CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700310

Synthesis of the Bicyclo[7.3.0]dodecadiyne Core of the Maduropeptin Chromophore

Kentaro Iso,[b] Masayuki Inoue,*[a] Nobuki Kato,[b] and Masahiro Hirama*[b]

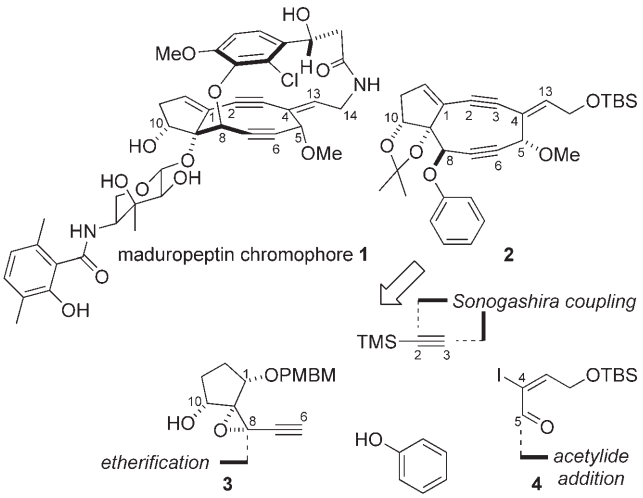
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: Maduropeptin, an extremely potent antitumor agent, consists of a 1:1 complex of a carrier protein and a chromophore. We report herein a general and efficient route for the synthesis of the highly strained bicyclo[7.3.0]dodecadiyne core of the chromophore. The key feature of the synthetic strategy is the use of two Sonogashira coupling reactions in a stepwise manner to construct the conjugated dienyne substructure of the fused-ring system, including the *Z* alkene at C4,C13.

Keywords: alkynes · antitumor agents · cyclization · natural products · palladium

Introduction

The chromoprotein maduropeptin, which comprises a 32-kDa apoprotein and the chromophore **1** (Scheme 1), displays potent antitumor activity.[1] The chromophore **1** is responsible for DNA recognition and damage, and the apoprotein functions as a drug-delivery system. The highly strained bicyclo[7.3.0]dodecadiyne structure of **1** is central to the potent biological activity of the chromoprotein. The chromophore components of related agents, such as C-1027,[2] kedarcidin,[3] and neocarzinostatin,[4,5] share a common bicyclo[7.3.0]dodecadiyne core, but differ in their degree of oxidation and unsaturation; **1** is the only chromophore that contains a C4,C13 *Z* olefin within the fifteen-membered ansamacrolactam. From a synthetic point of view, the stereoselective formation of the core structure is one of the most formidable challenges for the total synthesis of **1**. We therefore undertook the synthesis of the model bicyclic system **2**. Herein, we describe a general and efficient route for the synthesis of **2** on the basis of a newly developed synthetic strategy.[6–9]



Scheme 1. Structure of the maduropeptin chromophore and retrosynthesis of its core. PMBM = *p*-methoxybenzyloxymethyl, TBS = *tert*-butyldimethylsilyl.

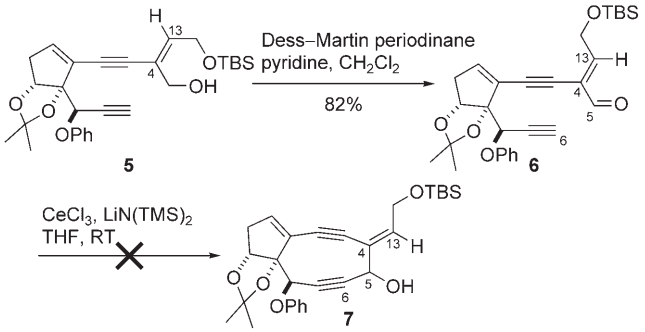
[a] Prof. Dr. M. Inoue
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-3395-5214
E-mail: inoue@mol.f.u-tokyo.ac.jp

[b] K. Iso, Dr. N. Kato, Prof. Dr. M. Hirama
Department of Chemistry
Graduate School of Science
Tohoku University
Sendai 980-8578 (Japan)
Fax: (+81) 22-217-6566
E-mail: hirama@mail.tains.tohoku.ac.jp

Results and Discussion

The stereoselective formation of the enyne-conjugated *Z* alkene at C4,C13 and the preservation of the required geome-

try during subsequent transformations present a unique synthetic challenge. The facile isomerization of the *Z* alkene to the corresponding *E* alkene has been observed in various highly conjugated intermediates, and suggests that the *Z* isomer is less thermodynamically stable than the *E* isomer (Scheme 2).[8c] In a previous study by our research group,[6a]



Scheme 2. Unsuccessful attempt at the synthesis of the bicyclo[7.3.0]dodecadiyne core of the maduropeptin chromophore. TMS = trimethylsilyl.

the oxidation of enediyne **5** with Dess–Martin periodinane[10] generated the C4,C13 *E* alkene **6** as the sole isomer after isomerization. Furthermore, the attempted $CeCl_3$/$LiN(TMS)_2$-mediated addition[11] of the corresponding acetylide to the aldehyde to transform **6** into **7** was unsuccessful, presumably as a result of the chemical lability of the conjugated aldehyde.

To avoid these problems, we decided to construct the conjugated enediyne moiety in the last stage of the synthesis. Compound **2** was divided retrosynthetically into four fragments (Scheme 1): The etherification of phenol with **3** and subsequent bond formation between C6 and C5 were to be followed by Sonogashira coupling reactions[12] at C3 and C2. The key to the success of the present synthetic strategy was the formation of the strained, highly unsaturated nine-membered ring of **2** by palladium chemistry.[13,14]

Our synthesis started with the previously reported alcohol **9**[6c] (Scheme 3). The protection of the secondary alcohol at C1 of **9** as the corresponding *p*-methoxybenzyloxymethyl (PMBM) ether followed by the removal of the TBS and TMS groups by treatment with TBAF afforded the alcohol **3** in 80% yield. The CsF-promoted addition[15] of phenol to the epoxide in **3** resulted in the formation of the diol **10** (78%), which was converted into the acetonide **11** (100%) under acidic conditions in the presence of 2,2′-dimethoxypropane. The coupling partner **4** was synthesized from the known compound **8**[8c] by oxidation with Dess–Martin periodinane. To our surprise, the α,β-unsaturated aldehyde **4** underwent alkene isomerization, even when kept in a freezer (−30 °C), to give an approximately 1:1 mixture of *E* and *Z* isomers after 5 h. Therefore, **4** was prepared and used immediately in the next reaction, without purification. The cerium acetylide generated from **11** upon treatment with $CeCl_3$ and $LiN(TMS)_2$ reacted with the aldehyde **4** to deliver the coupling adduct **12** in 100% yield as a 1:1 mixture of epimers at C5 without olefin isomerization. The failure of the corresponding lithium acetylide of **11** to react with **4** under similar conditions to give **12** indicates the superior nucleophilicity of the organocerium intermediate.[16] The methylation of the alcohol **12** with $LiN(TMS)_2$ and MeI, followed by the removal of the PMBM group with DDQ, provided **14**. The C5 epimers of **14** were separated by HPLC (silica gel) to produce **14A** (40%) and **14B** (37%), which were subjected separately to the remaining reactions in the synthesis.

