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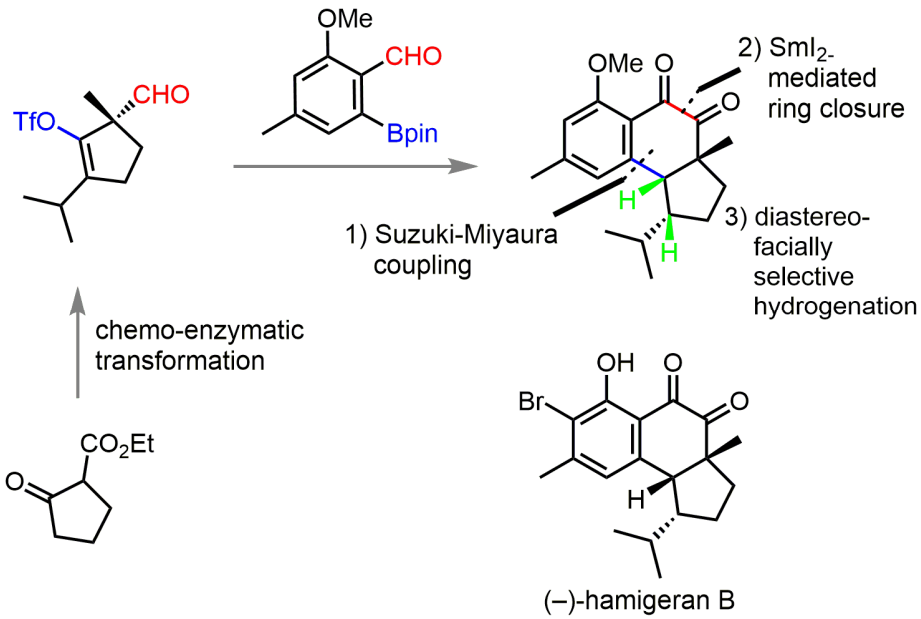

(–)-hamigeran B

Formal total synthesis of (–)-hamigeran B from a chemo-enzymatically prepared building block with quaternary chiral center

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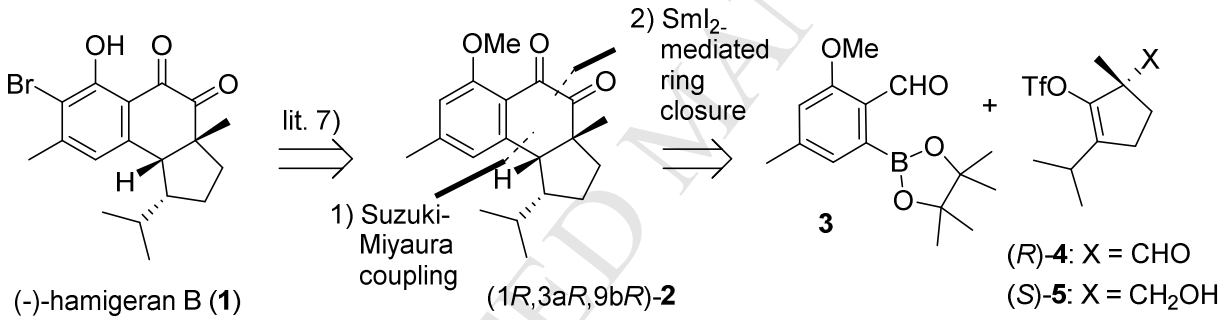
Abstract

A formal total synthesis of (–)-hamigeran B was achieved in 17 steps from commercially available ethyl 2-oxocyclopentanecarboxylate. Carbonyl reductase-catalyzed asymmetric reduction and the subsequent chemical transformations furnished an enantiomerically pure synthetic intermediate, (*R*)-5-formyl-2-isopropyl-5-methylcyclopent-1-en-1-yl trifluoromethylsulfonate. Suzuki-Miyaura coupling with Gao's arylboronate [2-(2-formyl-3-methoxy-5-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane], under $PdCl_2(dppf)•CH_2Cl_2$ catalysis, and the subsequent cyclization by way of intramolecular reductive SmI_2-mediated 1,2-diol formation provided a tricyclic skeleton with a tetrasubstituted double bond between C-1 and C-9b. Upon hydrogenation of this double bond, the proper stereochemistry of the remaining chiral centers was established. Exclusive addition of the hydrogen atom from the β-face occurred, owing to the shielding of the α-face with a bulky TBS protective group on the C-4 alcohol. The hydrogenation products were transformed into Clive's synthetic precursor for (–)-hamigeran B.

1. Introduction

In 2000, (–)-hamigeran B (**1**) was isolated from marine sponge, *Hamigera tarangaensis*, and found to show antiviral activity.[1] Since then, many efforts have been devoted to its chemistry and many total and formal total syntheses have been achieved.[2-16] We envisaged that Clive's diketone (1*R*,3a*R*,9b*R*)-**2**,[5] a synthetic precursor for **1**, could be synthesized by stepwise transformation involving: 1) Suzuki-Miyaura coupling between Gao's arylboronate **3**[17] and (*R*)-**4** with the proper branched side chain and quaternary chiral center; and 2) SmI_2-mediated ring closure[16] as the key steps (Scheme 1). The cyclopentenoid (*R*)-**4** would be available from (*S*)-**5**, and its alkenyl triflate moiety was expected to aid in the palladium-catalyzed C-C bond formation.

