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抗生素 Elansolid A 简化衍生物的不对称全合成

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摘要 Elansolid A 属于一类聚酮大环内酯天然产物, 具有良好的抗菌活性. 已经通过 28 步的最长线性合成步和总共 41 步反应实现了 elansolid A 的首次全合成. 在此基础上, 提出了 elansolid A 的简化类似物结构, 主要包含环己基稠合的 19 元大环内酯单元, 并采用汇聚式合成策略, 通过酸酐的去对称化醇解、钯催化的 Stille 偶联、Suzuki-Miyaura 偶联以及 Mukaiyama 环化等关键反应, 完成了此简化衍生物的不对称全合成.

关键词 不对称全合成; 偶联反应; 简化类似物; Elansolid A

Asymmetric Total Synthesis towards the Simplified Analogs of Antibiotic Elansolid A

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Abstract Natural product elansolid A belongs to one type of polyketide macrolactone with promising antibiotic activity. Previously, the first total synthesis of elansolid A in 28 longest linear sequence (LLS) and 41 steps in total has been achieved. Herein, the simplified analog of elansolid A, featured with a cyclohexyl-fused 19-memebered macrolactone, was proposed, and its asymmetric total synthesis based on a convergent strategy and key reactions exemplified by desymmetric alcoholysis of anhydride, Pd-catalyzed Stille coupling, Suzuki-Miyaura coupling as well as Mukaiyama macrolactonization was finished.

Keywords asymmetric total synthesis; coupling reaction; simplified analog; elansolid A

1 Introduction

The persistent occurrence of drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin intermediate *Staphylococcus aureus* (VISA) *etc.* has been a great threat to human beings, especially to those infected patients after encountering a surgery in clinic. Seeking novel antibiotics to combat with those drug-resistant bacteria thus becomes an emergent event.[1] The natural products elansolid family consisting of elansolids A (**1**/**1***),[2] A3 (**3**),[3] B1 (**2a**), B2 (**2b**),[2] *etc.* as showcased in Figure 1, were isolated from gliding bacterium *Chitinophaga sancti* (formerly *Flexibacter spec.*) and possessed antibacterial activities. For instance, elansolid A2 (**1***), showed activity against Gram-positive bacteria in the range of 0.2～64 μg/mL, while its atropisomer, elansolid A1 (**1**), was less active. In addition, the quinone methide elansolid A3 (**3**) was observed to possess a similarly promising minimal inhibit concentration (MIC) value against various MRSA as its counterpartner macrolactone elansolid A2 (**1***).[4] Previously, in the endeavor to elucidate the biosynthetic pathway of elansolid A1/A2 (**1**/**1***), we have totally synthesized the C^{20}-deoxy elansolid B1 (**2c**) as the proposed seco acid of elansolid A1/A2, and found that **2c** was also highly active against various MRSA, indicating the unnecessity of C^{20}-hydroxy function group for maintaining its antibiotic activity.[5] On the basis of the promising antibacterial activity profile of elansolid A2 (**1***), we anticipated that the 19-membered macrolactone motif might be a cru-

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cial pharmacophore to maintain the antibacterial activity, and on the other hand, the six-membered ring with a *cis*-C^{16}-C^{24} substitution may be also pivotal to keep the rigid conformation of this macrocycle. We are curious to know that whether the left five-membered ring motif on elansolid A1/A2 is still essential to maintain its antibiotic activity. Herein, we proposed the simplified structure (**4**) of antibiotic elansolid A1/A2, containing the cyclohexyl-fused 19-membered macrolactone, and performed its total synthesis as outlined in Scheme 1.[6]

The retrosynthetic analysis of the simplified analog **4** was outlined in Scheme 1, which basically followed the disconnection protocol as documented in our previous total synthesis of elansolid A1/A2 (**1**/**1***).[7-8] Derivative **4** could be assembled in a convergent manner from three fragments, vinyl iodide **5**, two-carbon unit **6** and unsaturated ester **7**. Fragments **5** and **7** could be welded by Pd-catalyzed Stille and Suzuki-Miyaura coupling reactions via a two-carbon unit **6**, and the macrocycle was able to be formed by Mukaiyama macrolactonization reaction.

2 Results and discussion

2.1 Synthesis of fragments

The synthesis of fragment **5** bearing three contiguous stereogenic centers commenced with the desymmetric alcoholysis of cyclic anhydrides **8** in the presence of cinchona catalyst $(DHQD)_2AQN$ to provide chiral carboxylic acid **9** following the known procedure (Scheme 2).[9] Then, two steps sequences including mixed-anhydride formation and subsequent reduction reaction afforded lactone **10**, which could be further reduced to form hemiacetal **11**. The subsequent alkyne formation[10] and Parikh-Doering oxidation delivered aldehyde **13**. Subsequently, the aromatic lithium species, generated by the exchange of *n*-BuLi and bromide **14**, attacked the resulting aldehyde **13** to furnish the alcohol **15** in a moderate diastereoselectivity (*dr*＝3∶1). The absolute configuration at the alcohol stereogenic center of **15** was assumed to be (*S*) according to the Cram-model as drawn in the **TS1**, which was further confirmed by Mosher ester analysis (Scheme 3).[11] Dess-Martin oxidation of **15** and lithium aluminum hydride reduction of the resulting ketone **16** afforded the (*R*)-configurated alcohol **17** in good *dr* (5∶1), of which the configuration at the alcohol stereocenter was consistent with elansolid A1/A2 (**1**/**1***) at C^{25} and validated again by Mosher ester analysis (Scheme 3). After acetylation and alkynyl iodination to generate **19**,[12] subsequent *cis*-reduction of the alkynyl iodide eventually led to the vinyl iodide fragment **5** (Scheme 2).[13]

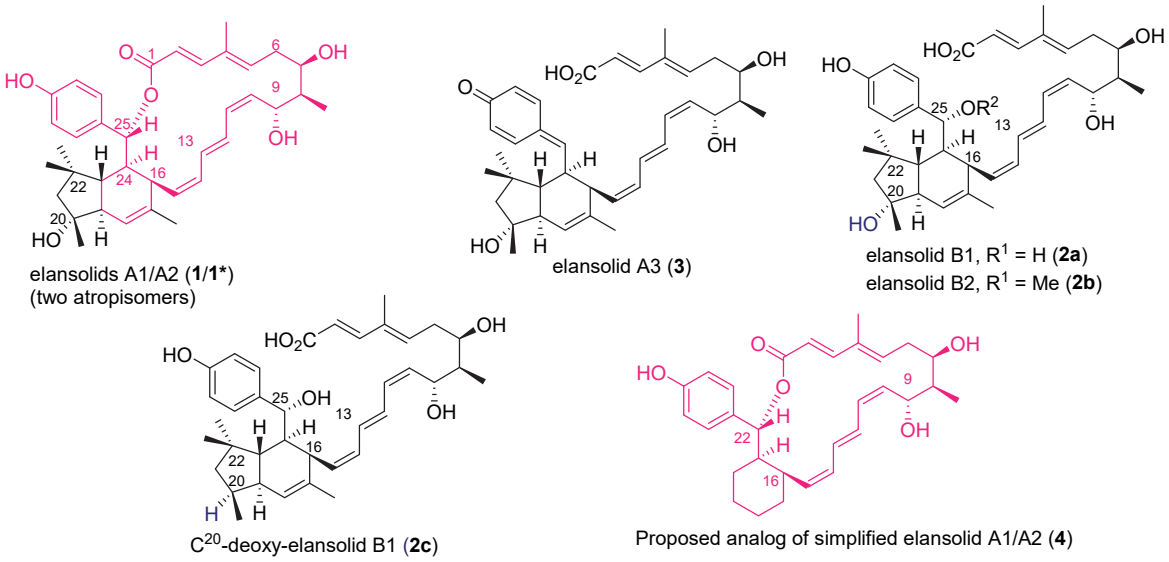
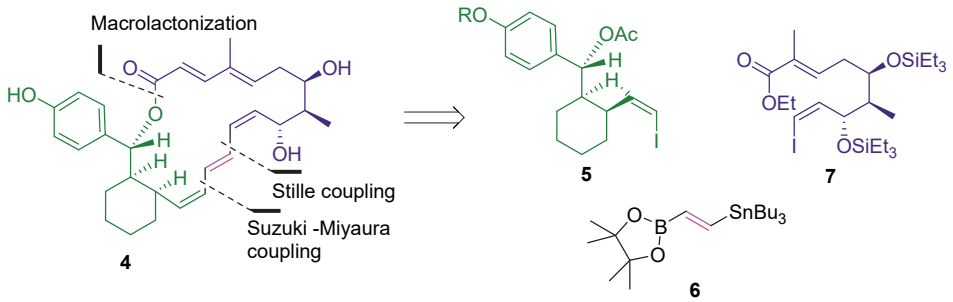
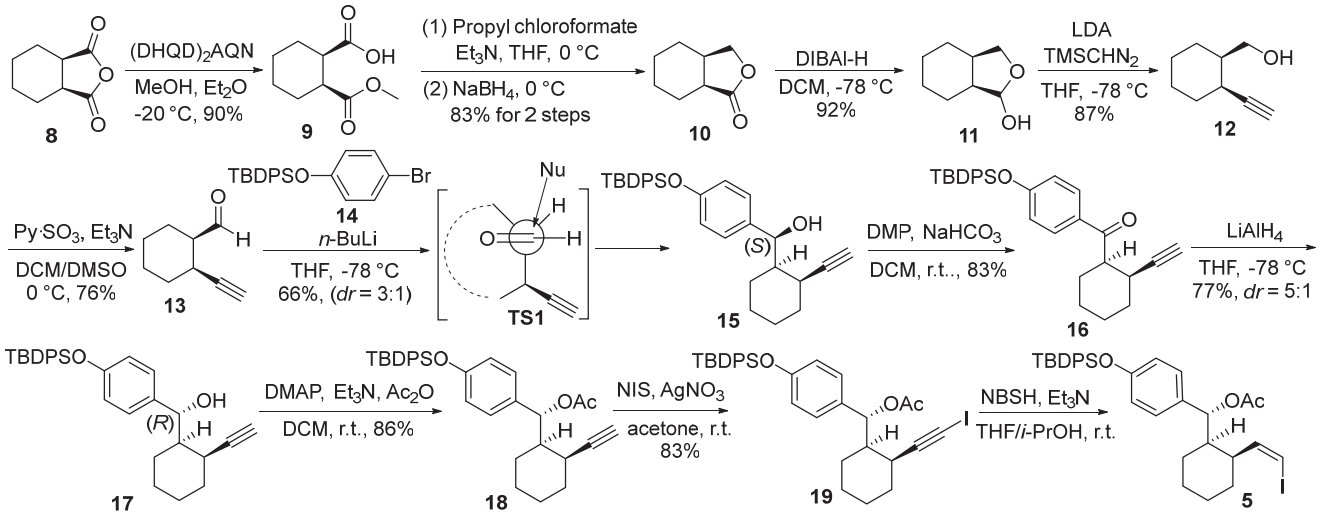


