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First total synthesis of modiolide A, based on the whole-cell yeast-catalyzed asymmetric reduction of a propargyl ketone

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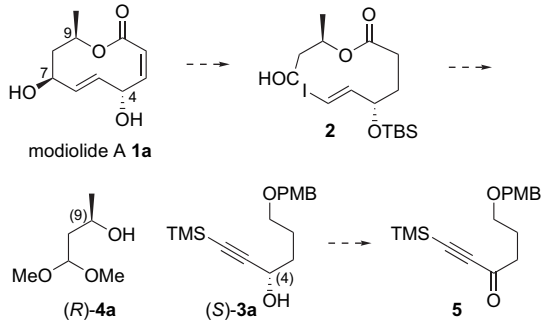
Abstract—While the first total synthesis of modiolide A (**1a**), a 10-membered ring lactone with a marine-origin was achieved, an important chiral building block for constructing the chirality at C-4 in **1a**, (*S*)-6-[(4-methoxybenzyl)oxy]-1-trimethylsilyl-1-hexyn-3-ol (**3a**) was obtained in as high as 96.1% ee. Asymmetric reduction of a silylated propargyl ketone (**5**) mediated by whole-cell of *Pichia minuta* IAM 12215 was established. This yeast-mediated reduction was also applicable to provide stereochemically pure (3*S*,5*R*)-5-[(4-methoxybenzyl)-oxy]-1-trimethylsilyl-1-hexyn-3-ol (**15**), a synthetic intermediate for the related 10-membered lactone, tuckolide (**16**).

1. Introduction

Naturally occurring 10-membered ring lactones from fungal metabolites present a wide variety of bioactive substances. Among them, modiolide A (**1a**) was isolated by Kobayashi and co-workers[1] as antibacterial and antifungal substance from marine-origin microorganisms.

Inspired by Pilli's approach to construct 10-membered ring lactones,[2,3] the synthesis of modiolide A (**1a**) was designed based on the intramolecular Nozaki–Hiyama–Kishi coupling reaction[4] of the intermediate **2** with the concomitant establishment of the C-7 stereogenic center (Scheme 1). The precursor **2** was further divided into two segments, a propargyl alcohol (*S*)-**3a**, which constitutes the chiral center at C-4 and an acetal alcohol (*R*)-**4a**[5,6] with the chiral center at C-9. We chose the whole-cell yeast-mediated reduction[7] of the corresponding propargyl ketone **5**. There are a number of methods for preparation of enantiomerically enriched forms of propargyl alcohols, for example, chirally modified boranes[8] or transition metal complex-mediated reduction[9] of propargyl ketones, and the addition of acetylides on aldehydes, in the presence of chiral Lewis bases.[10,11] Compared with them, the whole-cell yeast-catalyzed reduction has an advantage that the chiral catalyst is supplied in a large quantity and self-reproducible manner, by a simple incubation from a seed culture.



Scheme 1.

2. Results and discussion

2.1. Preparation of propargyl alcohol (*S*)-3a by whole-cell yeast-catalyzed reduction

The first task is the preparation of an propargylic synthon (*S*)-**3a** involving the C-4 chiral center. Toward this end, an aldehyde **6**[12] was treated with TMSCCLi and subsequent Dess–Martin periodinane oxidation provided the substrate **5** in 93% yield (Scheme 2). Then, cultured cells of four recently developed yeast strains, *Pichia minuta* IAM 12215, *Pichia angusta* IAM 12895, *Trichosporon cutaneum* IAM12206, *Candida floricola* IAM 13115, which were screened as the ones capable of reducing hydrophobic, bulky carbonyl compounds,[13] were applied. Among the above four strains, only *P. minuta* accepted the ketone **5** as the substrate.

The incubation conditions were summarized in Table 1. The reduction smoothly proceeded only under the following

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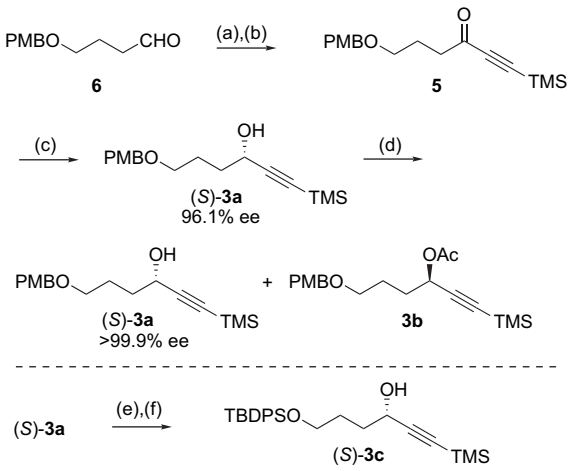


Scheme 2. (a) TMSCCLi, THF; (b) Dess–Martin periodinane, CH_2Cl_2 93%; (c) *P. minuta* IAM 12215, 88%; (d) *P. cepacia* lipase (Amano PS-C), vinyl acetate, *i*-Pr_2O, 94% recovery for **3a**; (e) DDQ, CH_2Cl_2–H_2O, 54%; (f) TBDPSCl, imidazole, DMF, quantitative.

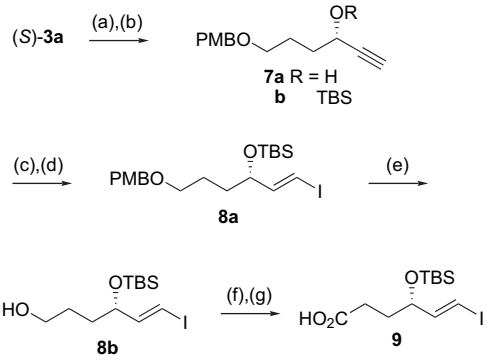
Table 1. *Picha minuta*-mediated reduction of **5**

Entry	Pre-incubation time (h)	Yield (**3a**, %)	ee (**3a**, %)
1	24	89	94.0
2	26	92	93.0
3	29	88	96.1
4	30	91	91.0
5	35	78	88.0
6	42	No reaction	NA

condition, due to the substantially inhibitory property of **5**. The substrate was directly introduced into the fermentation broth at low substrate concentration (0.2%). With a fixed charge of whole-cell yeast-enzyme catalysts [w/wcw (wet cell weight), 0.05], the period of pre-incubation was examined. Better rate of the reduction as well as the enantioselectivity were observed in yeast cells in the relatively younger stage, with the pre-incubation of 24–30 h (entries 1–4). (*S*)-Alcohol **3a** with 96.1% ee became available in 88% yield (entry 3). Along with the prolonged pre-incubation, the enantioselectivity decreased; finally, there was no reaction after 42 h pre-incubation (entry 6). It was noteworthy that the pre-incubation required plentiful oxygen supply (see Section 4.3), otherwise, there was observed almost no reduction.

The chiral starting materials with a supply in certain quantity as well as the consistent enantiomeric purity only deserve the chiral pool for natural product synthesis. For this purpose, integrated combination of asymmetric synthesis and enzyme-mediated kinetic resolution have so far been developed.[14–16] In this particular case, the ee of (*S*)-**3a** was further enhanced to be over 99.9% by the treatment with *Pseudomonas cepacia* lipase (Amano PS-C)[17] in the presence of vinyl acetate in 94% as the recovery even from the starting material with 92.4% ee (for detail, see Section 4.5), via the removal of contaminating (*R*)-**3a** as the acetate (*R*)-**3b**. The (*S*)-absolute configuration of the above-mentioned **3a** was confirmed by the derivatization to **3c**. The oxidative deprotection of PMB with DDQ (54%) and the subsequent regioselective protection on the primary hydroxyl group provided the known (*S*)-**3c**,[18] by comparison of the sign of rotation (Scheme 2, see Section 4.4.1).

