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Enantioselective Total Synthesis of (+)-Ottelione A, (−)-Ottelione B, (+)-3-*epi*-Ottelione A and Preliminary Evaluation of Their Antitumor Activity

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Abstract: Enantioselective total synthesis of (+)-ottelione A (**1**) and (−)-ottelione B (**2**), novel and potent antitumor agents from a freshwater plant, and (+)-3-*epi*-ottelione A (**3**), the earlier proposed stereostructure of **1**, was efficiently achieved starting from the known tricyclic compound **10**. The synthesis involved the following key steps: i) coupling reactions of aldehydes **8** and **9** with the aromatic portion **7** (**8**+**7**→**15** and **9**+**7**→**27**), ii) base-induced hemiacetal-opening/epimerization reactions of the cyclic hemiacetals **6** and **27** (**6**→**17** and **27a**→**26a**), and iii) Corey–Winter's reductive olefination of the cyclic thiocarbonates **21** and **36** (**21**→**22** and **36**→**37**). The present total synthesis fully established the absolute configuration of these natural products. The cell growth inhibition profile, COMPARE analysis, and tubulin inhibitory assay of (+)-3-*epi*-ottelione A (**3**) and its *O*-acetyl derivative **24** demonstrated that these unnatural substances could be prominent lead compounds for the development of anticancer agents with a novel mode of action.

Keywords: antitumor agents · natural products · otteliones · total synthesis · tubulin polymerization inhibitors

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Introduction

In 1998, Ayyad and Hoye et al. reported the isolation and structural elucidation of two novel diastereomeric natural products, otteliones A (**1**) and B (**2**) (Figure 1), from the freshwater plant *Ottelia alismoides* collected from the Nile Delta, Egypt.[1,2] These substances were found to exhibit prominent biological properties such as antitubercular[3] and antitumor activities.[1,2] Remarkably, these small-molecule

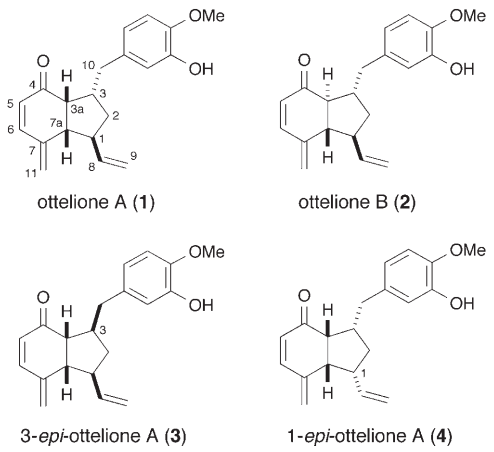


Figure 1. Structures of ottelione A (**1**), ottelione B (**2**), 3-*epi*-ottelione A (**3**), and 1-*epi*-ottelione A (**4**).

natural products were reported to display quite potent cytotoxicity at nanomolar to picomolar levels of IC_{50} values against a panel of 60 human tumor cell lines at the National Cancer Institute in the United States.[1] It has also been reported that ottelione A inhibits tubulin polymerization into microtubules similarly to the well-known alkaloids colchicine, vincristine, and vinbrastine.[4] In addition, ottelione A has been shown to inhibit doxorubicin-resistant leukemia cells (P388/DOX) with an IC_{50} value of $1.0\,ng\,mL^{-1}$ (3.0 nM).[1] Ottelione, therefore, are expected to be promising new leads for the development of cancer chemotherapeutic agents. However, detailed study of the biological properties of these natural products is severely limited by their scarcity. It has been reported that each 9.0 mg of ottelione A (**1**) and B (**2**) was isolated from 1.0 kg (dry weight) of the plant *O. alismoides* (each 0.0009 % isolated yield).[1]

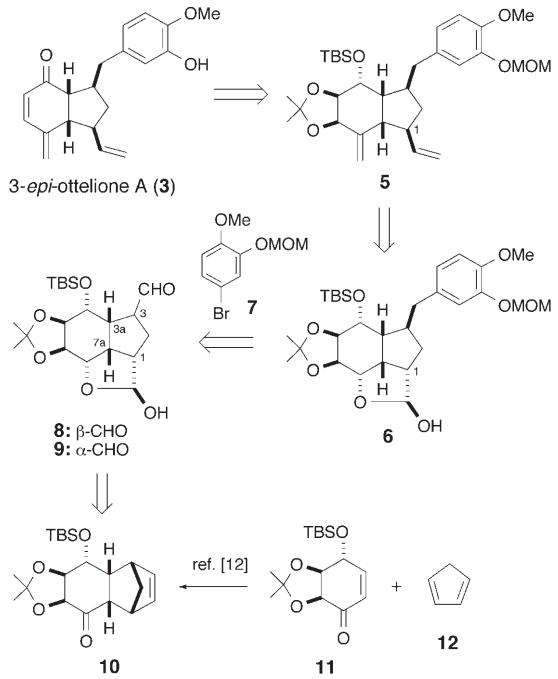
Structurally, ottelione A and B possess a novel bicyclic hydrindane skeleton with four contiguous asymmetric carbon centers, in which the rare and sensitive 4-methylene-2-cyclohexenone substructure is a special characteristic feature.[5] When these natural products were isolated, the relative configuration of ottelione B was elucidated as shown in formulation **2** (Figure 1) by the combination of molecular modeling and ^{1}H NMR studies; however, ottelione A could not be assigned unambiguously and both formulations **3** and **4** were proposed as possible stereostructures with more preference for **3**.[1] In 2000, scientists from Rhône-Poulenc Rorer (now Sanofi-Aventis) proposed an alternative stereostructure **1** for ottelione A, which was assigned based on the analysis of 2D-NMR spectra including COSY, HMQC, and NOESY experiments,[6] while its absolute configuration was not determined.

The remarkable biological properties, unique structural features, and limited availability from natural resources, as well as the necessity of confirming the absolute configuration, have made the ottelione exceptionally intriguing and timely targets for total synthesis. A number of synthetic approaches for ottelione A and B has been reported to date.[7] The first total synthesis of racemic (±)-ottelione A (**1**) and B (**2**) was reported by Mehta and Islam in 2002,[8] which verified their relative stereostructures. In the following year, Mehta and Islam[9] and our groups[10] independently accomplished the first enantioselective total synthesis of naturally occurring (+)-ottelione A (**1**) and (−)-ottelione B (**2**), leading to the establishment of their absolute configurations as depicted in Figure 1. In addition, we also achieved an enantioselective total synthesis of 3-*epi*-ottelione A (**3**),[7f] which represents the earlier proposed formulation of ottelione A. Recently, Clive and Liu reported the elegant total synthesis of (+)-**1** and (−)-**2** in an enantioselective manner.[11] In this paper, we describe the enantioselective total synthesis of ottelione A (**1**), ottelione B (**2**), and 3-*epi*-ottelione A (**3**). In addition, the cell growth inhibition analysis and tubulin polymerization assay of unnatural 3-*epi*-ottelione A (**3**) and its *O*-acetyl derivative **24** along with ottelione A (**1**) are also described.

Results and Discussion

Synthesis of 3-*epi*-ottelione A (3), an earlier proposed stereostructure of ottelione A (1)

Synthetic plan: At the beginning of this project (April 2000), formulation **3** was considered as the most likely stereostructure for ottelione A (**1**); therefore, our initial synthetic efforts were targeted toward structure **3**. Our synthetic plan for 3-*epi*-ottelione A (**3**) is outlined in Scheme 1. The

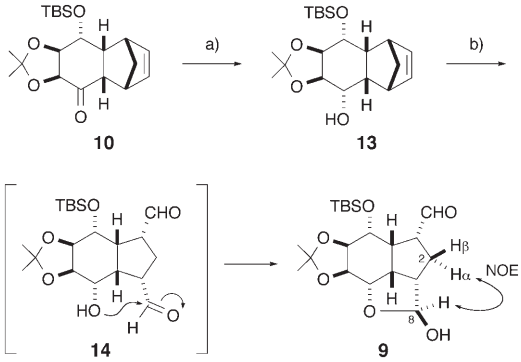


Scheme 1. Synthetic plan for 3-*epi*-ottelione A (**3**). TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

key feature of this plan is the utilization of the highly and appropriately functionalized intermediate **8**, which contains the requisite bicyclic hydrindane core framework possessing the correct stereochemistries at the C3, C3a, and C7a positions as well as the desirable functionalities for elaboration of the target molecule **3**. Intermediate **8** should be accessible from intermediate **9** by epimerization at the C3 position. The 4-methylene-2-cyclohexenone substructure present in molecule **3** was expected to be highly sensitive; therefore, we decided to elaborate this substructure at the final stage of the synthesis. Since the C1 formyl group of **8** is masked as an internal hemiacetal moiety, intermediate **6** would be constructed through the coupling reaction of **8** with the aryllithium generated from bromobenzene derivative **7**. Intermediate **6** would be converted into the target molecule **3** through the advanced key intermediate **5** by sequential functional group manipulation and deprotection or vice versa; the sequence involves base-induced hemiacetal-opening/epimerization at the masked C1 formyl group and subsequent construction of the 4-methylene-2-cyclohexenone substruc-

ture as the crucial steps. Intermediate **9** should in turn be accessed from the known tricyclic compound **10**, which was previously prepared in our laboratories by Diels–Alder cycloaddition between optically active cyclohexenone **11** and cyclopentadiene (**12**).[12]

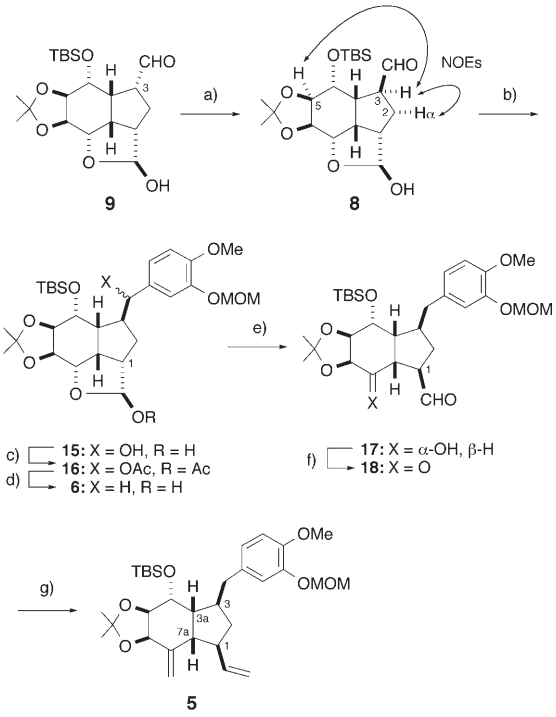
Synthesis of intermediate 9: First, as shown in Scheme 2, we pursued the synthesis of intermediate **9** starting from the known enantiomerically pure tricyclic compound **10**.[12] Thus, stereoselective reduction of the carbonyl group in **10** with $NaBH_4$ provided the expected alcohol **13** in 87% yield as a single stereoisomer. Subsequent Lemieux–Johnson oxidation (OsO_4/$NaIO_4$)[13] of **13** furnished the cyclic hemiacetal **9** in 75% yield through the intermediary dialdehyde **14**. The stereochemistry at the C8 position in **9** was assigned based on NOESY experiments in the 500 MHz ^{1}H NMR spectrum, in which a clear NOE interaction between C8-H and C2-Hα was observed.



Scheme 2. Synthesis of intermediate **9**. a) $NaBH_4$, THF/H_2O 10:1, 0°C, 87%; b) OsO_4, $NaIO_4$, *t*BuOH/THF/H_2O 8:6:3, 0°C→RT, 75%.

Synthesis of intermediate 5: Having obtained intermediate **9**, we next performed the synthesis of intermediate **5** possessing the requisite carbon skeleton and correct stereochemistries at the C1, C3, C3a and C7a positions as shown in Scheme 3. Epimerization at the C3 position of **9** occurred smoothly and cleanly by treatment with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in THF at ambient temperature for 2 h to give the desired β-formyl compound **8** in quantitative yield. The β-disposition of the C3 formyl group in **8** was confirmed by NOESY experiments, which showed clear NOE interactions between C3-H and C5-H, C2-Hα.

The crucial coupling reaction of **8** with the aromatic portion **7** was efficiently achieved by halogen/metal exchange of 4-bromo-1-methoxy-2-(methoxymethoxy)benzene (**7**)[14] with *n*BuLi in THF at −78°C followed by the addition of **8** at the same temperature; the desired coupling product **15** was obtained in quantitative yield as an inseparable mixture of epimeric alcohols (9:1 by 500 MHz ^{1}H NMR). All attempts to directly remove the benzylic hydroxy group from **15** under conventional conditions such as Barton–McCombie deoxygenation [$NaN(SiMe_3)_2$, CS_2, MeI; $(nBu)_3SnH$, AIBN] or Birch reductive deoxygenation (Li metal, liq.

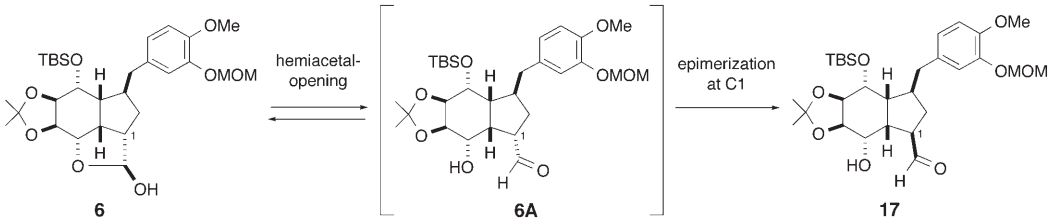


Scheme 3. Synthesis of intermediate **5**. a) DBU, THF, RT, quant.; b) 4-bromo-1-methoxy-2-(methoxymethoxy)benzene (**7**), *n*BuLi, THF, −78°C; at −78°C, add. **8**, quant.; c) Ac_2O, DMAP, pyridine, RT, quant.; d) Li, liq. NH_3, THF, −78°C, 87%; e) DBU, toluene, reflux, 52% (see entry 3 in Table 1); f) Dess–Martin periodinane, CH_2Cl_2, RT, 90%; g) $Ph_3P^+CH_3Br^-$, *t*BuOK, benzene, RT→reflux, 88%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine.

NH_3) were unsuccessful. This was attributed to the presence of reactive hemiacetal function in substrate **15**; therefore, we decided to protect the hydroxy group in the hemiacetal moiety. Thus, acetylation of the hydroxy groups in **15** followed by treatment of the resulting diacetates **16** with a large excess of Li metal (50 equiv) in liquid NH_3/THF at −78°C for 5 min resulted in the formation of the desired deoxygenated lactol **6** in 87% yield in two steps. In Birch reductive deacetoxylation, the best results were obtained with a large excess of Li metal at low temperature (−78°C) in a short time (5 min).

We next examined the base-induced hemiacetal-opening/epimerization reaction of **6** to obtain **17** possessing the requisite stereochemistry at the C1 position. The result summarized in Table 1 deserves some comments. This one-pot two-step reaction via the intermediary **6 A** was best achieved by treatment of **6** with DBU (20 equiv) in refluxing toluene for 1.5 h (entry 3), which provided the desired product **17** in 52% yield along with 40% recovery of the starting material **6**. The choice of the appropriate reaction conditions such as equivalent of DBU and temperature is very crucial in this reaction. By employing lower amounts of DBU (2–10 equiv) (entries 1, 2), a lower yield of **17** (14–25%) was produced and a large amount of the starting material **6** (86–70% yield) was recovered unchanged. When a large excess of DBU (50 equiv) was used (entry 4), only un-

Table 1. Base-induced hemiacetal-opening/epimerization reaction of intermediate **6** leading to intermediate **17**.

