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Alternative synthetic approach for (+)-phomopsidin via the highly stereoselective TADA reaction

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ABSTRACT

This manuscript describes an alternative synthetic approach for (+)-phomopsidin, which shows strong inhibitory activity against the assembly of microtubule proteins. We observed that the TADA reaction of the macrolactone **5** with the reversed C11 configuration provided the desired cycloadduct **6** in 86% yield with excellent stereoselectivity (dr=16:1). Luche reduction of the ketone derived from the major product of the TADA reaction resulted in a 91% yield with excellent stereoselectivity (dr=21:1), and the major product was successfully converted to the known compound in the previously reported total synthesis of (+)-phomopsidin, thereby accomplishing the formal total synthesis of (+)-phomopsidin.

1. Introduction

In 1997, (+)-phomopsidin (Fig. 1) was isolated from a marine-derived fungus, *Phomopsis* sp. strain TUF 95F47, that was collected in Pohnpei.[1] (+)-Phomopsidin was found to be a new inhibitor of microtubule assembly, showing strong inhibitory activity against the assembly of microtubule proteins derived from the porcine brain at an IC_{50} of 5.7 μM.[1] The relative configuration of (+)-phomopsidin was determined by NMR studies,[1,2] and its absolute configuration was elucidated by the exciton chirality method.[3]

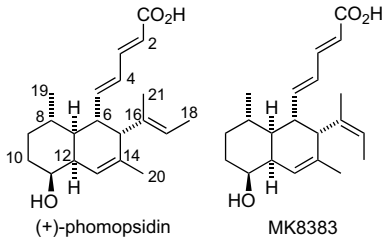
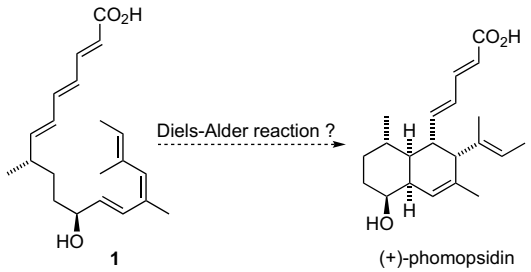


Figure 1. Respective structures of (+)-phomopsidin and MK8383.

(+)-Phomopsidin features a *cis*-dehydrodecaline core substituted with hydroxyl, methyl, (1*E*,3*E*)-4-carboxy-1,3-butadienyl, and (*E*)-1-methyl-1-propenyl groups, and six stereogenic centers are incorporated in this core. A structurally related natural product, MK8383,[4] the 16*Z*-isomer of (+)-phomopsidin, has been isolated and found to show a similar activity (IC_{50}=8.0 μM) to (+)-phomopsidin. Recently, carneic acid A,[5] which has a *trans*-dehydrodecaline core and the enantiomeric configuration of (+)-phomopsidin, has also been reported.

The potent inhibitory activity against the assembly of microtubule proteins and unique structure of (+)-phomopsidin makes it an attractive synthetic target; hence, we started the enantioselective total synthesis of (+)-phomopsidin. Radiolabeling studies of (+)-phomopsidin have confirmed that its biosynthesis proceeds through the polyketide pathway, suggesting that (+)-phomopsidin is derived from the acyclic precursor **1** through the Diels–Alder reaction (Scheme 1).[3]



Scheme 1.

Therefore, the acyclic precursor **1** was first considered for the total synthesis of (+)-phomopsidin featuring a biomimetic Diels–Alder reaction (Scheme 1). However, this route was not pursued because **1** possesses a sensitive triene, as well as (*E*,*Z*)-dienes that are

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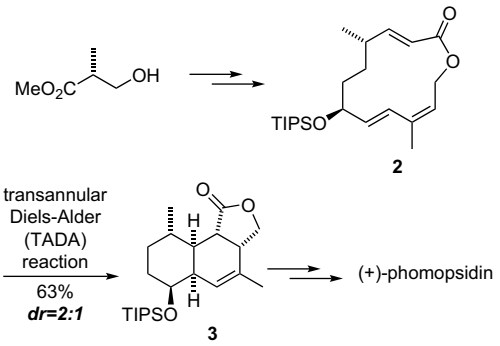
known to react poorly in Diels–Alder reactions owing to their energetically unfavorable *s-cis* conformation in the transition state. Thus, we decided to employ a transannular Diels–Alder (TADA) reaction[6,7] to generate the *cis*-dehydrodecaline skeleton of (+)-phomopsidin, and achieved the first enantioselective total synthesis of (+)-phomopsidin in 2004.[8]

The TADA reaction of the macrolactone **2** (Scheme 2), which resulted in excellent *exo*-selectivity and good yield,[8] was a key reaction in the first total synthesis of (+)-phomopsidin, but its stereoselectivity was unsatisfactory (dr=2:1). We have been interested in the low selectivity of the TADA reaction. Therefore, we decided to investigate the TADA reaction and report here the alternative synthetic route for (+)-phomopsidin via the highly stereoselective TADA reaction.



Scheme 2.

2. Results and discussions

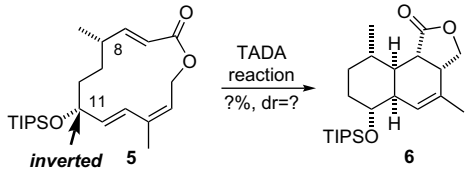
We analyzed the transition states of the TADA reaction of the macrolactone **2**. Scheme 3 shows the proposed transition states TS-3 and TS-4, which clearly explain the formation of the corresponding products **3** and **4**, respectively. In the TADA reaction of **2**, *exo*-adducts are formed exclusively because the formation of *endo*-adducts is restricted by the transannular reaction mode of **2**; therefore, the transition states providing *endo*-adducts are energetically unfavorable.

TS-3 incorporates a chair six-membered ring with the equatorial C11 OTIPS and C8 methyl groups, resulting in an energetically favorable transition state. By contrast, TS-4 is energetically unfavorable because it has a twist-boat six-membered ring with a pseudoaxial C8 methyl group. Consequently, the conformational analysis depicted in Scheme 3 suggests the predominant formation of the desired **3**.

However, the observed low product ratio of 2:1 could not be rationalized from only the conformational difference between TS-3 and TS-4 because the energy difference between the chair form and the twist-boat form of cyclohexane is at least 4.7 kcal/mol, suggesting that the product ratio should be expected to be more than 2:1.

