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Article

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Total Synthesis of (+)-Antrocin and Its Diastereomer and Clarification of the Absolute Stereochemistry of (-)-Antrocin

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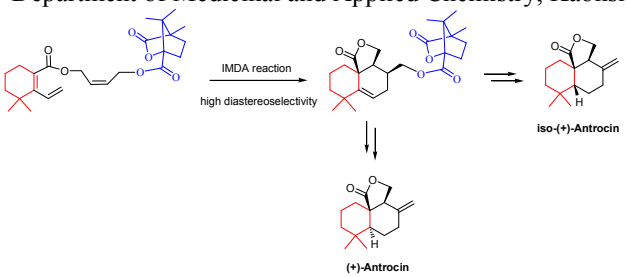


ABSTRACT: Using 2,2-dimethyl cyclohexanone as the starting compound, (+)-antrocin and its diastereomer have been synthesized. The absolute stereochemistry of (-)-antrocin, a natural sesqui-terpenoid and an antagonist in some types of cancer cells, was clarified using the character data of (+)-antrocin. The synthetic procedure involved two key steps: (1) the reaction of vinyl magnesium bromide with 2,2-dimethyl-6-*t*-butyl-dimethyl-silyoxy-methyl-1-cyclo-hexanone to give a vinyl cyclohexanol derivative and (2) a highly stereoselective intramolecular Diels-Alder (IMDA) reaction of the camphanate-containing triene intermediate. The relative energy levels of the possible transition states of the IMDA reaction of the camphanate-containing triene were obtained from density functional theory calculations, proving the stereospecific formation of the target molecule.

INTRODUCTION

Traditionally, *Antrodia camphorate* (also called "Niu-Zarng Jee"), a fungus that uniquely grows on the withered inner shell of a Taiwanese lauraceous tree called "Niu-Zarng", is utilized as a multi-functional folk medicine for the treatment of various diseases.[1-6] Two decades ago, (-)-antrocin (1, Fig. 1), one of the terpenoids contained in *Antrodia camphorata*,[1,7] was first isolated by Chiang et al.,[5] who further identified its relative molecular stereostructure based on its ORTEP diagram. Recently, antrocin was proven to be a potent antagonist in several types of cancer cells, especially in MDA-MB-231 breast cancer cells.[3] Currently, although *Antrodia camphorata* is highly valuable in east Asia,[6] "Niu-Zarng" trees are not readily available for several reasons,[8] creating an urgent need for the synthesis of antrocin, which has demonstrated significant biological activity.[9] In 2011, Yang and co-workers reported the synthesis of racemic antrocin via a cascade reaction of a 1,7-diyne analog with nucleophiles, using gold as the catalyst.[10] To obtain enantiomerically pure antrocin for medicinal purposes, we designed a synthetic route for the target product, and this retro-synthesis is illustrated in Figure 2.

The tricyclic molecule **B** is one of the key intermediates and may be furnished by the intramolecular Diels-Alder (IMDA) reaction of molecule **C**,[11] which is expected to be prepared from intermediate **D**. After molecule **E** is obtained, intermediate **D** can be prepared through the reaction of **E** with a Grignard reagent, followed by conversion of a functional group. Thus, the commercially available compound **F** should be the precursor of the target molecule. Herein, we report the total synthesis of (+)-antrocin as well as a clarification of the absolute stereochemistry of (-)-antrocin, a natural bioactive sesqui-terpenoid.

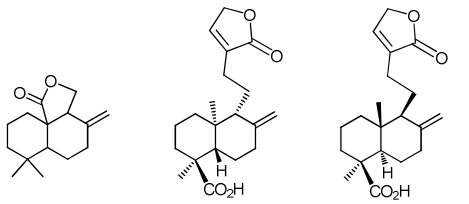


Figure 1. Molecular structures of some terpenoids isolated from the fruit of *Antrodia camphorata*.

RESULTS AND DISCUSSION

As shown in Scheme 1, formylation of commercially available 2,2-dimethyl cyclohexanone (**3**, i.e., compound **F** shown in Fig. 2) gave keto-enol **4**.[12] Reduction of **4** by sodium borohydride provided a diol, of which the primary hydroxyl group was then protected with TBSCl to give secondary alcohol **5.** Oxidation of **5** with PCC furnished the cyclohexanone derivative **6**. Reaction of vinyl magnesium bromide with **6** afforded the tertiary alcohol **7**.[13] The hydroxyl aldehyde **8** was then obtained after removal of the *tert*-butyl dimethyl silyl group in **7**, followed by oxidation of the primary hydroxyl group.[14]

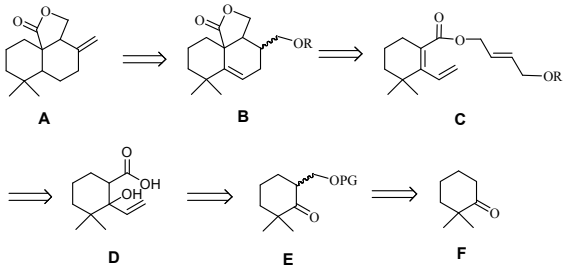
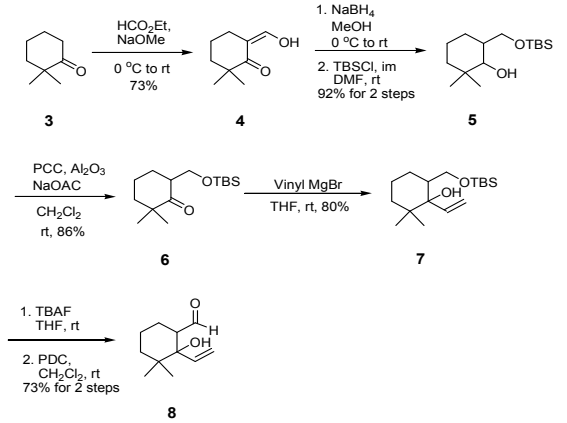


Figure 2. Retro-synthetic analysis of antrocin.

The formyl group on **8** was further oxidized to a carboxylic acid (Scheme 2),[15] which immediately underwent esterification with *E*-2-butenol camphanate (**8a**, Fig. 3)[16,17] in the presence of DCC to produce the *β*-hydroxyl ester **9**. Thionyl chloride was then employed for the dehydration of **9** to provide the key intermediate **10**. The IMDA reaction of **10**, using TEMPO as the catalyst, gave the lactone **11** as a single product in good yield.[18] Notably, none of the stereoisomers of **11** was detected after the IMDA reaction. Hydrogenation of **11** in methanol smoothly afforded the lactone **12** (Scheme 3). The individual absolute stereo-structures of **11** and **12** were confirmed by X-ray crystallography of the corresponding single crystals. Treatment of **12** with sodium carbonate furnished the hydroxyl lactone **13**. Iodination of **13** followed by an elimination produced alkene **2**, which turned out to be a diastereomer of (-)-antrocin.

Scheme 1. Synthesis of the aldehyde **8**.



Although compound **2** was not the original target molecule, our synthetic strategy for the natural product appeared to be feasible. Thus, to obtain natural (-)-antrocin, *Z*-2-butenol camphanate[16] (**8b**, Fig. 3) was adopted as one of the reactants for the preparation of the new key intermediate. As shown in Scheme 4, reaction of **8b** with the crude acid given by the oxidation of **8** provided the *β*-hydroxyl ester **14**. Dehydration of **14** under the same conditions as for that of **9** furnished the triene **15**. The lactone **16**, a stereoisomer of **11**, was then obtained from the IMDA reaction of **15**. Similar to the case of intermediate **10**, none of the stereoisomers of **16** was detected after the reaction.