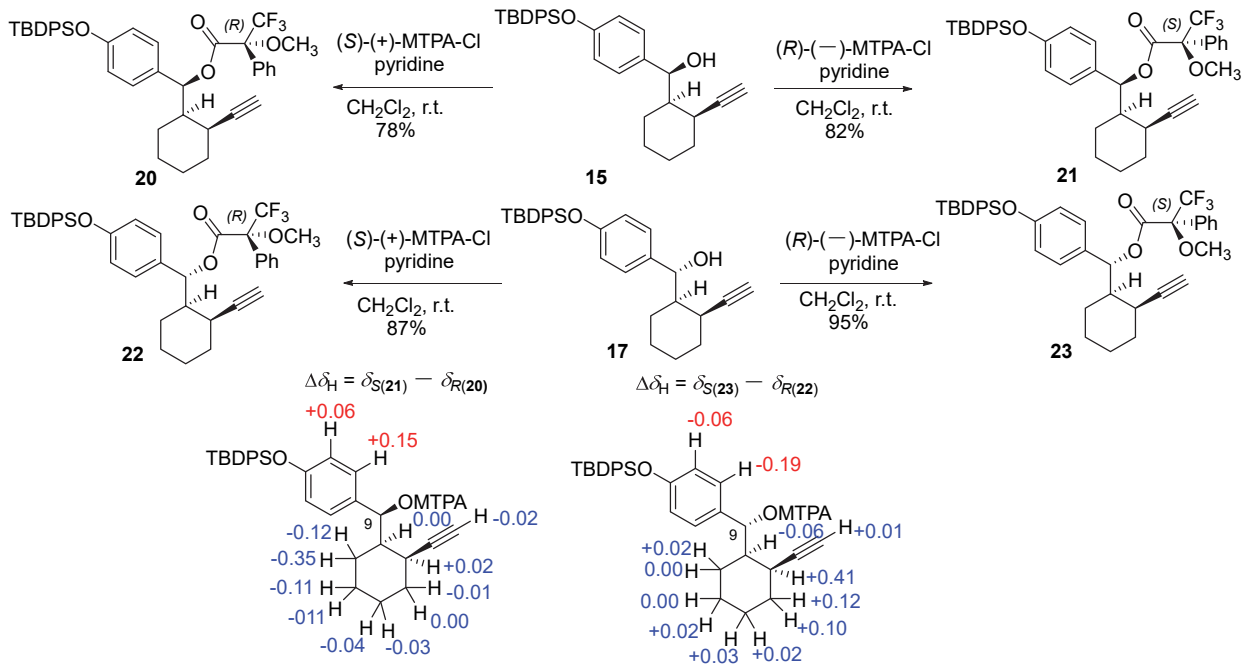
Figure 1 Polyketide family of elansolids **1**～**3** and proposed simplified analog **4** of elansolid A1/A2



Scheme 1 Retrosynthetic plan for analog **4**



Scheme 2 Synthesis of vinyl iodide fragment **5**



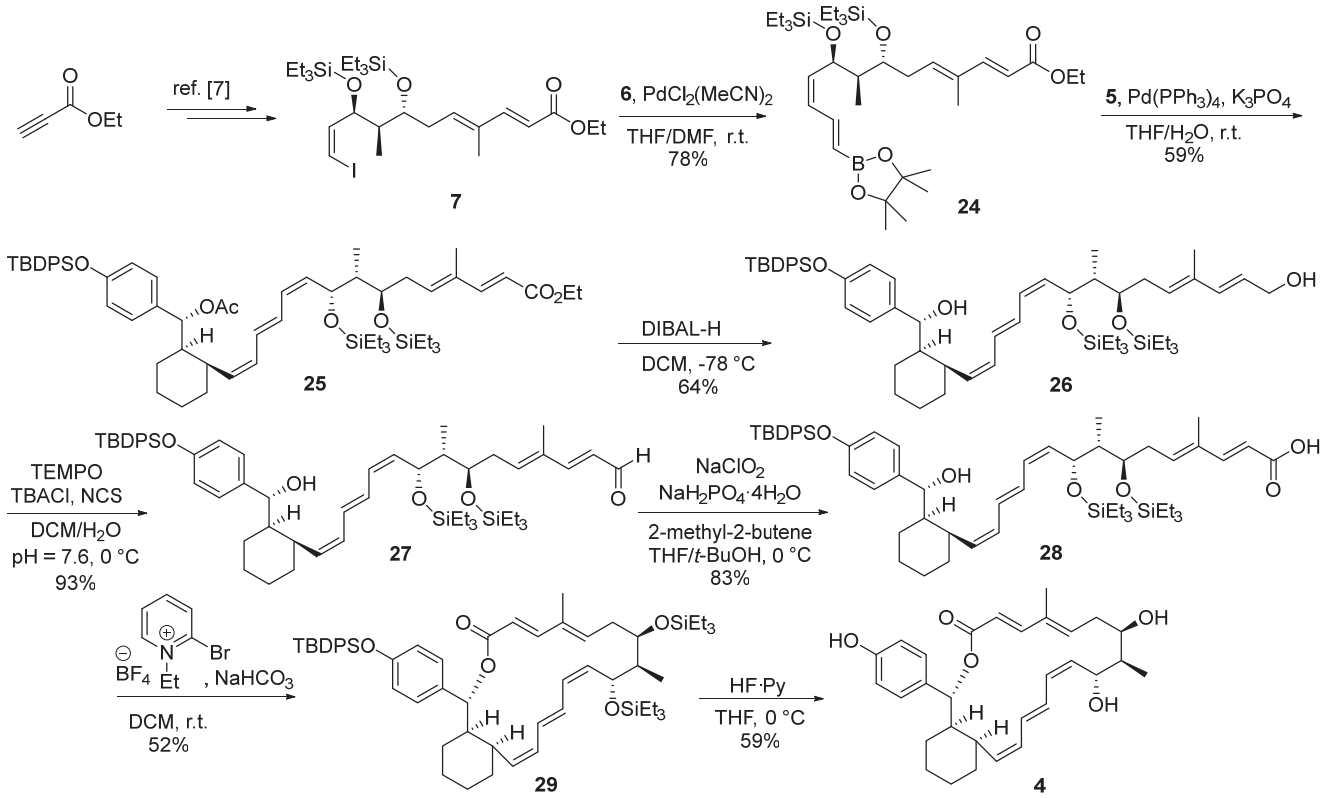
Scheme 3 Assignment of absolute configuration of secondary alcohol by Mosher ester analysis based on the ^{1}H NMR chemical shift

2.2 Completion of the total synthesis of analog **4**

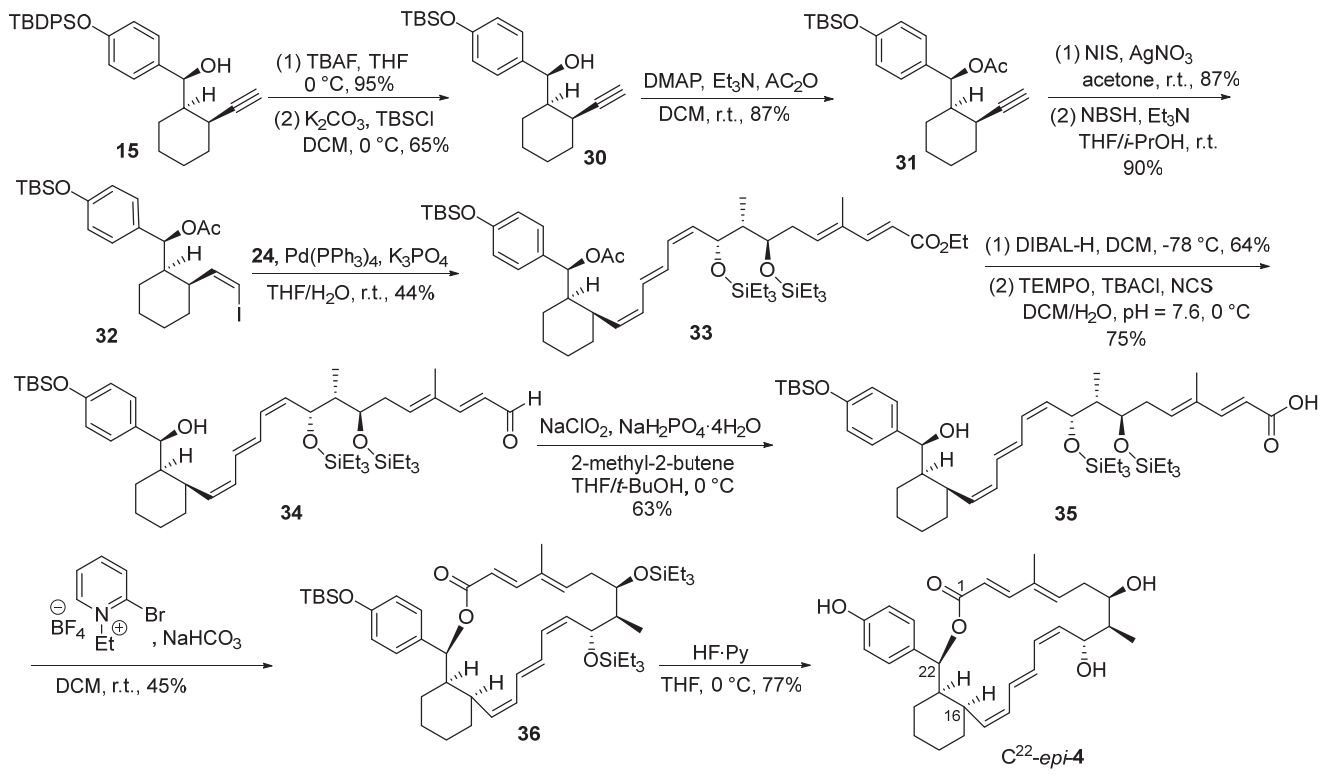
α,*β*-Unsaturated ester **7** was prepared from the ethyl propiolate by a 12-step sequence, and then converted into diene boronate **24**, adhering to our previous synthesis (Scheme 4).[7] The Suzuki-Miyaura cross-coupling reaction between diene boronate **24** and vinyl iodide **5** afforded the (*Z*,*E*,*Z*)-triene **25** without isomerization observed.[14] Subsequently, reduction of both the acetyl group and the terminal ethyl ester by diisobutylalumium hydride (DIBAL-H) formed diol **26**, which was then subjected to 2,2,6,6-tetramethylpiperidoxyl (TEMPO) oxidation condition to yield the unsaturated aldehyde **27** without affecting the benzylic alcohol.[15] In contrast, when Parikh-Doering oxidation condition was employed, both the primary and benzylic alcohols on diol **26** could be indistinguishably oxidized. Then, by Pinnick oxidation, aldehyde **27** was transformed to carboxylic acid **28**, which was subjected to the Mukaiyama macrolactonization condition to furnish macrolactone **29**.[16] After removal of silyl group under mild condition, the proposed analog **4** was successfully achieved (Scheme 4).

When evaluating the whole route for synthesizing elansolid derivate, we realized that (*S*)-configurated alcohol **15** as showcased in Scheme 1 should be an ideal intermediate for accessing the C^{22}-epimer of macrolatone **4** following the similar synthetic steps. With this idea in mind, we set out the synthesis of C^{22}-*epi*-**4** from the *t*-butyldimethylsilyl (TBS) protected alcohol **15**, and by 11 steps, the C^{22}-*epi*-**4** could be also smoothly furnished (Scheme 5). It should be

mentioned that exchange of *tert*-butyldiphenylsilyl (TBDPS) protecting group on **15** to TBS at the beginning would facilitate its cleavage in the final step toward C^{22}-*epi*-**4**. With those simplified analogs of elansolid A1/A2, macrolactone **4** and C^{22}-*epi*-**4** in hand, this would then lay the foundation for antibiotic activity test in the future.



Scheme 4 Total synthesis of analog **4**



Scheme 5 Total synthesis of C^{22}-*epi*-**4**

3 Conclusions

We have finished the asymmetric total synthesis of two simplified analogs of natural product elansolid A in a convergent way. This synthesis was featured by the key steps such as desymmetrisation of anhydride, Pd-catalyzed Stille coupling, Suzuki-Miyaura coupling as well as Mukaiyama macrolactonization. With those analogs in hand, the biological evaluation including antibiotic activity test would be performed in due course in the future.

