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Convergent approach to the maduropeptin chromophore: aryl ether formation of (*R*)-3-aryl-3-hydroxypropanamide and cyclization of macrolactam

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Abstract—Efficient enantioselective syntheses of the functionalized phenol and diethynylcyclopentene moiety of the maduropeptin chromophore were achieved. Their CsF-mediated coupling yielded a sterically congested aryl propargyl ether. The subsequent intramolecular Sonogashira coupling reaction between the vinyl iodide and diethynyl groups occurred at the appropriate position to yield a macrolactam, which was accompanied by Pd-mediated enyne-yne benzannulation.

1. Introduction

Maduropeptin, isolated from the broth filtrate of *Actinomadura madura*, consists of a 1:1 complex of an acidic carrier apoprotein (32 kDa) and a 9-membered enediyne chromophore, and exhibits potent antibacterial and antitumor activities.[1] The structure of the intact chromophore has not been concluded because it was too labile for isolation, and instead methanol adduct **1** was isolated from the methanol extract and characterized with the exception of the absolute stereochemistry.[1b] Compound **1** possesses a labile 9-membered diyne core, a macrolactam ansa-bridge, and an amino sugar. While there are several possibilities for the structure of the parent chromophore, the mechanism of action for **1** was proposed as shown in Scheme 1 on the basis of the isolation of cycloaromatization product **4**, as well as the enhancement of DNA cleavage under basic conditions. The amide nitrogen of **1** would attack C13, causing an S_N2' displacement of methoxy group to afford labile enediyne **2**, which undergoes cycloaromatizatin to *p*-benzyne biradical **3** capable of proton abstraction and DNA scission. The potent bioactivity and the novel structure of **1**, as well as the exploration of the structure of the intact chromophore stimulated the synthetic studies of **1**.[2]

The target of this study was *ent*-**1**, an enantiomer of the compound arbitrarily described in the literature,[1b] due to the structural similarity of **1** to the related chromophores of C-1027[3] and kedarcidin.[4–6] The retrosynthetic analysis of *ent*-**1** is outlined in Scheme 2. The construction of *ent*-**1** was thought to be accomplished by macro-ring cyclization using intramolecular Sonogashira coupling[7] of **5** and a subsequent internal addition of an alkyne to the aldehyde. The intermediate **5** was split into two fragments, 3-aryl-3(*R*)-hydroxypropanamide **6** and diethynylepoxycyclopentene **7** by disconnection of the aryl ether bond. The fragment **6** could be constructed from 3-aryl-3(*R*)-hydroxypropanoic acid **8** and amine **9**. The functionalized cyclopentene moiety **7** is to be generated from the previously synthesized chiral dihydroxycyclopentylidene **10**.[2f,8] In this paper, the enantioselective synthesis of **5**, through the efficient CsF-mediated aryl ether bond formation[9] between the sterically hindered phenol **6** and epoxide **7**, as well as macro-ring cyclization of **5**, is reported.

2. Results and discussion

Synthesis of allyl amine **15** is summarized in Scheme 3. Here, vinyl iodide **11**, prepared from 1,4-butynediol according to the literature procedure[2c] was treated with MPMBr in the presence of NaH to afford MPM ether **12** in a 60% yield. It is important to add NaH into a solution of **11** and MPMBr in small portions. An excess of NaH results in the production of bis-TBS ether, subsequently decreasing the yield of **12**. Deprotection of the TBS group of **12** and subsequent formation of phthalimide **14** via Mitsunobu reaction[10] followed by cleavage of the phthaloyl group with

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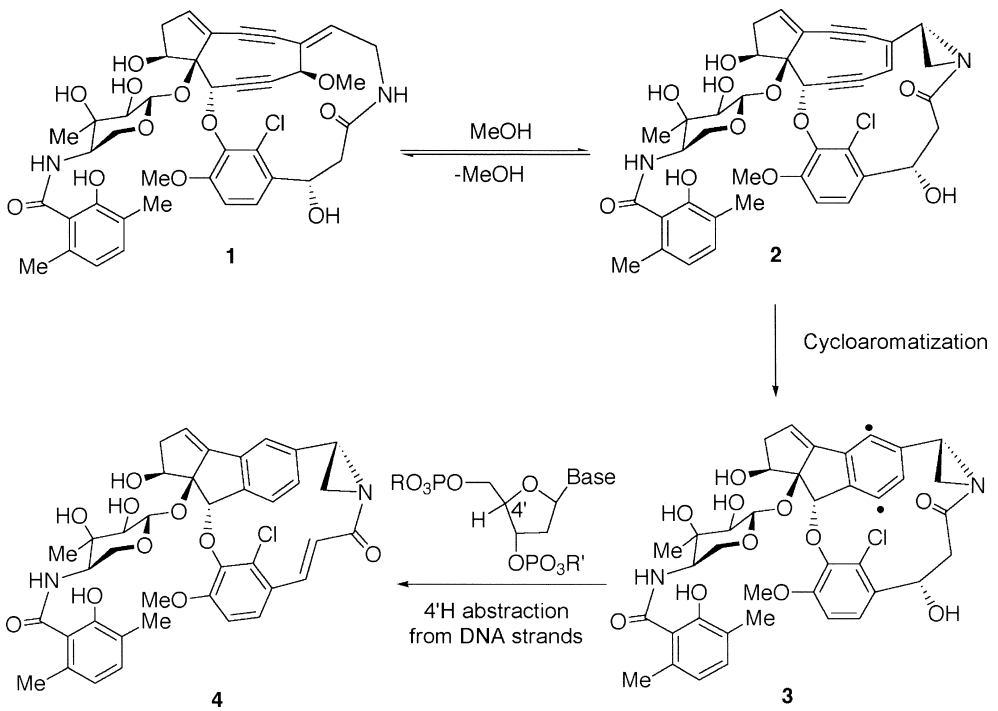
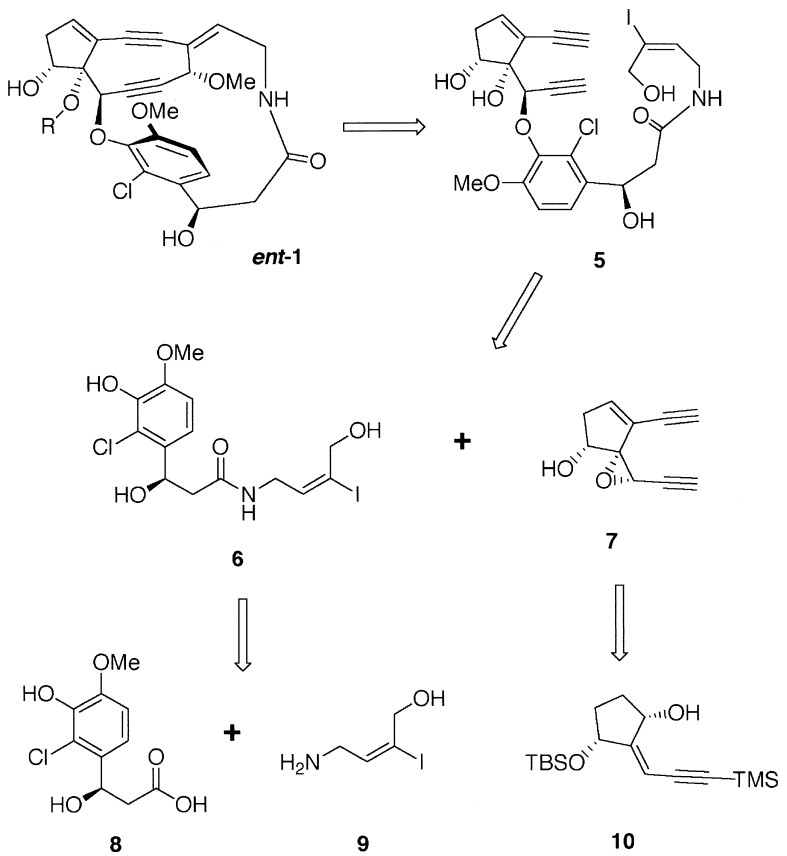


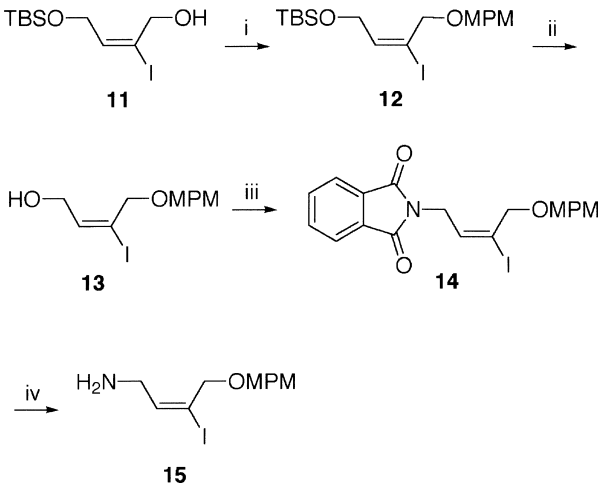
Scheme 1. Mechanism of action of methanol adduct **1** of the maduropeptin chromophore proposed by Schroeder et al.[1b]

hydrazine monohydrate gave allyl amine **15**, which was used for the next reaction without purification.