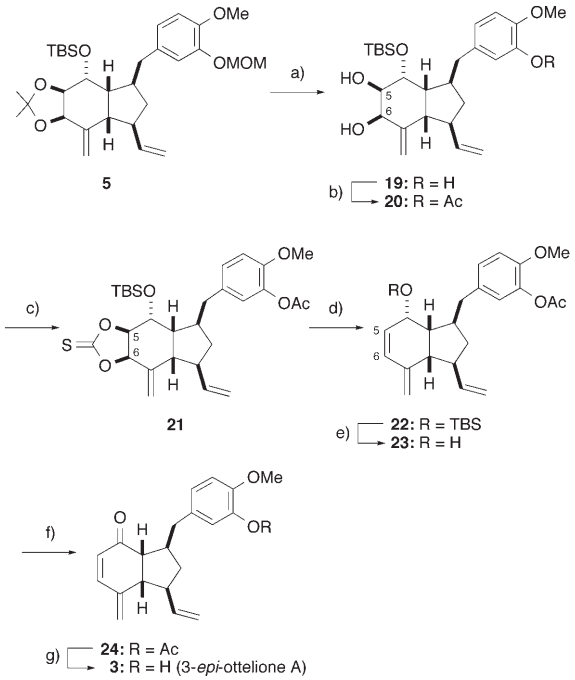


Entry	DBU [equiv]	Solvent	T[a] [°C]	t [h]	Yield [%][b]	
					17	**6**
1	2	toluene	110	10	14	86
2	10	toluene	110	5	25	70
3	20	toluene	110	1.5	52	40
4	50	toluene	110	1.5	decomposition	
5	20	benzene	80	1.5	no reaction	
6	20	xylene	140	1.5	decomposition	

[a] Reflux temperature. [b] Isolated yield.

identified decomposition products were generated in the reaction mixture. In addition, when the reaction was carried out at a lower temperature (80 °C) (entry 5), it did not proceed and substrate **6** was recovered quantitatively. At a higher temperature (140 °C) (entry 6), the complete decomposition of the materials was observed. To continue the synthesis (cf. Scheme 3), compound **17** was further converted to the key intermediate **5** in 79% overall yield via a two-step sequence involving Dess–Martin oxidation followed by twofold Wittig methylenation of the resulting keto-aldehyde **18**.

Completion of synthesis of (+)-3-*epi*-ottelione A (3): Having obtained the key intermediate **5** in an efficient way, we next investigated the synthesis of 3-*epi*-ottelione A (**3**), as shown in Scheme 4, which involves the crucial elaboration of the highly sensitive 4-methylene-2-cyclohexenone substructure. To this end, treatment of **5** with CF_3CO_2H in THF containing H_2O at 0 °C effected simultaneous deprotection of both the acetonide moiety and the MOM group to provide the corresponding triol **19** in 76% yield. Subsequent chemoselective acetylation of the phenolic hydroxy group in **19** afforded the acetate **20** in 90% yield. Installation of the C5–C6 double bond was successfully achieved by employing Corey-Winter's protocol[15] with some modifications to the reaction conditions. Thus, treatment of **20** with thiophosgene (2.0 equiv) in the presence of DMAP (5.0 equiv) followed by exposure of the resulting cyclic thiocarbonate **21** to refluxing triethyl phosphite, resulted in the formation of the requisite diene **22** in 73% yield in two steps. Subsequent selective removal of the TBS group in **22** was successfully attained via a one-pot two-step operation involving treatment with tetra-*n*-butylammonium fluoride (TBAF) followed by chemoselective acetylation of the liberated phenolic hydroxy group; the desired alcohol **23** was produced in 92% yield. Dess–Martin oxidation of **23** furnished dienone **24** possessing the sensitive 4-methylene-2-cyclohexenone substructure in 97% yield. Finally, the targeted 3-*epi*-ottelione A (**3**) was obtained in 98% yield upon deacetylation (K_2CO_3, MeOH, 0 °C) of **24**.



Scheme 4. Synthesis of 3-*epi*-ottelione A (**3**). a) CF_3CO_2H, THF/H_2O 10:1, 0 °C, 76%; b) Ac_2O, 2 M NaOH, *i*PrOH, RT, 90%; c) $CSCl_2$, DMAP, CH_2Cl_2, RT, 96%; d) $(EtO)_3P$, reflux, 68%; e) TBAF, THF, RT; Ac_2O, 92%; f) Dess–Martin periodinane, CH_2Cl_2, RT, 97%; g) K_2CO_3, MeOH, 0 °C, 98%. TBAF = tetra-*n*-butylammonium fluoride.

The structure and stereochemistry of **3**, the earlier proposed stereostructure of ottelione A (**1**), was unambiguously confirmed by extensive spectroscopic analysis including NOESY experiments in the 500 MHz ^{1}H NMR spectra. The selected NOESY correlation of **3** is depicted in Figure 2, wherein clear NOE interactions between H_{3a} and $H_{2\beta}$, H_{7a}, $H_{10\alpha}$, $H_{10\beta}$, between H_{7a} and $H_{2\beta}$, H_8, and between $H_{2\alpha}$ and H_3, H_1 are observed, revealing that both the C1 and C3 substituents are *syn* to the bridgehead protons H_{3a} and H_{7a} in the *cis*-fused hydrindane skeleton. To our disappointment,

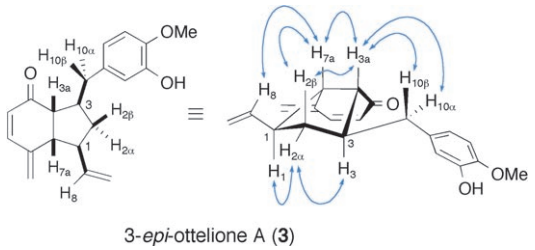
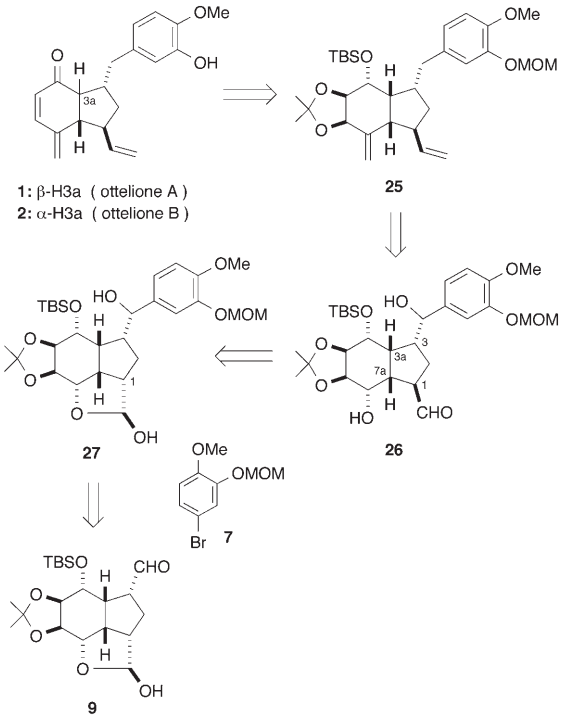


Figure 2. Selected NOESY correlation of 3-*epi*-ottelione A (**3**).

the ^{1}H NMR spectral data of the synthesized compound **3** did not match that of the natural product ottelione A; however, we achieved the first total synthesis of **3** (3-*epi*-ottelione A), the earlier proposed formulation of ottelione A (**1**), in an enantiomerically pure form.[7f] Coincidentally, at the time we completed the projected synthesis of **3**, the first total synthesis of (±)-ottelione A (**1**) and B (**2**) was reported by Mehta and Islam,[8] which verified their relative stereostructures as shown in Figure 1. Consequently, our synthetic efforts were directed toward formulations **1** and **2** (i.e., otteliones A and B). This is the subject of the following section.

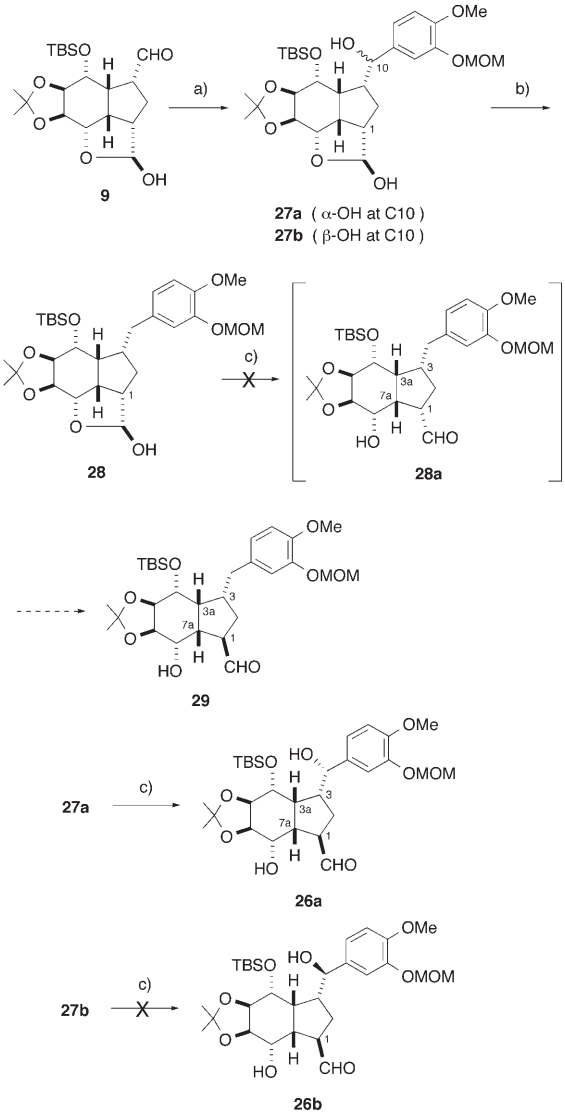
Synthesis of ottelione A (1) and ottelione B (2)

Synthetic plan: Our redesigned synthetic plan for ottelione A (**1**) and B (**2**) is outlined in Scheme 5, based on the synthesis of 3-*epi*-ottelione A (**3**) described above. We envisaged that the highly and appropriately elaborated intermediate **27** would be converted to the target molecules **1** and **2** via the intermediates **26** and **25** by a methodology similar to the synthesis of 3-*epi*-ottelione (**3**) from intermediate **9** (cf. Scheme 1 and two previous sections). Epimerization at the C3a position in ottelione A (**1**) would result in ottelione B (**2**). Intermediate **27** would, in turn, be produced through the coupling reaction of the common intermediate **9** and the aromatic portion **7**.



Scheme 5. Synthetic plan for ottelione A (**1**) and ottelione B (**2**).

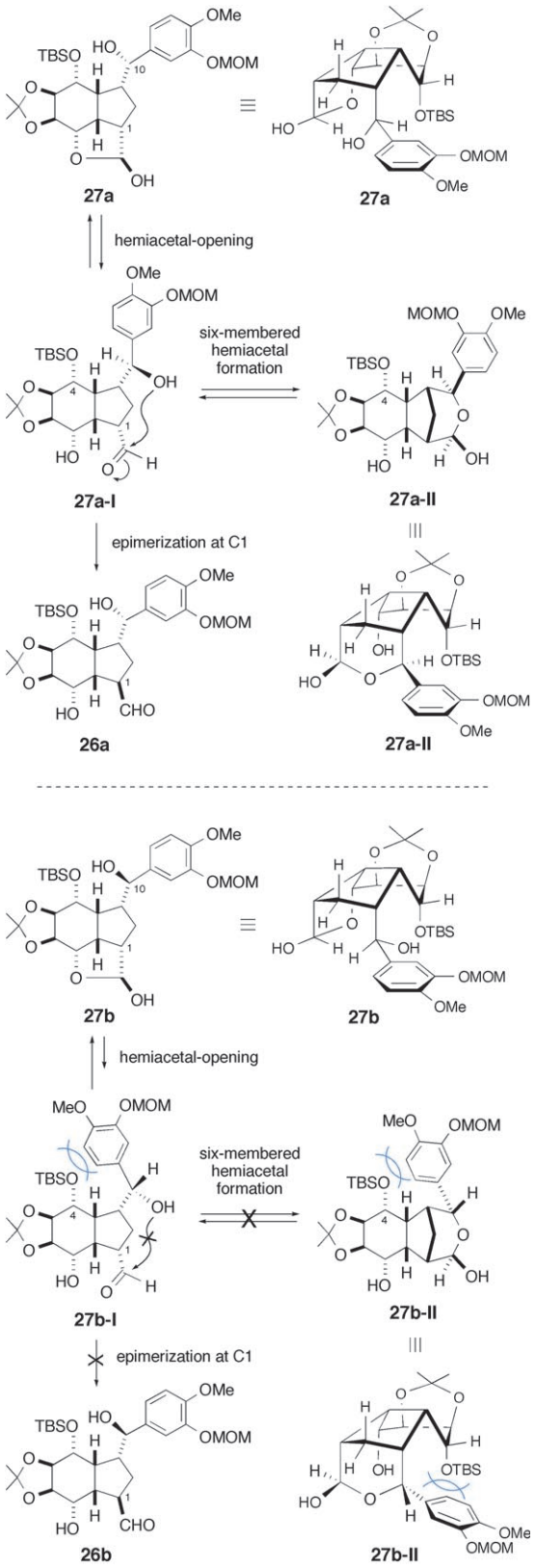
Synthesis of intermediate 26: As shown in Scheme 6, we initially investigated the synthesis of the advanced key intermediate **26a** possessing all four correct stereogenic centers (C1, C3, C3a, and C7a) and the proper functionalities for elaboration of the target molecules **1** and **2**. The coupling reaction of the aldehyde **9** with the aryllithium generated in



Scheme 6. Synthesis of intermediate **26a**. a) 4-bromo-1-methoxy-2-(methoxymethoxy)benzene (**7**), *n*BuLi, THF, −78 °C; at −78 °C, add. **9**, 80 % for **27a**, 20 % for **27b**; b) Li, liq. NH_3, THF, −78 °C, 73 % for **27a**→**28**, 75 % for **27b**→**28**; c) DBU, toluene, reflux, no reaction (recovery of **28**) for **28**→**29**; 30 % (65 % based on recycling four times) for **27a**→**26a** ; no reaction (recovery of **27b**) for **27b**→**26b**.

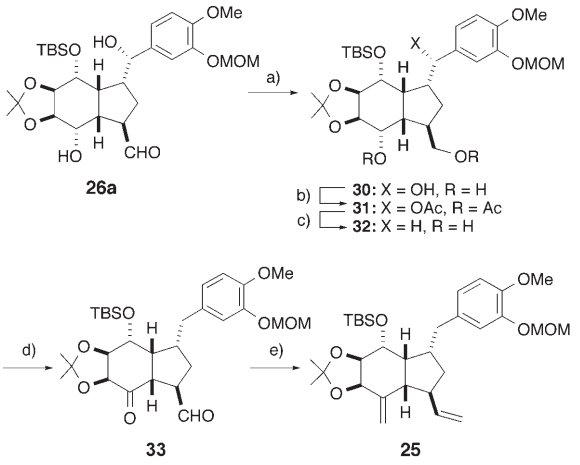
situ from **7** proceeded cleanly and smoothly to furnish the desired products **27a** (80% yield) and **27b** (20% yield) as a mixture of epimeric alcohols separated by column chromatography on silica gel. The stereochemistry at the benzylic C10 position in the coupling products **27a**,**b** was tentatively assigned based on the well-known Felkin-Anh model, while the stereogenic center disappeared at a later stage of the synthesis. The C10 hydroxy group in both **27a** and **27b** was removed under Birch reduction conditions (Li metal, liquid NH_3/THF, −78°C) to obtain the deoxygenated hemiacetal **28** in 73 and 75% yield, respectively. The crucial base-induced hemiacetal-opening/epimerization reaction of **28** leading to the hydroxy aldehyde **29** was attempted next under similar conditions (DBU, toluene, reflux) to those employed in the Section on intermediate **5** (cf. **6**→**17**, Scheme 3 and Table 1); however, the reaction did not proceed and the starting material **28** was recovered unchanged. We reasoned that substrate **28** might be thermodynamically much more stable than the hemiacetal-opened hydroxy aldehyde **28a**. Therefore, we next examined the hemiacetal-opening/epimerization reaction employing hemiacetals **27a**,**b** as the alternative substrates. Thus, in the case of **27a**, the expected hemiacetal-opening/epimerization reaction proceeded under the same conditions (DBU, toluene, reflux, 1.5 h) described above, which resulted in the formation of the desired product **26a** (30% yield) along with the starting material **27a** (60% yield). Since prolonged reaction time caused decomposition of **26a** and/or **27a**, the reaction was terminated when an approximately 1:2 mixture of **26a**/**27a** was generated. After recycling the recovered starting material **27a** four times, we could obtain 65% yield of the desired compound **26a**. On the contrary, the same treatment of the minor product **27b** turned out to be unsuccessful and the starting material was recovered unchanged. Therefore, the projected synthesis was conducted forward using only the major coupling product **27a**.