4 Experimental section

4.1 General information

NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400, 500, 600 or 800 MHz, and ^{13}C NMR spectra were recorded at 100, 125, 150 or 200 MHz (Bruker Avance 400 MHz, 500 MHz, 600 MHz, 800 MHz spectrometers), respectively, by using $CDCl_3$ or acetone as internal references. High resolution mass spectra were obtained on a Q-TOF-Premier mass spectrometer (Agilent 6540). Optical rotations were measured on an Autopol V Polarimeter (Rudolph Serial #91058) at 589 nm.

4.2 Synthesis of (1*R*,2*S*)-2-(methoxycarbonyl)-cyclohexane-1-carboxylic acid (**9**)

In a flame dried round bottom flask, anhydride **8** (1.0 g, 6.48 mmol) was dissolved with Et_2O (100.0 mL). The solution was cooled to −20 ℃ and then MeOH (2.63 mL) and 1,4-bis[(9*S*)-10,11-dihydro-6'-methoxycinchonan-9-yl]-9,10-anthracenedione ($(DHQD)_2AQN$, 278 mg, 0.32 mmol) were added in sequence. The mixture was vigorously stirred for 2 d at this temperature. The reaction mixture was quenched by slow addition of 1 mol/L HCl solution and extracted with Et_2O. The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give crude **9** as light oil (1.08 g, 5.83 mmol, 90%). R_f=0.70 [petroleum ether (PE)/EtOAc, V∶V=10∶1, visualized using an $KMnO_4$ stain]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 2.84 (br, 2H), 2.03～1.98 (m, 2H), 1.79～1.74 (m, 2H), 1.56～1.47 (m, 2H), 1.43～1.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.9, 174.0, 51.7, 42.5, 42.3, 26.2, 25.9, 23.7, 23.6; HRMS (ESI) calcd for $C_9H_{14}O_4Na$ $[M+Na]^+$ 185.0819, found 185.0819.

4.3 Synthesis of (3a*R*,7a*S*)-hexahydroisobenzofuran-1(3*H*)-one (**10**)

Methyl ester **9** (1.41 g, 7.57 mmol) was dissolved in tetrahydrofuran (THF) (40 mL) at 0 ℃, followed by addition of Et_3N (1.37 mL, 9.85 mmol). The mixture was stirred for 10 min. Propyl chloroformate (1.1 mL, 9.85 mmol) was added to this solution at this temperature. The reaction mixture was stirred for 1.5 h. After filtration to remove the resulting solid, $NaBH_4$ was added (1.0 g, 26.51 mmol) to the filtrate at 0 ℃ and the mixture was stirred for 1 h, then warmed to room temperature for another 2 h. The reaction was then quenched by H_2O. The aqueous solution was extracted with Et_2O. The organic phases were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the lactone **10** (887 mg, 6.33 mmol, 83%). R_f=0.45 (PE/EtOAc, V∶V=3∶1, visualized using an $KMnO_4$ stain); $[\alpha]_D^{20}$+43.38 (c 1.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (dd, J=5.0, 8.7 Hz, 1H), 3.88 (d, J=8.7 Hz, 1H), 2.58～2.55 (m, 1H), 2.43～2.36 (m, 1H), 2.06～2.02 (m, 1H), 1.78～1.72 (m, 1H), 1.63～1.51 (m, 3H), 1.20～1.10 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 178.5, 71.7, 39.4, 35.4, 27.1, 23.4, 22.9, 22.5; HRMS (ESI) calcd for $C_8H_{12}O_2Na$ $[M+Na]^+$ 163.0730, found 163.0730.

4.4 Synthesis of (1*S*,3a*R*,7a*S*)-octahydroisobenzofuran-1-ol (**11**)

Diisobutylaluminium hydride (DIBAL-H, 5.17 mL, 5.17 mmol, 1.0 mol/L in hexane) was slowly added to a solution of **10** (604 mg, 4.31 mmol) in CH_2Cl_2 (20 mL) at −78 ℃. The reaction mixture was stirred for 2 h at this temperature and then terminated by addition of saturated sodium potassium tartrate solution. The aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish alcohol **11** (567 mg, 3.99 mmol, 92%). R_f=0.55 (PE/EtOAc, V∶V=2∶1, visualized using an $KMnO_4$ stain); $[\alpha]_D^{20}$ +61.05 (c 1.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 (s, 1H), 3.97 (t, J=7.8 Hz, 1H), 3.63 (d, J=7.9 Hz, 1H), 2.53～2.43 (m, 1H), 1.99～1.95 (m, 1H), 1.60～1.42 (m, 4H), 1.37～1.32 (m, 2H), 1.28～1.18 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 104.8, 70.4, 44.0, 35.2, 24.2, 24.1, 23.4, 21.8; HRMS (ESI) calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0884, found 165.0886.

4.5 Synthesis of ((1*R*,2*S*)-2-ethynylcyclohexyl)methanol (**12**)

A flame dried round bottom flask equipped with a stirrer bar was charged with diisopropylamine (2.6 mL, 18.54 mmol) and THF (30 mL). Then the solution was cooled to −78 ℃ and *n*-BuLi (2.5 mol/L in hexane, 7.4 mL, 18.54 mmol) was added dropwise. The resulting mixture was stirred for 30 min at this temperature, followed by addition of (trimethylsilyl)diazomethane ($TMSCHN_2$, 6.46 mL, 12.93 mmol). After stirring for 40 min at −78 ℃, alcohol **11** (567 mg, 4.31 mmol) was added and the mixture was stirred for another 2.5 h at this temperature. The reaction was quenched by addition of saturated aq. NH_4Cl solution and extracted with Et_2O several times. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the alkyne **12** (523 mg, 3.78 mmol, 87%). R_f=0.56 (PE/EtOAc, V∶V=3∶1, visualized using an Annis stain); $[\alpha]_D^{20}$ +51.90 (c 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64 (dd, J=8.2, 10.7 Hz, 1H), 3.55 (dd, J=5.6, 10.7 Hz, 1H), 2.92 (br, 1H), 2.08 (d, J=2.5 Hz, 1H), 1.88～1.85 (m, 1H), 1.74～1.70 (m, 1H), 1.67～1.60 (m, 2H), 1.55～1.52 (m, 1H), 1.50～1.43 (m, 2H), 1.38～1.30 (m, 1H), 1.27～1.18 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 84.9, 71.2, 66.2, 42.2, 30.8,

28.9, 25.4, 24.5, 21.8; HREI (EI) calcd for $C_9H_{14}O$ 138.1039, found 138.1039.

4.6 Synthesis of (1*R*,2*S*)-2-ethynylcyclohexane-1-carbaldehyde (**13**)

Sulfur trioxide-pyridine (1.5 g, 9.46 mmol) was added to alcohol **12** (523 mg, 3.78 mmol) and Et_3N (1.32 ml, 9.46 mmol) in dimethyl sulfoxide (DMSO) (5 mL)/CH_2Cl_2 (5 mL) at 0 ℃. After stirring for 1 h, the reaction was terminated by addition of saturate aq. NH_4Cl solution. The aqueous solution was extracted with Et_2O. The combined organic phases were washed with water for three times and dried over Na_2SO_4. The organic phases were filtered and then concentrated under reduced pressure to provide the aldehyde **13** (396 mg, 2.90 mol, 76%). R_f = 0.66 (PE/EtOAc, V∶V=3∶1, visualized using an Annis stain); $[\alpha]_D^{20}$ +1.54 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.65 (s, 1H), 3.10～3.05 (m, 1H), 2.25～2.21 (m, 2H), 2.06 (d, J=2.4 Hz, 1H), 1.75～1.71 (m, 2H), 1.67～1.61 (m, 2H), 1.53～1.45 (m, 2H), 1.25～1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 202.8, 82.6, 70.8, 50.6, 29.6, 26.8, 23.3, 21.2, 20.8; HRMS (ESI) calcd for $C_9H_{11}O$ [M−H]$^-$ 135.0813, found 135.0815.

4.7 Synthesis of (*S*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)((1*R*,2*S*)-2-ethynylcyclohexyl)methanol (**15**)

A flame dried round bottom flask equipped with a stirrer bar was charged with THF (4 mL) and bromide **14** (920 mg, 2.23 mmol), and then cooled to −78 ℃. *n*-BuLi (2.5 mol/L in hexane, 0.89 mL, 2.23 mmol) was added dropwise. The resulting mixture was stirred for 2.5 h at this temperature. Aldehyde **13** (122 mg, 0.89 mmol) in THF (4.0 mL) was added dropwise and the resulting mixture was stirred for 2 h at −78 ℃. The reaction was terminated by addition of a saturated aq. NH_4Cl solution, and extracted with Et_2O. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the allylic alcohol **15** (247mg, 0.58 mmol, 66%). R_f = 0.57 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +39.65 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71～7.69 (m, 4H), 7.43～7.40 (m, 2H), 7.37～7.34 (m, 4H), 7.12 (d, J=8.5 Hz, 2H), 6.73 (d, J=8.5 Hz, 2H), 4.47 (d, J=8.2 Hz, 1H), 2.15 (br, 1H), 2.11 (d, J=2.4 Hz, 1H), 2.00～1.98 (m, 1H), 1.80～1.70 (m, 2H), 1.60～1.57 (m, 1H), 1.48～1.45 (m, 1H), 1.33～1.29 (m, 1H), 1.20～1.16 (m, 1H), 1.09 (s, 9H), 0.89～0.83 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.2, 135.8, 135.6, 133.0, 129.9, 127.8, 127.6, 119.6, 85.3, 77.1, 71.9, 47.7, 31.5, 29.6, 26.6, 25.8, 24.2, 21.6, 19.5; HRMS (ESI) calcd for $C_{31}H_{36}O_2SiNa$ [M+Na]$^+$ 491.2374, found 491.2377.

4.8 Synthesis of (4-((*tert*-butyldiphenylsilyl)oxy)phenyl)((1*R*,2*S*)-2-ethynylcyclohexyl)methanone (**16**)

Alcohol **15** (60 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (3 mL), followed by addition of $NaHCO_3$ (537 mg, 6.40 mmol). Dess-Martin periodinane (271 mg, 0.64 mmol) was added to the solution. The reaction mixture was stirred for 2 h at room temperature and then the reaction was terminated by addition of saturated aq. $Na_2S_2O_3$ solution. The aqueous solution was then extracted with Et_2O. The organic phases were combined and washed with saturated aq. NaCl solution. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the ketone **16** (52.2 mg, 0.10 mmol, 83%). R_f=0.62 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +74.74 (*c* 1.28, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67～7.10 (m, 6H), 7.44～7.42 (m, 2H), 7.39～7.36 (m, 4H), 6.78 (d, J=8.7 Hz, 2H), 3.23 (dt, J=3.4, 11.3 Hz, 1H), 3.07 (br, 1H), 2.07 (d, J=2.4 Hz, 1H), 1.98～1.93 (m, 2H), 1.83～1.79 (m, 1H), 1.72～1.67 (m, 1H), 1.65～1.61 (m, 1H), 1.59～1.57 (m, 1H), 1.33～1.27 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.4, 159.7, 135.4, 132.1, 130.1, 130.1, 129.5, 127.9, 119.7, 83.6, 71.9, 47.4, 31.4, 31.0, 26.4, 25.0, 23.7, 21.5, 19.4; HRMS (ESI) calcd for$C_{31}H_{34}O_2SiNa$ [M + Na]$^+$ 489.2220, found 489.2220.

