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Enantioselective synthesis of dictyoceratin-A (smenospondiol) and -C, hypoxia-selective growth inhibitors from marine sponge

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ABSTRACT

Total syntheses of (+)-dictyoceratin-C (**1**) and (+)-dictyoceratin-A (smenospondiol) (**2**), hypoxia-selective growth inhibitors isolated from marine sponge, were executed. The absolute stereochemistry of the each compound was determined through the enantioselective total syntheses of them. It revealed that the unnatural enantiomers of them also exhibited the hypoxia-selective growth inhibitory activity against human prostate cancer DU-145 cells.

1. Introduction

Over the past decades, a number of sesquiterpene phenols/quinones and the related compounds have been isolated from marine organisms, particularly from algae and sponges.[1,2] Some of these sesquiterpenoids have been found to exhibit a variety of attractive biological activities such as antimicrobial, antiviral, cytotoxic, and immunomodulatory activities. In many cases, however, further biological studies of these compounds have been limited mainly due to the scarcity of natural supply. Consequently, the secure supply through chemical synthesis and the precise evaluation are highly desirable from the viewpoint of medicinal chemistry and drug discovery.

It is known that hypoxia alters the metabolic and proliferative pathway of tumor cells. And the tumor cells, which have adapted to the hypoxic environment, aggravate pathology of cancer by promoting tumor growth, angiogenesis, metastasis, and response to chemotherapy and irradiation.[3] As the hypoxic environment is rarely observed in normal tissues, the new chemical entities, which exhibit the hypoxia-selective growth inhibitory activity, are highly needed as a novel and promising anticancer drug lead.

In our continuing search for novel hypoxia-selective growth inhibitors against human prostate cancer DU-145 cells, we re-discovered a sesquiterpene phenol dictyoceratin-C (**1**)[4] as an active constituent, from the Indonesian marine sponge of *Dactylospongia elegans* (Fig. 1). Structure–activity relationship study with some sponge-derived sesquiterpenoids revealed that dictyoceratin-A (smenospondiol) (**2**),[5,6] a closely related compound possessing a *para*-hydroxybenzoyl ester moiety, exhibited similar

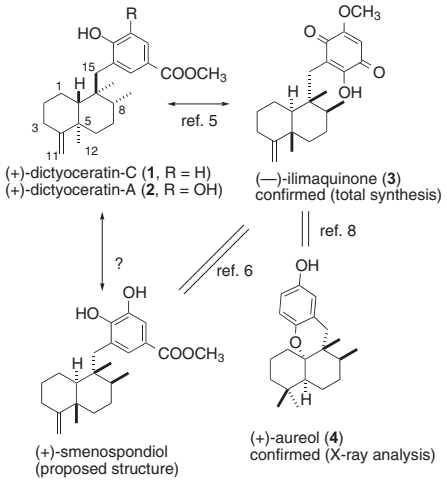

Figure 1. Proposed chemical structures of dictyoceratin-C (**1**) and dictyoceratin-A (smenospondiol) (**2**).

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hypoxia-selective growth inhibitory activity, whereas all the tested sesquiterpene quinones such as ilimaquinone (**3**) did not show hypoxia-selectivity.[7]

In order to supply sufficient amount of these compounds for further biological study including in vivo anti-tumor test and to develop a more promising anticancer drug lead, we engaged in their synthetic study. Here we report the first enantioselective total synthesis of **1** and **2** with confirming the absolute stereostructure and the biological evaluation of them.

2. Results and discussion

2.1. Enantioselective synthesis of (+)-dictyoceratin-C

To date, the absolute stereostructure of **1** and **2** remains unclear, although the structural similarity and the same sign of their specific rotation suggested that the absolute stereochemistry of the two compounds should be the same. There have been only a few reports regarding the absolute stereostructure of **2**. Nakamura and co-workers first reported the isolation and structure elucidation of dictyoceratin-A, in which they described that the specific rotation of its degradation product is antipodal to that derived from (−)-ilimaquinone (**3**) (Fig. 1).[5] Later, the absolute configuration of (−)-**3** was determined through the similar correlation study with (+)-aureol (**4**)[8] and total synthesis.[9] Considering these literatures and the opposite sign of the optical rotation, the absolute configuration of **2** might be deduced as shown in Figure 1. On the other hand, Kondracki and co-workers isolated a sesquiterpenoid having the same relative stereostructure as that of dictyoceratin-A named smenospondiol.[6] They supposed about the absolute configuration of smenospondiol to be antipodal of dictyoceratin-A through the chemical conversion, despite the same sign of the optical rotation for these two compounds was observed. Therefore, we decided to synthesize both enantiomers of **1** and **2**, to confirm their absolute stereostructure.

Today, several synthetic studies of these sesquiterpene quinones/phenols with various strategies have been reported.[10] One of the most popular strategy for the synthesis of *trans*-clerodane type compounds is that the quinone/phenol side chain is appended through one-pot Birch reduction–alkylation on the enone moiety of Wieland–Miescher-type diketone.[11] On the other hand, Samadi and co-workers developed a concise and scalable synthetic method of ilimaquinone (**3**) through appending the side chain by simple alkylation toward the enone **5**.[12] We envisioned that the similar strategy, as shown in Figure 2, would lead us to obtain sufficient amount of the compounds. Thus, the coupling reaction between the common enone **5** and the arylmethyl bromide, and the following introduction of 8-methyl group and 4-methylene group would afford **1** and **2**. Furthermore, the optically pure enone **5** and its enantiomer (*ent*-**5**) could be prepared using an amino acid (phenylalanine) as a chiral catalyst.[13]

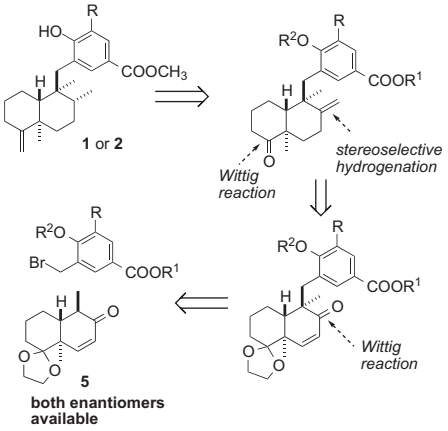


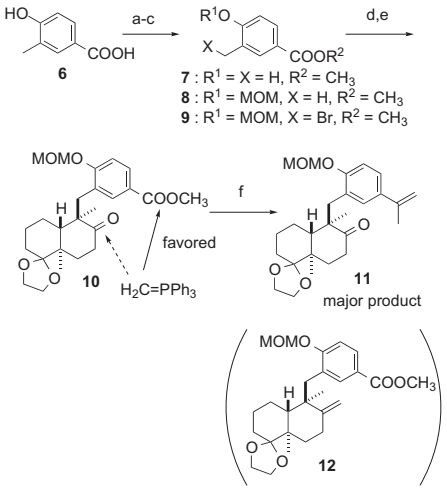
Figure 2. Synthetic strategy of **1** and **2**.

At first, the synthesis of the side chain part of **1** was executed (Scheme 1). Commercially available 4-hydroxy-3-methylbenzoic acid (**6**) was treated with H_2SO_4 in MeOH to give a corresponding methyl ester **7**.[14] After protection of the hydroxyl group of **7** as a methoxymethyl (MOM) ether, the resulting compound **8** was then subjected to radical bromination reaction to provide a bromide **9**, the coupling partner of enone **5**.

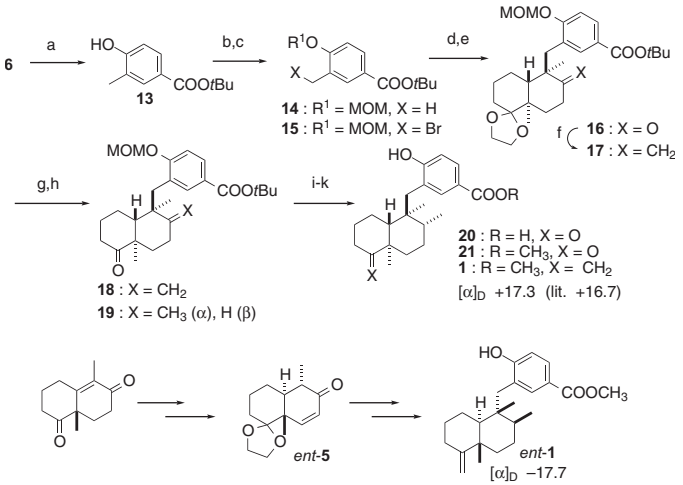
The coupling reaction of **5** and **9** using LHMDS as a base proceeded smoothly to provide a desired product as a single diastereomer, and the following hydrogenation gave a ketone **10** in good yield. Then, we examined the introduction of methyl group into the C-8 position by Wittig methylenation and stereoselective hydrogenation. To our disappointment, the methylenation reaction using excess Wittig reagent under heating conditions provided a styrene derivative **11** as a main product instead of the desired product **12**.[15] It clearly indicates that the C-8 ketone in **10** was less reactive in the Wittig methylenation than the carbonyl in the methyl ester, probably because of the steric hindrance. Reduction of the amount of the Wittig reagent or temperature (0 °C–rt) did not improve the selectivity.

Based on the initial results, we anticipated that the use of more bulky ester group would reduce the reactivity of the ester carbonyl and give the desired *exo*-olefin product, and decided to use *tert*-butyl ester as a bulky protecting group. Thus, the condensation of **6** and *tert*-BuOH with DCC[16] gave the *tert*-butyl ester **13**, and the following similar four-step transformation, as that used in the case of a methyl ester described above, provided the desired ketone **16** (Scheme 2). As expected, Wittig reaction toward the carbonyl group of the *tert*-butyl ester was completely inhibited, and the desired methylenation product **17** was obtained in good yield. The optimized reaction condition (55 °C, 16 h) improved the reaction yield up to 74%.

After removal of the ketal group under an acidic condition, the resulting ketone **18** was subjected to Pd–C catalyzed hydrogenation in Et_3N/MeOH (50:1)[17] to afford the desired product **19** as a single diastereomer. The stereochemistry of the resulting methyl group at C-8 was determined by NOE experiment. Acid treatment of **19** removed all the remained protecting groups providing **20**, which was converted to the methyl ester **21** in quantitative yield



Scheme 1. Synthesis of methyl ester **10** and attempted Wittig reaction. Reagents and conditions: (a) H_2SO_4, MeOH, 60 °C, 67%; (b) MOMCl, K_2CO_3, DMAP, CH_2Cl_2, 77%; (c) NBS, AIBN, benzene, 95 °C, 91%; (d) LHMDS, **5**, THF, 59%; (e) H_2, Pd–C, AcOEt, 84%; (f) KHMDS, Ph_3PCH_3Br, THF, 45 °C.



