JOC Article

Total Synthesis of Leustroducsin B

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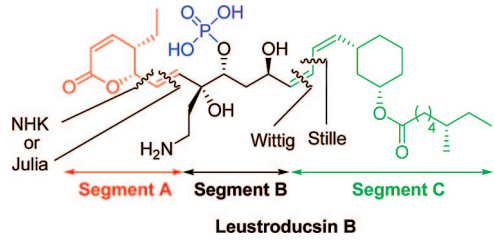

Leustroducsin B was synthesized via a convergent route based on division of the leustroducsin molecule into three segments A, B, and C. Two coupling reactions (Julia coupling reaction and Nozaki−Hiyama−Kishi (NHK) reaction) were employed for coupling of segments A and B: segment A_1 for the Julia coupling reaction was prepared by a combination of Sharpless asymmetric epoxidation and an epoxide-cleavage reaction with an organoaluminum reagent, while segment A_2 for the NHK reaction was synthesized from optically active alcohol that had previously been prepared by lipase-catalyzed kinetic resolution. Segment B, whose structure was modified with some functional groups, was synthesized from (*R*)-malic acid by a combination of Wittig reaction and Sharpless asymmetric dihydroxylation, and segment C, containing a cyclohexane moiety, was prepared by asymmetric Diels−Alder reaction. Segment B was first coupled with segment A_1 via the Julia coupling reaction, but the yield was low due to unexpected epimerization. The NHK reaction of segment A_2 proceeded to give the coupling product in good yield. This product was coupled with segment C via Wittig and Stille coupling reactions, and finally, phosphorylation was carried out by partial hydrolysis of a cyclic phosphate to give leustroducsin B.

Introduction

Leustroducsins A−C (**1a**−**c**), shown in Figure 1, were isolated from the culture broth of *Streptomyces platensis* SANK 60191 by Sankyo's groups in 1993.[1,2] These compounds have been found to show various biological activities, including induction of a colony-stimulating factor by NF-κB activation, thrombopoiesis, anti-infective activity, and antimetastatic activity.[3] An analogous natural product, fostriecin (**3**), has also attracted much attention due to its superior specific inhibitory activity against serine/threonine protein phosphatase (PP) 2A compared to that against PP1 among reported PP inhibitors, making compound **3** an attractive synthetic target.[4] Consequently, a number of synthetic studies on fostriecin (**3**), including some by our group, have been reported.[5,6] As expected based on its structural similarity to fostriecin (**3**), the hydrated analogue of leustroducsins, leustroducsin H (**1h**), is also known to be a potent PP2A inhibitor, suggesting a relationship between the

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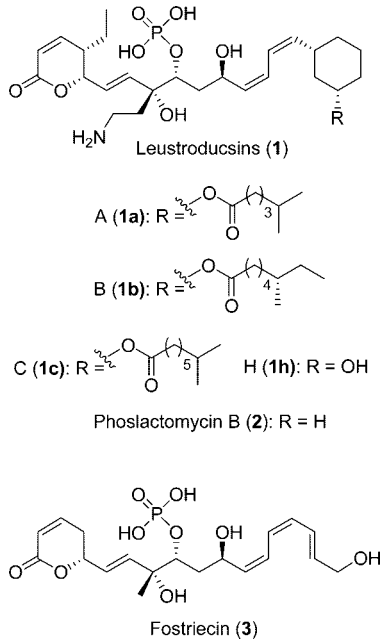

FIGURE 1. Structures of leustroducsins (**1**), phoslactomycin B (**2**), and fostriecin (**3**).

biological activity of leustroducsins and the PP2A-specific inhibitory activity.[7] Synthetic studies on this type have been reported by two groups in Japan. In 2003, Fukuyama and co-workers reported the first total synthesis of leustroducsin B (**1b**),[8] while in 2006, Kobayashi and co-workers successfully synthesized the analogous natural product, phoslactomycin B (**2**).[9,10] In this paper, we describe details of our total synthesis of leustroducsin B (**1b**).[11]

In our previous paper, we described the total synthesis of fostriecin (**3**) via a convergent route.[5] When planning the synthetic strategy, we paid particular attention to the possibility of synthesizing various derivatives, including not only analogous natural products but also artificial derivatives, using the same synthetic strategy. On the basis of this, fostriecin (**3**) was synthesized via a convergent route in which the molecule was constructed from three segments A′, B′, and C′, as shown in Figure 2. We also utilized this strategy in the synthesis of leustroducsin B (**1b**), dividing the structure into three segments A, B, and C, as shown in Figure 3.

In our consideration of the synthesis of segment A of leustroducsin (**1**), we noted that the most significant difference between leustroducsins (**1**) and fostriecin (**3**) was the additional stereogenic center at C(4) in **1**. For this reason, the Horner−Emmons reaction used our synthesis of fostriecin (**3**) was not suitable due to the possibility of epimerization of the C(4) stereogenic center.

We decided to examine two coupling reactions, the Julia coupling reaction[12] and the Nozaki−Hiyama−Kishi (NHK) reaction,[13] for the coupling of segment A with segment B (**6**). Segment A_1 (**4**), the substrate for the Julia coupling reaction, was to be prepared from *trans*-2-penten-1-ol (**9**) by Sharpless asymmetric epoxidation followed by an epoxide cleavage reaction with an alkynylaluminum reagent, while segment A_2 (**5**), the substrate for the NHK reaction with segment B, was to be synthesized from optically active alcohol **10**, which had already been prepared by Panek's group from ethylmalonate **11** using lipase-catalized kinetic resolution as a key step.[14]

Segment B (**6**), which contains a 2-aminoethyl group (another characteristic structural difference from fostriecin (**3**)) was to be obtained from (*R*)-malic acid (**13**): (1) the 2-aminoethyl group was to be introduced by a Wittig reagent with a lactone structure and (2) Sharpless asymmetric dihydroxylation of the resulting olefin **12** was to give the desired hydoxyl groups in a stereoselective manner. Segment B (**6**) was expected to serve as a common intermediate for the Julia and NHK substrate.

The structure of the right side of leustroducsins (**1**), the olefinic moiety, is largely different from that of fostriecin (**3**). However, we expected that the coupling of segment B (**6**) with segment C (**7**) could be achieved basically using the same reaction, the Stille coupling reaction. Segment C (**7**) was to be synthesized by homologation of optically active 3-cyclohexenecarboxylic acid (**14**), which was to be obtained by Diels−Alder reaction of **15** with 1,3-butadiene.

Results and Discussion

Synthesis of Segment A. Compound **4** (segment A_1 for the Julia coupling reaction) was synthesized from *trans*-2-penten-1-ol (**9**) as follows (Scheme 1). Sharpless asymmetric epoxidation of **9** with L-(+)-DIPT furnished epoxyalcohol **16** with greater than 20:1 stereoselectivity (determined after being derived from MTPA ester). The stereochemistry of the product **16** was assigned to be 2*S* and 3*S* from experimental prediction reported by Sharpless and co-workers,[15] but was eventually determined by comparison of the $[\alpha]_D$ value with that of authentic sample.[16] Cleavage of the epoxide bond of **16** with an alkynylaluminum reagent prepared from **17**[17] in cyclohexane yielded 1,2-diol **18a** as the major product, accompanying regioisomeric 1,3-diol **18b**. The reaction in toluene gave similar results, but with a slightly improved yield. The structures of **18a** and **18b** were confirmed by transformation into the cyclic

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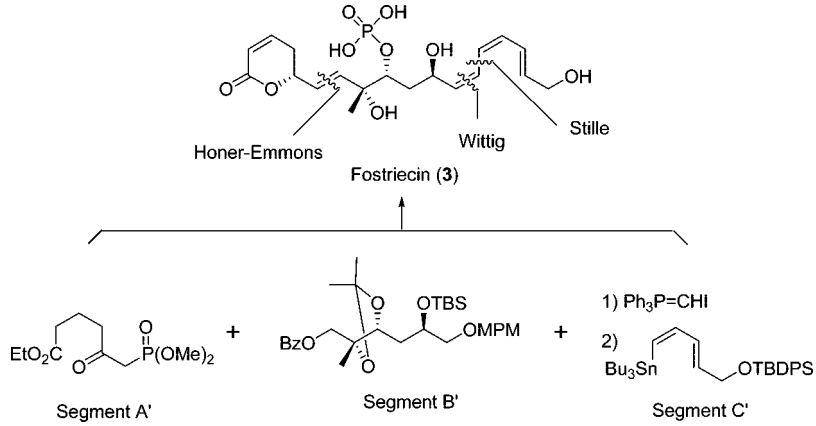

FIGURE 2. Total synthesis of fostriecin (**3**) from a previous study.[5]

