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Total Synthesis of Pteridic Acids A and B

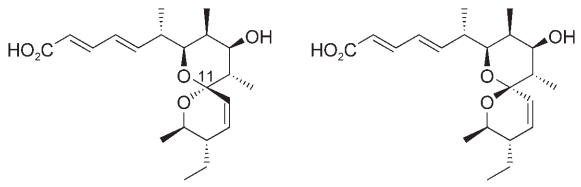
Takashi Nakahata, Shohei Fujimura, and Shigefumi Kuwahara*[a]

Abstract: Pteridic acid A (**1**) is a spirocyclic octaketide produced by the phytoepiphytic actinomycete *Streptomyces hygroscopicus* TP-A0451 and possesses potent plant-growth-promoting activity comparable to that of indole-3-acetic acid. The enantioselective total synthesis of this natural product was achieved by employing the $Sn(OTf)_2$-mediated Evans aldol reaction and the Fukuyama acetylenic coupling reaction as the key C–C bond-forming steps producing **1** through a 14-step sequence in 22% overall yield from a known oxazolidinone derivative. $MgBr_2$-mediated equilibration of an anomerically favored spirocyclic intermediate used for the synthesis of **1** brought about partial epimerization of the spirocenter to give the corresponding anomerically disfavored epimer, which was converted into pteridic acid B (11-*epi*-**1**), another plant-growth promoter of the same microbial origin.

Keywords: aldol reaction · natural products · polyketides · pteridic acid · total synthesis

Introduction

In the course of screening for plant-growth regulators produced by epiphytic microorganisms on live plants, Igarashi and co-workers discovered two novel spirocyclic polyketides, pteridic acids A (**1**) and B (**2**, 11-*epi*-**1**), from the fermentation broth of the actinomycete *Streptomyces hygroscopicus* TP-A0451, isolated from the stems of the bracken *Pteridium aquilinum* and determined their structures on the basis of extensive spectroscopic analyses including HMBC and NOESY experiments.[1] These two epimeric octaketides both exhibited potent promoting activity in the formation of adventitious roots in the hypocotyls of kidney beans comparable to that of indole-3-acetic acid (a natural plant hormone, auxin) at an extremely low concentration of 1 nM. This is the lowest value so far reported for the plant-growth-promoting activity of microbial secondary metabolites,[2] which might allow us to envisage the presence of a symbiosis-like interrelationship between phytoepiphytic actinomycetes and their host plants by secondary metabolites.[3] Our interest in such substantial biological roles of secondary metabolites of microbial origin in the natural ecosystem and in complex molecular architectures featuring a spiroacetal ring bearing eight stereogenic centers around it prompted us to embark on the total synthesis of pteridic acids, and our synthetic efforts recently culminated in the first enantioselective total synthesis of pteridic acid A (**1**).[4] We describe herein a full account of our synthetic study on **1**, together with the conversion of its synthetic intermediate into the other plant-growth promoter, pteridic acid B (**2**).

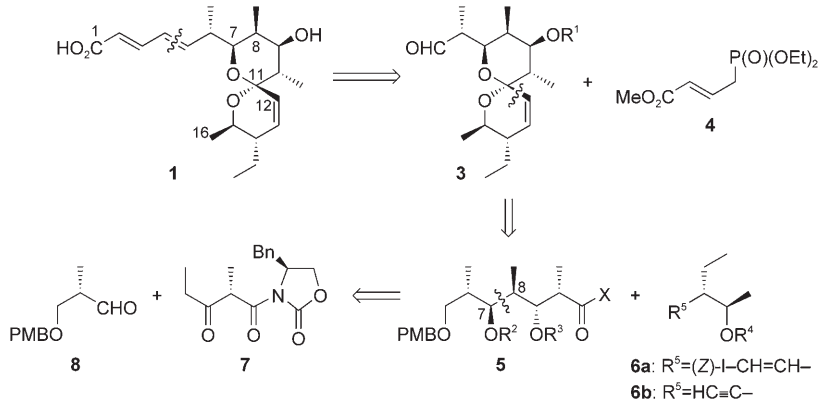


pteridic acid A (**1**) pteridic acid B (**2**) (11-*epi*-**1**)

Our retrosynthetic analysis of pteridic acid A (**1**) is shown in Scheme 1. The conjugated diene carboxylic acid moiety incorporated in **1** was considered to be readily installable by using the Horner–Wadsworth–Emmons olefination of aldehyde **3** with known phosphonate **4**. The spiroacetal **3** could be obtained either by the addition of an alkenyl anion derived from iodide **6a** or by the addition of an acetylide anion derived from **6b** to carbonyl compound **5** (X = H or an appropriate leaving group), followed by some additional

[a] T. Nakahata, S. Fujimura, Prof. Dr. S. Kuwahara
Laboratory of Applied Bioorganic Chemistry
Graduate School of Agricultural Science
Tohoku University, Tsutsumidori-Amamiyamachi
Aoba-ku, Sendai 981–8555 (Japan)
Fax: (+81) 22-717-8783
E-mail: skuwahar@biochem.tohoku.ac.jp

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author and contains ^1H and ^{13}C NMR spectra for all important compounds.

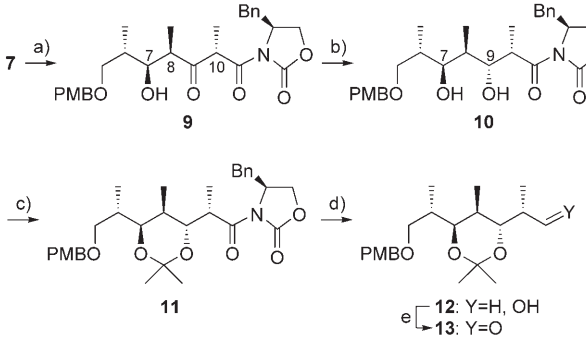


Scheme 1. Retrosynthetic analysis of pteridic acid A (**1**). PMB = *p*-methoxybenzyl.

transformations. Finally, retrosynthetic disconnection of the C7–C8 bond in **5** enabled us to think of its construction through an asymmetric aldol reaction between ketone **7** and aldehyde **8**. On the other hand, the synthesis of pteridic acid B (**2**), the 11-epimer of **1**, was anticipated to be more difficult due to its anomerically disfavored conformation at the spirocenter.[1] This potential difficulty was, however, successfully overcome by applying a $MgBr_2$-promoted epimerization reaction to a spirocyclic synthetic intermediate of **1** as described later in this paper.

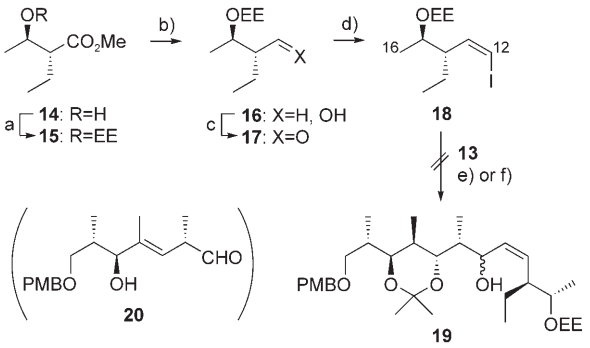
Results and Discussion

Preparation of the C5–C11 fragment 13: The preparation of our subtarget **13** (compound **5** in Scheme 1; X = H, R^1 and R^2 = acetonide) began with the diastereoselective aldol reaction of known aldehyde **8**[5] with β-keto imide derivative **7** developed by Evans et al.,[6] which produced an inseparable 13:1 mixture of the desired 7,8-*syn*-8,10-*anti*-aldol **9** and its (7*R*,8*S*)-diastereomer, as judged by the ^{1}H NMR analysis of the reaction product (Scheme 2). The mixture then underwent hydroxyl-directed diastereoselective reduction by treatment with $NaBH(OAc)_3$[7] to give 7,9-*anti*-diol **10** with considerably high diastereoselectivity (7,9-*anti*/7,9-*syn* approximately 10:1). The protection of diol **10** as acetonide **11** and subsequent reductive removal of the chiral auxiliary with $LiBH_4$ afforded stereochemically homogeneous alcohol **12** in 75% yield from **10** after chromatographic purification. The 7,9-*anti* relative stereochemistry of **12** was readily confirmed by analyzing its ^{13}C NMR spectrum, in which the signals assignable to the quaternary carbon and the two methyl carbon atoms of the acetonide moiety were observed at $\delta = 100.6$, 24.9, and 23.5 ppm, respectively, in good accordance with a general rule proposed for the assignment of the relative stereochemistry of 1,3-*syn*- and 1,3-*anti*-diol acetonides.[8] Finally, oxidation of **12** with Dess–Martin periodinane (DMP) completed the preparation of the C5–C11 fragment **13**.



Scheme 2. Preparation of the C5–C11 fragment **13**: a) $Sn(OTf)_2$, Et_3N, **8**, CH_2Cl_2, −78°C, 2 h (82%); b) $NaBH(OAc)_3$, AcOH, RT, 1.5 h (92%); c) $Me_2C(OMe)_2$, $TsOH{\cdot}H_2O$, acetone, RT, 24 h (96%); d) $LiBH_4$, MeOH, THF, RT, 3 h (78%); e) DMP, CH_2Cl_2, RT, 24 h (94%). DMP = Dess–Martin periodinane.

Preparation of the C12–C16 fragment 18 and its attempted coupling with 13: Next, we set about the preparation of alkenyl iodide **18** (compound **6a** in Scheme 1, R^4 = EE), one of the candidates for the coupling partner of **13** (Scheme 3).