Scheme 2. Synthesis of (+)-**1** and *ent*-**1**. Reagents and conditions: (a) DCC, *t*BuOH, DMAP, CH_2Cl_2, 99%; (b) MOMCl, K_2CO_3, DMAP, CH_2Cl_2, 45 °C, 70%; (c) NBS, AIBN, benzene, reflux, 76%; (d) LHMDS, **5**, THF, −78 °C to rt, 75%; (e) H_2, Pd–C, AcOEt, 99%; (f) KHMDS, Ph_3PCH_3Br, THF, 55 °C, 74%; (g) 5% HCl, THF; (h) H_2, Pd–C, Et_3N/MeOH, quant (2 steps); (i) 6 N HCl, THF; TFA, CH_2Cl_2, 97% (2 steps); (j) $SOCl_2$, MeOH, 45 °C, 89%; (k) KHMDS, Ph_3PCH_3Br, THF, 0 °C, 98%.

by using $SOCl_2$ in MeOH. Finally, Wittig methylenation toward the C-4 ketone in **21** proceeded to afford dictyoceratin-C (**1**) in good yield.

The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic dictyoceratin-C (**1**) were identical to those of natural product. In addition, the optical rotation of the synthetic **1** ($[\alpha]_D$ +17.3 (*c* 0.12, $CHCl_3$)) showed good agreement with that of the naturally occurring one ($[\alpha]_D$ +16.7 (*c* 0.03, $CHCl_3$)).[18] We also synthesized *ent*-dictyoceratin-C from *ent*-**5**, easily obtained by using L-phenylalanine as a chiral organocatalyst.[12] The optical rotation of *ent*-**1** ($[\alpha]_D$ −17.7 (*c* 0.28, $CHCl_3$)) was opposite to the natural **1**. Therefore, we determined the absolute stereochemistry of (+)-dictyoceratin-C, as 5*R*,8*R*,9*S*,10*R*.

2.2. Enantioselective synthesis of (+)-dictyoceratin-A (smenospondiol)

We next executed synthesis of **2**. At first, the aromatic fragment was prepared from commercially available 3-methylcatechol (**22**) (Scheme 3). Thus, the catechol moiety in **22** was reacted with 2-butanone to give an isobutylidene ketal **23**[19] in moderate yield. After regioselective Friedel–Crafts acetylation of **23** with $ZnCl_2$ in Ac_2O, the subsequent haloform reaction toward **24** by using $Ca(ClO)_2$[20] gave a benzoic acid **25**. Then compound **25** was converted to the corresponding *tert*-butyl ester **26** in moderate yield, by the treatment with $SOCl_2$ in CH_2Cl_2 and the following addition of *tert*-BuOK. The $SOCl_2$ treatment in *tert*-butanol gave **26** in low yield, and the carbodiimide-mediated esterification with *tert*-butanol did not proceed at all. Finally, radical bromination of the methyl group in **26** provided an aromatic fragment **27**.

Using the aromatic fragment **27** and the decalin part **5**, the same transformation sequence as that for **1** [LHMDS-mediated coupling under heating condition; stereoselective introduction of the C-8 methyl group; removal of all protecting groups by acid hydrolysis and conversion to the methyl ester; and Wittig olefination] smoothly proceeded to afford dictyoceratin-A (**2**). Additionally, *ent*-**2** was synthesized form *ent*-**5**.

The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic dictyoceratin-A were identical to those of natural product. The optical rotation of the synthetic **2** $[\alpha]_D$ +10.4 (*c* 0.19, $CHCl_3$) also showed good agreement with that of the naturally occurring one ($[\alpha]_D$ +5.8 (*c* 0.97, $CHCl_3$),[5] and that of *ent*-**2** ($[\alpha]_D$ −11.6 (*c* 0.96, $CHCl_3$)) was opposite. These results have confirmed the absolute stereostructure of **2** to be the same as that of **1**, as well as that smenospondiol is the same as dictyoceratin-A.

2.3. Biological evaluation of dictyoceratin-A and -C

With both enantiomers of **1** and **2** in hand, we next evaluated their growth inhibitory effects against DU145 cells under normoxic or hypoxic conditions. As shown in Figure 3, both synthetic **1** and **2** showed dose-dependent and hypoxia-selective growth inhibitory activity against DU145 cells, respectively. And, to our surprise, the *ent*-**1** and *ent*-**2** showed almost the same activity and selectivity as those for **1** and **2**, respectively. It implies that the pharmacophore of these compounds might be a *para*-hydroxybenzoyl ester moiety of the side chain and the decalin part might not play a crucial role.

3. Conclusion

In summary, we succeeded the total synthesis of (+)-dictyoceratin-C (**1**) and (+)-dictyoceratin-A (**2**), and also confirmed their absolute stereostructures. This is the first example of the enantioselective synthesis of **1** and **2**, although the racemic synthesis of **2** has been reported.[21] Through their biological evaluation, we found that the hypoxia-selective growth inhibitory activity of them was not dependent on the absolute stereochemistry. Development of more promising hypoxia-targeting anti-tumor drug candidate through structure–activity relationship study and target protein analysis of **1** and **2** are currently being studied.

4. Experimental section

4.1. General experimental

The following instruments were used to obtain physical data: a JASCO P-2200 digital polarimeter (*L* = 50 mm) for specific rotations; a JEOL ECS-300 (^1H NMR: 300 MHz, ^{13}C NMR: 75 MHz), ECA-500 (^1H NMR: 500 MHz, ^{13}C NMR: 125 MHz) and an Agilent NMR system (^1H NMR: 600 MHz, ^{13}C NMR: 150 MHz) spectrometer for ^1H and ^{13}C NMR data using tetramethylsilane as an internal standard; a JASCO FT/IR-5300 infrared spectrometer for IR spectra; a Waters Q-Tof Ultima API mass spectrometer for ESI-TOF MS. Silica gel (Kanto, 40–100 μm) and pre-coated thin layer chromatography (TLC) plates (Merck, $60F_{254}$) were used for column chromatography and TLC. Spots on TLC plates were detected by spraying acidic *p*-anisaldehyde solution (*p*-anisaldehyde: 25 mL, *c*-H_2SO_4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) or phosphomolybdic acid solution (phosphomolybdic acid: 25 g, EtOH: 500 mL) with subsequent heating. Unless otherwise noted, all the reaction was performed under a N_2 atmosphere. After workup, the organic layer was dried over Na_2SO_4.

4.2. Enantioselective synthesis of dictyoceratin-C (1)

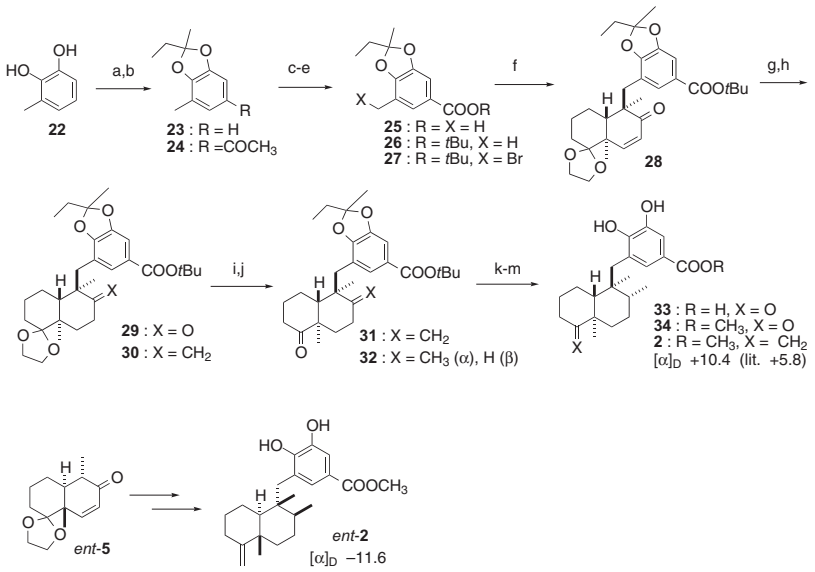
4.2.1. (4a*R*,5*R*,8a*R*)-5,8a-Dimethyl-3,4,4a,8a-tetrahydro-2*H*-spiro[naphthalene-1,2′-[1,3]dioxolan]-6(5*H*)-one (5)

The starting material, optically pure Wieland–Miescher-type diketone ((*R*)- or (*S*)-5,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione) was obtained through the reported method.[13]

(*R*)-Isomer: $[\alpha]_D^{26}$ −150 (*c* 1.0, CH_2Cl_2) {Lit. $[\alpha]_D^{20}$ −140 (*c* 0.20, CH_2Cl_2)[13]}.

(*S*)-Isomer: $[\alpha]_D^{26}$ +150 (*c* 1.0, CH_2Cl_2) {Lit. $[\alpha]_D^{20}$ +140 (*c* 0.20, CH_2Cl_2)[13]}.

Then, **5** and *ent*-**5** were prepared through the reported method,[12] starting from the above material of (*R*)- or (*S*)-isomer, respectively.



Scheme 3. Synthesis of (+)-**2** and *ent*-**2**. Reagents and conditions: (a) 2-butanone, P_2O_5, toluene, 75 °C, 70%; (b) $ZnCl_2$, Ac_2O, 55%; (c) $Ca(ClO)_2$, Na_2CO_3, NaOH, H_2O/1,4-dioxane, 70 °C, 89%; (d) $SOCl_2$, *t*BuOK, THF, 52%; (e) NBS, AIBN, benzene, reflux, 60%; (f) LHMDS, **5**, THF, −78 °C to 60 °C, 73%; (g) H_2, Pd–C, EtOH, 99%; (h) KHMDS, Ph_3PCH_3Br, toluene, 100 °C, 82%; (i) concd HCl, THF; (j) H_2, Pd–C, Et_3N/MeOH, 99% (2 steps); (k) TFA, THF/H_2O, 95%; (l) $SOCl_2$, MeOH, 60 °C, 85%; (m) KHMDS, Ph_3PCH_3Br, THF, 83%.

