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Stereoselective approach to potential scaffold of A-nor B-aromatic OSW-1 analogues via [4+2] cycloaddition of *o*-quinodimethane

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ABSTRACT

A-nor B-aromatic steroidal skeleton was efficiently constructed by means of *o*-quinodimethane chemistry with exclusive stereoselectivity. The benzocyclobutene substrate for generation of the *o*-quinodimethane intermediate and subsequent [4+2] cycloaddition could be synthesized via (*E*)-selective Julia–Kocienski olefination and diastereoselective Grignard addition reactions. The synthesized tricyclic steroid-like compound with a *trans*-diol substructure would be utilized for divergent syntheses of potentially antitumor OSW-1 analogues with the truncated steroidal aglycone.

1. Introduction

o-Quinodimethanes, generated by thermolytic 4π-ring cleavage of benzocyclobutene derivatives, have been extensively utilized in an organic synthesis field as a highly useful and reactive intermediate.[1] Complex organic molecules including fused polycyclic system, such as a steroidal skeleton, have been assembled via an intramolecular [4+2] cycloaddition reaction of these intermediates in a highly efficient manner. So-called '*o*-quinodimethane chemistry' is undoubtedly one of the most important strategies for the second-generation steroid syntheses.[2] In our group, great efforts have been devoted to this research field, and syntheses of tremendous types of steroidal and steroid-like polycyclic compounds have been accomplished and reported to date.[3] Among them, we have reported that *trans*-4,5-benzhydrindan-1-ones, such as **1** (Fig. 1) can be constructed by means of the *o*-quinodimethane chemistry, in an efficient and stereoselective fashion, in which *trans*-annulated CD ring and high enantio-purity are successfully established.[4] These compounds could be well adapted to converting into various A-nor steroidal bioactive compounds, including aglycone of A-nor B-aromatic OSW-1 analogues **2**.[4,5]

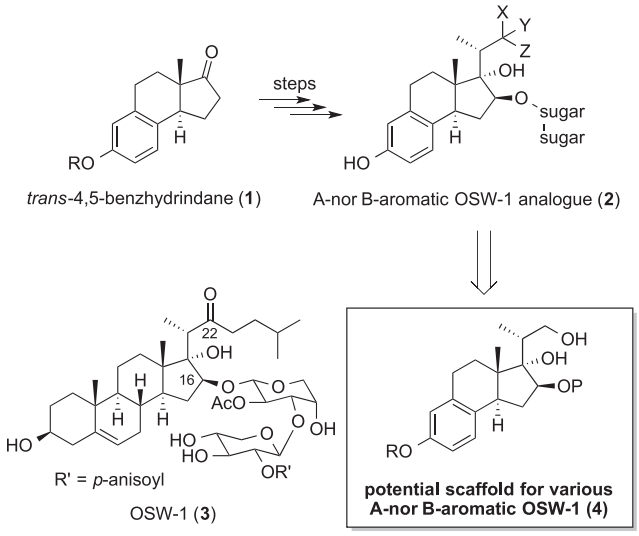

Fig. 1. Natural OSW-1 and its A-nor B-aromatic analogues.

OSW-1 (**3**) is known as an antitumor steroidal saponin, which exhibits extremely potent cytotoxicity against wide range of malignant tumor cells, and expected to be a promising candidate of novel anticancer drugs.[6] In the course of our studies on SAR of

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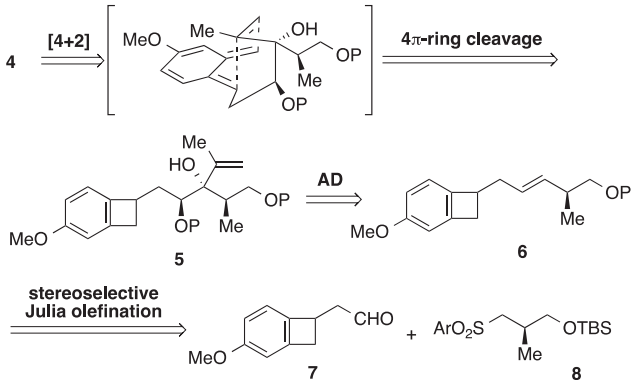
OSW-1, we have disclosed that simplification of the steroidal skeleton of OSW-1 can be an effective approach for new antitumor drug discovery, exemplified as A-aromatic (estrane) analogue[7] and des-AB-type analogue of OSW-1.[8] In this context, A-nor B-aromatic OSW-1 analogues **2** seem to be the next design of artificial compounds having a truncated aglycone part, which is accessible starting from *trans*-4,5-benzhydrindan-1-ones **1**, synthesized by the *o*-quinodimethane chemistry, as mentioned above.[4] This transformation, however, involves some embarrassing situations, such as circuitous installation of the *trans*-diol unit via a multi-step sequence.[4a] These drawbacks would be circumvented employing more suitably functionalized benzocyclobutene substrate for the *o*-quinodimethane chemistry, which will bring about straightforward construction of the CD ring with the *trans*-diol unit. Thus, we set compound **4** (Fig. 1) as a potential scaffold for various A-nor B-aromatic OSW-1 analogues containing protected secondary alcohol (on the C16 as steroidal numbering) and convertible primary alcohol (on the C22). The compound **4** should be a useful precursor of a wide variety of OSW-1 analogues (**2**) possessing various oxidation states at the C22 position, which would provide useful information on SAR of the side-chain.[9]

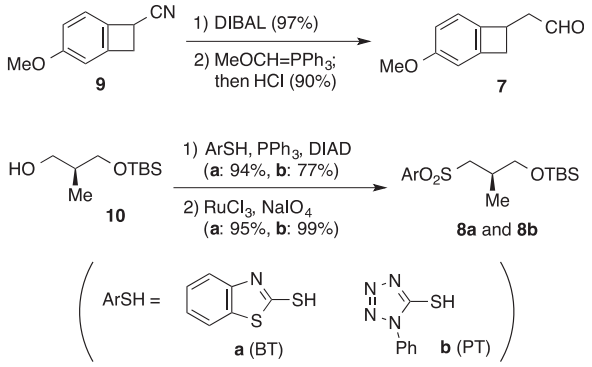
Synthetic plan for the target compound **4** is presented in Scheme 1. Tricyclic framework will be constructed at a time by successive pericyclic reactions (4π-ring cleavage and [4+2] cycloaddition) via *o*-quinodimethane intermediate, generated from highly oxygenated benzocyclobutene derivative **5**. The transition state of the [4+2] cycloaddition will be dictated by the most relaxed orientation of the substituents depicted in Scheme 1. The benzocyclobutene **5** will be obtained by Sharpless asymmetric dihydroxylation (AD)[10] followed by several transformations of alkene **6**, which will be synthesized by stereoselective modified Julia olefination reaction[11] between aldehyde **7** and sulfone **8**. In this paper, we describe the stereoselective synthesis of **4**, a core structure of A-nor B-aromatic OSW-1, especially emphasizing good applicability of the *o*-quinodimethane chemistry.