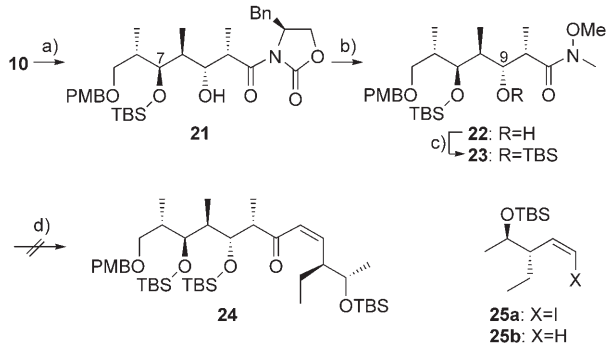


Scheme 3. Preparation of the C12–C16 fragment **18** and its coupling with **13**: a) CH_2=CHOEt, PPTS, CH_2Cl_2, RT, 24 h (quant); b) DIBAL, CH_2Cl_2, −78°C, 24 h (quant); c) DMSO, $(COCl)_2$, Et_3N, −78°C, 1 h (quant); d) $(Ph_3PCH_2I)^+I^-$, NaHMDS, THF, −20°C, 3 h (68%); e) *t*BuLi, THF, −78°C, 12 h; f) $CrCl_2$, $NiCl_2$, DMSO, DMF, RT, 24 h. EE = ethoxyethyl, PPTS = pyridinium *p*-toluenesulfonate; DIBAL = diisobutylaluminum hydride; HMDS = hexamethyldisilazide.

Protection of known hydroxy ester **14**[9] as its ethoxyethyl ether **15** was followed by reduction of the ester functionality to give alcoholic intermediate **16**, which was then exposed to Swern oxidation conditions to furnish protected aldehyde **17**. (*Z*)-Selective Wittig olefination of **17** with Ph_3P=CHI proceeded smoothly to afford **18** with >20:1 *Z*/*E* selectivity.[10]

The coupling of **18** with aldehyde **13** was examined in two ways: 1) addition of the alkenyllithium reagent prepared from **18** to **13**[11] and 2) direct coupling of the two components under the Nozaki–Hiyama–Kishi coupling conditions.[12] Under the former conditions, however, the only isolable product was the β-elimination product **20**, while under the latter conditions, no detectable product was obtained, resulting only in the recovery of the substrates.

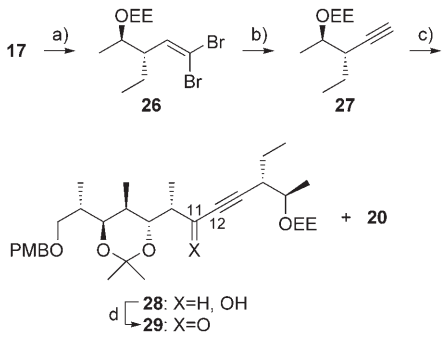
We also attempted the coupling of Weinreb's amide **23** and the alkenyllithium reagent derived from **25a** (Scheme 4), which in turn was obtained from **14** by the same



Scheme 4. Preparation of the C5–C11 fragment **23** and its coupling with **25a**: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −5 °C, 24 h; b) $AlMe_3$, (MeO)-MeNH·HCl, THF, −20 °C, 24 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 24 h (30% from **10**); d) **25a**, *t*BuLi, THF, −78 °C, 2.5 h. TBS = *tert*-butylsilyl; Tf = triflate.

procedure as described for **18** except for the protection step (TBSOTf/2,6-lutidine/CH_2Cl_2 instead of CH_2=CHOEt/PPTS/CH_2Cl_2). To prepare **23**, the C7−OH group of diol **10** was protected as its mono-TBS ether **21**, followed by the replacement of the chiral auxiliary with a methoxymethylamino group under conventional conditions to give **22**.[13] Finally, TBS-protection of the remaining hydroxyl at the C9 position produced the desired amide **23** in about 30% overall yield from **10** (the chemical yield was not optimized). The nucleophilic substitution of **23** with the alkenyl anion prepared by treating **25a** with *t*BuLi to form olefinic ketone **24**, however, did not proceed at all, giving only the starting amide **23** along with deiodinated terminal olefin **25b** generated from **25a**.

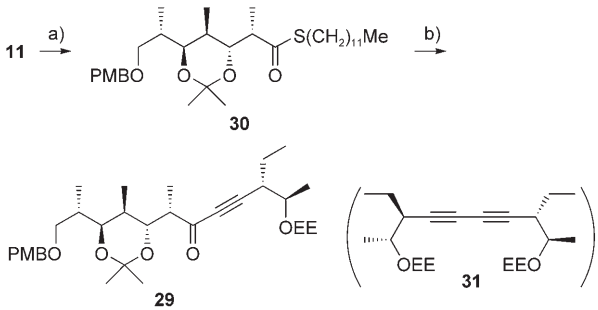
Preparation of the C12–C16 fragment 27 and its coupling with 13: To circumvent the difficulties encountered in the coupling reaction with alkenyl iodides **18** or **25a**, we turned our attention to the utilization of terminal acetylene **27** (compound **6b** in Scheme 1; R^4 = EE) for the construction of the C11−C12 bond (Scheme 5). The acetylenic segment was readily prepared by dibromomethylenation of aldehyde **17** in the presence of pyridine and subsequent treatment of the resulting dibromoolefin **26** with *n*BuLi.[14] The presence of pyridine as an additive was essential in this case, as its absence brought about complete deprotection of the ethoxyethyl group. After treatment of **27** with *n*BuLi, the resulting



Scheme 5. Preparation of the C12–C16 fragment **27** and its coupling with **13**: a) CBr_4, Ph_3P, Py, CH_2Cl_2, 0 °C, 1.5 h (64%); b) *n*BuLi, THF, −78 °C, 24 h (79%); c) *n*BuLi, **13**, −78 °C, 24 h (40%); d) DMP, CH_2Cl_2, 0 °C, 24 h (94%).

lithium acetylide was reacted successfully with aldehyde **13** to give a 40% yield of desired coupling product **28**, which was then oxidized to ketone **29**. In this coupling reaction, again, the main byproduct was the β elimination product **20** (approximately 40% yield). Use of the less basic magnesium acetylide prepared by treating **27** with EtMgBr in THF was not successful, resulting only in the recovery of **13** and **27**. The unexpected problems in this coupling step with aldehyde **13** as a precursor of **29** made us seek an alternative protocol for the formation of the C11−C12 linkage.

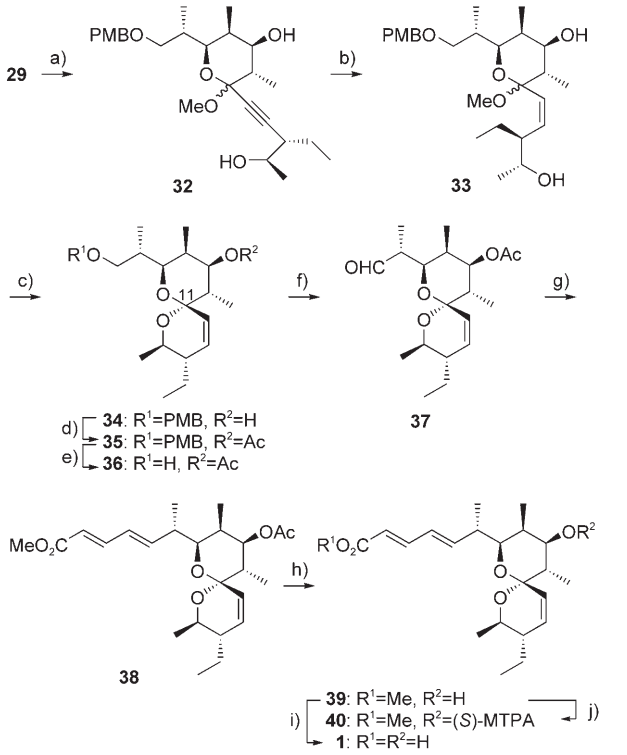
Construction of the C11−C12 bond via thiol ester intermediate 30: Although we could secure α,β-acetylenic ketone **29**, which was a requisite for the installation of the spiroacetal ring, by oxidation of **28** as just described, the low chemical yield (40%) and the formation of a substantial amount of byproduct **20** (approximately 40%), stemming from the β elimination of aldehyde **13** in the coupling step, called on us to alter our synthetic plan to a small extent. We envisaged obtaining **29** without the intervention of **13**. Among numerous methodologies so far reported for the preparation α,β-acetylenic ketones,[15] we adopted a protocol recently developed by Fukuyama and co-workers, which could effect the coupling of a variety of thiol esters and terminal acetylenes in the presence of [$PdCl_2$(dppf)] and CuI under mild reaction conditions (Scheme 6).[16] Thus, oxazolidinone deriva-



Scheme 6. Preparation of the C5–C11 fragment **30** and its coupling with **27**: a) *n*-$C_{12}H_{25}SH$, *n*BuLi, −78–−20 °C, 5 h (77%); b) [$PdCl_2$(dppf)], CuI, (2-furyl)$_3$P, Et_3N, **27**, DMF, 50 °C, 3 h (83%, 3 cycles). dppf = bis(diphenylphosphino)ferrocene.

tive **11** was first converted into the corresponding dodecanethiol ester **30** by treatment with lithium dodecanethiolate in THF.[16b] Gratifyingly, the palladium-catalyzed coupling reaction of **30** with terminal acetylene **27** (approximately 2 equiv) produced **29** cleanly, without the formation of any other products arising from **30**. This transformation was, however, accompanied by an oxidative homocoupling reaction of the acetylenic substrate **27** to afford the corresponding Glaser-type diyne compound **31**,[17] which competitively consumed **27** and, as a result, precluded the reaction from proceeding to completion. Thus, the chemical yield of this coupling reaction was approximately 40–45% per single operation, but the thiol ester substrate **30** could be recovered almost quantitatively, which made it possible to obtain an 83% yield of **29** in total by repeating the same operation two more times with recovered **30**. This alteration of the coupling protocol enabled us to not only reduce the number of synthetic steps, but also to improve the overall yield of **29** (five steps, 46% overall yield from **7**).