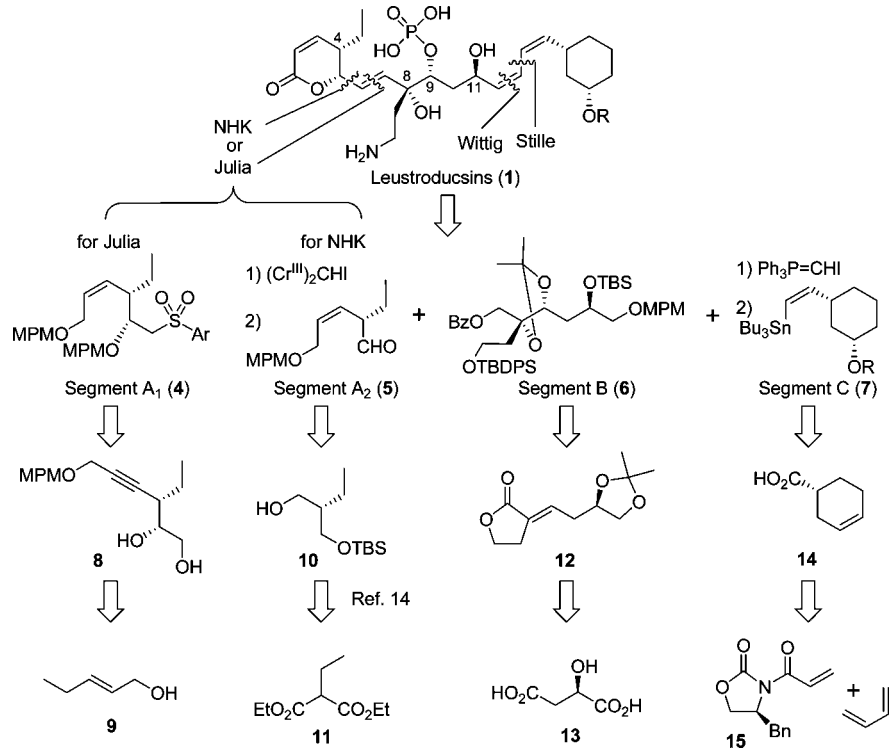

FIGURE 3. Retrosynthetic analysis of leustroducsins (**1**).

carbonates, **19a** and **19b**, the IR spectra of which showed maximum absorption at 1807 and 1756 cm^{-1} corresponding to 5-membered and 6-membered cyclic carbonates, respectively. The 1,2-diol **18a** was protected to give *p*-anisilidene acetal **20** as a diastereomeric mixture (ca. 2:3), and reduction of the triple bond of **20** was carried out without separation. Hydrogenation with Lindlar catalyst afforded a mixture of a saturated compound and the desired (*Z*)-olefinic compound **21**, which was hard to separate. We then employed activated Zn as an alternative method for the reaction,[18] which proceeded smoothly to give **21** in good yield. Reductive cleavage of the acetal bond of **21** with DIBAl-H took place regioselectively at −100 °C to yield primary alcohol **22**, and reaction of **22** with thiol **23** under Mitsunobu conditions afforded sulfide **24**, which was oxidized to give segment A_1 (**4**) for the Julia coupling reaction.

Aldehyde **5**, corresponding to segment A_2 for the NHK reaction, was prepared from known alcohol **10** as shown in Scheme 2.[14] Oxidation of **10** and subsequent treatment with Wittig reagent[19] afforded cis-unsaturated ester **26**. The ester group of **26** was reduced with DIBAl-H, and the hydroxyl group of the resultant **27** was protected with a MPM group, yielding **28**. The TBS group of **28** was removed by acidic treatment to give **29**, which was oxidized with Dess−Martin periodinane to yield the desired segment A_2 (**5**) for the NHK reaction.

Synthesis of Segment B (6). Segment B (**6**) was synthesized as shown in Scheme 3. Oxidation of alcohol **30**[20] followed by in situ treatment with Wittig reagent **31**,[21] containing a γ-lactone structure, afforded (*E*)-olefin **12** stereoselectively. The lactone moiety of **12** was reduced with DIBAl-H to give hydroxyalde-

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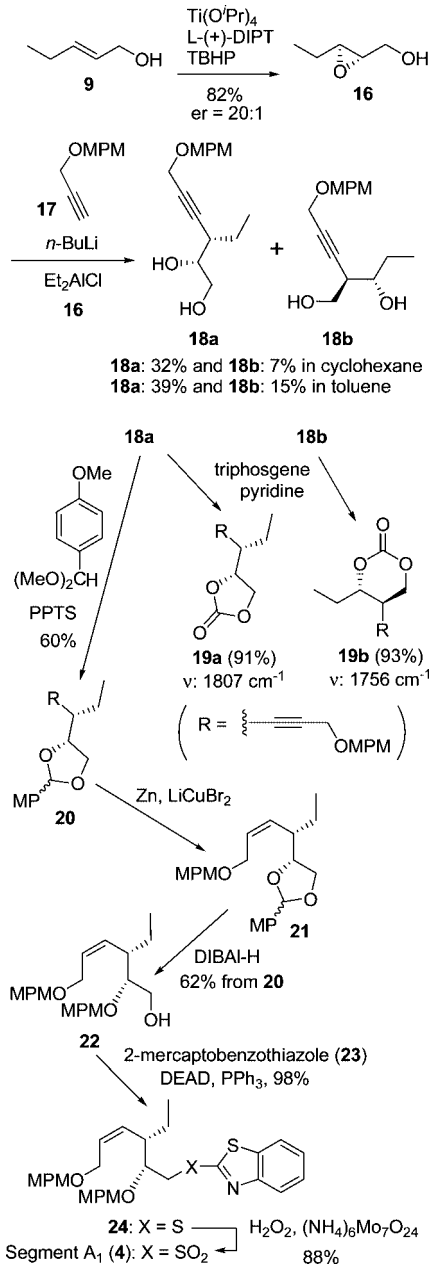
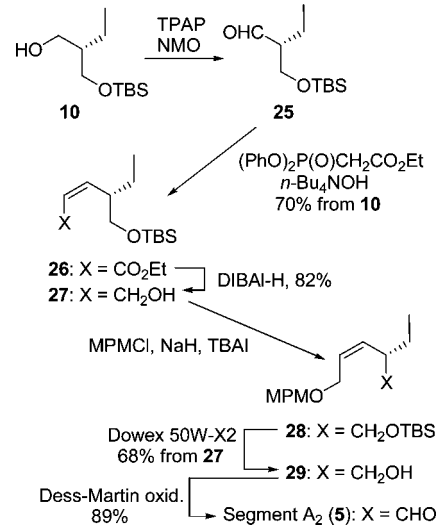
SCHEME 1. Synthesis of Segment A_1



hyde **32**, which was protected with a TBDPS group, affording aldehyde **33**. After reduction of **33**, the hydroxyl group of the resulting **34** was protected with a benzoyl group to give olefin **35**. Sharpless asymmetric dihydroxylation of **35** with the $(DHQD)_2PHAL$[22] ligand furnished diol **36** as a single isomer in good yield. The stereochemistry of **36** was expected to be as shown based on experimental prediction proposed by Sharpless and co-workers[22] and also from our previous result,[5] but was determined by modified Mosher's method.[23] Diol **36** was transformed into (*S*)- and (*R*)-MTPA monoesters, respectively,

SCHEME 2. Synthesis of Segment A_2



and the differences in the ^{1}H NMR chemical shifts ($\Delta\delta$) of the (*S*)- and (*R*)-monoesters are summarized in Figure 4. Thus, the stereochemistry at C(9) was unambiguously shown to have an (*R*)-configuration, which implies that the configuration at C(8) is also *R*.

Finally, compound **36** was transformed into segment B (**6**) as follows. The *vic*-diol moiety of **36** was protected with an acetonide group to give bisacetonide **37**. The terminal acetonide group of **37** was then selectively removed by zinc nitrate treatment, giving diol **38**, the primary hydroxyl group of which was selectively protected with a MPM group via cyclic stannane to give **39**. Finally, the secondary hydroxyl group of **39** was protected with a TBS group to give segment B (**6**).

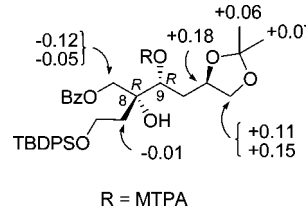


FIGURE 4. $\Delta\delta$ ($= \Delta\delta_S - \Delta\delta_R$) values (ppm) for MTPA esters of **36**.

