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Synthesis of two osteoclast-forming suppressors, demethylincisterol A_3 and chaxine A

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ABSTRACT

The synthesis of two potent osteoclast-forming suppressing agents isolated from the Chinese mushroom *Agrocybe chaxingu*, demethylincisterol A_3 and chaxine A, was accomplished using ergocalciferol as the starting material. Our methodology for the synthesis of demethylincisterol A_3 and chaxine A featured the construction of a butenolide moiety by the intramolecular Horner–Wadsworth–Emmons reaction under Masamune–Roush conditions. This is the first reported synthesis of chaxine A.

1. Introduction

An imbalance between bone formation, which is mediated by osteoblasts, and resorption, which is mediated by osteoclasts, is related to metabolic bone diseases, such as osteoporosis and osteopetrosis. Osteoclasts are multinucleated giant cells developed from hematopoietic stem cells of the monocyte–macrophage lineage.[1,2] The hematopoietic precursor cells differentiate into osteoclasts under the control of two critical cytokines, receptor activator of NFκB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). Tumor necrosis factor α (TNF-α) also accelerates osteoclastogenesis, particularly in states of inflammatory osteolysis causing rheumatoid arthritis.[3] Thus, an inhibitor or a suppressor of these cytokines that mediates osteoclast differentiation would be a candidate anti-osteoporosis chemotherapeutic agent. In 2006, Kawagishi and co-workers isolated the two potent osteoclast formation suppressing compounds from the mushroom *Agrocybe chaxingu*, which is found only in mountainous areas in South China (Fig. 1).[4,5] One of the two compounds, demethylincisterol A_3 (**2**), was first reported as a synthetic intermediate in the synthesis of 17-methylincisterol[6] and has been isolated from various fungi.[7] Mansoor and co-workers reported the isolation of **2** and the (17*S*)-isomer of **2** from a marine sponge; these compounds have cytotoxic effects on certain tumor cell lines.[8] The second compound was chaxine A, which is a previously unknown compound (**1**) (Fig. 1).

The stereochemistry of chaxine A was elucidated by extensive NMR analyses and comparison of the NMR data with those of **2**, but the absolute configuration of **1** remained undetermined. These two were shown to compounds significantly reduce the number of tartrate-resistant acid phosphatase (TRAP)-(+) multinucleated cells in a co-culture of osteoblastic cells and bone marrow cells without cytotoxicity in the presence of RANKL.[4,5] Because bone resorption can be suppressed by the inhibition of osteoclast formation, this result indicates that these two compounds might be candidate chemotherapeutic agents for the treatment of bone diseases, such postmenopausal osteoporosis. As mentioned above, the availability of *A. chaxingu*, from which **1** and **2** can be isolated, is limited, and

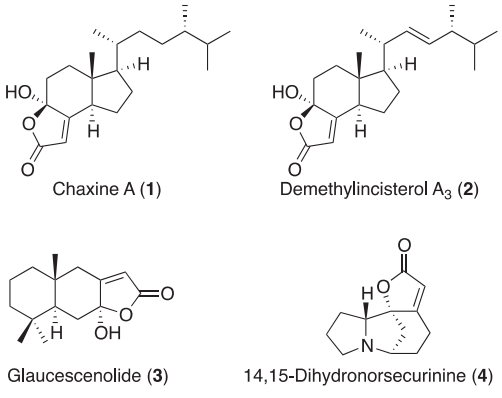

Fig. 1. The structures of demethylincisterol A_3, chaxine A, and related natural products.

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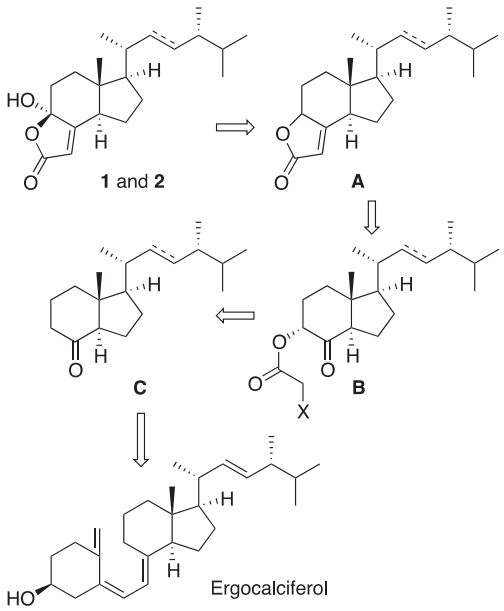
the contents of the compounds in the mushroom are low, i.e., 1.4 mg of **1** and 8.1 mg of **2** from 1.5 kg of dried fruiting bodies of *A. chaxingu*.[5] Furthermore, natural products containing a γ-hydroxybutenolide moiety related to chaxine A have been reported.[9] We were, therefore, interested in synthesizing demethylincisterol A_3 and chaxine A to establish a concise method for the synthesis of the characteristic moiety and also to confirm the stereostructure of chaxine A. This paper describes the results of our synthetic studies of demethylincisterol A_3 and the first synthesis of chaxine A.

2. Results and discussion

A wide variety of the synthetic approaches for γ-hydroxybutenolide derivatives have been reported. For example, Sodano and co-workers reported the synthesis of demethylincisterol A_3 (**2**) as a synthetic intermediate in the synthesis of 17-methylincisterol, employing the hetero Diels–Alder reaction of a diene with singlet oxygen as the key step.[6] Although the chemical yield was low (approximately 0.14%), Sakaguchi and co-workers directly prepared **2** using the photo-oxidative degradation of ergosterol.[10] These approaches require the use of photo-reaction equipment. Takikawa and co-workers synthesized a cytotoxic sesquiterpene, glaucescenolide (**3**), via a γ-ketoacid derivative as a precursor of butenolide.[11] The butenolide was oxidized via a furan derivative to give glaucescenolide in high yield.[12] This approach cannot be used for the synthesis of **1** or **2** because the appropriate starting material cannot be obtained easily. Our retrosynthetic analysis is summarized in Scheme 1. The γ-hydroxybutenolide moiety of **1** and **2** was introduced by oxidation of butenolide A constructed by an intramolecular cyclization reaction of B. The α-acyloxy ketone B was obtained from C, which can be derived from ergocalciferol.