Scheme 1. Synthetic plan for the target compound **4**.

2. Results and discussion

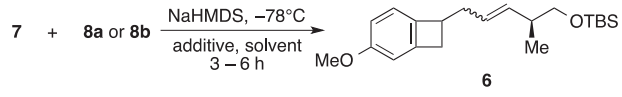
Already reported benzocyclobutenyl aldehyde **7**[12] was prepared as follows; readily available 1-cyano-4-methoxy benzocyclobutene **9**[13] was reduced by DIBAL, and the resulting aldehyde was reacted with methoxymethylene phosphorane followed by acid treatment to afford the homologated aldehyde **7** in good yields. On the other hand, known optically pure alcohol **10**[14] was transformed into the two types of heteroarylsulfone **8a** (benzothiazolyl; BT) and **8b** (phenyltetrazolyl; PT) through Mitsunobu reaction and subsequent oxidation of the heteroarylsulfides (Scheme 2).



Scheme 2. Preparation of the Julia substrates **7** and **8**.

With the aldehyde **7** and the sulfones **8** in hand, we examined modified Julia coupling of these compounds, and the results are summarized in Table 1. In general, modified Julia olefination could be expected to show (*E*)-selectivity[11] desired in this synthesis. We commenced the examination using BT sulfone **8a** and NaHMDS as a base in several solvents at −78 °C (entries 1–3). Although the reaction proceeded to give the coupling product **6**, the yields were moderate with low stereoselectivity. It has been reported that the selectivity is significantly influenced by surroundings of the counter cation of the α-sulfonyl carbanion (derived from the base).[15] Actually, these findings have been put to effective use for enhancement of (*E*)-selectivity of modified Julia olefination by adding several chelating agents.[16] Thus, we tried addition of HMPA or crown ether to improve the stereoselectivity (entries 4–6). Although addition of HMPA brought no positive effects, it was found that 18-crown-6 significantly improved (*E*)-selectivity of the reaction.[17] However, the chemical yields were still moderate and not so satisfactory. Then, we examined Julia–Kocienski olefination using PT sulfone **8b**, which was known to be easier to avoid self-condensation under basic conditions (entries 7–9).[16a] Expectedly the chemical yields were increased, and almost exclusive (*E*)-selectivity was obtained when adding crown ether similar to the case of **8a**. Use of 1 equiv of 18-crown-6 gave rise to the best result (entry 8). Effects of crown ether for the enhancement of (*E*)-selectivity of Julia–Kocienski olefination have been reasonably explained in the past literature.[16a] The explanation is based on the prevention of a closed transition state of the reaction between the sulfonyl carbanion and the aldehyde, which includes a fixed chair-form containing metal chelation leading to the (*Z*)-alkene product.

Table 1
Modified Julia olefination between aldehyde **7** and sulfone **8**

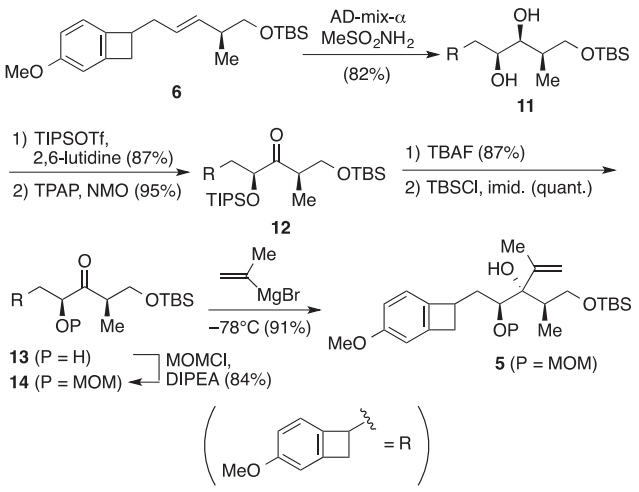


Entry[a]	Sulfone	Solvent	Additive (equiv)	Yield%[b] (*E*/*Z*)[c]
1	**8a** (BT)	THF	—	37 (60:40)
2	**8a** (BT)	Et_2O	—	55 (60:40)
3	**8a** (BT)	Toluene	—	62 (65:35)
4	**8a** (BT)	Toluene	HMPA (5)	61 (60:40)
5	**8a** (BT)	Toluene	18-crown-6 (1)	46 (90:10)
6	**8a** (BT)	Toluene	18-crown-6 (1)	56 (85:15)
7	**8b** (PT)	Toluene	—	82 (60:40)
8	**8b** (PT)	Toluene	18-crown-6 (1)	83 (>95:5)
9	**8b** (PT)	Toluene	18-crown-6 (2)	62 (>95:5)

[a] All reactions were carried out using 1.2 equiv of aldehyde, 1 equiv of sulfone, and 1.1 equiv of NaHMDS.
[b] Isolated yields.
[c] The ratio were estimated by ^{1}H NMR spectra of a mixture of geometric isomers (δ 5.56, J=15.0 Hz for *E*, and δ 5.24, J=11.0 Hz for *Z*).

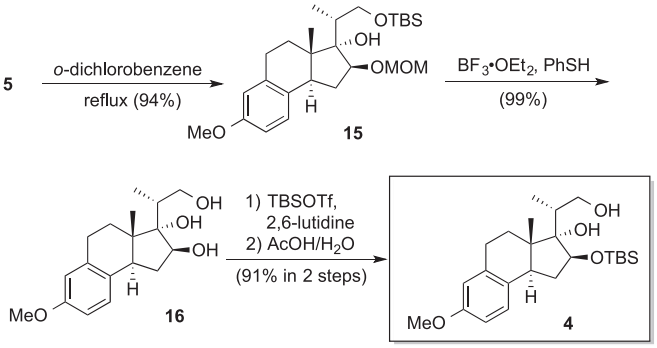
Under the influence of a high metal-abstracting character of the crown ether, the reaction proceeds via an opened transition state with the least steric repulsion between substituents on the sulfone and the aldehyde, and then (*E*)-isomer is preferably produced.[16a]