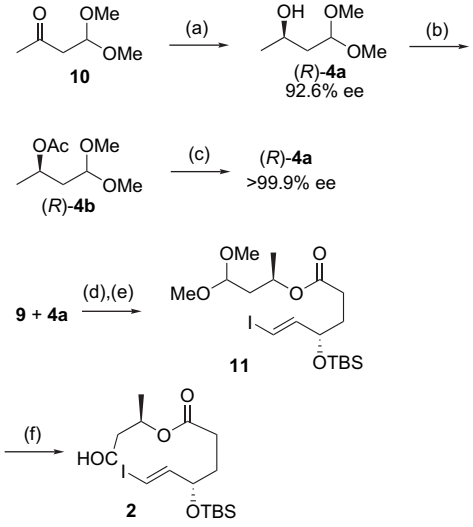
The acetylenic TMS group of (*S*)-**3a** was removed and the free hydroxyl group was then protected as TBS ether to give **7b** (99%, Scheme 3). The (*E*)-alkenyl iodide structure in **8a** was provided (74%) by way of an alkenylstannane. At this stage, the PMB protective group was removed (97%), and the subsequent oxidation of primary alcohol yielded the requisite carboxylic acid **9** (95%, Scheme 3).



Scheme 3. (a) K_2CO_3, MeOH; (b) TBSCl, imidazole, DMF, 99%; (c) *n*-Bu_3SnH (1.2 equiv), AIBN (0.04 equiv), benzene; (d) I_2, CH_2Cl_2, 74%; (e) DDQ (1.2 equiv), CH_2Cl_2–H_2O, 97%; (f) SO_3–pyridine, *i*-Pr_2NEt, DMSO, CH_2Cl_2; (g) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, aq *tert*-BuOH, 95%.

2.2. Combination with another chiral starting material (*R*)-4a toward acyclic precursor 2

The second task is the synthesis of another four-carbon synthon involving the chirality at C-9 in the lactones. Toward this end, an acetal alcohol (*R*)-**4a** of 92.6% ee was prepared (76%) by *Yamadazyma farinosa* NBRC 10896-mediated asymmetric reduction[5,6] of commercially available ketone **10** in a large scale (Scheme 4). Enantioselective enrichment



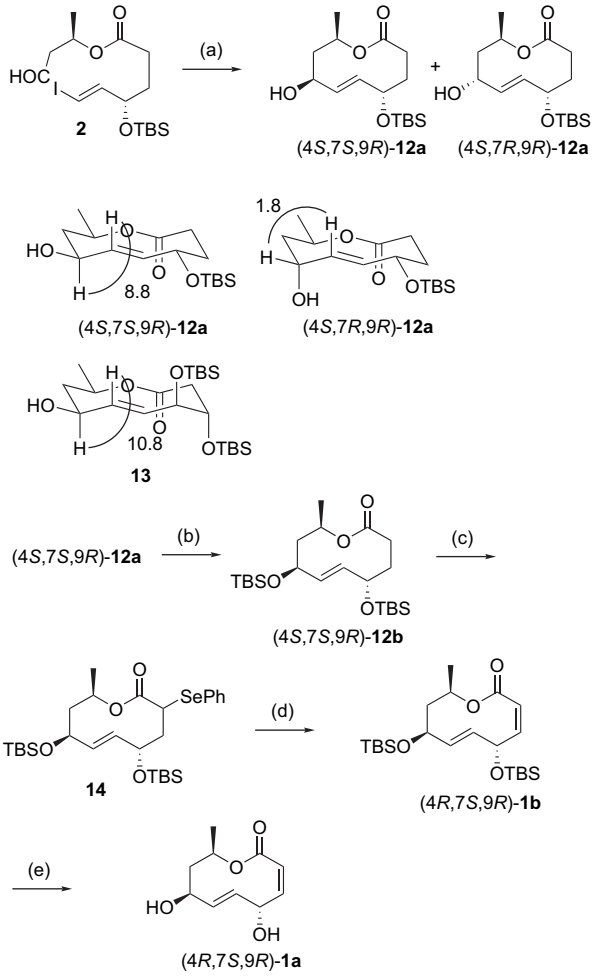
Scheme 4. (a) *Y. farinosa* NBRC 10896, 76%; (b) *P. cepacia* lipase (Amano PS-C), vinyl acetate, 58%; (c) K_2CO_3, MeOH, 98%; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; (e) DMAP, benzene, quantitative; (f) *p*-TsOH–H_2O, acetone.

was performed by treatment with lipase[6,19] in the presence of vinyl acetate to give an acetate (*R*)-**4b** (69% conversion, 58% yield, Scheme 4). This acetate was hydrolyzed to give the alcohol (*R*)-**4a** of >99.9% ee (98%). Then the acid **9** was condensed with alcohol (*R*)-**4a** to give an ester **11** (quantitative) by activating via Yamaguchi's mixed anhydride intermediate in the presence of DMAP.[20]

2.3. Stereoselective cyclization and derivation to modiolide A (1a)

After the cleavage of the dimethyl acetal in the above-mentioned **11** under acidic conditions, the resulted aldehyde **2** was submitted to the key-step, the intramolecular Nozaki–Hiyama–Kishi coupling. The reaction proceeded in a stereoselective manner, to give the desired (4*S*,7*S*,9*R*)-**12a** (52%) as the major product along with diastereomeric (4*S*,7*R*,9*R*)-**12a** (9%) as in Scheme 5. The control of the stereogenic center at C-7 was well understandable by the previous results for which the stereochemistry at C-7 was dominated by that at C-9, regardless of the stereochemistry at the C-4 chiral center.[2,3] The ^{1}H signal at C-7 (δ: 4.06, $J_{6,7}$=8.8 Hz) in (4*S*,7*S*,9*R*)-**12a** coincided well with those at C-7 (δ: 4.21, $J_{6,7}$=10.8 Hz) in **13**,[2] which is a key intermediate for Pilli's synthesis of 10-membered lactone, while that in (4*S*,7*R*,9*R*)-**12a** (δ=4.45, $J_{6,7}$=1.8 Hz) was far from **13**.

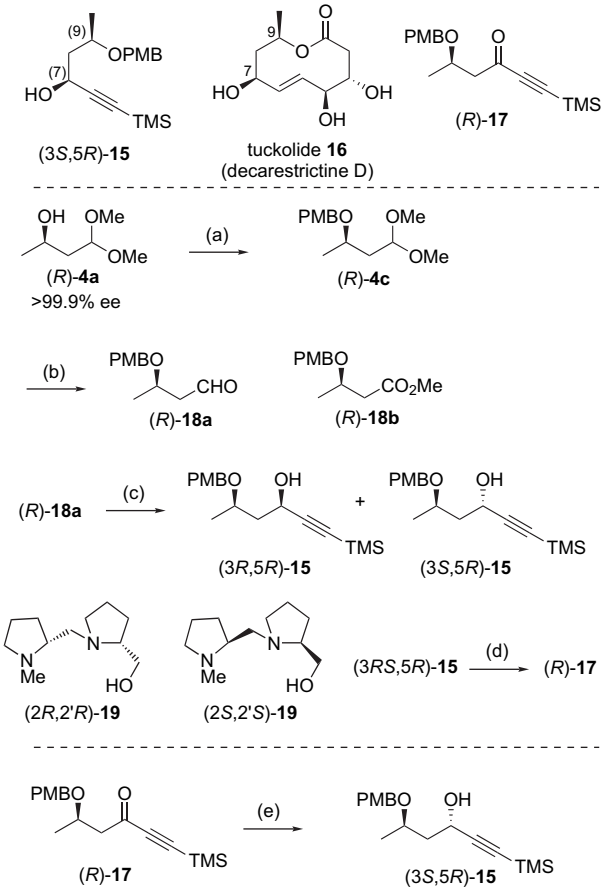
The final task was the introduction of a double bond at C-2 (Scheme 5). Toward the end, first, the free hydroxyl group at C-7 was protected by TBS ether (95%), and the resulted bis-TBS ether **12b** was phenylselenylated with phenylselenenyl chloride[21] to give **14** in 75% yield. Its ^{1}H NMR suggested the single isomer, we however, did not pursue the detail of its stereochemistry. Immediately, it was treated with H_2O_2 to promote oxidation to the corresponding selenoxide and the subsequent *syn*-elimination to give the requisite *cis*-double bond to afford (4*R*,7*S*,9*R*)-**1b** in 75% yield. Finally, two TBS ethers were deprotected (91%) with HF–pyridine,[22] to give (+)-modiolide A (**1a**, Scheme 5); mp 187–188 °C [lit.[23] mp 189–191 °C]; $[\alpha]_D^{21.8}$ +34.7 (*c* 0.250, MeOH) [lit.[1] $[\alpha]_D^{18}$ +42 (*c* 0.25, MeOH)]; whose spectral data coincided with those reported for the natural product.[1]