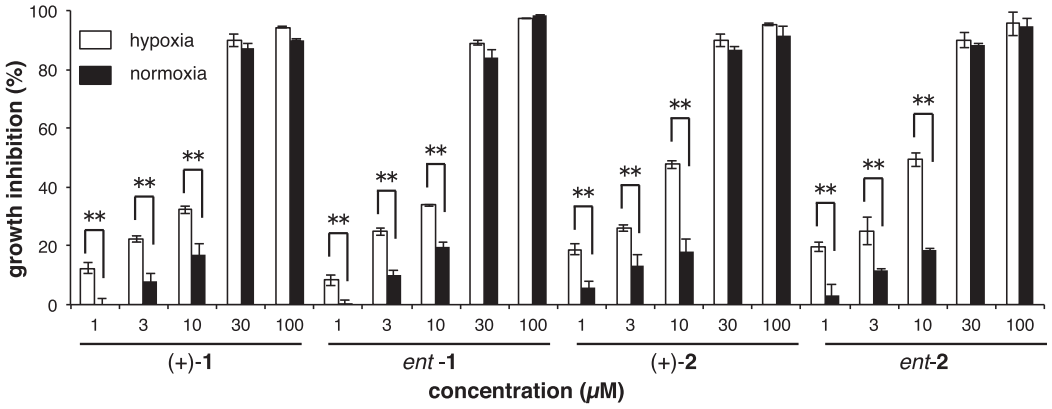


Figure 3. Growth inhibition activities of the synthetic **1**, *ent*-**1**, **2**, and *ent*-**2** against DU145 cells. $^{**}P$ <0.01.

4.2.2. Methyl 4-hydroxy-3-methylbenzoate (7)

Concd H_2SO_4 (2.0 mL) was added to a solution of 4-hydroxy-3-methylbenzoic acid (**6**) (2.0 g, 13.1 mmol) in anhydrous MeOH (20 mL), and the whole mixture was stirred for 12 h at 60 °C. The mixture was neutralized with 4 N NaOH and cold H_2O was added. The precipitate was filtered off and washed with cold H_2O. The crystals were dried in vacuo to give **7** (1.46 g, 67%) as a white solid.

The spectroscopic and physical data were identical to those reported.[14]

4.2.3. Methyl 4-(methoxymethoxy)-3-methylbenzoate (8)

K_2CO_3 (3.81 g, 27.6 mmol, 2.0 equiv) and MOMCl (1.26 mL, 16.5 mmol, 1.2 equiv) were added to a solution of **7** (2.29 g, 13.8 mmol) in anhydrous DMF (20 mL), and the whole mixture was stirred for 20 h at 55 °C. The residue mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in Et_2O and washed with satd NH_4Cl aq and brine. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (CH_2Cl_2) to give **8** (2.23 g, 77%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.83–7.82 (2H, m), 7.04 (1H, d, J = 8.9 Hz), 5.23 (2H, s), 3.86 (3H, s), 3.46 (3H, s), 2.25 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.9, 159.0, 132.2, 129.0, 127.1, 123.0, 112.6, 94.0, 56.1, 51.8, 16.2. IR (KBr): 2951, 1717, 1607, 1501, 1437, 1296, 1263 cm^{-1}. MS (ESI-TOF) m/z: 233 $[M+Na]^+$. HRMS (ESI-TOF) m/z: 233.0790 Calcd for $C_{11}H_{14}O_4Na$; Found: 233.0796.

4.2.4. Methyl 3-(bromomethyl)-4-(methoxymethoxy)benzoate (9)

NBS (1.94 g, 10.9 mmol, 1.05 equiv) and AIBN (136 mg, 0.83 mmol, 0.08 equiv) were added to a solution of **8** (2.18 g, 10.4 mmol) in anhydrous benzene (30 mL), and the whole mixture was stirred for 16 h at 80 °C. The whole reaction mixture was concentrated in vacuo, and the residue was dissolved in Et_2O and washed with satd $NaHCO_3$ aq. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 10:1) to give **9** (2.74 g, 91%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (1H, d, J = 2.3 Hz), 7.97 (1H, dd, J = 8.6, 2.3 Hz), 7.13 (1H, d, J = 8.6 Hz), 5.33 (2H, s), 4.57 (2H, s), 3.89 (3H, s), 3.52 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 158.5, 132.4, 131.9, 126.6, 123.3, 113.4, 93.8, 56.4, 51.9, 28.0. IR (KBr): 1705, 1609, 1503, 1445, 1275, 1150 cm^{-1}. MS (ESI-TOF)

m/*z*: 311/313 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 310.9895 Calcd for $C_{11}H_{13}{}^{79}BrO_4Na$; Found: 310.9898.

4.2.5. Methyl 3-[{(4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxooctahydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalen)-5′-yl}methyl]-4-(methoxymethoxy)benzoate (10)

Under an Ar atmosphere, *n*-BuLi (3.83 mL, of a 1.60 M solution in hexane, 6.13 mmol, 1.3 equiv) was added to a solution of HMDS (1.28 mL, 6.13 mmol, 1.3 equiv) in anhydrous THF (3.0 mL) at −78 °C, and the whole mixture was stirred for 5 min at −78 °C and for 10 min at rt. A solution of **5** (1.11 g, 4.71 mmol) in anhydrous THF (5.0 mL) was added dropwise to the mixture via cannula over 5 min at −50 °C, and the whole mixture was stirred for 45 min at 0 °C. A solution of bromide **9** (1.50 g, 5.19 mmol, 1.1 equiv) in anhydrous THF (5.0 mL) was added dropwise to the mixture via cannula over 5 min at −78 °C, and the whole mixture was stirred for 10 min at −78 °C, for 40 min at 0 °C and for 1 h at rt. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 3:1) to give a coupling product, Methyl 3-[{(4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxo-3′,4′,4a′,5′,6′,8a′-hexahydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalen)-5′-yl}methyl]-4-(methoxymethoxy)benzoate (1.24 g, 59%) as a white amorphous solid.

$[\alpha]_D^{26}$ +17.4 (*c* 1.18, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.82 (1H, d, *J* = 8.6 Hz), 7.70 (1H, s), 7.09 (1H, d, *J* = 8.6 Hz), 6.90 (1H, d, *J* = 10.3 Hz), 5.87 (1H, d, *J* = 10.3 Hz), 5.18 (1H, d, *J* = 6.9 Hz), 5.09 (1H, d, *J* = 6.9 Hz), 3.94–3.88 (4H, m), 3.81 (3H, s), 3.44 (3H, s), 3.06 (1H, d, *J* = 13.6 Hz), 2.87 (1H, d, *J* = 13.6 Hz), 2.25 (1H, d, *J* = 12.3 Hz), 1.64–1.60 (2H, m), 1.54–1.52 (1H, m), 1.42 (1H, qd, *J* = 12.5, 3.8 Hz), 1.30–1.28 (1H, m), 1.25–1.22 (1H, m), 1.17 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.7, 166.9, 159.7, 155.0, 133.5, 129.8, 127.4, 127.0, 122.9, 113.2, 111.6, 94.5, 64.9, 64.5, 56.2, 51.8, 48.9, 45.1, 41.9, 39.7, 29.2, 22.4, 22.0, 21.5, 19.7. IR (KBr): 2951, 1717, 1665, 1604, 1501, 1439, 1265, 1188 cm^{-1}. MS (ESI-TOF) *m*/*z*: 467 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 467.2046 Calcd for $C_{25}H_{32}O_7Na$; Found: 467.2057.

10% Pd–C (27 mg) was added to a solution of the above coupling product (124 mg, 0.279 mmol) in anhydrous MeOH (2.5 mL), and the whole mixture was stirred for 12 h under a H_2 atmosphere (balloon). The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 2:1) to give **10** (105 mg, 84%) as a white amorphous solid.

$[\alpha]_D^{26}$ −8.4 (*c* 0.58, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.86 (1H, dd, *J* = 8.7, 2.2 Hz), 7.71 (1H, d, *J* = 2.2 Hz), 7.11 (1H, d, *J* = 8.7 Hz), 5.18 (1H, d, *J* = 6.8 Hz), 5.11 (1H, d, *J* = 6.9 Hz), 3.94–3.91 (4H, m), 3.87 (3H, s), 3.48 (3H, s), 2.96 (1H, d, *J* = 13.4 Hz), 2.85 (1H, d, *J* = 13.4 Hz), 2.71–2.61 (1H, m), 2.34 (1H, q, *J* = 7.5 Hz), 2.30–2.24 (1H, m), 2.12–1.95 (1H, m), 1.72–1.67 (1H, m), 1.61–1.55 (2H, m), 1.53–1.38 (3H, m), 1.26–1.24 (1H, m), 1.04 (3H, s), 1.02 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.4, 166.8, 159.7, 133.5, 129.9, 126.5, 122.8, 113.1, 112.6, 94.6, 64.9, 64.6, 56.2, 51.8, 51.2, 46.1, 42.0, 39.6, 34.7, 29.7, 28.6, 22.7, 22.6, 19.9, 17.5. IR (KBr): 2949, 1715, 1605, 1501, 1439, 1262, 1134 cm^{-1}. MS (ESI-TOF) *m*/*z*: 469 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 469.2202 Calcd for $C_{25}H_{34}O_7Na$; Found: 469.2220.