4.9 Synthesis of (*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)((1*R*,2*S*)-2-ethynylcyclohexyl)methanol (**17**)

To a solution of ketone **16** (15.0 mg, 0.10 mmol) in THF (5.0 mL) at −78 ℃ was added $LiAlH_4$ (154 mg, 4.06 mmol). The resulting mixture was stirred for 3 h at this temperature and the reaction was terminated by addition of saturated sodium potassium tartrate solution. Then the mixture was extracted with Et_2O. The organic phases were combined, then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the alcohol **17** (38.8 mg, 0.08 mmol, 77%). R_f=0.58 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ + 6.53 (*c* 1.25, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70～7.69 (m, 4H), 7.43～7.40 (m, 2H), 7.37～7.34 (m, 4H), 7.03 (d, J=8.5 Hz, 2H), 6.72 (d, J=8.4 Hz, 2H), 4.42 (d, J=9.4 Hz, 1H), 3.22 (br, 1H), 2.13 (d, J=2.4 Hz, 1H), 1.91～1.89 (m, 1H), 1.61～1.55 (m, 2H), 1.50～1.48 (m, 1H), 1.45～1.39 (m, 1H), 1.27～1.24 (m, 1H), 1.23～1.17 (m, 1H), 1.09 (s, 9H), 1.06～1.02 (m, 1H), 0.93～0.91 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.1, 135.9, 135.5, 132.9, 129.8, 127.7, 127.7, 119.6, 85.4, 76.7, 71.3, 46.9, 30.9, 28.5, 26.5, 25.7, 24.5, 21.4, 19.4; HRMS (ESI) calcd for$C_{31}H_{36}O_2SiNa$ [M+Na]$^+$ 491.2374, found 491.2377.

4.10 Synthesis of (*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl) ((1*R*,2*S*)-2-ethynylcyclohexyl)methyl acetate (**18**)

To a stirred solution of alcohol **17** (36.0 mg, 0.07 mmol) in CH_2Cl_2 (1.5 mL) were added 4-dimethylaminopyridine (DMAP) (9.4 mg, 0.07 mmol), Et_3N (0.08 mL, 0.57 mmol) and Ac_2O (0.036 mL, 0.3840 mmol). The reaction mixture was stirred at ambient temperature for 24 h and the reaction was terminated by addition of water. Then the mixture was extracted with Et_2O for three times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column

chromatography to give **18** (33.9 mg, 0.06 mmol, 86%). R_f=0.68 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain); $[\alpha]_D^{20}$ +47.70 (*c* 1.48, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71～7.68 (m, 4H), 7.43～7.39 (m, 2H), 7.37～7.33 (m, 4H), 7.04 (d, J=8.5 Hz, 2H), 6.70 (d, J=8.5 Hz, 2H), 5.47 (d, J=10.6 Hz, 1H), 3.09 (br, 1H), 2.09 (d, J=2.5 Hz, 1H), 1.98 (s, 3H), 1.92～1.89 (m, 1H), 1.79～1.74 (m, 1H), 1.63～1.59 (m, 1H), 1.51～1.48 (m, 1H), 1.45～1.42 (m, 1H), 1.27～1.24 (m, 1H), 1.21～1.15 (m, 1H), 1.09 (s, 9H), 1.05～1.01 (m, 1H), 0.92～0.89 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.9, 155.2, 135.5, 132.9, 132.1, 129.8, 128.5, 127.7, 119.5, 84.1, 78.2, 71.6, 44.8, 30.8, 28.8, 26.5, 25.6, 24.0, 21.3, 21.1, 19.4; HRMS (ESI) calcd for $C_{33}H_{38}O_3SiNa$ $[M+Na]^+$ 533.2482, found 533.2482.

4.11 Synthesis of (*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)((1*R*,2*S*)-2-(iodoethynyl)cyclohexyl)methyl acetate (**19**)

A flame dried round bottom flask equipped with a stirrer bar was charged with acetone (1.5 mL), *N*-iodosuccinimide (8.86 mg, 0.039 mmol) and alkyne **18** (18.3 mg, 0.035 mmol). To the stirred solution, $AgNO_3$ (1.8 mg, 0.010 mmol) was added at room temperature, and the mixture was stirred for 1 h. Then the volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography to afford **19** (18.7 mg, 0.029 mmol, 83%). R_f=0.68 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain); $[\alpha]_D^{20}$ +31.29 (*c* 1.19, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70～7.68 (m, 4H), 7.43～7.40 (m, 2H), 7.36～7.33 (m, 4H), 7.03 (d, J=8.5 Hz, 2H), 6.69 (d, J=8.5 Hz, 2H), 5.40 (d, J=10.3 Hz, 1H), 3.23～3.22 (m, 1H), 1.98 (s, 3H), 1.91～1.88 (m, 1H), 1.74～1.70 (m, 1H), 1.63～1.58 (m, 1H), 1.50～1.47 (m, 1H), 1.42～1.35 (m, 1H), 1.19～1.13 (m, 2H), 1.09 (s, 9H), 1.04～1.01 (m, 1H), 0.95～0.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.8, 155.2, 135.5, 132.9, 132.1, 129.8, 128.4, 127.7, 119.5, 94.8, 78.2, 76.7, 45.4, 31.2, 30.9, 26.5, 25.6, 24.3, 21.5, 21.2, 19.4; HRMS (ESI) calcd for $C_{33}H_{37}IO_3SiNa$ $[M+Na]^+$ 659.1442, found 659.1449.

4.12 Synthesis of (*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl) ((1*R*,2*S*)-2-((*Z*)-2-iodovinyl)cyclohexyl)methyl acetate (**5**)

Alkynyl iodide **19** (12.7 mg, 0.019 mmol) was dissolved in a mixture of THF (1.0 mL) and *i*-PrOH (1.0 mL). Et_3N (7.9 μL, 0.057 mmol) and 2-nitrobenzylsulfonylhydrazine (NBSH) (7.4 mg, 0.034 mmol) were added and the reaction mixture was stirred for 24 h. Then, the volatiles were removed *in vacuo* at ambient temperature and the residue was purified by silica gel column chromatography to give vinyl iodide **5** (11.2 mg, 0.018 mmol, 92%). R_f=0.50 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −0.11 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70～7.67 (m, 4H), 7.41～7.39 (m, 2H), 7.37～7.33 (m, 4H), 6.99 (d, J=8.5 Hz, 2H), 6.69 (d, J=8.4 Hz, 2H), 6.45 (dd, J=7.4, 9.3 Hz, 1H), 6.28 (d, J=7.3 Hz, 1H), 5.10 (d, J=10.7 Hz, 1H), 3.06～3.05 (m, 1H), 2.01 (s, 3H), 1.94～1.92 (m, 1H), 1.76～1.73 (m, 1H), 1.69～1.66 (m, 1H), 1.52～1.46 (m, 2H), 1.20～1.12 (m, 2H), 1.08 (s, 9H), 1.06～1.03 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.1, 155.2, 140.0, 135.5, 132.9, 132.3, 129.8, 128.3, 127.7, 119.5, 83.5, 77.7, 44.3, 40.5, 31.0, 26.5, 25.7, 24.5, 21.8, 21.4, 19.4; HRMS (ESI) calcd for $[M+Na]^+$ $C_{33}H_{39}IO_3SiNa$ 661.1604, found 661.1605.

4.13 Synthesis of ethyl (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*R*)-acetoxy(4-((*tert*-butyldiphenylsilyl)oxy)phenyl)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenoate (**25**)

Vinyl iodide **5** (15.0 mg, 23.50 μmol) and boronate **24** (18.2 mg, 28.20 μmol) were dissolved in THF (2.4 mL) and H_2O (1.2 mL). To the stirred solution were sequentially added K_3PO_4 (29.9 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (8.1 mg, 7.05 μmol) at room temperature. The reaction mixture was stirred for 16 h and then water was added. The aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish the title triene **25** (14.4 mg, 13.93 μmol, 59%). R_f=0.55 (PE/EtOAc, V∶V=3∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −10.67 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.61～7.59 (m, 4H), 7.35～7.32 (m, 2H), 7.30～7.27 (m, 4H), 7.21 (d, J=15.6 Hz, 1H), 6.95 (d, J=8.5 Hz, 2H), 6.61 (d, J=8.5 Hz, 2H), 6.54 (dd, J=11.0, 14.5 Hz, 1H), 6.46 (dd, J=11.3, 14.5 Hz, 1H), 6.09～6.01 (m, 2H), 5.90 (t, J=7.2 Hz, 1H), 5.76 (t, J=11.0 Hz, 1H), 5.67 (d, J=15.6 Hz, 1H), 5.34 (t, J=10.1 Hz, 1H), 4.97 (d, J=10.8 Hz, 1H), 4.52 (dd, J=6.8, 8.9 Hz, 1H), 3.96 (q, J=7.1 Hz, 2H), 3.81～3.78 (m, 1H), 3.24～3.22 (m, 1H), 2.31～2.22 (m, 2H), 1.86～1.81 (m, 2H), 1.74 (s, 3H), 1.67 (s, 3H), 1.65～1.62 (m, 1H), 1.56～1.54 (m, 1H), 1.51～1.49 (m, 1H), 1.32～1.29 (m, 2H), 1.19～1.17 (m, 2H), 1.05 (t, J=7.1 Hz, 3H), 0.96 (s, 9H), 0.87 (d, J=6.9 Hz, 3H), 0.83～0.80 (m, 18H), 0.78～0.73 (m, 2H), 0.49～0.47 (m, 6H), 0.46～0.45 (m, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ: 169.5, 167.5, 156.0, 150.0, 140.0, 136.3, 134.8, 134.4, 133.6, 133.0, 131.0, 130.9, 130.4, 130.0, 129.5, 129.4, 128.9, 128.8, 120.1, 116.6, 78.6, 73.4, 70.9, 60.4, 48.4, 46.0, 33.7, 33.4, 33.2, 26.9, 26.7, 24.2, 21.5, 21.4, 19.9, 14.7, 12.8, 10.2, 7.3, 5.9, 5.8; HRMS (ESI) calcd for $C_{62}H_{92}O_7Si_3Na$ $[M+Na]^+$ 1055.6047, found 1055.6043.

4.14 Synthesis of (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)(hdroxy)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((tri-ethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaen-1-ol (**26**)

DIBAL-H (0.21 mL, 0.31 mmol, 1.5 mol/L in toluene) was slowly added to the solution of **25** (12.9 mg, 0.012 mmol) in CH_2Cl_2 (2 mL) at −78 ℃. The reaction mixture was stirred for 1 h at this temperature and then the reaction was terminated by addition of saturated sodium potassium tartrate solution. The aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhy-

drous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish diol **26** (7.3 mg, 7.60 μmol, 64%). R_f=0.5 (PE/EtOAc, V∶V=2∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +24.72 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70～7.68 (m, 4H), 7.41～7.39 (m, 2H), 7.36～7.33 (m, 4H), 6.96 (d, J=8.5 Hz, 2H), 6.70 (d, J=8.5 Hz, 2H), 6.58 (dd, J=11.3, 14.7 Hz, 1H), 6.40 (dd, J=11.6, 14.6 Hz, 1H), 6.20～6.13 (m, 2H), 6.00 (d, J=11.2 Hz, 1H), 5.87 (t, J=10.8 Hz, 1H), 5.60 (dt, J=5.9, 15.6 Hz, 1H), 5.48 (t, J=6.8 Hz, 1H), 5.39 (t, J=10.1 Hz, 1H), 4.50 (dd, J=6.6, 9.1 Hz, 1H), 4.10 (d, J=9.4 Hz, 1H), 4.02 (d, J=5.9 Hz, 2H), 3.75～3.72 (m, 1H), 3.34～3.31 (m, 1H), 2.26～2.16 (m, 2H), 1.69 (s, 3H), 1.67～1.65 (m, 1H), 1.60～1.59 (m, 1H), 1.56～1.54 (m, 2H), 1.42～1.40 (m, 2H), 1.15～1.12 (m, 2H), 1.09 (s, 9H), 0.98～0.91 (m, 21H), 0.82～0.79 (m, 2H), 0.58～0.56 (m, 6H), 0.55～0.53 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 154.9, 136.6, 136.4, 135.5, 134.3, 133.5, 132.9, 132.7, 130.5, 129.8, 129.7, 129.6, 128.7, 128.2, 127.7, 127.5, 124.9, 119.54, 76.7, 72.7, 69.9, 63.6, 47.6, 47.0, 32.8, 32.6, 31.9, 26.5, 26.2, 23.9, 20.9, 19.4, 12.8, 9.8, 7.0, 5.2, 5.1; HRMS (ESI) calcd for $C_{58}H_{88}O_5Si_3Na$ $[M+Na]^+$ 971.5832, found 971.5832.