Completion of the synthesis of pteridic acid A (1): The successful assembly of the C5–C16 segment **29** set the stage for the formation of the spiroacetal ring and subsequent four-carbon elongation toward the total synthesis of pteridic acid A (**1**, Scheme 7). Simultaneous removal of the two types of acetal-protecting groups of **29** in acidic methanol below 0°C brought about the formation of cyclic acetal **32** as an inseparable 3:1 diastereomeric mixture in 91% yield. Keeping the reaction temperature below 0°C was essential to obtain reproducibly high yields, as elevating the reaction temperature to 25°C resulted in considerably low yields (53–78%), producing unidentified byproducts. Exposure of **32** to catalytic semihydrogenation conditions followed by acidic treatment of the resulting olefin **33** afforded spiroacetal **34** as a single stereoisomer. The stereochemistry of the spirocenter of **34** was tentatively assigned based on the amomeric effect and the similarity in the ^{1}H NMR spectrum between **34** and pteridic acid A (**1**), and was eventually confirmed by its conversion to **1**. After protection of the hydroxyl group of **34** as its acetate **35**, the PMB-protecting group was removed by DDQ oxidation to give **36** without any epimerization at the spirocenter. In our previous communication,[4] we reported the occurrence of partial epimerization at the C11 spirocenter during the oxidation step, producing a 6:1 mixture of **36** and 11-*epi*-**36**. This small degree of epimerization, however, could be avoided by immediately conducting chromatographic purification of the crude reaction mixture. This finding made us suspect that the ring-opening/closure process leading to the epimeric mixture might have taken place as a result of exposure of the initially formed spiroacetal **36** to a high concentration of the considerably acidic 2,3-dichloro-5,6-dicyanohydroquinone generated from the oxidizing reagent DDQ, as in our previous experiment,[4] the crude reaction product was left to stand overnight at room temperature without purification after the evaporation of the EtOAc employed for extraction.

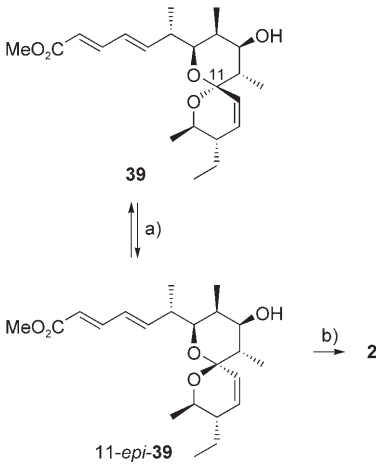


Scheme 7. Completion of the synthesis of pteridic acid A (**1**): a) CSA, MeOH, CH_2Cl_2, 0°C, 3 d (91%); b) Lindlar's catalyst, 1-hexene, EtOAc, RT, 15 min (89%); c) PPTS, toluene, RT, 1 h (99%); d) Ac_2O, DMAP, Py, RT, 24 h (quant); e) DDQ, H_2O, CH_2Cl_2, 0°C, 1 h (86%); f) DMP, Py, CH_2Cl_2, 0°C, 24 h (91%); g) **4**, LiHMDS, THF, −78°C, 3 h (94%); h) K_2CO_3, MeOH, RT, 3 h (83%); i) KOH, H_2O, MeOH, 6 h (99%); j) (*R*)-MTPACl, Py. CSA = camphorsulfonic acid; DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

The oxidation of alcohol **36** with DMP proceeded uneventfully to give aldehyde **37**, for which four-carbon elongation with phosphonate **4** furnished geometrically pure **38** possessing all the carbon atoms and stereochemically correct asymmetric centers of pteridic acid A (**1**). Finally, deprotection of the acetyl group by methanolysis to **39** and subsequent hydrolysis of the methyl ester moiety gave **1** ($[\alpha]_D^{24} = +24$ ($c = 0.15$ in $CHCl_3$); lit.[1] $[\alpha]_D^{24} = +22.3$ ($c = 1.0$ in $CHCl_3$)). ^{1}H and ^{13}C NMR spectra were identical to those of natural pteridic acid A.[1] The enantiomeric homogeneity of our synthetic pteridic acid A was confirmed by directly comparing the ^{1}H NMR spectrum of the (*S*)-MTPA ester (**40**) derived from **39** with those of the (*S*)- and (*R*)-MTPA esters prepared previously by Igarashi from natural pteridic acid A.[1]

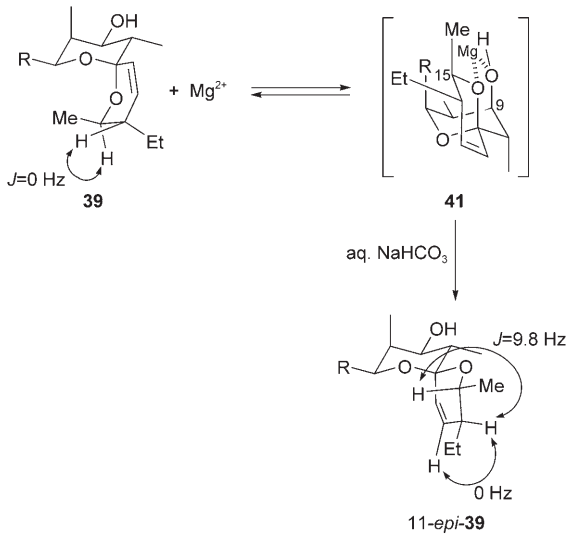
Synthesis of pteridic acid B through epimerization of intermediate 39: With the enantioselective total synthesis of **1** completed, we attempted the epimerization of the spirocenter of an appropriate synthetic intermediate for **1** to obtain pteridic acid B (**2**), the C11 epimer of pteridic acid A (**1**). As reported in our previous communication,[4] the epimerization must have occurred at the stage of the formation of

36 when the crude reaction product was exposed to a high concentration of the phenolic byproduct generated from DDQ, giving an inseparable 6:1 mixture of **36** and 11-*epi*-**36**; this epimeric mixture was converted through a three-step sequence into a separable mixture of **39** and 11-*epi*-**39**, the former of which was then successfully transformed into pteridic acid A (**1**) by saponification. Although the previous synthetic efforts failed to produce **2** in its chemically pure form due to its paucity,[4] the observation that **39** and 11-*epi*-**39** were separable, helped us chose **39** as a suitable epimerization substrate for the synthesis of **2**. Our literature search for reaction conditions used for analogous conversions suggested the utilization of $MgBr_2$, which had previously been employed as catalyst for the epimerization of a spiroacetal intermediate in the total synthesis of pinnatoxin A by Kishi et al.[18] Gratifyingly, treatment of a solution of **39** in CH_2Cl_2 with 3–4 equivalents of anhydrous $MgBr_2$ at room temperature brought about clean equilibration to give a separable 3:2 mixture of **39** and 11-*epi*-**39** without formation of any other detectable product (Scheme 8). Increasing the amount



Scheme 8. Synthesis of pteridic acid B (**2**) by epimerization of intermediate **39**: a) $MgBr_2$, CH_2Cl_2, RT, 3 h (40% for 11-*epi*-**39**, 60% for **39**); b) KOH, H_2O, MeOH, 6 h (99%).

of the Lewis acid catalyst did not improve the outcome, but merely promoted the gradual decomposition of the products, as judged by TLC monitoring. This successful equilibration yielding a considerably high proportion of anomerically disfavored 11-*epi*-**39** is in sharp contrast to the exclusive formation of anomerically favored spirocyclic compound **34** on treatment of **33** with a protic acid (PPTS in toluene, Scheme 7), which might allow us to assume some kind of positive participation of Mg^{2+} to promote the production of 11-*epi*-**39**. It might be possible to presume the intervention of a chelation-stabilized species, such as **41**, which could be formed from **39** through Lewis acid catalyzed epimerization at the spirocenter and conformational change at both of the two rings (Scheme 9). The conformation of **41** should be suitable for the formation of the magnesium chelate between the C9- and the C15-oxygen functionalities while



Scheme 9. A plausible mechanism for the formation of the anomerically disfavored spiroacetal, 11-*epi*-**39**.

keeping the anomerically favored conformation at the spirocenter. Quenching the equilibrium mixture with aqueous $NaHCO_3$ would then have led to the irreversible 3:2 mixture of the starting spiroacetal **39** and the epimerization product (11-*epi*-**39**, generated by an additional conformational change at the tetrahydropyran ring of **41** after the basic workup), probably reflecting the equilibrium ratio between some kind of magnesium complex of **39** and the chelation-stabilized intermediate **41**. Chromatographic separation of the mixture enabled us to isolate **39** (60%) and 11-*epi*-**39** (40%), the latter of which was then hydrolyzed to furnish pteridic acid B (**2**, $[\alpha]_D^{24} = -20.2$ ($c = 0.05$ in $CHCl_3$); lit.[1] $[\alpha]_D^{24} = -20.8$ ($c = 0.68$ in $CHCl_3$)). The ^1H and ^{13}C NMR spectra of **2** were identical to those of natural pteridic acid B.[1]

Conclusion

The enantioselective total synthesis of pteridic acid A (**1**) employing the $Sn(OTf)_2$-mediated Evans aldol reaction of oxazolidinone **7** with aldehyde **8** and the Fukuyama coupling reaction of thiol ester intermediate **30** with acetylene **27** as the key C–C bond-forming steps was accomplished in 22% overall yield from **7** through a considerably short 14-step sequence. $MgBr_2$-mediated equilibration of the spirocyclic intermediate **39** brought about partial epimerization of the spirocenter to give anomerically disfavored 11-*epi*-**39**, which was then converted into pteridic acid B (**2**).