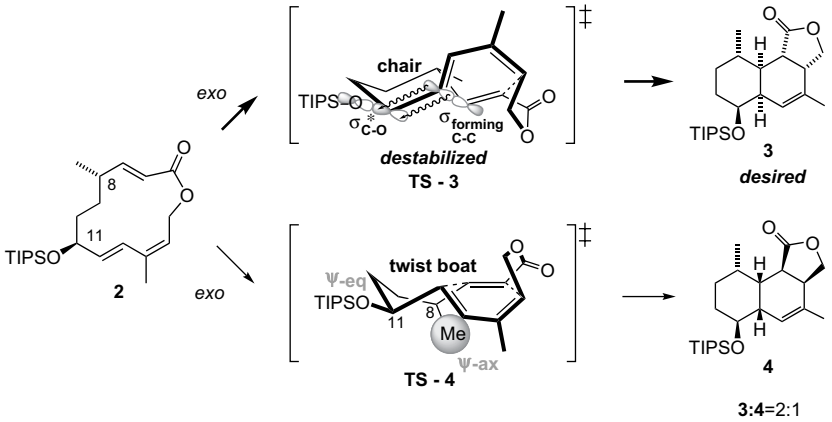
We turned our attention to another factor affecting the product ratio, and considered that the stereoelectronic effect induced by the C11 OTIPS group might explain the low stereoselectivity observed. That is, the C11 OTIPS group is equatorial; hence, the C–O bond at C11 is anti-periplanar to the forming C–C bond in TS-3. Therefore, the overlap between the bonding orbital of the forming C–C bond ($\sigma_{\text{forming C–C}}$) and the anti-bonding orbital of C–O ($\sigma^*_{\text{C–O}}$) at C11 would destabilize the forming C–C bond; therefore, the energy level of TS-3 would be higher.[9,10]

In other words, although TS-3 is more energetically favored than TS-4 by the conformational and steric factors, the stereoelectronic effect would destabilize TS-3, reducing the product ratio to 2:1. This analysis suggested that the inversion of the C11 configuration could improve the stereoselectivity of the TADA reaction. If the C–O bond at the inverted C11 position is not equatorial in TS-3, that is, if the C–O bond at C11 is orthogonal to the forming C–C bond in the TADA reaction, TS-3 would be relieved from the destabilization by the stereoelectronic effect and the stereoselectivity of the TADA reaction would be improved. Consequently, we examined the TADA reaction of the macrolactone **5** with the inverted C11 stereogenic center (Scheme 4).

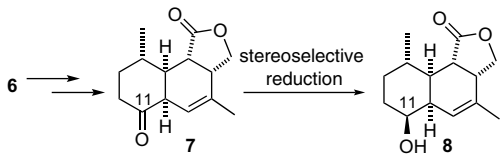


Scheme 4.

Although this tactic requires the re-inversion of the C11 configuration after the TADA reaction, the stereoselective reduction of the ketone **7**, which could be easily prepared from the TIPS ether **6**, was expected to provide the desired alcohol **8** with the correct stereochemistry because the stereoselective reduction of the



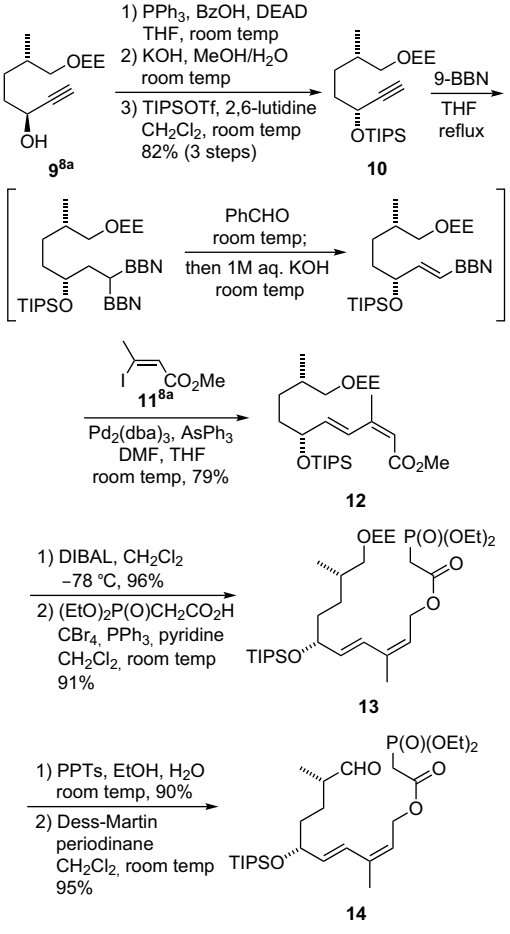
Scheme 3.



Scheme 5.

ketone **7** could be attained by selecting a suitable reducing reagent (Scheme 5).

The synthesis of the macrolactone **5** was started with the Mitsunobu reaction of the known alcohol **9** since more advanced intermediates resisted the Mitsunobu reaction of the C11 hydroxyl (Scheme 6). The benzoate thus obtained by the Mitsunobu reaction was subjected to hydrolysis to afford the corresponding alcohol, which was converted to the TIPS ether **10** (82%, three steps). The one-pot hydroboration of the TIPS ether **10** with 9-BBN and the subsequent Suzuki–Miyaura coupling reaction with the iodide **11** under conditions reported previously[8a,11] provided the methyl ester **12** in 79% yield. That is, the TIPS ether **10** was subjected to the reaction with 9-BBN first, followed by treatment with benzaldehyde to convert the by-product 1,1-bisboryl adduct to the desired *trans*-alkenylborane,[8a,12] and finally the reaction with methyl (*Z*)-3-iodo-2-butenoate under the conditions in Scheme 6 provided the methyl ester **12**. The methyl ester **12** was reduced with DIBAL (96%), followed by the condensation reaction with diethylphosphonoacetic acid using CBr_4 and PPh_3[13] to generate the phosphonate **13** (91%). The ethoxyethyl group in the phosphonate **13** was removed under



Scheme 6.

acidic condition (90%) and the subsequent Dess–Martin oxidation[14] provided the aldehyde **14** (95%).

Next we examined the intramolecular Horner–Wadsworth–Emmons (HWE) reaction of compound **14** (Table 1). The HWE reaction of **14** under the previously reported optimized conditions for the preparation of the macrolactone **2**[8a] resulted in 95% yield, but its *E*/*Z* ratio was low (1.5:1) (entry 1). Therefore, we optimized the reaction conditions for **14** and found that the use of $Ba(OH)_2$ improves *E*/*Z* ratio to 3.3:1, and the dimer was formed in 8% yield (entry 2).

On the other hand, the reaction under Masamune's conditions[15] afforded a product with an increased *E*/*Z* ratio of 9.1:1 with concomitant formation of the dimer (9%, entry 3). A highly diluted condition (0.5 mmol/L) was employed for this reaction (entry 4), which provided no dimer but the conversion was low even after 69 h (65% at 49% conversion, entry 4). However, the use of excess reagents under Masamune's conditions improved the yield (82%) and resulted in a good *E*/*Z* ratio (7.6:1) (entry 5).

