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Synthetic studies of kampanols, novel p21^{ras} farnesyltransferase inhibitors: an efficient synthesis of the tetracyclic ABCD ring system of kampanols

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Abstract—An enantioselective synthesis of the tetracyclic ABCD ring system (**4**) of kampanols, novel Ras farnesyltransferase inhibitors from a microorganism, was efficiently achieved for the first time starting from the known *trans*-decalone derivative **9**. The synthetic method involves the following two key steps: (i) a conjugate addition reaction between the α-methylene ketone **6** and the Grignard reagent (**7**) of the *ortho*-disubstituted bromobenzene derivative **8** to deliver the coupling product **21** with stereoselectivity at the C9 position and (ii) a phenylselenium-mediated cyclization reaction of the phenol derivative **5** to stereoselectively construct the requisite tetracyclic intermediate **25** possessing the *cis*-fused connectivity of the B/C rings.

1. Introduction

In 1998, the Merck research group reported the isolation and structure elucidation of three novel natural products, kampanols A (**1**), B (**2**), C (**3**) (Fig. 1), from the fungal culture broth of *Stachybotrys kampalensis*.[1] Kampanols A and B have been shown to be specific inhibitors of Ras protein farnesyltransferase (PFTase), while kampanol C is inactive against the enzyme.[1,2] PFTase catalyzes the S-farnesylation of a cystein residue in a conserved CAAX sequence (C: cystein, A: aliphatic amino acid, X: serine or methionine) located at the carboxy terminus of Ras p21 protein. This post-translational modification is an essential first step for plasma membrane association that is critical for triggering *ras* oncogene toward tumor formation.[3] Consequently, kampanols A and B are anticipated to be promising new leads for novel anticancer agents. The gross structure of kampanols including the relative stereochemistry was determined by extensive and incisive spectroscopic studies to have a novel pentacyclic (or tetracyclic) [ABCD(E)] ring system with five asymmetric carbons.[1,4,5] The attractive biological properties and unique structural features prompted us to undertake a project directed toward the total synthesis of kampanols in enantiomerically pure forms. Recently, we communicated our preliminary results concerning an efficient construction of the tetracyclic model compound **4** (ABCD ring system) possessing the requisite substituents and asymmetric carbons,[6] which, to our best knowledge, represents the first and only synthetic studies of these fascinating natural products.[7] In this paper, we wish to disclose the full details of our enantioselective synthesis of **4**.

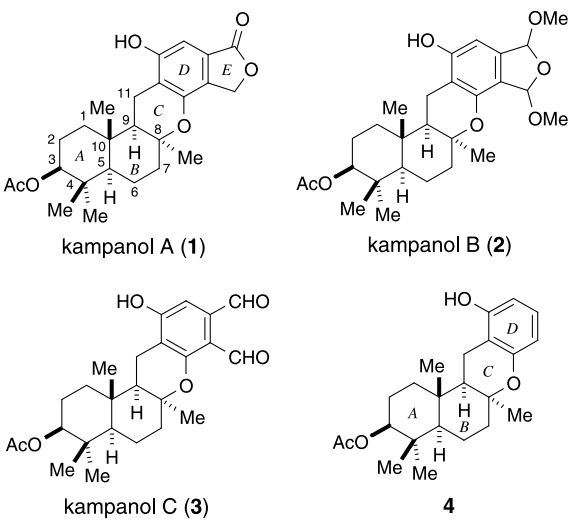

Figure 1. Structures of kampanols A (**1**), B (**2**), C (**3**) and the tetracyclic model compound **4**.

Keywords: kampanols; ras farnesyltransferase inhibitors; conjugate addition; phenylselenium-mediated cyclization.

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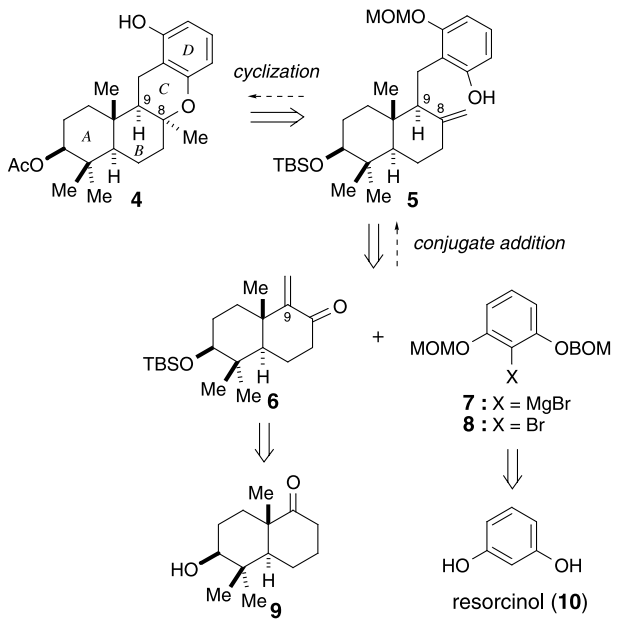


Scheme 1. Synthetic plan for the model compound **4**.

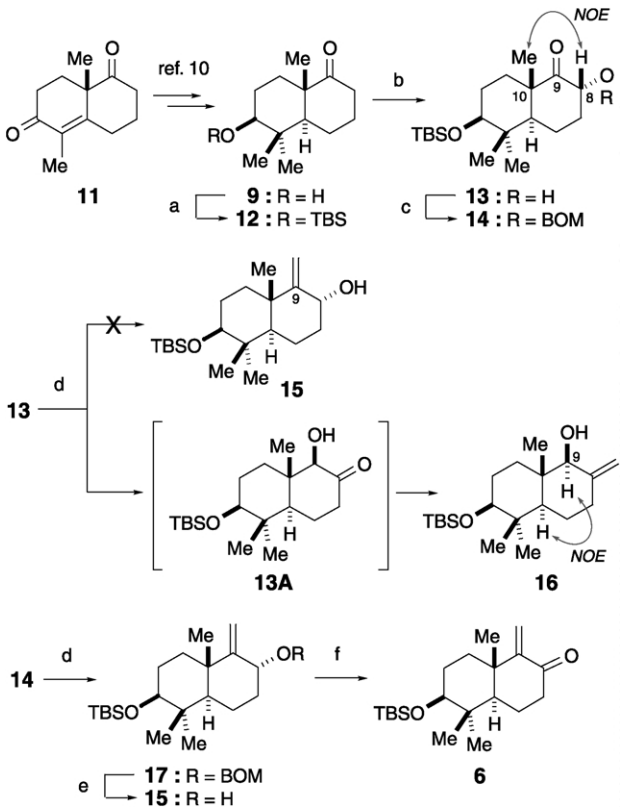
2. Results and discussion

2.1. Synthetic strategy

Our synthetic plan for the target molecule **4** is outlined in Scheme 1. The most crucial step in this scheme is envisioned to be the stereocontrolled cyclization reaction of the phenol derivative **5** to construct the dihydropyran C ring with the requisite *cis*-fused B/C ring juncture (**5**⟶**4**). This cyclization may involve an interesting possibility for controlling the stereochemistry at the C8 position (kampanols numbering) in **4** because the cyclization precursor **5** possesses an unusual *exo*-olefinic substituted pattern.[7a–g] The cyclization precursor **5** would be elaborated through the conjugate addition reaction[8] of the Grignard reagent **7**, derived from the *ortho*-disubstituted bromobenzene derivative **8**, with the α-methylene ketone **6** (**6**+**7**⟶**5**). Since the C9 substituent in the coupling product **5** is placed in an equatorial orientation, we expected that the requisite C9 stereocenter should be established under thermodynamically and/or kinetically controlled reaction conditions.[9] The decalin segment **6** and the aromatic segment **8**, in turn, would be prepared from the known *trans*-decalone **9**[10] and the commercially available resorcinol (**10**), respectively.

