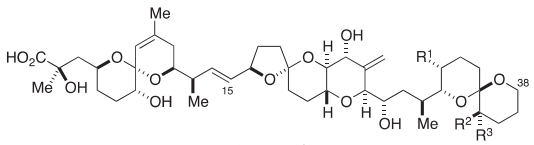
Keywords:
Marine toxins
Polyethers
Spiroacetals
Suzuki–Miyaura coupling
Anomeric sulfones

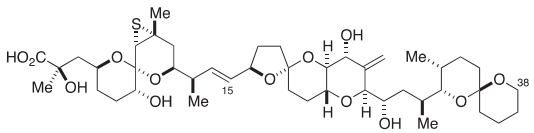
ABSTRACT

A marine polyether natural product okadaic acid is known to be a potent and specific inhibitor of protein phosphatases 1 and 2A. Herein, concise synthesis of the C15–C38 fragment of okadaic acid is reported. We investigated two different strategies for the construction of two spiroacetal substructures found in the target compound. The first strategy involved Suzuki–Miyaura coupling for the synthesis of endocyclic enol ethers and subsequent spiroacetalization. The second strategy exploited Suzuki–Miyaura coupling for the synthesis of *exo*-olefins as the precursor of spiroacetals. An alkynylaluminum–anomeric sulfone coupling effectively assembled the key spiroacetal substructures and completed the target compound.

1. Introduction

Okadaic acid (**1**, Fig. 1) was first isolated from the marine sponges *Halichondria okadai* and *Halichondria melanodocia*,[1] and subsequently discovered from the marine dinoflagellates *Prorocentrum lima* and *Dinophysis fortii* as a toxic constituent.[2] The complex structure of okadaic acid was established on the basis of an X-ray crystallographic analysis of the corresponding *o*-bromobenzyl ester.[1] A number of natural congeners of okadaic acid, including dinophysistoxin-1 (**2**)[3] and -2 (**3**),[4] and acanthifolicin (**4**),[5] have been identified so far. It is now considered that okadaic acid would be the secondary metabolite of symbiotic microorganisms.[6] It is known that okadaic acid and its congeners accumulate in shellfish and are responsible for diarrhetic shellfish poisoning.[7] Okadaic acid exhibits a wide range of biological activities, including tumor-promoting activity,[8] apoptosis-inducing activity,[9] and most notably, highly potent and specific inhibitory activity against protein phosphatases 1 and 2A (PP1 and PP2A, respectively).[10] PP1 and PP2A are known to dephosphorylate serine and threonine residues of proteins and play significant roles in controlling the phosphorylation level and activity of many proteins.[11] Thus, okadaic acid has





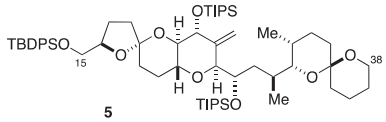


Fig. 1. Structures of okadaic acid (**1**), dinophysistoxin-1 (**2**), dinophysistoxin-2 (**3**), acanthifolicin (**4**), and the C15–C38 fragment **5** of okadaic acid.

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http://dx.doi.org/10.1016/j.tet.2015.04.001
0040-4020/

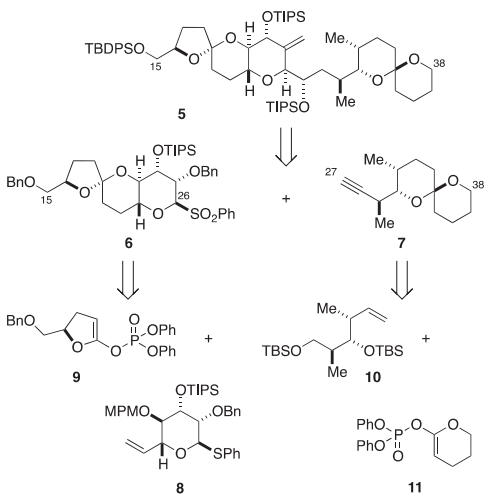
been widely utilized in cell biology as a potent and specific PP1/PP2A inhibitor, and its cellular effect has been investigated in several cell models.[12] James and co-workers have reported the crystallographic structure of okadaic acid bound to PP1 at a resolution of 1.9 Å.[13] Subsequently, Shi and colleagues have disclosed the X-ray crystallographic analysis of a co-crystal of okadaic acid and PP2A at 2.6 Å resolution.[14] These studies have established the binding mode of okadaic acid to PP1 and PP2A at the atomic level. Recent studies by Konoki et al. have identified new specific targets, okadaic acid-binding proteins (OABPs), from *H. okadai*, although their exact physiological role awaits elucidation.[15] Quite recently, a synthetic derivative of okadaic acid has been shown to display selective cytotoxicity against undifferentiated human pluripotent stem cells, where the different expression pattern of ATP-binding cassette (ABC) transporters between differentiated cells and pluripotent stem cells is responsible for the selectivity.[16]

The structure–activity relationship (SAR) of okadaic acid with respect to PP1/PP2A inhibitory activity has been investigated mainly by evaluating natural congeners and their derivatives.[17] The Isobe,[18] Forsyth,[19] and Ley[20] groups have independently achieved the total synthesis of okadaic acid, enabling the assessment of the PP1/PP2A inhibitory activity of selected synthetic compounds.[21] In contrast, neither the structural elements required for binding to OABPs nor those crucial for ABC transporter selectivity have not been investigated in detail. To help elucidate the SAR of okadaic acid, we embarked on the development of a concise synthetic entry to okadaic acid and its analogs. Herein, we report in detail our synthetic studies on the C15–C38 fragment **5** (Fig. 1) of okadaic acid.[22]

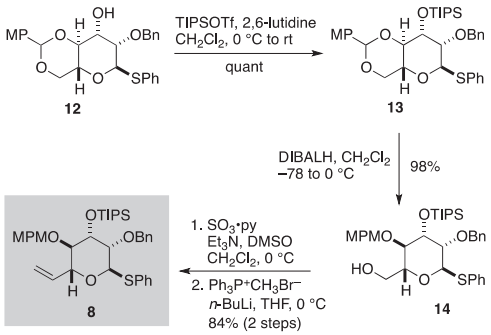
2. Results and discussion

2.1. Initial synthesis plan

The C15–C38 fragment **5**, the target compound of this study, would be derived from the sulfone **6** and the alkyne **7**[20] by considering an alkynylaluminum–anomeric sulfone coupling (Scheme 1). This strategy originally developed by the Ley group[20] should allow for a convergent and flexible access to the target compound **5** and its analogs. On the basis of our previous experience on spiroacetal synthesis,[23] we initially envisioned that **6** could be synthesized from the olefin **8** and the enol phosphate **9** (or its acyclic equivalent)[24] via a Suzuki–Miyaura coupling[25] and a spiroacetalization.[26] Likewise, **7** would be obtainable from the olefin **10** and the enol phosphate **11**.



Scheme 1. Initial synthesis plan toward **5**.



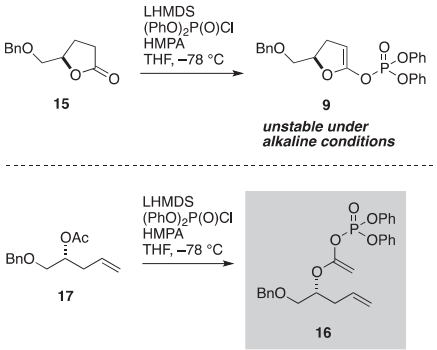
Scheme 2. Synthesis of olefin **8**.

2.2. Synthesis of olefin 8

The synthesis of the olefin **8** commenced with silylation of the alcohol **12**,[27] leading to the silyl ether **13** (Scheme 2). Regioselective reductive opening of the *p*-methoxybenzylidene acetal with DIBALH[28] delivered the alcohol **14**, which was oxidized[29] and then methylenated to afford the olefin **8**.

2.3. Synthesis of enol phosphates 9 and 16

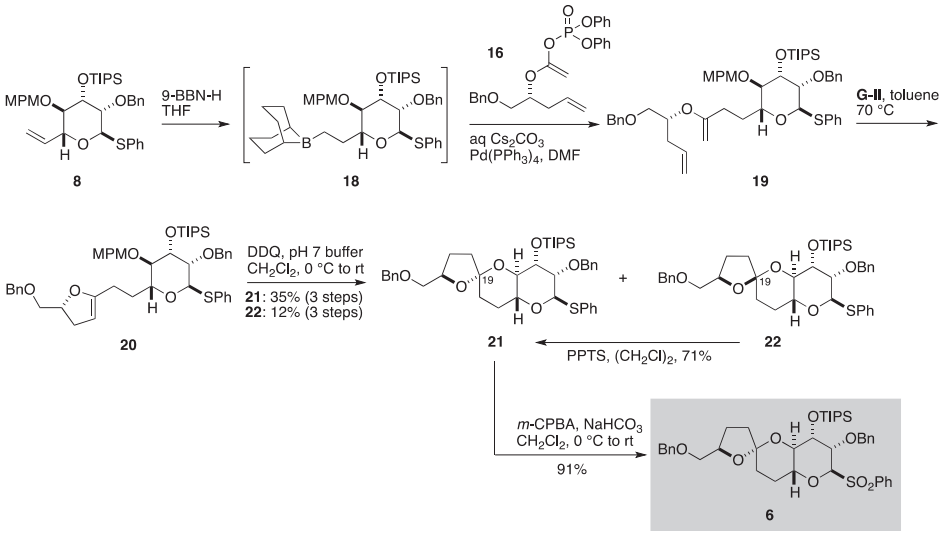
Next, we prepared the enol phosphate **9** from the lactone **15**[30] (Scheme 3). Treatment of **15** with LHMDS and $(PhO)_2P(O)Cl$[31] delivered the enol phosphate **9**. However, it was found that this compound readily underwent hydrolysis to give the lactone **15** under alkaline conditions and could not be used as an electrophile in Suzuki–Miyaura coupling.[25] This disappointing outcome prompted us to use the acyclic counterpart **16**.[23a] Exposure of the acetate **17**[32] to LHMDS in the presence of $(PhO)_2P(O)Cl$[31] delivered the enol phosphate **16**.



Scheme 3. Synthesis of enol phosphates **9** and **16**.

2.4. Synthesis of sulfone 6

The olefin **8** was reacted with 9-BBN-H to generate the alkylborane **18**, which was coupled with the enol phosphate **16** (prepared from 1.8 equiv of the acetate **17**, Scheme 3) under the influence of $Pd(PPh_3)_4$ and aqueous Cs_2CO_3 in DMF at room temperature to afford the diene **19** (Scheme 4). This was exposed to the second-generation Grubbs catalyst (**G-II**)[33] in toluene at 70 °C to provide the endocyclic enol ether **20**. Since **20** was quite sensitive to silica gel and too unstable to be isolated, it has to be immediately used in the next step without any purification. Finally, removal of the MPM group with DDQ and spontaneous spiroacetalization furnished the spiroacetal **21** (35% overall yield from **8**), along with its C19 diastereomer **22** (12% overall yield from **8**). Isomerization of **22** under mild acidic conditions provided additional **21**. The



Scheme 4. Synthesis of sulfone **6**.

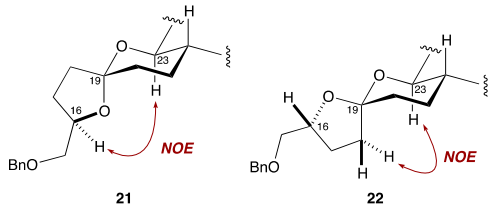
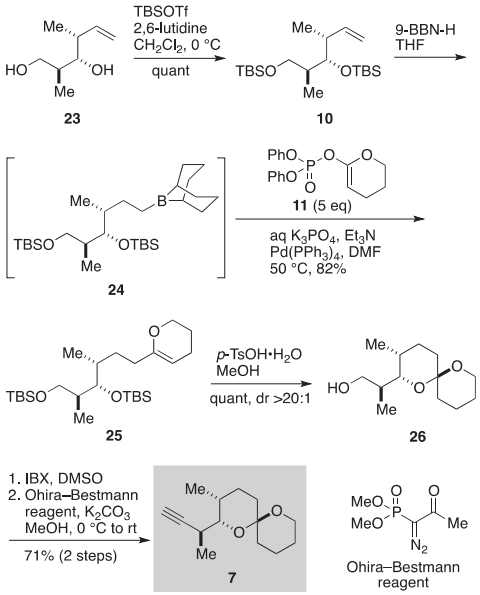


Fig. 2. Stereochemical analysis on **21** and **22**.

stereostructures of **21** and **22** were determined on the basis of NOE experiments, as shown in Fig. 2. Finally, oxidation of **21** with *m*-CPBA afforded the sulfone **6** in 91% yield.

2.5. Synthesis of alkyne 7 via spiroacetalization of endocyclic enol ether 25

The synthesis of alkyne **7** started from the diol **23**,[19a] which was prepared in four steps from (*S*)-Roche ester (Scheme 5). Silylation of **23** with TBSOTf/2,6-lutidine gave the bis-silyl ether **10** quantitatively. Hydroboration of **10** with 9-BBN-H followed by coupling of the derived alkylborane **24** with the enol phosphate **11**[34] (5 equiv) in the presence of $Pd(PPh_3)_4$ and aqueous K_3PO_4 in DMF at 50 °C afforded the endocyclic enol ether **25** in 82% yield. Excess molar amounts of **11** were indispensable for achieving the optimal product yield. Exposure of **25** to acidic MeOH at room temperature resulted in desilylation and concomitant spiroacetalization to deliver the alcohol **26**[19a] quantitatively as a single stereoisomer (dr >20:1). Oxidation of **26** with *o*-iodoxybenzoic acid (IBX)[35] and subsequent alkynylation using Ohira–Bestmann reagent[36] (K_2CO_3, MeOH, 0 °C to room temperature) furnished the alkyne **7** in 71% yield (two steps).