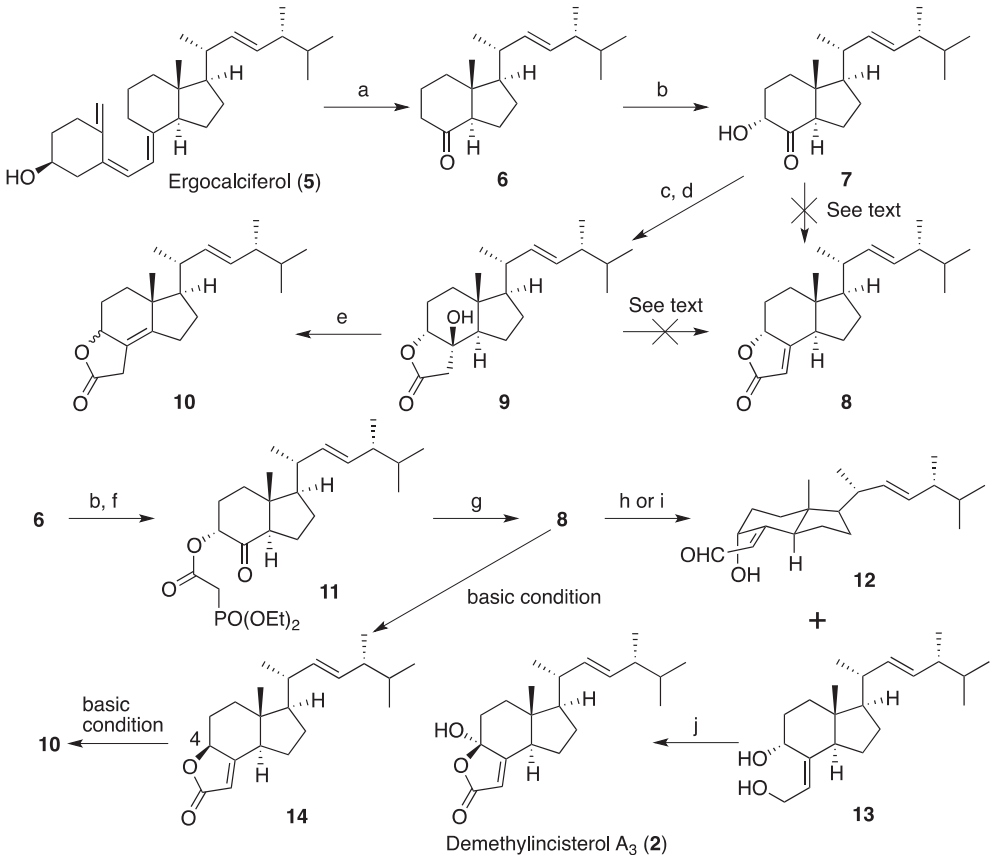


Scheme 1. Retrosynthetic analysis of demethylincisterol A_3 and chaxine A.

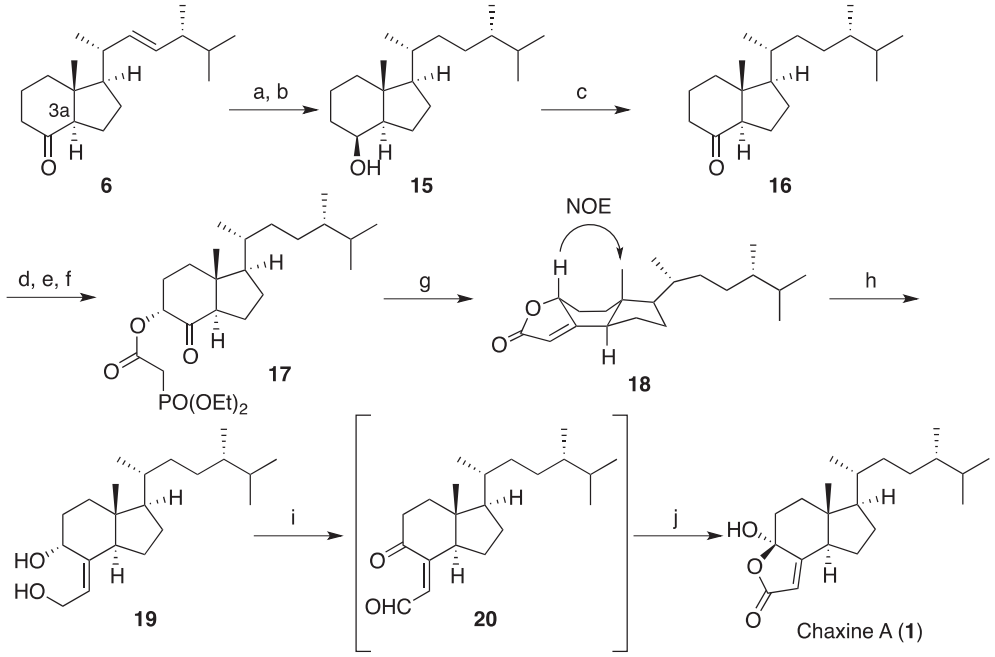
Weinreb and co-workers synthesized (+)-14,15-dihydronorsecurinine (**4**) and related alkaloids that contain fused butenolide ring systems via a tandem acylation-Wittig reaction of acyloin derivatives with the Bestmann ylide.[13] Because the butenolide can be converted into the corresponding γ-hydroxybutenolide via furan oxidation, we therefore employed these simple and successive approaches for the synthesis of demethylincisterol A_3. According to the literature,[14] ketone **6** was prepared from ergocalciferol (**5**) (Scheme 2). The corresponding silyl enol ether of **6** was oxidized with OsO_4 and NMO to yield the relatively unstable acyloin **7** as a single stereoisomer. The relative stereochemistry of **7** was confirmed after the construction of a butenolide ring (vide infra). Unfortunately, we could not obtain the desired butenolide **8** by the reaction of **7** with the Bestmann ylide[15] under various conditions, probably because of the instability of **7**. Next, we investigated the copper-catalyzed tandem acylation-Wittig reaction under the mild conditions developed by Matsuo and Shindo.[16] Under these conditions, the reaction of **7** with a modified thioester ($Ph_3P{=}CHCOSC_6H_3Me_2$) was not observed. With these disappointing results, we subsequently investigated an alternative approach.

In the total synthesis of dehydrololiolide, Mori and co-workers reported a simple approach employing an intramolecular Reformatsky reaction and a Horner–Wadsworth–Emmons (HWE) reaction to construct a butenolide moiety.[17] First, we applied the Reformatsky reaction for the construction of the butenolide ring. The acylation of **7** with bromoacetyl bromide, followed by the intramolecular Reformatsky reaction with zinc dust under sonication, gave hydroxylactone **9** in moderate yield. Unfortunately, however, the dehydration of **9** to obtain **8** was unsuccessful using various reagents, such as dehydrating reagents, acids, and bases. Moreover, it was notably difficult to convert the hydroxyl group of **9** into the corresponding ester or sulfonate, which might have been the result of the steric hindrance caused by the angular methyl group shielding the hydroxyl group. The only transformation that occurred was the dehydration of **9** with $SOCl_2$ under reflux conditions in pyridine to give undesired tetrasubstituted olefin **10**. This compound might be formed from **8** by isomerization because **10** would be thermodynamically favored over **8** (vide infra). Next, we examined the HWE approach, i.e., phosphonate **11** was subjected to the intramolecular HWE reaction under the optimized conditions, Masamune–Roush conditions,[18] to produce the desired butenolide **8** in 82% yield. However, the conversion of butenolide **8** into the corresponding furan was unsuccessful using DIBAL as a reducing agent.[19] The major products that we could isolate were the starting material and diol **13** together with hydroxyaldehyde **12** instead of a lactol. The favored conformation of hydroxyaldehyde **12** possesses an axially oriented hydroxyl group that would prevent the formation of the furan ring through a lactol. Furthermore, we observed an epimerization at C-4 of **8** to afford **14** under basic conditions, such as those of the intramolecular HWE reaction or the silyloxyfuran formation reaction conditions, that is, in the presence of TBSOTf and a base. The epimerized butenolide **14** was formed at first, and **14** was subsequently isomerized to yield the corresponding γ,δ-unsaturated lactone **10** after a prolonged reaction time. These results indicate that both of the ring systems of butenolides **8** and **14** are highly strained, which made it to difficult to form the furan derivatives. Because the obtained diol **13** was the synthetic intermediate of Sodano's synthesis of demethylincisterol A_3,[6] the stereochemistry of **13** was confirmed by a comparison of the ^1H NMR spectra. Finally, **13** was oxidized with the Jones reagent according to Sodano's method to afford demethylincisterol A_3 in a low yield. The overall yield of demethylincisterol A_3, based on ergocalciferol, was 11.4% after eight steps. This compound's properties, such as the NMR spectra, were identical to those of the reported data.[4] Although the overall chemical yield of our synthesis of demethylincisterol A_3 was lower than that of Sodano's synthesis, our synthesis is convenient and scalable.