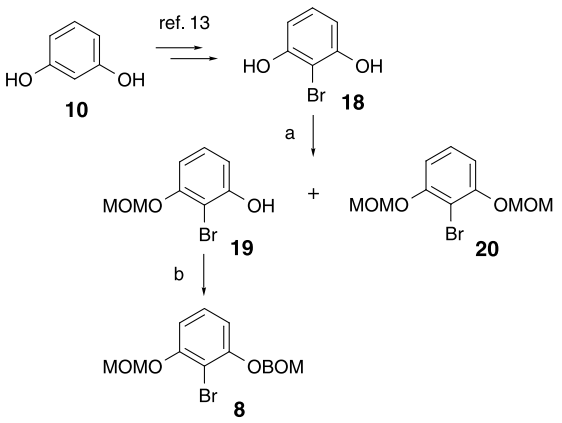
2.2. Synthesis of the decalin segment 6

At first, we investigated the synthesis of the decalin segment **6** as shown in Scheme 2. Compound **6** has been previously synthesized by Seifert et al.[9a] starting from the (+)-Wieland-Miescher ketone in 21% overall yield in nine steps; nevertheless, we sought an alternative, more efficient and reliable method for the synthesis of **6**. We have now found that **6** can be synthesized starting from (+)-Wieland-Miescher ketone analogue **11** in 44% overall yield in a 10-step sequence. The improved synthesis commenced with the known *trans*-decalone **9**,[10] readily and sufficiently



Scheme 2. Synthesis of the decalin segment **6**. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 99%; (b) $NaN(TMS)_2$, THF, −78°C; 2-phenylsolfonyl-3-phenyloxazindine, −78°C, 74%; (c) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 98%; (d) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 85% for **16**, 91% for **17**; (e) Li, liq. NH_3–THF, 80%; (f) Dess-Martin periodinane, CH_2Cl_2, rt, 98%.

prepared from (+)-**11** (>99% *ee*) in four steps [(1) ethylene glycol/*p*-TsOH/benzene, reflux, 95%; (2) Li/liquid NH_3/MeI/THF, reflux, 92%; (3) $NaBH_4$/EtOH, −40⟶−10°C, 99%; (4) 5% aqueous HCl/THF, rt, 99%] according to the Hagiwara protocol.[10] After protection of the hydroxy group in **9** as its *t*-butyldimethylsilyl (TBS) ether, the resulting ketone **12** was subjected to α-hydroxylation reaction by the use of $NaN(SiMe_3)_2$ and Davis reagent (2-phenylsulfonyl-3-phenyloxaziridine),[11] which led to the formation of the α-hydroxy ketone **13** as a single stereoisomer in 74% yield. The C8 stereochemistry of **13** was assigned based on the NOESY experiments, which show the interactions between C8-H and the angular methyl group (C10-Me). The stereoselectivity can be explained by the consideration that the oxidizing reagent (Davis reagent) accesses exclusively from the less hindered α-face of the enolate generated in situ from **12** under the influence of the *axial*-oriented methyl group at the ring juncture. To obtain the requisite *exo*-olefin **15** in a straightforward manner from the α-hydroxy ketone **13**, we initially attempted Wittig methylenation of **13** under standard reaction conditions. However, the expected compound **15** could not be detected: instead, the undesired methylenation product **16** was formed in 85% yield, whose structure and stereochemistry at the C9 position was assigned based on the NMR spectral analyses including NOESY experiments. The plausible mechanistic pathways for the formation of **16** from **13** may involve the intermediate **13A** generated in situ from **13** via a carbonyl transposition under the basic conditions. Therefore, we decided to prepare **15** in a stepwise manner. Thus,

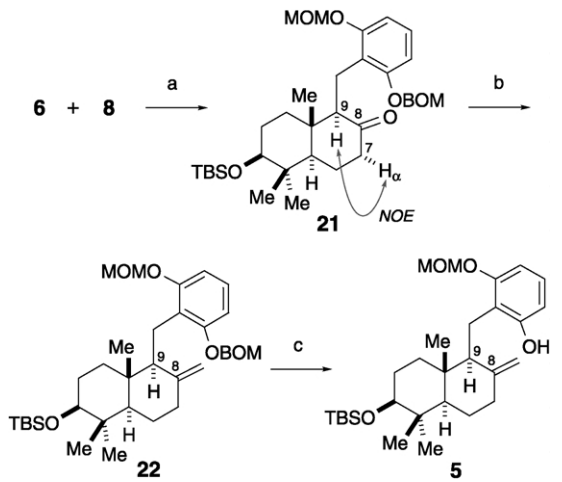


Scheme 3. Synthesis of the aromatic segment **8**. (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 44% for **19**, 29% for **20**; (b) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 96%.

protection of the hydroxy group in **13** as its benzyloxymethyl (BOM) ether followed by Wittig methylenation of the resulting BOM ether **14**, provided the *exo*-olefin **17**, whose BOM protecting group was subsequently removed under Birch conditions to give the desired **15** in 71% yield for the three steps. Finally, Dess-Martin oxidation[12] of **15** afforded the requisite decalin segment **6** in 98% yield.

2.3. Synthesis of the aromatic segment 8

The synthesis of the aromatic segment **8** was next pursued as shown in Scheme 3. The starting material, 2-bromoresorcinol (**18**), was prepared from the commercially available resorcinol (**10**) in two steps [(1) $Br_2/CHCl_3$, 0°C→rt, 99%; (2) Na_2SO_3/NaOH/MeOH–H_2O, rt, 99%] according to the literature.[13] Since it was necessary to discriminate between the two hydroxy groups of the aromatic moiety in the later stage of the synthesis,[14] the two hydroxy groups in **18** were separately protected at this stage. Thus, reaction of **18** with 1.0 equiv. of chloromethyl methyl ether (MOMCl) in the presence of 1.0 equiv. of *i*-Pr_2NEt furnished the mono-MOM ether **19** in 44% yield along with the bis-MOM ether **20** (29%) and the recovery of the starting material **18** (15%). Further protection of **19** as its BOM ether provided the requisite aromatic segment **8** in 96% yield.



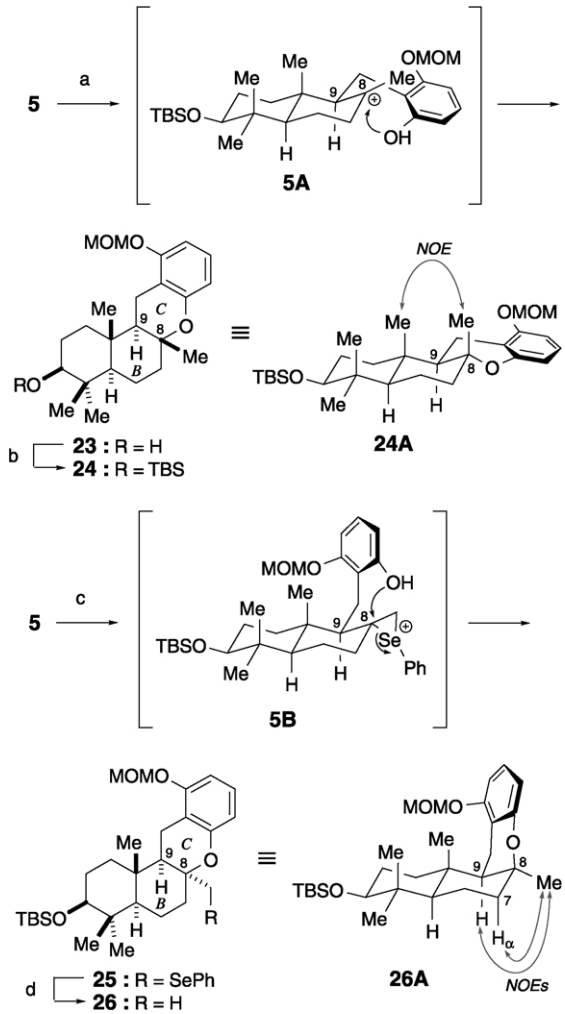
Scheme 4. Synthesis of the key cyclization precursor **5**. (a) **8**, Mg, 1,2-dibromoethane, Et_2O, reflux; add. **6**, 0°C→rt, 95%; (b) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 97%; (c) Li, liq. NH_3–THF, 95%.