Synthesis of Segment C (7). Several methods including optical resolution by recrystallization[24] and asymmetric Diels−Alder reaction[25−28] have been reported to give optically active 3-cyclohexenecarboxylic acid (**14**). However, the recrystallization procedure was found to be inefficient, and expensive chiral auxiliaries, sometimes with unnatural stereochemistry, are required to obtain the (*R*)-isomer **14** by asymmetric Diels−Alder reaction. On the basis of the report by Raw and Jang of an effective asymmetric Diels−Alder reaction with a crotonic acid derivative containing an (*R*)-benzyloxazolidinone structure as a chiral auxiliary,[29] we applied this reaction to acrylic acid derivative **15** (Scheme 4). The Diels−Alder reaction of **15** with

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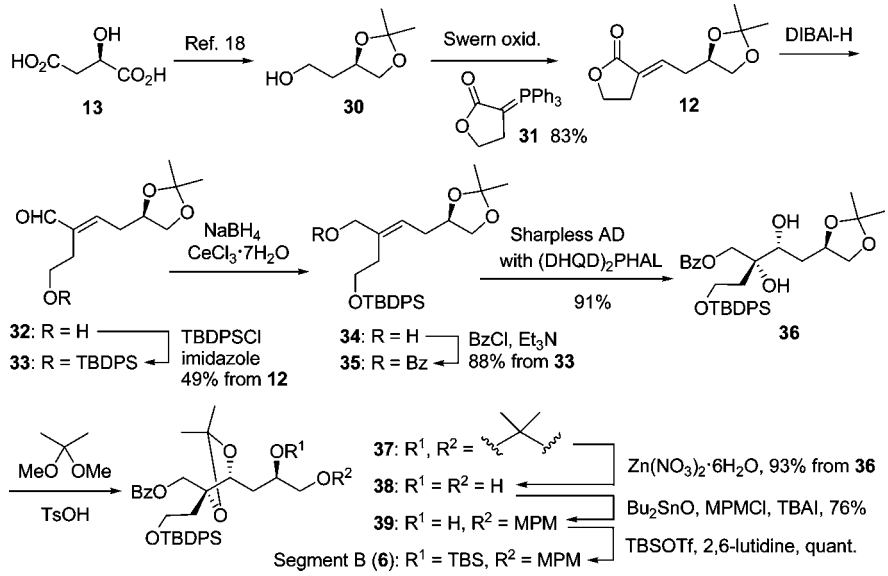
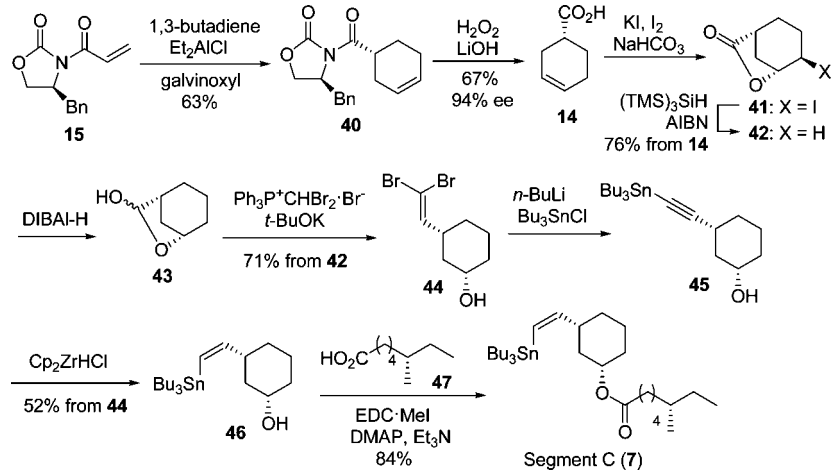
SCHEME 3. Synthesis of Segment B



SCHEME 4. Synthesis of Segment C



butadiene afforded **40** as a single diastereomer. The chiral auxiliary was removed by hydrolysis, and the resulting carboxylic acid **14** was converted to lactone **42** by iodolactonization and subsequent reduction of **41** with silane.[30] After reduction with DIBAl-H, dibromomethylenation of **43** by Wittig reaction afforded **44**, which was treated with *n*-butyllithium and tributyltin chloride without protecting the hydroxyl group to furnish acetylene **45**. This was reduced by hydozirconation to give cis-olefin **46**, which was finally esterified with carboxylic acid **47**[31]to afford segment C (**7**). It is notable that various segments C for other leustroducsins and phoslactomycins can be synthesized by using different types of carboxylic acid in the last step.

Coupling Reaction of Segment B (6) with Segment A. As is obvious from the structure of segment B (**6**), it can be coupled with either segment A or C by selective removal of one of the two terminal protecting groups (the benzoyl group and the MPM group). In view of the stability of the diene moiety of leustroducsins (**1**) and the diversity of the acyloxy side chain on the cyclohexane structure, segment A, rather than segment C, was initially used for the coupling reaction. For the Julia coupling reaction of segment B (**6**) with segment A_1 (**4**), segment B (**6**) was transformed into aldehyde **49** in good yield by selective removal of the terminal benzoyl group by methanolysis and oxidation with TPAP (Scheme 5).

Although the Julia coupling reaction of **49** with segment A_1 (**4**) using NaHMDS as a base afforded olefin **50** in 49% yield, it was found that unexpected epimerization at C(5) took place, resulting in the formation of a diastereomeric mixture. The mechanism of epimerization at C(5) is thought to be as shown in Figure 5: elimination of the *p*-methoxybenzyloxy group followed by re-addition of the *p*-methoxybenzyloxy anion to vinylsulfone.[32] On the basis of this, we attempted the reaction using a different base (LiHMDS). Interestingly, no epimerization was observed with this base, but the yield decreased considerably. This is probably due to the lower nucleophilicity of the lithium salt of the *p*-methoxybenzyloxy anion compared to the corresponding sodium salt. It is also noteworthy that the (*R*)-

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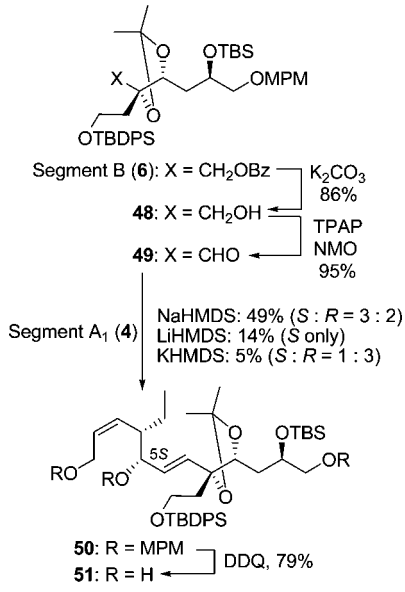
SCHEME 5. Julia Coupling Reaction of Segment A_1 with Segment B



diastereomer was obtained as a major product when KHMDS was used as a base, although the yield was much lower. The (*S*)-isomer **50** obtained with LiHMDS was transformed into triol **51** by removal of all MPM groups under oxidative conditions.

As the desired product **50** was obtained only in low yield under Julia reaction conditions, we attempted the NHK reaction (Scheme 6). In this case, aldehyde **49** was treated with iodoform and $CrCl_2$ to give *trans*-iodomethylene **52**,[33] which was coupled with segment A_2 (**5**) under NHK reaction conditions. The reaction took place smoothly but with unfavorable stereoselectivity, affording product **53** as a mixture of diastereomers which was separable by flash chromatography. The stereochemistry of **53** was determined by transformation of **53a** into triol **51**, which was identical with the compound derived from the product of the Julia coupling reaction. This result showed that the desired (*S*)-isomer **53a** was the minor product of the NHK reaction. It was also found that oxidation of the diastereomeric mixture of **53** and subsequent reduction of the resulting ketone **54** with L-selectride gave the (*R*)-isomer **53b** stereoselectively.[34] This stereochemical outcome, with preferential formation of the (*R*)-isomer **53b**, is thought to be affected by the neighboring stereogenic center in ketone **54**, and may be explained by consideration of the Felkin−Anh model shown in Figure 6. The (*R*)-isomer **53b** was converted into the desired (*S*)-isomer **53a** by the Mitsunobu reaction. Overall, the NHK reaction was concluded to be more effective than the Julia coupling reaction for coupling of segment A with segment B.

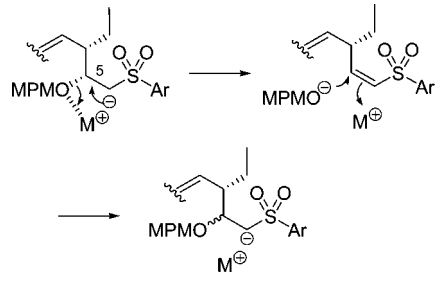
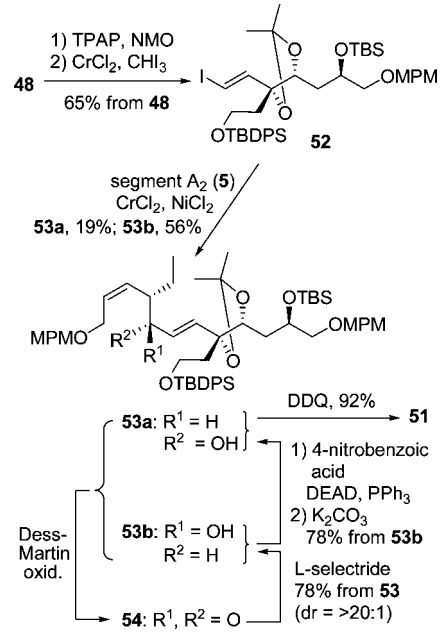


FIGURE 5. Possible mechanism for epimerization at C(5).

