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An Efficient Synthesis of Pironetins Employing a Useful Chiral Building Block, (*1S,5S,6R*)-5-Hydroxybicyclo[4.1.0]heptan-2-one

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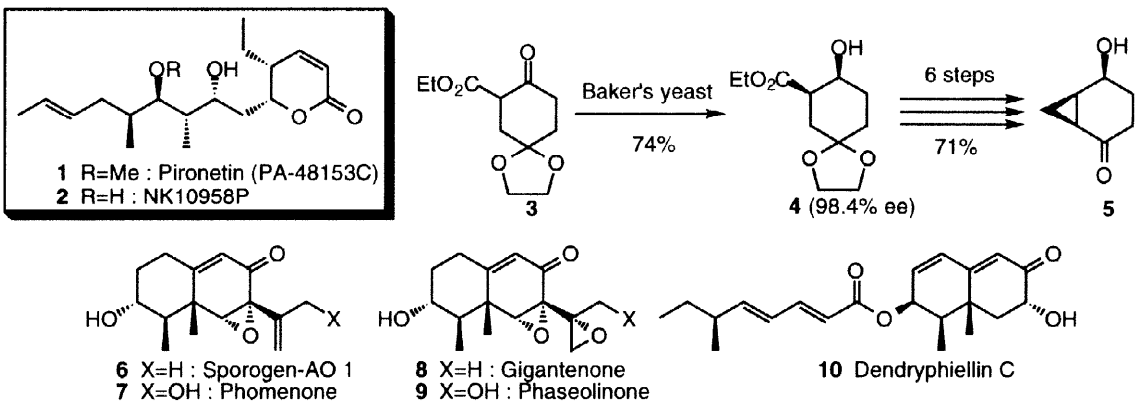
Abstract: A convergent total synthesis of pironetin **1** and related compound **2** using a chiral building block, (*1S,5S,6R*)-5-hydroxybicyclo[4.1.0]heptan-2-one **5** is described. Both the dithiane **47** and the epoxide **32** with proper substituents were employed as coupling partners to construct the whole carbon skeleton **48**, which was converted to (−)-pironetin **1** and (−)-**2** in few steps. The usefulness of **5** for polyketide synthesis was demonstrated.

Keywords: *pironetin; cell cycle inhibition; plant growth regulator; immunosuppressor; epoxide opening*

Introduction

Pironetin (PA-48153C) **1** and its demethyl analogue, NK10958P **2**, are novel unsaturated δ-lactone derivatives, which were independently isolated by two groups from the fermentation broths of *Streptomyces* sp. NK10958[1] and *Streptomyces prunicolor* PA-48153.[2] These compounds possess remarkable biological activities. One is a plant growth regulatory activity reported by Kobayashi and co-workers.[1a,d] The plant heights of sorghum and paddy rice are shortened by **1** or **2**, and it is expected that the use of these compounds will contribute to prevent lodging and subsequent loss of harvests. Another is an immunosuppressive activity described by Yoshida and co-workers.[2a] Recently, a study on the structure-activity relationships of the analogues of **1** was reported by the same group.[2b] They showed the suppressive effects of **1** on the responses of T and B lymphocytes to mitogens, while CsA and FK506 selectively inhibit T cell activation. More recently, Osada and co-workers reported the biological effects of **1** and its derivatives on cell cycle progression and antitumor activities.[3]