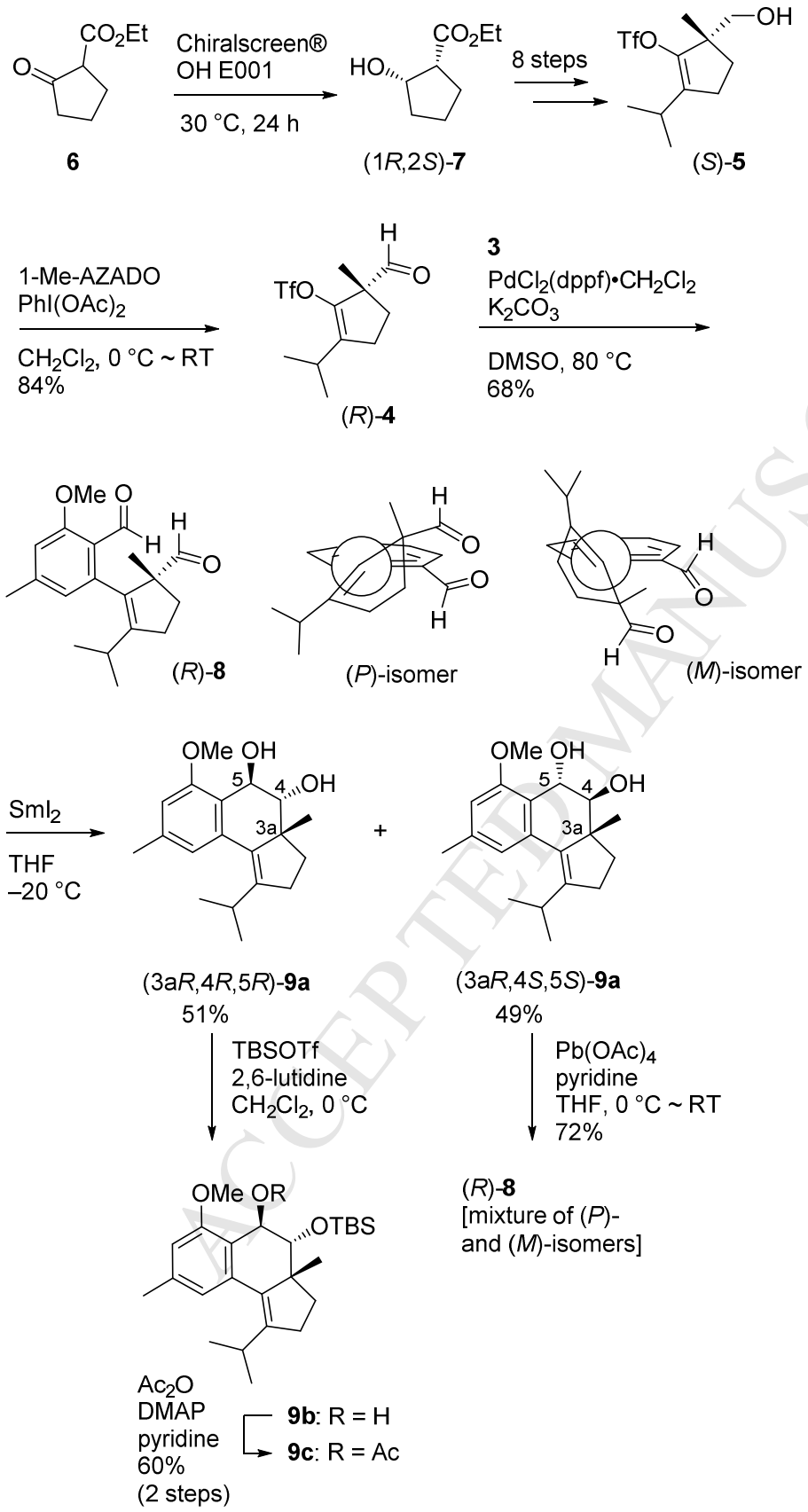


Scheme 1. Synthetic plan for (–)-hamigeran B (**1**) and the precursor (1*R*,3a*R*,9b*R*)-**2**, by the coupling between aromatic segment **3** and cyclopentenoid segment (*R*)-**4** and subsequent ring closure.

2. Results and discussion

To this end, in the same manner as the synthesis of its antipode (*R*)-**5**,[18] (*S*)-**5** was synthesized from **6** by enzyme-catalyzed asymmetric reduction and 8 additional chemical transformations of the resulting stereochemically pure (1*R*,2*S*)-**7**. 1-Methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO)-catalyzed oxidation of the primary alcohol furnished (*R*)-**4** in 84% yield (Scheme 2). Its

counterpart, arylboronate **3**, was prepared from 3,5-dihydroxytoluene[20] in 4 steps.[17,21,22]



Scheme 2. Suzuki-Miyaura coupling between **3** and (*R*)-**4** and the SmI_2-mediated ring closure.

Suzuki-Miyaura coupling between **3** and (*R*)-**4** was accomplished under Gao's conditions with $PdCl_2(dppf)•CH_2Cl_2$ as the catalyst to furnish (*R*)-**8** in 68% yield (Scheme 2). Switching the palladium catalyst to PEPPSI-IPr or PEPPSI-SIPr, which had been reported to be effective for the coupling of sterically hindered substrates,[23] the yield of **8** decreased (*ca*. 40%). When the coupling between **3** and another triflate (*S*)-**5** was attempted, only an undesired borate ester on the primary alcohol in **5** and a homo-coupling byproduct originating from **3** were observed. Moreover, all attempts at Stille coupling, which was successful with a very similar cyclopentenyl triflate and alkenylstannane[24] failed with the corresponding aryltrimethylstananne instead of **3**.

The coupling product (*R*)-**8** was revealed to be a 56:44 mixture of two rotamers judging by its ^{1}H NMR spectrum as shown in section 4.3. The next step, the ring closure of **8**, proceeded almost quantitatively by treatment with SmI_2 in tetrahydrofuran (THF) at –20 °C. In contrast to the normal facial selectivity which prefers *cis*-1,2-diol formation, the preference for the *trans*-isomer in an intramolecular fashion had been reported in a similar substrate with a rigid structure and bulky neighboring substituents.[16] In our case, two diastereomers (3a*R*,4*R*,5*R*)-**9a** (51%) and (3a*R*,4*S*,5*S*)-**9a** (49%) formed, which presumably originated from each rotamer in (*R*)-**8**, and were separated by silica gel column chromatography.