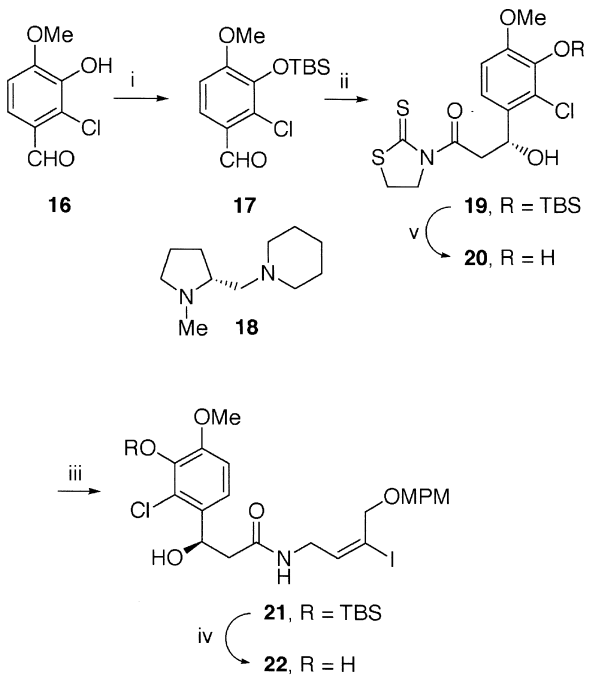
Synthesis of 3-aryl-3(*R*)-hydroxypropanamide fragment **21** began with readily available chloroisovanilin **16**[11] (Scheme 4). The phenol of **16** was protected as TBS ether **17** in 98% yield, and then subjected to asymmetric Mukaiyama aldol reaction with 3-acetylthiazolidine-2-thione in the presence of (*R*)-chiral diamine **18**[12] to afford (*R*)-aldol product **19** as a major enantiomer (75% ee by



Scheme 2. Retrosynthesis of artifact *ent*-**1** of the maduropeptin chromophore.



Scheme 3. Reagents and conditions: (i) MPMBr, NaH, THF/DMF (1:1), room temperature, 1 h, 60%; (ii) TBAF, THF, room temperature, 30 min, 87%; (iii) DEAD, PPh_3, phthalimide, THF, room temperature, 30 min, 98%; (iv) $H_2NNH_2{\cdot}H_2O$, THF, room temperature, 6 h, 99%.

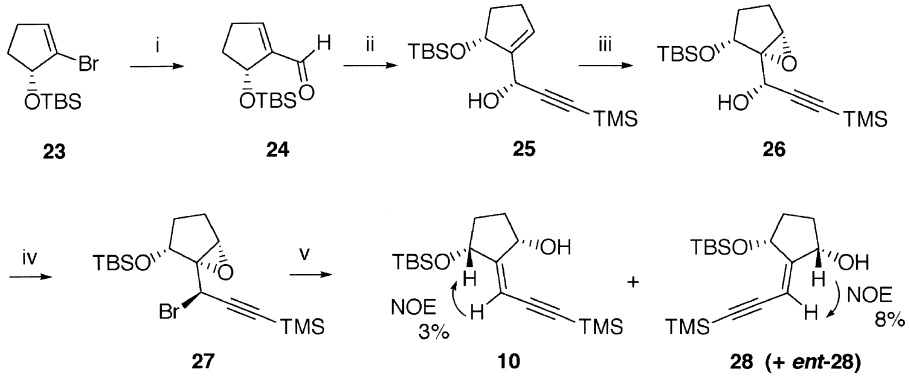


Scheme 4. Reagents and conditions: (i) TBSCl, imidazole, DMF, room temperature, 40 min, 96%; (ii) (*R*)-**18**, $Sn(OTf)_2$, 3-acetylthiazolidine-2-thione, *N*-ethylpiperidine, CH_2Cl_2, −95 °C, 10 h, 72%, 75%ee; recrystallization (AcOEt/hexane=1:50), 64%, >99%ee; (iii) **15**, CH_2Cl_2, room temperature, 2 h, 88%; (iv) TBAF, THF, room temperature, 30 min, 85%; (v) HF·pyridine, THF, room temperature, 12 h, 81%.

HPLC analysis). One recrystallization of thus obtained **19** yielded enantiomerically pure **19** in 49% yield. The absolute stereochemistry of **19** was unambiguously assigned by X-ray crystallographic analysis of **20**[13] after deprotection of the TBS ether. The activated ester **19** was directly treated with the amine **15** to afford amide **21** in 99% yield[14] and subsequent deprotection of the TBS group of **21** yielded **22** (85% yield).

Although several syntheses of compounds related to the enyne **10** have been achieved by trapping enols as triflates followed by Sonogashira coupling,[8] an alternative strategy is required for the syntheses of functionalized **10**. An efficient stereoselective route to **10** has been developed.[2f] Synthesis of **10** started from a readily available 2-bromo-3(*R*)-cyclopentenol derivative **23**,[15] which was formylated in the presence of BuLi and DMF[16] to afford unstable aldehyde **24** (Scheme 5). The aldehyde **24** was treated with lithium trimethylsilylacetylide without purification to give a single diastereomer of allylic alcohol **25** in an 88% yield. This stereoselectivity can be accounted by the transition state model shown in Figure 1, where the conjugated enal system of **24** should be almost planar. The *s-cis* enal conformation **A** is expected to be favored over that of the *s-trans* **B**, because **B** may exhibit some steric repulsion between the TBS ether group and the carbonyl oxygen coordinated with the lithium reagent. Epoxidation of **25** with *m*CPBA resulted in a 5:1 mixture of diastereomers in favor of **26**. On the other hand, Sharpless asymmetric epoxidation with (+)-DET[17] yielded **26** as the sole product. Under these conditions, a kinetic resolution occurred and the epoxy alcohol **26** was produced in enantiomerically pure form. The stereochemistry of **26** was unambiguously assigned by X-ray crystallographic analysis (Fig. 2).[18] The alcohol **26** was further converted to bromide **27** with a complete stereochemical inversion, using CBr_4 and PPh_3 in dry CH_2Cl_2. If the solvent was not dried, a dibromo alcohol (~20%) was formed via addition of HBr to the epoxide **27**.[19]

The subsequent reductive opening of the α-bromoepoxide **27** was attempted based on the assumption that anti-elimination using zinc would occur (Table 1).[20,21] Treatment with Zn–NaI in MeOH at −40 °C gave **10** and **28**



Scheme 5. Reagents and conditions: (i) BuLi, THF, −78 °C, 30 min; DMF, −78 °C, 30 min., (ii) TMSCCLi, THF, −78 °C, 1.5 h, 95% (2 steps); (iii) (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, MS4A, CH_2Cl_2, −20 °C, 10 h, 72%; (iv) CBr_4, PPh_3, CH_2Cl_2, 2 h, 89%; (v) see Table 1.

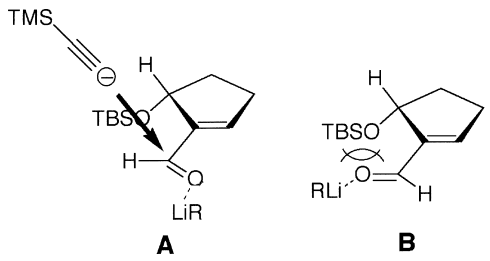


Figure 1. Stereoselective addition of lithium trimethylacetylide to the preferred *s-cis* enal conformation **A** of **24**.

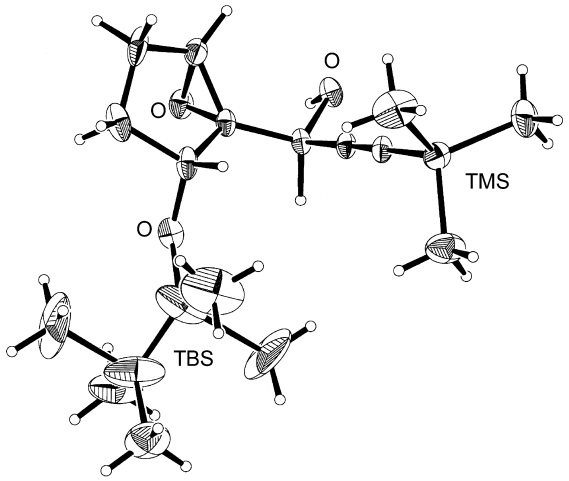
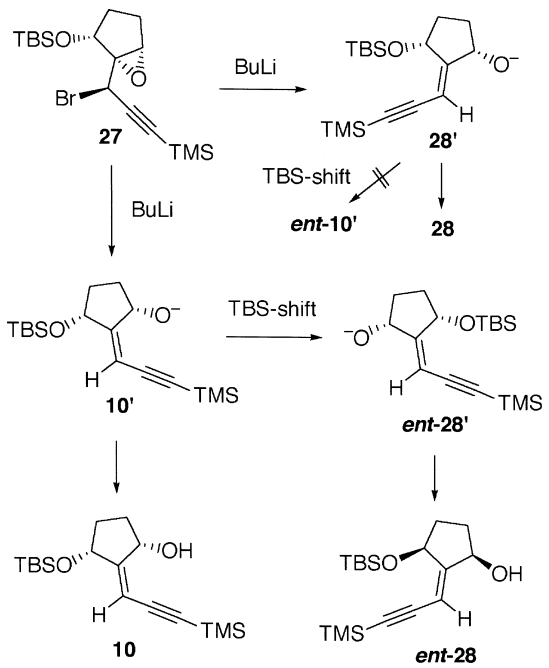