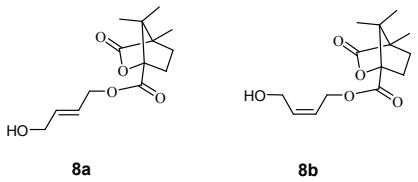
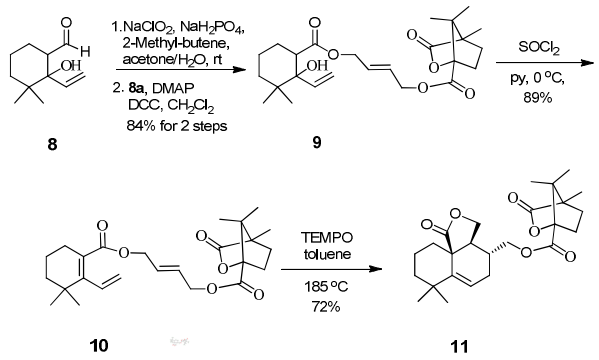
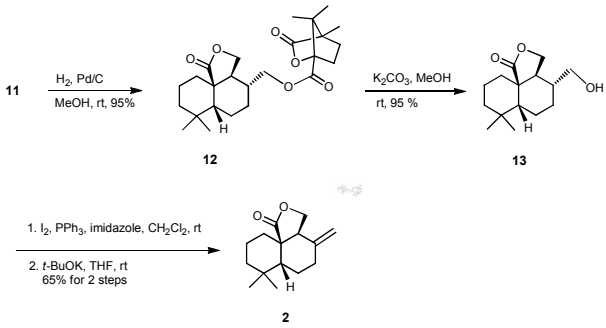


Figure 3. Molecular structures of **8a** and **8b**.

Scheme 2. Synthesis of lactone **11**.



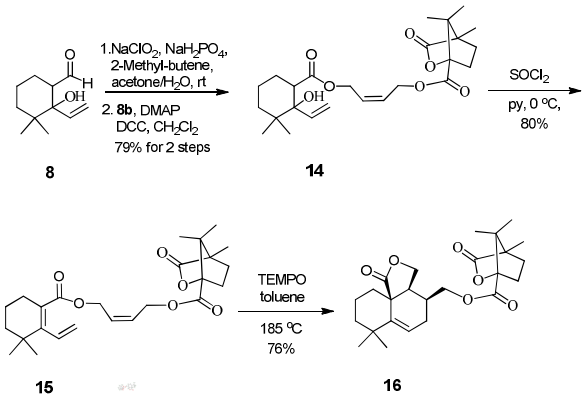
Scheme 3. Synthesis of alkene **2**.



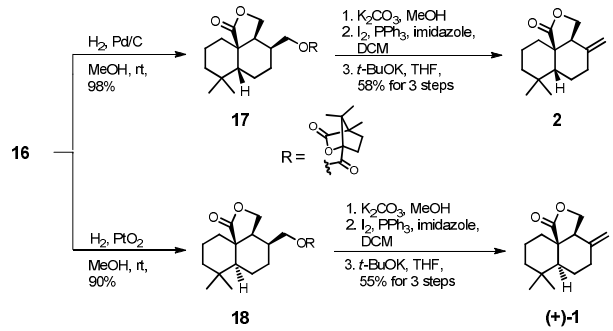
For the hydrogenation of **16**, the same conditions as for that of **11** were employed at first. Unexpectedly, however, the lactone **17** (Scheme 5) was exclusively obtained in good yield. Starting from **17**, compound **2** was then again provided in three steps: hydrolysis, iodination and elimination.[19] Thus, at this stage,[20] platinum dioxide instead of Pd/C was adopted as the catalyst for the hydrogenation of **16** in order to obtain the exact target molecule.[20(d)] Indeed, the reaction smoothly afforded the lactone **18** as the only product. Diastereospecific hydrogenations of compounds **11** and **16** in the presence of Pd/C to give **12** and **17**, respectively, could be attributed to a directing effect between the catalyst and the lactone moiety, which is oriented β-face.[20(c)] On the other hand, hydrogenation of **16** in the presence of PtO_2 to give stereospecific **18** was probably due to the steric hindrance caused on the β-face by the substituents on the ring.[20] Finally, the target molecule, compound **(+)-1**, was furnished after the same three reactions were carried out starting from **18**. Surprisingly, the sign of the optical rotation of product **(+)-1** was found to be positive, whereas

the ^{1}H-NMR and ^{13}C-NMR spectral data of **(+)-1** were in excellent agreement with those of the natural product reported in the literature.[5,21] As illustrated in Figure 4, upon comparison of the optical rotation ($[\alpha]_D$ = -112, C1.0, $CHCl_3$) of antrocin isolated by Chang and coworkers[5] with that ($[\alpha]_D$ = +116, C0.6, $CHCl_3$) of product **(+)-1** synthesized by us, the absolute stereo-structure of each of the two isomers was accordingly clarified.

Scheme 4. Synthesis of intermediate **16**.



Scheme 5. Synthesis of (+)-antrocin **1**.



To explore the theoretical basis for why only one isomer was furnished by the IMDA reaction of the triene **10**, on which an (*E*)-2-butene moiety is the dienophile, the spatial features of all possible transition states (**TS1** ~ **TS4**) were considered and are illustrated in Figure 5(a). Conformations **TS2** and **TS3** are unstable because of the A-strain. In addition, **TS4** is also unstable due to the steric effect between the chiral auxiliary (Xc) and ring methylene moiety, and/or that between Xc and pseudo-equatorial methyl group. It was hypothesized that **TS1** exclusively exists in *exo*-cycloaddition mode.[22] Thus, the diastereomer **11** rather than ***iso*-11** was furnished by the reaction.

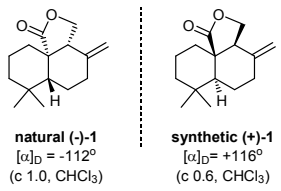


Figure 4. Comparison of the absolute stereo-structure of natural **(-)-1** with that of synthetic **(+)-1**.

On the other hand, the stereospecific formations of product **16** obtained from the IMDA reaction of triene **15**, on which a (*Z*)-2-butene moiety is the dienophile, might be attributable to the spatial features of transition states **TS5** ~ **TS8** illustrated in Figure 5(b). It is speculated that **TS7** and **TS8** should not exist because of the large steric effect caused by the chiral auxiliary (Xc) and the vinyl moiety of diene, and the repulsion effect between the two carbonyl groups. Therefore, ***iso*-16** could not be obtained at all from the reaction, and the reaction exclusively provided **16** via **TS5**, a predominant conformer compared to **TS6**.

To gain a better understanding about each of the IMDA reactions of **10** and **15**, which can afford the corresponding stereospecific products, the density functional theory (DFT) was thus performed.[23] It has to be mentioned here that a recent paper reported by Liptrot and Power demonstrated that the London dispersion forces could considerably influence the stability, structure and reactivity of molecules bearing large substituents.[24] Since it is well-known that the B97-D3 functional[25] can describe non-covalent interactions (for instance, the London dispersion) successfully,[24] computations were thus performed using the dispersion-corrected B97-D3/6-311G(d,p).[23] For each IMDA reaction, as illustrated in Figure 6, the diene and dienophile moieties on the reactant could interact at two different pairs of relative positions, constructing one transition state with high free energy and the other with low free energy. During the reaction of **10**, according to the calculation, the activation energy (16.8 kcal/mol) required to produce **11** was much lower than that (30.7 kcal/mol) required to produce ***iso*-11**, which was higher in Gibb's free energy than the former (**11**) by 0.9 kcal/mol as illustrated in Figure 6(a). On the other hand, for the reaction of **15**, compound **16** was exclusively furnished via the pathway possessing transition state **TS(15-16)**, which was lower in free energy than transition state **TS(15-*iso*-16)** by 12.1 kcal/mol as illustrated in Figure 6(b). Furthermore, compound **16** was lower in Gibb's free energy than compound ***iso*-16** by 1.6 kcal/mol. In addition, it is speculated that there are two possible reasons for the difference in energy (Fig. 6) between **TS(10-11)** and **TS(10-*iso*-11)**: (1) in the latter, a significant steric repulsion caused by the dienophile, which is connected to the camphanate moiety, and the diene, which is attached to the twisted six-membered ring (**TS3** or **TS4**), as shown in Figure 5, and (2) a large torsion of the dienophile moiety in **TS(10-*iso*-11)**. Two reasons, which are similar to the above, are for the difference in energy (Fig. 6) between **TS(15-16)** and **TS(15-*iso*-16)**. Furthermore, on the basis of the self-consistent reaction field (SCRF) method (SCRF = PCM)[26] in Gaussian programs,[23] corrections for solvation in dielectric medium with the toluene dielectric constant (ε = 2.38)[27] were utilized, whose theoretical data are also collected in Figure 6. As shown in Figure 6, it is apparent that the relative energies calculated with two methods for different systems, i.e., B97-D3/6-311G(d,p) and B97-D3/6-311G(d,p) + PCM (solvent = toluene)//B97-D3/6-311G(d,p) are quite similar to each other. As a consequence, the relative activation energy levels obtained computationally were in excellent agreement with the aforesaid relative free energy levels of the possible transition states illustrated in Figure 5, confirming the extremely high stereo-selectivity of each reaction.

