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Enantioselective Synthesis of (+)-Penostatin E

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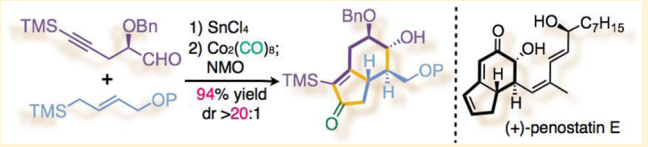
Supporting Information

ABSTRACT: The first enantioselective total synthesis of penostatin E has been accomplished. Two highly efficient and diastereoselective reactions, a Hosomi–Sakurai allylation and an intramolecular Pauson–Khand reaction, were utilized for the construction of the basic carbon framework of the target molecule as the key steps. A late-stage introduction of the side chain and a successful base-promoted elimination reaction afforded an efficient synthetic route to (+)-penostatin E.



INTRODUCTION

Penostatin E (**1**, Figure 1) is a secondary metabolite isolated from a strain of *Penicillium* sp. OUPS-79 separated from the

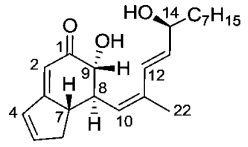
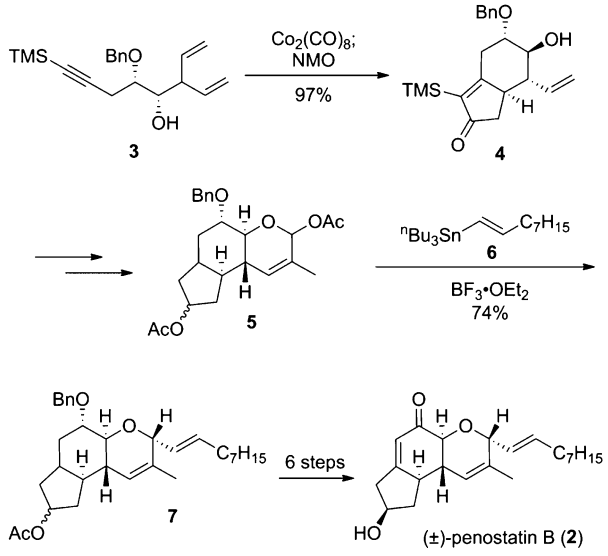


Figure 1. Structure of (+)-penostatin E (**1**).

marine alga *Enteromorpha intestinalis*.[1] The absolute and relative stereochemistry of **1** was established by a combination of NMR experiments, circular dichroism studies, and chemical transformations. The structure of **1** consists of a densely functionalized hydroindenone carbon framework with three contiguous stereogenic centers and the olefinic side chain bearing an allylic secondary alcohol at C14 with the (*S*)-configuration. Penostatin E exhibited promising cytotoxicity with an ED_{50} value of 0.9 μg/mL against P388 leukemia cell lines. Despite the interesting biological activity and the challenging molecular structure, no total synthesis of **1** has been reported to date. Herein we describe the first total synthesis of penostatin E in its enantiomerically pure form.

In a previous paper, we reported the first total synthesis of penostatin B (**2**) in racemic form[2] (Scheme 1) and showed that the 5,6-bicyclic enone **4**, with its three contiguous stereogenic centers corresponding to those in both **1** and **2**, could be prepared in excellent yield by the highly diastereoselective intramolecular Pauson–Khand reaction[3] of dienyne **3**. In order to allow for the successful introduction of the pseudoaxially oriented side chain, the bicycle **4** was further elaborated to the acetate **5**, which was reacted with the alkenyl stannane **6** in the presence of $BF_3{\cdot}OEt_2$ to give in 74% yield the tricycle **7**, which was transformed in six steps to (±)-penostatin B (**2**). Consequently, we decided to apply the synthetic technology

Scheme 1. Total Synthesis of (±)-Penostatin B (2)



of Scheme 1 (**3** → **4**) in the stereocontrolled construction of an analogous hydroindenone skeleton for penostatin E (**1**).

Retrosynthetically, we thought that (+)-**1** could be prepared via the selective elimination of one of the three acyloxy groups of the δ-oxyketone **8**, which would be generated from the triol **9**. This could be synthesized from the α,β-unsaturated lactone **10** by simultaneous reduction of both the lactone and enone carbonyl groups followed by Wittig reaction of the resulting lactol. We postulated that a *Z*-selective Ando variant[4] of the Horner–Wadsworth–Emmons olefination of the β-hydroxy aldehyde **12** with the phosphonate **11**[4c] would give the ester, which might undergo spontaneous lactonization, resulting in formation of the lactone **10** after desilylation of the TMS group.

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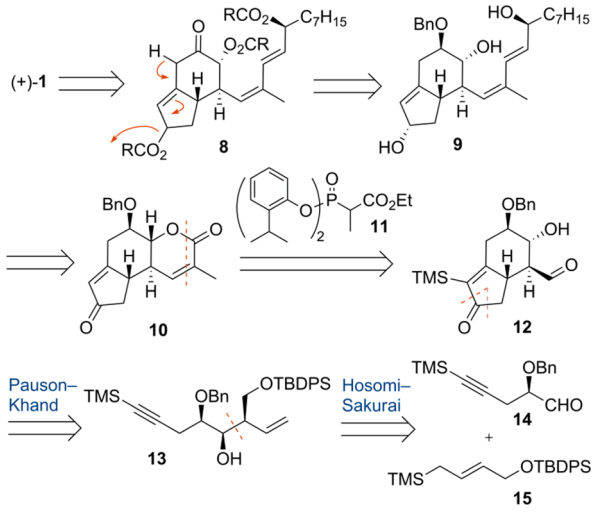
The bicycle **12** would be prepared via the intramolecular Pauson–Khand reaction of the enyne **13**, which would be assembled by the Hosomi–Sakurai allylation reaction[5] with the optically active aldehyde **14** and the allylsilane **15** (Scheme 2).

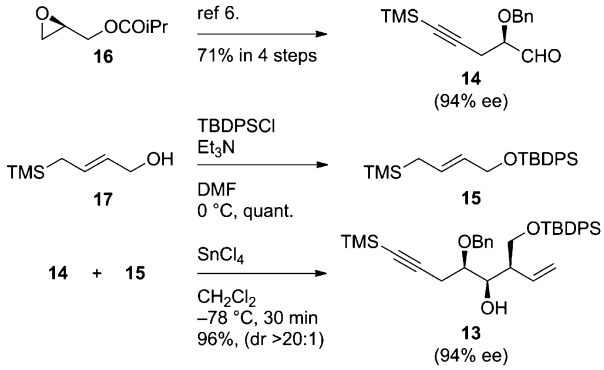
Scheme 2. Retrosynthetic Analysis of (+)-1



RESULTS AND DISCUSSION

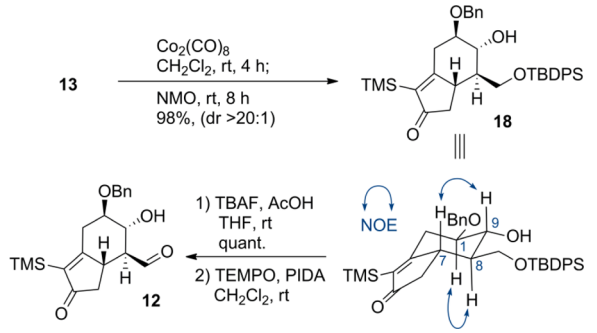
Our synthetic studies began with the preparation of the required *syn,syn*-stereotriad of **13**. First, the substrates **14** and **15** for the Hosomi–Sakurai allylation were synthesized as follows. The (*R*)-glycidyl isobutyrate **16** was converted to the α-benzyloxy aldehyde **14** (94% ee) following literature procedure.[6] The allylsilane **15** was prepared from the known alcohol **17**[7] by silylation. The resulting substrates **14** and **15** were reacted in the presence of $SnCl_4$ to give the desired alcohol **13** in 96% yield and with complete diastereoselectivity[5b,c] without any loss of enantiopurity of **14** (Scheme 3).