2.4. Synthesis of the key cyclization precursor 5 via the conjugate addition reaction between 6 and 8

Having obtained both the decalin segment **6** and the aromatic segment **8**, our next efforts were directed toward elaboration of the key cyclization precursor **5** through the coupling reaction of these two segments. As shown in Scheme 4, the critical conjugate addition of the Grignard reagent **7**, prepared from **8** and Mg powder in the presence of 1,2-dibromoethane in Et_2O, to the α-methylene ketone **6** proceeded smoothly and cleanly without the addition of any copper salts,[8,9] leading to the formation of the desired coupling product **21** in excellent yield (95%) with complete stereoselectivity at the C9 position. The C9 stereochemistry was confirmed by NOESY experiments in the ^1H NMR spectrum, in which a clear NOE interaction between C9-H and C7-H_α was observed. In general, the conjugate addition reaction of Grignard reagents to α,β-unsaturated ketones is carried out in the presence of copper salts in order to prevent the formation of 1,2-addition products.[8] However, in this case the 1,4-addition product **21** was exclusively formed: this must be attributed to the structure nature of the substrate **6**, which involves the highly reactive *exo*-olefin moiety toward conjugate addition of carbon nucleophiles. Related conjugate addition reactions without copper salts have been previously described in the literature;[9] however, to our knowledge, the conjugate addition reaction between **6** and the Grignard reagent prepared from sterically hindered *ortho*-disubstituted bromobenzene derivative such as **8** is unprecedented. To forward the synthesis, the conjugate addition product **21** was further converted to the phenol derivative **5**, the key cyclization precursor, in excellent overall yield via a two-step sequence involving Wittig methylenation of the carbonyl function in **21** (97%) followed by reductive removal of the BOM protecting group in the resulting *exo*-olefin **22** under the Birch conditions (95%).

2.5. The key cyclization reaction of 5 and the synthesis of the requisite tetracyclic intermediate 26

With the key cyclization precursor **5** in hand, we focused our attention on the crucial stereocontrolled cyclization reaction of **5** to construct the requisite tetracyclic ABCD ring system **26** as depicted in Scheme 5. We initially examined the acid-mediated cyclization of **5** by treatment with $BF_3{\cdot}Et_2O$ (10 equiv.) in dichloromethane at −60→−10°C for 5 h, which led to the formation of the undesired *trans*-cyclization product **23** as a single stereoisomer in 75% yield. Since the TBS protecting group was cleaved concomitantly in this acid-mediated cyclization reaction, the liberated hydroxy group in **23** was reprotected under standard conditions to afford the corresponding TBS ether **24** (85%). The β-disposition of the C8 methyl group in **24** was established by NOESY experiments as illustrated in the formula **24A**. The stereochemical outcome observed for this acid-mediated cyclization reaction can be rationalized by considering that the phenolic hydroxy group, as depicted in the formula **5A**, attacks the C8 tertiary carbocation, generated in situ by acid treatment, from the less hindered α-face of the molecule under the influence of the β-oriented axial methyl group at the decalin junction, leading to **23**. Eventually, to our delight, the desired *cis*-cyclization of **5** was successfully achieved by the use of an

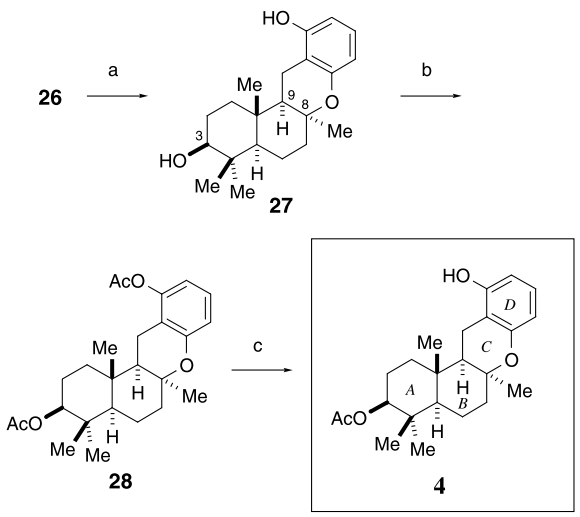


Scheme 5. The key cyclization of **5** to deliver the requisite tetracyclic intermediate **26**. (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −60⟶−10°C, 75%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 85%; (c) *N*-phenylselenophthalimide, $SnCl_4$, CH_2Cl_2, −78°C, 98%; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 78%.

organoselenenylating reagent.[15] Thus, **5** was treated with *N*-(phenylseleno)phthalimide (1.6 equiv.) in the presence of tin(IV) chloride (1.4 equiv.) in dichloromethane at −78°C for 2 h, resulting in the formation of the expected cyclization product **25** as the single diastereomer in 98% yield. The newly formed stereocenter at the C8 position in **25** was proven by NOESY experiments in the ^{1}H NMR spectrum of the deselenylated compound **26**, prepared by treating **25** with tri-*n*-butyltin hydride in the presence of 2,2′-azobis(isobutyronitrile) (AIBN). As pictured in the formula **26A**, two key NOEs between C8-Me and C9-H, C7-H_α were clearly observed, establishing the *cis*-fused connectivity of the B/C rings. This phenylselenium-mediated cyclization reaction would proceed through the transition state such as selenonium ion intermediate **5B**, where the selenonium ion would be opened by the attack of the inner phenolic hydroxy group from the β-face via a 6-*exo* cyclization mode, providing the desired product **25**.

2.6. Completion of the synthesis of the target tetracyclic model compound 4

Having established the method for the construction of the tetracyclic key intermediate **26** possessing the whole carbon framework with the requisite functionalities and asymmetric carbons, we next investigated the final transformation of **26** into the target molecule **4** to complete the project synthesis. As shown in Scheme 6, the route required only manipulation of the two hydroxy protecting groups in **26**. To this end, deprotection of both the TBS and MOM groups in **26** was carried out by reaction with 6 M HCl in MeOH at 50°C to provide diol **27** in 96% yield. Initial attempts at direct conversion of **27** to **4** by selective acetylation of the C3 hydroxy group were unfortunately fruitless. Therefore, we decided to look at chemoselective removal of the phenolic acetyl group in diacetate **28** prepared by complete acetylation of **27** in 85% yield. After several experiments, the requisite selective deacetylation of **28** was best achieved by exposure to potassium *t*-butoxide (1.05 equiv.) in THF–*t*-butyl alcohol (5:1) at room temperature, finally providing **4** in 96% yield. The stereostructure of the tetracyclic model compound **4** was unambiguously confirmed by extensive spectroscopic analysis including NOESY experiment in the 500 MHz ^{1}H NMR spectrum. The selected NOESY correlation of **4** is pictured in Figure 2, where key NOE interactions between C11-H_β and C10-Me, C1-H_β, and between C8-Me and C11-H_α, C7-H_α, C9-H are observed, indicating that the dihydropyran C ring takes a half-chair conformation in the *cis*-fused B/C rings.



Scheme 6. Synthesis of the tetracyclic model compound **4**. (a) 6 M HCl, MeOH, 50°C, 96%; (b) Ac_2O, DMAP, pyridine, rt, 85%; (c) *t*-BuOK, THF–*t*-BuOH (5:1), rt, 96%.

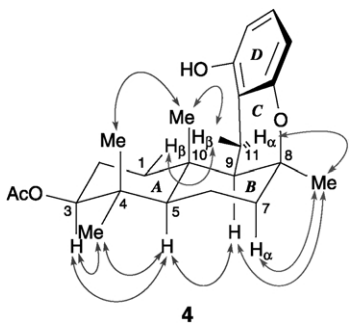


Figure 2. Selected NOESY correlation of the tetracyclic model compound **4**.

3. Conclusion

We have succeeded in developing a facile and efficient method for the construction of the tetracyclic ABCD ring system [(−)-**4**] of kampanols in an enantioselective manner starting from the known *trans*-decalone derivative **9**. The method features a conjugate addition reaction of the Grignard reagent (**7**) of the bromobenzene derivative **8** with the α-methylene ketone **6** to form the coupling product **21** as well as a phenylselenium-mediated cyclization reaction of the phenol derivative **5** to stereoselectively construct the tetracyclic key intermediate **25**. Further investigation toward the total synthesis of kampanols and analogues is now in progress and will be reported in due course.

4. Experimental

4.1. General methods

All reactions involving air and moisture-sensitive reagents were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction was carried out using glass-supported Merck Silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated.

All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone under argon.

Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with Brucker DRX-500 (500 MHz) spectrometers. Chemical shifts are expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra and high-resolution mass (HRMS) spectra were measured on a Hitachi M-80B spectrometer.