CONCLUSIONS

In conclusion, by starting with commercially available compound, we achieved the total synthesis of (+)-antrocin and its diastereomer. The highly stereo-selective IMDA reaction of each triene intermediate (**10** or **15**) containing a camphanate group was one of the crucial steps leading to the target molecule. DFT calculations of the activation energy of both reactions confirmed the rationale for the formations of the stereo-specific products **11** and **16**. The absolute stereo-structure of natural (-)-antrocin was finalized based on the optical rotation of (+)-antrocin, X-ray crystallography of the key intermediates and NMR spectra.[28,29]

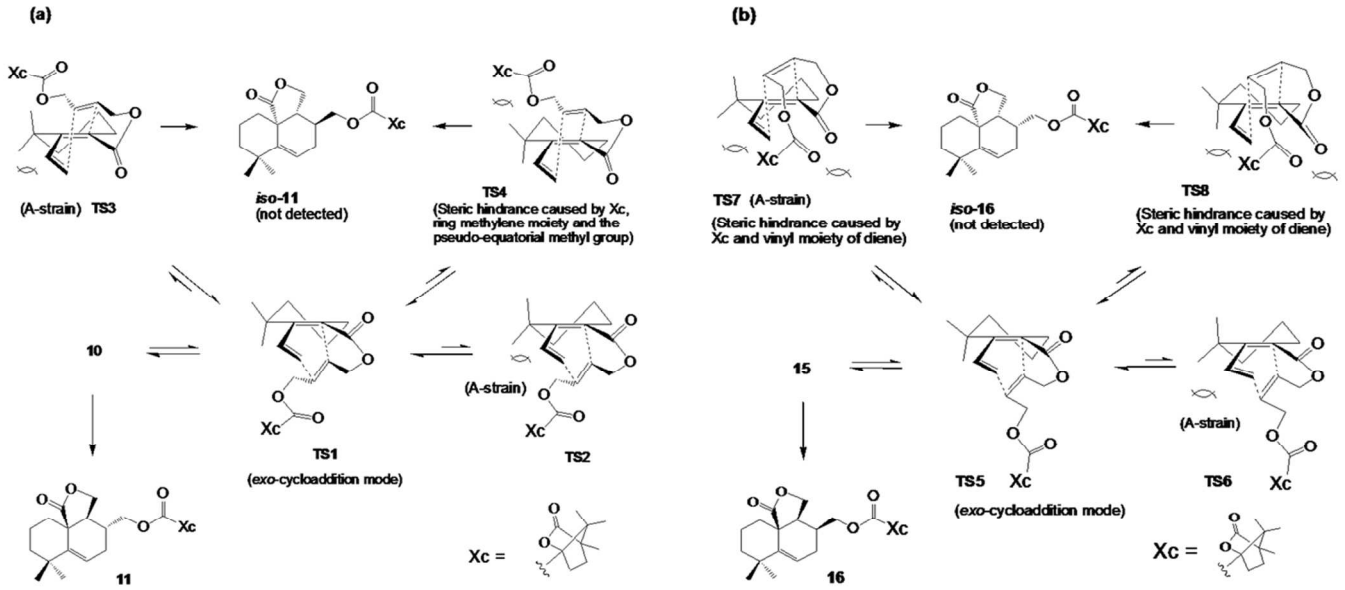


Figure 5. Structures of the possible transition states of the IMDA reactions of **10** and **15**.

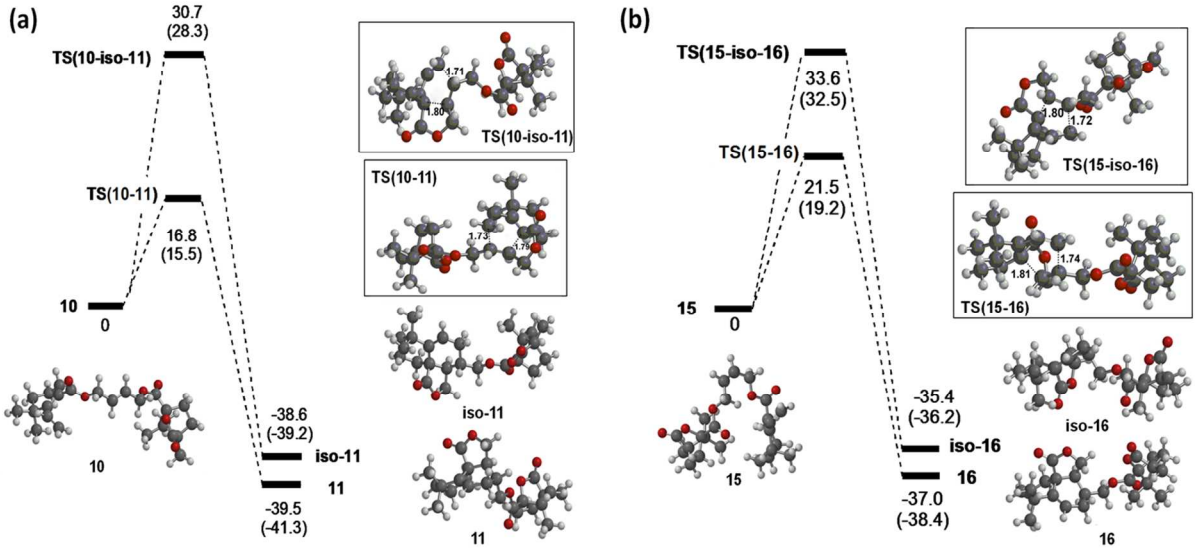


Figure 6. Potential energy surfaces of the reactants (**10** and **15**), transition states, and cycloaddition products (**11** and **16**) at the B97-D3/6-311G(d,p) level of theory. The solvent effect (SCRF= PCM, solvent = toluene) was utilized for the B97-D3/6-311G(d,p) + PCM (solvent = toluene)//B97-D3/6-311G(d,p) method, whose computational data are given in the parentheses. (For more information, see the text).

EXPERIMENTAL SECTION

General Procedures. Reactions were carried out in round bottom flasks fitted with rubber septa under argon. Crude product solutions were dried on Na_2SO_4 and concentrated with a rotary evaporator below 40 ^oC at ~ 30 Torr. Silica gel column chromatography was performed employing 230 - 400 mesh silica gel. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained using Bruker Avance II (300 MHz) NMR spectrometer. Chemical shifts (δ scale) are expressed in parts per million downfield from tetramethylsilane (δ = 0.00). 1H NMR data are presented as follows: chemical shift, multiplicity (s = singlet, br = broad singlet, d = doublet, t = triplet, m = multiplet and/or multiple resonances), coupling constant in Hz (Hertz), integration. High-resolution mass spectra were determined on a Jasco JMS-HX 110 spectrometer. Reactions were monitored by thin layer chromatography (TLC) on Silicycle siliaplate^{TM}G TLC plates (F-254 indicator). The optical rotation ($[\alpha]^{20}_D$) were recorded with a Jasco P-2000 polarimeter at 589 nm (sodium d-line) using thermostable optical glass cell (10 mm path length). HRMS measurements were performed using a magnetic sector mass analyzer.