Transformation of the compound **6** into the thermal reaction substrate **5** is presented in Scheme 3.[18] Stereoselective introduction of two hydroxyl groups onto the alkene of **6** was achieved utilizing Sharpless asymmetric dihydroxylation. Namely, the alkene **6** was reacted with AD-mix-α in the presence of methanesulfonamide to give the diol **11** as a sole diastereomer in 82% yield.[19] The next task was selective protection of one hydroxyl group far from the methyl group. After many complications, this was accomplished using a sterically-demanding triisopropylsilyl (TIPS) group as a protecting group. The other remaining hydroxyl group was then oxidized upon treatment with TPAP to afford the ketone **12**. Attempt to convert **12** directly to **5** (P=TIPS) via Grignard addition was unsuccessful probably due to steric hindrance of the TIPS group. Therefore, we had to change the bulky TIPS group to a less hindered group, and we chose the methoxymethyl (MOM) group to this end because of the assumption that a chelating ability of the MOM group would work well for realizing the desired diastereoselectivity of the subsequent Grignard addition reaction. Two silyl groups (TBS and TIPS) were removed by exposure to TBAF, and only the primary hydroxyl group was re-protected by the TBS group under mild conditions to form the secondary alcohol **13**, which was then methoxymethylated to give the MOM ether **14**. As expected, the isopropenyl Grignard addition reaction of **14** proceeded at −78 °C in 91% yield with exclusive stereoselectivity to furnish required product **5**. The stereochemical outcome could be reasoned considering a simple chelation model.[20]



Scheme 3. Synthesis of the substrate **5** for thermal pericyclic reaction.

The key thermal transformation of the compound **5** through the *o*-quinodimethane intermediate was performed in refluxing *o*-dichlorobenzene (ca. 180 °C). Gratifyingly, A-nor steroidal tricyclic framework was efficiently constructed through the successive pericyclic reactions in 94% yield in a highly stereoselective manner (Scheme 4). Judging from the stereochemistry of the product **15**,[21] the [4+2] cycloaddition reaction undoubtedly proceeded via the *exo* transition state depicted in Fig. 2 (*exo*-**TS1**), which should be the most stable among the possible four transition states.[22] Another *exo* transition state (*exo*-**TS2**), leading to the isomer **15′**, which could not be detected in this reaction, would have steric repulsion between substituent R and the *o*-quinodimethane moiety (Fig. 2). Both of the MOM and TBS protecting groups in **15** could be easily removed spontaneously by exposure to trifluoroborane and thiophenol to afford the triol **16** in a nearly quantitative yield. Because the primary alcohol moiety was intended to further transform into various side-chain in future, only the secondary hydroxyl group of **16** was protected as TBS ether through the two-step sequence, installation of the TBS group to both alcohol followed by removal of one on the primary alcohol by mild treatment with AcOH. Thus, highly efficient synthesis of the tricyclic system **4** containing five stereogenic centers was accomplished in 11 steps from known benzocyclobutenyl aldehyde **7** with 31.7% overall yield. This compound would be a very important scaffold for a variety of OSW-1 analogues with A-nor B-aromatic steroidal aglycone.



Scheme 4. Completion of synthesis of the target compound **4**.

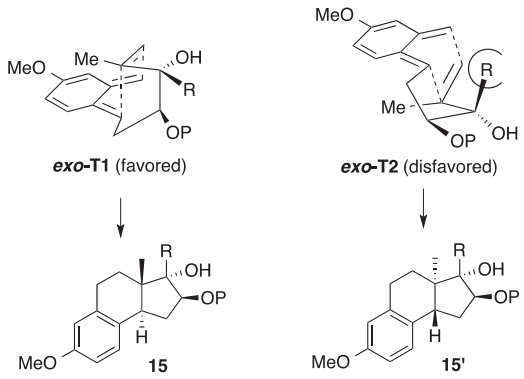


Fig. 2. Possible *exo* transition states for [4+2] cycloaddition.

3. Conclusion

In summary, we have established an efficient synthetic approach for the A-nor B-aromatic steroidal skeleton possessing a *trans*-diol unit on the D ring taking advantage of high generality and stereoselectivity of *o*-quinodimethane chemistry. This compound **4** would be a useful common starting point for divergent syntheses of A-nor B-aromatic OSW-1 analogues and provide a versatile scaffold of SAR studies of ring-truncated OSW-1 antitumor derivatives. Based on these results, we are presently grappling with transformation of the compound **4** into potentially antitumor derivatives with various side-chains including an ether, ester, or carbonyl linkage on the C22 position, as well as biological evaluations, and the results obtained from these efforts will be disclosed in due course.

4. Experimental section

4.1. General remarks

All chemical reagents were obtained from commercial suppliers (Aldrich, Kanto Chemical, Tokyo Chemical Industry (TCI), Wako

Pure Chemical Industries) and used without further purification. Anhydrous solvents were obtained from commercial sources or were prepared by distillation over the standard protocols. All nonaqueous reactions were carried out under Ar atmosphere. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel (Merck). Column chromatography was carried out on Cica Silica Gel 60N (spherical, neutral, 40–50 μm or 63–210 μm). ^{1}H NMR spectra were recorded in deuterated solvents on a VARIAN Gemini 300 (300 MHz) spectrometer, or a VARIAN UNITYplus 500 (500 MHz) spectrometer, using the residual solvent peak as an internal reference. ^{13}C NMR spectra were recorded in deuterated solvents on a Varian Gemini 300 (75 MHz) spectrometer. IR spectra were measured on a JNM FT/IR-460Plus spectrometer. Mass spectra were recorded on a JEOL D-200, JEOL JMS-GCmate II, SHIMADZU GCMS-QP 500, or JEOL AX 505 spectrometer. The optical rotations were determined on a JASCO DIP-1000 instrument. Melting points were taken with a Yanagimoto micro melting point apparatus and are uncorrected.

