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ENANTIOSELECTIVE TOTAL SYNTHESIS OF NOVEL DITERPENOID PYRONES (+)-SESQUICILLIN AND (–)-NALANTHALIDE FROM FUNGAL FERMENTATIONS

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Abstract – We efficiently synthesized (+)-sesquicillin (a glucocorticoid antagonist) and (–)-nalanthalide (a potassium channel Kv1.3 blocker) in a convergent and unified manner starting from (+)-5-methyl-Wieland–Miescher ketone. The synthesis involved the following key steps: (i) a [2,3]-Wittig rearrangement of a stannylmethyl ether to install the stereogenic center at C9 and the *exo*-methylene functionality at C8 present in the *trans*-decalin portion, (ii) a coupling reaction of a *trans*-decalin portion with a γ-pyrone moiety to assemble the requisite whole carbon framework, and (iii) a conversion of a γ-pyrone moiety to an α-pyrone ring to produce (+)-sesquicillin. The present total synthesis has verified the absolute configuration of these natural products.

INTRODUCTION

In recent years, a number of diterpenoid pyrones and related compounds have been isolated from microorganisms, particularly from fungal strains.[1–5] Several of these natural products have been reported to exhibit a wide variety of biological properties such as insecticidal,[1,2c] antihypertensive,[2d] bronchospasmolytic,[2d] anti-inflammatory,[2d] laxative,[2d] anticancer,[2e] and immunosuppressive[3–5] activities. In most cases, however, further biological studies including structure-activity relationships are severely restricted probably because of the scarcity of structural diversity of microorganisms. Consequently, the development of efficient and flexible synthetic routes for this class of natural products and related compounds is quite desirable and worthwhile from the viewpoint of medicinal chemistry and

This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

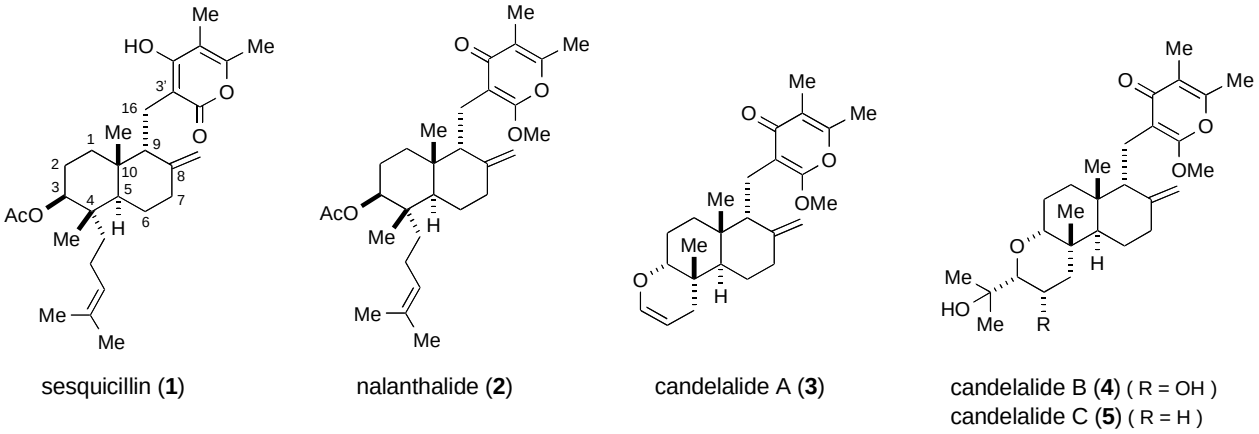


Figure 1. Structures of sesquicillin (**1**), nalanthalide (**2**), and candelalides A (**3**), B (**4**), C (**5**).

pharmaceuticals.

In 1998, Erkel *et al.*[2a] reported the isolation and structural elucidation of a novel diterpenoid pyrone, sesquicillin (**1**) (Figure 1), from the culture broth of *Acremonium* sp. This substance was first assigned as an inhibitor of glucocorticoid-mediated signal transduction.[2a] It has also been reported that sesquicillin strongly induced G1 phase arrest in human breast cancer cell lines.[2b] Recently, four additional and new sesquicillin analogues (named sesquicillin B–E) were isolated from the culture broth of *Albophoma* sp. and together with **1** (renamed sesquicillin A).[2c] These substances were reported to exhibit insecticidal and cytotoxic activities.[2c] The gross structure and stereochemistry of **1** have been determined by extensive NMR spectroscopic studies including COSY, HMQC, HMBC, and NOESY experiments,[2a] but the absolute configuration has not been assigned. This natural product consists of a *trans*-decalin skeleton connected to a fully substituted α-pyrone via a methylene linkage.[2]

A closely related diterpenoid pyrone, nalanthalide (**2**), was isolated from the culture broth of *Nalanthamala* sp. by the Merck research group in 2001.[4] This substance was found to be a blocker of the voltage-gated potassium channel Kv1.3 for a novel molecular-targeted immunosuppressive agent.[4,6,7] The gross structure of **2** including stereochemistry, wherein the α-pyrone ring of **1** is replaced by a γ-pyrone ring, has been determined using detailed NMR spectroscopic analysis,[4] however, the absolute configuration has not been disclosed. Subsequently, the Merck research group reported the isolation and structural determination of three novel diterpenoid pyrones, candelalides A (**3**), B (**4**), and C (**5**), from the culture broth of *Sesquicillium candelabrum* in 2002.[5] They found that these substances were also potential Kv1.3 blocking immunosuppressive agents.[5]

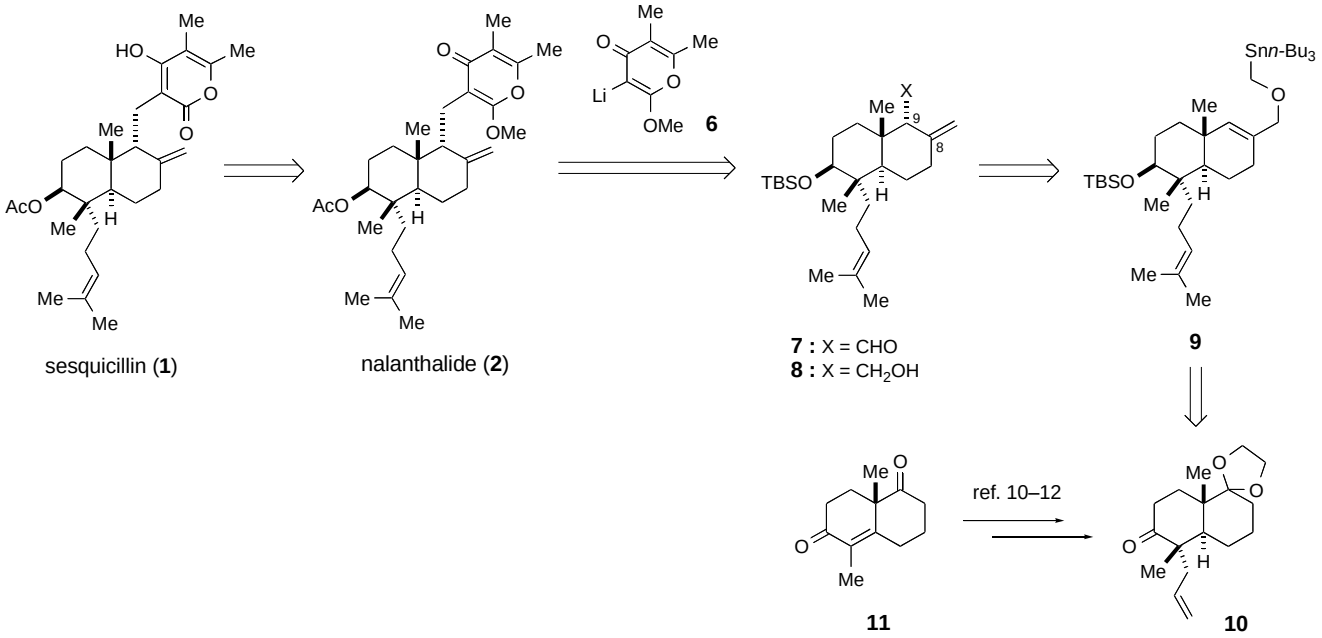
The attractive biological properties and unique structural features of **1**–**5** have made them intriguing targets for total synthesis. To date, only one total synthesis of (±)-**1** has been reported by Danishefsky and Zhang in 2002.[8] We have previously reported our preliminary results on the first total synthesis of (–)-**2**[9]

and (–)-**3**[10] in enantiomerically pure forms, leading to the confirmation of their absolute configurations. In addition, we also achieved an enatioselective total synthesis of candelalides B (**4**) and C (**5**).[11] In this paper, we describe the full details of our unified total synthesis of naturally occurring (+)-sesquicillin (**1**) and (–)-nalanthalide (**2**).