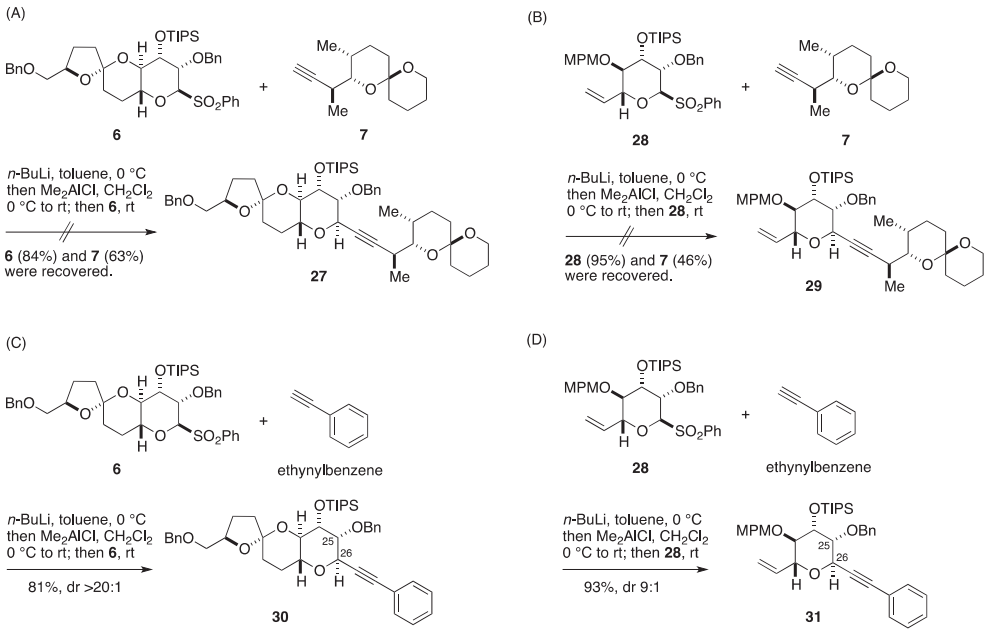


Scheme 5. Synthesis of alkyne **7** via spiroacetalization of endocyclic enol ether **25**.

2.6. Investigating alkynylaluminum–anomeric sulfone coupling

Next, we investigated the coupling of the sulfone **6** and the alkyne **7**, according to the procedure described by Ley et al.[20] (Scheme 6). Thus, deprotonation of the alkyne **7** (1.5 equiv) with *n*-BuLi (1.5 equiv, toluene, 0 °C) followed by addition of Me_2AlCl (1.5 equiv, diluted with CH_2Cl_2, 0 °C to room temperature) generated the corresponding alkynylaluminum, which was reacted with the sulfone **6** at room temperature. However, the coupling reaction did not take place at all and only returned the sulfone **6** (84%) and the alkyne **7** (63%) (Scheme 6A). The coupling of simpler sulfone **28**, prepared from **8**, with the alkyne **7** under the same conditions was also completely unsuccessful (Scheme 6B). In contrast, when we reacted the sulfone **6** with the alkynylaluminum prepared from ethynylbenzene under the same conditions, we found that the reaction proceeded smoothly to provide the coupling product **30** in 81% yield as a single stereoisomer (dr >20:1) (Scheme 6C). Similarly, coupling of **28** with ethynylbenzene was successful, giving the internal alkyne **31** in 93% yield (dr 9:1) (Scheme 6D). The configuration of the newly generated stereogenic center of **30** and **31** was determined on the basis of $^3J_{H,H}$ values, as shown in Fig. 3.

Here, we considered that the nucleophilicity of the alkynylaluminum species prepared from the alkyne **7** should be lower than that of dimethyl(2-phenylethynyl)aluminum because **7** has two Lewis basic oxygen atoms. The poor reactivity of alkynylaluminum reagents having an ether oxygen atom has been described in the



Scheme 6. Alkynylaluminum–anomeric sulfone coupling.

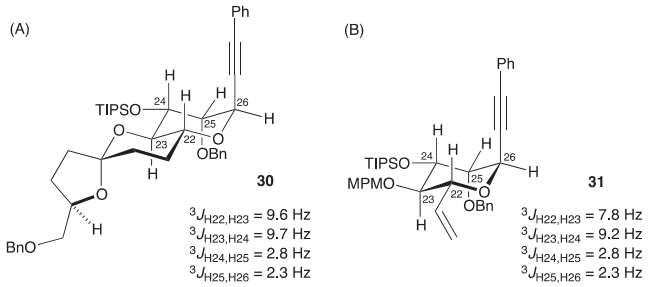


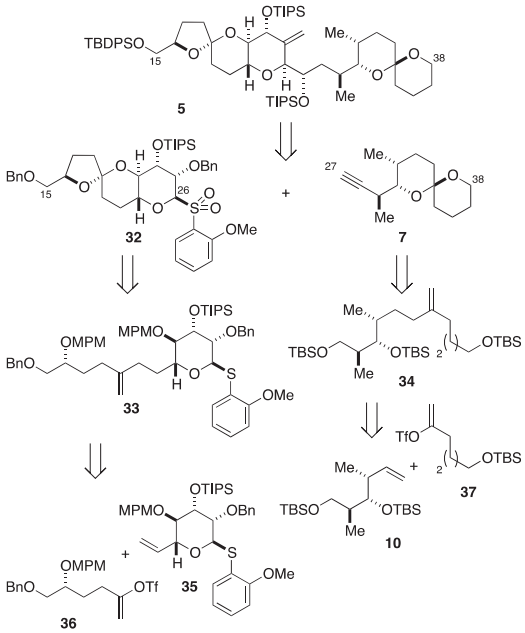
Fig. 3. (A) Stereochemical analysis on **30**. (B) Stereochemical analysis on **31**.

literature.[37] Ley et al. have overcome this problem by introducing an *ortho*-methoxy group to the sulfone benzene ring of the anomeric sulfone, thereby enhancing the coordinating ability of the sulfonyl group to incoming alkynylaluminum reagent.[38]

2.7. Revised synthesis plan

In our initial synthetic approach toward the C15–C38 fragment **5**, the two spiroacetal substructures were synthesized via Suzuki–Miyaura coupling[25] of the enol phosphates **11** and **16**. However, the low stability of **11** and **16** under alkaline conditions was rather problematic and necessitated their use in excess molar amounts. The endocyclic enol ether **20** was also found to be quite unstable and could not be isolated. The stability problem of these intermediates has turned out to be a serious drawback especially with regard to material throughput. In addition, the alkynylaluminum–anomeric sulfone coupling of **6** and **7** was completely ineffective presumably because of the low reactivity of **7** having Lewis basic oxygen atoms.

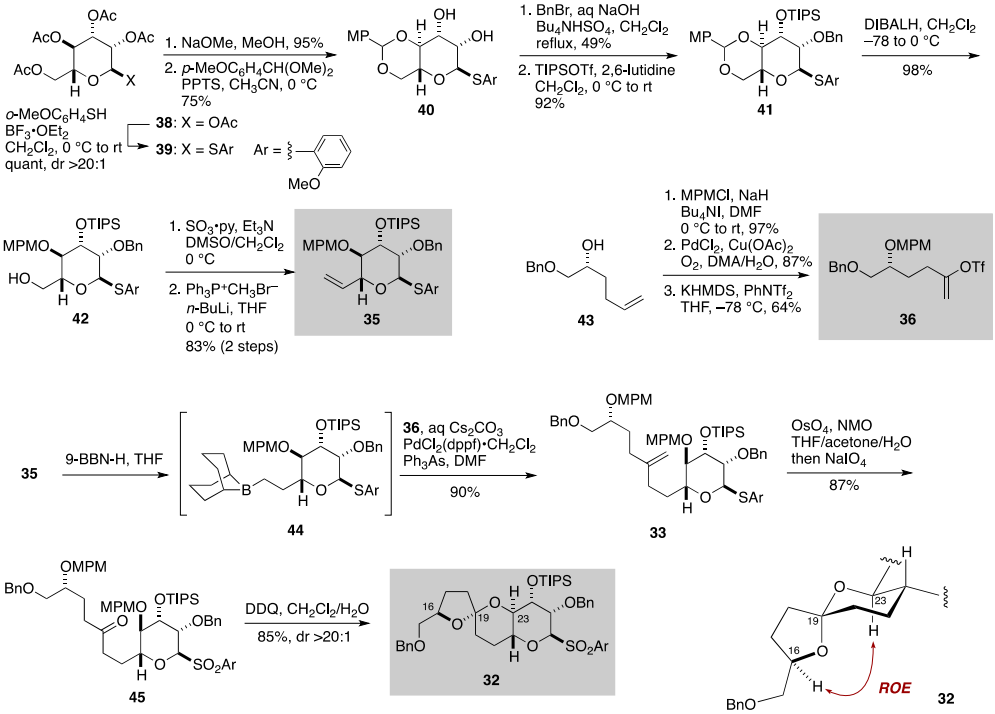
With these problems in mind, we revised our synthetic approach toward **5**, as depicted in Scheme 7. To improve the reactivity toward the alkynylaluminum species derived from **7**, we considered the *o*-methoxyphenyl counterpart of **6** as the C15–C26 sulfone (i.e., **32**). We envisioned a unified strategy for the synthesis of **32** and **7**. Given that the spiroacetal substructures are both thermodynamically favored by the virtue of anomeric effect, **32** and **7** should be easily obtainable from the respective *exo*-olefins **33** and **34** via an oxidative cleavage of the double bond followed by a spiroacetalization. The *exo*-olefin **33** could be synthesized via a Suzuki–Miyaura coupling[25] of the olefin **35** and the enol triflate **36**. The *exo*-olefin **34** could be prepared from the olefin **10** and the enol triflate **37** in the same manner.



Scheme 7. Revised synthesis plan.

2.8. Synthesis of sulfone 32

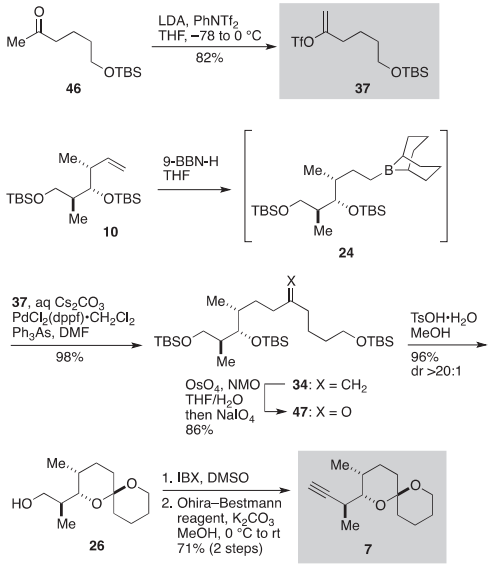
At first, the olefin **35** was synthesized from D-mannose pentaacetate (**38**) (Scheme 8). Thioglycosylation of **38** with *o*-MeOC$_6$H$_4$SH in the presence of $BF_3 \cdot OEt_2$ provided the thioglycoside **39** quantitatively (dr >20:1). After removal of the acetyl groups, the resultant tetraol was selectively protected as its *p*-methoxybenzylidene



Scheme 8. Synthesis of sulfone **32**.

acetal derivative to give the diol **40**. Selective benzylation of the axially oriented hydroxy group under phase-transfer conditions,[39] followed by silylation of the remaining alcohol, delivered the silyl ether **41**. This was elaborated to the olefin **35** in the same manner as that described for **8** (Scheme 2). Meanwhile, the enol triflate **36** was readily prepared from the alcohol **43**[40] in three steps. Protection of **43** as its MPM ether followed by Wacker oxidation[41] gave a methyl ketone, which was treated with KHMDS/$PhNTf_2$ to provide the enol triflate **36**.

Suzuki–Miyaura coupling[25] of the alkylborane **44**, derived from **35**, with the enol triflate **36** proceeded uneventfully under the influence of $PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$ and aqueous Cs_2CO_3 in DMF at room temperature[42] to afford the *exo*-olefin **33** in 90% yield. Oxidative cleavage of the double bond of **33** with concomitant oxidation of the sulfide led to the ketone **45**. Deprotection of the MPM groups with DDQ resulted in spontaneous spiroacetalization to furnish the sulfone **32** as a single stereoisomer (dr >20:1). The configuration of the C19 stereogenic center was determined on the basis of an ROE experiment, as shown. Thus, we were able to construct the spiroacetal substructure of **32** in just three steps from **35** and **36** in a highly stereocontrolled manner.



Scheme 9. Synthesis of alkyne **7** via spiroacetalization of ketone **47**.

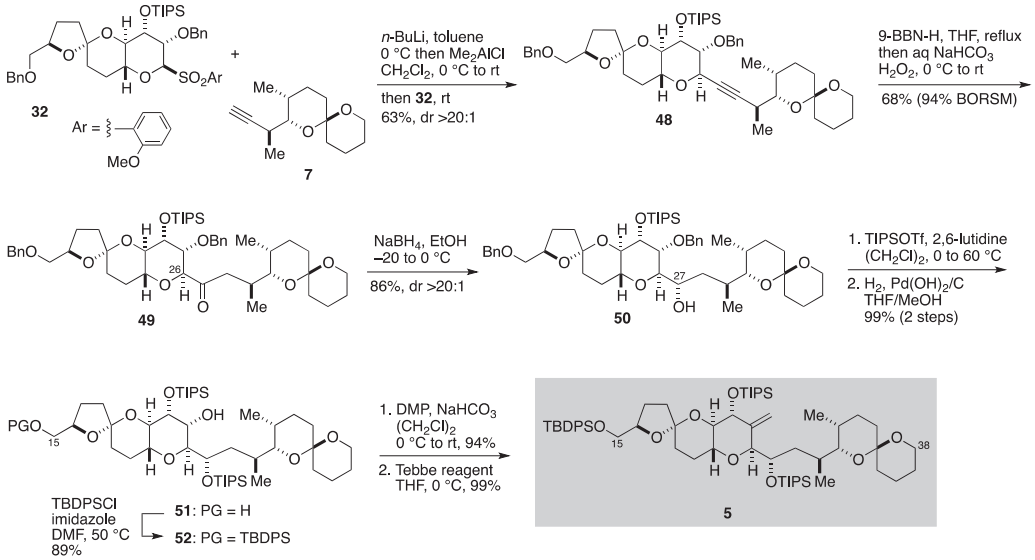
2.9. Synthesis of alkyne 7 via spiroacetalization of ketone 47

Hydroboration of the olefin **10** with 9-BBN-H followed by coupling of the resultant alkylborane **24** with the enol triflate **37** ($PdCl_2(dppf)\cdot CH_2Cl_2/Ph_3As$, aqueous Cs_2CO_3, DMF, room temperature)[42] provided the *exo*-olefin **34** (Scheme 9). The enol triflate **37** was prepared from the methyl ketone **46**[43] under standard conditions (LDA, $PhNTf_2$, THF, −78 to 0 °C). The double bond of **34** was cleaved to give the ketone **47**. Exposure of **47** to acidic methanol resulted in removal of the silyl groups and simultaneous spiroacetalization to afford the alcohol **26**[19a] as a single stereoisomer (dr >20:1). This was converted to the alkyne **7** as described above.

