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Headline Articles

Convenient Route to Both Enantiomerically Pure Forms of *trans*-4,5-Dihydroxy-2-cyclopenten-1-one: Efficient Synthesis of the Neocarzinostatin Chromophore Core

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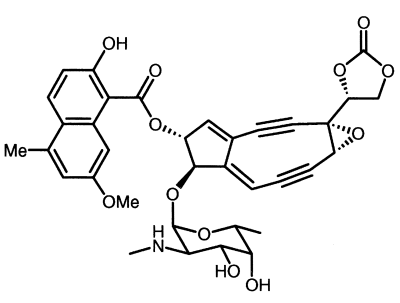
An enantioselective synthesis of an epoxybicyclo[7.3.0]dodecenediyne core system of the neocarzinostatin chromophore has been achieved via intramolecular acetylide addition and palladium-mediated coupling of iodocyclopentene **5** with alkyne **6**. The key cyclopentene moiety, *trans*-4,5-dihydroxy-2-cyclopenten-1-one **7**, was conveniently prepared in both enantiomerically pure forms via enzymatic desymmetrization of *meso*-3,4,5-*trans*,*trans*-trihydroxycyclopentene derivatives.

The chromphore structures of chromoprotein antitumor antibiotics such as neocarzinostatin **1**[1] and kedarcidin **2** possess a highly strained nine-membered cyclic diyne core that is tightly fused to a densely functionalized cyclopentene ring. In their total synthesis, concise approaches to prepare chiral *trans*-4,5-dihydroxy-2-cyclopenten-1-one derivatives[3,4] to serve as key intermediates are therefore required.[5,6] Described herein is a convenient synthesis of both enantiomers of a *trans*-4,5-dihydroxy-2-cyclopenten-1-one derivative, *en route* to the convergent construction of a functionalized bicyclo[7.3.0]dodecenediyne core system of **1** (Chart 1).

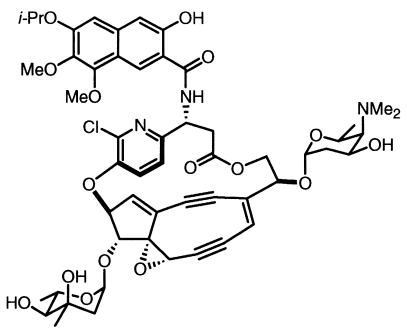
By analogy with previous processes from our group and others,[5f,5i,5l,5m] the epoxybicyclic core **3** would be accessible via an acetylide anion–aldehyde ring closure of **4**, which itself could be synthesized by palladium-mediated coupling of the iodocyclopentene **5** with the alkyne **6** (Scheme 1).[7] In turn, **5** and **6** would be derived from the enantiomerically pure cyclopentenone (−)-**7** and propargylic alcohol **8**,[3f,3l] respectively.

Results and Discussion

Expeditious Synthesis of Both Enantiomers of *trans*-4,5-Dihydroxy-2-cyclopenten-1-one. The retrosynthetic plan towards the highly oxygenated cyclopentenone (−)-**7** is outlined in Scheme 2. Enantiomerically pure (−)-**7** would be prepared from (−)-**9** via enzymatic desymmetization of meso-cyclopentenetriol **10**.[8] The most straightforward route to the key intermediate **10** would be a Diels–Alder type reaction between singlet oxygen and the alkoxy cyclopentadiene **13**. However, Diels–Alder reactions of **13** tend to favor *syn*-addition relative to the C_5 alkoxy substituent.[9] Therefore, the cyclopentadienyl-

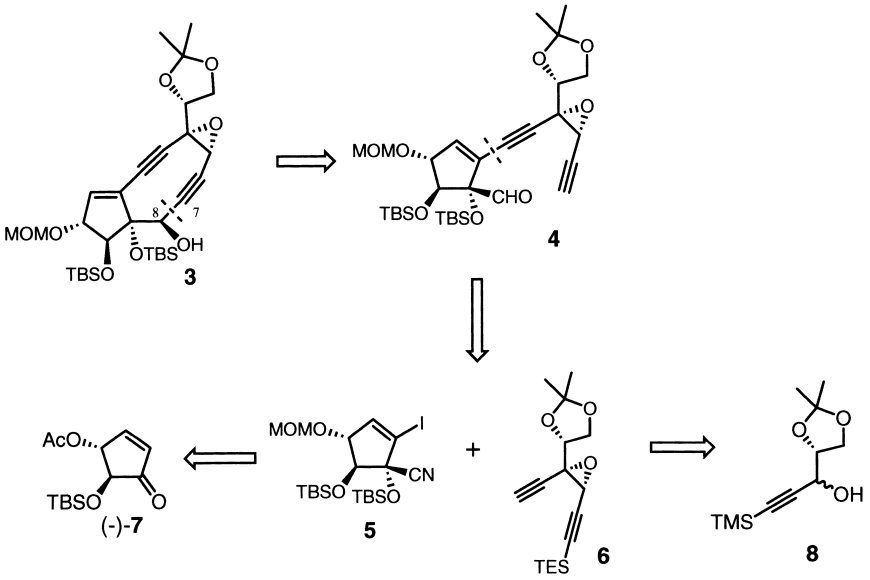


Neocarzinostatin chromophore (**1**)

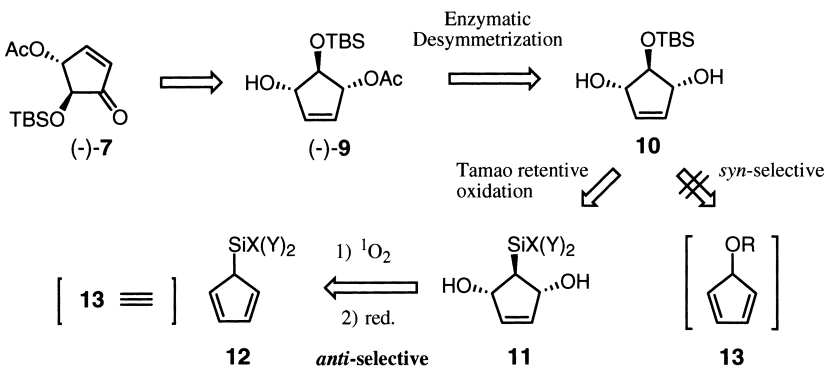


Kedarcidin chromophore (**2**, revised structure)

Chart 1.



Scheme 1.



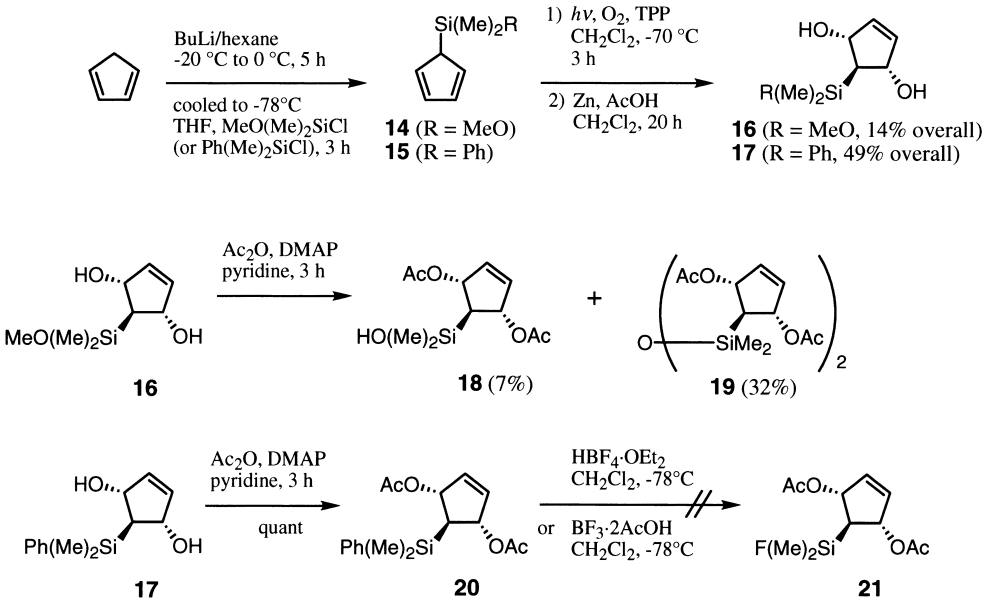
Scheme 2.

silane **12** was chosen as an alternative substrate for two main reasons:[10] firstly, high *anti* stereoselectivity has been demonstrated in analogous Diels–Alder reactions[10a] and, secondly, the C–Si bond can be oxidatively transformed to a C–O bond with stereochemical retention.[11,12]

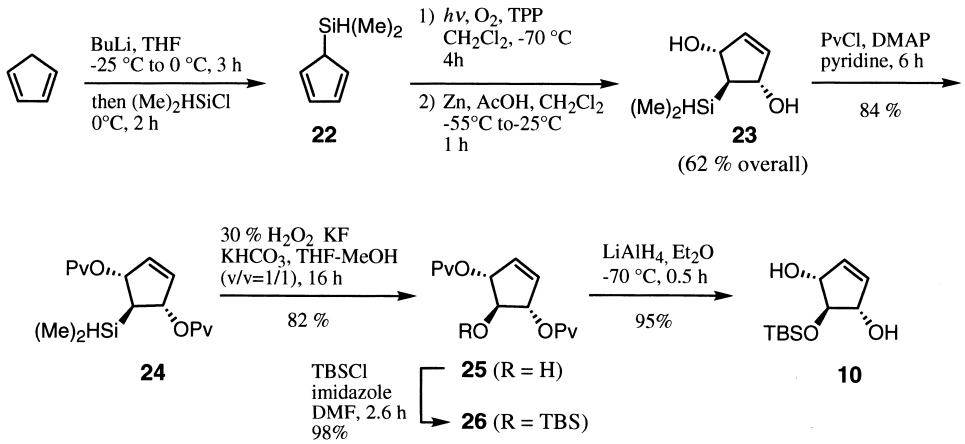
Preliminary experiments revealed that judicious choice of the silyl group in **11** was required for the successful formation of **10**. For example, lithium cyclopentadienide was silylated with methoxydimethylsilyl or dimethylphenylsilyl chloride to afford cyclopentadienylsilane **14** or **15**, respectively (Scheme 3). Subsequent reaction with singlet oxygen followed by reduction of the *endo*-peroxide produced the diol **16** or **17** in moderate yield. While the methoxydimethylsilane **16** was found to be too labile to acetylation, giving a mixture of silanol **18** and siloxane **19**, the dimethylphenylsilane **17** smoothly gave its diacetate **20**, but any further transformation of **20** was unsuccessful.[12]