4.15 Synthesis of (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)(hydroxy)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenal (**27**)

Alcohol **26** (33.0 mg, 0.034 mmol) was dissolved in CH_2Cl_2/H_2O (1.5 mL/1.5 mL, pH=7.6), followed by addition of tetrabutyl ammonium chloride (TBACl) (33.8 mg, 0.12 mmol) and TEMPO (17.1 mg, 0.11 mmol). Then *N*-chlorosuccinimide (NCS) (23.2 mg, 0.17 mmol) was added to the solution. The reaction mixture was stirred for 2 h at this temperature and then the reaction was terminated by addition of saturated aq. NH_4Cl solution. Then the mixture was extracted with Et_2O. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue was purified by silica gel chromatography to give the aldehyde **27** (30 mg, 0.031 mmol, 93%). R_f=0.65 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −12.56 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.75～7.73 (m, 4H), 7.49～7.46 (m, 2H), 7.43～7.40 (m, 4H), 7.28 (d, J=15.5 Hz, 1H), 7.02 (d, J=8.4 Hz, 2H), 6.78 (dd, J=11.3, 14.5 Hz, 1H), 6.72 (d, J=8.5 Hz, 2H), 6.58 (dd, J=11.7, 14.5 Hz, 1H), 6.22～6.13 (m, 3H), 6.02 (dd, J=7.7, 15.5 Hz, 1H), 5.94 (t, J=10.8 Hz, 1H), 5.47 (t, J=10.1 Hz, 1H), 4.74 (dd, J=5.8, 9.1 Hz, 1H), 4.08～4.04 (m, 1H), 3.98～3.96 (m, 1H), 3.46～3.45 (m, 1H), 2.46～2.44 (m, 2H), 1.84 (s, 3H), 1.76～1.73 (m, 1H), 1.69～1.67 (m, 1H), 1.61～1.55 (m, 2H), 1.46～1.42 (m, 2H), 1.16～1.12 (m, 3H), 1.09 (s, 9H), 0.99～0.98 (m, 2H), 0.97～0.94 (m, 18H), 0.84～0.81 (m, 2H), 0.63 (q, J=4.5 Hz, 6H), 0.60 (q, J=4.4 Hz, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ: 194.3, 158.1, 155.5, 142.1, 139.1, 136.4, 135.4, 134.4, 134.2, 133.8, 132.0, 131.0, 130.3, 130.1, 128.8, 128.6, 128.2, 127.7, 120.0, 76.5, 73.4, 70.7, 49.2, 48.3, 33.9, 33.7, 33.5, 27.1, 26.9, 24.6, 21.7, 20.0, 12.9, 10.0, 7.3, 5.9, 5.8; HRMS (ESI) calcd for $C_{58}H_{86}O_5Si_3Na$ $[M+Na]^+$ 969.5679, found 969.5675.

4.16 Synthesis of (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*R*)-(4-((*tert*-butyldiphenylsilyl)oxy)-phenyl)(hydroxy)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenoic acid (**28**)

To a stirred solution of the aldehyde **27** (25.0mg, 0.026 mmol) in THF (2.0 mL)/*t*-BuOH (2.0 mL) was added 2-methyl-2-butene (3.8 mL, 7.73 mmol, 2.0 mol/L in THF) at 0 ℃. Then a solution of $NaClO_2$ (72 mg, 0.79 mmol) and NaH_2PO_4•H_2O (198 mg, 1.26 mmol) in water (1.6 mL) was added to the mixture. After stirring overnight, the reaction was terminated by the addition of water, and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish acid **28** (21.3 mg, 0.030 mmol, 83%). R_f=0.5 (PE/EtOAc, V∶V=2∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −11.21 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.75～7.74 (m, 2H, H6'), 7.49～7.46 (m, 2H, H8'), 7.43～7.40 (m, 4H, H7'), 7.28 (d, J=15.6 Hz, 1H, H3), 7.03 (d, J=8.5 Hz, 2H, H24), 6.77 (dd, J=11.3, 14.6 Hz, 1H, H13), 6.72 (d, J=8.4 Hz, 2H, H25), 6.57 (dd, J=11.7, 14.5 Hz, 1H, H12), 6.20 (t, J=11.1 Hz, 1H, H14), 6.14 (t, J=11.2 Hz, 1H, H11), 6.01 (t, J=7.1 Hz, 1H, H5), 5.93 (t, J=10.8 Hz, 1H, H15), 5.78 (d, J=15.6 Hz, 1H, H2), 5.46 (t, J=10.1 Hz, 1H, H10), 4.72 (dd, J=5.9, 9.1 Hz, 1H, H9), 4.08 (d, J=9.6 Hz, 1H, H22), 3.96～3.94 (m, 1H, H7), 3.46～3.44 (m, 1H, H16), 2.42～2.40 (m, 2H, H6a, H6b), 1.81 (s, 3H, H1'), 1.76～1.73 (m, 1H, H8), 1.68～1.65 (m, 2H, H17b, H19b), 1.64～1.59 (m, 2H, H19a, H21), 1.55～1.58 (m, 1H, H17a), 1.47～1.41 (m, 2H, H18a, H18b), 1.16～1.12 (m, 1H, H20b), 1.09 (s, 9H, H4'), 0.99～0.98 (m, 3H, H2'), 0.98～0.95 (m, 18H, H10', H12'), 0.82～0.80 (m, 1H, H20a), 0.64～0.62 (m, 6H, H11'), 0.61～0.59 (m, 6H, H9'); ^{13}C NMR (151 MHz, acetone-d_6) δ: 168.4 (C1), 155.4 (C26), 150.2 (C3), 139.8 (C5), 139.2 (C23), 136.4 (C6'), 134.7 (C4), 134.4 (C15), 134.2 (C10), 133.8 (C5'), 132.0 (C13), 131.0 (C8'), 130.2 (C11), 130.1 (C14), 128.8 (C7'), 128.6 (C24), 128.2 (C12), 120.0 (C25), 116.9 (C2), 76.4 (C22), 73.5 (C7), 70.7 (C9), 49.2 (C21), 48.3 (C8), 33.9 (C16), 33.7 (C17), 33.3 (C6), 27.2 (C19), 26.9 (C4'), 24.6(C20), 21.7 (C18), 20.0 (C3'), 12.8 (C1'), 10.0 (C2'), 7.3 (C10', C12'), 5.9 (C11'), 5.8 (C9'); HRMS (ESI) calcd for $C_{58}H_{85}O_6Si_3$ $[M-H]^-$ 961.5657, found 961.5659.

4.17 Synthesis of (1*R*,4*E*,6*E*,9*R*,10*R*,11*R*,12*Z*,14*E*,16*Z*,17a*R*,21a*R*)-1-(4-((*tert*-butyldiphenylsilyl)oxy)phenyl)-10-methyl-9,11-bis((triethylsilyl)oxy)-8,9,10,11,17a,18,19,20,21,21a-decahydrobenzo[*c*][1]oxacyclononadecin-3(1*H*)-one (**29**)

Acid **28** (6.0 mg, 6.23 μmol) was dissolved in CH_2Cl_2

(8.0 mL). Then sodium bicarbonate (261.8 mg, 3.11 mmol) and Mukaiyama reagent (85.3 mg, 0.31 mmol) were added sequentially. After stirring for 18 h, the reaction was terminated by addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish macrolactone **29** (3.1 mg, 3.28 μmol, 52%). R_f=0.5 (PE/EtOAc, V∶V=2∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +113.58 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.74～7.73 (m, 2H, H6'), 7.48～7.45 (m, 2H, H8'), 7.43～7.40 (m, 4H, H7'), 7.14 (d, J=8.5 Hz, 2H, H24), 7.04 (d, J=15.7 Hz, 1H, H3), 6.76 (d, J=8.5 Hz, 1H, H25), 6.44 (dd, J=11.0, 14.6 Hz, 1H, H13), 6.34 (dd, J=11.3, 14.7 Hz, 1H, H12), 6.15～6.10 (m, 1H, H11), 6.00 (t, J=10.8 Hz, 1H, H14), 5.92～5.88 (m, 1H, H5), 5.77 (t, J=10.5 Hz, 1H, H15), 5.61 (d, J=15.5 Hz, 1H, H2), 5.44～5.43 (m, 1H, H10), 5.42～5.41 (m, 1H, H22), 4.55～4.25 (m, 1H, H9), 3.97～3.96 (m, 1H, H7), 3.16 (br, 1H, H16), 2.46～2.36 (m, 2H, H6a, H6b), 2.09～2.08 (m, 1H, H21), 1.78～1.77 (m, 1H, H8), 1.72 (s, 3H, H1'), 1.69～1.65 (m, 2H, H17b, H20b), 1.62～1.58 (m, 1H, H17a), 1.41～1.36 (m, 2H, H19a, H19b), 1.34～1.32 (m, 2H, H18b), 1.18～1.14 (m, 2H, H18a, H20a), 1.11～1.10 (m, 3H, H2'), 1.08 (s, 9H, H4'), 1.01～0.98 (m, 9H, H12'), 0.95～0.93 (m, 9H, H10'), 0.66 (q, J=7.9 Hz, 6H, H9'), 0.59 (t, J=7.9 Hz, 6H, H11'); ^{13}C NMR (151 MHz, acetone-d_6) δ: 167.1 (C1), 156.1 (C26), 150.3 (C3), 136.7 (C4), 136.3 (C6'), 135.9 (C5), 134.4 (C23), 134.0 (C15), 133.6 (C5'), 133.5 (C10), 131.0 (C8'), 131.0 (C11), 130.9 (C13), 130.2 (C12), 130.0 (C3'), 129.6 (C24), 128.8 (C7'), 120.2 (C25), 117.2 (C2), 77.4 (C22), 71.4 (C7), 70.4 (C9), 50.3 (C8), 45.4 (C21), 34.2 (C16), 34.1 (C6), 33.2 (C17), 26.9 (C4'), 26.1 (C20), 25.6 (C18), 22.4 (C19), 19.9 (C3'), 12.7 (C1'), 11.2 (C2'), 7.4 (C10', C12'), 6.4 (C11'), 5.7 (C9'); HRMS (ESI) calcd for $C_{58}H_{84}O_5Si_3Na$ $[M+Na]^+$ 961.5516, found 967.5519.