(Z)-6-(Hydroxymethylene)-2,2-dimethylcyclohexanone (4) [12]. To a stirred suspension of NaOMe (16.3 g, 302.85 mol) in dry toluene (300 mL) was added dropwise 2,2-dimethylcyclohexanone (20 g, 158.49 mmol) during 30 min at room temperature, the mixture being stirred throughout this period. To this was added

dropwise HCO_2Et (34.9 mL, 406.58 mol) during 15 min at 0 °C and the reaction mixture stirred for 12 h at room temperature before being poured into ice cooled water. The reaction mixture was acidified with 10% HCl aq, extracted with EA (3 x 100 mL), washed with water (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:20) gave **4** (17.8 g, 73%): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.68 (s, 1H), 2.32 (t, *J* = 6.3 Hz, 2H), 1.62 – 1.70 (m, 2H), 1.52 – 1.56 (m, 2H), 1.19 (s, 6H); [lit.[12(b)] NMR ($CDCl_3$): δ 14.40 (1H, broad, s), 8.54 (1H, s), 1.5~2.4 (6H), 1.18 (6H, s)]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.4, 188.8, 107.2, 37.4, 27.0, 24.3, 19.5.

Alcohol 5. To a stirred solution of **4** (15 g, 97.34 mmol) in MeOH (150 mL) at 0 °C was added $NaBH_4$ (5.5 g, 145.91 mol).The reaction mixture was allowed to stir for 1 h at 0 °C and quenched with water. The reaction mixture was extracted with EA (3 x 50 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated. The crude product was used for the next step without purification. To a stirred solution of crude diol (11.14 g, 70.38 mmol) in DMF (150 mL) was added imidazole (9.58 g, 140.71 mol) and TBDMSCl (15.9 g, 105.56 mol) at 0 °C. After stirring at room temperature for 5 h. The reaction mixture was dilutes with water followed by extraction with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:20) gave **5** (24.3 g, 92% for 2 steps): IR (KBr): 3399, 2954, 2929, 2857, 1461, 1251, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.09 (s, 1H), 3.68 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.56 (t, *J* = 9 Hz, 1H), 3.18 (d, *J* = 9 Hz, 1H), 1.73 – 1.60 (m, 1H), 1.53 – 1.36 (m, 4H), 1.16 – 1.11 (m, 2H), 1.00 (s, 3H), 0.90 (s, 12H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.1, 69.7, 40.5, 39.2, 35.5, 29.2, 27.7, 26.0, 20.9, 18.6, 18.2, -5.4; Anal calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84; found: C, 66.35; H, 11.88.

Ketone 6. To a stirred solution of **5** (9 g, 33.24 mmol) in CH_2Cl_2 (100 mL) was added pyridinium chlorochromate (28.6 g, 132.94 mol) at room temperature. Stirring was continued at room temperature until the starting material was disappeared on TLC. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (3 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:40) gave **6** (7.7 g, 86%): IR (KBr): 2954, 2930, 2884, 2857, 1703, 1471, 1463, 1254, 1122, 1103, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.50 (dd, *J* = 10.2, 8.4 Hz, 1H), 2.78 – 2.67 (m, 1H), 2.38 – 2.29 (m, 1H), 1.87 – 1.63 (m, 3H), 1.59 – 1.50 (m, 1H), 1.34 – 1.24 (m, 1H), 1.18 (s, 3H), 1.02 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.2, 62.9, 48.5, 45.5, 41.8, 31.8, 26.0, 25.4, 25.2, 21.2, 18.4, -5.2, -5.3; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{30}O_2Si$ 270.2015; found 270.2012.

Vinly alcohol 7. To a solution of **6** (17.9 g, 66.32 mmol) in THF (100 mL) was added vinyl magnesium bromide (12.54 g, 95.59 mmol). The mixture was stirred at room temperature for 1 h and quenched with saturated aqueous NH_4Cl solution (50 mL) at 0 °C. The system was extracted by CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:50) gave **7** (16.2 g, 80%): IR (KBr): 2936, 2860, 1471, 1464, 1389, 1257, 1084 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.43 (dd, *J* = 17.1, 2.4 Hz, 1H), 5.21 (dd, *J* = 10.5, 2.4 Hz, 1H), 3.98 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 1H), 3.47 (dd, *J* = 9.6, 2.1 Hz, 1H), 2.05 – 1.79 (m, 2H), 1.68 – 1.50 (m, 3H), 1.40 – 1.33 (m, 1H), 1.13 – 1.07 (m, 1H), 0.92 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 114.6, 79.5, 67.0, 39.9, 37.6, 36.1, 25.9, 24.7, 24.6, 23.5, 21.7, 18.2, -5.6, -5.7; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{17}H_{34}O_2Si$ 298.2328; found 298.2329.

Hydroxyl aldehyde 8. To a stirred solution of **7** (1.59 g, 5.33 mmol) in THF (80 mL) was added TBAF (1 M in THF, 10.6 mL, 10.6 mmol) at room temperature. The reaction mixture was stirred for 12 h, then concentrated under reduced pressure. Purification by silica gel flash column chromatography (EA-hexanes, 1:4) gave corresponding alcohol **S-1** (8.8 g, 80%): IR (KBr): 3322, 2980, 2865 1459, 1385, 1249, 1071, 1004cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.37 (dd, *J* = 17.4, 1.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.89 (dd, *J* = 10.8, 2.1 Hz, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 2.77 (s, 1H), 2.30 (br, 1H), 1.90 – 1.84 (m, 1H), 1.81 – 1.71 (m, 2H), 1.64 – 1.55 (m, 2H), 1.53 – 1.47 (m, 1H), 1.20 – 1.14 (m, 1H), 0.95 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 114.4, 80.1, 65.6, 40.0, 37.6, 36.0, 24.3, 24.2, 23.5, 21.3; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{11}H_{20}O_2$ 184.1463; found 184.1462.

To a stirred solution of the alcohol **S-1** (4.4 g, 24.16 mmol) in CH_2Cl_2 (150 mL) was added PDC (36 g, 95.69 mmol) at room temperature. The reaction mixture was stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (240 mL) and washed with water (3 x 80 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:5) gave **8** (3.9 g, 91%): IR (KBr): 2937, 2868, 1713, 1455, 1388, 1195 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (s , 1H), 5.99 (dd, *J* = 17.4, 7.4 Hz, 1H), 5.29 (m, 2H), 2.73 (m, 1H), 1.76 – 1.61 (m, 5H), 1.26 – 1.21 (m, 1H), 0.99 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.3, 139.9, 115.2, 77.0, 52.0, 37.2, 35.3, 23.7, 23.1, 21.8, 20.3; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{11}H_{18}O_2$ 182.1307; found 182.1305.

Butenol camphanate 8a. To a stirred solution of trans-2-butene-1,4-diol (1.7 g, 19.29 mmol) in CH_2Cl_2 (50 mL) was added (1*S*)-(-)-camphanic chloride (4 g, 18.51 mmol) at room temperature. The mixture was stirred at room temperature for 4 h and quenched with water (50 mL). The aqueous layer was extracted by CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:5) gave **8a** (4.2 g, 82%): IR (KBr):3662, 2971, 1783, 1736, 1450, 1311, 1228 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 – 5.93 (m , 1H), 5.88 – 5.81 (m, 1H), 4.73 (d, *J* = 5.7 Hz, 2H), 4.17 (d, *J* = 4.8 Hz, 2H), 2.42 (td, *J* = 11.4, 4.8 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.93 – 1.87 (m, 1H), 1.72 – 1.63 (m, 1H), 1.10 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 167.1, 134.7, 123.5, 91.0, 65.2, 62.2, 54.6, 54.1,

30.5, 28.7, 16.6, 9.5; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{14}H_{20}O_5$ 268.1311; found 268.1304.