2.10. Completion of the synthesis of the C15–C38 fragment 5

Coupling of the sulfone **32** with the alkynylaluminum species prepared from the alkyne **7** afforded the coupling product **48** in 60–63% yield as a single stereoisomer (dr >20:1) (Scheme 10). It was found that more than 2 equiv of **7** was required for complete consumption of **32**. However, the excess **7** could be recovered after aqueous workup and purification by flash column chromatography using silica gel. Hydroboration of **48** with 9-BBN-H in refluxing THF followed by alkaline oxidative workup provided the ketone **49** (68%, 94% based on recovered starting material (BORSM)). The regioselectivity of the hydroboration could be ascribed to the electronic effect induced by the C26 ether oxygen atom.[44] Here, the

Please cite this article in press as: Fuwa, H.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.001



Scheme 10. Synthesis of the C15–C38 fragment **5**.

configuration of the C26 stereogenic center was established by a conformational analysis on the basis of NOE experiments and $^{3}J_{H,H}$ values (Fig. 4A). Treatment of **49** with $NaBH_4$ (EtOH, −20 to 0 °C) gave the alcohol **50** in 86% yield as a single stereoisomer (dr >20:1). The newly generated C27 stereogenic center was assigned on the basis of a modified Mosher analysis (Fig. 4B).[45] The stereoselectivity could be rationalized by considering a polar Felkin–Anh model.[18d,46] Silylation of **50** with TIPSOTf/2,6-lutidine and cleavage of the benzyl ethers by hydrogenolysis gave the diol **51**. Selective silylation of the C15 alcohol led to the alcohol **52**. Oxidation of **52** with Dess–Martin periodinane (DMP)[47] followed by methylenation of the derived ketone by using Tebbe reagent[48] furnished the C15–C38 fragment **5**.

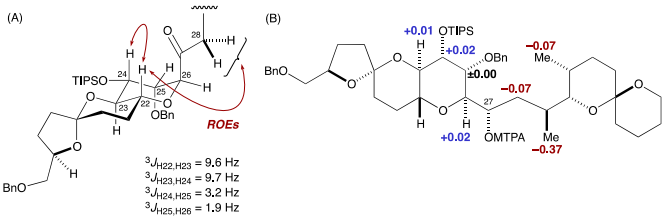


Fig. 4. (A) Stereochemical analysis on **49**. (B) Determination of the absolute configuration of the C27 stereogenic center of **50**.

3. Conclusions

In this paper, we described a concise synthesis of the C15–C38 fragment **5** of okadaic acid. Two different approaches were investigated for the construction of the spiroacetal substructures of **5**. Our initial approach involved Suzuki–Miyaura coupling of enol phosphates and subsequent spiroacetalization of the resultant endocyclic enol ethers for the synthesis of the sulfone **6** and the alkyne **7**. However, sufficient quantities of these important intermediates could not be obtained because of the low material throughput that could be at least partly ascribed to the instability of the intermediary enol phosphates (i.e., **11** and **16**). Furthermore, the reactivity of the sulfone **6** toward the alkynylaluminum prepared from **7** proved to be insufficient. Accordingly, we devised a more robust approach that featured the synthesis of the *exo*-olefins **33** and **34** via Suzuki–Miyaura coupling. The derived *exo*-olefins **33** and **34** were efficiently converted to the sulfone **32** and the alkyne **7**, respectively. An alkynylaluminum–anomeric sulfone coupling of **32** and **7** and subsequent functional group manipulations completed the synthesis of the C15–C38 fragment **5**. The present synthesis proceeded in only 19 linear steps from commercially available D-mannose pentaacetate, demonstrating the efficiency of our synthetic strategy. Work toward the synthesis and evaluation of okadaic acid analogs will be reported in due course.

4. Experimental section

4.1. General remark

All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co. Inc. and used directly without further drying unless otherwise noted. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene were purchased from Wako Pure Chemical Industries, Ltd. and further purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. 1,2-Dichloroethane (DCE), diisopropylamine, diisopropylethylamine, 2,6-lutidine, methanol (MeOH), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride under an atmosphere of argon. *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from magnesium sulfate under reduced pressure. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride under reduced pressure. All other chemicals were purchased at highest commercial grade and used directly. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} plates (0.25-mm thickness). Flash column chromatography was carried out using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). Optical rotations were recorded on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM ECA-600 spectrometer, and chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal residual solvent [^{1}H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15), CHD_2OD (3.31), CHD_2COCD_3 (2.05); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0), CD_3OD

(49.8), $(CD_3)_2CO$ (29.8)]. Coupling constants (J) are reported in Hertz (Hz). The following abbreviations were used to designate the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; br=broad. ESI-TOF mass spectra were measured on a Bruker microTOFfocus spectrometer. Diastereomer ratio (dr) and *E*/*Z* isomer ratio were estimated by ^{1}H NMR spectroscopic analysis (600 MHz), unless otherwise noted.

4.2. Silyl ether 13

To a solution of alcohol **12** (178 mg, 0.370 mmol) in CH_2Cl_2 (3.7 mL) at 0 °C were added 2,6-lutidine (0.130 mL, 1.11 mmol) and TIPSOTf (0.150 mL, 0.555 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave silyl ether **13** (253 mg, quant) as a colorless oil: $[\alpha]_D^{24}$ +116.4 (*c* 1.00, benzene); ^{1}H NMR (600 MHz, C_6D_6) δ 7.53–7.52 (m, 2H), 7.45–7.41 (m, 4H), 7.20–7.17 (m, 2H), 7.08 (m, 1H), 7.01–6.94 (m, 3H), 6.83–6.80 (m, 2H), 5.76 (d, J=1.4 Hz, 1H), 5.26 (s, 1H), 4.65 (d, J=11.0 Hz, 1H), 4.61 (dd, J=10.1, 3.3 Hz, 1H), 4.57 (ddd, J=10.1, 10.1, 5.0 Hz, 1H), 4.45 (d, J=11.0 Hz, 1H), 4.35 (dd, J=9.7, 9.7 Hz, 1H), 4.16 (dd, J=3.2, 1.4 Hz, 1H), 4.13 (dd, J=10.1, 5.1 Hz, 1H), 3.66 (dd, J=10.1, 10.1 Hz, 1H), 3.23 (s, 3H), 1.18–1.15 (m, 21H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.3, 138.5, 131.7 (2C), 129.4 (2C), 128.34 (2C), 128.29 (4C), 128.0 (2C), 127.9, 127.6, 113.5 (2C), 102.7, 87.6, 82.5, 79.7, 73.7, 71.6, 68.6, 66.4, 54.6, 18.4 (6C), 12.9 (3C); HRMS (ESI) calcd for $C_{36}H_{49}O_6SSi$ [$(M+H)^+$] 637.3014, found 637.3021.

4.3. Alcohol 14

To a solution of silyl ether **13** (0.955 g, 1.50 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DIBALH (1.02 M solution in *n*-hexane, 5.90 mL, 6.00 mmol), and the resultant solution was allowed to warm to 0 °C over a period of 3 h. The reaction was quenched with MeOH at 0 °C. The resultant mixture was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution, and stirred vigorously at room temperature until the layers became clear. The organic layer was separated and washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes) gave alcohol **14** (0.936 g, 98%) as a colorless oil: $[\alpha]_D^{23}$ +116.2 (*c* 1.00, benzene); IR (film) 3503, 2943, 2866, 1514, 1248, 1086 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.51–7.50 (m, 2H), 7.39–7.38 (m, 2H), 7.26–7.25 (m, 2H), 7.18–7.17 (m, 2H), 7.07–7.01 (m, 3H), 6.96 (m, 1H), 6.79–6.77 (m, 2H), 5.71 (d, J=1.9 Hz, 1H), 4.90 (d, J=11.0 Hz, 1H), 4.61 (d, J=11.5 Hz, 1H), 4.56 (dd, J=9.6, 2.8 Hz, 1H), 4.47 (d, J=11.5 Hz, 1H), 4.41 (d, J=11.5 Hz, 1H), 4.30 (ddd, J=9.6, 3.7, 3.7 Hz, 1H), 4.25 (dd, J=9.6, 9.6 Hz, 1H), 4.11 (dd, J=2.8, 1.9 Hz, 1H), 3.80–3.77 (m, 2H), 3.27 (s, 3H), 1.25–1.18 (m, 21H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.6, 138.7, 135.2, 132.0, 131.2 (2C), 129.3 (2C), 129.2 (2C), 128.5 (2C), 128.3 (2C), 127.8 (2C), 127.7, 114.0, 86.3, 81.9, 76.3, 75.0, 74.6, 74.3, 72.3, 62.4, 54.7, 18.5 (6C), 13.3 (3C); HRMS (ESI) calcd for $C_{36}H_{50}O_6SSiNa$ [$(M+Na)^+$] 661.2990, found 661.2990.

4.4. Olefin 8

To a solution of alcohol **14** (49 mg, 0.077 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 0.78 mL) at 0 °C were added Et_3N (0.045 mL, 0.32 mmol) and SO_3·pyridine (38 mg, 0.24 mmol), and the resultant mixture was stirred at 0 °C for 45 min. The reaction mixture was diluted with Et_2O, washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual aldehyde was passed through a short pad of silica gel and used in the next reaction without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (84 mg, 0.24 mmol) in THF (0.40 mL) at 0 °C was added *n*-BuLi (2.69 M solution in *n*-hexane, 0.080 mL, 0.22 mmol), and the resultant mixture was stirred at 0 °C for 30 min. To this mixture was added a solution of the above aldehyde in THF (0.4 mL), and the resultant mixture was stirred at 0 °C for 35 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave olefin **8** (42 mg, 84% for the two steps) as a colorless oil: $[\alpha]_D^{21}$ +124.3 (*c* 1.00, $CHCl_3$); IR (film) 2943, 1727, 1514, 1464, 1248, 1080 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.41 (m, 2H), 7.38–7.37 (m, 2H), 7.36–7.33 (m, 2H), 7.27–7.22 (m, 6H), 6.85–6.82 (m, 2H), 5.96 (ddd, J=16.9, 10.1, 6.9 Hz, 1H), 5.54 (d, J=1.9 Hz, 1H), 5.41 (d, J=16.9 Hz, 1H), 5.22 (d, J=10.1 Hz, 1H), 4.72 (d, J=11.0 Hz, 1H), 4.69 (d, J=11.9 Hz, 1H), 4.65 (d, J=11.9 Hz, 1H), 4.54 (d, J=11.0 Hz, 1H), 4.48 (dd, J=9.2, 6.9 Hz, 1H), 4.22 (dd, J=9.2, 2.8 Hz, 1H), 3.98 (dd, J=2.8, 1.9 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J=9.2, 9.2 Hz, 1H), 1.12–1.08 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.3, 135.3, 134.8, 131.8, 131.5 (2C), 130.8, 129.2 (2C), 129.0 (2C), 128.2 (2C), 127.5 (2C), 127.3 (2C), 118.3, 113.5, 85.7, 79.7, 77.2, 76.8, 74.4, 73.3, 72.2, 55.3, 18.2 (6C), 12.9 (3C); HRMS (ESI) calcd for $C_{37}H_{50}O_5SiSNa$ [$(M+Na)^+$] 657.3040, found 657.3037.

4.5. Enol phosphate 16

To a solution of acetate **17** (354 mg, 1.51 mmol) in THF (15 mL) at −78 °C were added HMPA (0.80 mL, 4.6 mmol), $(PhO)_2P(O)Cl$ (0.45 mL, 2.2 mmol), and LHMDS (1.0 M solution in THF, 2.0 mL, 2.0 mmol), and the resultant solution was stirred at −78 °C for 1 h. The reaction was quenched with 3% NH_4OH solution. The resultant mixture was stirred vigorously at room temperature for 30 min and then extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual enol phosphate **16** was immediately used in the next reaction without further purification.

4.6. Spiroacetals 21 and 22

To a solution of olefin **8** (292 mg, 0.460 mmol) in THF (2 mL) was added a solution of 9-BBN-H dimer (151 mg, 0.604 mmol) in THF (1.6 mL+1.0 mL rinse), and the resultant solution was stirred at room temperature for 3 h. To this solution was added 3 M aqueous Cs_2CO_3 solution (0.50 mL, 1.5 mmol), and the resultant mixture was stirred at room temperature for 20 min. To this mixture was added a solution of the above enol phosphate **16** in DMF (2.6 mL+2.0 mL rinse) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol), and the resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with Et_2O and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual enol ether **19** was rapidly passed through a short pad of silica gel to remove baseline impurities and used immediately in the next reaction without further purification.

To a solution of the above enol ether **19** in toluene (70 mL) was added a solution of the second-generation Grubbs catalyst (**G-II**) (39 mg, 0.061 mmol) in toluene (22 mL), and the resultant solution was stirred at 70 °C for 1 h. The reaction mixture was cooled to room temperature, stirred at room temperature under air for 2 h, and then concentrated under reduced pressure. The residual endocyclic enol ether **20** was used in the next reaction without any purification.