Scheme 5. (a) $CrCl_2$ (12 equiv), $NiCl_2$, (0.5 mol %), DMF, 52% for (4*S*,7*S*,9*R*)-**12a** and 9% for (4*S*,7*R*,9*R*)-**12a**; (b) TBSCl, imidazole, DMF, 95%; (c) LDA (2.1 equiv), PhSeCl (2.2 equiv), HMPA (1.5 equiv), THF, 75%; (d) H_2O_2, $NaHCO_3$, THF, 75%; (e) HF–pyridine, THF, pyridine, 91%.

2.4. Application of the whole-cell reduction to another propargyl ketone 17

In the course of the present study, we became interested in the whole-cell yeast-mediated reduction of propargyl ketones. A propargyl alcohol (3*S*,5*R*)-**15** (Scheme 6) was selected as the next target. This alcohol is the key intermediate[24] for another naturally occurring 10-membered



Scheme 6. (a) PMBCl, NaH, DMF, quantitative; (b) AcOH–H_2O, 94%; (c) TMSCCLi, THF, 82%; (d) Dess–Martin periodinane, CH_2Cl_2 87%; (e) *P. minuta* IAM 12215, 61%.

ring lactone, tuckolide (decarestrictine D, **16**),[25,26] which had been isolated as the substance with inhibitory activity on cholesterol biosynthesis and synthesized by several groups.[12,24,27–29]

The substrate (*R*)-**17** for yeast-catalyzed reduction was prepared as in Scheme 6, and we have some comments on the route to its precursor **18a**. First, the hydroxyl group of the starting material, (*R*)-**4a** synthesized as above was protected in a conventional manner (quantitative), by treatment with *p*-methoxybenzyl chloride and NaH, and the subsequent hydrolysis of the dimethyl acetal in (*R*)-**4c** (94%) provided β-PMBoxy aldehyde **18a**.[24] The choice of (*R*)-**4c** as the intermediate enabled avoiding the use of *p*-methoxybenzyl trichloroacetimidate, which had been necessary for the preparation of the so far reported starting material, (*R*)-**18b**, a β-PMBoxy ester. Second, as Andrus had stated before,[24] in the course of the addition of TMS acetylide on aldehyde (*R*)-**18a**, the undesired (3*R*,5*R*)-**15** predominated over (3*S*,5*R*)-isomer (2.6:1). The addition proceeded strongly in substrate-controlled manner, influenced by the chelation between pre-existing PMBoxy group. Attempts to change this situation into 'reagent control' were in vain. Even the addition of either enantiomer of diamines (2*R*,2′*R*)-**19** or (2*S*,2′*S*)-**19**[30] only slightly changed the ratio of the resulting both diastereomers, (3*R*,5*R*)-**15** and (3*S*,5*R*)-**15** in 4.0:1 or 3.0:1. In our hand, a mixture of diastereomers (3*RS*,5*R*)-**15** without separation was directly oxidized to the substrate (*R*)-**17**.

As in the same manner for ynone **5** (Scheme 2), only *P. minuta* accepted **17** as the substrate, among the aforementioned four yeast strains under pH-controlled (6.0) conditions. This substrate **17** was less toxic compared with **5**, then the reduction proceeded more smoothly. The desired alcohol (3*S*,5*R*)-**15** was obtained as a single isomer in 61% yield with the recovery of **17** (9%, Table 2, entry 1). Increase of the cell mass applied (=lower substrate/cell catalysts) and prolonged reaction time (entry 2) lowered the yield of the desired product as well as the recovery of the unreacted substrate.

Table 2. *Picha minuta*-mediated reduction of **17**

Entry	Sub/WCW	Time (h)	Yield [(3*S*,5*R*)-**15**, %]	Recovery (**17**, %)
1	0.02	28	61	9
2	0.01	52	57	3

WCW=wet cell weight; for detail, see Section 4.4.2.

3. Conclusion

We established a first total synthesis of (+)-modiolide A, based on the whole-cell yeast-catalyzed reduction of carbonyl precursor for providing the key-intermediates. Especially, newly developed conditions for asymmetric reduction of propargyl ketones worked very well in a preparative scale.

4. Experimental

4.1. Materials and methods

Merck silica gel 60 F_{254} thin-layer plates (1.05744, 0.5 mm thickness) and silica gel 60 (spherical and neutral; 100–210 μm, 37560-79) from Kanto Chemical Co. were used for preparative thin-layer chromatography and column chromatography, respectively. Peptone and yeast extract were purchased from Kyokuto Pharmaceutical Co., for the cultivation of microorganism. Yeast strains are available from Institute of Applied Microbiology Culture Collection; Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan.

4.2. Analytical methods

All mps are uncorrected. IR spectra were measured as films for oils or KBr disks of solids on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ at 400 MHz on a Jeol JNM GX-400 spectrometer, and ^{13}C NMR spectra were measured in $CDCl_3$ at 100 MHz on a Jeol GX-400 spectometer, unless otherwise stated. HPLC data were recorded on Jasco PU-2080 and MD-2010 liquid chromatographs. Optical rotation values were recorded on a Jasco DIP 360 and P-1010 polarimeter.

4.3. Pre-incubation of *P. minuta* IAM 12215[13]

A small portion of yeast cells of *P. minuta* IAM 12215 grown on the agar-plate culture was aseptically inoculated to a glucose medium [containing glucose (20 g), peptone (8.0 g), yeast extract (2.0 g), KH_2PO_4 (1.2 g), K_2HPO_4 (0.8 g), at pH 6.5, total volume of 400 mL] in four 500-mL baffled Erlenmeyer cultivating flasks. The flask was loosely capped with sterilized filter paper, instead of conventional foamed polyurethane plug, for a plenty of oxygen supply, and then shaken on a gyratory shaker (180 rpm) for 29 h at 30 °C. The OD (660 nm) reached 1.37.