A successful route to the *meso*-diol **10** is outlined in Scheme 4. Lithium cyclopentadienide was treated with dimethylsilyl chloride to give the cyclopentadienyldimethylsilane **22**, which was exposed to singlet oxygen at low temperature. The resulting *endo*-peroxide was reduced with zinc in acetic acid to give the desired *trans*-cyclopentenediol **23** in 62% overall yield. After pivaloylation, **24** was treated according to Tamao conditions (30% hydrogen peroxide, potassium fluoride, and potassium hydrogencarbonate) causing oxidative cleavage of the C–Si bond to generate **25** in good yield.[11] Protection of the alcohol **25** as its *t*-butyldimethylsilyl (TBS) ether followed by reductive cleavage of the pivalate groups with LiAlH4, afforded the key *meso*-compound **10** in near quantitative yield.

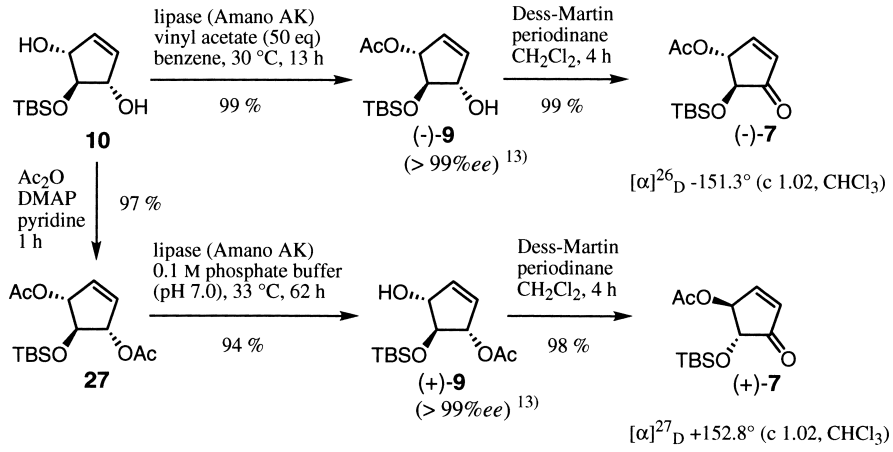
Syntheses of both enantiomers of the enone **7** are shown in Scheme 5. Lipase (Amano AK) catalyzed asymmetric acylation[8] of the diol **10** gave monoacetate (−)-**9** quantitatively in excellent enantioselectivity.[13] Dess–Martin oxidation[14] of (−)-**9** provided the enantiomerically pure enone (−)-**7**;[15] other oxidations with MnO_2, PDC, SO_3·pyridine, or Swern conditions gave lower yields. On the other hand, the *meso*-diacetate **27**, derived from diol **10**, was converted to enantiomerically pure (+)-**9** via asymmetric hydrolysis with lipase (Amano AK) and oxidation gave the antipodal enone (+)-**7**, which is useful for synthesis of kedarcidin chromophore **2**.[2b] In short, both (−)-**7** and (+)-**7** were readily obtained in enanantiomerically pure form and on a preparative scale (ca. 0.1 molar) within 8 or 9 steps from cyclopentadiene.



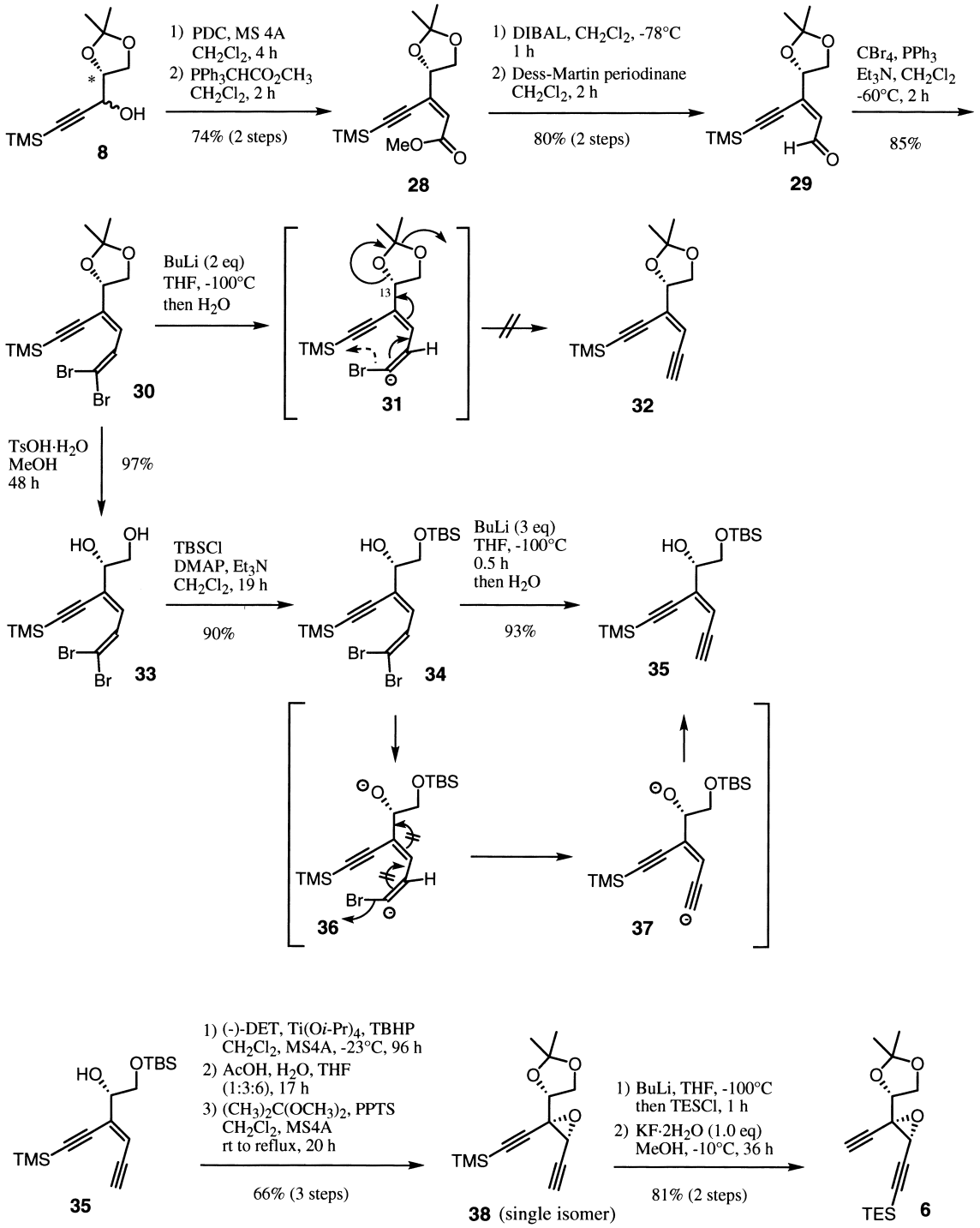
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

Synthesis of the Epoxydiyne Moiety. Synthesis of the epoxy diyne fragment **6** commenced with the propargylic alcohol **8**, which is readily available from D-mannitol (Scheme 6).[5f,51] Oxidation of **8** with PDC followed by Wittig reaction gave the (*E*)-α,β-unsaturated ester **28** exclusively. Reduction of **28** with DIBAL gave a mixture of aldehyde and primary alcohol, which was treated with Dess–Martin periodinane to give the aldehyde **29**. By use of the Corey procedure, transformation to the alkyne **32** was attempted and the 1,1-dibromoalkene **30** was formed by treatment of **29** with triphenylphosphine and tetrabromomethane in the presence of triethylamine.[16] However, as illustrated in Scheme 6, metalation of **30** with butyllithium gave complex mixtures, conceivably due to the carbanion intermediate **31** undergoing competitive elimination of the C13-ether functionality prior to α-bromide elimination. Therefore, the partially protected diol **34** was selected as a substrate, since the resulting allylic alkoxide would prevent this unproductive type of elimination. To this end, the acetonide of **30** was removed with *p*-toluenesulfonic acid in methanol and the resulting free diol **33** was selectively silylat-

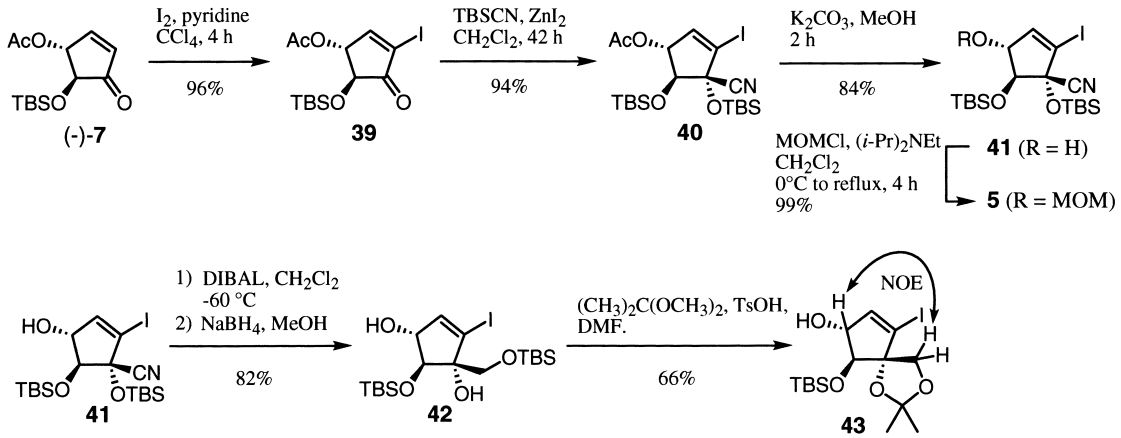
ed at the primary position to afford **34**. Gratifyingly, the reaction of **34** with butyllithium efficiently generated the enediyne **35** in 93% yield. Subsequent Sharpless asymmetric epoxidation of **35** with (−)-diethyl tartrate,[5b,5h,5j] followed by protecting group manipulation, gave the epoxy diyne **38** as a single stereoisomer. Lastly, the terminal alkyne of **38** was silylated with TESCl and the TMS group was selectively removed with $KF{\cdot}2H_2O$ in methanol at −10 °C to give the desired epoxydiyne fragment **6**.