Experimental Section

General methods: IR spectra were measured by a Jasco FTIR-4100 spectrometer. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer (300 MHz for ^1H and

75 MHz for ^{13}C NMR spectra), a Varian UNITY plus-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C NMR spectra), or a Varian UNITY plus-600 spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C NMR spectra). Optical rotation values were measured with a Jasco DIP-371 polarimeter, and mass spectra were obtained with a Jeol JMS-700 spectrometer operated in the EI or FAB mode. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography. Solvents for reactions were distilled prior to use: THF from Na and benzophenone, MeOH from Mg and I_2, CH_2Cl_2 and DMF from CaH_2, and toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

(2*S*,4*R*,5*S*,6*S*)-1-[(*S*)-4-Benzyl-2-oxooxazolidin-3-yl]-5-hydroxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylheptane-1,3-dione (9): Et_3N (1.21 mL, 8.71 mmol) was added to a stirred suspension of stannous triflate (3.03 g, 7.26 mmol) in CH_2Cl_2 (30 mL) at room temperature. The resultant pale yellow slurry was immediately cooled to −20 °C and stirred for 10 min before a solution of **7** (1.40 g, 4.84 mmol) in CH_2Cl_2 (12 mL) was added dropwise over 5 min. The resulting almost clear solution was stirred at −20 °C for 1 h and then cooled to −78 °C. A solution of **8** (1.13 g, 5.81 mmol) in CH_2Cl_2 (5 mL) was then added to the solution, and the resulting mixture was stirred at −78 °C for a further 2 h before being poured into a vigorously stirred mixture of CH_2Cl_2 (200 mL) and $NaHSO_4$ (1 M, 200 mL) at 0 °C. The mixture was stirred for 30 min and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **9** (1.98 g, 82 %) as a pale yellow oil. The ^{1}H NMR spectrum indicated that the product was a mixture of **9** and its (4*S*,5*R*)-diastereomer. $[\alpha]_D^{24} = +36.3$ ($c = 1.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 7.1$ Hz, 3H), 1.47 (d, $J = 7.2$ Hz, 3H), 1.85–1.95 (m, 1H), 2.76 (dd, $J = 13.5$, 9.6 Hz, 1H), 2.91 (dq, $J = 3.0$, 7.1 Hz, 1H), 3.30 (dd, $J = 13.5$, 3.6 Hz, 1H), 3.42 (d, $J = 2.6$ Hz, 1H; OH), 3.54 (d, $J = 5.8$ Hz, 2H), 3.80 (s, 3H), 3.90 (ddd, $J = 8.8$, 3.0, 2.6 Hz, 1H), 4.11–4.24 (m, 2H), 4.45 (s, 2H), 4.67–4.76 (m, 1H), 4.94 (q, $J = 7.2$ Hz, 1H), 6.87 (deformed d, $J = 8.5$ Hz, 2H), 7.18–7.37 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.0$, 13.4, 13.9, 35.9, 37.9, 47.4, 50.9, 55.3, 55.4, 66.4, 73.1, 74.1, 74.5, 113.8, 127.4, 129.0, 129.3, 129.4, 130.0, 135.0, 153.6, 159.2, 170.5, 210.4 ppm; IR (film): $\tilde{\nu} = 3475$ (m), 3050 (w), 3020 (w), 1770 (vs), 1710 (s), 1690 (s), 1610 (m), 1510 (s), 1240 (s), 755 cm^{-1} (s); HRMS (FAB): *m*/*z*: calcd for $C_{28}H_{35}NO_7Na$: 520.2311; found: 520.2313 $[M+Na]^+$.

(*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*,5*S*,6*S*)-3,5-dihydroxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylheptanoyl]oxazolidin-2-one (10): To stirred acetic acid (neat, 80 mL) was added portionwise $NaBH_4$ (1.87 g, 50 mmol) at 0 °C. After hydrogen evolution ceased, the mixture was warmed to room temperature, and stirred for 1 h. To this solution was added a solution of **9** (2.40 g, 4.95 mmol) in acetic acid (28 mL) over a period of 5 min, and the resulting mixture was stirred for 1.5 h, and then concentrated in vacuo. The resulting oily product was diluted with toluene, concentrated again in vacuo to remove residual acetic acid, and finally mixed with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 3:1) to give **10** (2.28 g, 92 %) as a colorless oil. The ^{1}H NMR spectrum indicated that the product contained the (5*R*)-isomer of **10** (**10**/(5*R*)-**10** approximately 10:1) together with a minute amount of other diastereomers. $[\alpha]_D^{24} = +30.0$ ($c = 1.40$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.72$ (d, $J = 7.2$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 1.32 (d, $J = 6.9$ Hz, 3H), 1.26 (s, 1H; OH), 1.67–1.76 (m, 1H), 1.93–2.05 (m, 1H), 2.78 (dd, $J = 13.4$, 9.3 Hz, 1H), 3.27 (dd, $J = 13.4$, 3.3 Hz, 1H), 3.46 (t, $J = 9.1$ Hz, 1H), 3.57 (dd, $J = 9.1$, 3.8 Hz, 1H), 5.59 (d, $J = 4.9$ Hz, 1H; OH), 3.80 (s, 3H), 3.89–4.06 (m, 3H), 4.13–4.22 (m, 2H), 4.42 (d, $J = 11.4$ Hz, 1H), 4.48 (d, $J = 11.4$ Hz, 1H), 4.62–4.70 (m, 1H), 6.88 (deformed d, $J = 8.5$ Hz, 2H), 7.16–7.37 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.3$, 11.6, 12.9, 35.6, 36.5, 37.6, 40.2, 55.2 (two overlapping peaks), 66.0, 69.6, 73.1, 74.2, 76.1, 113.9, 127.4, 129.0, 129.4, 129.5, 129.6, 135.2, 153.0, 159.4, 177.5 ppm; IR (film): $\tilde{\nu} = 3450$ (m), 3050 (w), 1770 (vs), 1685 (s), 1605 (s), 1505 (s), 1240 (s), 750 cm^{-1} (s); HRMS (FAB): *m*/*z*: calcd for $C_{28}H_{37}NO_7Na$: 522.2468; found: 522.2471 $[M+Na]^+$.

(*S*)-4-Benzyl-3-((*S*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}propanoyl)oxazolidin-2-one (11): $TsOH{\cdot}H_2O$ (25 mg, 0.13 mmol) was added to a stirred solution of **10** (665 mg, 1.33 mmol) and 2,2-dimethoxypropane (5 mL) in acetone (5 mL) at room temperature. After 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 3:1) to give **11** (688 mg, 96 %) as a pale yellow oil. $[\alpha]_D^{24} = +37.1$ ($c = 1.10$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.26 (s, 3H), 1.27 (d, $J = 7.1$ Hz, 3H), 1.29 (s, 3H), 1.76–1.88 (m, 1H), 1.88–1.99 (m, 1H), 2.76 (dd, $J = 13.5$, 9.9 Hz, 1H), 3.32 (dd, $J = 13.5$, 3.0 Hz, 1H), 3.38 (dd, $J = 8.5$, 6.0 Hz, 1H), 3.53 (dd, $J = 8.5$, 3.0 Hz, 1H), 3.56–3.64 (m, 2H), 3.80 (s, 3H), 4.01 (dq, $J = 4.7$, 7.1 Hz, 1H), 4.09–4.20 (m, 2H), 4.41 (s, 2H), 4.59–4.67 (m, 1H), 6.86 (deformed d, $J = 8.8$ Hz, 2H), 7.20–7.38 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.6$, 11.8, 13.2, 23.6, 24.9, 33.7, 34.8, 37.7, 41.2, 55.2, 55.8, 66.0, 70.0, 72.1, 72.8, 75.7, 100.6, 113.7, 127.4, 129.0, 129.2, 129.5, 131.1, 135.5, 153.3, 159.1, 175.0 ppm; IR (film): $\tilde{\nu} = 3060$ (w), 1780 (vs), 1700 (s), 1615 (m), 1515 (s), 1250 (s), 760 cm^{-1} (s); HRMS (FAB): *m*/*z*: calcd for $C_{31}H_{42}NO_7$: 540.2961; found: 540.2961 $[M+H]^+$.

(*R*)-2-{(4*S*,5*S*,6*S*)-6-[(*S*)-2-(4-Methoxybenzyloxy)-1-methylethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-1-propanol (12): $LiBH_4$ (63 mg, 2.89 mmol) was added portionwise to a stirred solution of **11** (788 mg, 1.45 mmol) and MeOH (0.12 mL) in THF (3 mL) at 0 °C, and the resulting mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with saturated aqueous Rochelle's salt, and the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **12** (411 mg, 78 %) as a pale yellow oil. $[\alpha]_D^{24} = +0.55$ ($c = 1.37$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 1.27 (s, 3H), 1.34 (s, 3H), 1.76–1.95 (m, 3H), 2.42–2.53 (br s, 1H; OH), 3.39 (dd, $J = 8.8$, 6.0 Hz, 1H), 3.48–3.55 (m, 2H), 3.57–3.68 (m, 3H), 3.80 (s, 3H), 4.41 (s, 2H), 6.88 (deformed d, $J = 8.5$ Hz, 2H), 7.26 ppm (deformed d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.7$, 12.1, 13.4, 23.5, 24.9, 33.7, 34.1, 37.6, 55.2, 67.0, 70.2, 72.0, 72.8, 77.8, 100.6, 113.6, 129.1, 130.9, 159.0 ppm; IR (film): $\tilde{\nu} = 3420$ (m), 1610 (m), 1510 (s), 1250 (vs), 1220 (s), 1035 (s), 760 cm^{-1} (s); HRMS (FAB): *m*/*z*: calcd for $C_{21}H_{35}O_5$: 367.2484; found: 367.2487 $[M+H]^+$.

(*S*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-Methoxybenzyloxy)-1-methylethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}propanal (13): Dess–Martin periodinane (463 mg, 1.09 mmol) was added portionwise to a stirred solution of **12** (286 mg, 0.78 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give (267 mg, 94 %) of **13** as a pale yellow oil. $[\alpha]_D^{24} = +22.0$ ($c = 0.50$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.25 (s, 3H), 1.32 (s, 3H), 1.79–1.95 (m, 2H), 2.42 (ddq, $J = 1.1$, 3.3, 6.9 Hz, 1H), 3.41 (dd, $J = 8.4$, 6.0 Hz, 1H), 3.52 (dd, $J = 8.4$, 3.3 Hz, 1H), 3.62 (dd, $J = 10.7$, 4.4 Hz, 1H), 3.75 (dd, $J = 7.4$, 3.3 Hz, 1H), 3.81 (s, 3H), 4.41 (s, 2H), 6.87 (deformed d, $J = 8.8$ Hz, 2H), 7.25 (deformed d, $J = 8.8$ Hz, 2H), 9.70 ppm (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.8$, 11.8, 13.3, 23.4, 24.6, 33.6, 34.5, 49.0, 55.2, 70.1, 72.0, 72.9, 74.1, 100.9, 113.7, 129.2, 131.1, 159.2, 204.6 ppm; IR (film): $\tilde{\nu} = 2720$ (w), 1725 (s), 1610 (m), 1510 (s), 1250 (s), 1220 cm^{-1} (s); HRMS (FAB): *m*/*z*: calcd for $C_{21}H_{32}O_5Na$: 387.2147; found: 387.2148 $[M+Na]^+$.