Hydroxyl ester 9. To a stirred solution of **8** (3 g, 16.47 mmol) in acetone/H_2O = 3:1 (40 mL) was added 2-methyl-butene (7 mL, 65.87 mmol), NaH_2PO_4 (2.27 g, 16.45 mmol), and $NaClO_2$ (4.4 g, 49.42 mmol), and the mixture was stirred at room temperature for 4 h. Then the reaction mixture was diluted with EA (50 mL), washed with ice cooled aqueous 0.1 M HCl and brine, then dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give a crude acid, which was directly used in next step.

To a stirred solution of the crude acid (2.44 g, 12.32 mmol) in CH_2Cl_2 (80 mL) was added **8a** (3.04 g, 11.34 mmol), *N,N'*-dicyclohexylcarbodiimide (4.6 g, 22.29 mmol), and DMAP (0.13 g, 1.06 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was filtered through celite and rinsed with CH_2Cl_2 (3 x 25 mL). The filtrate was washed with water (3 x 50 mL), brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:30) gave **9** (6.2 g, 73% for 2 steps): IR (KBr): 3088, 2941, 1790, 1731, 1522, 1447, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87 (m , 3H), 5.30 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.15 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.73 (m, 2H), 4.55 (m, 2H) 3.66 (s, 1H), 2.83 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.49－2.39 (m, 1H), 2.08－2.04 (m, 1H), 1.94－1.87 (m, 3H), 1.74－1.70 (m, 2H), 1.61－1.55 (m, 2H), 1.19 (m, 1H), 1.13 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 176.2, 167.1, 140.1, 128.7, 127.2, 115.3, 90.9, 75.9, 64.7, 63.6, 54.7, 54.2, 46.4, 36.8, 35.0, 30.6, 28.8, 25.2, 24.5, 22.9, 20.7, 16.7, 9.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{36}O_7$ 448.2461; found 448.2465.

Triene 10. To a stirred solution of **9** (1.5 g, 3.39 mmol) in pyridine (50 mL) was added $SOCl_2$ (0.72 mL, 9.92 mmol). The mixture was stirred at room temperature for 2 h and quenched with saturated aqueous $NaHCO_3$ solution (50 mL) at 0 °C. The mixture layer was extracted by CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:4) gave **10** (1.29 g, 89%): IR (KBr): 3082, 2934, 1790, 1731, 1639, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.36 (ddt, *J* = 17.4, 11.1, 1.8 Hz, 1H), 5.89 (m, 2H), 5.06 (ddd, *J* = 20.7, 17.4, 1.8 Hz, 2H), 4.74 (d, *J* = 4.2 Hz, 2H), 4.58 (d, *J* = 4.2 Hz, 2H), 2.44 (ddd, *J* = 12.3, 10.5, 3.9 Hz, 1H), 2.27 (td, *J* = 7.2, 1.8 Hz, 2H), 2.09－1.89 (m, 2H), 1.75－1.63 (m, 3H), 1.52－1.48 (m, 2H), 1.12 (s, 3H), 1.06 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 170.6, 167.1, 148.8, 135.4, 129.3, 127.0, 126.8, 117.6, 90.9, 64.9, 63.5, 54.7, 54.2, 38.2, 34.0, 30.6, 28.8, 27.9, 27.4, 18.4, 16.7, 9.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2364.

Lactone 11. To a stirred solution of **10** (0.56 g, 1.30 mmol) in anhydrous degassed toluene (5 mL) was added TEMPO (0.05 g, 10 mol%) and heated in a sealed tube under argon at 185 °C for 5 d. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (3 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:10) gave **11** (0.4 g, 72%): IR (KBr): 2929, 1787, 1459, 1313, 1273, 1171 cm^{-1}; $[\alpha]^{20}_D$ = +51.8 (c 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.82-5.81 (m, 1H), 4.46－4.40 (m, 1H), 4.33－4.24 (m, 3H), 2.48－2.39 (m, 1H), 2.30－2.47 (m, 2H), 2.10－1.90 (m, 6H), 1.75－1.66 (m, 2H), 1.60－1.53 (m, 1H), 1.46－1.40 (m, 1H), 1.36 (s, 3H), 1.27 (m, 1H), 1.17 (s, 3H), 1.13(s, 3H), 1.06 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 177.1, 167.3, 139.9, 121.9, 90.8, 66.7, 66.4, 54.5, 54.0, 47.6, 45.7, 45.6, 40.2, 36.0, 35.0, 32.8, 32.0, 30.4, 28.8, 28.6, 27.0, 18.1, 16.5, 9.4; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2359.

Tricyclic camphanate 12. To a stirred solution of **11** (0.2 g, 0.46mmol) in MeOH (50 mL) was added 10% Pd/C (0.02 g, 10 mol%), and the mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. Then the mixture was filtered through a celite-sintered funnel and extracted with EA (3 x 20 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated in *vacuo* gave **12** (0.19 g, 95%): IR (KBr): 2927, 2854, 1782, 1667, 1626, 1457cm^{-1}; $[\alpha]^{20}_D$ = +80.2 (c 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.39-4.34 (m, 1H), 4.23-4.19 (m, 2H), 4.13-4.09 (m, 1H),2.49－2.20 (m, 1H) 2.18 (m, 1H), 1.99－1.86 (m, 5H), 1.74－1.60 (m, 3H), 1.40－1.34 (m, 5H), 1.13 (s, 3H), 1.07 (s, 3H), 1.02(s, 3H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.3, 177.9, 167.7, 91.0, 69.7, 68.4, 54.7, 54.2, 46.7, 42.6, 40.2, 38.8, 36.4, 33.7, 31.7, 30.6, 28.8, 27.1, 23.3, 22.0, 18.6, 16.8, 16.7, 9.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{36}O_6$ 432.2512; found 432.2518.

Tricyclic alcohol 13. To a stirred solution of **12** (0.2 g, 0.46 mmol) in MeOH (20 mL) was added K_2CO_3 (0.1 g, 0.72 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted by CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:5) gave **13** (0.11 g, 95%): IR (KBr): 3686, 2918, 2857, 1762, 1453, 1373cm^{-1}; $[\alpha]^{20}_D$ = +90.6 (c 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.34 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.13 (d, *J* = 9.3 Hz, 1H), 3.64 (d, *J* = 4.5 Hz, 2H),2.28－2.23 (m, 1H), 1.95－1.84 (m, 3H), 1.69 (br, 1H), 1.60－1.56 (m, 2H), 1.51－ 1.46 (m, 3H), 1.37－1.32 (m, 4H), 1.06 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 70.2, 66.3, 46.7, 42.6, 40.3, 38.9, 38.7, 33.7, 31.8, 31.7, 27.2, 23.0, 22.1, 18.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{24}O_3$ 252.1725; found 252.1720.

Tricyclic alkene 2. To a stirred solution of **13** (80 mg, 0.31 mmol) in DCM (10 mL) was added PPh_3 (0.13 g, 0.49 mmol), imidazole (69 mg, 1.01 mmol), and I_2 (160 mg, 0.63 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, quenched with saturated aqueous $Na_2S_2O_3$ solution (15 mL), and extracted with EA (3 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:6) gave corresponding lactone **S-2** (0.11 g, 82%): IR (KBr): 2929, 1769, 1481, 1455, 1367, 1195cm^{-1}; $[\alpha]^{20}_D$ = 78.1 (c

0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.34 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.38－3.25 (m, 2H), 2.22 (dd, *J* = 10.2, 4.2 Hz, 1H), 1.97－1.91 (m, 2H), 1.85 (m, 1H), 1.64－1.52 (m, 5H), 1.48－1.41 (m, 1H), 1.39－1.31(m, 3H), 1.07 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.3, 69.4, 46.9, 42.6, 42.3, 40.1, 37.8, 33.6, 31.9, 31.8, 27.3, 26.9, 22.0, 18.7, 14.7; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{23}IO_2$ 362.0743; found 362.0746.