Construction of Epoxybicyclo[7.3.0]dodecenediyne Moiety. Preparation of the iodocyclopentene **5** is shown in Scheme 7. α-Iodination of cyclopentenone (−)-**7** led to **39** in near quantitative yield.[17] Treatment of **39** with *t*-butyldimethylsilyl cyanide in the presence of zinc iodide[18] gave the protected cyanohydrin **40** as a single isomer. After methanolysis of **40**, the alcohol **41** was protected to give the desired methoxymethyl (MOM) ether **5**. Confirmation of the stereochemistry of these products were determined by NOE difference experiments on the acetonide **43**, which was derived from **41** via the tetraol **42**.

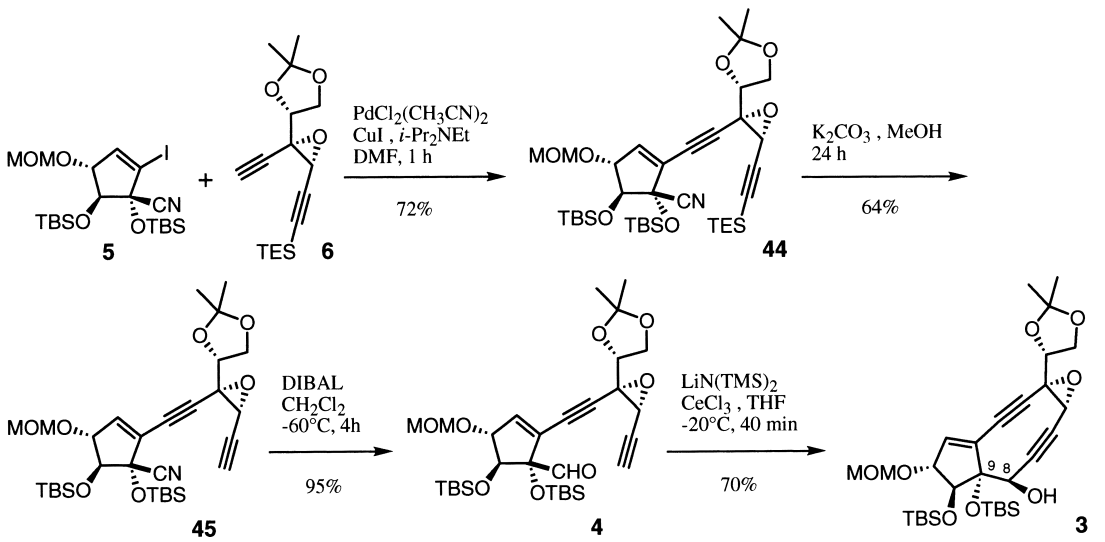
Using $PdCl_2(CH_3CN)_2$ as catalyst under Sonogashira-type conditions, coupling of **5** with the epoxy diyne unit **6** proceeded readily and gave **44** in 72% yield (Scheme 8).[7] After removal of the acetylenic TES group using potassium carbonate in methanol, the nitrile **45** was reduced with DIBAL and the resulting unstable aldehyde **4** was immediately treated with a large excess of lithium hexamethyldisilazide and cerium (III) chloride in THF at −20 °C. Under these conditions, the desired nine-membered ring closure reaction proceeded smoothly and afforded the strained bicyclic epoxy enediyne **3** in 70% yield.[5f,5i,5m] The stereochemistry of the C8 was unambiguously determined by NOE experiments.

Conclusion

In summary, an expeditious synthesis of both enantiomerically pure forms of *trans*-4-acetoxy-5-*t*-butyldimethylsilyloxy-2-cyclopenten-1-one, (−)-**7** and (+)-**7**, was achieved via enzymatic desymmetrization of *meso*-3,4,5-*trans*,*trans*-trihydroxycyclopentene derivatives, **10** and **27**, respectively. In turn, **10**



Scheme 7.



Scheme 8.

and **27** were readily prepared by the photosensitized oxidation of 5-dimethylsilylcyclopentadiene **22** followed by retentive Tamao oxidation of the C–Si bond. Through a series of reactions involving $[PdCl_2(CH_3CN)_2]$-mediated coupling of iodocyclopentene **5** with epoxy alkyne **6**, the aldehyde-acetylenic cyclization precursor **4** was synthesized and subsequently treated with excess $LiN(TMS)_2/CeCl_3$ at −20 °C to afford the highly strained bicyclo[7.3.0]dodecenediyne **3**. Advanced studies directed toward the total synthesis of the chromophore **1**, as well as **2**, are actively being pursued in our laboratory and will be the subject of future work.

Experimental

General. NMR spectra were recorded using Varian Gemini-200, Varian Mercury-200, JEOL GX-400, or Bruker AM-600 spectrometers, and referenced to chloroform as an internal standard. IR spectra were recorded on a JASCO FT/IR-7000 spectrometer. Optical rotations were performed by a JASCO DIP-370 polarimeter. Mass and high-resolution mass spectra (HRMS) were recorded on a JEOL HX-110 mass spectrometer. Elemental analysis was obtained on a Yanagimoto CHN corder/MT-5 instrument. Melting points were measured on a Yanagimoto micro-melting point apparatus.

Unless noted otherwise, solvents were dried and purified before use. THF was distilled from sodium-benzophenone. Anhydrous grade diethyl ether was purchased from Kanto Chemical Co. Ltd., and used without further purification. Benzene, dichloromethane, DMF, pyridine, and toluene were distilled over calcium hydride. Air- and moisture-sensitive reactions were carried out under an argon atmosphere and anhydrous conditions. All reactions were monitored by TLC on 0.25 mm Merck Kieselgel TLC plate (60F-254) using UV light, I_2, ethanolic phosphomolybdic acid, or *p*-anisaldehyde and sulfuric acid solution as developing agents when heated. Merck Kieselgel 60 (70–230 mesh) and (230–400 mesh) were used for silica-gel and flash silica-gel column chromatography, respectively. Yields refer to chromatographically and spectroscopically pure materials.

5-Dimethylsilylcyclopentadiene (22). To a mechanically stirred solution of cyclopentadiene (64.4 mL, 0.780 mol) in THF (800 mL) was added dropwise a solution of butyllithium (1.56 M) in hexane (500 mL, 0.780 mol) at −25 °C over 1 h and the resulting solution was stirred for 0.5 h. After chlorodimethylsilane (95.2 mL, 0.858 mol) was added, the reaction mixture was allowed to stand at 0 °C over 2 h, after which the reaction mixture was diluted with pentane (150 mL) and quenched with water (200 mL). The organic layer was washed with cold water (500 mL × 2) and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under aspirator vacuum at 10–15 °C to give the crude product **22**.

5-Dimethylsilyl-2-cyclopentene-1,4-diol (23). A catalytic amount of 5,10,15,20-tetraphenylporphyrin (TPP, 240 mg) was added to a solution of the crude diene **22** in commercially available CH_2Cl_2 (3500 mL). After O_2 was bubbled for 30 min, the reaction mixture was cooled to −80 °C, and irradiated with a 400-W high pressure mercury lamp, while bubbling O_2 through the reaction mixture and continually stirring over 2.5 h at this temperature. During the reaction, TPP (240 mg × 4) was added in four portions at 30 min intervals. To the peroxide solution was added a suspension of zinc (226.5 g, 3.12 mol) and acetic acid (134 mL, 2.34 mol) in CH_2Cl_2 (300 mL) and then the mixture was activated by sonication. The reaction mixture was allowed to warm to −25 °C and stirred for 1 h, filtered through Celite, and concentrated. The remaining brownish residue was purified by column chromatography (silica-gel, hexane/ethyl acetate, 1/0 → 6/1 → 4/1 → 1/2) to yield diol **23** (76.51 g, 62.0% from cyclopentadiene) as a pale brown amorphous solid. **23**: R_f 0.15 (hexane/ethyl acetate, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (2H, d, J = 0.8 Hz), 4.47 (2H, dd, J = 3.7, 0.8 Hz), 3.87–3.95 (1H, m), 1.07 (1H, q, J = 3.7 Hz), 0.14 (6H, d, J = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.56, 77.80, 42.92, -5.76; IR (thin film) 3360, 3062, 2962, 2902, 2118, 1684, 1615, 1419, 1342, 1255, 1189, 1118, 1071, 884, 845, 735, 650, 596, 458 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_7H_{13}O_2Si$ $(M - H)^+$, 157.0685; found, 157.0684.