Figure 2. ORTEP drawing of **26**.

in a 2.7:1 ratio with 70% yield (entry 1). The *E* and *Z* stereochemistry was assigned based on the results of NOE experiments. A slightly higher ratio (3.1:1) was obtained with Zn–Cu in refluxing ethanol (entry 2). The best result (**10**–**28**=6.5–7:1, 99% yield) was achieved using BuLi at −90 °C in THF (entry 3). If a migration of TBS group occurs between the pseudo-axial hydroxyl groups under the basic reaction conditions, the alkoxide **10′** would produce *ent*-**28′** and the alkoxide **28′** would afford *ent*-**10′** (Scheme 6). Therefore, the enantiomeric purities of **10** and **28** were determined by HPLC with a chiral column. Interestingly, the major product **10** was always enantiomerically pure and the absolute configuration of **10** corresponded to that of **26**,[22] whereas **28** was not enantiomerically pure; the ratio of **28** and *ent*-**28** greatly varied from 3:1 to 1:2. These results indicated that the only alkoxide **10′** underwent the TBS group migration. No simple explanation for the different migration reactivity observed between the alkoxides **10′** and **28′** can be offered at present. A reductive anti-elimination leading to **10** predominated in the reaction of α-bromoepoxide **27** with BuLi.

Thus obtained **10** was stereoselectively converted to epoxide **29** by hydroxy-directed *m*CPBA epoxidation in an 86% yield (Scheme 7). The stereochemistry of **29** was



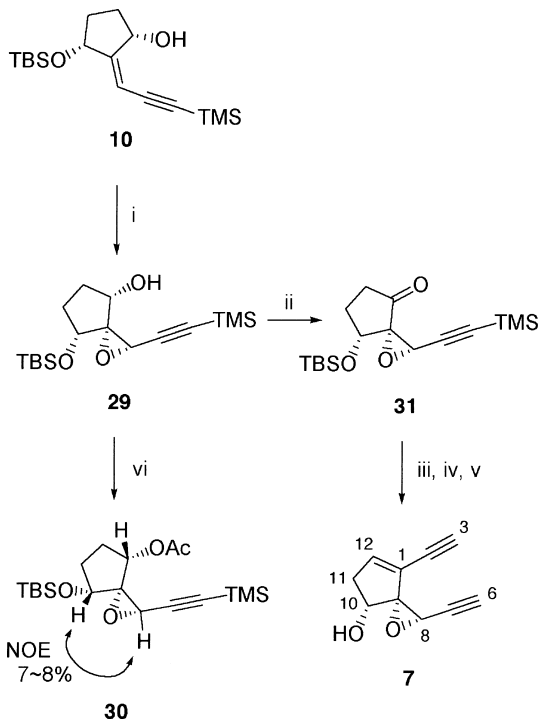
Scheme 6. Proposed reaction pathways to produce **10**, **28**, and *ent*-**28** in the BuLi-mediated reductive opening of α-bromoepoxide **27**.

confirmed by NOE experiments for acetate **30**. Dess–Martin oxidation[23] of **29** gave ketone **31** (84%), to which lithium trimethylsilylacetylide was added and the resulting epimeric mixture of alcohols were dehydrated with methanesulfonyl anhydride in the presence of triethylamine at 40 °C. Subsequent removal of the silyl groups with TBAF yielded diethynylcyclopentene **7** from **31** in a 57% overall yield. The absolute configuration of enantiomerically pure **7** was confirmed by NMR comparison of the corresponding (*S*)- and (*R*)-MTPA esters.[22]

The two key fragments **7** and **22** in hand were then assembled. Our coupling method,[9a,b] employing CsF in DMF at 60 °C, proved to be effective for the sterically congested *o*,*o*,*m*-tri-substituted phenol **22**. The coupling of these compounds resulted into aryl ether **32** in a 50% yield (Scheme 8). Thus obtained diyne alkenyl iodide **32** was subjected to the most critical step in this study, an intramolecular Sonogashira reaction under the previously established optimized conditions.[7] A regioselective cyclization between C3 and C4 forming a 16-membered ring was expected to be favored over the formation of the more strained 14-membered ansa-macro ring through C4–C6 coupling. The reaction at room temperature for 3.5 h afforded product in a 7% yield. The reaction mixture was subsequently heated at 60 °C to increase the yield of the product to 40% yield. This product was not the desired **33**. The product was deduced to be **34** by detailed NMR analysis using HMBC (see Experimental), HMQC, and NOE

Table 1. Reductive opening of the α-bromoepoxide **27**

Entry	Reaction conditions	Product ratio (**10**/**28**)	Combined yield (%)
1	Zn (3.0 equiv.), NaI (1.7 equiv.), MeOH, −40 °C, 1 h	73/27	70
2	Zn–Cu (3.0 equiv.), EtOH, reflux, 30 min	76/24	90
3	BuLi (1.5 equiv.), THF, −90 °C, 15 min	87/13	99



Scheme 7. Reagents and conditions: (i) *m*CPBA, Na_2HPO_4, CH_2Cl_2, room temperature, 16 h, 86%; (ii) Dess–Martin periodinane, room temperature, 30 min, 84%; (iii) TMSCCLi, −78 °C, THF, 3 h; (iv) Ms_2O, Et_3N, dichloroethane, 40 °C, 3 h; (v) TBAF, THF, room temperature, 0 °C, 57% (3 steps); (vi) Ac_2O, pyridine, 50 °C, 11 h, 73%.

experiments (Fig. 3). The product **34**, however, clearly indicated the intermediacy of **33**, which underwent a concomitant Pd-mediated benzannulation reaction between the enyne and alkyne functionalities.[24]

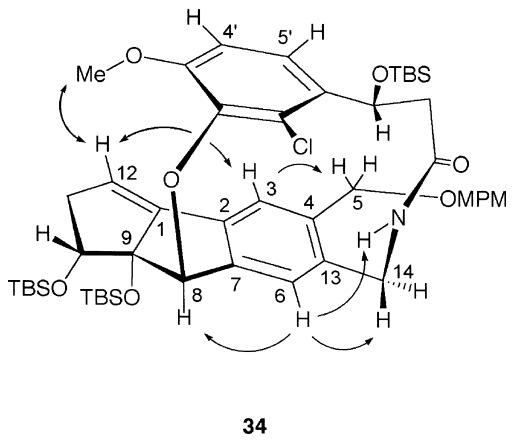
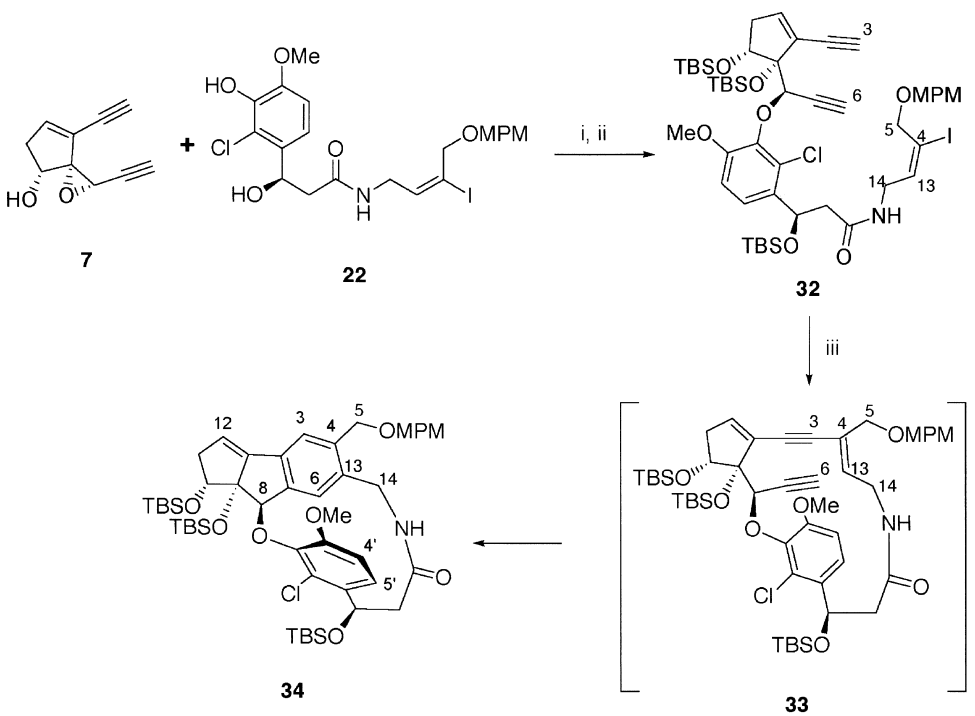


Figure 3. NOEs observed for **34**.