The macrolactone **5** containing a geometrical isomer was used for the next TADA reaction under the previously reported optimized conditions for compound **2** (Scheme 7). That is, the TADA reaction of the macrolactone **5** was carried out in toluene under a highly diluted condition at reflux temperature for 63 h to provide the desired compound **6** (81%) and its isomer **15** (5%).[16] The structure of the former was determined by converting it to a known compound while the structure of the latter was successfully determined by NOE experiments (Fig. 2).

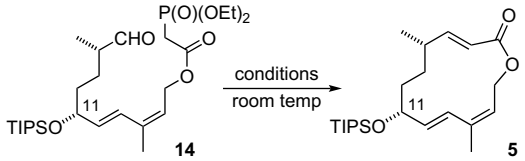
The combined yield (86%) and the diastereomer ratio (dr=16/1)[17] were greater than those of the macrolactone **2** (63%, dr=2/1). As in the TADA reaction of the macrolactone **2** (Scheme 3), it was expected that the *exo*-adducts would generate exclusively and the important transition states would be TS-6 and TS-15 (Scheme 8). Although TS-6 involves an axial C11 OTIPS group, TS-6 is energetically more favorable than TS-15 due to the following reasons: (1) TS-6 incorporates a chair six-membered ring with an equatorial C8 methyl group while TS-15 has a twist-boat six-membered ring with the 1,4-interaction derived from pseudoaxial C11 OTIPS and C8 methyl groups; and (2) TS-5 is relieved of the destabilization induced by the stereoelectronic effect arising from the overlap between the bonding orbital of the forming C–C bond ($\sigma_{\text{forming C–C}}$) and the anti-bonding orbital of C–O ($\sigma^*_{\text{C–O}}$) at C11 because the C11 OTIPS group is axial. Therefore, these factors would improve the stereoselectivity of the TADA reaction of macrolactone **5**.

Since the desired cycloadduct **6** was obtained in high yield with excellent stereoselectivity, we next examined the inversion of the C11 configuration via the oxidation and stereoselective reduction sequence. The cycloadduct **6** was treated with TBAF to afford the alcohol **16** (Scheme 9), which was converted to the ketone **7** by Dess–Martin oxidation[14] (78%, two steps) to examine stereoselective reduction (Table 2). The reduction with a bulky reagent, L-Selectride [Li(*sec*-Bu)$_3$BH], produced the undesired alcohol **16** as the major product (quant., **8**/**16**=1:2, entry 1). Since L-Selectride is an well-known reagent that is capable of an equatorial attack of a hydride against cyclohexenone derivatives,[18] this result indicated that the equatorial attack of a hydride took place preferentially to provide the alcohol **16**.

Therefore, we next examined the reduction with $NaBH_4$ because $NaBH_4$ is a well-known reagent that is capable of an axial attack of a hydride.[18] As the result, the stereoselectivity was reversed (10:1) in the reaction of $NaBH_4$ at room temperature (89%, entry 2). The ratio was improved to 15:1 in the reaction at −78 °C (entry 3), and finally, the desired product was obtained in 91% yield with excellent selectivity (21:1)[17] at −78 °C under Luche's conditions[19] (entry 4).

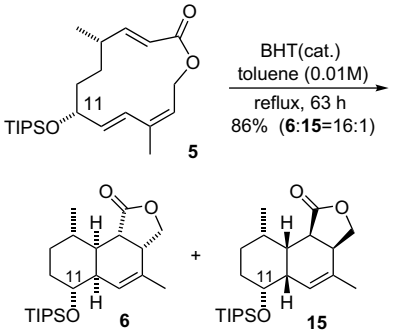
Although products **8** and **16** were inseparable at this stage, we anticipated that the alcohol **8** would be selectively silylated with a bulky silylating reagent because **8** had a reactive C11 equatorial

Table 1
Intramolecular Horner–Wadsworth–Emmons reaction of compound **14**



Entry	Conditions (equiv)	Concd (mmol/L)	Time (h)	Yield[a] (%)	*E*:*Z*[b]
1	K_2CO_3 (5.0), 18-crown-6 (5.0), toluene	3.5	41	95	1.5:1
2	$Ba(OH)_2 \cdot 8H_2O$ (1.2), THF/H_2O (40:1)	3.5	5	58 (dimer 8%)	3.3:1
3	LiCl (6.0), DIPEA (5.0), CH_3CN	3.5	5	44 (dimer 9%)	9.1:1
4	LiCl (6.0), DIPEA (5.0), CH_3CN	0.5	39	65 (at 49% conv)	5.6:1
5	LiCl (21), DIPEA (20), CH_3CN	0.5	47.5	82	7.6:1

[a] Isolated yield.
[b] *E*/*Z* determined by ^{1}H NMR.



Scheme 7.

hydroxyl while **16** had a hindered C11 axial hydroxyl. Indeed, **8** with a small amount of **16** reacted with TIPSOTf to provide the TIPS ethers **3** (93%) and **16** (4%) expectedly remained unreacted (Scheme 9). The synthesized TIPS ether **3** was spectroscopically identical in all respects to the synthetic intermediate in the previously reported total synthesis of (+)-phomopsidin,[8a] indicating the completion of the structural determination of product **6** in the TADA reaction and the formal total synthesis of (+)-phomopsidin.

3. Conclusion

In summary, based on the analysis of the transition state of the TADA reaction of the macrolactone **2**, we postulated that the stereoelectronic effect arising from the overlap between the bonding orbital of the forming C–C bond ($\sigma_{\text{forming C–C}}$) and the anti-bonding orbital of C–O ($\sigma^*_{\text{C–O}}$) at C11 would be a factor in the low stereoselectivity. Consequently, we carried out the TADA reaction of the macrolactone **5** with the reversed C11 configuration and observed that the TADA reaction expectedly provided the desired cycloadduct **6** in excellent yield (86%) with high stereoselectivity

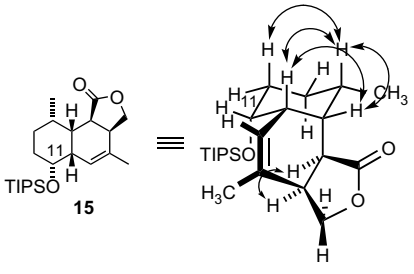


Figure 2.

(dr=16:1). Compared with the TADA reaction of the macrolactone **2** that of the macrolactone **5** showed greatly improved stereoselectivity (from 2:1 to 16:1). In addition to the successful TADA reaction of macrolactone **5**, we observed that the Luche reduction of the ketone derived from the major product of the TADA reaction proceeded in high yield (91%) with high stereoselectivity (21:1). The major compound obtained was successfully converted to the known compound in the previously reported total synthesis of (+)-phomopsidin, thereby accomplishing the formal total synthesis of (+)-phomopsidin.