4.4. Reduction of propargyl ketones with whole cells of *P. minuta* IAM 12215

4.4.1. (*S*)-(+)-6-[(4-Methoxybenzyl)oxy]-1-trimethylsilyl-1-hexyn-3-ol 3a. To a 100 mL of grown broth as above was directly added **5** (210 mg, 0.690 mmol), and the mixture was stirred at 30 °C for 22 h. Then the reaction mixture was saturated with sodium chloride and mixed with ethyl acetate (100 mL). The mixture was stirred for 1 h and filtered through a pad of Celite. The organic layer of the filtrate was separated and the aqueous layer was further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (15 g). Elution with hexane–ethyl acetate (2:1) afforded **3a** (185.2 mg, 88%); $[\alpha]_D^{25.5}$ +0.85 (*c* 2.69, EtOH); ^{1}H NMR δ: 0.17 (s, 9H), 1.70–1.92 (m, 4H), 2.88 (d, *J*=5.9 Hz, 1H), 3.51 (m, 2H), 3.81 (s, 3H), 4.41 (ddd, *J*=5.6, 5.6, 5.9 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 4.48 (d, *J*=11.6 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 7.63 (d, *J*=8.7 Hz, 2H); ^{13}C NMR δ: 0.0, 25.5, 35.2, 55.3, 62.5, 69.8, 72.6, 89.1, 106.7, 113.8, 129.3, 130.0, 159.1; IR ν_{max} 3404, 2956, 2861, 2170, 1613, 1514, 1456, 1362, 1250, 844 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3Si$: C 66.62, H 8.55. Found: C 66.43, H 8.54. HPLC analysis [column, Daicel Chiralcel OD–H, 0.46 cm×25 cm; hexane–*i*-PrOH (20:1); flow rate 0.5 mL/min]: t_R (min)=20.4 [1.9%, (*R*)-**3a**]; 24.0 [98.0%, (*S*)-**3a**]; 96.1% ee.

This was converted to (*S*)-**3c** in conventional two steps. (*S*)-**3c**: $[\alpha]_D^{23.0}$ +5.9 (*c* 0.570, $CHCl_3$) [lit.[18] $[\alpha]_D^{22}$ −5.7 (*c* 0.525, $CHCl_3$) for (*R*)-isomer]; ^{1}H NMR δ: 0.18 (s, 9H), 1.06 (s, 9H), 1.66–1.91 (m, 4H), 2.75 (d, *J*=5.9 Hz, 1H), 3.70 (m, 2H), 4.44 (ddd, *J*=5.7, 5.7, 5.9 Hz, 1H), 7.41 (m, 4H), 7.68 (m, 6H); ^{13}C NMR δ: 0.01, 19.2, 26.9, 28.3, 35.1, 62.6, 63.9, 89.2, 106.7, 127.6, 129.6, 133.4, 135.5; IR ν_{max} 3387, 2957, 2931, 2858, 2170, 1428, 1251, 1112, 1009, 844, 702, 614 cm^{-1}.

4.4.2. (3*S*,5*R*)-(−)-5-[(4-Methoxybenzyl)oxy]-1-trimethylsilyl-1-hexyn-3-ol 15. Pre-incubation of *P. minuta* was carried out as above for 36 h at 30 °C. The wet cells were harvested by centrifugation (3000 rpm) and washed with phosphate buffer (0.1 M, pH 6.0). The weight of combined wet cells was ca. 5.1 g from 100 mL of the broth. Harvested cells of *P. minuta* (9.5 g) were applied for the reduction of **17** (199.6 mg, 0.656 mmol) at 30 °C for 28 h. During the reaction, its pH was occasionally adjusted to 6.0 by the addition of aqueous sodium hydroxide solution with an automatic pH controller. The product was extracted in the same manner as described before, and the residue was purified by silica gel column chromatography (12.5 g). Elution with hexane–ethyl acetate (15:1 to 6:1) afforded (3*S*,5*R*)-**15** (121.6 mg, 61%); $[\alpha]_D^{23.2}$ −86.5 (*c* 1.12, $CHCl_3$); ^{1}H NMR δ: 0.19 (s, 9H), 1.26 (d, *J*=6.3 Hz, 3H), 1.83 (ddd, *J*=2.9, 6.1, 14.4 Hz, 1H), 1.95 (ddd, *J*=1.6, 9.3, 14.4 Hz, 1H), 3.58 (d, *J*=7.9 Hz, 1H), 3.80 (s, 3H), 4.10 (ddq, *J*=2.9, 9.3, 6.3 Hz, 1H), 4.40 (d, *J*=10.7 Hz, 1H), 4.56 (d, *J*=10.7 Hz, 1H), 4.56 (ddd, *J*=1.6, 6.1, 7.9 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.29 (d, *J*=8.6 Hz, 2H); ^{13}C NMR δ: 0.0, 19.4, 43.1, 55.3, 61.1, 70.6, 73.3, 89.1, 106.7, 113.8, 129.5, 130.1, 159.2; IR ν_{max} 3423, 2962, 2837, 2170, 1614, 1587, 1514, 1464, 1421, 1375, 1342, 1302, 1250, 1174, 1142, 1111, 1036, 941, 845, 760 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_3Si$: C 66.62, H 8.55. Found: C 66.67, H 8.42. Its NMR spectra were identical with those reported previously.[24] The crude product of yeast reduction contained only (3*S*,5*R*)-**15** [R_f 0.64, hexane–AcOEt (2:1)], and no diastereomeric (3*R*,5*R*)-**15** [R_f 0.54, hexane–ethyl acetate (2:1)] was observed. ^{1}H NMR spectrum of the crude sample showed no signals assigned for (3*R*,5*R*)-**15**, for example, δ: 3.83 [ddq, *J*=6.1, 3.5, 9.5 Hz, 1H (H-5)]. Moreover, no (3*R*,5*R*)-**15** isomer was observed by ^{13}C NMR. ^{13}C NMR spectrum for authentic (3*R*,5*R*)-**15**, δ: 0.0, 19.6, 44.7, 55.3, 62.0, 70.2, 74.0, 88.9, 106.3, 113.8, 129.3, 130.1, 159.1. As the 100% of stereochemical purity at C-5 had already been confirmed in the course of preparation of the substrate (*R*)-**17**, the results show the present sample is a single stereoisomer.

4.5. Lipase-catalyzed enantiomeric enhancement of 3a

To a solution of **3a** (92.4% ee, 1.05 g, 3.43 mmol) in diisopropyl ether (12.3 mL) was added vinyl acetate (6.1 mL) and lipase (Amano PS-C, 1.06 g), and stirred at room temperature for 32.5 h. Then to the mixture was further added Amano PS-C (527.7 mg) and stirring was continued at room temperature. After stirring for 36 h, an additional amount of Amano PS-C (530.7 mg) was added, and stirring was further continued for 47 h, so that the total reaction time reached 115.5 h. The mixture was passed through a pad of Celite and the filtrate was concentrated in vacuo. The residue was charged on a silica gel column (125 g), and eluted with hexane–ethyl acetate (4:1 to 2:1). First, less polar acetate **3b** [R_f=0.57 (hexane–ethyl acetate=2:1)] was eluted, and further elution afforded **3a** (987.2 mg, 98%) as a pale yellow oil. R_f=0.40 (hexane–ethyl acetate=2:1); $[\alpha]_D^{29.2}$ +0.57 (*c* 2.66, EtOH); HPLC analysis [column, Daicel Chiralcel OD–H, 0.46 cm×25 cm; hexane–*i*-PrOH (20:1); flow rate 0.5 mL/min]: t_R(min)=23.6 [single peak, (*S*)-**3a**]. Its IR and NMR spectra were identical with those as above.

4.6. Preparation of substrates 5 and (*R*)-17

4.6.1. 6-[(4-Methoxybenzyl)oxy]-1-trimethylsilyl-1-hexyn-3-one 5. To a solution of trimethylsilylacetylene (3.9 mL, 28.2 mmol) in anhydrous THF (20.2 mL) was added dropwise *n*-BuLi (2.46 M in hexane, 10.5 mL, 25.9 mmol) at 0 °C for 30 min. To a stirred solution of an aldehyde **6**[12] (4.9 g, 23.5 mmol) in anhydrous THF (20.2 mL) at −78 °C was added the pre-formed solution of lithium trimethylsilylacetylide via a cannula. After the mixture had been stirred at −78 °C for 40 min, the reaction was gradually warmed to room temperature. After stirring at room temperature for 30 min, the reaction was quenched by addition of saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (360 g), and eluted with hexane–ethyl acetate (4:1 to 2:1) afforded racemic **3a** (6.85 g, 95%) as a pale yellow oil.

