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Stereoselective synthesis of the left wing of Caribbean ciguatoxin

Shuji Yamashita *, Ryohei Uematsu, Masahiro Hirama *

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

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ABSTRACT

Ciguatoxins, the principal causative toxins of ciguatera seafood poisoning, are potent toxic polycyclic ethers. In this paper, we report a stereoselective and secure route to the left wing of Caribbean ciguatoxin on the basis of a 6-*exo* radical cyclization strategy.

1. Introduction

Ciguatera seafood poisoning, an important medical issue in tropical and subtropical regions, causes gastrointestinal, cardiovascular, and neurological disorders that may last for weeks or even years.[1] Alhough ciguatera had been localized to the islands of the Pacific Ocean, Indian Ocean, and the Caribbean Sea, it has become a global problem due to expanding tourism and trade. Ciguatoxins (CTXs), the principal causative toxins of ciguatera, are ladder-like polycyclic ethers 3 nm in length with ring sizes ranging from five- to nine-members.[2] Ciguatoxins exhibit their potent toxicities (LD_{50}=0.25–4 μg/kg, mice) by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes.[3,4] Recent progress in analytical technology reveals that the ciguatoxins are structurally varied according to geographical region.[5] Caribbean ciguatoxin C-CTX-1 (**1**, Fig. 1) was isolated from the carnivorous fish horse-eye jack (*Caranx latus*) as the main toxin of ciguatera in the Caribbean Sea.[5a] In contrast to the typical Pacific ciguatoxins, CTX3C (**2**) and 51-hydroxyCTX3C (**3**),[6] **1** possesses 14 ether rings with a more complicated architecture.

We have successfully synthesized three Pacific ciguatoxins (**2**, **3**, and CTX1B)[7] and developed a sandwich enzyme-linked immunosorbent assay (ELISA) for their detection.[8,9] Moreover, we have reported the syntheses of ABCDE-,[10] M-,[11] and LMN-ring[12] fragments of **1**. However, more practical and secure methods to prepare sufficient amounts of the fragments are still required for the total synthesis of **1**. Recently, we developed three efficient routes for constructing *trans*-fused polyethers based on radical

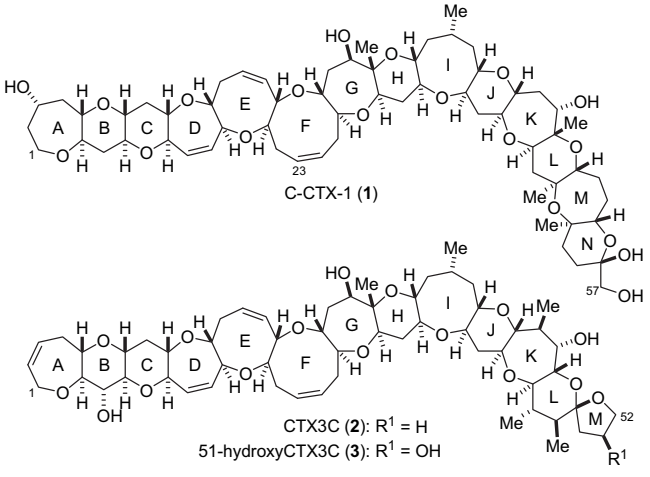

Fig. 1. Structures of ciguatoxins.

* Corresponding authors. Tel.: +81 22 795 6564; fax: +81 22 795 6566; e-mail addresses: s-yamashita@m.tohoku.ac.jp (S. Yamashita), hirama@m.tohoku.ac.jp (M. Hirama).

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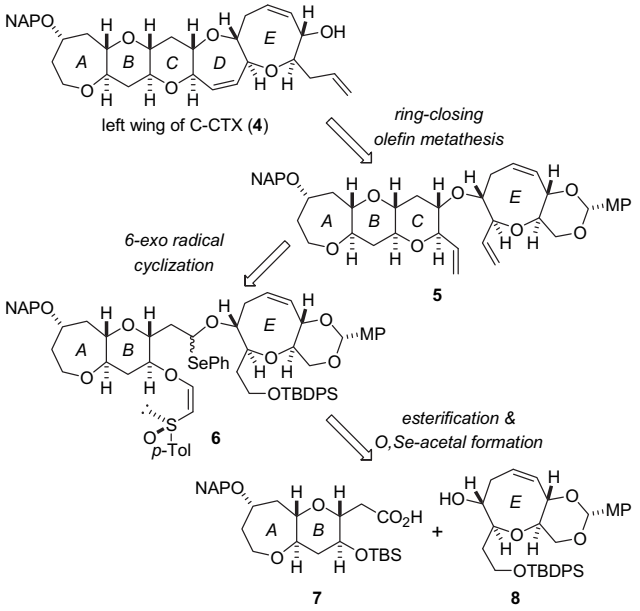
reactions: (i) an acyl radical cyclization/reductive etherification sequence,[13] (ii) a 7-*exo* radical cyclization using an electron-deficient acrylate/ring-closing olefin metathesis (RCM) sequence,[7,14] and (iii) a 6-*exo* radical cyclization using a *cis*-vinyl sulfoxide/RCM sequence.[7h] Herein, we describe an advanced synthetic route to the left wing of **1** utilizing method (iii) as the key strategy.

2. Results and discussion

A new synthesis plan of the left wing (**4**) of **1** is summarized in Scheme 1. The seven-membered D-ring was retrosynthetically cleaved to triene **5**, which could be generated from *O*,*Se*-acetal **6** by the key 6-*exo* radical cyclization. The intermediate **6** would be prepared from bicycles **7** and **8** via esterification and *O*,*Se*-acetal formation.

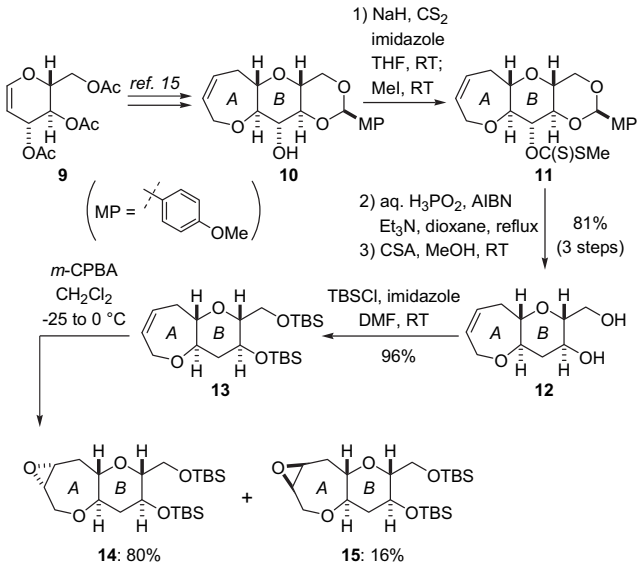


Scheme 1. Retrosynthesis of the left wing of C-CTX-1 (**1**).

We first improved the synthesis of the AB-ring of C-CTX-1 from the known alcohol **10**, which was prepared from tri-*O*-acetyl-D-glucal **9** (Scheme 2).[15] Deoxygenation of the B-ring alcohol of **10** was achieved by Barton radical reduction.[16] Successive treatment of **10** with NaH, carbon disulfide, and MeI afforded xanthate **11**. Removal of xanthate by the action of aqueous phosphinic acid and AIBN in the presence of Et_3N in dioxane furnished the C-CTX-1 type B-ring. Subsequent acid treatment to cleave the anisylidene acetal moiety provided diol **12** in 81% overall yield from **10**. After TBS protection of the two hydroxy groups of **12**, epoxidation of the resulting TBS ether **13** with *m*-CPBA in CH_2Cl_2 at low temperature afforded α-epoxide **14** in 80% yield along with its diastereomer **15** (16%).

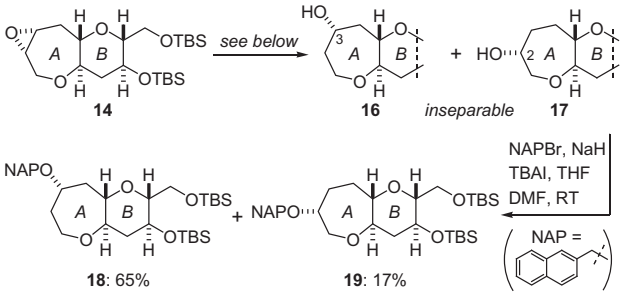
Reductive opening of epoxide **14** was explored as summarized in Table 1. Treatment of **14** with lithium triethylborohydride ($LiBHEt_3$) gave an inseparable 1:1 mixture of the desired C3-alcohol **16** and its regioisomer **17** in 95% yield (entry 1). L-Selectride [$LiBH(s\text{-}Bu)_3$], Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$], and DIBAL gave unsatisfactory results (entries 2–4). After considerable experimentation we eventually found that treatment of **14** with $LiAlH_4$ in Et_2O at −30 to −20 °C provided **16** as the major product (4:1) in 100% combined yield. The secondary alcohols, **16** and **17**, were protected as 2-naphthylmethyl (NAP)[7b,17] ethers to give **18** and **19**, which were isolated in 65% and 17% yields, respectively.

Selective cleavage of the less-hindered TBS ether of **18** was achieved by exposure to CSA in MeOH at 0 °C to give primary



Scheme 2. Synthesis of epoxide **14**.

Table 1
Regioselective cleavage of epoxide **14**

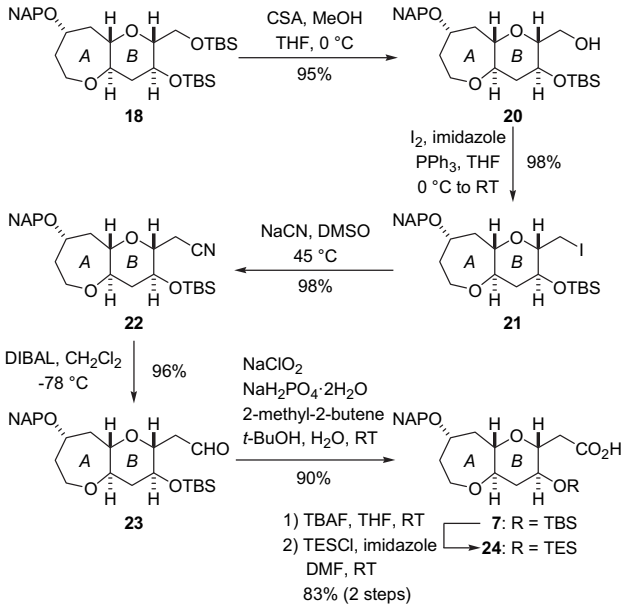


Entry	Conditions	Combined Yield	**16**:**17**[a]
1	$LiBHEt_3$, THF, −20 °C	95%	1:1
2	$LiBH(s\text{-}Bu)_3$, THF, −20 °C to RT	41%	1:1
3	Red-Al,THF, −20 to 0 °C	17%	1:1
4	DIBAL, CH_2Cl_2, 0 °C	decomposed	–
5	$LiAlH_4$, Et_2O, −30 to −20 °C	100%	4:1

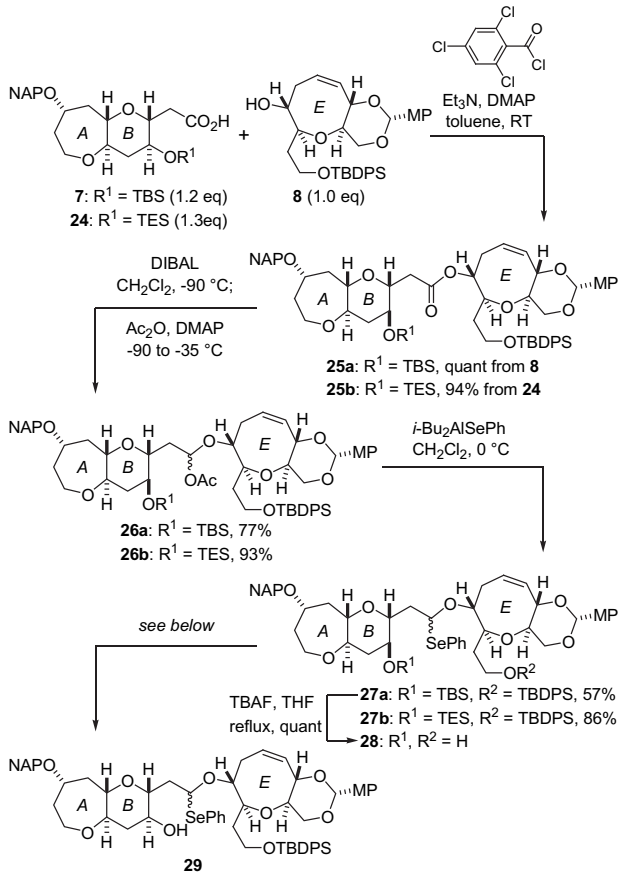
[a] The ratio of **16**:**17** was determined by ^{1}H-NMR analysis

alcohol **20** (Scheme 3). Following the method developed by Sammuelsson,[18] the hydroxy group of **20** was converted to the iodide **21** in 93% yield from **18**. After the one carbon homologation of **21** by substitution of iodide with sodium cyanide, nitrile **22** was transformed to the carboxylic acid **7** through DIBAL reduction and Pinnick oxidation in 85% overall yield from **21**. The TES-protected AB-ring carboxylic acid **24** was also prepared from **7** in two steps.

As shown in Scheme 4, the AB-ring carboxylic acid **7** was condensed with the E-ring alcohol **8**[7h] by Yamaguchi esterification[19] to afford ester **25a**. The ester was treated with DIBAL in CH_2Cl_2 at −90 °C followed by acetylation with Ac_2O and DMAP to produce acetate **26a** of the hemiacetal.[20] The acetate group of **26a** was substituted with the phenylselenyl group by the action of $i\text{-}Bu_2AlSePh$, which was freshly prepared from DIBAL and $(PhSe)_2$,[21] to give *O*,*Se*-acetal **27a** in 57% yield. Although selective removal of the TBS group of **27a** was attempted, cleavage of the TBDPS ether always occurred competitively. We thus examined protection of the primary alcohol of the corresponding diol **28**. Although a variety of experimental conditions was tested, including treatment of **28** with



Scheme 3. Synthesis of the AB-ring.



Entry	Conditions	Results
1 (**28**)	TBDPSCl (1.1 eq), imidazole, DMF, RT	**29**: 32%, **28**: 60%
2 (**28**)	TBDPSCl (2.0 eq), imidazole, DMF, 0 °C	**29**: 30%, **28**: 20%
3 (**27b**)	TBAF, THF, -30 °C	**29**: 95%

Scheme 4. Coupling of the AB- and the E-rings.