4.2.6. (4a′*R*,5′*R*,8a′*R*)-5′-(2-(Methoxymethoxy)-5-(prop-1-en-2-yl)benzyl)-5′,8a′-dimethylhexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (11)

Under an Ar atmosphere, KHMDS (0.60 mL of a 0.5 M solution in toluene, 0.30 mmol, 5.0 equiv) was added to Ph_3PCH_3Br (107 mg, 0.30 mmol, 5.0 equiv) in anhydrous THF (0.3 mL), and the whole mixture was stirred for 45 min at rt. Above solution was added dropwise to a solution of **10** (26.7 mg, 0.06 mmol) in anhydrous THF (0.3 mL) at rt, and the whole mixture was stirred for 5 h at 45 °C. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 8:1) to give **11** (14.9 mg, 58%) as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$) δ: 7.26 (1H, dd, *J* = 8.6, 2.2 Hz), 7.12 (1H, d, *J* = 2.2 Hz), 7.05 (1H, d, *J* = 8.6 Hz), 5.25 (1H, s), 5.15 (1H, d, *J* = 6.6 Hz), 5.07 (1H, d, *J* = 6.6 Hz), 4.97 (1H, s), 3.92–3.86 (4H, m), 3.47 (3H, s), 2.93 (1H, d, *J* = 13.5 Hz), 2.84 (1H, d, *J* = 13.5 Hz), 2.56–2.49 (1H, m), 2.34–2.27 (2H, m), 2.10 (3H, s), 1.98–1.95 (1H, m), 1.70–1.68 (1H, m), 1.59–1.54 (3H, m), 1.47–1.40 (3H, m), 1.06 (3H, s), 1.03 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 217.1, 155.6, 142.7, 134.2, 129.3, 126.3, 124.9, 113.5, 112.8, 110.9, 94.8, 65.0, 64.7, 56.0, 51.6, 45.4, 42.1, 39.8, 35.2, 29.8, 28.5, 22.8, 22.7, 21.9, 20.6, 17.4. IR (KBr): 2950, 1704, 1501, 1459, 1240 cm^{-1}. MS (ESI-TOF) *m*/*z*: 451 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 451.2460 Calcd for $C_{26}H_{36}O_5Na$; Found: 451.2463.

4.2.7. *tert*-Butyl 4-hydroxy-3-methylbenzoate (13)

A solution of DCC (14.9 g, 72.5 mmol, 1.1 equiv) in anhydrous THF (65 mL) was added dropwise to a solution of **6** (10.0 g, 65.9 mmol), DMAP (0.80 g, 6.59 mmol, 0.1 equiv) and *tert*-butanol (220 mL) in anhydrous THF (30 mL) over 30 min, and the whole mixture was stirred for 20 h at rt. The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 5:1) to give **13** (13.6 g, 99%) as a white solid.

^1H NMR (500 MHz, $CDCl_3$) δ: 7.78–7.73 (2H, m), 6.85 (1H, s), 6.82 (1H, dd, *J* = 8.0, 3.4 Hz), 2.27 (3H, s), 1.59 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.7, 158.4, 132.6, 129.1, 124.0, 123.6, 114.5, 81.0, 28.2 (3C), 15.7. IR (KBr): 3341, 1678, 1607 cm^{-1}. MS (ESI-TOF) *m*/*z*: 231 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 231.0997 Calcd for $C_{12}H_{16}O_3Na$; Found: 231.1030.

4.2.8. *tert*-Butyl 4-(methoxymethoxy)-3-methylbenzoate (14)

K_2CO_3 (36.0 g, 261 mmol, 4.0 equiv) and MOMCl (9.9 mL, 130 mmol, 2.0 equiv) were added to a solution of **13** (13.5 g, 65.1 mmol) in anhydrous DMF (70 mL), and the whole mixture was stirred for 20 h at 45 °C. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in Et_2O and washed with satd NH_4Cl aq and brine. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 20:1) to give **14** (11.6 g, 70%) as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$) δ: 7.80–7.78 (2H, m), 7.03 (1H, d, *J* = 8.6 Hz), 5.24 (2H, s), 3.47 (3H, s), 2.26 (3H, s), 1.57 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.7, 158.6, 132.0, 128.8, 126.8, 124.9, 112.5, 94.0, 80.4, 56.0, 28.2 (3C), 16.2. IR (KBr): 1709, 1609, 1501, 1300 cm^{-1}. MS (ESI-TOF) *m*/*z*: 275 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 275.1259 Calcd for $C_{14}H_{20}O_4Na$; Found: 275.1253.

4.2.9. *tert*-Butyl 3-(bromomethyl)-4-(methoxymethoxy)benzoate (15)

NBS (8.16 g, 45.9 mmol, 1.1 equiv) and AIBN (342 mg, 2.09 mmol, 0.05 equiv) were added to a solution of **14** (10.5 g, 41.7 mmol) in anhydrous benzene (130 mL), and the whole mixture was stirred for 16 h under reflux. The mixture was concentrated in vacuo, and the residue was dissolved in Et_2O and washed with satd $NaHCO_3$ aq. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 20:1) to give **15** (10.5 g, 76%) as a white solid and recovered starting material (2.55 g, 24%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (1H, s), 7.91 (1H, d, J = 8.6 Hz), 7.10 (1H, d, J = 8.6 Hz), 5.31 (2H, s), 4.56 (2H, s), 3.51 (3H, s), 1.58 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 158.2, 132.2, 131.8, 126.4, 125.3, 113.3, 93.9, 80.9, 56.4, 28.4, 28.2 (3C). IR (KBr): 2363, 1709, 1609, 1501 cm^{-1}. MS (ESI-TOF) m/z: 355/353 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 353.0364 Calcd for $C_{14}H_{19}{}^{79}BrO_4Na$; Found: 353.0367.

4.2.10. *tert*-Butyl 3-[{(4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxooctahydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalen)-5′-yl}methyl]-4-(methoxymethoxy)benzoate (16)

Under an Ar atmosphere, LHMDS (15.9 mL of a 0.89 M solution, 14.2 mmol, 1.6 equiv, prepared from *n*-BuLi (1.60 M solution in hexane), HMDS and THF) was added dropwise to a solution of **5** (2.10 g, 8.90 mmol) in anhydrous THF (9.0 mL) via cannula over 5 min at −45 °C, and the whole mixture was stirred for 50 min at 0 °C. A solution of **15** (3.54 g, 10.7 mmol, 1.2 equiv) in anhydrous THF (9.0 mL) was added dropwise to the mixture via cannula over 10 min at −78 °C, and the whole mixture was stirred for 10 min at −78 °C, 40 min at 0 °C, and 1 h at rt. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 4:1) to give a coupling product, 3-[{(4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxo-3′,4′,4a′,5′,6′,8a′-hexahydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalen)-5′-yl}methyl]-4-(methoxymethoxy)benzoate (3.26 g, 75%) as a white amorphous solid.

$[\alpha]_D^{27}$ +17.8 (*c* 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (1H, dd, J = 8.6, 2.0 Hz), 7.65 (1H, d, J = 2.0 Hz), 7.07 (1H, d, J = 8.6 Hz), 6.91 (1H, d, J = 10.3 Hz), 5.87 (1H, d, J = 10.3 Hz), 5.17 (1H, d, J = 6.9 Hz), 5.10 (1H, d, J = 6.9 Hz), 3.97–3.87 (2H, m), 3.83–3.82 (2H, m), 3.44 (3H, s), 3.06 (1H, d, J = 13.9 Hz), 2.86 (1H, d, J = 13.9 Hz), 2.30 (1H, dd, J = 12.7, 2.7 Hz), 1.62–1.58 (2H, m), 1.54 (9H, s), 1.54–1.52 (2H, m), 1.44–1.38 (1H, m), 1.26–1.24 (1H, m), 1.18 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.6, 165.6, 159.3, 154.8, 133.4, 129.4, 127.5, 126.7, 124.8, 113.1, 111.6, 94.5, 80.3, 64.9, 64.5, 56.1, 48.9, 45.0, 41.9, 39.6, 29.3, 28.2 (3C), 22.4, 22.0, 21.5, 19.7. IR (KBr): 2976, 1709, 1669, 1605 cm^{-1}. MS (ESI-TOF) m/z: 509 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 509.2515 Calcd for $C_{28}H_{38}O_7Na$; Found: 509.2531.

10% Pd–C (617 mg) was added to a solution of the above coupling product (3.09 g, 6.34 mmol) in AcOEt (30 mL), and the whole mixture was stirred for 2 h under a H_2 atmosphere (balloon). The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 3:1) to give **16** (3.05 g, 99%) as a white amorphous solid.

$[\alpha]_D^{26}$ −8.1 (*c* 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (1H, dd, J = 8.6, 2.0 Hz), 7.62 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 8.6 Hz), 5.14 (1H, d, J = 6.9 Hz), 5.07 (1H, d, J = 6.9 Hz), 3.88–3.84 (4H, m), 3.43 (3H, s), 2.91 (1H, d, J = 13.6 Hz), 2.83 (1H, d, J = 13.6 Hz), 2.63–2.57 (1H, m), 2.32–2.24 (2H, m), 2.05–1.99 (1H, m), 1.66–1.64 (1H, m), 1.54 (9H, s), 1.52–1.36 (6H, m), 1.00 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.4, 165.5, 159.3, 133.3, 129.6, 126.2, 124.6, 113.0, 112.6, 94.5, 80.3, 64.9, 64.6, 56.1, 51.2, 45.9, 42.0, 39.5, 34.8, 29.7, 28.6, 28.1 (3C), 22.7, 22.6, 20.0, 17.5. IR (KBr): 1707, 1605, 1298 cm^{-1}. MS (ESI-TOF) m/z: 511 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 511.2672 Calcd for $C_{28}H_{40}O_7Na$; Found: 511.2695.

4.2.11. *tert*-Butyl 3-[{(4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-methyleneoctahydro-2′*H*-spiro([1,3]dioxolane-2,1′-naphthalen)-5′-yl}methyl]-4-(methoxymethoxy)benzoate (17)

Under an Ar atmosphere, KHMDS (45.3 mL of a 0.5 M solution in toluene, 22.6 mmol, 8.0 equiv) was added to Ph_3PCH_3Br (8.09 g, 22.6 mmol, 8.0 equiv), and the whole mixture was stirred for 1 h at rt. A solution of **16** (1.38 g, 2.83 mmol) in anhydrous THF (20 mL) was added dropwise to the mixture via cannula at 0 °C, and the whole mixture was stirred for 16 h at 55 °C. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 8:1) to give **17** (1.02 g, 74%) as a white amorphous solid.