RESULTS AND DISCUSSION

Synthetic plan for (+)-sesquicillin (1) and (–)-nalanthalide (2)

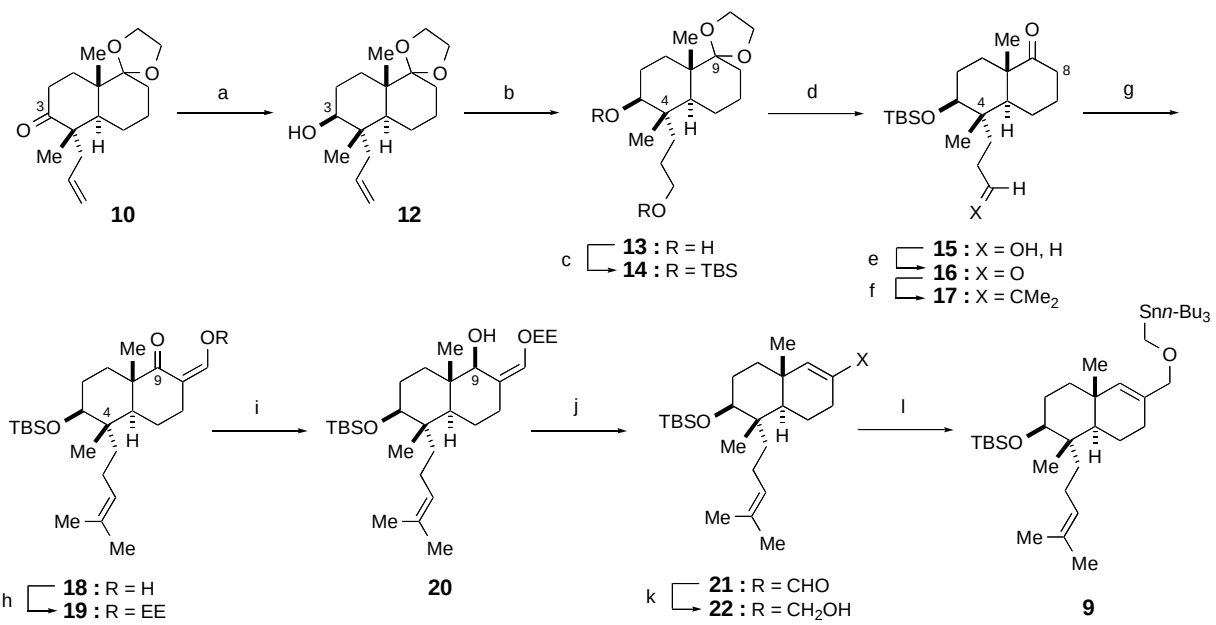
The synthetic plan for (+)-sesquicillin (**1**) and (–)-nalanthalide (**2**) is outlined in Scheme 1. The γ-pyrone moiety present in **2** is considered to be an equivalent to vinylogous ester; therefore, hydrolysis of this moiety followed by its spontaneous tautomerization to α-pyrone would deliver sesquicillin (**1**). To the best of our knowledge, the method for conversion of **2** to **1** was hitherto unknown, and hence this reaction posed a considerable challenge from the synthetic viewpoint. Nalanthalide (**2**) would be produced through a coupling reaction of the appropriately substituted *trans*-decalin segment **7** (accessible from alcohol **8**) with the fully substituted γ-pyrone **6**.[10,11] The advanced key intermediate **8**, having both a hydroxymethyl group at C9 and an *exo*-methylene moiety at C8, would be formed through the strategic [2,3]-Wittig rearrangement of stannylmethyl ether **9**, where we believed that the C9 stereogenic center and the C8 *exo*-methylene moiety in the product **8** would be established simultaneously. The intermediate **9** should, in turn, be accessed from the known *trans*-decalone **10**,[10–12] which is readily prepared in an enantiomerically pure form from (+)-5-methyl-Wieland–Miescher ketone (**11**), by sequential functional group manipulation and deprotection or vice versa.



Scheme 1. Synthetic plan for sesquicillin (**1**) and nalanthalide (**2**).

Synthesis of the substrate 9 for the [2,3]-Wittig rearrangement

As shown in Scheme 2, we initially pursued the synthesis of the intermediate **9**, a substrate for the critical [2,3]-Wittig rearrangement, starting from the known enantiomerically pure *trans*-decalone **10**[10–12] (>99% ee). Our route to the allyl alcohol **22** from **10** was based on the procedures established by Danishefsky *et al.*[8] with some improvements in the reaction steps and conditions, which eventually allowed for an increase of the total yield of **22** (49% overall yield in eleven steps versus 30% overall yield from those same steps). Thus, stereoselective reduction of the C3 carbonyl group in **10** with lithium aluminum hydride produced the desired β-alcohol **12** in 98% yield as a single stereoisomer. Subsequent hydroboration of **12** (BH_3·THF, THF, 0 °C→rt) followed by hydrogen peroxide oxidation (30% aq. H_2O_2, 3M NaOH, 0 °C→rt) delivered the requisite diol **13** in 85% yield. The two hydroxy groups in **13** were simultaneously protected as the bis(*tert*-butyldimethylsilyl) (TBS) ethers to furnish the corresponding disilyl ether **14** in quantitative yield. Compound **14** was then converted to the aldehyde **16** via a two-step operation including selective deprotection of the TBS group on the C4 side chain and ethylene acetal moiety at C9 by acid treatment [AcOH/THF/H_2O (3:1:1), 50 °C, 4 h, 90%], followed by Dess–Martin oxidation[13] (96%). To set up the requisite homoprenyl side chain at the C4 position, compound **16** was subjected to a Wittig reaction using isopropylidene(triphenyl)phosphorane providing the desired product **17** in 86% yield.



Scheme 2. Synthesis of the key intermediates **9**. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O, –45°C to rt, 1.5 h, 98%; (b) BH_3·THF, THF, 0°C to rt, 1 h; 30% aq. H_2O_2, 3M NaOH, 0°C to rt, 1.5 h, 85%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 30 min, quant.; (d) AcOH/THF/H_2O (3:1:1), 50°C, 4 h, 90%; (e) Dess-Martin periodinane, CH_2Cl_2, rt, 96%; (f) Ph_3PCHMe_2I, *n*-BuLi, THF, 0°C, 1 h, 86%; (g) ethyl formate, NaH, THF, 0° to rt, 1 h, quant.; (g) ethyl vinyl ether, PPTS, rt, 4 h, 91%; (i) $NaBH_4$, EtOH, 0°C to rt, 2 h, 92%; (j) MsCl, Et_3N, CH_2Cl_2, 0°C, 30 min, 94% (k) $NaBH_4$, EtOH, 0°C to rt, 30 min, quant.; (l) *n*-Bu_3SnCH_2I, KH, 18-crown-6, THF, 0°C to rt, 1 h, 98%

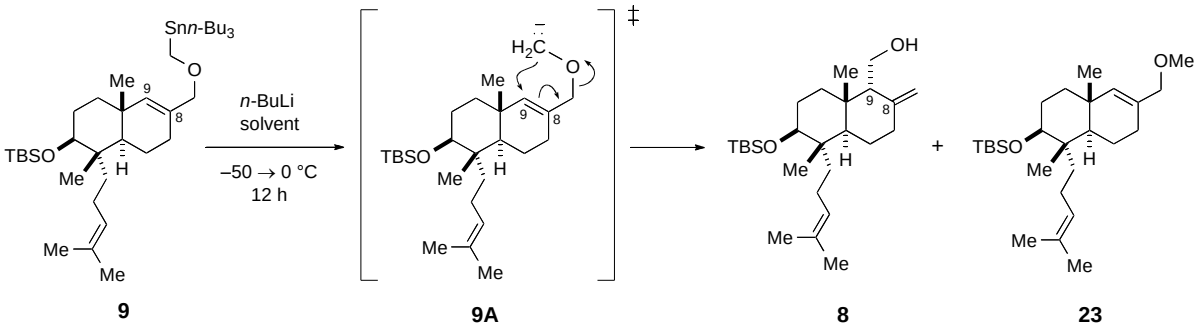
To introduce a formyl group at the C8 position, compound **17** was treated with ethyl formate in the presence of sodium hydride to afford the enol **18** in quantitative yield, whose hydroxy group was then protected as its ethoxyethyl (EE) ether to produce the enol ether **19** in 91% yield. Subsequent sodium borohydride reduction of **19** provided the alcohol **20** in 92% yield as a single stereoisomer with respect to the C9 position. Simultaneous dehydration of the C9 hydroxy function and deprotection of the EE group within **20** was efficiently achieved by reaction with methanesulfonyl chloride (MsCl) in the presence of triethylamine at 0 °C for 30 min, which provided the desired α,β-unsaturated aldehyde **21** in 94% yield. Finally, compound **21** was converted to the requisite stannylmethyl ether **9** having 98% overall yield through a two step sequence involving sodium borohydride reduction of the formyl group, followed by stannylmethylation[14] of the resulting alcohol **22** with iodomethyl tri-*n*-butyltin in the presence of potassium hydride and 18-crown-6.

Synthesis of the *trans*-decalin segment 7

With the key intermediate **9** synthesized, we then conducted the synthesis of the *trans*-decalin segment **7** (Table 1 and Scheme 3). The sequence involved the critical stereocontrolled [2,3]-Wittig rearrangement[15,16] of **9** to construct the requisite decalin system **8**, having both a hydroxymethyl group at C9 with correct stereochemistry and an *exo*-methylene functionality at C8. After screening several reaction conditions (Table 1), we found that the designed [2,3]-Wittig rearrangement of **9** proceeded smoothly and cleanly in a completely stereoselective manner by treatment with *n*-butyllithium in hexane from −50 to 0 °C for 12 h. The expected rearrangement product **8** was obtained in 92% yield as a single stereoisomer with respect to the C9 position (entry 1). The structure and stereochemistry of **8** was confirmed by extensive spectroscopic analysis including 600 MHz ^{1}H NMR NOESY experiments. The selected NOESY correlation of **8** is depicted in Figure 2.

Note that the use of hexane as the solvent was crucial in this reaction. When THF or Et_2O was used instead of hexane, the yield of the desired rearrangement product **8** was reduced to 46–69% (entries 2 and 3), and in addition, the undesired methyl ether **23** was obtained in 23–43% yield as a byproduct. The byproduct **23** was probably formed by protonation of the intermediary carboanion **9A**, generated in situ by tin/lithium exchange; this reactive species might have brought about a proton abstraction from the ethereal solvents such as THF and Et_2O because the methylene position adjacent to oxygen atom in those solvents is relatively activated. To continue the synthesis (Scheme 3), the rearrangement product **8** was then subjected to Dess–Martin oxidation[13] to give the requisite *trans*-decalin segment **7** in quantitative yield.