4.2. Synthesis of 4, a core structure of A-nor B-aromatic OSW-1

*4.2.1. (3-Methoxybicyclo[4.2.0]octa-1,3,5-triene-7-yl)-acetaldehyde (**7**).* Under an Ar atmosphere, to a solution of 1-cyano-4-methoxybenzocyclobutane (**9**)[13] (1.60 g, 10.1 mmol) in CH_2Cl_2 (30.0 mL) was added dropwise DIBAL (0.95 M in hexane, 12.7 mL, 12.1 mmol) at −78 °C, and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with satd NH_4Cl aq, and the mixture was stirred for 30 min at the room temperature. The insoluble precipitate was filtered off through a Celite pad and the filtrate was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=4:1) to afford 3-methoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbaldehyde (1.59 g, 97%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.67 (1H, d, *J*=2.4 Hz), 7.07 (1H, d, *J*=7.7 Hz), 6.81 (1H, dd, *J*=7.7, 1.1 Hz), 6.74 (1H, d, *J*=1.1 Hz), 4.17–4.13 (1H, m), 3.79 (3H, s), 3.46–3.36 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.8, 160.4, 144.9, 132.0, 124.1, 114.3, 108.9, 55.5, 52.9, 30.3; IR (neat) 2715, 1716, 1387 cm^{-1}; MS (EI) *m*/*z*: 162 (M^+); HRMS (EI) calcd for $C_{10}H_{10}O_2$: 162.0680 (M^+), found: 162.0650.

Under an Ar atmosphere, to a solution of (methoxymethyl)triphenylphosphonium chloride (9.4 g, 27.4 mmol) in THF (30.0 mL) was added dropwise phenyllithium (1.90 M in *n*-butyl ether, 12.2 mL, 23.2 mmol) at 0 °C, and the mixture was stirred for 10 min at the room temperature. The solution was cooled to 0 °C again, and to the above reaction mixture was added 3-methoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbaldehyde (1.5 g, 9.25 mmol), and the mixture was stirred for 1 h at the same temperature. The reaction mixture was extracted with Et_2O, and then the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=7:1) to afford compound **7** (1.5 g, 90%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.88 (1H, t, *J*=1.4 Hz), 7.00 (1H, d, *J*=8.1 Hz), 6.75 (1H, dd, *J*=8.1, 2.2 Hz), 6.68 (1H, s), 3.82–3.76 (1H, m), 3.78 (3H, s), 3.41 (1H, dd, *J*=14.0, 5.2 Hz), 2.85 (2H, dd, *J*=7.7, 1.4 Hz), 2.77 (1H, dd, *J*=14.0, 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 160.0, 144.0, 139.3, 123.5, 113.7, 109.1, 55.7, 48.9, 36.2, 35.8; IR (neat) 2721, 1721, 1387 cm^{-1}; MS (EI) *m*/*z*: 176 (M^+); HRMS (EI) calcd for $C_{11}H_{12}O_2$: 176.0837 (M^+), found: 176.0851.

*4.2.2. (−)-2-[3-(tert-Butyldimethylsilanyloxy)-2-methylpropane-1-sulfonyl]-benzothiazole (**8a**).* Under an Ar atmosphere, to a solution of (−)-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropane-1-ol (**10**)[14] (3.3 g, 16.2 mmol), triphenylphosphine (5.1 g, 19.4 mmol), and 2-mercaptobenzthiazol (3.25 g, 19.4 mmol) in THF (90.0 mL) was added DIAD (3.83 mL, 19.4 mmol) at 0 °C, and the mixture was stirred for 2 h at the room temperature. The reaction mixture was diluted with Et_2O, and then the organic layer was washed with satd $NaHCO_3$ aq. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=5:1) to afford (−)-2-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropylsulfanyl]-benzothiazole (5.38 g, 94%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (1H, ddd, *J*=8.2, 1.1, 0.6 Hz), 7.74 (1H, ddd, *J*=8.0, 1.1, 0.6 Hz), 7.40 (1H, ddd, *J*=8.2, 7.1, 1.1 Hz), 7.14 (1H, ddd, *J*=8.0, 7.1, 1.1 Hz), 3.67 (1H, dd, *J*=9.9, 5.2 Hz), 3.59–3.49 (2H, m), 3.24 (1H, dd, *J*=13.0, 7.1 Hz), 2.17–2.11 (1H, m), 1.08 (3H, d, *J*=6.9 Hz), 0.92 (9H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 153.1, 134.9, 125.7, 123.8, 121.2, 120.6, 66.3, 36.9, 35.9, 25.9, 18.3, 16.2, −5.4; MS (EI) *m*/*z*: 353 (M^+); HRMS (EI) calcd for $C_{17}H_{27}NOS_2Si$: 353.1303 (M^+), found: 353.1286; $[\alpha]_D^{26}$ −4.59 (*c* 1.10, $CHCl_3$).

To a solution of (−)-2-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropylsulfanyl]-benzothiazole (2.0 g, 5.66 mmol) and sodium periodate (3.6 g, 17.0 mmol) in CCl_4 (11.0 mL), CH_3CN (11.0 mL), and H_2O (22.0 mL) was added $RuCl_3 \cdot nH_2O$ (0.6 mg, 2.8 μmol) at the room temperature, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with satd $NaHCO_3$ aq, and then with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=4:1) to afford compound **8a** (2.1 g, 95%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (1H, d, *J*=8.0 Hz), 8.01 (1H, d, *J*=7.7 Hz), 7.66–7.26 (2H, m), 3.83 (1H, dd, *J*=14.0, 4.2 Hz), 3.64 (1H, dd, *J*=9.5, 4.2 Hz), 3.46–3.40 (1H, m), 3.33–3.25 (1H, m), 2.42–2.40 (1H, m), 1.13 (3H, d, *J*=7.4 Hz), 0.82 (9H, s), 0.00 (3H, s), −0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 152.4, 136.5, 127.8, 127.4, 125.2, 122.2, 66.2, 57.5, 31.6, 25.8, 18.2, 16.8, −5.4; IR (neat) 1309, 1144 cm^{-1}; MS (EI) *m*/*z*: 385 (M^+); HRMS (EI) calcd for $C_{17}H_{27}NO_3S_2Si$: 385.1202 (M^+), found: 385.1225; $[\alpha]_D^{26}$ −7.36 (*c* 1.00, $CHCl_3$).

*4.2.3. (−)-5-[3-(tert-Butyldimethylsilanyloxy)-2-methylpropane-1-sulfonyl]-1-phenyl-1H-tetrazole (**8b**).* Under an Ar atmosphere, to a solution of (−)-3-(*tert*-butyldimethylsilanyloxy)-2-methylpropane-1-ol (**10**)[14] (11.0 g, 53.8 mmol), triphenylphosphine (16.9 g, 64.6 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (11.5 g, 64.6 mmol) in THF (150.0 mL) was added DIAD (12.7 mL, 64.6 mmol) at 0 °C, and the mixture was stirred for 2 h at the room temperature. The reaction mixture was diluted with Et_2O, and then the organic layer was washed with satd $NaHCO_3$ aq. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=5:1) to afford (+)-5-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropylsulfanyl]-1-phenyl-1*H*-tetrazole (15.0 g, 77%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.53 (5H, m), 3.64 (1H, dd, *J*=10.0, 4.8 Hz), 3.55–3.47 (2H, m), 3.37 (1H, dd, *J*=13.0, 6.6 Hz), 2.20–2.13 (1H, m), 1.05 (3H, d, *J*=6.9 Hz), 0.88 (9H, s), 0.03 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 133.4, 129.6, 129.4, 123.4, 66.0, 36.7, 35.4, 25.7, 18.1, 16.0, −5.4; MS (EI) *m*/*z*: 307 (M^+−57); HRMS (EI) calcd for $C_{13}H_{18}N_4OSSi$: 307.1049 (M^+−57), found: 307.1046; $[\alpha]_D^{26}$ +2.59 (*c* 1.00, $CHCl_3$).