Methyl (2*R*,3*R*)-3-(1-ethoxyethoxy)-2-ethylbutanoate (15): Ethyl vinyl ether (1.48 g, 20.5 mmol) was added dropwise to a stirred solution of **14** (1.00 g, 6.84 mmol) and PPTS (0.17 g, 0.68 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 24 h. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concen-

trated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 6:1) to give (1.49 g, quant) of **15**. $[\alpha]_D^{24}=-5.51$ ($c=1.70$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.89$ (t, $J=7.4$ Hz, 1.5H), 0.90 (t, $J=7.4$ Hz, 1.5H), 1.15 (d, $J=6.3$ Hz, 1.5H), 1.18 (t, $J=7.0$ Hz, 1.5H), 1.19 (t, $J=7.0$ Hz, 1.5H), 1.22 (d, $J=6.3$ Hz, 1.5H), 1.23 (d, $J=5.5$ Hz, 1.5H), 1.29 (d, $J=5.5$ Hz, 1.5H), 1.50–1.61 (m, 2H), 2.36–2.47 (m, 1H), 3.41 (dq, $J=9.2$, 7.0 Hz, 0.5H), 3.49 (dq, $J=9.2$, 7.0 Hz, 0.5H), 3.60 (dq, $J=9.2$, 7.0 Hz, 0.5H), 3.61 (dq, $J=9.2$, 7.0 Hz, 0.5H), 3.69 (s, 3H), 3.80 (dq, $J=8.1$, 6.3 Hz, 0.5H), 3.91 (dq, $J=8.1$, 6.3 Hz, 0.5H), 4.68 (q, $J=5.5$ Hz, 0.5H), 4.75 ppm (q, $J=5.5$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.8$, 11.9, 15.1, 15.2, 17.6, 18.8, 20.3, 20.5, 21.1, 21.2, 51.2 (two overlapping peaks), 54.2, 54.3, 59.8, 60.0, 72.0, 75.2, 97.9, 100.7, 174.9, 175.7 ppm; IR (film): $\tilde{\nu}=1730$ (s), 1190 (m), 1080 cm^{-1} (m); HRMS (FAB): m/z: calcd for $C_{11}H_{22}O_4Na$: 241.1416; found: 241.1422 $[M+Na]^+$.

(2*S*,3*R*)-3-(1-Ethoxyethoxy)-2-ethyl-1-butanol (16): DIBAL (1M in hexane, 20 mL, 20 mmol) was added dropwise to a stirred solution of **15** (1.50 g, 6.87 mmol) in CH_2Cl_2 (10 mL) at −78°C. After 24 h, the reaction was quenched with saturated aqueous potassium sodium tartrate and the mixture was warmed gradually to room temperature and stirred for 24 h. After this time, the mixture was extracted with EtOAc, and the extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **16** (1.56 g, quant). $[\alpha]_D^{24}=-28.3$ ($c=2.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.96$ (t, $J=7.2$ Hz, 3H), 1.20 (t, $J=7.0$ Hz, 1.5H), 1.20 (d, $J=6.0$ Hz, 1.5H), 1.22 (t, $J=7.0$ Hz, 1.5H), 1.28 (d, $J=6.0$ Hz, 1.5H), 1.31 (d, $J=5.2$ Hz, 1.5H), 1.32 (d, $J=5.2$ Hz, 1.5H), 1.30–1.48 (m, 3H), 2.70 (dd, $J=6.6$, 5.1 Hz, 0.5H; OH), 3.17 (dd, $J=8.1$, 5.1 Hz, 0.5H; OH), 3.44–3.68 (m, 3H), 3.68–3.81 (m, 1H), 3.84–3.97 (m, 1H), 4.69 (q, $J=5.2$ Hz, 0.5H), 4.70 ppm (q, $J=5.2$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.7$, 11.8, 15.1 (two overlapping peaks), 18.3, 19.4, 20.3, 20.5, 21.0, 21.2, 47.6, 48.0, 60.3, 60.9, 61.6, 62.5, 74.4, 77.2, 98.2, 100.5 ppm; IR (film): $\tilde{\nu}=3425$ (m), 1130 (s), 1080 (s), 1050 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{10}H_{23}O_3$: 191.1647; found: 191.1651 $[M+H]^+$.

(2*R*,3*R*)-3-(1-Ethoxyethoxy)-2-ethylbutanal (17): A solution of dimethyl sulfoxide (1.53 g, 19.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of oxalyl chloride (1.24 g, 9.81 mmol) in CH_2Cl_2 (10 mL) at −78°C, and the mixture was stirred for 30 min. After this time, a solution of **16** (1.56 g, 8.17 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the mixture at −78°C. After 1.5 h, Et_3N (4.56 mL, 32.7 mmol) was added dropwise, and the resulting mixture was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **17** (1.56 g, quant). $[\alpha]_D^{24}=-27.0$ ($c=1.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.93$ (t, $J=7.5$ Hz, 3H), 1.19 (t, $J=7.1$ Hz, 1.5H), 1.196 (d, $J=6.3$ Hz, 1.5H), 1.198 (t, $J=7.1$ Hz, 1.5H), 1.26 (d, $J=6.3$ Hz, 1.5H), 1.286 (d, $J=5.2$ Hz, 1.5H), 1.288 (d, $J=5.2$ Hz, 1.5H), 1.51–1.65 (m, 1H), 1.65–1.80 (m, 1H), 2.18–2.32 (m, 1H), 3.41–3.54 (m, 1H), 3.54–3.67 (m, 1H), 3.94 (quin, $J=6.3$ Hz, 0.5H), 4.06 (quin, $J=6.3$ Hz, 0.5H), 4.72 (q, $J=5.2$ Hz, 0.5H), 4.77 (q, $J=5.2$ Hz, 0.5H), 9.69 (d, $J=3.3$ Hz, 0.5H), 9.70 ppm (d, $J=3.3$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.59$, 11.64, 15.1, 15.2, 17.9, 18.7, 19.1, 19.2, 20.1, 20.3, 59.4, 59.6, 59.8, 59.9, 70.6, 73.0, 97.5, 100.2, 204.9, 205.1 ppm; IR (film): $\tilde{\nu}=2720$ (w), 1720 (s), 1135 (s), 1080 (s), 1060 cm^{-1} (m); HRMS (FAB): m/z: calcd for $C_{10}H_{19}O_3$: 187.1334; found: 187.1348 $[M-H]^-$.

(3*S*,4*R*)-4-(1-Ethoxyethoxy)-3-ethyl-1-iodo-1-pentene (18): NaHMDS (1M in THF, 1.03 mL, 1.03 mmol) was added dropwise to a stirred suspension of iodomethyltriphenylphosphonium iodide (0.55 g, 1.03 mmol) in THF (3.9 mL) at room temperature. After 10 min, a solution of **17** (0.16 g, 0.82 mmol) in THF (1 mL) was added dropwise at −20°C and the resulting mixture was stirred for 3 h before being gradually warmed to room temperature. Hexane (5 mL), Celite (1.5 g) and water (0.5 mL) were then successively added to the mixture and the resulting slurry was stirred for a few minutes. After filtration, the filtrate was concentrated in vacuo and the resulting residue was diluted with water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 20:1) to give **18** (0.18 g, 68%) as a pale yellow oil. $[\alpha]_D^{24}=+33.1$ ($c=2.63$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$ (t, $J=7.5$ Hz, 1.5H), 0.91 (t, $J=7.5$ Hz, 1.5H), 1.09 (d, $J=6.3$ Hz, 1.5H), 1.15 (d, $J=6.3$ Hz, 1.5H), 1.20 (t, $J=7.2$ Hz, 1.5H), 1.21 (t, $J=7.2$ Hz, 1.5H), 1.29 (d, $J=5.2$ Hz, 1.5H), 1.31 (d, $J=5.2$ Hz, 1.5H), 1.38–1.54 (m, 1H), 1.54–1.70 (m, 1H), 2.39–2.50 (m, 1H), 3.42–3.58 (m, 1H), 3.58–3.70 (m, 1H), 3.71 (dq, $J=3.3$, 6.3 Hz, 0.5H), 3.80 (dq, $J=3.3$, 6.3 Hz, 0.5H), 4.736 (q, $J=5.2$ Hz, 0.5H), 4.743 (q, $J=5.2$ Hz, 0.5H), 6.03 (dd, $J=9.9$, 7.2 Hz, 0.5H), 6.06 (dd, $J=9.9$, 7.2 Hz, 0.5H), 6.346 (d, $J=7.2$ Hz, 0.5H), 6.353 ppm (d, $J=7.2$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.6$, 11.7, 15.1, 15.2, 17.6, 18.5, 20.4, 20.6, 22.6, 23.1, 52.06, 52.11, 59.97, 60.00, 72.4, 74.8, 84.0, 84.2, 97.7, 100.0, 142.2, 142.3 ppm; IR (film): $\tilde{\nu}=3070$ (w), 1610 (w), 1130 (s), 1085 (s), 1055 cm^{-1} (s); HRMS (EI): m/z: calcd for $C_{11}H_{21}IO_2$: 312.0587; found: 312.0589 $[M]^+$.

(3*S*,4*R*)-1,1-Dibromo-4-(1-ethoxyethoxy)-3-ethyl-1-pentene (26): A solution of CBr_4 (2.22 g, 6.69 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred mixture of Ph_3P (3.51 g, 13.0 mmol) and pyridine (1.1 mL) in CH_2Cl_2 (10 mL) at 0°C, and the mixture was stirred for 15 min. A solution of **17** (600 mg, 3.19 mmol) in CH_2Cl_2 (5 mL) was then added, and the resulting mixture was stirred at 0°C for 1.5 h before being diluted with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 20:1) to give **26** (700 mg, 64%) as a pale yellow oil. $[\alpha]_D^{24}=+18.0$ ($c=1.82$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.91$ (t, $J=7.2$ Hz, 1.5H), 0.92 (t, $J=7.2$ Hz, 1.5H), 1.10 (d, $J=6.3$ Hz, 1.5H), 1.17 (d, $J=6.3$ Hz, 1.5H), 1.20 (t, $J=7.0$ Hz, 3H), 1.29 (d, $J=5.2$ Hz, 1.5H), 1.30 (d, $J=5.2$ Hz, 1.5H), 1.35–1.51 (m, 1H), 1.51–1.66 (m, 1H), 2.31–2.42 (m, 1H), 3.43–3.54 (m, 1H), 3.57–3.68 (m, 1H), 3.69 (dq, $J=3.6$, 6.3 Hz, 0.5H), 3.79 (dq, $J=3.6$, 6.3 Hz, 0.5H), 4.69 (q, $J=5.2$ Hz, 0.5H), 4.73 (q, $J=5.2$ Hz, 0.5H), 6.30 (d, $J=9.9$ Hz, 0.5H), 6.33 ppm (d, $J=9.9$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=11.7$, 11.8, 15.19, 15.24, 17.9, 19.0, 20.3, 20.5, 23.1, 23.4, 51.66, 51.68, 59.8, 59.9, 71.9, 74.5, 89.2, 89.4, 97.6, 100.3, 139.8, 140.0 ppm; IR (film): $\tilde{\nu}=1130$ (s), 1090 (s), 1060 (m), 760 (s), 670 cm^{-1} (m); HRMS (EI): m/z: calcd for $C_{11}H_{20}{}^{79}Br_2O_2$: 341.9830; found: 341.9837 $[M]^+$.