Table 1. [2,3]-Wittig rearrangement of the stannylmethyl ether **9**.



9 **9A** **8** **23**

Entry	Solvent	Yield [%][a]	
		8	**23**
1	hexane	92	0
2	THF	46	43
3	Et_2O	69	23

[a] Isolated yield.

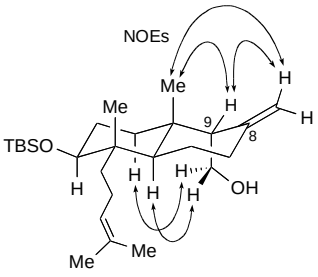


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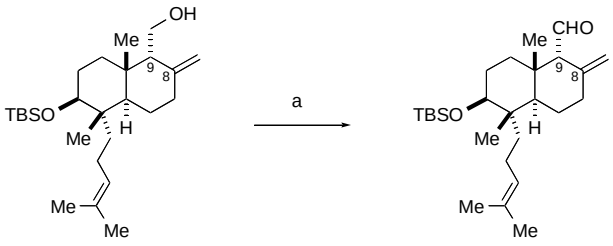
Figure 2. Selected NOESY correlation of **8**.

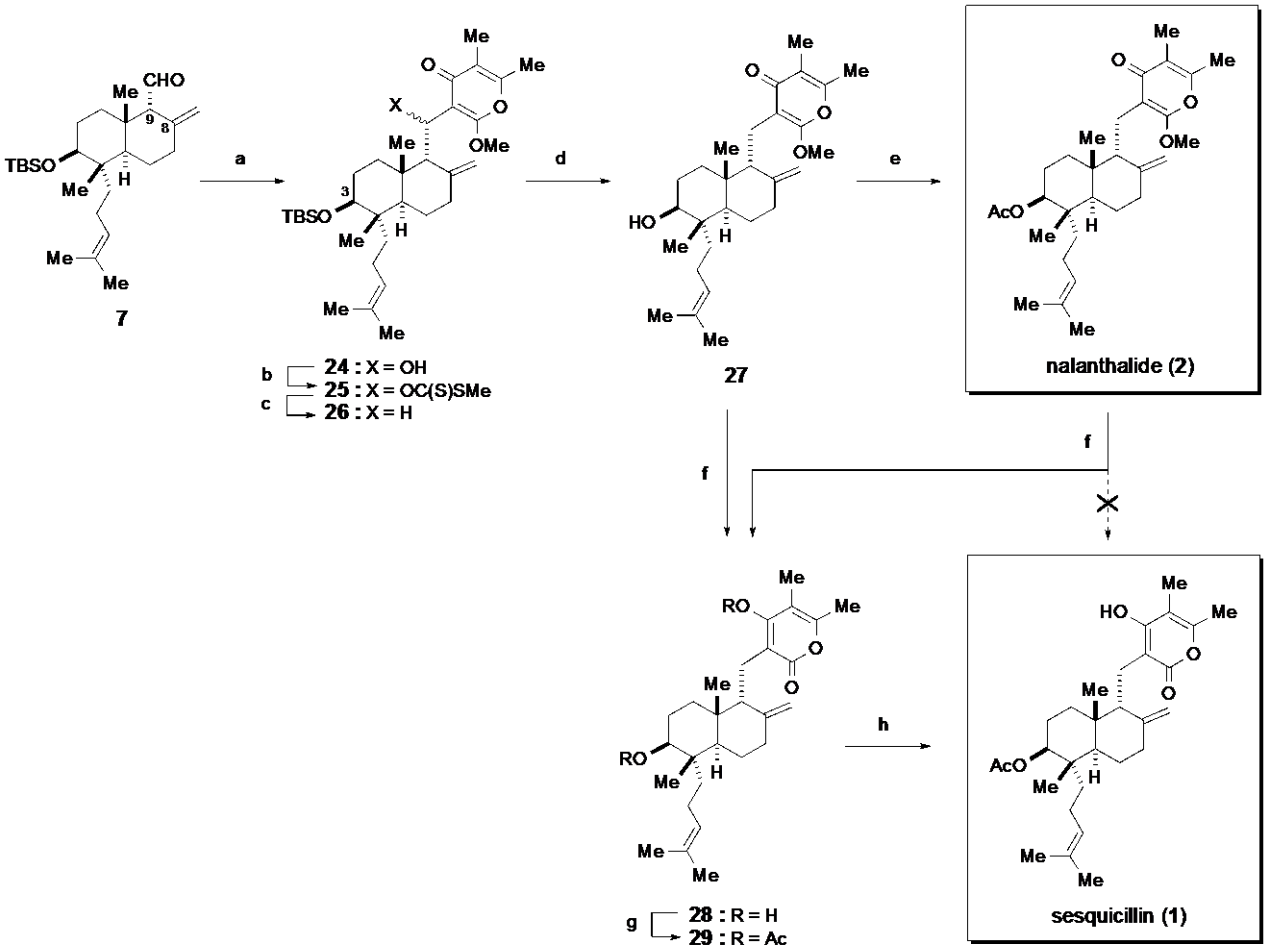


8 **7**

Scheme 3. Synthesis of the decalin segment (**7**). *Reagents and conditions*: (a) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h, quant.

Synthesis of (–)-nalanthalide (2) and (+)-sesquicillin (1)

Having obtained the requisite *trans*-decalin segment **7** efficiently, we then investigated the synthesis of the first target nalanthalide (**2**) by assembling the *trans*-decalin and γ-pyrone segments (Scheme 4). The crucial coupling reaction of **7** with the 3-lithio-γ-pyrone **6**[10] was successfully achieved by an initial bromine/lithium exchange of 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one and subsequent reaction



Scheme 4. Synthesis of sesquicillin (**1**) and nalanthalide (**2**). *Reagents and conditions*: (a) 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one, *n*-BuLi, THF, –78°C, 5 min; at –78°C, add **7**, –78 to –55°C, 1 h, 87% (b) $NaN(SiMe_3)_2$, CS_2, MeI, THF, –78°C, 2 h (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 6 h, 82% (2 steps); (d) BF_3-Et_2O, MeCN, 0°C to rt, 4 h, 95%; (e) Ac_2O, DMAP, pyridine, rt, 1 h, 86%; (f) 1M NaOH, MeOH, reflux, 12 h; (g) Ac_2O, Et_3N, DMAP, 0°C, 1 h, 70% (2 steps); (h) 1M NaOH, THF, 0°C, 30 min, 88%

with **7** from −78 to −55 °C for 1 h. The desired coupling product **24** was obtained in 87% yield as a mixture of epimeric alcohols (ca. 1:1 by 400 MHz ^{1}H NMR) that was very difficult to separate. Note that the regiochemical integrity of the sensitive *exo*-methylene moiety at C8 was maintained during the coupling reaction. Removal of the sterically hindered hydroxy group in **24** was achieved smoothly by applying the Barton–McCombie procedure[17] with some improvements in the reaction conditions. Thus, treatment of a mixture of **24** and carbon disulfide in THF with sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$] at −78 °C followed by addition of iodomethane at the same temperature provided the corresponding methyl xanthate **25**, which was further treated with tri-*n*-butyltin hydride and 2,2'-azobis(isobutyronitrile) (AIBN) in refluxing toluene to produce the desired deoxygenated product **26** in 82% overall yield. The sterically congested TBS group in **26** was deprotected by exposure to $BF_3 \cdot Et_2O$ in acetonitrile at room temperature, affording de-*O*-acetylnalanthalide (**27**) in 95% yield. When this deprotection was performed using the conventional procedure (TBAF, THF, rt→reflux), the yield of the

desired product **27** was reduced to ~40% because the γ-pyrone moiety was labile under these basic conditions. Finally, acetylation of **27** under standard conditions (Ac_2O, pyridine, DMAP, rt) resulted in the targeted (–)-nalanthalide (**2**) in 86% yield. The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic sample **2** were identical to those of natural **2**.[4] The optical rotation of the synthetic **2** {$[\alpha]_D^{25}$ –48.3 (*c* 1.02, $CHCl_3$)} was in good agreement with that of natural **2** {lit.,[4] $[\alpha]_D^{25}$ –58.2 (*c* 0.275, $CHCl_3$)},[18] leading to the assignment of the absolute configuration of natural **2**.

Having successfully synthesized the first target nalanthalide (**2**), we next directed our attention to the synthesis of the second target sesquicillin (**1**). Initial attempts to realize the direct conversion of **2** to **1** under conventional basic conditions (e.g. 1 M NaOH, MeOH, rt→reflux) were unsuccessful. The expected hydrolysis of the γ-pyrone moiety in **2** followed by tautomerization of the γ-pyrone to α-pyrone proceeded smoothly and cleanly at reflux temperature; however, unfavorable deprotection of the acetyl group took place during the reaction, producing de-*O*-acetylsesquicillin (**28**) in good yield (83%). Therefore, we decided to pursue the synthesis of **1** in a step-by-step manner from the intermediate **27**. Thus, hydrolysis of the γ-pyrone moiety in **27** under basic conditions (1 M NaOH, MeOH, reflux, 12 h) provided the desired **28**, having an α-pyrone ring, whose two hydroxy groups were simultaneously acetylated (Ac_2O, Et_3N, DMAP, 0 °C, 1 h) to form the corresponding diacetate **29** in 70% overall yield from **27**. Finally, chemoselective deprotection of the acetyl group on the pyrone ring in **29** under mild basic conditions (1 M NaOH, THF, 0 °C, 30 min) resulted in the formation of (+)-sesquicillin (**1**) in 88% yield. The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic sample **1** were identical to those of natural **1**.[2a] The optical rotation of the synthetic **1** {$[\alpha]_D^{25}$ +7.1 (*c* 0.36, $CHCl_3$)} was essentially identical to that of natural **1** {lit.,[2a] $[\alpha]_D^{22}$ +10 (*c* 0.8, $CHCl_3$)},[18] verifying the absolute configuration of natural **1**.