1.1 or 2.0 equiv of TBDPSCl in the presence of imidazole (Scheme 4, entries 1 and 2), the desired secondary alcohol **29** was obtained in only 30–32% yield. Based on these unsuccessful protecting group manipulations, we decided to alter the TBS-protecting group of the secondary alcohol on the B-ring to the more labile TES group. The TES derivative **27b** was prepared from **24** and **8** following the same reaction sequence described above. Treatment of **27b** with TBAF at −30 °C selectively cleaved the TES ether and gave secondary alcohol **29** in 95% yield (Scheme 4, entry 3).

With the requisite **29** in hand, construction of the C- and D-rings was performed (Scheme 5). The reaction of acetylene sulfoxide **30**[22] with the alkoxide, which was generated from alcohol **29** and NaH, furnished the *cis*-vinyl sulfoxide **6** in 65% yield along with starting material **29** (30%). It is noteworthy that the addition of 1 equiv of H_2O improved the yield as well as reproducibility, while the reaction in the absence of H_2O gave **6** in 8–54% yield and recovered **29** in 35–90% yield.[23] Radical cyclization to construct the C-ring was carried out under the previously optimized conditions.[7h,24] Treatment of **6** with *n*-Bu_3SnH and Et_3B at low temperature afforded the six-membered ether **31** exclusively in 70% yield. Sulfoxide **31** was converted to the terminal olefin **32** via Pummerer rearrangement[25] and subsequent Wittig olefination. After cleavage of the TBDPS ether by TBAF, alcohol **33** was transformed to phenylselenide **34** using PhSeCN and *n*-Bu_3P in THF. Oxidation of selenide **34** with hydrogen peroxide in the presence of $NaHCO_3$ provided the corresponding selenoxide, which underwent β-elimination at 40 °C to furnish the triene **5** in 82% yield from **32**. RCM reaction of **5** using Grubbs' first generation catalyst (**35**)[26] formed the seven-membered D-ring, and acid treatment gave diol **36**. Selective tosylation of the primary alcohol of **36** followed by cyanation afforded nitrile **37** in 78% yield. Synthesis of the left wing fragment **4** was finally accomplished from **37** by DIBAL reduction and Wittig olefination in 72% yield for the two steps.

3. Conclusion

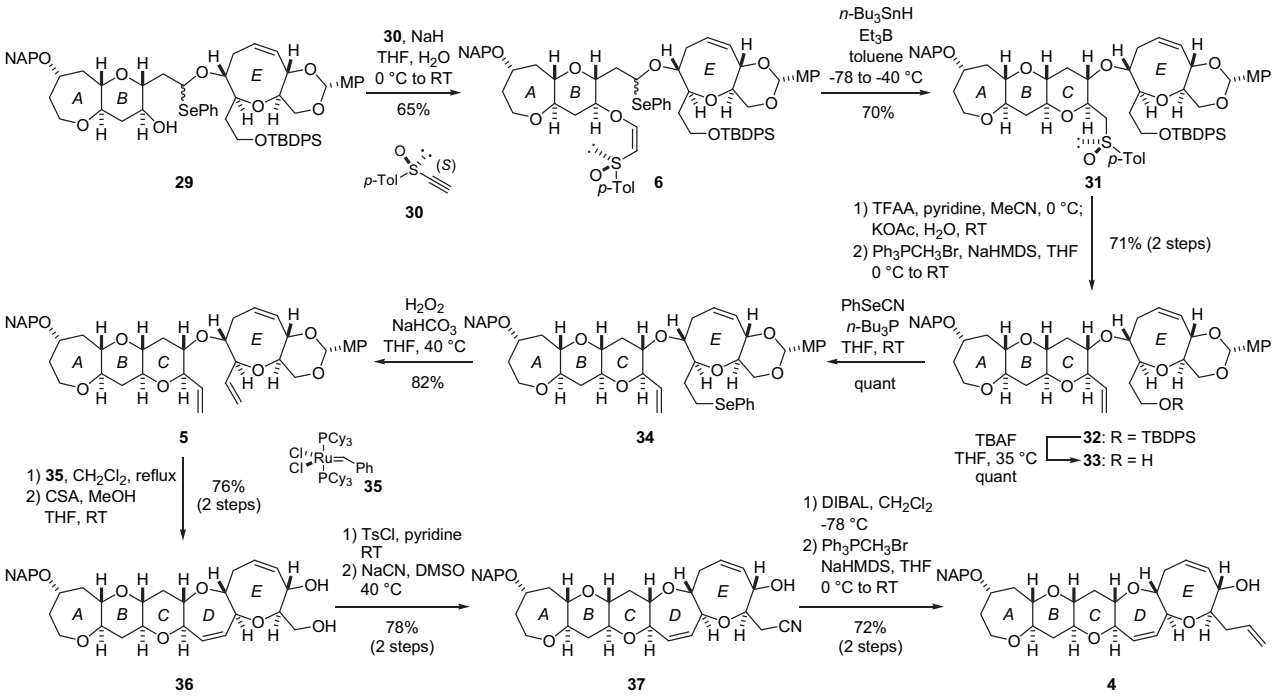
We have devised a practical and stereoselective route to construct the C-CTX-1 left wing. The features of the present synthesis are (i) an improved preparation of the AB-ring, (ii) an efficient coupling of the AB- and the E-rings through Yamaguchi esterification followed by *O*,*Se*-acetal formation, (iii) a completely stereocontrolled construction of the C-ring via 6-*exo* radical cyclization using *cis*-vinyl sulfoxide, and (iv) RCM reaction to build the seven-membered D-ring. The new method enabled us to synthesize **4** via 39 steps in 0.62% overall yield from commercially available materials (cf. previous synthesis: 39 steps in 0.25%).[10] The left wing prepared herein will play a key role in the total synthesis of C-CTX-1, which is currently under investigation in our laboratory.

4. Experimental

4.1. General experimental procedures

All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Chemical shifts of NMR spectra are reported in δ (ppm) down field from tetramethylsilane with reference to solvent signals [^{1}H NMR: $CHCl_3$ (7.26), C_6D_5H (7.16), ^{13}C NMR: $CDCl_3$ (77.0), C_6D_6 (128.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak.

*4.1.1. Diol **12**.* To a solution of alcohol **10** (930 mg, 2.78 mmol) in THF (19 mL) were added NaH (60% in oil, 278 mg, 6.95 mmol) and imidazole (95 mg, 1.39 mmol) at room temperature. After being stirred for 30 min, the mixture was added CS_2 (420 μL, 6.95 mmol) at



Scheme 5. Synthesis of the left wing of Caribbean ciguatoxin.

room temperature. After being stirred for 40 min, the reaction mixture was treated with MeI (517 μL, 8.28 mmol). After being stirred for 1 h, the mixture was treated with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 1:1) afforded xanthate **11**, which was used in the next reaction without further purification.

To a mixture of **11** (~2.78 mmol) and Et_3N (5.83 mL, 41.7 mmol) in dioxane (28 mL) and H_2O (2 mL) were added H_3PO_2 (1.2 mL, 27.8 mmol) and AIBN (457 mg, 2.78 mmol). After being stirred for 5 h at 90 °C, additional reagents (Et_3N, 5.8 mL; H_2O, 1.8 mL; H_3PO_2, 1.2 mL; AIBN, 457 mg) were added. After being stirred for 3 h at 90 °C, the mixture was cooled to room temperature, quenched with brine, and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. Filtration through the pad of silica gel (hexane/EtOAc 10:1–3:1) gave crude product, which was used in the next reaction without further purification.

To a solution of tricyclic compound (~2.78 mmol) in MeOH (140 mL) was added CSA (194 mg, 834 μmol) at room temperature. After being stirred for 2 h, the mixture was treated with Et_3N (800 μL) and concentrated. Purification by column chromatography (hexane/EtOAc 4:1–1:3) gave diol **12** (453 mg, 2.26 mmol) in 81% from **10**: colorless oil; colorless solid; mp 196 °C; $[\alpha]_D^{22}$ + 17.2 (*c* 1.01, $CHCl_3$); IR (film) ν 3357, 2943, 2863, 1426, 1277, 1129, 1097, 1083, 1052, 1030, 1017, 707, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, dddd, *J*=14.5, 6.3, 3.7, 3.7 Hz, H2), 5.86 (1H, dddd, *J*=14.5, 8.0, 3.1, 3.1 Hz, H3), 4.22 (1H, dd, *J*=14.9, 6.3 Hz, H1), 3.99 (1H, ddd, *J*=1.9, 3.7, 3.1 Hz, H1), 3.86 (1H, dd, *J*=11.5, 4.1 Hz, H10), 3.76 (1H, dd, *J*=11.5, 5.1 Hz, H10), 3.68 (1H, ddd, *J*=11.3, 9.4, 4.7 Hz, H8), 3.31 (1H, ddd, *J*=11.3, 8.8, 4.7 Hz, H6), 3.20 (1H, ddd, *J*=9.4, 5.1, 4.1 Hz, H9), 3.14 (1H, ddd, *J*=10.6, 8.8, 3.7 Hz, H5), 2.57 (1H, ddd, *J*=15.8, 8.4, 3.7 Hz, H4), 2.42 (1H, ddd, *J*=1.3, 4.7, 4.7 Hz, H7), 2.34 (1H, dddd, *J*=15.8, 10.6, 3.7, 3.1 Hz, H4), 1.92 (2H, br, OH ×2), 1.57 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1 (CH, C2), 128.3 (CH, C3), 82.11 (CH, C6), 80.77 (CH, C9), 77.73 (CH, C5), 67.67 (CH_2, C1), 66.91 (CH, C8), 63.18 (CH_2, C10), 40.31 (CH_2, C1), 34.42 (CH_2, C4); HRESIMS *m*/*z* 223.0940 $[M+Na]^+$ (calcd for $C_{10}H_{16}NaO_4$ 223.0941).

*4.1.2. Bis-TBS ethers **13**.* To a mixture of diol **12** (9.22 g, 46 mmol) and imidazole (11.1 g, 161 mmol) in DMF (92 mL) was added TBSCl (20.8 g, 138 mmol) at room temperature. After being stirred for 12 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with hexane and EtOAc (1:1). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc 1:0–5:1) afforded bis-TBS ethers **13** (18.9 g, 44 mmol) in 96% yield: colorless amorphous; $[\alpha]_D^{22}$ + 41.4 (*c* 1.01, $CHCl_3$); IR (film) ν 2952, 2929, 2856, 1471,1462, 1252, 1146, 1096, 1059, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95–5.82 (2H, m, H2, H3), 4.20 (1H, dd, *J*=14.7, 5.9 Hz, H1), 3.98 (1H, ddd, *J*=14.7, 2.0, 2.0 Hz, H1), 3.83 (1H, dd, *J*=11.3, 1.7 Hz, H10), 3.70 (1H, dd, *J*=11.3, 4.9 Hz, H10), 3.62 (1H, ddd, *J*=11.0, 9.0, 4.7 Hz, H8), 3.24 (1H, ddd, *J*=11.0, 8.8, 4.7 Hz, H6), 3.10–3.05 (2H, m, H5, H9), 2.57 (1H, ddd, *J*=15.9, 8.2, 3.5 Hz, H4), 2.36–2.26 (2H, m, H4, H7), 1.54 (1H, ddd, *J*=11.0, 11.0, 11.0 Hz, H7), 0.89 (9H, s, TBS), 0.87 (9H, s, TBS), 0.07 (6H, s, TBS), 0.05 (6H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0 (CH, C2), 128.8 (CH, C3), 82.52 (CH, C6), 82.46 (CH, C9), 77.52 (CH, C5), 67.60 (CH_2, C1), 66.15 (CH, C8), 62.91 (CH_2, C10), 41.14 (CH, C7), 34.65 (CH_2, C4), 26.11 (CH_3 ×3, TBS), 25.89 (CH_3 ×3, TBS), 18.64 (C, TBS), 18.07 (C, TBS), −4.21 (CH_3, TBS), −4.78 (CH_3 ×2, TBS), −5.01 (CH_3, TBS); HRESIMS *m*/*z* 451.2670 $[M+Na]^+$ (calcd for $C_{22}H_{44}NaO_4Si_2$ 451.2670).

*4.1.3. Epoxide **14**.* To a solution of **13** (7.59 g, 17.7 mmol) in CH_2Cl_2 (350 mL) was added *m*-CPBA (70% purity, 10.7 g, 43 mmol) at −25 °C. After being stirred for 6 h at 0 °C, *m*-CPBA (3.25 g, 13.2 mmol) was added and the mixture was stirred for additional 10 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 50:1–10:1) gave epoxide **14** (6.30 g, 14.1 mmol) in 80% yield along with its diastereomer **15** (1.29 g, 2.89 mmol) in 16% yield. **14**: colorless solid; mp 84 °C; $[\alpha]_D^{19}$ + 29.9 (*c* 1.01, $CHCl_3$); IR (film) ν 2953, 2928, 2855, 1472, 1251, 1144, 1100, 1075, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (1H, dd, *J*=14.5, 3.3 Hz, H1), 3.81 (1H, dd, *J*=11.3, 1.8 Hz, H10), 3.78 (1H, dd,

J=14.5, 14.5 Hz, H1), 3.66 (1H, dd, *J*=11.3, 4.9 Hz, H10), 3.53 (1H, ddd, *J*=11.4, 9.0, 4.7 Hz, H8), 3.25 (1H, ddd, *J*=11.0, 9.0, 4.5 Hz, H5), 3.20 (1H, dd, *J*=4.5, 4.5 Hz, H3), 3.02–2.98 (2H, m, H2, H9), 2.78 (1H, ddd, *J*=11.4, 9.0, 4.7 Hz, H6), 2.74 (1H, ddd, *J*=15.3, 4.5, 4.5 Hz, H4), 2.25 (1H, ddd, *J*=11.4, 4.7, 4.7 Hz, H7), 1.93 (1H, dd, *J*=15.3, 11.0 Hz, H4), 1.50 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H7), 0.88 (9H, s, TBS), 0.86 (9H, s, TBS), 0.05 (6H, s, TBS), 0.04 (6H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.10 (CH, C9), 80.55 (CH, C6), 76.54 (CH, C5), 66.25 (CH_2, C1), 65.62 (CH, C8), 62.74 (CH_2, C10), 55.55 (CH_2, C2), 52.65 (CH_2, C3), 40.53 (CH, C7), 33.67 (CH, C4), 26.08 (CH_3 ×3, TBS), 25.86 (CH_3 ×3, TBS), 18.61 (C, TBS), 18.05 (C, TBS), −4.24 (CH_3, TBS), −4.79 (CH_3 ×2, TBS), −5.00 (CH_3, TBS); HRESIMS *m*/*z* 467.2619 $[M+Na]^+$ (calcd for $C_{22}H_{44}NaO_5Si_2$ 467.2619).