(3*S*,4*R*)-4-(1-Ethoxyethoxy)-2-ethyl-1-pentyne (27): *n*BuLi (1.6M in hexane, 5.11 mL, 8.18 mmol) was added dropwise to a stirred solution of **26** (700 mg, 2.05 mmol) in THF (4 mL) at −78°C, and the solution was stirred for 24 h. After this time, the reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated at atmospheric pressure. The residue was chromatographed over silica gel (pentane/ether 20:1) to give **27** (297 mg, 79%) as a pale yellow oil. $[\alpha]_D^{24}=+22.2$ ($c=1.65$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.040$ (t, $J=7.4$ Hz, 1.5H), 1.044 (t, $J=7.4$ Hz, 1.5H), 1.195 (t, $J=7.1$ Hz, 1.5H), 1.203 (t, $J=7.1$ Hz, 1.5H), 1.21 (d, $J=6.2$ Hz, 1.5H), 1.26 (d, $J=6.2$ Hz, 1.5H), 1.31 (d, $J=5.2$ Hz, 1.5H), 1.32 (d, $J=5.2$ Hz, 1.5H), 1.36–1.55 (m, 1H), 1.55–1.71 (m, 1H), 2.08 (d, $J=2.5$ Hz, 0.5H), 2.09 (d, $J=2.5$ Hz, 0.5H), 2.35–2.47 (m, 1H), 3.45–3.56 (m, 1H), 3.58–3.71 (m, 1H), 3.79 (dq, $J=4.2$, 6.2 Hz, 0.5H), 3.83 (dq, $J=4.2$, 6.2 Hz, 0.5H), 4.77 (q, $J=5.2$ Hz, 0.5H), 4.78 ppm (q, $J=5.2$ Hz, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=12.0$, 12.1, 15.2 (two overlapping peaks), 16.9, 18.0, 20.3, 20.5, 22.4, 22.6, 39.8, 40.0, 59.8, 60.2, 70.5 (two overlapping peaks), 72.4, 74.3, 85.2, 98.3, 99.9 ppm; IR (film): $\tilde{\nu}=3300$ (m), 2250 (w), 2110 (w), 1125 (s), 1080 (s), 1060 (s), 760 cm^{-1} (vs); HRMS (FAB): m/z: calcd for $C_{11}H_{19}O_2$: 183.1385; found: 183.1386 $[M-H]^-$.

***S*-Dodecyl (*S*)-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}propanethioate (30)**: *n*BuLi (1.6M in hexane, 0.66 mL, 1.06 mmol) was added dropwise to a stirred solution of dodecanethiol (225 mg, 1.11 mmol) in THF (3.5 mL) at −5°C. After 30 min, the reaction mixture was cooled to −78°C and a solution of **11** (150 mg, 0.278 mmol) in THF (1 mL) was added. The resulting solution was stirred for 2 h at −78°C and was then gradually warmed to 0°C over a period of 3 h before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt, and the extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue

was chromatographed over silica gel (hexane/EtOAc 20:1) to give **30** (120 mg, 77%) as a pale yellow oil. $[\alpha]_D^{24} = +18.2$ ($c = 6.35$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.9$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 3H), 1.18–1.37 (m, 21H), 1.31 (s, 3H), 1.48–1.60 (m, 2H), 1.75–1.93 (m, 2H), 2.72 (quin, $J = 6.9$ Hz, 1H), 2.82 (dt, $J = 13.2$, 7.1 Hz, 1H), 2.91 (dt, $J = 13.2$, 7.1 Hz, 1H), 3.39 (dd, $J = 8.8$, 6.3 Hz, 1H), 3.53 (dd, $J = 8.8$, 2.7 Hz, 1H), 3.58 (dd, $J = 6.9$, 5.8 Hz, 1H), 3.62 (dd, $J = 10.7$, 4.1 Hz, 1H), 3.81 (s, 3H), 4.41 (s, 2H), 6.87 (deformed d, $J = 8.8$ Hz, 2H), 7.25 ppm (deformed d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.9$, 12.6, 13.2, 14.0, 22.6, 23.7, 24.9, 28.7, 28.8, 29.0, 29.2, 29.4 (two overlapping peaks), 29.48, 29.53 (two overlapping peaks), 31.8, 33.6, 35.4, 52.4, 55.2, 69.9, 72.1, 72.8, 76.2, 100.8, 113.7, 129.2, 131.1, 159.2, 201.9 ppm; IR (film): $\tilde{\nu} = 1680$ (s), 1610 (m), 1510 (s), 1250 (s), 1220 cm^{-1} (s); HRMS (EI): m/z: calcd for $C_{33}H_{56}O_5S$: 564.3848; found: 564.3852 $[M]^+$.

(2*S*,6*S*,7*R*)-7-(1-Ethoxyethoxy)-6-ethyl-2-{(4*R*,5*R*,6*S*)-6-[(*S*)-2-(4-methoxybenzyloxy-1-methylethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl]-4-octyn-3-one (29): A solution of **30** (120 mg, 0.212 mmol) in DMF (0.5 mL) was added to a stirred mixture of $[PdCl_2(dppf)]$ (17 mg, 0.020 mmol), CuI (69 mg, 0.36 mmol), tri(2-furyl)phosphine (12 mg, 0.050 mmol), and Et_3N (0.3 mL) in DMF (1.0 mL) at room temperature. A solution of **27** (74 mg, 0.404 mmol) in DMF (0.3 mL) was then added at 50 °C, and the resulting mixture was stirred for 3 h. After this time, the mixture was diluted with EtOAc and brine, and was filtered through a Celite pad. The filtrate was extracted with EtOAc, and the extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 20:1) to give **29** (45 mg, 39%) as a pale yellow oil together with recovered **30** (74 mg, 61%). The recovered thiol ester was retreated with same reaction conditions to give a mixture of **29** and **30**, the latter of which was, after chromatographic separation, treated once more to the same operation to eventually provide a maximum yield of **29** (96 mg, 83% in total). $[\alpha]_D^{24} = +11.4$ ($c = 4.65$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.05 (t, $J = 7.4$ Hz, 3H), 1.16–1.37 (m, 18H), 1.45–1.96 (m, 4H), 2.52–2.65 (m, 2H), 3.39 (dd, $J = 8.8$, 6.0 Hz, 1H), 3.44–3.65 (m, 4H), 3.76–3.95 (m, 2H), 3.81 (s, 3H), 4.41 (s, 2H), 4.75 (q, $J = 5.4$ Hz, 0.5H), 4.76 (q, $J = 5.4$ Hz, 0.5H), 6.87 (deformed d, $J = 8.8$ Hz, 2H), 7.25 ppm (deformed d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.5$, 11.6, 12.2, 13.3, 15.2, 17.2 (0.5C), 18.3 (0.5C), 20.2 (0.5C), 20.4 (0.5C), 22.0 (0.5C), 22.4 (0.5C), 23.5, 24.6, 33.7, 35.1, 40.4 (0.5C), 40.7 (0.5C), 51.6, 55.2, 59.8 (0.5C), 60.0 (0.5C), 70.0, 72.1, 72.9, 73.3 (0.5C), 73.6 (0.5C), 75.0, 77.2, 96.1, 98.1 (0.5C), 99.9 (0.5C), 100.8, 113.7, 129.2, 131.0, 159.2, 186.2 ppm; IR (film): $\tilde{\nu} = 2200$ (m), 1670 (s), 1610 (m), 1510 (vs), 1250 (vs), 1225 (vs), 1080 cm^{-1} (vs); HRMS (FAB): m/z: calcd for $C_{32}H_{50}O_7Na$: 569.3454; found: 569.3459 $[M+Na]^+$.

(2*S*,3*S*,4*R*,5*S*,6*S*)-2-[(3*S*,4*R*)-3-Ethyl-4-hydroxy-1-pentynyl]-2-methoxy-6-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-3,5-dimethyltetrahydropyran-4-ol (32): Camphorsulfonic acid (1.3 mg, 5.5 μmol) was added to a stirred solution of **29** (12 mg, 22 μmol) and MeOH (0.2 mL) in CH_2Cl_2 (1.5 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 3 d. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 5:1) to give **32** (9.0 mg, 91%) as a pale yellow oil. The ^1H NMR spectrum indicated that the product was a 3:1 mixture of **32** and its C2-epimer. $[\alpha]_D^{24} = -65.4$ ($c = 1.65$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 1.05 (t, $J = 7.2$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.27 (d, $J = 6.9$ Hz, 3H), 1.50–1.64 (m. 3H), 1.75–1.95 (br s, 2H; 2×OH), 1.88–2.03 (m, 2H), 2.32–2.41 (m, 1H), 3.25 (s, 3H), 3.52–3.58 (m, 3H), 3.72–3.81 (m, 2H), 3.81 (s, 3H), 4.41 (s, 2H), 6.87 (deformed d, $J = 8.8$ Hz, 2H), 7.25 ppm (deformed d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.3$, 11.9, 12.3, 13.1, 21.2, 24.3, 34.7, 35.5, 41.7, 42.3, 50.2, 55.2, 69.0, 71.7, 71.9, 72.2, 72.7, 81.7, 84.1, 98.8, 113.7, 129.1, 130.9, 159.1 ppm; IR (film): $\tilde{\nu} = 3400$ (s), 2230 (w), 1610 (s), 1510 (s), 1250 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{26}H_{40}O_6Na$: 471.2723; found: 471.2727 $[M+Na]^+$.