CONCLUSION

We have accomplished the enantioselective total synthesis of (+)-sesquicillin (**1**) and (–)-nalanthalide (**2**) in a convergent and unified manner starting from (+)-5-methyl-Wieland–Miescher ketone (**11**). The key steps of the synthesis were (i) highly stereoselective [2,3]-Wittig rearrangement of stannylmethyl ether **9** to produce the requisite decalin portion **8**, having both a hydroxymethyl group at C9 with the correct stereochemistry and an *exo*-methylene functionality at C8 (**9**→**8**, Table 1), (ii) straightforward coupling of the *trans*-decalin segment **7** with the γ-pyrone segment **6** to construct the desired carbon framework **24** (**7**+**6**→**24**, Scheme 4), and (iii) strategic conversion of the γ-pyrone moiety present in de-*O*-acetylnalanthalide (**27**) to the corresponding α-pyrone **28** to approach sesquicillin (**1**) (**27**→**28**, Scheme 4). This synthesis has verified the absolute configurations of these natural products. On the basis of the present study, we are currently synthesizing the analogues of **1** and **2** with the aim of exploring

their structure–activity relationships and will report our results in the future.

EXPERIMENTAL

General Procedures: All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction 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. Tetrahydrofuran (THF) and Et_2O were freshly distilled from Na metal/benzophenone under argon. Toluene was distilled from Na metal under argon. *N*,*N*-Dimethylformamide (DMF), CH_2Cl_2, pyridine, and hexane were distilled from CaH under argon.Measurements of optical rotations were performed with a JASCO DIP-370 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a JEOL AL-400 (400MHz) or a JEOL JNM-LA600 (600 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si (δ=0) as an internal standard. The following abbreviations are used: singlet (s), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectra measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and High-resolution mass (MS and HRMS) spectra were measured on a JEOL JMS-DX 303/JMA-DA 5000 SYSTEM high resolution mass spectrometer.

(4a*S*,5*S*,6*S*,8a*S*)-5-Allyl-5,8a-dimethyl-6-(hydroxy)decahydronaphthalen-1-one 1-ethylene acetal (12): A solution of **11**[10,11] (4.54g, 16 mmol) in dry Et_2O (50 mL) was added to a stirred suspension of $LiAlH_4$ (683 mg, 18 mmol) in dry Et_2O (200 mL) at −45 °C under argon, and the mixture was warmed up to rt over 1.5 h. The reaction was quenched by the successive addition of 1 M NaOH (0.7 mL), H_2O (0.7 mL), and brine (0.7 mL) at 0 °C. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane/EtOAc, 6:1) to give **12** (4.49 g, 98%) as a colorless viscous oil. $[\alpha]_D^{20}$ −11.5° (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, s), 1.07 (3H, s), 1.29–1.70 (11H, m), 2.02 (1H, dd, J = 7.8, 14.2 Hz), 2.30 (1H, dd, J = 7.3, 14.2 Hz), 3.46–3.50 (1H, m), 3.79–3.85 (1H, m), 3.88–3.94 (3H, m), 5.00–5.11 (2H, m), 5.82–5.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8, 16.9, 20.3, 22.8, 26.8, 28.5, 30.4, 42.0, 42.6, 43.0, 43.5, 64.7, 65.3, 73.9, 113.2, 117.5, 135.2; IR (neat) 3443, 3072, 2945, 2872, 2677, 1636, 1475, 1450, 1382, 1335, 1280, 1200, 1176, 1128, 1105, 1036, 907, 759, 732, 703 cm^{-1}; HREIMS (*m/z*) calcd for $C_{17}H_{28}O_3$ (M^+), 280.2038, found 280.2038.

(4a*S*,5*S*,6*S*,8a*S*)-5,8a-Dimethyl-6-hydroxy-5-(3-hydroxypropyl)decahydronaphthalen-1-one-1-

ethylene acetal (13): A solution of BH_3·THF in THF (1.00 M solution, 32.3 mL, 32 mmol) was added dropwise to a stirred solution of **12** (4.52 g, 16 mmol) in dry THF (160 mL) at 0 °C under argon. After 1 h, 3 M NaOH (16.1 mL, 48 mmol) and 30% aqueous H_2O_2 (18.3 mL, 0.16 mol) was added to the mixture at 0 °C, and stirring was continued for 1.5 h at rt. The reaction was quenched with H_2O (160 mL) at 0°C, and the resulting mixture was extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 1:2 → 0:1) to give **13** (4.09 g, 85%) as a white solid. Recrystallization from acetone afford colorless needles, mp 138–139 °C; $[\alpha]_D^{20}$ −9.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, s), 1.07 (3H, s), 1.25–1.34 (2H, m), 1.38–1.47 (4H, m), 1.50–1.61 (6H, m), 1.62–1.71 (3H, m), 1.67 (2H, br s), 3.46–3.50 (1H, m), 3.56–3.68 (2H, m), 3.80–3.86 (1H, m), 3.88–3.94 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 17.1, 20.2, 23.0, 25.9, 26.9, 28.6, 30.4, 33.2, 40.8, 42.4, 42.9, 63.6, 64.8, 65.3, 73.0, 113.3; IR (KBr) 3359, 2941, 2871, 2308, 1684, 1652, 1456, 1383, 1337, 1281, 1199, 1176, 1130, 1104, 1045, 907, 754 cm^{-1}; HREIMS (*m/z*) calcd for $C_{17}H_{30}O_4$ (M^+), 298.2144, found 298.2144. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.55; H, 10.59.

(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5-(*tert*-butyldimethylsiloxypropyl)-5,8a-(dimethyl)-decahydronaphthalen-1-one 1-ethylene acetal (14): *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (8.71 mL, 38 mmol) was added dropwise to a stirred solution of **13** (3.77 g, 13 mmol) in dry CH_2Cl_2 (150 mL) containing 2,6-lutidine (5.89 mL, 51 mmol) at 0 °C under argon. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 150 mL). The combined extracts were washed with brine (2 x 70 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 50:1→30:1) to give **14** (6.65 g, 100%) as a colorless viscous liquid. $[\alpha]_D^{20}$ +2.4° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.04 (9H, s), 0.76 (3H, s), 0.87 (9H, s), 0.89 (9H, s), 1.06 (3H, s), 1.16–1.21 (1H, m), 1.27 (1H, dd, *J* = 3.9, 13.0 Hz), 1.33 (1H, dt, *J* = 3.4, 12.7 Hz), 1.37–1.40 (6H, m), 1.45–1.50 (1H, m), 1.52–1.66 (5H, m), 3.44 (1H, dd, *J* = 4.9, 10.5 Hz), 3.47–3.51 (2H, m), 3.56–3.61 (1H, m), 3.78–3.84 (1H, m), 3.87–3.94 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.29, –5.25, –4.9, –3.6, 17.1, 17.7, 18.1, 18.5, 20.3, 23.0, 25.9 (3 carbons), 26.1 (3 carbons), 26.4, 27.4, 28.5, 30.5, 33.0, 41.2, 42.3, 42.8, 64.3, 64.7, 65.3, 73.7, 113.5; IR (neat) 2950, 2858, 1471, 1462, 1384, 1361, 1254, 1106, 1007, 908, 836, 773, 666 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{58}O_4Si_2$ (M^+): 526.3874, found 526.3871.

(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-5-(3-hydroxypropyl)decahydro-

naphthalen-1-one (15): A solution of **14** (5.83 g, 11 mmol) in AcOH/THF/H_2O (3:1:1) (150 mL) was stirred at 50 °C for 4 h. The reaction mixture was basified with 1 M NaOH (50 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 200 mL). The combine extracts were washed brine (2 x 100mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 4:1→3:1) to give **15** (3.67 g, 90%) as a white solid. Recrystallization from Et_2O afford colorless needles, mp 104–105 °C; $[\alpha]_D^{20}$ −8.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.06 (3H, s), 0.88 (3H, s), 0.89 (9H, s), 1.16 (3H, s), 1.21–1.33 (3H, m), 1.37–1.47 (1H, m), 1.50–1.72 (9H, m), 2.05–2.09 (1H, m), 2.17–2.22 (1H, m), 2.56 (1H, td, *J* = 6.8, 13.7 Hz), 3.41 (1H, dd, *J* = 3.4, 5.4 Hz), 3.51–3.57 (1H, m), 3.60–3.65 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.0, –3.7, 17.9, 18.0, 19.0, 20.5, 25.8 (3 carbons), 26.1, 26.2, 27.0, 30.9, 32.9, 37.4, 42.1, 47.0, 48.2, 63.4, 73.0, 215.5; IR (KBr) 3426, 2939, 2859, 2247, 1756, 1471, 1383, 1253, 1113, 1099, 1075, 961, 836, 773, 669 cm^{-1}; HREIMS (*m/z*) calcd for $C_{21}H_{40}O_3Si$ (M^+), 368.2747, found 368.2729. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94: C, 68.65; H, 11.46.