Scheme 3. Preparation of the Alcohol 13 by a Hosomi–Sakurai Reaction



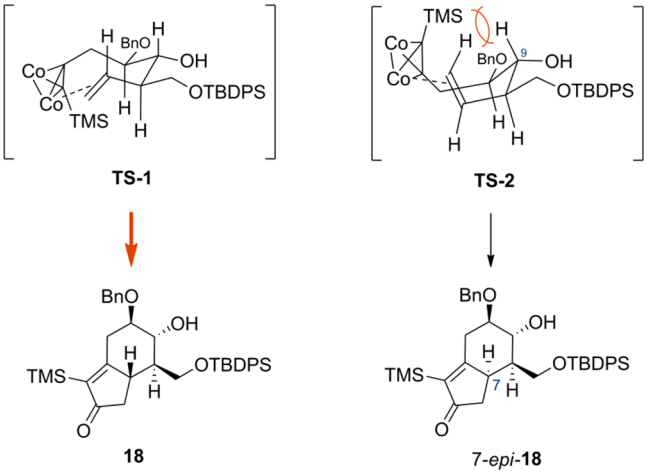
The enyne **13** thus obtained was first treated with $Co_2(CO)_8$ in CH_2Cl_2 and then with NMO.[8] The intramolecular Pauson–Khand reaction was quite effective and proceeded smoothly to give the bicyclic enone **18** in 98% yield with complete diastereoselectivity. The desired stereochemistries were supported by the observed NOE interactions between H1 and H8 and H7 and H9. The silyl ether **18** was deprotected with TBAF/AcOH, and the resulting primary alcohol was then oxidized with TEMPO/PIDA to afford aldehyde **12**, which was used immediately in the next reaction (Scheme 4).

Scheme 4. Pauson–Khand Reaction and NOE Experiment



This stereochemical outcome can be explained by considering the two transition states TS-1 and TS-2. The cyclization occurs exclusively through the more favorable TS-1[9] thus avoiding unfavorable steric interactions between H9 and the vinyl proton in the boat-like conformation in TS-2 (Scheme 5).

Scheme 5. Plausible Mechanism of the Pauson–Khand Reaction



With the construction of the bicycle core secured, our attention turned to finding suitable conditions for the lactone ring formation by the *Z*-selective olefination and spontaneous ring closure of **12**. While an initial attempt using NaH with Ando's phosphonate **11**[4c] was unsuccessful, employing DBU/NaI[4e] with **11** worked efficiently. Under these conditions, the olefination/lactonization reaction of the aldehyde **12** proceeded smoothly. During the conversion, desilylation of the TMS group occurred simultaneously to afford the desired lactone **10** in 75% yield (2 steps) along with 12% of **19**, which could be converted to **10** in 71% yield by treating with a combination of DBU and NaI. This is the first example of desilylation during an Emmons type olefination with DBU/NaI. It should be noted that the unprecedented mild desilylation conditions were crucial in obtaining the desired tricycle **10**. Attempted desilylation of **19** to obtain **10** under various conditions (e.g., TBAF, TBAF/AcOH, K_2CO_3/MeOH) resulted only in decomposition. Eventually we successfully developed a one-pot process for the preparation of **10** in a three-step sequence: *Z*-olefination, lactonization, and desilylation (Scheme 6).

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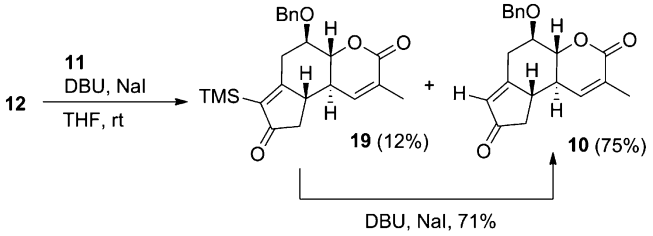
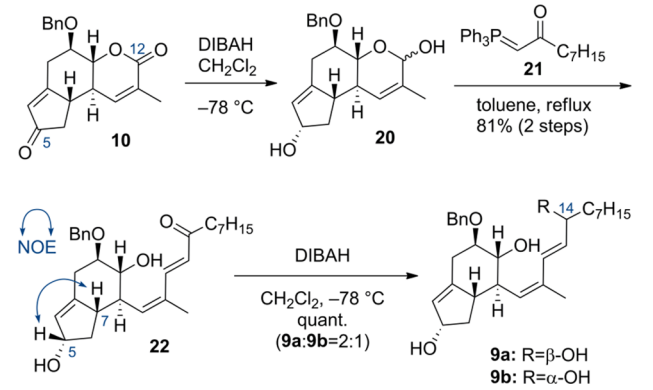
Scheme 6. One-Pot *Z*-Olefination, Lactonization, and Desilylation Sequence



Our next task involved the introduction of the side chain bearing a stereogenic center at a position (C14) remote from the hydroindenone core. First, the carbonyl groups of both the lactone (C12) and the enone moiety (C5) of **10** were reduced with DIBAH to afford the lactol **20** as a mixture of diastereomers, with the ^{1}H NMR spectrum showing two peaks at 5.17 and 5.41 ppm that corresponded to the methine protons of the lactol moiety (H12). Based on the integration ratio of the two signals, the lactol **20** was identified as an approximately 3:2 mixture of stereoisomers. The diastereomeric mixture of **20** and the phosphorus ylide **21**[10] was heated in a pressure tube at 140 °C to give the dienone **22** as a single product in 81% yield for the two steps. NOE correlation of the resulting **22** was observed between the two protons at C5 and C7, indicating the relative stereochemistry at C5, as shown in Scheme 7. The reduction of the C5 carbonyl group occurred

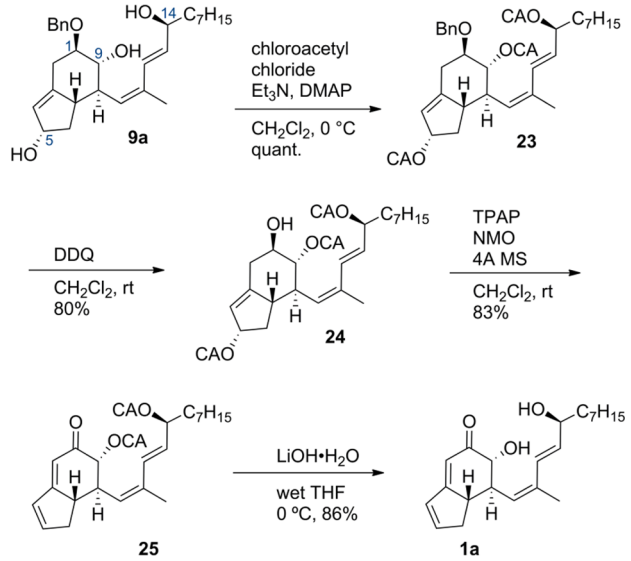
Scheme 7. Side Chain Introduction: Synthesis of the Triols 9a and 9b



from the convex *β*-face.[2] Then **22** was reduced with DIBAH at −78 °C to provide the diallyl alcohols **9a** and **9b** in quantitative yield but with low stereoselectivity (*dr* 2:1) as a chromatographically separable mixture. To improve the diastereoselectivity, several reduction procedures, e.g., oxazaborolidine/BH_3[11] systems, Noyori asymmetric hydrogenation,[12] etc., were attempted; however, none of them gave satisfactory results. At this stage, although the absolute configuration at C14 of **9a** and **9b** could not be assigned, for convenience, the stereochemistries of **9a** and **9b** were depicted as (*S*) and (*R*), respectively. Both isomers **9a** and **9b** were independently converted to the natural product for determination of the configuration at C14 (Scheme 7).