Scheme 1



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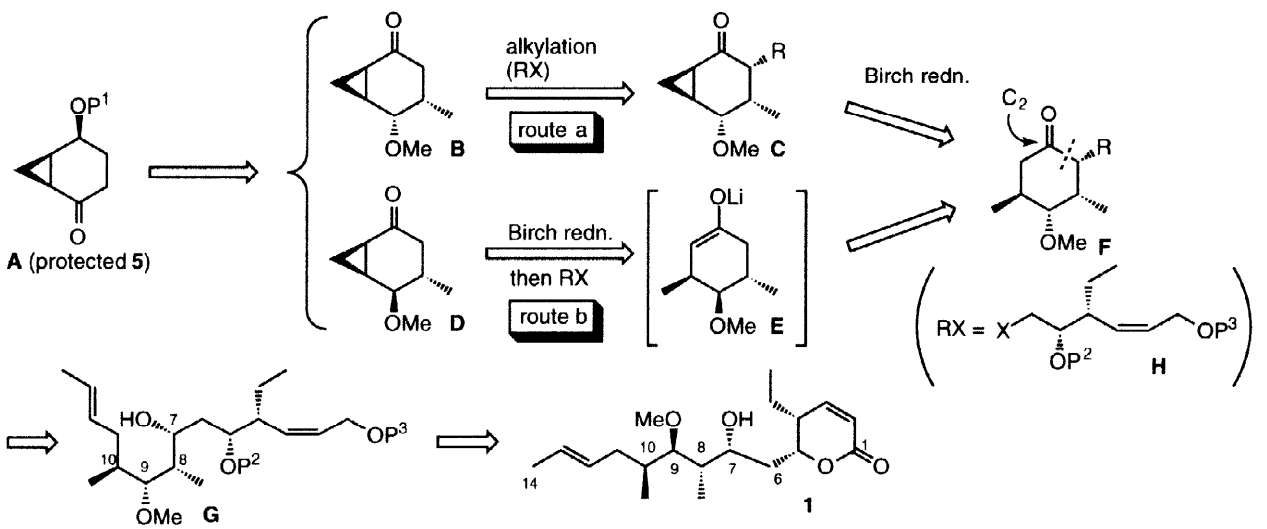
Not only these interesting activities but also the unique and simple structures make **1** and **2** attractive synthetic targets and four total syntheses of **1** have been reported only in the past five years.[4] We show here an alternative approach to **1** and **2** *via* an efficient and convergent route[5] using our chiral building block, (*1S,5S,6R*)-5-hydroxybicyclo[4.1.0]heptan-2-one **5**.[6] The chiral ketone **5** is available in large quantity by simple operation starting from a β-ketoester **3**,[6a,b] from which we synthesized several natural products **6**-**10** (Scheme 1).[6b-d] Through these syntheses, the ketone **5** has been proved to be useful for the construction of eremophilanes and related ring systems, but we considered that it could be a useful chiral starting material for polyketide synthesis. The basic plan is shown in Scheme 2. Methylation at the α-position of the ketone **A** (= protected **5**), reduction of the ketone followed by etherification, and deprotection-oxidation would lead to the key intermediates **B** and/or **D**. We envisioned two routes using **B** and **D**. Introduction of the C1-C6 unit to **B** would be attained by alkylation using **H** to give **C**, and Birch reduction of the cyclopropane ring would afford **F** (route a). Alternatively, Birch reduction of **D** and the subsequent alkylation of the resulting enolate **E** could also afford **F** (route b). The Baeyer-Villiger oxidation of **F** followed by two carbon-unit introduction would give a linear precursor **G**, which would be led to **1** by oxidative lactonization in the final stage.

Scheme 2

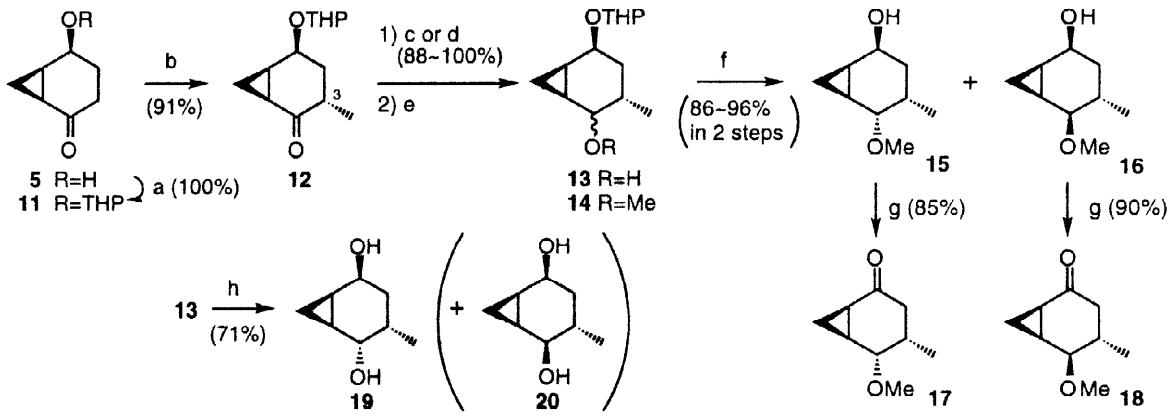


Results and Discussion

Preparation of the key intermediates 17 and 18: The protection of **5** as THP ether followed by methylation of the enolate generated by LDA in HMPA-THF at –78°C afforded the ketone **12** in 91% yield (Scheme 3). The diastereoisomer at C3 position could not be detected. The reduction of **12** with L-Selectride® at –78°C gave **13** as an inseparable mixture of four diastereomers (**13** and their diastereomers due to the THP group) in quantitative yield. Treatment of **13** with NaH-MeI in THF in the presence of a catalytic amount of TBAI and subsequent removal of the THP group under acidic conditions gave separable isomers **15** and **16** (2 steps 96%) in a ratio of 13:1. On the other hand, reduction of **12** with $NaBH_4$ in absolute ethanol at 0°C (88%) followed by the same two steps, etherification–deprotection, led to **15** and **16** in an inverse ratio of 1:4 (2 steps 86%). The alcohols **15** and **16** were separately oxidized with Dess-Martin periodinane[7] to give ketones **17** (85%) and **18** (90%), respectively. Consequently, either of the two isomers, **17** (= **B**) and **18** (= **D**), could be prepared selectively using the different reducing agents (**17**, 69% yield from **5**; **18**, 47% yield from **5**). The ^{1}H-NMR spectra of **15**/**16** and **17**/**18** did not indicate the clear stereochemistries of the newly-introduced methyl and

methoxy groups, but they were determined unambiguously by X-ray analysis of a crystalline diol **19** as shown in Figure 1. The diol **19** was prepared as a major isomer (71%, **19**:**20**=14:1) by the deprotection of **13**, which was prepared by L-Selectride® reduction (*ca.* 13:1 mixture).