4.1.1. (4a*S*,6*S*,8a*S*)-6-*tert*-Butyldimethylsiloxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (12). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.02 ml, 4.4 mmol) was added dropwise to a stirred solution of (4a*S*,6*S*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (**9**)[10] (621 mg, 3.0 mmol) in dichloromethane (8.0 ml) containing 2,6-lutidine (0.55 ml, 4.7 mmol) at room temperature under argon. After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (15 ml), and the mixture was extracted with diethyl ether (3×40 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 50:1) to give **12** (945 mg, 99%) as a white solid. Recrystallization from hexane afforded an analytical sample of **12** as colorless plates, mp 93–94°C; $[\alpha]_D^{20}=-15.7°$ (*c* 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.86 (3H, s), 0.89 (9H, s), 0.93 (3H, s), 1.11 (1H, dd, *J*=3.2, 12.0 Hz), 1.14 (3H, s), 1.46–1.53 (1H, m), 1.57–1.67 (4H, m), 1.67–1.82 (2H, m), 2.03–2.11 (1H, m), 2.16–2.24 (1H, m), 2.54 (1H, dt, *J*=14.0, 7.0 Hz), 3.13–3.18 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −3.8, 16.3, 18.1, 18.7, 21.0, 25.9 (three carbons), 26.4, 27.3, 28.4, 31.1, 37.5, 40.3, 48.6, 52.7, 78.7, 215.5; IR (KBr) 2949, 2857, 1703, 1472, 1391, 1366, 1318, 1250, 1204, 1100, 1076, 1007, 988, 943, 893, 835, 772, 671, 604, 475, 446 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{19}H_{37}O_2Si$ [(M+H)$^+$], 325.2563, found 325.2538.

4.1.2. (2*R*,4a*S*,6*S*,8a*S*)-6-*tert*-Butyldimethylsiloxy-2-hydroxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (13). A solution of **12** (357 mg, 1.1 mmol) in dry tetrahydrofuran (3.0 ml) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)-amide in tetrahydrofuran (1.0 M solution, 1.76 ml, 1.8 mmol) at −78°C under argon. After 1.5 h, a solution of 2-phenylsulfonyl-3-phenyloxaziridine[11] (Davis reagent) (517 mg, 2.0 mmol) in dry tetrahydrofuran (3.0 ml) was added slowly to the above mixture at −78°C, and the resulting mixture was further stirred for 2 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride (10 ml), and the mixture was extracted with diethyl ether (3×40 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 50:1→20:1) to give **13** (275 mg, 74%) as a white solid. Recrystallization from hexane afforded an analytical sample of **13** as colorless plates, mp 82–84°C; $[\alpha]_D^{20}=-8.3°$ (*c* 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.87 (3H, s), 0.89 (9H, s), 0.94 (3H, s), 1.11 (1H, dd, *J*=3.7, 11.6 Hz), 1.17 (3H, s), 1.24–1.36 (1H, m), 1.57–1.90 (6H, m), 2.44–2.51 (1H, m), 3.14–3.20 (1H, m), 3.59 (1H, d, *J*=3.9 Hz), 4.40 (1H, ddd, *J*=3.9, 7.4, 11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −3.9, 16.2, 18.0, 18.4, 19.5, 25.8 (three carbons), 26.7, 28.3, 30.8, 36.3, 40.4, 47.5, 53.4, 71.4, 78.4, 214.8; IR (KBr) 3883, 3823, 3746, 3491, 2951, 2857, 1703, 1472, 1391, 1364, 1250, 1142, 1103, 1076, 1055, 1009, 990, 949, 889, 837, 774, 673, 596, 511 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{19}H_{37}O_3Si$ [(M+H)$^+$], 341.2512, found 341.2502.

4.1.3. (1*S*,4a*S*,6*S*,8a*S*)-6-*tert*-Butyldimethylsiloxy-2-methylene-5,5,8a-(trimethyl)decahydronaphthalen-1-ol (16). A suspension of potassium *tert*-butoxide (507 mg, 4.4 mmol) and methyltriphenylphosphonium bromide (1.60 g, 4.4 mmol) in benzene (15 ml) was heated at reflux for 3 h under argon, and then roughly half-volume of the solvent was removed in vacuo. A solution of **13** (299 mg, 0.88 mmol) in benzene (15 ml) was added to the above mixture, and the resulting mixture was then refluxed for 16 h under argon. After cooling, the reaction was quenched with water (10 ml), and the mixture was extracted with

diethyl ether (3×50 ml). The combined extracts were washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 100:1) to give **16** (253 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$=+15.4° (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (3 H, s), 0.05 (3H, s), 0.75 (3H, s), 0.77 (3H, s), 0.89 (9H, s), 0.93 (3H, s), 1.03 (1H, dd, *J*=2.8, 12.5 Hz), 1.19–1.28 (1H, m), 1.31–1.42 (1H, m), 1.51 (1H, d, *J*=5.7 Hz), 1.57–1.63 (2H, m), 1.64–1.69 (1H, m), 1.84 (1H, dt, *J*=3.5, 13.3 Hz), 2.01 (1H, dt, *J*=5.3, 13.4 Hz), 2.39–2.45 (1H, m), 3.20–3.26 (1H, m), 3.59 (1H, d, *J*=4.7 Hz), 4.81 (2H, dd, *J*=1.8, 25.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, 12.4, 16.1, 18.1, 22.8, 25.9 (three carbons), 27.9, 28.6, 34.2, 35.9, 39.5, 40.6, 52.0, 79.4, 82.1, 104.9, 148.6; IR (neat) 3441, 2936, 2855, 1655, 1460, 1387, 1252, 1101, 1007, 941, 885, 835, 774, 667 cm^{-1}; HRFABMS (*m/z*) calcd for $C_{20}H_{39}O_2Si$ [(M+H)$^+$], 339.2719, found 339.2722.

4.1.4. (2*R*,4a*S*,6*S*,8a*S*)-2-Benzyloxymethoxy-6-*tert*-butyldimethylsiloxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (14). Benzyl chloromethyl ether (0.90 ml, 5.9 mmol) was added dropwise to a stirred solution of **13** (287 mg, 0.84 mmol) in dichloromethane (5.0 ml) containing diisopropylethylamine (1.17 ml, 6.7 mmol) at room temperature under argon. After 15 h, the reaction was quenched with saturated aqueous ammonium chloride (5.0 ml), and the resulting mixture was extracted with ethyl acetate (3×30 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **13** (379 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$=+51.2° (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.85 (3H, s), 0.89 (9H, s), 0.93 (3H, s), 1.11 (1H, dd, *J*=3.1, 12.2 Hz), 1.13 (3H, s), 1.45–1.54 (2H, m), 1.58–1.67 (2H, m), 1.67–1.89 (3H, m), 2.28–2.36 (1H, m), 3.16 (1H, dd, *J*=5.0, 10.6 Hz), 4.54 (1H, dd, *J*=7.1, 12.5 Hz), 4.61 (1H, d, *J*=11.8 Hz), 4.67 (1H, d, *J*=11.8 Hz), 4.77 (1H, d, *J*=7.1 Hz), 4.87 (1H, d, *J*=7.1 Hz), 7.27–7.37 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −3.8, 16.2, 18.1, 18.4, 20.1, 25.9 (three carbons), 27.0, 28.3, 30.8, 33.7, 40.4, 48.5, 52.9, 69.9, 75.8, 78.5, 93.7, 127.7, 127.8, 127.9, 128.0, 128.5, 137.8, 211.5; IR (neat) 2951, 2857, 2363, 1723, 1460, 1385, 1364, 1254, 1182, 1107, 1057, 1022, 986, 970, 949, 887, 837, 775, 737, 698, 671 cm^{-1}; HREIMS (*m/z*) calcd for $C_{27}H_{44}O_4Si$ (M$^+$), 460.3009, found 460.3016.