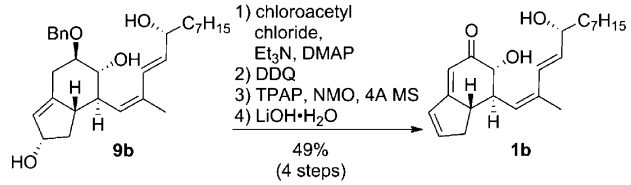
With the triols **9a,b** in hand, we next turned our attention to the elaboration of a conjugated dienone moiety in the bicyclic core by the *δ*-elimination of the C5 hydroxyl group. Accordingly, we chose the acetyl moiety as the protecting group for the three secondary alcohols at C5, C9, and C14, which would work well for *δ*-elimination of the C5 hydroxyl group. An initial attempt to utilize the acetyl group was unsuccessful. Although the requisite dienone was generated efficiently via the *δ*-elimination after debenzylation/oxidation of the C1-OH, the attempted deprotection of the two remaining acetyl groups did not work well. The substrate proved to be unstable to the deprotection reaction, since it was gradually decomposed under hydrolysis conditions using LiOH. This result suggested that a more reactive acyl protecting group would be necessary. Consequently, we chose the chloroacetyl (CA) group, which turned out to be effective. Thus, the triol **9a** was converted to the tris(chloroacetyl) ester **23** in quantitative yield. The benzyl group of **23** was deprotected with DDQ to afford the alcohol **24**, which was exposed to the oxidation conditions with TPAP/NMO to provide the requisite dienone **25** in 83% yield via ketone formation at C1 followed by spontaneous *δ*-elimination of the chloroacetate group as we expected. Finally deprotection of the remaining two CA groups was successfully realized by treatment with LiOH·H_2O in wet THF at 0 °C in 5 min, producing **1a** in 86% yield (Scheme 8).

Scheme 8. Elaboration of the Bicyclic Core Structure



In a similar manner the triol **9b**, the minor isomer, was transformed to **1b** in 49% overall yield for the four steps (Scheme 9).

Scheme 9. Conversion of 9b to 1b



The comparison of the ^{1}H and ^{13}C NMR chemical shifts of the synthetic **1a** and **1b** with those reported for natural penostatin E is shown in Table 1. From these data, it was difficult to determine which isomer was the natural penostatin E (**1**) (Table 1).

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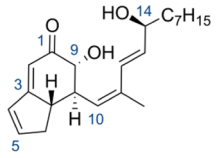
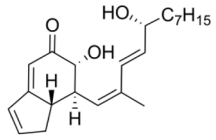
Table 1. Comparison of the ^{1}H and ^{13}C NMR Spectra



1a



1b

		synthetic[b]				synthetic[b]	
H	natural[a]	**1a**[c]	**1b**[c]	C	natural[a]	**1a**[c]	**1b**[c]
2	6.02	6.02 (0)	6.02 (0)	1	199.21	199.12 (+0.07)	199.17 (+0.04)
4	6.49	6.48 (+0.01)	6.48 (+0.01)	2	114.86	114.93 (−0.07)	114.88 (−0.02)
5	6.73	6.74 (−0.01)	6.72 (+0.01)	3	173.49	173.27 (+0.22)	173.37 (+0.12)
6a	2.29	2.26 (+0.03)	2.29 (0)	4	132.06	132.10 (−0.04)	132.05 (−0.01)
6b	2.70	2.69 (+0.01)	2.69 (+0.01)	5	149.86	149.63 (+0.23)	149.75 (+0.11)
7	2.87	2.87 (0)	2.86 (+0.01)	6	37.65	37.63 (+0.02)	37.66 (−0.01)
8	3.02	3.01 (+0.01)	3.01 (+0.01)	7	45.86	45.87 (−0.01)	45.89 (−0.03)
9	3.97	3.96 (+0.01)	3.96 (+0.01)	8	48.21	48.21 (−0.02)	48.24 (−0.03)
10	5.41	5.40 (+0.01)	5.40 (+0.01)	9	77.23	77.23 (0)	77.24 (−0.01)
12	6.61	6.59 (+0.02)	6.60 (+0.01)	10	129.22	129.23 (−0.01)	129.20 (+0.02)
13	5.78	5.78(0)	5.77 (+0.01)	11	135.21	135.16 (+0.05)	135.20 (+0.01)
14	4.18	4.16 (+0.02)	4.16 (+0.02)	12	127.03	127.11 (−0.08)	127.05 (−0.02)
15	1.53	1.53 (0)	1.53 (0)	13	134.20	134.33 (−0.13)	134.19 (+0.01)
16	1.27	1.26 (+0.01)	1.27 (0)	14	73.17	73.17(0)	73.14 (+0.03)
17	1.27	1.26 (+0.01)	1.27 (0)	15	37.50	37.63 (−0.13)	37.53 (−0.03)
18	1.27	1.26 (+0.01)	1.27 (0)	16	29.52	29.50 (+0.02)	29.52 (0)
19	1.27	1.26 (+0.01)	1.27 (0)	17	29.25	29.27 (−0.01)	29.23 (+0.02)
20	1.27	1.26 (+0.01)	1.27 (0)	18	25.45	25.50 (−0.05)	25.44 (+0.01)
21	0.88	0.87 (+0.01)	0.88 (0)	19	31.80	31.79 (+0.01)	31.80 (0)
22	1.94	1.94 (0)	1.94 (0)	20	22.65	22.64 (+0.01)	22.64 (+0.01)
9-OH	3.89	3.88 (+0.01)	3.87 (+0.02)	21	14.11	14.08 (+0.03)	14.08 (+0.03)
14-OH	1.55	1.55 (0)	1.47 (+0.08)	22	21.06	20.99 (+0.07)	21.03 (+0.03)

[a] ^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz. [b] ^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz. [c] The chemical shift differences are given in parentheses.

In order to establish the absolute configuration at C14 of the synthetic **1a** and **1b**, we used the chiral anisotropic reagent 2-naphthylmethoxyacetic acid (NMA).[13] The $\Delta\delta$ values of the corresponding NMA esters of **1a** and **1b** are shown in Figure 2. They enabled us to assign the *S* configuration to **1a** and the *R* to **1b**, respectively, and it was thought that the major isomer **1a** would be the natural penostatin E. The comparison of the optical rotations of **1a,b** with that of the natural product {$[\alpha]_D^{21}$ +9.00 (*c* 0.96, $CHCl_3$) for **1a** and $[\alpha]_D^{21}$ −7.24 (*c* 0.96, $CHCl_3$) for **1b**; $[\alpha]_D$ +48.5 (*c* 0.16, $CHCl_3$)[1] for the natural penostatin E} supported this conclusion. Although the discrepancy[14] in the magnitude of the rotation remains unclear, the circular dichroism data of **1a** were also identical with those reported for the natural product.[1] Therefore, we have concluded that **1a** is the natural penostatin E. Thus, we have completed the first enantioselective total synthesis of (+)-penostatin E (**1**).

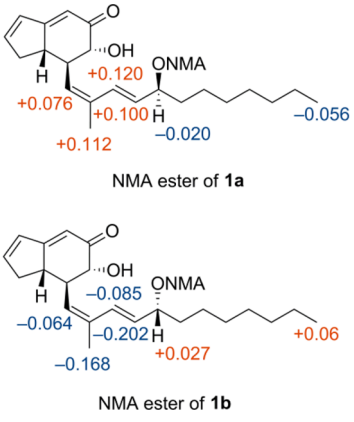


Figure 2. Comparison of the $\Delta\delta$ values of NMA esters. ($\Delta\delta = \delta_R - \delta_S$ ppm, 400 MHz).