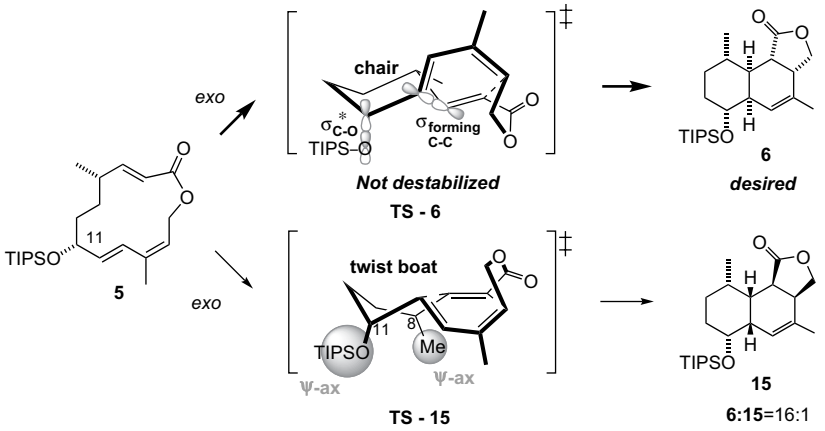
4. Experimental

4.1. General

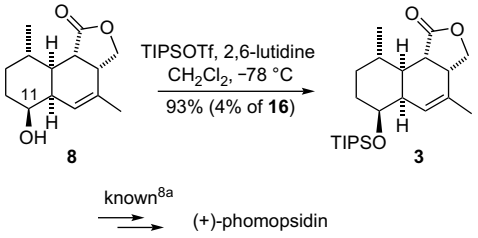
^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yanaco melting point apparatus equipped with a digital thermometer. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis was performed on a JASCO PU-980 and UV-970. Mass spectrometric analyses and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates ($60F_{254}$). THF was distilled from sodium/benzophenone ketyl and methylene chloride (CH_2Cl_2) from calcium hydride. Toluene was distilled from sodium. Acetonitrile and DMF were distilled from CaH_2 under reduced pressure. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.

4.2. (3*R*,6*S*)-7-(1-Ethoxyethoxy)-6-methylhept-1-yn-3-yl benzoate (9a)

To a stirred solution of alcohol **9** (2.05 g, 9.57 mmol) in THF (90 mL) were added PPh_3 (3.51 g, 13.3 mmol), BzOH (2.33 g,



Scheme 8.



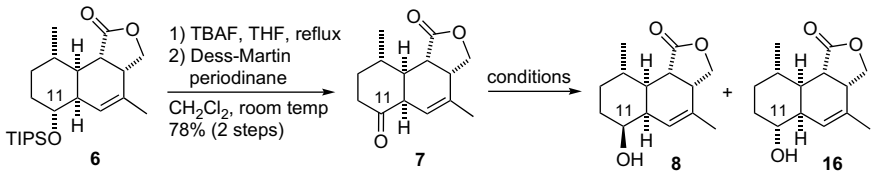
Scheme 9.

19.1 mmol), and after a while, DEAD (6.09 mL, 13.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (80 mL) and the aqueous layer was extracted with Et_2O (100 mL×3), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated. To the residue was added hexane (50 mL) and precipitates were filtered off. Evaporation of the filtrate and the residue was purified by silica gel chromatography (hexane/ethyl acetate=10:1) to give the benzoate **9a** as a colorless oil, which was used for the next step: R_f=0.49 (hexane/ethyl acetate=3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.00 (2H, m), 7.65–7.53 (1H, m), 7.55–7.41 (2H, m), 5.65–5.55 (1H, m), 4.67 (1H, q, J=5.4 Hz), 3.70–3.60 (2/2H, m), 3.53–3.36 (4/2H, m), 3.32–3.21 (2/2H, m), 2.49 (1H, d, J=1.5 Hz), 2.05–1.87 (2H, m), 1.83–1.64 (2H, m), 1.45–1.34 (1H, m), 1.30 (3H, d, J=5.4 Hz), 1.19 (3H, t, J=7.1 Hz), 0.97 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 133.2, 129.8, 128.4, 99.7, 81.2, 73.7, 70.3, 70.2, 64.5, 60.7, 60.7, 33.2, 32.3, 28.9, 19.8, 17.0, 15.3; IR (neat) ν_{max} 3300, 3272, 3068, 2980, 2932, 2880, 2364, 2340, 1726, 1454, 1382, 1342, 1318, 1270, 1178, 1134, 1108, 1070, 1028, 994, 954, 878, 712 cm^{-1}; FABMS $[M-H]^+$ calculated for $C_{19}H_{25}O_4$: 317.1753, found: 317.1756.

4.3. (3*R*,6*S*)-6-(1-Ethoxyethoxymethyl)hept-1-yn-3-ol (9b)

To a stirred solution of the benzoate **9a** in a mixture of methanol and water (5:1, 120 mL) was added KOH (1.34 g, 23.8 mmol) portionwise at 0 °C and the resultant mixture was stirred at room temperature for 30 min. To the reaction mixture were added water (100 mL) and Et_2O (100 mL), and the aqueous layer separated was extracted with Et_2O (100 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was roughly purified by silica gel chromatography (hexane/ethyl acetate=4:1) to give the alcohol **9b** as a colorless oil, which was used for the next step: R_f=0.19 (hexane/ethyl acetate=4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, q, J=5.4 Hz), 4.36 (1H, dt, J=6.6, 2.0 Hz), 3.71–3.60 (2/2H, m), 3.53–3.35 (4/2H, m), 3.28 (1/2H, dd, J=9.3, 6.1 Hz), 3.23 (1/2H, dd, J=9.3, 6.3 Hz), 2.46 (1H, d, J=2.0 Hz), 1.85–1.67 (3H, m), 1.66–1.55 (1H, m), 1.38–1.20 (4H, m), 1.20 (3H, t, J=7.1 Hz), 0.95 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.7, 84.9, 72.9, 70.4, 70.4, 62.5, 60.8, 60.7, 35.1, 35.0, 33.3, 29.0, 19.8, 17.1, 15.3; IR (neat) ν_{max} 3420, 3296, 3044, 2980, 2936, 2360, 1458, 1382, 1342, 1132, 1086, 1056, 946, 932, 880 cm^{-1}; FABMS $[M-EtO]^+$ calculated for $C_{10}H_{17}O_2$: 169.1229, found: 169.1229.

Table 2
Preparation and stereoselective reduction of ketone **7**



Entry	Reagents (equiv)	Solvent	Temp (°C)	Time (min)	Yield[a] (%)	**8**/**16**[b]
1	L-Selectride (2.0)	THF	−78	45	quant.[c]	1/2
2	$NaBH_4$ (excess)	MeOH	room temperature	10	89	10/1
3	$NaBH_4$ (excess)	MeOH	−78	25	quant.	15/1
4	$NaBH_4$ (excess) $CeCl_3 \cdot 7H_2O$ (1.9)	MeOH	−78	60	91	21/1

[a] Isolated yield.
[b] *E*/*Z* ratio determined by ^{1}H NMR.
[c] At 96% conversion.