4-Dimethylsilyl-3,5-bis(2,2-dimethylpropanoyloxy)cyclopentene (24). Diol **23** (30.57 g, 0.193 mol) and 4-dimethylaminopyridine (1.18 g, 9.66 mmol) were dissolved in pyridine (193 mL). The solution was cooled to 0 °C and 2,2-dimethylpropanoyl chloride (71.3 mL, 0.579 mol) was added dropwise. The reaction mixture was stirred for 6 h at room temperature and evaporated in vacuo. The residue was dissolved in diethyl ether (250 mL) and partitioned with water (100 mL). The organic layer was separated, the aqueous layer extracted with diethyl ether (100 mL × 3), and the combined organic extracts washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 10/1) to yield dipivalate **24** (52.79 g, 83.8%) as a pale yellow oil. **24**: R_f 0.68 (hexane/ethyl acetate, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (2H, d, J = 1.1 Hz), 5.43 (2H, dd, J = 3.9, 1.1 Hz), 3.89–3.96 (1H, m), 1.41 (1H, dt, J = 3.9, 3.2 Hz), 1.19 (18H, s), 0.15 (6H, d, J = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.19, 135.11, 78.73, 38.30, 35.54, 27.05, −5.67; IR (thin film) 2974, 2876, 2124, 1729, 1541, 1483, 1462, 1398, 1369, 1325, 1282, 1255, 1149, 1085, 1033, 938, 882, 835, 772, 706, 656, 584 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{17}H_{30}O_4Si$ M^+, 326.1903; found, 326.1885.

2,5-Bis(2,2-dimethylpropanoyloxy)-3-cyclopenten-1-ol (25). The reaction flask was kept open to air throughout this reaction. A solution of dipivalate **24** (52.70 g, 0.161 mol) in commercially available THF (160 mL) and methanol (160 mL) was treated with anhydrous potassium fluoride (19.02 g, 0.327 mol, Nakalai Tesque Co. Ltd.) and potassium hydrogencarbonate (16.10 g, 0.161 mmol). A solution of 30% hydrogen peroxide in water (65.0 mL, 0.575 mol) was added to the stirred mixture portionwise over 15 min. After several minutes an exothermic reaction began, which was controlled by intermittent and brief cooling with a water bath to maintain the reaction temperature *between 40–45 °C*. The exothermic reaction ceased after a few hours and the reaction mixture was then stirred over 16 h at room temperature and quenched with 50% sodium thiosulfate pentahydrate (75 mL) while the temperature was maintained near 30 °C. The formed precipitate was filtered off, the filtrate was evaporated, and the residue was diluted with diethyl ether (200 mL). After separation of phases, the aqueous layer was extracted with ether (100 mL × 3) and the combined organic extracts was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 20/1 → 10/1) to yield alcohol **25** (37.53 g, 82.0%) as a colorless oil. **25** R_f 0.33 (hexane/ethyl acetate, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (2H, s), 5.36 (2H, d, J = 4.0 Hz), 4.15 (1H, brt, J = 4.0 Hz), 3.83 (1H, brs), 1.23 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.37, 132.14, 84.20, 83.88, 38.66, 27.08; IR (thin film) 3516, 2976, 2938, 2914, 2878, 1734, 1483, 1462, 1400, 1371, 1325, 1282, 1232, 1152, 1089, 1035, 984, 961,

882, 806, 775, 576, 489 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{15}H_{24}O_5$ M^+, 284.1616; found, 284.1620.

4-*t*-Butyldimethylsilyloxy-3,5-bis(2,2-dimethylpropanoyloxy)cyclopentene (26). Alcohol **25** (37.69 g, 0.133 mol) was dissolved in DMF (45 mL) and the solution was treated with *t*-butyldimethysilyl chloride (23.86 g, 0.158 mol) and imidazole (18.21 g, 0.267 mol). The reaction mixture was stirred for 2.6 h and then purified by column chromatography (silica-gel, hexane/ethyl acetate, 1/0 → 20/1) to yield silyl ether **26** (51.62 g, 97.7%) as a colorless oil. **26**: R_f 0.60 (hexane/ethyl acetate, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (2H, s), 5.38 (2H, d, J = 4.0 Hz), 4.36 (1H, t, J = 4.0 Hz), 1.23 (18H, s), 0.87 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.04, 132.47, 82.73, 82.36, 38.67, 27.19, 25.62, 17.91, −4.85; IR (thin film) 2984, 2936, 2864, 1736, 1481, 1464, 1398, 1367, 1325, 1280, 1143, 1033, 1007, 984, 963, 942, 882, 862, 839, 779, 671, 578, 491 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{21}H_{38}O_5Si$ M^+, 398.2489; found, 398.2496.

5-*t*-Butyldimethylsilyloxy-2-cyclopentene-1,4-diol (10). To a suspension of lithium aluminium hydride (14.82 g, 0.391 mol) in diethyl ether (200 mL) was added dropwise a solution of dipivaloate **26** (51.20 g, 0.128 mol) in diethyl ether (250 mL) over 30 min at −70 °C. The suspension was stirred for 0.5 h at this temperature, warmed to 0 °C and quenched with water (15 mL). The reaction mixture was diluted with diethyl ether (200 mL), treated with 15% sodium hydroxide (15 mL) followed by water (45 mL), and filtered. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica-gel, hexane/ethyl acetate, 10/1 → 1/1 → 1/2), to yield *meso*-diol **10** (28.01 g, 94.6%) as colorless needles. **10**: R_f 0.37 (hexane/ethyl acetate, 1/1); mp 117.6–118.0 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (2H, s), 4.42 (2H, brdd, J = 6.0, 4.0 Hz), 3.92 (1H, t, J = 4.0 Hz), 2.19 (2H, brs), 0.92 (9H, s), 0.15 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.98, 89.92, 81.33, 25.82, 18.06, −4.57; IR (KBr) 3296, 3070, 2956, 2930, 2904, 2860, 1475, 1381, 1352, 1323, 1253, 1212, 1158, 1102, 1023, 975, 872, 837, 783, 737, 727, 671, 601 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{10}H_{19}O_3Si$ $(M - CH_3)^+$, 215.1104; found, 215.1107; Anal. calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63%, found: C, 57.38; H, 9.42%.

(1*S*,4*R*,5*R*)-4-Acetoxy-5-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol ((−)-9). To a solution of *meso*-diol **10** (16.41 g, 71.2 mmol) in benzene (300 mL) and vinyl acetate (328 mL, 3.56 mol) was added lipase Amano AK (12.32 g, Amano Pharmaceutical Co. Ltd.) at 30 °C. After stirring for 13 h, the suspension was filtered through Celite and the solvent was removed. The residue was purified by column chromatography (silica-gel, hexane/ethyl acetate, 10/1 → 5.6/1 → 2.7/1) to yield acetate (−)-**9** (19.17 g, 98.8%) as a colorless oil. (−)-**9**: R_f 0.47 (hexane/ethyl acetate, 3/1); $[\alpha]_D^{25}$ −66.3° (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, dt, J = 6.1, 1.5 Hz), 5.81 (1H, dt, J = 6.1, 1.5 Hz), 5.32 (1H, dtd, J = 4.2, 1.5, 1.0 Hz), 4.47 (1H, dddt, J = 6.9, 4.2, 1.5, 1.0 Hz), 4.13 (1H, t, J = 4.2 Hz), 2.07 (3H, s), 2.00 (1H, d, J = 6.9 Hz), 0.90 (9H, s), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.62, 135.63, 130.61, 86.14, 82.94, 80.79, 25.69, 21.01, 18.00, −4.73, −4.79; IR (thin film) 3460, 3070, 2934, 2900, 2862, 1744, 1475, 1375, 1328, 1255, 1129, 1027, 967, 897, 864, 839, 781, 746, 673, 609, 582, 545 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_9H_{16}O_4Si$ $(MH - C_4H_9)^+$, 216.0818; found, 216.0824.

(4*R*,5*S*)-4-Acetoxy-5-*t*-butyldimethylsilyloxy-2-cyclopenten-1-one ((−)-7). To a suspension of Dess–Martin periodinane (44.31 g, 104.2 mmol) in CH_2Cl_2 (140 mL) was added dropwise a solution of alcohol (−)-**9** (18.98 g, 69.7 mmol) in CH_2Cl_2 (140 mL) over 5 min. The reaction mixture was stirred for 4 h, diluted with diethyl ether (500 mL), cooled to 0 °C, and quenched with 25% $Na_2S_2O_3{\cdot}5H_2O$–saturated $NaHCO_3$ solution (500 mL). After stirring for 20 min at room temperature, the organic layer was separated and the aqueous layer was extracted with ether (150 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated, and the remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 10/1 → 6/1) to yield acetate (−)-**7** (19.00 g, 100.0%) as a colorless oil. (−)-**7**: R_f 0.29 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{26}$ −151.3° (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, dd, J = 6.2, 1.9 Hz), 6.30 (1H, dd, J = 6.2, 1.4 Hz), 5.68 (1H, ddd, J = 3.1, 1.9, 1.4 Hz), 4.28 (1H, d, J = 3.1 Hz), 2.14 (3H, s), 0.92 (9H, s), 0.17 (3H, s), 0.13 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.42, 170.26, 155.34, 134.13, 78.83, 78.16, 25.62, 20.81, 18.32, −4.66, −5.28; IR (thin film) 2934, 2890, 2862, 1742, 1591, 1475, 1371, 1344, 1234, 1143, 1064, 1035, 982, 926, 841, 783, 681, 605, 538, 435 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{12}H_{19}O_4Si$, $(M - CH_3)^+$, 255.1053; found, 255.1050.