Please cite this article in press as: Fuwa, H.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.001

To a solution of the above endocyclic enol ether **20** in CH_2Cl_2/pH 7 buffer (10:1, v/v, 4.6 mL) at 0 °C was added DDQ (104 mg, 0.458 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first-round: 2–8% EtOAc/hexanes; second-round: benzene) gave spiroacetal **21** (113 mg, 35% for the three steps) as a colorless oil, along with its diastereomer **22** (39 mg, 12% for the three steps) as a colorless oil.

To a solution of spiroacetal **22** (39 mg, 0.055 mmol) in $(CH_2Cl)_2$ (0.55 mL) was added PPTS (4.5 mg, 0.018 mmol), and the resultant solution was stirred at room temperature overnight. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 4–8% EtOAc/hexanes) gave additional spiroacetal **21** (28 mg, 71%) as a colorless oil.

21: $[\alpha]_D^{24}$ +63.9 (*c* 1.0, $CHCl_3$); IR (film) 3734, 2942, 2864, 2361, 2324, 1456, 1146, 1028, 736 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.44–7.21 (m, 15H), 5.49 (d, *J*=1.9 Hz, 1H), 4.71 (d, *J*=11.9 Hz, 1H), 4.68 (d, *J*=11.9 Hz, 1H), 4.57 (s, 2H), 4.37 (m, 1H), 4.17 (dd, *J*=10.1, 3.2 Hz, 1H), 4.08 (dd, *J*=10.1, 10.1 Hz, 1H), 3.99 (dd, *J*=3.2, 1.9 Hz, 1H), 3.91 (ddd, *J*=10.1, 10.1, 4.1 Hz, 1H), 3.55 (dd, *J*=10.5, 4.1 Hz, 1H), 3.51 (dd, *J*=10.1, 5.5 Hz, 1H), 2.10 (m, 1H), 2.02–1.89 (m, 3H), 1.87–1.79 (m, 2H), 1.76 (m, 1H), 1.70 (m, 1H), 1.50 (s, 21H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.7, 139.6, 135.7, 132.7 (2C), 130.2 (2C), 129.3 (3C), 129.0 (2C), 128.8 (2C),128.7, 128.6 (2C), 128.5, 107.9, 88.1, 83.0, 78.9, 74.2, 74.1, 73.5, 73.3, 72.6, 71.3, 37.6, 34.3, 27.2, 26.8, 18.8 (6C), 13.9 (3C); HRMS (ESI) calcd for $C_{41}H_{56}O_6SSiNa$ ($[M+Na]^+$) 727.3459, found 727.3466.

22: $[\alpha]_D^{24}$ +92.2 (*c* 0.5, $CHCl_3$); IR (film) 3649, 2942, 2865, 2361, 2311, 1457, 1151, 1038, 737 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.53–7.52 (m, 2H), 7.37–7.35 (m, 4H), 7.21–6.94 (m, 9H), 5.80 (d, *J*=1.4 Hz, 1H), 4.60 (d, *J*=11.9 Hz, 1H), 4.90–4.54 (m, 3H), 4.43 (d, *J*=11.5 Hz, 1H), 4.26–4.19 (m, 2H) 4.12 (dd, *J*=3.2, 1.4 Hz, 1H), 3.96 (dd, *J*=9.7, 9.7 Hz, 1H), 3.80 (dd, *J*=9.7, 6.4 Hz, 1H), 3.59 (dd, *J*=9.7, 5.5 Hz, 1H), 2.02 (ddd, *J*=11.9, 7.3, 1.8 Hz, 1H), 1.95 (ddd, *J*=13.3, 13.3, 4.6 Hz, 1H), 1.81–1.73 (m, 2H), 1.64–1.56 (m, 2H), 1.44 (ddd, *J*=13.3, 4.1, 4.1 Hz, 1H), 1.26 (m, 21H), 1.03 (ddd, *J*=11.9, 11.9, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 139.1, 138.5, 130.9 (2C), 130.7, 129.1 (2C), 128.2 (2C), 128.0 (2C), 127.7 (2C), 127.5, 127.5 (2C), 127.3, 127.0, 108.5, 86.6, 82.2, 79.3, 75.7, 74.4, 73.3, 72.8, 71.9, 70.1, 34.4, 32.4, 28.0, 27.2, 18.4 (6C), 12.9 (3C); HRMS (ESI) calcd for $C_{41}H_{56}O_6SSiNa$ [$(M+Na)^+$] 727.3459, found 727.3466.

4.7. Sulfone 6

To a solution of spiroacetal **21** (50.0 mg, 0.0709 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C were added $NaHCO_3$ (36.3 mg, 0.465 mmol) and *m*-CPBA (43.0 mg, 0.254 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3% Et_2O/benzene) gave sulfone **6** (49.5 mg, 91%) as a colorless oil: $[\alpha]_D^{23}$ +23.4 (*c* 1.0, $CHCl_3$); IR (film) 2943, 2865, 2360, 1490, 1456, 1308, 1159, 1123, 1078, 1026 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.69–7.68 (m, 2H), 7.53 (m, 1H), 7.44–7.41 (m, 2H), 7.21–7.12 (m, 10H), 4.75 (d, *J*=11.9 Hz, 1H), 4.58 (s, 1H), 4.48–4.40 (m, 5H), 4.23 (m, 1H), 4.06 (m, 1H), 3.98 (dd, *J*=5.0, 5.0 Hz, 1H), 3.39–3.37 (m, 2H), 1.99 (m, 1H), 1.84–1.58 (m, 7H), 1.09–1.02 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 137.9, 137.2, 134.0, 129.1 (2C), 128.7 (2C), 128.31 (2C), 128.29 (2C), 127.8 (2C), 127.7, 127.6 (2C), 127.4, 106.2, 92.9, 77.5, 76.0, 74.3, 73.8, 73.1, 72.3, 71.3, 70.5, 36.7, 33.1, 26.3, 26.2, 18.2 (3C), 18.1 (3C), 12.6 (3C); HRMS (ESI) calcd for $C_{41}H_{56}O_8SSiNa$ [$(M+Na)^+$] 759.3357, found 759.3353.

4.8. Bis-silyl ether 10

To a solution of diol **23** (166 mg, 1.15 mmol) in CH_2Cl_2 (12 mL) at 0 °C were added 2,6-lutidine (0.40 mL, 3.5 mmol) and TBSOTf (0.58 mL, 2.5 mmol), and the resultant solution was stirred at 0 °C for 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, hexanes) gave bis-silyl ether **10** (430.3 mg, quant) as a colorless oil: $[\alpha]_D^{24}$ +21.2 (*c* 1.00, $CHCl_3$); IR (film) 2956, 2929, 2858, 1472, 1254, 1105, 1052, 856, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddd, *J*=17.9, 10.3, 7.6 Hz, 1H), 4.98–4.91 (m, 2H), 3.66 (dd, *J*=6.8, 2.4 Hz, 1H), 3.42 (dd, *J*=9.7, 7.9 Hz, 1H), 3.33 (dd, *J*=9.7, 6.5 Hz, 1H), 2.33 (ddd, *J*=7.6, 6.8, 6.8 Hz, 1H), 1.75 (m, 1H), 0.98 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.77 (d, *J*=6.8 Hz, 3H), 0.04 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.2, 113.3, 74.9, 66.0, 42.8, 38.8, 26.2, 25.9, 18.5, 18.2, 16.9 (3C), 10.6 (3C), −3.7, −4.1, −5.27, −5.32; HRMS (ESI) calcd for $C_{20}H_{44}O_2Si_2Na$ [$(M+Na)^+$] 395.2772, found 395.2766.

4.9. Endocyclic enol ether 25

To a solution of bis-silyl ether **10** (45.0 mg, 1.21 mmol) in THF (1.2 mL) was added 9-BBN-H dimer (40.6 mg, 1.66 mmol), and the resultant solution was stirred at room temperature for 2.5 h. To this solution was added 3 M aqueous K_3PO_4 solution (0.14 mL, 0.42 mmol), and the resultant mixture was stirred at room temperature for 20 min. To this mixture was added a solution of enol phosphate **11** (prepared from δ-valerolactone (0.55 mL, 0.61 mmol) immediately prior to use) in DMF (2.4 mL), Et_3N (0.040 mL, 0.26 mmol), and $Pd(PPh_3)_4$ (10.0 mg, 0.00865 mmol), and the resultant mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with Et_2O, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1% Et_3N/hexanes) gave endocyclic enol ether **25** (45.3 mg, 82%) as a colorless oil: $[\alpha]_D^{24}$ +13.8 (*c* 1.00, benzene); IR (film) 1716, 1472, 1388, 1361, 1006 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 4.53 (dd, *J*=3.8, 3.8 Hz, 1H), 3.81–3.76 (m, 3H), 3.56 (dd, *J*=9.6, 7.6 Hz, 1H), 3.43 (dd, *J*=9.6, 6.2 Hz, 1H), 2.26 (m, 1H), 2.11 (m, 1H), 1.98–1.82 (m, 4H), 1.74 (m, 1H), 1.51–1.40 (m, 3H), 1.03–0.98 (m, 24H), 0.15 (s, 3H), 0.14 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 155.2, 95.1, 75.5, 66.3, 66.0, 39.4, 37.7, 33.0, 31.4, 26.4 (3C), 26.1 (3C), 22.8, 20.6, 18.7, 18.4, 16.1, 12.3, −3.6, −3.9, −5.2 (2C); HRMS (ESI) calcd for $C_{25}H_{52}O_3Si_2Na$ [$(M+Na)^+$] 479.3347, found 479.3370.

4.10. Alcohol 26 (from 25)

To a solution of endocyclic enol ether **25** (256 mg, 0.560 mmol) in MeOH (6.0 mL) at 0 °C was added *p*-TsOH·H_2O (32 mg, 0.17 mmol), and the resultant solution was stirred at room temperature for 20.5 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5–15% EtOAc/hexanes) gave alcohol **26** (128 mg, quant, dr >20:1) as a colorless oil: $[\alpha]_D^{24}$ +92.2 (*c* 1.00, $CHCl_3$); IR (film) 3397, 2937, 2874, 1452, 1384, 1234, 1044, 998, 976 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.67–3.63 (m, 2H), 3.56–3.52 (m, 2H), 3.47 (m, 1H), 2.01 (m, 1H), 1.88–1.74 (m, 3H), 1.62 (ddd, *J*=13.3, 1.9, 1.9 Hz, 1H), 1.59–1.47 (m,

4H), 1.43 (dd, J=13.3, 4.1 Hz, 1H), 1.39–1.33 (m, 2H), 1.11 (d, J=6.9 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H), one proton missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 95.7, 72.6, 64.9, 60.4, 37.5, 35.8, 30.3, 28.0, 26.5, 25.4, 18.7, 14.4, 11.3; HRMS (ESI) calcd for $C_{13}H_{24}O_3Na$ [$(M+Na)^+$] 251.1618, found 251.1600.

4.11. Alkyne 7

To a solution of alcohol **26** (143.3 mg, 0.6280 mmol) in DMSO (6.3 mL) was added 2-iodoxybenzoic acid (IBX, 352 mg, 1.26 mmol), and the resultant solution was stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O and washed successively with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude aldehyde, which was used in the next reaction without further purification.

To a solution of the above aldehyde in MeOH (6.3 mL) at 0 °C were added Ohira–Bestmann reagent (180 mg, 0.938 mmol) and K_2CO_3 (218 mg, 1.58 mmol), and the resultant mixture was allowed to warm to room temperature over a period of 3 h. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was separated and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1% Et_2O/hexanes) gave alkyne **7** (99.0 mg, 71% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +94.2 (c 1.00, $CHCl_3$); IR (film) 3310, 2938, 2874, 2359, 2324, 1062, 997, 983 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.62 (dd, J=11.0, 2.7 Hz, 1H), 3.56 (m, 1H), 3.52 (dd, J=10.6, 2.3 Hz, 1H), 2.48, (m, 1H), 2.12 (m, 1H), 2.04 (m, 1H), 2.01 (d, J=2.8 Hz, 1H), 1.81 (m, 1H), 1.59–1.46 (m, 5H), 1.43 (dd, J=13.3, 4.1 Hz, 1H), 1.41–1.36 (m, 2H), 1.31 (d, J=6.4 Hz, 3H), 0.93 (d, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 95.8, 85.9, 74.1, 69.4, 60.4, 35.7, 30.1, 28.9, 28.3, 26.1, 25.3, 18.7, 18.4, 10.9; HRMS (ESI) calcd for $C_{14}H_{23}O_2$ [$(M+H)^+$] 223.1693, found 223.1701.

4.12. Sulfone 28

To a solution of olefin **8** (115 mg, 0.180 mmol) in CH_2Cl_2 (1.8 mL) at 0 °C were added $NaHCO_3$ (76.0 mg, 0.974 mmol) and m-CPBA (95.2 mg, 0.562 mmol), and the resultant mixture was stirred at room temperature for 2.5 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, benzene) gave sulfone **28** (96.9 mg, 81%) as a colorless oil: $[\alpha]_D^{23}$ +62.5 (c 1.0, $CHCl_3$); IR (film) 2942, 2866, 1514, 1457, 1249, 1152, 1126, 1079, 1036 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.62 (m, 1H), 7.52–7.50 (m, 2H), 7.37–7.36 (m, 2H), 7.33–7.30 (m, 2H), 7.27 (m, 1H), 7.20–7.18 (m, 2H), 6.84–6.83 (m, 2H), 5.75 (ddd, J=16.9, 10.5, 6.4 Hz, 1H), 5.22 (d, J=16.9 Hz, 1H), 5.12 (d, J=10.5 Hz, 1H), 4.78–4.75 (m, 2H), 4.68–4.54 (m, 5H), 4.50 (d, J=11.0 Hz, 1H), 3.79 (s, 3H), 3.62 (m, 1H), 1.29–1.07 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 137.7, 137.2, 135.1, 133.9, 129.1 (4C), 129.0 (4C), 128.9 (2C), 128.3 (4C), 127.9, 127.8, 113.5 (2C), 73.34 (2C), 55.3 (3C), 18.2 (6C),13.0 (3C); HRMS (ESI) calcd for $C_{37}H_{50}O_7SSiNa$ [$(M+Na)^+$] 689.2939, found 689.2945.