To a solution of racemic **3a** (1.17 g, 3.83 mmol) in dichloromethane (38 mL) was added Dess–Martin periodinane (2.21 g, 5.22 mmol), and the mixture was stirred for 6 h at room temperature. The workup as before and the purification with silica gel column (75 g) afforded **5** (1.14 g, 98%) as a pale yellow oil. ^{1}H NMR δ: 0.00 (s, 9H), 1.72 (tt, *J*=6.4, 7.3 Hz, 2H), 2.44 (t, *J*=7.3 Hz, 2H), 3.23 (t, *J*=6.4 Hz, 2H), 3.57 (s, 3H), 4.18 (s, 2H), 6.64 (d, *J*=8.5 Hz, 2H), 7.02 (d, *J*=8.5 Hz, 2H); ^{13}C NMR δ: −0.68, 24.1, 42.1, 55.3, 68.7, 72.5, 97.7, 101.9, 113.7, 129.1, 130.3, 159.0, 187.2; IR ν_{max} 2958, 2900, 2859, 2149, 2091, 1678, 1613, 1514, 1360, 1303, 1250, 1098, 1037, 847, 762 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_3Si$: C 67.06, H 7.95. Found: C 67.23, H 8.00.

4.6.2. (*R*)-4,4-Dimethoxy-2-butanol 4a. According to the reported procedure,[5,6] 4,4-dimethoxy-2-butanone (**10**) was incubated with the harvested cells of *Y. farinosa* NBRC 10896 to give (*R*)-**4a** (76%); $[\alpha]_D^{20.0}$ +12.0 (*c* 1.00, $CHCl_3$). The ee of **4a** was determined by HPLC analysis of the corresponding benzoate **4d**. HPLC [column, Daicel Chiralcel OJ, 0.46 cm×25 cm; hexane–*i*-PrOH (9:1); flow rate 0.5 mL/min]: t_R (min)=11.9 (96.3%), 12.8 (3.7%); 92.6% ee. This was treated with *P. cepacia* lipase (Amano PS-C) and vinyl acetate to give the corresponding acetate (*R*)-**4b** (58%). To the solution of **4b** (3.1 g, 17.5 mmol) in methanol (43 mL) was added potassium carbonate (2.4 g, 17.4 mmol) and the mixture was stirred at 0 °C for 3 h. Then the reaction mixture was poured into 40 mL of saturated aqueous ammonium chloride solution and evaporated. The mixture was extracted with ethyl acetate and organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Bulb-to-bulb distillation afforded

(*R*)-**4a** (2.3 g, 98%) as a pale yellow oil. This was over 99.9% ee, judged by the HPLC analysis of **4d** as described above.

4.6.3. (*R*)-1,1-Dimethoxy-3-[(4-methoxybenzyl)oxy]butane 4c. To a dispersion of sodium hydride (55% in paraffin, 240 mg, 5.5 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF, 3.5 mL) was added dropwise a solution of **4a** (399 mg, 3.0 mmol) in anhydrous DMF (0.7 mL). The mixture was stirred at room temperature for 20 min, and 4-methoxybenzyl chloride (564 mg, 3.6 mmol) was added dropwise. After stirring at room temperature overnight, the reaction was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (38 g), and eluted with hexane–ethyl acetate (4:1 to 3:1) to afford **4c** (748.5 mg, 99%) as a pale yellow oil; $[\alpha]_D^{20.0}$ −50.7 (*c* 0.975, $CHCl_3$); ^{1}H NMR (Jeol JNM-270, 270 MHz, $CDCl_3$) δ: 1.21 (d, *J*=6.1 Hz, 3H), 1.70 (ddd, *J*=4.4, 7.5, 14.0 Hz, 1H), 1.87 (ddd, *J*=4.4, 8.5, 14.0 Hz, 1H), 3.29 (s, 3H), 3.30 (s, 3H), 3.64 (m, 1H), 3.80 (s, 3H), 4.36 (d, *J*=11.0 Hz, 1H), 4.51 (d, *J*=11.0 Hz, 1H), 4.54 (dd, *J*=4.4, 7.5 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 2H), 7.26 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ: 19.8, 40.1, 52.6, 53.2, 55.2, 70.1, 71.2, 102.2, 113.7, 129.2, 130.9, 159.0; IR ν_{max} 2933, 2834, 2061, 1613, 1586, 1514, 1465, 1375, 1347, 1302, 1249, 1173, 1122, 1054, 960, 910, 872, 822, 754, 708 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$: C 66.12, H 8.72. Found: C 66.17, H 8.58.

4.6.4. (*R*)-3-[(4-Methoxybenzyl)oxy]butanal 18a. Acetal **4c** (555.3 mg, 2.18 mmol) was stirred in 20 mL of a mixed solvent of acetic acid and water (1:1) at room temperature overnight. To the resulting solution was added dropwise a cooled aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (25 g), and eluted with hexane–ethyl acetate (3:1) to afford **18a** (427.1 mg, 94%) as a pale yellow oil; $[\alpha]_D^{19.0}$ −40.2 (*c* 0.975, $CHCl_3$); ^{1}H NMR δ: 1.28 (d, *J*=6.1 Hz, 3H), 2.50 (ddd, *J*=2.2, 5.0, 16.0 Hz, 1H), 2.68 (ddd, *J*=2.2, 7.4, 16.0 Hz, 1H), 3.80 (s, 3H), 4.06 (m, 1H), 4.41 (d, *J*=11.0 Hz, 1H), 4.54 (d, *J*=11.0 Hz, 1H), 6.87 (d, *J*=8.8 Hz, 2H), 7.24 (d, *J*=8.8 Hz, 2H), 9.77 (t, *J*=2.2 Hz, 1H); ^{13}C NMR δ: 19.7, 50.4, 55.2, 69.8, 70.2, 113.8, 129.2, 130.2, 159.2, 201.5; IR ν_{max} 2971, 2934, 2905, 2837, 2727, 2547, 2058, 1887, 1724, 1613, 1586, 1514, 1465, 1377, 1338, 1302, 1248, 1174, 1110, 1035, 954, 822, 756, 708 cm^{-1}; Anal. Calcd for $C_{12}H_{16}O_3$: C 69.21, H 7.74. Found: C 69.00, H 7.68. Its NMR spectra were identical with that reported previously.[24]

4.6.5. (*R*)-5-[(4-Methoxybenzyl)oxy]-1-trimethylsilyl-1-hexyn-3-one 17. To a solution of (3*RS*,5*R*)-**15** [328.7 mg, 1.07 mmol, prepared from (*R*)-**18a** according to the previous report[24]] in dichloromethane (11.9 mL) was added Dess–Martin periodinane (687.3 mg, 1.62 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 4 h, and quenched with a mixture of saturated aqueous sodium thiosulfate and sodium hydrogen carbonate solution (3:1). The reaction mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (18 g), and eluted with hexane–ethyl acetate (15:1 to 10:1) to afford (*R*)-**17** (283.5 mg, 87%) as a pale yellow oil; $[\alpha]_D^{22.7}$ −9.52 (*c* 1.35, $CHCl_3$); ^{1}H NMR δ: 0.23 (s, 9H), 1.25 (d, *J*=6.3 Hz, 3H), 2.62 (dd, *J*=5.4, 15.9 Hz, 1H), 2.91 (dd, *J*=7.5, 15.9 Hz, 1H), 3.79 (s, 3H), 4.12 (ddq, *J*=5.4, 7.5, 6.3 Hz, 1H), 4.43 (d, *J*=11.0 Hz, 1H), 4.50 (d, *J*=11.0 Hz, 1H), 6.86 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ: −0.7, 19.9, 52.4, 55.3, 70.6, 71.0, 98.1, 102.1, 113.7, 129.2, 130.4, 159.0, 185.4; IR ν_{max} 2964, 2933, 2902, 2837, 1678, 1614, 1514, 1464, 1375, 1338, 1302, 1250, 1174, 1128, 1066, 866, 847, 762 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_3Si$: C 67.06, H 7.95. Found: C 67.42, H 7.98.