Scheme 3



Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, r.t.; (b) LDA, HMPA, THF, –78°C then MeI; (c) LiB(*sec*-butyl)$_3$H, THF, –78°C; (d) $NaBH_4$, EtOH, 0°C; (e) NaH, MeI, TBAI, THF, 60°C; (f) aq. HCl, MeOH, 0°C; (g) Dess-Martin periodinane, CH_2Cl_2, 0°C; (h) TsOH, MeOH, r.t.

Preparation of the C1-C6 unit: The benzoate **22** of the known epoxy alcohol **21**[8c] (93% ee) was treated with acetylenic alanate, which was prepared from TBS propargyl ether, *n*-BuLi and trimethylaluminum, in the presence of $BF_3 \cdot OEt_2$ to give the homopropargyl alcohol **23** in 43% yield[9] (Scheme 4). Although a considerable amount of an unidentified byproduct was observed, the regioisomer on the epoxide opening was not detected. Hydrogenation of **23** over Lindlar catalyst in methanol at room temperature gave a (*Z*)-homoallylic alcohol **24** in quantitative yield without generation of the undesired (*E*)-isomer or saturated compound. The secondary hydroxyl group of **24** was protected as TBS ether to give **25**. Removal of the benzoate was executed by treatment with two equivalents of MeLi in ether to give alcohol **26** in 85% yield, while methanolysis of **25** (K_2CO_3, MeOH) resulted in a low yield of **26** due to 1,2-shift of the TBS group. Triflylation of the resulting hydroxyl group afforded a triflate **27** as a C1-C6 unit. The other C1-C6 units, an iodide **31** and an epoxide **32**, were prepared easily from **24** in the usual manner. Methanolysis of the benzoate **24** (99%), selective monotosylation of the resulting primary hydroxyl group (76%), silylation of the remaining secondary hydroxyl group (100%) and iodination of the tosylate (83%) gave **31**. Treatment of **29** with a base afforded epoxide **32** in 89% yield.

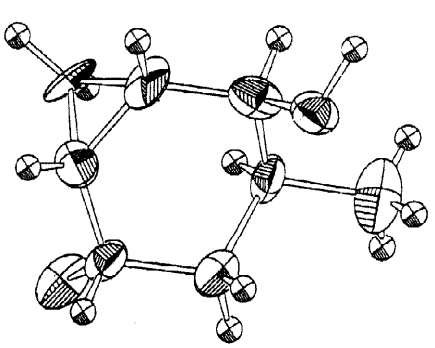
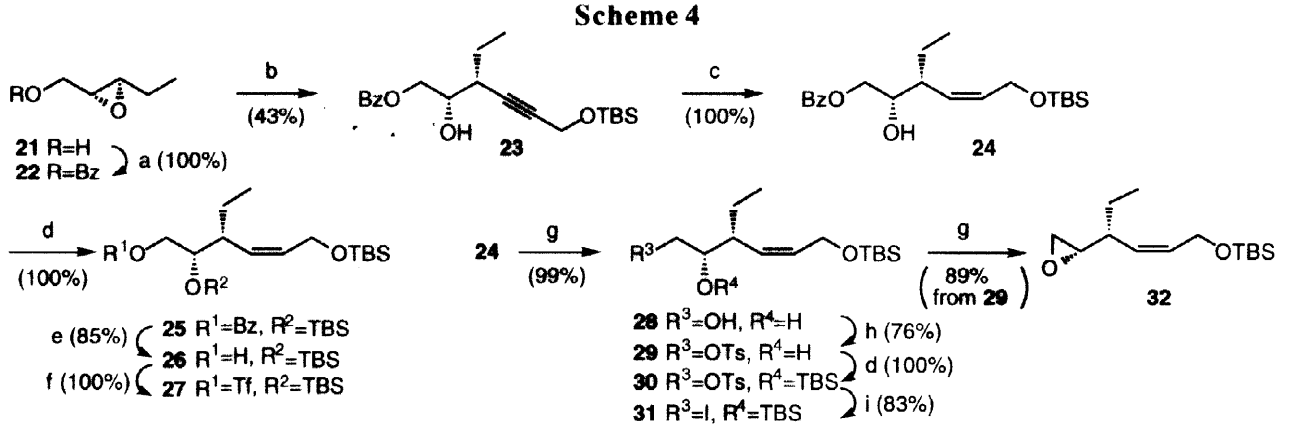


Figure 1. ORTEP view of compound **19**.