From these results, it is evident that the stereochemistry of the C10 hydroxy group in substrates **27a**,**b** plays an important role in the hemiacetal-opening/epimerization reaction. The difference in reactivity between **27a** and **27b** is not clear, but can be rationalized by the tentative mechanistic route depicted in Scheme 7. Thus, in the case of **27a**, the formation of six-membered hemiacetal **27a**-II would participate in the equilibrium event between **27a** and **27a**-I;[16] this may bring about an equilibrium shift to **27a**-I, facilitating the production of the desired **26a** upon epimerization at C1 in **27a**-I. On the other hand, in the case of **27b**, the formation of the six-membered hemiacetal **27b**-II would be precluded due to a severe steric interaction between the aromatic ring and the C4-OTBS group in the intermediary **27b**-I; this phenomenon would prohibit the desired production of **26b**.

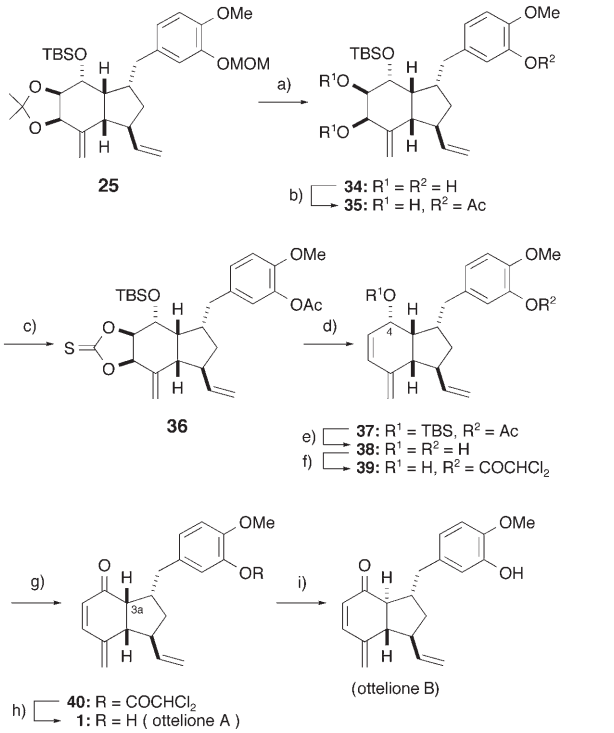


Scheme 7. Tentative mechanistic route in the hemiacetal-opening/epimerization reaction of **27a**,**b**.

Synthesis of intermediate 25: In the next stage, we pursued the synthesis of the key intermediate **25** as shown in Scheme 8. Thus, reduction of the formyl group in compound **26a** with $LiAlH_4$ followed by complete acetylation of the



Scheme 8. Synthesis of intermediate **25**. a) $LiAlH_4$, THF, 0 °C, 96 %; b) Ac_2O, DMAP, pyridine, RT, 95 %; c) Li, liq. NH_3, THF, −78 °C, 98 %; d) Dess–Martin periodinane, CH_2Cl_2, RT, 90 %; e) $Ph_3P^+CH_3Br^-$, *t*BuOK, benzene, RT→reflux, 95 %.



Scheme 9. Synthesis of ottelione A (**1**) and ottelione B (**2**). a) CF_3CO_2H, THF/H_2O 10:1, 0 °C, 86 %; b) Ac_2O, 2 M NaOH, *i*PrOH, RT, 91 %; c) $CSCl_2$, DMAP, CH_2Cl_2, RT, 93 %; d) $(EtO)_3P$, reflux, 78 %; e) TBAF, THF, RT, 83 %; f) $(CHCl_2CO)_2O$, pyridine, CH_2Cl_2, RT, 79 %; g) Dess–Martin periodinane, CH_2Cl_2, RT, 95 %; h) 50 % aqueous $NaHCO_3$/MeCN 1:1, RT, 90 %; i) *t*BuOK, *t*BuOH, RT, 79 % (**1**/**2** 23:77 by 500 MHz ^1H NMR); isolation of **2** by HPLC, 23 %.

three hydroxy groups in the resulting alcohol **30** furnished triacetate **31** in 91 % overall yield in two steps. Subsequent reaction of **31** with a large excess of Li metal (100 equiv) in liquid NH_3/THF at −78 °C resulted in the desired deoxygenated diol **32** in 98 % yield. Simultaneous oxidation of the primary and secondary hydroxy groups in **32** with Dess–Martin periodinane provided the corresponding keto-aldehyde **33** in 90 % yield, which was then subjected to twofold Wittig methylenation to give the requisite key intermediate **25** in 95 % yield.

Completion of the total synthesis of (+)-ottelione A (1) and (−)-ottelione B (2): The final route that led to the completion of the total synthesis of the targeted ottelione A (**1**) and ottelione B (**2**) is summarized in Scheme 9. The key intermediate **25** was initially converted to the triene **37** in four steps in 57 % overall yield by the same reaction sequence described for the synthesis of 3-*epi*-ottelione A (**3**) from diene **5** (cf. **5**→**19**→**20**→**21**→**22**, Scheme 4). Thus, deprotection of both the acetonide moiety and the MOM group in **25** by exposure to CF_3CO_2H/H_2O at 0 °C followed by chemoselective acetylation of the phenolic hydroxy group in the resulting triol **34** afforded acetate **35** in 78 % yield in two steps. Subsequent treatment of the diol **35** with thiophosgene in the presence of DMAP furnished the cyclic thiocarbonate **36** in 93 % yield, which was then heated in triethyl phosphite, resulted in the desired diene **37** in 78 % yield. Treatment of **37** with TBAF effected simultaneous deprotection of the TBS and acetyl groups to give the diol **38** in 83 % yield. Chemoselective dichloroacetylation of the phenolic hydroxy group in **38** furnished the dichloroacetate **39** in 79 % yield. It is noteworthy that selection of this dichloroacetyl group proved useful at a later deprotection stage (cf. **40**→**1**) (vide infra). Finally, compound **39** was efficiently converted to ottelione A (**1**) in 86 % overall yield via a two-step sequence of reactions involving Dess–Martin oxidation of the C4 hydroxy group and removal of the dichloroacetyl group in the resulting dienone **40** by brief exposure to 50 % aqueous $NaHCO_3$ in MeCN at ambient temperature. In the last deprotection step (**40**→**1**), selection of the dichloroacetyl group proved important because this protecting group could be smoothly and cleanly removed under mild conditions without appreciable epimerization at the C3a position. In our preliminary experiment, we had prepared an *O*-acetyl variant of **40** (R = Ac); unfortunately, all attempts to remove the *O*-acetyl group from this compound under standard conditions (e.g., aq. NaOH, aq. KOH in MeOH or THF; K_2CO_3, NaOMe in MeOH) resulted in partial epimerization at the C3a position. We emphasize here that a only small amount of contamination of the C3a-epimerized product [ottelione B (**2**)] should be precluded for accurately measuring the optical rotation of ottelione A (**1**), because the absolute value of $[\alpha]_D$ for ottelione B (vide infra) is much greater than that for ottelione A.

The spectroscopic properties (IR, ^1H and ^{13}C NMR, MS) of the synthetic sample **1** were identical to those of the natural product **1**. Comparison of the optical rotation [synthetic **1**, $[\alpha]_D^{25} = +17.3$ (c=0.55 in $CHCl_3$); natural **1**, $[\alpha]_D^{25} = +14.0$ (c = 0.87 in $CHCl_3$)[17,18] established the absolute configuration of (+)-ottelione A (**1**) to be (1*S*,3*S*,3a*R*,7a*S*) as shown in Scheme 9.

Conversion of ottelione A (**1**) to ottelione B (**2**) was successfully achieved via epimerization at the C3a position by exposure to *t*BuOK in *t*BuOH at room temperature for 2 h, which resulted in a 23:77 mixture of **1** and **2**. Isolation of **2** from this mixture by column chromatography on silica gel was not effective; therefore, we performed the isolation using HPLC (DAICEL CHIRALPAK AD-H) to yield an entirely pure sample of **2**, whose spectroscopic properties (IR, ^{1}H and ^{13}C NMR, MS) were identical to those of natural **2**. The optical rotation of a pure synthetic sample of **2** {$[\alpha]_D^{25} = -333.0$(c=0.18 in $CHCl_3$)} was essentially identical to that of natural **2** (contaminated with a small amount of **1**, **2**/**1** 85:15) {$[\alpha]_D^{25} = -276$ (c = 0.20 in $CHCl_3$)},[17,18] indicating that natural **2** possesses (1*S*,3*S*,3a*S*,7a*S*) absolute configuration as depicted in Scheme 9.

Preliminary biological evaluation of (+)-ottelione A (1), (+)-3-*epi*-ottelione A (3), and (+)-*O*-acetyl-3-*epi*-ottelione A (24)

Biological evaluation of unnatural 3-*epi*-ottelione A (**3**) and *O*-acetyl-3-*epi*-ottelione A (**24**) along with (−)-ottelione A (**1**) is of great interest from the viewpoint of structure–activity relationships. To this end, we used a panel of 39 human cancer cell lines (termed JFCR39) coupled to a drug activity database[19] comparable to the panel developed by the National Cancer Institute.[20] The cell growth inhibition profiles against the JFCR39 (herein termed fingerprints) of more than 60 standard anticancer drugs were compared using COMPARE analysis,[19a,c] which showed that this is an information-rich approach for identifying the molecular target of a new compound, as described by Paull et al.[20a] This system can be used to predict the molecular target or the mode of action of test compounds by assessing the correlation coefficient between the fingerprints mediated by such test compounds and various reference compounds with known modes of action.[21]

The growth inhibitory activity of **1**, **3**, and **24** was evaluated by JFCR39 in the Japanese Foundation for Cancer Research.[19] The number of cell lines and their origin (organ) are as follows: five breast, six central nervous system (brain), one melanoma, five ovary, two kidney, six stomach, and two prostate cancers. Dose-response curves were measured at five different concentrations (10^{-10}–10^{-6} M, one log interval) for each compound, and the concentration causing 50% cell growth inhibition (GI_{50}) was compared with the control. The results are presented in Table 2 as log GI_{50} values. It was evident that the test compounds exhibited extremely potent cytotoxic activity against almost all of the 39 cell lines [log $GI_{50} = -10.0$ (1.0×10^{-10} M)–−6.0 (1.0×10^{-6} M)]. The order of the potency was estimated by MG-MID value (mean value of log GI_{50} over all cell lines tested) to be **1** (−8.44) > **3** (−8.26) = **24** (−8.22). The delta values (the difference in log GI_{50} value of the most sensitive cell and MG-MID value) and the range values (the difference in log GI_{50} values of the most sensitive cell and the least sensitive cell) were 1.52 and 4.00 for **1**, 1.31 and 4.00 for **3**, and 1.32 and 3.55 for **24** (effective value: delta ≥ 0.5 as well as range ≥ 1.0), respectively, indicating that all of these compounds showed pronounced selective cytotoxic activity.

Table 2. Growth inhibition of compounds **1**, **3**, and **24** against a panel of 39 human cancer cell lines.

Origin of cancer	Cell line	log GI_{50}[a] [M] **1**	**3**	**24**
breast	HBC-4	−8.46	−8.39	−8.32
	BSY-1	−10.0[c]	−9.51	−9.40
	HBC-5	−9.74	−8.11	−6.51
	MCF-7	−8.47	−8.16	−8.13
	MDA-MB-231	−9.13	−8.49	−8.47
central nervous system (brain)	U-251	−8.40	−8.42	−8.35
	SF-268	−8.42	−8.43	−8.60
	SF-295	−8.34	−8.66	−8.40
	SF-539	−9.48	−8.95	−9.46
	SNB-75	−8.55	−7.47	−6.62
	SNB-78	−9.36	−8.71	−8.62
colon	HCC2998	8.66	−8.55	−8.66
	KM-12	−9.41	−9.30	−9.33
	HT-29	−6.40	−6.22	−6.42
	HCT-15	−8.46	−8.45	−8.61
	HCT-116	−9.14	−8.30	−8.38
lung	NCI-H23	−8.49	−8.34	−8.28
	NCI-H226	−8.84	−7.49	−6.77
	NCI-H522	−9.67	−9.56[c]	−9.55[c]
	NCI-H460	−8.48	−8.19	−8.13
	A549	−7.55	−7.94	−8.23
	DMS273	−9.56	−8.53	−8.65
	DMS114	−9.40	−8.50	−8.65
melanoma	LOX-IMVI	−9.03	−8.44	−8.75
ovary	OVCAR-3	−9.80	−8.53	−8.53
	OVCAR-4	−8.44	−7.09	−7.17
	OVCAR-5	−8.09	−7.08	−7.25
	OVCAR-8	−8.50	−8.31	−8.42
	SK-OV-3	−8.45	−8.41	−8.45
kidney	RXF-631 L	−7.02	−6.00[b]	−6.71
	ACHN	−6.00[b]	−8.55	−8.35
stomach	St-4	−6.29	−6.00[b]	−6.00[b]
	MKN1	−9.12	−8.71	−8.91
	MKN7	−8.58	8.90	−9.11
	MKN28	−9.14	−9.27	−9.24
	MKN45	−8.26	−7.12	−7.20
	MKN74	−9.41	−9.21	−8.43
prostate	DU-145	−6.00[b]	−8.52	−8.50
	PC-3	−6.00[b]	−9.18	−9.15
MG-MID[d]		−8.44	−8.26	−8.22
delta[e]		1.52	1.31	1.32
range[f]		4.00	3.56	3.55

[a] Log concentration that induces 50% inhibition of cell growth compared to control. [b] The least sensitive cell. [c] The most sensitive cell. [d] Mean value of log GI_{50} over all cell lines tested. [e] The difference in log GI_{50} value of the most sensitive cell and MG-MID value. [f] The difference in log GI_{50} value of the most sensitive cell and the least sensitive cell.

Next, the pattern of differential cytotoxicity was analyzed using COMPARE analysis,[19a,c,21] which indicated that (+)-ottelione A (**1**) was acting via a mechanism similar to vincristine (r = 0.816) that is widely used in cancer chemotherapy as a prominent tubulin polymerization inhibitor. Interestingly, the modes of action for 3-*epi* analogues **3** and **24** did not correlate with that shown by any other anticancer drugs

developed to date (**3**/$r=0.481$, **24**/$r=0.422$), suggesting that these compounds may represent new leads for anticancer agents with a novel action mechanism.

In order to confirm that compounds **1**, **3**, and **24** actually inhibit the polymerization of tubulin, we employed the two-step bioassay for tubulin inhibitors established by the Screening Committee of New Anticancer Agents in Japan.[22] The results summarized in Table 3 clearly show

Table 3. Inhibitory activity of compounds **1**, **3**, and **24** against tubulin polymerization.

	1	**3**	**24**	Vincristine[b]
EC[a] [M]	$\geqslant 10^{-10}$	$>10^{-10}$	$\geqslant 10^{-9}$	$\geqslant 10^{-9}$

[a] Effective concentration that induces inhibition of tubulin polymerization. [b] Positive control as a representative tubulin polymerization inhibitor.

that all of these compounds exhibit potent inhibitory activity against tubulin polymerization. Compound **1** was found to exhibit ≈ 10 times more potent activity compared to vincristine, a reference compound. Furthermore, the potency of 3-*epi* analogues **3** and **24** was similar or superior to that of vincristine. Considering the results obtained by both the COMPARE analysis and tubulin inhibitory assay, 3-*epi* analogues **3** and **24** could be promising candidates or potential lead compounds for the development of novel anticancer agents targeting tubulin, albeit the binding sites are unknown at present.

Conclusion

We initially achieved the total synthesis of (+)-3-*epi*-ottelione A (**3**), the earlier proposed stereostructure of (+)-ottelione A (**1**) starting from the known, readily available tricyclic compound **10**. Subsequently, by applying this approach, we accomplished the total synthesis of (+)-ottelione A (**1**) and (−)-ottelione B (**2**); this synthesis resulted in the establishment of their absolute configurations. Importantly, the routes explored have potential for preparing various types of ottelione analogues in enantiomerically pure forms due to their generality and flexibility. Preliminary biological evaluation of the synthetic (+)-ottelione A (**1**), (+)-3-*epi*-ottelione A (**3**), and (+)-*O*-acetyl-3-*epi*-ottelione A (**24**) revealed that all of the test compounds exhibited significant tumor growth inhibitory activity as well as extremely potent tubulin inhibitory potency. It was evident that unnatural 3-*epi* analogues **3** and **24** displayed a unique tumor growth inhibitory profile. On the basis of the present study, further investigations concerning structure–activity relationships and in vivo antitumor activity are currently under way and will be reported in due course.