4.4. (3*R*,6*S*)-7-(1-Ethoxyethoxy)-6-methylhept-1-yn-3-yloxytriisopropylsilane (10)

To a stirred solution of the alcohol **9b** in CH_2Cl_2 (90 mL) were added 2,6-lutidine (2.14 mL, 18.3 mmol) and TIPSOTf (3.95 mL, 14.7 mmol) successively at 0 °C and the resultant mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL×3), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=40:1) to give TIPS ether **10** (2.89 g, 82% three steps) as a colorless oil: R_f=0.66 (hexane/ethyl acetate=4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (1H, q, J=5.4 Hz), 4.43 (1H, dt, J=6.1, 1.5 Hz), 3.70–3.58 (1H, m), 3.50–3.38 (1.5H, m), 3.34 (0.5H, dd, J=9.0, 6.8 Hz), 3.24 (0.5H, dd, J=9.0, 6.1 Hz), 3.18 (0.5H, dd, J=9.0, 6.8 Hz), 2.37 (1H, d, J=1.5 Hz), 1.83–1.52 (5H, m), 1.27 (3H, d, J=5.4 Hz), 1.17 (3H, t, J=7.1 Hz), 1.14–1.01 (21H, m), 0.91 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.7, 85.6, 72.1, 70.6, 63.1, 60.7, 36.3, 33.4, 28.8, 19.8, 18.0, 17.1, 15.3, 12.2; IR (neat) ν_{max} 3316, 2948, 2896, 2872, 1466, 1382, 1342, 1134, 1098, 1062, 882 cm^{-1}; FABMS $[M-H]^+$ calculated for $C_{21}H_{41}O_3Si$: 369.2825, found: 369.2830.

4.5. (2*Z*,4*E*,6*R*,9*S*)-Methyl 10-(1-ethoxyethoxy)-3,9-dimethyl-6-triisopropylsilyloxydeca-2,4-dienoate (12)

To a stirred solution of TIPS ether **10** (1.51 g, 4.07 mmol) was added a solution of 9-BBN in THF (20.4 mL, 0.5 M) at 0 °C and the resultant mixture was refluxed for 1 h. The reaction mixture was cooled to 0 °C, and to the reaction mixture was added benzaldehyde (2.48 mL, 24.4 mmol) at room temperature. After 6 h, to the reaction mixture was added aqueous 1 M KOH (12 mL) and stirring was continued for further 30 min. The reaction mixture was added to a stirred solution of (*Z*)-iodoalkene **11** (1.38 g, 6.11 mmol), $Pd_2(dba)_3$ (0.0381 g, 0.0416 mmol), and $AsPh_3$ (0.0634 g, 0.207 mmol) in DMF (40 mL) and the reaction mixture was stirred at room temperature for 12 h. To the reaction mixture were added water (50 mL) and Et_2O (50 mL), and the aqueous layer separated was extracted with Et_2O (50 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=30:1) to give the ester **12** (1.51 g, 79%) as a colorless oil: R_f=0.38 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, J=16.1 Hz), 6.05 (1H, dd, J=16.1, 7.1 Hz), 5.67 (1H, s), 4.66 (1H, q, J=5.4 Hz), 4.38–4.31 (1H, m), 3.69 (3H, s), 3.69–3.60 (1H, m), 3.50–3.38 (1.5H, m), 3.33 (0.5H, dd, J=9.2, 6.8 Hz), 3.25 (0.5H, dd, J=9.3, 5.9 Hz), 3.17 (0.5H, dd, J=9.2, 6.8 Hz), 1.99 (3H, s), 1.72–1.41 (5H, m), 1.28 (3H, d, J=5.4 Hz), 1.19 (3H, t, J=7.1 Hz), 1.07–1.03 (21H, m), 0.91 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.6, 141.2, 126.6, 116.9, 99.6, 99.6, 74.0, 70.6, 60.6, 50.9, 36.0, 33.7, 28.7, 21.1, 19.8, 19.8, 18.2, 18.1, 18.0, 17.1, 15.3, 12.3; IR (neat) ν_{max} 2948, 2872, 1722, 1640, 1606, 1458, 1342, 1228, 1160, 1138, 1088, 1062, 986, 882, 794 cm^{-1}; FABMS $[M-H]^+$ calculated for $C_{26}H_{49}O_5Si$: 469.3350, found: 469.3345.

4.6. (2*Z*,4*E*,6*R*,9*S*)-10-(1-Ethoxyethoxy)-3,9-dimethyl-6-triisopropylsilyloxydeca-2,4-dien-1-ol (12a)

To a stirred solution of the ester **12** (6.43 g, 13.7 mmol) in CH_2Cl_2 (140 mL) was added DIBAL in hexane (36.3 mL, 0.94 M) at −78 °C and the reaction mixture was stirred at the same temperature for 30 min. To the reaction mixture was added MeOH at −78 °C until no gas evolution was observed and the mixture was warmed up to room temperature. To the mixture was added saturated aqueous Rochelle salt (100 mL) and the resultant mixture was stirred at room temperature for 30 min. The aqueous layer separated was extracted with EtOAc (150 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=8:1) to give the alcohol **12a** (5.80 g, 96%) as a colorless oil: R_f=0.17 (hexane/ethyl acetate=2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, d, J=15.6 Hz), 5.73 (1H, dd, J=15.6, 6.3 Hz), 5.54 (1H, t, J=6.8 Hz), 4.69–4.61 (1H, m), 4.34–4.24 (3H, m), 3.65 (1H, dq, J=14.1, 7.1 Hz), 3.52–3.42 (1H, m), 3.39 (0.5H, dd, J=9.3, 6.1 Hz), 3.34 (0.5H, dd, J=9.3, 6.6 Hz), 3.25 (0.5H, dd, J=9.3, 6.1 Hz), 3.19 (0.5H, dd, J=9.3, 6.6 Hz), 1.85 (3H, s), 1.72–1.40 (5H, m), 1.29 (3H, d, J=5.4 Hz), 1.19 (3H, t, J=7.1 Hz), 1.08–1.03 (21H, m), 0.91 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.9, 127.8, 125.3, 99.7, 99.7, 73.8, 70.7, 60.7, 60.7, 58.4, 36.0, 33.6, 33.6, 28.6, 20.5, 19.8, 18.1, 18.1, 17.1, 15.3, 15.3, 12.4; IR (neat) ν_{max} 3416, 2944, 2868, 1464, 1380, 1342, 1136, 1088, 1060, 1014, 966, 882 cm^{-1}; FABMS [M] calculated for $C_{25}H_{50}O_4Si$: 442.3478, found: 442.3479.