*4.1.4. NAP ether **18**.* To a suspension of $LiAlH_4$ (175 mg, 4.62 mmol) in Et_2O (8 mL) was added a solution of **14** (585 mg, 1.32 mmol) in Et_2O (4 mL) at −30 °C. After being stirred for 5 h at −30 to −20 °C, the reaction mixture was quenched with saturated aqueous Roschell's salt and stirred for 2 h. The mixture was extracted with EtOAc and the organic layer was washed with brine. Concentration and column chromatography (hexane/EtOAc 5:1–3:1) afforded a mixture of alcohols **16** and **17** (592 mg, 1.32 mmol) in quantitative yield.

To a solution of alcohols **16** and **17** in THF (3.3 mL) and DMF (1.1 mL) was added NaH (60% in oil, 158 mg, 3.96 mmol) at 0 °C. After being stirred for 30 min, the mixture were added NAPBr (583 mg, 2.64 mmol) and TBAI (97.5 mg, 264 μmol) at room temperature. After being stirred for 15 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 1:0–30:1) gave NAP ether **18** (515 mg, 877 μmol) in 65% yield along with the regioisomer **19** (134 mg, 228 μmol) in 17% yield. **18**: colorless amorphous; $[\alpha]_D^{19}$ +29.7 (*c* 1.01, $CHCl_3$); IR (film) ν 2951, 2928, 2855, 1471, 1462, 1251, 1095, 856, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (4H, m, NAP), 4.49–7.44 (3H, m, NAP), 4.74 (1H, d, *J*=12.3 Hz, NAP), 4.67 (1H, d, *J*=12.3 Hz, NAP), 3.97 (1H, ddd, *J*=12.9, 5.9, 3.9 Hz, H1), 3.87 (1H, dddd, *J*=7.4, 5.9, 5.1, 3.5 Hz, H3), 3.82 (1H, dd, *J*=11.3, 1.8 Hz, H10), 3.69 (1H, dd, *J*=11.3, 4.7 Hz, H10), 3.60 (1H, ddd, *J*=11.9, 9.2, 4.9 Hz, H8), 3.52 (1H, ddd, *J*=12.9, 9.4, 2.9 Hz, H1), 3.50 (1H, ddd, *J*=9.2, 9.2, 3.4 Hz, H5), 3.12 (1H, ddd, *J*=11.9, 9.2, 4.9 Hz, H6), 3.08 (1H, ddd, *J*=9.2, 4.7, 1.8 Hz, H9), 2.39 (1H, ddd, *J*=14.7, 5.1, 3.7 Hz, H4), 2.25 (1H, ddd, *J*=11.9, 4.9, 4.9 Hz, H7), 2.11 (1H, dddd, *J*=15.0, 5.9, 5.9, 2.9 Hz, H2), 1.97 (1H, dddd, *J*=15.0, 9.4, 7.4, 3.9 Hz, H2), 1.91 (1H, ddd, *J*=14.7, 9.2, 3.5 Hz, H4), 1.53 (1H, ddd, *J*=11.9, 11.9, 11.9 Hz, H7), 0.89 (9H, s, TBS), 0.87 (9H, s, TBS), 0.06 (6H, s, TBS), 0.05 (6H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (C, NAP), 133.4 (C, NAP), 133.1 (C, NAP), 128.3 (CH, NAP), 128.0 (CH, NAP), 127.8 (CH, NAP), 126.3 (CH, NAP), 126.2 (CH, NAP), 125.9 (CH, NAP), 125.8 (CH, NAP), 82.74 (CH, C9), 78.75 (CH, C6), 76.71 (CH, C5), 72.96 (CH, C3), 70.49 (CH_2, NAP), 66.58 (CH_2, C1), 66.08 (CH, C8), 62.89 (CH_2, C10), 40.56 (CH_2, C7), 38.64 (CH_2, C4), 37.02 (CH_2, C2), 26.11 (CH_3 ×3, TBS), 25.89 (CH_3 ×3, TBS), 18.62 (C, TBS), 18.06 (C, TBS), −4.21 (CH_3, TBS), −4.70 (CH_3, TBS), −4.78 (CH_3, TBS), −4.96 (CH_3, TBS); HRESIMS *m*/*z* 609.3402 $[M+Na]^+$ (calcd for $C_{33}H_{54}NaO_5Si_2$ 609.3402).

*4.1.5. Alcohol **20**.* To a solution of **18** (3.27 g, 5.57 mmol) in MeOH (34 mL) and THF (34 mL) was added CSA (77 mg, 334 μmol) at 0 °C. After being stirred for 6 h at the same temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (henxane/EtOAc 30:1–3:1) afforded alcohol **20** (2.49 g, 5.26 mmol) in 95% yield: colorless amorphous; $[\alpha]_D^{19}$ +36.3 (*c* 1.00, $CHCl_3$); IR (film) ν 3474, 2950, 2928, 2856, 1471, 1462, 1360, 1252, 1095, 857, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (4H, m, NAP), 7.50–7.45 (3H, m, NAP), 4.74 (1H, d, *J*=12.3 Hz, NAP), 4.71 (1H, d, *J*=12.3 Hz, NAP), 3.99 (1H, ddd, *J*=12.9, 6.1, 3.9 Hz, H1), 3.89 (1H, dddd, *J*=8.6, 7.0, 4.9, 3.5 Hz, H3), 3.80 (1H, ddd, *J*=11.4, 6.7, 3.0 Hz, H10), 3.62–3.54 (3H, m, H5, H8, H10), 3.52 (1H, ddd, *J*=12.9, 9.0, 2.9 Hz, H1), 3.18 (1H, ddd, *J*=11.3, 5.7, 3.0 Hz, H9), 3.15 (1H, ddd, *J*=11.6, 9.2, 4.5 Hz, H6), 2.37 (1H, ddd, *J*=14.7, 4.9, 3.9 Hz, H4), 2.27 (1H, ddd, *J*=11.6, 4.5, 4.5 Hz, H7), 2.12 (1H, dddd, *J*=15.0, 8.6, 6.1, 2.9 Hz, H2), 1.99 (1H, dddd, *J*=15.0, 9.0, 7.0, 3.9 Hz, H2), 1.94 (1H, m, OH), 1.90 (1H, ddd, *J*=14.7, 9.4, 3.5 Hz, H4), 1.57 (1H, ddd, *J*=11.6, 11.6, 11.6 Hz, H7), 0.87 (9H, s, TBS), 0.08 (3H, s, TBS), 0.07 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (C, NAP), 133.4 (C, NAP), 133.1 (C, NAP), 128.3 (CH, NAP), 127.9 (CH, NAP), 127.8 (CH, NAP), 126.3 (CH, NAP), 126.2 (CH, NAP), 126.0 (CH, NAP), 125.8 (CH, NAP), 81.74 (CH, C9), 78.55 (CH, C6), 76.93 (CH, C5), 72.66 (CH, C3), 70.60 (CH_2, NAP), 66.94 (CH, C8), 66.44 (CH_2, C1), 62.77 (CH_2, C10), 40.79 (CH_2, C7), 38.67 (CH_2, C4), 36.55 (CH_2, C2), 25.02 (CH_3 ×3, TBS), 18.01 (C, TBS), −4.09 (CH_3, TBS), −4.81 (CH_3, TBS); HRESIMS *m*/*z* 495.2534 $[M+Na]^+$ (calcd for $C_{27}H_{40}NaO_5Si$ 495.2537).

*4.1.6. Iodide **21**.* To a solution of **20** (3.20 g, 6.77 mmol) in THF were added imidazole (740 mg, 10.8 mmol), PPh_3 (2.83 g, 10.8 mmol), and I_2 (2.41 g, 9.48 mmol) at 0 °C. After being stirred for 1 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl and extracted with hexane/EtOAc (4:1). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 80:1–10:1) gave iodide **21** (3.88 g, 6.66 mmol) in 98% yield: colorless amorphous; $[\alpha]_D^{23}$ +22.3 (*c* 1.01, $CHCl_3$); IR (film) ν 2950, 2927, 2856, 1470, 1360, 1252, 1096, 854, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.79 (4H, m, NAP), 7.50–7.46 (3H, m, NAP), 4.76 (1H, d, *J*=12.2 Hz, NAP), 4.68 (1H, d, *J*=12.2 Hz, NAP), 3.97 (1H, ddd, *J*=12.9, 6.0, 3.9 Hz, H1), 3.90 (1H, dddd, *J*=8.8, 6.8, 5.4, 3.3 Hz, H3), 3.61 (1H, ddd, *J*=9.4, 9.4, 3.5 Hz, H5), 3.52 (1H, ddd, *J*=12.9, 9.0, 3.1 Hz, H1), 3.47 (1H, dd, *J*=10.5, 2.7 Hz, H10), 3.46 (1H, ddd, *J*=11.3, 8.4, 4.5 Hz, H8), 3.28 (1H, dd, *J*=10.5, 5.7 Hz, H10), 3.19 (1H, ddd, *J*=11.3, 9.4, 4.5 Hz, H6), 2.84 (1H, ddd, *J*=8.4, 5.6, 2.7 Hz, H9), 2.43 (1H, *J*=14.8, 5.4, 3.5 Hz, H4), 2.27 (1H, ddd, *J*=11.3, 4.5, 4.5 Hz, H7), 2.10 (1H, dddd, *J*=15.3, 8.8, 6.0, 3.1 Hz, H2), 1.96 (1H, dddd, *J*=15.3, 9.0, 6.8, 3.9 Hz, H2), 1.90 (1H, ddd, *J*=14.8, 9.4, 3.3 Hz, H4), 1.59 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H7), 0.88 (9H, s, TBS), 0.12 (3H, s, TBS), 0.10 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (C, NAP), 133.4 (C, NAP), 133.1 (C, NAP), 128.3 (CH, NAP), 128.0 (CH, NAP), 127.8 (CH, NAP), 126.4 (CH, NAP), 126.2 (CH, NAP), 126.0 (CH, NAP), 125.9 (CH, NAP), 79.88 (CH, C9), 78.43 (CH, C6), 77.11 (CH, C5), 72.55 (CH, C3), 70.52 (CH_2, NAP), 70.39 (CH, C8), 66.38 (CH_2, C1), 40.45 (CH_2, C7), 38.23 (CH_2, C4), 36.60 (CH_2, C2), 25.87 (CH_3 ×3, TBS), 17.97 (C, TBS), 8.76 (CH_2, C10), −3.87 (CH_3, TBS), −4.37 (CH_3, TBS); HRESIMS *m*/*z* 605.1558 $[M+Na]^+$ (calcd for $C_{27}H_{39I}NaO_4Si$ 605.1555).

*4.1.7. Nitrile **22**.* To a solution of iodide **21** (4.18 g, 7.17 mmol) in DMSO (14 mL) was added NaCN (703 mg, 14.3 mmol) at room temperature. After being stirred for 20 h at 45 °C, the mixture was treated with saturated aqueous $NaHCO_3$ and extracted with hexane/EtOAc (4:1). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 1:0–10:1) gave nitrile **22** (3.40 g, 7.06 mmol) in 98% yield: colorless amorphous; $[\alpha]_D^{30}$ +12.9 (*c* 0.68, CH_2Cl_2); IR (film) ν 3056, 2952, 2931, 2858, 1737, 1509, 1467, 1098, 839, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (4H, m, NAP), 7.51–7.45 (3H, m, NAP), 4.75 (1H, d, *J*=12.3 Hz, NAP), 4.69 (1H, d, *J*=12.3 Hz, NAP), 3.98 (1H, ddd, *J*=12.7, 6.0, 3.9 Hz, H1), 3.90 (1H, m, H3), 3.58–3.52 (2H, m, H1, H5), 3.50 (1H, ddd, *J*=12.1, 9.0, 4.5 Hz, H8), 3.28 (1H, ddd, *J*=9.0, 5.7, 3.5 Hz, H9), 3.20 (1H, ddd, *J*=12.1, 9.2 4.3 Hz, H6), 2.70 (1H, dd, *J*=16.6, 3.5 Hz, H10), 2.55 (1H, dd, *J*=16.6, 5.7 Hz, H10), 2.40 (1H, ddd, *J*=14.7, 4.6, 3.7 Hz, H4), 2.31 (1H, ddd,

J=12.1, 4.5, 4.5 Hz, H7), 2.10 (1H, dddd, J=15.5, 8.8, 6.0, 2.9 Hz, H2), 1.98 (1H, dddd, J=15.5, 8.8, 7.1, 3.9 Hz, H2), 1.89 (1H, ddd, J=14.7, 9.4, 3.3 Hz, H4), 1.54 (1H, ddd, J=12.1, 12.1, 12.1 Hz, H7), 0.87 (9H, s, TBS), 0.11 (3H, s, TBS), 0.10 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (C, NAP), 133.5 (C, NAP), 133.2 (C, NAP), 128.5 (CH, NAP), 128.1 (CH, NAP), 128.0 (CH, NAP), 126.5 (CH, NAP), 126.4 (CH, NAP), 126.1 (CH, NAP), 126.0 (CH, NAP), 117.6 (C, C11), 78.17 (CH, C6), 77.66 (CH, C5), 77.16 (CH, C9), 72.62 (CH, C3), 70.52 (CH_2, NAP), 69.43 (CH, C8), 66.63 (CH_2, C1), 40.61 (CH_2, C1), 38.44 (CH_2, C1), 36.54 (CH_2, C2), 25.94 (CH_3 ×3, TBS), 21.25 (CH_2, C10), 18.09 (C, TBS), −3.78 (CH_3, TBS), −4.59 (CH_3, TBS); HRESIMS m/z 504.2543 $[M+Na]^+$ (calcd for $C_{28}H_{39}NNaO_4Si$ 504.2541).