(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-5-(3-oxopropyl)decahydronaphthalen-1-one (16): Dess–Martin periodinane (5.60 g, 13 mmol) was added in small portions to a stirred solution of **16** (4.08 g, 11 mmol) in dry CH_2Cl_2 (110 mL) containing $NaHCO_3$ (9.28 g, 0.11 mmol) at rt. After 30 min, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (50 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined extracts were washed with 1 M NaOH (50 mL) and brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 50:1→10:1) to give **16** (3.89 g, 96%) as a white solid. Recrystallization from Et_2O afford colorless needles, mp 83–84 °C; $[\alpha]_D^{20}$ −17.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 0.94 (3H, s), 1.12 (1H, dd, *J* = 2.4, 12.2 Hz), 1.17 (3H, s), 1.46–1.63 (5H, m), 1.65–1.69 (2H, m), 1.70–1.79 (1H, m), 1.86–1.94 (1H, m), 2.05–2.17 (2H, m), 2.17–2.23 (1H, m), 2.26–2.35 (1H, m), 2.57 (1H, td, *J* = 6.8, 13.7 Hz), 3.33 (1H, dd, *J* = 5.4, 9.8 Hz), 9.74 (1H, t, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.6, 17.6, 18.0, 18.9, 20.5, 25.8 (3 carbons), 26.1, 26.9, 28.7, 30.9, 37.3, 37.9, 42.0, 47.2, 48.2, 73.0, 201.8, 214.9; IR (KBr) 3430, 3395, 2951, 2882, 2858, 2713, 1726, 1713, 1471, 1385, 1253, 1113, 1005, 962, 900, 836, 773, 668 cm^{-1}; HREIMS (*m/z*) calcd for $C_{21}H_{38}O_3Si$ (M^+), 366.2590, found 366.2595. Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45: C, 68.98; H, 10.87.

(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-5-(4-methylpent-3-enyl)decahydronaphthalen-1-one (17): *n*-BuLi in hexane (1.58 M, 12 mL, 19 mmol) was added dropwise to a stirred suspension of isopropyltriphenylphosphonium iodide (9.80 g, 23 mmol) in dry THF (70 mL) at 0 °C

under argon. After 30 min, a solution of **16** (2.76 g, 7.5 mmol) in dry THF (30 mL) was added dropwise to the above mixture at 0 °C, and it was allowed to stand at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and the resulting mixture was extracted with EtOAc (3 x 60 mL). The combined extracts were washed with brine (2 x 50 mL), and dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 100:1→50:1) to give **17** (2.54 g, 86%) as a white solid. Recrystallization from Et_2O afford colorless needles, mp 63–64 °C; $[\alpha]_D^{20}$ +5.7° (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.05 (3H, s), 0.86 (3H, s), 0.88 (9H, s), 1.12–1.20 (1H, m), 1.16 (3H, s), 1.30 (1H, dd, *J* = 2.9, 11.7 Hz), 1.46–1.60 (8H, m), 1.61–1.69 (6H, m), 1.72–1.82 (2H, m), 2.05–2.09 (1H, m), 2.20 (1H, dd, *J* = 4.4, 14.1 Hz), 2.57 (1H, td, *J* = 7.3, 13.9 Hz), 3.43–3.47 (1H, m), 5.00 (1H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1, −3.7, 17.7, 17.9 18.0, 18.9, 20.7, 21.4, 25.7 (3 carbons), 25.8, 26.2, 27.1, 31.0, 36.9, 37.5, 42.4, 47.0, 48.3, 72.9, 124.4, 131.0, 215.5; IR (KBr) 2935, 2859, 2360, 1709, 1471, 1453, 1382, 1361, 1253, 1099, 1067, 1006, 960, 836, 773 cm^{-1}; HREIMS (*m/z*) calcd for $C_{24}H_{44}O_2Si$ (M^+), 392.3111, found 392.3110. Anal. Calcd for $C_{24}H_{44}O_2Si$: C, 73.41; H, 11.29: C, 73.46; H, 11.66.

(*Z*)-(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-2-hydroxymethylene-5-(4-methyl-pent-3-enyl)decahydronaphthalen-1-one (18): A solution of **17** (2.12 g, 5.4 mmol) in dry THF (20 mL) containing ethyl formate (6.54 mL, 81 mmol) was added to a stirred suspension of NaH (60% dispersion in mineral oil) (3.23 g, 81 mmol) in dry THF (40 mL) at 0 °C under argon, and stirring was continued at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 50:1) to give **18** (2.27 g, 100%) as a pale yellow viscous liquid. $[\alpha]_D^{20}$ +36.2° (*c* 1.02, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$): δ 0.03 (3H, s), 0.06 (3H, s), 0.80 (3H, s), 0.88 (9H, s), 1.22 (3H, s), 1.31–1.41 (2H, m), 1.47–1.62 (2H, m), 1.59 (3H, s), 1.66–1.74 (3H, m), 1.68 (3H, s), 1.77–1.83 (2H, m), 2.01 (1H dt, *J* = 3.4, 13.7 Hz), 2.30–2.38 (1H, m), 2.45–2.50 (1H, m), 3.52 (1H, dd, *J* = 6.3, 9.3 Hz), 5.01–5.05 (1H, m), 8.53–8.54 (1H, m), 14.66 (1H, d, *J* = 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1, −3.7, 17.7, 17.9, 18.0, 18.1, 20.6, 21.5, 23.4, 25.7, 25.8 (3 carbons), 27.4, 31.9, 36.9, 41.3, 41.6, 42.5, 73.0, 105.8, 124.4, 131.0, 186.3, 193.7; IR (neat) 2953, 2857, 2735, 1634, 1583, 1471, 1455, 1380, 1360, 1333, 1255, 1209, 1103, 1070, 1006, 942, 890, 836, 773, 669 cm^{-1}; HREIMS (*m/z*) calcd for $C_{25}H_{44}O_3Si$ (M^+), 420.3060, found 420.3057.

(*Z*)-(4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-2-(ethoxyethan-1-yl)oxymethylene-5,8a-dimethyl-5-(4-methylpent-3-enyl)decahydronaphthalen-1-one (19): Pyridinium *p*-toluenesulfonate (PPTS) (133

mg, 0.53 mmol) was added to a stirred solution of **18** (2.22 g, 5.3 mmol) in dry THF (60 mL) containing ethyl vinyl ether (10.1 mL, 0.11 mmol) at rt. After 4 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (40 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 40:1→10:1) to give **19** (1:1 diastereomeric mixture caused by the EE group) (2.37 g, 91%) as a pale yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.06 (3H, s), 0.83 (3H, s), 0.88 (9H, s), 1.12 (3H, s), 1.208 (3/2H, t, *J* = 6.8 Hz), 1.213 (3/2H, t, *J* = 6.8 Hz), 1.24–1.27 (2H, m), 1.34–1.39 (1H, m), 1.423 (3/2H, d, *J* = 5.3 Hz), 1.433 (3/2H, d, *J* = 5.3 Hz), 1.50–1.56 (3H, m), 1.59 (3H, s), 1.61–1.65 (2H, m), 1.68 (3H, s), 1.79–1.82 (2H, m), 1.94 (1H, dt, *J* = 3.4, 13.7 Hz), 2.18–2.27 (1H, m), 2.72 (1H, dd, *J* = 4.4, 16.6 Hz), 3.45–3.51 (2H, m), 3.67–3.75 (1H, m), 5.02–5.10 (2H, m), 7.43 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1, −3.7, 14.90, 14.94, 17.7, 17.9, 18.0, 19.5, 21.1, 21.6, 22.6, 25.7, 25.8 (3 carbons), 27.4, 32.4, 36.7, 42.1, 42.5, 46.0, 63.6 (1/2 carbon), 63.7 (1/2 carbon), 73.1, 103.5 (1/2 carbon), 103.7 (1/2 carbon), 113.7 (1/2 carbon), 113.9 (1/2 carbon), 124.6, 130.9, 151.5 (1/2 carbon), 151.7 (1/2 carbon), 206.3; IR (neat) 2934, 2858, 1681, 1594, 1454, 1381, 1360, 1253, 1207, 1103, 1071, 1042, 970, 950, 893, 836, 773, 667 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{52}O_4Si$ (M^+), 492.3635, found 492.3630.

(*Z*)-(1*R*,4a*S*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-2-(ethoxyethan-1-yl)oxymethylene-5,8a-dimethyl-5-(4-methylpent-3-enyl)decahydronaphthalen-1-ol (20): $NaBH_4$ (954.4 mg, 25.23 mmol) was added in small portions to a stirred solution of **19** (2.49 g, 5.1 mmol) in EtOH (50 mL) at 0 °C, and stirring was continued at rt for 2 h. The reaction was quenched with 10% aqueous AcOH (30 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 30:1→5:1) to give **20** (1:1 diastereomeric mixture caused by EE group) (2.30 g, 92%) as a colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.05 (3H, s), 0.76 (3H, s), 0.78 (3H, s), 0.88 (9H, s), 1.11–1.16 (3H, m), 1.20 (3/2H, t, *J* = 6.8 Hz), 1.21 (3/2H, t, *J* = 6.8 Hz), 1.22–1.28 (1H, m), 1.36 (3H, d, *J* = 5.3 Hz), 1.45–1.62 (5H, m), 1.62 (3H, s), 1.67 (3H, s), 1.76–1.86 (3H, m), 2.91 (1H, d, *J* = 14.5 Hz), 3.44–3.53 (2H, m), 3.63–3.65 (1H, m), 3.69–3.78 (1H, m), 4.87–4.93 (1H, m), 5.04 (1H, t, *J* = 7.2 Hz), 6.24–6.25, (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.7, 12.8, 15.1 (1/2 carbon), 15.2 (1/2 carbon), 17.70, 17.74 (1/2 carbon), 17.8 (1/2 carbon), 18.1, 20.46 (1/2 carbon), 20.54 (1/2 carbon), 21.31 (1/2 carbon), 21.33 (1/2 carbon), 21.5, 24.2, 25.7, 25.8 (3 carbons), 27.7, 35.61 (1/2 carbon), 35.63 (1/2 carbon), 36.8, 40.1 (1/2 carbon), 40.2 (1/2 carbon), 41.5, 45.7, 62.2 (1/2 carbon), 62.4 (1/2carbon), 73.6, 81.1, 100.8, 118.6 (1/2 carbon), 118.7 (1/2 carbon), 124.8, 130.8, 133.4 (1/2 carbon),

133.8 (1/2 carbon); IR (neat) 3490, 2935, 2857, 1685, 1451, 1382, 1253, 1147, 1102, 1056, 940, 893, 835, 772, 671 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{54}O_4Si$ (M^+), 494.3791, found 494.3792.