$[\alpha]_D^{26}$ −58.9 (*c* 0.91, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (1H, dd, J = 8.6, 2.3 Hz), 7.64 (1H, d, J = 2.3 Hz), 7.05 (1H, d, J = 8.6 Hz), 5.15 (1H, d, J = 6.9 Hz), 5.10 (1H, d, J = 6.9 Hz), 4.70 (1H, s), 4.16 (1H, s), 3.99–3.92 (4H, m), 3.46 (3H, s), 2.78 (1H, d, J = 13.2 Hz), 2.67 (1H, d, J = 13.2 Hz), 2.38–2.36 (1H, m), 2.12–2.09 (2H, m), 1.98–1.95 (1H, m), 1.70–1.68 (1H, m), 1.62–1.54 (3H, m), 1.56 (9H, s), 1.46–1.44 (2H, m), 1.19–1.17 (1H, m), 1.05 (3H, s), 0.92 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.9, 159.9, 153.1, 134.0, 128.9, 127.2, 123.9, 113.6, 112.6, 107.6, 94.7, 80.2, 64.8, 64.4, 56.1, 46.7, 43.4, 42.8, 39.5, 32.0, 29.7, 29.4, 28.2 (3C), 23.1, 22.8, 20.9, 19.9. IR (KBr): 1709, 1604, 1497 cm^{-1}. MS (ESI-TOF) m/z: 509 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 509.2879 Calcd for $C_{29}H_{42}O_6Na$; Found: 509.2861.

4.2.12. *tert*-Butyl 3-[{(1*R*,4a*R*,8a*R*)-1,4a-dimethyl-2-methylene-5-oxodecahydronaphthalen-1-yl}methyl]-4-(methoxymethoxy)benzoate (18)

5% HCl (15 mL) was added to a solution of **17** (606 mg, 1.24 mmol) in THF (20 mL) at 0 °C, and the whole mixture was stirred for 6 h at rt. Satd $NaHCO_3$ aq was added to the mixture, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a **18** as a colorless amorphous solid, which was used for the next reaction without further purification.

$[\alpha]_D^{27}$ −70.6 (*c* 1.46, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (1H, dd, J = 8.6, 2.3 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.06 (1H, d, J = 8.6 Hz), 5.16 (1H, d, J = 6.9 Hz), 5.12 (1H, d, J = 6.9 Hz), 4.78 (1H, s), 4.33 (1H, s), 3.46 (3H, s), 2.80 (1H, d, J = 13.2 Hz), 2.69 (1H, d, J = 13.2 Hz), 2.52 (1H, td, J = 14.3, 6.3 Hz), 2.43–2.21 (4H, m), 2.08–2.05 (1H, m), 1.83–1.78 (3H, m), 1.56 (9H, s), 1.52–1.46 (1H, m), 1.41–1.37 (1H, m), 1.14 (3H, s), 1.06 (3H, s), 0.88 (1H, t, J = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.1, 165.7, 159.7, 151.7, 133.9, 129.2, 126.7, 124.2, 112.7, 108.8, 94.7, 80.4, 56.2, 49.7, 49.1, 44.0, 39.6, 38.0, 31.5, 28.6, 28.2 (3C), 25.4, 23.3, 22.6, 20.8. IR (KBr): 1707, 1604 cm^{-1}. MS (ESI-TOF) m/z: 465 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 465.2617 Calcd for $C_{27}H_{38}O_5Na$; Found: 465.2634.

4.2.13. *tert*-Butyl 4-(methoxymethoxy)-3-[{(1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl}methyl]benzoate (19)

10% Pd–C (1.22 g) was added to a solution of the above product **18** in Et_3N/MeOH (30 mL, 50:1), and the whole mixture was stirred for 12 h under a H_2 atmosphere (balloon). The mixture was diluted with small amount of $CHCl_3$ and filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 1:1) to give **19** (554 mg, quantitative yield for two steps) as a colorless viscous liquid.

$[\alpha]_D^{27}$ +18.7 (*c* 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (1H, dd, J = 8.6, 2.3 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.08 (1H, d, J = 8.6 Hz), 5.18 (1H, d, J = 6.9 Hz), 5.16 (1H, d, J = 6.9 Hz), 3.44 (3H, s), 2.81 (1H, d, J = 14.3 Hz), 2.63–2.54 (2H, m), 2.21–2.18 (2H, m), 2.13–2.10 (1H, m), 1.85–1.79 (1H, m), 1.71–1.61 (1H, m), 1.56 (9H, s), 1.47 (1H, dt, J = 13.0, 2.4 Hz), 1.43–1.38 (1H, m), 1.34–1.18 (3H, m), 1.15 (3H, s), 1.02 (3H, d, J = 5.7 Hz), 0.93 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.0, 165.5, 159.6, 133.6, 129.4, 127.0, 124.6, 113.3, 94.4, 80.5, 56.2, 49.1, 47.3, 42.3, 37.4, 37.2, 35.8, 32.3, 28.2 (3C), 26.8, 25.3, 22.0, 18.8, 18.0, 17.6. IR (KBr):

1707, 1605, 1456 cm^{-1}. MS (ESI-TOF) *m*/*z*: 467 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 467.2773 Calcd for $C_{27}H_{40}O_5Na$; Found: 467.2793.

4.2.14. 4-Hydroxy-3-[{(1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl}methyl]benzoic acid (20)

6 N HCl (20 mL) was added to a solution of **19** (541 mg, 1.24 mmol) in THF (20 mL) at 0 °C and stirred for 12 h at rt. The whole mixture was concentrated in vacuo. TFA (10 mL) was added to a solution of the above residue in dry CH_2Cl_2 (10 mL) at 0 °C, and the whole mixture was stirred for 2 h at rt. The mixture was concentrated in vacuo to give a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 1:1 contained with 1% AcOH) to give **20** (414 mg, 97%) as a white solid.

$[\alpha]_D^{27}$ +26.7 (*c* 1.05, MeOH). ^1H NMR (500 MHz, CD_3COCD_3) δ: 7.76 (1H, d, *J* = 2.3 Hz), 7.72 (1H, dd, *J* = 8.3, 2.3 Hz), 6.91 (1H, d, *J* = 8.3 Hz), 2.78 (1H, d, *J* = 14.2 Hz), 2.73 (1H, d, *J* = 14.2 Hz), 2.63 (1H, td, *J* = 14.0, 7.1 Hz), 2.31 (1H, dd, *J* = 13.7, 2.0 Hz), 2.09–2.00 (3H, m), 1.88–1.83 (1H, m), 1.67–1.63 (1H, m), 1.38–1.34 (4H, m), 1.17 (1H, d, *J* = 2.0 Hz), 1.15 (3H, s), 1.05 (3H, d, *J* = 6.0 Hz), 0.96 (3H, s). ^{13}C NMR (125 MHz, CD_3OD) δ: 219.0, 170.2, 162.3, 135.9, 130.7, 125.9, 121.8, 115.7, 50.5, 49.3, 43.4, 38.4, 37.9, 37.0, 33.8, 27.8, 26.8, 23.0, 19.3, 18.4, 17.9. IR (KBr): 3156, 1682, 1603, 1279 cm^{-1}. MS (ESI-TOF) *m*/*z*: 367 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 367.1885 Calcd for $C_{21}H_{28}O_4Na$; Found: 367.1887.

4.2.15. Methyl 4-hydroxy-3-[{(1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl}methyl]benzoate (21)

$SOCl_2$ (0.35 mL, 4.82 mmol, 4.5 equiv) was added to a solution of **20** (367 mg, 1.06 mmol) in anhydrous MeOH (11 mL), and the whole mixture was stirred for 24 h at 45 °C. Removal of the solvent from the mixture under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 2:1) to give **21** (338 mg, 89%) as a white solid.

$[\alpha]_D^{27}$ +25.9 (*c* 1.07, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75–7.72 (2H, m), 6.75 (1H, d, *J* = 8.0 Hz), 6.58 (1H, br s), 3.86 (3H, s), 2.73 (1H, d, *J* = 14.3 Hz), 2.67 (1H, d, *J* = 14.3 Hz), 2.58 (1H, td, *J* = 14.0, 7.2 Hz), 2.24 (1H, d, *J* = 12.9 Hz), 2.17 (1H, dd, *J* = 14.3, 5.2 Hz), 2.09–2.05 (1H, m), 1.79 (1H, qd, *J* = 12.9, 6.4 Hz), 1.65–1.62 (1H, m), 1.48–1.45 (1H, m), 1.41–1.38 (1H, m), 1.28–1.25 (3H, m), 1.16 (3H, s), 1.14–1.13 (1H, m), 1.02 (3H, d, *J* = 5.7 Hz), 0.94 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 217.3, 167.2, 159.3, 134.8, 129.5, 124.7, 121.6, 115.3, 51.9, 49.2, 47.5, 42.3, 37.5, 37.1, 35.7, 32.3, 26.7, 25.2, 22.0, 18.9, 18.0, 17.5. IR (KBr): 3333, 1688, 1603, 1427, 1283 cm^{-1}. MS (ESI-TOF) *m*/*z*: 381 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 381.2042 Calcd for $C_{22}H_{30}O_4Na$; Found: 381.2047.

4.2.16. (+)-Dictyoceratin-C (1)

Under an Ar atmosphere, KHMDS (12.3 mL of a 0.5 M solution in toluene, 6.14 mmol, 9.5 equiv) was added to Ph_3PCH_3Br (2.19 g, 6.14 mmol, 9.5 equiv), and the whole mixture was stirred for 1 h at rt. A solution of **21** (231 mg, 0.643 mmol) in anhydrous THF (12 mL) was added dropwise to the mixture via cannula at 0 °C, and the whole mixture was stirred for 12 h at rt. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 8:1) to give **1** (205 mg, 98%) as a white solid.

$[\alpha]_D^{27}$ +17.3 (*c* 0.12, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.77 (1H, s), 7.77–7.74 (1H, m), 6.77 (1H, d, *J* = 8.0 Hz), 6.01 (1H, s), 4.41 (1H, s), 4.36 (1H, s), 3.87 (3H, s), 2.68 (1H, d, *J* = 14.3 Hz), 2.64 (1H, d, *J* = 14.3 Hz), 2.33 (1H, td, *J* = 13.7, 5.2 Hz), 2.08 (2H, d, *J* = 13.7 Hz), 1.93–1.89 (1H, m), 1.61–1.56 (1H, m), 1.47 (1H, dt, *J* = 12.2, 3.2 Hz), 1.41–1.38 (3H, m), 1.31–1.27 (1H, m), 1.22–1.19 (1H, m), 1.06 (3H, s), 1.02 (3H, d, *J* = 6.9 Hz), 0.96 (1H, dd, *J* = 12.0, 1.7 Hz), 0.88 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.6, 160.0, 159.2, 135.0, 129.3, 125.2, 121.6, 115.3, 102.8, 52.0, 48.0, 42.0, 40.2, 37.0, 36.5, 36.3, 33.0, 27.8, 27.7, 23.2, 20.5, 17.62, 17.59. IR (KBr): 3341, 1686, 1601, 1426, 1287 cm^{-1}. MS (ESI-TOF) *m*/*z*: 379 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 379.2249 Calcd for $C_{23}H_{32}O_3Na$; Found: 379.2266.