*4.1.8. Aldehyde **23**.* To a solution of **22** (3.40 g, 7.06 mmol) in CH_2Cl_2 (70 mL) was added DIBAL (1.0 M in hexane, 21 mL, 21 mmol) at −80 °C. After being stirred for 1 h at the same temperature, EtOAc (15 mL) and saturated aqueous Rochell's salt were added and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 30:1–3:1) gave aldehyde **23** (3.27 g, 6.79 mmol) in 96% yield: Colorless amorphous; $[\alpha]_D^{29}$ +30.2 (c 1.00, $CHCl_3$); IR (film) ν 2928, 2856, 1727, 1461, 1361, 1252, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s, CHO), 7.78–7.85 (1H, m, NAP), 7.45–7.5 (1H, m, NAP), 4.72 (1H, d, J=12.4 Hz, NAP), 4.66 (1H, d, J=12.4 Hz, NAP), 3.97 (1H, ddd, J=12.8, 6.0, 3.6 Hz, H1), 3.85–3.90 (1H, m, H3), 3.55–3.65 (2H, m, H5, H9), 3.51 (1H, ddd, J=12.8, 9.6, 3.2 Hz, H1), 3.41 (1H, ddd, J=11.2, 8.8, 4.0 Hz, H8), 3.17 (1H, ddd, J=11.2, 9.2, 4.0 Hz, H6), 2.73 (1H, dd, J=15.2, 2.0 Hz, H10), 2.40 (1H, ddd, J=14.8, 8.4, 3.6 Hz, H4), 2.28–2.39 (2H, m, H10, H7), 2.11 (1H, dddd, J=14.8, 6.0, 6.0, 3.2 Hz, H2), 1.97 (1H, dddd, J=14.8, 9.6, 7.2, 3.6 Hz, H2), 1.84 (1H, ddd, J=14.8, 10.0, 3.2 Hz, H4), 1.58 (1H, ddd, J=11.2, 11.2, 11.2 Hz, H7), 0.087 (9H, s, TBS), 0.06 (6H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6 (CHO), 136.2 (NAP), 133.4 (NAP), 133.1 (NAP), 128.3 (NAP), 128.0 (NAP), 127.8 (NAP), 126.4 (NAP), 126.3 (NAP), 126.0 (NAP), 125.8 (NAP), 78.5 (CH, C8), 77.6 (CH, C5), 77.3 (CH, C9), 72.6 (CH, C3), 70.6 (CH_2, NAP), 70.5 (CH, C6), 66.5 (CH_2, C1), 46.4 (CH_2, C10), 40.9 (CH_2, C7), 38.5 (CH_2, C4), 36.6 (CH_2, C2), 25.9 (TBS), 18.0 (TBS), −3.9 (TBS), −4.6 (TBS); HRESIMS m/z 507.2534 $[M+Na]^+$ (calcd for $C_{28}H_{40}NaO_5Si$ 507.2543).

*4.1.9. Carboxylic acid **7**.* To a mixture of aldehyde **23** (980 mg, 2.03 mmol), $NaH_2PO_4\cdot 2H_2O$ (550 mg, 4.58 mmol), and 2-methyl-2-butene (1.7 mL, 16.2 mmol) in t-BuOH (8 mL) and H_2O (2 mL) was added $NaClO_2$ (550 mg, 6.09 mmol) at room temperature. After being stirred for 3 h at room temperature, the mixture was treated with saturated aqueous $Na_2S_2O_3$ and NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 10:1–3:1) gave carboxylic acid **7** (920 mg, 1.83 mmol) in 90% yield: colorless solid; mp 102 °C; $[\alpha]_D^{29}$ +34.2 (c 1.00, $CHCl_3$); IR (film) ν 2929, 2857, 1713, 1462, 1360, 1254, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.77 (4H, m, NAP), 7.48–7.46 (3H, m, NAP), 4.72 (1H, d, J=12.4 Hz, NAP), 4.66 (1H, d, J=12.4 Hz, NAP), 3.97 (1H, ddd, J=12.8, 6.0, 4.0 Hz, H1), 3.85 (1H, m, H3), 3.57 (1H, ddd, J=14.4, 8.8, 3.6 Hz, H9), 3.54 (1H, m, H5), 3.51 (1H, ddd, J=12.8, 8.4, 3.2 Hz, H1), 3.42 (1H, ddd, J=11.6, 8.8, 4.4 Hz, H8), 3.18 (1H, ddd, J=11.6, 9.2, 4.4 Hz, H6), 2.83 (1H, dd, J=15.6, 3.6 Hz, H10), 2.39 (1H, dd, J=15.6, 14.4 Hz, H10), 2.38 (1H, ddd, J=14.4, 4.0, 4.0 Hz, H4), 2.29 (1H, ddd, J=11.6, 4.4, 4.4 Hz, H7), 2.07 (1H, dddd, J=15.2, 11.6, 6.0, 3.2 Hz, H2), 1.95 (1H, dddd, J=15.2, 8.4, 5.6, 4.0 Hz, H2), 1.84 (1H, ddd, J=14.4, 9.6, 3.2 Hz, H4), 1.57 (1H, ddd, J=11.6, 11.6, 11.6 Hz, H7), 1.26 (1H, t, J=7.2 Hz, OH), 0.87 (9H, s, TBS), 0.07 (6H, d, J=4.0 Hz, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (CO_2H), 136.1 (NAP), 133.4 (NAP), 133.1 (NAP), 128.3 (NAP), 128.0 (NAP), 127.8 (NAP), 126.5 (NAP), 126.2 (NAP), 125.93 (NAP), 125.91 (NAP), 78.6 (CH, C9), 78.3 (CH, C6), 77.3 (CH, C5), 72.6 (CH, C3), 70.5 (CH_2, NAP), 70.1 (CH, C8), 66.4 (CH_2, C1), 40.8 (CH_2, C7), 38.4 (CH_2, C4), 37.6 (CH_2, C10), 36.6 (CH_2, C2), 25.8 (TBS), 18.0 (TBS), −3.9 (TBS), −4.7 (TBS); HRESIMS m/z 523.2494 $[M+Na]^+$ (calcd for $C_{28}H_{40}NaO_6Si$ 523.2490).

*4.1.10. TES ether **24**.* To a solution of carboxylic acid **7** (415 mg, 829 μmol) in THF (16.5 mL) was added TBAF (1.0 M in THF, 1.7 mL, 1.7 mmol) at room temperature. After being stirred for 4 h at 45 °C, the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 3:1–0:1) gave the corresponding alcohol **S1** (228 mg, 745 μmol) in 90% yield: colorless amorphous; $[\alpha]_D^{25}$ +9.2 (c 1.01, $CHCl_3$); IR (film) ν 3423, 2938, 2870, 1712, 1352, 1272, 1192, 1123, 1069 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91–7.81 (4H, m, NAP), 7.51–7.45 (3H, m, NAP), 4.41 (1H, d, J=12.0 Hz, NAP), 4.67 (1H, d, J=12.0 Hz, NAP), 3.93 (1H, ddd, J=12.7, 5.9, 3.9 Hz, H1), 3.76 (1H, dddd, J=6.9, 5.9, 5.1, 3.3 Hz, H3), 3.57 (1H, ddd, J=12.7, 8.4, 3.3 Hz, H1), 3.53 (1H, ddd, J=9.4, 9.4, 2.7 Hz, H9), 3.50 (1H, ddd, J=9.4, 9.2, 3.9 Hz, H5), 3.31 (1H, ddd, J=11.5, 9.4, 4.7 Hz, H8), 3.21 (1H, ddd, J=11.5, 9.2, 4.7 Hz, H6), 2.87 (1H, dd, J=16.0, 2.7 Hz, H10), 2.36 (1H, ddd, J=14.7, 5.1, 3.9 Hz, H4), 2.34 (1H, ddd, J=11.5, 4.7, 4.7 Hz, H7), 2.31 (1H, dd, J=16.0, 9.4 Hz, H10), 2.12 (1H, dddd, J=15.0, 5.9, 5.9, 3.3 Hz, H2), 1.94 (1H, dddd, J=15.0, 8.4, 6.9, 3.9 Hz, H2), 1.89 (1H, ddd, J=14.7, 9.4, 3.3 Hz, H4), 1.52 (1H, ddd, J=11.5, 11.5, 11.5 Hz, H7); ^{13}C NMR (100 MHz, CD_3OD) δ 175.6 (C, C11), 137.5 (C, NAP), 134.6 (C, NAP), 134.3 (C, NAP), 129.0 (CH, NAP), 128.9 (CH, NAP), 128.6 (CH, NAP), 127.3 (CH, NAP), 127.1 (CH, NAP), 126.9 (CH, NAP), 126.8 (CH, NAP), 80.04 (CH, C9), 79.58 (CH, C6), 78.31 (CH, C5), 74.14 (CH, C3), 71.28 (CH_2, NAP), 69.80 (CH, C8), 67.21 (CH_2, C1), 41.13 (CH_2, C7), 39.19 (CH_2, C4), 38.60 (CH_2, C10), 37.26 (CH_2, C2); HRESIMS m/z 409.1617 $[M+Na]^+$ (calcd for $C_{22}H_{26}NaO_6$ 409.1622).

To a solution of the above alcohol **S1** (228 mg, 745 μmol) in DMF (6 mL) were added imidazole (305 mg, 4.48 mmol) and TESCl (338 mg, 2.24 mmol) at room temperature. After being stirred for 2 h at room temperature, the mixture was treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The aqueous layer was added solid NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 10:1–1:1) gave TES ether **24** (342 mg, 683 μmol) in 92% yield: colorless amorphous; $[\alpha]_D^{25}$ +20.9 (c 1.01, $CHCl_3$); IR (film) ν 2953, 2875, 1714, 1456, 1238, 1094, 1006, 821, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (4H, m, NAP), 7.39–7.33 (3H, m, NAP), 4.60 (1H, d, J=12.3 Hz, NAP), 4.52 (1H, d, J=12.3 Hz, NAP), 3.86 (1H, ddd, J=12.7, 5.7, 3.7 Hz, H1), 3.74 (1H, dddd, J=8.8, 5.7, 4.9, 3.3 Hz, H3), 3.50 (1H, ddd, J=9.4, 9.2, 4.9 Hz, H5), 3.45 (1H, ddd, J=9.2, 8.8, 3.3 Hz, H9), 3.42 (1H, ddd, J=12.7, 7.2, 3.1 Hz, H1), 3.33 (1H, ddd, J=11.4, 9.2, 4.5 Hz, H8), 3.07 (1H, ddd, J=11.4, 9.2, 4.5 Hz, H6), 2.75 (1H, dd, J=15.7, 3.3 Hz, H10), 2.30 (1H, dd, J=15.7, 8.8 Hz, H10), 2.27 (1H, ddd, J=14.6, 4.9, 4.9 Hz, H4), 2.19 (1H, ddd, J=11.4, 4.5, 4.5 Hz, H7), 1.99 (1H, dddd, J=15.3, 5.7, 5.7, 3.1 Hz, H2), 1.84 (1H, dddd, J=15.3, 8.8, 7.2, 3.7 Hz, H2), 1.73 (1H, ddd, J=14.6, 9.4, 3.3 Hz, H4), 1.46 (1H, ddd, J=11.4, 11.4, 11.4 Hz, H7), 0.84 (9H, t, J=8.0 Hz, TES), 0.49 (6H, q, J=8.0 Hz, TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO_2H), 136.1 (NAP), 133.4 (NAP), 133.1 (NAP), 128.3 (NAP), 128.0 (NAP), 127.8 (NAP), 126.5 (NAP), 126.2 (NAP), 125.9 (NAP), 78.6 (CH, C9), 78.3 (CH, C6), 77.2 (CH, C5), 72.5 (CH, C3), 70.5 (CH_2, NAP), 70.1 (CH, C8), 66.4 (CH_2, C1), 40.9 (CH_2,C7), 38.3 (CH_2, C4), 36.5 (CH_2, C10), 36.5 (CH_2, C2), 6.92 (CH_2, TES), 5.13 (CH_3, TES); HRESIMS m/z 523.2485 $[M+Na]^+$ (calcd for $C_{28}H_{40}NaO_6Si$ 523.2486).

*4.1.11. Ester **25b**.* To a mixture of carboxylic acid **24** (1.75 g, 3.50 mmol) and alcohol **8** (1.48 g, 2.57 mmol) were added Et_3N (2.2 mL, 15.4 mmol) and 2,4,6-trichlorobenzoyl chloride (1.6 mL, 10.3 mmol) at room temperature. After being stirred for 30 min, the mixture was added DMAP (3.14 g, 25.7 mmol) and stirred for additional 1 h. The reaction mixture was quenched with H_2O and

extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 10:1–1:1) afforded ester **25b** (2.56 g, 2.42 mmol) in 94% yield: colorless amorphous; $[\alpha]_D^{25}$ −31.5 (*c* 1.03, $CHCl_3$); IR (film) ν 2930, 2856, 1740, 1518, 1250, 1105 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.84–7.60 (8H, m, MP, NAP, TBDPS), 7.49–7.34 (11H, m, MP, NAP, TBDPS), 6.91 (2H, d, *J*=8.8 Hz), 5.99 (1H, dd, *J*=11.0, 5.0 Hz, H19), 5.74 (1H, ddd, *J*=11.0, 10.3, 6.5 Hz, H18), 5.39 (1H, s, MP), 4.87 (1H, ddd, *J*=9.6, 2.9, 2.9 Hz, H16), 4.25 (1H, m, H20), 4.00 (1H, ddd, *J*=12.5, 5.9, 3.7 Hz, H1), 3.89–3.82 (3H, m, H3, H15, H22), 3.81 (3H, s, MP), 3.69 (1H, ddd, *J*=10.3, 7.0, 3.5 Hz, H13′), 3.62 (1H, ddd, *J*=10.3, 10.3, 4.9 Hz, H13′), 3.58–3.43 (5H, m, H1, H5, H8, H9, H22), 3.35 (1H, ddd, *J*=14.3, 14.3, 5.1 Hz, H21), 3.18 (1H, ddd, *J*=11.4, 9.2, 4.3 Hz, H6), 2.76 (1H, dd, *J*=14.3, 3.1 Hz, H10), 2.69 (1H, ddd, *J*=13.7, 10.3, 2.9 Hz, H17), 2.46 (1H, ddd, *J*=13.7, 6.5, 2.9 Hz, H17), 2.34–2.28 (3H, m, H4, H7, H10), 2.10 (1H, dddd, *J*=15.1, 5.9, 5.9, 2.8 Hz, H2), 1.95–1.78 (3H, m, H2, H4, H14), 1.59 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H7), 1.40 (1H, m, H14), 1.11 (9H, s, TBDPS), 0.96 (9H, t, *J*=8.0 Hz, TES), 0.62 (6H, q, *J*=8.0 Hz, TES); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C, C11), 160.2 (C, MP), 136.1 (C, NAP), 135.7 (CH ×4, TBDPS), 134.2 (CH, C19), 133.7 (C ×2, TBDPS), 133.3 (C, NAP), 133.1 (C, NAP), 130.3 (C, MP), 129.9–129.8 (CH ×2, MP, NAP), 128.3–126.4 (CH ×9, TBDPS ×6, NAP ×3), 126.2 (CH, C18), 125.94 (CH, NAP), 125.91 (CH, NAP), 125.8 (CH, NAP), 113.8 (CH, MP), 100.9 (CH, MP), 79.77 (CH, C20), 79.43 (CH, C9), 78.49 (CH, C6), 77.23 (CH, C8), 77.06 (CH, C16), 76.06 (CH, C15), 75.84 (CH, C21), 72.66 (CH, C3), 70.50 (CH_2, NAP), 70.20 (CH, C5), 69.29 (CH_2, C22), 66.67 (CH_2, C1), 59.86 (CH_2, 13′), 55.42 (CH_3, MP), 40.98 (CH_2, C7), 38.66 (CH_2, C4), 38.28 (CH_2, C10), 36.68 (CH_2, C2), 36.13 (CH_2, C14), 29.90 (CH_2, C17), 27.09 (CH_3 ×6, TBDPS), 19.29 (C ×2, TBDPS), 6.98 (CH_3 ×3, TES), 5.12 (CH_2 ×3, TES); HRESIMS *m*/*z* 1123.5392 $[M+Na]^+$ (calcd for $C_{64}H_{84}NaO_{12}Si_2$ 1123.5394).