The stage was now set for the crucial Sonogashira coupling reactions. The secondary alcohol **14** was first converted into the enol triflate **15** in a two-step sequence involving oxidation with Dess–Martin periodinane and triflate formation in the presence of $LiN(TMS)_2$ and the Comins reagent[17] (**15A**: 66%, **15B**: 59%). Upon the treatment of **15** with trimethylsilylacetylene in the presence of catalytic $[Pd(PPh_3)_4]$ and CuI in iPr_2NEt and THF at room temperature, the C4 iodide reacted in a completely chemoselective fashion in the presence of the potentially reactive C1 triflate to provide the coupling product **16** in quantitative yield.[18] In preparation for the second palladium-mediated reaction, the acetylenic TMS group of **16** was removed selectively at low temperature to give **17** (100%). When **17A** was subjected to the same Sonogashira reaction conditions ($[Pd(PPh_3)_4]$/CuI), the product obtained was not the desired product **2A**, but the dimer **18** (55%) formed by Glaser coupling.[19]

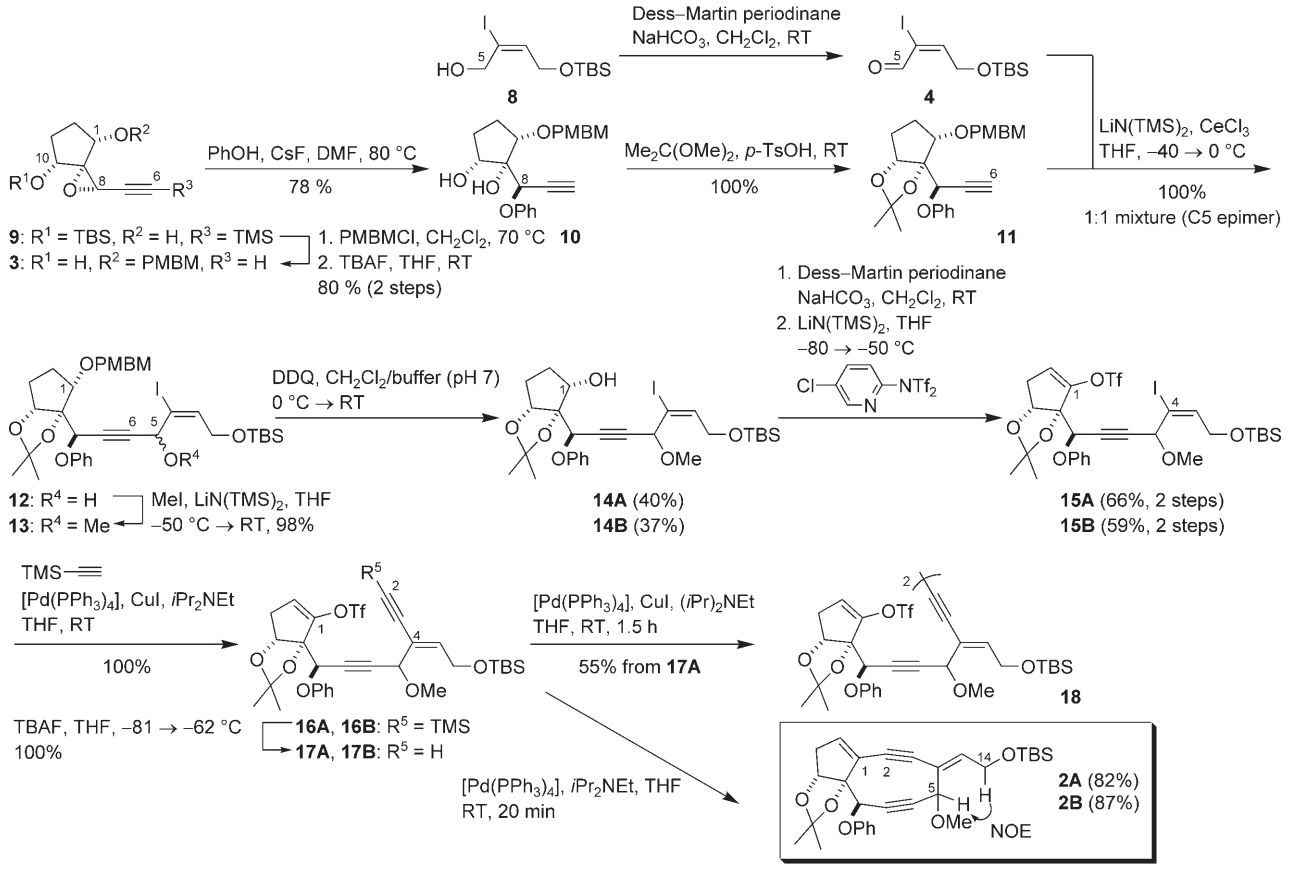
In exploring possible reagents, we found that $[Pd(PPh_3)_4]$ enabled cyclization in the absence of CuI. Thus, **17A** and **17B** were each treated with $[Pd(PPh_3)_4]$ (10 mol%) and iPr_2NEt in THF at room temperature[20] to furnish the desired compounds **2A** (82%) and **2B** (87%), respectively, with a nine-membered diyne ring, without formation of the dimer.[21] The presence of a *Z* alkene at C4,C13 of both **2A** and **2B** was confirmed unambiguously by NOE experiments.[22]

Conclusions

We have described a new strategy for the synthesis of the highly strained bicyclo[7.3.0]dodecadiyne core of the maduropeptin chromophore. The key feature of the synthesis is a pair of Sonogashira coupling reactions used to construct the conjugated dienyne substructure, including the *Z* alkene at C4,C13, in the fused-ring system. The application of the present methodology to the synthesis of the maduropeptin

Abstract in Japanese:
強力な抗腫瘍活性を有するマデュロペプチンは、クロモフォアとキャリアータンパク質の 1:1 複合体である。我々は、マデュロペプチンクロモフォアの歪みの高いビシクロ[7.3.0]ドデカジエン骨格構造の新規効率的構築法を開発した。園頭反応を二回利用し、C4,13-*Z*-オレフィンを有する高度に共役した環構造を、立体選択的に得た。

CHEMISTRY
AN ASIAN JOURNAL



Scheme 3. Synthesis of the bicyclo[7.3.0]dodecadiyne core of the maduropeptin chromophore. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

chromophore **1** and other enediyne natural products is under way in our laboratory.

Experimental Section

General Methods

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 under reduced pressure from sodium/benzophenone, dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and diisopropylethylamine (iPr_2NEt) from calcium hydride, and DMF from calcium hydride. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed with E. Merck silica gel 60 F254 precoated plates. Column chromatography was performed with 100–210-μm silica gel 60N (Kanto Chemical Co.); for flash column chromatography, 40–50-μm silica gel 60N (Kanto Chemical Co.) was used.

^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 500 (500 MHz) or Varian INOVA 600 (600 MHz) spectrometer. Chemical shifts are reported in δ (ppm) downfield from tetramethylsilane with reference to the solvent signal (^{1}H NMR: 7.26; ^{13}C NMR: 77.0 ($CHCl_3$)). Signal patterns are indicated as s = singlet, d = doublet, t = triplet, m = multiplet. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Optical rotation measurements were made with a Jasco DIP-370 polarimeter. Mass spectra were recorded on a Bruker APEX III (EI and ESI-TOF MS, HRMS), a PerSeptive BioSystems Mariner (ESI-TOF MS), or a PerSeptive BioSystems Voyager DE STR instrument (MALDI-TOF MS). Melting points were measured on a Yanaco MP-S3 micro-melting-point apparatus. Elemental analyses were performed with a Yanaco CHN-Corder MT-6 instrument.