Using the developed methodology, we synthesized chaxine A by starting from **6** (Scheme 3). The reduction of the double bond of **6** was found to be quite difficult. Namely, under standard catalytic hydrogenation conditions, epimerization at C-3a adjacent to the carbonyl group occurred. As in the case of the intramolecular HWE reaction described above, the ring system of **8** is highly strained, probably because of the repulsion between the angular methyl group and the bulky side chain. Therefore, we tentatively reduced



Scheme 2. Synthesis of demethylincisterol A_3. Reagents, conditions, and yields: (a) Ref. 14: (i) $KMnO_4$, EtOH, H_2O, −15 °C; (ii) $Pb(OAc)_4$, pyridine, CH_2Cl_2, −15 °C, 80% in two steps; (b) LDA or LiHMDS, TMSCl, THF, −78 °C; (b) OsO_4, NMO, THF, H_2O, *t*-BuOH; (c) $BrCH_2COBr$, pyridine, DMAP, CH_2Cl_2, 59% in three steps; (d) Zn, HMPA, THF, sonication, 66%; (e) $SOCl_2$, pyridine, reflux, 82%; (f) $(EtO)_2POCH_2COOH$, EDC, DMAP, CH_2Cl_2, 53% in three steps; (g) LiCl, DBU, THF, 0 °C, 82%; (h) DIBAL (4 equiv), CH_2Cl_2, −78 °C, 50–60% of **13**, and 30–40% of **12**; (i) DIBAL (7 equiv), CH_2Cl_2, toluene, −78 °C, 84%; (j) Jones reagent, acetone, 0 °C, 39%.



Scheme 3. Synthesis of chaxine A. Reagents, conditions, and yields: (a) $NaBH_4$, MeOH; (b) H_2, PtO_2, AcOH, 89% in two steps; (c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 93%; (d) LiHMDS, TMSCl, THF, −78 °C; (e) OsO_4, NMO, THF, H_2O, *t*-BuOH; (f) $(EtO)_2POCH_2COCl$, pyridine, DMAP, CH_2Cl_2, 52% in three steps; (g) LiCl, DBU, THF, 0 °C, 86%; (h) DIBAL (7 equiv), CH_2Cl_2, toluene, −78 °C, 95%; (i) 1-Me-AZADO, NaOCl, KBr, TBAB, $NaHCO_3$, CH_2Cl_2, H_2O; (j) Jones reagent, acetone, 0 °C, 67% in two steps.

the carbonyl group of **6** with $NaBH_4$ to avoid the undesired epimerization. The resulting alcohol whose stereochemistry was deduced by its ^1H NMR spectrum[20] was subjected to catalytic hydrogenation with Adams' catalyst in acetic acid under a hydrogen atmosphere to give **15** (89%). Oxidation of the hydroxyl group with Dess–Martin periodinane gave **16** (93%). Phosphonate **17** was prepared by the developed method via an acyloin (52% in three steps), and the intramolecular HWE reaction under carefully controlled conditions gave butenolide **18** in 86%. The stereochemistry of **18** was confirmed by NOE experiments. Diol **19** was obtained by the reduction of **18** with an excess amount of DIBAL, and the subsequent Jones oxidation of **19** gave chaxine A in 38% yield. Although the synthesis of chaxine A was achieved, we further investigated the final oxidation reaction to improve the yield. Under the Jones oxidation conditions, we observed multiple products using TLC analysis. To avoid the side reactions, we investigated the step-wise oxidation processes. Namely, we assumed that the mild oxidation of diol **19** into the corresponding ketoaldehyde **20** without reformation of lactone **18** would be possible because we obtained hydroxyaldehyde **12** in the previous reaction shown in Scheme 2. As expected, the 1-Me-AZADO-mediated oxidation developed by Iwabuchi[21] of diol **19** proceeded smoothly to give ketoaldehyde **20**, and, subsequently, the resulting ketoaldehyde was directly oxidized under Lindgren–Kraus–Pinnick condition[22] in one pot to afford **1** in moderate yield (57%). Finally, we obtained **1** by the step-wise oxidation of **19** using Iwabuchi oxidation and Jones oxidation with a 67% yield. The overall yield of chaxine A, based on ergocalciferol, was 18.8% after ten steps. The ^1H and ^{13}C NMR spectra of the synthetic **1** were identical with those of the reported data, and the optical rotation value of the synthetic **1** was in good accord with that of the natural product.[4] The absolute stereochemistry of chaxine A was confirmed to be that proposed by Kawagishi.

3. Conclusion

We achieved the synthesis of demethylincisterol A_3 and the first synthesis of chaxine A employing the intramolecular HWE reaction as a key step to construct the tricyclic ring systems of these compounds. The proposed stereochemistry of natural chaxine A was confirmed by direct comparison of the physical properties between the synthetic and the natural **1**. Because the developed method to construct a fused γ-hydroxybutenolide structure, specifically, butenolide formation by the intramolecular HWE reaction under Masamune–Roush conditions followed by reduction and oxidation by the combination of Iwabuchi and Jones oxidations, is versatile and practical, it is applicable to the synthesis of related natural products and may be useful for the syntheses of the analogues of chaxine A including chaxines B–E[23] to develop an anti-osteoporosis chemotherapeutic agent.

4. Experimental

4.1. General

Optical rotations were measured on a Jasco P-2100 polarimeter. IR spectra were measured on a Jasco IR-4100 spectrometer. ^1H NMR spectra were recorded on a Jeol ECS400 (400 MHz) spectrometer using $CDCl_3$ at δ=7.26 or CD_3OD at δ=3.30 as an internal standard. ^{13}C NMR spectra were recorded on a Jeol ECS400 (100 MHz) spectrometer using $CDCl_3$ at δ=77.0 or CD_3OD at δ=49.0 as an internal standard. Elemental compositions were analyzed on a J-Science MICROCORDER JM10 apparatus. High-resolution EI-MS and ESI-MS data were recorded on Jeol JMS-HX110 and Waters SYNAPT G2 spectrometers. Column chromatography was performed with Wakogel-C200 silica gel.