4.2.17. (−)-Dictyoceratin-C (*ent*-1)

ent-**1** was synthesized through the same procedures as those for **1**, using *ent*-**5** as a starting material. $[\alpha]_D^{26}$ −17.7 (*c* 0.28, $CHCl_3$).

4.3. Enantioselective synthesis of dictyoceratin-A (2)

4.3.1. 2-Ethyl-2,4-dimethylbenzo[*d*][1,3]dioxole (23)

A solution of P_2O_5 (12.6 g, 88.8 mmol, 1.0 equiv) in 2-butanone (162 mL) was added to a solution of 2,3-dihydroxytoluene (**22**) (10.9 g, 87.8 mmol) in anhydrous toluene (162 ml), and the whole mixture was stirred for overnight at 75 °C. The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane) to give **23**[19] (11.0 g, 70%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$) δ: 6.67 (1H, t, *J* = 8.0 Hz), 6.59 (1H, d, *J* = 8.0 Hz), 6.58 (1H, d, *J* = 8.0 Hz), 2.20 (3H, s), 1.94 (2H, q, *J* = 7.4 Hz), 1.61 (3H, s), 1.01 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.1, 146.0, 122.7, 120.4, 118.9, 118.6, 105.7, 32.2, 24.0, 14.7, 7.5.

4.3.2. 1-(2-Ethyl-2,7-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethanone (24)

$ZnCl_2$ (4.68 g, 34.3 mmol, 1.0 equiv) was added to a solution of **23** (6.10 g, 34.2 mmol) in Ac_2O (31 mL) at 0 °C, and the whole mixture was stirred for 2.5 h at 0 °C and for 1.5 h at rt. The mixture was concentrated in vacuo. Satd $NaHCO_3$ aq was added to the residue, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 20:1) to give **24** (4.12 g, 55%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$) δ: 7.34 (1H, d, *J* = 1.1 Hz), 7.19 (1H, d, *J* = 1.1 Hz), 2.51 (3H, s), 2.24 (3H, s), 1.96 (2H, q, *J* = 7.4 Hz), 1.63 (3H, s), 1.01 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.3, 150.3, 147.5, 130.9, 125.6, 120.6, 117.7, 105.2, 32.2, 26.2, 23.9, 14.5, 7.2. IR (KBr): 2982, 1676, 1489, 1427, 1302, 1235 cm^{-1}. MS (ESI-TOF) *m*/*z*: 243 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 243.0997 Calcd for $C_{13}H_{16}O_3Na$; Found: 243.1000.

4.3.3. 2-Ethyl-2,7-dimethylbenzo[*d*][1,3]dioxole-5-carboxylic acid (25)

$Ca(ClO)_2$ (16.8 g, 118 mmol, 5.0 equiv) was dissolved in H_2O (23.6 mL) and stirred for 10 min at 60 °C. A solution of Na_2CO_3 (12.5 g, 118 mmol, 5.0 equiv) and NaOH (3.6 g, 89.7 mmol, 3.8 equiv) in H_2O (23.6 mL) was added dropwise to the mixture at rt, and the whole mixture was stirred for 5 min at 60 °C. The mixture was filtered, and the filtrate was stirred at 60 °C. A solution of **24** (5.20 g, 23.6 mmol) in 1,4-dioxane (23.6 mL) was added dropwise to the mixture, and the whole mixture was stirred for 3 h at 70 °C. Satd $NaHSO_3$ aq was added to the mixture, and the whole mixture was stirred for 1 h at rt. 5% HCl was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt/AcOH = 25:5:3) to give **25** (4.69 g, 89%) as a white solid.

^1H NMR (500 MHz, $CDCl_3$) δ: 12.29 (1H, br), 7.54 (1H, d, *J* = 1.1 Hz), 7.30 (1H, d, *J* = 1.1 Hz), 2.24 (3H, s), 1.98 (2H, q, *J* = 7.4 Hz), 1.65 (3H, s), 1.02 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.3, 151.0, 147.3, 127.2, 122.0, 120.9 118.1, 107.2, 32.3, 24.0, 14.5, 7.3. IR (KBr): 2980, 2943, 1684, 1424, 1306, 1225, 1182 cm^{-1}. MS (ESI-TOF) *m*/*z*: 245 $[M+Na]^+$.

HRMS (ESI-TOF) *m*/*z*: 245.0791 Calcd for $C_{12}H_{14}O_4Na$; Found: 245.0790.

4.3.4. *tert*-Butyl 2-ethyl-2,7-dimethylbenzo[*d*][1,3]dioxole-5-carboxylate (26)

$SOCl_2$ (2.0 mL, 27.4 mmol, 2.0 equiv) was added to a solution of **25** (3.00 g, 13.5 mmol) in anhydrous THF (27 mL) at 0 °C, and the whole mixture was stirred for 30 min at rt. *tert*-BuOK (54.0 mL of a 1.0 M solution in THF, 54.0 mmol, 4.0 equiv) was added dropwise to the mixture at 0 °C, and the whole mixture was stirred for 30 min at rt. H_2O was added to the mixture and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 30:1) to give **26** (1.95 g, 52%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (1H, s), 7.18 (1H, s), 2.21 (3H, s), 1.95 (2H, q, *J* = 7.4 Hz), 1.62 (3H, s), 1.56 (9H, s), 1.00 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 149.6, 147.0, 125.7, 124.6, 120.2, 117.5, 106.6, 80.1, 32.1, 28.0 (3C), 23.8, 14.4, 7.2. IR (KBr): 2980, 1709, 1312, 1169 cm^{-1}. MS (ESI-TOF) *m*/*z*: 301 [M+Na]$^+$. HRMS (ESI-TOF) *m*/*z*: 301.1416 Calcd for $C_{16}H_{22}O_4Na$; Found: 301.1429.

4.3.5. *tert*-Butyl 7-(bromomethyl)-2-ethyl-2-methylbenzo[*d*][1,3]dioxole-5-carboxylate (27)

NBS (1.76 g, 9.89 mmol, 1.1 equiv) and AIBN (118 mg, 0.72 mmol, 0.08 equiv) were added to a solution of **26** (2.50 g, 8.98 mmol) in anhydrous benzene (36 mL), and the whole mixture was stirred for 2 h under reflux. Satd $NaHCO_3$ aq was added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 20:1) to give **27** (1.91 g, 60%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53 (1H, d, *J* = 1.1 Hz), 7.28 (1H, d, *J* = 1.1 Hz), 4.46 (1H, d, *J* = 10.1 Hz), 4.42 (1H, d, *J* = 10.1 Hz), 1.99 (2H, q, *J* = 7.4 Hz), 1.66 (3H, s), 1.56 (9H, s), 1.01 (3H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 149.7, 147.9, 125.5, 125.0, 122.1, 117.9, 109.1, 80.9, 32.4, 28.2 (3C), 26.5, 24.2, 7.2. IR (KBr): 2980, 1711, 1485, 1447, 1312, 1235, 1165 cm^{-1}. MS (ESI-TOF) *m*/*z*: 379/381 [M+Na]$^+$. HRMS (ESI-TOF) *m*/*z*: 379.0521 Calcd for $C_{16}H_{21}{}^{79}BrO_4Na$; Found: 379.0541.

4.3.6. *tert*-Butyl 7-(((4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxo-3′,4′,4a′,5′,6′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-5′-yl)methyl)-2-ethyl-2-methylbenzo[*d*][1,3]dioxole-5-carboxylate (28)

Under an Ar atmosphere, LHMDS (6.2 mL of a 1.0 M solution in THF, 6.2 mmol, 1.5 equiv) was added dropwise to a solution of **5** (980 mg, 4.15 mmol) in anhydrous THF (5.5 mL) via cannula over 5 min at −78 °C, and the whole mixture was stirred for 1 h with gradually warming to 0 °C. A solution of **27** (1.78 g, 4.98 mmol, 1.2 equiv) in anhydrous THF (10 mL) was added dropwise to the mixture via cannula over 5 min at −78 °C, and the whole mixture was stirred for 1.5 h with gradually warming to 60 °C and for 12 h at 60 °C. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with CH_2Cl_2. Removal of the solvent from the CH_2Cl_2 extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 5:1) to give **28** (1.55 g, 73%, inseparable diastereomeric mixture) as a white amorphous.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (0.5H, d, *J* = 1.7 Hz), 7.23 (0.5H, d, *J* = 1.7 Hz), 7.18 (0.5H, d, *J* = 1.7 Hz), 7.17 (0.5H, d, *J* = 1.7 Hz), 6.95 (0.5H, d, *J* = 10.3 Hz), 6.93 (0.5H, d, *J* = 9.7 Hz), 5.90 (0.5H, d, *J* = 9.7 Hz), 5.85 (0.5H, d, *J* = 10.3 Hz), 3.98 (1H, q, *J* = 6.9 Hz), 3.92 (1H, q, *J* = 6.8 Hz), 3.88–3.81 (2H, m), 3.12 (0.5H, d, *J* = 13.7 Hz), 3.02 (0.5H, d, *J* = 13.7 Hz), 2.71 (0.5H, d, *J* = 13.7 Hz), 2.68 (0.5H, d, *J* = 13.7 Hz), 2.40–2.35 (1H, m), 1.96–1.91 (2H, m), 1.69–1.66 (1H, m), 1.63–1.56 (6H, m), 1.55 (9H, s), 1.50–1.44 (2H, m), 1.232 (1.5H, s), 1.225 (1.5H, s), 1.21 (1.5H, s), 1.20 (1.5H, s), 1.02 (1.5H, t, *J* = 7.4 Hz), 0.98 (1.5H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.5 (0.5C), 203.3 (0.5C), 165.56 (0.5C), 165.54 (0.5C), 155.2 (0.5C), 155.0 (0.5C), 150.4 (0.5C), 150.2 (0.5C), 147.09 (0.5C), 147.06 (0.5C), 127.6 (0.5C), 127.5 (0.5C), 127.1 (0.5C), 126.9 (0.5C), 124.73 (0.5C), 124.71 (0.5C), 120.5 (0.5C), 120.4 (0.5C), 118.3 (0.5C), 118.1 (0.5C), 111.7, 107.1 (0.5C), 107.0 (0.5C), 80.3, 65.0, 64.50 (0.5C), 64.47 (0.5C), 49.3, 45.13 (0.5C), 45.07 (0.5C), 41.6 (0.5C), 41.4 (0.5C), 38.8 (0.5C), 38.7 (0.5C), 32.3 (0.5C), 32.2 (0.5C), 29.31 (0.5C), 29.28 (0.5C), 28.2 (3C), 24.1 (0.5C), 23.7 (0.5C), 22.4 (0.5C), 22.34 (0.5C), 22.33 (0.5C), 22.28 (0.5C), 21.13 (0.5C), 21.07 (0.5C), 19.7 (0.5C), 19.6 (0.5C), 7.5 (0.5C), 7.3 (0.5C). IR (KBr): 2980, 1707, 1669, 1437, 1381, 1304, 1167 cm^{-1}. MS (ESI-TOF) *m*/*z*: 535 [M+Na]$^+$. HRMS (ESI-TOF) *m*/*z*: 535.2672 Calcd for $C_{30}H_{40}O_7Na$; Found: 535.2682.