Experimental Section

General techniques: All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were 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 following exceptions. THF was freshly distilled from Na metal/benzophenone under argon. Toluene was distilled from Na metal under argon. CH_2Cl_2, benzene, and pyridine were distilled from CaH_2 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. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-500 (500 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si ($\delta=0$) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Copies of ^1H and ^{13}C NMR spectra for all new compounds are shown in the Supporting Information. Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra was measured on a Shimadzu GCMS-QP2010. High-resolution mass (HRMS) spectra was measured on a JEOL MStation JMS-700 mass spectrometer. Elemental analyses were performed with a Perkin Elmer 2400II apparatus.

(1*R*,4*S*,4a*R*,5*R*,6*R*,7*R*,8*S*,8a*S*)-5-*tert*-Butyldimethylsiloxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-methanonaphthalen-8-ol (13): $NaBH_4$ (153 mg, 4.0 mmol) was added to a stirred solution of (1*R*,4*S*,4a*S*,5*R*,6*S*,7*S*,8a*S*)-5-*tert*-butyldimethylsiloxy-6,7-*O*-isopropylidenedioxy-1,4,4a,5,6,7,8,8a-octahydro-*endo*-methanonaphthalen-8-one (**10**)[12] (737 mg, 2.0 mmol) in THF/H_2O 10:1 (22 mL) at 0 °C. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) at 0 °C. The reaction mixture was extracted with Et_2O (2×100 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (2×50 mL) and brine (2×50 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1→4:1) to give **13** (644 mg, 87%) as a white solid. Recrystallization from hexane/Et_2O afforded colorless needles. M.p. 147.0–147.7 °C; $[\alpha]_D^{20}=-25.1$ ($c=0.98$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.10$ (s, 6H), 0.90 (s, 9H), 1.23–1.34 (m, 4H), 1.38–1.49 (m, 4H), 2.58–2.79 (m, 2H), 2.80–3.05 (m, 2H), 3.80–4.30 (m, 4H), 6.03 (s, 1H), 6.09 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.95$, −4.71, 18.0, 23.8, 25.8, 25.9, 26.6, 44.9, 51.7, 78.1, 107.7, 134.5 ppm; IR (KBr): $\tilde{\nu}=3426$, 2934, 2858, 2363, 1630, 1381, 1251, 1207, 1167, 1111, 1064, 898, 862, 837, 777 cm^{-1}; MS (CI): m/z: 367 $[M+H]^+$; elemental analysis calcd (%) for $C_{20}H_{34}O_4Si$: C 65.53, H 9.35; found: C 65.57, H 9.35.

(2*S*,2a*S*,4*R*,4a*S*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-5-*tert*-Butyldimethylsiloxy-2-hydroxy-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan-4-carbaldehyde (9): OsO_4 in *t*BuOH (0.04 M solution, 1.35 mL, 55 mmol) and $NaIO_4$ (467 mg, 2.2 mmol) were added successively to a stirred solution of **13** (200 mg, 0.55 mmol) in *t*BuOH/THF/H_2O 8:6:3 (10 mL) at 0 °C, and the mixture was allowed to warm up to room temperature. After 12 h, the reaction was quenched with 20% aqueous NaS_2O_3 (10 mL), and the resulting mixture was extracted with Et_2O (2×50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2×25 mL) and brine (2×25 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 5:1) to give **9** (163 mg, 75%) as a white solid. Recrystallization from hexane/Et_2O afforded colorless needles. M.p. 120.7–121.5 °C; $[\alpha]_D^{20}=+19.0$ ($c=0.99$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.06$ (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.34 (s, 3H), 1.44 (s, 3H), 2.07–2.15 (m, 1H), 2.18–2.25 (m, 1H), 2.26 (d, 1H, $J=2.3$ Hz), 2.74–2.91 (m, 3H), 2.91–2.97 (m, 1H), 4.17 (dd, 1H, $J=6.7$, 4.5 Hz), 4.23 (s, 1H), 4.46 (dd, 1H, $J=12.2$, 6.7 Hz), 4.47 (dd, 1H, $J=12.2$, 6.7 Hz), 5.27 (d, 1H, $J=2.3$ Hz), 9.93 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.43$, −4.37, 18.2, 24.3, 25.9, 27.0, 30.2, 40.6, 41.9, 52.0, 55.8, 69.4, 73.6,

75.7, 76.0, 103.1, 107.7, 202.9 ppm; IR (KBr): $\tilde{\nu}$ = 3433, 2955, 2928, 2854, 1714, 1469, 1371, 1246, 1221, 1151, 1103, 1057, 1012, 956, 898, 860, 831, 775, 511 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{20}H_{34}O_6Si$: 398.2125, found 398.2124 $[M]^+$.

(2*S*,2a*S*,4*S*,4a*S*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-5-*tert*-Butyldimethylsiloxy-2-hydroxy-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan-4-carbaldehyde (8): DBU (0.50 mL, 3.3 mmol) was added to a stirred solution of **9** (657 mg, 1.6 mmol) in dry THF (20 mL) at room temperature under argon. After 2 h, the mixture was diluted with Et_2O (100 mL) and the organic layer was washed successively with 3% aqueous HCl (2×50 mL), saturated aqueous $NaHCO_3$ (2×50 mL), and brine (50 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **8** (657 mg, quant.) as a white solid. Recrystallization from hexane/CH_2Cl_2 afforded colorless needles. M.p. 108.7–110.0 °C; $[\alpha]_D^{20}$ = −25.0 (*c* = 0.93 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.36 (s, 3H), 1.48 (s, 3H), 1.72–1.79 (m, 1H), 1.95–2.05 (m, 1H), 2.31 (d, 1H, *J* = 2.2 Hz), 2.46 (ddd, 1H, *J* = 12.5, 7.8, 4.6 Hz), 2.59–2.67 (m, 1H), 2.83–2.88 (m, 1H), 3.00–3.02 (m, 1H), 3.89 (dd, 1H, *J* = 7.8, 4.6 Hz), 4.13 (dd, 1H, *J* = 7.8, 6.2 Hz), 4.49 (d, 1H, *J* = 6.2 Hz), 4.56 (d, 1H, *J* = 7.3 Hz), 5.22 (d, 1H, *J* = 2.2 Hz), 9.50 ppm (d, 1H, *J* = 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.51, −4.31, 18.1, 25.5, 25.8, 28.1, 31.4, 42.7, 49.5, 50.3, 51.7, 71.9, 76.4, 76.6, 76.8, 103.3, 107.5, 202.0 ppm; IR (KBr): $\tilde{\nu}$ = 3391, 2937, 2891, 1707, 1471, 1386, 1246, 1219, 1089, 1014, 904, 829, 779, 667 cm^{-1}; MS (CI): *m/z*: 399 $[M+H]^+$; elemental analysis cald (%) for $C_{20}H_{34}O_6Si$: C 60.27, H 8.64; found: C 60.25, H 8.32.

(2*S*,2a*S*,4*S*,4a*R*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-5-*tert*-Butyldimethylsiloxy-4-[1-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl]-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan-2-ol (15): *n*BuLi in *n*hexane (1.55 M solution, 3.10 mL, 4.8 mmol) was added dropwise to a stirred solution of 4-bromo-1-methoxy-2-(methoxymethoxy)benzene (**7**) (1.50 g, 5.2 mmol) in dry THF (50 mL) at −78 °C under argon. After 30 min, a solution of **8** (510 mg, 1.3 mmol) in dry THF (25 mL) was added dropwise to the above mixture at −78 °C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the reaction mixture was extracted with Et_2O (2×100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×30 mL) and brine (2×30 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 2:1→1:1) to give **15** (724 mg, quant.) as an inseparable mixture of two diastereomers (9:1) as a colorless viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.16 (s, 3H), 0.18 (s, 3H), 0.94 (s, 9H), 1.34 (s, 3H), 1.46 (s, 3H), 1.31–1.39 (m, 1H), 1.90–1.94 (m, 1H), 2.12–2.20 (m, 1H), 2.17 (s, 1H), 2.31–2.36 (m, 1H), 2.47 (d, 1H, *J* = 4.4 Hz), 2.54–2.57 (m, 1H), 2.93–2.99 (m, 1H), 3.51 (s, 3H), 3.86 (s, 3H), 3.94 (dd, 1H, *J* = 7.4, 4.1 Hz), 4.25–4.30 (m, 1H), 4.40 (dd, 1H, *J* = 8.4, 2.3 Hz), 4.42 (dd, 1H, *J* = 7.4, 2.3 Hz), 5.01–5.05 (m, 1H), 5.09 (s, 1H), 5.19–5.24 (m, 2H), 6.85 (d, 1H, *J* = 8.4 Hz), 6.92 (dd, 1H, *J* = 8.4, 1.9 Hz), 7.08 ppm (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.07, −3.82, 18.5, 23.7, 26.1, 26.4, 32.7, 36.6, 42.1, 52.1, 52.4, 53.4, 55.9, 56.1, 68.6, 74.9, 76.0, 95.6, 103.6, 107.4, 111.7, 114.9, 120.5, 136.6, 146.7, 149.4 ppm; IR (neat): $\tilde{\nu}$ = 3420, 2934, 2858, 1720, 1608, 1512, 1464, 1381, 1257, 1155, 1078, 1005, 912, 837, 779 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{29}H_{45}O_9Si$: 565.2833, found 565.2831 $[M-H]^+$.

(2*R*,2a*S*,4*S*,4a*R*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-2-Acetoxy-5-*tert*-butyldimethylsiloxy-4-[1-acetoxy-[4-methoxy-3-(methoxymethoxy)phenyl]methyl]-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan (16): $(CH_3CO)_2O$ (1.17 mL, 12 mmol) and 4-dimethylaminopyridine (DMAP) (15.0 mg, 0.12 mmol) were added to a stirred solution of **15** (700 mg, 1.2 mmol) in pyridine (12 mL) at room temperature. After 3 h, the mixture was diluted with Et_2O (120 mL). The organic layer was washed with 3% aqueous HCl (4×30 mL), saturated aqueous $NaHCO_3$ (2×30 mL), and brine (30 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **16** (804 mg, quant.) as a colorless viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.10 (s, 6H), 0.91 (s, 9H), 1.29 (s, 3H), 1.34 (s, 3H), 1.78–1.85 (m, 1H), 2.02 (s, 3H), 2.08 (s, 3H), 2.03–2.07 (m, 1H), 2.10–2.16 (m, 1H), 2.43–2.50 (m, 1H), 2.83–2.92 (m, 2H), 3.50 (s, 3H), 3.83 (t, 1H, *J* = 4.4 Hz), 3.86 (s, 3H), 4.17 (dd, 1H, *J* = 6.9, 4.4 Hz), 4.36 (dd, 1H, *J* = 6.9, 1.9 Hz), 4.44 (dd, 1H, *J* = 6.9, 2.0 Hz), 5.20 (s, 2H), 5.67 (d, 1H, *J* = 6.9 Hz), 5.92 (s, 1H), 6.83 (d, 1H, *J* = 8.3 Hz), 6.88 (dd, 1H, *J* = 8.3, 1.9 Hz), 7.06 ppm (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.82, −4.45, 18.3, 21.3, 21.3, 24.4, 25.9, 26.9, 31.0, 41.7, 49.0, 51.1, 55.9, 56.1. 71.0, 73.9, 75.7, 76.8, 77.2, 79.0, 95.6, 103.7, 107.7, 111.5, 114.5, 120.6, 132.8, 140.6, 149.3, 170.2, 170.3 ppm; IR (neat): $\tilde{\nu}$ = 2934, 1741, 1514, 1464, 1373, 1234, 1155, 1134, 1080, 1005, 837, 777, 733 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{33}H_{50}NaO_{11}Si$: 673.3020, found 673.3022 $[M+Na]^+$.

(2*S*,2a*S*,4*R*,4a*R*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-5-*tert*-Butyldimethylsiloxy-4-[4-methoxy-3-(methyoxymethoxy)benzyl]-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan-2-ol (6): A solution of **16** (420 mg, 0.62 mmol) in dry THF (20 mL) was added dropwise to a stirred solution of Li metal (215 mg, 31 mmol) in liquid NH_3 (40 mL) at −78 °C under argon. After 5 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at the same temperature. The mixture was then allowed to stand at room temperature for 4 h in order to evaporate off excess NH_3. The mixture was extracted with EtOAc (3×100 mL) and the extracts were washed with saturated aqueous $NaHCO_3$ (2×60 mL) and brine (60 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **6** (299 mg, 87%) as a white solid. Recrystallization from hexane/Et_2O afforded colorless needles. M.p. 112.8–113.5 °C; $[\alpha]_D^{20}$ = −36.6 (*c* = 0.77 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.36 (s, 3H), 1.47 (s, 3H), 1.43–1.49 (m, 1H), 1.62 (ddd, 1H, *J* = 13.5, 6.3, 3.0 Hz), 1.90–1.95 (m, 1H), 1.96–2.03 (m, 1H), 2.07 (dd, 1H, *J* = 13.1, 10.4 Hz), 2.15 (d, 1H, *J* = 2.1 Hz), 2.65–2.70 (m, 1H), 2.93–2.99 (m, 1H), 3.34 (dd, 1H, *J* = 13.1, 3.7 Hz), 3.52 (s, 3H), 3.85 (s, 3H), 3.93 (dd, 1H, *J* = 7.7, 4.23–4.27 Hz), 4.25 (m, 1H), 4.46–4.49 (m, 2H), 5.07 (d, 1H, *J* = 2.1 Hz), 5.20 (s, 2H), 6.79 (dd, 1H, *J* = 8.2, 1.9 Hz), 6.80 (d, 1H, *J* = 8.2 Hz), 6.91 ppm (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.50, −4.42, 18.2, 25.2, 25.9, 27.8, 36.8, 41.1, 42.4, 43.8, 49.0, 49.5, 55.9, 56.2, 72.8, 76.3, 76.9, 77.8, 95.7, 103.4, 107.3, 111.7, 117.4, 122.5, 134.6, 146.1, 148.0 ppm; IR (KBr): $\tilde{\nu}$ = 3449, 2955, 1516, 1257, 1132, 1082, 1006, 837, 779 cm^{-1}; MS (EI): *m/z*: 550 $[M]^+$; elemental analysis calcd (%) for $C_{29}H_{46}O_8Si$: C 63.24, H 8.42; found: C 63.39, H 8.55.

(1*R*,3*R*,3a*R*,4*R*,5*R*,6*R*,7*S*,7a*R*)-4-*tert*-Butyldimethylsiloxy-7-hydroxy-5,6-*O*-isopropylidenedioxy-3-[4-methoxy-3-(methoxymethoxy)benzyl]octahydroinden-1-carbaldehyde (17): DBU (2.6 mL, 17 mmol) was added to a stirred solution of **6** (480 mg, 0.87 mmol) in dry toluene (10 mL) at room temperature under argon. The mixture was heated at reflux for 1.5 h. After cooling, the mixture was directly subjected to column chromatography on silica gel eluting with EtOAc in order to remove excess DBU. The fractions containing **17** and starting material **6** were collected and then concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 4:1) to give less polar **17** (250 mg, 52%, colorless viscous liquid) and more polar starting material **6** (192 mg, 40%). **17**: $[\alpha]_D^{20}$ = +7.09 (*c* = 0.92 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.18 (s, 6H), 0.93 (s, 9H), 1.35 (s, 3H), 1.46 (s, 3H), 1.32–1.40 (m, 1H), 1.96–2.03 (m, 1H), 2.13–2.19 (m, 1H), 2.26–2.35 (m, 1H), 2.40 (dd, 1H, *J* = 13.4, 9.5 Hz), 2.66–2.73 (m, 1H), 2.85 (dd, 1H, *J* = 13.4, 9.5 Hz), 3.04–3.12 (m, 1H), 3.50 (s, 3H), 3.86 (s, 3H), 3.89 (ddd, 1H, *J* = 12.5, 5.0, 2.9 Hz), 4.01–4.04 (m, 1H), 4.20 (d, 1H, *J* = 12.5 Hz), 4.33 (dd, 1H, *J* = 7.1, 2.8 Hz), 4.53 (dd, 1H, *J* = 7.1, 2.9 Hz), 5.20 (s, 2H), 6.76 (dd, 1H, *J* = 8.2, 1.9 Hz), 6.81 (d, 1H, *J* = 8.2 Hz), 6.97 (d, 1H, *J* = 1.9 Hz), 9.73 ppm (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.33, −3.85, 18.0, 23.6, 25.7, 26.2, 32.9, 38.5, 40.0, 41.4, 41.7, 52.3, 55.9, 56.1, 67.0, 69.8, 75.5, 76.3, 95.6, 108.3, 111.7, 117.1, 122.5, 132.9, 146.5, 148.2, 203.1 ppm; IR (neat): $\tilde{\nu}$ = 3418, 2932, 1722, 1514, 1263, 1157, 1026, 839 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{29}H_{46}O_8Si$: 550.2962, found 550.2939 $[M]^+$.