4.1.12. Acetate ***26b***. To a solution of ester **25b** (635 mg, 601 μmol) in CH_2Cl_2 (10 mL) was added DIBAL (1.0 M in hexane, 900 μL, 900 μmol) at −90 °C. After being stirred for 1 h at the same temperature, a mixture of Ac_2O (142 mL, 1.5 mmol) and DMAP (293 mg, 2.4 mmol) in CH_2Cl_2 was added. The reaction mixture was allowed to warm up to 0 °C over 2 h. The mixture was quenched with saturated aqueous Rochell's salt and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 15:1–2:1) gave acetate **26b** (613 mg, 557 μmol) in 93% yield: colorless amorphous; IR (film) ν 2954, 2875, 1736, 1615, 1518, 1248, 1110, 823, 744, 703 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 8.00–7.35 (19H, m, NAP, TBDPS, MP), 6.95 (3/4H, d, *J*=8.4 Hz, MP), 6.93 (5/4H, d, *J*=8.8 Hz, MP), 6.82 (5/8H, dd, *J*=10.6, 3.4 Hz, H11), 6.75 (3/8H, dd, *J*=8.8, 2.4 Hz, H11), 6.16 (3/8H, dd, *J*=11.1, 4.9 Hz, H19), 6.11 (5/8H, dd, *J*=11.0, 4.9 Hz, H19), 6.05 (3/8H, m, H18), 5.84 (5/8H, m, H18), 5.39 (3/8H, s, MP), 5.35 (5/8H, s, MP), 4.84 (5/8H, d, *J*=12.2 Hz, NAP), 4.61 (5/8H, d, *J*=12.2 Hz, NAP), 4.49 (3/8H, d, *J*=12.5 Hz, NAP), 4.44 (3/8H, d, *J*=12.5 Hz, NAP), 4.40 (3/8H, m, H20), 4.32 (5/8H, m, H20), 4.16 (5/8H, dd, *J*=9.6, 3.9 Hz, H22), 4.12 (3/8H, m, H15), 4.03–3.85 (35/8H, m, H1, H5, H13′, H15, H16, H22), 3.81–3.77 (1H, m, H5, H9), 3.70–3.64 (13/8H, m, H3, H8), 3.60–3.43 (29/8H, m, H8, H9, H13′, H21, H22), 3.38 (9/8H, s, MP), 3.37 (15/8H, m, MP), 3.36–3.22 (19/8H, m, H1, H6, H22), 2.82 (3/8H, m, H17), 2.79–2.48 (37/8H, m, H4, H7, H10, H14, H17), 2.34 (3/8H, m, H14), 2.16 (5/8H, ddd, *J*=13.3, 10.6, 2.9 Hz, H10), 2.06–1.87 (35/8H, m, H2 ×2, H4, H7, H10), 1.82 (9/8H, s, Ac), 1.75 (15/8H, s, Ac), 1.60 (1H, m, H14), 1.37 (27/8H, s, TBDPS), 1.28 (45/8H, s, TBDPS), 1.07 (15/8H, t, *J*=8.0 Hz, TES), 1.03 (9/8H, t, *J*=8.0 Hz, TES), 0.67 (5/4H, q, *J*=8.0Hz, TES), 0.62 (3/4H, q, TES); HRESIMS *m*/*z* 1123.5392 $[M+Na]^+$ (calcd for $C_{64}H_{84}NaO_{12}Si_2$ 1123.5394).

4.1.13. O,Se-Acetal ***27b***. To a solution of $(PhSe)_2$ (677 mg, 2.17 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (1.0 M in hexane, 3.3 mL, 3.3 mmol), and the mixture was stirred for 1 h at room temperature. To a solution of acetal **26b** (1.84 g, 1.67 mmol) in CH_2Cl_2 (53 mL) at 0 °C was added freshly prepared *i*-$Bu_2AlSePh$. After being stirred for 1 h at 0 °C, the mixture was quenched with EtOAc and saturated aqueous Rochell's salt. After being stirred for 1 h, the mixture was extracted with EtOAc, and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 20:1–1:1) gave *O*,*Se*-acetal **27b** (1.71 g, 1.43 mmol) in 86% yield: colorless amorphous; IR (film) ν 3069, 3062, 2953, 2874, 1737, 1615, 1518, 1101, 823, 738 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.94–7.04 (24H, m, NAP, TBDPS, MP, Ph), 6.95 (1H, d, *J*=8.8 Hz, MP), 6.92 (1H, d, *J*=8.8 Hz, MP), 6.17–6.15 (1H, m, H11, H18), 6.13 (1/2H, dd, *J*=11.0, 4.9 Hz), 5.84–5.77 (3/2H, m, H11, H18), 5.38 (1/2H, s, MP), 5.36 (1/2H, s, MP), 4.64 (1/2H, d, *J*=12.4 Hz, NAP), 4.60 (1/2H, d, *J*=12.4 Hz, NAP), 4.50 (1H, s, NAP), 4.39–4.33 (1H, m, H20), 4.22 (1/2H, m, H16), 4.20 (1/2H, dd, *J*=10.4, 4.7 Hz, H22), 4.12 (1/2H, ddd, *J*=10.1, 10.1, 1.5 Hz, H15), 4.04 (1/2H, ddd, *J*=9.4, 9.4, 1.6 Hz, H15), 4.00–3.58 (15/2H, m, H1, H3, H5, H8, H9, H13′ ×2, H16, H21), 3.53 (1/2H, dd, *J*=10.4, 10.4 Hz, H22), 3.46–3.41 (2H, m, H8, H17, H21, H22), 3.39 (3/2H, s, MP), 3.36 (3/2H, s, MP), 3.33–3.17 (2H, m, H1, H6), 2.98–2.88 (1H, m, H10), 2.81 (1/2H, m, H17), 2.65–2.47 (7/2H, m, H4, H7, H14, H17), 2.38 (1/2H, ddd, *J*=13.9, 9.4, 3.9 Hz, H10), 2.30–2.17 (1H, m, H10, H14), 2.10–1.87 (4H, m, H2 ×2, H4, H7), 1.77 (1/2H, m, H14), 1.56 (1/2H, m, H14), 1.33 (9/2H, s, TBDPS), 1.29 (9/2H, s, TBDPS), 1.04 (3/2H, t, *J*=7.9 Hz, TES), 0.96 (3/2H, t, *J*=7.9 Hz, TES), 0.63 (1H, q, *J*=7.9 Hz, TES), 0.50 (1H, q, *J*=7.9 Hz, TES); HRESIMS *m*/*z* 1221.4817 $[M+Na]^+$ (calcd for $C_{68}H_{86}NaO_{10}SeSi_2$ 1221.4819).

4.1.14. Alcohol ***29***. To a solution of *O*,*Se*-acetal **27b** (40.5 mg, 33.8 μmol) in THF (1.7 mL) at −45 °C was added TBAF (1.0 M in THF, 135 μL, 135 μmol). After being stirred for 3 h at −30 °C, the mixture was added TBAF (65 μL, 65 μmol) and stirred for additional 3 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 20:1–1:1) gave alcohol **29** (34.9 mg, 32.2 μmol) in 95% yield: colorless amorphous; IR (film) ν 3462, 3050, 2929, 2856, 1734, 1615, 1249, 1103, 822, 738 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.85–6.90 (24H, m, NAP, MP, TBDPS, Ph), 6.84 (1H, d, *J*=9.0 Hz, MP), 6.82 (1H, d, *J*=9.0 Hz, MP), 6.11–6.04 (1H, m, H18, H19), 6.02 (1/2H, dd, *J*=11.0, 4.7 Hz, H19), 5.66 (1/2H, dd, *J*=8.2, 4.3 Hz, H11), 5.64 (1/2H, m, H18), 5.62 (1/2H, dd, *J*=10.6, 2.6 Hz, H11), 5.27 (1/2H, s, MP), 5.25 (1/2H, s, MP), 4.49 (1/2H, d, *J*=12.7 Hz, NAP), 4.46 (1/2H, d, *J*=12.7 Hz, NAP), 4.36 (1H, s, NAP), 4.27 (1/2H, dd, *J*=9.0, 3.9 Hz, H20), 4.22 (1/2H, dd, *J*=6.9, 5.5 Hz, H20), 4.14–4.02 (3/2H, m, H15, H16, H22), 3.92 (1/2H, m, H15), 3.84–3.77 (3/2H, m, H1, H13′), 3.74 (1/2H, dd, *J*=10.4, 4.8 Hz, H22), 3.71–3.62 (3/2H, m, H5, H16), 3.57–3.30 (9/2H, m, H3, H9, H13′, H21, H22), 3.28 (3/2H, s, MP), 3.26 (3/2H, s, MP), 3.24–3.22 (1H, m, H8, H17), 3.17–3.09 (1H, m, H1), 3.06–2.83 (2H, m, H6, H8, H10), 2.72–2.64 (1H, m, H10, H17), 2.52–2.35 (2H, m, H4, H14, H17), 2.26 (1/2H, ddd, *J*=11.6, 4.3, 4.3 Hz, H7), 2.23–2.09 (5/2H, m, H7, H10, H14, H17), 1.92–1.65 (7/2H, m, H2 ×2, H4, H14), 1.57 (1/2H, ddd, *J*=11.7, 11.7, 11.7 Hz, H7), 1.49 (1/2H, ddd, *J*=11.6, 11.6, 11.6 Hz, H7), 1.42 (1/2H, m, H14); HRESIMS *m*/*z* 1107.3953 $[M+Na]^+$ (calcd for $C_{62}H_{72}NaO_{10}SeSi$ 1107.3952).

4.1.15. Vinyl sulfoxide ***6***. To a solution of alcohol **29** (930 mg, 854 μmol) in THF (65 mL) at 0 °C was added NaH (60% in oil, 102 mg, 2.56 mmol) and the mixture was warmed to room temperature. After being stirred for 1 h, the reaction mixture was added a solution of sulfoxide **30** (210 mg, 1.28 mmol) and H_2O (15 mL, 854 μmol) in THF (0.5 mL). After being stirred for 40 min, the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4.

Concentration and purification by flash column chromatography (hexane/EtOAc 10:1–1:1) gave vinyl sulfoxide **6** (690 mg, 553 μmol) in 65% yield along with recovered **29** (278 mg, 256 μmol) in 30% yield. **6**: colorless amorphous; IR (film) ν 2929, 2856, 1735, 1617, 1248, 1103, 1041, 822, 738, 704 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.85–6.82 (30H, m, NAP, MP, TBDPS, Ph, *p*-Tol), 6.08 (1/2H, dd, *J*=11.1, 4.9 Hz, H19), 6.05–6.01 (1H, m, H18, H19), 5.87 (1/2H, d, *J*=5.7 Hz, H12), 5.80 (1/2H, m, H18), 5.68 (1/2H, m, H11), 5.64 (1/2H, d, *J*=5.5 Hz, H12), 5.59 (1/2H, m, H11), 5.30 (1/2H, d, *J*=5.7 Hz, H13), 5.28 (1/2H, s, MP), 5.24 (1/2H, s, MP), 5.22 (1/2H, d, *J*=5.5 Hz, H13), 4.52 (1/2H, d, *J*=12.1 Hz, NAP), 4.48 (1/2H, d, *J*=12.1 Hz, NAP), 4.39 (1H, s, NAP), 4.25–4.22 (1H, m, H20), 4.16 (1/2H, m, H16), 4.12–4.04 (2H, m, H13′, H16, H22), 4.01 (1/2H, m, H15), 3.96 (1/2H, m, H15), 3.86–3.61 (11/2H, m, H1, H5, H6, H9, H13′, H21, H22), 3.58–3.53 (1H, m, H3), 3.45–3.34 (3/2H, m, H8, H17, H22), 3.29–3.22 (1H, m, H21, H22), 3.27 (3/2H, s, MP), 3.25 (3/2H, s, MP), ; 3.18–3.07 (3/2H, m, H1, H8), 3.04–2.96 (1H, m, H6), 2.88 (1/2H, m, H10), 2.71–2.60 (1H, m, H10, H17), 2.52–2.34 (3H, m, H4, H14, H17 ×2), 2.31–2.19 (3/2H, m, H7, H10), 2.12 (1/2H, m, H10), 1.96 (3/2H, s, *p*-Tol), 1.94 (3/2H, m, *p*-Tol), 1.88–1.66 (9/2H, m, H2 ×2, H4, H7, H14), 1.25 (1/2H, m, H14), 1.20 (9/2H, s, TBDPS), 1.14 (9/2H, s, TBDPS); HRESIMS *m*/*z* 1271.4247 $[M+Na]^+$ (calcd for $C_{71}H_{80}NaO_{11}SSeSi$ 1271.4248).