4.3.7. *tert*-Butyl 7-(((4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxooctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-5′-yl)methyl)-2-ethyl-2-methylbenzo[*d*][1,3]dioxole-5-carboxylate (29)

10% Pd–C (1.0 g) was added to a solution of **28** (2.13 g, 4.16 mmol) in EtOH (20 mL), and the whole mixture was stirred for 2 h under a H_2 atmosphere (balloon). The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave **29** (2.05 g, 99%, diastereomeric mixture) as a white amorphous, which was used for the next reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (0.5H, s), 7.26 (0.5H, s), 7.194 (0.5H, s), 7.191 (0.5H, s), 3.95–3.80 (4H, m), 2.96 (0.5H, d, *J* = 13.7 Hz), 2.88 (0.5H, d, *J* = 13.7 Hz), 2.69 (0.5H, d, *J* = 13.7 Hz), 2.66 (0.5H, d, *J* = 13.7 Hz), 2.51–2.32 (2H, m), 2.23–2.20 (1H, m), 1.99–1.85 (3H, m), 1.68–1.64 (2H, m), 1.61 (1.5H, s), 1.57 (1.5H, s), 1.54 (9H, s), 1.48–1.41 (5H, m), 1.09 (4.5H, s), 1.07 (1.5H, s), 1.02 (1.5H, t, *J* = 7.7 Hz), 0.99 (1.5H, t, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.3 (0.5C), 216.0 (0.5C), 165.53 (0.5C), 165.51 (0.5C), 150.5 (0.5C), 150.3 (0.5C), 147.0, 126.83 (0.5C), 126.75 (0.5C), 124.7, 120.54 (0.5C), 120.50 (0.5C), 118.3 (0.5C), 118.2 (0.5C), 112.7 (0.5C), 112.6 (0.5C), 107.19 (0.5C), 107.16 (0.5C), 80.3, 64.94 (0.5C), 64.92 (0.5C), 64.7, 51.8 (0.5C), 51.6 (0.5C), 44.8 (0.5C), 44.7 (0.5C), 42.12 (0.5C), 42.07 (0.5C), 38.6 (0.5C), 38.5 (0.5C), 35.2 (0.5C), 35.0 (0.5C), 32.3 (0.5C), 32.1 (0.5C), 29.9, 28.2 (3C), 28.1 (0.5C), 28.0 (0.5C), 23.9 (0.5C), 23.8 (0.5C), 22.6, 22.5 (0.5C), 22.4 (0.5C), 21.32 (0.5C), 21.30 (0.5C), 16.74 (0.5C), 16.73 (0.5C), 7.5 (0.5C), 7.4 (0.5C). IR (KBr): 2978, 1707, 1439, 1304, 1165 cm^{-1}. MS (ESI-TOF) *m*/*z*: 537 [M+Na]$^+$. HRMS (ESI-TOF) *m*/*z*: 537.2828 Calcd for $C_{30}H_{42}O_7Na$; Found: 537.2844.

4.3.8. *tert*-Butyl 7-(((4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-methyleneoctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-5′-yl)methyl)-2-ethyl-2-methylbenzo[*d*][1,3]dioxole-5-carboxylate (30)

Under an Ar atmosphere, KHMDS (56 mL of a 0.5 M solution in toluene, 28 mmol, 7.2 equiv) was added to Ph_3PCH_3Br (11.1 g, 30.7 mmol, 7.9 equiv), and the whole mixture was stirred for 1 h at 100 °C. A solution of **29** (2.00 g, 3.89 mmol) in anhydrous toluene (19.5 mL) was added dropwise to the mixture via cannula at rt, and the whole mixture was stirred for 1.5 h at 100 °C. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave a crude product, which was purified by SiO_2 column (*n*-hexane/AcOEt = 18:1) to give **30** (1.64 g, 82%, diastereomeric mixture) as a white amorphous.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (0.5H, d, *J* = 1.7 Hz), 7.29 (0.5H, d, *J* = 1.7 Hz), 7.17 (1H, br s), 4.75 (1H, d, *J* = 1.1 Hz), 4.39

(0.5H, d, J = 1.1 Hz), 4.37 (0.5H, d, J = 1.1 Hz), 3.99–3.89 (4H, m), 2.68–2.57 (2H, m), 2.29–2.27 (1H, m), 2.18–2.11 (1H, m), 2.05–2.00 (1H, m), 1.94–1.91 (3H, m), 1.69–1.67 (1H, m), 1.62–1.56 (3H, m), 1.55 (9H, s), 1.54–1.42 (5H, m), 1.22–1.14 (1H, m), 1.061 (1.5H, s), 1.058 (1.5H, s), 1.01–0.98 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.7, 153.01 (0.5C), 152.98 (0.5C), 150.83 (0.5C), 150.78 (0.5C), 146.6, 127.5, 123.7 (0.5C), 123.6 (0.5C), 120.1 (0.5C), 120.0 (0.5C), 119.2 (0.5C), 119.1 (0.5C), 113.48 (0.5C), 113.46 (0.5C), 108.12 (0.5C), 108.07 (0.5C), 106.64 (0.5C), 106.61 (0.5C), 80.1, 65.0 (0.5C), 64.4 (0.5C), 46.1 (0.5C), 46.0 (0.5C), 43.30 (0.5C), 43.27 (0.5C), 42.80 (0.5C), 42.77 (0.5C), 39.9 (0.5C), 39,7 (0.5C), 32.2 (0.5C), 32.0 (0.5C), 31.8 (0.5C), 31.7 (0.5), 29.74 (0.5C), 29.67 (0.5C), 29.5 (0.5C), 29.4 (0.5C), 28.2 (3C), 23.8, 22.81 (0.5C), 22.78 (0.5C), 22.72, 20.7, 20.6, 20.5, 7.4 (0.5C), 7.3 (0.5C). IR (KBr): 2982, 2943, 1707, 1439, 1377, 1304, 1165 cm^{-1}. MS (ESI-TOF) m/z: 535 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 535.3036 Calcd for $C_{31}H_{44}O_6Na$; Found: 535.3052.

4.3.9. *tert*-Butyl 7-(((1*R*,4a*R*,8a*R*)-1,4a-dimethyl-2-methylene-5-oxodecahydronaphthalen-1-yl)methyl)-2-ethyl-2-methylbenzo[*d*][1,3]dioxole-5-carboxylate (31)

Concd HCl (5 mL) was added to a solution of **30** (1.61 g, 3.14 mmol) in THF (45 mL) at 0 °C, and the whole mixture was stirred for 30 min at rt. H_2O was added to the mixture, and the whole mixture was extracted with Et_2O. Removal of the solvent from the Et_2O extract under reduced pressure gave **31** (1.50 g, quant, diastereomeric mixture) as a white amorphous, which was used next reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (0.5H, d, J = 1.7 Hz), 7.31 (0.5H, d, J = 1.7 Hz), 7.18 (1H, s), 4.84 (1H, s), 4.54 (0.5H, d, J = 1.1 Hz), 4.51 (0.5H, d, J = 1.1 Hz), 2.71 (0.5H, d, J = 14.0 Hz), 2.70 (0.5H, d, J = 14.0 Hz), 2.61 (0.5H, d, J = 14.0 Hz), 2.60 (0.5H, d, J = 14.0 Hz), 2.54–2.52 (1H, m), 2.34–2.24 (4H, m), 2.09–2.04 (1H, m), 1.93–1.90 (2H, m), 1.86–1.72 (3H, m), 1.57 (1.5H, s), 1.56 (1.5H, s), 1.55 (9H, s), 1.47–1.42 (2H, m), 1.15 (3H, s), 1.13 (1.5H, s), 1.11 (1.5H, s), 1.00–0.98 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.03 (0.5C), 215.01 (0.5C), 165.57 (0.5C), 165.56 (0.5C), 151.6 (0.5C), 151.5 (0.5C), 150.7 (0.5C), 150.6 (0.5C), 146.8, 127.2, 124.1 (0.5C), 124.0 (0.5C), 120.3 (0.5C), 120.2 (0.5C), 118.7 (0.5C), 118.6 (0.5C), 109.3 (0.5C), 109.2 (0.5C), 107.0 (0.5C), 106.9 (0.5C), 80.4, 49.4 (0.5C), 49.2 (0.5C), 49.1 (0.5C), 49.0 (0.5C), 43.94 (0.5C), 43.92 (0.5C), 39.68 (0.5C), 39.66 (0.5C), 37.90 (0.5C), 37.88 (0.5C), 32.2 (0.5C), 32.0 (0.5C), 31.54 (0.5C), 31.52 (0.5C), 28.6, 28.2 (3C), 25.41 (0.5C), 25.38 (0.5C), 23.8, 23.02 (0.5C), 22.99 (0.5C), 22.2 (0.5C), 22.1 (0.5C), 21.7 (0.5C), 21.5 (0.5C), 7.5 (0.5C), 7.3 (0.5C). IR (KBr): 2982, 2944, 1707, 1439, 1377, 1304, 1165 cm^{-1}. MS (ESI-TOF) m/z: 491 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 491.2773 Calcd for $C_{29}H_{40}O_5Na$; Found: 491.2793.