The *trans*-stereochemistries of both diastereomers were assigned by the comparison of nuclear Overhauser effect (nOe) and coupling constants in ^{1}H NMR spectra as depicted in Figure 1. Upon irradiation at methyl group at C-3a, nOe was observed at H-4 (4.0%) for (3a*R*,4*R*,5*R*)-**9a**, but at H-3 (2.0%) for (3a*R*,4*S*,5*S*)-**9a**. Coupling constants between H-4 and H-5 were agreeable for *trans*-isomers; 0 Hz for (3a*R*,4*R*,5*R*)-**9a** and 7.4 Hz for (3a*R*,4*S*,5*S*)-**9a** as shown in Figure 1. It is also

noted that both of ^{1}H NMR spectra of (3a*R*,4*R*,5*R*)-**9a** and (3a*R*,4*S*,5*S*)-**9a** were different from that of previously reported corresponding *cis*-**9a**.[17]

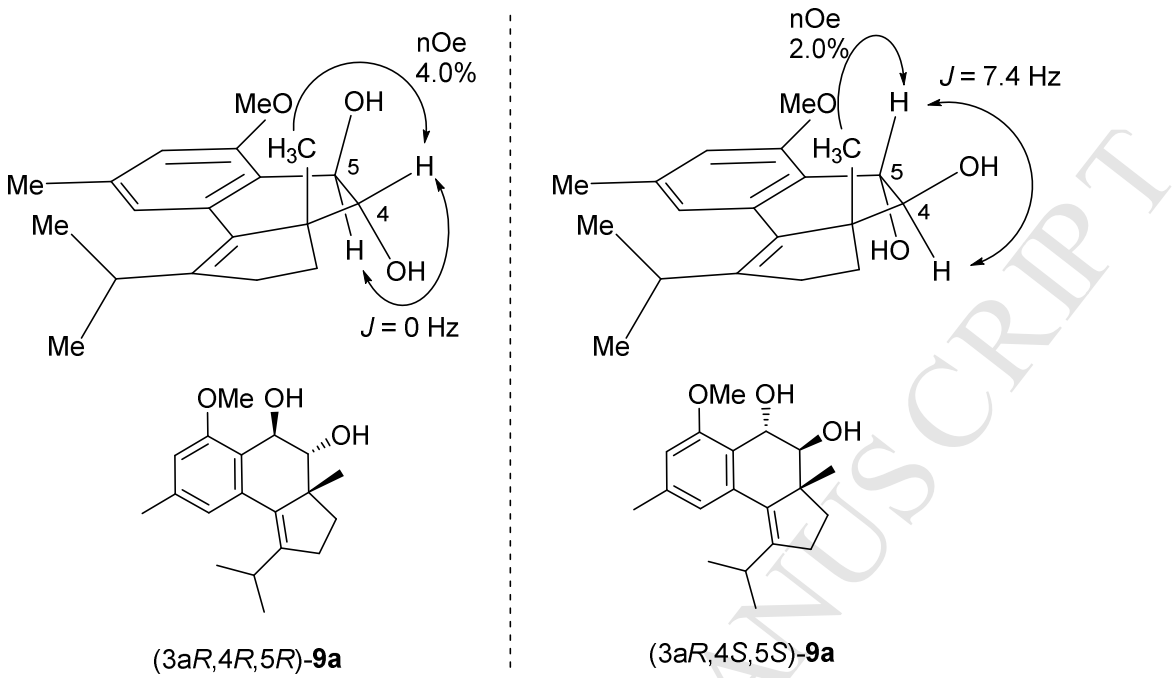


Figure 1. Assignment of the stereochemistry by NMR analyses of SmI_2-mediated ring closure products, (3a*R*,4*R*,5*R*)-**9a** and the diastereomeric (3a*R*,4*S*,5*S*)-**9a**.

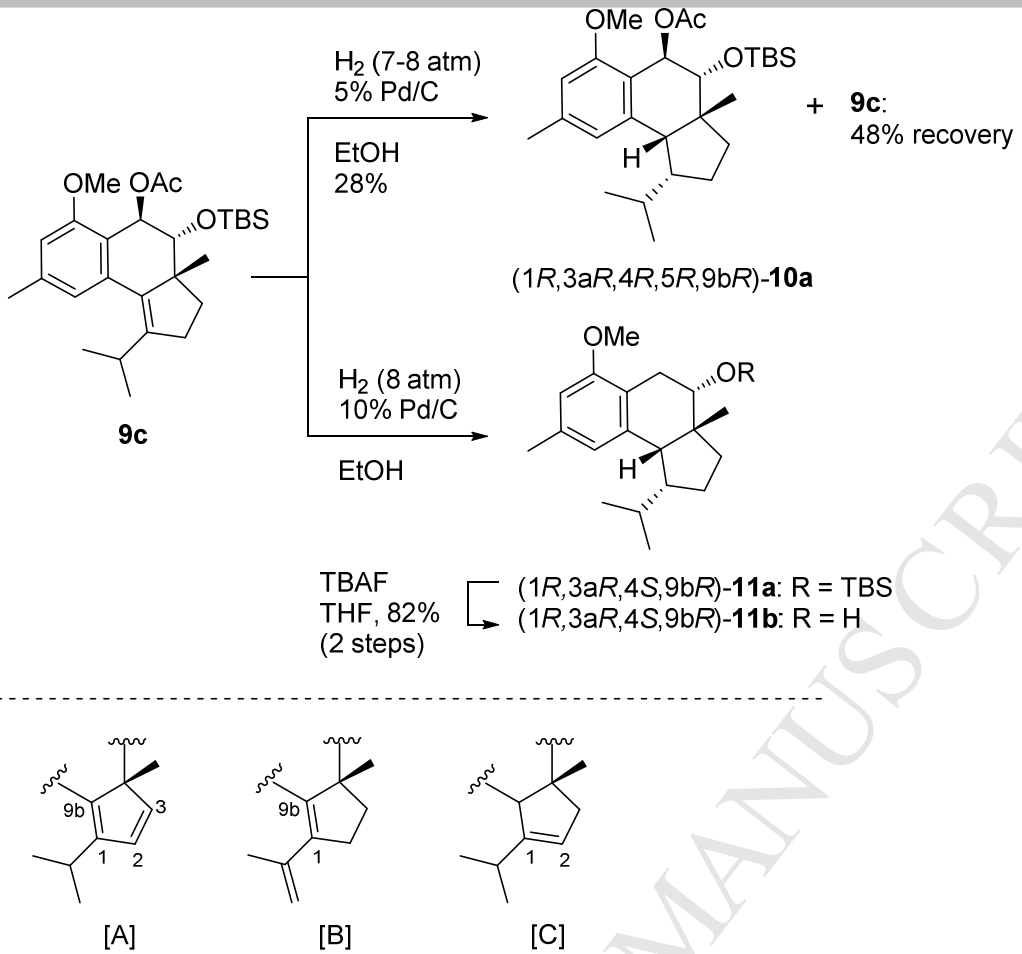
The final task was the installation of the correct stereochemistry at C-1 and C-9b by hydrogenation. Clive's pioneering work[7] revealed that a large substituent oriented over the α-face at C-4 is necessary to control the stereochemistry at C-1 and C-9b to yield the desired (1*R*,9b*R*)-stereochemistry upon hydrogenation of the double bond between C-1 and C-9b.