SCHEME 6. NHK Reaction of Segment A_2 with Segment B



Synthesis of Leustroducsin B (1b). Before construction of the entire carbon skeleton of leustroducsin B (**1b**) by coupling with segment C (**7**), the amino group at C(25) was introduced as follows (Scheme 7). Triol **51** was oxidized with TEMPO, affording lactone-aldehyde **55** in a one-pot reaction. Compound **55** was subjected to the Wittig reaction, affording (*Z*)-iodomethylene **56** as a major product. After removal of two silyl groups of **56** to give **57**, both hydroxyl groups were again protected with a TBS group, and the primary hydroxyl group was regenerated by careful acidic hydrolysis, giving the alcohol **58**. An azide group was introduced via standard protocols, and the resulting azide **59** was reduced and protected with an Alloc group to give **60** in a one-pot reaction. Acidic treatment resulted in simultaneous removal of the acetonide and TBS groups to afford triol **61**, which was then coupled with segment C (**7**) under Pd(0)-catalyzed conditions, producing **62**, which contains the entire carbon skeleton of leustroducsin B (**1b**).

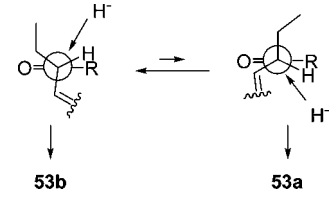
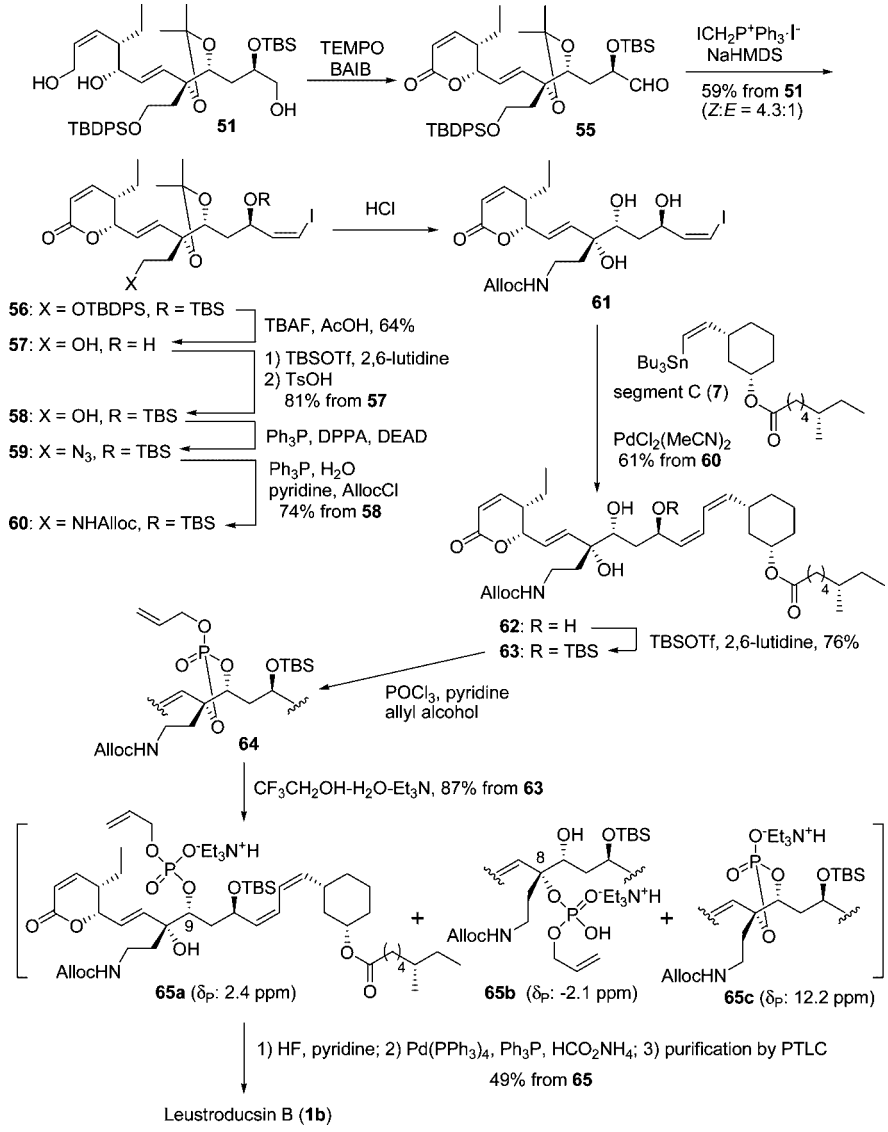


FIGURE 6. Stereoselectivity for reduction of ketone **54**.

The final stage, regioselective introduction of the phosphate function, was achieved via a cyclic phosphate, using a method we developed and employed in the total synthesis of fostriecin.[5b] The hydroxyl group at C(11) was regioselectively protected with a TBS group at −78 °C, giving diol **63**. Formation of a cyclic phosphate triester followed by partial hydrolysis of **64** successfully produced **65a**, a fully protected form of leustroducsin B (**1b**), as a major product, accompanied by C(8) *O*-phosphate **65b** and cyclic phosphate diester **65c** (**65a**:**65b**:**65c** = 71:22:7). The structures of these compounds **65a**−**c** were confirmed by comparison of their characteristic ^{31}P NMR chemical shifts, as shown in Scheme 7.[5b] As it was difficult to separate these phosphate diesters **65** at this stage, the final transformations were

SCHEME 7. Total Synthesis of Leustroducsin B: Final Steps



carried out with the unseparated mixture. First, the TBS group of **65** was deprotected, and then the allyl protecting groups were removed.[35] The resulting product was purified by PTLC to afford leustroducsin B (**1b**), the $[\alpha]_D$ value and ^1H and ^{13}C NMR data for which were identical with those of authentic sample.

Conclusion

A total synthesis of leustroducsin B (**1b**) was achieved via a convergent route involving a three-segment coupling process, employing a strategy that was basically the same as that used for our total synthesis of fostriecin (**3**). This synthetic strategy provides an efficient method for synthesis not only of fostriecin-type natural products but also of various derivatives, including compounds lacking sections of the structure of the parent natural products and hybrid analogues of fostriecin (**3**) and leustroducsins (**1**), and would contribute to studies in chemical biology and medicinal chemistry, particularly in the area of serine/threonine protein phosphatases.

Experimental Section

(2*R*,3*R*,5*R*)-5-*tert*-Butyldimethylsiloxy-2-(2-*tert*-butyldiphenylsiloxyethyl)-2,3-isopropylidenedioxy-6-(4-methoxybenzyloxy)-1-hexanol (48). To a stirred solution of **6** (870 mg, 1.05 mmol) in methanol (10 mL) was added K_2CO_3 (436 mg, 3.15 mmol), and the reaction was stirred at room temperature for 4 h. After filtration, the resulting filtrate was diluted with ether, washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:6) to give **48** (621 mg, 86%) as a colorless oil: $[\alpha]^{21}_D$ −2.92 (*c* 1.92, $CHCl_3$); IR ν_{max} (KBr) 3382, 2930, 1462 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.05 (9H, s), 1.29 (3H, s), 1.34 (3H, s), 1.48−1.82 (4H, m), 2.65 (1H, br s), 3.34 (1H, dd, J = 5, 10 Hz), 3.40 (1H, dd, J = 5, 10 Hz), 3.52 (1H, m), 3.76 (1H, m), 3.80 (3H, s), 3.89−4.00 (2H, m), 4.22 (1H, d, J = 9 Hz), 4.52 (2H, s), 6.88 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.35−7.46 (6H, m), 7.64−7.70 (4H, m); ^{13}C NMR (67.8 MHz,

(33) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
(34) Although we examined reductions of the corresponding ketone including asymmetric reductions, the results were unsatisfactory.
(35) When deprotection procedures were carried out in reverse (allyl protecting groups followed by the TBS group), in the same sequence as used in our fostriecin synthesis, purification was more difficult and we were unable to isolate pure leustroducsin B.
(36) Goering, H. L.; Serres, C., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 5908–5912.

$CDCl_3$) δ_C −4.9, −4.1, 18.1, 19.0, 25.9 (3C), 26.8 (3C), 27.0, 28.5, 34.3, 34.6, 55.2, 59.8, 64.7, 68.7, 72.9, 74.8, 76.6, 83.1, 107.5, 113.7 (2C), 127.7 (2C), 127.7 (2C), 129.3 (2C), 129.7, 129.7, 130.4, 133.1, 133.2, 135.5 (2C), 135.6 (2C), 159.1; mass (FAB) *m*/*z* 723 (M + H^+); HRMS calcd for $C_{41}H_{63}O_7Si_2$ 723.4113, found 723.4094.