3. Conclusion

An enantioselective synthesis of (*R*)-3-aryl-3-hydroxypropanamide fragment **22** of maduropeptin chromophore artifact *ent*-**1** was achieved via asymmetric Mukaiyama aldol reaction, whereas a stereoselective route to diethynylcyclopentene moiety **7** was developed using a novel BuLi-mediated reductive opening of α-bromoepoxide **27**. The CsF-mediated coupling strategy between highly congested phenol derivative **22** and epoxide **7** successfully constructed a key aryl ether structure **32**. A critical intramolecular Sonogashira macro-ring cyclization of diyne vinyl iodide **32** was demonstrated to proceed in the desired manner forming the 16-membered ring intermediate **33**, which underwent a concomitant Pd-mediated benzannulation of an enyne–yne system, leading to the 13-membered lactam **34**. Based on the chemistry described



Scheme 8. Synthesis of **32** and Pd-catalyzed macrocyclization. Reactions and conditions: (i) CsF, DMF, 60 °C, 8 h, 50%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 77%; (iii) $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, *i*-Pr_2NEt, DMF, 60 °C, 3 h, 40%.

herein, further studies directed toward the total synthesis of *ent*-**1** are currently underway.

4. Experimental

4.1. General

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. THF was distilled from sodium/benzophenone just prior to use. CH_2Cl_2, DMF and dichloroethane were distilled from calcium hydride. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica Gel 0.25 mm pre-coated plates (60F-254). Column chromatography was performed using Silica Gel 60 (E. Merck, 70–230 mesh) or 100–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and for flash column chromatography 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used. HPLC was performed on Hitachi D-7000 HPLC System using a UV detector (254 nm).

^{1}H- and ^{13}C NMR spectra were recorded on a Varian INOVA 500 or a JEOL α-500 spectrometer. Chemical shifts are reported in δ (ppm) using residual $CHCl_3$ as an internal standard of δ 7.26 and 76.9 for ^{1}H and ^{13}C NMR, respectively. IR spectra were recoded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. MALDI-TOF mass spectra were recorded on a Applied Biosystems Voyager DE STR SI-3 instrument, and ESI-TOFMS were on a Applied Biosystems Mariner. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Elemental analysis was conducted with a Yanaco CHN corder MT-5. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

4.1.1. MPM ether 12. To a solution of **11** (1.98 g, 6.04 mmol) and MPMBr (3.04 g, 15.1 mmol) in DMF–THF (1:1, 20 ml) was slowly added NaH (60% dispersion in mineral oil, 400 mg, 16.7 mmol) in small portions at 0 °C. After stirring for 1 h at room temperature, to the reaction mixture were added MeOH (2 ml) and sat. NH_4Cl aq. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=20:1) to afford **12** (1.63 g, 60%) as a colorless oil. IR (neat) ν 2954, 2930, 2856, 1613, 1514, 1250, 1088, 1037, 837, 778 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 3.81 (s, 3H), 4.13 (brs, 2H), 4.15 (d, 2H, *J*=6.4 Hz), 4.43 (s, 2H), 6.55 (brd, 1H, *J*=6.4 Hz), 6.89 (d, 2H, *J*=8.7 Hz), 7.30 (d, 2H, *J*=8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.38, 18,17, 25.73, 55.16, 61.09, 70.98, 71.19, 100.13, 113.72, 129.24, 129.53, 144.25, 159.25. MALDI-TOFMS (positive-ion) calcd for $C_{18}H_{29}IO_3SiNa$: $(M+Na)^+$ 471.0828; found: 471.0606.

4.1.2. TBS ether 13. To a solution of **12** (3.20 g, 7.14 mmol) in THF (50 ml) was added to TBAF (1.0 M THF solution, 11 ml, 11.0 mmol) at 0 °C. After stirring for 30 min, the reaction quenched with sat. NH_4Cl aq. The water layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=3:1) to afford **13** (2.07 g, 87%) as a colorless oil. IR (neat) ν3 418, 2933, 1614, 1515, 1249, 1175, 1033, 820, 759 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (brs, 1H), 3.81 (s, 3H), 4.08 (brd, 2H, *J*=6.7 Hz), 4.19 (s, 2H), 4.46 (s, 2H), 6.63 (t, 1H, *J*=6.7 Hz), 6.89 (d, 2H, *J*=8.4 Hz), 7.29 (d, 2H, *J*=8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.16, 60.28, 71.45, 71.92, 101.26, 113.77, 129.14, 129.56, 143.37, 159.32. ESI-TOFMS (positive-ion) calcd for $C_{12}H_{15}IO_3H$: $(M+H)^+$ 335.0144; found: 335.0126, calcd for $C_{12}H_{15}IO_3NH_4$: $(M+NH_4)^+$ 352.0140; found 352.0464, calcd for $C_{12}H_{15}IO_3Na$: $(M+Na)^+$ 356.9964; found: 357.0032, calcd for $C_{12}H_{15}IO_3K$: $(M+K)^+$ 372.9703; found 372.9713.

4.1.3. Phthalimide 14. To a solution of **13** (2.95 g, 8.81 mmol), PPh_3 (3.50 g 13.3 mmol) and phthalimide (1.98 g, 13.5 mmol) in dry THF (20 ml) was added DEAD (5.5 ml, 72.4 mmol) at 0 °C under argon, and the mixture was stirred at room temperature for 30 min. The solvent was removed, and the residue was added diethyl ether. Then, the precipitate was removed by filtration and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=7:1) to afford **14** (4.00 g, 98%) as needles. Mp 78–80 °C (from hexane/AcOEt). IR (film) ν 2835, 2066, 1722, 1714, 1611, 1513, 1393, 1248, 1087, 1033, 721, 529 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.29 (d, 2H, *J*=7.4 Hz), 4.37 (s, 2H), 4.51 (s, 2H), 6.48 (t, 1H, *J*=7.4 Hz), 6.90 (d, 2H, *J*=6.9 Hz), 7.36 (d, 2H, *J*=6.9 Hz), 7.72 (dd, 2H, *J*=5.9, 3.3 Hz), 7.84 (dd, 2H, *J*=5.9, 3.3 Hz). ^{13}C NMR (125 MHz, CDCl3) δ 36.83, 55.17, 71.33, 104.54, 113.75, 123.29, 129.58, 131.87, 134.02, 137.08, 159.25, 167.41. ESI-TOFMS (positive-ion) calcd for $C_{20}H_{18}INO_4NH_4$: $(M+NH_4)^+$ 481.0624; found 481.0462, calcd for $C_{20}H_{18}INO_4Na$: $(M+Na)^+$ 486.0178; found: 486.0185, calcd for $C_{20}H_{18}INO_4K$: $(M+K)^+$ 501.9918; found 501.9926. Anal. Calcd for $C_{20}H_{18}INO_4$: C, 51.85; H, 3.92; N, 3.02. Found: C, 51.80; H, 4.06; N, 2.85.

4.1.4. Amine 15. To a solution of **14** (185 mg, 0.399 mmol) in THF (5 ml) was added hydrazine monohydrate (150 μl, 3.09 mmol), and the mixture was stirred at room temperature. After stirring for 30 min, the solvent was removed in vacuo. The residue was treated with sat. NaOH aq. and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **15** (132 mg, 99%) as a pale yellow oil. IR (neat) ν 3364, 2999, 2906, 2856, 1613, 1514, 1249, 1174, 1085, 1033, 820 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (brs, 2H), 3.28 (d, 2H, *J*=7.3 Hz), 3.79 (s, 3H), 4.13 (s, 2H), 4.43 (s, 2H), 6.52 (t, 1H, *J*=7.3 Hz), 6.87 (d, 2H, *J*=8.6 Hz), 7.28 (d, 2H, *J*=8.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.65, 55.11, 71.04, 71.10, 99.71, 113.67, 129.40, 145.63, 159.20. ESI-TOFMS (positive-ion) calcd for $C_{12}H_{16}INO_2H$: $(M+H)^+$ 334.0304; found: 334.0295.

4.1.5. TBS ether 17. To a solution of **16** (3.42 g, 18.4 mmol) and imidazole (2.83 g, 42.2 mmol) in DMF (20 ml) was added TBSCl (3.68 g, 24.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 45 min. The

reaction quenched with sat. NH_4Cl aq. The aqueous layer was extracted with hexane, and the combined organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=20:1) to afford **17** (4.24 g, 96%) as a colorless oil. Mp 41–43 °C (from MeOH/H_2O). IR (film) ν 2931, 2858, 1689, 1580, 1494, 1312, 1282, 1043, 875, 838, 785 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 6H), 1.05 (s, 9H), 3.89 (s, 3H), 6.86 (d, 1H, J=8.7 Hz), 7.59 (d, 1H, J=8.7 Hz), 10.35 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −4.09, 18.78, 25.75, 55.38, 109.23, 122.66, 126.42, 129.56, 141.71, 156.10, 189.36.. ESI-TOFMS (positive-ion) calcd for $C_{14}H_{21}ClO_3SiH$: $(M+H)^+$ 301.1027; found: 301.0943. Anal. Calcd for $C_{14}H_{21}ClO_3Si$: C, 55.89; H, 7.04; Cl, 11.78. Found C, 55.73; H, 7.05; Cl, 11.68.