CONCLUSION

In summary, the first asymmetric total synthesis of penostatin E has been accomplished. The unique features of this work include the very high stereoselectivities observed in the two key reactions, the Hosomi−Sakurai allylation reaction to prepare the *syn,syn*-stereotriad and the intramolecular Pauson−Khand reaction to construct the bicyclic carbon framework. We have also successfully developed an efficient one-pot olefination/lactonization/desilylation sequence to obtain the tricyclic compound **10** from the *β*-hydroxy aldehyde **12**. Furthermore, it was clarified that the ^{1}H and ^{13}C NMR spectra of penostatin E and 14-*epi*-penostatin E proved to be quite similar and that both diastereomers could be distinguished spectroscopically by means of the chiral anisotropic reagent 2-naphthylmethoxyacetic acid. The synthetic route developed here is general and efficient and would be applicable to the synthesis of other penostatins.

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EXPERIMENTAL SECTION

General Procedure. All reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocols. Column chromatography was performed on silica gel 60N (70−230 mesh) using the indicated solvent. NMR spectra were recorded on a 400 and 500 MHz NMR instrument. ^{1}H NMR was measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm). ^{13}C NMR was measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm). Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. High-resolution mass spectra were recorded in positive ion mode using electrospray ionization and a time-of-flight mass analyzer.

(*E*)-*tert*-Butyldiphenyl-((4-(trimethylsilyl)but-2-en-1-yl)oxy)-silane (15). To a solution of allyl alcohol **17** (10.0 g, 69.3 mmol) in DMF (135 mL) were added Et_3N (19.3 mL, 138 mmol) and TBDSCl (19.8 mL, 76.2 mmol) at 0 °C. After stirring was continued for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (97/3) afforded silyl ether **15** as a colorless oil (26.5 g, quant.); IR (neat) ν_{max} 2955, 1112, 850, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.69 (4H, m), 7.43−7.34 (6H, m), 5.65 (1H, m), 5.57 (1H, ddt, J = 15.2, 5.2, and 1.2 Hz), 4.14 (2H, d, J = 5.2 Hz), 1.46 (2H, d, J = 8.0 and 1.2 Hz), 1.05 (9H, br s), 0.00 (9H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (×4), 134.1 (×2), 129.5 (×2), 127.9, 127.6 (×4), 127.3, 64.9, 26.8 (×3), 22.6, 19.2, −2.00 (×3); HRMS (ESI) calcd for $C_{23}H_{34}NaOSi_2$ $[M + Na]^+$: 405.2046, found: 405.2052.

(3*R*,4*R*,5*R*)-5-(Benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)-methyl)-8-(trimethylsilyl)oct-1-en-7-yn-4-ol (13). To a solution of aldehyde **14** (7.00 g, 26.9 mmol) in CH_2Cl_2 (30 mL) was added tin chloride (IV) (1 M in CH_2Cl_2, 26.9 mL, 26.9 mmol) at −78 °C, and the reaction mixture was stirred for 30 min at the same temperature. And then to it was added a solution of allylsilane **15** (16.5 g, 43.1 mmol) in CH_2Cl_2 (5 mL). After 30 min, saturated aqueous $NaHCO_3$ was added to the reaction mixture, and then the mixture was filtered through a Celite pad. The filtrate was extracted with AcOEt, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (95/5) afforded enyne **13** as a colorless oil (14.7 g, 96%, 94% ee). The enantiomeric excess was determined by HPLC analysis [CHIRALCEL AD-H column, 15% isopropanol/hexane, 0.5 mL/min, retention times 15.5 (*R*) and 18.9 (*S*)]; $[\alpha]_D^{28}$ −3.74 (*c* 1.00 $CHCl_3$); IR (neat) ν_{max} 3566, 2957, 2930, 2175, 1112, 843, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (5H, m), 7.43−7.28 (10H, m), 5.73 (1H, dtd, J = 17.2, 10.4, and 1.2 Hz), 5.10 (1H, dd, J = 10.4 and 1.2 Hz), 5.00 (1H, dt, J = 17.2 and 1.2 Hz), 4.73 (1H, d, J = 11.2 Hz), 4.48 (1H, dd, J = 11.2 Hz), 3.87 (2H, dd, J = 10.0 and 4.8 Hz), 3.81 (1H, dd, J = 10.0 and 5.6 Hz), 3.71 (1H, dt, J = 6.8 and 1.6 Hz), 2.66 (2H, d, J = 6.4 Hz), 2.55−2.48 (2H, m), 1.04 (9H, s), 0.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.9, 135.64 (×2), 135.62 (×2), 133.4, 133.3, 129.62, 129.60, 128.3 (×2), 127.8 (×2), 127.7, 127.62 (×2), 127.60 (×2), 117.8, 103.9, 86.6, 77.6, 72.8, 72.3, 65.5, 49.0, 26.8 (×3), 22.1, 19.2, 0.0 (×3); HRMS (ESI) calcd for $C_{35}H_{46}NaO_3Si_2$ $[M + Na]^+$: 593.2883, found: 593.2901.

(5*R*,6*R*,7*R*,7a*S*)-5-(Benzyloxy)-7-(((*tert*-butyldiphenylsilyl)-oxy)methyl)-6-hydroxy-3-(trimethylsilyl)-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (18). To a solution of enyne **13** (12.5 g, 21.9 mmol) in CH_2Cl_2 (43 mL) was added $Co_2(CO)_8$ (8.23 g, 24.1 mmol), and the reaction mixture was stirred at rt for 8 h. The mixture was diluted with CH_2Cl_2 (172 mL), and to the solution was added NMO (25.6 g, 219 mmol) at 0 °C. After the mixture was stirred for 8 h at rt, purple precipitates were removed through a short silica gel pad, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (90/10) afforded tetrahydroindanone **18** as a colorless oil (12.8 g, 98%); $[\alpha]_D^{28}$ +3.76 (*c* 1.00 $CHCl_3$); IR (neat) ν_{max} 3446, 2856, 1708, 1113, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.65 (5H, m), 7.48−7.35 (10H, m), 4.76 (1H, d, J = 11.2 Hz), 4.67 (1H, d, J = 11.2 Hz), 4.14 (1H, d, J = 10.4 Hz), 4.00 (1H, t, J = 9.6 Hz), 3.61 (1H, dd, J = 10.4 and 2.8 Hz), 3.43−3.33 (2H, m), 3.03 (1H, br s), 2.90 (1H, t, J = 8.4 Hz), 2.36 (1H, ddd, J = 18.4, 6.8, and 0.8 Hz), 2.29 (1H, t, J = 12.0 Hz), 1.88 (1H, d, J = 18.4 Hz), 1.27 (1H, t, J = 10.8 Hz), 1.08 (9H, d, J = 1.2 Hz), 0.21 (9H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 185.3, 139.8, 138.4, 136.02 (×2), 135.96 (×2), 133.6, 133.5, 130.33, 130.28, 129.1 (×2), 128.6, 128.4 (×2), 128.3 (×2), 128.2 (×2), 82.5, 73.2, 72.7, 62.4, 45.0, 42.7, 41.4, 35.1, 27.4 (×3), 19.8, 0.0 (×3); HRMS (ESI) calcd for $C_{36}H_{47}O_4Si_2$ $[M + H]^+$: 599.3013, found: 599.3025.