(2*R*,4*R*,5*R*,6*E*,8*S*,9*S*,10*Z*)-2-*tert*-Butyldimethylsiloxy-5-(2-*tert*-butyldiphenylsiloxyethyl)-9-ethyl-4,5-isopropylidenedioxy-8,12-bis(4-methoxybenzyloxy)-6,10-dodecadiene (50). To a stirred solution of **48** (53 mg, 0.073 mmol) in CH_2Cl_2 (0.8 mL) were added molecular sieves 4A (110 mg), *N*-methylmorpholine -*N*-oxide (26 mg, 0.110 mmol), and tetrapropylammonium perruthenate (2.1 mg, 8 mol%) at room temperature, and the reaction was stirred at the same temperature for 2 h. After filtration, the reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:8) to give **49** (49 mg, 95%). To a stirred solution of **49** (49 mg, 0.068 mmol) and the segment A_1 (**4**) (79 mg, 0.136 mmol) in THF (0.7 mL) was added sodium bis(trimethylsilyl)amide (1.1 M in THF, 123 μL, 0.136 mmol) at −78 °C, and the reaction was stirred at the same temperature for 1 h. After being warmed to 0 °C for 1 h, the reaction mixture was diluted with ether, washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:8) to give **50** (37 mg, 49%) as a colorless oil: $[\alpha]^{22}_D$ +58.6 (*c* 0.55, $CHCl_3$); IR ν_{max} (KBr) 2851, 1685, 1650, 1613, 1511, 1460 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.75 (3H, t, *J* = 7 Hz), 0.85 (9H, s), 1.03, (9H, s), 1.03−1.13 (1H, m), 1.26 (3H, s), 1.29 (3H, s), 1.43−1.56 (2H, m), 1.62−1.79 (2H, m), 1.96 (1H, dt, *J* = 5, 12 Hz), 2.32−2.43 (1H, m), 3.38 (2H, ddd, *J* = 5, 10, 13 Hz), 3.51 (1H, dd, *J* = 6, 8), 3.75−4.10 (7H, m), 3.79 (6H, s), 3.80 (3H, s), 4.24 (1H, d, *J* = 12 Hz), 4.33 (1H, d, *J* = 12 Hz), 4.35 (1H, d, *J* = 12 Hz), 4.47 (1H, d, *J* = 12 Hz), 4.49 (2H, d, *J* = 12 Hz), 5.16 (1H, t, *J* = 11 Hz), 5.40 (1H, d, *J* = 15 Hz), 5.53 (1H, dd, *J* = 8, 15 Hz), 5.61 (1H, td, *J* = 6, 11 Hz), 6.79 (2H, d, *J* = 9 Hz), 6.84 (2H, d, *J* = 9 Hz), 6.89 (2H, d, *J* = 9 Hz), 7.05 (2H, d, *J* = 9 Hz), 7.19 (2H, d, *J* = 9 Hz), 7.26−7.37 (8H, m), 7.61−7.65 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C: −4.7, −4.1, 11.8, 18.2, 19.2, 24.3, 26.0 (3C), 26.7, 27.0 (3C), 28.4, 33.9, 36.9, 44.6, 55.3, 55.3, 55.3, 60.7, 66.3, 68.6, 69.7, 71.7, 72.9, 74.9, 79.4, 82.2, 82.8, 107.8, 113.5 (2C), 113.6 (2C), 113.6 (2C), 127.5 (2C), 127.5 (2C), 128.2, 128.5, 129.1 (2C), 129.2 (2C), 129.2 (2C), 129.4 (2C), 130.3, 130.5, 130.6, 132.9, 133.7, 133.8, 134.6, 135.3 (2C), 135.4 (2C), 158.7, 158.9, 159.0; mass (FAB) *m*/*z* 1110 (M + Na^+); HRMS calcd for $C_{65}H_{90}O_{10}Si_2Na$ 1109.5970, found 1109.5970.

Reactions with lithium and potassium bis(trimethylsilyl)amide were also carried out similarly.

(2*R*,4*R*,5*R*,6*E*,8*S*,9*S*,10*Z*)-2-*tert*-Butyldimethylsiloxy-5-(2-*tert*-butyldiphenylsiloxyethyl)-9-ethyl-4,5-isopropylidenedioxy-6,10-dodecadiene-1,8,12-triol (51). To a stirred solution of **50** (349 mg, 0.321 mmol) in CH_2Cl_2 (3 mL) containing water (0.3 mL) was added DDQ (291 mg, 1.28 mmol) at room temperature, and the reaction was stirred vigorously at room temperature for 1 h. After addition of saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate. Combined organic layers were washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by passing through a silica gel short column (ethyl acetate−hexane = 1:2) to give **51** (183 mg, 79%) as a colorless oil: $[\alpha]^{23}_D$ +6.99 (*c* 0.41, $CHCl_3$); IR ν_{max} (KBr) 3070, 2854, 1612, 1513 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.09 (3H s), 0.81 (3H, t, *J* = 7 Hz), 0.88 (9H, s), 1.04 (9H, s), 1.04−1.14 (1H, m), 1.29 (6H, s), 1.40−1.50 (1H, m), 1.53−1.74 (3H, m), 1.90−2.00 (1H, m), 2.05 (1H, br s), 2.45−2.57 (1H, m), 3.51 (1H, d, *J* = 12 Hz), 3.63−3.84 (4H, m), 3.86−3.99 (3H, m), 4.14 (1H, dd, *J* = 9, 12 Hz), 5.09 (1H, t, *J* = 11 Hz), 5.46 (1H, d, *J* = 15 Hz), 5.69 (1H, dd, *J* = 7, 15 Hz), 5.82 (1H, td, *J* = 7, 11 Hz), 7.33−7.44 (6H, m), 7.63−7.67 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.6, −4.2, 12.0, 18.1, 19.2, 24.7, 25.9 (3C), 26.7, 26.9 (3C), 28.3, 33.3, 36.6, 45.2, 57.9, 60.3, 67.2, 70.3, 74.3, 80.0, 82.9, 107.9, 127.5 (2C), 127.5 (2C), 129.5, 129.5, 130.1, 131.7, 132.6, 133.1, 133.7, 133.9, 135.4 (4C); mass (FAB) *m*/*z* 749 (M + Na^+); HRMS calcd for $C_{41}H_{66}O_7Si_2Na$ 749.4245, found 749.4251.

(2*R*,4*R*,5*R*)-2-*tert*-Butyldimethylsiloxy-7-*tert*-butyldiphenylsiloxy-5-[(*E*)-2-iodovinyl]-4,5-isopropylidenedioxy-1-(4-methoxybenzyloxy)heptane (52). To a stirred solution of **48** (740 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) were added powdered MS4A (1.6 g), *N*-methylmorpholine *N*-oxide (155 mg, 1.33 mmol), and tetrabutylammonium perruthenate (29 mg, 8 mol%), and the reaction was stirred at room temperature for 1 h. After filtration, the solvent was evaporated off under reduced pressure, and the resulting residue was passed through a silica gel short column (ethyl acetate−hexane = 1:8) to give aldehyde (733 mg), which was immediately employed for the next reaction. To a stirred suspension of $CrCl_2$ (753 mg, 6.12 mmol) in THF (7.0 mL) was added dropwise a THF (7.0 mL) solution of the aldehyde (733 mg) and iodoform (801 mg, 2.03 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with ether, washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:20) to afford **52** (562 mg, 65% from **48**) as a colorless oil: $[\alpha]^{25}_D$ +6.51 (*c* 3.40, $CHCl_3$); IR ν_{max} (KBr) 3070, 2930, 2856, 1611, 1588, 1513 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.88 (9H, s), 1.06 (9H, s), 1.26 (3H, s), 1.29 (3H, s), 1.44−1.89 (4H, m), 3.37 (2H, ddd, *J* = 5, 10, 13 Hz), 3.68−3.81 (2H, m), 3.81 (3H, s), 3.89−3.98 (2H, m), 4.47 (1H, d, *J* = 12 Hz), 4.49 (1H, d, *J* = 12 Hz), 6.30 (1H, d, *J* = 15 Hz), 6.38 (1H, d, *J* = 15 Hz), 6.90 (1H, d, *J* = 9 Hz), 7.26 (1H, d, *J* = 9 Hz), 7.33−7.47 (6H, m), 7.61−7.68 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.8, −3.9, 18.2, 19.2, 26.0 (3C), 26.6, 27.0 (3C), 28.3, 33.9, 36.5, 55.3, 59.9, 68.7, 72.9, 74.6, 76.8, 79.3, 85.4, 108.1, 113.6 (2C), 127.5 (2C), 127.6 (2C), 129.2 (2C), 129.5 (2C), 130.2, 133.7, 133.7, 135.4 (2C), 135.5 (2C), 146.3, 159.0; mass (FAB) *m*/*z* 867 (M + Na^+); HRMS calcd for $C_{42}H_{61}O_6Si_2NaI$ 867.2949, found 867.2979.