Syntheses

3: SO_2Cl_2 (2.22 mL, 26.5 mmol) was added to a solution of *p*-methoxybenzyloxymethyl methyl sulfide (4.38 g, 22.1 mmol) in CH_2Cl_2 (37 mL) at −78 °C. The resulting mixture was warmed to room temperature, stirred for 3 h, and then concentrated. The residue was dissolved in $(CH_2Cl)_2$ (50 mL) and cooled to 0 °C. iPr_2NEt (11.4 mL, 65.7 mmol) was then added, followed by a solution of **9** (5.0 g, 14.6 mmol) in $(CH_2Cl)_2$ (23 mL). The mixture was heated at reflux for 12 h and then concentrated. The residue was dissolved in THF (68 mL), TBAF (1 M in THF, 44 mL, 44 mmol) was added at room temperature, and the reaction mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 7:1–1:2) gave **3** (3.55 g, 11.7 mmol, 80 %) as a pale-yellow oil. $[\alpha]_D^{25} = -8.3$ ($c = 0.970$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3448$, 3276, 2944, 1612, 1514, 1248, 1174, 1100, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.92$–2.05 (m, 3H), 2.07–2.15 (m, 2H), 2.46 (d, $J = 0.8$ Hz, 1H), 3.60 (d, $J = 1.2$ Hz, 1H), 3.80 (s, 3H), 3.87–3.91 (m, 1H), 4.26–4.28 (m, 1H), 4.55 (d, $J = 9.0$ Hz, 1H), 4.59 (d, $J = 9.0$ Hz, 1H), 4.81 (d, $J = 5.4$ Hz, 1H), 4.83 (d, $J = 5.4$ Hz, 1H), 6.85–6.91 (m, 2H), 7.25–7.31 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.7$, 30.5, 49.7, 55.2, 69.1, 70.7, 71.4, 73.8, 75.5, 78.0, 93.5, 113.7, 129.5, 129.8, 159.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{20}NaO_5$: 327.1203 $[M+Na]^+$; found: 327.1203.

10: CsF (3.3 g, 21.7 mmol) was added to a solution of **3** (2.2 g, 7.23 mmol) and phenol (2.05 g, 21.8 mmol) in DMF (37 mL) at room temperature.

The resulting mixture was stirred for 19 h at 80 °C, then diluted with Et_2O (15 mL). Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 2:1–1:1) gave **10** (2.25 g, 5.66 mmol, 78%) as a colorless oil. $[\alpha]_D^{24} = -83.0$ ($c = 1.074$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3475, 3284, 2949, 1612, 1589, 1514, 1494, 1247, 1033\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.75$–1.85 (m, 1H), 1.90–2.05 (m, 3H), 2.49 (d, $J = 2.0$ Hz, 1H), 2.76 (d, $J = 5.4$ Hz, 1H), 3.80 (s, 3H), 3.83 (s, 1H), 4.23 (dd, $J = 10.2$, 5.1 Hz, 1H), 4.44 (dd, $J = 5.4$, 5.1 Hz, 1H), 4.61 (s, 2H), 4.86 (d, $J = 5.4$ Hz, 1H), 4.89 (d, $J = 2.0$ Hz, 1H), 4.91 (d, $J = 5.4$ Hz, 1H), 6.85–6.90 (m, 2H), 7.00–7.04 (m, 3H), 7.27–7.33 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.2$, 29.7, 55.2, 69.5, 71.1, 72.8, 76.1, 77.3, 79.0, 79.6, 94.0, 113.9, 115.9, 122.1, 129.4, 129.5, 129.6, 157.0, 159.3 ppm; HRMS (ESI): m/z calcd for $C_{23}H_{26}NaO_6$: 421.1622 $[M+Na]^+$; found: 421.1623.

11: *p*-TsOH (36.0 mg, 0.2 mmol) was added to a solution of **10** (1.52 g, 3.8 mmol) in acetone dimethyl acetal (30 mL). The reaction mixture was stirred for 2 h at room temperature, then diluted with EtOAc (10 mL). The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 1:2) gave **11** (1.66 g, 3.79 mmol, 100%) as colorless crystals. M.p.: 85.5–86.6 °C; $[\alpha]_D^{21} = -114.5$ ($c = 1.11$, $CHCl_3$); IR (film): $\tilde{\nu} = 3282, 2938, 1598, 1514, 1495, 1249, 1045\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (s, 3H), 1.45–1.55 (m, 4H), 1.76–1.84 (m, 1H), 1.84–1.95 (m, 1H), 2.03–2.08 (m, 1H), 2.40 (d, $J = 1.6$ Hz, 1H), 3.67 (s, 3H), 4.19 (dd, $J = 8.5$, 5.5 Hz, 1H), 4.45 (d, $J = 9.0$ Hz, 1H), 4.56 (d, $J = 9.0$ Hz, 1H), 4.63 (d, $J = 3.1$ Hz, 1H), 4.79 (d, $J = 5.8$ Hz, 1H), 4.83 (d, $J = 5.8$ Hz, 1H), 4.92 (d, $J = 1.6$ Hz, 1H), 6.69–6.74 (m, 2H), 6.87–6.94 (m, 3H), 7.14–7.21 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.8$, 27.5, 27.8, 29.1, 55.2, 69.4, 69.7, 76.2, 78.6, 79.5, 82.7, 89.6, 94.8, 112.2, 113.8, 115.8, 121.9, 129.4, 129.7, 129.9, 157.2, 159.2 ppm; elemental analysis: calcd (%) for $C_{26}H_{30}O_6$: C 71.21, H 6.90; found: C 70.97, H 6.95; HRMS (ESI): m/z calcd for $C_{26}H_{30}NaO_6$: 461.1935 $[M+Na]^+$; found: 461.1937.

4: $NaHCO_3$ (718 mg, 8.55 mmol) and Dess–Martin periodinane (1.45 g, 3.42 mmol) were added to a solution of **8** (561 mg, 1.71 mmol) in CH_2Cl_2 (17 mL), and the resulting mixture was stirred for 30 min at room temperature. The reaction was then quenched with aqueous $Na_2S_2O_3$, and the mixture was extracted with hexane. The organic layer was washed with brine and dried over Na_2SO_4. The residue was used directly in the next reaction.