To a stirred solution of Lactone **S-2** (70 mg, 0.15 mmol) in THF (10 mL) was added *t*-BuOK (50 mg, 0.45 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted by CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:6) gave tricyclic alkene **2** (20 mg, 78%): IR (KBr): 2930, 2361, 1768, 1647, 1275, 1158 cm^{-1}; $[\alpha]^{20}_D$ = +120.3 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.84 (d, *J* = 15.6 Hz, 2H), 4.24-4.21 (m, 1H), 2.83 (t, *J* = 7.5 Hz, 1H), 2.25－2.13 (m, 3H), 1.97－1.91 (m, 1H), 1.84 (m, 1H), 1.52－1.35 (m, 5H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 143.9, 112.0, 68.9, 50.7, 46.3, 41.6, 36.0, 33.7, 29.8, 29.6, 29.2, 29.0, 23.9, 18.3; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{22}O_2$ 234.1620; found 234.1626.

Butenol camphanate 8b. To a stirred solution of cis-2-butene-1,4-diol (2 g, 22.69 mmol) in CH_2Cl_2 (50 mL) was added (-)-camphanic chloride (4.7 g, 21.77 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (50 mL). The mixture was extracted by CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:5) gave **8b** (4.8 g, 80%): IR (KBr): 3661, 2971, 1788, 1736, 1450, 1312, 1228 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92－5.87 (m , 1H), 5.69－5.64 (m, 1H), 4.85 (d, *J* = 6.9 Hz, 2H), 4.29 (d, *J* = 6.3 Hz, 2H), 2.43 (td, *J* = 12.1, 4.2 Hz, 1H), 2.08－1.88 (m, 3H), 1.73－1.65 (m, 1H), 1.12 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 167.3, 134.3, 124.1, 90.8, 61.0, 58.1, 54.6, 54.1, 30.3, 28.7, 16.5, 16.5, 9.4; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{14}H_{20}O_5$ 268.1311; found 268.1300.

Hydroxyl ester 14. To a stirred solution of **8** (4 g, 21.96 mmol) in acetone/H_2O = 3:1 (44 mL) was added 2-methyl-butene (9.3 g, 87.82 mmol), NaH_2PO_4 (3.02 g, 21.93 mmol), and $NaClO_2$ (5.96 g, 65.89 mmol) at room temperature. After 4 h, the reaction mixture was diluted with EtOAc (20 mL), washed with ice cooled aqueous 0.1 M HCl and brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give a crude acid, which was directly used in next step.

To a stirred solution of the crude acid (3 g, 15.14 mmol) in CH_2Cl_2 (50 mL) was added **8b** (3.74 g, 13.94 mmol), *N,N'*-dicyclohexylcarbodiimide (5.6 g, 27.4 mmol), and DMAP (0.15 g, 1.3 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was filtered through celite and rinsed with CH_2Cl_2 (3 x 25 mL). The filtrate was washed with water (3 x 50 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:5) gave **14** (7.78 g, 79% for 2 steps): IR (KBr): 3060, 2967, 1790, 1715, 1639, 1447, 1379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90－5.72 (m , 3H), 5.31－5.12 (m, 2H), 4.81 (d, *J* = 5.4 Hz, 2H), 4.66 (d, *J* = 5.1 Hz, 2H), 3.62 (s, 1H), 2.80 (dd, *J* = 12.9, 3.9 Hz, 1H), 2.83 (dd, *J* = 12.1, 3.9 Hz, 1H), 2.06－2.01 (m, 1H), 1.98－1.82 (m, 3H), 1.73－1.66 (m, 3H), 1.58 (m, 1H), 1.18 (m, 1H), 1.17 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 176.2, 167.2, 140.1, 128.6, 127.3, 115.2, 90.8, 75.9, 60.7, 59.7, 54.7, 54.2, 46.4, 36.8, 35.0, 30.5, 28.8, 25.1, 24.5, 22.8, 20.7, 16.6, 9.6; HRMS (EI/ magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{36}O_7$ 448.2461; found 448.2452.

Triene 15. To a stirred solution of **14** (2 g, 4.46 mmol) in pyridine (50 mL) was added $SOCl_2$ (0.94 mL, 13.05 mmol). The mixture was stirred at room temperature for 2 h and quenched with saturated aqueous $NaHCO_3$ solution (50 mL) at 0 ºC. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:4) gave **15** (1.53 g, 80%)l: IR (KBr): 3079, 2934, 1790, 1731, 1639, 1453 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.37 (dd, *J* = 17.4, 11.4 Hz, 1H), 5.83－5.74 (m, 2H), 5.08 (ddd, *J* = 13.2, 11.4, 2.1 Hz, 2H), 4.85 (d, *J* = 5.7 Hz, 2H), 4.70 (d, *J* = 5.4 Hz, 2H), 2.44 (td, *J* = 10.8, 4.5 Hz, 1H), 2.27 (td, *J* = 6.3, 2.1 Hz, 2H), 2.09－1.89 (m, 2H), 1.75－1.66 (m, 3H), 1.52－1.50 (m, 2H), 1.22 (s, 3H), 1.07 (s, 9H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 170.7, 167.2, 148.8, 135.4, 128.9, 127.0, 117.7, 90.9, 61.0, 59.7, 54.7, 54.2, 38.3, 34.0, 30.6, 29.6, 28.3, 28.0, 27.5, 18.5, 16.7, 9.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2364.

Lactone 16. To a stirred solution of **15** (0.8 g, 1.85 mmol) in anhydrous degassed toluene (5 mL) was added TEMPO (0.08 g, 10 mol%) and heated in a sealed tube under argon at 185 ºC for 5 d. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (3 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:10) gave **16** (0.42 g, 76%): IR (KBr): 2929, 1787, 1760, 1459, 1274, 1017 cm^{-1}; $[\alpha]^{20}_D$ = +41.1 (c 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, , *J* = 6.3 Hz, 1H), 4.23－4.13 (m, 4H), 2.58－2.38 (m, 3H), 2.18－1.98 (m, 6H), 1.81－1.66 (m, 2H), 1.53－1.45 (m, 2H), 1.27－1.17 (m, 1H), 1.17 (s, 3H), 1.12(s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 177.9, 167.5, 141.9, 121.4, 91.0, 67.1, 64.7, 54.8, 54.3, 46.9, 45.5, 45.4, 41.1, 37.9, 36.6, 32.7, 30.8, 30.4, 28.9, 26.4, 24.5, 18.6, 16.9, 9.7; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2348.

Tricyclic camphanate 17. To a stirred solution of **16** (0.3 g, 0.69 mmol) in MeOH (50 mL) was added 10% Pd/C (0.03, 10 mol%), and the mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. Then the mixture was filtered through a celite-sintered funnel and extracted with EA (3 x 20 mL). The organic layers were combined, dried with anhydrous

$MgSO_4$ and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:5) gave **17** (0.29 g, 98%): IR (KBr): 2928, 2854, 1782, 1627, 1450, 1175 cm^{-1}; $[\alpha]^{20}_D$ = +58.1 (c 0.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.3 (td, *J* = 9.3, 1.8 Hz, 1H), 4.08 (m, 3H), 2.47－2.40 (m, 2H), 2.30 (m, 1H), 2.07－1.88 (m, 4H), 1.74－1.66 (m, 3H), 1.64－1.48 (m, 5H), 1.44 (m, 2H) 1.28 (s, 6H), 1.27 (s, 3H), 1.05(s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 177.8, 167.3, 90.8, 67.2, 64.3, 54.6, 54.1, 46.0, 45.9, 43.6, 41.6, 33.9, 33.7, 32.3, 31.9, 30.6, 28.7, 28.1, 27.4, 23.8, 22.9, 18.1, 16.6, 9.5; HRMS (EI/ magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{36}O_6$ 432.2512; found 432.2514.