4.7. Total synthesis of modiolide A (1a)

4.7.1. (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-[(4-methoxybenzyl)oxy]-1-hexyne 7b. To a solution of **3a** (100% ee, 934.0 mg, 3.05 mmol) in methanol (30.5 mL) was added potassium carbonate (425.9 mg, 3.08 mmol) and the mixture was stirred at 0 °C for 5 h. Then the mixture was poured into 35 mL of saturated aqueous ammonium chloride solution and concentrated in vacuo. The mixture was extracted with ethyl acetate and organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was charged on a silica gel column (50 g) and eluted with hexane–ethyl acetate (1:1) to afford **7a** (704.9 mg, 99%) as a pale yellow oil; $[\alpha]_D^{22.9}$ −3.6 (*c* 1.52, EtOH); ^{1}H NMR δ: 1.74–1.95 (m, 4H), 2.46 (d, *J*=2.0 Hz, 1H), 3.52 (m, 2H), 3.81 (s, 3H), 4.42 (ddd, *J*=2.0, 5.9, 5.9 Hz, 1H), 4.45 (d, *J*=11.5 Hz, 1H), 4.49 (d, *J*=11.5 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 2H), 7.27 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ: 25.4, 35.2, 55.3, 61.8, 69.7, 72.6, 84.9, 113.7, 129.3, 129.9, 159.1; IR ν_{max} 3396, 3288, 2955, 2932, 2863, 1612, 1586, 1514, 1456, 1361, 1248, 1175, 1033, 821, 638 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C 71.77, H 7.74. Found: C 71.55, H 7.77.

To a solution of **7a** (597.4 mg, 2.55 mmol) in *N*,*N*-dimethylformamide (DMF, 7.3 mL) was added imidazole (349.5 mg, 5.13 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl, 469.2 mg, 3.11 mmol). After stirring at room temperature overnight, the reaction was quenched by addition of water (20 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (75 g), and eluted with hexane–ethyl acetate (8:1) to afford **7b** (887.9 mg, quantitative) as a pale yellow oil; $[\alpha]_D^{26.4}$ −27.3 (*c* 1.76, EtOH); ^{1}H NMR δ: 0.10 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.76 (m, 4H), 2.38 (d, *J*=2.0 Hz, 1H), 3.48 (m, 2H), 3.81 (s, 3H), 4.38 (ddd, *J*=2.0, 5.6, 5.6 Hz, 1H), 4.44 (s, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 7.27 (d, *J*=8.8 Hz, 2H); ^{13}C NMR δ: −5.0, −4.5, 18.2, 25.5, 25.8, 35.3, 55.3, 62.5, 69.7, 72.1, 72.4, 85.4, 113.7, 129.1, 130.6, 159.0; IR ν_{max} 3307, 2954, 2857, 1613, 1514, 1464, 1361, 1302, 1249, 1173, 1096, 1038, 1005, 838, 778, 666 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3Si$: C 68.92, H 9.25. Found: C 68.57, H 9.10.

4.7.2. (1*E*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-6-[(4-methoxybenzyl)oxy]-1-hexene 8a. To a stirred solution

of **7b** (887.9 mg, 2.55 mmol) in anhydrous benzene (50.9 mL) under an argon atmosphere were added tri-*n*-butylstannyl hydride (279.0 mg, 1.08 mmol) and azobisisobutyronitrile (AIBN, 16.5 mg, 0.10 mmol). The reaction mixture was refluxed for 12 h and then concentrated in vacuo. The residue was charged on a silica gel column (200 g) and eluted with hexane–ethyl acetate (30:1 to 20:1) to afford an alkenylstannane (1.21 g, 74%) as a pale yellow oil. This was dissolved in dichloromethane (18.9 mL), and to this was added iodine (482.9 mg, 1.90 mmol) at 0 °C. After the mixture was stirred at 0 °C for 30 min, the reaction was quenched by addition of saturated aqueous sodium thiosulfate solution. The mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (100 g) and eluted with hexane–ethyl acetate (30:1) to afford **8a** (937.2 mg, quantitative) as a pale yellow oil; $[\alpha]_D^{23.4}$ −16.3 (*c* 1.60, EtOH); ^{1}H NMR *δ*: 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.53–1.67 (m, 4H), 3.43 (t, *J*=6.1 Hz, 1H), 3.81 (s, 3H), 4.10 (dt, *J*=6.1, 4.9 Hz, 1H), 4.42 (s, 2H), 6.19 (d, *J*=14.3 Hz, 1H), 6.50 (dd, *J*=6.1, 14.3 Hz, 1H), 6.88 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H); ^{13}C NMR δ: −4.8, −4.5, 18.2, 25.2, 25.9, 34.1, 55.3, 69.8, 72.5, 74.9, 75.8, 113.7, 129.2, 130.5, 148.9, 159.0; IR ν_{max} 2952, 2929, 2855, 1611, 1463, 1361, 1249, 1361, 1096, 1038, 836, 776 cm^{-1}. Anal. Calcd for $C_{20}H_{33}IO_3Si$: C 50.42, H 6.98. Found: C 50.52, H 7.05.

4.7.3. (5*E*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-iodo-5-hexen-1-ol 8b. To a stirred solution of **8a** (291.1 mg, 0.611 mmol) in dichloromethane (5.8 mL) were added water (0.29 mL) and DDQ (166.6 mg, 0.734 mmol) at 0 °C. After stirring at 0 °C for 3 h, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (25 g) and eluted with toluene–ethyl acetate (12:1) to afford **8b** (210.6 mg, 97%) as a pale yellow oil; $[\alpha]_D^{24.8}$ −33.4 (*c* 1.49, EtOH); ^{1}H NMR *δ*: 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.53–1.65 (m, 4H), 1.75 (s, 1H), 3.59–3.66 (m, 2H), 4.17 (dt, *J*=6.1, 5.1 Hz, 1H), 6.22 (d, *J*=14.3 Hz, 1H), 6.52 (dd, *J*=6.1, 14.3 Hz, 1H); ^{13}C NMR *δ*: −4.8, −4.5, 18.2, 25.8, 27.9, 33.9, 62.8, 74.8, 76.0, 148.6; IR ν_{max} 3330, 2952, 2929, 2857, 1607, 1471, 1361, 1255, 1096, 1062, 944, 837, 776 cm^{-1}. Anal. Calcd for $C_{12}H_{25}IO_2Si$: C 40.45, H 7.07. Found: C 40.63, H 7.15.

4.7.4. (4*S*,5*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-iodo-5-hexenoic acid 9. To a stirred solution of **8b** (215.6 mg, 0.605 mmol) in dichloromethane (5.1 mL) was added diisopropylethylamine (0.72 mL, 4.24 mmol) and the resulting mixture was stirred at 0 °C for 5 min. Then, dimethyl sulfoxide (0.43 mL, 6.51 mmol) was added and the mixture stirred at 0 °C for another 10 min. At this time, SO_3–pyridine (387.9 mg, 2.44 mmol) was added and the mixture stirred at 0 °C for 20 min. The reaction was quenched by addition of water (10 mL) and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous ammonium chloride solution, sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (20 g) and eluted with hexane–ethyl acetate (16:1 to 8:1) to afford an aldehyde (204.3 mg, 95%) as a pale yellow oil.