4.13. Alkyne 30

To a solution of ethynylbenzene (0.011 mL, 0.10 mmol) in toluene (0.2 mL) at 0 °C was added n-BuLi (1.64 M solution in n-hexane, 0.061 mL, 0.10 mmol), and the resultant solution was stirred at 0 °C for 30 min. To this solution were added Me_2AlCl (1.0 M solution in n-hexane, 0.10 mL, 0.10 mmol) and CH_2Cl_2 (0.20 mL), and the resultant solution was stirred at room temperature for 30 min. To this solution was added a solution of sulfone **6** (24.1 mg, 0.0327 mmol) in CH_2Cl_2 (0.2 mL+0.2 mL rinse), and the resultant solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave alkyne **30** (18.7 mg, 81%, dr >20:1) as a colorless oil: $[\alpha]_D^{25}$ +54.6 (c 1.0, $CHCl_3$); IR (film) 3030, 2942, 2864, 2360, 1490, 1456, 1362, 1249, 1122, 1101, 1028, 882 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.39 (m, 4H), 7.33–7.29 (m, 9H), 7.26–7.23 (m, 2H), 4.92 (d, J=2.3 Hz, 1H), 4.82 (d, J=12.4 Hz, 1H), 4.71 (d, J=12.4 Hz, 1H), 4.59 (d, J=12.4 Hz, 1H), 4.56 (d, J=12.4 Hz 1H), 4.38 (dd, J=9.6, 2.8 Hz 1H), 4.33 (m, 1H), 4.05 (dd, J=9.7, 9.6 Hz 1H), 3.87 (dd, J=2.8, 2.3 Hz, 1H), 3.65 (ddd, J=11.5, 9.6, 4.1 Hz, 1H), 3.54–3.49 (m, 2H), 2.10–1.98 (m, 2H), 1.92–1.81 (m, 4H), 1.77–1.68 (m, 2H), 1.14–1.08 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.61, 138.58, 131.7 (2C), 128.7, 128.33 (2C), 128.29 (2C), 128.2 (2C), 127.6 (2C), 127.5 (2C), 127.4 (2C), 122.2, 106.2, 88.3, 84.6, 81.9, 77.4, 73.13, 73.08, 72.3, 72.1, 71.9, 71.6, 67.8, 36.8, 33.4, 26.3, 26.2, 18.23 (3C), 18.16 (3C), 12.7 (3C); HRMS (ESI) calcd for $C_{43}H_{56}O_6SiNa$ [$(M+Na)^+$] 719.3738, found 719.3761.

4.14. Alkyne 31

To a solution of ethynylbenzene (0.010 mL, 0.091 mmol) in toluene (0.3 mL) at 0 °C was added n-BuLi (1.63 M solution in n-hexane, 0.056 mL, 0.091 mmol), and the resultant solution was stirred at 0 °C for 30 min. To this solution were added Me_2AlCl (1.0 M solution in n-hexane, 0.091 mL, 0.091 mmol) and CH_2Cl_2 (0.3 mL), and the resultant solution was stirred at room temperature for 30 min. To this solution was added a solution of sulfone **28** (47.7 mg, 0.0715 mmol) in CH_2Cl_2 (0.3 mL+0.3 mL rinse), and the resultant solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5–20% EtOAc/hexanes) gave alkyne **31** (41.8 mg, 93%, dr 9:1) as a colorless oil: $[\alpha]_D^{26}$ +27.4 (c 1.0, $CHCl_3$); IR (film) 3734, 2942, 2865, 2361, 1514, 1457, 1248, 1247, 1089, 1037, 756 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.41 (m, 2H), 7.38–7.28 (m, 8H), 7.23–7.21 (m, 2H), 6.83–6.81 (m, 2H), 5.98 (ddd, J=17.5, 10.6, 6.9 Hz, 1H), 5.44 (d, J=17.5 Hz, 1H), 5.24 (d, J=10.6 Hz, 1H), 5.00 (d, J=2.3 Hz, 1H), 4.74 (s, 2H), 4.71 (d, J=10.5 Hz, 1H), 4.53 (d, J=10.5 Hz, 1H), 4.52 (dd, J=9.2, 2.8 Hz, 1H), 4.27 (dd, J=7.8, 7.8 Hz, 1H), 3.91 (dd, J=2.8, 2.3 Hz, 1H), 3.78 (s, 3H), 3.64 (dd, J=9.2, 7.8 Hz, 1H), 1.10–1.09 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.4, 135.6, 131.7 (2C), 130.7, 129.4 (2C), 128.7, 128.3 (2C), 128.2 (2C), 127.50 (2C), 127.46 (2C), 122.0, 118.1, 113.5 (2C), 79.7 (2C), 76.3 (2C), 74.5, 73.3, 72.3, 55.2 (2C), 18.24 (3C), 18.20 (3C),13.0 (3C); HRMS (ESI) calcd for $C_{39}H_{50}O_5SiNa$ [$(M+Na)^+$] 649.3320, found 649.3345.

4.15. Thioglycoside 39

To a solution of D-mannose pentaacetate (**38**) (1.20 g, 3.07 mmol) and o-$MeOC_6H_4SH$ (0.49 mL, 4.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added $BF_3\cdot OEt_2$ (1.90 mL, 15.4 mmol), and the resultant solution was stirred at 0 °C for 30 min and then at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of

Please cite this article in press as: Fuwa, H.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.001

the residue by flash column chromatography (silica gel, 10–40% EtOAc/hexanes) gave thioglycoside **39** (1.49 g, quant, dr >20:1) as a yellow oil: $[\alpha]_D^{24}$ +122.8 (*c* 1.00, $CHCl_3$); IR (film) 2942, 1749, 1370, 1245, 1227, 1063 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, *J*=7.8, 1.8 Hz, 1H), 7.26 (m, 1H), 6.90–6.86 (m, 2H), 5.61 (d, *J*=1.4 Hz, 1H), 5.49 (dd, *J*=3.7, 1.8 Hz, 1H), 5.41 (dd, *J*=9.7, 3.2 Hz, 1H), 5.30 (dd, *J*=10.1, 10.1 Hz, 1H), 4.48 (ddd, *J*=10.1, 5.5, 2.3 Hz, 1H), 4.25 (dd, *J*=12.4, 5.5 Hz, 1H), 3.96 (dd, *J*=12.4, 2.3 Hz, 1H), 3.86 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.9, 169.8 (2C), 158.7, 134.0, 129.9, 121.1, 119.4, 111.0, 83.1, 70.8, 69.5, 69.4, 66.3, 62.3, 55.8, 20.9, 20.70, 20.66, 20.63; HRMS (ESI) calcd for $C_{21}H_{26}O_{10}SNa$ [$(M+Na)^+$] 493.1139, found 493.1143.

4.16. Diol 40

To a solution of thioglycoside **39** (1.39 g, 3.07 mmol) in MeOH (10 mL) was added NaOMe (324 mg, 6.00 mmol), and the resultant solution was stirred at room temperature for 16 h. The reaction mixture was neutralized with Amberlyst® 15 ion-exchange resin, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, $CHCl_3$ to 20% MeOH/$CHCl_3$) gave a tetraol (0.88 g, 95%) as a pale yellow foam: $[\alpha]_D^{24}$ +190.2 (*c* 1.00, $CHCl_3$); IR (film) 3365, 2934, 1580, 1477, 1246, 1065, 796 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (dd, *J*=8.0, 1.6 Hz, 1H), 7.16 (m, 1H), 6.82–6.76 (m, 2H), 5.58 (s, 1H), 5.34–5.11 (m, 3H), 4.41 (s, 1H), 4.18 (s, 1H), 4.10–3.90 (m, 2H), 3.93–3.90 (m, 2H), 3.75 (s, 3H), 3.60 (d, *J*=11.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 133.2, 129.0, 121.2, 121.1, 110.8, 86.0, 73.4, 72.5, 72.1, 66.4, 60.9, 55.7; HRMS (ESI) calcd for $C_{13}H_{18}O_6SNa$ [$(M+Na)^+$] 325.0716, found 325.0724.

To a solution of the above tetraol (8.39 g, 27.8 mmol) in CH_3CN (270 mL) at 0 °C were added *p*-methoxybenzaldehyde dimethyl acetal (7.10 mL, 41.7 mmol) and PPTS (1.40 g, 5.57 mmol), and the resultant solution was stirred at 0 °C for 70 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2/hexanes to give diol **40** (6.11 g, 52%) as colorless crystals. The mother liquor was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 50% EtOAc/hexanes then 10% MeOH/$CHCl_3$) to give additional diol **40** (2.71 g, 23%) as colorless crystals. Total yield: 8.82 g, 75%. Data for **40**: mp 122–123 °C (recrystallized from CH_2Cl_2/hexanes); $[\alpha]_D^{24}$ +269.5 (*c* 1.00, $CHCl_3$); IR (KBr) 3418, 1518, 1477, 1248, 1092, 1068, 1026 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.52 (dd, *J*=7.8, 1.9 Hz, 1H), 7.42–7.40 (m, 2H), 7.31 (m, 1H), 7.03 (dd, *J*=8.2, 1.4 Hz, 1H), 6.97–6.90 (m, 3H), 5.64 (s, 1H), 5.55 (s, 1H), 4.47 (d, *J*=5.5 Hz, 1H), 4.45 (d, *J*=3.2 Hz, 1H), 4.21–4.17 (m, 2H), 4.02 (ddd, *J*=9.6, 5.5, 3.7 Hz, 1H), 3.99–3.95 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H) 3.72 (dd, *J*=10.5, 10.1 Hz, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 161.0, 159.7, 134.2, 131.6, 130.0, 128.5 (2C), 122.1, 121.9, 114.0 (2C), 112.0, 102.5, 87.6, 80.0, 73.6, 69.7, 69.0, 65.9, 56.2, 55.5; HRMS (ESI) calcd for $C_{21}H_{24}O_7SNa$ [$(M+Na)^+$] 443.1135, found 443.1121.

4.17. Silyl ether 41

To a solution of diol **40** (2.08 g, 4.95 mmol) in CH_2Cl_2 (50 mL) were added Bu_4NHSO_4 (337.7 mg, 0.9946 mmol), BnBr (0.70 mL, 5.9 mmol), and 3 M aqueous NaOH solution (4.0 mL, 12 mmol), and the resultant biphasic mixture was heated to reflux for 10 h. The resultant mixture was cooled to room temperature, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was roughly purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) and then by recrystallization from EtOAc/hexanes to give a benzyl ether (1.05 g, 41%) as colorless crystals. The mother liquor was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 20% EtOAc/hexanes) and then by recrystallization from EtOAc/hexanes to give additional benzyl ether (0.21 g, 8%) as colorless crystals (total yield: 1.26 g, 49%): mp 150–151 °C (recrystallized from EtOAc/hexanes); $[\alpha]_D^{24}$ +165.2 (*c* 1.00, C_6H_6); IR (KBr) 3476, 2901, 1248, 1093, 751 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.50 (dd, *J*=7.8, 1.8 Hz, 1H), 7.47–7.42 (m, 4H), 7.37–7.28 (m, 4H), 7.03 (dd, *J*=8.3, 0.9 Hz, 1H), 6.96–6.91 (m, 3H), 5.77 (s, 1H), 5.58 (s, 1H), 4.80 (s, 2H), 4.32 (d, *J*=6.4 Hz, 1H), 4.18 (ddd, *J*=10.1, 5.0, 5.0 Hz, 1H), 4.11–4.06 (m, 2H), 4.02–3.90 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.74 (dd, *J*=10.1, 10.1 Hz, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 160.9, 159.6, 139.5, 134.1, 131.6, 130.1, 129.0 (2C), 128.7 (2C), 128.6 (2C), 128.3, 123.0, 121.9, 114.0 (2C), 112.1, 102.5, 85.4, 81.6, 80.3, 73.7, 70.1, 68.9, 66.3, 56.2, 55.5; HRMS (ESI) calcd for $C_{28}H_{30}O_7SNa$ [$(M+Na)^+$] 533.1604, found 533.1581.

To a solution of the above benzyl ether (1.04 g, 2.04 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added 2,6-lutidine (0.650 mL, 5.61 mmol) and TIPSOTf (0.700 mL, 2.60 mmol), and the resultant solution was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave silyl ether **41** (1.25 g, 92%) as a pale yellow oil: $[\alpha]_D^{23}$ +129.1 (*c* 1.00, $CHCl_3$); IR (film) 2941, 2865, 1519, 1477, 1463, 1248, 1096 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.51 (dd, *J*=7.8, 1.8 Hz, 1H), 7.45–7.42 (m, 4H), 7.37–7.28 (m, 4H), 7.04 (dd, *J*=8.2, 1.4 Hz, 1H), 6.96–6.90 (m, 3H), 5.78 (d, *J*=1.4 Hz, 1H), 5.59 (s, 1H), 4.82 (d, *J*=11.5 Hz, 1H), 4.79 (d, *J*=11.5 Hz, 1H), 4.40 (dd, *J*=9.6, 3.2 Hz, 1H), 4.21 (ddd, *J*=9.6, 4.6, 4.6 Hz, 1H), 4.10–4.00 (m, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.76 (dd, *J*=10.2, 10.1 Hz, 1H), 1.07–1.05 (m, 21H); ^{13}C NMR (150 MHz, acetone-d_6) δ 161.0, 159.6, 139.6, 134.3 (2C), 132.2, 130.2, 129.0 (2C), 128.7 (2C), 128.5 (2C), 128.3, 121.9, 121.8, 113.9, 112.1, 102.9, 85.6, 82.5, 80.2, 73.8, 71.8, 68.9, 66.8, 56.2, 55.5, 18.5 (6C), 13.2 (3C); HRMS (ESI) calcd for $C_{37}H_{50}O_7SSiNa$ [$(M+Na)^+$] 689.2939, found 689.2947.