4.1.5. (2*R*,4a*S*,6*S*,8a*S*)-2-Benzyloxymethoxy-6-*tert*-butyldimethylsiloxy-1-methylene-5,5,8a-(trimethyl)decahydronaphthalene (17). A suspension of potassium *tert*-butoxide (507 mg, 4.4 mmol) and methyltriphenylphosphonium bromide (1.60 g, 4.4 mmol) in dry benzene (15 ml) was heated at reflux for 3 h under argon, and then roughly half-volume of the solvent was removed in vacuo. A solution of **14** (403 mg, 0.88 mmol) in benzene (15 ml) was added to the above mixture, and the resulting solution was refluxed for 16 h under argon. After cooling, the reaction was quenched with water (10 ml), and the mixture was extracted with diethyl ether (3×50 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 100:1) to give **17** (365 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$=+10.6° (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.78 (3H, s), 0.89 (12H, s), 0.93 (1H, dd, *J*=3.0, 12.6 Hz), 1.04 (3H, s), 1.20–1.32 (1H, m), 1.54–1.79 (6H, m), 2.16–2.23 (1H, m), 3.20 (1H, dd, *J*=4.4, 11.0 Hz), 4.30 (1H, dd, *J*=5.3, 11.9 Hz), 4.60 (1H, d, *J*=11.7 Hz), 4.68 (1H, s), 4.70 (1H, d, *J*=11.7 Hz), 4.74 (1H, d, *J*=6.9 Hz), 4.86 (1H, d, *J*=6.9 Hz), 4.92 (1H, s), 7.26–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, 15.7, 18.1, 20.6, 20.8, 25.9 (three carbons), 27.9, 28.5, 35.2, 35.3, 39.8, 39.9, 52.8, 69.4, 74.5, 79.2, 93.2, 100.1, 127.7, 127.9 (two carbons), 128.4 (two carbons), 138.0, 158.8; IR (neat) 2936, 2859, 1642, 1462, 1387, 1364, 1252, 1175, 1111, 1047, 995, 903, 889, 870, 837, 774, 735, 696, 673 cm^{-1}; HRFABMS (*m/z*) calcd for $C_{28}H_{45}O_3Si$ [(M−H)$^+$], 457.3138, found 457.3121.

4.1.6. (2*R*,4a*S*,6*S*,8a*S*)-6-*tert*-Butyldimethylsiloxy-1-methylene-5,5,8a-(trimethyl)decahydronaphthalen-2-ol (15). A solution of **17** (618 mg, 1.3 mmol) in dry tetrahydrofuran (20 ml) was added dropwise to a stirred solution of lithium (281 mg, 41 mmol) in liquid ammonia (ca. 80 ml) at −78°C under argon. The resulting solution was allowed to warm at reflux of liquid ammonia for 1 h. Furthermore, the mixture was allowed to stand at room temperature for 5 h in order to remove ammonia. After addition of saturated aqueous ammonium chloride (20 ml), the resulting mixture was extracted with ethyl acetate (3×30 ml). The combined extracts were washed with brine, and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1) to give **15** (367 mg, 80%) as a white solid. Recrystallization from hexane/diethyl ether (10:1) afforded an analytical sample of **15** as colorless needles, mp 114–115°C; $[\alpha]_D^{20}$=−34.0° (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.06 (3H, s), 0.79 (3H, s), 0.85–0.95 (1H, m), 0.90 (12H, s), 1.05 (3H, s), 1.11–1.22 (1H, m), 1.40 (1H, d, *J*=6.3 Hz), 1.55–1.82 (6H, m), 2.19–2.26 (1H, m), 3.19 (1H, dd, *J*=4.3, 11.0 Hz), 4.27–4.34 (1H, m), 4.70 (1H, s), 4.90 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, 15.8, 18.1, 20.7, 20.8, 25.9 (three carbons), 26.0, 27.8, 28.5, 35.4, 37.7, 39.9, 52.8, 69.7, 79.3, 99.3, 161.9; IR (KBr) 3304, 2934, 2857, 1642, 1460, 1387, 1364, 1252, 1105, 1061, 1007, 968, 953, 889, 870, 837, 772, 673 cm^{-1}; HRFABMS (*m/z*) calcd for $C_{20}H_{39}O_2Si$ [(M+H)$^+$], 339.2719, found 339.2722.

4.1.7. (4a*R*,6*S*,8a*S*)-6-*tert*-Butyldimethylsiloxy-5,5,8a-trimethyl-1-methylene-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1*H*)-one (6). Dess-Martin periodinane (327 mg, 0.80 mmol) was added in small portions to a stirred solution of **15** (135 mg, 0.40 mmol) in dry dichloromethane (5.0 ml) at room temperature. After 1 h, the reaction was quenched with 15% aqueous sodium thiosulfate (3.0 ml), and the resulting mixture was extracted with diethyl ether (3×30 ml). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate and brine,

then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1) to give **6** (132 mg, 98%) as a white powder, mp 60–62°C; $[\alpha]_D^{20}=-39.0°$ (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.07 (3H, s), 0.86 (3H, s), 0.91 (9H, s), 0.99 (3H, s), 1.03 (3H, s), 1.40 (1H, dd, *J*=3.0, 12.5 Hz), 1.58 (1H, dt, *J*=12.5, 4.5 Hz), 1.64–1.73 (2H, m), 1.76 (1H, dt, *J*=3.3, 12.5 Hz), 1.85 (1H, dq, *J*=5.5, 12.5 Hz), 1.94–2.01 (1H, m), 2.31 (1H, ddd, *J*=7.9, 12.5, 17.0 Hz), 2.66 (1H, ddd, *J*=1.8, 5.5, 17.0 Hz), 3.28 (1H, dd, *J*=5.4, 10.0 Hz), 5.00 (1H, d, *J*=0.9 Hz), 5.55 (1H, d, *J*=0.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −3.8, 15.9, 18.1, 20.4, 21.4, 25.9 (three carbons), 27.7, 28.6, 35.2, 40.0, 40.3, 40.6, 49.9, 79.1, 113.8, 158.5, 203.6; IR (KBr) 2955, 2895, 2857, 2708, 1723, 1698, 1613, 1472, 1389, 1362, 1285, 1254, 1215, 1177, 1101, 1071, 1005, 968, 941, 885, 870, 837, 774, 669, 590, 534, 486 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{20}H_{36}O_2Si$ (M^+), 336.2485, found 336.2479.

4.1.8. 2-Bromo-3-(methoxymethoxy)phenol (19) and 2-bromo-1,3-bis(methoxymethoxy)benzene (20). Chloromethyl methyl ether (0.32 ml, 4.2 mmol) was added dropwise to a stirred solution of 2-bromoresorsinol[13] (**18**) (800 mg, 4.2 mmol) in dry dichloromethane (14.0 ml) containing diisopropylethylamine (0.74 ml, 4.2 mmol) at room temperature under argon. After 1 h, the reaction was quenched with 3% aqueous hydrochloric acid (8.0 ml), and the resulting mixture was extracted with ethyl acetate (3×60 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1) to give more polar **19** (430 mg, 44%) (colorless oil) and less polar **20** (337 mg, 29%) (colorless oil). **19**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (3H, s), 5.25 (2H, s), 5.62 (1H, s), 6.70–6.72 (1H, m), 6.72–6.74 (1H, m), 7.15 (1H, t, *J*=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 95.1, 101.3, 107.4, 109.5, 128.7, 153.5, 154.3; IR (neat) 3426, 2932, 1593, 1466, 1385, 1321, 1260, 1190, 1154, 1088, 1034, 926, 772, 581 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_8H_9BrO_3$ (M^+), 231.9735, found 231.9740. **20**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (6H, s), 5.25 (4H, s), 6.84 (1H, d, *J*=8.3 Hz), 7.18 (1H, t, *J*=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4 (two carbons), 95.2, 103.9 (two carbons), 109.6 (two carbons), 128.2, 155.1 (two carbons); IR (neat) 2957, 1595, 1468, 1250, 1204, 1155, 1086, 1038, 922, 772, 656 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{10}H_{13}BrO_4$ (M^+), 275.9997, found 275.9990.

4.1.9. 1-Benzyloxymethoxy-2-bromo-3-(methoxymethoxy)benzene (8). Benzyl chloromethyl ether (0.43 ml, 2.8 mmol) was added dropwise to a stirred solution of **19** (430 mg, 1.9 mmol) in dry dichloromethane (8.0 ml) containing diisopropylethylamine (0.54 ml, 3.2 mmol) at room temperature under argon. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride (8.0 ml), and the mixture was extracted with ethyl acetate (3×60 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1) to give **8** (629 mg, 96%) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 3.53 (3H, s), 4.77 (2H, s), 5.26 (2H, s), 5.37 (2H, s), 6.85 (1H, dd, *J*=1.2, 8.3 Hz), 6.91 (1H, dd, *J*=1.2, 8.3 Hz), 7.19 (1H, t, *J*=8.3 Hz), 7.33–7.40 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 70.3, 92.9, 95.2, 103.9, 109.6, 109.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 137.0, 155.0, 155.1; IR (neat) 2905, 1721, 1593, 1466, 1385, 1246, 1206, 1155, 1086, 1042, 891, 772, 739, 698, 606 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{16}H_{17}BrO_4$ (M^+), 352.0310, found 352.0309.