4.7. (2*Z*,4*E*,6*R*,9*S*)-10-(1-Ethoxyethoxy)-3,9-dimethyl-6-triisopropylsilyloxydeca-2,4-dienyl diethoxyphosphorylacetate (13)

To a stirred solution of pyridine (0.152 mL, 1.88 mmol), diethylphosphonoacetic acid (0.234 g, 1.19 mmol), and the alcohol **12a** (0.417 g, 0.942 mmol) in CH_2Cl_2 (10 mL) were added CBr_4 (0.473 g, 1.43 mmol) and PPh_3 (0.350 g, 1.33 mmol) successively at room temperature and the resultant mixture was stirred at the same temperature for 1 h. The reaction mixture was evaporated and precipitates were filtered off. The filtrate was evaporated and the residue was purified by silica gel chromatography (hexane/ethyl acetate=1:1) to give the phosphonate **13** (0.530 g, 91%) as a colorless oil: R_f=0.14 (hexane/ethyl acetate=2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, d, J=15.6 Hz), 5.78 (1H, dd, J=15.6, 6.6 Hz), 5.46 (1H, t, J=7.3 Hz), 4.78 (2H, d, J=7.3 Hz), 4.66 (1H, q, J=5.4 Hz), 4.31 (1H, q, J=5.9 Hz), 4.22–4.12 (4H, m), 3.79–3.59 (1H, m), 3.51–3.39 (1.5H, m), 3.34 (0.5H, dd, J=9.3, 6.8 Hz), 3.25 (0.5H, dd, J=9.3, 6.1 Hz), 3.18 (0.5H, dd, J=9.3, 6.6 Hz), 2.97 (2H, d, J=21.5 Hz), 1.86 (3H, s), 1.77–1.55 (5H, m), 1.52–1.40 (1H, m), 1.34 (6H, t, J=7.1 Hz), 1.29 (3H, d, J=5.4 Hz), 1.19 (3H, t, J=7.1 Hz), 1.14–1.00 (21H, m), 0.91 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.3, 136.4, 124.9, 121.8, 99.7, 99.6, 73.8, 70.6, 62.7, 62.7, 61.4, 60.6, 36.1, 34.9, 33.7, 28.6, 20.5, 19.8, 18.1, 18.0, 17.2, 16.3, 16.3, 15.3, 12.4; IR (neat) ν_{max} 3508, 2948, 2872, 1740, 1460, 1382, 1270, 1110, 1058, 1028, 970, 882 cm^{-1}; FABMS $[M+Na]^+$ calculated for $C_{31}H_{61}NaO_8PSi$: 643.3771, found: 643.3777.

4.8. (2*Z*,4*E*,6*R*,9*S*)-10-Hydroxy-3,9-dimethyl-6-triisopropylsilyloxydeca-2,4-dienyl diethoxyphosphorylacetate (13a)

To a stirred solution of the phosphonate **13** (0.530 g, 0.854 mmol) in EtOH (10 mL) was added PPTS (0.0873 g, 0.347 mmol) and the mixture was stirred at room temperature for 41 h. The reaction was quenched with Et_3N (0.1 mL) and the resultant solution was evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=1:1) to give the alcohol **13a** (0.423 g, 90%) as a colorless oil: R_f=0.21 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, d, J=15.6 Hz), 5.77 (1H, dd, J=15.6, 6.8 Hz), 5.47 (1H, t, J=7.3 Hz), 4.91–4.69 (2H, m), 4.33 (1H, q, J=6.3 Hz), 4.22–4.11 (4H, m), 3.48–3.38 (2H, m), 2.96 (2H, d, J=21.5 Hz), 1.86 (3H, s), 1.66–1.54 (3H, m), 1.50–1.40 (1H, m), 1.33 (6H, t, J=7.1 Hz), 1.17–1.00 (22H, m), 0.91 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.8, 136.3, 125.1, 121.6, 73.7, 68.2, 62.7, 61.3, 35.7, 35.0, 33.6, 27.9, 20.5, 18.1, 18.0, 16.4, 16.3, 12.3; IR (neat) ν_{max} 3464, 2948, 2872, 1742, 1464, 1392, 1262, 1112, 1030, 970, 882, 784 cm^{-1}; FABMS $[M+Na]^+$ calculated for

$C_{27}H_{53}NaO_7PSi$: 571.3196, found: 571.3193; $[\alpha]_D^{24}$ −18.8 (*c* 1.3, $CHCl_3$).

4.9. (2*Z*,4*E*,6*R*,9*S*)-3,9-Dimethyl-10-oxo-6-triisopropylsilyloxydeca-2,4-dienyl diethoxyphosphorylacetate (14)

To a stirred solution of the alcohol **13a** (0.158 g, 0.288 mmol) in CH_2Cl_2 (3 mL) was added Dess–Martin reagent (0.371 g, 0.874 mmol) at room temperature. After 2 h, to the reaction mixture were added Et_2O (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous $Na_2S_2O_3$ (20 mL) successively and the resultant mixture was stirred for 30 min. The aqueous layer was separated and extracted with Et_2O (20 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=2:1) to give the aldehyde **14** (0.149 g, 95%) as a colorless oil: R_f 0.31 (hexane/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, d, *J*=1.7 Hz), 6.52 (1H, d, *J*=15.6 Hz), 5.77 (1H, dd, *J*=15.6, 6.3 Hz), 5.48 (1H, t, *J*=7.1 Hz), 4.78 (2H, d, *J*=7.1 Hz), 4.40–4.34 (1H, m), 4.21–4.12 (4H, m), 2.97 (2H, d, *J*=21.5 Hz), 2.38–2.28 (1H, m), 1.86 (3H, s), 1.84–1.36 (4H, m), 1.34 (6H, t, *J*=7.1 Hz), 1.10 (3H, d, *J*=7.1 Hz), 1.07–1.03 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 165.6, 137.1, 135.7, 125.3, 122.1, 73.2, 62.7, 61.3, 46.2, 35.7, 34.9, 33.6, 25.3, 20.5, 18.0, 18.0, 16.3, 13.3, 12.3; IR (neat) ν_{max} 2948, 2868, 1738, 1458, 1388, 1270, 1110, 1054, 1028, 972, 882 cm^{-1}; FABMS $[M+Na]^+$ calculated for $C_{27}H_{51}NaO_7PSi$: 569.3040, found: 569.3032; $[\alpha]_D^{25}$ −0.516 (*c* 1.1, $CHCl_3$).