4.18 Synthesis of (1*R*,4*E*,6*E*,9*R*,10*R*,11*R*,12*Z*,14*E*,16*Z*,17a*R*,21a*R*)-9,11-dihydroxy-1-(4-hydroxyphenyl)-10-methyl-8,9,10,11,17a,18,19,20,21,21a-decahydrobenzo[*c*][1]oxacyclononadecin-3(1*H*)-one (**4**)

Macrolactone **29** (8.0 mg, 8.46 μmol) was dissolved in THF (1.0 mL) and the solution was cooled to 0 ℃. A solution of diluted hydrogen fluoride pyridine complex (1.0 mL), which was prepared by mixing hydrogen fluoride (2 mL, hydrogen fluoride ω≈70%) with pyridine (5.6 mL) in THF (9.8 mL), was added at 0 ℃. The reaction mixture was stirred for 10 h at this temperature and the reaction was terminated by addition of saturated aq. $NaHCO_3$ solution. The aqueous solution was extracted with Et_2O for three times and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to furnish derivative **4** (2.4 mg, 5.01 μmol, 59%). R_f=0.56 (EtOAc, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +124.4 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (800 MHz, acetone-d_6) δ: 8.36 (s, 1H, OH26), 7.19 (d, J=8.2 Hz, 2H, H24), 7.05 (d, J=15.4 Hz, 1H, H3), 6.78 (d, J=8.1 Hz, 1H, H25), 6.41 (dd, J=10.9, 14.7 Hz, 1H, H13), 6.34 (dd, J=11.2, 14.6 Hz, 1H, H12), 6.09 (t, J=10.7 Hz, 1H, H11), 6.00 (t, J=10.8 Hz, 1H, H14), 5.94 (t, J=7.8 Hz, 1H, H5), 5.76 (t, J=10.3 Hz, 1H, H15), 5.60 (d, J=15.5 Hz, 1H, H2), 5.47 (t, J=9.6 Hz, 1H, H10), 5.42 (d, J=10.5 Hz, 1H, H22), 4.40～4.25 (m, 1H, H9), 3.93 (br, 1H, H7), 3.82 (s, 1H, OH), 3.50 (d, J=4.9 Hz, 1H, OH), 3.23 (br, 1H, H16), 2.48～2.47 (m, 1H, H6b), 2.38～2.34 (m, 1H, H6a), 2.14～2.11 (m, 1H, H21), 1.79～1.76 (m, 1H, H8), 1.71 (s, 3H, H1'), 1.69～1.67 (m, 2H, H17b), 1.66～1.63 (m, 2H, H19a), 1.63～1.59 (m, 2H, H17a), 1.43～1.40 (m, 1H, H19b), 1.38～1.35 (m, 2H, H19a), 1.33～1.31 (m, 1H, H18b), 1.21～1.19 (m, 1H, H18a), 1.17～1.15 (m, 1H, H20a), 1.11 (d, J=6.7 Hz, 3H, H2'); ^{13}C NMR (201 MHz, acetone-d_6) δ: 167.0 (C1), 158.0 (C26), 150.3 (C3), 136.7 (C4), 135.9 (C5), 134.9 (C10), 133.0 (C15), 132.4 (C23), 131.4 (C11), 130.3 (C13), 130.3 (C12), 130.2 (C14), 130.0 (C24), 117.3 (C2), 115.8 (C25), 77.6 (C22), 70.9 (C7), 68.4 (C9), 47.7 (C8), 45.41(C21), 34.1 (C16), 33.8 (C6), 33.1 (C17), 26.2 (C20), 25.5 (C18), 22.4 (C19), 12.5 (C1'), 11.1 (C2'); HRMS (ESI) calcd for $C_{30}H_{38}O_5Na$ $[M+Na]^+$ 501.2611, found 501.2611.

4.19 Synthesis of (*R*)-MTPA-ester (**20**)

The secondary alcohol **15** (5.0 mg, 10.66 μmol) was dissolved in CH_2Cl_2 (0.5 mL). Then pyridine (0.0050 mL, 62.83 μmol) and (*S*)-(+)-MTPA-Cl (0.0035 mL, 20.26 μmol) were added sequentially. After stirring for 2 h, the reaction was terminated by addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish ester **20** (5.7 mg, 8.31 μmol, 78%). R_f=0.55 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +60.39 (*c* 0.57, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) δ: 7.71～7.69 (m, 4H, H12'), 7.42～7.41 (m, 2H, H14'), 7.36～7.33 (m, 4H, H13'), 7.28～7.26 (m, 1H, H6'), 7.16 (d, J=7.7 Hz, 2H, H4'), 7.11 (t, J=7.5 Hz, 2H, H5'), 7.00 (d, J=7.9 Hz, 2H, H11), 6.68 (d, J=7.9 Hz, 2H, H12), 5.64 (d, J=10.7 Hz, 1H, H9), 3.45 (s, 3H, H8'), 2.15 (s, 1H, H1), 2.07 (br, 1H, H3), 1.89～1.87 (m, 1H, H7b), 1.80～1.78 (m, 1H, H8), 1.76～1.75 (m, 1H, H6b), 1.74～1.71 (m, 1H, H4b), 1.64～1.61 (m, 1H, H5b), 1.52～1.50 (m, 1H, H5a), 1.49～1.48 (m, 1H, H7a), 1.24～1.23 (m, 1H, H4a), 1.18～1.15 (m, 1H, H6a), 1.10 (s, 9H, H10'); ^{13}C NMR (201 MHz, $CDCl_3$) δ: 165.7 (C1'), 155.7 (C13), 135.5 (C12'), 132.8 (C7'), 132.7 (C11'), 132.2 (C3'), 130.1 (C10), 129.9 (C14'), 129.2 (C6'), 128.8 (C11), 128.0 (C5'), 127.7 (C13'), 127.2 (C4'), 119.5 (C12), 84.6 (C2'), 83.9 (C2), 82.1 (C9), 72.4 (C1), 55.7 (C8'), 44.6 (C8), 31.0 (C4), 28.6 (C3), 26.4 (10'), 25.3 (C6), 24.7 (C7), 21.2 (C5), 19.4 (C9'); HRMS (ESI) calcd for $C_{41}H_{43}O_4F_3SiNa$ $[M+Na]^+$ 707.2772, found 707.2775.

4.20 Synthesis of (*S*)-MTPA-ester (**21**)

The secondary alcohol **15** (5.0 mg, 10.66 μmol) was dissolved in CH_2Cl_2 (0.5 mL). Then pyridine (0.0050 mL, 62.83 μmol) and (*R*)-(−)-MTPA-Cl (0.0035 mL, 20.26 μmol) were added sequentially. After stirring for 2 h, the reaction was terminated with water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish ester **21** (6.0 mg, 8.74 μmol, 82%). R_f=0.55 (PE/EtOAc, *V*∶*V*=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +1.43 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) *δ*: 7.70～7.68 (m, 4H, H12'), 7.43～7.41 (m, 2H, H14'), 7.36～7.33 (m, 4H, H13'), 7.33～7.31 (m, 1H, H6'), 7.29 (d, *J*=7.8 Hz, 2H, H4'), 7.21 (t, *J*=7.6 Hz, 2H, H5'), 7.15 (d, *J*=8.3 Hz, 2H, H11), 6.74 (d, *J*=8.2 Hz, 2H, H12), 5.76 (d, *J*=10.7 Hz, 1H, H9), 3.30 (s, 3H, H8'), 2.13 (s, 1H, H1), 2.09 (br, 1H, H3), 1.81～1.79 (m, 1H, H8), 1.72～1.70 (m, 1H, H4b), 1.66～1.64 (m, 1H, H6b), 1.60～1.58 (m, 1H, H5b), 1.55～1.53 (m, 1H, H7b), 1.47～1.45 (m, 1H, H5a), 1.39～1.36 (m, 1H, H7a), 1.24～1.22 (m, 1H, H4a), 1.10 (s, 9H, H10'), 1.06～1.05 (m, 1H, H6a); ^{13}C NMR (201 MHz, $CDCl_3$) *δ*: 165.9 (C1'), 155.9 (C13), 135.5 (C12'), 132.7 (C7'), 132.6 (C11'), 132.5 (C3'), 130.1 (C10), 129.9 (C14'), 129.3 (C6'), 129.1 (C11), 128.1 (C5'), 127.7 (C13'), 127.2 (C4'), 119.7 (C12), 84.3 (C2'), 83.8 (C2), 81.5 (C9), 72.3 (C1), 55.4 (C8'), 44.5 (C8), 31.0 (C4), 28.6 (C3), 26.4 (10'), 25.2 (C6), 24.3 (C7), 21.2 (C5), 19.4 (C9'); HRMS (ESI) calcd for $C_{41}H_{43}O_4F_3SiNa$ $[M+Na]^+$ 707.2772, found 707.2775.

4.21 Synthesis of (*R*)-MTPA-ester (**22**)

The secondary alcohol **17** (5.0 mg, 10.66 μmol) was dissolved in CH_2Cl_2 (0.5 mL). Then pyridine (0.0050 mL, 62.83 μmol) and (*S*)-(+)-MTPA-Cl (0.0035 mL, 20.26 μmol) were added sequentially. After stirring for 2 h, the reaction was terminated by addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish ester **22** (6.4 mg, 9.34 μmol, 87%). R_f=0.57 (PE/EtOAc, *V*∶*V*=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +66.35 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) *δ*: 7.70～7.66 (m, 4H, H12'), 7.43～7.40 (m, 2H, H14'), 7.37～7.35 (m, 4H, H13'), 7.35～7.34 (m, 1H, H6'), 7.33 (d, *J*=7.6 Hz, 2H, H4'), 7.25～7.24 (m, 2H, H5'), 7.10 (d, *J*=8.4 Hz, 2H, H11), 6.73 (d, *J*=8.4 Hz, 2H, H12), 5.72 (d, *J*=10.9 Hz, 1H, H9), 3.27 (s, 3H, H8'), 2.65 (br, 1H, H3), 2.16 (s, 1H, H1), 1.87～1.84 (m, 1H, H8), 1.77～1.75 (m, 1H, H4b), 1.60～1.59 (m, 1H, H6b), 1.57～1.55 (m, 1H, H5b), 1.48～1.45 (m, 1H, H5a), 1.30～1.28 (m, 1H, H4a), 1.20～1.15 (m, 1H, H7b), 1.10 (s, 9H, H10'), 1.02～0.98 (m, 1H, H6a), 0.92～0.90 (m, 1H, H7a); ^{13}C NMR (201 MHz, $CDCl_3$) *δ*: 165.5 (C1'), 155.8 (C13), 135.5 (C12'), 132.9 (C7'), 132.7 (C11'), 132.6 (C3'), 130.4 (C10), 129.9 (C14'), 129.3 (C6'), 129.2 (C11), 128.1 (C5'), 127.7 (C13'), 127.2 (C4'), 119.8 (C12), 84.3 (C2'), 83.8 (C2), 80.6 (C9), 72.0 (C1), 55.5 (C8'), 43.8 (C8), 30.4 (C4), 28.4 (C3), 26.4 (10'), 25.4 (C6), 23.8 (C7), 21.2 (C5), 19.4 (C9'); HRMS (ESI) calcd for $C_{41}H_{43}O_4F_3SiNa$ $[M+Na]^+$ 707.2772, found 707.2775.