4.1.1. (1R,3aR,5R,7aR,1′R,2′E,4′R)-5,6,7,7a-Tetrahydro-5-bromoacetoxy-7a-methyl-1-(1′,4′,5′-trimethyl-2′-hexenyl)-3aH-indan-4-one. To a stirred solution of LDA [prepared from 87.6 μl (624 μmol) of diisopropylamine and *n*-BuLi (378 μl, 624 μmol, 1.65 M solution in hexane)] in THF (1 ml) at −78 °C was added **6**[14] (143 mg, 520 μmol) and HMPA (66 μl) in THF (2 ml) was added dropwise, and the mixture was stirred for 45 min. After addition of TMSCl (107 μl, 624 μmol), the reaction mixture was stirred for 1.5 h at the same temperature. Next, the mixture was poured into water. The aqueous phase was extracted with ether. The combined organic layers were washed with water and brine and dried with Na_2SO_4. Removal of the solvent in vacuo yielded the crude silyl enol ether. A stirred solution of the silyl enol ether and *N*-methylmorpholine-*N*-oxide (216 μl, 1.04 mmol, 4.8 M solution in water) in THF/H_2O (3/1, 14 ml) was treated with 264 μl of 1% (w/v) *t*-BuOH solution of OsO_4 (10 μmol). The resulting yellow solution was stirred at room temperature overnight, followed by the addition of 100 mg of $NaHSO_3$, filtration, and the removal of the THF in vacuo. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo afforded a dark brown oil. This oil was dissolved in CH_2Cl_2 (2.5 ml), and DMAP (ca. 4 mg), pyridine (84 μl, 1.04 mmol), and bromoacetyl bromide (90 μl, 1.04 mmol) were successively added to the resulting solution at 0 °C. After stirring for 1.5 h, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and were dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=80/1) to give the titled compound (126 mg, 59% in three steps) as a yellow oil; $[\alpha]_D^{25}$ −36.1 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 2958, 2871, 1749, 1458, 1385, 1267, 1159, 1108, 995, 971, 886, 870 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.66 (s, 3H), 0.82 (d, *J*=6.8 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 1.2–2.2 (m, 12H), 3.16 (dd, *J*=7.3, 11.4 Hz, 1H), 3.85 (s, 2H), 4.95 (dd, *J*=3.0, 3.0 Hz, 1H), 5.17 (dd, *J*=8.5, 15.5 Hz, 1H), 5.24 (dd, *J*=7.8, 15.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.5, 17.6, 18.5, 19.6, 20.0, 21.0, 25.4, 27.7, 29.5, 33.0, 34.3, 39.9, 42.8, 50.9, 56.7, 58.4, 78.2, 132.8, 134.6, 165.9, 205.7. HRMS (ESI): M+Na^+, observed 435.1499; expected for $C_{21}H_{33}O_3NaBr$: 435.1511.

*4.1.2. (3aR,3bR,5aR,6R,8aR,1′R,2′E,4′R)-3a,3b,4,5,5a,7,8,8a-Octahydro-3a-hydroxy-5a-methyl-6-(1′,4′,5′-trimethyl-2′-hexenyl)-2H-indeno[5,4-b]dihydrofuran-2-one (**9**).* The suspension of the above compound (50.0 mg, 121 μmol), zinc powder (2.76 g, 42.2 mmol), and HMPA (20.9 μl, 121 μmol) in THF (1 ml) was sonicated for 2 h. Next, the mixture was poured into 2 N HCl solution and filtered. The aqueous phase was extracted with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine and were dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=10/1) to give the titled compound **9** (26.6 mg, 66%) as a white powder; $[\alpha]_D^{25}$ +15.9 (*c* 0.67, $CHCl_3$); ν_{max} (KBr) 3538, 2959, 2930, 2871, 1744, 1459, 1369, 1206, 1190, 1107, 1004, 969 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (d, *J*=6.8 Hz, 3H), 0.85 (d, *J*=6.9 Hz, 3H), 0.89 (s, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.15–1.86 (m, 14H), 2.03 (m, 3H), 2.58 (d, *J*=16.5 Hz, 1H), 2.61 (d, *J*=16.5 Hz, 1H), 4.38 (dd, *J*=3.0, 3.0 Hz, 1H), 5.14 (dd, *J*=7.8, 15.5 Hz, 1H), 5.22 (dd, *J*=7.8, 15.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.3, 17.6, 18.9, 19.6, 20.0, 20.8, 22.0, 27.0, 33.1, 33.7, 39.8, 40.9, 42.8, 44.8, 50.9, 55.9, 76.0, 82.1, 132.5, 134.9, 174.3. HRMS (ESI): M+Na^+, observed 357.2397; expected for $C_{21}H_{34}O_3Na$: 357.2406.

*4.1.3. (3bRS,5aR,6R,1′R,2′E,4′R)-3b,4,5,5a,7,8-Hexahydro-5a-methyl-6-(1′,4′,5′-trimethyl-2′-hexenyl)-2H-indeno[5,4-b]dihydrofuran-2-one (**10**).* To a stirred solution of **9** (10 mg, 30 μmol) in pyridine (1 ml) was added $SOCl_2$ (11 μl, 150 μmol), and the mixture was

stirred for 30 min at room temperature. After addition of an additional $SOCl_2$ (11 μl, 150 μmol), the reaction mixture was stirred for 30 min at 110 °C. Next, the mixture was cooled and poured into water. The aqueous phase was extracted with ether. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ solution, and brine and were dried with Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=80/1) to give the titled compound **10** (8.2 mg, 86%) as a yellow oil; $[\alpha]_D^{25}$ +17.5 (*c* 0.10, $CHCl_3$); ν_{max} (liquid film) 2958, 2929, 2871, 1784, 1465, 1370, 1260, 1174, 1138, 1010, 973, 803 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82–0.86 (m, 6H), 0.89 (s, 3H), 0.92, 0.93 (each d, *J*=6.8 Hz, total 3H), 1.01, 1.06 (each d, *J*=6.4 Hz, total 3H), 1.25–1.90 (m, H), 2.05–2.25 (m, 4H), 2.99 (d, *J*=20.6 Hz, 1H), 3.08 (m, 1H), 4.82 (m, 1H), 5.21 (dd, *J*=7.8, 15.5 Hz, 1H), 5.26 (dd, *J*=7.8, 15.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 14.1, 17.6, 19.7, 20.0, 20.5, 21.5, 25.9, 26.6, 28.1, 29.7, 31.9, 32.0, 32.7, 33.1, 39.2, 42.8, 42.9, 43.7, 53.8, 68.5, 78.8, 121.9, 132.8, 134.7, 146.9, 175.6. HRMS (ESI): $M+H^+$, observed 317.2479; expected for $C_{21}H_{33}O_2$: 317.2481.