4.18. Alcohol 42

To a solution of silyl ether **41** (1.25 g, 1.87 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added DIBALH (1.02 M solution in *n*-hexane, 7.40 mL, 7.55 mmol), and the resultant solution was allowed to warm to 0 °C over a period of 4 h. The reaction was quenched with MeOH at 0 °C. The resultant solution was diluted with EtOAc and saturated aqueous potassium sodium tartrate solution. The resultant biphasic mixture was stirred vigorously at room temperature until the layers became clear and then separated. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes) gave alcohol **42** (1.23 g, 98%) as a colorless oil: $[\alpha]_D^{24}$ +134.7 (*c* 1.00, $CHCl_3$); IR (film) 3485, 2942, 2866, 1514, 1247, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, *J*=7.3, 1.9 Hz, 1H), 7.38–7.31 (m, 4H), 7.27–7.23 (m, 4H), 6.90–6.84 (m, 4H), 5.68 (d, *J*=1.4 Hz, 1H), 4.84 (d, *J*=11.5 Hz, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 4.66 (d, *J*=12.0 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.36 (dd, *J*=8.7, 2.8 Hz, 1H), 4.05 (ddd, *J*=9.6, 4.6, 3.2 Hz, 1H), 4.00 (dd, *J*=1.8, 1.4 Hz, 1H), 3.90 (dd, *J*=9.2, 9.2 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.68–3.60 (m, 2H), 1.65 (m, 1H), 1.15–1.10 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 158.6, 138.4, 134.2 (2C), 130.6, 129.5, 129.3 (2C), 128.3 (2C), 127.5, 127.4 (2C), 121.2, 121.1, 113.7 (2C), 111.0, 83.3, 81.2, 74.7, 73.7, 73.6, 72.2, 62.3, 55.8, 55.3,

18.22 (3C), 18.17 (3C), 12.9 (3C); HRMS (ESI) calcd for $C_{37}H_{52}O_7SSiNa$ [(M+Na)$^+$] 691.3095, found 691.3118.

4.19. Olefin 35

To a solution of alcohol **42** (3.98 g, 5.95 mmol) and Et_3N (3.40 mL, 24.4 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 58 mL) at 0 °C was added SO_3·pyridine (2.86 g, 18.0 mmol), and the resultant solution was stirred at 0 °C for 40 min. The reaction mixture was diluted with Et_2O and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give crude aldehyde, which was used in the next reaction without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (6.38 g, 17.9 mmol) in THF (58 mL) at 0 °C was added *n*-BuLi (2.65 M solution in *n*-hexane, 6.40 mL, 17.0 mmol), and the resultant suspension was stirred at 0 °C for 30 min. To this suspension was added a solution of the above aldehyde in THF (5 mL+5 mL rinse), and the resultant mixture was allowed to warm to room temperature over a period of 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave olefin **35** (3.30 g, 83% for the two steps) as a pale yellow oil: $[\alpha]_D^{24}$ +110.4 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2865, 1514, 1463, 1247, 1087, 1068 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, *J*=7.3, 1.8 Hz, 1H), 7.43–7.41 (m, 2H), 7.36–7.34 (m, 2H), 7.30–7.24 (m, 4H), 6.90 (dd, *J*=7.3, 1.4 Hz, 1H), 6.92–6.85 (m, 3H), 5.95 (ddd, *J*=17.5, 10.6, 6.9 Hz, 1H), 5.73 (s, 1H), 5.37 (d, *J*=17.5 Hz, 1H), 5.19 (d, *J*=10.6 Hz, 1H), 4.75 (d, *J*=11.0 Hz, 1H), 4.74–4.70 (m, 2H), 4.57 (d, *J*=10.6 Hz, 1H), 4.51 (dd, *J*=9.1, 6.8 Hz, 1H), 4.36 (dd, *J*=8.7, 3.2 Hz, 1H), 4.05 (s, 1H), 3.85 (s, 3H) 3.80 (s, 3H), 3.72 (dd, *J*=9.2, 9.2 Hz, 1H), 1.16–1.14 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 158.3, 138.5, 135.4, 133.5, 130.8, 129.1 (2C), 128.9, 128.2 (2C), 127.4 (2C), 121.8, 121.1, 118.1, 113.4 (2C), 110.8, 83.3, 81.3, 79.7, 77.2, 74.5, 74.4, 73.2, 72.0, 55.8, 55.2, 18.23 (3C), 18.19 (3C), 12.8 (3C); HRMS (ESI) calcd for $C_{38}H_{52}O_6SSiNa$ [(M+Na)$^+$] 687.3146, found 687.3133.

4.20. Enol triflate 36

To a solution of (*R*)-1-benzyloxyhex-5-en-2-ol (**43**) (496 mg, 2.40 mmol) in DMF (8 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 192 mg, 4.80 mmol), and the resultant mixture was stirred at room temperature for 15 min. To this mixture at 0 °C were added MPMCl (0.400 mL, 2.96 mmol) and Bu_4NI (89.0 mg, 0.241 mmol), and the resultant mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 10% *t*-BuOMe/hexanes; second round: 5% *t*-BuOMe/hexanes) gave an MPM ether (761 mg, 97%) as a colorless oil: $[\alpha]_D^{24}$ +17.0 (*c* 1.00, $CHCl_3$); IR (film) 2912, 2857, 1612, 1513, 1268 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.36 (m, 4H), 7.32–7.29 (m, 3H), 6.88 (d, *J*=8.7 Hz, 2H), 5.81 (ddt, *J*=17.4, 10.1, 6.4 Hz, 1H), 5.02 (dd, *J*=17.4, 1.4 Hz, 1H), 4.96 (d, *J*=10.1 Hz, 1H), 4.64 (d, *J*=11.5 Hz, 1H), 4.57 (s, 2H), 4.51 (d, *J*=11.5 Hz, 1H), 3.80 (s, 3H), 3.64–3.52 (m, 3H) 2.20 (m, 1H), 2.12 (m, 1H) 1.71–1.64 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.4, 138.3, 130.9, 129.3 (2C), 128.3 (2C), 127.50 (2C), 127.46, 114.6, 113.6 (2C), 77.0, 73.2, 72.7, 71.6, 55.2, 31.2, 29.6; HRMS (ESI) calcd for $C_{21}H_{26}O_3Na$ [(M+Na)$^+$] 349.1774, found 349.1746.

To a solution of the above MPM ether (740 mg, 2.26 mmol) in *N*,*N*-dimethylacetamide (DMA)/H_2O (7:1, v/v, 24 mL) were added $Cu(OAc)_2$ (861 mg, 4.74 mmol) and $PdCl_2$ (80 mg, 0.45 mmol), and the resultant mixture was stirred at room temperature under an atmosphere of O_2 (balloon) for 9 h 20 min. The resultant mixture was cooled to 0 °C, diluted with H_2O, stirred at room temperature for 15 min, and then filtered through a pad of Celite to remove insoluble materials. The filtrate was diluted with *t*-BuOMe and washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 10–30% EtOAc/hexanes; second round: 30% *t*-BuOMe/hexanes) gave a methyl ketone (672 mg, 87%) as a pale yellow oil: $[\alpha]_D^{24}$ +27.9 (*c* 1.00, $CHCl_3$); IR (film) 2858, 1714, 1513, 1246, 1030 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.32 (m, 4H), 7.29–7.22 (m, 3H), 6.85 (d, *J*=8.3 Hz, 2H), 4.59 (d, *J*=11.5 Hz, 1H), 4.53 (s, 2H), 4.43 (d, *J*=11.5 Hz, 1H), 3.78 (s, 3H), 3.57 (m, 1H), 3.53 (dd, *J*=10.1, 5.5 Hz, 1H), 3.48 (dd, *J*=10.1, 4.6, 1H), 2.52–2.40 (m, 2H), 2.05 (s, 3H), 1.87 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.6, 159.1, 138.2, 130.7, 129.4 (2C), 128.3 (2C), 127.55 (2C), 127.53, 113.7 (2C), 76.4, 73.3, 72.5, 71.5, 55.2, 39.3, 29.8, 25.9; HRMS (ESI) calcd for $C_{21}H_{26}O_4Na$ [(M+Na)$^+$] 365.1723, found 365.1712.

To a solution of the above methyl ketone (383.4 mg, 1.120 mmol) in THF (11 mL) at −78 °C was added KHMDS (0.5 M solution in toluene, 2.7 mL, 1.4 mmol), and the resultant solution was stirred at −78 °C for 20 min. To this solution was added a solution of $PhNTf_2$ (480.3 mg, 1.344 mmol) in THF (1 mL), and the resultant solution was stirred at −78 °C for 50 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at −78 °C. The resultant mixture was allowed to warm to room temperature and then extracted with *t*-BuOMe. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5–10% Et_2O/hexanes) gave enol triflate **36** (338.4 mg, 64%) as a colorless oil, which was contaminated with a small amount of unidentified impurities. This material was immediately used in the next reaction without further purification. Data for **36**: ^{1}H NMR (600 MHz, C_6D_6) δ 7.27–7.25 (m, 2H), 7.21–7.17 (m, 4H), 7.10 (m, 1H), 6.80–6.78 (m, 2H), 4.69 (d, *J*=3.7 Hz, 1H), 4.51 (d, *J*=11.5 Hz, 1H), 4.30–4.28 (m, 3H), 4.25 (d, *J*=3.7 Hz, 1H), 3.41–3.33 (m, 1H), 3.30 (s, 3H), 3.21 (dd, *J*=9.6, 5.0 Hz, 1H), 2.29 (ddd, *J*=15.5, 7.8, 7.8 Hz, 1H), 2.13 (ddd, *J*=15.5, 8.3, 7.8 Hz, 1H), 1.60–1.55 (m, 3H); HRMS (ESI) calcd for $C_{22}H_{25}F_3O_6SNa$ [(M+Na)$^+$] 497.1216, found 497.1216.

4.21. *exo*-Olefin 33

To a solution of olefin **35** (308.4 mg, 0.4638 mmol) in THF (3 mL) was added a solution of 9-BBN-H dimer (184.2 mg, 0.7548 mmol) in THF (2 mL+1 mL rinse), and the resultant solution was stirred at room temperature for 3 h. To this solution was added 3 M aqueous Cs_2CO_3 solution (0.460 mL, 1.38 mmol), and the resultant mixture was stirred at room temperature for 20 min. To this mixture were added a solution of enol triflate **36** (338.4 mg, 0.7131 mmol) in DMF (2.5 mL), $PdCl_2(dppf)\cdot CH_2Cl_2$ (38.9 mg, 0.0476 mmol), and Ph_3As (58.0 mg, 0.189 mmol), and the resultant mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with *t*-BuOMe and H_2O and stirred at room temperature for a while. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 5–10% EtOAc/hexanes; second round: 1% EtOAc/benzene) gave *exo*-olefin **33** (413.0 mg, 90%) as a colorless oil: $[\alpha]_D^{24}$ +93.4 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2865, 1513, 1247, 1090 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (dd, *J*=7.8, 1.8 Hz, 1H), 7.39–7.38 (m, 2H), 7.33–7.30 (m, 6H), 7.27–7.20 (m, 6H), 7.16 (m, 1H), 6.86–6.79 (m,

6H), 5.75 (d, J=1.4 Hz, 1H), 4.83 (d, J=11.0 Hz, 1H), 4.70 (d, J=11.5 Hz, 1H), 4.66 (d, J=11.5 Hz, 1H), 4.59–4.50 (m, 6H), 4.43 (d, J=11.5 Hz, 1H), 4.32 (dd, J=9.2, 2.8 Hz, 1H), 3.97 (s, 1H), 3.87 (ddd, J=9.2, 9.1, 1.4 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.61 (dd, J=9.2, 9.2 Hz, 1H), 3.51–3.43 (m, 3H), 2.00 (m, 1H), 1.92–1.82 (m, 3H), 1.70 (m, 1H), 1.57–1.53 (m, 3H), 1.43 (m, 1H), 1.11 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 158.1, 149.2, 138.50, 138.45, 133.3, 131.1, 130.8, 129.35 (2C), 129.31 (2C), 128.8, 128.3 (2C), 128.2 (2C), 127.57 (2C), 127.51, 127.4 (4C), 121.8, 121.1, 113.68 (2C), 113.64 (2C), 110.7, 108.5, 82.4, 81.3, 79.8, 77.4, 74.9, 73.9, 73.3, 72.98, 72.92, 72.1, 71.6, 55.7, 55.25, 55.22, 32.2, 31.6, 30.0, 29.5, 18.29 (3C), 18.24 (3C), 13.0 (3C); HRMS (ESI) calcd for $C_{59}H_{78}O_9SSiNa$ [(M+Na)$^+$] 1013.5028, found 1013.5035.

4.22. Ketone 45

To a solution of *exo*-olefin **33** (402.0 mg, 0.4059 mmol) in THF/acetone/H_2O (5:5:1, v/v, 11 mL) were added NMO (4.8 M solution in H_2O, 0.72 mL, 3.5 mmol) and OsO_4 (10 mg/mL solution in *t*-BuOH, 1.0 mL, 0.039 mmol), and the resultant solution was stirred at room temperature for 14 h. To this solution was added $NaIO_4$ (436.1 mg, 2.039 mmol), and the resultant mixture was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20–40% EtOAc/hexanes) gave ketone **45** (361.6 mg, 87%) as a pale yellow oil: $[\alpha]_D^{23}$ +71.0 (*c* 1.00, $CHCl_3$); IR (film) 2941, 2865, 1713, 1612, 1513, 1248 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, J=7.8, 1.4 Hz, 1H), 7.45 (m, 1H), 7.35–7.19 (m, 14H), 7.00 (dd, J=7.8, 7.8 Hz, 1H), 6.90, (d, J=8.2 Hz, 1H), 6.84–6.82 (m, 4H), 5.36 (d, J=4.1 Hz, 1H), 4.71 (m, 1H), 4.66 (d, J=11.5 Hz, 2H), 4.56 (d, J=11.5 Hz, 2H), 4.51 (s, 2H), 4.47 (m, 2H), 4.39 (d, J=11.5 Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.52–3.43 (m, 4H), 2.28–2.09 (m, 2H), 1.85–1.83 (m, 2H), 1.77–1.62 (m, 3H), 1.42 (m, 1H), 1.07 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.7, 159.2 (2C), 157.5, 138.2, 137.8, 135.7, 131.0, 130.7, 130.2, 129.36 (2C), 129.32 (2C), 128.38 (2C), 128.31, 128.2 (2C), 127.8 (2C), 127.63 (3C), 127.59 (2C), 120.5, 113.72 (2C), 113.70 (2C), 112.1, 89.4, 76.5, 73.4, 73.0, 72.5, 71.5, 60.3, 56.2, 55.2 (2C), 38.2* (2C), 29.3* (1C), 25.8* (2C), 21.0, 18.2 (6C), 14.2, 12.8 (3C), signals with asterisk were assigned on the basis of HMQC spectrum; HRMS (ESI) calcd for $C_{58}H_{76}O_{12}SSiNa$ [(M+Na)$^+$] 1047.4719, found 1047.4719.