*4.1.16. Sulfoxide **31**.* To a mixture of **6** (387 mg, 310 μmol) and *n*-Bu_3SnH (750 μL, 2.79 mmol) in toluene (103 mL) at −78 °C was added Et_3B (1.0 M in THF, 2.5 mL, 2.5 mmol). After being stirred for 3 h at −40 °C, the reaction mixture was concentrated and directly subjected to flash column chromatography (hexane/EtOAc 4:1–1:3) to give sulfoxide **31** (236 mg, 216 μmol) in 70% yield: colorless amorphous; $[\alpha]_D^{22}$ −60.4 (*c* 1.01, $CHCl_3$); IR (film) ν 2930, 2856, 1616, 1517, 1459, 1427, 1387, 1249, 1104, 1038, 823, 754, 703 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.82–7.21 (21H, m, MP, NAP, TBDPS, *p*-Tol), 6.89–6.82 (4H, m, MP, *p*-Tol), 6.02 (1H, dd, *J*=10.9, 4.7 Hz, H19), 5.63 (1H, m, H18), 5.38 (1H, s, MP), 4.52 (1H, d, *J*=12.3 Hz, NAP), 4.47 (1H, d, *J*=12.3 Hz, NAP), 4.30 (1H, m, H20), 4.09 (1H, dd, *J*=16.0, 10.6 Hz, H22), 3.89–3.69 (7H, m, H1, H5, H11, H13′ ×2, H15, H16), 3.58 (1H, m, H3), 3.47 (2H, m, H21, H22), 3.36 (1H, ddd, *J*=9.0, 4.3, 4.3 Hz, H12), 3.26 (3H, s, MP), 3.22–3.14 (2H, m, H1, H13), 3.08 (1H, ddd, *J*=11.4, 9.4, 4.3 Hz, H6), 2.95–2.83 (2H, m, H8, H13), 2.80 (1H, ddd, *J*=11.6, 3.9, 3.9 Hz, H9), 2.62 (1H, m, H17), 2.51 (1H, ddd, *J*=15.0, 4.1, 3.1 Hz, H4), 2.44 (1H, ddd, *J*=11.9, 4.3, 4.3 Hz, H7), 2.33 (1H, ddd, *J*=11.6, 4.3, 4.3 Hz, H10), 2.31–2.24 (2H, m, H14, H17), 1.95 (3H, s, *p*-Tol), 1.91 (1H, m, H2), 1.84–1.75 (3H, m, H2, H4, H7), 1.63–1.53 (1H, m, H14), 1.43 (1H, ddd, *J*=11.6, 11.6, 11.6 Hz, H10); ^{13}C NMR (100 MHz, C_6D_6) δ 160.5 (C, MP), 143.2 (C, *p*-Tol), 140.9 (C, *p*-Tol), 136.9 (C, NAP), 136.0 (CH, H19), 134.0–124.4 (30C, NAP, MP, TBDPS, *p*-Tol), 126.5 (CH, C18), 113.8 (CH, *p*-Tol), 101.1 (CH, MP), 83.69 (CH, C16), 80.20 (CH, C20), 79.63 (CH, C6), 77.67 (CH, C15), 77.52 (CH, C5), 77.14 (CH, C8), 76.95 (CH, C12), 76.19 (CH, C21), 75.72 (CH, C9), 74.64 (CH, C11), 73.01 (CH, C3), 70.56 (CH_2, NAP), 69.64 (CH_2, C22), 66.29 (CH_2, C1), 60.72 (CH_2, C13′), 60.15 (CH_2, C13), 54.78 (CH_3, MP), 39.06 (CH_2, C4), 38.21 (CH_2, C10), 37.36 (CH_2, C2), 37.27 (CH_2, C4), 36.89 (CH_2, C7), 30.67 (CH_2, C17), 27.19 (CH_3 ×3, TBDPS), 21.12 (CH_3, *p*-Tol), 19.38 (C, TBDPS); HRESIMS *m*/*z* 1115.4768 $[M+Na]^+$ (calcd for $C_{65}H_{76}NaO_{11}SSi$ 1115.4770).

*4.1.17. Diene **32**.* To a mixture of sulfoxide **31** (236 mg, 216 μmol) and pyridine (105 μL, 1.30 mmol) in CH_3CN (4.3 mL) at 0 °C was added TFAA (90 μL, 648 μmol). After being stirred 2 h, the mixture was added a solution of KOAc (636 mg, 6.48 mmol) in H_2O (4.0 mL) and stirred for 12 h at room temperature. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 4:1–1:2) gave the corresponding aldehyde **S2** (174 mg, 180 μmol) in 83% yield: colorless amorphous; $[\alpha]_D^{24}$ −55.2 (*c* 1.00, $CHCl_3$); IR (film) ν 2930, 2857, 1740, 1615, 1517, 1461, 1427, 1385, 1249, 1103, 823, 754, 703 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 9.47 (1H, s, H13), 7.85–7.24 (19H, m, MP, NAP, TBDPS), 6.83 (2H, d, *J*=9.2 Hz, MP), 6.04 (1H, dd, *J*=10.9, 5.0 Hz, H19), 5.63 (1H, m, H18), 5.33 (1H, s, MP), 4.52 (1H, d, *J*=125 Hz, NAP), 4.49 (1H, d, *J*=12.5 Hz, NAP), 4.31 (1H, m, H20), 4.10 (1H, dd, *J*=10.1, 4.7 Hz, H22), 3.88–3.78 (4H, m, H1, H13′ ×2, H15), 3.71 (1H, ddd, *J*=9.8, 9.8, 2.5 Hz, H5), 3.57–3.49 (2H, m, H3, H21), 3.45 (1H, dd, *J*=10.1, 10.1 Hz, H22), 3.40–3.36 (2H, m, H12, H16), 3.27 (3H, s, MP), 3.24–3.13 (2H, m, H1, H11), 3.04 (1H, ddd, *J*=11.3, 9.0, 4.5 Hz, H6), 2.78 (1H, ddd, *J*=11.3, 9.2, 4.5 Hz, H8), 2.67 (1H, ddd, *J*=11.5, 9.2, 4.0 Hz, H9), 2.58–2.50 (2H, m, H4, H17), 2.43 (1H, ddd, *J*=11.3, 4.5, 4.5 Hz, H7), 2.26 (1H, ddd, *J*=11.5, 4.0, 4.0 Hz, H10), 2.21–2.16 (1H, m, H14), 2.12–2.06 (1H, m, H17), 1.95–1.88 (2H, m, H2 ×2), 1.82–1.78 (1H, m, H4), 1.74 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H7), 1.54–1.47 (1H, m, H14), 1.46 (1H, ddd, *J*=11.5, 11.5, 11.5 Hz, H10); ^{13}C NMR (100 MHz, C_6D_6) δ 196.7 (CH, C13), 160.3 (C, MP), 136.6–135.8 (×2, NAP, TBDPS), 134.0 (CH, C19), 133.8–126.2 (22C, MP, NAP, TBDPS), 126.0 (CH, C18), 125.9 (CH, NAP), 125.7 (CH, NAP), 113.6 (CH, MP), 100.9 (CH, MP), 83.78 (CH, C16), 83.08 (CH, C12), 80.00 (CH, C20), 79.29 (CH, C6), 77.50 (CH, C5), 77.40 (CH, C15), 76.20 (CH, C8), 76.00 (CH, C21), 74.99 (CH, C9), 72.75 (CH, C3), 72.27 (CH, C11), 70.38 (CH_2, NAP), 69.44 (CH_2, C22), 66.13 (CH_2, C1), 60.38 (CH_2, C13′), 54.58 (CH_3, MP), 38.84 (CH_2, C4), 37.49 (CH_2, C10), 36.93 (CH_2, C7), 36.49 (CH_2, C14), 36.46 (CH_2, C2), 30.41 (CH_2, C17), 26.97 (CH_3 ×3, TBDPS), 19.17 (C, TBDPS); HRESIMS *m*/*z* 991.4417 $[M+Na]^+$ (calcd for $C_{58}H_{68}NaO_{11}Si$ 991.4423).

To a suspension of methyltriphenylphosphonium bromide (579 mg, 1.62 mmol) in THF (10 mL) was added NaHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol) at 0 °C. To the reaction mixture was added a solution of aldehyde **S2** (174 mg, 180 μmol) in THF (4 mL). After being stirred for 1 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 10:1–2:1) gave diene **32** (149 mg, 154 μmol) in 86% yield: colorless amorphous; mp 236–239 °C; $[\alpha]_D^{24}$ −56.6 (*c* 1.00, $CHCl_3$); IR (film) ν 2930, 2857, 1615, 1517, 1461, 1427, 1385, 1249, 1089, 823, 755, 703 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.95–7.21 (19H, m, MP, NAP, TBDPS), 6.11 (1H, ddd, *J*=17.2, 10.7, 5.3 Hz, H13), 6.04 (1H, dd, *J*=11.2, 5.0 Hz, H19), 5.70 (1H, m, H18), 5.63 (1H, ddd, *J*=17.2, 1.6, 1.6 Hz, H14′), 5.33, (1H, s, MP), 5.26 (1H, ddd, *J*=10.7, 1.6, 1.6 Hz, H14′), 4.52 (1H, d, *J*=12.3 Hz, NAP), 4.49 (1H, d, *J*=12.3 Hz, NAP), 4.30 (1H, m, H20), 4.12 (1H, dd, *J*=10.3, 4.7 Hz, H22), 3.85–3.75 (5H, m, H1, H5, H13′ ×2, H15), 3.68 (1H, dddd, *J*=9.0, 5.3, 1.6, 1.6 Hz, H12), 3.61–3.51 (2H, m, H3, H21), 3.46 (1H, dd, *J*=10.3, 10.3 Hz, H22), 3.30 (1H, m, H16), 3.27 (3H, s, MP), 3.16 (1H, ddd, *J*=12.3, 9.4, 2.5 Hz, H1), 3.04 (1H, ddd, *J*=11.4, 9.0, 4.5 Hz, H6), 3.03–2.97 (2H, m, H8, H11), 2.84 (1H, ddd, *J*=11.1, 9.0, 4.3 Hz, H9), 2.58–2.53 (3H, m, H4, H7, H17), 2.32 (1H, ddd, *J*=11.1, 4.3, 4.3 Hz, H10), 2.25 (1H, m, H14), 2.15 (1H, ddd, *J*=10.6, 6.8, 2.9 Hz, H17), 1.94–1.73 (4H, m, H2 ×2, H4, H7), 1.56 (1H, ddd, *J*=11.1, 11.1, 11.1 Hz, H10), 1.39 (1H, m, H14); ^{13}C NMR (100 MHz, C_6D_6) δ 160.5 (C, MP), 136.9 (C, NAP), 136.5 (CH, C13), 136.0–126.0 (25C, MP, NAP, TBDPS), 133.5 (CH, C19), 126.7 (CH, C18), 117.1 (CH, C14′), 113.8 (CH, MP), 101.2 (CH, MP), 83.76 (CH, C16), 81.29 (CH, C12), 80.23 (CH, C20), 79.72 (CH, C6), 77.93 (CH, C15), 77.77 (CH ×2, C5, C11), 76.62 (CH, C8), 76.32 (CH, C21), 75.22 (CH, C9), 73.14 (CH, C3), 70.57 (CH_2, NAP), 69.70 (CH_2, C22), 66.39 (CH_2, C1), 60.60 (CH_2, C13′), 54.83 (CH_3, MP), 39.18 (CH_2, C4), 38.08 (CH_2, C10), 37.61 (CH_2, C7), 36.98 (CH_2, C14), 36.85 (CH_2, C2), 30.95 (CH_2, C17), 27.14 (CH_3 ×3, TBDPS), 19.38 (C, TBDPS); HRESIMS *m*/*z* 989.4630 $[M+Na]^+$ (calcd for $C_{59}H_{70}NaO_{10}Si$ 989.4630).

*4.1.18. Alcohol **33**.* To a solution of diene **32** (149 mg, 150 μmol) in THF (15 mL) at room temperature was added TBAF (1.0 M in THF,

450 μL, 450 μmol). After being stirred for 3 h at 35 °C, the mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 5:1–0:1) gave alcohol **33** (111 mg, 152 μmol) in quantitative yield: colorless solid; mp 174–177 °C; $[\alpha]_D^{25}$ −78.2 (*c* 1.00, $CHCl_3$); IR (film) *ν* 3347,2932, 2870, 1615, 1517, 1462, 1382, 1250, 1094, 1039, 821, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.88–7.79 (4H, m, MP, NAP), 7.52–7.40 (5H, m, MP, NAP), 6.88 (2H, d, *J*=8.8 Hz, MP), 5.87 (1H, ddd, *J*=17.0, 10.7, 6.5 Hz, H13), 5.84 (1H, dd, *J*=10.6, 4.3 Hz, H19), 5.74 (1H, m, H18), 5.42 (1H, s, MP), 5.40 (1H, d, *J*=17.0 Hz, H14′), 5.28 (1H, d, *J*=10.7 Hz, H14′), 4.73 (1H, d, *J*=12.5 Hz, NAP), 4.70 (1H, d, *J*=12.5 Hz, NAP), 4.42 (1H, m, H20), 4.43 (1H, dd, *J*=10.8, 5.2 Hz, H22), 3.99 (1H, ddd, *J*=12.7, 10.0, 4.0 Hz, H1), 3.91 (1H, m, H3), 3.80 (3H, s, MP), 3.77–3.71 (2H, m, H13′ ×2), 3.63–3.41 (7H, m, H1, H5, H12, H15, H16, H21, H22), 3.26–3.21 (2H, m, H6, H11), 3.08–3.00 (2H, H8, H9), 2.62 (1H, m, H17), 2.45–2.33 (4H, m, H4, H7, H10, H17), 2.15–1.95 (3H, m, H2 ×2, H14), 1.87 (1H, ddd, *J*=14.4, 9.6, 3.2 Hz, H4), 1.58–1.45 (3H, H7, H10, H14); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.1 (C, MP), 136.2 (C, NAP), 135.7 (CH, C13), 133.4 (CH, C19), 133.38–133.0 (C ×2, NAP, MP), 130.1 (C, NAP), 128.2–126.3 (CH, ×5, NAP, MP), 126.2 (CH, C18), 126.2 (CH, NAP), 125.9 (CH, NAP), 125.7 (CH, NAP), 119.1 (CH, C14′), 113.7 (CH, MP), 100.8 (CH, MP), 83.43 (CH, C16), 81.47 (CH, C15), 79.79 (CH, C20), 78.81 (CH, C12), 78.67 (CH, C6), 77.32 (CH, C5), 77.01 (CH, C11), 76.04 (CH, C9), 75.91 (CH, C21), 75.78 (CH, C8), 72.60 (CH, C3), 70.51 (CH_2, NAP), 69.41 (CH_2, C22), 66.43 (CH_2, C1), 59.52 (CH_2, C13′), 55.33 (CH_3, MP), 38.39 (CH_2, C4), 37.62 (CH_2, C10), 36.83 (CH_2, C7), 36.23 (CH_2, C2), 36.04 (CH_2, C14), 30.09 (CH_2, C17); HRESIMS *m*/*z* 751.3453 $[M+Na]^+$ (calcd for $C_{43}H_{52}NaO_{10}$ 751.3454).