(4a*R*,5*S*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-5-(4-methylpent-3-enyl)-3,4,4a,5,6,7,8,8a-octahydronaphthlene-2-carbaldehyde (21): Methanesulfonyl chloride (MsCl) (3.41 mL, 44 mmol) was added dropwise to a stirred solution of **20** (2.18 g, 4.4 mmol) in dry CH_2Cl_2 (50 mL) containing Et_3N (7.38 mL, 53 mmol) at 0 °C under argon. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 70 mL). The combined extracts were washed with brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 40:1→30:1) to give **21** (1.68 g, 94%) as a colorless viscous liquid. $[\alpha]_D^{20}$ +43.8° (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.06 (3H, s), 0.80 (3H, s), 0.90 (9H, s), 1.07, (3H, s), 1.18–1.28 (2H, m), 1.31–1.49 (2H, m), 1.54–1.65 (2H, m), 1.58 (3H, s), 1.68 (3H, s), 1.71–1.82 (4H, m), 2.04–2.14 (1H, m), 2,42 (1H, dd, *J* = 5.9, 18.0 Hz), 3.55 (1H, dd, *J* = 4.9, 11.2 Hz), 5.01–5.05 (1H, m), 6.41 (1H, s), 9.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1, −3.7, 17.4, 17.6 (2 carbons), 18.0, 20.7, 21.4, 22.8, 25.7, 25.8 (3 carbons), 27.6, 36.1, 36.3, 36.9, 41.4, 44.1, 73.2, 124.4, 131.0, 137.7, 162.0, 194.8; IR (neat) 2928, 2856, 2711, 1692, 1683, 1643, 1471, 1379, 1254, 1188, 1102, 1066, 995, 949, 888, 836, 773, 723, 672 cm^{-1}; HREIMS (*m/z*) calcd for $C_{25}H_{44}O_2Si$ (M^+), 404.3111, found 404.3107.

(4a*R*,5*S*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-5-(4-methylpent-3-enyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-2-methanol (22): $NaBH_4$ (239 mg, 6.3 mmol) was added in small portions to a stirred solution of **21** (1.70 g, 4.2 mmol) in EtOH (50 mL) at 0 °C, and stirring was continued at rt for 30 min. The reaction was quenched with 10% aqueous AcOH (20 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 20:1→10:1) to give **22** (1.69 g, 100%) as a colorless viscous liquid. $[\alpha]_D^{20}$ +31.9° (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.05 (3H, s), 0.76 (3H, s), 0.88 (9H, s), 0.96 (3H, s), 1.16–1.26 (3H, m), 1.42–1.57 (4H, m), 1.59 (3H, s), 1.62–1.74 (2H, m), 1.68 (3H, s), 1.78–1.84 (2H, m), 1.98–2.07 (1H, m), 2.12 (1H, dd, *J* = 6.3, 17.6 Hz), 3.53 (1H, dd, *J* = 4.9, 11.2 Hz), 3.96 (2H, s), 5.04 (1H, t, *J* = 6.8 Hz), 5.36 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1, −3.7, 17.6, 17.7, 18.1, 18.3, 21.5, 21.8, 25.7, 25.9 (3 carbons), 27.1, 28.0, 34.6, 37.0, 37.3, 41.2, 44.4, 67.1, 73.6, 124.8, 130.7, 133.7, 136.4; IR (neat) 3315, 2934, 2857, 1461, 1382, 1361, 1253, 1102, 1068, 998, 945, 887, 836, 772 cm^{-1}; HREIMS (*m/z*) calcd for $C_{25}H_{46}O_2Si$ (M^+), 406.3267, found 406.3268.

(4a*R*,5*S*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)-2-(tri-*n*-butylstannylmethoxymethyl)-5,8a-dimethyl-5-(4-methylpent-3-enyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene (9): KH (30% dispersion in mineral oil) (1.63 g, 12 mmol), 18-crown-6 (3.17 g, 12 mmol), and iodomethyl tri-*n*-buthyltin (2.40 mL, 8.0 mmol) were added successively to a stirred solution of **22** (1.63 g, 4.0 mmol) in dry THF (60 mL) at 0 °C under argon, and stirring was continued at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 70 mL). The combined extracts were washed with brine (2 x 50 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 200:1) to give **9** (2.79 g, 98%) as a colorless viscous liquid. $[\alpha]_D^{20}$ +16.9° (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.76 (3H, s), 0.87–0.92 (24H, m), 0.97 (3H, s), 1.15–1.35 (10H, m), 1.39–1.54 (10H, m), 1.59 (3H, s), 1.63–1.74 (1H, m), 1.68 (3H, s), 1.73–1.88 (2H, m), 1.91–2.00 (1H, m), 2.07 (1H, dd, *J* = 5.9, 17.6 Hz), 3.53 (1H, dd, *J* = 4.9, 11.2 Hz), 3.61–3.72 (4H, m), 5.04 (1H, t, *J* = 6.8 Hz), 5.32 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.7, 9.0 (3 carbons), 13.7 (3 carbons), 17.6, 17.7, 18.1, 18.3, 21.5, 21.9, 25.8, 25.9 (3 carbons), 27.3 (3 carbons), 27.4, 28.1, 29.2 (3 carbons), 34.8, 37.0, 37.4, 41.2, 44.4, 60.6, 73.7, 79.3, 124.9, 130.7, 131.2, 138.0; IR (neat) 2956, 2926, 2854, 1734, 1671, 1460, 1378, 1254, 1186, 1102, 1065, 945, 887, 836, 773, 730, 666 cm^{-1}; HREIMS (*m/z*) calcd for $C_{38}H_{74}O_2SiSn$ (M^+), 710.4480, found 710.4478.

(1*R*,4a*R*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydronaphthalene-1-methanol (8) and (4a*R*,5*S*,6*S*,8a*R*)-6-(*tert*-butyldimethylsiloxy)-2-methoxymethyl-5,8a-dimethyl-5-(4-methylpent-3-enyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene (23): *n*-BuLi in hexane (1.57 M solution, 12.1 mL, 19 mmol) was added dropwise to a stirred solution of **9** (2.70 g, 3.8 mmol) in dry hexane (200 mL) at −50 °C under argon. The mixture was gradually warmed up to 0 °C over 4 h, and stirring was continued at 0 °C for 8 h. The reaction was quenched with saturated aqueous NH_4Cl (2 x 50 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (50mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 1:0→20:1) to give **8** (1.47 g, 92%) as a colorless viscous oil.

8: $[\alpha]_D^{20}$ +4.7° (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.75 (3H, s), 0.87 (9H, s), 0.98 (3H, s), 1.16–1.18 (1H, m), 1.20–1.28 (2H, m), 1.38–1.48 (3H, m), 1.51–1.60 (3H, m), 1.60 (3H, s), 1.68 (3H, s), 1.73 (1H, dd, *J* = 2.9, 13.2 Hz), 1.81 (1H, d, *J* = 7.8 Hz), 1.84 (1H, d, *J* = 7.8 Hz), 1.93 (1H, dd, *J* = 5.4, 10.7 Hz), 2.05–2.13 (1H, m), 2.26–2.29 (1H, m), 3.46 (1H, dd, *J* = 4.9, 11.2 Hz), 3.55–3.61 (1H, m), 3.76 (1H, dt, *J* = 4.9, 9.8 Hz), 4.76 (1H, t, *J* = 1.9 Hz), 4.94 (1H, t, *J* = 1.9 Hz),

5.04 (1H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.6, 17.7, 18.05, 18.07, 21.6, 22.7, 23.1, 25.7, 25.8 (3 carbons), 27.7, 31.0, 34.4, 36.9, 37.1, 39.9, 41.7, 59.0, 60.3, 73.8, 113.1, 124.7, 130.8, 146.8; IR (neat) 3398, 3067, 2928, 2884, 2857, 1641, 1471, 1452, 1384, 1361, 1254, 1099, 1065, 1024, 933, 891, 836, 773, 665 cm^{-1}; HREIMS (*m/z*) calcd for $C_{26}H_{48}O_2Si$ (M^+), 420.3424, found 420.3420.

When THF was used as a solvent instead of hexane, **8** and **23** were obtained in 46% and 43% yields, respectively. In the case of using Et_2O as a solvent instead of hexane, **8** and **23** were obtained in 69% and 23% yields, respectively.

23: colorless viscous liquid. $[\alpha]_D^{20}$ +30.6° (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.05 (3H, s), 0.76 (3H, s), 0.88 (9H, s), 0.97 (3H, s), 1.51–1.27 (3H, m), 1.41–1.53 (4H, m), 1.59 (3H, s), 1.61–1.74 (2H, m), 1.68 (3H, s), 1.73–1.88 (2H, m), 1.95–2.04 (1H, m), 2.10 (1H, dd, *J* = 5.9, 17.6 Hz), 3.28 (3H, s), 3.53 (1H, dd, *J* = 4.9, 10.7 Hz), 3.74 (2H, s), 5.04 (1H, t, *J* = 6.8 Hz), 5.36 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.7, 17.6, 17.7, 18.1, 18.3, 21.5, 21.8, 25.8, 25.9 (3 carbons), 27.4, 28.1, 34.8, 37.0, 37.3, 41.2, 44.3, 57.6, 73.6, 76.9, 124.9, 130.7, 130.8, 138.5; IR (neat) 2934, 2856, 1471, 1451, 1381, 1360, 1254, 1188, 1103, 1065, 1006, 943, 915, 887, 836, 773, 666 cm^{-1}; HREIMS (*m/z*) calcd for $C_{26}H_{48}O_2Si$ (M^+), 420.3424, found 420.3437.