3,5-Diacetoxy-4-*t*-butyldimethylsilyloxycyclopentene (27). Diol **10** (382.1 mg, 1.66 mmol) and 4-dimethylaminopyridine (27.7 mg, 0.14 mmol) were dissolved in pyridine (8.0 mL). The solution was cooled to 0 °C and acetic anhydride (470 μL, 4.98 mmol) was added dropwise. The reaction mixture was stirred for 1 h at room temperature and evaporated in vacuo. The residue was dissolved in diethyl ether (20 mL) and partitioned with water (3 mL). The organic layer was separated, the aqueous layer was extracted with diethyl ether (5 mL × 3), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 10/1) to yield diacetate **27** (504.2 mg, 96.7%) as a colorless oil. **27**: R_f 0.60 (hexane/ethyl acetate, 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (2H, s), 5.40 (2H, d, J = 4.3 Hz), 4.34 (1H, t, J = 4.3 Hz), 2.09 (6H, s), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.47, 132.38, 82.59, 82.33, 25.60, 20.96, 17.97, −4.92; IR (thin film) 2960, 2934, 2902, 2862, 1746, 1475, 1365, 1323, 1226, 1135, 1108, 1027, 969, 897, 861, 839, 781, 675, 605, 497 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{15}H_{26}O_5Si$, M^+, 314.1549; found, 314.1556.

(1*R*,4*S*,5*S*)-4-Acetoxy-5-*t*-butyldimethylsilyloxy-2-cyclopenten-1-ol ((+)-9). To a suspension of *meso*-diacetate **27** (465.5 mg, 1.48 mmol) in 0.1 M (1 M = 1 mol dm^{-3}) phosphate buffer (pH 7.0, 14.8 mL) and MeOH (2.9 mL) was added lipase Amano PS (341.1 mg) at 30 °C. After stirring for 62 h, the reaction mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous layer was extracted with ethyl acetate (20 mL × 3), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 10/1 → 5.6/1 → 2.7/1) to yield acetate (+)-**9** (380.9 mg, 94.5%) as a colorless oil. (+)-**9**: $[\alpha]_D^{27}$ +67.2° (*c* 1.00, $CHCl_3$).

(4*S*,5*R*)-4-Acetoxy-5-*t*-butyldimethylsilyloxy-2-cyclopenten-1-one ((+)-7). To a suspension of Dess–Martin periodinane (887 mg, 2.09 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of alcohol (+)-**9** (380 mg, 1.4 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 4 h, diluted with diethyl ether (10 mL), cooled to 0 °C and quenched with 25% $Na_2S_2O_3{\cdot}5H_2O$-saturated $NaHCO_3$ solution (10 mL). After stirring for 20 min at

room temperature, the organic layer was separated and the aqueous layer was extracted with ether (5 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated, and the remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 10/1 → 6/1) to yield acetate (+)-**7** (371 mg, 98%) as a colorless oil. (+)-**7**: $[\alpha]_D^{27}$ +152.8° (*c* 1.02, $CHCl_3$).

Methyl (2*E*)-3-[(1*S*)-1,2-Isopropylidenedioxyethyl]-5-trimethylsilypent-2-en-4-ynoate (28). To a mixture of pyridinium dichromate (217.4 g, 0.577 mol) and powdered dry molecular sieves 3A (132.5 g) in CH_2Cl_2 (500 mL) was added dropwise a solution of alcohol **8** (65.90 g, 0.289 mol) in CH_2Cl_2 (250 mL) at room temperature over 30 min. The reaction mixture was stirred for 4 h; then the precipitate was filtered off and washed with ether. The filtrate was washed sequentially with saturated aqueous potassium hydrogensulfate (300 mL × 3) and then with saturated aqueous sodium hydrogencarbonate (200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by evaporation. The crude product was purified through column chromatography (florisil, hexane/ether, 3/1) to yield the corresponding ynone as a concentrate (ca. 60 g).

To a solution of the ynone in CH_2Cl_2 (510 mL) was added $Ph_3PCHCO_2CH_3$ at room temperature. After stirring for 2 h, the reaction mixture was diluted with hexane (1000 mL), filtered, and concentrated. The remaining residue was diluted with hexane (1000 mL) and the precipitate was filtered. The filtrate was concentrated and purified by column chromatography (silica-gel, hexane/ethyl acetate, 20/1) to yield **28** (60.30 g, 74%) as a colorless oil. **28**: R_f 0.58 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{25}$ +39.60° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (1H, d, J = 1.5 Hz), 4.62 (1H, td, J = 6.8, 1.5 Hz), 4.27 (1H, dd, J = 8.6, 6.7 Hz), 3.93 (1H, dd, J = 8.6, 6.7 Hz), 3.76 (3H, s), 1.46 (3H, s), 1.42 (3H, s), 0.24 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.17, 136.92, 123.53, 110.83, 109.04, 99.36, 77.58, 68.99, 51.43, 26.13, 25.71, −0.44; IR (thin film) 2992, 2960, 2904, 2152, 1734, 1626, 1458, 1437, 1375, 1317, 1253, 1212, 1154, 1073, 1036, 969, 919, 845, 762, 702, 636, 509 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{14}H_{22}O_4Si$, M^+, 282.1287; found, 282.1289.

(2*E*)-3-[(1*S*)-1,2-Isopropylidenedioxyethyl]-5-trimethylsilylpent-2-en-4-ynal (29). To a solution of ester **28** (136.26 g, 0.483 mol) in CH_2Cl_2 (200 mL) and hexane (1000 mL) was added dropwise a solution of DIBAL (1.0 M) in hexane (1000 mL, 1.00 mol) at −78 °C over 50 min. The reaction mixture was stirred for 1 h, allowed to warm up to 0 °C, and then diluted with ethyl acetate (900 mL). The reaction was quenched with saturated aqueous ammonium chloride (350 mL), saturated aqueous Rochelle salt (650 mL), and water (150 mL). After stirring overnight at room temperature, the two phases which formed were separated. The aqueous layer was extracted with ethyl acetate (800 mL), and the combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by evaporation. A solution of the crude product in commercially available CH_2Cl_2 (500 mL) was treated with Dess–Martin periodinane (224.0 g, 0.526 mol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The solution was diluted with ether (1200 mL), cooled to 0 °C, and then saturated aqueous sodium hydrogencarbonate solution containing 25% sodium thiosulfate pentahydrate (2700 mL) was poured into the reaction mixture portionwise. After stirring for 20 min at room temperature, the organic layer was separated and the aqueous layer was extracted with ether (750 mL × 2). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated, and the remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 20/1) to yield aldehyde **29** (97.3 g, 80.0%) as a colorless oil. **29**: R_f 0.55 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ +25.51° (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (1H, d, J = 8.1 Hz), 6.52 (1H, dd, J = 8.1, 1.5 Hz), 4.68 (1H, td, J = 6.6, 1.5 Hz), 4.30 (1H, dd, J = 8.6, 6.9 Hz), 3.97 (1H, dd, J = 8.6, 6.3 Hz), 1.47 (3H, s), 1.43 (3H, s), 0.24 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.30, 144.24, 133.34, 111.08, 109.38, 97.35, 77.05, 68.77, 26.10, 25.60, −0.56; IR (thin film) 2992, 2964, 2904, 2148, 1684, 1599, 1458, 1383, 1253, 1222, 1156, 1114, 1071, 959, 847, 762, 704 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{13}H_{20}O_3Si$, M^+, 252.1182; found, 252.1193.

(3*E*)-1,1-Dibromo-4-[(1*S*)-1,2-isopropylidenedioxyethyl]-6-trimethylsilylhexa-1,3-dien-5-yne (30). To a solution of carbon tetrabromide (78.5 g, 0.237 mol) in CH_2Cl_2 (140 mL) was added a solution of triphenylphosphine (64.4 g, 0.246 mol) in CH_2Cl_2 (120 mL) was added at −20 °C. After stirring for 40 min at this temperature, a solution of aldehyde **29** (20.7 g, 77.3 mmol) and triethylamine (13.0 mL, 93.3 mmol) in CH_2Cl_2 (150 mL) was added to the reaction mixture at −60 °C. The mixture was stirred for 2 h, allowed to warm to room temperature, diluted with hexane (900 mL), filtered, and concentrated. The remaining residue was diluted with hexane (500 mL) and the precipitate was filtered. The filtrate was evaporated and then purified by column chromatography (silica-gel, hexane/ethyl acetate, 50/1) to yield 1,1-dibromoalkene **30** (27.0 g, 86%) as a pale yellow oil. **30**: R_f 0.66 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ −11.9° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, d, J = 10.9 Hz), 6.62 (1H, dd, J = 10.9, 1.1 Hz), 4.54 (1H, td, J = 6.8, 1.1 Hz), 4.18 (1H, dd, J = 8.1, 6.5 Hz), 3.91 (1H, dd, J = 8.2, 7.1 Hz), 1.48 (3H, s), 1.42 (3H, s), 0.23 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.46, 132.51, 126.10, 110.36, 105.54, 99.87, 95.76, 77.69, 68.78, 26.27, 25.93, −0.27; IR (thin film) 2990, 2964, 2882, 2140, 1557, 1458, 1381, 1373, 1253, 1222, 1154, 1069, 969, 886, 845, 808, 760, 729, 702, 636, 555 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{14}H_{20}Br_2O_2Si$, M^+, 405.9599; found, 405.9636.