(1*R*,3*R*,3a*R*,4*R*,5*R*,6*S*,7a*R*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-3-[4-methoxy-3-(methoxymethoxy)benzyl]-7-oxooctahydroinden-1-carbaldehyde (18): Dess–Martin periodinane (865 mg, 2.0 mmol) was added to a stirred solution of **17** (375 mg, 0.68 mmol) in dry CH_2Cl_2 (7 mL) at room temperature. After 1 h, the reaction was quenched with

10% aqueous $Na_2S_2O_3$ (3 mL), and the resulting mixture was extracted with EtO_2 (2×50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 3:1) to give **18** (336 mg, 90%) as a colorless viscous liquid. $[\alpha]_D^{20}=+17.8$ ($c=1.19$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.03$ (s, 3H), 0.04 (s, 3H), 0.82 (s, 9H), 1.34 (s, 3H), 1.30–1.39 (m, 1H), 1.57 (s, 3H), 1.95–2.02 (m, 1H), 2.24–2.33 (m, 1H), 2.58 (dd, 1H, $J=13.5$, 8.2 Hz), 2.70 (dd, 1H, $J=13.5$, 6.7 Hz), 2.85 (ddd, 1H, $J=11.8$, 7.9, 1.7 Hz), 2.99–3.07 (m, 1H), 3.42 (dd, 1H, $J=11.8$, 10.4 Hz), 3.51 (s, 3H), 3.65 (dd, 1H, $J=3.5$, 1.7 Hz), 3.86 (s, 3H), 4.26 (d, 1H, $J=7.4$ Hz), 4.41 (dd, 1H, $J=7.4$, 3.5 Hz), 5.21 (s, 2H), 6.75 (dd, 1H, $J=8.2$, 1.9 Hz), 6.82 (d, 1H, $J=8.2$ Hz), 6.96 (d, 1H, $J=1.9$ Hz), 9.82 ppm (d, 1H, $J=1.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.67$, −4.48, 17.8, 23.9, 25.5, 26.1, 33.0, 40.5, 42.7, 46.4, 46.5, 53.2, 56.0, 56.1, 69.3, 76.77, 77.3, 80.5, 95.6, 111.8, 112.0, 117.0, 122.5, 132.9, 146.6, 148.2, 202.5, 206.0 ppm; IR (neat): $\tilde{\nu}=2932$, 1728, 1512, 1466, 1383, 1261, 1209, 1157, 1076, 1006, 839, 777 cm^{-1}; HRMS (EI): m/z: calcd for $C_{29}H_{44}O_8Si$: 548.2805, found 548.2806 $[M]^+$.

(1*S*,3*R*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-3-[4-methoxy-3-(methoxymethoxy)benzyl]-7-mehtylene-1-(vinyl)octahydroindene (5): Wittig reagent ($Ph_3P=CH_2$) in benzene solution was first prepared as follows: a suspension of $Ph_3P^+CH_3Br^-$ (1.0 g, 2.8 mmol) and *t*BuOK (314 mg, 2.8 mmol) in dry benzene (6 mL) were heated at reflux for 4 h under argon, and the solution was cooled to room temperature. A solution of the Wittig reagent in benzene (1.0 mL, 0.47 mmol) was added very slowly to a stirred solution of **18** (257 mg, 0.47 mmol) in dry benzene (20 mL) at room temperature under argon. After the first methylenation of the C1-formyl group was completed (monitored by TLC), a solution of the Wittig reagent in benzene (4 mL, 1.9 mmol) was added once again and the resulting mixture was heated under reflux for 30 min to pursue the second methylenation of the C7-carbonyl group. After cooling, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2× 50 mL). The organic layer was washed with brine (2×20 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 20:1) to give **5** (224 mg, 88%) as a colorless viscous liquid. $[\alpha]_D^{20}=+9.75$ ($c=0.77$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.03$ (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.08–1.19 (m, 1H), 1.35 (s, 3H), 1.49 (s, 3H), 1.78–1.84 (m, 1H), 2.18–2.26 (m, 1H), 2.26–2.32 (m, 1H), 2.45 (dd, 1H, $J=13.4$, 8.9 Hz), 2.46–2.54 (m, 1H), 2.61–2.68 (m, 1H), 2.78 (dd, 1H, $J=13.4$, 5.5 Hz), 3.50 (s, 3H), 3.64–3.67 (m, 1H), 3.85 (s, 3H), 4.18 (dd, 1H, $J=7.4$, 3.0 Hz), 4.61 (d, 1H, $J=7.4$ Hz), 4.94 (dd, 1H, $J=10.3$, 1.0 Hz), 5.00–5.08 (m, 3H), 5.18–5.23 (m, 2H), 5.81 (ddd, 1H, $J=17.4$, 10.3, 7.3 Hz), 6.77 (dd, 1H, $J=8.2$, 1.9 Hz), 6.80 (d, 1H, $J=8.2$ Hz), 6.97 ppm (d, 1H, $J=1.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.73$, −4.37, 17.9, 24.0, 25.6, 26.3, 40.5, 41.0, 41.1, 42.8, 45.0, 48.3, 55.9, 56.1, 70.2, 78.3, 79.1, 95.6, 108.7, 111.6, 112.2, 113.6, 117.2, 122.5, 134.1, 143.0, 145.6, 146.3, 147.8 ppm; IR (neat): $\tilde{\nu}=2928$, 2856, 1512, 1462, 1379, 1261, 1209, 1155, 1080, 1030, 902, 837, 810, 775 cm^{-1}; HRMS (EI): m/z: calcd for $C_{31}H_{48}O_6Si$: 544.3220, found 544.3224 $[M]^+$.

(1*S*,3*R*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-4-*tert*-Butyldimethylsiloxy-3-(3-hydroxy-4-methoxybenzyl)-7-methylene-1-(vinyl)octahydroinden-5,6-diol (19): A solution of CF_3CO_2H/H_2O 10:1 (11 mL) was added to a stirred solution of **5** (230 mg, 0.42 mmol) in THF (1 mL) at 0°C. After 10 min, the mixture was neutralized with 6 M NaOH and then extracted with EtOAc (3× 40 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (2×20 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 3:1) to give **19** (148 mg, 76%) as a colorless viscous liquid. $[\alpha]_D^{20}=+15.1$ ($c=0.93$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.08$ (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.14 (ddd, 1H, $J=13.1$, 10.1, 6.9 Hz), 1.70 (d, 1H, $J=5.9$ Hz), 1.91 (d, 1H, $J=7.4$ Hz), 2.06–2.15 (m, 2H), 2.35–2.43 (m, 1H), 2.47–2.60 (m, 3H), 2.73–2.82 (m, 1H), 3.72–3.75 (m, 1H), 3.81–3.85 (m, 1H), 3.86 (s, 3H), 4.61–4.65 (m, 1H), 4.87 (d, 1H, $J=17.0$ Hz), 4.93 (d, 1H, $J=10.2$ Hz), 4.99 (s, 1H), 5.18–5.20 (m, 1H), 5.52 (s, 1H), 5.57 (ddd, 1H, $J=17.0$, 10.2, 7.9 Hz), 6.62 (dd, 1H, $J=8.0$, 1.8 Hz), 6.73 (d, 1H, $J=1.8$ Hz), 6.74 ppm (d, 1H, $J=8.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.78$, −4.43, 17.8, 25.8, 39.5, 39.8, 43.1, 45.7, 48.9, 52.6, 55.9, 68.1, 74.1, 75.7, 110.5, 111.4, 114.2, 114.9, 120.1, 134.6, 141.7, 144.7, 145.3, 145.4 ppm; IR (neat): $\tilde{\nu}=$ 3429, 2930, 2856, 1591, 1512, 1442, 1273, 1076, 875, 835, 775, 505, 430, 407 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{26}H_{40}NaO_5Si$: 483.2543, found, 483.2546 $[M+Na]^+$.

(1*S*,3*R*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-3-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-7-methylene-1-(vinyl)octahydroinden-5,6-diol (20): 2 M NaOH (0.42 mL, 0.84 mmol) and $(CH_3CO)_2O$ (79 μL, 0.84 mmol) were added dropwise to a stirred solution of **19** (140 mg, 0.30 mmol) in 2-propanol (3.5 mL) at room temperature. After 30 min, the mixture was diluted with EtOAc (50 mL). The organic layer was washed with H_2O (2× 15 mL) and brine (15 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc 2:1) to give **20** (138 mg, 90%) as a colorless viscous liquid. $[\alpha]_D^{20}=+6.16$ ($c=0.97$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.04$ (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.14 (ddd, 1H, $J=$ 12.9, 10.3, 7.3 Hz), 1.94–1.99 (m, 2H), 2.08–2.14 (m, 1H), 2.14–2.18 (m, 1H), 2.29 (s, 3H), 2.31–2.39 (m, 1H), 2.46–2.54 (m, 2H), 2.67 (dd, 1H, $J=13.5$, 6.7 Hz), 2.72–2.81 (m, 1H), 3.58–3.62 (m, 1H), 3.79–3.84 (s, 3H), 3.82 (m, 1H), 4.56–4.60 (m, 1H), 4.87 (d, 1H, $J=17.1$ Hz), 4.93 (d, 1H, $J=10.2$ Hz), 4.96 (s, 1H), 5.18–5.22 (m, 1H), 5.56 (ddd, 1H, $J=17.1$, 10.2, 7.9 Hz), 6.84 (d, 1H, $J=2.1$ Hz), 6.87 (d, 1H, $J=8.3$ Hz), 6.98 ppm (dd, 1H, $J=2.1$, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.90$, −4.40, 17.8, 20.7, 25.7, 39.7, 39.9, 42.5, 45.2, 48.9, 52.5, 55.9, 68.9, 74.1, 75.5, 111.3, 112.3, 114.3, 123.3, 126.9, 134.1, 139.3, 141.5, 145.5, 149.1, 169.3 ppm; IR (neat): $\tilde{\nu}=3452$, 2930, 2856, 1768, 1639, 1512, 1460, 1369, 1263, 1205, 1122, 1066, 1018, 902, 835, 775, 408 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{28}H_{42}NaO_6Si$: 525.2648, found, 525.2634 $[M+Na]^+$.

(3a*R*,4*R*,4a*R*,5*R*,7*S*,7a*S*)-5-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-8-methylene-7-(vinyl)octahydroindeno[5,6-*d*,1,3]dioxol-2-thione (21): A solution of $CSCl_2$ (50 μL, 0.66 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise to a stirred solution of **20** (165 mg, 0.33 mmol) in dry CH_2Cl_2 (6 mL) containing DMAP (200 mg, 1.7 mmol) at room temperature. After 1 h, silica gel (2.0 g) was added to the reaction mixture, and the solvent was carefully evaporated off in vacuo. The resulting solid was charged on the top of a silica gel column chromatography, and elution with hexane/EtOAc 10:1 gave **21** (172 mg 96%) as a colorless viscous liquid. $[\alpha]_D^{20}=+5.04$ ($c=0.91$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.01$ (s, 3H), 0.02 (s, 3H), 0.81 (s, 9H), 1.15–2.24 (m, 1H), 1.87–1.94 (m, 1H), 2.11–2.16 (m, 1H), 2.16–2.24 (m, 1H), 2.31 (s, 3H), 2.48–2.55 (m, 1H), 2.57 (d, 1H, $J=18.3$, 8.0 Hz), 2.61–2.72 (m, 2H), 3.66–3.70 (m, 1H), 3.81 (s, 3H), 4.81 (dd, 1H, $J=8.6$, 3.2 Hz), 5.00 (d, 1H, $J=10.2$ Hz), 5.07 (d, 1H, $J=17.2$ Hz), 5.19 (d, 1H, $J=2.5$ Hz), 5.28 (d, 1H, $J=8.6$ Hz), 5.32 (d, 1H, $J=2.5$ Hz), 5.78 (ddd, 1H, $J=17.2$, 7.6, 10.2 Hz), 6.82 (d, 1H, $J=2.1$ Hz), 6.90 (d, 1H, $J=8.3$ Hz), 6.97 ppm (dd, 1H, $J=8.3$, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.78$, −4.69, 17.8, 20.7, 25.5, 40.4, 40.5, 41.1, 44.4, 48.8, 56.0, 68.0, 77.2, 81.9, 85.5, 112.5, 114.6, 116.7, 123.2, 126.9, 133.2, 139.6, 140.6, 141.7, 149.5, 168.9, 191.0 ppm; IR (neat): $\tilde{\nu}=2930$, 2856, 1768, 1512, 1460, 1367, 1329, 1269, 1203, 1093, 995, 916, 833, 777 cm^{-1}; HRMS (EI): m/z: calcd for $C_{29}H_{40}O_6SSi$: 544.2315, found 544.2303 $[M]^+$.

(1*S*,3*R*,3a*R*,4*S*,7a*S*)-3-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroindene (22): A solution of **21** (153 mg, 0.28 mmol) in $(EtO)_3P$ (20 mL) was heated at reflux for 2 h under argon. After cooling, excess $(EtO)_3P$ was removed through short column chromatography eluting with hexane. The combined fractions were concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/EtOAc 100:1) to give **21** (89.0 mg, 68%) as a colorless viscous liquid. $[\alpha]_D^{20}=+103.3$ ($c=1.06$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.04$ (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.15 (ddd, 1H, $J=13.1$, 8.9, 5.7 Hz), 1.98–2.02 (m, 1H), 2.09 (dt, 1H, $J=$ 13.1, 8.2 Hz), 2.26 (dd, 1H, $J=13.5$, 7.6 Hz), 2.30 (s, 3H), 2.46–2.54 (m, 2H), 2.66–2.75 (m, 1H), 2.71 (dd, 1H, $J=13.5$, 8.3 Hz), 3.80 (s, 3H), 4.06 (t, 1H, $J=5.0$ Hz), 4.81 (s, 1H), 4.88 (d, 1H, $J=17.0$ Hz), 4.94 (d, 1H, $J=10.2$ Hz), 4.99 (s, 1H), 5.65–5.73 (m, 2H), 6.09 (d, 1H, $J=9.8$ Hz), 6.85 (d, 1H, $J=2.1$ Hz), 6.86 (d, 1H, $J=8.3$ Hz), 6.99 ppm (dd, 1H, $J=$ 8.3, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.80$, −4.05, 18.0, 20.6,

25.8, 38.8, 40.4, 42.4, 47.1, 47.1, 50.0, 55.9, 66.6, 112.2, 114.1, 114.7, 123.1, 126.9, 129.8, 130.1, 134.7, 139.4, 142.1, 143.1, 149.0, 169.0 ppm; IR (neat): $\tilde{\nu}$ = 2928, 2854, 1770, 1512, 1460, 1367, 1265, 1201, 1124, 1028, 885, 835, 773, 432, 414 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{28}H_{41}O_4Si$: 469.2774, found 469.2771 $[M+H]^+$.

(1*S*,3*R*,3a*R*,4*S*,7a*S*)-3-(Acetoxy-4-methoxybenzyl)-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroinden-4-ol (23): Tetra-*n*-butylammonium fluoride (TBAF) in THF (1 M solution, 0.90 mL, 0.90 mmol) was added to a stirred solution of **22** (105 mg, 0.22 mmol) in THF (5 mL) at room temperature. After 16 h, $(CH_3CO)_2O$ (62 μL, 0.66 mmol) was added very slowly to the reaction mixture. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), and the resulting mixture was extracted with EtOAc (2×50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration of solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 4:1) to give **23** (73 mg, 92%) as a colorless viscous liquid. $[\alpha]_D^{20}$ = +61.8 (*c* = 0.78 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18–1.35 (m, 2H), 2.02–2.06 (m, 1H), 2.15–2.22 (m, 1H), 2.30 (s, 3H), 2.50–2.59 (m, 2H), 2.60–2.69 (m, 3H), 3.80 (s, 3H), 4.03 (t, 1H, *J* = 5.1 Hz), 4.89 (s, 1H), 4.91 (d, 1H, *J* = 17.1 Hz), 4.96 (d, 1H, *J* = 10.2 Hz), 5.04 (s, 1H), 5.68 (ddd, 1H, *J* = 17.1, 10.2, 7.8 Hz), 5.84 (dd, 1H, *J* = 9.8, 5.1 Hz), 6.18 (d, 1H, *J* = 9.8 Hz), 6.87 (d, 1H, *J* = 8.3 Hz), 6.90 (d, 1H, *J* = 2.1 Hz), 7.02 ppm (dd, 1H, *J* = 8.3, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 38.9, 40.3, 42.4, 46.7, 46.7, 50.7, 55.9, 65.7, 112.2, 114.6, 116.0, 123.1, 127.0, 128.5, 131.4, 134.2, 139.5, 141.4, 142.8, 149.2, 169.1 ppm; IR (neat): $\tilde{\nu}$ = 3516, 1766, 1639, 1512, 1442, 1369, 1267, 1205, 1122, 1014, 904, 810 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{22}H_{26}O_4$: 354.1831, found 354.1843 $[M]^+$.