4.1.10. (1*R*,4a*R*,6*S*,8a*S*)-1-[2-Benzyloxymethoxy-6-(methoxymethoxy)benzyl]-6-*tert*-butyldimethylsiloxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphtalen-2-one (21). Ethylene dibromide (79.0 μl, 0.91 mmol) was added dropwise to a stirred suspension of magnesium powder (132 mg, 5.4 mmol) in dry diethyl ether (1.0 ml) at room temperature under argon. Immediately, a solution of **8** (1.28 g, 3.6 mmol) in dry diethyl ether (5.0 ml) was added slowly to the above mixture, and the resulting mixture was gently refluxed for 1 h to complete the formation of the Grignard reagent. A solution of **6** (203 mg, 0.60 mmol) in dry diethyl ether (4.0 ml) was added to the above mixture at 0°C, and the mixture was further stirred for 5 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (4.0 ml), and the mixture was extracted with ethyl acetate (3×50 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 50:1) to give **21** (349 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{20}=-26.3°$ (*c* 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.79 (3H, s), 0.85–0.90 (1H, m), 0.87 (3H, s), 0.88 (9H, s), 0.96 (3H, s), 1.18–1.29 (1H, m), 1.42–1.50 (1H, m), 1.57–1.68 (1H, m), 1.74 (1H, dq, *J*=4.9, 13.2 Hz), 1.92 (1H, dt, *J*=13.5, 3.4 Hz), 1.97–2.08 (1H, m), 2.27 (1H, dt, *J*=6.9, 13.2 Hz), 2.35–2.42 (1H, m), 2.61–2.70 (2H, m), 2.66 (1H, s), 3.19–3.26 (1H, m), 3.23 (1H, dd, *J*=4.3, 11.9 Hz), 3.49 (3H, s), 4.72 (2H, dd, *J*=11.8, 16.6 Hz), 5.17 (2H, dd, *J*=6.6, 8.4 Hz), 5.28 (2H, s), 6.75 (1H, d, *J*=8.3 Hz), 6.83 (1H, d, *J*=8.3 Hz), 7.06 (1H, t, *J*=8.3 Hz), 7.27–7.37 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, 14.4, 15.8, 16.6, 18.1, 23.9, 25.9 (three carbons), 27.9, 28.8, 36.1, 39.8, 42.1, 43.1, 53.9, 56.1, 63.7, 70.1, 79.1, 92.6, 94.8, 108.1, 121.2, 126.8, 127.9, 128.0, 128.1 (two carbons), 128.5 (two carbons), 137.4, 156.0, 156.1, 211.3; IR (neat) 2955, 2857, 1715, 1593, 1470, 1389, 1366, 1325, 1254, 1211, 1155, 1086, 1044, 885, 837, 775, 737, 698, 669 cm^{-1}; HREIMS (*m*/*z*) for $C_{36}H_{54}O_6Si$ (M^+), 610.3690, found 610.3680.

4.1.11. (1*S*,4a*R*,6*S*,8a*R*)-1-[2-Benzyloxymethoxy-6-(methoxymethoxy)benzyl]-6-*tert*-butyldimethylsiloxy-5,5,8a-trimethyl-2-methylene-3,4,4a,5,6,7,8,8a-octahydronaphtalene (22). A stirred suspension of potassium *tert*-butoxide (330 mg, 2.9 mmol) and methyltriphenylphosphonium bromide (1.04 g, 2.9 mmol) in dry benzene (5.0 ml) was heated at reflux for 3 h under argon, and then roughly half-volume of the solvent was removed in vacuo. A solution of **21** (349 mg, 0.57 mmol) in dry benzene

(5.0 ml) was added to the above mixture, and the resulting solution was refluxed for 13 h under argon. After cooling, the reaction was quenched with water (5.0 ml), and the mixture was extracted with diethyl ether (2×60 ml). The combined extracts were washed with 10% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 50:1) to give **22** (338 mg, 97%) as a colorless viscous oil. $[\alpha]_D^{20}=-20.6°$ (*c* 1.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.76 (3H, s), 0.85 (3H, s), 0.89 (9H, s), 0.90 (3H, s), 1.10 (1H, dd, *J*=2.6, 12.5 Hz), 1.24–1.33 (1H, m), 1.39 (1H, dq, *J*=4.2, 12.9 Hz), 1.48–1.55 (1H, m), 1.57–1.67 (1H, m), 1.68–1.76 (1H, m), 1.82–1.96 (2H, m), 2.29–2.36 (1H, m), 2.55 (1H, dd, *J*=4.2, 8.9 Hz), 2.77 (1H, dd, *J*=4.2, 13.9 Hz), 2.91 (1H, dd, *J*=8.9, 13.9 Hz), 3.08–3.12 (1H, m), 3.50 (3H, s), 4.71 (1H, s), 4.73 (2H, s), 4.98 (1H, s), 5.19 (2H, dd, *J*=6.6, 13.1 Hz), 5.29 (2H, s), 6.75 (1H, d, *J*=8.2 Hz), 6.83 (1H, d, *J*=8.2 Hz), 7.05 (1H, t, *J*=8.2 Hz), 7.27–7.37 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.7, 14.2, 16.0, 18.1, 19.9, 24.5, 25.9 (three carbons), 28.5, 28.9, 36.6, 38.7, 39.8, 40.1, 55.0, 55.2, 56.2, 70.0, 79.5, 92.3, 94.7, 106.6, 107.9, 108.0, 120.8, 126.7, 127.9, 128.0 (two carbons), 128.5 (two carbons), 137.3, 149.5, 156.2, 156.3; IR (neat) 2934, 2855, 1593, 1468, 1385, 1254, 1192, 1155, 1100, 1046, 941, 887, 837, 774, 698, 666 cm^{-1}; HREIMS (*m*/*z*) for $C_{37}H_{56}O_5Si$ (M^+), 608.3897, found 608.3902.

4.1.12. (1*S*,4a*R*,6*S*,8a*R*)-1-[2-Hydroxy-6-(methoxymethoxy)benzyl]-6-*tert*-butyldimethylsiloxy-5,5,8a-trimethyl-2-methylene-3,4,4a,5,6,7,8,8a-octahydronaphtalene (5). A solution of **22** (338 mg, 0.56 mmol) in dry tetrahydrofuran (7.0 ml) was added dropwise to a stirred solution of lithium (116 mg, 17 mmol) in liquid ammonia (ca. 20 ml) at −78°C under argon. The resulting solution was allowed to warm at reflux of liquid ammonia for 1 h. After addition of saturated aqueous ammonium chloride (10 ml), the mixture was allowed to stand for 4 h at room temperature in order to remove ammonia. The mixture was extracted with ethyl acetate (3×40 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **5** (258 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{20}=-12.6°$ (*c* 0.79, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.76 (3H, s), 0.82 (3H, s), 0.88 (9H, s), 0.89 (3H, s), 1.11 (1H, dd, *J*=2.7, 12.5 Hz), 1.22–1.33 (1H, m), 1.35–1.46 (1H, m), 1.50–1.56 (1H, m), 1.58–1.68 (1H, m), 1.70–1.79 (1H, m), 1.88–2.01 (2H, m), 2.30–2.41 (2H, m), 2.76 (1H, dd, *J*=8.1, 14.6 Hz), 2.86 (1H, dd, *J*=3.7, 14.6 Hz), 3.20 (1H, dd, *J*=4.5, 11.4 Hz), 3.50 (3H, s), 4.82 (1H, d, *J*=1.1 Hz), 4.89 (1H, s), 5.04 (1H, d, *J*=1.1 Hz), 5.17 (1H, d, *J*=6.6 Hz), 5.20 (1H, d, *J*=6.6 Hz), 6.43 (1H, dd, *J*=0.8, 8.2 Hz), 6.66 (1H, dd, *J*=0.8, 8.2 Hz), 6.98 (1H, t, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, 14.2, 15.9, 18.1, 19.2, 24.4, 25.9 (three carbons), 28.5, 28.7, 36.5, 38.5, 39.8, 40.3, 54.9, 55.5, 56.2, 79.4, 94.7, 106.6, 106.7, 109.5, 118.2, 126.8, 150.3, 155.0, 156.2; IR (neat) 3420, 2936, 2855, 1719, 1647, 1595, 1466, 1385, 1254, 1194, 1154, 1094, 1044, 941, 887, 835, 774, 731, 664 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{29}H_{48}O_4Si$ (M^+), 488.3322, found 488.3325.