(5*R*,6*R*,7*R*,7a*S*)-5-(Benzyloxy)-6-hydroxy-7-(hydroxymethyl)-3-(trimethylsilyl)-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one. To a solution of tetrahydroindanone **18** (1.50 g, 2.50 mmol) in THF (8.3 mL) were added TBAF (1 M in THF, 12.5 mL, 12.5 mmol) and AcOH (1.00 mL, 17.5 mmol) at rt, and the reaction mixture was stirred for 30 min at the same temperature. After the mixture was quenched with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with AcOEt. The organic phase was then dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (80/20) afforded diol as a white solid (901 mg, quant.); mp 64.1−70.0 °C (recryst. from Et_2O/Hex); $[\alpha]_D^{28}$ +19.60 (*c* 1.00 $CHCl_3$); IR (neat) ν_{max} 3406, 2953, 1688, 1592, 1071, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (5H, m), 4.72 (1H, d, J = 11.2 Hz), 4.58 (1H, d, J = 11.2 Hz), 3.87 (1H, m), 3.71 (1H, dd, J = 10.8 and 9.2 Hz), 3.69 (1H, d, J = 10.8 and 6.8 Hz), 3.42−3.33 (2H, m), 3.10 (1H, s), 2.81 (1H, br s), 2.57−2.47 (2H, m), 2.20 (1H, t, J = 12.0 Hz), 2.08 (1H, m), 1.41 (1H, m), 0.26 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 183.7, 140.4, 138.2, 129.2 (×2), 128.7, 128.3 (×2), 81.9, 76.8, 72.4, 65.3, 49.4, 41.9, 41.5, 34.8, 0.0 (×3); HRMS (ESI) calcd for $C_{20}H_{29}O_4Si$ $[M + H]^+$: 361.1835, found: 361.1846.

(4a*R*,5*R*,9a*S*,9b*S*)-5-(Benzyloxy)-2-methyl-5,6,9,9a-tetrahydrocyclopenta[*f*]chromene-3,8(4a*H*,9b*H*)-dione (10) and (4a*R*,5*R*,9a*S*,9b*S*)-5-(Benzyloxy)-2-methyl-7-(trimethylsilyl)-5,6,9,9a-tetrahydrocyclopenta[*f*]chromene-3,8(4a*H*,9b*H*)-dione (19). To a solution of diol (2.20 g, 6.10 mmol) in CH_2Cl_2/MeCN (1/1) (56 mL) were added TEMPO (190 mg, 1.22 mmol) and PIDA (1.76 g, 5.49 mmol) at rt, and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. Then the aqueous layer was extracted with AcOEt, and the organic phase was then washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was diluted with Et_2O, passed through a silica gel pad, and concentrated to give crude aldehyde **12** as a yellow oil. It was used for the next reaction without further purification. To a suspension of NaI (1.83 g, 12.2 mmol) in THF (50 mL) was added DBU (1.82 mL, 12.2 mmol) at rt. The mixture was stirred for 10 min, and then a solution of phosphonate **11** (5.10 g, 12.2 mmol) in THF (5 mL) was added slowly to the reaction mixture at 0 °C. The reaction mixture was stirred for 10 min at rt, and crude aldehyde **12** in THF (5 mL) was added at 0 °C. After the mixture was stirred at rt for 4 h, 30 mL of 6 M HCl were added, followed by stirring at rt for an additional 1 min. Then the aqueous layer was extracted with AcOEt, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (80/20) afforded tricycle **10** and **19** as a white solid (1.49 g, 75%) and a yellow oil (290 mg, 12%); for **10**, mp 152.6−154.0 °C (recryst. from Et_2O/Hex); $[\alpha]_D^{25}$ +94.32 (*c* 0.78 $CHCl_3$); IR (neat) ν_{max} 2924, 2364, 1711, 1629, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (5H, m), 6.43 (1H, dd, J = 1.6 and 1.2 Hz), 5.99 (1H, t, J = 1.2 Hz), 4.97 (1H, d, J = 11.6 Hz), 4.75 (1H, d, J = 11.6 Hz), 4.30 (1H, dd, J = 11.6 and 9.0 Hz), 3.77 (1H, ddd, J = 10.8, 9.2, and 5.6 Hz), 3.23 (1H, dd, J = 14.4 and 5.6 Hz), 2.69 (1H, dd, J = 18.0 and 6.6 Hz), 2.61 (1H, m), 2.45 (1H, t, J = 12.0 Hz), 2.18 (2H, m), 1.98 (3H, t, J = 2.0 Hz);

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^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 175.6, 164.9, 140.5, 138.5, 130.9, 130.5, 129.0 (×2), 128.47, 128.45 (×2), 84.1, 77.6, 74.2, 42.8, 42.8, 39.9, 35.8, 17.6; HRMS (ESI) calcd for $C_{20}H_{21}O_4$ $[M + H]^+$: 325.1440, found: 325.1456; for **19**, $[\alpha]_D^{25}$ +86.42 (*c* 1.05 $CHCl_3$); IR (neat) ν_{max} 1725, 1694, 843 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.26 (5H, m), 6.42 (1H, s), 4.97 (1H, d, *J* = 12.0 Hz), 4.75 (1H, d, *J* = 12.0 Hz), 4.30 (1H, dd, *J* = 11.6 and 9.2 Hz), 3.69 (1H, ddd, *J* = 10.8, 9.2, and 5.2 Hz), 3.31 (1H, dd, *J* = 14.2 and 5.2 Hz), 2.62 (1H, dd, *J* = 18.0 and 7.2 Hz), 2.54 (1H, m), 2.35 (1H, dd, *J* = 13.8 and 11.2 Hz), 2.13 (1H, m), 2.09 (1H, dd, *J* = 18.6 and 2.6 Hz), 1.97 (3H, s), 0.16 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 181.4, 164.7, 141.1, 140.7, 138.1, 129.9, 128.7 (×2), 128.14, 128.10 (×2), 83.8, 77.1, 73.7, 44.0, 42.5, 39.8, 36.0, 17.2, −0.5 (×3); HRMS (ESI) calcd for $C_{23}H_{29}O_4Si$ $[M + H]^+$: 397.1835, found: 397.1816.

(1*Z*,3*E*)-1-((2*S*,5*R*,6*R*,7*S*,7a*S*)-5-(Benzyloxy)-2,6-dihydroxy-2,4,5,6,7,7a-hexahydro-1*H*-inden-7-yl)-2-methyldodeca-1,3-dien-5-one (22). To a solution of lactone **10** (650 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added DIBAH (1 M in toluene, 4.40 mL, 4.40 mmol) at −78 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with a minimum amount of water (a few drops). After stirring was continued for 1 h, the mixture was filtered through a Celite pad and concentrated to give crude lactol **20** as a colorless oil. It was used for the next reaction without further purification. To a solution of crude lactol **20** in toluene (10 mL) was added (2-oxononanylidene)triphenylphosphorane **21** (1.61 g, 4.00 mmol) at rt, and stirring was continued for 4 h at 140 °C. The reaction mixture was diluted with Hexane. Then it was passed through Celite and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (70/30) afforded dienone **22** as a white solid (691 mg, 81%); mp 152.6−154.0 °C (recryst. from Et_2O/Hex); $[\alpha]_D^{25}$ −19.72 (*c* 0.61 $CHCl_3$); IR (neat) ν_{max} 3391, 2927, 1654, 1589, 1075 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 15.5 Hz), 7.37−7.28 (5H, m), 6.22 (1H, d, *J* = 15.5 Hz), 5.58 (1H, d, *J* = 10.0 Hz), 5.53 (1H, q, *J* = 2.0 Hz), 4.79 (1H, br s), 4.73 (1H, d, *J* = 11.5 Hz), 4.56 (1H, d, *J* = 11.5 Hz), 3.46 (1H, q, *J* = 9.0 Hz), 3.43 (1H, ddd, *J* = 10.5, 9.0, and 5.0 Hz), 2.98 (1H, dd, *J* = 13.5 and 5.0 Hz), 2.59 (1H, m), 2.56 (1H, t, *J* = 7.5 Hz), 2.55 (1H, q, *J* = 10.0 Hz), 2.39 (1H, dt, *J* = 13.5 and 8.0 Hz), 2.27 (1H, m), 2.05 (1H, t, *J* = 12.0 Hz), 1.94 (3H, d, *J* = 1.0 Hz), 1.75 (1H, br), 1.61 (2H, quint, *J* = 7.0 Hz), 1.32−1.20 (10H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 143.7, 139.6, 139.1, 138.1, 134.0, 128.6, 128.0 (×2), 127.8, 127.5 (×2), 127.2, 81.5, 76.8, 76.1, 71.6, 48.9, 47.7, 41.1, 39.3, 31.75, 31.71, 29.3, 29.2, 24.3, 22.6, 20.5, 14.1; HRMS (ESI) calcd for $C_{29}H_{41}O_4$ $[M + H]^+$: 453.3005, found: 453.2995.