To a solution of (+)-5-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropylsulfanyl]-1-phenyl-1*H*-tetrazole (2.0 g, 5.49 mmol) and sodium periodate (3.5 g, 16.5 mmol) in CCl_4 (10.0 mL), CH_3CN (10.0 mL), and H_2O (20.0 mL) was added $RuCl_3 \cdot nH_2O$ (0.6 mg, 2.8 μmol) at the room temperature, and the mixture was stirred for 5 h at the same temperature. The reaction mixture was extracted

with Et_2O. The combined organic layers were washed with satd $NaHCO_3$ aq, and then with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=4:1) to afford compound **8b** (2.2 g, 99%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.57 (5H, m), 4.05 (1H, dd, J=15.0, 4.7 Hz), 3.72 (1H, dd, J=10.0, 4.7 Hz), 3.59–3.47 (2H, m), 2.51–2.44 (1H, m), 1.16 (3H, d, J=6.9 Hz), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 133.1, 131.5, 129.7, 125.2, 66.3, 58.7, 31.4, 26.1, 18.5, 17.1, −5.1; IR (neat) 1335, 1153 cm^{-1}; MS (EI) m/z: 339 (M^+−57); HRMS (EI) calcd for $C_{13}H_{19}N_4O_3SSi$: 339.0947 (M^+−57), found: 339.0936; $[\alpha]_D^{26}$ −5.22 (c 1.10, $CHCl_3$).

*4.2.4. (+)-tert-Butyl-[5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methylpent-3-enyloxy]-dimethylsilane (**6**).* Under an Ar atmosphere, to a solution of compound **8b** (60 mg, 0.15 mmol) in toluene (1.0 mL) was added dropwise NaHMDS (1.0 M in THF, 0.17 mL, 0.17 mmol) at −78 °C, and the mixture was stirred for 30 min at the same temperature. To the above reaction mixture was added dropwise a solution of 18-crown-6 (40 mg, 0.15 mmol) in toluene (1.0 mL) at −78 °C, and the mixture was stirred for 30 min at the same temperature. Then, to the reaction mixture was added dropwise a solution of compound **7** (40 mg, 0.15 mmol) in toluene (1.0 mL) at −78 °C, and the mixture was stirred for 3 h at the same temperature. The reaction was quenched with H_2O, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=20:1) to afford compound **6** (43 mg, 83%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (1H, dd, J=8.0 2.7 Hz), 6.74–6.68 (2H, m), 5.56 (1H, dt, J=15.0, 6.3 Hz), 5.42 (1H, dd, J=15.0, 2.2 Hz), 3.77 (3H, s), 3.53–3.47 (1H, m), 3.43–3.36 (2H, m), 3.24 (1H, dd, J=14.0, 5.0 Hz), 2.71 (1H, dd, J=14.0, 2.5 Hz), 2.37–2.27 (3H, m), 1.00 (3H, d, J=6.7 Hz), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 144.2, 141.0, 134.2, 127.8, 122.9, 112.9, 108.9, 68.3, 55.4, 42.0, 39.6, 37.9, 35.2, 26.0, 18.5, 16.9, −5.1; IR (neat) 1589, 1025 cm^{-1}; MS (EI) m/z: 346 (M^+); HRMS (EI) calcd for $C_{21}H_{34}O_2Si$: 346.2328 (M^+), found: 346.2336; $[\alpha]_D^{25}$ +0.29 (c 1.30, $CHCl_3$).

*4.2.5. (−)-5-(tert-Butyldimethylsilanyloxy)-1-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-4-methylpentane-2,3-diol (**11**).* A mixture of methanesulfonamide (549 mg, 5.8 mmol), AD-mix-α (8.1 g) in t-BuOH (30 mL), and H_2O (30 mL) was stirred at 0 °C for 15 min. Compound **6** (2.0 g, 5.8 mmol) was added to the solution at 0 °C, and the mixture was stirred for 24 h at the same temperature. Then, sodium hydrogen sulfite (8.0 g) was added to the solution at 0 °C, and the mixture was stirred for 1 h at the room temperature. The reaction mixture was extracted with AcOEt. The combined organic layers were washed with satd 2 N KOH aq, and then with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=4:1) to afford compound **11** (1.8 g, 82%) as a colorless oil and **11**-stereoisomer (220 mg, 10%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02–6.98 (1H, m), 6.73 (1H, dd, J=8.0, 2.2 Hz), 6.69 (1H, d, J=2.2 Hz), 3.93–3.87 (1H, m), 3.81 (1H, dd, J=10.0, 2.9 Hz), 3.77 (3H, s), 3.70–3.52 (3H, m), 3.36–3.29 (1H, m), 3.10–2.95 (2H, br), 2.74 (1H, dd, J=14.0, 2.5 Hz), 2.04–1.91 (1H, m), 1.87–1.66 (2H, m), 0.99–0.88 (3H, m), 0.89 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 144.0, 140.7, 122.7, 112.8, 108.7, 78.4, 70.4, 66.2, 55.2, 39.3, 38.2, 37.8, 35.5, 25.8, 18.1, 11.6, −5.6; IR (neat) 3414 cm^{-1}; MS (EI) m/z: 380 (M^+); HRMS (EI) calcd for $C_{21}H_{36}O_4Si$: 380.2383 (M^+), found: 380.2419; $[\alpha]_D^{26}$ −14.00 (c 1.10, $CHCl_3$).