(1*R*,4a*R*,5*S*,6*S*,8a*S*)-6-(*tert*-butyldimethylsiloxy)-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydronaphthalene-1-carbaldehyde (7): Dess–Martin periodinane (568 mg, 1.3 mmol) was added in small portions to a stirred solution of **8** (282 mg, 0.67 mmol) containing $NaHCO_3$ (563 mg, 6.70 mmol) in dry CH_2Cl_2 (60 mL) at rt. After 1 h, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (20 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 60 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 30 mL), and brine (2 x 30 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 100:1) to give **7** (281 mg, 100%) as a colorless viscous liquid. $[\alpha]_D^{20}$ +46.2° (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.77 (3H, s), 0.87 (9H, s), 0.97 (3H, s), 1.15-1.23 (1H, m), 1.36–1.46 (1H, m), 1.47 (1H, dd, *J* = 4.4, 13.2 Hz), 1.51–1.59 (3H, m), 1.60 (3H, s), 1.65-1.72 (2H, m), 1.68 (3H, s), 1.82–1.88 (3H, m), 2.22–2.45 (1H, m), 2.42–2.45 (1H, m), 2.61 (1H, d, *J* = 3.9 Hz), 3.51 (1H, dd, *J* = 4.4, 10.7 Hz), 4.77 (1H, t, *J* = 2.0 Hz), 4.94 (1H, t, *J* = 2.0 Hz), 5.02–5.06 (1H, m), 9.89 (1H, d, *J* = 3.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.7, 17.7, 17.9, 18.0, 21.6, 21.9, 22.5, 25.7, 25.8 (3 carbons), 27.7, 32.9, 35.0, 36.8, 38.8, 41.2, 41.8, 71.0, 73.5, 113.9, 124.6, 130.9, 142.1, 202.4; IR (neat) 2948, 2929, 2883, 2857, 1717, 1646, 1453, 1385, 1360, 1253, 1100, 1064, 891, 836, 773 cm^{-1}; HREIMS (*m/z*) calcd for $C_{26}H_{46}O_2Si$ (M^+), 418.3267, found 418.3277.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*S*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-

enyl)decahydronaphthalen-1-yl]hydroxymethyl-5,6-dimethyl-2-methoxy-4*H*-pyran-4-one (24): *n*-BuLi in hexane (1.57 M solution, 0.59 mL, 0.93 mmol) was added dropwise to a stirred solution of 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one (231 mg, 0.99 mmol) in dry THF (15 mL) at −78 °C under argon. After 5 min, a solution of **7** (83 mg, 0.20 mmol) in dry THF (5 mL) was added to the above mixture at −78 °C, and the resulting mixture was warmed up to −55 °C over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) at −55 °C, and the mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were washed brine (2 x 40 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 4:1) to give **24** (1:1 diastereomeric mixture) (101 mg, 87%) as a white amorphous powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04–0.52 (6H, m), 0.75 (3/2H, s), 0.76 (3/2H, s), 0.88 (9H, s), 0.92 (3/2H, s), 0.97 (3/2H, s), 1.10–1.21 (1H, m), 1.26–1.49 (3H, m), 1.52–1.57 (2H, m), 1.60–1.70 (8H, m), 1.75–1.79 (1H, m), 1.86 (3/2H, s), 1.88 (3/2H, s), 1.91–2.04 (3H, m), 2.23–2.33 (1H, m), 2.26 (3/2H, s), 2.28 (3/2H, s), 2.44–2.50 (1H, m), 3.55–3.61 (1H, m), 3.91 (3/2H, s), 3.97 (3/2H, s), 4.37–5.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.1 (1/2 carbon), −5.0 (1/2 carbon), −3.7 (1/2 carbon), −3.6 (1/2 carbon), 9.4 (1/2 carbon), 9.6 (1/2 carbon), 16.9, 17.6, 17.7, 17.9 (1/2 carbon), 18.0 (1/2 carbon), 21.5 (1/2 carbon), 21.6 (1/2 carbon), 22.9 (1/2 carbon), 23.0 (1/2 carbon), 23.1, 25.6 (1/2 carbon), 25.7 (1/2 carbon), 25.8 (3/2 carbon), 25.9 (3/2 carbon), 27.9 (1/2 carbon), 28.0 (1/2 carbon), 32.4 (1/2 carbon), 33.9 (1/2 carbon), 34.2 (1/2 carbon), 35.1 (1/2 carbon), 37.0 (1/2 carbon), 37.1 (1/2 carbon), 37.8 (1/2 carbon), 37.9 (1/2 carbon), 39.2 (1/2 carbon), 39.5 (1/2 carbon), 41.5 (1/2 carbon), 41.8 (1/2 carbon), 55.4 (1/2 carbon), 55.5 (1/2 carbon), 61.4 (1/2 carbon), 64.4 (1/2 carbon), 67.0 (1/2 carbon), 67.6 (1/2 carbon), 73.8 (1/2 carbon), 73.9 (1/2 carbon), 105.2 (1/2 carbon), 105.4 (1/2 carbon), 110.7 (1/2 carbon), 111.7 (1/2 carbon), 119.4 (1/2 carbon), 119.5 (1/2 carbon), 124.9 (1/2 carbon), 125.0 (1/2 carbon), 130.4 (1/2 carbon), 130.6 (1/2 carbon), 147.9 (1/2 carbon), 148.1 (1/2 carbon), 155.5 (1/2 carbon), 155.8 (1/2 carbon), 160.4 (1/2 carbon), 160.5 (1/2 carbon), 181.9 (1/2 carbon), 182.0 (1/2 carbon); IR (KBr) 3445, 2953, 2929, 2857, 1669, 1592, 1463, 1423, 1377, 1319, 1253, 1151, 1097, 1063, 936, 888, 836, 772, 757, 665 cm^{-1}; HREIMS (*m/z*) calcd for $C_{34}H_{56}O_5Si$ (M^+), 572.3897, found 572.3899.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*R*)-6-(*tert*-Butyldimethylsiloxy)-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydronaphthalen-1-yl]methyl-5,6-dimethyl-2-methoxy-4*H*-pyran-4-one (26): $NaN(SiMe_3)_2$ in THF (1.0 M solution, 0.25 mL, 0.25 mmol) was added dropwise to a stirred solution of **24** (109 mg, 0.19 mmol) in dry THF (8 mL) containing CS_2 (0.12 mL, 1.90 mmol) at −78 °C under argon. After 1 h, MeI (0.12 mL, 1.90 mmol) was added dropwise to the mixture at −78 °C, and the resulting solution was further stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) at −78 °C, and the resulting mixture was extracted with EtOAc (3 x 30 mL). The combined

extracts were washed with brine (2 x 20 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded crude methyl xanthate **25** (112 mg), which was used for the next reaction without purification.

n-Bu_3SnH (0.15 mL, 0.55 mmol) and 2,2'-azobisisobutyronitrile (AIBN) (15.1 mg, 0.09 mmol) were added successively to a stirred solution of the crude methyl xanthate **25** (112 mg, 0.17 mmol) in dry toluene (5 mL) at rt. For the deaeration of the reaction mixture, it was frozen using liquid nitrogen, and the reaction vessel was evacuated *in vacuo* for 30 min followed by filled with dry argon. The mixture was heated at reflux for 2 h under argon. After cooling, the reaction mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (benzene/EtOAc, 30:1) to give **26** (86 mg, 82%, 2 steps) as a colorless viscous liquid. $[\alpha]_D^{20}$ −30.1° (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.06 (3H, s), 0.75 (3H, s), 0.88 (9H, s), 0.93 (3H, s), 1.14–1.22 (1H, m), 1.26–1.42 (4H, m), 1.50–1.54 (1H, m), 1.58–1.63 (2H, m), 1.64 (3H, s), 1.69 (3H, s), 1.73–1.77 (1H, m), 1.80–1.85 (1H, m), 1.88–1.98 (2H, m), 1.90 (3H, s), 2.09 (1H, dd, *J* = 3.4, 14.0 Hz), 2.24 (3H, s), 2.31–2.45 (2H, m), 2.69 (1H, dd, *J* = 3.4, 13.0 Hz), 3.52 (1H, dd, *J* = 4.8, 10.9 Hz), 3.83 (3H, s), 4.17–4.18 (1H, m), 4.50 (1H, t, *J* = 2.4 Hz), 5.06–5.10 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.0, −3.6, 10.0, 17.0, 17.7, 17.8, 18.1, 19.9, 21.8, 22.9, 23.1, 25.8, 25.9 (3 carbons), 28.0, 30.8, 34.0, 37.0, 37.5, 38.5, 41.6, 55.3, 55.9, 74.3, 103.5, 109.1, 118.6, 125.2, 130.6, 149.2, 154.9, 162.9, 180.4; IR (neat) 2951, 2927, 2856, 1671, 1604, 1461, 1415, 1375, 1317, 1254, 1097, 1063, 1005, 934, 888, 836, 772 cm^{-1}; HREIMS (*m/z*) calcd for $C_{34}H_{56}O_4Si$ (M^+), 556.3948, found 556.3961.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*R*)-5,8a-Dimethyl-2-methylene-5-(4-methylpent-3-enyl)-(6-hydroxy)decahydro-naphthalen-1-yl]methyl-5,6-dimethyl-2-methoxy-4*H*-pyran-4-one (27): $BF_3 \cdot OEt_2$ (88 μL, 0.67 mmol) was added dropwise to a stirred solution of **26** (74 mg, 0.13 mmol) in CH_3CN (4 mL) at 0 °C under argon, and stirring was continued at rt for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (2 x 30 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 2:1→1:1) to give **27** (56 mg, 95%) as a colorless amorphous powder. $[\alpha]_D^{20}$ −43.1° (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (3H, s), 0.94 (3H, s), 1.25–1.42 (6H, m), 1.48–1.61 (2H, m), 1.64–1.75 (2H, m), 1.66 (3H, s), 1.69 (3H, s), 1.90 (3H, s), 1.92–2.00 (3H, m), 2.08–2.13 (1H, m), 2.24 (3H, s), 2.32–2.45 (2H, m), 2.69 (1H, dd, *J* = 3.4, 12.9 Hz), 3.56 (1H, t, *J* = 7.8 Hz), 3.84 (3H, s), 4.19 (1H, s), 4.51–4.52 (1H, m), 5.14 (1H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0, 16.9, 17.0, 17.6, 19.9, 21.8, 22.85, 22.89, 25.7, 27.7, 30.7, 34.1, 37.5, 37.6, 38.9, 41.0, 55.3, 55.8, 73.9, 103.3, 109.2, 118.6, 125.0, 131.1, 148.9, 154.9, 162.9, 180.3; IR (KBr) 3419, 2928, 2871, 1669, 1588, 1462, 1419, 1376, 1319, 1256, 1163, 1149,