(2*S*,5*R*,6*R*,7*S*,7a*S*)-5-(Benzyloxy)-7-((*S*,1*Z*,3*E*)-5-hydroxy-2-methyldodeca-1,3-dien-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diol (9a) and (2*S*,5*R*,6*R*,7*S*,7a*S*)-5-(Benzyloxy)-7-((*R*,1*Z*,3*E*)-5-hydroxy-2-methyldodeca-1,3-dien-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diol (9b). To a solution of dienone **22** (250 mg, 0.55 mmol) in CH_2Cl_2 (6 mL) was added DIBAH (1 M in toluene, 0.64 mL, 0.64 mmol) at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with a minimum amount of water (a few drops). After stirring was continued for 1 h, it was filtered through a Celite pad and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (60/40) afforded alcohol (**9a**/**9b** = 2/1) as a colorless oil (251 mg, quant.). The diastereomers were separated by HPCL (Kanto Chemical Co. INC Mightysil Si 60 250−20 (5 mm), AcOEt/Hexane = 50/50, 3.8 mL/min); for **9a**, $[\alpha]_D^{26}$ −13.23 (*c* 0.85 $CHCl_3$); IR (neat) ν_{max} 3368, 2926, 2855, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (5H, m), 6.67 (1H, d, *J* = 15.6 Hz), 5.76 (1H, dd, *J* = 15.6 and 6.0 Hz), 5.47 (1H, d, *J* = 1.6 Hz), 5.15 (1H, d, *J* = 10.0 Hz), 4.77 (1H, br s), 4.72 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 11.6 Hz), 4.16 (1H, q, *J* = 6.0 Hz), 3.46−3.37 (2H, m), 2.94 (1H, dd, *J* = 13.2 and 4.4 Hz), 2.56−2.45 (2H, m), 2.36 (1H, dt, *J* = 14.2 and 8.0 Hz), 2.20 (1H, m), 2.05 (1H, t, *J* = 11.2 Hz), 1.89 (3H, d, *J* = 1.2 Hz), 1.56−1.45 (2H, m), 1.34−1.18 (13H, m), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 138.7, 134.9, 133.8, 130.4, 128.6 (×2), 127.79, 127.74 (×2), 127.10, 127.08, 81.7, 77.2, 76.9, 72.8, 71.7, 48.5, 48.2, 38.8, 37.5, 32.0, 31.8, 29.6, 29.2, 35.6, 22.6, 20.9, 14.1; HRMS (ESI) calcd for $C_{29}H_{43}O_4$ $[M + H]^+$: 455.3161, Found: 455.3160; for **9b**, $[\alpha]_D^{28}$ −40.70 (*c* 1.35 $CHCl_3$); IR (neat) ν_{max} 3368, 2926, 2855, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (5H, m), 6.65 (1H, d, *J* = 15.6 Hz), 5.74 (1H, dd, *J* = 15.6 and 6.6 Hz), 5.49 (1H, q, *J* = 1.6 Hz), 5.16 (1H, d, *J* = 10.0 Hz), 4.79 (1H, br s), 4.72 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 11.6 Hz), 4.17 (1H, q, *J* = 6.4 Hz), 3.41 (2H, m), 2.95 (1H, dd, *J* = 13.2 and 4.4 Hz), 2.48 (1H, br s), 2.45 (1H, q, *J* = 10.0 Hz), 2.37 (1H, dt, *J* = 14.8 and 8.0 Hz), 2.22 (1H, m), 2.05 (1H, t, *J* = 11.2 Hz), 1.90 (3H, d, *J* = 1.2 Hz), 1.52 (2H, m), 1.42−1.22 (13H, m), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.3, 135.0, 133.8, 130.5, 128.5, 127.83, 127.79, 127.78, 127.74, 127.73, 127.3, 81.7, 77.2, 76.6, 73.0, 71.7, 48.6, 48.3, 38.9, 37.5, 32.0, 31.8, 29.6, 29.2, 25.5, 22.6, 21.0, 14.1; HRMS (ESI) calcd for $C_{29}H_{42}O_4Na$ $[M + Na]^+$: 477.2981, found: 477.2988.

(2*S*,5*R*,6*R*,7*S*,7a*S*)-7-((*R*,1*Z*,3*E*)-5-(2-Chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-5-hydroxy-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diyl Bis(2-chloroacetate) (23). To a solution of alcohol **9a** (174 mg, 0.383 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (637 μL, 4.60 mmol), chloroacetyl chloride (183 μL, 2.30 mmol), and DMAP (139 mg, 1.15 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic layer was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (90/10) afforded chloroacetate **23** as a colorless oil (262 mg, quant.); $[\alpha]_D^{28}$ −50.15 (*c* 1.02 $CHCl_3$); IR (neat) ν_{max} 2928, 1755, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (5H, m), 6.60 (1H, d, *J* = 15.6 Hz), 5.69 (1H, br s), 5.61 (1H, dd, *J* = 15.6 and 8.0 Hz), 5.54 (1H, q, *J* = 1.6 Hz), 5.36 (1H, dd, *J* = 7.6 and 6.0 Hz), 5.11 (1H, d, *J* = 9.6 Hz), 4.97 (1H, dd, *J* = 10.0 and 9.2 Hz), 4.66 (1H, d, *J* = 12.0 Hz), 4.55 (1H, d, *J* = 12.0 Hz), 4.06 (2H, s), 4.03 (2H, d, *J* = 0.8 Hz), 3.83 (2H, d, *J* = 0.8 Hz), 3.60 (1H, ddd, *J* = 10.8, 9.2, and 5.4 Hz), 3.00 (1H, dd, *J* = 13.2 and 5.4 Hz), 2.57−2.46 (2H, m), 2.40 (1H, m), 2.21 (1H, t, *J* = 12.8 Hz), 1.80 (3H, d, *J* = 1.2 Hz), 1.73 (1H, m), 1.61 (1H, m), 1.37 (1H, dt, *J* = 14.4 and 4.4 Hz), 1.32−1.21 (10H, br), 0.88 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.8, 166.7, 147.0, 138.2, 135.1, 130.6, 130.3, 128.5 (×2), 128.3, 127.8, 127.4 (×2), 123.4, 81.9, 78.6, 78.4, 77.6, 72.1, 47.8, 47.2, 41.2, 41.0, 40.8, 35.4, 34.6, 32.7, 31.8, 29.3, 29.1, 25.2, 22.6, 20.5, 14.1; HRMS (ESI) calcd for $C_{35}H_{45}O_7NaCl_3$ $[M + Na]^+$: 705.2129, found: 705.2142.