4.22 Synthesis of (*S*)-MTPA-ester (**23**)

The secondary alcohol **17** (5.0 mg, 10.66 μmol) was dissolved in CH_2Cl_2 (0.5 mL). Then pyridine (0.0050 mL, 62.83 μmol) and (*R*)-(−)-MTPA-Cl (0.0035 mL, 20.26 μmol) were added sequentially. After stirring for 2 h, the reaction was terminated by addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish ester **23** (7.0 mg, 10.22 μmol, 95%). R_f=0.56 (PE/EtOAc *V*∶*V*=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +1.08 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (800 MHz, $CDCl_3$) *δ*: 7.72～7.69 (m, 4H, H12'), 7.43～7.40 (m, 2H, H14'), 7.37～7.34 (m, 4H, H13'), 7.26 (m, 1H, H6'), 7.19 (d, *J*=7.8 Hz, 2H, H4'), 7.12 (t, *J*=7.6 Hz, 2H, H5'), 6.91 (d, *J*=8.2 Hz, 2H, H11), 6.67 (d, *J*=8.3 Hz, 2H, H12), 5.56 (d, *J*=10.8 Hz, 1H, H9), 3.50 (s, 3H, H8'), 3.06 (br, 1H, H3), 2.17 (s, 1H, H1), 1.89～1.87 (m, 1H, H4b), 1.81～1.78 (m, 1H, H8), 1.62～1.60 (m, 1H, H6b), 1.59～1.57 (m, 1H, H5b), 1.50～1.49 (m, 1H, H5a), 1.40～1.37 (m, 1H, H4a), 1.22～1.17 (m, 1H, H7b), 1.10 (s, 9H, H10'), 1.02～0.99 (m, 1H, H6a), 0.92～0.91 (m, 1H, H7a); ^{13}C NMR (201 MHz, $CDCl_3$) *δ*: 165.4 (C1'), 155.6 (C13), 135.5 (C12'), 132.8 (C7'), 132.7 (C11'), 132.5 (C3'), 130.5 (C10), 129.9 (C14'), 129.2 (C6'), 129.0 (C11), 128.0 (C5'), 127.7 (C13'), 127.2 (C4'), 119.5 (C12), 84.5 (C2'), 83.8 (C2), 81.2 (C9), 72.2 (C1), 55.7 (C8'), 44.0 (C8), 30.5 (C4), 28.7 (C3), 26.4 (10'), 25.4 (C6), 23.8 (C7), 21.2 (C5), 19.4 (C9'); HRMS (ESI) calcd for $C_{41}H_{43}O_4F_3SiNa$ $[M+Na]^+$ 707.2772, found 707.2775.

4.23 Synthesis of (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)((1*R*,2*S*)-2-ethynylcyclohexyl)methyl acetate (**31**)

To a stirred solution of alcohol **30** (36 mg, 0.07 mmol) in CH_2Cl_2 (1.5 mL) were added DMAP (9.4 mg, 0.07 mmol), Et_3N (0.08 mL, 0.57 mmol) and Ac_2O (0.036 ml, 0.38 mmol). The mixture was stirred at ambient temperature for 24 h and the reaction was terminated by addition of water. Then the mixture was extracted with Et_2O three times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give **31** (33.9 mg, 0.06 mmol, 87%). R_f=0.63 (PE/EtOAc, *V*∶*V*=5∶1, visualized using an Annis stain); $[\alpha]_D^{20}$ +50.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.27～7.26 (m, 2H), 6.78 (d, *J*=8.4 Hz, 2H), 5.63 (d, *J*=10.4 Hz, 1H), 2.18～2.15 (m, 2H), 2.01 (s, 3H), 1.83～1.78 (m, 1H), 1.76～1.73 (m, 1H), 1.65～1.62 (m, 1H), 1.52～1.48 (m, 1H), 1.33～1.27 (m, 2H), 1.23～1.18 (m, 2H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ*: 170.5, 155.6, 132.1, 128.7, 119.9, 84.4, 78.8, 72.4, 45.8, 45.0, 31.4, 29.0, 25.8, 24.9, 21.6, 21.4, 18.3, −4.1; HRMS (ESI) calcd for

$C_{23}H_{34}O_3SiNa$ $[M+Na]^+$ 409.2169, found 409.2166.

4.24 Synthesis of (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)((1*R*,2*S*)-2-((*Z*)-2-iodovinyl)cyclohexyl) methyl acetate (**32**)

A flame dried round bottom flask equipped with a stirrer bar was charged with acetone (1.5 mL), *N*-iodosuccinimide (8.8 mg, 0.039 mmol) and alkyne **31** (18.3 mg, 0.035 mmol). To the stirred solution, $AgNO_3$ (1.8 mg, 0.010 mmol) was added at room temperature, and the mixture was stirred for 1 h. Then the volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography to afford alkynyl iodide (18.7 mg, 0.029 mmol, 87%).

Alkynyl iodide (12.7 mg, 0.019 mmol) was dissolved in a mixture of THF (1.0 mL) and *i*-PrOH (1.0 mL). Et_3N (7.9 μL, 0.057 mmol) and NBSH (7.4 mg, 0.034 mmol) were added and the reaction mixture was stirred for 24 h. Then, the volatiles were removed *in vacuo* at ambient temperature and the residue was purified by silica gel column chromatography to give vinyl iodide **32** (11.2 mg, 0.018 mmol, 90%). R_f=0.50 (PE/EtOAc V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −0.11 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12 (d, J=8.4 Hz, 2H), 6.77 (d, J=8.4 Hz, 2H), 6.53 (t, J=8.2 Hz, 1H), 6.30 (d, J=7.3 Hz, 1H), 5.34 (d, J=10.5 Hz, 1H), 2.24～2.22 (m, 1H), 2.03～1.98 (m, 4H), 1.85～1.83 (m, 1H), 1.66～1.63 (m, 1H), 1.52～1.50 (m, 1H), 1.39～1.33 (m, 2H), 1.31～1.21 (m, 2H), 0.97 (s, 9H), 0.18 (d, J=2.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.5, 155.5, 140.1, 131.5, 129.0, 120.3, 84.0, 78.3, 45.0, 40.8, 31.7, 29.9, 25.9, 25.1, 21.8, 21.4, 18.3, −4.0; HRMS (ESI) calcd for $C_{33}H_{39}IO_3SiNa$ $[M+Na]^+$ 661.1604, found 661.1605.

4.25 Synthesis of ethyl (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*S*)-acetoxy(4-((*tert*-butyldimethylsilyl)oxy)phenyl)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenoate (**33**)

Vinyl iodide **32** (60.0 mg, 11.66 μmol) and boronate **24** (136 mg, 21.00 μmol) were dissolved in THF (2.0 mL) and H_2O (1.0 mL). To the stirred solution were sequentially added K_3PO_4 (148 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (26.9 mg, 23.32 μmol) at room temperature. The reaction mixture was stirred for 16 h and then water was added. The aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish the title triene **33** (48 mg, 52.82 μmol, 44%). R_f=0.45 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +17.75 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone d_6) δ: 7.31 (d, J=15.6 Hz, 1H, H3), 7.14 (d, J=8.4 Hz, 1H, H24), 6.75 (d, J=8.4 Hz, 1H, H25), 6.58 (dd, J=11.7, 14.5 Hz, 1H, H12), 6.18 (t, J=11.2 Hz, 1H, H14), 6.07 (t, J=7.2 Hz, 1H, H5), 5.96～5.90 (m, 2H, H11, H15), 5.86～5.81 (m, 2H, H2, H13), 5.45 (t, J=10.1 Hz, 1H, H10), 5.38 (d, J=10.6 Hz, 1H, H22), 4.70 (dd, J=6.0, 9.1 Hz, 1H, H9), 4.11 (q, J=7.1 Hz, 2H, H1'), 3.98～3.96 (m, 1H, H7), 2.50～2.48 (m, 1H, H16), 2.44～2.42 (m, 2H, H6a, H6b), 2.10～2.06 (m, 1H, H21), 1.95 (s, 3H, H6'), 1.85 (s, 3H, H3'), 1.84～1.83 (m, 1H, H20a), 1.82～1.80 (m, 1H, H19a), 1.80～1.78 (m, 1H, H8), 1.56～1.52 (m, 1H, H18b), 1.52～1.50 (m, 1H, H17b), 1.49～1.47 (m, 1H, H20a), 1.46～1.45 (m, 1H, H17a), 1.45～1.44 (m, 1H, H18a), 1.34～1.33 (m, 1H, H19a), 1.20 (t, J=7.1 Hz, 3H, H2'), 1.03 (d, J=6.9 Hz, 3H, H4'), 1.01～0.99 (m, 18H, H8', H13'), 0.95～0.93 (m, 9H, H11'), 0.67～0.57 (m, 12H, H10', H12'), 0.21 (s, 6H, H9'); ^{13}C NMR (151 MHz, acetone d_6) δ: 170.2 (C5'), 167.4 (C1), 156.2 (C26), 149.8 (C3), 140.1 (C5), 134.7 (C4), 134.6 (C10), 133.0 (C23), 132.9 (C15), 131.0 (C13), 130.2 (C24), 130.1 (C14), 130.0 (C11), 128.7 (C12), 120.4 (C25), 116.8 (C2), 78.7 (C22), 73.8 (C7), 70.9 (C9), 60.4 (C1'), 48.4 (C8), 46.3 (C21), 34.3 (C16), 34.2 (C17), 33.3 (C6), 26.8 (C19), 26.1 (C8'), 24.2(C20), 21.8 (C18), 21.1 (C6'), 18.8 (C7'), 14.6 (C2'), 12.9 (C3'), 10.0 (C4'), 7.4 (C13'), 7.3 (C11'), 5.9 (C10', C12'), − 4.0 (C9'); HRMS (ESI) calcd for $C_{52}H_{88}O_7Si_3Na$ $[M+Na]^+$ 931.5730, found 931.5735.

4.26 Synthesis of (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*S*)-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)(hydroxy)methyl)cyclohexyl)-4,8-dimethyl-7,9-bis((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenal (**34**)

DIBAL-H (0.88 mL, 1.32 mmol, 1.5 mol/L in toluene) was slowly added to a solution of **33** (48.0 mg, 52.82 μmol) in CH_2Cl_2 (1.5 mL) at −78 ℃. The mixture was stirred for 1 h at this temperature and then the reaction was terminated by addition of a saturated sodium potassium tartrate solution. The aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish the diol (28.0 mg, 33.90 μmol, 64%). R_f=0.55 (PE/EtOAc, V∶V=2∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +78.98 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.10 (d, J=8.4 Hz, 1H), 6.72 (d, J=8.4 Hz, 1H), 6.53 (dd, J=11.7, 14.5 Hz, 1H), 6.25 (d, J=15.5 Hz, 1H), 6.12 (t, J=11.2 Hz, 1H), 5.97～5.92 (m, 3H), 5.91～5.87 (m, 1H), 5.70 (dt, J=5.6, 15.6 Hz, 1H), 5.56 (t, J=6.8 Hz, 1H), 5.42 (t, J=10.0 Hz, 1H), 4.66 (dd, J=6.8, 8.9 Hz, 1H), 4.12～4.05 (m, 3H), 3.90～3.88 (m, 1H), 2.41～2.39 (m, 1H), 2.35～2.31 (m, 2H), 2.20～2.17 (m, 1H), 1.86～1.84 (m, 1H), 1.78 (s, 3H), 1.77～1.72 (m, 2H), 1.50～1.48 (m, 2H), 1.46～1.44 (m, 1H), 1.43～1.41 (m, 2H), 1.35～1.32 (m, 1H), 1.02 (d, J=6.8 Hz, 3H), 1.01～0.99 (m, 18H), 0.94 (t, J=7.9 Hz, 9H), 0.65 (q, J=7.9 Hz, 6H), 0.58 (q, J=7.9 Hz, 6H), 0.21 (d, J=2.5 Hz, 6H,); ^{13}C NMR (151 MHz, acetone-d_6) δ: 155.5, 138.5, 135.5, 134.9, 134.7, 134.0, 131.2, 130.1, 130.0, 129.5, 129.4, 128.4, 127.9, 120.2, 76.7, 74.0, 71.0, 63.4, 49.3, 48.3, 34.6, 34.5, 32.6, 27.1, 26.1, 24.3, 22.0, 18.8, 13.3, 10.2, 7.5, 7.3, 5.9, −4.0; HRMS (ESI) calcd for $C_{48}H_{84}O_5Si_3Na$ $[M+Na]^+$ 847.5519, found 847.5513.