12: Anhydrous $CeCl_3$ (2.81 g, 11.4 mmol) was dried at 90 °C under high vacuum for 2 h with vigorous stirring to afford a fine white powder of $CeCl_3$. THF (50 mL) was added to the flask at 0 °C, and the resulting mixture was stirred vigorously for 2 h at 0 °C, then for 16 h at room temperature. *n*BuLi (1.56 M in hexane, 6.9 mL, 10.8 mmol) was added to a solution of $HN(TMS)_2$ (2.41 mL, 11.4 mmol) in THF (10 mL) at 0 °C. The resulting solution of LiHMDS was stirred at 0 °C for 0.5 h, then added to the suspension of $CeCl_3$ at −78 °C. The mixture was allowed to warm to −55 °C over 1.5 h, and then a solution of **11** (500 mg, 1.14 mmol) in THF (20 mL) was added. After 1 min, **4** (crude, as 1.71 mmol) was added at −50 °C. The resulting mixture was stirred for 10 min at the same temperature, then warmed to 0 °C. The reaction was quenched with aqueous phosphate buffer (pH 7) at 0 °C, then celite was added. The slurry was filtered through a pad of celite, which was then washed with EtOAc. The organic layer was washed with aqueous NH_4Cl, then brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 5:1–4:1) gave a 1:1 diastereomeric mixture of the coupling product **12** (873 mg, 1.14 mmol, 100%) as a pale-yellow oil. IR (film): $\tilde{\nu} = 3419, 2934, 2857, 1598, 1514, 1494, 1379, 1250, 1105, 1041\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3/2H), 0.03 (s, 3/2H), 0.04 (s, 3/2H), 0.04 (s, 3/2H), 0.85 (s, 9/2H), 0.87 (s, 9/2H), 1.50 (s, 3/2H), 1.52 (s, 3/2H), 1.56 (s, 6/2H), 1.64–1.72 (m, 2/2H), 1.88–2.04 (m, 4/2H), 2.13–2.19 (m, 2/2H), 2.93 (d, $J = 7.9$ Hz, 1/2H), 2.95 (d, $J = 7.8$ Hz, 1/2H), 3.77 (s, 3/2H), 3.77 (s, 3/2H), 4.11 (dd, $J = 14.2$, 6.4 Hz, 1/2H), 4.14 (dd, $J = 14.2$, 5.4 Hz, 1/2H), 4.18 (dd, $J = 14.2$, 6.4 Hz, 1/2H), 4.20 (dd, $J = 14.2$, 5.9 Hz, 1/2H), 4.31 (dd, $J = 9.8$, 6.9 Hz, 1/2H), 4.36 (dd, $J = 9.8$, 6.9 Hz, 1/2H), 4.55 (d, $J = 11.2$ Hz, 1/2H), 4.57 (d, $J = 11.2$ Hz, 1/2H), 4.65 (d, $J = 11.2$ Hz, 1/2H), 4.67 (d, $J = 11.2$ Hz, 1/2H), 4.74 (d, $J = 3.9$ Hz, 1/2H), 4.76 (d, $J = 4.4$ Hz, 1/2H), 4.85 (d, $J = 7.3$ Hz, 1/2H), 4.86 (d, $J = 6.9$ Hz, 1/2H), 4.96–5.06 (m, 6/2H), 6.34 (dd, $J = 5.4$, 5.4 Hz, 1/2H), 6.35 (dd, $J = 5.4$, 5.4 Hz, 1/2H), 6.78–6.81 (m, 4/2H), 6.95–7.00 (m, 6/2H), 7.24–7.28 ppm (m, 8/2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.5$, −5.4, 14.2, 18.1, 21.0, 25.7, 26.8, 26.9, 27.4, 27.4, 27.7, 27.9, 29.5, 29.5, 55.2, 55.2, 60.4, 61.6, 61.7, 63.1, 63.2, 69.4, 69.4, 70.0, 70.2, 78.4, 78.6, 82.0, 82.0, 82.7, 82.8, 87.0, 87.0, 90.1, 90.1, 94.3, 94.5, 105.4, 105.6, 112.4, 113.7, 113.8, 115.9, 116.0, 121.7, 121.8, 129.4, 129.4, 129.7, 129.7, 129.8, 142.0, 142.1, 157.3, 159.2 ppm; HRMS (ESI): m/z calcd for $C_{36}H_{49}INaO_8Si$: 787.2134 $[M+Na]^+$; found: 787.2135.

13: MeI (2.43 mL, 39 mmol) was added to a solution of **12** (1.48 g, 1.95 mmol) in THF (30 mL). LiHMDS (prepared from $HN(TMS)_2$ (1.66 mL, 7.8 mmol), *n*BuLi (1.56 M in hexane, 3.78 mL, 5.9 mmol), and THF (10 mL)) was added to the reaction mixture at −50 °C. The resulting mixture was stirred for 16 h, during which time it was allowed to warm gradually to room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, then brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 10:1–5:1) gave a 1:1 diastereomeric mixture of **13** (1.49 g, 1.92 mmol, 98%) as a pale-yellow oil. IR (film): $\tilde{\nu} = 2933, 2857, 1598, 1514, 1494, 1379, 1250, 1104, 1043\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.03$ (s, 3/2H), 0.03 (s, 3/2H), 0.04 (s, 3/2H), 0.04 (s, 3/2H), 0.86 (s, 9/2H), 0.87 (s, 9/2H), 1.54 (s, 3/2H), 1.55 (s, 3/2H), 1.57 (s, 3/2H), 1.57 (s, 3/2H), 1.59–1.74 (m, 2/2H), 1.87–2.04 (m, 4/2H), 2.12–2.20 (m, 2/2H), 3.25 (s, 3/2H), 3.26 (s, 3/2H), 3.76 (s, 6/2H), 4.10–4.22 (m, 4/2H), 4.30 (dd, $J = 9.8$, 9.8 Hz, 1/2H), 4.32 (dd, $J = 9.8$, 9.8 Hz, 1/2H), 4.51 (d, $J = 5.9$ Hz, 1/2H), 4.52 (d, $J = 5.4$ Hz, 1/2H), 4.68 (d, $J = 11.3$ Hz, 2/2H), 4.69 (s, 2/2H), 4.80–4.93 (m, 6/2H), 5.13 (d, $J = 1.0$ Hz, 1/2H), 5.14 (d, $J = 1.5$ Hz, 1/2H), 6.46 (dd, $J = 5.9$, 5.4 Hz, 1/2H), 6.50 (dd, $J = 5.9$, 5.4 Hz, 1/2H), 6.74–6.78 (m, 4/2H), 6.94–6.98 (m, 6/2H), 7.20–7.27 ppm (m, 8/2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.4$, 18.2, 25.8, 26.8, 27.6, 27.9, 27.9, 29.3, 29.3, 55.2, 55.8, 55.9, 61.7, 61.7, 69.4, 69.5, 69.5, 70.7, 70.8, 79.8, 79.8, 82.0, 82.1, 82.5, 82.6, 85.2, 90.1, 90.2, 95.1, 95.2, 101.2, 101.4, 112.3, 112.3, 113.7, 115.9, 116.0, 121.6, 129.3, 129.7, 129.7, 129.8, 129.9, 144.2, 157.4, 157.5, 159.1, 159.1 ppm; HRMS (ESI): m/z calcd for $C_{37}H_{51}INaO_8Si$: 801.2290 $[M+Na]^+$; found: 801.2293.