(2*S*,5*R*,6*R*,7*S*,7a*S*)-7-((*R*,1*Z*,3*E*)-5-(2-Chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-5-hydroxy-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diyl Bis(2-chloroacetate) (24). To a solution of dienone **23** (280 mg, 0.409 mmol) in CH_2Cl_2 (4 mL) was added DDQ (929 mg, 4.09 mmol) at rt, and stirring was continued for 48 h at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (80/20) afforded alcohol **24** as a colorless oil (194 mg, 80%); $[\alpha]_D^{23}$ −54.80 (*c* 1.03 $CHCl_3$); IR (neat) ν_{max} 3504, 2927, 1750, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, d, *J* = 15.2 Hz), 5.71 (1H, br s), 5.67 (1H, t, *J* = 8.0 Hz), 5.58 (1H, t, *J* = 2.0 Hz), 5.35 (1H, dt, *J* = 7.2 and 6.4 Hz), 5.11 (1H, d, *J* = 9.6 Hz), 4.80 (1H, t, *J* = 9.6 Hz), 4.05 (2H, s), 4.03 (2H, s), 4.01 (1H, d, *J* = 14.8 Hz), 3.90 (1H, d, *J* = 14.8 Hz), 3.82 (1H, ddd, *J* = 11.2, 9.2, and 5.2 Hz), 2.96 (1H, dd, *J* = 13.6 and 5.2 Hz), 2.56 (1H, dt, *J* = 14.4 and 7.6 Hz), 2.49 (1H, dd, *J* = 10.4 and 9.6 Hz), 2.43 (1H, br), 2.21 (1H, dt, *J* = 11.2 and 1.6 Hz), 1.80 (3H, d, *J* = 1.6 Hz), 1.74 (1H, br), 1.62 (1H, m), 1.44−1.16 (12H, m), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.0, 166.8, 146.7, 135.2, 130.6, 130.1, 128.4, 123.6, 81.8, 80.3, 77.7, 71.6, 47.9, 47.0, 41.1, 41.0, 40.8, 35.4, 34.7, 34.6, 31.7, 29.3, 29.1, 25.1, 22.3, 20.5, 14.0; HRMS (ESI) calcd for $C_{28}H_{39}O_7NaCl_3$ $[M + Na]^+$: 615.1659, found: 615.1667.

(6*R*,7*S*,7a*S*)-7-((*R*,1*Z*,3*E*)-5-(2-Chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-5-oxo-5,6,7,7a-tetrahydro-1*H*-inden-6-yl

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2-chloroacetate (25). To a solution of alcohol **24** (110 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) were added 4 Å MS (100 mg), NMO (130 mg, 1.1 mmol), and TPAP (20 mg, 0.056 mmol) at rt. After stirring was continued for 8 h, black precipitates were removed through a Celite pad, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (90/10) afforded dienone **25** as a colorless oil (76 mg, 83%); $[\alpha]_D^{21}$ −65.76 (*c* 1.03 $CHCl_3$); IR (neat) ν_{max} 2927, 1750, 1668, 1620, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, dt, *J* = 5.6 and 2.4 Hz), 6.58 (1H, d, *J* = 15.6 Hz), 6.47 (1H, dt, *J* = 5.6 and 2.4 Hz), 5.97 (1H, d, *J* = 2.4 Hz), 5.67 (1H, dd, *J* = 15.6 and 7.2 Hz), 5.33 (1H, q, *J* = 6.8 Hz), 5.30−5.18 (2H, m), 4.18 (1H, d, *J* = 15.2 Hz), 4.08 (1H, d, *J* = 15.2 Hz), 4.03 (2H, s), 3.25 (1H, dt, *J* = 11.2 and 9.2 Hz), 2.96 (1H, m), 2.73 (1H, dddd, *J* = 18.4, 7.2, 2.8, and 1.6 Hz), 2.24 (1H, m), 1.85 (3H, d, *J* = 1.2 Hz), 1.70 (1H, m), 1.62 (1H, m), 1.33−1.19 (10H, br s), 0.87 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 171.5, 167.1, 166.7, 149.1, 135.8, 132.1, 129.4, 129.1, 128.7, 116.5, 77.2, 77.0, 45.5, 45.3, 41.1, 40.8, 37.7, 34.5, 31.7, 29.4, 29.1, 25.2, 22.6, 20.6, 14.1; HRMS (ESI) calcd for $C_{26}H_{35}O_5Cl_2$ $[M + H]^+$: 497.1862, found: 497.1867.

Penostatin E (1a). To a solution of dienone **25** (20 mg, 40 μmol) in THF/H_2O (3/1) (1 mL) was added LiOH·H_2O (6.4 mg, 160 μmol) at 0 °C and stirred for 5 min at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ether. The combined organic layer was washed brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (75/25) afforded penostatin E (**1a**) as a colorless oil (12 mg, 86%); $[\alpha]_D^{21}$ +9.00 (*c* 0.96 $CHCl_3$); IR (neat) ν_{max} 3431, 2926, 1659, 1618, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (1H, dt, *J* = 6.0 and 3.0 Hz), 6.59 (1H, d, 15.5 Hz), 6.48 (1H, dt, *J* = 6.0 and 3.0 Hz), 6.02 (1H, d, *J* = 2.5 Hz), 5.78 (1H, dd, *J* = 15.6 and 6.8 Hz), 5.40 (1H, br d, *J* = 10.0 Hz), 4.16 (1H, q, *J* = 6.5 Hz), 3.96 (1H, dd, *J* = 10.5 and 1.0 Hz), 3.88 (1H, d, *J* = 1.0 Hz), 3.01 (1H, d, *J* = 10.5 Hz), 2.87 (1H, dddd, *J* = 10.0, 6.5, 4.5, and 2.5 Hz), 2.69 (1H, dddd, *J* = 10.0, 6.5, 3.0, and 2.5 Hz), 2.26 (1H, dddd, *J* = 18.0, 6.5, 3.0, and 2.5 Hz), 1.94 (1H, d, *J* = 1.0 Hz), 1.55 (1H, br s), 1.26 (10H, br s), 0.87 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.12, 173.27, 149.63, 135.16, 134.33, 132.10, 129.23, 127.11, 114.93, 77.23, 73.17, 48.21, 45.87, 37.63, 37.33, 31.79, 29.50, 29.27, 25.50, 22.64, 20.99, 14.08; HRMS (ESI) calcd for $C_{22}H_{33}O_3$ $[M + H]^+$: 345.2430, found: 345.2437; CD λ (*c* 1.93 × 10^{-4} M in EtOH) nm 211 ($\Delta\varepsilon$ −2.15), 233 (−7.59), 248 (0), 258 (+2.59), 273 (0), 292 (−5.15), 310 (0), 329 (+3.96) and 390 (0).

(2*S*,5*R*,6*R*,7*S*,7a*S*)-5-(Benzyloxy)-7-((*R*,1*Z*,3*E*)-5-(2-chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diyl Bis(2-chloroacetate) (14-*epi*-23). To a solution of alcohol **9b** (91 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (330 μL, 2.4 mmol), chloroacetyl chloride (97 μL, 1.2 mmol), and DMAP (78 mg, 0.60 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic layer was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (90/10) afforded triacylate as a colorless oil (132 mg, 97%); $[\alpha]_D^{28}$ −62.98 (*c* 1.02 $CHCl_3$); IR (neat) ν_{max} 2928, 1752, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (5H, m), 6.59 (1H, d, *J* = 15.6 Hz), 5.69 (1H, br s), 5.61 (1H, dd, *J* = 15.6 and 7.6 Hz), 5.54 (1H, d, *J* = 1.2 Hz), 5.35 (1H, q, *J* = 7.2 Hz), 5.11 (1H, d, *J* = 10.0 Hz), 4.98 (1H, t, *J* = 10.0 Hz), 4.67 (1H, d, *J* = 12.0 Hz), 4.54 (1H, d, *J* = 12.0 Hz), 4.15 (1H, d, *J* = 14.8 Hz), 4.09 (1H, d, *J* = 14.8 Hz), 4.03 (2H, s), 3.78 (2H, s), 3.66 (1H, ddd, *J* = 10.8, 9.6, and 5.2 Hz), 3.01 (1H, dd, *J* = 13.2 and 5.2 Hz), 2.53 (1H, q, *J* = 10.2 Hz), 2.48 (1H, dd, *J* = 8.0 and 7.2 Hz), 2.38 (1H, m), 2.20 (1H, t, *J* = 12.4 Hz), 1.79 (3H, s), 1.72 (1H, m), 1.60 (1H, m), 1.40 (1H, dt, *J* = 14.6 and 4.0 Hz), 1.38−1.16 (10H, br s), 0.89 (3H, dd, *J* = 7.2 and 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.6, 166.5, 147.0, 138.2, 135.0, 130.2, 130.1, 128.4 (×2), 128.2, 127.7, 127.5 (×2), 123.5, 81.7, 78.63, 78.60, 77.3, 72.0, 47.9, 47.2, 41.2, 41.1, 40.6, 35.2, 34.6, 32.6, 31.7, 29.3, 29.1, 25.2, 22.6, 20.4, 14.1; HRMS (ESI) calcd for $C_{35}H_{46}O_7Cl_3$ $[M + H]^+$: 683.2320, found: 683.2309.