Thus, (3a*R*,4*R*,5*R*)-**9a** was submitted to the following sequence to form **2**. As expected from the 1,3-diaxial repulsion of bulky protective group on the C-5 hydroxy group and C-3a methyl group, less sterically hindered alcohol at C-4 was protected with a *tert*-butyldimethylsilyl (TBS) group (Scheme 2). The remaining *pseudo*-axially oriented secondary alcohol at C-5 was then protected with a small acetyl group to minimize the blocking of the β-face upon hydrogenation.

In contrast, such desired approach of hydrogen atoms from the β-face cannot be expected for (3a*R*,4*S*,5*S*)-**9a** which has both substituents at C-4 and C-5 in the *pseudo*-equatorial orientation, as shown in Figure 1. Therefore, this diastereomer was recycled into the cyclization precursor (*R*)-**8**, by C-C bond cleavage of the *trans*-1,2-diol moiety by oxidation with lead tetraacetate in 72% yield (Scheme 2). The resulting (*R*)-**8** became a mixture of rotamers again, as in almost same ratio as the above-mentioned Suzuki-Miyaura coupling product, as indicated by the ^{1}H NMR spectrum.

The hydrogenation of **9c** catalyzed by Pd (5%) on charcoal was sluggish even under high pressure of hydrogen gas. Desired (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10a** was obtained only in as low as 28% yield with recovery of starting material (48%) (Scheme 3). To overcome the low efficiency, the catalyst loading was increased from 5% to 10% under a higher concentration of the substrate in ethanol. Under these conditions, deoxygenation at the benzylic C-5 position also occurred, and (1*R*,3a*R*,4*S*,9b*R*)-**11a** was the major product with complete consumption of the starting material. Hydrogenolysis at the benzylic position alleviated the steric hindrance, possibly promoting hydrogenation of the tetrasubstituted double bond, although an intermediate for this pathway was not detected in the crude products of the reaction. $Pd(OH)_2$ brought about the same deoxygenation at the benzylic C-5 position. Subsequent deprotection of the TBS ether in **11a** furnished **11b** in 82% yield from **9c**.

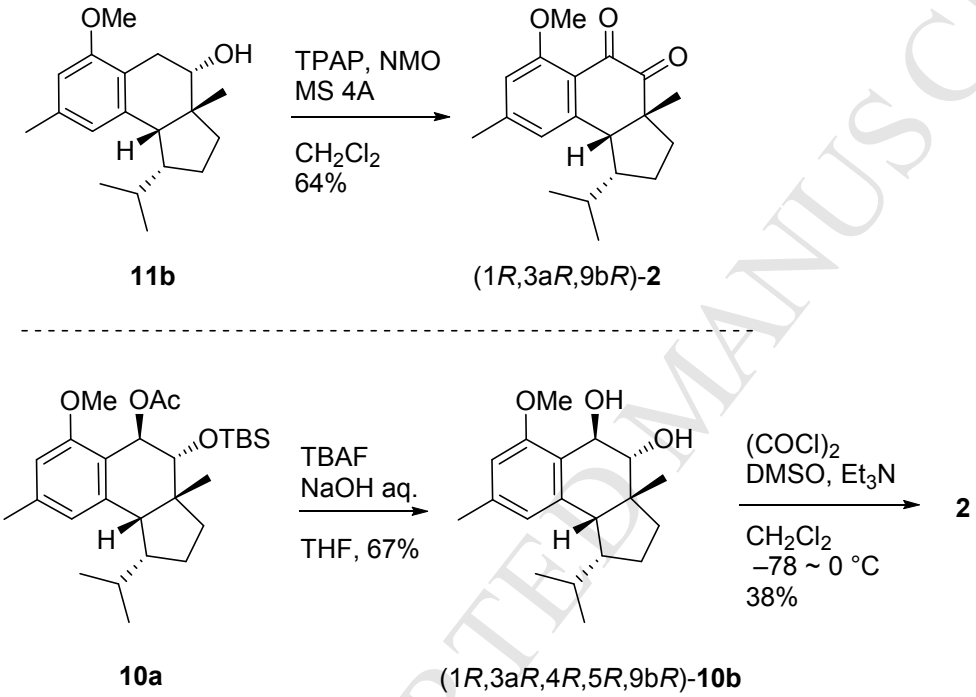
In contrast to the hydrogenation of conjugated tetrasubstituted bond (type A[6-8] and type B[12]), nobody has achieved the hydrogenation of an isolated double bond between C-1 and C-9b such as in **9c**. A possible intermediate, in which the double bond was isomerized to the disubstituted, sterically less hindered C-1 and C-2 positions (type C)[3-5,9,10] was not detected in our experiments.