14: DDQ (1.18 g, 5.2 mmol) was added to a solution of **13** (1.62 g, 2.08 mmol) in CH_2Cl_2 (42 mL) and phosphate buffer (pH 7, 2.1 mL) at 0 °C, and the resulting mixture was stirred for 3 h at room temperature. The reaction was then quenched with aqueous $Na_2S_2O_3$ and $NaHCO_3$, and the mixture was extracted twice with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 5:1–4:1) gave a 1:1 diastereomeric mixture of **14** (1.07 g, 1.70 mmol, 82%). The mixture was separated by HPLC (YMC Pack, SIL-06, 250×20 mm; detection at 254 nm; hexane/EtOAc 5:1; 9.9 mL min^{-1}) to afford **14A** (40%) and **14B** (37%), each as a pale-yellow oil. **14A**: $[\alpha]_D^{21} = -106.6$ ($c = 0.97$, $CHCl_3$); IR (film): $\tilde{\nu} = 3525, 2933, 2857, 1598, 1494, 1381, 1252, 1232, 1093\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.53 (s, 3H, acetonide), 1.55 (s, 3H, acetonide), 1.65–1.77 (m, 2H, 11-H, 12-H), 1.85–1.94 (m, 1H, 11-H), 2.09–2.18 (m, 1H, 12-H), 2.57 (d, $J = 9.0$ Hz, 1H, 1-OH), 3.28 (s, 3H, Me), 4.17 (dd, $J = 14.0$, 6.0 Hz, 1H, 14-H), 4.22 (dd, $J = 14.0$, 6.0 Hz, 1H, 14-H), 4.26 (td, $J = 9.0$, 7.0 Hz, 1H, 1-H), 4.75 (s, 1H, 5-H), 4.85 (d, $J = 2.5$ Hz, 1H, 10-H), 4.95 (s, 1H, 8-H), 6.49 (dd, $J = 6.0$, 6.0 Hz, 1H, 13-H), 6.99–7.04 (m, 3H, Ph), 7.27–7.31 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.4$, 18.2, 25.8, 26.4, 27.4, 27.7, 31.7, 55.9, 61.8, 69.3, 70.8, 73.0, 81.8, 82.2, 85.2, 89.3, 101.1, 112.3, 115.9, 121.9, 129.5, 144.2, 157.4 ppm; HRMS (ESI): m/z calcd for $C_{28}H_{41}INaO_6Si$: 651.1609 $[M+Na]^+$; found: 651.1608. **14B**: $[\alpha]_D^{21} = -82.7$ ($c = 0.94$, $CHCl_3$); IR (film): $\tilde{\nu} = 3525, 2933, 2857, 1598, 1494, 1380, 1252, 1232, 1093\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.53 (s, 3H, acetonide), 1.55 (s, 3H, acetonide), 1.62 (dddd, $J = 13.0$, 10.0, 5.5, 3.5 Hz, 1H, 11-H), 1.72 (ddd, $J = 12.0$, 9.0, 6.0 Hz, 1H, 12-H), 1.88 (dd, $J = 13.0$, 6.5 Hz, 1H, 11-H), 2.12–2.19 (m, 1H, 12-H), 2.57 (d, $J = 9.0$ Hz, 1H, 1-OH), 3.30 (s, 3H, Me), 4.17 (dd, $J = 14.0$,

6.0 Hz, 1H, 14-H), 4.22 (dd, J=14.0, 6.0 Hz, 1H, 14-H), 4.29 (ddd, J=9.0, 9.0, 6.5 Hz, 1H, 1-H), 4.75 (s, 1H, 5-H), 4.82 (d, J=3.5 Hz, 1H, 10-H), 4.96 (s, 1H, 8-H), 6.50 (dd, J=6.0, 6.0 Hz, 1H, 13-H), 6.98–7.05 (m, 3H, Ph), 7.27–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4, 18.2, 25.8, 26.4, 27.4, 27.7, 31.7, 55.9, 61.8, 69.2, 70.8, 73.0, 81.9, 82.2, 85.2, 89.3, 101.2, 112.3, 115.8, 121.9, 129.5, 144.2, 157.3 ppm; HRMS (ESI): m/z calcd for $C_{28}H_{41}INaO_6Si$: 651.1609 $[M+Na]^+$; found: 651.1607.

15A: $NaHCO_3$ (361 mg, 4.3 mmol) and Dess–Martin periodinane (456 mg, 1.07 mmol) were added to a solution of **14A** (135 mg, 215 μmol) in CH_2Cl_2 (4.3 mL) at room temperature, and the resulting mixture was stirred for 30 min. Additional Dess–Martin periodinane (111 mg, 0.2 mmol) was then added, and the reaction mixture was stirred for a further 10 min. The reaction was quenched with aqueous $Na_2S_2O_3$, and the mixture was extracted twice with EtOAc. The organic layer was washed with aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 10:1) gave the ketone (135 mg, 215 μmol, 100%), which was used in the next reaction without further purification. LiHMDS (483 μL, 1 M in THF) was added to a mixture of the ketone (101 mg, 161 μmol) and the Comins reagent (161 mg, 417 μmol) in THF (16 mL) at −80 °C, and the resulting mixture was stirred for 1.2 h. The reaction was then quenched with saturated aqueous NH_4Cl at −50 °C, and the mixture was extracted twice with EtOAc. The organic layer was washed with aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 25:1) gave **15A** (80.7 mg, 106 μmol, 66%) as a pale-yellow oil. $[\alpha]_D^{21}$=−109.5 (c=1.054, CH_2Cl_2); IR (film): $\tilde{\nu}$=2992, 2932, 2858, 1657, 1598, 1494, 1426, 1218, 1141, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.05 (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.56 (dd, J=17.0, 2.5 Hz, 1H, 11-H), 2.86 (ddd, J=17.0, 5.5, 2.0 Hz, 1H, 11-H), 3.27 (s, 3H, Me), 4.16 (dd, J=14.5, 5.5 Hz, 1H, 14-H), 4.23 (dd, J=14.5, 5.5 Hz, 1H, 14-H), 4.73 (d, J=1.5 Hz, 1H, 5-H), 5.00 (dd, J=5.5, 1.0 Hz, 1H, 10-H), 5.03 (d, J=1.5 Hz, 1H, 8-H), 5.88 (ddd, J=2.5, 2.0, 1.0 Hz, 1H, 12-H), 6.49 (dd, J=6.0, 6.0 Hz, 1H, 13-H), 6.99–7.06 (m, 3H, Ph), 7.26–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4, 18.2, 25.8, 26.6, 27.5, 34.0, 55.9, 61.8, 67.4, 70.7, 78.1, 80.2, 85.2, 92.1, 100.7, 113.2, 116.1, 118.7, 122.2, 129.5, 144.3, 146.4, 157.4 ppm; HRMS (ESI): m/z calcd for $C_{29}H_{38}F_3INaO_8SSi$: 781.0946 $[M+Na]^+$; found: 781.0944.

15B: Prepared by the same procedure (59% from **14B**) as a pale-yellow oil. $[\alpha]_D^{21}$=−88.1 (c=1.115, CH_2Cl_2); IR (film): $\tilde{\nu}$=2992, 2932, 2858, 1657, 1598, 1495, 1426, 1218, 1141, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.05 (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.55 (dd, J=17.5, 3.0 Hz, 1H, 11-H), 2.81 (ddd, J=17.5, 5.5, 2.0 Hz, 1H, 11-H), 3.28 (s, 3H, Me), 4.17 (dd, J=14.5, 6.0 Hz, 1H, 14-H), 4.21 (dd, J=14.5, 6.0 Hz, 1H, 14-H), 4.73 (1H, d, J=1.0 Hz, 5-H), 4.99 (dd, J=5.5, 1.0 Hz, 1H, 10-H), 5.04 (d, J=1.0 Hz, 1H, 8-H), 5.90 (ddd, J=3.0, 2.0, 1.0 Hz, 1H, 12-H), 6.49 (dd, J=6.0, 6.0 Hz, 1H, 13-H), 6.99–7.06 (m, 3H, Ph), 7.28–7.32 ppm (m, 1H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4, 18.2, 25.8, 26.6, 27.5, 34.0, 55.9, 61.8, 67.2, 70.7, 78.0, 80.3, 85.2, 92.2, 100.8, 113.2, 116.1, 118.7, 122.2, 129.5, 144.1, 146.4, 157.4 ppm; HRMS (ESI): m/z calcd for $C_{29}H_{38}F_3INaO_8SSi$: 781.0946 $[M+Na]^+$; found: 781.0945.