*4.1.4. (1R,3aR,5R,7aR,1′R,2′E,4′R)-5,6,7,7a-Tetrahydro-5-(diethylphosphonoacetoxy)-7a-methyl-1-(1′,4′,5′-trimethyl-2′-hexenyl)-3aH-indan-4-one (**11**).* To a stirred solution of **6**[14] (15.8 mg, 57.4 μmol) in THF (0.5 ml) at −78 °C was added dropwise LiHMDS (68.8 μl, 68.8 μmol, 1.0 M solution in THF), and the mixture was stirred for 45 min. After addition of TMSCl (6 μl, 69 μmol), the reaction mixture was stirred for 2 h at the same temperature. Next, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with ether. The combined organic layers were washed with brine and dried with $MgSO_4$. Removal of the solvent in vacuo yielded the crude silyl enol ether. A stirred solution of the silyl enol ether and *N*-methylmorpholine-*N*-oxide (29 μl, 143 μmol, 4.8 M solution in water) in THF/H_2O (3/1, 2 ml) was treated with 32 μl of a 1% (w/v) *t*-BuOH solution of OsO_4 (1 μmol). The resulting yellow solution was stirred at room temperature overnight, followed by the addition of 5 mg of $NaHSO_3$, filtration, and the removal of the THF in vacuo. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent in vacuo afforded a dark brown oil. This oil was dissolved in CH_2Cl_2 (0.5 ml), and DMAP (ca. 5 mg), diethylphosphonoacetic acid (18 μl, 110 μmol), and EDC (19.8 mg, 115 μmol) were successively added to the resulting solution at 0 °C. After stirring for 48 h at room temperature, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, saturated aqueous NH_4Cl solution, and brine and were dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=2/1) to give the titled compound **11** (14.4 mg, 53% in three steps) as a colorless oil; [found: C, 63.58; H, 9.07. $C_{25}H_{43}O_6P$ requires C, 63.81; H, 9.21%]; $[\alpha]_D^{26}$ −17.8 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3470, 2960, 2872, 1746, 1461, 1386, 1268, 1114, 1025, 973, 905, 869, 836 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.65 (s, 3H), 0.82 (d, *J*=7.3 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H), 1.4–1.9 (m, 9H), 1.34 (t, *J*=6.9 Hz, 6H), 2.04 (m, 2H), 2.13 (m, 1H), 3.00 (d, *J*=21.5 Hz, 2H), 3.03 (dd, *J*=7.3, 11.5 Hz, 1H), 4.16 (m, 4H), 4.91 (t, *J*=3.4 Hz, 1H), 5.16 (dd, *J*=7.8, 15.5 Hz, 1H), 5.23 (dd, *J*=7.8, 15.5 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.5, 16.3, 16.4, 17.6, 18.5, 19.6, 20.0, 21.0, 27.8, 29.6, 33.0, 33.8, 34.3, 35.1, 39.8, 42.9, 51.1, 56.7, 58.1, 62.71, 62.76, 62.83, 77.9, 132.8, 134.6, 164.5, 164.6, 205.7. HRMS (ESI): $M+Na^+$, observed 493.2674; expected for $C_{25}H_{43}O_6NaP$: 493.2695.

*4.1.5. (3bR,5aR,6R,8aR,1′R,2′E,4′R)-3a,3b,4,5,5a,7,8,8a-Octahydro-5a-methyl-6-(1′,4′,5′-trimethyl-2′-hexenyl)-2H-indeno[5,4-b]furan-2-one (**8**).* To a stirred and cooled (0 °C) solution of **11** (240 mg, 508 μmol) in THF (3 ml) under an Ar atmosphere were added LiCl (32.3 mg, 761 μmol) and DBU (83.4 μl, 558 μmol). The mixture was stirred for 1 h at 0 °C and subsequently quenched with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate=20/1) to give the titled compound **8** (132 mg, 82%) as a colorless oil; [found: C, 79.52; H, 9.92. $C_{21}H_{32}O_2$ requires C, 79.70; H, 10.19%]; $[\alpha]_D^{26}$ −91.3 (*c*=1.0, $CHCl_3$); ν_{max} (liquid film) 2958, 2873, 1754, 1641, 1460, 1384, 1329, 1156, 1084, 1018, 972, 941, 897, 849, 805 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (d, *J*=6.8 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.91 (s, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.4 Hz, 3H), 1.25–1.60 (m, 5H), 1.83–2.13 (m, 6H), 2.31 (m, 1H), 2.69 (m, 1H), 5.15 (dd, *J*=7.8, 15.5 Hz, 1H), 5.26 (dd, *J*=7.8, 15.5 Hz, 1H), 5.30 (m, 1H), 5.70 (dd, *J*=2.2, 2.2 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 17.6, 19.0, 19.6, 19.9, 20.6, 22.3, 26.1, 29.2, 33.0, 34.2, 40.1, 41.5, 42.8, 49.5, 56.8, 80.6, 113.3, 133.0, 134.4, 174.1, 174.8. HRMS (ESI): $M+H^+$, observed 317.2478; expected for $C_{21}H_{33}O_2$: 317.2481. The prolonged reaction time resulted in isomerization of C-4 to give **14**. Properties of **14**: $[\alpha]_D^{25}$ +233.2 (*c*=0.485, $CHCl_3$); ν_{max} (liquid film) 2956, 2872, 1749, 1654, 1457, 1383, 1153, 1129, 1060, 1003, 889, 851 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.60 (s, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.84 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.04 (d, *J*=6.8 Hz, 3H), 1.22–1.64 (m, 6H), 1.74 (m, 1H), 1.88 (m, 2H), 2.05 (m, 2H), 2.29–2.43 (m, 2H), 4.65 (ddd, *J*=0.9, 7.3, 10.5 Hz, 1H), 5.16 (dd, *J*=8.2, 15.5 Hz, 1H), 5.25 (dd, *J*=7.8, 15.5 Hz, 1H), 5.63 (br dd, *J*=1.9, 1.9 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.2, 17.6, 19.6, 19.9, 21.0, 28.9, 29.7, 30.8, 33.0, 35.6, 40.1, 42.8, 48.0, 52.2, 55.4, 81.8, 111.1, 132.9, 134.6, 172.7, 173.9. HRMS (ESI): $M+H^+$, observed 317.2475; expected for $C_{21}H_{33}O_2$: 317.2481.

*4.1.6. (1R,3aR,4Z,5R,7aR,1′R,2′E,4′R)-5,6,7,7a-Tetrahydro-4-(2-hydroxyethylidene)-7a-methyl-1-(1′,4′,5′-trimethyl-2′-hexenyl)-3aH-indan-5-ol (**13**).* To a stirred and cooled (−78 °C) solution of **8** (106 mg, 333 μmol) in CH_2Cl_2 (3 ml) was added DIBAL (1.55 ml, 2.33 mmol, 1.5 M solution in toluene). The mixture was stirred for 1.5 h at −78 °C and was quenched by the careful addition of MeOH. The mixture was then warmed to room temperature and diluted with aqueous Rochelle's salt solution and ether. The mixture was stirred vigorously for 2 h. Next, the aqueous phase was extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$. After concentration of the solvent in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=1/1) to give the titled compound **13** (89.7 mg, 84%) as a white powder; [found: C, 78.95; H, 11.13. $C_{21}H_{36}O_2$ requires C, 78.69; H, 11.32%]; $[\alpha]_D^{25}$ +1.7 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3403 (br), 2957, 2927, 2872, 1462, 1371, 1262, 1075, 1013, 973, 804, 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.55 (s, 3H), 0.83 (d, *J*=6.4 Hz, 3H), 0.84 (d, *J*=6.4 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.03 (d, *J*=6.3 Hz, 3H), 1.25–1.55 (m, 7H), 1.75–1.90 (m, 6H), 2.02 (m, 1H), 2.52 (m, 1H), 4.20 (ddd, *J*=0.9, 6.8, 12.4 Hz, 1H), 4.33 (ddd, *J*=1.4, 7.8, 12.4 Hz, 1H), 4.73 (t, *J*=1.5 Hz, 1H), 5.18 (dd, *J*=7.8, 15.5 Hz, 1H), 5.21 (dd, *J*=7.8, 15.5 Hz, 1H), 5.35 (dt, *J*=2.0, 7.3 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 11.4, 17.6, 19.6, 20.0, 21.1, 22.1, 27.7, 30.2, 33.1, 34.5, 40.4, 42.8, 44.9, 49.7, 56.2, 57.8, 64.4, 122.5, 132.1, 135.5, 144.8. HRMS (ESI): $M+Na^+$, observed 343.2592; expected for $C_{21}H_{36}O_2Na$: 343.2613. By using less amount of DIBAL, the corresponding aldehyde **12** was obtained in 30–40% yield. Properties of **12**: white powder, $[\alpha]_D^{25}$ +130.8 (*c* 0.68, $CHCl_3$); ν_{max} (KBr) 3399 (br), 2956, 2872, 1664, 1458, 1372, 1136, 1028, 971 cm^{-1}; δ_H (400 MHz, CD_3OD) 0.63 (s, 3H), 0.84 (d, *J*=7.3 Hz, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.9 Hz, 3H), 1.05 (d, *J*=6.4 Hz, 3H), 1.25–1.55 (m, 6H), 1.76–1.95 (m, 6H), 2.05 (m, 1H), 2.86 (m, 1H), 5.21 (dd, *J*=7.8, 15.5 Hz, 1H), 5.25 (dd, *J*=7.8, 15.5 Hz, 1H), 5.33 (m, 1H), 5.67 (dd. *J*=1.3, 8.3 Hz, 1H), 10.08 (d, *J*=8.3 Hz, 1H); δ_C (100 MHz, CD_3OD) 12.1, 18.2, 20.1, 20.5, 21.6, 22.6, 28.8, 32.0, 34.4, 35.6, 41.7, 44.4, 51.8, 58.0, 64.1, 125.9, 133.6, 136.7, 169.0, 191.9.