4.10. (9*E*,11*Z*,5*S*,8*R*)-5,11-Dimethyl-8-triisopropylsilyloxy-oxacyclotrideca-3,9,11-trien-2-one (5)

To a stirred solution of the aldehyde **14** (0.0514 g, 0.0940 mmol) in MeCN (190 mL) were added LiCl (0.0800 g, 1.89 mmol) and DIPEA (0.328 mL, 1.88 mmol) at room temperature. After 47.5 h, the reaction was quenched with saturated aqueous NH_4Cl (200 mL) and the aqueous layer was extracted with Et_2O (200 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate/Et_2O=60:1:1) to give the macrolactone **5** (0.0302 g, 82%, a mixture of isomers; *E*/*Z*=7.6:1) as a colorless oil: R_f=0.43 (hexane/ethyl acetate=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 ((*E*)-1H, dd, *J*=15.9, 8.5 Hz), 6.51 ((*Z*)-1H, d, *J*=15.9 Hz), 6.28 ((*E*)-1H, d, *J*=16.1 Hz), 5.79–5.53 ((*E*)-3H, (*Z*)-4H, m), 4.95 ((*E*)-1H, dd, *J*=13.9, 2.4 Hz), 4.79 ((*Z*)-1H, dd, *J*=12.7, 5.9 Hz), 4.69 ((*Z*)-1H, dd, *J*=12.7, 7.3 Hz), 4.51 ((*E*)-1H, dd, *J*=13.9, 6.3 Hz), 4.47–4.40 ((*E*)-1H, m), 4.40–4.32 ((*Z*)-1H, m), 3.18–3.05 ((*Z*)-1H, m), 2.35–2.21 ((*E*)-1H, m), 1.89 ((*Z*)-3H, s), 1.86 ((*E*)-3H, s), 1.85–1.23 ((*E*)-4H, (*Z*)-4H, m), 1.10–1.01 ((*E*)-24H, (*Z*)-24H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.0, 151.1, 140.1, 137.7, 134.8, 132.9, 130.9, 129.6, 129.0, 122.6, 121.4, 119.2, 118.5, 73.2, 73.1, 60.8, 59.1, 36.7, 34.1, 33.4, 32.1, 31.5, 30.3, 20.6, 19.3, 18.1, 18.0, 17.3, 12.3 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{23}H_{41}O3Si$: 393.2825, found: 393.2814.

4.11. (3a*S*,5a*S*,6*R*,9*S*,9a*R*,9b*S*)-3,3a,5a,6,7,8,9,9a-Octahydro-4,9-dimethyl-6-triisopropylsilyloxynaphtho[2,1-*c*]furan-1(9b*H*)-one (6) and (3a*R*,5a*R*,6*R*,9*S*,9a*S*,9b*R*)-3,3a,5a,6,7,8,9,9a-octahydro-4,9-dimethyl-6-triisopropylsilyloxynaphtho[2,1-*c*]furan-1(9b*H*)-one (15)

A mixture of macrolactone **5** (0.0302 g, 0.0769 mmol, *E*/*Z*=7.6:1 (determined by 400 MHz ^{1}H NMR)) and BHT (0.8 mg) in toluene (8 mL) was refluxed for 63 h. The reaction mixture was evaporated and the residue was purified by silica gel chromatography (hexane/ethyl acetate=30:1) to give compounds **6** (0.0245 g, 81%) and **15** (0.0015 g, 5%) as a colorless oil. Compound **6**: R_f=0.13 (hexane/ethyl acetate=8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, s), 4.21 (2H, d, *J*=3.7 Hz), 3.90–3.85 (1H, m), 2.95 (1H, dd, *J*=7.6, 3.2 Hz), 2.77–2.70 (1H, m), 2.36–2.28 (1H, m), 2.17–2.10 (1H, m), 1.66–1.63 (3H, m), 1.58–1.45 (2H, m), 1.40–1.20 (3H, m), 1.01–0.98 (21H, m), 0.88 (3H, d, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 130.7, 127.1, 71.3, 69.9, 41.0, 39.2, 38.3, 35.2, 29.4, 29.2, 28.0, 20.8, 19.8, 18.1, 18.1, 12.2; IR (neat) ν_{max} 2944, 2872, 1776, 1464, 1374, 1212, 1186, 1156, 1142, 1124, 1112, 1098, 1052, 976, 882, 804 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{23}H_{41}O_3Si$: 393.2825, found: 393.2840; $[\alpha]_D^{26}$ +74.3 (*c* 1.2, $CHCl_3$). Compound **15**: R_f=0.20 (hexane/ethyl acetate=8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, d, *J*=1.2 Hz), 4.19 (1H, d, *J*=9.0 Hz), 4.14 (1H, dd, *J*=9.0, 5.9 Hz), 4.10–4.07 (1H, m), 2.98 (1H, dd, *J*=7.3, 3.7 Hz), 2.85–2.79 (1H, m), 2.29–2.16 (1H, m), 2.03–1.97 (1H, m), 1.75–1.58 (5H, m), 1.56–1.38 (3H, m), 1.00–0.96 (21H, m), 0.91 (3H, d, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 131.6, 130.2, 71.1, 69.3, 42.1, 41.8, 39.0, 37.4, 33.5, 31.1, 29.8, 20.4, 19.1, 18.2, 18.1, 12.8; IR (neat) ν_{max} 2940, 2868, 1768, 1466, 1378, 1370, 1214, 1152, 1140, 1078, 1066, 1028, 990, 922, 882 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{23}H_{41}O_3Si$: 393.2825, found: 393.2823; $[\alpha]_D^{22}$ −28.2 (*c* 1.0, $CHCl_3$).

4.12. (3a*S*,5a*S*,6*R*,9*S*,9a*R*,9b*S*)-3,3a,5a,6,7,8,9,9a-Octahydro-6-hydroxy-4,9-dimethylnaphtho[2,1-*c*]furan-1(9b*H*)-one (16)

To a stirred solution of compound **6** (0.391 g, 0.996 mmol) in THF (10 mL) was added TBAF (2.20 mL, 1.0 M in THF) and the mixture was refluxed for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the aqueous layer was extracted with Et_2O (20 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2/ethyl acetate=8:1) to give the alcohol **16** as a colorless oil, which was used for the next step: R_f=0.19 (hexane/ethyl acetate=2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (1H, s), 4.32 (1H, dd, *J*=9.0, 6.1 Hz), 4.28 (1H, dd, *J*=9.0, 1.7 Hz), 3.92–3.87 (1H, m), 3.04 (1H, dd, *J*=7.8, 3.4 Hz), 2.88–2.81 (1H, m), 2.42–2.33 (1H, m), 2.19–2.10 (2H, m), 1.75–1.70 (3H, m), 1.70–1.63 (1H, m), 1.56–1.35 (4H, m), 0.97 (3H, d, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 131.0, 126.7, 70.7, 70.2, 40.9, 38.9, 38.3, 35.1, 29.1, 28.2, 27.7, 20.8, 19.5; IR (neat) ν_{max} 3464, 2876, 1766, 1454, 1376, 1214, 1180, 1156, 1112, 1034, 1010, 974, 928, 890, 864, 822 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{14}H_{21}O_3$: 237.1490, found: 237.1500; $[\alpha]_D^{19}$ +129.0 (*c* 1.2, $CHCl_3$).