16A: Trimethylsilylacetylene (4.4 μL, 31.6 μmol) was added to a mixture of $[Pd(PPh_3)_4]$ (6.2 mg, 5.4 μmol), CuI (2.1 mg, 11.1 μmol), and **15A** (24 mg, 31.6 μmol) in THF (2.4 mL) and iPr$_2$NEt (1.6 mL) at room temperature, and the resulting mixture was stirred for 20 min. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with aqueous NH_4Cl and then brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 20:1) gave **16A** (23.0 mg, 31.6 μmol, 100%) as a pale-yellow oil. $[\alpha]_D^{20}$=−67.5 (c=1.077, CH_2Cl_2); IR (film): $\tilde{\nu}$=2956, 2932, 2899, 2858, 2148, 1657, 1598, 1495, 1428, 1217, 1142, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.04 (s, 6H, TBS), 0.18 (s, 9H, TMS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.53 (dd, J=17.5, 3.0 Hz, 1H, 11-H), 2.82 (ddd, J=17.5, 5.0, 2.5 Hz, 1H, 11-H), 3.28 (s, 3H, Me), 4.26 (dd, J=15.0, 6.0 Hz, 1H, 14-H), 4.30 (dd, J=15.0, 6.0 Hz, 1H, 14-H), 4.74 (d, J=1.5 Hz, 1H, 5-H), 4.99 (d, J=5.0 Hz, 1H, 10-H), 5.03 (d, J=1.5 Hz, 1H, 8-H), 5.82 (dd, J=3.0, 2.5 Hz, 1H, 12-H), 6.13 (dd, J=6.0, 6.0 Hz, 1H, 13-H), 6.99–7.05 (m, 3H, Ph), 7.27–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4, −0.1, 18.2, 25.8, 26.6, 27.6, 34.0, 56.1, 59.7, 67.2, 68.3, 78.0, 80.1, 84.8, 92.3, 94.8, 102.9, 113.1, 116.0, 118.3, 120.9, 122.1, 129.5, 142.4, 146.6, 157.5 ppm; HRMS (ESI): m/z calcd for $C_{34}H_{47}F_3NaO_8SSi_2$: 751.2374 $[M+Na]^+$; found: 751.2374.

16B: Prepared by the same procedure (100% from **15B**) as a pale-yellow oil. $[\alpha]_D^{21}$=−89.9 (c=0.979, CH_2Cl_2); IR (film): $\tilde{\nu}$=2956, 2932, 2858, 2148, 1657, 1598, 1494, 1427, 1217, 1142, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.04 (s, 6H, TBS), 0.17 (s, 9H, TMS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.54 (dd, J=17.5, 3.5 Hz, 1H, 11-H), 2.82 (ddd, J=17.5, 5.5, 2.0 Hz, 1H, 11-H), 3.29 (s, 3H, Me), 4.28 (d, J=6.0 Hz, 2H, 14-H), 4.70 (d, J=1.5 Hz, 1H, 5-H), 4.98 (dd, J=5.5, 1.0 Hz, 1H, 10-H), 5.02 (d, J=1.5 Hz, 1H, 8-H), 5.86 (ddd, J=3.0, 2.0, 1.0 Hz, 1H, 12-H), 6.12 (t, J=6.0 Hz, 1H, 13-H), 6.99–7.05 (m, 3H, Ph), 7.27–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4, −0.1, 18.2, 25.8, 26.5, 27.5, 34.0, 56.3, 59.7, 67.2, 68.6, 78.1, 80.1, 84.8, 92.3, 94.6, 102.9, 113.2, 116.0, 118.5, 120.7, 122.1, 129.5, 142.4, 146.6, 157.5 ppm; HRMS (ESI): m/z calcd for $C_{34}H_{47}F_3NaO_8SSi_2$: 751.2374 $[M+Na]^+$; found: 751.2373.

17A: TBAF (1 M in THF, 17.8 μL, 17.8 μmol) was added to a solution of **16A** (13 mg, 17.8 μmol) in THF (4 mL) at −81 °C, and the resulting mixture was stirred for 25 min, during which time the temperature increased to −62 °C. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The organic layer was washed with aqueous NH_4Cl and then brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 10:1) gave **17A** (11.7 mg, 17.8 μmol, 100%) as a pale-yellow oil. $[\alpha]_D^{21}$=−87.6 (c=0.658, CH_2Cl_2); IR (film): $\tilde{\nu}$=3297, 2933, 2858, 1658, 1598, 1494, 1426, 1218, 1141, 1088 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.05 (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.54 (dd, J=17.0, 3.0 Hz, 1H, 11-H), 2.81 (ddd, J=17.0, 5.5, 2.0 Hz, 1H, 11-H), 2.84 (s, 1H, 2-H), 3.30 (s, 3H, Me), 4.26 (dd, J=15.0, 6.0 Hz, 1H, 14-H), 4.31 (dd, J=15.0, 6.0 Hz, 1H, 14-H), 4.81 (d, J=1.5 Hz, 1H, 5-H), 4.99 (dd, J=5.5, 1.0 Hz, 1H, 10-H), 5.05 (d, J=1.5 Hz, 1H, 8-H), 5.83 (ddd, J=3.0, 2.0, 1.0 Hz, 1H, 12-H), 6.17 (dd, J=6.0, 6.0 Hz, 1H, 13-H), 6.99–7.05 (m, 3H, Ph), 7.27–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.38 (TBS), 18.2 (TBS), 25.8 (TBS), 26.6 (acetonide), 27.5 (acetonide), 33.9 (C11), 56.3 (Me), 59.6 (C14), 67.2 (C8), 68.0 (C5), 77.6 (C2), 78.0 (C10), 80.3 (C6), 81.4 (C3), 84.7 (C7), 92.2 (C9), 113.1 (acetonide), 116.0 (Ph), 118.4 (C12), 120.1 (C4), 122.1 (Ph), 129.5 (Ph), 142.5 (C13), 146.6 (C1), 157.4 ppm (Ph; one CF_3 carbon atom could not identified as a result of C,F coupling); HRMS (ESI): m/z calcd for $C_{31}H_{39}F_3NaO_8SSi$: 679.1979 $[M+Na]^+$; found: 679.1976.