1114, 1035, 996, 885, 731 cm^{-1}; HREIMS (*m/z*) calcd for $C_{28}H_{42}O_4$, 442.3083, found 442.3072.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*R*)-6-Acetoxy-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydro-naphthalen-1-yl]methyl-5,6-dimethyl-2-methoxy-4*H*-pyran-4-one [(−)-nalanthalide] (2): Ac_2O (47 μL, 0.50 mmol) was added to a stirred solution of **27** (44.2 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) containing Et_3N (97 μL, 0.70 mmol) and 4-dimethylaminopyridine (DMAP) (1.23 mg, 0.01 mmol) at 0 °C. After 1 h, the reaction was quenched with 1 M aqueous HCl (2 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 x 40 mL). The combined extracts were washed with brine (2 x 20 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 3:1) to give **2** (41.6 mg, 86%) as a colorless amorphous powder. $[\alpha]_D^{25}$ −48.3° (*c* 1.02, $CHCl_3$) {lit.,[4] $[\alpha]_D^{25}$ −58.2° (*c* 0.275, $CHCl_3$)}. The ^1H and ^{13}C NMR, IR, and MS spectra (see below) are identical to those of natural (−)-nalantalide. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, s), 0.96 (3H, s), 1.14–1.22 (1H, m), 1.26–1.33 (2H, m), 1.35–1.39 (2H, m), 1.50–1.54 (1H, m), 1.61 (3H, s), 1.68 (3H, s), 1.71–1.78 (3H, m), 1.90 (3H, s), 1.92–2.00 (2H, m), 1.98 (1H, dd, *J* = 2.9, 11.7 Hz), 2.04 (3H, s), 2.01–2.12 (1H, m), 2.24 (3H, s), 2.33–2.46 (2H, m), 2.68 (1H, dd, *J* = 3.4, 12.7 Hz), 3.85 (3H, s), 4.20 (1H, t, *J* = 1.3 Hz), 4.52 (1H, t, *J* = 2.2 Hz), 4.82 (1H, dd, *J* = 7.3, 9.1 Hz), 5.07 (1H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.0, 16.9, 17.5, 18,1, 19.9, 21.3, 21.7, 22.7, 22.9, 24.1, 25.7, 30.7, 33.8, 37.4, 37.9, 39.2, 40.0, 55.3, 55.6, 76.3, 103.2, 109.4, 118.6, 124.6, 131.3, 148.7, 154.8, 162.8, 170.6, 180.3; IR (KBr) 2928, 2877, 1732, 1672, 1603, 1456, 1416, 1374, 1317, 1253, 1242, 1076, 1027, 983, 882 cm^{-1}; HREIMS (*m/z*) calcd for $C_{30}H_{44}O_5$ (M^+), 484.3189, found 484.3168.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*R*)-6-Acetoxy-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydro-naphthalen-1yl]methyl-4-acetoxy-5,6-dimethyl-2*H*-pyran-2-one (29): 1 M NaOH (1.40 mL, 1.4 mmol) was added dropwise to a stirred solution of **27** (33.8 mg, 76 mmol) in MeOH (2 mL) at rt. The mixture was heated at reflux for 24 h. The reaction was quenched with 1 M HCl (1.40 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 30 mL). The combined extracts were washed with brine (2 x 20 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded the corresponding α-pyrone **28** (31.4 mg) as a colorless amorphous powder, which was used for the next reaction without purification.

Ac_2O (36.0 μL, 0.38 mmol) was added to a stirred solution of the crude α-pyrone **28** (31.4 mg) in CH_2Cl_2 (3 mL) containing Et_3N (74.0 μL, 0.54 mmol) and DMAP (0.80 mg, 6.6 μmol) at 0 °C, and stirring was continued for 1 h at rt. The reaction was quenched with 1 M HCl (1 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), then dried over $MgSO_4$. Concentration of the

solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane/EtOAc, 2:1) to give **29** (27.5 mg, 70%, 2 steps) as a colorless amorphous powder. $[\alpha]_D^{20}$ −14.2° (*c* 0.352, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, s), 0.98 (3H, s), 1.14–1.22 (1H, m), 1.26–1.29 (2H, m), 1.32–1.43 (1H, m), 1.53–1.57 (1H, m), 1.59 (3H, s), 1.62–1.64 (1H, m), 1.67 (3H, s), 1.73–1.88 (4H, m), 1.78 (3H, s), 1.93–2.02 (1H, m), 2.04 (3H, s), 2.06–2.10 (1H, m), 2.14–2.18 (1H, m), 2.22 (3H, s), 2.30 (3H, s), 2.32–2.46 (1H, m), 2.53–2.55 (2H, m), 4.36 (1H, s), 4.58 (1H, t, *J* = 2.0 Hz), 4.79 (1H, dd, *J* = 7.2, 8.2 Hz), 5.05 (1H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 17.41, 17.44, 18.1, 20.3, 21.2, 21.7, 22.5, 22.9, 24.0, 25.7, 30.67, 30.72, 34.0, 37.4, 37.8, 39.3, 39.9, 55.4, 76.0, 107.9, 111.0, 116.2, 124.2, 131.5, 147.2, 156.0, 159.4, 164.0, 167.0, 170.7; IR (KBr) 2931, 2872, 1773, 1723, 1651, 1579, 1454, 1369, 1242, 1193, 1180, 1088, 1023, 893, 735 cm^{-1}; HREIMS (*m/z*) calcd for $C_{31}H_{44}O_6$ (M^+), 512.3138, found 512.3146.

3-[(1*R*,4a*R*,5*S*,6*S*,8a*R*)-6-Acetoxy-5,8a-dimethyl-2-methylene-5-(4-methylpent-3-enyl)decahydro-naphthalene-1-yl]methyl-5,6-dimethyl-4-hydroxy-2*H*-pyran-2-one [(+)-sesquicillin] (1): 1 M NaOH (0.54 mL, 0.54 mmol) was added dropwise to a stirred solution of **29** (27.5 mg, 54 μmol) in THF (0.54 mL) at 0 °C. After 30 min, he reaction was quenched with 1 M HCl (0.6 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3 x 30 mL). The combined extracts were washed with brine (2 x 20 mL), then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded the residue, which was purified by column chromatography (hexane/EtOAc, 3:1) to give **1** (22.2 mg, 88%) as a colorless amorphous powder. $[\alpha]_D^{25}$ +7.1° (*c* 0.36, $CHCl_3$) {lit.,[2a] $[\alpha]_D^{22}$ +10° (*c* 0.8, $CHCl_3$)}. The ^1H and ^{13}C NMR spectra (see below) are identical to those reported.[2a] ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, s), 0.97 (3H, s), 1.19 (1H, td, *J* = 4.9, 12.2 Hz), 1.24–1.32 (2H, m), 1.41 (1H, ddd, *J* = 4.4, 13.2, 25.9 Hz), 1.54–1.61 (1H, m), 1.58 (3H, s), 1.67–1.78 (3H, m), 1.67 (3H, s), 1.83–1.89 (1H, m), 1.92 (3H, s), 1.95–1.99 (3H, m), 2.04 (3H, s), 2.19 (3H, s), 2.22–2.25 (1H, m), 2.42 (1H, td, *J* = 5.4, 13.7 Hz), 2.54 (1H, dd, *J* = 10.7, 14.2 Hz), 2.75 (1H, dd, *J* = 3.4, 14.1 Hz), 4.45 (1H, s), 4.65 (1H, s), 4.80–4.84 (1H, m), 5.05 (1H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.9, 17.3, 17.5, 18.0, 21.2, 21.7, 22.1, 22.6, 22.8, 24.0, 25.7, 30.9, 33.8, 37.6, 37.8, 39.3, 40.0, 56.4, 76.2, 103.0, 106.1, 111.0, 124.4, 131.4, 148.9, 155.7, 164.3, 165.1, 170.8; IR (KBr) 3254, 2932, 2877, 1776, 1731, 1667, 1567, 1454, 1389, 1346, 1242, 1116, 1076, 1027, 887, 756 cm^{-1}; HREIMS (*m/z*) calcd for $C_{29}H_{42}O_5$ (M^+), 470.3032, found 470.3022.

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18. Although the absolute value of the synthetic material is somewhat smaller than that of natural product for some reason, we believe that the synthetic material is enantiomerically pure.