Scheme 4



Reagents and conditions: (a) PhCOCl, Et_3N, CH_2Cl_2, 0°C; (b) $TBSOCH_2C{\equiv}CH$, *n*-BuLi, Me_3Al, $BF_3{\cdot}OEt_2$, ether, –78°C; (c) H_2, Lindlar cat., MeOH, r.t.; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (e) MeLi, THF, –78°C; (f) Tf_2O, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 0°C; (g) K_2CO_3, MeOH, r.t.; (h) TsCl, Et_3N, DMAP, CH_2Cl_2, 0°C; (i) NaI, $NaHCO_3$, DMF, 90°C.

Coupling of the cyclohexanone ring with the C1-C6 unit: We investigated introduction of the C1-C6 unit to the ketone **17** or **18** (Scheme 5). A simple alkylating reagent, such as methyl or isobutyl iodide, reacted with a lithium enolate of **17** (LHMDS, HMPA, THF, 0°C) to give **33** (R= Me, isobutyl) in 60-70% yield as a diastereomeric mixture due to the R group. However, treatment of the triflate **27** or the iodide **31** with the enolate under the same conditions resulted in no reaction. The other enolate **E** (in Scheme 2) generated by Birch reduction of **18** (Li, *t*-BuOH, liq. NH_3, THF, –78°C) also did not react with **27** or **31** and a non-alkylated ketone **34** was obtained.

Scheme 5

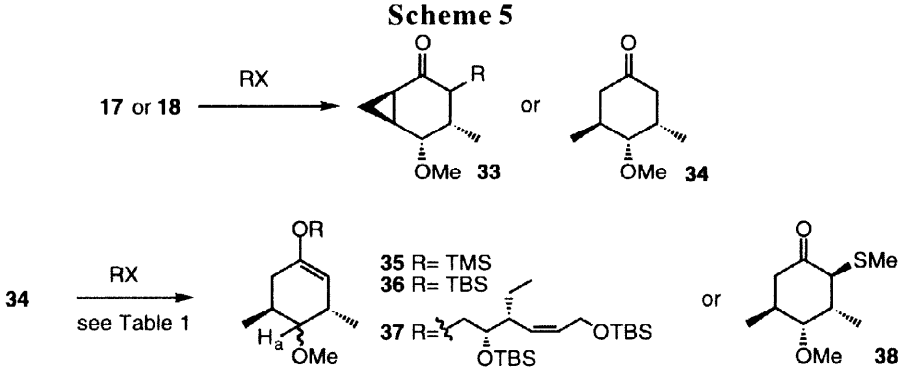
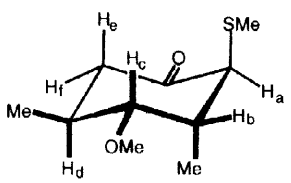


Table 1: Reaction of the enolate of **34**.

Entry	Conditions	RX	Product (%)	Ratio [a]
1	LDA, THF, –78°C	TMSCl	**35** (67)	1 : 1
2	KHMDS, THF, –78°C	TMSCl	**35** (83)	1 : 3
3	$BrMgNPr^i_2$, Et_3N, Et_2O, r.t. [b]	TMSCl	**35** (60)	1.7 : 1
4	Et_3N, CH_2Cl_2, 0°C	TBSOTf	**36** (92)	1 : 1.5
5	LDA, THF, –78°C	$MeSSO_2Me$ [c]	**38** (100) [d]	–
6	LDA, THF, –78°C	**31** [c]	**37** (32) [d]	1 : 1

a) The ratio was determined by ^{1}H-NMR (integration of H_a) and the stereochemistries were not confirmed. b) See reference 10. c) 0.5 equiv. of RX was used. d) Yield based on RX.