Tricyclic alkene 2 (from **17**). To a stirred solution of **17** (30 mg, 0.06 mmol) in MeOH (10 mL) was added K_2CO_3 (20 mg, 0.14 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EA-hexanes, 1:3) gave **S-3** (16 mg, 93%): IR (KBr): 3435, 2933, 2870, 1762, 1627, 1457, 1268 cm^{-1}; $[\alpha]^{20}_D$ = +109.8 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.29 (t, *J* = 9 Hz, 1H), 4.14 (d, *J* = 8.7 Hz, 1H), 3.57－3.50 (m, 2H), 2.42－2.38 (m, 2H), 1.92－1.87 (m, 2H), 1.69－1.59 (m, 4H), 1.53 (m, 2H), 1.44 (m, 1H), 1.39 (m, 1H), 1.14 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9, 65.1, 64.8, 46.0, 43.7, 42.0, 35.2, 34.0, 33.9, 28.2, 27.5, 23.9, 23.2, 21.0, 18.3; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{24}O_3$ 252.1725; found 252.1729.

To a stirred solution of **S-3** (40 mg, 0.15 mmol) in DCM (10 mL) was added PPh_3 (60 mg, 0.22 mmol), imidazole (30 mg, 0.45 mmol), and I_2 (76 mg, 0.30 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL), and extracted with EA (3 x 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:6) gave **S-4** (5 mg, 75%): IR (KBr): 2924, 1769, 1481, 1455, 1367, 1195 cm^{-1}; $[\alpha]^{20}_D$ = +88.1 (c 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.18－4.09 (m, 2H), 3.09－3.04 (m, 1H), 2.89 (t, *J* = 9.9 Hz, 1H), 2.47－2.45 (m, 2H), 1.89－1.82 (m, 3H), 1.58－1.48 (m, 4H), 1.43－1.25 (m, 3H), 1.16－1.12 (m, 1H), 1.04 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 64.1, 49.4, 46.9, 43.1, 42.0, 37.5, 35.9, 33.2, 33.0, 24.9, 22.1, 19.6, 18.4, 8.6; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{23}IO_2$ 362.0743; found 362.0741.

To a stirred solution of **S-4** (50 mg, 0.10 mmol) in THF (10 mL) was added *t*-BuOK (46 mg, 0.40 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:20) gave tricyclic alkene **2** (0.02 g, 79%). All the characterized data were in excellent agreement with those of tricyclic alkene **2** obtained from tricyclic alcohol **13**.

Tricyclic camphanate 18. To a stirred solution of **16** (0.1 g, 0.23 mmol) in MeOH (20 mL) was added 10% PtO_2 (0.01, 10 mol%), and the mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. Then the mixture was filtered through a celite-sintered funnel and extracted with EA (3 x 20 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:5) gave **18** (0.09 g, 90%): IR (KBr): 2926, 2864, 1785, 1740, 1630, 1422, 1116 cm^{-1}; $[\alpha]^{20}_D$ = +64.4 (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.32－4.08 (m, 4 Hz, 1H), 2.47－2.29 (m, 3H), 2.15－2.02 (m, 2H), 1.99－1.90 (m, 1H), 1.81－1.80 (m, 1H), 1.76－1.56 (m, 5H), 1.52－1.44 (m, 2H) 1.41－1.37 (m, 2H), 1.26 (m, 1H), 1.19 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H), 0.96 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 177.9, 167.3, 908, 66.3, 64.8, 54.6, 54.1, 46.8, 46.7, 46.3, 43.5, 41.8, 37.3, 33.2, 33.0, 32.1, 30.6, 28.7, 22.0, 21.0, 19.0, 18.3, 16.6, 9.5; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{25}H_{36}O_6$ 432.2512; found 432.2514.

(+)-Antrocin (1). To a stirred solution of **18** (50 mg, 0.1 mmol) in MeOH (20 mL) was added K_2CO_3 (4 mg, 0.28 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted by CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:3) gave corresponding alcohol **S-5** (20 mg, 95%): IR (KBr): 3447, 2932, 2870, 1762, 1636, 1457, 1097 cm^{-1}; $[\alpha]^{20}_D$ = +101.9 (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.35－4.23 (m, 2H), 3.67－3.51 (m, 2H), 2.42－2.36 (m, 1H), 2.14－2.10 (m, 2H), 1.86－1.70 (m, 4H), 1.58－1.50 (m, 3H), 1.49－1.38 (m, 2H), 1.32－1.29 (m, 1H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 70.8, 62.1, 58.8, 55.5, 51.0, 50.5, 47.1, 42.2, 39.0, 38.5, 33.9, 32.7, 28.9, 21.3, 20.3, 18.6; HRMS (EI/ magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{24}O_3$ 252.1725; found 252.1733.

To a stirred solution of alcohol **S-5** (21 mg, 0.08 mmol) in DCM (10 mL) was added PPh_3 (35 mg, 0.13 mmol), imidazole (18 mg, 0.27 mmol), and I_2 (43 mg, 0.17 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL), and extracted with EA (3 x 20 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:6) gave corresponding lactone **S-6** (22 mg, 73%): IR (KBr): 2928, 1769, 1481, 1455, 1195, 1127 cm^{-1}; $[\alpha]^{20}_D$ = +85.9 (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.31 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.10 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.25 (dd, *J* = 10.2, 6.3 Hz, 1H), 2.95 (t, *J* = 10.2 Hz, 1H), 2.45 (t, *J* = 6.3 Hz, 1H), 2.23－2.21 (m, 2H), 1.84－1.70 (m, 3H), 1.53－1.52 (m, 2H), 1.49－1.40 (m, 3H), 1.38－1.28 (m, 2H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.2, 64.3, 49.5, 47.0, 43.2, 42.1, 37.6, 36.1, 33.4, 33.2, 25.1, 22.2, 19.8, 18.6, 8.8; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{23}IO_2$ 362.0743; found 362.0748.

To a stirred solution of lactone **S-6** (20 mg, 0.06 mmol) in THF (10 mL) was added *t*-BuOK (18 mg, 0.17 mmol). The mixture was stirred at room temperature for 4 h and quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. Purification by silica gel flash column chromatography (EtOAc-hexanes, 1:20) gave **(+)-1** (11 mg, 78%): IR (KBr): 2922, 1769, 1459, 1366, 1158 cm^{-1}; $[\alpha]^{20}_D$ = +116.1 (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.83 (d, *J* = 10.2 Hz, 2H), 4.48 (dd, *J* = 9.3, 6.6 Hz, 1H), 4.16 (dd, *J* = 9.6, 1.2 Hz, 1H), 2.68 (d, *J* = 6.6 Hz, 1H), 2.41－2.22 (m, 2H), 2.20－2.14 (m, 1H), 1.86－1.74 (m, 2H), 1.58－1.49 (m, 2H), 1.48－1.44 (m, 1H), 1.40－1.33 (m, 2H), 1.27－1.22 (m, 1H), 1.19 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 146.7, 111.2, 69.4, 54.2, 48.5, 46.6, 42.0, 36.8, 33.3, 33.2, 30.4, 22.4, 22.2, 18.7; HRMS (EI/magnetic sector) m/z: $[M]^+$ calcd for $C_{15}H_{22}O_2$ 234.1620; found 234.1614.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for all the new compounds, X-ray crystallographic data

Crystallographic data of **11**

Crystallographic data of **12**

Crystallographic data of **16**

Crystallographic data of **1**

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Notes:

The authors declare no competing financial interest.