4.1.13. (3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-3-Hydroxy-11-methoxymetoxy-4,4,6a,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (23). Boron trifluoride diethyl etherate (10.0 μl, 82 μmol) was added dropwise to a stirred solution of **5** (4.0 mg, 8.2 μmol) in dry dichloromethane (0.5 ml) at −60°C under argon. The mixture was gradually warmed up to −10°C during 5 h. The reaction was quenched with saturated aqueous sodium hydrogencarbonate (2.0 ml), and the resulting mixture was extracted with ethyl acetate (3×4 ml). The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **23** (2.3 mg, 75%) as a colorless viscous oil. $[\alpha]_D^{20}=+23.2°$ (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s), 0.93 (3H, s), 1.03 (3H, s), 0.99–1.03 (1H, m), 1.09–1.17 (1H, m), 1.19 (3H, s), 1.39–1.50 (1H, m), 1.55–1.60 (1H, m), 1.62–1.74 (4H, m), 1.75–1.81 (1H, m), 1.84 (1H, dt, *J*=13.1, 3.5 Hz), 2.08 (1H, dt, *J*=12.5, 3.1 Hz), 2.34 (1H, dd, *J*=13.2, 17.0 Hz), 2.69 (1H, dd, *J*=5.0, 17.0 Hz), 3.23–3.29 (1H, m), 3.49 (3H, s), 5.19 (2H, s), 6.46 (1H, d, *J*=8.2 Hz), 6.59 (1H, dd, *J*=0.8, 8.2 Hz), 7.01 (1H, t, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 15.6, 17.4, 19.5, 20.6, 27.2, 28.2, 36.7, 37.5, 38.8, 41.0, 51.5, 55.2, 56.1, 70.6, 78.7, 94.5, 104.8, 110.7, 112.0, 126.9, 154.0, 155.7; IR (neat) 3443, 2928, 2855, 1726, 1591, 1468, 1381, 1333, 1263, 1225, 1192, 1154, 1127, 1096, 1051, 922, 777, 718 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{23}H_{34}O_4$ (M^+), 374.2457, found 374.2446.

4.1.14. (3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-3-*tert*-Butyldimethylsiloxy-11-methoxymetoxy-4,4,6a,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (24). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (12 μl, 51 μmol) was added dropwise to a stirred solution of **23** (1.9 mg, 5.1 μmol) in dry dichloromethane (0.5 ml) containing 2,6-lutidine (9.0 μl, 61 μmol) at room temperature under argon. After 24 h, the reaction was quenched with saturated aqueous ammonium chloride (2.0 ml), and the mixture was extracted with ethyl acetate (2×4 ml). The combined extracts were washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **24** (2.1 mg, 85%) as colorless viscous oil. $[\alpha]_D^{20}=+31.9°$ (*c* 0.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.79 (3H, s), 0.90 (9H, s), 0.92 (3H, s), 0.94 (3H, s), 0.99 (1H, dd, *J*=1.9, 12.0 Hz), 1.03–1.11 (1H, m), 1.18 (3H, s), 1.43 (1H, dq, *J*=3.1, 13.6 Hz), 1.51–1.55 (1H, m), 1.61–1.71 (3H, m), 1.73–1.82 (2H, m), 2.06 (1H, dt, *J*=3.1, 12.4 Hz), 2.33 (1H, dd, *J*=13.2, 17.1 Hz), 2.68 (1H, dd, *J*=5.1, 17.1 Hz), 3.21 (1H, dd, *J*=4.7, 11.3 Hz), 3.49 (3H, s), 5.19 (2H, dd, *J*=6.5, 9.6 Hz), 6.46 (1H, d, *J*=8.2 Hz), 6.59 (1H, d, *J*=8.2 Hz), 7.01 (1H, t, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.7, 14.9, 16.1, 17.4, 18.1, 19.7, 20.6, 25.9 (three carbons), 27.6, 28.6, 29.7, 36.6, 37.5, 41.1, 51.6, 55.3, 56.1, 76.5, 79.2, 94.5, 104.7, 110.8, 112.2, 126.9, 154.0, 155.7; IR (neat) 2928, 2855, 1738, 1607, 1591,

1468, 1387, 1331, 1262, 1225, 1192, 1154, 1127, 1098, 1053, 966, 924, 883, 837, 804, 777, 720, 667, 608 cm^{-1}; HRFABMS *m/z* calcd for $C_{29}H_{48}O_4Si$ (M^+), 488.3322, found 488.3311.

4.1.15. (3*S*,4a*R*,6a*S*,12a*R*,12b*S*)-3-*tert*-Butyldimethylsilyoxy-11-methoxymethoxy-4,4,12b-trimethyl-6a-phenylselenylmethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (25). *N*-(Phenylseleno)phtalimide (86.0 mg, 0.28 mmol) in dry dichloromethane (10 ml) and tin(IV) chloride in dichloromethane (1.0 M solution, 0.25 ml, 0.25 mmol) were added dropwise to a stirred solution of **5** (114 mg, 0.23 mmol) in dry dichloromethane (8.0 ml) at −78°C under argon. After 1 h, the reaction mixture was concentrated in vacuo to afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **25** (147 mg, 98%) as a pale yellow viscous oil. $[\alpha]_D^{20}=+21.5°$ (*c* 1.04, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.69 (3H, s), 0.74 (3H, s), 0.88 (9H, s), 0.89–0.92 (1H, m), 0.94 (3H, s), 1.01–1.12 (1H, m), 1.45–1.53 (1H, m), 1.55–1.61 (2H, m), 1.61–1.75 (2H, m), 1.75–1.88 (2H, m), 2.15–2.24 (1H, m), 2.44 (1H, dd, *J*=8.4, 18.7 Hz), 2.73 (1H, d, *J*=18.7 Hz), 3.09 (2H, s), 3.23 (1H, dd, *J*=4.7, 11.3 Hz), 3.45 (3H, s), 5.17 (2H, d, *J*=1.6 Hz), 6.43 (1H, dd, *J*=0.8, 8.2 Hz), 6.56 (1H, dd, *J*=0.8, 8.2 Hz), 6.98 (1H, t, *J*=8.2 Hz), 7.14–7.23 (3H, m), 7.40–7.47 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.7, 14.2, 16.0, 18.1, 19.9, 24.5, 25.9 (three carbons), 28.5, 28.9, 36.6, 38.7, 39.8, 40.1, 55.0, 55.2, 56.2, 70.0, 79.5, 92.3, 94.7, 106.6, 107.9, 108.0, 120.8, 126.7, 127.9, 128.0, 128.5, 137.3, 149.5, 156.2, 156.3; IR (neat) 2951, 2855, 1730, 1591, 1468, 1389, 1360, 1254, 1155, 1098, 1053, 953, 924, 883, 837, 774, 737, 691, 529, 467 cm^{-1}; HREIMS (*m/z*) calcd for $C_{35}H_{52}O_4SeSi$ (M^+), 644.2800, found 644.2794.