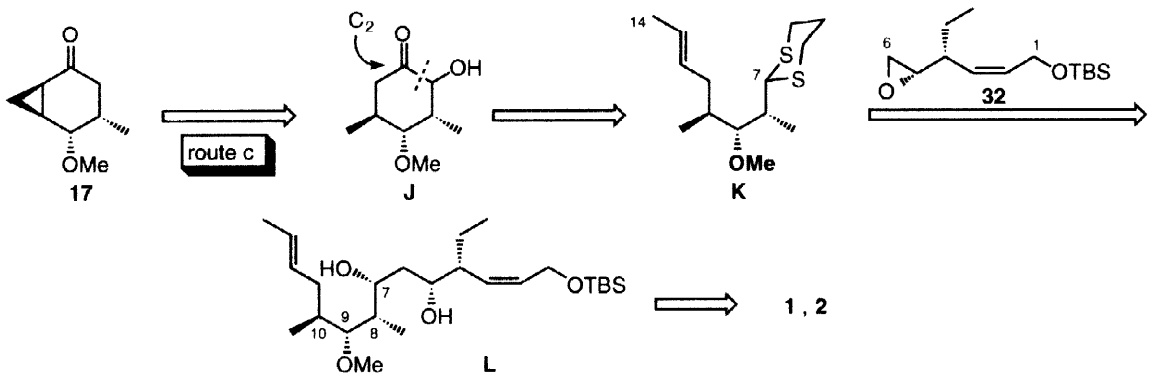
H_a: dd, J= 1.6, 4.0 Hz
H_e: dd, J= 11.2, 14.5 Hz
H_f : ddd, J= 1.6, 5.2, 14.5 Hz

Figure 2

The ketone **34** was prepared from either **17** and **18** in good yield (Li, liq. NH_3, THF, –78°C then NH_4Cl; 75-78% yield) and we then tried the regioselective enolate formation (Table 1). Although no remarkable selectivity was observed under the thermodynamic[10] or kinetic conditions (entry 1-4), we found the lithium enolates have different reactivities (entry 5). A mixture of the enolate (1:1) reacted with 0.5 equivalent of $MeSSO_2Me$ to give 2-methylthiocyclohexanone **38** in quantitative yield (= 50%) as a single diastereomer together with recovery of the unreacted **34** (25%). The regio- and stereochemistries were determined by ^{1}H-NMR. Long range-coupling constant (1.6 Hz) of H_a-H_f and vicinal coupling constant (11.2 Hz) of H_d-H_e indicated the configuration of **38** to be that as shown in Figure 2. To our disappointment, treatment of the enolate with 0.5 equivalent of the iodide **31** under the same conditions afforded an *O*-alkylated product **37** in 32% yield (entry 6). Consequently, introduction of the C1-C6 unit to the α-position of ketone **17**, **18** or **34** could not be accomplished and these results might be due to the lower reactivity of both the enolate and the alkylating reagent. Although cross-aldol reaction of **17** with an aldehyde of the C1-C6 unit (prepared from **26** by Swern oxidation in 92% yield) afforded the desired product in 74% yield, removal of the hydroxl group resulted in disappointing yield.

Revised route: Higher nucleophilicity, therefore, should be essential for the coupling with the C1-C6 unit and we adopted route c, which involves an epoxide opening with the anion of 1,3-dithiane (Scheme 6). Hydroxylation of the ketone **17** and the reductive cleavage of the cyclopropane ring would afford **J**. Oxidative cleavage of the α-ketol moiety of **J** and two carbon-unit introduction would give C7-C14 unit **K**. Coupling of the dithiane **K** with the epoxide **32** followed by hydrolysis and stereoselective reduction at C7 would afford **L** which is equivalent to **G** in Scheme 2.

Scheme 6



Treatment of the silyl enol ether of **17** with osmium tetroxide[11] in THF-H_2O gave an inseparable mixture of α-ketol **39** and **40** (2:3) in quantitative yield (Table 2, entry 4). On the other hand, oxidation using Davis' reagent[12] (entry 1) or lead tetraacetate[13] (entry 2), and *m*-CPBA oxidation of the silyl enol ether[14] (entry 3) gave **39** or **40** selectively but in lower yields. Reductive cleavage of the cyclopropyl ketone moiety by Birch reduction afforded a separable mixture of **41** and **42** in 54% yield in a ratio of 2:3. In this reaction, pre-formation of the alkoxide using LHMDS was essential to avoid the undesired reductive cleavage of the hydroxyl group. The moderate yield of the Birch reduction was unimproved even by changing several conditions (alkali metal, concentration and scale, reaction time, and the workup procedures), although this reaction seemed to be clean and only both epimers, **41** and **42**, were observed on TLC of SiO_2. The stereochemistries of **39**-**42** were confirmed by ^{1}H NMR. Coupling constants of H_b and H_d were 12.2 Hz and 11.2 Hz, respectively, which clearly show 1,2-diaxial relationship between vicinal protons on the cyclohexane ring.

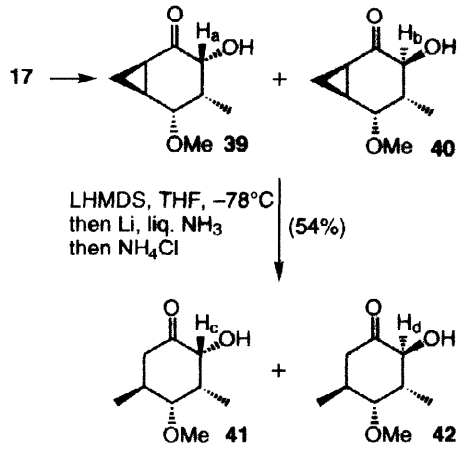
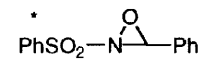


Table 2: Hydroxylation of **17**.