4.1.6. Thiazolidinethione 19. To a suspension of stannous triflate (1.02 g, 2.45 mmol) and *N*-ethyl piperidine (386 μl, 2.85 mmol) in CH_2Cl_2 (10 ml) was dropwise added 3-acetylthiazolidine-2-thione (637 mg, 3.96 mmol) in CH_2Cl_2 (1.5 ml) at −78 °C under argon. After the mixture was stirred for (*R*)-**18** (501 mg, 2.75 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise, and the mixture was stirred for 5 min at this temperature. Then the mixture was cooled to −95 °C and **17** (598 mg, 2.21 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise. The mixture was further stirred for 1 h at this temperature, and then quenched with 0.1 M HCl. The organic layer was extracted with diethyl ether and the extracts were washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (hexane/AcOEt=20:1) to afford **19** (673 mg, 72%) as a yellow solid. To a solution of **19** (673 mg, 75%ee) in ethyl acetate (1 ml) was added hexane (50 ml) at 50 °C, and the mixture was allowed to stand at room temperature for 3 h. The mixture was filtered through a sintered-glass funnel, and the crystals were repeatedly rinsed with hexane (3×30 ml) to afford enantiomerically pure **19** (431 mg, 64%, >99%ee) as yellow needles. Mp 119–121 °C. $[\alpha]_D^{23}$=+73.7 (*c* 0.88, $CHCl_3$). IR (film) ν 3500, 2930, 2857, 1694, 1494, 1277, 1157, 1046, 829 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.20 (s, 3H), 1.02 (s, 9H), 3.32 (t, 2H, J=7.6 Hz), 3.34 (d, 1H, J=2.8 Hz), 3.59 (dd, 1H, J=18.0, 9.2 Hz), 3.66 (dd, 1H, J=18.0, 2.8 Hz), 3.80 (s, 3H), 4.63 (t, 2H, J=7.6 Hz), 5.53 (dt, 1H, J=9.2, 2.8 Hz), 6.81 (d, 1H, J=8.8 Hz), 7.15 (d, 1H, J=8.8 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −4.16, −4.07, 18.78, 25.80, 28.30, 46.06, 55.19, 55.55, 67.06, 109.78, 118.47, 123.50, 132.51, 141.34, 150.44, 173.55, 201.48. ESI-TOFMS (positive-ion) calcd for $C_{19}H_{28}ClNO_4S_2SiH$: $(M+H)^+$ 462.0996; found: 462.1161, calcd for $C_{19}H_{28}ClNO_4S_2SiNH_4$: $(M+NH_4)^+$ 479.1261; found: 479.1351, calcd for $C_{19}H_{28}ClNO_4S_2SiNa$: $(M+Na)^+$ 484.0815; found: 484.0904, calcd for $C_{19}H_{28}ClNO_4S_2SiK$: $(M+K)^+$ 500.0555; found 500.0643. Anal. Calcd for $C_{19}H_{28}ClNO_4S_2Si$: C, 49.38; H, 6.11; N, 3.03. Found C, 49.25; H, 6.27; N, 3.01.

The ee of **19** was determined as follows. To a solution of chromatographically purified **19** (46.4 mg, 108 μmol) in MeOH (3 ml) was added K_2CO_3 (8.4 mg, 60.9 μmol) and the mixture was stirred at room temperature for 20 min, then added NaCl. The organic layer was extracted with ether and the extracts were washed with brine, and dried over $MgSO_4$. The residue was purified by silica-gel column chromatography (hexane/AcOEt=4:1) to afford methyl ester (30.3 mg, 82%) as a colorless oil, which was analyzed to be 75%ee by HPLC using Chiralcel OJ-R column 4.6ϕ×150 mm (MeOH/H_2O=7:3): $[\alpha]_D^{20}$=+54.6 (2.62, $CHCl_3$). IR (neat) ν 3500, 2931, 2858, 1731, 1592, 1494, 1258, 1046, 830 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 1.02 (s, 9H), 2.58 (dd, 1H, J=16.5, 9.2 Hz), 2.83 (dd, 1H, J=16.5, 2.4 Hz), 3.40 (brd, 1H, J=3.4 Hz, OH), 3.73 (s, 3H), 3.79(s, 3H), 5.42 (ddd, 1H, J=9.2, 3.4, 2.4 Hz), 6.79 (d, 1H, J=8.8 Hz), 7.14 (d, 1H, J=8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.20, −4.14, 18.75, 25.77, 41.36, 51.75, 55.14, 67.07, 109.68, 118.11, 123.34, 132.64, 141.32, 150.38, 172.87. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{27}ClO_5SiNH_4$: $(M+NH_4)^+$ 392.1600; found: 392.1509.

4.1.7. Propanamide 21. To a solution of **15** (3.52 g, 28.9 mmol) in CH_2Cl_2 (20 ml) was added **19** (5.5 ml, 72.4 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with sat. NH_4Cl aq.. The water layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=3:2) to afford **21** (3.89 g, 88%) as a colorless oil. $[\alpha]_D^{26}$=+49.9 (*c* 1.6, $CHCl_3$). IR (film) ν 3313, 2930, 2856, 1651, 1514, 1493, 1250, 1045, 839 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 1.02 (s, 9H), 2.39 (dd, 1H, J=15.1, 8.7 Hz), 2.61 (dd, 1H, J=15.1, 2.3 Hz), 3.76–3.82 (m, 7H), 3.87 (ddd, 1H, J=15.0, 6.6, 5.8 Hz), 4.19 (s, 2H), 4.30 (brs, 1H), 4.45 (s, 2H), 5.32 (dd, 1H, J=8.7, 2.3 Hz), 5.96 (brs, 1H), 6.36 (t, 1H, J=6.6 Hz), 6.81 (d, 1H, J=8.7 Hz), 6.88 (d, 2H, J=8.7 Hz), 7.11 (d, 1H, J=8.7 Hz), 7.29 ((d, 2H, J=8.7 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −4.17, −4.07, 18.79, 25.81, 38.76, 42.20, 55.16, 55.19, 67.69, 71.56, 71.93, 101.89, 109.73, 113.82, 118.29, 122.13, 129.30, 129.51, 132.87, 139.72, 141.32, 150.37, 159.38, 171.56. ESI-TOFMS (positive-ion) calcd for $C_{28}H_{39}ClINO_6SiH$: $(M+H)^+$ 676.1358; found: 676.1198, calcd for $C_{28}H_{39}ClINO_6SiNa$: $(M+Na)^+$ 698.1178; found: 698.0712, calcd for $C_{28}H_{39}ClINO_6SiK$: $(M+K)^+$ 714.0917; found 714.0647.

4.1.8. Phenol propanamide 22. To a solution of **21** (1.48 g, 4.45 mmol) in THF (10 ml) was added to TBAF (1.0 M THF solution, 5.6 ml, 5.60 mmol) at 0 °C. After stirring at same temperature for 30 min, the reaction quenched with phosphate buffer (pH 7.0). The water layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The reaction mixture was purified by silica-gel column chromatography (hexane/AcOEt=1:1) to afford **22** (2.08 g, 85%) as a white solid. $[\alpha]_D^{26}$=+44.4 (*c* 1.4, $CHCl_3$). IR (film) ν 3340, 2937, 1650, 1612, 1513, 1493, 1282, 1249, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, 1H, J=15.1, 8.3 Hz), 2.61 (dd, 1H, J=15.1, 3.1 Hz), 3.76–3.82 (m, 4H), 3.85–3.90 (m, 4H), 4.19 (s, 2H), 4.45 (s, 2H), 5.32 (dd, 1H, J=8.3, 3.1 Hz), 5.98 (brs, 1H), 6.01 (brt, 1H, J=5.7 Hz), 6.35 (t, 1H, J=7.3 Hz), 6.83 (d, 1H, J=8.8 Hz), 6.87 (d, 2H, J=8.3 Hz), 7.08 (d, 1H, J=8.8 Hz), 7.28 (d, 2H, J=8.3 Hz). ^{13}C NMR (125 MHz, CDCl3) δ 38.74, 42.11, 55.15, 56.24, 67.39, 71.53, 71.86, 101.80, 109.08, 113.79,

116.91, 117.12, 129.28, 129.48, 133.06, 139.77, 141.73, 146.46, 159.31, 171.48. ESI-TOFMS (positive-ion) calcd for $C_{22}H_{25}ClINO_6H$: $(M+H)^+$ 562.0493; found: 562.0275, calcd for $C_{22}H_{25}ClINO_6Na$: $(M+Na)^+$ 584.0313; found: 583.9929, calcd for $C_{22}H_{25}ClINO_6K$: $(M+K)^+$ 600.0052; found 599.9821.