4.1.16. (3*S*,4a*R*,6a*S*,12a*R*,12b*S*)-3-*tert*-Butyldimethylsilyoxy-11-methoxymethoxy-4,4,6a,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (26). Tributyltin hydride (102 μl, 0.37 mmol) and 2,2′-azobisisobutyronitrile (2.0 mg, 12 μmol) were added successively to a stirred solution of **25** (79.1 mg, 0.12 mmol) in dry toluene (3.0 ml) at room temperature. The mixture was frozen using liquid nitrogen, and then the reaction bottle was evacuated in vacuo followed by filled with dry argon. After warming to room temperature, the mixture was heated at reflux for 7 h under argon. After cooling, the reaction mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/ethyl acetate, 50:1→20:1) to give **26** (47.0 mg, 78%) as a colorless oil. $[\alpha]_D^{20}=-13.8°$ (*c* 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.69 (3H, s), 0.74 (3H, s), 0.84–0.91 (1H, m), 0.88 (9H, s), 0.93 (3H, s), 0.97–1.10 (1H, m), 1.16 (3H, s), 1.32 (1H, d, *J*=8.2 Hz), 1.45–1.63 (4H, m), 1.64–1.74 (1H, m), 1.80–1.89 (1H, m), 2.11–2.21 (1H, m), 2.63 (1H, dd, *J*=8.2, 18.5 Hz), 2.80 (1H, d, *J*=18.5 Hz), 3.20 (1H, dd, *J*=4.6, 11.4 Hz), 3.49 (3H, s), 5.20 (2H, s), 6.44 (1H, d, *J*=8.2 Hz), 6.56 (1H, d, *J*=8.2 Hz), 6.99 (1H, t, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.7, 14.2, 16.2, 17.7, 18.1, 18.2, 25.9 (three carbons), 27.0, 27.6, 29.0, 38.0, 38.3, 39.4, 40.8, 49.0, 54.5, 56.0, 75.0, 79.5, 94.4, 104.9, 110.9, 112.4, 126.4, 154.8, 155.6; IR (neat) 2930, 1591, 1470, 1389, 1256, 1155, 1134, 1098, 1055, 941, 883, 837, 774, 708 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{48}O_4Si$ (M^+), 488.3322, found 488.3355.

4.1.17. (3*S*,4a*R*,6a*S*,12a*R*,12b*S*)-4,4,6a,12b-Tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-3,11-diol (27). 6 M Hydrochloric acid (0.36 ml, 2.2 mmol) was added to a stirred solution of **26** (106 mg, 0.22 mmol) in methanol (4.0 ml) at room temperature, and then the mixture was heated at 50°C for 3 h. After cooling, the reaction was diluted with ethyl acetate (60 ml). The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **27** (68.8 mg, 96%) as a white solid. Recrystallization from hexane/diethyl ether (4:1) afforded an analytical sample of **27** as white fine needles, mp 108–109°C; $[\alpha]_D^{20}=-40.6°$ (*c* 0.91, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (3H, s), 0.79 (3H, s), 0.89–0.95 (1H, m), 1.03 (3H, s), 1.04–1.12 (1H, m), 1.17 (3H, s), 1.37 (1H, d, *J*=7.8 Hz), 1.55–1.62 (3H, m), 1.62–1.75 (2H, m), 1.92 (1H, dt, *J*=13.0, 3.6 Hz), 2.14–2.21 (1H, m), 2.17 (1H, s), 2.65 (1H, dd, *J*=7.7, 17.8 Hz), 2.73 (1H, d, *J*=17.8 Hz), 3.21–3.27 (1H, m), 4.63 (1H, s), 6.30 (1H, dd, *J*=1.0, 8.1 Hz), 6.37 (1H, dd, *J*=1.0, 8.1 Hz), 6.92 (1H, t, *J*=8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.1, 15.6, 17.4, 17.9, 26.9, 27.0, 28.5, 38.1, 38.2, 38.8, 40.6, 48.8, 54.3, 75.0, 79.1, 106.2, 109.5, 126.5, 153.5, 155.8; IR (KBr) 3439, 2928, 1616, 1593, 1466, 1370, 1273, 1169, 1134, 1026, 903, 775 cm^{-1}; HRFABMS (*m/z*) calcd for $C_{21}H_{30}O_3$ (M^+), 330.2195, found 330.2226.

4.1.18. (3*S*,4a*R*,6a*S*,12a*R*,12b*S*)-3,11-Diacetoxy-4,4,6a,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (28). Acetic anhydride (0.172 ml, 1.8 mmol) was added dropwise to a stirred solution of **27** (60.4 mg, 0.18 mmol) in pyridine (1.0 ml) containing 4-(dimethylamino)pyridine (11.0 mg, 92 μmol) at room temperature. After 18 h, the reaction mixture was diluted with ethyl acetate (10 ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1) to give **28** (64.4 mg, 85%) as a amorphous white powder, mp 144–146°C; $[\alpha]_D^{20}=-8.3°$ (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.72 (3H, s), 0.85 (3H, s), 0.90 (3H, s), 0.96–1.01 (1H, m), 1.07–1.15 (1H, m), 1.17 (3H, s), 1.33 (1H, d, *J*=7.8 Hz), 1.54–1.63 (2H, m), 1.63–1.77 (3H, m), 1.83 (1H, dt, *J*=13.1, 3.6 Hz), 2.05 (3H, s), 2.14–2.21 (1H, m), 2.32 (3H, s), 2.56 (1H, d, *J*=18.1 Hz), 2.63 (1H, dd, *J*=7.8, 18.1 Hz), 4.49 (1H, dd, *J*=4.8, 11.6 Hz), 6.56 (1H, dd, *J*=1.0, 8.1 Hz), 6.65 (1H, dd, *J*=1.0, 8.1 Hz), 7.07 (1H, t, *J*=8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.8, 17.7, 17.8, 20.8, 21.3, 23.4, 26.8, 28.4, 37.7, 37.8, 37.9, 40.4, 48.6, 54.4, 75.3, 80.7, 113.1, 114.8, 115.7, 126.7, 148.9, 155.7, 169.1, 171.0; IR (KBr) 2971, 2932, 2886, 1753, 1723, 1615, 1584, 1466, 1372, 1318, 1252, 1209, 1165, 1136, 1086, 1030, 1009, 974, 916, 893, 876, 849, 804, 785, 725, 706, 658, 598, 557, 527 cm^{-1}; HRFABMS (*m/z*) calcd for $C_{25}H_{34}O_5$ (M^+), 414.2406, found 414.2420.

4.1.19. (3*S*,4a*R*,6a*S*,12a*R*,12b*S*)-3-Acetoxy-11-hydroxy-4,4,6a,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene (4). Potassium *tert*-butoxide (51.7 mg, 0.48 mmol) was added in small portions to a stirred solution of **28** (61.9 mg, 0.15 mmol) in THF-*tert*-butyl alcohol (5:1) (3.0 ml) at room temperature under argon. After 20 min, the reaction was quenched with saturated aqueous ammonium chloride (5.0 ml), and the mixture was extracted with ethyl acetate (3×20 ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 10:1→2:1) to give **4** (53.4 mg, 96%) as a white solid. Recrystallization from hexane/diethyl ether (20:1) afforded an analytical sample of **4** as white fine needles, mp 233–234°C; $[\alpha]_D^{20}=-10.4°$ (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (3H, s), 0.86 (3H, s), 0.90 (3H, s), 0.97–1.03 (1H, m), 1.09–1.21 (1H, m), 1.18 (3H, s), 1.38 (1H, d, *J*=7.5 Hz), 1.49–1.77 (5H, m), 1.91 (1H, dt, *J*=13.2, 3.5 Hz), 2.05 (3H, s), 2.12–2.21 (1H, m), 2.66 (1H, dd, *J*=7.5, 17.9 Hz), 2.72 (1H, d, *J*=17.9 Hz), 4.50 (1H, dd, *J*=4.7, 11.7 Hz), 4.77 (1H, s), 6.30 (1H, dd, *J*=0.8, 8.0 Hz), 6.37 (1H, d, *J*=8.0 Hz), 6.92 (1H, t, *J*=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 16.8, 17.4, 17.8, 21.3, 23.4, 26.8, 28.4, 37.7, 37.8, 38.0, 40.5, 48.7, 54.4, 75.0, 81.1, 106.2, 109.5, 109.8, 126.6, 153.5, 155.8, 171.4; IR (KBr) 3447, 2946, 2361, 1699, 1616, 1595, 1468, 1377, 1277, 1169, 1136, 1084, 1030, 972, 905, 777, 561 cm^{-1}; HREIMS (*m*/*z*) calcd for $C_{23}H_{32}O_4$ (M^+), 372.2301, found 372.2298: Anal. calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66, found C, 74.25; H, 8.53.

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References

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2. Kampanols A (**1**) and B (**2**) inhibit Ras farnesyltransferase (PFTase) with IC_{50} values of 13 μM and 7 μM, respectively, while kampanol C is inactive and displays an IC_{50} value of 560 μM. Additionally, it is also reported that all kampanols are inactive against human geranyl–geranyl protein transferase (GGTase) (IC_{50}>100 μM) (Ref. 1).
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