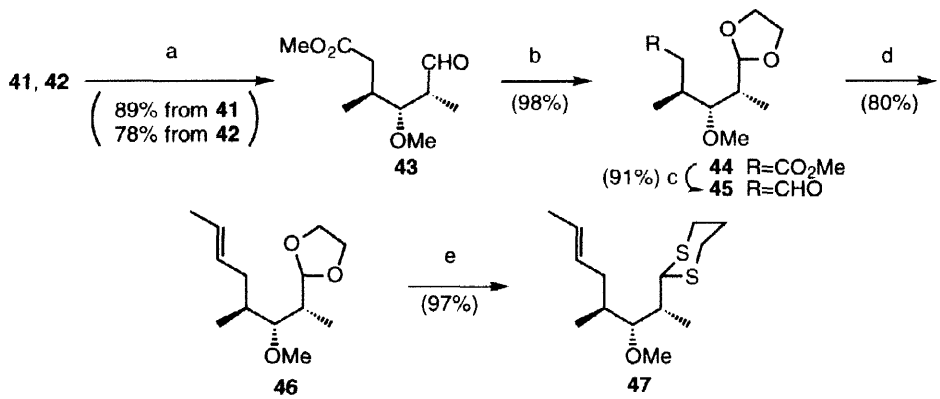
Entry	Conditions	Products	Yield (%)
1	KHMDS, THF, -78°C then Davis reagent *	**40**	28
2	1) $Pb(OAc)_4$, C_6H_6, reflux 2) K_2CO_3, MeOH	**40**	40
3	1) TBSOTf, Et_3N, CH_2Cl_2, 0°C then *m*-CPBA 2) aq. HF, MeCN, r.t.	**39**	65
4	1) TBSOTf, Et_3N, CH_2Cl_2, 0°C 2) cat. OsO_4, NMO, THF, H_2O, r.t.	**39** + **40** (2 : 3)	100

(H_a: t, J= 3.5 Hz; H_b: d, J= 12.2 Hz; H_c: d, J= 5.7 Hz; H_d: br d, J= 11.2 Hz)



The α-ketol moiety of both **41** and **42** was oxidatively cleaved with lead tetraacetate in benzene-methanol solution (4:1)[15] to give the same product **43** in 89% and 78% yield, respectively (Scheme 7). Acetalization of **43** followed by reduction with DIBAL at –78°C in CH_2Cl_2 gave aldehyde **45** (2 steps 89%). Introduction of the two carbon-unit to the formyl group was accomplished by Takai's protocol.[16] Treatment of **45** with CH_3CHI_2 in the presence of $CrCl_2$ in THF afforded the desired (*E*)-olefin **46** in 80% yield exclusively. Transacetalization of **46** with 1,3-propanedithiol in the presence of $BF_3 \cdot OEt_2$ afforded the dithiane **47** in 97% yield as a C7-C14 unit of pironetin (overall 14 steps, 21% from **5**). Although thioacetalization of **43** is a straightforword route to **47**, decomposition of the dithiane function resulted in poor yield in the Takai reaction.