17B: Prepared by the same procedure (100% from **16B**) as a pale-yellow oil. $[\alpha]_D^{21}$=−102.9 (c=0.652, CH_2Cl_2); IR (film): $\tilde{\nu}$=3297, 2933, 2858, 1658, 1598, 1494, 1426, 1218, 1141, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.05 (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.47 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 2.54 (dd, J=17.5, 3.0 Hz, 1H, 11-H), 2.75 (ddd, J=17.5, 5.5, 2.0 Hz, 1H, 11-H), 2.85 (s, 1H, 2-H), 3.31 (s, 3H, Me), 4.28 (d, J=6.0 Hz, 2H, 14-H), 4.81 (d, J=1.5 Hz, 1H, 5-H), 4.97 (dd, J=5.5, 1.0 Hz, 1H, 10-H), 5.06 (d, J=1.5 Hz, 1H, 8-H), 5.85 (ddd, J=3.0, 2.0, 1.0 Hz, 1H, 12-H), 6.16 (t, J=6.0 Hz, 1H, 13-H), 6.99–7.06 (m, 3H, Ph), 7.24–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.4 (TBS), 18.2 (TBS), 25.8 (TBS), 26.6 (acetonide), 27.5 (acetonide), 33.9 (C11), 56.3 (Me), 59.6 (C14), 67.0 (C8), 68.0 (C5), 77.6 (C2), 77.9 (C10), 80.4 (C6), 81.2 (C3), 84.7 (C7), 92.3 (C9), 113.2 (acetonide), 116.0 (Ph), 118.4 (C12), 120.3 (C4), 122.1 (Ph), 129.5 (Ph), 142.2 (C13), 146.5 (C1), 157.4 ppm (Ph); HRMS (ESI): m/z calcd for $C_{31}H_{39}F_3NaO_8SSi$: 679.1979 $[M+Na]^+$; found: 679.1981.

2A: Compound **17A** (4.6 mg, 7.0 μmol) was added as a solution in THF (2.6 mL) and iPr$_2$NEt (1.2 mL) to a solution of $[Pd(PPh_3)_4]$ (0.35 mM in THF, 2 mL, 0.7 μmol) at room temperature, and the resulting mixture was stirred for 20 min at room temperature. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The organic layer was washed with aqueous NH_4Cl

and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexane/EtOAc 40:1–20:1) gave **2A** (2.9 mg, 5.7 μmol, 82%) as a pale-yellow oil. $[\alpha]_D^{21} = -99.9$ ($c = 0.791$, $CHCl_3$); IR (film): $\tilde{\nu} = 2930, 2856, 1598, 1494, 1372, 1256, 1226, 1076\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H, TBS), 0.89 (s, 9H, TBS), 1.43 (s, 3H, acetonide), 1.46 (s, 3H, acetonide), 2.62 (dd, $J = 19.0$, 3.0 Hz, 1H, 11-H), 2.84 (ddd, $J = 19.0$, 5.5, 2.0 Hz, 1H, 11-H), 3.09 (s, 3H, Me), 4.31 (dd, $J = 15.5$, 5.0 Hz, 1H, 14-H), 4.35 (dd, $J = 15.5$, 7.0 Hz, 1H, 14-H), 4.71 (d, $J = 5.5$ Hz, 1H, 10-H), 4.76 (d, $J = 2.0$ Hz, 1H, 8-H), 5.05 (dd, $J = 2.0$, 1.5 Hz, 1H, 5-H), 6.10 (dd, $J = 3.0$, 2.0 Hz, 1H, 12-H), 6.18 (ddd, $J = 7.0$, 5.0, 1.5 Hz, 1H, 13-H), 6.96–7.04 (m, 3H, Ph), 7.27–7.33 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.3$ (TBS), −5.2 (TBS), 18.3 (TBS), 25.9 (TBS), 27.2 (acetonide), 27.7 (acetonide), 38.6 (C11), 53.5 (Me), 59.9 (C14), 71.3 (C5), 72.7 (C8), 81.9 (C10), 88.5 (C7), 91.3 (C6), 95.4 (C2), 96.5 (C3), 97.3 (C9), 112.0 (acetonide), 115.8 (Ph), 122.0 (Ph), 123.0 (C4), 125.8 (C1), 129.4 (Ph), 135.3 (C12), 138.2 (C13), 156.9 ppm (Ph); HRMS (ESI): m/z calcd for $C_{30}H_{38}NaO_5Si$: 529.2381 $[M+Na]^+$; found: 529.2381.

2B: Prepared by the same procedure (87% from **17B**) as a pale-yellow oil. $[\alpha]_D^{19} = -218.1$ ($c = 0.677$, CH_2Cl_2); IR (film): $\tilde{\nu} = 2932, 2857, 1599, 1494, 1372, 1256, 1227, 1071\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H, TBS), 0.88 (s, 9H, TBS), 1.42 (s, 3H, acetonide), 1.43 (s, 3H, acetonide), 2.61 (dd, $J = 19.0$, 3.0 Hz, 1H, 11-H), 2.83 (ddd, $J = 19.0$, 5.0, 2.5 Hz, 1H, 11-H), 3.37 (s, 3H, Me), 4.34 (d, $J = 6.5$ Hz, 2H, 14-H), 4.66 (d, $J = 5.0$ Hz, 1H, 10-H), 4.81 (s, 1H, 8-H), 4.99 (d, $J = 1.5$ Hz, 1H, 5-H), 6.10 (dd, $J = 3.0$, 2.5 Hz, 1H, 12-H), 6.16 (td, $J = 6.5$, 1.5 Hz, 1H, 13-H), 6.95–6.99 (m, 2H, Ph), 6.99–7.03 (m, 1H, Ph), 7.28–7.32 ppm (m, 2H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = -5.3$ (TBS), −5.2 (TBS), 18.2 (TBS), 25.8 (TBS), 27.3 (acetonide), 27.8 (acetonide), 38.7 (C11), 53.7 (Me), 59.9 (C14), 71.1 (C5), 72.6 (C8), 82.0 (C10), 88.4 (C7), 91.3 (C6), 96.1 (C2), 96.8 (C3), 98.4 (C9), 111.7 (acetonide), 115.5 (Ph), 121.9 (Ph), 123.2 (C4), 125.9 (C1), 129.5 (Ph), 135.4 (C12), 138.3 (C13), 156.9 ppm (Ph); HRMS (ESI): m/z calcd for $C_{30}H_{38}NaO_5Si$: 529.2381 $[M+Na]^+$; found: 529.2379.

Acknowledgements

This research was supported by CREST and SORST, Japan Science and Technology Agency (JST).

[1] a) N. Zein, W. Solomon, K. L. Colson, D. R. Schroeder, *Biochemistry* **1995**, *34*, 11591–11597; b) D. R. Schroeder, K. L. Colson, S. E. Klohr, N. Zein, D. R. Langley, M. S. Lee, J. A. Matson, T. W. Doyle, *J. Am. Chem. Soc.* **1994**, *116*, 9351–9352; c) M. Hanada, H. Ohkuma, T. Yonemoto, K. Tomita, M. Ohbayashi, H. Kamei, T. Miyaki, M. Konishi, H. Kawaguchi, S. Forenza, *J. Antibiot.* **1991**, *44*, 403–414.

[2] a) T. Otani, Y. Minami, T. Marunaka, R. Zhang, M.-Y. Xie, *J. Antibiot.* **1988**, *41*, 1580–1585; b) Y. Zhen, S. Ming, Y. Bin, T. Otani, H. Saito, Y. Yamada, *J. Antibiot.* **1989**, *42*, 1294–1298.