4.23. Sulfone 32

To a solution of ketone **45** (330.9 mg, 0.3227 mmol) in CH_2Cl_2/H_2O (10:1, v/v, 3.3 mL) at 0 °C was added DDQ (186.4 mg, 0.8211 mmol), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave sulfone **32** (211.2 mg, 85%, dr >20:1) as a pale yellow oil: $[\alpha]_D^{24}$ +34.3 (*c* 1.00, $CHCl_3$); IR (film) 2943, 2865, 2360, 2341, 1155, 1117 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (dd, J=7.8, 1.9 Hz, 1H), 7.51 (m, 1H), 7.29–7.16 (m, 10H), 7.01 (m, 1H), 6.91 (d, J=8.2 Hz, 1H), 5.28 (s, 1H), 4.80 (d, J=11.9 Hz, 1H), 4.57 (d, J=11.9 Hz, 1H), 4.52–4.46 (m, 3H), 4.40 (d, J=3.7 Hz, 1H), 4.27 (m, 1H), 4.01 (dd, J=10.1, 9.6 Hz, 1H), 3.92 (m, 1H), 3.76 (s, 3H), 3.44–3.41 (m, 2H), 2.01 (m, 1H), 1.85 (m, 1H), 1.76–1.60 (m, 5H), 1.48 (m, 1H), 1.06 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.5 (2C), 138.5, 138.2, 135.9, 131.2, 128.24 (2C), 128.22 (2C), 127.50 (2C), 127.46 (3C), 127.4, 125.1, 120.7, 112.3, 106.2, 91.2, 77.4, 76.2, 73.83, 73.76, 73.0, 72.3, 71.3, 70.7, 56.2, 36.6, 33.0, 26.2, 18.2 (3C), 18.1 (3C), 12.6 (3C); HRMS (ESI) calcd for $C_{42}H_{58}O_9SSiNa$ [(M+Na)$^+$] 789.3463, found 789.3439.

4.24. Enol triflate 37

To a solution of *i*-Pr_2NH (0.640 mL, 4.57 mmol) in THF (19 mL) at 0 °C was added *n*-BuLi (2.65 M solution in *n*-hexane, 1.70 mL, 4.51 mmol), and the resultant solution was stirred at 0 °C for 20 min. To this solution at −78 °C was added a solution of 6-*tert*-butyldimethylsilyloxyhexan-2-one (**46**) (821.2 mg, 3.564 mmol) and $PhNTf_2$ (1.63 g, 4.56 mmol) in THF (3 mL+1 mL rinse), and the resultant solution was stirred at −78 °C for 1 h and then allowed to warm to 0 °C over a period of 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% Et_2O/hexanes) gave enol triflate **37** (1.057 g, 82%) as a pale yellow oil: IR (film) 2955, 2931, 2859, 1671, 1419, 1252, 1211 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 4.71 (d, J=3.2 Hz, 1H), 4.29 (ddd, J=3.7, 1.4, 0.9 Hz, 1H), 3.34 (t, J=5.9 Hz, 2H), 1.93 (m, 2H), 1.33–1.28 (m, 2H), 1.25–1.20 (m, 2H), 0.96 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 157.1, 121.0 (q, J=246 Hz, 1C), 104.0, 62.4, 33.5, 31.7, 26.0 (3C), 22.6, 18.4, −5.3 (2C); HRMS (ESI) calcd for $C_{13}H_{25}F_3O_4SSiNa$ [(M+Na)$^+$] 385.1087 found 385.1086.

4.25. *exo*-Olefin 34

To a solution of bis-silyl ether **10** (897.0 mg, 2.407 mmol) in THF (12 mL) was added a solution of 9-BBN-H dimer (648.0 mg, 2.655 mmol) in THF (8 mL+4 mL rinse), and the resultant solution was stirred at room temperature for 1 h. To this solution was added 3 M aqueous Cs_2CO_3 solution (2.40 mL, 7.20 mmol), and the resultant mixture was stirred at room temperature for 20 min. To this mixture were added a solution of enol triflate **37** (1.057 g, 2.916 mmol) in DMF (12 mL+12 mL rinse), $PdCl_2(dppf)\cdot CH_2Cl_2$ (193.8 mg, 0.2373 mmol), and Ph_3As (294.6 mg, 0.9202 mmol), and the resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with *t*-BuOMe and washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% Et_2O/hexanes) gave *exo*-olefin **34** (1.384 g, 98%) as a pale yellow oil: $[\alpha]_D^{24}$ +8.7 (*c* 1.00, $CHCl_3$); IR (film) 2954, 2929, 2894, 2858, 1472, 1463, 1254, 1100, 836, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.67 (s, 2H), 3.63–3.56 (m, 3H), 3.43 (dd, J=9.6, 6.8 Hz, 1H), 3.33 (dd, J=9.6, 6.8 Hz, 1H), 2.06–1.98 (m, 3H), 1.89 (m, 1H), 1.73 (ddd, J=13.7, 6.8, 3.2 Hz, 1H), 1.63–1.41 (m, 6H), 1.16 (m, 1H), 0.88–0.86 (m, 27H), 0.84 (d, J=6.8 Hz, 3H), 0.81 (d, J=6.9 Hz, 3H), 0.03 (s, 9H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2, 108.6, 75.3, 66.2, 63.1, 38.9, 37.9, 35.9, 34.2, 32.6, 31.8, 26.1 (3C), 26.0 (3C), 25.9 (3C), 24.0, 18.44, 18.36, 18.22, 15.6, 12.1, −3.8, −4.1, −5.27 (2C), −5.33, −5.36; HRMS (ESI) calcd for $C_{32}H_{70}O_3Si_3Na$ [(M+Na)$^+$] 609.4525, found 609.4524.

4.26. Ketone 47

To a solution of *exo*-olefin **34** (1.384 g, 2.349 mmol) in THF/H_2O (2:1, v/v, 24 mL) were added NMO (4.8 M solution in H_2O, 1.5 mL, 7.2 mmol) and OsO_4 (37.3 mg, 0.147 mmol), and the resultant mixture was stirred at room temperature for 10 h. To this mixture was added $NaIO_4$ (2.01 g, 9.40 mmol), and the resultant mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic

layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 3% Et_2O/hexanes) gave ketone **47** (1.188 g, 86%) as a pale yellow oil: $[\alpha]_D^{24}$ +12.4 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2929, 2886, 2857, 1717, 1472, 1254, 1098, 1048, 836, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.60 (dd, *J*=5.0, 3.2 Hz, 1H), 3.59 (d, *J*=6.4 Hz, 1H), 3.58 (d, *J*=6.4 Hz, 1H), 3.41 (dd, *J*=9.6, 7.4 Hz, 1H), 3.33 (dd, *J*=9.6, 6.4 Hz, 1H), 2.43–2.37 (m, 3H), 2.32 (ddd, *J*=16.0, 10.1, 5.9 Hz, 1H), 1.77–1.70 (m, 2H), 1.62–1.57 (m, 2H), 1.55–1.51 (m, 2H), 1.50–1.45 (m, 2H), 1.32 (m, 1H), 0.873 (s, 9H), 0.866 (s, 9H), 0.865 (s, 9H), 0.83 (d, *J*=6.9 Hz, 3H), 0.81 (d, *J*=6.8 Hz, 3H), 0.02 (s, 9H), 0.010 (s, 3H), 0.008 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.3, 75.0, 66.0, 62.8, 42.5, 41.2, 38.8, 37.7, 32.3, 27.6, 26.1 (3C), 26.0 (3C), 25.9 (3C), 20.3, 18.4, 18.3, 18.2, 15.7, 11.9, −3.8, −4.1, −5.3 (3C), −5.4; HRMS (ESI) calcd for $C_{31}H_{68}O_4Si_3Na$ [(M+Na)$^+$] 611.4318, found 611.4321.

4.27. Alcohol 26 (from ketone 47)

To a solution of ketone **47** (1.188 g, 2.016 mmol) in MeOH (20 mL) was added $TsOH\cdot H_2O$ (116.2 mg, 0.6109 mmol), and the resultant solution was stirred at room temperature for 18 h. The reaction mixture was neutralized with Et_3N and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes) gave spiroacetal **26** (440.5 mg, 96%, dr >20:1) as a colorless oil.

4.28. Alkyne 48

To a solution of alkyne **7** (132.0 mg, 0.5937 mmol) in toluene (0.25 mL) at 0 °C was added *n*-BuLi (2.65 M solution in *n*-hexane, 0.230 mL, 0.610 mmol), and the resultant solution was stirred at 0 °C for 30 min. To this solution were added CH_2Cl_2 (0.20 mL) and Me_2AlCl (1.0 M solution in *n*-hexane, 0.59 mL, 0.59 mmol), and the resultant solution was stirred at room temperature for 30 min. To this solution was added a solution of sulfone **32** (197.4 mg, 0.2573 mmol) in CH_2Cl_2 (0.2 mL+0.4 mL rinse), and the resultant solution was stirred at room temperature for 4.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, first round: 5–10% EtOAc/hexanes; second round: 2% Et_2O/benzene) gave alkyne **48** (132.7 mg, 63%, dr >20:1) as a pale yellow oil: $[\alpha]_D^{24}$ +55.0 (*c* 1.00, $CHCl_3$); IR (film) 2939, 2865, 2229, 1454, 1383, 1092, 996, 879 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.36 (m, 2H), 7.33–7.27 (m, 6H), 7.26–7.21 (m, 2H), 4.79 (d, *J*=11.9 Hz, 1H), 4.69 (dd, *J*=1.9, 1.8 Hz, 1H), 4.67 (d, *J*=11.9 Hz, 1H), 4.58 (d, *J*=12.4 Hz, 1H), 4.55 (d, *J*=12.4 Hz, 1H), 4.32 (m, 1H), 4.25 (dd, *J*=9.7, 2.8 Hz, 1H), 3.99 (dd, *J*=9.7, 9.6 Hz, 1H), 3.72 (dd, *J*=2.8, 2.3 Hz, 1H), 3.62 (ddd, *J*=11.9, 11.0, 2.8 Hz, 1H), 3.57 (m, 1H), 3.54–3.48 (m, 4H), 2.52 (dqd, *J*=10.6, 6.4, 1.8 Hz, 1H), 2.10–1.95 (m, 4H), 1.90 (m, 1H), 1.85–1.77 (m, 4H), 1.76–1.67 (m, 2H), 1.62–1.48 (m, 5H), 1.44 (dd, *J*=13.3, 4.1 Hz, 1H), 1.41–1.36 (m, 2H), 1.30 (d, *J*=6.4 Hz, 3H), 1.10–1.09 (m, 21H), 0.92 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 138.6, 128.3 (2C), 128.2 (2C), 127.6 (2C), 127.44 (2C), 127.40, 127.3, 106.2, 95.8, 90.3, 82.1, 77.3, 74.0, 73.1, 73.0, 72.3, 71.9, 71.8, 71.5, 67.6, 60.4, 36.8, 35.6, 33.5, 30.1, 29.2, 28.7, 27.0, 26.3, 26.12, 26.08, 25.3, 18.7, 18.4, 18.2 (3C), 18.1 (3C), 12.6 (3C), 11.0; HRMS (ESI) calcd for $C_{49}H_{72}O_8SiNa$ [(M+Na)$^+$] 839.4889, found 839.4910.

4.29. Ketone 49

Alkyne **48** (13.6 mg, 0.0166 mmol) was mixed with 9-BBN-H (0.5 M solution in THF, 0.160 mL, 0.0800 mmol), and the resultant solution was heated to reflux for 14 h. The resultant solution was cooled to 0 °C and treated sequentially with H_2O (10 μL), saturated aqueous $NaHCO_3$ solution (100 μL), and 30% aqueous H_2O_2 solution (50 μL). The resultant mixture was diluted with THF (320 μL) and stirred at 0 °C for 1 h and then at room temperature for 2.5 h. The resultant mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous Na_2SO_3 solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% EtOAc/hexanes) gave ketone **49** (9.5 mg, 68%, 94% based on recovered starting material) as a colorless oil, along with recovered **48** (3.7 mg, 27%) as a colorless oil. **49**: $[\alpha]_D^{24}$ +4.65 (*c* 1.00, $CHCl_3$); IR (film) 2940, 2865, 1714, 1454, 1131, 1099, 1066, 999 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.36 (m, 2H), 7.32–7.22 (m, 8H), 4.87 (d, *J*=11.9 Hz, 1H), 4.61, (d, *J*=11.9 Hz, 1H), 4.57 (d, *J*=12.4 Hz, 1H), 4.55 (d, *J*=12.4 Hz, 1H), 4.32 (m, 1H), 4.25 (dd, *J*=3.2, 1.9 Hz, 1H), 4.17 (d, *J*=1.9 Hz, 1H), 4.03 (dd, *J*=9.7, 9.6 Hz, 1H), 3.77 (dd, *J*=9.7, 3.2 Hz, 1H), 3.62 (ddd, *J*=11.9, 11.0, 2.3 Hz, 1H) 3.54 (m, 1H), 3.50–3.49 (m, 2H), 3.35 (dd, *J*=10.1, 2.3 Hz, 1H), 2.94 (m, 1H), 2.42 (dd, *J*=16.5, 10.1 Hz, 1H) 2.33 (dd, *J*=16.5, 3.2 Hz, 1H), 2.12–1.96 (m, 4H), 1.89–1.76 (m, 5H), 1.75–1.59 (m, 4H), 1.57–1.45 (m, 4H), 1.42 (dd, *J*=13.3, 4.1 Hz, 1H), 1.40–1.35 (m, 2H), 1.10–1.09 (m, 21H), 0.97 (d, *J*=6.8 Hz, 3H), 0.87 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.8, 138.8, 138.6, 128.3 (2C), 128.2 (2C), 127.61 (2C), 127.55 (2C), 127.4, 106.1, 95.6, 83.6, 77.9, 77.5, 74.6, 74.0, 73.7, 73.1, 72.3, 71.9, 71.4, 60.4, 40.7, 36.7, 35.8, 34.7, 33.3, 31.5, 30.1, 27.7, 26.41, 26.36, 26.2, 25.4, 22.6, 18.7, 18.2 (3C), 18.1 (3C), 12.6 (3C), 11.0; HRMS (ESI) calcd for $C_{49}H_{74}O_9SiNa$ [(M+Na)$^+$] 857.4994, found 857.5004.