4.1.9. Phenol thiazolidinethione 20. To a solution of **19** (88.7 mg, 0.191 mmol) in THF (3.5 ml) was added to HF·pyridine (280 μl) at 0 °C. After stirring at room temperature for 12 h, the reaction quenched with sat. KF aq. The water layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by silica-gel column chromatography (hexane/AcOEt=4:1) to afford **20** (53.8 mg, 81%) as yellow needles. Mp 160–162 °C (from hexane/AcOEt). $[\alpha]_D^{22}=+92.7$ (*c* 0.51, EtOH). IR (film) ν 3304, 1673, 1497, 1349, 1288, 1162, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.32 (t, 2H, *J*=7.5 Hz), 3.38 (brd, 1H, *J*=3.3 Hz), 3.59 (dd, 1H, *J*=17.5, 9.2 Hz), 3.68 (dd, 1H, *J*=17.5, 3.3 Hz), 3.91 (s, 3H), 4.63 (t, 2H, *J*=7.5 Hz), 5.54 (dt, 1H, *J*=9.2, 3.3 Hz), 5.91 (s, 1H), 6.84 (d, 1H, *J*=8.6 Hz), 7.13 (d, 1H, *J*=8.6 Hz). ^{13}C NMR (125 MHz, CDCl3) δ 28.29, 46.11, 55.53, 56.23, 66.73, 109.12, 117.23, 117.37, 132.67, 141.76, 146.53, 173.41, 201.55. ESI-TOFMS (positive-ion) calcd for $C_{13}H_{14}ClINO_4S_2Na$: $(M+Na)^+$ 369.9950; found: 369.9979, calcd for $C_{13}H_{14}ClINO_4S_2K$: $(M+K)^+$ 385.9690; found 385.9736. Anal. Calcd for $C_{13}H_{14}ClINO_4S_2$: C, 44.89; H, 4.06; N, 4.03. Found C, 44.96; H, 4.30; N, 3.88.

4.1.10. Aldehyde (24). To a solution of **23** (33.9 g, 122 mmol, ~90%ee) in THF (100 ml) was slowly added *n*-BuLi (1.61 M hexane solution, 91.0 ml, 147 mmol) at −78 °C. After stirred for 30 min at the same temperature, DMF (15 ml, 194 mmol) was added and the mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched with sat. NH_4Cl aq. The water layer was extracted with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford **24** (27.8 g, crude) as a pale yellow oil. $[\alpha]_D^{27}=-6.8$ (*c* 0.50, $CHCl_3$). IR (neat) ν 2955, 2930, 2856, 1693, 1251, 1075, 837, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 1.83–1.89 (m, 1H), 2.20–2.27 (m, 1H), 2.41–2.48 (m, 1H), 2.72–2.80 (m, 1H), 5.09 (dt, 1H, *J*=7.4, 2.4 Hz), 6.94 (t, 1H, *J*=2.4 Hz), 9.78 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −5.09, −5.00, 18.10, 25.67, 31.16, 34.33, 73.35, 148.40, 153.68, 188.75. ESI-TOFMS (positive-ion) calcd for $C_{12}H_{22}O_2SiNa$: $(M+Na)^+$ 249.1287; found: 249.1286, calcd for $C_{12}H_{22}O_2SiK$: $(M+K)^+$ 265.1026; found 265.1048.

4.1.11. Alkyne (25). To a solution of trimethyl acetylene (35.0 ml, 245 mmol) in THF (100 ml) was added dropwise *n*-BuLi (1.61 M hexane solution, 115 ml, 185 mmol) at −78 °C and stirred at −78 °C for 20 min. To the acetylide solution, a solution of **24** (27.8 g, crude) prepared above in THF (100 ml) added slowly at −78 °C and the mixture was stirred at −78 °C for 1.5 h. The reaction mixture was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with hexane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=25:1) to afford **25** (37.5 g, 2 steps 95%) as a pale yellow oil: $[\alpha]_D^{24}=+4.3$ (*c* 0.62, $CHCl_3$). IR (neat) ν 3416, 2957, 2929, 1250, 1065, 841, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.18 (s, 9H), 0.89 (s, 9H), 1.76 (ddt, 1H, *J*=12.6, 9.1, 6.3 Hz), 2.21–2.35 (m, 2H), 2.45 (ddq, 1H, *J*=15.9, 9.1, 1.9 Hz), 3.29 (d, 1H, *J*=2.9 Hz), 4.94 (brt, 1H, *J*=6.3 Hz), 5.05 (brs, 1H), 6.05 (brs, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −5.10, −4.29, −0.26, 17.76, 25.65, 29.41, 34.84, 61.15, 79.36, 89.84, 103.60, 129.56, 143.29. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{32}O_2Si_2Na$: $(M+Na)^+$ 347.1839; found: 347.1828, calcd for $C_{17}H_{32}O_2Si_2K$: $(M+K)^+$ 363.1578; found 363.1584.

4.1.12. Epoxide (26). Activated MS4A (1.21 g) suspended in CH_2Cl_2 (5 ml) was vigorously stirred at −20 °C under argon for 10 min. (+)-DET (68 μl, 0.40 μmol) and Ti(O-*i*-Pr)$_4$ (75 μl, 0.25 mmol) were added sequentially with stirring. The reaction mixture was stirred at −20 °C as TBHP (5.2 M CH_2Cl_2 solution, 1.2 ml, 6.03 mmol) was added. The resulting mixture was stirred at −20 °C for 30 min. **25** (1.63 g, 5.03 mmol), dissolved in CH_2Cl_2 (5 ml), was slowly added at −20 °C. and the reaction mixture was stirred at −20 °C for 10 h. The reaction mixture was quenched with 30% NaOH in saturated brine. The water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=20:1) to afford **26** (1.22 g, 72%) as colorless needles. Mp 132 °C (from hexane/AcOEt). $[\alpha]_D^{25}=-25.8$ (*c* 0.97, $CHCl_3$). IR (film) ν 3512, 2956, 2360, 2178, 1249, 1073, 846, 776, 668 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.17 (s, 9H), 0.89 (s, 9H), 1.46 (tt, 1H, *J*=8.4, 7.8 Hz), 1.63 (dddd, 1H, *J*=14.2, 12.0, 8.4, 1.1 Hz), 1.85 (dt, 1H, *J*=12.0, 7.8 Hz), 2.03 (dd, 1H, *J*=14.2, 8.4 Hz), 2.38 (brs, 1H), 3.56 (s, 1H), 4.50 (t, 1H, *J*=7.8 Hz), 4.91 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −5.06, −4.63, −0.38, 17.94, 24.29, 25.68, 28.13, 58.02, 58.61, 69.45, 72.19, 91.57, 101.44. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{32}O_3Si_2H$: $(M+H)^+$ 341.1968; found: 341. 1920, calcd for $C_{17}H_{32}O_3Si_2NH_4$: $(M+NH_4)^+$ 358.2234; found 358.2132. Anal. Calcd for $C_{17}H_{32}O_3Si_2$: C, 59.95; H, 9.47. Found C, 59.97; H, 4.40.

4.1.13. Bromide (27). To a solution of **26** (14.2 g, 41.8 mmol) and CBr_4 (17.1 g, 51.7 mmol) in CH_2Cl_2 (120 ml) was added PPh_3 (22.0 g, 83.4 mmol) at room temperature under argon, and the mixture was stirred at room temperature for 2 h. The reaction mixture was added ether and filtered through Celite. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (hexane/AcOEt=50:1) to afford **27** (15.0 g, 89%) as a pale yellow oil. $[\alpha]_D^{23}=-20.1$ (*c* 0.50, $CHCl_3$). IR (neat) ν 2957, 2858, 2360, 2179, 1472, 1373, 1250, 1118, 846 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.13 (s, 3H), 0.17 (s, 9H), 0.90 (s, 9H), 1.46 (ddt, 1H, *J*=14.0, 11.0, 7.8 Hz), 1.63 (ddd, 1H, *J*=11.0, 8.6, 7.8 Hz), 1.83 (dt, 1H, *J*=12.2, 7.8 Hz), 2.00 (dd, *J*=14.0, 8.6 Hz), 3.59 (s, 1H), 4.70 (t, 1H, *J*=7.8 Hz), 4.88 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −4.81, −4.53, −0.48, 17.91, 24.39, 25.71, 28.34, 33.53, 60.56, 66.77, 70.92,

93.86, 99.21. MALDI-TOFMS (positive-ion) calcd for $C_{17}H_{31}BrO_2Si_2K$: $(M+K)^+$ 441.0683; found: 441.0239.

4.1.14. Enynes (10 and 28). To a solution of **27** (3.48 g, 8.64 mmol) in THF (30 ml) was added *n*-BuLi (1.61 M hexane solution, 8 ml, 12.9 mmol) at −90 °C under argon, and the mixture was stirred at this temperature for 15 min. The mixture was quenched with sat. NH_4Cl aq.. The aqueous layer was extracted with hexane. The combined organic layer was washed with sat. NH_4Cl aq. solution, brine, and dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=50:1) to afford **10** (2.42 g, 86%) and **28** (0.366 g, 13%). The enantiomeric purities of **10** and **28** were determined by HPLC with CHIRALCEL OJ-R column (4.6ϕ×150 mm; MeOH/water=75:25) and CHIRALCEL OD-R column (4.6ϕ×250 mm; MeOH/water=80:20), respectively. *Compound* **10**. Pale yellow oil. $[\alpha]_D^{24}$=+71.2 (*c* 0.60, $CHCl_3$); 100% ee. IR (neat) ν 3352, 2957, 2857, 2131, 1722, 1620, 1471, 1360, 1250, 1161, 842 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.19 (s, 9H), 0.90 (s, 9H), 1.74–1.88 (m, 4H), 2.86 (brs, 1H), 4.42 (ddd, 1H, *J*=8.2, 4.7, 2.0 Hz), 4.78 (brdd, 1H, *J*=5.0, 2.0 Hz), 5.66 (t, 1H, *J*=2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.93, −4.64, −0.29, 18.01, 25.69, 29.68, 32.64, 70.56, 74.85, 101.33, 101.51, 104.68, 164.18. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{32}O_2Si_2H$: $(M+H)^+$ 325.2019; found: 325.1832, calcd for $C_{17}H_{32}O_2Si_2NH_4$: $(M+NH_4)^+$ 342.2285; found 342.2111. *Compound* **28**. Pale yellow oil. $[\alpha]_D^{23}$=−66.4 (*c* 0.66, $CHCl_3$); 50% ee. IR (neat) ν 3348, 2957, 2930, 1250, 842 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.19 (s, 9H), 0.89 (s, 9H), 1.63–1.66 (m, 1H), 1.84–1.88 (m, 2H), 1.99–2.03 (m, 1H), 2.30 (brs, 1H), 4.30 (brdd, 1H, *J*=6.6, 4.3 Hz), 4.78 (d, 1H, *J*=4.5 Hz), 5.72 (brs, 1H). ^{13}C NMR (125 MHz, CDCl3) δ −4.91, −4.54, −0.22, 17.84, 25.70, 32.73, 32.85, 72.03, 74.58, 99.57, 101.64, 106.63, 159.51. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{32}O_2Si_2H$: $(M+H)^+$ 325.2019; found: 325.2039, calcd for $C_{17}H_{32}O_2Si_2Na$: $(M+Na)^+$ 347.1839; found 347.1805.