The obtained diol (20.0 mg, 24.25 μmol) was dissolved in

CH_2Cl_2/H_2O (1.0 mL/1.0 mL, pH=7.6), followed by addition of TBACl (27.3 mg, 98.23 μmol) and TEMPO (13.6 mg, 87.3 μmol). Then NCS (21.8 mg, 163.7 μmol) was added to the solution. The reaction mixture was stirred for 2 h at this temperature and then the reaction was terminated by addition of a saturated aq. NH_4Cl solution. Then the mixture was extracted with Et_2O. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the aldehyde **34** (15.0 mg, 18.21 μmol, 75%). R_f=0.62 (PE/EtOAc, V∶V=5∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ +51.20 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, acetone-d_6) δ: 7.29 (d, J=15.5 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 6.71 (d, J=8.4 Hz, 1H), 6.56 (dd, J=11.7, 14.4 Hz, 1H), 6.22 (t, J=7.1 Hz, 1H), 6.13 (t, J=11.1 Hz, 1H), 6.04 (dd, J=7.7, 15.5 Hz, 1H), 5.98～5.91 (m, 3H), 5.45 (t, J=10.1 Hz, 1H), 4.71 (dd, J=6.1, 9.1 Hz, 1H), 4.13～4.11 (m, 1H), 4.01～3.98 (m, 1H), 2.49～2.47 (m, 2H), 2.42～2.40 (m, 1H), 2.20～2.17 (m, 1H), 1.89 (s, 3H), 1.87～1.85 (m, 1H), 1.81～1.77 (m, 2H), 1.50～1.47 (m, 2H), 1.46～1.45 (m, 1H), 1.44～1.41 (m, 2H), 1.35～1.32 (m, 1H), 1.04 (d, J=6.9 Hz, 3H), 1.01～0.98 (m, 18H), 0.94 (t, J=7.9 Hz, 9H), 0.66 (q, J=7.9 Hz, 6H), 0.59 (q, J=7.9 Hz, 6H), 0.20 (d, J=2.5 Hz, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ: 194.2, 157.9, 155.5, 142.3, 138.5, 135.4, 134.5, 134.3, 131.3, 130.1, 129.4, 129.3, 128.4, 127.8, 120.2, 76.8, 73.7, 70.9, 49.3, 48.4, 34.6, 34.6, 33.5, 27.1, 26.1, 24.4, 22.0, 18.8, 13.0, 9.9, 7.4, 7.3, 5.9, −4.0; HRMS (ESI) calcd for $C_{48}H_{82}O_5Si_3Na$ $[M+Na]^+$ 845.5362, found 845.5366.

4.27 Synthesis of (2*E*,4*E*,7*R*,8*R*,9*R*,10*Z*,12*E*,14*Z*)-15-((1*R*,2*R*)-2-((*S*)-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)(hy-droxy)methyl)cyclohexyl-4,8-dimethyl-7,9-bis-((triethylsilyl)oxy)pentadeca-2,4,10,12,14-pentaenoic acid (**35**)

To a stirred solution of the aldehyde **34** (20.2mg, 24.53 μmol) in THF (1.4 mL)/*t*-BuOH (1.4 mL) was added 2-methyl-2-butene (3.59 mL, 7.18 mmol, 2.0 mol/L in THF) 0 ℃. Then a solution of $NaClO_2$ (66.5 mg, 0.73 mmol) and NaH_2PO_4•H_2O (183.7 mg, 1.17 mmol) in water (1.5 mL) was added to the mixture. After stirring overnight, the reaction was terminated by the addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish acid **35** (13 mg, 15.50 μmol, 63%). R_f=0.4 (PE/EtOAc, V∶V=2∶1, visualized using an Annis stain or UV light). Compound **35** was set out to next reaction directly.

4.28 Synthesis of (1*S*,4*E*,6*E*,9*R*,10*R*,11*R*,12*Z*,14*E*,16*Z*,17a*R*,21a*R*)-1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-10-methyl-9,11-bis((triethylsilyl)oxy)-8,9,10,11,17a,18,19,20,21,21a-decahydrobenzo[*c*][1]oxacyclononadecin-3(1*H*)-one (**36**)

Acid **35** (12.0 mg, 14.31 μmol) was dissolved in CH_2Cl_2 (20.0 mL). Then sodium bicarbonate (601.1 mg, 7.15 mmol) and the Mukaiyama reagent (195.9 mg, 0.71 mmol) were added sequentially. After stirring for 18 h at room temperature, the reaction was terminated by addition of water and the aqueous solution was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish macrolactone **36** (5.4 mg, 6.58 μmol, 45%). R_f=0.68 (PE/EtOAc, V∶V=10∶1, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −20.51 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (800 MHz, acetone-d_6) δ: 7.17～7.15 (m, 3H, H3, H24), 6.82 (d, J=8.3 Hz, 2H, H25), 6.45 (t, J=12.2 Hz, 1H, H13), 6.33 (t, J=13.0 Hz, 1H, H12), 6.04～6.01 (m, 1H, H11), 5.99～5.96 (m, 2H, H14, H15), 5.95～5.94 (m, 1H, H22), 5.90～5.85 (m, 1H, H5), 5.79 (d, J=15.7 Hz, 1H, H2), 5.58～5.50 (m, 1H, H10), 4.23～4.20 (m, 1H, H9), 3.91 (br, 1H, H7), 3.13～3.12 (m, 1H, H16), 2.68～2.65 (m, 1H, H6), 2.14～2.12 (m, 1H, H21), 1.88 (s, 3H, H1'), 1.74～1.73 (m, 1H, H19b), 1.71～1.68 (m, 2H, H8, H17b), 1.63～1.61 (m, 1H, H17a), 1.48～1.42 (m, 2H, H18b, H20b), 1.38～1.37 (m, 1H, H18a), 1.28～1.25 (m, 1H, H20a), 1.23～1.17 (m, 1H, H19a), 1.03～1.01 (m, 9H, H9'), 0.98～0.96 (m, 18H, H7', H5'), 0.94～0.92 (m, 3H, H2'), 0.74～0.68 (m, 6H, H8'), 0.63～0.60 (m, 6H, H6'), 0.20 (s, 6H, H3'); ^{13}C NMR (151 MHz, acetone-d_6) δ: 167.7 (C1), 155.4 (C26), 150.6 (C3), 135.7 (C15), 134.8 (C5), 134.7 (C4), 134.1 (C23), 131.6 (C10), 129.7 (C13), 129.6 (C12), 128.3 (C24), 127.8 (C14), 120.2 (C25), 118.1 (C11), 116.5 (C2), 78.7 (C22), 74.7 (C7), 68.3 (C9), 47.3 (C21), 39.7 (C8), 36.9 (C16), 35.6 (C17), 34.2 (C6), 27.5 (C19), 26.0 (C5'), 24.5 (C20), 21.7 (C18), 18.8 (C4'), 13.0 (C1'), 11.3 (C2'), 7.3 (C7', C9'), 6.3 (C6'), 5.7 (C8'), −4.0 (C3'); HRMS (ESI) calcd for $C_{58}H_{84}O_5Si_3Na$ $[M+Na]^+$ 843.5206, found 843.5204.

4.29 Synthesis of (1*S*,4*E*,6*E*,9*R*,10*R*,11*R*,12*Z*,14*E*,16*Z*,17a*R*,21a*R*)-9,11-dihydroxy-1-(4-hydroxyphenyl)-10-methyl-8,9,10,11,17a,18,19,20,21,21a-decahydrobenzo[*c*][1]oxacyclononadecin-3(1*H*)-one (C_{22}-*epi*-**4**)

Macrolactone **36** (5.1 mg, 6.21 μmol) was dissolved in THF (1.0 mL) and the solution was cooled to 0 ℃. A solution of diluted hydrogen fluoride pyridine complex (1.0 mL), which was prepared by mixing hydrogen fluoride (2 mL, ω≈70%) with pyridine (5.6 mL) in THF (9.8 mL), was added at 0 ℃. The mixture was stirred for 10 h at this temperature and the reaction was terminated by addition of a saturated aq. $NaHCO_3$ solution. The aqueous solution was extracted with Et_2O for three times and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to furnish C_{22}-*epi*-**4** (2.3 mg, 4.80 μmol, 77%). R_f=0.56 (EtOAc, visualized using an Annis stain or UV light); $[\alpha]_D^{20}$ −10.20 (*c* 0.2, acetone); ^{1}H NMR (800 MHz, acetone- d_6) δ: 8.22 (s, OH), 7.12 (d, J=15.6 Hz, 1H, H3), 7.07 (d, J=8.4 Hz, 2H, H24), 6.79 (d, J=8.3 Hz, 2H, H25), 6.34 (dd, J=11.1, 14.6 Hz, 1H, H13), 6.27 (dd, J=11.1, 14.5 Hz, 1H, H12), 6.03 (t, J=10.9 Hz, 1H, H15), 5.96～5.91 (m, 2H, H11, H14), 5.86 (d, J=15.6

Hz, 1H, H2), 5.82～5.80 (m, 1H, H5), 5.80～5.78 (m, 1H, H22), 5.55 (t, J=9.7 Hz, 1H, H10), 4.85～4.82 (m, 1H, H9), 4.24～4.12 (m, 1H, OH7), 3.94～3.91 (m, 1H, H7), 3.71～3.69 (m, 1H, OH9), 3.04～3.03 (m, 1H, H16), 2.74～2.69 (m, 1H, H6a), 2.55～2.54 (m, 1H, H6b), 2.03～2.01 (m, 1H, H21),1.97 (s, 3H, H1'), 1.75～1.73 (m, 1H, H19b), 1.71～1.68 (m, 1H, H17a), 1.66～1.63 (m, 1H, H8), 1.62～1.61 (m, 1H, H17b), 1.58～1.56 (m, 2H, H20a, H20b), 1.50～1.46 (m, 1H, H18a), 1.41～1.39 (m, 1H, H18b), 1.18～1.13 (m, 1H, H19a), 1.06 (d, J=6.9 Hz, 3H, H2'); ^{13}C NMR (151 MHz, acetone-d_6) δ: 167.9 (C1), 157.1 (C26), 150.0 (C3), 138.3 (C5), 135.7 (C10), 135.3 (C4), 134.8 (C15), 132.2 (C23), 129.7 (C12), 128.5 (C13), 127.6 (C24, C11), 127.5 (C14), 116.6 (C2), 115.5 (C25), 79.6 (C22), 75.2 (C7), 66.5 (C9), 48.2 (C21), 42.8 (C8), 37.5 (C16), 35.6 (C17), 34.5 (C6), 27.4 (C19), 26.2 (C20), 21.6 (C18), 13.0 (C1'), 10.6 (C2'); HRMS (ESI) calcd for $C_{30}H_{38}O_5Na$ $[M+Na]^+$ 477.2643, found 477.2646.

Supporting Information Experimental procedures, characterizations, analytical data of new compounds and NMR spectra. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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