This was dissolved in a mixture of *tert*-butyl alcohol and water [3.3:5 (v/v), 7.3 mL], and to the solution were added 2-methyl-2-butene (970.2 mg, 13.8 mmol) and sodium dihydrogen phosphate (557.4 mg, 4.65 mmol) at room temperature. Then sodium chlorite (653 mg, ca. 80% purity, 5.77 mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (10 mL) and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (15 g) and eluted with hexane–ethyl acetate (2: 1) to afford **9** (214.2 mg, quantitative) as a pale yellow oil; $[\alpha]_D^{24.7}$ −30.8 (*c* 1.11, EtOH); ^{1}H NMR *δ*: 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.75–1.97 (m, 2H), 2.34–2.48 (m, 2H), 4.20 (dt, *J*=5.9, 5.4 Hz, 1H), 6.27 (d, *J*=14.4 Hz, 1H), 6.49 (dd, *J*=5.9, 14.4 Hz, 1H); ^{13}C NMR *δ*: −4.9, −4.5, 18.2, 25.8, 29.0, 31.8, 73.7, 76.7, 147.9, 179.5; IR ν_{max} 3045, 2954, 2929, 2895, 2857, 2674, 1710, 1607, 1471, 1463, 1414, 1362, 1256, 1102, 946, 837, 777 cm^{-1}. Anal. Calcd for $C_{12}H_{23}IO_3Si$: C 38.92, H 6.26. Found: C 38.86, H 6.34.

4.7.5. (4*S*,5*E*,1′*R*)-3′,3′-Dimethoxy-1-methylpropyl 4-[(*tert*-butyldimethylsilyl)oxy]-6-iodo-5-hexenoate 11. To a mixture of **9** (549.8 mg, 1.485 mmol) and Et_3N (165.3 mg, 1.633 mmol) in THF (26.5 mL) was added 2,4,6-trichlorobenzoyl chloride (398.3 mg, 1.633 mmol). The mixture was stirred at room temperature for 5 h. The white precipitate was removed by filtration with a sintered glass funnel under N_2, and the precipitate was washed with dry THF. The combined filtrate and washings were concentrated in vacuo by a stream of Ar. The residue was diluted with dry benzene (36.9 mL). To this mixture were added alcohol (*R*)-**4a** (265.4 mg, 1.978 mmol) and DMAP (390.0 mg, 3.192 mmol) in dry benzene (16.1 mL). The reaction mixture was stirred at room temperature for 8.5 h. Then the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate solution (50 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (75 g) and eluted with hexane–ethyl acetate (5:1) to afford **11** (720.3 mg, quantitative) as a pale yellow oil; $[\alpha]_D^{22.6}$ −34.3 (*c* 1.49, EtOH); ^{1}H NMR *δ*: 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.24 (d, *J*=6.4 Hz, 3H), 1.78 (ddd, *J*=4.8, 5.0, 14.3 Hz, 1H; dd, *J*=5.5, 7.7 Hz, 2H), 1.92 (ddd, *J*=4.7, 7.8, 14.3 Hz, 1H), 2.31 (t, *J*=7.7 Hz, 1H), 2.32 (t, *J*=7.7 Hz, 1H), 3.30 (s, 6H), 4.18 (ddt, *J*=1.0, 5.9, 5.5 Hz, 1H), 4.42 (dd, *J*=4.7, 4.8 Hz, 1H), 5.00 (ddq, *J*=7.8, 5.0, 6.4 Hz, 1H), 6.24 (dd, *J*=1.0, 14.2 Hz, 1H), 6.49 (dd, *J*=5.9, 14.2 Hz, 1H); ^{13}C NMR *δ*: −4.9, −4.5, 18.2, 20.5, 25.8, 29.5, 32.2, 39.0, 52.4, 53.2, 67.9, 73.8, 76.4, 101.6, 148.2, 172.6; IR ν_{max} 2955, 2930, 2857, 1732, 1607, 1463, 1362, 1256, 1185, 1096, 947, 838, 778 cm^{-1}. Anal. Calcd for $C_{18}H_{35}IO_5Si$: C 44.44, H 7.25. Found: C 44.59, H 7.34.

4.7.6. (4*S*,5*E*,7*S*,9*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7-hydroxy-9-methyl-5-nonen-9-olide 12a and its (4*S*,7*R*,9*R*)-isomer. To a stirred solution of **11** (227.8 mg, 0.468 mmol) in acetone (35.5 mL) was added *p*-toluenesulfonic acid monohydrate (20.2 mg, 0.106 mmol). The reaction mixture was stirred at room temperature for 3 h. Then the mixture was poured into phosphate buffer solution (0.5 M, pH 7.0, 30 mL) and concentrated in vacuo. The mixture was extracted with chloroform and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The very unstable aldehyde **2** was employed for the next step immediately without further purification.

To a stirred solution of chromium(II) chloride (696.9 mg, 5.67 mmol) and nickel(II) chloride (3.6 mg, 0.028 mmol) in degassed DMF (78.9 mL) at 0 °C was added the above-mentioned crude aldehyde in degassed DMF (14.8 mL) via a cannula. The reaction mixture was gradually warmed to room temperature and stirred for 11 h. Then the mixture was concentrated in vacuo and poured into water (50 mL). The mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (15 g) and eluted with hexane–ethyl acetate (3:1). Some contaminated fractions were further purified with preparative TLC with hexane–ethyl acetate (3:1, developed twice). Pure (4*S*,7*S*,9*R*)-**12a** (77.0 mg, 52%) and (4*S*,7*R*,9*R*)-**12a** (13.3 mg, 9%) were totally obtained through the above-mentioned column chromatography and preparative TLC. These were recrystallized from diethyl ether–hexane to give analytical samples as colorless needles, respectively.

(4*S*,7*S*,9*R*)-**12a**: R_f=0.40 (hexane–ethyl acetate=3:1, developed twice). Mp 64.5–65.5 °C; $[\alpha]_D^{24.5}$ +28.2 (*c* 1.49, EtOH); ^{1}H NMR δ: 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.21 (d, *J*=6.4 Hz, 3H), 1.75 (ddd, *J*=11.0, 11.2, 13.9 Hz, 1H), 1.92 (m, 2H), 2.05 (m, 2H), 2.25 (m, 1H), 4.06 (m, 2H), 5.14 (ddq, *J*=1.5, 11.2, 6.4 Hz, 1H), 5.42 (dd, *J*=8.3, 15.6 Hz, 1H), 5.49 (dd, *J*=8.8, 15.6 Hz, 1H); ^{13}C NMR δ: −4.6, −4.2, 18.2, 21.4, 25.8, 31.5, 35.6, 43.4, 67.4, 72.3, 75.2, 133.8, 134.5, 174.2; IR ν_{max} 3469, 2954, 2930, 2857, 1728, 1365, 1336, 1249, 1158, 1119, 994, 978, 892, 837, 776 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_4Si$: C 61.11, H 9.61. Found: C 60.89, H 9.41.

(4*S*,7*R*,9*R*)-**12a**: R_f=0.47 (hexane–ethyl acetate=3:1, developed twice). Mp 95–96 °C; $[\alpha]_D^{24.4}$ −13.6 (*c* 1.02, EtOH); ^{1}H NMR δ: 0.01 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.21 (d, *J*=6.4 Hz, 3H), 1.77 (ddd, *J*=2.2, 11.0, 14.6 Hz, 1H), 1.87 (m, 1H; ddd, *J*=2.1, 5.1, 14.6 Hz, 1H), 1.94–2.11 (m, 2H), 2.25 (m, 1H), 4.06 (ddd, *J*=4.2, 8.6, 9.5 Hz, 1H), 4.45 (ddd, *J*=1.8, 2.2, 5.1 Hz, 1H), 5.38 (ddq, *J*=2.1, 11.0, 6.4 Hz, 1H), 5.45 (dd, *J*=8.6, 16.1 Hz, 1H), 5.65 (dd, *J*=1.8, 16.1 Hz, 1H); ^{13}C NMR δ: −4.6, −4.2, 18.2, 21.1, 25.9, 31.8, 35.1, 42.4, 64.7, 67.6, 75.5, 129.5, 132.8, 175.2. Anal. Calcd for $C_{16}H_{30}O_4Si$: C 61.11, H 9.61. Found: C 60.95, H 9.50.