(2*S*,5*R*,6*R*,7*S*,7a*S*)-7-((*R*,1*Z*,3*E*)-5-(2-Chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-5-hydroxy-2,4,5,6,7,7a-hexahydro-1*H*-indene-2,6-diyl Bis(2-chloroacetate) (14-*epi*-24). To a solution of dienone (110 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added DDQ (350 mg, 1.6 mmol) at rt, and stirring was continued for 48 h at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (80/20) afforded alcohol as a colorless oil (76 mg, 80%); $[\alpha]_D^{23}$ −66.19 (*c* 0.72 $CHCl_3$); IR (neat) ν_{max} 2927, 1747, 1741, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, d, *J* = 15.6 Hz), 5.70 (1H, br s), 5.63 (1H, dd, *J* = 15.6 and 7.6 Hz), 5.58 (1H, br s), 5.35 (1H, q, *J* = 6.8 Hz), 5.11 (1H, d, *J* = 10.0 Hz), 4.82 (1H, t, *J* = 9.6 Hz), 4.15 (1H, d, *J* = 14.8 Hz), 4.09 (1H, d, *J* = 14.8 Hz), 4.05 (2H, s), 3.97 (1H, d, *J* = 14.8 Hz), 3.87 (1H, d, *J* = 14.8 Hz), 3.81 (1H, ddd, *J* = 15.6, 11.2, and 5.6 Hz), 2.97 (1H, dd, *J* = 13.6 and 5.6 Hz), 2.58−2.48 (2H, m), 2.40 (1H, m), 2.21 (1H, t, *J* = 12.4 Hz), 1.80 (3H, s), 1.72 (1H, m), 1.63 (1H, m), 1.40 (1H, dt, *J* = 14.6 and 4.0 Hz), 1.34−1.23 (11H, br s), 0.88 (3H, dd, *J* = 6.4 and 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 167.2, 164.6, 146.6, 135.1, 130.0, 129.9, 128.7, 123.7, 81.6, 80.6, 77.2, 71.8, 48.1, 46.9, 41.2, 41.1, 40.7, 35.3, 34.9, 34.6, 31.7, 29.3, 29.1, 25.2, 22.6, 20.5, 14.1; HRMS (ESI) calcd for $C_{28}H_{39}O_7NaCl_3$ $[M + Na]^+$: 615.1659, found: 615.1658.

(6*R*,7*S*,7a*S*)-7-((*R*,1*Z*,3*E*)-5-(2-Chloroacetoxy)-2-methyldodeca-1,3-dien-1-yl)-5-oxo-5,6,7,7a-tetrahydro-1*H*-inden-6-yl 2-chloroacetate (14-*epi*-25). To a solution of alcohol (31 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added 4 Å MS (30 mg), NMO (37 mg, 0.31 mmol), and TPAP (3.5 mg, 0.010 mmol) at rt. After stirring was continued for 8 h, black precipitates were removed through a Celite pad, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (90/10) afforded dienone as a colorless oil (21 mg, 81%); $[\alpha]_D^{22}$ −52.85 (*c* 0.83 $CHCl_3$); IR (neat) ν_{max} 2927, 1757, 1667, 1620, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (1H, q, *J* = 2.4 Hz), 6.60 (1H, d, *J* = 15.6 Hz), 6.47 (1H, d, *J* = 5.2 Hz), 5.97 (1H, d, *J* = 2.0 Hz), 5.66 (1H, dd, *J* = 15.6 and 7.6 Hz), 5.34 (1H, dd, *J* = 14.4 and 7.2 Hz), 5.27 (2H, d, *J* = 9.6 Hz), 4.14 (1H, d, *J* = 14.8 Hz), 4.04 (1H, s), 4.02 (1H, d, *J* = 14.8 Hz), 3.29 (1H, m), 2.96 (1H, ddd, *J* = 10.8, 6.6, and 3.6 Hz), 2.71 (1H, ddt, *J* = 18.4, 7.2, and 2.0 Hz), 2.30 (1H, d, *J* = 18.4 Hz), 1.86 (3H, s), 1.71 (1H, m), 1.63 (1H, m), 1.33−1.21 (10H, br s), 0.88 (3H, dd, *J* = 6.8 and 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 171.8, 166.9, 166.7, 149.4, 135.8, 132.0, 129.9, 128.9, 128.7, 116.4, 77.3, 77.2, 45.6, 45.3, 41.2, 40.6, 37.6, 34.5, 31.7, 29.3, 29.1, 25.2, 22.6, 20.5, 14.1; HRMS (ESI) calcd for $C_{26}H_{35}O_5Cl_2$ $[M + H]^+$: 497.1862, found: 497.1874.

14-*epi*-Penostatin E (1b). To a solution of dienone (20 mg, 40 μmol) in THF/H_2O (3/1) (1 mL) was added LiOH·H_2O (6.4 mg, 0.16 mmol) at 0 °C and stirred for 5 min at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ether. The combined organic layer was washed brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography. Elution with hexane/AcOEt (75/25) afforded 14-*epi*-penostatin E (**1b**) as a colorless oil (12 mg, 78%); $[\alpha]_D^{21}$ −7.24 (*c* 0.96 $CHCl_3$); IR (neat) ν_{max} 3448, 2926, 1655, 1617, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (1H, dt, *J* = 6.0 and 2.5 Hz), 6.60 (1H, d, *J* = 16.0 Hz), 6.48 (1H, dt, *J* = 6.0 and 2.5 Hz), 6.02 (1H, d, *J* = 2.5 Hz), 5.77 (1H, dd, *J* = 16.0 and 6.5 Hz), 5.40 (1H, br d, *J* = 10.0 Hz), 4.16 (1H, q, *J* = 6.5 Hz), 3.96 (1H, dd, *J* = 11.0 and 1.5 Hz), 3.87 (1H, d, *J* = 1.5 Hz), 3.01 (1H, d, *J* = 10.5 Hz), 2.86 (1H, dddd, *J* = 10.0, 6.5, 4.5, and 2.5 Hz), 2.69 (1H, dddd, *J* = 10.0, 6.5, 3.0, and 2.5 Hz), 2.29 (1H, dddd, *J* = 18.0, 6.5, 3.0, and 2.5 Hz), 1.47 (1H, br s), 1.27 (10H, br s), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.17, 173.37, 149.75, 135.20, 134.19, 132.05, 129.20, 127.05, 114.88, 77.24, 73.14, 48.24, 45.89, 37.66, 37.53, 31.80, 29.52, 29.23, 25.44, 22.64, 21.03,

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14.08; HRMS (ESI) calcd for $C_{22}H_{33}O_3$ $[M + H]^+$: 345.2430, found: 345.2437.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) According to the suggestion of one of the reviewers, the optical rotations were measured in almost the same concentrations as those with the literature. The values are as follows: $[\alpha]_D^{29}$ +14.1 (*c* 0.12, $CHCl_3$) for **1a** and $[\alpha]_D^{31}$ −9.36 (*c* 0.11, $CHCl_3$) for **1b**