(2*S*,3*E*)-6,6-Dibromo-3-trimethylsilylethynyl-3,5-hexadiene-1,2-diol (33). A solution of acetonide **30** (26.2 g, 64.3 mmol) in methanol (175 mL) was treated with 4-toluenesulfonic acid monohydrate (6.12 g) at room temperature. The reaction mixture was stirred for 48 h at this temperature, and the solvent was removed. The residue was diluted with ether (200 mL), and washed with saturated aqueous sodium hydrogencarbonate (20 mL). The aqueous layer was extracted with ether (100 mL × 2), and the combined organic layer was washed with water (20 mL), then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining residue was purified by column chromatography (silica-gel, hexane /ethyl acetate, 50/1) to yield diol **33** (22.9 g, 97%) as a colorless amorphous solid. **33**: R_f 0.48 (hexane/ethyl acetate, 3/1); $[\alpha]_D^{25}$ −4.11° (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42 (1H, d, J = 10.7 Hz), 6.64 (1H, dd, J = 10.7, 1.0 Hz), 4.27 (1H, m), 3.84 (1H, brd, J = 10.9 Hz), 3.65 (1H, brdd, J = 10.9, 7.0 Hz), 3.31 (1H, brd, J = 5.3 Hz), 2.78 (1H, brs), 0.23 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.48, 132.25, 126.72, 106.24, 100.02, 95.76, 74.03, 65.50, −0.22; IR (thin film) 3374, 3024, 2962, 2900, 2142, 1551, 1410, 1311, 1253, 1178, 1125, 1089, 1046, 984, 932, 843, 801, 760, 741, 702, 638, 543 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{11}H_{16}Br_2O_2Si$, M^+, 365.9286; found, 365.9281.

(3*S*,3*E*)-6,6-Dibromo-1-*t*-butyldimethylsilyloxy-3-trimethylsilylethynyl-3,5-hexadien-2-ol (34). To a solution of diol **33**

(22.4 g, 60.8 mmol) in CH_2Cl_2 (160 mL) were was added *t*-butyldimethylsilyl chloride (10.1 g, 66.8 mmol), 4-dimethylaminopyridine (0.371 g, 3.04 mmol), and triethylamine (14.3 mL, 102 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 19 h. The solution was diluted with ether (240 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (40 mL × 2), and the combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 20/1) to yield **34** (26.4 g, 90%) as a colorless oil. **34**: R_f 0.42 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{20}$ −19.5° (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 10.7 Hz), 6.65 (1H, dd, J = 10.7, 1.5 Hz), 4.20 (1H, m), 3.85 (1H, dd, J = 10.1, 3.8 Hz), 3.64 (1H, brdd, J = 10.1, 6.3 Hz), 0.90 (9H, s), 0.23 (9H, s), 0.082 (3H, s), 0.075 (3H,s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.70, 131.96, 127.15, 105.46, 100.51, 94.99, 73.57, 65.70, 25.85, 18.32, −0.19, −5.37; IR (thin film) 3412, 2960, 2930, 2886, 2862, 2144, 1549, 1473, 1392, 1363, 1309, 1253, 1180, 1114, 1006, 934, 843, 779, 760, 700, 638, 420 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{17}H_{30}Br_2O2Si_2$, M^+, 480.0151; found, 480.0161.

(2*S*,3*E*)-1-*t*-Butyldimethylsilyloxy-3-trimethylsilylethynyl-hex-3-ene-5-yn-2-ol (35). To a solution of 1,1-dibromoalkene **34** (26.4 g, 54.8 mmol) in THF (556 mL) was added dropwise a solution of *n*-butyllithium (1.56 M) in hexane (110 mL, 0.172 mol) was added dropwise over 30 min at −100 °C. The mixture was stirred at this temperature for 0.5 h and quenched with saturated aqueous ammonium chloride (80 mL). After separation of the layers, the aqueous layer was extracted with ether (40 mL), and the combined organic layer was washed with saturated aqueous ammonium chloride (40 mL) and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by column chromatography (silica-gel, hexane/ethyl acetate, 50/1) to yield **35** (16.4 g, 93%) as a colorless amorphous solid. **35**: R_f 0.52 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{22}$ +23.6° (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (1H, dd, J = 2.4, 2.0 Hz), 4.23 (1H, m), 3.87 (1H, dd, J = 10.2, 3.9 Hz), 3.64 (1H, dd, J = 10.2, 6.4 Hz), 3.31 (1H, dd, J = 2.4, 0.8 Hz), 2.76 (1H, brd, J = 4.4 Hz), 0.90 (9H, s), 0.22 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.86, 114.92, 104.66, 100.63, 84.32, 80.84, 73.32, 65.75, 25.82, 18.30, −0.20, −5.38, −5.44; IR (thin film) 3454, 3318, 2960, 2932, 2862, 2148, 1473, 1392, 1363, 1309, 1253, 1114, 1007, 891, 841, 779, 762, 698, 634 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{17}H_{30}O_2Si_2$, M^+, 322.1784; found, 322.1770.

(3*S*,4*R*)-3,4-Epoxy-3-[(1*R*)-1,2-isopropylidenedioxyethyl]-1-trimethylsilyl-1,5-hexadiyne (38). To a suspension of powdered molecular sieves 4A (45.8 g) in CH_2Cl_2 (400 mL) cooled at −23 °C, was added titanium(IV) isopropoxide (72.0 mL, 0.244 mol) and D-(−)-diethyl tartrate (45.9 mL, 0.269 mol), and the mixture was stirred for 20 min. To the stirred solution at −23 °C were added a solution of enediyne **35** (73.3 g, 0.227 mmol) in CH_2Cl_2 (160 mL) and then a solution of *t*-butyl hydroperoxide (5 M) in CH_2Cl_2 (260 mL, 1.30 mol) was added. The reaction mixture was stirred for 96 h while maintaining the temperature at −23 °C. The reaction was quenched with saturated aqueous sodium thiosulfate (1000 mL), and the solution was diluted with ether (1200 mL) and washed with water (300 mL). The precipitate was filtered and washed with ether. After separation of layers, the aqueous layer was extracted with ether (700 mL), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. After the remaining oil was dissolved in THF (240 mL) and cooled to 0 °C, acetic acid (30 mL) and water (120 mL) were added to the mixture. The reaction mixture was allowed to warm to room temperature and was then stirred for 17 h. The solution was diluted with ether (300 mL), then cooled to 0 °C, and quenched with saturated aqueous sodium bicarbonate (750 mL). The aqueous layer was separated and extracted with ether (120 mL × 2). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. After purification through column chromatography (silica, hexane/ethyl acetate, 2.8/1), the corresponding epoxy diol was dissolved in CH_2Cl_2 (450 mL). The solution was treated with a mixture of 2,2-dimethoxypropane (81.0 mL, 0.659 mol) and pyridinium 4-toluenesulfonate (5.77 g, 23.0 mmol) at room temperature. The mixture was stirred for 18 h at this temperature, followed by refluxing with molecular sieves **4A** for 2 h. After cooling to room temperature, the solution was diluted with hexane (400 mL), and washed with water (100 mL) and saturated aqueous sodium hydrogencarbonate (60 mL). The aqueous layer was extracted with hexane (120 mL), and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining residue was purified by column chromatography (silica-gel, hexane/ethyl acetate, 80/1 → 60/1) to yield **38** (39.9 g, 66%) as a colorless oil. **38**: R_f 0.43 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ +65.8° (*c* 1.05, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.21 (1H, dd, J = 8.6, 6.7 Hz), 4.10 (1H, dd, J = 8.6, 6.1 Hz), 4.01 (1H, t, J = 6.6 Hz), 3.63 (1H, d, J = 1.6 Hz), 2.47 (1H, d, J = 1.6 Hz), 1.45 (3H, s), 1.35 (3H, s), 0.18 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.95, 97.69, 93.81, 77.53, 75.80, 74.62, 67.05, 57.87, 49.52, 26.06, 25.28, −0.42; IR (thin film) 3288, 2992, 2966, 2904, 2182, 2132, 1458, 1375, 1253, 1218, 1156, 1077, 1009, 951, 847, 762, 702, 663, 586, 540, 509, 426 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{14}H_{20}O_3Si$, M^+, 264.1182; found, 264.1183.

(3*R*,4*S*)-3,4-Epoxy-4-[(1*R*)-1,2-isopropylidenedioxyethyl]-1-triethylsilyl-1,5-hexadiyne (6). To a solution of alkyne **38** (39.9 g, 0.151 mol) in THF (600 mL) was added a solution of *n*-butyllithium (1.56 M) in hexane (107 mL, 0.167 mol) dropwise over 20 min at −100 °C. After stirring for 30 min at this temperature, the mixture was treated with triethylsilyl chloride (30.5 mL, 0.182 mol), and then stirred for a further 30 min. The reaction was quenched with water (120 mL), and the solution was allowed to warm to room temperature. The separated aqueous layer was extracted with hexane (80 mL), and the combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue obtained was dissolved in methanol (400 mL), and then the solution was treated with potassium fluoride dihydrate (14.4 g, 0.152 mol) at −10 °C. After stirring for 36 h at this temperature, the reaction was diluted with hexane (600 mL) and then quenched with water (200 mL). After separation of layers, the aqueous layer was extracted with hexane (200 mL × 2), and the combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining oil was purified by column chromatography (silica-gel, hexane /ethyl acetate, 100/1 → 50/1) to yield **6** (34.5 g, 81%) as a colorless oil. **6**: R_f 0.56 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{22}$ +64.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1H, dd, J = 8.6, 6.7 Hz), 4.10 (1H, dd, J = 8.6, 6.2 Hz), 4.05 (1H, t, J = 6.4 Hz), 3.63 (1H, s), 2.47 (1H, s), 1.47 (3H, s), 1.35 (3H, s), 0.99 (9H, t, J = 7.8 Hz), 0.61 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.97, 99.41, 90.29, 77.16, 75.79, 75.41, 66.82, 57.89, 49.85, 26.03, 25.11, 7.30, 4.08; IR (thin film) 3284, 2960, 2916, 2880, 2188, 2130, 1460, 1375, 1263,

1218, 1156, 1077, 1019, 967, 949, 891, 855, 824, 739, 576, 513, 416 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{17}H_{26}O_3Si$, M^+, 306.1652; found, 306.1644.