*4.1.19. Selenide **34**.* To a mixture of alcohol **33** (204 mg, 280 μmol) and PhSeCN (344 μL, 2.80 mmol) in THF (56 mL) was added *n*-Bu_3P (699 μL, 2.80 mmol). After being stirred 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 10:1–2:1) gave selenide **34** (245 mg, 280 μmol) in quantitative yield: colorless solid; mp 66–70 °C; $[\alpha]_D^{24}$ −68.0 (*c* 1.02, $CHCl_3$); IR (film) *ν* 2931, 2869, 1615, 1517, 1438, 1382, 1249, 1103, 1039, 823, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.84–7.78 (4H, m, MP, NAP), 7.52–7.25 (10H, m, MP, NAP, Ph), 6.88 (2H, d, *J*=8.8 Hz, MP), 5.86 (1H, dd, *J*=11.0, 4.9 Hz, H19), 5.75 (1H, m, H18), 5.71 (1H, ddd, *J*=17.2, 10.5, 6.6 Hz, H13), 5.41 (1H, s, MP), 5.22 (1H, ddd, *J*=17.2, 1.2, 1.2 Hz, H14′), 5.11 (1H, ddd, *J*=10.5, 1.2, 1.2 Hz, H14′), 4.73 (1H, d, *J*=12.5 Hz, NAP), 4.70 (1H, d, *J*=12.5 Hz, NAP), 4.40 (1H, m, H20), 4.25 (1H, dd, *J*=10.8, 5.1 Hz, H22), 3.95 (1H, ddd, *J*=12.7, 10.0, 3.9 Hz, H1), 3.91 (1H, m, H3), 3.80 (3H, s, MP), 3.59 (1H, dd, *J*=10.8, 10.8 Hz, H22), 3.56–3.38 (6H, m, H1, H5, H12, H15, H16, H21), 3.25–3.18 (2H, m, H6, H11), 3.06–2.94 (3H, m, H8, H9, H13′), 2.85 (1H, ddd, *J*=16.4, 8.8, 7.5 Hz, H13′), 2.58 (1H, m, H7), 2.43–2.32 (4H, m, H4, H7, H10, H17), 2.13–2.07 (2H, m, H2, H14), 1.99 (1H, m, H2), 1.87 (1H, ddd, *J*=14.7, 9.8, 3.3 Hz, H4), 1.67 (1H, m, H14), 1.55–1.46 (2H, m, H7, H10); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.1 (C, MP), 136.2 (C, NAP), 135.5 (CH, C13), 133.4 (CH, C19), 133.3–125.7 (×18, MP, NAP, Ph), 126.2 (CH, C18), 119.4 (CH, C14′), 113.7 (CH ×2, MP), 100.8 (CH, MP), 83.64 (CH, C21), 81.57 (CH, C12), 80.99 (CH, C15), 79.79 (CH, C20), 78.84 (CH, C6), 77.35 (CH, C5), 77.15 (CH, C11), 76.27 (CH, C16), 76.06 (CH, C9), 75.78 (CH, C8), 72.61 (CH, C3), 70.54 (CH_2, NAP), 69.41 (CH_2, C22), 66.46 (CH_2, C1), 55.37 (CH_3, MP), 38.44 (CH_2, C4), 37.62 (CH_2, C7), 36.87 (CH_2, C10), 36.26 (CH_2, C2), 34.62 (CH_2, C14), 30.20 (CH_2, C17), 22.83 (CH_2, C13′); HRESIMS *m*/*z* 891.2980 $[M+Na]^+$ (calcd for $C_{49}H_{56}NaO_9Se$ 891.2982).

*4.1.20. Triene **5**.* To a mixture of selenide **34** (245 mg, 280 mmol) and $NaHCO_3$ (470 mg, 5.6 mmol) in THF (56 mL) was added H_2O_2 (34.5% in H_2O, 2.6 mL, 28.0 mmol) at room temperature. After being stirred for 10 h at room temperature, the mixture was warmed to 40 °C and stirred for additional 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$, extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 15:1–2:1) gave triene **5** (163 mg, 230 μmol) in 82% yield: colorless solid; mp 194–195 °C; $[\alpha]_D^{22}$ −67.8 (*c* 1.01, $CHCl_3$); IR (film) *ν* 2930, 2868, 1614, 1517, 1440, 1382, 1250, 1091, 1038, 821, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.88–7.79 (4H, m, NAP), 7.54–7.40 (5H, m, MP, NAP), 6.91 (2H, d, *J*=8.8 Hz, MP), 5.98 (1H, ddd, *J*=17.1, 10.6, 4.3 Hz, H14), 5.90 (1H, dd, *J*=11.0, 6.5 Hz, H19), 5,87 (1H, ddd, *J*=17.4, 7.6, 6.1 Hz, H13), 5.75 (1H, dddd, *J*=12.1, 12.1, 6.5, 1.6 Hz, H18), 5.44 (1H, s, MP), 5.38 (1H, ddd, *J*=17.4, 1.5, 1.5 Hz, H14′), 5.27 (1H, ddd, *J*=17.1, 1.8, 1.8 Hz, C13′), 5.24 (1H, ddd, *J*=7.6, 1.5, 1.5 Hz, H14′), 5.10 (1H, ddd, *J*=10.6, 1.8, 1.8 Hz, H13′), 4.74 (1H, d, *J*=12.3 Hz, NAP), 4.69 (1H, d, *J*=12.3 Hz, NAP), 4.44 (1H, ddd, *J*=11.0, 4.9, 1.6 Hz, H20), 4.30 (1H, dd, *J*=11.0, 5.3 Hz, H22), 3.98 (1H, ddd, *J*=12.7, 6.1, 3.9 Hz, H1), 3.91 (1H, m, H3), 3.85 (1H, m, H15), 3.80 (3H, s, MP), 3.66 (1H, dd, *J*=11.0, 11.0 Hz, H22), 3.63–3.47 (4H, m, H1, H5, H12, H16), 3.41 (1H, ddd, 11.0, 11.0, 5.3 Hz, H21), 3.23 (2H, ddd, *J*=11.1, 9.2, 4.5 Hz, H6, H11), 3.06 (1H, ddd, *J*=11.4, 9.0, 4.3 Hz, H8), 3.00 (1H, ddd, *J*=11.1, 9.2, 4.1 Hz, H9), 2.65 (1H, ddd, *J*=12.1, 9.4, 2.7 Hz, H17), 2.48–2.32 (4H, m, H4, H7, H10, H17), 2.09 (1H, dddd, *J*=14.9, 6.1, 6.1, 2.9 Hz, H2), 1.99 (1H, dddd, *J*=14.9, 8.8, 7.2, 4.1 Hz, H2), 1.87 (1H, ddd, *J*=13.1, 9.8, 3.5 Hz, H4), 1.55 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H7), 1.52 (1H, ddd, *J*=11.1, 11.1, 11.1 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.1 (C, MP), 137.1 (CH, C14), 136.2 (C, NAP), 135.6 (CH, C13), 133.7 (CH, C19), 133.3–125.7 (12C, MP, NAP), 126.3 (CH, C18), 118.4 (CH, C14′), 114.7 (CH, C13), 113.7 (CH ×2, MP), 100.9 (CH, MP), 83.13 (CH, C16), 81.22 (CH, C12), 81.13 (CH, C15), 79.87 (CH, C20), 78.86 (CH, C6), 77.35 (CH, C5), 77.31 (CH, C11), 76.10 (CH, C8), 75.80 (CH, C9), 75.54 (CH, C21), 72.64 (CH, C3), 70.55 (CH_2, NAP), 69.57 (CH_2, C22), 66.44 (CH_2, C1), 55.37 (CH_3, MP), 38.44 (CH_2, C4), 37.46 (CH_2, C10), 36.87 (CH_2, C7), 36.28 (CH_2, C2), 30.74 (CH_2, C17); HRESIMS *m*/*z* 733.3350 $[M+Na]^+$ (calcd for $C_{43}H_{50}NaO_9$ 733.3347).

*4.1.21. Diol **36**.* To a solution of **5** (84.6 mg, 119 μmol) in CH_2Cl_2 (60 mL) was added Grubbs' catalyst **35** (49 mg, 60 μmol). After being stirred for 12 h under reflux conditions, the reaction mixture was quenched with Et_3N at room temperature. After being stirred for 10 h at room temperature, the mixture was concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (hexane/EtOAc 5:1–1:1) to give diene **S3** (71.5 mg, 105 μmol) in 88% yield: colorless solid; mp 236–239 °C; $[\alpha]_D^{22}$ −98.1 (*c* 0.48, $CHCl_3$); IR (film) *ν* 2931, 2876, 1614, 1518, 1440, 1388, 1173, 1101, 998, 831, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.85–7.79 (4H, m, NAP), 7.52–7.41 (5H, m, MP, NAP), 6.91 (2H, d, *J*=8.8 Hz, MP), 5.88–5.80 (2H, m, H18, H19), 5.74 (1H, ddd, *J*=12.7, 1.4, 1.4 Hz, H13), 5.57 (1H, ddd, *J*=12.7, 1.2, 1.2 Hz, H14), 5.43 (1H, s, MP), 4.74 (1H, d, *J*=12.3 Hz, NAP), 4.71 (1H, d, *J*=12.3 Hz, NAP), 4.43 (1H, dd, *J*=8.8, 2.4 Hz, H20), 4.27 (1H, dd, *J*=10.8, 5.1 Hz, H22), 4.18 (1H, dd, *J*=8.6, 2.1 Hz, H15), 3.99 (1H, ddd, *J*=12.7, 6.0, 3.9 Hz, H1), 3.90 (1H, m, H3), 3.80 (3H, s, MP), 3.78 (1H, m, H12), 3.64 (1H, m, H16), 3.62 (1H, dd, *J*=10.8, 10.8 Hz, H22), 3.55–3.45 (3H, m, H1, H5, H21), 3.25 (1H, ddd, *J*=13.5, 9.0, 4.5 Hz, H11), 3.20 (1H, ddd, *J*=13.3, 9.2, 4.3 Hz, H6), 2.99–2.92 (2H, m, H8, H9), 2.73 (1H, ddd, *J*=12.7, 8.8, 3.7 Hz, H17), 2.41–2.25 (3H, m, H4, H7, H17), 2.23 (1H, ddd, *J*=13.5, 4.5, 4.5 Hz, H10), 2.09 (1H, dddd, *J*=15.1, 6.0, 6.0, 3.1 Hz, H2), 1.97 (1H, ddd, *J*=15.1, 8.6, 6.7, 3.9 Hz, H2), 1.89 (1H, ddd, *J*=14.5, 9.6, 3.3 Hz, H4), 1.52 (1H, ddd, *J*=13.3, 13.3, 13.3 Hz, H7), 1.46 (1H, ddd, *J*=13.5, 13.5, 13.5 Hz, H10); ^{13}C NMR (100 MHz, C_6D_6) *δ* 160.2 (C, MP), 136.2 (C, NAP), 135.2 (CH, C13), 133.7 (C, NAP), 133.1 (CH, C19), 133.1 (C, NAP), 131.0 (CH, C14), 130.2 (C, MP), 128.3 (CH, NAP), 127.9 (CH, NAP), 127.8 (CH, NAP), 127.5 (CH ×2, MP), 127.0 (CH, C18), 126.3

(CH, NAP), 126.2 (CH, NAP), 125.9 (CH, NAP), 125.8 (CH, NAP), 113.7 (CH ×2, MP), 100.8 (CH, MP), 85.01 (CH, C16), 81.05 (CH, C15), 80.64 (CH, C12), 79.76 (CH, C20), 78.86 (CH, C6), 78.57 (CH, C11), 77.32 (CH, C5), 76.12 (CH, C8), 76.00 (CH, C9), 75.93 (CH, C21), 72.63 (CH, C3), 70.56 (CH_2, NAP), 69.76 (CH_2, C22), 66.45 (CH_2, C1), 55.40 (CH_3, MP), 38.50 (CH_2, C4), 36.98 (CH_2, C10), 36.80 (CH_2, C7), 36.31 (CH_2, C2), 32.76 (CH_2, C17); HRESIMS *m*/*z* 705.3035 $[M+Na]^+$ (calcd for $C_{41}H_{46}NaO_9$ 705.3034).

To a solution of the above diene **S3** (71.5 mg, 105 μmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) was added CSA (2.4 mg, 10 μmol). After being stirred for 10 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by flash column chromatography (hexane/EtOAc 3:1–1:5) gave diol **36** (51 mg, 90 μmol) in 86% yield: colorless solid; mp 198–202 °C; $[\alpha]_D^{22}$ −95.6 (*c* 0.99, $CHCl_3$); IR (film) *ν* 3394, 2930, 2871, 1454, 1353, 1284, 1094, 1076, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.84–7.78 (4H, m, NAP), 7.52–7.45 (3H, m, NAP), 5.82–5.71 (3H, m, H13, H18, H19), 5.56 (1H, ddd, *J*=12.7, 2.3, 2.3 Hz, H14), 4.74 (1H, d, *J*=12.2 Hz, NAP), 4.70 (1H, d, *J*=12.2 Hz, NAP), 4.46 (1H, dd, *J*=9.2, 4.7 Hz, H20), 4.13 (1H, dd, *J*=9.0, 2.3 Hz, H15), 3.97 (1H, ddd, *J*=12.7, 6.0, 3.9 Hz, H1), 3.91–3.88 (2H, m, H3, H21), 3.80–3.74 (2H, m, H12, H22), 3.60 (1H, ddd, *J*=9.0, 3.7, 3.0 Hz, H16), 3.54–3.49 (2H, m, H1, H5), 3.41 (1H, ddd, *J*=9.4, 4.7, 4.1 Hz, H21), 3.27–3.18 (2H, m, H6, H11), 2.98–2.91 (2H, m, H8, H9), 2.69 (1H, ddd, *J*=12.9, 9.0, 3.7 Hz, H17), 2.38 (1H, ddd, *J*=14.7, 4.5, 3.7 Hz, H4), 2.33–2.27 (2H, m, H7, H17), 2.22 (1H, ddd, *J*=11.9, 3.7, 3.7 Hz, H10), 2.09 (1H, dddd, *J*=15.2, 6.0, 6.0, 3.3 Hz, H2), 1.97 (1H, dddd, *J*=15.2, 8.8, 6.9, 3.9 Hz, H2), 1.87 (1H, ddd, *J*=14.7, 9.4, 3.3 Hz, H4), 1.58 (2H, br, OH ×2), 1.50 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H7), 1.45 (1H, ddd, *J*=11.9, 11.9, 11.9 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.5 (C, C19), 136.2 (C, NAP), 135.1 (CH, C13), 133.4 (C, NAP), 133.1 (C, NAP), 130.9 (CH, C14), 128.3 (CH, NAP), 127.9 (CH, NAP), 127.8 (CH, NAP), 126.8 (CH, C18), 126.4 (CH, NAP), 126.2 (CH, NAP), 126.0 (CH, NAP), 125.8 (CH, NAP), 85.06 (CH, C21), 84.79 (CH, C16), 81.20 (CH, C15), 80.69 (CH, C12), 78.85 (CH, C6), 78.53 (CH, C11), 77.31 (CH, C5), 76.10 (CH, C9), 75.93 (CH, C8), 72.61 (CH, C3), 70.56 (CH_2, NAP), 70.16 (CH, C20), 66.44 (CH_2, C1), 64.53 (CH_2, C22), 38.47 (CH_2, C4), 36.96 (CH_2, C10), 36.77 (CH_2, C7), 36.27 (CH_2, C2), 32.63 (CH_2, C17); HRESIMS *m*/*z* 587.2614 $[M+Na]^+$ (calcd for $C_{33}H_{40}NaO_8$ 587.2615).