Scheme 3. Catalytic hydrogenation of tetrasubstituted double bond in **9c** to **10a** and **11a**,

Alcohol **11b** had been synthesized as an intermediate for (–)-hamigeran B by Taber and co-workers. According to their procedure,[10] **11b** was submitted to tetra-*n*-propylammonium perruthenate (TPAP)-catalyzed oxidation with *N*-methylmorpholine-*N*-oxide (NMO) as co-oxidant to give Clives' precursor **2** in 64% yield (Scheme 4). Physicochemical and spectral properties were in good accordance with those of the previously reported sample [$[\alpha]_D^{21}$ –228 (*c* 0.35, CH_2Cl_2); lit.[8] $[\alpha]_D$ –187.1 (*c* 0.124, CH_2Cl_2)]. Then, transformation of **10a** to **2** was also attempted. Deprotection of the acetyl and TBS groups of the alcohols on C-4 and C-5 were performed by sequential one-pot treatment with aqueous sodium hydroxide and tetra-*n*-butylammonium fluoride (TBAF) solution in THF, to give (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10b** in 67% yield.

Dess-Martin periodinane-mediated transformation of **10b** preferred the oxidation at benzylic position. The product was a 1:1.7 mixture of **2** and the corresponding hydroxyketone whose hydroxy group at C-4 was intact. Instead, Swern oxidation proceeded on both secondary alcohols at C-4 and C-5 to furnish **2**, but the yield was as low as 38% (Scheme 4). The combined yield of **2** from **9c** through **11b** (52%) was much higher than that through **10a** (7%).



Scheme 4. Transformation of **11b** and **10a** to (1*R*,3a*R*,9b*R*)-**2**, the intermediate of natural (–)-hamigeran B *via* oxidation of the precursors.

3. Conclusion

The aldehyde (*R*)-**4** with a cyclopentene skeleton and stereochemically pure chiral center was effectively utilized in the formal total synthesis of (–)-hamigeran B. The tricyclic structure was obtained by successive Suzuki-Miyaura coupling of two segments, and subsequent cyclization mediated by the reductive coupling of two aldehydes with SmI_2. Upon hydrogenation, the

stereochemistries of the remaining chiral centers at C-1 and C-9b were controlled with exclusive selectivity, by the introduction of a bulky protective group at C-4. In this way, we achieved a formal synthesis of (–)-hamigeran B in 17 steps from commercially available **6**.

4. Experimental

4.1. General

Hydrogenation under high pressure was performed in a pressure vessel with inner vessel and impeller, EYELA HIP-60. IR spectra were measured as ATR on a Jeol FT-IR SPX60 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ at 400 MHz on a VARIAN 400-MR spectrometer or at 500 MHz on a VARIAN 500-MR spectrometer and ^{13}C NMR spectra were measured in $CDCl_3$ at 100 MHz on a VARIAN 400-MR spectrometer or at 125 MHz on a VARIAN 500-MR spectrometer. Merck silica gel 60 N (spherical, neutral, 63-210 μm, 37565-84) from Kanto Chemical Co. was used for column chromatography, respectively. Optical rotation values were recorded on a Jasco P-1010 polarimeter.

4.2. (*R*)-5-Formyl-2-isopropyl-5-methylcyclopent-1-ene-1-yl trifluoromethylsulfonate 4

To a solution of alcohol (*S*)-**5** (71.8 mg, 0.238 mmol) in CH_2Cl_2 (2.0 mL) were added 1-Me-AZADO (1.1 mg, 0.006 mmol) and $PhI(OAc)_2$ (81.0 mg, 0.251 mmol) at 0 °C and stirred for 4 h at that temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (60:1–10:1) to give an aldehyde (*R*)-**4** (60.2

mg, 84%) as a colorless oil. $[\alpha]_D^{24}$ +125.5 (*c* 1.14, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* = 6.9 Hz), 1.08 (3H, d, *J* = 6.9 Hz), 1.29 (3H, s), 1.80 (1H, ddd, *J* = 13.4, 8.0, 4.4 Hz), 2.31 (1H, ddd, *J* = 13.5, 8.0, 4.4 Hz), 2.38–2.48 (2H, m), 2.92 (1H, qq, *J* = 6.9, 6.9 Hz), 9.56 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 20.2, 20.5, 24.4, 26.1, 31.0, 58.0, 117.1, 118.3 (q, *J* = 319.6 Hz), 139.3, 144.5, 199.2; IR ν_{max} 2970, 2937, 1732, 1410, 1212 cm^{-1}. HRMS (DART) $[M+H]^+$ calculated for $C_{11}H_{16}F_3O_4S_1$: 301.1721, found: 301.0719.