HRMS (ESI): M+Na^+, observed 341.2445; expected for $C_{21}H_{34}O_2Na$: 341.2456.

*4.1.7. Demethylincisterol A_3 (**2**).* To a solution of **13** (5 mg, 16 μmol) in acetone (0.5 ml), Jones reagent was added dropwise until an orange-brown color persisted. Thereafter, the reaction mixture was poured into water, the aqueous mixture was extracted with three portions of EtOAc, and the organic phases were washed successively with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexane/EtOAc=5/1) to give the titled compound **2** (2 mg, 39%) as a colorless oil; $[\alpha]_D^{25}$ +130.0 (*c* 0.35, MeOH), lit.[4] $[\alpha]_D$ +130 (*c* 0.69, MeOH); ν_{max} (liquid film) 3266 (br), 2953, 2871, 1759, 1730, 1667, 1465, 1378, 1342, 1131, 1115, 1054, 970, 948, 904, 852 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.61 (s, 3H), 0.83 (d, *J*=6.9 Hz, 3H), 0.84 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.04 (d, *J*=6.4 Hz, 3H), 0.93–1.00 (m, 2H), 1.10–2.10 (m, 14H), 2.27 (ddd, *J*=2.3, 3.6, 13.7 Hz, 1H), 2.65 (m, 1H), 2.76 (br s, 1H), 5.17 (dd, *J*=8.2, 15.2 Hz, 1H), 5.25 (dd, *J*=7.8, 15.2 Hz, 1H), 5.64 (d, *J*=1.8 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 11.7, 17.6, 19.6, 20.0, 21.0, 21.4, 28.8, 33.0, 35.0, 35.3, 40.1, 42.8, 48.8, 50.3, 55.3, 104.7, 112.3, 132.9, 134.6, 170.5, 170.7. HRMS (EI): M^+, observed 332.2351; expected for $C_{21}H_{32}O_3$: 332.2354. The ^1H and ^{13}C NMR spectra of the synthetic **2** are identical with those of the natural product. The purity of the synthetic **2** is >98% as judged by the NMR spectra.

*4.1.8. (1R,3aR,4S,7aR,1′R,4′S)-Hexahydro-7a-methyl-1-(1′,4′,5′-trimethylhexyl)-indan-4-ol (**15**).* To a stirred and cooled (−7 °C) solution of **6**[14] (766 mg, 2.77 mmol) in MeOH (8 ml) was added $NaBH_4$ (146 mg, 3.86 mmol). After stirring for 1 h at room temperature, the reaction was quenched with water. The aqueous phase was extracted with EtOAc, and the organic extract was washed with saturated aqueous $NaHCO_3$ solution, water, and brine and was dried with $MgSO_4$. Removal of the solvent in vacuo gave the crude alcohol. The obtained crude alcohol was dissolved in acetic acid (10 ml), and PtO_2 (6.3 mg, 28 μmol) was added to the solution. The mixture was stirred under H_2 (balloon) for 24 h at room temperature. The mixture was subsequently diluted with EtOAc and filtered through a Celite pad. After evaporation of the solvents, the residue was purified by column chromatography (hexane/ethyl acetate=90/1) to give the titled compound **15** (692 mg, 89% in two steps) as a colorless oil; [found: C, 81.05; H, 13.01. $C_{19}H_{36}O$ requires C, 81.36; H, 12.94%]; $[\alpha]_D^{25}$ +23.6 (*c* 1.0, $CHCl_3$). ν_{max} (liquid film): 3431 (br), 2957, 2873, 1465, 1377, 1242, 1166, 1066, 990, 942, 887 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.78 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.9 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 0.87–0.98 (m, 3H), 0.90 (d, *J*=6.4 Hz, 3H), 0.93 (s, 3H), 1.00–1.92 (m, 16H), 2.00 (m, 1H), 4.07 (br s, 1H); δ_C (400 MHz, $CDCl_3$) 13.5, 15.4, 17.4, 17.6, 18.7, 20.5, 22.5, 27.1, 30.6, 31.5, 33.5, 33.6, 35.7, 39.1, 40.4, 41.8, 52.6, 56.6, 69.5. HRMS (EI): M^+, observed 280.2761; expected for $C_{19}H_{36}O$: 280.2766.

*4.1.9. (1R,3aR,7aR,1′R,4′S)-5,6,7,7a-Tetrahydro-7a-methyl-1-(1′,4′,5′-trimethylhexyl)-3aH-indan-4-one (**16**).* To a stirred and cooled (0 °C) solution of **15** (8.7 mg, 31.1 μmol) in CH_2Cl_2 (0.5 ml) was added $NaHCO_3$ (13.0 mg, 155 μmol) and Dess–Martin periodinane (20.0 mg, 62.2 μmol). After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the organic extract was washed with saturated aqueous $NaHCO_3$ solution, water, and brine and was dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=60/1) to afford the titled compound **16** (8.2 mg, 95%) as a colorless oil; [found: C, 81.81; H, 12.48. $C_{19}H_{34}O$ requires C, 81.95; H, 12.31%]; $[\alpha]_D^{25}$ −3.6 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 2956, 2872, 1715, 1465, 1378, 1307, 1241, 1226, 1056, 942, 874, 836 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.63 (s, 3H), 0.78 (d, *J*=6.9 Hz, 3H), 0.79 (d, *J*=6.9 Hz, 3H), 0.85 (d, *J*=6.6 Hz, 3H), 0.90–1.20 (m, 2H), 0.95 (d, *J*=6.4 Hz, 3H), 1.10–2.30 (m, 16H), 2.44 (dd, *J*=7.5, 11.6 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.5, 15.4, 17.6, 18.9, 19.1, 20.5, 24.1, 27.5, 30.5, 31.5, 33.5, 35.9, 38.98, 39.01, 41.0, 49.9, 56.6, 62.0, 212.1. HRMS (ESI): M+Na^+, observed 301.2498; expected for $C_{19}H_{34}ONa$: 301.2507.