(2*Z*,4*S*,5*S*,6*E*,8*R*,9*R*,11*R*)-11-*tert*-Butyldimethylsiloxy-8-(2-*tert*-butyldiphenylsiloxyethyl)-4-ethyl-8,9-isopropylidenedioxy-1,12-bis(4-methoxybenzyloxy)-2,6-dodecadien-5-ol (53a). To a stirred solution of segment A_2 (**5**) (30 mg, 0.121 mmol) and **52** (133 mg, 0.157 mmol) in degassed DMSO (0.6 mL) were added $NiCl_2$ (0.6 mg, 4 mol%) and $CrCl_2$ (60 mg, 0.484 mmol), and the reaction was stirred at room temperature for 2 h. After being diluted with ether, the reaction mixture was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (ethyl acetate−hexane = 1:6) to give **53a** (22 mg, 19%, **53a**:**53b** = >20:1) and **53b** (66 mg, 56%, **53a**:**53b** = 1:14) as a colorless oil, respectively. Compound **53a**: $[\alpha]^{25}_D$ +18.5 (*c* 0.78, $CHCl_3$); IR ν_{max} (KBr) 3471, 3070, 2931, 2856, 1612, 1587, 1513. cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.78 (3H, t, *J* = 7 Hz), 0.84 (9H, s), 1.03 (9H, s), 1.08 (1H, m), 1.25 (3H, s), 1.27 (3H, s), 1.38−1.48 (2H, m), 1.61 (1H, m), 1.70 (1H, m), 1.92−1.98 (2H, m), 2.41 (1H, m), 3.36 (2H, ddd, *J* = 3, 5, 9 Hz), 3.68 (1H, m), 3.76−3.84 (2H, m), 3.80 (3H, s), 3.80 (3H, s), 3.88−4.01 (4H, m), 4.42 (1H, d, *J* = 12 Hz), 4.43 (1H, d, *J* = 12 Hz), 4.46 (1H, d, *J* = 12 Hz), 4.48 (1H, d, *J* = 12 Hz), 5.16 (1H, t, *J* = 11 Hz), 5.42 (1H, d, *J* = 16 Hz), 5.64 (1H, dd, *J* = 7, 16 Hz), 5.71 (1H, td, *J* = 7, 11 Hz), 6.87 (2H, d, *J* = 9 Hz), 6.89 (2H, d, *J* = 9 Hz), 7.26 (2H, d, *J* = 9 Hz), 7.27 (2H, d, *J* = 9 Hz), 7.33−7.40 (6H, m), 7.64−7.65 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.7, −4.0, 12.1, 18.2, 19.2, 24.3, 26.0 (3C), 26.7, 27.0 (3C), 28.4, 33.8, 36.8, 45.8, 55.3 (2C), 60.5, 65.5, 68.7, 72.1, 72.9, 74.5, 74.9, 79.6, 82.8, 107.6, 113.6 (2C), 113.7 (2C), 127.5 (4C), 129.2 (2C), 129.3, 129.4 (2C), 129.4 (2C), 129.7, 130.1, 130.3, 132.2, 133.7, 133.8, 133.9, 135.4 (4C), 159.0, 159.0; mass (FAB) *m*/*z* 990 (M + Na^+); HRMS calcd for $C_{57}H_{82}O_9Si_2Na$ 989.5395, found 989.5408. Compound **53b**: $[\alpha]^{25}_D$ +12.1 (*c* 1.08, $CHCl_3$);

IR ν_{max} (KBr) 3480, 3070, 2931, 2856, 1613, 1587, 1514. cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.71 (3H, t, J = 7 Hz), 0.85 (9H, s), 0.96 (1H, m), 1.03 (9H, s), 1.08 (1H, m), 1.27 (3H, s), 1.28 (3H, s), 1.36 (1H, m), 1.47 (1H, m), 1.58−1.77 (2H, m), 1.95 (1H, m), 2.19 (1H, m), 3.37 (2H, ddd, J = 5, 10, 15 Hz), 3.68−3.73 (2H, m), 3.78−3.88 (2H, m), 3.79 (3H, s), 3.80 (3H, s), 3.93−4.03 (3H, m), 4.40 (1H, d, J = 12 Hz), 4.41 (1H, d, J = 12 Hz), 4.46 (1H, d, J = 12 Hz), 4.49 (1H, d, J = 12 Hz), 5.28 (1H, t, J = 11 Hz), 5.46 (1H, d, J = 16 Hz), 5.65 (1H, dd, J = 7, 16 Hz), 5.82 (1H, td, J = 7, 11 Hz), 6.86 (2H, d, J = 9 Hz), 6.89 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz), 7.28 (2H, d, J = 9 Hz), 7.33−7.40 (6H, m), 7.63−7.65 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.7, −4.0, 11.8, 18.2, 19.2, 23.8, 26.0 (3C), 26.8, 27.0 (3C), 28.4, 33.9, 36.9, 46.3, 55.3, 55.3, 60.5, 65.8, 68.8, 72.0, 72.9, 74.8 (2C), 79.7, 82.7, 107.7, 113.6 (2C), 113.7 (2C), 127.5 (2C), 127.5 (2C), 129.2 (2C), 129.3, 129.4 (2C), 129.7 (2C), 130.2, 130.3, 130.7, 133.0, 133.8, 133.9, 134.2, 135.4 (4C), 159.0, 159.0; HRMS calcd for $C_{57}H_{82}O_9Si_2Na$ 989.5395, found 989.5408.

Deprotection of MPM Groups of 53a. To a stirred solution of **53a** (73 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) containing water (0.1 mL) was added DDQ (43 mg, 0.189 mmol), and the reaction was stirred at room temperature for 1 h. After addition of saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate. The organic solution was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:2) to give **51** (50 mg, 92%).

Oxidation and Reduction with L-Selectride. To a stirred solution of **53** (18 mg, 0.018 mmol, **53a**:**53b** = ca. 1:2.3) in CH_2Cl_2 (0.4 mL) was added Dess−Martin periodinane (7.9 mg, 0.024 mmol), and the reaction was stirred at room temperature for 30 min. A mixture of saturated $NaHCO_3$ solution and saturated $Na_2S_2O_3$ solution (1:2, one drop) was added to the reaction mixture, which was then stirred for 10 min. After extraction with ether, the ethereal layer was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give crude ketone **54** (17 mg). To a stirred solution of the ketone **54** (17 mg) in THF (0.4 mL) was added lithium tributylborohydride (1.0 M in THF, 30 μL, 0.030 mmol) at −78 °C, and the reaction was stirred at the same temperature for 1 h. After addition of saturated NH_4Cl solution, the reaction mixture was stirred vigorously for 30 min and extracted with ethyl acetate. The organic solution was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:6) to give **53b** (14 mg, 78% from **53**, **53a**:**53b** = 1:>20).

Transformation of 53b into 53a via Mitsunobu Reaction. To a solution of **53b** (66 mg, 0.068 mmol) in toluene (0.6 mL) were added triphenylphosphine (36 mg, 0.137 mmol), *p*-nitrobenzoic acid (18 mg, 0.109 mmol), and diethyl azodicarboxylate (2.2 M in toluene, 62 μL, 0.137 mmol), and the reaction was stirred at room temperature for 3 h. After being diluted with ether, the reaction mixture was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:6) to give *p*-nitrobenzoate (81 mg), which was treated with K_2CO_3 (19 mg, 0.137 mmol) in methanol (1.0 mL) at room temperature for 1 h. After being diluted with ether, the reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (ethyl acetate−hexane = 1:6) to give **53a** (51 mg, 78%, **53a**:**53b** = >20:1)

(5*S*,6*S*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*)-6-*tert*-Butyldimethylsiloxy-3-(2-*tert*-butyldiphenylsiloxyethyl)-8-iodo-3,4-isopropylidenedioxy-1,7-octadienyl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (56). To a stirred solution of **51** (230 mg, 0.358 mmol) in CH_2Cl_2 (4 mL) were added diacetoxyiodobenzene (404 mg, 1.25 mmol) and 2,2,6,6-tetramethylpiperidine 1-oxyl (11 mg, 0.072 mmol), and the reaction was stirred at room temperature for 1.5 h. After addition of saturated $Na_2S_2O_3$ solution, the reaction mixture was extracted with ether. Combined ethereal layers were washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was passed through a silica gel short column (ethyl acetate−hexane = 1:6) to give **55** (236 mg), which was immediately employed for the next reaction. To a stirred solution of (iodomethyl)triphenylphosphonium iodide (208 mg, 0.393 mmol) in THF (1.9 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 350 μL, 0.35 mmol) at room temperature. The reaction mixture was stirred at room temeperature for 3 min and then cooled to −60 °C. After addition of HMPA (285 μL, 1.64 mmol) at the same temperature, the reaction mixture was cooled to −100 °C, to which a solution of **55** (236 mg) in THF (1.5 mL) was added slowly. The reaction mixture was stirred at −100 °C for 10 min, then warmed to 0 °C and stirred at the same temperature for 20 min. After addition of saturated NH_4Cl solution, the reaction mixture was extracted with ether. Combined ethereal layers were washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform−hexane = 7:2) to give a geometric mixture of **56** (*Z*:*E* = 4.3:1, 179 mg, 59% from **51**) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.07 (3H s), 0.76 (3H, t, J = 7 Hz), 0.85 (9H, s), 1.03, (9H, s), 1.11−1.42 (3H, m), 1.29 (3H, s), 1.34 (3H, s), 1.48−1.67 (2H, m), 1.98 (1H, m), 2.25 (1H, m), 3.66 (1H, dt, J = 5, 11 Hz), 3.79 (1H, m), 3.87 (1H, dd, J = 2, 10 Hz), 4.52 (1H, ddd, J = 3, 6, 10 Hz), 4.90 (1H, m), 5.64 (2H, m), 6.01 (1H, d, J = 10 Hz), 6.19−6.24 (2H, m), 6.90 (1H, dd, J = 6, 10 Hz), 7.32−7.42 (6H, m), 7.62−7.66 (4H, m); mass (FAB) *m*/*z* 867 (M + Na^+); HRMS calcd for $C_{42}H_{61}O_6Si_2NaI$ 867.2949, found 867.2919.