Scheme 7

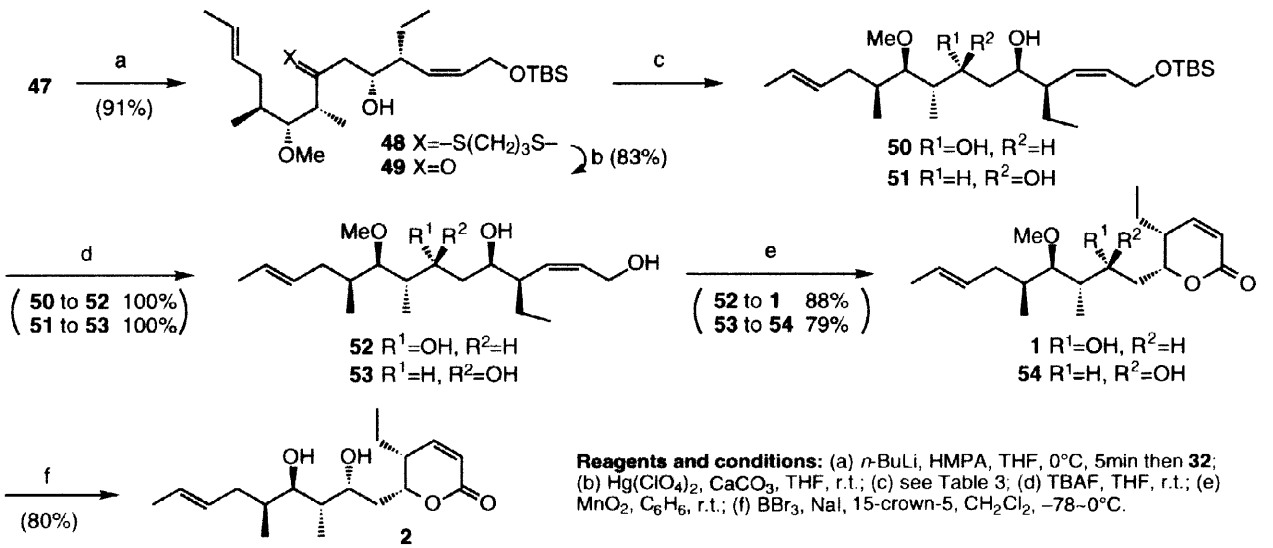


Reagents and conditions: (a) $Pb(OAc)_4$, C_6H_6, MeOH, r.t.; (b) $HO(CH_2)_2OH$, TsOH, C_6H_6, reflux; (c) DIBAL, CH_2Cl_2, –78°C; (d) CH_3CHI_2, $CrCl_2$, THF, r.t.; (e) $HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$, CH_2Cl_2, –78°C.

Coupling reaction of two units, the dithiane **47** and the epoxide **32**, successfully gave the whole skeleton **48** in 91% yield (Scheme 8). The key feature of this reaction is the anion formation and the best yield was obtained when the dithiane **47** was treated with *n*-BuLi at 0°C for a short period (5 minutes). The same treatment for a longer period resulted in the complete recovery of the substrates, probably because of the protone-abstraction from THF. The reaction under the usual conditions, such as *t*-BuLi at lower temperature (–78°C), gave no products. Similar successful conditions (1,3-dithiane, *n*-BuLi, THF, r.t., 5 min. then epoxide) were reported independently by Ide and co-workers.[17] Mercuric ion-assisted hydrolysis of the thioacetal **48** gave β-ketol **49** in 83% yield. Stereoselective reduction of the ketone was investigated to introduce the last chiral center

at the C7 position (Table 3). Reduction with sodium[18] or tetramethylammonium triacetoxyborohydride,[19] both of which are known as effective methods for the stereoselective reduction to *anti*-diol, gave disappointing results (entry 1–3). Also, reduction with a bulky reagent such as L-Selectride® at –78°C (entry 4) and the intramolecular Tischenko reaction[20] (entry 7) gave unsatisfactory results. We then tried Mori's method using excess $LiAlH_4$[21a,b] or $LiAlH(OBu^t)_3$[21c] in the presence of lithium iodide in ether at –78°C. Although the reduction with $LiAlH_4$ mainly afforded the undesired *syn*-isomer **51** predominantly (entry 5), the use of $LiAlH(OBu^t)_3$ gave the desired **50** in high selectivity of 91:9 (entry 6). These selectivities can be explained according to Mori's report.[21c] The chelation of the lithium cation between the ketone and the methoxy group gave a transition state as shown in Figure 3. The free hydroxyl group would be protected as an aluminum alkoxide and the second hydride attacks the carbonyl group. A small hydride such as $LiAlH_4$ attacks from the axial face to give a *syn*-product and alternatively, a bulky hydride such as $LiAlH(OBu^t)_3$ attacks from the less-hindered equatorial face to give an *anti*-product. The stereochemistries of **50** and **51** were determined by converting them into **1** and its C7-epimer **54**.

Scheme 8



Reagents and conditions: (a) *n*-BuLi, HMPA, THF, 0°C, 5min then **32**; (b) $Hg(ClO_4)_2$, $CaCO_3$, THF, r.t.; (c) see Table 3; (d) TBAF, THF, r.t.; (e) MnO_2, C_6H_6, r.t.; (f) BBr_3, NaI, 15-crown-5, CH_2Cl_2, –78~0°C.

Desilylation of **50** and **51** with TBAF followed by oxidative lactonization with manganese dioxide afforded pironetin **1** and its C7-epimer **54**, respectively. In addition to that, we achieved the synthesis of **2** by the demethylation of **1** with BBr_3 in the presence of sodium iodide and 15-crown-5 at –78 to 0°C, a mild demethylation condition reported by Niwa and co-workers.[22] The ^{1}H-NMR, ^{13}C-NMR and IR spectral data, specific rotations, melting points of **1** and **2** were identical with those reported.[1a,1d,2a]

Table 3: Reduction of **49** to *anti/syn*-diol **50** and **51**.