(1*S*,3*R*,3a*R*,7a*S*)-3-(3-Acetoxy-4-methoxybenzyl)-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroinden-4-one (24): Dess–Martin periodinane (81.0 mg, 0.51 mmol) was added in small portions to a stirred solution of **23** (90.0 mg, 0.25 mmol) in dry CH_2Cl_2 (6 mL) at room temperature. After 30 min, the reaction was quenched with 20% aqueous $Na_2S_2O_3$ (1.5 mL), and the mixture was extracted with EtOAc (2×25 mL). The combined extracts were washed with brine (2×15 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 5:1) to give **24** (74.9 mg, 84%) as a white cloudy oil. $[\alpha]_D^{20}$ = +18.0 (*c* = 0.67 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (ddd, 1H, *J* = 13.0, 10.6, 7.5 Hz), 1.99 (dt, 1H, *J* = 13.0, 7.7 Hz), 2.24 (m, 1H), 2.30 (s, 3H), 2.57 (dd, 1H, *J* = 8.2, 3.6 Hz), 2.61 (dd, 1H, *J* = 13.9, 8.6 Hz), 2.72 (dd, 1H, *J* = 10.6, 8.2 Hz), 2.84 (dd, 1H, *J* = 13.0, 7.0 Hz), 2.90–2.99 (m, 1H), 3.80 (s, 3H), 4.87 (d, 1H, *J* = 17.0 Hz), 5.00 (d, 1H, *J* = 10.2 Hz), 5.21 (s, 1H), 5.36 (s, 1H), 5.62 (ddd, 1H, *J* = 17.0, 10.2, 8.1 Hz), 5.90 (d, 1H, *J* = 9.4 Hz), 6.88 (d, 1H, *J* = 8.3 Hz), 6.92 (d, 1H, *J* = 2.1 Hz), 6.95 (d, 1H, *J* = 9.4 Hz), 7.08 ppm (dd, 1H, *J* = 8.3, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 37.6, 41.2, 41.7, 48.7, 50.2, 53.7, 55.9, 112.3, 116.0, 121.6, 123.4, 126.5, 133.2, 139.5, 140.3, 140.5, 145.7, 149.4, 169.1, 199.7, 127.1 ppm; IR (neat): $\tilde{\nu}$ = 2934, 1766, 1664, 1581, 1512, 1442, 1369, 1267, 1203, 1124, 1028, 906, 812, 779 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{22}H_{24}O_4$: 352.1675, found 352.1674 $[M]^+$.

(1*S*,3*R*,3a*R*,7a*S*)-3-(3-Hydroxy-4-methoxybenzyl)-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroinden-4-one (3) (3-*epi*-ottelione A): K_2CO_3 (29.0 mg, 0.21 mmol) was added in small portions to a stirred solution of **24** (74.0 mg, 0.21 mmol) in MeOH (4 mL) at 0°C. After 30 min, the mixture was diluted with EtOAc (30 mL). The organic layer was washed successively with 3% aqueous HCl (2×6 mL), saturated aqueous $NaHCO_3$ (2×6 mL) and brine (3 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane/EtOAc 4:1) to give **3** (63.8 mg, 98%) as a white cloudy oil. $[\alpha]_D^{20}$ = +15.6 (*c* = 0.32 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (ddd, 1H, *J* = 17.7, 10.3, 7.4 Hz), 1.98 (dt, 1H, *J* = 13.1, 7.8 Hz), 2.19–2.28 (m, 1H), 2.54–2.60 (m, 2H), 2.73 (dd, 1H, *J* = 10.6, 8.4 Hz), 2.79 (dd, 1H, *J* = 13.7, 7.1 Hz), 2.90–2.98 (m, 1H), 3.85 (s, 3H), 4.87 (d, 1H, *J* = 17.0 Hz), 4.99 (d, 1H, *J* = 10.2 Hz), 5.21 (s, 1H), 5.36 (s, 1H), 5.53 (s, 1H), 5.64 (ddd, 1H, *J* = 17.0, 10.2, 8.1 Hz), 5.88–5.92 (m, 1H), 6.73 (dd, 1H, *J* = 8.1, 1.9 Hz), 6.77 (d, 1H, *J* = 8.1 Hz), 6.81 (d, 1H, *J* = 1.9 Hz), 6.94 ppm (d, 1H, *J* = 9.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.5, 41.3, 41.9, 48.7, 50.2, 53.7, 56.0, 110.6, 115.4, 115.9, 120.3, 121.5, 126.5, 133.9, 140.5, 140.7, 144.9, 145.3, 145.6, 199.8 ppm; IR (neat): $\tilde{\nu}$ = 3423, 2920, 1655, 1589, 1510, 1440, 1273, 1234, 1130, 1028, 912, 804, 760 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{20}H_{22}O_3$: 310.1569, found 310.1565 $[M]^+$.

(2*S*,2a*S*,4*R*,4a*R*,5*R*,6*R*,7*R*,7a*S*,7b*R*)-5-*tert*-Butyldimethylsiloxy-4-[1-hydroxy-[4-methoxy-3-(methoxymethoxy)phenyl]methyl]-6,7-(*O*-isopropylidenedioxy)decahydroindeno[7,1-*bc*]furan-2-ol (27a,b): *n*BuLi in *n*hexane (1.55 M solution, 4.50 mL, 7.0 mmol) was added dropwise to a stirred solution of 4-bromo-1-methoxy-2-(methoxymethoxy)benzene (**7**) (2.30 g, 7.7 mmol) in dry THF (40 mL) at −78°C under argon. After 1 h, a solution of **9** (930 mg, 2.3 mmol) in dry THF (30 mL) was added to the above mixture at −78°C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with Et_2O (2×100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×30 mL) and brine (30 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 2:1→1:1) to give **27a** (1.06 g, 80%, more polar) and **27b** (263 mg, 20%, less polar).

27a: colorless oil; $[\alpha]_D^{20}$ = +20.1 (*c* = 0.74 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17 (s, 3H), 0.24 (s, 3H), 0.95 (s, 9H), 1.26 (s, 6H), 1.81 (br s, 1H), 1.88 (br s, 1H), 1.98–2.08 (m, 1H), 2.27 (br s, 1H), 2.29 (d, 1H, *J* = 2.4 Hz), 2.47–2.56 (m, 1H), 2.76–2.87 (m, 2H), 3.51 (s, 3H), 3.88 (s, 3H), 3.99 (t, 1H, *J* = 3.4 Hz), 4.20–4.25 (m, 1H), 4.42–4.49 (m, 1H), 4.47 (dd, 1H, *J* = 7.1, 1.6 Hz), 4.82–4.89 (m, 1H), 5.23 (s, 2H), 5.27 (d, 1H, *J* = 2.5 Hz), 6.88 (d, 1H, *J* = 8.3 Hz), 7.03 (dd, 1H, *J* = 8.3, 1.9 Hz), 7.22 ppm (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.07, −3.82, 18.5, 23.7, 26.1, 26.4, 32.7, 36.6, 42.1, 52.1, 52.4, 53.4, 55.9, 56.1, 68.6, 73.9, 74.9, 76.0, 95.6, 103.6, 107.4, 111.7, 114.9, 120.5, 136.6, 146.7, 149.4 ppm; IR (neat): $\tilde{\nu}$ = 3423, 2932, 2856, 1606, 1510, 1464, 1385, 1259, 1211, 1155, 1132, 1080, 1012, 868, 835, 775 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{29}H_{46}O_9Si$: 566.2911, found 566.2904 $[M]^+$.

27b: colorless oil; $[\alpha]_D^{20}$ = +12.5 (*c* = 0.74 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.20 (s, 3H), 0.24 (s, 3H), 0.97 (s, 9H), 1.26 (s, 3H), 1.36–1.44 (m, 1H), 1.44 (s, 3H), 1.67–1.78 (m, 1H), 1.77 (m, 1H), 2.15–2.18 (m, 1H), 2.36–2.40 (m, 1H), 2.51–2.58 (m, 1H), 2.63–2.72 (m, 1H), 2.84–2.93 (m, 1H), 3.51 (s, 3H), 3.84–3.90 (m, 3H), 4.36 (m, 1H), 4.48 (d, 1H, *J* = 7.0 Hz), 4.54 (d, 1H, *J* = 6.4 Hz), 4.55–4.60 (m, 1H), 4.86 (d, 1H, *J* = 10.7 Hz), 5.18 (s, 1H), 5.21 (s, 2H), 6.87 (d, 1H, *J* = 8.3 Hz), 6.97 (d, 1H, *J* = 7.7 Hz), 7.19 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −3.81, −3.66, 18.5, 23.7, 25.8, 26.2, 26.5, 32.6, 36.4, 42.0, 52.6, 53.1, 68.3, 72.4, 73.8, 74.5, 75.1, 95.6, 103.8, 107.5, 111.6, 114.8, 120.0, 137.6, 146.4, 149.3 ppm; IR (neat): $\tilde{\nu}$ = 3435, 2934, 1510, 1464, 1383, 1261, 1157, 1078, 1049, 1006, 868, 835, 775 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{29}H_{46}O_9Si$: 566.2911, found 566.2914 $[M]^+$.

(1*R*,3*R*,3a*R*,4*R*,5*R*,6*R*,7*S*,7a*S*)-4-*tert*-Butyldimethylsiloxy-7-hydroxy-3-[(1*S*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl]-5,6-(*O*-isopropylidenedioxy)octahydroinden-1-carbaldehyde (26a): DBU (4.70 mL, 32 mmol) was added to a stirred solution of **27a** (900 mg, 1.6 mmol) in dry toluene (30 mL) at room temperature under argon. The mixture was heated at reflux for 1.5 h. After cooling, the mixture was directly subjected to column chromatography eluting with EtOAc in order to remove excess DBU. The fractions containing **26a** and starting material **27a** were collected and then concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 2:1→1:1) to give less polar **26a** (270 mg, 30%) as a colorless viscous liquid and more polar starting material **27a** (540 mg, 60%).

26a: $[\alpha]_D^{20}$ = −34.3 (*c* = 0.98 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.23 (s, 6H), 0.31 (s, 3H), 0.97 (s, 9H), 1.24 (d, 6H, *J* = 2.0 Hz), 2.01–2.12 (m, 1H), 2.22–2.43 (m, 3H), 3.02–3.09 (m, 1H), 3.37–3.43 (m, 1H), 3.50 (s, 3H), 3.82–3.89 (m, 2H), 3.87 (s, 3H), 4.02 (ddd, 1H, *J* = 10.8, 6.6, 4.1 Hz), 4.14–4.21 (m, 1H), 4.45 (br, 1H), 4.73 (br, 1H), 6.87 (d, 1H, *J* = 8.3 Hz), 6.99 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.18 (d, 1H, *J* = 2.0 Hz), 9.73 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.33, −3.84, 14.2, 18.1, 21.0, 23.8, 25.9, 26.1, 50.7, 55.9, 56.2, 60.3, 75.7, 75.9, 77.2, 95.6, 108.5, 111.8, 114.9, 120.1, 135.9, 146.7, 203.0 ppm; IR (neat): $\tilde{\nu}$ = 3422, 2934, 2860, 1718, 1512, 1383, 1261, 1211, 1155, 1078, 1022, 864, 839, 781 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{29}H_{46}O_9Si$: 566.2911, found 566.2916 $[M]^+$.

(1*R*,3*R*,3a*S*,4*S*,5*R*,6*R*,7*R*,7a*R*)-7-*tert*-Butyldimethylsiloxy-1-[(1*S*)-hydroxy[4-methoxy-3-(methoxymethoxy)phenyl]methyl]-3-hydroxymethyl-5,6-(*O*-isopropylidenedioxy)octahydroinden-4-ol (30): A solution of **26a** (306 mg, 0.54 mmol) in dry THF (6 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (41.0 mg, 1.1 mmol) in dry THF (4 mL) at 0 °C under argon. After 1 min, H_2O (40 μL), 15 % aqueous NaOH (40 μL), H_2O (0.12 mL), and Na_2SO_4 (500 mg) were added successively to the reaction mixture at 0 °C, and the resulting mixture was further stirred for 30 min at room temperature. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/EtOAc 1:1→EtOAc) to give **30** (294 mg, 96 %) as a colorless viscous liquid. $[\alpha]_D^{20}=-36.6$ ($c=0.83$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.22$ (s, 3H), 0.27 (s, 3H), 0.96 (s, 9H), 1.26 (s, 6H), 1.63 (br, 1H), 1.74 (br, 1H), 1.91–1.99 (m, 1H), 2.31–2.39 (m, 2H), 2.46–2.54 (m, 1H), 2.68 (br, 1H), 3.43 (m, 1H), 3.51 (s, 3H), 3.48–3.56 (m, 1H), 3.55–3.62 (m, 1H), 3.83–3.90 (m, 1H), 3.87 (s, 3H), 4.04 (br, 1H), 4.17–4.22 (m, 1H), 4.42 (dd, 1H, $J=7.3$, 5.2 Hz), 4.80–4.84 (m, 1H), 5.23 (s, 2H), 6.87 (d, 1H, $J=8.3$ Hz), 7.01 (dd, 1H, $J=8.3$, 2.0 Hz), 7.19 ppm (d, 1H, $J=2.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.31$, −3.99, 18.1, 24.0, 25.9, 26.1, 26.2, 30.2, 40.0, 43.7, 49.0, 55.9, 56.2, 67.3, 67.4, 72.0, 73.0, 76.4, 76.5, 95.5, 108.5, 111.5, 114.5, 120.0, 136.4, 146.5, 149.1 ppm; IR (neat): $\tilde{\nu}=3435$, 2932, 1512, 1383, 1259, 1155, 1078, 1018, 864, 837, 779 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{29}H_{48}O_9Si$: 568.3068, found 568.3085 $[M]^+$.

(1*R*,3*R*,3a*S*,4*S*,5*R*,6*R*,7*R*,7a*R*)-4-Acetoxy-3-acetoxymethyl-7-*tert*-butyldimethylsiloxy-1-[(1*S*)-acetoxy[4-methoxy-3-(methoxymethoxy)phenyl]-methyl]-5,6-(*O*-isopropylidenedioxy)octahydroindene (31): $(CH_3CO)_2O$ (1.50 mL, 16 mmol) and DMAP (19.0 mg, 0.16 mmol) were added to a stirred solution of **30** (294 mg, 0.52 mmol) in pyridine (5 mL) at room temperature. After 1 h, the mixture was diluted with Et_2O (50 mL). The organic layer was washed successively with 3 % aqueous HCl (2×10 mL), saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc 1:1) to give **31** (341 mg, 95 %) as a colorless viscous liquid. $[\alpha]_D^{20}=-38.8$ ($c=1.16$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.20$ (s, 3H), 0.33 (s, 3H), 0.96 (s, 9H), 1.13 (s, 3H), 1.21 (s, 3H), 1.62 (ddd, 1H, $J=12.6$, 8.6, 3.8 Hz), 1.99 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 1.96–2.13 (m, 2H), 2.31–2.37 (m, 1H), 2.65–2.76 (m, 1H), 2.76–2.84 (m, 1H), 3.51 (s, 3H), 3.86 (s, 3H), 3.84–3.89 (m, 1H), 3.94–4.03 (m, 2H), 4.06 (dd, 1H, $J=6.3$, 2.4 Hz), 4.21 (dd, 1H, $J=6.3$, 4.9 Hz), 5.20–5.26 (m, 2H), 5.43 (dd, 1H, $J=8.4$, 4.7 Hz), 5.82 (d, 1H, $J=10.6$ Hz), 6.86 (d, 1H, $J=8.3$ Hz), 7.05 (dd, 1H, $J=8.3$, 1.9 Hz), 7.23 ppm (d, 1H, $J=1.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-3.96$, −3.89, 18.1, 20.9, 21.2, 24.7, 26.0, 26.4, 31.9, 37.3, 39.7, 41.8, 46.0, 55.9, 56.2, 68.2, 68.8, 69.3, 73.5, 76.6, 77.1, 95.6, 108.1, 111.3, 115.4, 121.7, 132.5, 146.5, 149.6, 169.9, 170.4, 171.3 ppm; IR (neat): $\tilde{\nu}=$ 2935, 2856, 1738, 1608, 1516, 1466, 1371, 1238, 1157, 1371, 1238, 1157, 1132, 1078, 1024, 869, 837, 775, 607, 518, 412 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{35}H_{54}O_{12}Si$: 694.3385, found 694.3380 $[M]^+$.