11-*stereoisomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (1H, d, J=8.2 Hz), 6.73 (1H, dd, J=8.2, 2.2 Hz), 6.68 (1H, d, J=2.2 Hz), 3.85–3.57 (7H, m), 3.46–3.38 (1H, m), 3.32 (1H, dd, J=14.0, 5.2 Hz), 3.25–2.80 (2H, br), 2.74 (1H, dd, J=14.0, 2.5 Hz), 2.12–1.91 (2H, m), 1.83–1.71 (1H, m), 0.94–0.90 (12H, m), 0.92 (9H, s), 0.11 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 144.2, 141.0, 123.0, 113.0, 108.9, 78.7, 71.1, 67.7, 55.5, 39.6, 39.2, 37.2, 35.6, 25.9, 18.2, 14.2, −5.5; IR (neat) 3454 cm^{-1}; MS (EI) m/z: 380 (M^+); HRMS (EI) calcd for $C_{21}H_{36}O_4Si$: 380.2383 (M^+), found: 380.2402; $[\alpha]_D^{26}$ −7.65 (c 0.80, $CHCl_3$).

*4.2.6. (+)-1-(tert-Butyldimethylsilanyloxy)-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methyl-4-triisopropylsilanyloxypentan-3-one (**12**).* Under an Ar atmosphere, to a solution of compound (**11**) (1.5 g, 3.94 mmol) in CH_2Cl_2 (12.0 mL) was added 2,6-lutidine (1.37 mL, 11.8 mmol) and TIPSOTf (1.06 mL, 3.94 mmol) at 0 °C, and the mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2, and then the organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=10:1) to afford (+)-1-(*tert*-butyldimethylsilanyloxy)-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methyl-4-triisopropylsilanyloxypentan-3-ol (1.84 g, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (1H, d, J=7.9 Hz), 6.74 (1H, d, J=7.9 Hz), 6.69 (1H, s), 3.86–3.45 (5H, m), 3.78 (3H, s), 3.38–3.29 (1H, m), 2.78 (1H, d, J=14.0 Hz), 2.16–2.00 (1H, m), 1.95–1.83 (2H, m), 1.17–1.12 (21H, m), 1.02 (3H, d, J=6.8 Hz), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 144.2, 140.4, 123.0, 113.1, 108.8, 73.2, 72.9, 66.3, 55.4, 39.4, 38.5, 36.4, 31.7, 26.0, 22.8, 18.3, 14.2, 13.1, −5.3; IR (neat) 3545 cm^{-1}; MS (EI) m/z: 536 (M^+); HRMS (EI) calcd for $C_{30}H_{56}O_4Si_2$: 536.3717 (M^+), found: 536.3703; $[\alpha]_D^{26}$ +2.08 (c 0.75, $CHCl_3$).

Under an Ar atmosphere, to a solution of (+)-1-(*tert*-butyldimethylsilanyloxy)-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methyl-4-triisopropylsilanyloxypentan-3-ol (326 mg, 0.61 mmol) in CH_2Cl_2 (6.0 mL) was added MS4A (300 mg), NMO (213 mg, 1.82 mmol), and TPAP (43 mg, 0.12 mmol) at the room temperature, and the mixture was stirred for 2 h at the same temperature. The insoluble precipitate was filtered off through a Celite pad and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=20:1) to afford compound **12** (306 mg, 95%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02–6.92 (1H, m), 6.76–6.71 (1H, m), 6.67 (1H, s), 4.55–4.40 (1H, m), 3.90–3.83 (1H, m), 3.77 (3H, s), 3.67–3.46 (2H, m), 3.33–3.26 (1H, m), 3.21–3.13 (1H, m), 2.80–2.70 (1H, m), 2.26–1.93 (2H, m), 1.20–1.01 (24H, m), 0.91 (9H, s), 0.01 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.5, 159.5, 143.9, 140.2, 123.0, 113.1, 108.9, 78.0, 64.7, 55.4, 43.9, 39.5, 38.7, 36.0, 31.6, 25.9, 18.2, 14.4, 12.8, −5.4; IR (neat) 1715 cm^{-1}; MS (EI) m/z: 534 (M^+); HRMS (EI) calcd for $C_{30}H_{54}O_4Si_2$: 534.3561 (M^+), found: 534.3572; $[\alpha]_D^{25}$ +17.62 (c 1.32, $CHCl_3$).

*4.2.7. (+)-1-(tert-Butyldimethylsilanyloxy)-4-hydroxy-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methylpentan-3-one (**13**).* Under an Ar atmosphere, to a solution of compound **12** (264 mg, 0.50 mmol) in THF (3.0 mL) was added dropwise TBAF (1 M in THF, 1.50 mL, 1.50 mmol) at the room temperature, and the mixture was stirred for 3 h at the same temperature. The reaction was quenched with satd NH_4Cl aq, and the reaction mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=2:3) to afford (+)-1,4-dihydroxy-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methylpentan-3-one (114 mg, 87%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 and 6.95 (1H, d, J=8.2 and 8.0 Hz), 6.72–6.65 (2H, m), 4.44–4.32 (1H, m), 4.11–3.56 (6H, m),

3.29 (1H, d, J=14.0, 5.2 Hz), 3.15–2.98 (1H, m), 2.80–2.70 (1H, m), 2.06–1.74 (2H, m), 1.01 and 0.98 (3H, d, J=7.4 and 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.7, 159.5, 144.1, 139.8, 123.1, 113.1, 108.9, 75.0, 64.0, 55.4, 43.4, 39.2, 38.1, 35.6, 13.7; IR (neat) 3445, 1709 cm^{-1}; MS (EI) m/z: 246 (M^+); HRMS (EI) calcd for $C_{15}H_{20}O_4$: 264.1362 (M^+), found: 264.1336; $[\alpha]_D^{26}$ +35.41 (c 1.35, $CHCl_3$).

Under an Ar atmosphere, to a solution of (+)-1.4-dihydroxy-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-2-methylpentan-3-one (98 mg, 0.37 mmol) in DMF (3.0 mL) was added imidazole (51 mg, 0.41 mmol) and TBSCl (62 mg, 0.41 mmol) at 0 °C, and the mixture was stirred for 2 h at the room temperature. The reaction mixture was diluted with H_2O, and was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=2:1) to afford compound **13** (140 mg, quant.) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 and 6.99 (1H, d, J=7.9 Hz), 6.77–6.68 (2H, m), 4.38 and 4.28 (1H, dd, J=9.6, 3.1 and 9.4, 3.3 Hz), 3.83–3.53 (6H, m), 3.34 (1H, dd, J=14.0, 5.2 Hz), 3.23–3.11 (1H, m), 2.85–2.73 (1H, m), 2.18–2.05 (2H, m), 1.92–1.75 (1H, m), 1.07–1.00 (3H, m), 0.86 and 0.85 (9H, s), 0.03–0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.3, 159.5, 144.3, 140.2, 123.2, 113.1, 108.8, 75.7, 65.5, 55.4, 43.6, 39.4, 38.2, 35.9, 25.9, 18.3, 13.7, −5.5; IR (neat) 3481, 1713 cm^{-1}; MS (EI) m/z: 378 (M^+); HRMS (EI) calcd for $C_{21}H_{34}O_4Si$: 378.2226 (M^+), found: 378.2252; $[\alpha]_D^{26}$ +12.97 (c 1.40, $CHCl_3$).