(5*S*,6*S*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*)-6-Hydroxy-3-(2-hydroxyethyl)-8-iodo-3,4-isopropylidenedioxy-1,7-octadienyl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (57). To a stirred solution of **56** (74 mg, 0.088 mmol) in THF (1.1 mL) were added acetic acid (30 μL, 0.53 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 263 μL, 0.263 mmol) at room temperature, and the reaction was stirred at room temperature for 6 h. Again, acetic acid (30 μL, 0.53 mmol) and then tetrabutylammonium fluoride (1.0 M in THF, 263 μL, 0.263 mmol) were added to the reaction mixture, which was stirred at room temperature overnight. After addition of saturated $NaHCO_3$ solution at 0 °C, the reaction mixture was extracted with ethyl acetate. Combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 2:1) to give geometrically pure *Z*-isomer **57** (27 mg, 63%) as a colorless oil: $[\alpha]^{23}_D$ +114.0 (*c* 4.80, $CHCl_3$); IR ν_{max} (KBr) 3390, 2968, 2881, 1716, 1378 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 8 Hz), 1.25 (3H, s), 1.40−1.68 (3H, m), 1.53 (3H, s), 1.73−1.93 (2H, m), 2.05 (1H, m), 2.34 (1H, d, J = 5 Hz), 2.44 (1H, m), 2.60 (1H, dd, J = 2, 8 Hz), 3.69 (1H, m), 3.83 (1H, m), 4.04 (1H, dd, J = 3, 10 Hz), 4.60 (1H, m), 5.06 (1H, dd, J = 2, 4 Hz), 5.89 (1H, d, J = 15 Hz), 5.93 (1H, dd, J = 2, 15 Hz), 6.07 (1H, d, J = 10 Hz), 6.34 (1H, t, J = 8 Hz), 6.38 (1H, d, J = 8 Hz), 7.00 (1H, dd, J = 5, 10 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C 11.1, 21.7, 26.4, 28.2, 33.8, 35.4, 39.2, 59.6, 72.1, 79.3, 79.6, 82.5, 85.4, 108.6, 120.8, 125.2, 132.6, 142.6, 149.9, 163.7; mass (FAB) *m*/*z* 515 (M + Na^+); HRMS calcd for $C_{20}H_{29}O_6NaI$ 515.0906, found 515.0903.

(5*S*,6*S*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*)-6-*tert*-Butyldimethylsiloxy-3-(2-hydroxyethyl)-8-iodo-3,4-isopropylidenedioxy-1,7-octadienyl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (58). To a stirred solution of **57** (25 mg, 0.051 mmol) and 2,6-lutidine (35 μL, 0.31 mmol) in CH_2Cl_2 (0.5 mL) was added *tert*-butyldimethylsilyl triflate (35 mL, 0.15 mmol) at −78 °C, and the reaction was stirred at the same

temperature for 1 h. After addition of saturated $NaHCO_3$ solution, the reaction mixture was warmed to room temperature and extracted with ethyl acetate. Combined organic layers were washed successively with water, 0.5 M $KHSO_4$ solution, water, saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting bis-TBDMS ether was dissolved in THF (0.2 mL), to which *p*-toluenesulfonic acid monohydrate (0.3 mg, 3 mol%) was added at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate. Combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:2) to give **58** (26 mg, 81%) as a colorless oil: $[\alpha]^{22}_D$ +68.6 (*c* 1.60, $CHCl_3$); IR ν_{max} (KBr) 3451, 2938, 2889, 1725, 1612, 1464, 1376 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 0.95 (3H, t, J = 7 Hz), 1.25 (3H, s), 1.37−1.71 (5H, m), 1.52 (3H, s), 2.03 (1H, m), 2.41 (1H, m), 2.69 (1H, d, J = 8 Hz), 3.68 (1H, m), 3.81 (1H, dt, J = 4, 11 Hz), 3.99 (1H, dd, J = 2, 11 Hz), 4.53 (1H, m), 5.04 (1H, t, J = 4 Hz), 5.86 (1H, d, J = 15 Hz), 5.94 (1H, dd, J = 4, 15 Hz), 6.06 (1H, dd, J = 10 Hz), 6.20 (1H, t, J = 8 Hz), 6.22 (1H, d, J = 8 Hz), 6.98 (1H, dd, J = 6, 10 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.8, −4.1, 11.1, 18.1, 21.6, 25.8 (3C), 26.5, 28.3, 35.3, 35.4, 39.3, 59.7, 72.6, 78.8, 79.5, 80.1, 85.0, 108.3, 120.8, 124.8, 133.1, 144.1, 149.8, 163.7; mass (FAB) *m*/*z* 629 (M + Na^+); HRMS calcd for $C_{26}H_{23}O_6SiNaI$ 629.1772, found 629.1755.

(5*S*,6*S*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*)-3-[2-(Allyloxylcarbonylamino)-ethyl]-6-*tert*-butyldimethylsiloxy-8-iodo-3,4-isopropylidenedioxy-1,7-octadienyl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (60). To a stirred solution of **58** (26 mg, 0.043 mmol), triphenylphosphine (22 mg, 0.086 mmol), and diphenylphosphoryl azide (18 μL, 0.086 mmol) in THF (0.6 mL) was added diethyl azodicarboxylate (2.2 M in toluene, 39 μL, 0.086 mmol), and the reaction was stirred at room temperature for 1 h. After being diluted with ether, the reaction mixture was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was passed through a silica gel short column (ethyl acetate−hexane = 1:2) to give azide **59** (30 mg), which was immediately employed for the next reaction. To a stirred solution of **59** (30 mg) in THF (0.6 mL) were added triphenylphosphine (22 mg, 0.086 mmol) and water (8 μL, 0.428 mmol) at room temperature. After stirring at room temperature for 12 h, pyridine (21 μL, 0.26 mmol) and allyl chloroformate (14 μL, 0.13 mmol) were added to the reaction mixture, which was stirred at room temperature for 20 min and then diluted with ethyl acetate. The organic solution was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:2) to give **60** (20 mg, 74% from **58**) as a colorless oil: $[\alpha]^{23}_D$ +81.2 (*c* 2.20, $CHCl_3$); IR ν_{max} (KBr) 3348, 3071, 2955, 2931, 2884, 2857, 1724, 1519, 1463, 1380 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 0.95 (3H, t, J = 8 Hz), 1.36 (3H, s), 1.39−1.67 (5H, m), 1.51 (3H, s), 1.85 (1H, m), 2.41 (1H, m), 3.12−3.37 (2H, m), 3.96 (1H, d, J = 9 Hz), 4.48−4.54 (3H, m), 5.02 (1H, t, J = 4 Hz), 5.18 (1H, d, J = 11 Hz), 5.27 (1H, d, J = 17 Hz), 5.79−5.97 (3H, m), 6.06 (1H, d, J = 10 Hz), 6.19 (1H, t, J = 8 Hz), 6.22 (1H, d, J = 8 Hz), 6.97 (1H, dd, J = 5, 10 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C −4.8, −4.1, 11.1, 18.1, 21.6, 25.8 (3C), 26.6, 28.4, 33.4, 35.3, 36.9, 39.3, 65.3, 72.6, 78.8, 79.6, 80.0, 83.9, 108.2, 117.3, 120.8, 125.0, 133.0, 133.3, 144.2, 149.8, 155.9, 163.7; mass (FAB) *m*/*z* 690 (M + H^+); HRMS calcd for $C_{30}H_{49}O_7NSiI$ 690.2379, found 690.2351.