4.3.10. *tert*-Butyl 2-ethyl-2-methyl-7-(((1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl)methyl)benzo[*d*][1,3]dioxole-5-carboxylate (32)

10% Pd–C (2.11 g) was added to a solution of **31** (1.47 g, 3.14 mmol) in Et_3N (29.5 mL) and MeOH (2 drops), and the whole mixture was stirred for 6 h under a H_2 atmosphere (balloon). The mixture was filtered through short pad of Celite. Removal of the solvent from the filtrate under reduced pressure gave **32** (1.46 g, 99%) as a white amorphous, which was used for the next reaction without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.253 (0.5H, s), 7.249 (0.5H, s), 7.21 (0.5H, d, J = 1.1 Hz), 7.20 (0.5H, d, J = 1.1 Hz), 2.66–2.54 (3H, m), 2.18–2.13 (3H, m), 1.94–1.91 (2H, m), 1.83–1.78 (1H, m), 1.71–1.64 (1H, m), 1.58 (1.5H, s), 1.56 (1.5H, s), 1.54 (9H, s), 1.51–1.49 (1H, m), 1.35–1.25 (4H, m), 1.24–1.21 (1H, m), 1.15 (3H, s), 1.00–0.97 (6H, m), 0.92 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.89 (0.5C), 215.87 (0.5C), 165.3, 150.8 (0.5C), 150.7 (0.5C), 147.2 (0.5C), 147.1 (0.5C), 126.9 (0.5C), 126.8 (0.5C), 124.6 (0.5C), 124.5 (0.5C), 120.0, 118.6 (0.5C), 118.5 (0.5C), 107.24 (0.5C), 107.16 (0.5C), 80.5, 49.0, 47.42 (0.5C), 47.35 (0.5C), 42.3, 37.4, 37.24 (0.5C), 37.22 (0.5), 36.1 (0.5C), 36.0 (0.5C), 32.4, 32.18 (0.5C), 32.16 (0.5C), 28.2 (3C), 26.8 (0.5C), 26.7 (0.5C), 25.4 (0.5C), 25.3 (0.5C), 24.2 (0.5C), 23.4 (0.5C), 21.6 (0.5C), 17.9 (0.5C), 17.8 (0.5C), 17.3 (0.5C), 17.2 (0.5C), 7.5 (0.5C), 7.2 (0.5C). IR (KBr): 2976, 2934, 1707, 1435, 1304, 1165 cm^{-1}. MS (ESI-TOF) m/z: 493 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 493.2930 Calcd for $C_{29}H_{42}O_5Na$; Found: 493.2941.

4.3.11. 3,4-Dihydroxy-5-(((1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl)methyl)benzoic acid (33)

TFA (40 mL) was added to a solution of **32** (1.34 g, 2.95 mmol) in THF/H_2O (7:3, 10 mL) at 0 °C, and the whole mixture was stirred for 4 h at 40 °C and for 1 h at 50 °C. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column ($CHCl_3$/MeOH/H_2O = 30:3:1, lower phase) to give **33** (1.01 g, 95%) as a white amorphous.

$[\alpha]_D^{26}$ +23.8 (c 0.932, MeOH). ^{1}H NMR (500 MHz, CD_3COCD_3) δ: 8.92 (1H, br), 7.88 (1H, br), 7.38 (1H, d, J = 1.7 Hz), 7.35 (1H, d, J = 1.7 Hz), 2.75 (1H, d, J = 14.0 Hz), 2.71 (1H, d, J = 14.0 Hz), 2.60 (1H, td, J = 14.2, 7.4 Hz), 2.28 (1H, br d, J = 12.0 Hz), 2.02–1.97 (2H, m), 1.81 (1H, qd, J = 13.0, 3.4 Hz), 1.69–1.59 (1H, m), 1.35–1.32 (4H, m), 1.18–1.15 (2H, m), 1.12 (3H, s), 1.03 (3H, d, J = 5.7 Hz), 0.93 (3H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ: 214.8, 167.9, 150.3, 144.7, 127.1, 125.3, 121.1, 114.7, 49.7, 48.6, 42.9, 37.8, 37.6, 36.6, 33.5, 27.5, 26.1, 22.6, 19.1, 18.3, 17.9. IR (KBr): 3206, 2955, 1688, 1439, 1296, 1225 cm^{-1}. MS (ESI-TOF) m/z: 383 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 383.1834 Calcd for $C_{21}H_{28}O_5Na$; Found: 383.1852.

4.3.12. Methyl 3,4-dihydroxy-5-(((1*S*,2*R*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-oxodecahydronaphthalen-1-yl)methyl)benzoate (34)

$SOCl_2$ (0.44 mL, 6.00 mmol, 4.0 equiv) was added to a solution of **33** (538 mg, 1.49 mmol) in anhydrous MeOH (7.5 mL), and the whole mixture was stirred for 2.5 h with gradually warming to 60 °C and for 30 min at 60 °C. Removal of the solvent from the filtrate under reduced pressure gave a crude product, which was purified by SiO_2 column (n-hexane/AcOEt = 2:1) to give **34** (477 mg, 85%) as a white solid.

$[\alpha]_D^{26}$ +24.8 (c 1.05, MeOH). ^{1}H NMR (500 MHz, CD_3COCD_3) δ: 8.89 (1H, s), 7.95 (1H, s), 7.38 (1H, d, J = 2.3 Hz), 7.34 (1H, d, J = 2.3 Hz), 3.78 (3H, s), 2.78 (1H, d, J = 14.0 Hz), 2.75 (1H, d, J = 14.0 Hz), 2.64 (1H, td, J = 13.9, 7.1 Hz), 2.31 (1H, br d, J = 15.5 Hz), 2.10–2.08 (1H, m), 1.87 (1H, qd, J = 13.0, 3.7 Hz), 1.73–1.64 (1H, m), 1.41–1.29 (4H, m), 1.21–1.19 (2H, m), 1.16 (3H, s), 1.06 (3H, d, J = 6.3 Hz), 0.97 (3H, s). ^{13}C NMR (125 MHz, CD_3COCD_3) δ: 214.9, 167.2, 150.3, 144.7, 126.7, 125.3, 120.8, 114.3, 51.9, 49.7, 48.5, 42.9, 37.8, 37.6, 36.6, 33.4, 27.5, 26.0, 22.5, 19.0, 18.3, 17.9. IR (KBr): 3355, 2953, 1701, 1439, 1302, 1225 cm^{-1}. MS (ESI-TOF) m/z: 397 [M+Na]$^+$. HRMS (ESI-TOF) m/z: 397.1991 Calcd for $C_{22}H_{30}O_5Na$; Found: 397.1997.

4.3.13. (+)-Dictyoceratin-A (2)

Under an Ar atmosphere, KHMDS (13.2 mL of a 0.5 M solution in toluene, 6.6 mmol, 10.3 equiv) was added to Ph_3PCH_3Br (2.62 g, 7.33 mmol, 11.5 equiv), and the whole mixture was stirred for 1 h at rt. Above solution (24 mL, about 4.2 mmol of $Ph_3P{=}CH_2$, 6.6 equiv) was added dropwise to a solution of **34** (241 mg, 0.64 mmol) in anhydrous THF (24.5 mL), and the whole mixture was stirred for 1 h at rt. Satd NH_4Cl aq was added to the mixture, and the whole mixture was extracted with AcOEt. Removal of the solvent from the AcOEt extract under reduced pressure gave a crude product, which was purified by SiO_2 column (n-hexane/

AcOEt = 18:1) to give dictyoceratin-A (**2**) (200 mg, 83%) as a white solid.

$[\alpha]_D^{26}$ +10.4 (*c* 0.19, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.49 (1H, d, *J* = 2.0 Hz), 7.40 (1H, d, *J* = 2.0 Hz), 5.90 (2H, S), 4.41 (1H, s), 4.37 (1H, s), 3.87 (3H, s), 2.68 (1H, d, *J* = 14.3 Hz), 2.65 (1H, d, *J* = 14.3 Hz), 2.34 (1H, td, *J* = 13.7, 5.0 Hz), 2.09 (2H, d, *J* = 14.3 Hz), 1.93–1.91 (1H, m), 1.60–1.55 (1H, m), 1.47 (1H, dt, *J* = 11.6, 2.7 Hz), 1.43–1.35 (3H, m), 1.33–1.19 (2H, m), 1.06 (3H, s), 1.03 (3H, d, *J* = 6.3 Hz), 0.96 (1H, d, *J* = 11.5 Hz), 0.88 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.7, 160.1, 148.7, 142.3, 127.4, 125.2, 120.3, 114.0, 102.8, 52.1, 48.0, 42.1, 40.2, 37.0, 36.5, 36.3, 33.0, 27.9, 27.7, 23.2, 20.6, 17.64, 17.59. IR (KBr): 3341, 1686, 1601, 1426, 1287 cm^{-1}. MS (ESI-TOF) *m*/*z*: 395 $[M+Na]^+$. HRMS (ESI-TOF) *m*/*z*: 395.2198 Calcd for $C_{23}H_{32}O_4Na$; Found: 395.2214.

4.3.14. (–)-Dictyoceratin-A (*ent*-2)

ent-**2** was synthesized through the same procedures as those for **2**, using *ent*-**5** as a starting material. $[\alpha]_D^{26}$ −11.6 (*c* 0.96, $CHCl_3$).

4.4. Biological evaluation of dictyoceratin-C (1), dictyoceratin-A (2) and those enantiomers

4.4.1. Cell cultures

Human prostate cancer cell line DU145 was cultured in RPMI 1640 supplemented with heat-inactivated 10% fetal bovine serum (FBS) and kanamycin (50 μg/mL) in a humidified atmosphere of 5% CO_2 at 37 °C.

4.4.2. Assay for anti-proliferative activity under hypoxic condition

The DU145 cells in the culture medium were plated into each well of 96-well plates (1×10^4 cells/well/200 μL) for 4 h in a humidified atmosphere of 5% CO_2 at 37 °C (normoxic condition). Then, the plates were incubated for 12 h in the 94% nitrogen, 5% CO_2, and 1% O_2 (hypoxic condition) inducing hypoxia related genes, such as HIF-1α. After 12 h incubation, testing compounds were added, and then the plates were incubated for an additional 24 h in the hypoxic condition. The cell proliferation was detected by the MTT method. The growth inhibition rate was calculated as percentage of parallel negative controls. The anti-proliferative activities of the testing compounds under normoxic condition were also evaluated by MTT method.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2015.01.021.

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