4.7.7. (4*S*,5*E*,7*S*,9*R*)-4,7-Bis[(*tert*-butyldimethylsilyl)oxy]-9-methyl-5-nonen-9-olide 12b. To a solution of **12a** (158.9 mg, 0.505 mmol) in DMF (1.4 mL) were added imidazole (68.9 mg, 1.01 mmol) and TBSCl (92.1 mg, 0.611 mmol). After stirring at room temperature for 15 h, the reaction was quenched by addition of water (10 mL). The mixture was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (10 g) and eluted with hexane–ethyl acetate (10:1) to afford **12b** (206.7 mg, 95%) as a colorless oil; $[\alpha]_D^{26.2}$ +16.0 (*c* 1.88, EtOH); ^{1}H NMR δ: 0.02 (s, 6H), 0.04 (s, 6H), 0.85 (s, 9H), 0.86 (s, 9H), 1.19 (d, *J*=6.3 Hz, 3H), 1.77 (m, 2H), 1.89 (m, 1H), 2.02 (m, 2H), 2.24 (m, 1H), 4.02 (m, 2H), 5.09 (ddq, *J*=2.8, 9.9, 6.3 Hz, 1H), 5.30 (dd, *J*=8.8, 15.6 Hz, 1H), 5.45 (dd, *J*=9.3, 15.6 Hz, 1H); ^{13}C NMR δ: −4.67, −4.65, −4.4, −4.2, 18.2, 21.5, 25.8, 31.6, 35.6, 44.9, 67.5, 73.0, 75.3, 132.3, 135.1, 174.3; IR ν_{max} 2959, 2930, 2857, 1731, 1472, 1362, 1252, 1162, 1113, 1082, 837, 776 cm^{-1}. Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C 61.63, H 10.34. Found: C 61.01, H 10.43.

4.7.8. (2*Z*,4*S*,5*E*,7*S*,9*R*)-4,7-Bis[(*tert*-butyldimethylsilyl)oxy]-9-methyl-2,5-nonadien-9-olide 1b. To a solution of diisopropylamine (113.5 mg, 1.11 mmol) in dry THF (2.6 mL) was added dropwise *n*-BuLi (2.46 M in hexane, 0.411 mL, 1.01 mmol) at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. Then a solution of **12b** (206.7 mg, 0.482 mmol) in dry THF (9.7 mL) was added to the cooled reaction mixture. After stirring at −78 °C for 1 h, a solution of phenylselenenyl chloride (206.0 mg, 1.08 mmol) and hexamethylphosphoric triamide (HMPA, 129.6 mg, 0.723 mmol) in dry THF (6.5 mL) were added dropwise. The reaction mixture was stirred at −78 °C for 45 min, then further at −40 °C for 45 min. Then the reaction was quenched by addition of saturated aqueous ammonium chloride solution (20 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (30 g) and eluted with toluene–ethyl acetate (100:1) to afford α-phenylselenylated lactone **14** (209.6 mg, 75%) as colorless solid.

To a solution of above **14** (209.6 mg, 0.359 mmol) in dry THF (3.8 mL) were added sodium hydrogen carbonate (86.6 mg, 1.03 mmol) and aqueous hydrogen peroxide solution (30%, 0.132 mL, 1.29 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 16 h. Then the reaction mixture was refluxed for 42 h, and the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate solution (10 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was charged on a silica gel column (15 g) and eluted with hexane–ethyl acetate (10:1) and some contaminated fractions were further purified with preparative TLC with hexane–ethyl acetate (10:1). Bis-TBS ether **1b** (115.3 mg, 75%) was totally obtained through the above-mentioned column chromatography and preparative TLC as colorless solid. Mp 49.5–51.0 °C; $[\alpha]_D^{22.9}$ +35.1 (*c* 1.22, EtOH); ^{1}H NMR δ: 0.03 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.87 (s, 18H), 1.23 (d, *J*=6.3 Hz, 3H), 1.77 (ddd, *J*=3.6, 4.4, 14.2 Hz, 1H), 1.83 (ddd, *J*=9.0, 9.5, 14.2 Hz, 1H), 4.18 (ddd, *J*=4.4, 8.3, 9.0 Hz, 1H), 4.73 (dd, *J*=2.0, 7.8 Hz, 1H), 5.28 (ddq, *J*=3.6, 9.5, 6.3 Hz, 1H), 5.54 (dd, *J*=8.3, 16.1 Hz, 1H), 5.61 (dd, *J*=7.8, 16.1 Hz, 1H), 5.74 (dd, *J*=2.0, 12.7 Hz, 1H), 5.78 (d, *J*=12.7 Hz, 1H); ^{13}C NMR δ: −4.73, −4.66,

−4.3, −4.2, 18.2, 21.5, 25.8, 44.1, 68.6, 72.5, 72.7, 120.8, 129.5, 137.8, 168.1; IR ν_{max} 2959, 2930, 2887, 2857, 1723, 1472, 1389, 1253, 1212, 1107, 1079, 1006, 978, 954, 887, 861, 836, 777, 670 cm^{-1}. Anal. Calcd for $C_{22}H_{42}O_4Si_2$: C 61.92, H 9.92. Found: C 61.51, H 9.80.

4.7.9. (2*Z*,4*S*,5*E*,7*S*,9*R*)-4,7-Dihydroxy-9-methyl-2,5-nonadien-9-olide [(+)-modiolide A] 1a. In a polypropylene-made vessel, bis-TBS ether **1b** (120.1 mg, 0.2814 mmol) was dissolved in dry THF (0.10 mL) and pyridine (0.01 mL) and treated with a stock solution of HF–pyridine–THF[22] (1.28 M, 1.77 mL, 2.27 mmol) at room temperature for 27 h. At the intervals of 25.5 h, the above-mentioned HF–pyridine–THF solution (1.0 mL, 1.28 mmol) was added twice and the stirring was continued totally for 82.5 h. The workup as above and the purification by preparative TLC, which was developed with ethyl acetate, afforded **1a** (50.8 mg, 91%). This was recrystallized from ethyl acetate–diethyl ether to give an analytical sample as colorless needles. Mp 187–188 °C [lit.[23] 189–191 °C; $[\alpha]_D^{21.8}$ +34.7 (*c* 0.250, MeOH) [lit.[1] $[\alpha]_D^{18}$ +42 (*c* 0.25, MeOH)]; ^1H NMR (400 MHz, CD_3OD) δ: 1.22 (d, *J*=6.4 Hz, 3H), 1.71 (ddd, *J*=11.2, 11.2, 14.0 Hz, 1H), 1.87 (ddd, *J*=1.8, 3.5, 14.0 Hz, 1H), 4.12 (ddd, *J*=3.5, 8.5, 11.2 Hz, 1H), 4.68 (ddd, *J*=1.5, 2.9, 7.6 Hz, 1H), 5.25 (ddq, *J*=1.8, 11.2, 6.4 Hz, 1H), 5.55 (dd, *J*=8.5, 15.9 Hz, 1H), 5.62 (dd, *J*=7.6, 15.9 Hz, 1H), 5.82 (dd, *J*=2.9, 12.7 Hz, 1H), 5.87 (dd, *J*=1.5, 12.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ: 21.6, 44.0, 70.0, 72.2, 72.8, 122.8, 130.9, 137.7, 138.6, 170.0; IR ν_{max} 3279, 2976, 2915, 2885, 1713, 1398, 1236, 1220, 1113, 1049, 1028, 947 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C 60.59, H 7.12. Found: C 60.43, H 7.13. Its NMR spectra were in good accordance with those reported for isolated natural product.[1]

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