(5*S*,6*S*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*)-3-[2-(Allyloxylcarbonylamino)-ethyl]-6-*tert*-butyldimethylsiloxy-3,4-dihydroxy-10-{(1*R*,3*S*)-3-[(6*S*)-methyloctanoyloxy]cyclohexyl}-1,7,9-decatrienyl]-5-ethyl-5,6-dihydro-2*H*-pyran-2-one (63). A solution of **60** (38 mg, 0.060 mmol) in conc. HCl−methanol (1:30. 0.7 mL) was stirred at room temperature for 15 h. Evaporation of the solution under reduced pressure gave crude triol **61** (36 mg). To a solution of **61** (36 mg) and segment C (**7**) (111 mg, 0.202 mmol) in degassed DMF (0.6 mL) was added bis(acetonitrile)dichloropalladium (3.3 mg, 10 mol%), and the reaction was stirred at room temperature for 1 h. After concentration under reduced pressure, the resulting residue was passed through a silica gel short column (chloroform−hexane = 1:1) to give **62** (85 mg), which was dissolved in CH_2Cl_2 (0.8 mL) containing 2,6-lutidine (23 μL, 0.20 mmol). To the solution was added *tert*-butyldimethylsilyl triflate (23 μL, 0.10 mmol) at −78 °C, and the reaction was stirred at the same temperature for 30 min. After addition of saturated $NaHCO_3$ solution, the reaction mixture was warmed to room temperature and extracted with ethyl acetate. Combined organic layers were washed successively with water, 0.5 M $KHSO_4$ solution, water, saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate−hexane = 1:1) to give **63** (28 mg, 60% from **60**) as a colorless oil: $[\alpha]^{26}_D$ +89.9 (*c* 0.99, $CHCl_3$); IR ν_{max} (KBr) 3401, 2932, 2858, 1727, 1521, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.83 (3H, d, J = 6 Hz), 0.84 (3H, t, J = 7 Hz), 0.87 (9H, s), 0.95 (3H, t, J = 8 Hz), 1.01−1.67 (19H, m), 1.78−1.84 (2H, m), 1.90−1.98 (2H, m), 2.26 (2H, t, J = 8 Hz), 2.43 (1H, m), 2.57 (1H, m), 3.06 (1H, br s), 3.16 (1H, m), 3.34 (1H, m), 3.77−3.80 (2H, m), 4.54 (2H, d, J = 5 Hz), 4.74 (1H, m), 4.96 (1H, m), 5.06 (1H, t, J = 4 Hz), 5.19 (1H, dd, J = 1, 11 Hz), 5.29 (1H, dd, J = 1, 17 Hz), 5.34 (1H, t, J = 11 Hz), 5.52 (1H, t, J = 11 Hz), 5.81−5.95 (3H, m), 6.05 (1H, d, J = 10 Hz), 6.05 (1H, t, J = 11 Hz), 6.21 (1H, t, J = 11 Hz), 6.95 (1H, dd, J = 6, 10 Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ_C −5.2, −4.4, 11.0, 11.4, 18.0, 19.1, 21.6, 23.6, 25.4, 25.7 (3C), 26.6, 29.4, 31.3, 31.9, 34.2, 34.6, 34.7, 35.0, 36.1, 36.7, 37.4, 38.0, 39.3, 65.5, 67.8, 72.1, 73.9, 76.9, 79.9, 117.5, 120.9, 121.5, 123.1, 125.5, 133.0, 133.3, 136.0, 138.2, 149.9, 156.4, 163.9, 173.3; mass (FAB) *m*/*z* 810 (M + Na^+); HRMS calcd for $C_{44}H_{73}O_9NSiNa$ 810.4952, found 810.4948.

Allyl (1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*)-3-[2-(Allyloxylcarbonylamino)-ethyl]-6-*tert*-butyldimethylsiloxy-3,4-dihydroxy-10-{(1*R*,3*S*)-3-[(6*S*)-methyloctanoyloxy]cyclohexyl}-1-[(5*S*,6*S*)-5-ethyl-5,6-dihydro-2-oxo-2*H*-pyran-6-yl]-1,7,9-decatrien-4-yl Triethylammonium Phosphate (65a). To a stirred solution of **63** (8.7 mg, 0.011 mmol) in pyridine (0.2 mL) was added phosphorus oxychloride (5 μL, 0.055 mmol) at 0 °C, and the reaction was stirred at 0 °C for 1.5 h. At 0 °C, allyl alcohol (80 μL, 1.11 mmol) was added to the reaction mixture, which was stirred for 20 min and then diluted with ethyl acetate. The reaction mixture was washed successively with saturated $NaHCO_3$ solution, 0.5 M $KHSO_4$ solution, water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to give cyclic phosphate **64**, which was dissolved in a mixture of trifluoroethanol, triethylamine, and water (20:1:1, 1 mL). After being stirred at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure to give a mixture of **65a**, **65b**, and **65c** as a colorless oil, which was employed for the next reaction without separation: IR ν_{max} (KBr) 3320, 2933, 2858, 2675, 1726, 1516, 1463, 1382 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 0.00 (3H, s), 0.08 (3H, s), 0.84−0.87 (15H, m), 0.91 (3H, t, J = 7 Hz), 1.02−1.62 (19H, m), 1.24 (9H, t, J = 8 Hz), 1.70−1.95 (4H, m), 2.23 (2H, t, J = 8 Hz), 2.48 (1H, m), 2.62 (1H, m), 3.00−3.02 (6H, m), 3.11−3.18 (2H, m), 4.13 (1H, t, J = 9 Hz), 4.33−4.46 (4H, m), 4.70 (1H, m), 4.89 (1H, br t, J = 9 Hz), 5.01 (1H, m), 5.23−5.43 (4H, m), 5.76−6.02 (5H, m), 6.14−6.25 (2H, m), 7.03 (1H, dd, J = 5, 10 Hz), 11.3 (1H, br s); ^{31}P NMR (202.35 MHz, CD_3CN) δ_P 2.4; minor isomers δ_P −2.1, 12.2; mass (FAB) *m*/*z* 1010 (M + H^+); HRMS calcd for $C_{53}H_{94}O_{12}N_2SiP$ 1009.6314, found 1009.6303.

Leustroducsin B (1b). A solution of **65** (5.0 mg, 0.005 mmol) in a mixture of 48% HF, acetonitrile, and pyridine (1:19:5, 0.5 mL) was stirred at room temperature for 10 h. After being neutralized

with saturated $NaHCO_3$ solution, the reaction mixture was concentrated under reduced pressure. The resulting residue was passed through a reversed phase silica gel short column (water−acetonitrile = 40:1 to 2:1) to give crude product (2.9 mg), which was dissolved in THF (0.1 mL) and treated with triphenylphosphine (1.2 mg, 0.005 mmol), ammonium formate (6.1 mg, 0.097 mmol), and tetrakis(triphenylphosphine)palladium (0.9 mg, 0.001 mmol) at 50 °C for 3 h. The solvent was evaporated off under reduced pressure, and the resulting residue was purified by preparative silica gel TLC (methanol) and then reversed phase silica gel TLC (water−acetonitrile = 40:1 and then 1:2) to give leustroducsin B (**1b**) (1.6 mg, 49% from **65**) as a white solid: $[\alpha]^{25}_{D}$ +98.8 (*c* 0.050, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.86 (3H, d, J = 6 Hz), 0.88 (3H, t, J = 7 Hz), 0.96 (3H, t, J = 8 Hz), 1.03−1.19 (3H, m), 1.24−1.74 (15H, m), 1.81−1.96 (4H, m), 2.18 (1H, m), 2.28 (2H, t, J = 7 Hz), 2.54−2.67 (2H, m), 2.97−3.11 (2H, m), 4.29 (1H, dt, J = 3, 10 Hz), 4.72 (1H, m), 4.95 (1H, br t, J = 8 Hz), 5.10 (1H, dd, J = 4, 6 Hz), 5.31 (1H, br t, J = 9 Hz), 5.46 (1H, br t, J = 8 Hz), 5.95 (1H, d, J = 16 Hz), 6.02 (1H, dd, J = 1, 10 Hz), 6.07 (1H, dd, J = 6, 16 Hz), 6.24−6.33 (2H, m), 7.09 (1H, dd, J = 5, 10 Hz); ^{13}C NMR (125.65 MHz, CD_3OD) δ_C 11.4, 11.7, 19.6, 22.7, 24.6, 26.4, 27.6, 30.5, 32.4, 33.0, 34.3, 35.4, 35.5, 36.1, 37.1, 37.3, 39.4, 40.5 (2C), 64.6, 73.9, 77.7, 78.4, 82.3, 121.0, 123.7, 124.2, 127.6, 135.2, 137.2, 138.2, 152.7, 166.4, 175.0; mass (FAB) *m*/*z* 692 ($M + Na^+$); HRMS calcd for $C_{34}H_{56}O_{10}NPNa$ 692.3539, found 692.3554.

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Supporting Information Available: Experimental details for the syntheses of compounds **4**−**7**, **12**, **14**, **16**, **18**−**20**, **22**, **24**, **26**, **27**, **29**, **33**, **35**, **36**, **38**−**40**, **42**, **44**, and **46** and ^{1}H and ^{13}C NMR spectra for compounds **1b**, **4**−**7**, **12**, **14**, **16**, **18**−**20**, **22**, **24**, **26**, **27**, **29**, **33**, **35**, **36**, **38**−**40**, **42**, **44**, **46**, **48**, **50**−**53**, **56**−**58**, **60**, **63**, and **65**. This material is available free of charge via the Internet at http://pubs.acs.org.

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