(1*S*,3*R*,3a*S*,4*S*,5*R*,6*R*,7*R*,7a*R*)-7-*tert*-Butyldimethylsiloxy-3-hydroxymethyl-5,6-*O*-isopropylidenedioxy-1-[4-methyoxy-3-(methoxymethoxy)benzyl]-octahydroinden-4-ol (32): A solution of **31** (340 mg, 0.49 mmol) in dry THF (15 mL) was added dropwise to a stirred solution of Li metal (100 mg, 9.0 mmol) in liquid NH_3 (30 mL) at −78 °C under argon. After 5 min, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) at the same temperature. The mixture was then allowed to stand at room temperature for 4 h in order to evaporate off excess NH_3. The mixture was extracted with EtOAc (2×100 mL) and the extracts were washed with saturated aqueous $NaHCO_3$ (2×50 mL) and brine (50 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 1:1) to give **32** (265 mg, 98 %) as a colorless viscous liquid. $[\alpha]_D^{20}=-27.7$(c=0.91 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.23$ (s, 3H), 0.26 (s, 3H), 0.97 (s, 9H), 1.34 (s, 3H), 1.44 (s, 3H), 1.42–1.49 (m, 1H), 1.64–1.71 (m, 1H), 1.81 (br, 1H), 2.26–2.38 (m, 2H), 2.50–2.57 (m, 2H), 2.61–2.69 (m, 1H), 2.88 (dd, 1H, $J=13.3$, 4.6 Hz), 3.43 (dd, 1H, $J=10.3$, 7.3 Hz), 3.51 (m, 1H), 3.52 (s, 3H), 3.86 (s, 3H), 3.90–4.04 (m, 2H), 4.06 (t, 1H, $J=3.0$ Hz), 4.28 (dd, 1H, $J=7.2$, 2.9 Hz), 4.50–4.55 (m, 1H), 5.19–5.23 (m, 2H), 6.77 (dd, 1H, $J=8.2$, 1.9 Hz), 6.82 (d, 1H, $J=8.2$ Hz), 6.99 ppm (d, 1H, $J=1.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.46$, −3.56, 18.1, 24.0, 25.9, 26.4, 33.8, 35.4, 40.1, 40.6, 42.4, 42.8, 55.9, 56.1, 67.1, 67.3, 71.6, 76.1, 76.3, 95.5, 108.4, 111.6, 116.9, 122.1, 134.3, 146.3, 147.8 ppm; IR (neat): $\tilde{\nu}=3433$, 2932, 2858, 1512, 1466, 1383, 1261, 1211, 1155, 1134, 1078, 1016, 923, 868, 837, 808, 779 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{29}H_{48}O_8Si$: 552.3118, found 552.3129 $[M]^+$.

(1*R*,3*S*,3a*R*,4*R*,5*R*,6*S*,7a*R*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidene-3-[4-methoxy-3-(methoxymethoxy)benzyl]-7-oxooctahydroinden-1-carbaldehyde (33): Dess–Martin periodinane (609 mg, 1.4 mmol) was added in small portions to a stirred solution of **32** (265 mg, 0.48 mmol) in dry CH_2Cl_2 (10 mL) at room temperature. After 30 min, the reaction was quenched with 10 % aqueous $Na_2S_2O_3$ (3 mL), and the resulting mixture was extracted with Et_2O (2×50 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 6:1) to give **33** (237 mg, 90 %) as a colorless viscous oil. $[\alpha]_D^{20}=+24.5$ ($c=$ 2.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.16$ (s, 3H), 0.22 (s, 3H), 0.86 (s, 9H), 1.34 (s, 3H), 1.57 (s, 3H), 1.82–1.92 (m, 2H), 2.13–2.23 (m, 1H), 2.57 (dd, 1H, $J=13.5$, 10.0 Hz), 2.81 (dd, 1H, $J=13.5$, 5.3 Hz), 3.13–3.18 (m, 1H), 3.47–3.54 (m, 1H), 3.51 (s, 3H), 3.68 (dd, 1H, $J=9.6$, 5.1 Hz), 3.86 (s, 3H), 4.09–4.12 (m, 1H), 4.33 (d, 1H, $J=7.4$ Hz), 4.40 (dd, 1H, $J=7.4$, 3.1 Hz), 5.21 (s, 2H), 6.75 (dd, 1H, $J=8.2$, 1.9 Hz), 6.82 (d, 1H, $J=8.2$ Hz), 6.97 (d, 1H, $J=1.9$ Hz), 9.63 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.07$, −3.56, 17.9, 24.0, 25.6, 25.9, 30.5, 35.2, 43.3, 44.1, 44.8, 52.1, 55.9, 56.1, 68.8, 77.2, 80.4, 95.5, 111.7, 112.0, 116.7, 121.9, 133.2, 146.4, 148.0, 201.9, 206.2 ppm; IR (neat): $\tilde{\nu}=2932$, 2858, 1728, 1514, 1466, 1383, 1263, 1209, 1157, 1134, 1060, 1006, 925, 858, 837, 808, 777, 538, 468, 405 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{29}H_{44}O_8Si$: 548.2805, found 548.2801 $[M]^+$.

(1*S*,3*S*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-4-*tert*-Butyldimethylsiloxy-5,6-*O*-isopropylidenedioxy-3-[4-methoxy-3-(methoxymethoxy)benzyl]-7-methylene-1-(vinyl)octahydroindene (25): Wittig reagent ($Ph_3P=CH_2$) in benzene solution was first prepared as follows: a suspension of $Ph_3P^+CH_3Br^-$ (1.22 g, 3.4 mmol) and *t*BuOK (380 mg, 3.4 mmol) in dry benzene (10 mL) were heated at reflux for 4 h under argon, and the solution was cooled to room temperature. A solution of the Wittig reagent in benzene (1.0 mL, 0.34 mmol) was added very slowly to a stirred solution of **33** (187 mg, 0.34 mmol) in dry benzene (8 mL) at room temperature under argon. After the first methylenation of the C1-formyl group was completed (monitored by TLC), a solution of the Wittig reagent in benzene (4.0 mL, 1.36 mmol) was added once again and the resulting mixture was heated under reflux for 30 min to pursue the second methylenation of the C7-carbonyl group. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (2×50 mL). The organic layer was washed with brine (2×30 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 20:1→10:1) to give **25** (176 mg, 95 %) as a colorless viscous liquid. $[\alpha]_D^{20}=-21.9$ ($c=0.93$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.14$ (s, 3H), 0.18 (s, 3H), 0.88 (s, 9H), 1.35 (s, 3H), 1.41 (ddd, 1H, $J=12.2$, 8.4, 3.6 Hz), 1.45 (s, 3H), 1.91–2.00 (m, 1H), 2.36–2.45 (m, 1H), 2.53 (dd, 1H, $J=13.3$, 10.3 Hz), 2.58–2.63 (m, 1H), 2.72–2.78 (m, 1H), 2.83 (dd, 1H, $J=13.3$, 5.2 Hz), 2.85–2.93 (m, 1H), 3.51 (s, 3H), 3.84 (s, 3H), 3.95–3.98 (m, 1H), 4.15 (dd, 1H, $J=7.3$, 2.4 Hz), 4.62 (d, 1H, $J=7.3$ Hz), 4.84–4.88 (m, 1H), 4.93–4.99 (m, 1H), 5.14–5.17 (m, 1H), 5.21–5.24 (s, 2H), 5.22 (m, 1H), 5.88 (ddd, 1H, $J=17.8$, 10.2, 7.8 Hz), 6.78–6.81 (m, 2H), 7.00 ppm (d, 1H, $J=1.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.15$, −3.57, 18.0, 24.2, 25.8, 26.4, 36.2, 38.2, 42.0, 43.0, 44.8, 49.2, 55.9, 56.1, 70.0, 78.5, 78.8, 95.6, 108.6, 111.6, 111.7, 114.1, 117.0, 122.2, 134.6, 145.8, 146.1, 146.3, 147.8 ppm; IR (neat): $\tilde{\nu}=2932$, 2858, 1637, 1512, 1464, 1381, 1259, 1209, 1157, 1134, 1078, 1059, 1030, 1005, 908, 864, 835, 810, 775 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{31}H_{48}O_6Si$: 544.3220, found 544.3224 $[M]^+$.

(1*S*,3*S*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-4-*tert*-Butyldimethylsiloxy-3-(3-hydroxy-4-methoxybenzyl)-7-methylene-1-vinyloctahydroinden-5,6-diol (34): A solution of TFA/H_2O 10:1 (11 mL) was added dropwise to a stirred solution of **25** (177 mg, 0.33 mmol) in THF (1 mL) at 0 °C. After 10 min, the reaction mixture was neutralized with 6 M NaOH and extracted with EtOAc

(3×40 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (30 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 3:1) to give **34** (129 mg, 86%) as a colorless viscous liquid. $[\alpha]_D^{20}=+19.2$ ($c=1.97$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.22$ (s, 3H), 0.26 (s, 3H), 0.98 (s, 9H), 1.59 (ddd, 1H, $J=15.8$, 10.0, 5.7 Hz), 1.74 (d, 1H, $J=6.1$ Hz), 1.93 (d, 1H, $J=7.5$ Hz), 1.96–2.00 (m, 1H), 2.27–2.33 (m, 1H), 2.41–2.51 (m, 2H), 2.69 (dd, 1H, $J=13.6$, 8.9 Hz), 2.77–2.86 (m, 2H), 3.86 (s, 3H), 3.95–3.99 (m, 1H), 4.26 (t, 1H, $J=4.0$ Hz), 4.70–4.74 (m, 1H), 4.80–4.85 (m, 1H), 4.86–4.90 (m, 1H), 4.95 (s, 1H), 5.15 (t, 1H, $J=1.8$ Hz), 5.54 (s, 1H), 5.62 (ddd, 1H, $J=18.3$, 10.1, 8.3 Hz), 6.66 (dd, 1H, $J=8.2$, 2.1 Hz), 6.76 (d, 1H, $J=8.2$ Hz), 6.78 ppm (d, 1H, $J=2.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.05$, −3.37, 18.1, 26.1, 35.5, 37.1, 43.2, 44.2, 47.5, 54.3, 56.0, 68.2, 72.7, 75.4, 110.6, 110.8, 113.4, 114.6, 119.6, 135.3, 142.8, 144.7, 145.4, 145.8 ppm; IR (neat): $\tilde{\nu}=3422$, 2932, 2858, 1639, 1591, 1512, 1442, 1259, 1130, 1062, 1037, 904, 873, 835, 775, 706 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{26}H_{41}O_5Si$: 461.2723, found 461.2697 $[M+H]^+$.

(1*S*,3*S*,3a*R*,4*R*,5*R*,6*R*,7a*S*)-3-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-7-methylene-1-(vinyl)octahydroinden-5,6-diol (35): 2 M NaOH (0.40 mL, 0.80 mmol) and $(CH_3CO)_2O$ (76 μL, 0.80 mmol) were added dropwise to a stirred solution of **34** (128 mg, 0.28 mmol) in 2-propanol (2 mL) at room temperature. After 30 min, the reaction mixture was diluted with EtOAc (70 mL). The organic layer was washed with H_2O (2×20 mL) and brine (2×20 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (benzene/EtOAc 10:1) to give **35** (127 mg, 91%) as a colorless viscous liquid. $[\alpha]_D^{20}=+20.9$ ($c=0.80$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.21$ (s, 3H), 0.24 (s, 3H), 0.97 (s, 9H), 1.56–1.63 (m, 1H), 1.78 (d, 1H, $J=5.8$ Hz), 1.92 (d, 1H, $J=7.6$ Hz), 1.95–2.00 (m, 1H), 2.27–2.33 (m, 1H), 2.31 (s, 3H), 2.39–2.49 (m, 2H), 2.72 (dd, 1H, $J=13.7$, 8.8 Hz), 2.82 (dd, 1H, $J=13.7$, 6.3 Hz), 2.77–2.87 (m, 1H), 3.80 (s, 3H), 3.95–3.99 (m, 1H), 4.22–4.26 (m, 1H), 4.68–4.73 (m, 1H), 4.80–4.85 (m, 1H), 4.88 (dd, 1H, $J=10.0$, 1.3 Hz), 4.94 (s, 1H), 5.14–5.17 (m, 1H), 5.62 (ddd, 1H, $J=17.1$, 10.0, 8.3 Hz), 6.85 (d, 1H, $J=2.1$ Hz), 6.87 (d, 1H, $J=8.3$ Hz), 7.00 ppm (dd, 1H, $J=8.3$, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.06$, −3.36, 18.1, 20.7, 26.1, 35.3, 37.1, 43.1, 44.2, 47.5, 54.3, 55.9, 68.2, 72.7, 75.4, 110.9, 112.4, 113.5, 122.6, 126.4, 134.6, 139.5, 142.7, 145.7, 149.1, 168.3 ppm; IR (neat): $\tilde{\nu}=3449$, 2955, 2932, 2858, 1768, 1639, 1512, 1464, 1442, 1369, 1263, 1205, 1122, 1062, 1035, 902, 873, 835, 775, 706 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{28}H_{43}O_6Si$: 503.2829, found 503.2832 $[M+H]^+$.

(3a*R*,4*R*,4a*R*,5*S*,7*S*,7a*S*)-5-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-8-methylene-7-(vinyl)octahydroindeno[5,6-*d*]1,3]dioxol-2-thione (36): A solution of $CSCl_2$ (18 μL, 0.24 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise to a stirred mixture of **35** (60.0 mg, 0.12 mmol) in dry CH_2Cl_2 containing DMAP (72.0 mg, 0.60 mmol) at room temperature. After 30 min, silica gel (1.0 g) was added to the reaction mixture, and the solvent was carefully evaporated off in vacuo. The resulting solid was charged on the top of a silica gel column chromatography, and elution using hexane/EtOAc 10:1 gave **36** (60.3 mg, 93%) as a colorless viscous liquid. $[\alpha]_D^{20}=+25.3$ ($c=0.60$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.16$ (s, 3H), 0.22 (s, 3H), 0.87 (s, 9H), 1.44–1.50 (m, 1H), 1.88–1.96 (m, 1H), 2.31 (s, 3H), 2.30–2.34 (m, 1H), 2.40–2.52 (m, 2H), 2.79–2.85 (m, 1H), 2.86–2.93 (m, 2H), 3.80 (s, 3H), 4.15–4.18 (m, 1H), 4.85 (dd, 1H, $J=8.5$, 2.4 Hz), 4.91 (d, 1H, $J=10.1$ Hz), 4.94–4.99 (m, 1H), 5.28–5.33 (m, 2H), 5.47 (d, 1H, $J=2.5$ Hz), 5.85 (ddd, 1H, $J=17.2$, 10.1, 7.8 Hz), 6.82 (d, 1H, $J=2.1$ Hz), 6.89 (d, 1H, $J=8.3$ Hz), 6.97 ppm (dd, 1H, $J=8.3$, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.41$, −3.49, 17.9, 20.7, 25.6, 35.7, 38.0, 42.5, 43.0, 43.9, 49.6, 55.9, 67.6, 82.1, 85.3, 112.5, 112.6, 118.8, 122.7, 126.5, 133.5, 139.6, 141.1, 144.6, 149.4, 169.0, 190.8 ppm; IR (neat): $\tilde{\nu}=3076$, 2955, 2932, 2858, 1768, 1639, 1583, 1512, 1464, 1442, 1369, 1331, 1267, 1205, 1163, 1124, 1089, 1064, 1032, 995, 958, 904, 866, 837, 777, 758 cm^{-1}; HRMS (EI): m/z: calcd for $C_{29}H_{40}O_6SSi$: 544.2315, found 544.2316 $[M]^+$.