*4.2.8. (−)-1-(tert-Butyldimethylsilanyloxy)-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-4-methoxymethoxy-2-methylpentan-3-one (**14**).* Under an Ar atmosphere, to a solution of compound **13** (171 mg, 0.45 mmol) in CH_2Cl_2 (3.0 mL) was added diisopropylethylamine (348 μL, 2.0 mmol) and MOMCl (103 μL, 1.35 mmol) at 0 °C, and the mixture was stirred for 20 h at the room temperature. The reaction mixture was diluted with CH_2Cl_2, and then the organic layer was washed with 10% HCl aq, satd $NaHCO_3$ aq and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=3:1) to afford **14** (159 mg, 84%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 and 6.97 (1H, d, J=7.9 Hz), 6.77–6.68 (2H, m), 4.73–4.60 (2H, m), 4.43 and 4.27 (1H, dd, J=9.6, 3.0 and 8.7, 4.3 Hz), 3.88–3.80 (1H, m), 3.78 and 3.77 (3H, s), 3.65–3.58 (1H, m), 3.53–3.46 (1H, m), 3.41 and 3.38 (3H, s), 3.38–3.28 (1H, m), 3.09–2.97 (1H, m), 2.12–1.89 (2H, m), 1.03 and 1.01 (3H, d, J=7.0 and 7.0 Hz), 0.83 and 0.82 (9H, s), 0.01 and 0.00 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.7, 159.6, 143.8, 139.9, 123.0, 113.2, 108.8, 96.0, 80.3, 64.8, 56.0, 55.4, 45.0, 39.3, 35.7, 35.3, 25.9, 18.3, 13.8, −5.4,; IR (neat) 1729 cm^{-1}; MS (EI) m/z: 422 (M^+); HRMS (EI) calcd for $C_{23}H_{38}O_5Si$: 422.2489 (M^+), found: 422.2498; $[\alpha]_D^{26}$ −9.58 (c 0.90, $CHCl_3$).

*4.2.9. (−)-3-[2-(tert-Butyldimethylsilanyloxy)-1-methylethyl]-5-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-4-methoxymethoxy-2-methylpent-1-en-3-ol (**5**).* Under an Ar atmosphere, to a solution of compound **14** (90 mg, 0.21 mmol) in THF (10.0 mL) was added isopropenyl magnesium bromide (0.50 M in THF, 1.9 mL, 0.96 mmol) at −78 °C, and the mixture was stirred for 19 h at the same temperature. The reaction was quenched with satd NH_4Cl aq. The reaction mixture was extracted with Et_2O, and then the organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=7:1) to afford compound **5** (91 mg, 91%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04–7.00 (1H, m), 6.74–6.69 (2H, m), 5.12 (1H, d, J=2.5 Hz), 4.99 (1H, d, J=2.5 Hz), 4.84–4.69 (2H, m), 4.39–4.31 (2H, m), 3.92–3.63 (2H, m), 3.77 (3H, s), 3.43–3.22 (1H, m), 3.39 (3H, s), 2.78–2.68 (1H, m), 2.26–2.20 (1H, m), 1.92–1.77 (1H, m), 1.85 (3H, s), 1.29–0.87 (12H, m), 0.15–0.12 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 145.7, 144.2, 141.2, 122.7, 112.9, 108.9, 97.7, 97.2, 82.5, 81.3, 65.9, 56.0, 55.4, 40.3, 36.3, 36.0, 35.5, 25.9, 20.7, 18.2, 12.7, −5.6; IR (neat) 3458, 1588 cm^{-1}; MS (EI) m/z: 464 (M^+); HRMS (EI) calcd for $C_{26}H_{44}O_5Si$: 464.2958 (M^+), found: 464.2950; $[\alpha]_D^{26}$ −18.0 (c 1.35, $CHCl_3$).

*4.2.10. (+)-3-[2-(tert-Butyldimethylsilanyloxy)-1-methylethyl]-7-methoxy-2-methoxymethoxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalene-3-ol (**15**).* Under an Ar atmosphere, compound **5** (80 mg, 0.17 mmol) was dissolved in *o*-dichlorobenzene (10.0 mL), and the solution was refluxed on a heating oil bath for 7 h. Then, the solvent was evaporated off under a reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt=7:1) to afford compound **15** (75 mg, 94%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (1H, dd, J=8.5, 1.2 Hz), 6.71–6.67 (2H, m), 4.74 (1H, d, J=6.5 Hz), 4.65 (1H, d, J=6.5 Hz), 4.32 (1H, dd, J=9.8, 1.7 Hz), 4.13 (1H, dd, J=7.7, 3.8 Hz), 3.78 (3H, s), 3.63 (1H, dd, J=9.8, 2.5 Hz), 3.41 (3H, s), 3.21 (1H, dd, J=12.0, 8.1 Hz), 2.81 (2H, t, J=7.7 Hz), 2.74 (4H, m), 2.78–2.68 (1H, m), 2.38–2.32 (1H, m), 2.20–2.16 (1H, m), 1.68–1.62 (1H, m), 1.60–1.54 (2H, m), 1.16 (3H, d, J=7.3 Hz), 0.93 (9H, m), 0.59 (3H, s), 0.11 and 0.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 138.2, 133.1, 125.7, 113.0, 110.4, 96.3, 87.5, 87.0, 68.8, 56.5, 55.1, 47.4, 43.0, 34.2, 32.6, 30.0, 27.8, 25.9, 18.2, 14.9, 13.4, −5.6; IR (neat) 3455 cm^{-1}; MS (EI) m/z: 464 (M^+); HRMS (EI) calcd for $C_{26}H_{44}O_5Si$: 464.2958 (M^+), found: 464.2986; $[\alpha]_D^{26}$ +47.36 (c 1.05, $CHCl_3$).