[3] a) J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle, J. A. Matson, *J. Am. Chem. Soc.* **1992**, *114*, 7946–7948; b) S. Kawata, S. Ashizawa, M. Hirama, *J. Am. Chem. Soc.* **1997**, *119*, 12012–12013.

[4] *Neocarzinostatin* (Eds.: H. Maeda, K. Edo, N. Ishida), Springer, Tokyo, **1997**.

[5] For a review on chromoprotein antibiotics and other enediyne natural products, see: Z. Xi, I. H. Goldberg in *Comprehensive Natural Products Chemistry, Vol. 7* (Eds.: D. H. R. Barton, K. Nakanishi), Elsevier, Amsterdam, **1999**, pp. 553–592.

[6] For synthetic studies on the maduropeptin chromophore by our research group, see: a) N. Kato, S. Shimamura, Y. Kikai, M. Hirama, *Synlett* **2004**, 2107–2110; b) N. Kato, S. Shimamura, S. Khan, F. Takeda, Y. Kikai, M. Hirama, *Tetrahedron* **2004**, *60*, 3161–3172; c) S. Khan, N. Kato, M. Hirama, *Synlett* **2000**, 1494–1496.

[7] We recently synthesized the aglycon of the maduropeptin chromophore by using a different strategy: K. Komano, S. Shimamura, M. Inoue, M. Hirama, *J. Am. Chem. Soc.* **2007**, *129*, 14184–14186.

[8] For synthetic studies on the maduropeptin chromophore by other research groups, see: a) W. M. Dai, K. C. Fong, C. W. Lau, L. Zhou, W. Hamaguchi, S. Nishimoto, *J. Org. Chem.* **1999**, *64*, 682–683; b) C. Roger, D. S. Grierson, *Tetrahedron Lett.* **1998**, *39*, 27–30; c) J. Suffert, D. Toussaint, *Tetrahedron Lett.* **1997**, *38*, 5507–5510; d) K. C. Nicolaou, K. Koide, J. Xu, M. H. Izraelewicz, *Tetrahedron Lett.* **1997**, *38*, 3671–3674; e) K. C. Nicolaou, K. Koide, *Tetrahedron Lett.* **1997**, *38*, 3667–3670; f) P. Magnus, R. Carter, M. Davies, J. Elliott, T. Pitterna, *Tetrahedron* **1996**, *52*, 6283–6306.

[9] Total syntheses of nine-membered-ring enediynes have been reported; for N-1999-A2, see: a) T. A. Dineen, M. A. Zajac, A. G. Myers, *J. Am. Chem. Soc.* **2006**, *128*, 16406–16409; b) S. Kobayashi, S. Ashizawa, Y. Takahashi, Y. Sugiura, M. Nagaoka, M. J. Lear, M. Hirama, *J. Am. Chem. Soc.* **2001**, *123*, 11294–11295; for the neocarzinostatin chromophore, see: c) S. Kobayashi, M. Hori, G. X. Wang, M. Hirama, *J. Org. Chem.* **2006**, *71*, 636–644; d) A. G. Myers, R. Glatthar, M. Hammond, P. M. Harrington, E. Y. Kuo, J. Liang, S. E. Schaus, Y. Wu, J.-N. Xiang, *J. Am. Chem. Soc.* **2002**, *124*, 5380–5401; e) A. G. Myers, J. Liang, M. Hammond, P. M. Harrington, Y. Wu, E. Y. Kuo, *J. Am. Chem. Soc.* **1998**, *120*, 5319–5320; for the proposed structure of kedarcidin, see: f) F. Ren, P. C. Hogan, A. J. Anderson, A. G. Myers, *J. Am. Chem. Soc.* **2007**, *129*, 5381–5383.

[10] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[11] a) K. Iida, M. Hirama, *J. Am. Chem. Soc.* **1994**, *116*, 10310–10311; b) A. G. Myers, P. M. Harrington, E. Y. Kuo, *J. Am. Chem. Soc.* **1991**, *113*, 694–695; c) T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233–4236.

[12] a) K. Sonogashira in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, London, **1990**, pp. 521; b) K. Sonogashira, Y. Tohda, N. Hagiwara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

[13] For reviews on the synthesis of enediyne compounds, see: a) K. C. Nicolaou, W. M. Dai, *Angew. Chem.* **1991**, *103*, 1453–1481; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387–1416; b) S. J. Danishefsky, M. D. Shair, *J. Org. Chem.* **1996**, *61*, 16–44; c) J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453–6518; d) R. Brückner, J. Suffert, *Synlett* **1999**, 657.

[14] For related strategies, see: a) H. Tanaka, H. Yamada, A. Matsuda, T. Takahashi, *Synlett* **1997**, 381–383; b) M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefksy, *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525; c) M. D. Shair, T. Y. Yoon, S. J. Danishefsky, *Angew. Chem.* **1995**, *107*, 1883–1885; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1721–1723; d) M. D. Shair, T. Y. Yoon, S. J. Danishefsky, *J. Org. Chem.* **1994**, *59*, 3755–3757.

[15] S. Kawata, M. Hirama, *Tetrahedron Lett.* **1998**, *39*, 8707–8710.

[16] T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, Y. Kamiya, *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

[17] D. L. Comins, A. Dehghani, *Tetrahedron Lett.*. **1992**, *33*, 6299–6302.

[18] For representative examples of related chemoselective coupling reactions, see: a) D. J. Armitt, G. T. Crisp, *Tetrahedron* **2006**, *62*, 1485–1493; b) A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer, M. M. Weiss, *J. Am. Chem. Soc.* **2003**, *125*, 6261–6271; c) M. Lu, Y. Pan, Z. Peng, *Tetrahedron Lett.* **2002**, *43*, 7903–7906; d) T. Mizutani, S. Honzawa, S. Tosaki, M. Shibasaki, *Angew. Chem.* **2002**, *114*, 4874–4876; *Angew. Chem. Int. Ed.* **2002**, *41*, 4680–4682; e) A. M. Echavarren, J. K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.

[19] a) Q. Liu, D. J. Burton, *Tetrahedron Lett.* **1997**, *38*, 4371–4374; b) R. Rossi, A. Carpita, C. Begelli, *Tetrahedron Lett.* **1985**, *26*, 523–526; c) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320–3321; for a review of alkyne coupling, see: d) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[20] For recent advances in Cu^I-free Sonogashira coupling, see: a) A. Tougerti, S. Negri, A. Jutand, *Chem. Eur. J.* **2007**, *13*, 666–676; b) J. H. Li, X. D. Zhang, Y. X. Xie, *Eur. J. Org. Chem.* **2005**, 4256–

CHEMISTRY
AN ASIAN JOURNAL

4259; c) S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752–5755; d) A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer, D. L. Hughes, *Org. Lett.* **2003**, *5*, 4191–4194.

[21] In sharp contrast to a bicyclo[7.3.0]dodecatrienediyne core structure of the C-1027 chromophore (M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi, M. Hirama, *Org. Lett.* **2004**, *6*, 3833–3836), compounds **2A** and **2B** are stable at room temperature.

[22] We were unable to determine the configuration of **2A** and **2B** at C5 despite extensive NMR spectroscopic experiments.

Received: September 19, 2007
Published online: January 7, 2008