4.13. (3a*S*,5a*S*,9*S*,9a*R*,9b*S*)-3,3a,7,8,9,9a-Hexahydro-4,9-dimethylnaphtho[2,1-*c*]furan-1,6(5a*H*,9b*H*)-dione (7)

To a stirred solution of the alcohol **16** in CH_2Cl_2 (10 mL) was added Dess–Martin reagent (1.24 g, 2.93 mmol) at room temperature. After 1 h, to the reaction mixture were added Et_2O (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous $Na_2S_2O_3$ (20 mL) successively and the resultant mixture was stirred for 30 min. The aqueous layer was separated and extracted with Et_2O (20 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was subjected to recrystallization (CH_2Cl_2/hexane) to give the ketone **7** (0.183 g, 78%, two steps) as a colorless needle: R_f=0.64 (benzene/ethyl acetate=1:1); mp 153–155 °C (CH_2Cl_2/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, s), 4.36 (1H, dd, *J*=9.3, 6.1 Hz), 4.30 (1H, dd, *J*=9.3, 2.0 Hz), 3.13–3.06 (1H, m), 2.98 (1H, dd, *J*=7.6, 3.9 Hz), 2.96–2.90 (1H, m), 2.44–2.31 (2H, m), 2.26–2.18 (1H, m), 2.03–1.95 (1H, m), 1.90–1.80 (1H, m), 1.80–1.76 (3H, m), 1.58–1.46 (1H, m), 1.09 (3H, d, *J*=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 177.4, 132.6, 132.6, 122.8, 69.9, 47.6, 40.7, 39.8, 38.6, 37.5, 32.9, 28.9, 20.9, 18.9; IR (KBr) ν_{max} 2956, 1766, 1701, 1414, 1371, 1325, 1219, 1176, 1149, 1105, 1029, 975, 843 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{14}H_{19}O_3$: 235.1334, found: 235.1335; $[\alpha]_D^{25}$ −80.4 (*c* 1.0, $CHCl_3$).

4.14. (3a*S*,5a*S*,6*S*,9*S*,9a*R*,9b*S*)-3,3a,5a,6,7,8,9,9a-Octahydro-6-hydroxy-4,9-dimethylnaphtho[2,1-*c*]furan-1(9b*H*)-one (8)

To a stirred solution of the ketone **7** (0.0343 g, 0.146 mmol) in MeOH (1.8 mL) were added $CeCl_3\cdot 7H_2O$ (0.105 g, 0.281 mmol) and $NaBH_4$ (0.0622 g, 1.64 mmol) at −78 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (3 mL) and the aqueous layer was extracted with Et_2O (6 mL×3). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel chromatography (benzene/ethyl acetate=5:1) to give the alcohol **8** (0.0316 g, 91%) including the inseparable minor isomer **16**. Pure **8** was prepared from its TIPS ether to take the following data. Compound **8**: R_f 0.61 (benzene/ethyl acetate=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, s), 4.35–4.29 (2H, m), 3.78 (1H, ddd, J=11.7, 4.8, 4.0 Hz), 3.01 (1H, dd, J=7.9, 3.1 Hz), 2.88–2.81 (1H, m), 2.54–2.48 (1H, m), 2.01–1.89 (1H, m), 1.81 (1H, ddd, J=10.8, 3.7, 3.7 Hz), 1.75 (3H, s), 1.71–1.64 (2H, m), 1.44–1.29 (2H, m), 1.14–1.03 (1H, m), 0.93 (3H, d, J=6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 131.3, 124.2, 71.5, 70.3, 41.6, 39.4, 38.3, 38.2, 32.7, 29.9, 28.5, 20.9, 19.1; IR (neat) ν_{max} 3452, 2928, 2864, 1766, 1456, 1378, 1216, 1180, 1148, 1118, 1104, 1078, 1058, 1036, 980, 940, 890, 862, 840, 816 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{14}H_{21}O_3$: 237.1490, found: 237.1498; $[\alpha]_D^{19}$ +30.7 (*c* 0.4, $CHCl_3$).

4.15. (3a*S*,5a*S*,6*S*,9*S*,9a*R*,9b*S*)-3,3a,5a,6,7,8,9,9a-Octahydro-4,9-dimethyl-6-triisopropylsilyloxynaphtho[2,1-*c*]furan-1(9b*H*)-one (3)

To a stirred solution of the alcohol **8** (0.0316 g, 0.134 mmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (0.0312 mL, 0.268 mmol) and TIPSOTf (0.115 mL, 0.428 mmol) successively at −78 °C and the resultant mixture was stirred at room temperature for 40 min. The reaction was quenched with saturated aqueous NH_4Cl (4 mL) and the aqueous layer was extracted with CH_2Cl_2 (6 mL×3), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel chromatography (hexane/ethyl acetate=8:1) to give TIPS ether **3** (0.0489 g, 93%) as a colorless oil and the unreacted alcohol **16** (0.0014 g, 4%). The TIPS ether **3** was spectroscopically identical in all respect to the previously reported TIPS ether: R_f=0.71 (benzene/ethyl acetate=5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, s), 4.32–4.28 (2H, m), 3.80 (1H, dt, J=11.5, 4.6 Hz), 2.98 (1H, dd, J=7.8, 2.9 Hz), 2.85–2.79 (1H, m), 2.56–2.50 (1H, m), 1.79 (1H, ddd, J=11.0, 3.7, 3.7 Hz), 1.75 (3H, s), 1.70–1.60 (2H, m), 1.44–1.24 (3H, m), 1.11–1.10 (21H, m), 0.92 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 130.4, 125.2, 72.3, 70.2, 41.7, 39.7, 38.7, 38.4, 33.1, 31.4, 28.7, 21.0, 19.2, 18.1, 12.3; IR (neat) ν_{max} 2941, 2866, 1774, 1464, 1377, 1213, 1184, 1146, 1111, 1092, 1068, 1036, 980, 883, 822, 812 cm^{-1}; FABMS $[M+H]^+$ calculated for $C_{23}H_{41}O_3Si$: 393.2825, found: 393.2823; $[\alpha]_D^{23}$ +43.8 (*c* 1.1, $CHCl_3$).

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Supplementary data

Supplementary data for this article (^{1}H and ^{13}C NMR spectra of compounds **3**, **5**–**10**, and **12**–**16**) can be found online. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.030.

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