4.30. Alcohol 50

To a solution of ketone **49** (41.8 mg, 0.0500 mmol) in EtOH (0.5 mL) at −20 °C was added $NaBH_4$ (37.7 mg, 0.997 mmol), and the resultant solution was stirred at −20 °C for 15 min and then at 0 °C for 14 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10–20% EtOAc/hexanes) gave alcohol **50** (36.2 mg, 86%, dr >20:1) as a colorless oil: $[\alpha]_D^{24}$ +9.9 (*c* 1.00, $CHCl_3$); IR (film) 3443, 2941, 2865, 1454, 1384, 1065, 999, 879 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.35 (m, 2H), 7.32–7.27 (m, 6H), 7.26–7.21 (m, 2H), 4.82 (d, *J*=11.9 Hz, 1H), 4.61 (d, *J*=11.9 Hz, 1H), 4.58 (d, *J*=12.4 Hz, 1H), 4.55 (d, *J*=12.4 Hz, 1H), 4.32 (m, 1H), 4.08 (dd, *J*=9.6, 9.6 Hz, 1H), 3.93–3.90 (m, 2H), 3.67–3.63 (m, 2H), 3.57–3.49 (m, 4H), 3.28 (m, 1H), 3.20 (dd, *J*=10.1, 2.3 Hz, 1H), 2.51 (s, 1H), 2.09–1.96 (m, 3H), 1.95–1.68 (m, 9H), 1.64–1.48 (m, 5H), 1.44 (dd, *J*=13.3, 4.1 Hz, 1H), 1.41–1.37 (m, 2H), 1.09–1.08 (m, 21H), 1.02 (d, *J*=6.4 Hz, 3H), 0.87 (d, *J*=6.8 Hz, 3H), 0.68 (dd, *J*=12.4, 10.9 Hz, 1H), one proton missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.55, 138.51, 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.6 (2C), 127.5, 127.4, 106.2, 95.6, 81.9, 77.7, 77.5, 75.1, 73.5, 73.2, 72.3, 71.9, 71.6, 71.1, 63.4, 60.3, 36.7, 36.4, 35.9, 33.4, 30.9, 30.3, 27.4, 26.4, 26.3 (2C), 25.4, 18.7, 18.3 (3C), 18.2 (3C), 16.3, 12.8 (3C), 10.6; HRMS (ESI) calcd for $C_{49}H_{76}O_9SiNa$ [(M+Na)$^+$] 859.5151, found 859.5122.

4.31. Diol 51

To a solution of alcohol **50** (17.5 mg, 0.0209 mmol) in $(CH_2Cl)_2$ (0.3 mL) at 0 °C were added 2,6-lutidine (0.015 mL, 0.13 mmol) and TIPSOTf (0.015 mL, 0.056 mmol), and the resultant solution was stirred at 60 °C for 3 h. The reaction mixture was cooled to 0 °C and treated with additional portions of 2,6-lutidine (0.010 mL,

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0.086 mmol) and TIPSOTf (0.010 mL, 0.037 mmol), and the resultant solution was stirred at 60 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% Et_2O/hexanes) gave a silyl ether (33.2 mg), which was contaminated with TIPSOH. This material was used in the next reaction without further purification.

To a solution of the above silyl ether in THF/MeOH (1:1, v/v, 0.5 mL) was added 20% $Pd(OH)_2/C$ (1.5 mg), and the resultant mixture was stirred at room temperature under an atmosphere of H_2 (balloon) for 15 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% Et_2O/hexanes) gave diol **51** (16.9 mg, 99% for the two steps) as a colorless oil: $[\alpha]_D^{24}$ +6.9 (*c* 1.00, $CHCl_3$); IR (film) 3443, 2942, 2892, 2867, 1464, 1384, 1096, 1065, 999, 880 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.20–4.12 (m, 2H), 4.05 (d, *J*=3.7 Hz, 1H), 3.98 (dd, *J*=9.7, 4.1 Hz, 1H), 3.96 (d, *J*=4.6 Hz, 1H), 3.84 (dd, *J*=9.7, 9.6 Hz, 1H), 3.70–3.62 (m, 3H), 3.54 (m, 1H), 3.46 (m, 1H), 3.30 (dd, *J*=9.1, 1.8 Hz, 1H), 3.05 (s, 1H), 2.02–1.96 (m, 2H), 1.91 (dd, *J*=12.4, 3.2 Hz, 1H), 1.89–1.65 (m, 10H), 1.61 (m, 1H), 1.59–1.47 (m, 5H), 1.42 (dd, *J*=13.3, 4.1 Hz, 1H), 1.39–1.35 (m, 2H), 1.28 (ddd, *J*=15.1, 9.1, 5.9 Hz, 1H), 1.08–1.05 (m, 45H), 0.88 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.3, 95.7, 80.7, 78.5, 75.2, 73.1, 72.2, 71.8, 71.5, 71.2, 64.9, 60.4, 37.5, 37.1, 35.9, 33.1, 31.8, 30.3, 27.8, 26.66, 26.63, 25.4, 25.3, 18.7, 18.4 (6C), 18.0 (3C), 17.9 (3C), 17.1, 13.7 (3C), 12.4 (3C), 11.3; HRMS (ESI) calcd for $C_{44}H_{84}O_9Si_2Na$ [$(M+Na)^+$] 835.5546, found 835.5533.

4.32. Alcohol 52

To a solution of diol **51** (21.6 mg, 0.0266 mmol) in DMF (0.3 mL) were added imidazole (39.0 mg, 0.573 mmol) and TBDPSCl (0.070 mL, 0.27 mmol), and the resultant solution was stirred at 50 °C for 9 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with *t*-BuOMe, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% Et_2O/hexanes) gave alcohol **52** (25.0 mg, 89%) as a colorless oil: $[\alpha]_D^{24}$ +5.7 (*c* 1.00, $CHCl_3$); IR (film) 3443, 2942, 2893, 2866, 1463, 1112, 1100, 998, 880 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.41–7.34 (m, 6H), 4.21–4.16 (m, 2H), 4.05 (d, *J*=3.7 Hz, 1H), 4.00–3.96 (m, 2H), 3.87 (dd, *J*=9.7, 9.6 Hz, 1H), 3.69 (dd, *J*=10.5, 4.1 Hz, 1H), 3.65 (m, 1H), 3.62 (dd, *J*=10.6, 4.1 Hz, 1H), 3.54 (m, 1H), 3.31 (dd, *J*=9.6, 1.8 Hz, 1H), 3.04 (s, 1H), 2.10–1.89 (m, 3H), 1.88–1.73 (m, 9H), 1.64–1.47 (m, 6H), 1.42 (dd, *J*=13.3, 4.1 Hz, 1H), 1.38 (m, 2H), 1.29 (ddd, *J*=12.8, 9.2, 5.9 Hz, 1H), 1.09–1.06 (m, 45H), 1.02 (s, 9H), 0.88 (d, *J*=7.3 Hz, 3H), one proton missing due to H/D exchange; ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.63 (2C), 135.59 (2C), 133.7, 133.6, 129.56, 129.51, 127.6 (4C), 106.4, 95.7, 80.7, 79.0, 77.2, 75.3, 72.9, 72.2, 71.9, 71.7, 71.1, 66.0, 60.4, 37.6, 37.0, 35.9, 33.2, 31.8, 30.3, 27.8, 26.8 (3C), 26.7, 25.8, 25.5, 19.2, 18.7, 18.4 (6C), 18.0 (3C), 17.9 (3C), 17.1, 13.7 (3C), 12.4 (3C), 11.3; HRMS (ESI) calcd for $C_{60}H_{102}O_9Si_3Na$ [$(M+Na)^+$] 1073.6724, found 1073.6746.

4.33. C15–C38 fragment 5

To a solution of alcohol **52** (17.9 mg, 0.0170 mmol) in $(CH_2Cl)_2$ (0.5 mL) at 0 °C were added $NaHCO_3$ (15.8 mg, 0.188 mmol) and Dess–Martin periodinane (36.1 mg, 0.0851 mmol), and the resultant mixture was stirred at room temperature for 3 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was diluted with EtOAc and stirred at room temperature for 10 min. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% Et_2O/hexanes) gave a ketone (16.8 mg, 94%) as a colorless oil: $[\alpha]_D^{24}$ +28.5 (*c* 1.00, $CHCl_3$); IR (film) 2943, 2893, 2866, 1732, 1464, 1148, 1113, 1087, 998, 881 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4H), 7.41–7.34 (m, 6H), 4.32 (m, 1H), 4.25–4.19 (m, 2H), 4.10 (ddd, *J*=10.1, 10.1, 5.0 Hz, 1H), 4.05 (d, *J*=4.1 Hz, 1H), 3.83 (dd, *J*=10.1, 9.6 Hz, 1H), 3.69 (dd, *J*=10.5, 4.1 Hz, 1H), 3.64–3.60 (m, 2H), 3.52 (m, 1H), 3.28 (dd, *J*=9.6, 2.3 Hz, 1H), 2.10 (m, 1H), 2.01–1.77 (m, 10H), 1.66 (m, 1H), 1.62–1.57 (m, 2H), 1.56–1.46 (m, 3H), 1.42 (dd, *J*=13.3, 4.1 Hz, 1H), 1.39–1.29 (m, 3H), 1.09–1.03 (m, 45H), 1.02 (s, 9H), 0.87 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.5, 135.64 (2C), 135.60 (2C), 133.72, 133.65, 129.58, 129.53, 127.61 (2C), 127.58 (2C), 105.9, 95.7, 85.7, 79.14, 79.12, 77.2, 76.1, 75.0, 71.6, 66.1, 60.3, 36.8, 36.1, 35.8, 32.6, 31.9, 30.3, 27.8, 26.8 (3C), 26.6, 26.5, 25.7, 25.4, 19.3, 18.7, 18.32 (3C), 18.28 (3C), 18.0 (6C), 17.3, 13.6 (3C), 12.7 (3C), 11.4; HRMS (ESI) calcd for $C_{60}H_{100}O_9Si_3Na$ [$(M+Na)^+$] 1071.6567, found 1071.6576.

To a solution of the above ketone (15.8 mg, 0.0151 mmol) in THF (0.5 mL) at 0 °C was added Tebbe reagent (0.5 M solution in toluene, 0.15 mL, 0.08 mmol), and the resultant solution was stirred at 0 °C for 40 min. The reaction was quenched with 1 M aqueous NaOH solution at 0 °C. The resultant mixture was diluted with *t*-BuOMe and stirred at room temperature for 30 min. Insoluble material was filtered off, and the filtrate was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% Et_2O/hexanes) gave C15–C38 fragment **5** (15.7 mg, 99%) as a colorless oil: $[\alpha]_D^{24}$ −4.6 (*c* 1.00, $CHCl_3$); IR (film) 2942, 2865, 1463, 1145, 1112, 1081, 999, 881 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.41–7.34 (m, 6H), 5.35 (s, 1H), 5.02 (s, 1H), 4.40 (dd, *J*=9.1, 8.3 Hz, 1H), 4.21 (m, 1H), 4.13–4.09 (m, 2H), 3.69 (dd, *J*=11.0, 4.1 Hz, 1H), 3.65–3.60 (m, 2H), 3.53–3.47 (m, 2H), 3.42 (dd, *J*=9.6, 9.2 Hz, 1H), 3.17 (dd, *J*=10.1, 2.3 Hz, 1H), 2.06 (m, 1H), 1.99–1.74 (m, 9H), 1.63 (d, *J*=13.3 Hz, 1H), 1.57–1.47 (m, 4H) 1.42 (dd, *J*=13.3, 4.1 Hz, 1H), 1.39–1.28 (m, 3H), 1.27–1.23 (m, 2H), 1.10–1.06 (m, 42H), 1.03 (d, *J*=6.4 Hz, 3H), 1.02 (s, 9H), 0.87 (d, *J*=6.8 Hz, 3H), 0.80 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 135.64 (2C), 135.59 (2C), 133.8, 133.7, 129.55, 129.50, 127.6 (4C), 112.8, 106.2, 95.6, 87.3, 78.92, 77.88, 75.6, 72.7, 71.4, 67.2, 66.0, 60.1, 37.8, 36.9, 35.9, 33.3, 30.8, 30.4, 29.7, 27.4, 26.7 (3C), 26.5, 25.7, 25.5, 19.3, 18.8, 18.6 (6C), 18.3 (3C), 18.1 (3C), 16.1, 13.8 (3C), 12.8 (3C), 10.8; HRMS (ESI) calcd for $C_{61}H_{102}O_8Si_3Na$ [$(M+Na)^+$] 1069.6775, found 1069.6777.

Acknowledgements

We thank Professor Keiichi Konoki (Tohoku University) for helpful discussions. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas 'Chemical Biology of Natural Products' (No. 26102708) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.[49]

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Please cite this article in press as: Fuwa, H.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.04.001