*4.2.11. (+)-3-(2-Hydroxy-1-methylethyl)-7-methoxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalene-2,3-diol (**16**).* Under an Ar atmosphere, to a solution of compound **15** (656 mg, 1.41 mmol) in CH_2Cl_2 (2.0 mL) was added thiophenol (1.45 mL, 14.1 mmol) and $BF_3\cdot Et_2O$ (0.72 mL, 5.65 mmol) at 0 °C, and the mixture was stirred for 12 h at the room temperature. The reaction was diluted with AcOEt, and then the organic layer was washed with 5% NaOH aq, and then with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=1:2) to afford compound **16** (427 mg, 99%) as a colorless crystal.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (1H, d, J=8.1 Hz), 6.72–6.68 (2H, m), 4.22 (1H, dd, J=7.5, 5.0 Hz), 3.93–3.82 (1H, dd, J=18.0, 10.0 Hz), 3.78 (3H, s), 3.73 (1H, dd, J=10.0, 3.5 Hz), 3.14 (1H, dd, J=12.5, 7.5 Hz), 2.92–2.78 (2H, m), 2.74 (1H, ddd, J=12.5, 7.5, 7.5 Hz), 2.56–2.46 (1H, m), 2.40–1.50 (3H, br), 2.08 (1H, ddd, J=12.5, 8.5, 8.5 Hz), 1.74–1.60 (2H, m), 1.00 (3H, d, J=7.0 Hz), 0.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 137.5, 132.5, 126.2, 113.1, 110.8, 85.8, 81.8, 66.1, 55.2, 47.9, 43.4, 35.6, 34.0, 30.4, 27.6, 14.5, 12.7; IR (neat) 3376 cm^{-1}; MS (EI) m/z: 306 (M^+); HRMS (EI) calcd for $C_{18}H_{26}O_4$: 306.1831 (M^+), found: 306.1825; $[\alpha]_D^{25}$ +80.20 (c 0.26, $CHCl_3$); mp 191–193 °C.

*4.2.12. (+)-2-(tert-Butyldimethylsilanyloxy)-3-(2-hydroxy-1-methylethyl)-7-methoxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalene-3-ol (**4**).* Compound **16** (37 mg, 0.12 mmol) in CH_2Cl_2 (2.0 mL) was added 2,6-lutidine (0.11 mL, 0.97 mmol) and TBSOTf (0.14 mL, 0.60 mmol) at 0 °C, and the mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2, and then the organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=6:1) to afford (+)-3-[2-(*tert*-butyldimethylsilanyloxy)-1-methylethyl]-7-methoxy-2-*tert*-butyldimethylsilanyloxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-3-ol (65 mg, quant.) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95–6.91 (1H, m), 6.72–6.68 (2H, m), 4.68–4.60 (1H, m), 4.34–4.26 (2H, m), 3.78 (3H, s), 3.59 (1H, dd,

J=10.0, 2.7 Hz), 3.21–3.15 (1H, m), 2.84–2.79 (2H, m), 2.74–2.64 (1H, m), 2.37–2.21 (2H, m), 1.63–1.53 (2H, m), 1.16 (3H, d, J=7.1 Hz), 0.94 (9H, s), 0.88 (9H, s), 0.63 (3H, s), 0.12–0.03 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 138.3, 133.3, 125.7, 113.1, 110.4, 87.5, 82.5, 68.9, 55.2, 47.3, 43.0, 36.1, 34.0, 30.2, 27.8, 25.9, 25.8, 18.2, 17.8, 14.8, 13.4, −2.8, −5.4; IR (neat) 3477 cm^{-1}; MS (EI) m/z: 516 (M^+−18); $[\alpha]_D^{25}$ +46.10 (c 0.23, $CHCl_3$).

To a solution of (+)-3-[2-(*tert*-butyldimethylsilanyloxy)-1-methylethyl]-7-methoxy-2-*tert*-butyldimethylsilanyloxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene-3-ol (59 mg, 0.11 mmol) in THF (0.6 mL) and H_2O (0.6 mL) was added dropwise AcOH (1.8 mL) at the room temperature, and the mixture was stirred for 9 h at the same temperature. To the resulting solution was added satd NH_4Cl aq. The reaction mixture was extracted with AcOEt, and then the organic layer was washed with satd NH_4Cl aq. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (hexane/AcOEt=1:1) to afford compound **4** (42 mg, 91%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (1H, d, J=8.5 Hz), 6.72–6.69 (2H, m), 4.29 (1H, dd, J=7.7, 4.4 Hz), 4.17 (1H, dd, J=11.0, 2.5 Hz), 3.78 (3H, s), 3.67 (1H, dd, J=11.0, 3.3 Hz), 3.17–3.11 (1H, m), 2.86–2.81 (2H, m), 2.69 (1H, dt, J=14.0, 7.7 Hz), 2.31–2.13 (2H, m), 2.05–1.90 (2H, br), 1.70–1.50 (2H, m), 1.19 (3H, d, J=7.4 Hz), 0.86 (9H, s), 0.67 (3H, s), 0.15 and 0.13 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 137.8, 132.8, 126.0, 113.2, 110.7, 88.1, 81.7, 67.9, 55.2, 47.3, 43.1, 36.1, 34.6, 30.2, 27.6, 25.9, 17.8, 14.4, 12.7, −3.2, −5.4; IR (neat) 3432 cm^{-1}; MS (EI) m/z: 420 (M^+); HRMS (EI) calcd for $C_{24}H_{40}O_4Si$: 420.2696 (M^+), found: 420.2722; $[\alpha]_D^{26}$ +52.80 (c 1.19, $CHCl_3$).

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Supplementary data

NMR charts for all new compounds and stereostructure determination data are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.079.

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17. Although the combination of NaHMDS/18-crown-6 was reported not to be so effective (Ref. 16a), this combination brought good effect in our present reaction system.
18. Because we used racemic aldehyde 7, the compound **6** (as well as **5** and **11**–**14**) was a mixture of two diastereomers due to a chiral center on the cyclobutene ring. These isomers could not be distinguished in the ^{1}H NMR spectra.
19. A small amount of another diastereomer was also obtained (10%). Absolute configuration of the diol was presumed from the empirical model.
20. Relative configuration of the tertiary hydroxyl group was confirmed based on an NOE experiment after conversion to the compound **16** having a rigid tricyclic system. Details are described in Supplementary data.
21. The observed stereochemistry of the stereogenic centers on the D ring was supported by good similarity of 1H NMR spectra of the compound **16** with that of A-nor B-aromatic OSW-1 aglycone with the same tricyclic framework and *trans*-diol unit, reported by our group (Ref. 4a).
22. The two *endo* transition states, leading to *cis*-fused cycloadducts, should have a severe steric repulsion between the aromatic ring and the alkyl chain.