(2*R*,3*S*,4*R*,5*S*,6*S*)-2-[(1*Z*,3*S*,4*R*)-3-Ethyl-4-hydroxy-1-pentenyl]-2-methoxy-6-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-3,5-dimethyltetrahydropyran-4-ol (33): A mixture of **32** (28 mg, 0.062 mmol), Lindlar's catalyst (approximately 200 mg) and 1-hexene (0.5 mL) in EtOAc (1 mL) was vigorously stirred for 15 min at room temperature under a hydrogen atmosphere. After this time, the mixture was filtered through a Celite pad and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 5:1) to give **33** (25 mg, 89%) as a pale yellow oil. $[\alpha]_D^{24} = -62.6$ ($c = 1.65$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.50–1.81 (m, 4H; H-3+OH), 1.88–2.05 (m, 2H), 2.60–2.73 (m, 1H), 3.04 (br s, 1H; OH), 3.15 (s, 3H), 3.41 (dd, $J = 7.7$, 6.0 Hz, 1H), 3.51–3.58 (m, 2H), 3.71–3.88 (m, 2H), 3.79 (s, 3H), 4.36 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 11.5$ Hz, 1H), 5.36 (dd, $J = 12.1$, 10.9 Hz, 1H), 5.72 (d, $J = 12.1$ Hz, 1H), 6.86 (deformed d, $J = 8.5$ Hz, 2H), 7.23 ppm (deformed d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.1$, 11.4, 12.0, 13.3, 21.9, 24.5, 35.1, 35.6, 41.9, 48.2, 48.6, 55.2, 69.4, 71.9, 72.3, 72.4, 72.6, 102.7, 113.7, 129.2, 130.9, 133.4, 137.1, 159.1 ppm; IR (film): $\tilde{\nu} = 3425$ (m), 1610 (m), 1510 (s), 1250 (s), 1035 (s), 760 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{26}H_{42}O_6Na$: 473.2879; found: 473.2882 $[M+Na]^+$.

(2*S*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Ethyl-2-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-4-ol (34): A catalytic amount of PPTS was added to a stirred solution of **33** (25 mg, 0.056 mmol) in toluene (1.5 mL) and the mixture was stirred at room temperature for 1 h. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 5:1) to give 23 mg (99%) of **34** as a pale yellow oil. $[\alpha]_D^{24} = -5.3$ ($c = 1.55$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.941 (d, $J = 6.9$ Hz, 3H), 0.944 (t, $J = 7.4$ Hz, 3H), 1.26 (s, 1H; OH), 1.31 (d, $J = 6.6$ Hz, 3H), 1.47 (quin, $J = 7.4$ Hz, 2H), 1.55–1.71 (m, 2H), 1.87–1.97 (m, 1H), 1.97–2.07 (m, 1H), 3.29 (dd, $J = 8.9$, 7.2 Hz, 1H), 3.58 (dd, $J = 8.9$, 3.3 Hz, 1H), 3.77–3.87 (m, 2H), 3.80 (s, 3H), 3.93 (q, $J = 6.6$ Hz, 1H), 4.36 (s, 2H), 5.53 (dd, $J = 10.3$, 1.3 Hz, 1H), 5.99 (ddd, $J = 10.3$, 5.4, 0.8 Hz, 1H), 6.86 (deformed d, $J = 8.6$ Hz, 2H), 7.24 ppm (deformed d, $J = 8.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.3$, 11.8, 12.4, 13.3, 21.7, 26.1, 35.3, 36.0, 40.2, 40.9, 55.2, 71.2, 71.9, 72.5 (three overlapping peaks), 96.8, 113.7, 127.9, 129.3, 130.1, 131.0, 159.1 ppm; IR (film): $\tilde{\nu} = 3450$ (m), 3030 (w), 1610 (m), 1510 (s), 1250 (s), 1030 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{25}H_{38}O_5Na$: 441.2617; found: 441.2623 $[M+Na]^+$.

(2*S*,3*R*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Ethyl-2-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-4-yl acetate (35): Acetic anhydride (20 μL, 0.21 mmol) and a catalytic amount of DMAP was added to a stirred solution of **34** (10 mg, 0.024 mmol) in pyridine (0.3 mL) at room temperature. After 24 h, the mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **35** (11 mg quant) as a pale yellow oil. $[\alpha]_D^{24} = -17.0$ ($c = 1.65$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.93 (t, $J = 7.4$ Hz, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.40–1.51 (m, 2H), 1.61–1.70 (m, 1H), 1.80 (dq, $J = 11.6$, 6.6 Hz, 1H), 1.84–1.95 (m, 1H), 2.06 (s, 3H), 2.11–2.20 (m, 1H), 3.27 (dd, $J = 8.7$, 7.5 Hz, 1H), 3.59 (dd, $J = 8.7$, 3.3 Hz, 1H), 3.80 (s, 3H), 3.88 (dd, $J = 10.5$, 2.1 Hz, 1H), 3.94 (q, $J = 6.8$ Hz, 1H), 4.36 (s, 2H), 5.07 (dd, $J = 11.6$, 4.7 Hz, 1H), 5.54 (dd, $J = 10.2$, 1.4 Hz, 1H), 6.00 (ddd, $J = 10.2$, 5.8, 0.8 Hz, 1H), 6.86 (deformed d, $J = 8.8$ Hz, 2H), 7.24 ppm (deformed d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.2$, 11.8, 12.4, 13.3, 21.0, 21.7, 26.0, 33.4, 35.3, 38.0, 40.8, 55.2, 71.2, 71.3, 72.5 (two overlapping peaks), 75.4, 96.7, 113.7, 127.5, 129.2, 130.6, 131.0, 159.1, 170.7 ppm; IR (film): $\tilde{\nu} = 3020$ (w), 1735 (s), 1610 (m), 1510 (s), 1230 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{27}H_{40}O_6Na$: 483.2723; found: 483.2727 $[M+Na]^+$.

(2*S*,3*R*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Ethyl-2-[(*S*)-2-hydroxy-1-methylethyl]-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-4-yl acetate (36): DDQ (25 mg,

0.11 mmol) was added to a stirred mixture of **35** (36.0 mg, 0.078 mmol) and water (0.2 mL) in CH_2Cl_2 (1 mL) at 0 °C. After 1 h, the mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 30:1) to give 23 mg (86 %) of **36** as a pale yellow oil. $[\alpha]_D^{24} = -21.9$ ($c = 1.15$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.77$ (d, $J = 6.8$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H), 1.26 (br s, 1H; OH), 1.39 (d, $J = 6.8$ Hz, 3H), 1.37–1.53 (m, 2H), 1.68–1.77 (m, 1H), 1.83 (dq, $J = 11.5$, 6.8 Hz, 1H), 1.90–2.01 (m, 1H), 2.07 (s, 3H), 2.12–2.22 (m, 1H), 3.45 (br d, $J = 10.7$ Hz, 1H), 3.64 (dd, $J = 10.7$, 8.5 Hz, 1H), 3.99 (br q, $J = 6.8$ Hz, 1H), 4.01 (dd, $J = 10.2$, 2.5 Hz, 1H), 5.09 (dd, $J = 11.5$, 4.8 Hz, 1H), 5.54 (dd, $J = 10.2$, 1.4 Hz, 1H), 6.03 ppm (ddd, $J = 10.2$, 5.5, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.4$, 11.6, 12.3, 12.7, 21.0, 21.2, 25.9, 33.7, 36.3, 38.1, 40.6, 68.5, 71.7, 74.7, 76.9, 97.0, 126.9, 131.6, 170.7 ppm; IR (film): $\tilde{\nu} = 3500$ (m), 1720 (s), 1240 (s), 1030 (s), 990 (s), 760 cm^{-1} (vs); HRMS (FAB): m/z: calcd for $C_{19}H_{33}O_5$: 341.2328; found: 341.2333 $[M+H]^+$.

(2*R*,3*R*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Ethyl-3,5,8-trimethyl-2-[(*R*)-1-methyl-2-oxoethyl]-1,7-dioxaspiro[5.5]undec-10-en-4-yl acetate (37): Dess–Martin periodinane (43 mg, 0.10 mmol) was added to a stirred solution of **36** (23 mg, 0.068 mmol) and pyridine (30 μL) in CH_2Cl_2 (2 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 10:1) to give **37** (21 mg, 91 %) as a pale yellow oil. $[\alpha]_D^{24} = -40.9$ ($c = 1.05$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (d, $J = 6.8$ Hz, 3H), 0.925 (t, $J = 7.4$ Hz, 3H), 0.929 (d, $J = 7.1$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 1.23 (d, $J = 6.9$ Hz, 3H), 1.39–1.50 (m, 2H), 1.61–1.71 (m, 1H), 1.84 (dq, $J = 11.7$, 6.8 Hz, 1H), 2.08 (s, 3H), 2.14–2.24 (m, 1H), 2.55 (ddq, $J = 10.4$, 3.2, 6.9 Hz, 1H), 3.96 (q, $J = 6.9$ Hz, 1H), 4.24 (dd, $J = 10.4$, 2.2 Hz, 1H), 5.10 (dd, $J = 11.7$, 4.9 Hz, 1H), 5.53 (dd, $J = 10.4$, 1.4 Hz, 1H), 6.00 (ddd, $J = 10.2$, 5.8, 1.1 Hz, 1H), 9.73 ppm (d, $J = 3.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.3$, 9.6, 11.7, 12.3, 21.0, 22.2, 26.0, 33.2, 38.1, 40.7, 47.6, 71.4, 71.5, 74.7, 97.1, 126.9, 131.0, 170.6, 205.2 ppm; IR (film): $\tilde{\nu} = 3030$ (w), 1735 (s), 1730 (s), 1240 (s), 990 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{19}H_{31}O_5$: 339.2172; found: 339.2177 $[M+H]^+$.