(1*S*,3*S*,3a*R*,4*S*,7a*S*)-3-(3-Acetoxy-4-methoxybenzyl)-4-*tert*-butyldimethylsiloxy-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroindene (37): A solution of **36** (48.0 mg, 88 μmol) in $(EtO)_3P$ (8.8 mL) was heated at reflux for 2 h under argon. After cooling, excess $(EtO)_3P$ was removed using short column chromatography eluting with hexane. The combined fractions were concentrated in vacuo to afford a residue, which was purified by column chromatography (benzene/EtOAc 100:1) to give **37** (32.2 mg, 78%) as a colorless viscous liquid. $[\alpha]_D^{20}=+98.4$ ($c=1.07$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.11$ (s, 3H), 0.16 (s, 3H), 0.92 (s, 9H), 1.50–1.57 (m, 1H), 1.93 (ddd, 1H, $J=12.7$, 10.1, 8.3 Hz), 2.13 (m, 1H), 2.30 (s, 3H), 2.38–2.50 (m, 2H), 2.70 (dd, 1H, $J=13.7$, 9.3 Hz), 2.78–2.87 (m, 1H), 2.96 (dd, 1H, $J=13.7$, 6.0 Hz), 3.80 (s, 3H), 4.45 (t, 1H, $J=4.9$ Hz), 4.84–4.92 (m, 3H), 4.95 (s, 1H), 5.73 (ddd, 1H, $J=16.9$, 10.0, 8.8 Hz), 5.83 (dd, 1H, $J=9.7$, 4.9 Hz), 6.13 (d, 1H, $J=9.8$ Hz), 6.85–6.89 (m, 2H), 7.01 ppm (dd, 1H, $J=8.3$, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=-4.08$, −3.29, 18.1, 20.7, 26.0, 35.7, 43.9, 45.9, 47.9, 49.6, 55.9, 65.5, 112.2, 113.5, 114.3, 122.8, 126.6, 129.9, 131.1, 135.4, 139.5, 143.3, 144.0, 148.9, 169.0 ppm; IR (neat): $\tilde{\nu}=2928$, 2857, 1771, 1512, 1464, 1368, 1262, 1204, 1125, 1030, 882, 835, 773 cm^{-1}; HRMS (EI): m/z: calcd for $C_{28}H_{40}O_4Si$: 468.2696, found 468.2700 $[M]^+$.

(1*S*,3*S*,3a*R*,4*S*,7a*S*)-3-(3-Hydroxy-4-methoxybenzyl)-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroinden-4-ol (38): Tetra-*n*-butylammonium fluoride (TBAF) in THF (1 M solution, 0.86 mL. 0.86 mmol) was added to a stirred solution of **37** (40.0 mg, 85 μmol) in THF (2 mL) at room temperature. After 48 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), and extracted with EtOAc (2×30 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (benzene/EtOAc 4:1) to give **38** (22.1 mg, 83%) as a colorless viscous liquid. $[\alpha]_D^{20}=+74.6$ ($c=0.35$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.05$ (br, 1H), 1.65 (ddd, 1H, $J=16.1$, 10.1, 6.0 Hz), 1.99–2.03 (m, 1H), 2.04–2.09 (m, 1H), 2.44 (dd, 1H, $J=10.8$, 6.3 Hz), 2.47–2.54 (m, 1H), 2.55–2.61 (m, 1H), 2.87 (dd, 1H, $J=13.7$, 8.3 Hz), 2.98 (dd, 1H, $J=13.7$, 7.2 Hz), 3.86 (s, 3H), 4.36 (br, 1H), 4.83–4.88 (m, 2H), 4.90 (dd, 1H, $J=10.0$, 1.9 Hz), 4.99–5.03 (m, 1H), 5.54 (br, 1H), 5.70 (ddd, 1H, $J=18.7$, 10.0, 8.8 Hz), 5.93 (dd, 1H, $J=9.7$, 5.6 Hz), 6.19 (d, 1H, $J=9.7$ Hz), 6.73 (dd, 1H, $J=8.2$, 1.9 Hz), 6.76 (d, 1H, $J=8.2$ Hz), 6.84 ppm (d, 1H, $J=1.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=36.7$, 37.9, 44.4, 44.9, 48.6, 49.9, 55.9, 64.3, 110.4, 113.9, 114.7, 115.8, 119.9, 128.1, 131.5, 135.8, 142.0, 143.7, 144.5, 145.3 ppm; IR (neat): $\tilde{\nu}=3510$, 2924, 1591, 1512, 1442, 1273, 1130, 1008, 904, 802, 761 cm^{-1}; HRMS (EI): m/z: calcd for $C_{20}H_{24}O_3$: 312.1725, found 312.1729 $[M]^+$.

(1*S*,3*S*,3a*R*,4*S*,7a*S*)-3-(3-Dichloroacetoxy-4-methoxybenzyl)-7-methylene-1-vinyl-1,2,3,3a,7,7a-hexahydroinden-4-ol (39): A solution of $(CHCl_2CO)_2O$ (10 μL, 65 μmol) in dry CH_2Cl_2 (0.2 mL) was added very slowly to a stirred solution of **38** (17.0 mg, 54 μmol) in dry CH_2Cl_2 (0.8 mL) containing pyridine (9.0 μL, 0.1 mmol) at room temperature. The reaction mixture was diluted with EtOAc (10 mL), and the organic layer was washed with brine (3 mL), and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (benzene/EtOAc 20:1) to give **39** (18.2 mg, 79%) as a white cloudy oil. $[\alpha]_D^{20}=+71.5$ ($c=0.37$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.02$ (d, 1H, $J=6.3$ Hz), 1.64 (ddd, 1H, $J=19.0$, 10.1, 6.0 Hz), 1.99–2.03 (m, 1H), 2.05–2.10 (m, 1H), 2.43–2.62 (m, 3H), 2.93 (dd, 1H, $J=13.9$, 8.6 Hz), 3.03 (dd, 1H, $J=13.9$, 6.9 Hz), 3.82 (s, 3H), 4.30–4.36 (m, 1H), 4.83–4.85 (m, 1H), 4.86–4.89 (m, 1H), 4.92 (dd, 1H, $J=9.9$, 1.8 Hz), 5.01–5.04 (m, 1H), 5.70 (ddd, 1H, $J=18.7$, 9.9, 8.8 Hz), 5.91–5.96 (m, 1H), 6.18 (s, 1H), 6.20 (d, 1H, $J=9.6$ Hz), 6.91 (d, 1H, $J=8.4$ Hz), 7.01 (d, 1H, $J=2.0$ Hz), 7.14 ppm (dd, 1H, $J=8.4$, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=35.9$, 37.8, 44.3, 44.9, 48.6, 49.9, 56.1, 64.0, 64.3, 112.6, 114.0, 116.0, 121.9, 127.6, 128.0, 131.6, 135.4, 138.8, 141.9, 143.5, 148.6, 162.5 ppm; IR (neat): $\tilde{\nu}=3568$, 2926, 2345, 1782, 1512, 1269, 1141, 1028, 815, 407 cm^{-1}; HRMS (EI): m/z: calcd for $C_{22}H_{24}Cl_2O_4$: 422.1052, found 422.1050 $[M]^+$.

(1*S*,3*S*,3a*S*,7a*S*)-3-(3-Dichloroacetyl-4-methoxybenzyl)-1,2,3,3a,7,7a-hexahydro-7-methylene-1-(vinyl)inden-4-one (40): Dess–Martin periodinane (34.0 mg, 81 μmol) was added to a stirred solution of **39** (17.0 mg, 40 μmol) in dry CH_2Cl_2 (1.2 mL) at room temperature. After 15 min, the reaction was quenched with 20% aqueous $Na_2S_2O_3$ (0.5 mL), and the mixture was extracted with EtOAc (2×15 mL). The combined extracts

were washed with brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 4:1) to give **40** (16.0 mg, 95%) as a white cloudy oil. $[\alpha]_D^{20} = +22.4$ ($c = 0.83$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.58$–1.63 (m, 1H), 1.69–1.77 (m, 1H), 2.47 (m, 1H), 2.54–2.63 (m, 2H), 2.73–2.78 (m, 1H), 2.78–2.83 (m, 1H), 3.16 (dd, 1H, $J =$ 13.6, 6.9 Hz), 3.80 (s, 3H), 4.90–4.95 (m, 1H), 4.96–5.00 (m, 1H), 5.29 (d, 1H, $J = 1.1$ Hz), 5.32 (s, 1H), 5.75 (ddd, 1H, $J = 18.3$, 10.1, 8.2 Hz), 5.92 (dd, 1H, $J = 9.9$, 0.6 Hz), 6.18 (s, 1H), 6.89 (d, 1H, $J = 8.4$ Hz), 6.97 (d, 1H, $J = 8.4$ Hz), 6.98 (d, 1H, $J = 2.1$ Hz), 7.11 ppm (dd, 1H, $J = 8.4$, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 35.5$, 35.6, 46.3, 48.7, 49.1, 51.0, 56.1, 64.0, 112.6, 114.5, 120.1, 122.2, 128.0, 128.3, 134.8, 138.7, 141.6, 142.5, 145.8, 148.8, 162.5, 200.2 ppm; IR (neat): $\tilde{\nu} = 2932$, 1784, 1660, 1512, 1442, 1267, 1217, 1141, 1028, 912, 814 cm^{-1}; HRMS (EI): m/z: calcd for $C_{22}H_{22}Cl_2O_4$: 420.0895, found 420.0888 $[M]^+$.

(1*S*,3*S*,3a*R*,7a*S*)-1,2,3,3a,7,7a-Hexahydro-3-(3-hydroxy-4-methoxybenzyl)-7-methylene-1-(vinyl)inden-4-one (1) [(+)-ottelione A]: Compound **40** (13.0 mg, 31 μmol) was dissolved in a solution of 50% aqueous $NaHCO_3$/CH_3CN 1:1 (2.0 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with EtOAc (20 mL), and the organic layer was washed with brine (2×5 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (benzene/EtOAc 20:1) to give **1** (8.6 mg, 90%) as white cloudy oil. $[\alpha]_D^{25} = +17.3$ ($c = 0.55$ in $CHCl_3$). The ^{1}H NMR, ^{13}C NMR, IR, and MS spectra (see below) are compatible with those of natural (+)-ottelione A. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.52$–1.61 (m, 1H), 1.69–1.76 (m, 1H), 2.48–2.54 (m, 2H), 2.58–2.66 (m, 1H), 2.78 (t, 1H, $J = 8.2$ Hz), 2.86 (dd, 1H, $J = 8.2$, 5.9 Hz), 3.01–3.09 (m, 1H), 3.85 (s, 3H), 4.91–4.99 (m, 2H), 5.30–5.33 (m, 2H), 5.53 (br, 1H), 5.76 (ddd, 1H, $J = 18.2$, 10.1, 8.2 Hz), 5.93 (d, 1H, $J = 10.0$ Hz), 6.68 (dd, 1H, $J = 8.2$, 2.0 Hz), 6.75 (d, 1H, $J = 8.2$ Hz), 6.79 (d, 1H, $J = 2.0$ Hz), 6.99 ppm (d, 1H, $J = 9.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 35.6$, 35.8, 46.3, 48.5, 49.0, 51.4, 55.9, 110.4, 114.4, 114.9, 119.9, 120.2, 128.3, 135.1, 141.8, 142.9, 144.6, 145.2, 145.9, 200.4 ppm; IR (neat): $\tilde{\nu} = 3439$, 2926, 1658, 1589, 1510, 1440, 1275, 1236, 1130, 1030, 958, 800, 760 cm^{-1}; HRMS (EI): m/z: calcd for $C_{20}H_{22}O_3$: 310.1569, found 310.1571 $[M]^+$.

(1*S*,3*S*,3a*S*,7a*S*)-1,2,3,3a,7,7a-Hexahydro-3-(3-hydroxy-4-methoxybenzyl)-7-methylene-1-(vinyl)inden-4-one (2) [(+)-ottelione B]: *t*BuOK (8.0 mg, 0.13 mmol) was added in small portions to a stirred solution of ottelione A (**1**) (8.0 mg, 26 μmol) in *t*BuOH (1 mL) at room temperature. After 5 h, the reaction mixture was diluted with EtOAc (20 mL). The organic layer was washed with saturated aqueous NH_4Cl (2×4 mL), saturated aqueous $NaHCO_3$ (2×4 mL) and brine (4 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 4:1) to give a mixture of **2** and **1** (6.3 mg, 79%, **2**/**1** 77:23 determined by 500 MHz ^{1}H NMR) as a colorless viscous liquid. Isolation of **2** from this mixture was performed by means of HPLC (DAICEL CHIRALPAK AD-H, i.d. 4.6×250 mm, hexane/2-propanol 4:1, 0.5 mL min^{-1}; measurement of UV 254 nm absorbance, t_R-**2**: 34.7 min, t_R-**1**: 29.6 min) to give **2** (1.8 mg, 23%) as a white crystal, m.p. 142.2–143.0 °C; $[\alpha]_D^{25} = -330.0$ ($c = 0.18$ in $CHCl_3$). The ^{1}H NMR, ^{13}C NMR, IR, and MS (FAB) spectra (see below) are compatible with those of natural (−)-ottelione B. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.59$ (ddd, 1H, $J = 13.8$, 10.2, 8.2 Hz), 1.78 (ddd, 1H, $J = 13.8$, 9.8, 6.7 Hz), 2.27 (dd, 1H, $J = 13.9$, 9.8 Hz), 2.34 (dd, 1H, $J = 13.9$, 10.2 Hz), 2.46–2.56 (m, 2H), 2.69–2.77 (m, 1H), 3.14 (dd, 1H, $J = 13.4$, 3.6 Hz), 3.86 (s, 3H), 4.98–5.01 (m, 1H), 5.06–5.11 (m, 1H), 5.29–5.32 (m, 1H), 5.43–5.45 (m, 1H), 5.52 (br, 1H), 5.74 (ddd, 1H, $J = 18.2$, 10.2, 8.0, Hz), 5.94 (d, 1H, $J = 9.7$ Hz), 6.69 (dd, 1H, $J = 8.1$, 2.0 Hz), 6.76 (d, 1H, $J =$ 8.1 Hz), 6.80 (d, 1H, $J = 2.0$ Hz), 6.98–7.02 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 36.9$, 37.9, 40.6, 44.5, 50.5, 55.9, 58.3, 110.5, 114.6, 115.3, 117.1, 120.5, 128.7, 134.1, 141.5, 144.8, 144.9, 145.2, 147.6, 200.6 ppm; IR (KBr): $\tilde{\nu} = 3395$, 2930, 1664, 1589, 1512, 1440, 1275, 1176, 1126, 1035, 916, 808, 761 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{20}H_{23}O_3$: 311.1647, found 311.1633 $[M+H]^+$.

Cell-growth inhibition assay:[19] This experiment was carried out at the Cancer Chemotherapy Center, Japanese Foundation for Cancer Research. The screening panel consisted of the following 39 human cancer cell lines (HCC panel): breast cancer HBC-4, BSY-1, HBC-5, MCF-7, and MDA-MB-231; brain cancer U-251, SF-268, SF-295, SF-539, SNB-75, and SNB-78; colon cancer HCC2998, KM-12, HT-29, HCT-15, and HCT-116; lung cancer NCI-H23, NCI-H226, NCI-H522, NCI-H460, A549, DMS273, and DMS114; melanoma LOX-IMVI; ovarian cancer OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3; renal cancer RXF-631 L and ACHN; stomach cancer St-4, MKN1, MKN7, MKN28, MKN45, and MKN74; prostate cancer DU-145 and PC-3. The GI_{50} (50% cell growth inhibition) value for these cell lines was determined by using the sulforhodamine B colorimetric method.

Tubulin polymerization assay:[22] Ability of the test compounds to interfere with the polymerization dynamics of tubulin was examined by the two-step bioassay. In brief, the nerve growth factor (NGF)/rat pheochromocytoma (PC12) cell system was utilized in the first step to examine whether the test compounds had the ability to affect the polymerization dynamics of tubulin. In the second step, effect of the test compounds on the microtuble structures was examined in HT1080 human fibrosarcoma cells to distinguish whether they inhibited the polymerization of tubulin (to destabilize microtubule structures) or the depolymerization of tubulin (to stabilize microtubule structures).

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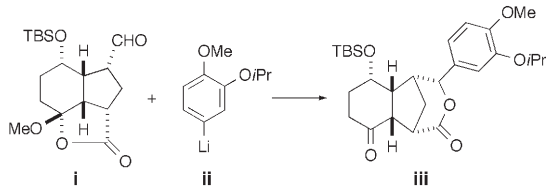

[17] Private communication from Professor Thomas R. Hoye of University of Minnesota. The value of optical rotation for natural otteliones A (**1**) and B (**2**) was not recorded in the literature.[1]
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