4.1.15. Epoxide (29). To a solution of **10** (2.56 g, 7.90 mmol) in CH_2Cl_2 (30 ml) was added Na_2HPO_4 (4.71 g, 33.2 mmol). After stirring for 10 min at room temperature, *m*CPBA (3.27 g, 19.0 mmol) was added to the white suspension and stirring continued at this temperature for 16 h. The reaction mixture was quenched with sat. Na_2SO_3 aq. The aqueous layer was extracted with hexane, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford **29** (2.31 g, 86%) as a white solid. $[\alpha]_D^{25}$=−6.0 (*c* 0.50, $CHCl_3$). IR (film) ν 3555, 2958, 2361, 2183, 1473, 1252, 1062, 845, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.17 (s, 9H), 0.86 (s, 9H), 1.83 (dtd, 1H, *J*=12.9, 7.2, 5.4 Hz), 1.90 (dddd, 1H, *J*=12.9, 7.8, 7.2, 5.4 Hz), 1.98–2.02 (m, 2H), 2.27 (d, 1H, *J*=4.8 Hz), 3.49 (s, 1H), 3.93 (t, 1H, *J*=5.4 Hz), 4.09 (dd, 1H, *J*=9.8, 4.8 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −4.96, −4.92, −0.47, 18.02, 25.59, 30.21, 30.89, 48.88, 68.71, 71.23, 72.64, 92.96, 99.19. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{32}O_3Si_2H$: $(M+H)^+$ 341.1968; found: 341.1961, calcd for $C_{17}H_{32}O_3Si_2NH_4$: $(M+NH_4)^+$ 358.2234; found 358.2241, calcd for $C_{17}H_{32}O_3Si_2Na$: $(M+Na)^+$ 363,1788; found: 363.1779, calcd for $C_{17}H_{32}O_3Si_2K$: $(M+K)^+$ 379.1527; found 379.1561.

4.1.16. Acetate (30). To a solution of **29** (108 mg, 0.317 mmol) in pyridine (3 ml) was added Ac_2O (1.5 ml) at room temperature and the mixture was stirred at 50 °C for 11 h. The reaction mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with hexane, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **30** (88.6 mg, 73%) as a colorless oil: $[\alpha]_D^{21}$=+36.1 (*c* 0.48, $CHCl_3$). IR (film) ν 2956, 2929, 1743, 1250, 1060, 844 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.15 (s, 9H), 0.87 (s, 9H), 1.76 (dddd, 1H, *J*=13.1, 8.8, 8.0, 5.0 Hz), 1.85 (ddt, 1H, *J*=13.1, 8.8, 5.0 Hz), 1.99 (ddt, 1H, *J*=14.1, 5.0, 8.0 Hz), 2.04 (s, 3H), 2.23 (dddd, 1H, *J*=14.1, 8.0, 7.6, 5.0 Hz), 3.41 (s, 1H), 3.83 (t, 1H, *J*=5.0 Hz), 5.17 (dd, 1H, *J*=7.6, 5.0 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −5.11, −4.85, −0.54, 18.02, 21.00, 25.55, 29.18, 30.91, 49.16, 69.68, 70.37, 72.78, 92.90, 98.88, 170.08. ESI-TOFMS (positive-ion) calcd for $C_{19}H_{34}O_4Si_2H$: $(M+H)^+$ 383.2074; found: 383.2034, calcd for $C_{19}H_{34}O_4Si_2NH_4$: $(M+NH_4)^+$ 400.2339; found 400.2313, calcd for $C_{19}H_{34}O_4Si_2Na$: $(M+Na)^+$ 405.1893; found: 405.1864, calcd for $C_{19}H_{34}O_4Si_2K$: $(M+K)^+$ 421.1633; found 421.1612.

4.1.17. Ketone (31). To a solution of **29** (4.32 g, 12.7 mmol) in CH_2Cl_2 (30 ml) was added Dess–Martin periodinane (8.08 g, 19.1 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane, and the combined organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt=30:1) to afford **31** (3.59 g, 84%) as needles. Mp 112–113 °C (from hexane/AcOEt) $[\alpha]_D^{23}$=−121.3 (*c* 0.50, $CHCl_3$). IR (film) ν 2955, 2853, 1747, 1401, 1249, 838 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.03 (s, 3H), 0.16 (s, 9H), 0.84 (s, 9H), 2.15–2.21 (m, 2H), 2.37 (dtd, 1H, *J*=18.9, 3.7, 3.0 Hz), 2.64 (dt, 1H, *J*=18.9, 10.5 Hz), 3.66 (s, 1H), 4.07 (brt, 1H, *J*=1.8 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −5.31, −4.83, −0.56, 17.99, 25.48, 28.06, 33.12, 50.57, 69.89, 71.68, 93.33, 96.61, 207.69. ESI-TOFMS (positive-ion) calcd for $C_{17}H_{30}O_3Si_2H$: $(M+H)^+$ 339.1812; found: 339.1636. Anal. Calcd for $C_{17}H_{30}O_3Si_2$: C, 60.30; H, 8.93. Found C, 60.11; H, 8.95.

4.1.18. Diyne (7). To a solution of trimethylsilylacetylene (320 μl, 2.24 mmol) in THF (4 ml) was added dropwise *n*-BuLi (1.61 M hexane solution, 990 μl, 1.60 mmol) at −78 °C and stirred at −78 °C for 50 min. A solution of **31** (261 mg, 77.1 μmol) in THF (4 ml) was then slowly added at −78 °C and the reaction mixture was stirred at −78 °C for 3 h. The reaction mixture was quenched with sat. NH_4Cl aq. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford a crude mixture of epimeric alcohols (304 mg) as a yellow oil. To the mixture in dichloroethane (2 ml) were added Et_3N (600 μl, 7.64 mmol) and Ms_2O (274 mg, 1.57 mmol) at room temperature and the reaction mixture was stirred at

40 °C for 3 h. The reaction quenched with sat. NH_4Cl aq. The aqueous layer was extracted with hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford a crude mixture of mesylates (330 mg). To a solution of the mixture in THF (10 ml) was added TBAF (1.0 M THF solution, 3.5 ml, 3.50 mmol) at 0 °C. After stirring at the same temperature for 20 min, the reaction quenched with phosphate buffer (pH 7.0). The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by silica-gel column chromatography (hexane/AcOEt=1:1) to afford **7** (70.6 mg, 57% in 2 steps) as colorless plates. Mp 86 °C (from hexane/AcOEt). $[\alpha]_D^{20}$=+36.6 (*c* 0.36, $CHCl_3$). IR (film) ν 3263, 905, 644 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (brs, 1H), 2.50 (dt, 1H, *J*=19.1, 2.6 Hz), 2.53 (d, 1H, *J*=2.0 Hz), 2.83 (ddd, 1H, *J*=19.1, 6.3, 2.6 Hz), 3.04 (s, 1H), 3.74 (d, 1H, *J*=2.0 Hz), 4.20 (dd, 1H, *J*=6.3, 2.6 Hz), 6.62 (t, 1H, *J*=2.6 Hz), ^{13}C NMR (125 MHz, CDCl3) δ 38.42, 50.23, 69.70, 72.96, 76.41, 76.70, 77.06, 82.31, 119.95, 145.73. ESI-TOFMS (positive-ion) calcd for $C_{10}H_8O_2NH_4$: $(M+NH_4)^+$ 178.0868; found: 178.0699, calcd for $C_{10}H_8O_2Na$: $(M+Na)^+$ 183.0422; found: 183.0216, calcd for $C_{10}H_8O_2K$: $(M+K)^+$ 199.0161; found 198.9940.