4.3. (*R*)-5-(5'-Formyl-2'-isopropyl-5'-methylcyclopent-1'-enyl)-6-methoxy-4-methylbenzaldehyde 8

To a mixture of $PdCl_2$(dppf)•CH_2Cl_2 (10.5 mg, 0.013 mmol) and K_2CO_3 was added a solution of boronate **3** (81.5 mg, 0.295 mmol) and triflate (*R*)-**4** (80.5 mg, 0.268 mmol) in DMSO (4.0 mL) and stirred for 12 h at 80 °C under argon atmosphere. The reaction was quenched with H_2O and organic materials were extracted with EtOAc twice. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–20:1) to furnish a 56:44 rotamer mixture of **8** (55.1 mg, 68%,) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (1.32H, d, *J* = 8.7 Hz), 0.89 (1.32H, d, *J* = 6.9 Hz), 0.91 (1.68H, d, *J* = 6.9 Hz), 0.93 (1.68H, d, *J* = 6.9 Hz), 1.04 (1.68H, s), 1.10 (1.32H, s), 1.77–1.81(0.44H, m), 1.88 (0.56H, ddd, *J* = 13.2, 9.3, 9.3 Hz), 2.17–2.20 (0.56H, m), 2.28–2.38 (1H, m), 2.34 (1.68H, s), 2.38 (1.32H, s), 2.47–2.60 (2.56H, m), 3.88 (1.32H, s), 3.91 (1.68H, s), 6.25 (0.56H, s), 6.40 (0.44H, s), 6.72 (0.56H, s), 6.73 (0.44 H, s), 9.53 (0.44H, s), 9.61 (0.56H, s), 10.25 (0.56H, s), 10.31 (0.44H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 19.8, 19.9, 20.4, 21.1, 21.7, 22.3, 22.3, 28.2, 28.5, 28.7, 28.9, 32.7, 33.2, 55.7, 55.8, 63.7, 64.1,

111.5, 111.5, 121.2, 121.9, 123.2, 124.9, 131.9, 134.9, 139.0, 141.3, 145.4, 146.0, 147.9, 152.4, 161.1, 162.3, 190.2, 190.9, 201.9, 203.7; IR ν_{max} 2958, 2927, 1718, 1688, 1599, 1568, 1449, 1401, 1289 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{24}NaO_3$: 323.1623, found: 323.1650.

4.4. (3a*R*,4*R*,5*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,4,5-tetrahydro-3a*H*-cyclopenta[a]naphthalene-4,5-diol 9a and (3a*R*,4*S*,5*S*)-9a

To a solution of SmI_2 (0.1 M in THF, 1.9 mL) was added a solution of aldehyde **8** (5.8 mg, 0.019 mmol) at –20 °C and stirred at that temperature for 5 h under argon atmosphere. The reaction was quenched with saturated sodium/potassium tartrate aq. solution and the organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–1:1) to furnish (3a*R*,4*R*,5*R*)-**9a** (3.0 mg, 51%) and (3a*R*,4*S*,5*S*)-**9a** (2.9 mg, 49%) as colorless oil.

(3a*R*,4*R*,5*R*)-**9a**: R_f = 0.50 (hexane:EtOAc = 2:1). $[\alpha]_D^{25}$ –154 (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.6 Hz), 1.15 (3H, s), 1.22 (3H, d, *J* = 6.8 Hz), 1.25 (1H, d, *J* =10.0 Hz), 1.63 (1H, ddd, *J* = 13.2, 9.8, 4.9 Hz), 2.22 (1H, ddd, *J* = 13.2, 10.0, 6.8 Hz), 2.35 (3H, s), 2.46–2.60 (2H, m), 3.16 (1H, s), 3.24 (1H, qq, *J* = 6.8, 6.6 Hz), 3.76 (1H, d, *J* = 10.0 Hz), 3.89 (3H, s), 4.83 (1H, s), 6.67 (1H, s), 6.88 (1H, s); ^{13}C NMR of (3a*R*,4*R*,5*R*)-**9a** (125 MHz, $CDCl_3$): δ 21.5, 21.9, 22.0, 23.4, 27.4, 29.8, 31.8, 51.4, 55.4, 70.3, 76.8, 110.1, 120.4, 121.6, 130.5, 132.5, 138.2, 148.5, 158.4; IR ν_{max} 3427, 2956, 1607, 1572, 1455, 1343 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{26}NaO_3$: 325.1779, found: 325.1773.

(3a*R*,4*S*,5*S*)-**9a**: R_f = 0.20 (hexane:EtOAc = 2:1). $[\alpha]_D^{22}$ –158 (*c* 0.64, $CHCl_3$). ^{1}H NMR

(500 MHz, $CDCl_3$): δ 0.95 (3H, s), 1.01 (3H, d, *J* = 6.6 Hz), 1.18 (3H, d, *J* = 6.8 Hz), 1.72 (1H, ddd, *J* = 13.2, 8.8, 4.4 Hz), 1.99 (1H, ddd, *J* = 13.2, 9.5, 8.1 Hz), 2.35 (3H, s), 2.40–2.43 (1H, br-s) 2.49–2.59 (2H, m), 3.20 (1H, qq, *J* = 6.8, 6.6 Hz), 3.76 (1H, d, *J* = 7.4 Hz), 3.89 (3H, s), 4.03 (1H, s), 4.84 (1H, d, *J* = 7.4 Hz), 6.60 (1H, s,), 6.85 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 21.2, 21.5, 21.9, 27.4, 29.7, 33.8, 53.2, 55.4, 73.0, 81.0, 109.6, 120.7, 122.6, 133.3, 134.7, 138.3, 145.0, 157.9; IR ν_{max} 3437, 2958, 1607, 1573, 1456, 1342 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{26}NaO_3$: 325.1779, found: 325.1787.

4.5. (3a*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-1-isopropyl-6-methoxy-3a,8-dimethyl-2,3,4,5-tetrahydro-3a*H*-cyclopenta[a]naphthalene-5-yl acetate 9c

To a solution of (3a*R*,4*R*,5*R*)-**9a** (9.2 mg, 0.030 mmol) in CH_2Cl_2 (0.7 mL) was added 2,6-lutidine (21 μL, 0.179 mmol) and TBSOTf (17 μL, 0.074 mmol) at 0 °C, and the mixture was stirred for 30 min at that temperature. The reaction was quenched with phosphate buffer solution (pH 7.0, 0.1 M), and the organic materials were extracted with EtOAc twice. The combined extract was washed with brine and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to furnish crude TBS ether (3a*R*,4*R*,5*R*)-**9b**. To this was added pyridine (0.4 mL), Ac_2O (0.4 mL) and 4-dimethylaminopyridine (DMAP, 4.6 mg, 0.038 mmol), and the mixture was stirred for 16 h at room temperature. The reaction was quenched with H_2O and the organic materials were extracted with EtOAc twice. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–20:1) to furnish (3a*R*,4*R*,5*R*)-**9c** (8.4 mg, 60%) as a colorless amorphous powder. $[\alpha]_D^{22}$ –129 (*c* 0.32, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ

0.12 (3H, s), 0.20 (3H, s), 0.78 (9H, s), 0.97 (3H, d, *J* = 6.8 Hz), 1.05 (3H, s), 1.19 (3H, d, *J* = 7.0 Hz), 1.44 (1H, ddd, *J* = 12.7, 9.0, 3.9 Hz), 2.00 (3H, s), 2.12 (1H, ddd, *J* = 12.7, 10.0, 7.5 Hz), 2.37 (3H, s), 2.40–2.51 (2H, m), 3.26 (1H, qq, *J* = 7.0, 6.8 Hz), 3.69 (1H, d, *J* = 1.7 Hz), 3.78 (3H, s), 5.88 (1H, d, *J* = 1.7 Hz), 6.60 (1H, s), 6.91 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ –5.2, –4.0, 18.0, 21.1, 21.5, 22.1, 23.4, 25.9 (3C), 27.5, 29.6, 31.7, 51.4, 55.4, 70.0, 75.7, 109.6, 117.6, 120.1, 131.2, 134.8, 138.3, 145.9, 158.8, 170.0; IR ν_{max} 2955, 2928, 1732, 1607, 1574, 1462, 1235 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{42}NaO_4Si$: 481.2750, found: 481.2718.

4.6. C-C bond cleavage of (3a*R*,4*S*,5*S*)-9a

To a solution of (3a*R*,4*S*,5*S*)-**9a** (7.8 mg, 0.026 mmol) in THF (600 μL) was added pyridine (50 μL, 0.619 mmol) and $Pb(OAc)_4$ (41 mg, 0.092 mmol) at 0 °C, and the mixture was gradually warmed to room temperature with stirring for 2 h. The reaction was quenched with saturated $Na_2S_2O_3$ aq. solution and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–10:1) to furnish **8** (5.6 mg, 72%) as a pale-yellow oil. The ^{1}H NMR spectrum was identical to that of **8** in section 4.3.

4.7. (1*R*,3a*R*,4*R*,5*R*,9b*R*)-4-*tert*-Butyldimethylsilyloxy-1-isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[a]naphthalene-5-yl acetate 10a

To a solution of **9c** (6.4 mg, 0.014 mmol) in EtOH (2.0 mL) was added Pd/C (5% on carbon, 10.2 mg) in a pressure vessel as shown in section 4.1. The mixture was stirred under H_2

atmosphere (8 atm) for 39 h. Then the mixture was then filtered through a pad of Celite, and the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–40:1) to furnish (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10a** (1.8 mg, 28%) as a colorless oil and (3a*R*,4*R*,5*R*)-**9c** (3.1 mg, 48% recovery). (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.59 (3H, d, *J* = 6.6 Hz), 0.89 (9H, s), 0.97 (3H, d, *J* = 6.4 Hz), 0.97–1.54 (3H, m), 1.23 (3H, s), 1.34–1.42 (1H, m), 1.85–1.91 (1H, m), 2.07 (3H, s), 2.29 (3H, s), 2.29–2.34 (1H, m), 3.02 (1H, d, *J* = 6.8 Hz), 3.65 (1H, d, *J* = 7.8 Hz), 3.74 (3H, s), 6.13 (1H, d, *J* = 7.8 Hz), 6.52 (1H, s), 6.61 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ –3.8, –3.7, 18.3, 21.5, 21.6, 21.9, 23.8, 26.0 (3C), 26.4, 28.4, 30.8, 33.1, 43.8, 53.9, 53.2, 55.3, 70.4, 77.8, 109.4, 121.4, 122.8, 137.0, 138.2, 157.2, 170.9; IR ν_{max} 2954, 2928, 1745, 1610, 1579, 1235 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{44}NaO_4Si$: 483.2907, found: 483.2906.

4.8. (1*R*,3a*R*,4*S*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[a]naphthalen-4-ol 11b

In a similar manner as described in the section 4.7, a mixture of **9c** (22.0 mg, 0.048 mmol) and Pd/C (10% on carbon, 21.0 mg) in EtOH (3.0 mL) was stirred under H_2 atmosphere (8 atm) for 20 h. The mixture was filtered through a pad of Celite, and the combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in a mixture of hexane/EtOAc (40:1), and the solution was filtered through short pad of silica gel to furnish **11a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.00 (3H, s), 0.07 (3H, s), 0.63 (1H, d, *J* = 6.7 Hz), 0.91 (9H, s), 0.97–1.03 (1H, m), 1.07 (1H, d, *J* = 6.2 Hz), 1.19 (3H, s), 1.39–1.43 (1H, m), 1.79–1.88 (1H, m), 2.21–2.27 (1H,

m), 2.30 (3H, s), 2.34 (1H, dd, *J* = 15.6, 11.2 Hz), 2.90 (1H, dd, *J* = 15.6, 4.3 Hz), 2.95 (1H, d, *J* = 7.0 Hz), 3.48 (1H, dd, *J* = 11.2, 4.3 Hz), 3.79 (3H, s), 6.50 (1H, s), 6.60 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ –4.9, –3.9, 18.1, 21.5, 21.7, 23.9, 25.9 (3C), 26.5, 28.6, 29.8, 30.4, 32.6, 46.1, 53.7, 53.8, 55.4, 76.0, 108.2, 122.8, 123.1, 134.8, 138.5, 156.4. This was employed for the next step without further purification.