(4*S*,5*R*)-4-Acetoxy-5-*t*-butyldimethylsilyloxy-2-iodo-2-cyclopenten-1-one (39). To a solution of cyclopentenone (−)-**7** (5.94 g, 22.0 mmol) in carbon tetrachloride (25 mL) and pyridine (25 mL) was added dropwise a solution of iodine (11.15 g, 43.9 mmol) in carbon tetrachloride (40 mL) and pyridine (40 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 4 h. The mixture was diluted with ether (200 mL) and washed with water (150 mL). The separated aqueous layer was extracted with ether (100 mL × 2), and the combined organic extracts were washed with 1 M HCl (150 mL × 2), water (100 mL), and saturated $Na_2S_2O_3$ (60 mL), and dried over anhydrous magnesium sulfate. After filtration and concentration, the remaining oil was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 10/1) to yield iodocyclopenenone **39** (8.41 g, 96.6%) as a pale yellow oil. **39**: R_f 0.70 (hexane/ethyl acetate, 3/1); $[\alpha]_D^{25}$ −143.9° (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 2.7 Hz), 5.60 (1H, dd, J = 2.8,2.2 Hz), 4.33 (1H, d, J = 2.8 Hz), 2.14 (3H, s), 0.92 (9H, s), 0.18 (3H, s), 0.14 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.56, 169.96, 160.94, 103.83, 79.84, 75.65, 25.50, 20.65, 18.21, −4.56, −5.39; IR (thin film) 2958, 2934, 2888, 2862, 1744, 1576, 1473, 1373, 1255, 1228, 1168, 1141, 1087, 1036, 980, 888, 841, 783, 756, 698, 677, 547 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_9H_{12}IO_4Si$, $(M - C_4H_9)^+$, 338.9550; found, 338.9546.

(1*R*,4*R*,5*S*)-4-Acetoxy-1,5-bis(*t*-butyldimethylsilyloxy)-2-iodo-2-cyclopentene-1-carbonitrile (40). Cyclopentenone **39** (5.15 g, 13.0 mmol) was azeotroped with toluene (10 mL × 3). A solution of enone **39** in CH_2Cl_2 (26 mL) was treated with *t*-butyldimethylsilyl cyanide (2.87 g, 20.3 mmol) and then anhydrous ZnI_2 (1.09 g, 3.40 mmol) at room temperature and stirred for 42 h. The mixture was diluted with ether (100 mL) and quenched with water (10 mL). The aqueous layer was extracted with ether (10 mL × 3), and the combined organic layers were washed with brine (8 mL), then dried over anhydrous magnesium sulfate. Purification by flash column chromatography (silica-gel, hexane/ethyl acetate, hexane → 40/1 → 30/1) provided nitrile **40** (6.71 g, 95.9%) as a colorless oil. **40**: R_f 0.68 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ −76.8° (*c* 1.05, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.46 (1H, dd, J = 2.0, 0.7 Hz), 5.22 (1H, dd, J = 4.1, 2.0 Hz), 4.29 (1H, dd, J = 4.1, 0.7 Hz), 2.09 (3H, s), 0.95 (9H, s), 0.94 (9H, s), 0.44 (3H, s), 0.30 (3H, s), 0.18 (3H, s), 0.12 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.98, 141.20, 116.32, 103.63, 84.44, 81.87, 25.72, 25.50, 20.73, 18.13, 18.02, −2.78, −3.01, −4.20, −4.82; IR (thin film) 2960, 2934, 2900, 2862, 1750, 1473, 1392, 1365, 1255, 1228, 1143, 1081, 1027, 980, 940, 876, 841, 783, 679 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{19}H_{33}INO_4Si_2$, $(M - CH_3)^+$, 522.0992; found, 522.0994.

(1*R*,4*R*,5*S*)-1,5-Bis(*t*-butyldimethylsilyloxy)-2-cyclopentene-1-carbonitrile (41). To a solution of acetate **40** (6.62 g, 12.32 mmol) in methanol (26 mL) was added K_2CO_3 (435.0 mg, 3.15 mmol) at room temperature. The reaction mixture turned black immediately and was stirred for 2 h. The solvent was removed under aspirator vacuum and the residue was dissolved in ether (50 mL) and water (10 mL). After separation of the phases, the aqueous layer was extracted with ether (10 mL × 2). The combined organic extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The remaining residue was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 20/1) to yield alcohol **41** (5.23 g, 85.6%) as a colorless amorphous solid. **41**: R_f 0.46 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{23}$ −14.4° (*c* 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.43 (1H, dd, J = 2.0, 0.5 Hz), 4.42 (1H, ddd, J = 8.0, 4.2, 2.0 Hz), 4.07 (1H, dd, J = 4.2, 0.5 Hz), 2.00 (1H, d, J = 8.0 Hz), 0.96 (9H, s), 0.93 (9H, s), 0.42 (3H, s), 0.29 (3H, s), 0.20 (3H, s), 0.18 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.85, 116.62, 101.68, 88.03, 84.57, 80.51, 25.85, 25.55, 18.13, 18.10, −2.85, −2.99, −3.92, −4.85; IR (thin film) 3458, 2934, 2902, 2862, 2248, 1597, 1473, 1408, 1365, 1311, 1259, 1195, 1151, 1110, 1067, 1031, 1007, 977, 940, 839, 783 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{17}H_{33}INO_3Si_2$, $(M - CH_3)^+$, 480.0886; found, 480.0882.

(1*R*,4*R*,5*S*)-1,5-Bis(*t*-butyldimethylsilyloxy)-2-iodo-4-methoxymethoxy-2-cyclopentene-1-carbonitrile (5). A solution of alcohol **41** (1.10 g, 2.22 mmol) in CH_2Cl_2 (2.2 mL) at 0 °C was treated with diisopropylethylamine (1.16 mL, 6.66 mmol) and chloromethyl methyl ether (253 μL, 3.33 mmol), stirred at 0 °C for 30 min and then refluxed at 40 °C for 4 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue was dissolved in ether (30 mL). The solution was washed with saturated NH_4Cl (10 mL), and the aqueous layer was extracted with ether (10 mL × 2). The combined organic extracts were washed with brine (8 mL), dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 50/1) to yield ether **5** (1.19 g, 99.3%). **5**: R_f 0.74 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ −9.8° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, dd, J = 1.6, 0.4 Hz), 4.72 (1H, d, J = 6.8 Hz), 4.68 (1H, d, J = 6.8 Hz), 4.20 (1H, dd, J = 4.4, 1.6 Hz), 4.18 (1H, dd, J = 4.4, 0.4 Hz), 3.39 (3H, s), 0.96 (9H, s), 0.93 (9H, s), 0.44 (3H, s), 0.29 (3H, s), 0.17 (3H, s), 0.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.31, 116.64, 101.44, 97.39, 87.50, 86.16, 83.75, 55.78, 25.83, 25.59, 18.20, 18.06, −2.54, −2.88, −4.00, −4.76; IR (thin film) 2934, 2862, 1603, 1473, 1365, 1305, 1257, 1216, 1152, 1038, 1000, 940, 920, 841, 781, 712, 679 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{19}H_{35}INO_4Si_2$, $(M - CH_3)^+$, 524.1148; found, 524.1160.

(1*R*,4*R*,5*S*)-1,5-Bis(*t*-butyldimethylsilyloxy)-2-{(3*S*,4*R*)-3,4-epoxy-3-[(1*R*)-1,2-isopropylidenedioxyethyl]-6-triethylsilyl-1,5-hexadiynyl}-4-methoxymethoxy-2-cyclopentene-1-carbonitrile (44). A degassed solution of iodocyclopentene **5** (0.340 g, 0.572 mmol), alkyne **6** (0.316 g, 1.03 mmol) and *N*,*N*-diisopropylethylamine (0.95 mL, 1.85 mmol) in DMF (0.9 mL) was added to a suspension of bis(acetonitorile)dichloropalladium(II) (15.3 mg, 59.0 μmol) and copper(I) iodide (22.5 mg, 0.118 mmol) in DMF (1.0 mL) at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous ammonium chloride, diluted with ether, and the aqueous layer was extracted with ether. The combined organics were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 50/1) to yield enediyne **44** (0.288 g, 72%) as a colorless oil. **44**: R_f 0.43 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{27}$ +21.8° (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (1H, d, J = 2.0 Hz), 4.71 (1H, d, J = 7.2 Hz), 4.67 (1H, d, J = 7.2 Hz), 4.26 (1H, dd, J = 5.0, 2.0 Hz), 4.20 (1H, dd, J = 8.1, 6.4 Hz), 4.15 (1H, dd, J = 6.4, 6.0 Hz), 4.11 (1H, d, J = 5.0 Hz), 4.05 (1H, dd, J = 8.1, 6.0 Hz), 3.71 (1H, s), 3.10 (3H, s), 1.46 (3H, s), 1.35 (3H, s), 0.98 (9H, t, J = 7.9 Hz), 0.94 (9H, s), 0.92 (9H, s), 0.61 (6H, q, J = 7.9 Hz), 0.38 (3H, s), 0.29 (3H, s), 0.15 (3H, s), 0.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.83, 126.57, 116.40, 110.99, 99.22, 97.45, 90.86, 88.65, 87.53, 84.80, 80.27, 79.93, 77.32, 75.48, 66.85, 58.27, 55.62, 49.88, 26.01, 25.73, 25.54, 25.08, 18.14, 17.97, 7.36, 7.05, −2.84, −3.09, −4.22, −4.78; IR (thin film)

2960, 2934, 2890, 2864, 1464, 1375, 1303, 1259, 1216, 1154, 1079, 1042, 1006, 843, 783, 729, 681, 582, 435 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{37}H_{63}O_7Si_3$, M^+, 717.3913; found, 717.3915.