*4.1.10. (1R,3aR,5R,7aR,1′R,4′S)-5,6,7,7a-Tetrahydro-5-(diethylphosphonoacetoxy)-7a-methyl-1-(1′,4′,5′-trimethylhexyl)-3aH-indan-4-one (**17**).* To a stirred solution of **16** (100 mg, 359 μmol) in THF (2 ml) at −78 °C was added dropwise LiHMDS (430 μl, 430 μmol, 1.0 M solution in THF), and the mixture was stirred for 45 min. After addition of TMSCl (37 μl, 430 μmol), the reaction mixture was stirred for 2 h at the same temperature. Next, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with ether. The combined organic layers were washed with brine and dried with $MgSO_4$. Removal of the solvent in vacuo yielded the crude silyl enol ether. A stirred solution of the silyl enol ether and *N*-methylmorpholine-*N*-oxide (150 μl, 718 μmol, 4.8 M solution in water) in THF/H_2O (3/1, 10 ml) was treated with 181 μl of a 1% (w/v) *t*-BuOH solution of OsO_4 (7 μmol). The resulting yellow solution was stirred at room temperature overnight, followed by the addition of 25 mg of $NaHSO_3$, filtration, and the removal of the THF in vacuo. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent in vacuo afforded a dark brown oil. This oil was dissolved in CH_2Cl_2 (1 ml), and pyridine (43.5 μl, 538 μmol), and diethylphosphonoacetyl chloride[24] (153 mg, 716 μmol) were added to the resulting solution at 0 °C. After stirring for 1 h at 0 °C, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate=2/1) to give the titled compound **17** (88.2 mg, 52% in three steps) as a white solid; mp 100–102 °C; [found: C, 63.55; H, 9.90. $C_{25}H_{45}O_6P$ requires C, 63.54; H, 9.60%]; $[\alpha]_D^{25}$ −7.9 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3471, 2958, 2872, 1746, 1601, 1465, 1387, 1324, 1263, 1162, 1112, 1018, 973, 904, 869, 835 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.64 (s, 3H), 0.78 (d, *J*=6.8 Hz, 6H), 0.79 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=6.4 Hz, 3H), 0.94–1.25 (m, 3H), 1.30–1.62 (m, 4H), 1.34 (t, *J*=6.9 Hz, 6H), 1.82–2.13 (m, 6H), 2.98 (s, 1H), 3.01 (dd, *J*=7.3, 12.0 Hz, 1H), 3.03 (s, 1H), 4.16 (m, 4H), 4.91 (t, *J*=3.4 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 12.3, 15.4, 16.3, 16.4, 17.6, 18.5, 18.9, 20.5, 27.5, 29.6, 30.4, 31.5, 33.5, 33.8, 34.4, 35.1, 35.9, 39.0, 51.2, 56.7, 58.0, 62.68, 62.74, 62.76, 62.82, 77.9, 164.5, 164.6, 205.8. HRMS (ESI): M+Na^+, observed 495.2842; expected for $C_{25}H_{45}O_6NaP$: 495.2851.

*4.1.11. (3bR,5aR,6R,8aR,1′R,4′S)-3a,3b,4,5,5a,7,8,8a-Octahydro-5a-methyl-6-(1′,4′,5′-trimethylhexyl)-2H-indeno[5,4-b]furan-2-one (**18**).* To a stirred and cooled (0 °C) solution of **17** (88 mg, 186 μmol) in THF (1 ml) under an Ar atmosphere were added LiCl (11.8 mg, 278 μmol) and DBU (30.5 μl, 204 μmol). The mixture was stirred for 1 h at 0 °C and subsequently quenched with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate=20/1) to give the titled compound **18** (50.9 mg, 86%) as a colorless oil; $[\alpha]_D^{25}$ −71.6 (*c*=1.0, $CHCl_3$); ν_{max} (liquid film) 2957, 2872, 1755, 1643, 1467, 1378, 1329, 1284, 1153, 1087, 1021, 977, 941, 898, 847, 805 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.79 (d, *J*=6.8 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 0.90 (s, 3H), 0.92 (d, *J*=6.4 Hz, 3H), 0.94–1.00 (m, 2H), 1.16–1.62 (m, 9H), 1.82–2.13 (m, 4H), 2.31 (m, 1H), 2.69 (m, 1H), 5.30 (dddd, *J*=1.8, 1.8, 5.7, 13.2 Hz, 1H), 5.70 (dd, *J*=2.2, 2.2 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 15.4, 17.6, 18.5,

18.9, 20.5, 22.4, 26.2, 28.8, 30.6, 31.5, 33.2, 34.4, 36.1, 39.0, 41.7, 49.3, 56.8, 80.7, 113.2, 174.1, 174.9. HRMS (EI): M^+, observed 318.2528. $C_{21}H_{34}O_2$ requires 318.2559.

*4.1.12. (1R,3aR,4Z,5R,7aR,1′R,4′S)-5,6,7,7a-Tetrahydro-4-(2-hydroxyethylidene)-7a-methyl-1-(1′,4′,5′-trimethylhexyl)-3aH-indan-5-ol (**19**).* To a stirred and cooled (−78 °C) solution of **18** (10.0 mg, 31.4 μmol) in CH_2Cl_2 (1 ml) was added DIBAL (219 μl, 219 μmol, 1.0 M solution in toluene). The mixture was stirred for 1.5 h at −78 °C and was quenched by the careful addition of MeOH. The mixture was then warmed to room temperature and diluted with aqueous Rochelle's salt solution and ether. The mixture was stirred vigorously for 2 h. Next, the aqueous phase was extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$. After concentration of the solvent in vacuo, the residue was purified by column chromatography (hexane/ethyl acetate=1/1) to give the titled compound **19** (9.5 mg, 95%) as a white solid; mp 80–82 °C; [found: C, 77.90; H, 11.84. $C_{21}H_{38}O_2$ requires C, 78.20; H, 11.18%]; $[\alpha]_D^{25}$ +16.6 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3255, 2959, 2871, 1467, 1377, 1337, 1252, 1214, 1155, 1100, 1054, 1007, 960, 922, 893, 853 cm^{-1} δ_H (400 MHz, $CDCl_3$) 0.54 (s, 3H), 0.78 (d, *J*=6.6 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.8 Hz, 3H), 0.88–1.02 (m, 2H), 0.93 (d, *J*=6.0 Hz, 3H), 1.10–2.30 (m, 17H), 2.51 (dd, *J*=7.3, 10.9 Hz, 1H), 4.18 (dd, *J*=6.1, 12.0 Hz, 1H), 4.33 (ddd, *J*=1.1, 8.2, 12.0 Hz, 1H), 4.73 (br s, 1H), 5.35 (dt, *J*=1.6, 7.3 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 11.1, 15.5, 17.6, 19.0, 20.5, 22.2, 27.5, 30.3, 30.6, 31.5, 33.6, 34.6, 36.5, 39.1, 45.1, 49.6, 56.2, 57.8, 64.4, 122.6, 144.9. HRMS (ESI): $M+Na^+$, observed 345.2757; $C_{21}H_{38}O_2Na$ requires: 345.2770.