To a solution of the above-mentioned **11a** in THF (400 μL) was added TBAF (1.0 M in THF, 400 μL) and the mixture was stirred at 40 °C for 15 h. The reaction was quenched with H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with hexane/EtOAc (20:1–5:1) to furnish (1*R*,3a*R*,4*S*,9b*R*)-**11b** (11.3 mg, 82% from **9c**) as a colorless solid. $[\alpha]_D^{21}$ +70 (*c* 0.56, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.66 (3H, d, *J* = 6.6 Hz), 0.96 (1H, m), 1.09 (3H, d, *J* = 6.1 Hz), 1.13 (1H, m), 1.30 (3H, s), 1.48 (1H, m), 1.61 (1H, m), 2.11 (1H, m), 2.30 (3H, s), 2.38 (1H, dd, *J* = 15.4, 11.5 Hz), 3.00 (1H, d, *J* = 6.4 Hz), 3.02 (1H, dd, *J* = 15.4, 4.4 Hz), 3.55 (1H, dd, *J* = 11.5, 4.4 Hz), 3.79 (3H, s), 6.51 (1H, s), 6.60 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 21.7, 23.9, 26.4, 28.3, 29.6, 29.7, 31.9, 45.7, 53.4, 53.9, 55.3, 75.7, 108.3, 122.5, 122.7, 135.0, 138.2, 156.3; IR ν_{max} 2939, 2867, 1463, 1272 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{28}NaO_2$: 311.1987, found: 311.1962. Its NMR and IR spectra were identical with those reported previously.[11]

4.9. (1*R*,3a*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[a]naphthalene-4,5-dione 2

To a suspension of **11b** (8.5 mg, 0.030 mmol) and powdered 4A molecular sieve (93.6 mg) in CH_2Cl_2 (1.0 mL) were added NMO (41.0 mg, 0.350 mmol) and TPAP (6.0 mg, 0.017 mmol), and stirred under argon atmosphere for 4 h. The reaction mixture was directly purified by silica gel column chromatography with hexane/EtOAc (10:1-2:1) to furnish a diketone **2** (5.7 mg, 64%) as a pale-yellow oil. $[\alpha]_D^{21}$ –228 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.44 (3H, d, *J* = 6.6 Hz), 0.57 (3H, d, *J* = 6.6 Hz), 1.14–1.23 (1H, m), 1.27 (3H, s), 1.48–1.59 (2H, m), 1.75–1.81 (1H, m), 2.20–2.28 (1H, m), 2.41 (3H, s), 2.47–2.52 (1H, m), 3.35 (1H, d, *J* = 9.5 Hz), 3.93 (3H, s), 6.71 (1H, s), 6.77 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 22.4, 23.1, 24.2, 28.0, 28.6, 35.4, 51.9, 55.1, 56.0 (2C), 110.9, 120.6, 124.4, 145.9, 147.2, 161.4, 180.8, 201.7; IR ν_{max} 2955, 1721, 1677, 1604 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{24}NaO_3$: 323.1623, found: 323.1634. Its NMR, IR and MS spectra were identical with those reported previously.[8]

4.10. (1*R*,3a*R*,4*R*,5*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[a]naphthalene-4,5-diol 10b

To (1*R*,3a*R*,4*R*,5*R*,9b*R*)-**10a** (1.8 mg, 3.9 μmol) were added TBAF (1.0 M in THF, 500 μL) and NaOH (2.0 M in H_2O, 120 μL) and the mixture was stirred at 70 °C for 45 h. The reaction was quenched with H_2O and organic materials were extracted with EtOAc three times. The combined extract was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with hexane/EtOAc (10:1–2:1) to furnish (1*R*,3a*R*,4*S*,9b*R*)-**10b** (0.8 mg, 67%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.61 (3H, d, *J* = 6.6 Hz), 0.75–0.85 (1H, m), 1.07 (3H, d, *J* = 6.4 Hz), 1.18 (1H, ddd, *J* = 14.1, 12.0, 7.3 Hz), 1.31–1.39 (1H, m), 1.35 (3H, s), 1.54–1.60 (1H, m), 1.60–

1.68 (1H, m), 2.19 (1H, m), 2.30 (3H, s), 3.01 (1H, d, *J* = 6.7 Hz), 3.46 (1H, d, *J* = 9.0 Hz), 3.87 (3H, s), 4.73 (1H, d, *J* = 9.0 Hz), 6.58 (1H, s), 6.64 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 21.6, 23.8, 26.3, 28.8, 29.6, 32.3, 43.0, 53.0, 53.1, 55.4, 69.5, 79.9, 109.4, 123.7, 124.4, 136.7, 137.5, 156.8; IR ν_{max} 3493, 2952, 2866, 1612, 1577, 1462 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{28}NaO_3$: 327.1936, found: 327.1955.

4.11. Synthesis of (1*R*,3a*R*,9b*R*)-2 by the oxidation of 10b

To a solution of $(COCl)_2$ (5 μL, 0.058 mmol) in CH_2Cl_2 (200 μL) was added a solution of dimethyl sulfoxide (DMSO, 6 μL, 0.084 mmol) in CH_2Cl_2 (200 μL) at –78 °C, and the mixture was stirred under argon atmosphere at that temperature for 30 min. To the mixture was added a solution of the diol (1*R*,3a*R*,4*S*,9b*R*)-**11b** (0.8 mg, 2.6 μmol) in CH_2Cl_2 (200 μL) and the stirring was continued at the same temperature. After 30 min, Et_3N (40 μL, 0.288 mmol) was added to the mixture, and the temperature was gradually raised to 0 °C for over 2 h with stirring. The reaction was quenched with saturated NH_4Cl aq. and the organic materials were extracted with EtOAc twice. The combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:0–20:1) to furnish (1*R*,3a*R*,9b*R*)-**2** (0.3 mg, 38%) as a pale-yellow oil. Its ^{1}H NMR spectrum was identical to that in section 4.9. HRMS (ESI) $[M+Na]^+$ calculated for $C_{19}H_{24}NaO_3$: 323.1623, found: 323.1639.

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