(1*R*,4*R*,5*S*)-1,5-Bis(*t*-butyldimethylsilyloxy)-2-{(3*S*,4*R*)-3,4-epoxy-3-[(1*R*)-1,2-isopropylidenedioxyethyl]-1,5-hexadiynyl}-4-methoxymethoxy-2-cyclopentene-1-carbonitrile (45). A solution of silylalkyne **44** (0.415 g, 0.578 mmol) in methanol (7.0 mL) was treated with potassium carbonate (43.6 mg, 0.316 mmol) at room temperature, and the mixture was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was diluted with ether (10 mL). The solution was washed with water (10 mL), and the aqueous layer was extracted with ether (5 mL × 2), and the combined organic extracts were washed with brine, then dried over anhydrous magnesium sulfate. After filtration and concentration, the remaining oil was purified by flash column chromatography (silica-gel, hexane/ethyl acetate, 10/1) to yield alkyne **45** (0.223 g, 64%) as a colorless oil. **45**: R_f 0.22 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{26}$ +22.4° (*c* 1.02, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (1H, d, J = 2.1 Hz), 4.71 (1H, d, J = 6.9 Hz), 4.67 (1H, d, J = 6.9 Hz), 4.26 (1H, dd, J = 4.4, 2.0 Hz), 4.23 (1H, dd, J = 8.5, 6.1 Hz), 4.14 (1H, t, J = 6.1 Hz), 4.12 (1H, d, J = 3.5 Hz), 4.07 (1H, dd, J = 8.6, 6.1 Hz), 3.70 (1H, d, J = 1.7 Hz), 3.37 (3H, s), 2.49 (1H, d, J = 1.7 Hz), 1.47 (3H, s), 1.35 (3H, s), 0.94 (9H, s), 0.90 (9H, s), 0.35 (3H, s), 0.29 (3H, s), 0.16 (3H, s), 0.13 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.30, 122.64, 116.52, 110.06, 97.30, 88.05, 87.15, 85.21, 80.99, 80.10, 77.06, 75.54, 75.41, 66.90, 58.07, 55.65, 49.37, 26.02, 25.72, 25.51, 25.08, 18.10, 17.96, −2.82, −3.19, −4.31, −4.83; IR (thin film) 3312, 2934, 2894, 2862, 1475, 1375, 1259, 1216, 1154, 1104, 1077, 1042, 1004, 978, 922, 841, 782, 677, 441 cm^{-1}; MS (EI, 70 eV) m/z (rel intensity) 588 (26), 546 (100), 516 (62).

(1*R*,4*R*,5*S*)-1,5-Bis(*t*-butyldimethylsilyloxy)-2-{(3*S*,4*R*)-3,4-epoxy-3-[(1*R*)-1,2-isopropylidenedioxyethyl]-1,5-hexadiynyl}-4-methoxymethoxy-2-cyclopentene-1-carbaldehyde (4). To a solution of nitrile **45** (112.5 mg, 0.186 mmol) in CH_2Cl_2 (2 mL) was added a solution of diisobutylalminium hydride (0.96 M) in hexane (290 μL, 0.278 mmol) at −60 °C. The mixture was stirred for 4 h and then allowed to warm to 0 °C. The reaction was quenched with saturated aqueous ammonium chloride (1.0 mL); then ethyl acetate (15 mL), saturated aqueous Rochelle salt (12 mL), and water were added to the solution. After vigorous stirring for 2 h, the mixture turned clear and the phases were separated. The aqueous layer was extracted with ethyl acetate (10 mL), and the combined organic phase was washed with brine, dried over anhydrous magnesium sulfate, filtrated, and concentrated. The remaining oil was purified by flash column chromatography (silica gel, hexane/ethyl acetate, hexane → 6/1) to yield aldehyde **4** (107.80 mg, 95%) as a colorless oil. (Aldehyde **4**): R_f 0.22 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{26}$ −39.8° (*c* 1.13, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.37 (1H, s), 6.50 (1H, t, J = 1.6 Hz), 4.74 (1H, d, J = 6.9 Hz), 4.69 (1H, d, J = 6.9 Hz), 4.34 (2H, d, J = 1.6 Hz), 4.24–3.88 (3H, m), 3.66 (1H, d, J = 1.9 Hz), 3.40 (3H, s), 2.42 (1H, d, J = 1.9 Hz), 1.44 (3H, s), 1.35 (3H, s), 0.93 (9H, s), 0.84 (9H, s), 0.23 (3H, s), 0.22 (3H, s), 0.09 (3H, s), 0.06 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.12, 143.18, 125.69, 110.95, 97.26, 92.02, 89.53, 87.05, 86.00, 81.26, 77.24,, 75.37, 75.15, 66.84, 58.01, 55.63, 49.23, 25.90, 25.61, 25.50, 25.07, 18.55, 17.83, −2.05, −2.29, −4.41, −5.18; IR (thin film) 3314, 2934, 2894, 2862, 1746, 1475, 1375, 1257, 1216, 1154, 1102, 1077, 1042, 1006, 922, 841, 781, 677, 433, 414 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{31}H_{50}O_8Si_2$, M^+, 606.3044; found, 606.3041.

(1*R*,2*R*,5*R*,6*S*,11*R*,12*S*)-1,12-Bis(*t*-butyldimethylsilyloxy)-5,6-epoxy-6-[(1*R*)-1,2-isopropylidenedioxyethyl]-11-methoxymethoxybicyclo[7.3.0]dodec-9-ene-3,7-diyn-2-ol (3). A suspension of anhydrous cerium chloride (520.1 mg, 2.11 mmol) in THF (10 mL, freshly distilled from sodium-benzophenone) was initially stirred over 12 h. To a separate solution of butyllithium (1.56 M) in hexane (1.60 mL, 2.50 mmol) was added hexamethyldisilazane (680 μL, 3.22 mmol) dropwise at 0 °C. The solution of lithium amide was stirred for 30 min and then added to the suspension of cerium(III) chloride at −40 °C. The mixture was allowed to warm to −20 °C gradually and then stirred for 1 h. To the mixture of cerium chloride and lithium amide was added a solution of aldehyde **4** (107.8 mg, 0.178 mmol) in THF (35 mL) dropwise at −20 °C. After stirring for 40 min, the reaction was quenched with saturated aqueous ammonium chloride; the precipitate which formed was filtered off and then washed with ethyl acetate. The filtrate was washed with saturated aqueous ammonium chloride and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, then concentrated, and the remaining residue was purified by flash column chromatography (florisil, hexane/ethyl acetate, 10/1) to yield the desired bicyclo[7.3.0]dodecenediyne **3** (75.5 mg, 70%) as a colorless oil. 3: R_f 0.18 (hexane/ethyl acetate, 6/1); $[\alpha]_D^{28}$ −19.8° (*c* 1.10, CHCl3); 1H NMR (600 MHz, $CDCl_3$) δ 6.32 (1H, t, J = 1.3 Hz, C12H), 4.71 (1H, d, J = 6.8 Hz, OCH_2OCH_3), 4.68 (1H, d, J = 6.8 Hz, OCH_2OCH_3), 4.47 (1H, dd, J = 4.7, 1.6 Hz, C8H), 4.26 (1H, t, J = 6.7 Hz, C1′H), 4.246 (1H, dd, J = 5.0, 1.3 Hz, C11H), 4.243 (1H, d, J = 5.0 Hz, C10H), 4.20 (1H, dd, J = 8.4, 6.7 Hz, C2′H), 4.04 (1H, dd, J = 8.4, 6.7 Hz, C2′H), 3.58 (1H, d, J = 1.6 Hz,C5H), 3.37 (3H, s, OCH_2–OCH_3), 2.88 (1H, d, J = 4.6 Hz, C8OH), 1.39 (3H, s, $C(CH_3)_2$), 1.35 (3H, s, $C(CH_3)_2$), 0.91 (9H, s, $Si(CH_3)_2C(CH_3)_3$), 0.90 (9H, s, $Si(CH_3)_2C(CH_3)_3$), 0.19 (3H, s, $Si(CH_3)_2C(CH_3)_3$), 0.17 (3H, s, $Si(CH_3)_2C(CH_3)_3$), 0.14 (3H, s, $Si(CH_3)_2C(CH_3)_3$), 0.12 (3H, s, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.85, 127.53, 110.78, 97.00, 96.10, 88.55, 88.49, 88.42, 87.35, 87.19, 85.43, 74.60, 67.65, 67.03, 63.73, 55.55, 53.54, 26.18, 25.80, 25.66, 25.23, 18.31, 17.91, −2.18, −2.66, −4.41, −5.00; IR (thin film) 3524, 2934, 2892, 2862, 1744, 1473, 1375, 1257, 1216, 1152, 1100, 1040, 1006, 965, 920, 839, 758, 677, 565, 507 cm^{-1}; HRMS (EI, 70 eV) *m/z*: calcd for $C_{31}H_{50}O_8Si_2$, M^+, 606.3044; found, 606.3056.

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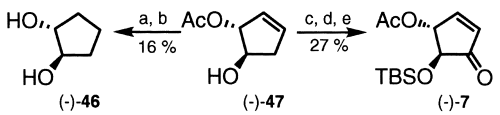

(-)-**46** (-)-**47** (-)-**7**

a) H_2, 5% Pd-C, MeOH, 19 h. b) K_2CO_3, MeOH, 6 h. c) TBSCl, imidazole, DMF, 2.5 h. d) NBS, pyridine, CCl_4, *hν*, 2h. e) DMSO, $NaHCO_3$, 50 °C, 13 h.

Scheme 9.