4.1.22. Nitrile ***37***. To a solution of diol **36** (41.6 mg, 73.7 μmol) in pyridine (7.4 mL) at room temperature was added TsCl (140 mg, 737 μmol). After being stirred for 8 h, the reaction mixture was quenched and saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (×3), and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 2:1–1:1) gave the corresponding tosylate **S4** (46.6 mg, 64.9 μmol) in 88% yield: colorless solid; mp 94 °C; $[\alpha]_D^{22}$ −92.2 (*c* 0.75, CH_2Cl_2); IR (film) *ν* 3455, 2931, 2871, 1598, 1356, 1094, 1074, 814, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.73–7.67 (6H, m, NAP, Ts), 7.41–7.35 (3H, m, NAP), 7.23 (2H, d, *J*=9.6 Hz, Ts), 5.66 (1H, dddd, *J*=11.2, 10.9, 6.7, 1.9 Hz, H18), 5.57 (1H, ddd, *J*=12.7, 2.7, 2.7 Hz, H13), 5.55 (1H, dd, *J*=11.2, 5.7 Hz, H19), 5.39 (1H, ddd, *J*=12.7, 2.3, 2.3 Hz, H14), 4.63 (1H, d, *J*=12.5 Hz, NAP), 4.58 (1H, d, *J*=12.5 Hz, NAP), 4.27 (1H, ddd, *J*=9.4, 5.7, 1.9 Hz, H20), 4.18 (2H, d, *J*=3.9 Hz, H22), 3.90 (1H, ddd, *J*=10.9, 2.7, 2.3 Hz, H15), 3.87 (1H, ddd, *J*=12.7, 6.0, 3.9 Hz, H1), 3.78 (1H, dddd, *J*=9.6, 6.8, 4.7, 3.6 Hz, H3), 3.60 (1H, ddd, *J*=11.3, 4.7, 2.7 Hz, H12), 3.44 (1H, ddd, *J*=11.4, 3.5, 3.5 Hz, H5), 3.42 (1H, ddd, *J*=10.9, 3.5, 2.5 Hz, H16), 3.39 (1H, ddd, *J*=12.7, 8.8, 8.6 Hz, H1), 3.35 (1H, dt, *J*=9.4, 3.9 Hz, H21), 3.10 (1H, ddd. *J*=11.4, 11.4, 3.9 Hz, H6), 3.08 (1H, ddd, *J*=11.3, 11.3, 4.7 Hz, H11), 2.84–2.81 (2H, m, H8, H9), 2.50 (1H, ddd, *J*=13.7, 10.9, 3.5 Hz, H17), 2.34 (3H, s, Ts), 2.27 (1H, ddd, *J*=14.6, 4.7, 3.5 Hz, H4), 2.20 (1H, ddd, *J*=13.7, 6.7, 2.5 Hz, H7), 2.08 (1H, ddd, *J*=11.3, 4.7, 4.7 Hz, H10), 2.00 (1H, dddd, *J*=15.4, 8.8, 6.0, 3.6 Hz, H2), 1.86 (1H, dddd, *J*=15.5, 8.6, 6.8, 3.9 Hz, H2), 1.75 (1H, ddd, *J*=14.6, 9.6, 3.5 Hz, H4), 1.38 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H7), 1.30 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 145.0 (C, Ts), 136.2 (C, NAP), 135.6 (CH, C19), 134.9 (CH, C13), 133.3 (C, NAP), 130.0 (C, Ts), 133.0 (C, NAP), 130.7 (NH, C14), 130.0 (CH ×2, Ts), 128.3 (CH, NAP), 128.1 (CH ×2, Ts), 127.9 (CH, NAP), 127.8 (CH, NAP), 127.5 (CH,C18), 126.3 (CH, NAP), 126.2 (CH, NAP), 125.9 (CH, NAP), 125.8 (CH, NAP), 84.57 (CH, C16), 83.29 (CH, C21), 81.54 (CH, C15), 80.71 (CH, C12), 78.87 (CH, C6), 78.49 (CH, C11), 77.32 (CH, C5), 76.12 (CH, C9), 75.92 (CH, C8), 72.64 (CH, C3), 71.31 (CH_2, C22), 70.57 (CH_2, NAP), 68.62 (CH, C20), 66.45 (CH_2, C1), 38.50 (CH_2, C4), 36.79 (CH_2, C7), 36.31 (CH_2, C2), 32.58 (CH_2, C17), 21.79 (CH_2, Ts); HRESIMS *m*/*z* 741.2703 $[M+Na]^+$ (calcd for $C_{40}H_{46}NaO_{10}S$ 741.2704).

To a solution of the above tosylate **S4** (110 mg, 153 μmol) in DMSO (22 mL) at room temperature was added NaCN (75 mg, 1.53 mmol). After being stirred for 20 h at 45 °C, the reaction mixture was quenched with EtOAc and saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (×3), and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 10:1–1:1) gave nitrile **37** (78 mg, 136 μmol) in 89% yield: colorless solid; mp 113 °C; $[\alpha]_D^{22}$ −97.7 (*c* 0.37, CH_2Cl_2); IR (film) *ν* 3381, 2932, 2872, 2248, 1438, 1353, 1283, 1093, 909, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.84–7.78 (4H, m, NAP), 7.49–7.46 (3H, m, NAP), 5.93 (1H, ddd, *J*=10.2, 2.6, 2.6 Hz, H13), 5.85 (1H, dddd, *J*=11.0, 10.4, 6.4, 1.4 Hz, H18), 5.67 (1H, dd, *J*=11.0, 5.0 Hz, H19), 5.58 (1H, ddd, *J*=10.2, 2.4, 2.4 Hz, H14), 4.73 (1H, d, *J*=12.5 Hz, NAP), 4.69 (1H, d, *J*=12.5 Hz, NAP), 4.27 (1H, m, H20), 4.13 (1H, ddd, *J*=8.6, 2.6, 2.4 Hz, H15), 3.97 (1H, ddd, *J*=12.7, 6.0, 3.9 Hz, H1), 3.90 (1H, dddd, *J*=9.6, 7.3, 6.0, 3.7 Hz, H3), 3.74 (1H, ddd, *J*=10.2, 2.6, 2.4 Hz, H12), 3.61 (1H, ddd, *J*=8.6, 31.1, 3.1 Hz, H16), 3.57 (1H, ddd, *J*=8.6, 8.6, 3.1 Hz, H21), 5.54 (1H, ddd, *J*=9.2, 4.6, 3.3 Hz, H5), 3.50 (1H, ddd, *J*=12.7, 9.0, 3.1 Hz, H1), 3.23 (1H, ddd, *J*=11.3, 9.0, 4.7 Hz, H11), 3.21 (1H, ddd, *J*=11.3, 9.2, 4.5 Hz, H6), 2.98–2.91 (2H, m, H9, H8), 2.90 (1H, dd, *J*=16.8, 3.1 Hz, H22), 2.69 (1H, ddd, *J*=10.4, 10.4, 3.1 Hz, H17), 2.58 (1H, dd, *J*=16.8, 8.6 Hz, H22), 2.38 (1H, ddd, *J*=14.7, 4.6, 3.7 Hz, H4), 2.33–2.29 (2H, m, H7, H17), 2.22 (1H, ddd, *J*=11.3, 4.7, 4.7 Hz, H10), 2.09 (1H, dddd, *J*=15.3, 6.0, 6.0, 3.1 Hz, H2), 1.97 (1H, dddd, *J*=15.3, 9.0, 7.3, 3.9 Hz, H2), 1.85 (1H, ddd, *J*=14.7, 9.6, 3.3 Hz, H4), 1.56 (1H, s, OH), 1.51 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H7), 1.43 (1H, ddd, *J*=11.3, 11.3, 11.3 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.2 (C, NAP), 135.4 (CH,C19), 134.4 (CH, C13), 133.4 (C, NAP), 133.1 (C, NAP), 131.1 (CH, C14), 128.6 (CH, C18), 128.3 (CH, NAP), 127.9 (CH, NAP), 127.8 (CH, NAP), 126.4 (CH,NAP), 126.2 (CH, NAP), 126.0 (CH, NAP), 125.8 (CH, NAP), 118.3 (C, CN), 84.25 (CH, C16), 81.49 (CH, C15), 81.42 (CH, C21), 80.73 (CH, C12), 78.88 (CH, C6), 78.52 (CH, C11), 77.32 (CH, C5), 76.14 (CH, C9), 75.91 (CH, C8), 72.65 (CH, C3), 71.44 (CH, C20), 70.57 (CH_2, NAP), 66.45 (CH_2, C1), 38.52 (CH_2, C4), 36.98 (CH_2, C10), 36.78 (CH_2, H7), 36.30 (CH_2, C2), 32.63 (CH_2, C17), 22.78 (CH_2, C22); HRESIMS *m*/*z* 596.2619 $[M+Na]^+$ (calcd for $C_{34}H_{39}NNaO_7$ 596.2619).

4.1.23. C-CTX left wing ***4***. To a solution of the nitrile **37** (53.1 mg, 92.6 μmol) in CH_2Cl_2 (9.3 mL) at −78 °C was added DIBAL (1.0 M in hexane, 370 μL, 370 μmol). After being stirred for 1 h at −78 °C, the reaction mixture was quenched with EtOAc and saturated aqueous Rochell's salt. The mixture was extracted with EtOAc (×3), and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and filtration through a pad of flash silica gel gave the aldehyde, which was used in the next reaction without further purification.

To a suspension of Ph_3PCH_3Br (200 mg, 556 mmol) in THF (4.6 mL) at 0 °C was added NaHMDS (1.0 M in THF, 370 μL, 370 μmol). After being stirred for 1 h, a solution of the above aldehyde in THF (4 mL) was added to the reaction mixture at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was quenched with aqueous saturated NH_4Cl. The mixture was extracted with EtOAc (×3), and the organic layer was washed with

brine and dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAc 10:1–3:1) gave the left wing fragment **4** (38.2 mg, 66.5 mmol) in 72% yield over two steps: colorless solid; mp 91 °C; $[\alpha]_D^{22}$ −91.9 (*c* 1.07, $CHCl_3$); IR (film) ν 3448, 2930, 2871, 1723, 1641, 1453, 1437, 1353, 1090, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (4H, m, NAP), 7.49–7.46 (3H, m, NAP), 5.93 (1H, dddd, *J*=16.8, 10.2, 7.4, 6.4 Hz, H23), 5.81–5.73 (2H, m, H13, H18), 5.69 (1H, dd, *J*=11.0, 4.9 Hz, H19), 5.52 (1H, ddd, *J*=12.7, 2.5, 2.5 Hz, H14), 5.15 (1H, dd, *J*=16.8, 1.9 Hz, H24), 5.11 (1H, dd, *J*=7.4, 1.9 Hz, H24), 4.74 (1H, d, *J*=12.5 Hz, NAP), 4.69 (1H, d, *J*=12.5 Hz, NAP), 4.22 (1H, m, H20), 4.06 (1H, ddd, *J*=8.8, 56.1, 2.5 Hz, H15), 3.98 (1H, ddd, *J*=12.7, 6.0, 3.7 Hz, H1), 3.89 (1H, m, H3), 3.74 (1H, ddd, *J*=9.2, 4.5, 2.5 Hz, H12), 3.59 (1H, ddd, *J*=8.8, 3.5, 3.5 Hz, H16), 3.55–3.48 (2H, m, H1, H5), 3.33 (1H, ddd, *J*=9.0, 9.0, 2.9 Hz, H21), 3.23 (1H, ddd, *J*=11.4, 9.2, 4.7 Hz, H11), 3.19 (1H, ddd, *J*=11.4, 9.1, 4.4 Hz, H6), 2.97–2.90 (2H, m, H8, H9), 2.71 (1H, ddd, *J*=13.1, 9.4, 3.5 Hz, H17), 2.63 (1H, ddd, *J*=12.8, 6.4, 2.9 Hz, H22), 2.38 (1H, ddd, *J*=14.7, 4.7, 3.7 Hz, H4), 2.34–2.17 (4H, m, H7, H10, H17, H22), 2.10 (1H, dddd, *J*=15.2, 6.0, 6.0, 3.0 Hz, H2), 1.99 (1H, dddd, *J*=15.3, 8.6, 6.8, 3.7 Hz, H2), 1.87 (1H, ddd, *J*=14.7, 9.6, 3.5 Hz, H4), 1.63 (1H, s, OH), 1.51 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H7), 1.43 (1H, ddd, *J*=11.4, 11.4, 11.4 Hz, H10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (CH, C19), 136.2 (C, NAP), 135.5 (CH, C23), 135.4 (CH, C13), 133.4 (C, NAP), 133.1 (C, NAP), 130.6 (CH, C14), 128.3 (CH, NAP), 128.0 (CH, NAP), 127.8 (CH, NAP), 127.0 (CH, C18), 126.3 (CH, NAP), 126.2 (CH, NAP), 126.0 (CH, NAP), 125.8 (CH, NAP), 117.3 (CH, C24), 85.75 (CH, C21), 84.70 (CH, C16), 81.13 (CH, C15), 80.81 (CH, C12), 78.92 (CH, C6), 78.49 (CH, C11), 77.32 (CH, C5), 76.13 (CH, C9), 75.98 (CH, C8), 72.65 (CH, C3), 72.22 (CH, C20), 70.58 (CH_2, NAP), 66.47 (CH_2, C1), 38.05 (CH_2, C4), 37.51 (CH_2, C22), 37.01 (CH_2, C10), 36.83 (CH_2, C7), 36.35 (CH_2, C2), 32.68 (CH_2, C17); HRESIMS *m*/*z* 597.2824 $[M+Na]^+$ (calcd for $C_{35}H_{42}NaO_7$ 597.2823).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.080.

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