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REFERENCES AND NOTES

(1) Geethangili, M.; Tzeng, Y.-M. *Evidence-Based Complementary and Alternative Medicine* **2009**, *Article ID 212641*, 1-17. doi: 10.1093/ecam/nep108.

(2) Geethangili, M.; Fang, S. H.; Lai, C. H.; Rao, Y. K.; Lien, H. M.; Tzeng, Y. M. *Food Chem*. **2010**, *119*, 149-153.

(3) Rao, Y. K.; Wu, A. T. H. M.; Geethangili, M. -T.; Huang, W.; Chao,-J.; Wu, C. -H.; Deng, W. -P.; Yeh, C. -T.; Tzeng, Y. -M. *Chem. Res. Toxicol.* **2011**, *24*, 238-245.

(4) Wu, D. -P.; Chiang, H. -C. *J. Chin. Chem. Soc.*, **1995**, *42*, 797-800.

(5) Chiang, H. -C.; Wu, D. -P.; Cherng, I. -W.; Ueng, C. -H. *Phytochemistry,* **1995**, *39*, 613-616.

(6) Chen, J. C. "King of Ganoderma: Antrodia Camphorata in Taiwan", Yuen Chi Jai Book Publishing: Taipei, Taiwan, 2nd Ed. **2008**.

(7) (a) Chen, C. -C.; Shiao, Y. -J.; Lin, R. -D.; Shao, Y. -Y.; Lai, M. -N.; Lin, C. -C.; Ng, L. -T.; Kuo, Y. -H. *J. Natural Products.* **2006**, *69*, 689-891. (b) Han, B. H.; Yang, H. O.; Kang, Y. H.; Suh, D. Y.; Go, H. J.; Song, W. J.; Kim, Y. C.; Park, M. K. *J. Med. Chem.* **1998**, *41*, 2626-2630. (c) Chiang, Y. M.; Liu, H. K.; Lo, J. M.; Chien, S. C.; Chan, Y. F.; Lee, T. H.; Su, J. K.; Kuo, Y. H. *J. Chin. Chem. Soc.* **2003**, *50*, 161-166. (d) Rojas, E. T.; Rodriguez-Hahn, L. *Phytochemistry,* **1978**, *17*, 574-575.

(8) Wu, S. -H.; Ryvarden, L.; Chang, T. -T. *Botanical Bulletin of Academia Sinica.* **1997**, *38*, 273-275.

(9) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012-3043.

(10) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-C.; Luo T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944-14947.

(11) For examples of the intramolecular Diels-Alder (IMDA) reaction, please see : (a) Lilly, M. J.; Sherburn, M. S. *Chem. Commun.* **1997**, 967-968. (b) Suzuki, Y.; Ohara, A.; Sugaya, K.; Takao, K. -i.; Tadano, K. -i. *Tetrahedron*, **2001**, *57*, 7291-7301. (c) Suzuki, Y.; Nishimaki, R.; Ishikawa, M.; Murata, T.; Takao, K. -i.; Tadano, K. -i. *J. Org. Chem.*, **2000**, *65*, 8595-8607. (d) Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387-4390. (e) Usui, K.; Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2015**, *56*, 1247-1251. (f) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D. *J. Org. Chem.* **1999**, *64*, 1932-1940. (g) Jauch, J. *Angew. Chem. Int. Ed.* **2000**. *39,* 2764-2765. (h) Zhao, Y. -M.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 1223-1226.

(12) (a) Bourdron, J.; Commeiras, L.; Audran, G.; Vanthuyne, N.; Hubaud, J. C.; Parrain, J. -L. *J. Org. Chem.* **2007**, *72*, 3770-3775. (b) Kawanobe, T.; Kogami, K.; Hayashi, K.; Matsui, M. *Agric. Biol. Chem.* **1984**, *48*, 461-464.

(13) Abad, A.; Agullo, C.; Castelblanque, L.; Cunat, A. C. I.; Navarro, M.; de Arellano, C. R. *J. Org. Chem.* **2000**, *65*, 4189-4192.

(14) Ravindar, K.; Caron, P. -Y.; Deslongchamps, P. *Org. Lett.* **2013**, *15*, 6270-6273.

(15) Kudoh, T.; Park, C. S.; Lefurgy, S. T.; Sun, M.; Michels, T.; Leyh, T. S.; Silverman, R. B. *Bioorg. Med. Chem.* **2010**, *18*, 1124-1134.

(16) Compounds **8a** and **8b** were obtained from the individual reactions of (1*S*)-(-)-camphanic chloride with *trans*-2-butene-1,4-diol and *cis*-2-butene-1,4-diol (Fig. 3), respectively. See the *Experimental Section* for the procedure.

(17) For the reaction of (1*S*)-(-)-camphanic chloride with alcohols, please see: (a) Bieliunas, V.; Rackauskaite, D.; Orentas, E.; Stoncius, S. *J. Org. Chem.* **2013**, *78*, 5339-5348. (b) Nicolaou, K. C.; Yang, Z.; Liu, J. -J. Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645-652.

(18) For the example of utilizing TEMPO as catalyst for IMDA reaction, see Chackalamannil, S.; Davies, R. J.; Wang, Y,; Asberom, T.; Doller, D.; Wong, J.; Leone, D. *J. Org. Chem.* **1999**, *64*, 1932-1940.

(19) Imuta, S.; Tanimoto, H.; Momose, M. K. N. Chida, *Tetrahedron* **2006**, *62*, 6926-6944.

(20) (a) Tapia, R.; Bouanou, H.; Alvarez, E.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2014**, *79*, 4405-4413. (b) Cheung, W. S.; Wong, H. N. C. *Tetrahedron* **1999**, *55*, 11001-11016.

(c) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655-2661. (d) The hydrogenation of lactone **11** in the presence of PtO_2 gave exactly the same product (**12**) as that in the presence of Pd/C did.

(21) The chemical shift difference between their corresponding ^{13}C NMR signals was found to be ≤ 0.2 ppm.

(22) Usui, K.; Kanbe, M.; Nakada, M. *Org. Lett.* **2014**, *16*, 4734-4737.

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G. V.; Barone, B.; Mennucci, G.; Petersson, A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, Jr., T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Ada-

mo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian, Inc*., Wallingford CT, 2013.
(24) Liptrot, D. J.; Power, P. P. *Nat. Rev. Chem.* **2017**, *1*, 4-12.
(25) Grimme, S. *J. Comput. Chem*. **2006**, *27*, 1787-1796.
(26) (a) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327-335. (b) Cances, M. T.; Mennucci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032-3041. (c) Barone, V.; Cossi, M.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210-3222. (d) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253-260. (e) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404-417.
(27) Wohlfarth, C. In *Dielectric constant of toluene*; Lechner, M., Ed.; Supplement to IV/6 Landolt-Börnstein-Group IV Physical Chemistry; Springer: Berlin, Heidelberg, 2008; Vol. 17.

(28) For the asymmetric synthesis of (-)-antrocin, see (a) Tai, D. -F.; Angamuthu, V.; Tzeng, Y. -M. U.S. Patent 0096324 A1, Apr. 18, 2013. (b) Li, F. -Z.; Li, S.; Zhang, P. -P.; Huang, Z. -H.; Zhang, W. -B.; Gong, J.; Yang, Z. *Chem. Commun*. **2016**, *52*, 12426-12429.
(29) It has to be noted that the absolute stereo-structure of synthetic (+)-**1** (Fig. 4) is exactly the same as that of synthetic (-)-**1** reported in the literature (ref. 28). Thus, it is worth emphasis that the absolute configuration of (+)-**1** (Fig. 4) was determined in terms of the X-ray crystallography of intermediates **11** (Scheme 2), **12** (Scheme 3) and **16** (Scheme 4), in which the absolute configuration of (-)-camphanic moiety was known. Please see the Supporting Information for all the CIF data of **11**, **12**, **16** and (+)-**1** (Scheme 5).