Methyl (*S*)-6-[(2*S*,3*R*,4*R*,5*S*,6*R*,8*R*,9*S*)-4-acetoxy-9-ethyl-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-2,4-heptadienoate (38): LiHMDS (1 M in hexane, 36 μL, 0.036 mmol) was added dropwise to a stirred solution of **4** (8.7 mg, 0.037 mmol) in THF (0.3 mL) at −78 °C. After 20 min, **37** (6.0 mg, 0.018 mmol) in THF (0.5 mL) was added and the resulting mixture was stirred at −78 °C for 3 h. After this time, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 50:1) to give **38** (7.0 mg, 94 %) as a pale yellow oil. $[\alpha]_D^{24} = +17.3$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.92 (t, $J = 7.3$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.38–1.49 (m, 2H), 1.58–1.68 (m, 1H), 1.80 (dq, $J = 11.7$, 6.9 Hz, 1H), 2.07 (s, 3H), 2.15–2.25 (m, 1H), 2.37–2.50 (m, 1H), 3.73 (s, 3H), 3.84 (dd, $J = 9.9$, 2.1 Hz, 1H), 3.93 (q, $J = 6.9$ Hz, 1H), 5.06 (dd, $J = 11.7$, 4.8 Hz, 1H), 5.52 (dd, $J = 10.2$, 1.2 Hz, 1H), 5.78 (d, $J = 15.3$ Hz, 1H), 5.97 (ddd, $J = 10.2$, 5.8, 1.0 Hz, 1H), 6.10–6.23 (m, 2H), 7.18 ppm (dd, $J = 15.3$, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 5.2$, 11.8, 12.3, 15.1, 21.0, 22.7, 26.1, 33.5, 38.0, 38.3, 40.8, 51.3, 71.5, 73.7, 75.3, 96.8, 118.9, 127.1, 127.2, 130.8, 145.5, 148.8, 167.9, 170.7 ppm; IR (film): $\tilde{\nu} = 3020$ (w), 1720 (vs), 1640 (s), 1620 (m), 1240 (vs), 1000 (vs), 760 cm^{-1} (vs); HRMS (FAB): m/z: calcd for $C_{24}H_{37}O_6$: 421.2590; found: 421.2594 $[M+H]^+$.

Methyl (*S*)-6-[(2*S*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-ethyl-4-hydroxy-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-2,4-heptadienoate (39): A catalytic amount of K_2CO_3 was added to a stirred solution of **38** (12 mg, 0.029 mmol) in MeOH (1 mL) and the mixture was stirred at room temperature for 3 h. After this time, the mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 30:1) to give **39** (9.0 mg, 83 %) as a pale yellow oil. $[\alpha]_D^{24} = +23.4$ ($c = 0.55$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.46 (quin, $J = 7.2$ Hz, 2H), 1.54–1.67 (m, 2H), 2.01–2.11 (m, 1H), 2.42–2.51 (m, 1H), 3.72 (s, 3H), 3.75 (dd, $J = 9.9$, 2.1 Hz, 1H), 3.84 (dd, $J = 11.1$, 4.7 Hz, 1H), 3.91 (q, $J = 6.6$ Hz, 1H), 5.51 (dd, $J = 10.4$, 1.5 Hz, 1H), 5.78 (d, $J = 15.3$ Hz, 1H), 5.96 (dd, $J = 10.4$, 5.7 Hz, 1H), 6.17 (dd, $J = 15.3$, 10.2 Hz, 1H), 6.18 (dd, $J = 15.3$, 7.0 Hz, 1H), 7.19 ppm (dd, $J = 15.5$, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.4$, 11.8, 12.4, 15.1, 22.8, 26.1, 36.2, 38.4, 40.3, 40.8, 51.4, 71.6, 72.4, 74.5, 96.9, 118.9, 127.0, 127.6, 130.3, 145.6, 149.1, 167.9 ppm; IR (film): $\tilde{\nu} = 3475$ (m), 1700 (s), 1640 (s), 1620 (m), 1270 (s), 1220 (s), 1150 (s), 1030 (s), 1000 (s), 760 cm^{-1} (vs); HRMS (FAB): m/z: calcd for $C_{22}H_{35}O_5$: 379.2484; found: 379.2485 $[M+H]^+$.

(*S*)-6-[(2*S*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Ethyl-4-hydroxy-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-2,4-heptadienoic acid (1): A solution of KOH (0.5 M in MeOH, 0.2 mL, 0.1 mmol) was added to a mixture of **39** (7.0 mg, 0.018 mmol) and water (0.1 mL), and the resulting mixture was stirred at room temperature for 6 h. After this time, the mixture was extracted with ether and the aqueous layer was acidified to pH 2 with aqueous HCl (0.5 M) and then extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by using preparative TLC (Merck silica gel 60 F_{254}, 0.5 mm thick; $CHCl_3$/EtOAc 20:1) to give **1** (6.7 mg (99 %) as a colorless oil. $[\alpha]_D^{24} = +24$ ($c = 0.15$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.93 (t, $J = 7.3$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.46 (quin, $J = 7.3$ Hz, 2H), 1.56–1.67 (m, 2H), 2.03–2.10 (m, 1H), 2.49 (ddq, $J = 9.8$, 6.8, 6.8 Hz, 1H), 3.75 (dd, $J = 9.8$, 2.0 Hz, 1H), 3.85 (dd, $J = 11.2$, 4.9 Hz, 1H), 3.91 (br q, $J = 6.8$ Hz, 1H), 5.51 (d, $J = 10.3$ Hz, 1H), 5.78 (d, $J = 15.1$ Hz, 1H), 5.96 (dd, $J = 10.3$, 5.4 Hz, 1H), 6.19 (dd, $J = 15.4$, 10.0 Hz, 1H), 6.25 (dd, $J = 15.4$, 6.8 Hz, 1H), 7.25 ppm (dd, $J = 15.1$, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 4.5$, 11.9, 12.5, 15.2, 22.9, 26.2, 36.2, 38.5, 40.3, 40.8, 71.6, 72.5, 74.5, 96.8, 118.1, 126.8, 127.5, 130.2, 147.5, 150.1, 171.0 ppm; IR (film): $\tilde{\nu}$3400 (m), 3020 (w), 2960 (s), 2925 (s), 2875 (s), 2650 (w), 1680 (s), 1635 (m), 1610 (m), 1455 (m), 1370 (w), 1300 (w), 1270 (m), 1200 (w), 1020 (m), 990 (s), 960 cm^{-1} (m); HRMS (FAB): m/z: calcd for $C_{21}H_{32}O_5Na$: 387.2147; found: 387.2151 $[M+Na]^+$.

Methyl (*S*)-6-[(2*S*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*)-9-ethyl-4-hydroxy-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-2,4-heptadienoate (11-*epi*-39): Anhydrous $MgBr_2$ (9.0 mg, 0.049 mmol) was added to a stirred solution of **39** (5.0 mg, 0.013 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/EtOAc 20:1) to give 11-*epi*-**39** (2.0 mg, 40 %) as a pale yellow oil together with recovered **39** (3.0 mg, 60 %). $[\alpha]_D^{24} = -22.3$ ($c = 0.10$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.4$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 7.1$ Hz, 3H), 1.16–1.28 (m, 1H), 1.22 (d, $J = 6.0$ Hz, 3H), 1.44–1.55 (m, 1H), 1.78 (dq, $J = 11.3$, 6.9 Hz, 1H), 1.81–1.90 (m, 1H), 1.95–2.12 (m, 2H; H-1 + OH), 2.52 (ddq, $J = 9.8$, 6.6, 6.6 Hz, 1H), 3.26 (dd, $J = 9.8$, 1.6 Hz, 1H), 3.69 (dd, $J = 11.0$, 4.7 Hz, 1H), 3.73 (s, 3H), 3.90 (dq, $J = 9.8$, 6.0 Hz, 1H), 5.77 (d, $J = 15.4$ Hz, 1H), 5.89 (d, $J = 11.2$ Hz, 1H), 5.93 (dd, $J = 11.2$, 1.6 Hz, 1H), 6.09 (dd, $J = 15.4$, 6.6 Hz, 1H), 6.21 (dd, $J = 15.4$, 10.4 Hz, 1H), 7.20 ppm (dd, $J = 15.4$, 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 4.8$, 9.9, 11.4, 15.3, 19.5, 23.3, 36.2, 38.2, 40.7, 42.2, 51.4, 68.1, 74.3, 75.6, 97.9, 118.8, 123.5, 127.6, 134.0, 145.7, 148.3, 168.0 ppm; IR (film): $\tilde{\nu} = 3450$ (m), 3030 (w), 1720 (s), 1640 (s), 1260 (m), 1000 cm^{-1} (s); HRMS (FAB): m/z: calcd for $C_{22}H_{35}O_5$: 379.2484; found: 379.2489 $[M+H]^+$.

(*S*)-6-[(2*S*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*)-9-Ethyl-4-hydroxy-3,5,8-trimethyl-1,7-dioxaspiro[5.5]undec-10-en-2-yl]-2,4-heptadienoic acid (2): By the same protocol as that described for the preparation of **1**, 11-*epi*-**39** (2.0 mg, 5.3 μmol) was converted into **2** (1.9 mg, 99 %, colorless oil). $[\alpha]_D^{24} = -20.2$ ($c = 0.05$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz,

3H), 1.16–1.25 (m, 1H), 1.22 (d, $J=6.2$ Hz, 3H), 1.45–1.54 (m, 1H), 1.78 (dq, $J=11.2$, 6.6 Hz, 1H), 1.82–1.88 (m, 1H), 2.04–2.10 (m, 1H), 2.53 (ddq, $J=9.8$, 6.8, 6.8 Hz, 1H), 3.26 (dd, $J=9.8$, 1.8 Hz, 1H), 3.69 (dd, $J=11.2$, 4.7 Hz, 1H), 3.89 (dd, $J=9.8$, 6.2 Hz, 1H), 5.77 (d, $J=15.5$ Hz, 1H), 5.89 (d, $J=11.0$ Hz, 1H), 5.93 (dd, $J=11.0$, 2.1 Hz, 1H), 6.14 (dd, $J=15.4$, 6.8 Hz, 1H), 6.24 (dd, $J=15.4$, 10.9 Hz, 1H), 7.26 ppm (dd, $J=15.5$, 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=4.7$, 9.8, 11.4, 15.2, 19.4, 23.3, 36.1, 38.3, 40.7, 42.2, 68.1, 74.2, 75.6, 97.9, 118.2, 123.5, 127.5, 134.1, 147.8, 149.5, 171.7 ppm; HRMS (FAB): m/z: calcd for $C_{21}H_{31}O_5$: 363.2172; found: 363.2175 $[M-H]^-$.

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