*4.1.13. Chaxine A (**1**).* A 10 ml flask was charged with a solution of **19** (10.0 mg, 31.0 μmol), 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO, 52 μg, 0.31 μmol) in CH_2Cl_2 (0.2 ml) and a saturated aqueous solution of $NaHCO_3$ (42.0 μl) containing KBr (368 μg, 3.09 μmol) and *n*-Bu_4NBr (TBAB, 238 μg, 1.54 μmol). To this cooled (0 °C) and stirred mixture, a pre-mixed solution of aqueous NaOCl and a saturated aqueous solution of $NaHCO_3$ (304 μl, 1:1.4 v/v) was added dropwise over 6 min. The mixture was stirred for 1 h at 0 °C and was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (0.2 ml). The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to afford the crude ketoaldehyde. To a stirred solution of the resulting ketoaldehyde in acetone (0.2 ml), the Jones reagent (2.67 M, 161 μl, 4.29 μmol) was added dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C and then poured into water. The aqueous phase was extracted with EtOAc. The combined organic extracts were washed successively with water and brine and dried with $MgSO_4$. After evaporation of the solvents, the residue was purified by column chromatography (hexane/ethyl acetate=4/1) to give the titled compound **1** (6.6 mg, 67%) as a colorless oil; $[\alpha]_D^{24}$ +136.8 (*c* 0.37, MeOH), lit.[4] $[\alpha]_D$+133 (*c* 0.1, MeOH); ν_{max} (liquid film) 3359 (br), 2959, 1746, 1663, 1465, 1378, 1338, 1214, 1177, 1127, 1048, 960, 905, 854 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.59 (s, 3H), 0.78 (d, *J*=6.9 Hz, 6H), 0.86 (d, *J*=6.9 Hz, 3H), 0.95 (d, *J*=6.4 Hz, 3H), 0.93–1.00 (m, 2H), 1.10–1.65 (m, 9H), 1.75 (m, 1H), 1.86 (ddd, *J*=4.5, 14.2, 18.8 Hz, 1H), 2.00 (ddd, *J*=2.3, 4.6, 13.3 Hz, 1H), 2.08 (m, 1H), 2.27 (ddd, *J*=2.3, 4.2, 14.3 Hz, 1H), 2.64 (ddd, *J*=1.8, 6.5, 11.6 Hz, 1H), 3.04 (br s, 1H), 5.63 (d, *J*=1.8 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 11.5, 15.4, 17.6, 18.9, 20.5, 21.4, 28.6, 30.5, 31.5, 33.5, 35.2, 35.3, 36.2, 39.0, 49.0, 50.3, 55.4, 104.9, 112.2, 170.8, 171.1. HRMS (EI): M^+, observed 334.2515; expected for $C_{21}H_{34}O_3$: 334.2508. The ^1H and ^{13}C NMR spectra of the synthetic **1** are identical with those of the natural product. The purity of the synthetic **1** is >98% as judged by the NMR spectra.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.057.

References and notes

1. Suda, T. *Proc. Jpn. Acad., Ser. B* **2004**, *80*, 407–421.
2. Udagawa, N.; Takahashi, N.; Akatsu, T.; Tanaka, H.; Sasaki, T.; Nishihara, T.; Koga, T.; Martin, J.; Suda, T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 7260–7264.
3. Teitelbaum, S. L. *Am. J. Pathol.* **2007**, *170*, 427–435.
4. Kawagishi, H.; Akachi, T.; Ogawa, T.; Masuda, K.; Yamaguchi, K.; Yazawa, K.; Takahashi, M. *Heterocycles* **2006**, *69*, 253–258.
5. Kawagishi, H.; Takahashi, M.; Yamaguchi, K.; Yazawa, K. Jpn. Kokai Tokkyo Koho JP 2008019223, 2008.
6. De Riccardis, F.; Spinella, A.; Izzo, I.; Giordano, A.; Sodano, G. *Tetrahedron Lett.* **1995**, *36*, 4303–4306.
7. (a) Ohta, K.; Yaoita, Y.; Matsuda, N.; Kikuchi, M. *Natural Med.* **1996**, *50*, 179–181; (b) Akihisa, T.; Nakamura, Y.; Tagata, M.; Tokuda, H.; Yasukawa, K.; Uchiyama, E.; Suzuki, T.; Kimura, Y. *Chem. Biodiversity* **2007**, *4*, 224–231; (c) Ueguchi, Y.; Matsunami, K.; Otsuka, H.; Kondo, K. *J. Nat. Med.* **2011**, *65*, 307–312.
8. Mansoor, T. A.; Hong, J.; Lee, C.-O.; Bae, S.-J.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2005**, *68*, 331–336.
9. For example: (a) Fascio, M.; Mors, W. B.; Gilbert, B.; Mahajan, J. R.; Monteiro, M. B.; Dos Santos Filho, D.; Vichnewski, W. *Phytochemistry* **1976**, *15*, 201–203; (b) Ayer, W. A.; Dufresne, C. *Bull. Soc. Chim. Belg.* **1986**, *95*, 699–706; (c) Scher, J. M.; Burgess, E. J.; Lorimer, S. D.; Perry, N. B. *Tetrahedron* **2002**, *58*, 7875–7882; (d) Nishimura, K.; Hitotsuyanagi, Y.; Sugeta, N.; Sakakura, K.; Fujita, K.; Fukaya, H.; Aoyagi, Y.; Hasuda, T.; Kinoshita, T.; He, D.-H.; Otsuka, H.; Takeda, Y.; Takeya, K. *Tetrahedron* **2006**, *62*, 1512–1519; (e) Yadav, P. P.; Arora, A.; Bid, H. K.; Konwar, R. R.; Kanojiya, S. *Tetrahedron Lett.* **2007**, *48*, 7194–7198; (f) Matuo, Y.; Deguchi, J.; Hosoya, T.; Hirasawa, Y.; Hirobe, C.; Shiro, M.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 976–979.
10. Togashi, H.; Mizushima, Y.; Takemura, M.; Sunagawara, F.; Koshino, H.; Esumi, Y.; Uzawa, J.; Kumagai, H.; Matsukage, A.; Yoshida, S.; Sakaguchi, K. *Biochem. Pharmacol.* **1998**, *56*, 583–590.
11. Takikawa, H.; Ueda, K.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 5569–5571.
12. Miles, W. H.; Connell, K. B. *Tetrahedron Lett.* **2003**, *44*, 1161–1163.
13. Han, G.; KaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293–6306.
14. De Riccardis, F.; Izzo, I.; Di Filippo, M.; Sodano, G.; D'Acquisto, F.; Carnuccio, R. *Tetrahedron* **1997**, *53*, 10871–10882.
15. Bestmann, H. J.; Sandmeier, D. *Chem. Ber.* **1980**, *113*, 274–277.
16. Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346–5349.
17. Tamura, H.; Fujita, A.; Takagi, Y.; Kitahara, T.; Mori, K. *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1902–1903.
18. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
19. Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 377–379.
20. (a) Inhoffen, H. H.; Quinkert, G.; Schütz, S.; Kampe, D.; Domagk, G. F. *Chem. Ber.* **1957**, *90*, 664–673; (b) Blalemore, P. R.; Kocienski, P. J.; Marzcak, S.; Wicha, J. *Synthesis* **1999**, 1209–1215.
21. Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.
22. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890; (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825–4830; (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
23. Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015–5024.
24. Choi, J.-H.; Ogawa, A.; Abe, N.; Masuda, K.; Koyama, T.; Yazawa, K.; Kawagishi, H. *Tetrahedron* **2009**, *65*, 9850–9853.