The absolute configuration of **7** was confirmed by the modified Mosher method using (*R*)- and (*S*)-MTPA esters of **7**:

Position	(*R*)-MTPA-**7** δ (ppm)	(*S*)-MTPA-**7** δ (ppm)	$\Delta\delta=\delta_S-\delta_R$
H-3	3.050	3.062	0.012
H-6	2.505	2.513	0.007
H-8	4.000	4.017	0.017
H-11	2.739	2.543	−0.196
H-11	3.043	2.955	−0.088
H-12	6.582	6.542	−0.040

4.1.19. Aryl ether (32). To a solution **7** (52.0 mg, 0.324 mmol) and CsF (53.0 mg, 0.349 mmol) in DMF (2 ml) was added a solution of **22** (97.0 mg, 0.173 mmol) in DMF (2 ml) at room temperature and the mixture was stirred at 60 °C for 12 h. The reaction was quenched with phosphate buffer (pH 7.0) at room temperature. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by silica-gel column chromatography (hexane/AcOEt=1:4) to afford triol (62.0 mg, 50%): $[\alpha]_D^{23}$=−2.9 (*c* 0.92, $CHCl_3$). IR (film) ν 3287, 1651, 1514, 1487, 1249, 1037 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (dd, 1H, *J*=15.2, 8.3 Hz), 2.41 (d, 1H, *J*=2.0 Hz), 2.47 (ddd, 1H, *J*=17.8, 5.3, 2.0 Hz), 2.58 (dd, 1H, *J*=15.2, 3.1 Hz), 2.82 (ddd, 1H, *J*=17.8, 7.3, 3.1 Hz), 3.04 (s, 1H), 3.37 (brd, 1H, *J*=2.4 Hz), 3.72–3.79 (m, 4H), 3.83–3.89 (m, 4H), 4.11 (s, 1H), 4.15 (d, 1H, *J*=13.0 Hz), 4.18 (d, 1H, *J*=13.0 Hz), 4.43 (s, 2H), 4.79 (brd, 1H, *J*=3.1 Hz), 4.94 (ddd, 1H, *J*=7.3, 5.3, 2.4 Hz), 5.27 (dt, 1H, *J*=8.3, 3.1 Hz), 5.53 (d, 1H, *J*=2.0 Hz), 6.31 (t, 1H, *J*=7.0 Hz), 6.32 (dd, 1H, *J*=3.1, 2.0 Hz), 6.36 (t, 1H, *J*=5.8 Hz), 6.86 (d, 3H, *J*=8.8 Hz), 7.27 (d, 2H, *J*=8.8 Hz), 7.29 (d, 1H, *J*=8.8 Hz). ^{13}C NMR (125 MHz, CDCl3) δ 38.33, 38.68, 41.74, 55.12, 56.00, 67.30, 71.12, 71.47, 71.66, 76.33, 77.46, 77.59, 78.30, 80.47, 84.27, 101.81, 110.38, 113.73, 122.19, 124.52, 125.72, 129.18, 129.50, 133.12, 139.76, 141.12, 141.61, 152.21, 159.25, 171.57. ESI-TOFMS (positive-ion) calcd for $C_{32}H_{33}ClINO_8H$: $(M+H)^+$ 722.1018; found: 722.0996, calcd for $C_{32}H_{33}ClINO_8NH_4$: $(M+NH_4)^+$ 739.1283; found 739.1238, calcd for $C_{32}H_{33}ClINO_8Na$: $(M+Na)^+$ 744.0837; found: 744.0787, calcd for $C_{32}H_{33}ClINO_8K$: $(M+K)^+$ 760.0577; found 760.0441.

To a solution of the above triol (53.3 mg, 73.8 μmol) and 2,6-lutidine (130 μl, 1.12 mmol) in CH_2Cl_2 (1 ml) was added a solution of TBSOTf (100 μl, 435 μmol) at −78 °C and the mixture was stirred at room temperature for 12 h. The reaction was quenched with phosphate buffer (pH 7.0). The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by silica-gel column chromatography (hexane/AcOEt=1:1) to afford **32** (60.2 mg, 77%) as amorphous solid: $[\alpha]_D^{23}$=+34.5 (0.60, $CHCl_3$). IR (film) ν 3311, 2954, 2930, 2856, 1659, 1651, 1514, 1487, 1251, 837, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ −0.19 (s, 3H), 0.02 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.12 (s, 3H), 0.21 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 0.92 (s, 9H), 2.21 (d, 1H, *J*=2.6 Hz), 2.32 (dd, 1H, *J*=14.1, 8.8 Hz), 2.39 (ddd, 1H, *J*=16.7, 7.3, 2.6 Hz), 2.53 (dd, 1H, *J*=14.1, 3.0 Hz), 2.62 (ddd, 1H, *J*=16.7, 7.3, 2.6 Hz), 3.04 (s, 1H), 3.79–3.94 (m, 8H), 4.21 (s, 2H), 4.46 (s, 2H), 4.63 (t, 1H, *J*=7.3 Hz), 5.36 (d, 1H, *J*=2.6 Hz), 5.43 (dd, 1H, *J*=8.8, 3.0 Hz), 6.12 (t, 1H, *J*=5.8 Hz), 6.33 (t, 1H, *J*=2.6 Hz), 6.44 (t, 1H, *J*=7.2 Hz), 6.84 (d, 1H, *J*=8.6 Hz), 6.89 (d, 2H, *J*=8.3 Hz), 7.17 (d, 1H, *J*=8.6 Hz), 7.31 (d, 2H, *J*=8.3 Hz). ^{13}C NMR (125 MHz, CDCl3) δ −5.45, −5.03, −4.78, −4.57, −2.63, −2.61, 17.95, 18.07, 18.71, 25.66, 25.95, 25.99, 38.80, 38.82, 45.74, 55.14, 55.52, 68.58, 71.35, 71.40, 72.42, 73.61, 76.48, 79.63, 79.88, 81.73, 85.14, 102.10, 110.09, 113.75, 121.89, 126.27, 127.12, 129.39, 129.52, 130.71, 140.28, 141.60, 142.07, 152.53, 159.27, 169.93. MALDI-TOFMS (positive-ion) calcd for $C_{50}H_{75}ClINO_8Si_3Na$: $(M+Na)^+$ 1086.3431; found: 1086.3484, calcd for $C_{50}H_{75}ClINO_8Si_3K$: $(M+K)^+$ 1102.3171; found 1102.3180.

4.1.20. Macrolactam (34). To a degassed solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (26.9 mg, 26.0 μmol) and CuI (9.9 mg, 52.0 μmol) in DMF (13 ml) was added a degassed solution of **32** (27.7 mg, 26.0 μmol) and $(i\text{-}Pr)_2NEt$ (160 μl) in DMF (13 ml) at 60 °C. The mixture was stirred at 60 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to afford **34** (9.7 mg, 40%) as colorless needles, mp 210–213 °C (from hexane/AcOEt): $[\alpha]_D^{20}$=−35.5 (0.16, $CHCl_3$). IR (film) ν 3287, 2929, 2856, 1634, 1253, 1090, 1072, 837, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ −0.38 (s, 3H), −0.14 (s, 3H), −0.05 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.21 (s, 3H), 0.77 (s, 9H), 0.83 (s, 9H), 0.95 (s, 9H), 2.02 (t, 1H, *J*=10.7 Hz), 2.82–2.87 (m, 2H), 2.94 (ddd, 1H, *J*=15.5, 7.8, 1.4 Hz), 3.30 (s, 3H, C3′-OMe), 3.57 (dd, 1H, *J*=14.1,

2.3 Hz, CH_2N), 3.83 (s, 3H), 4.19 (d, 1H, J=11.7 Hz, CH_2OMPM), 4.20 (d, 1H, J=11.2 Hz), 4.27 (d, 1H, J=11.2 Hz), 4.62 (d, 1H, J=11.7 Hz, CH_2OMPM), 4.88 (dd, 1H, J=14.1, 10.8 Hz, CH_2N), 5.00 (dd, 1H, J=10.8, 2.3 Hz, NH), 5.22 (t, 1H, J=7.8 Hz), 5.35 (s, 1H, H-8), 5.61 (dd, 1H, J=10.7, 4.8 Hz), 5.87 (dd, 1H, J=3.5, 1.4 Hz, H-12), 6.34 (d, 1H, J=8.3 Hz, H-4′), 6.86 (d, 1H, J=8.3 Hz, H-5′), 6.92 (d, 2H, J=8.8 Hz), 7.04 (s, 1H, H-3), 7.18 (d, 2H, J=8.8 Hz), 7.30 (s, 1H, H-6). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.17, −5.03, −4.77, −4.39, −3.21, −3.06, 17.77, 18.13, 18.42, 25.61, 25.66, 26.00, 38.47 (C14), 43.55, 48.98, 54.88, 55.24, 67.54, 70.39 (C5), 70.57, 70.79, 83.76 (C8), 92.45 (C9), 110.19, 113.88, 120.24, 121.91 (C3), 122.10, 128.97, 129.21, 129.72, 131.44 (C6), 133.47, 135.81 (C4), 136.12 (C2), 138.96 (C13), 142.33, 144.30 (C7), 150.06 (C1), 153.95, 159.33, 168.34. HMBC correlations: H3−C1, H3−C7, H3−C5, H3−C13; H5−C3, H5−C4, H5−C13; H6−C2, H6−C4, H6−C8, H6−C14. MALDI-TOFMS (positive-ion) calcd for $C_{50}H_{74}ClNO_8Si_3$-Na: $(M+Na)^+$ 958.4308; found: 958.4375, calcd for $C_{50}H_{74}ClNO_8Si_3K$: $(M+K)^+$ 974.4048; found 974.4182.

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