Entry	Reagents and conditions	**50** (*anti*) : **51** (*syn*)	Yield(%)
1	$NaBH(OAc)_3$, AcOH, MeCN, 0°C	49 : 51	77
2	$Me_4NBH(OAc)_3$, AcOH, MeCN, –20°C	64 : 36	94
3	$Me_4NBH(OAc)_3$, acetone, –78°C	59 : 41	86
4	L-Selectride®, THF, –78°C	62 : 38	90
5	$LiAlH_4$, LiI, ether, –78°C	30 : 70	92
6	$LiAlH(OBu^t)_3$, LiI, ether, –78°C	91 : 9	quant.
7	isobutyraldehyde, SmI_2, THF, –10°C	–	No reaction

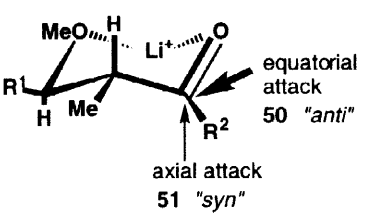


Figure 3

In conclusion, we have succeeded in efficient total synthesis of pironetins *via* a convergent route (13% overall yield of **1** in 19 steps from **5**). Furthermore, our chiral building block **5** was proved to be extremely versatile for natural product synthesis. Further studies on the synthesis and biological activities of the analogs are in progress and will be reported in due course.

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Experimental

All boiling points (bps) and melting points (mps) were uncorrected. Infrared spectra (IR) were measured on a Jasco FT/IR-230 spectrometer. Proton and carbon-13 magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on a BRUKER AC300 or a JEOL JNM α-500 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal chloroform (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). Optical rotations were measured on a Jasco DIP 1000 polarimeter. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm Merck silica gel 60 F_{254} precoated glass-backed plates. Compounds were visualized by ultraviolet light (254 nm), iodine vapor, or phosphomolybdic acid spray reagent. Preparative TLC was carried out using 0.5 mm Merck silica gel 60 F_{254} precoated glass-backed plates. All column chromatography was performed on Merck silica gel 60. All solvents were reagent grade. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride and stored over 4A-molecular seives. Methanol and absolute ethanol were used without purification.

*(1S,5S,6R)-5-(2-Tetrahydropyranyloxy)bicyclo[4.1.0]heptan-2-one (**11**)*

To a solution of **5**[6b] (6.0 g, 48 mmol) in dichloromethane (60 mL) were added 3,4-dihydro-2*H*-pyran (8.0 g, 95 mmol) and pyridinium *p*-toluenesulfonate (0.1 g, 0.4 mmol). After being stirred at room temperature for 30 min, the solution was poured into saturated aqueous sodium bicarbonate (200 mL) and extracted with diethyl ether (300 mL). The organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (200 g) eluted with *n*-hexane/ethyl acetate (5:1–3:1) to give **11** (10.2 g, quantitative). Two diastereomers (*ca.* 1:1) due to the THP group were inseparable and were employed in the next step without further purification; colorless oil; $[\alpha]_D^{21}$ –52.3°(*c* 0.45, $CHCl_3$); IR (film) ν_{max} 2944, 1695, 1442, 1342, 1255, 1201, 1154, 1133, 1077, 1029, 968, 883, 813 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.11–1.21 (1H, m), 1.39–2.20 (12H, m), 2.32–2.37 and 2.38–2.43 (total 1H, each m), 3.49–3.57 (1H, m), 3.85–4.02 (1H, m), 4.30–4.43 (1H, m), 4.75 and 4.88 (total 1H, each dd, *J*= 2.7, 4.6 and 2.7, 4.4 Hz); Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.64. Found: C, 68.23; H, 8.64.

*(1S,3S,5S,6R)-3-Methyl-5-(2-tetrahydropyranyloxy)bicyclo[4.1.0]heptan-2-one (**12**)*

To a solution of diisopropylamine (8.7 mL, 62 mmol) in THF (350 mL) under nitrogen atmosphere at 0°C was added *n*-buthyllithium (35.9 mL of 1.59 M solution in *n*-hexane, 57 mmol) over 20 min. After 15 min, HMPA (41 mL, 238 mmol) was added and the temperature was lowered to –78°C. A solution of **11** (10.0 g, 48 mmol) in THF (50 mL) was added over 30 min. After 1 hr, iodomethane (3.6 mL, 58 mmol) in THF (15 mL) was added over 30 min. The reaction mixture was allowed to warm to 0°C over 2 hr and stirred for 1 hr at the

same temperature. The solution was poured into cold water (500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (300 g) eluted with *n*-hexane/ethyl acetate (7:1–5:1) to give **12** (9.7 g, 91%). Two diastereomers (*ca.* 1:1) due to the THP group were inseparable and were employed in the next step without further purification; colorless oil; $[\alpha]_D^{24}$ –29.8° (*c* 0.68, $CHCl_3$); IR (film) ν_{max} 3447, 2939, 1695, 1454, 1377, 1200, 1132, 1022, 993, 870 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.02 and 1.05 (total 3H, each d, *J*= 6.8 and 7.1 Hz), 1.13–1.23 and 1.30–1.37 (total 1H, each m), 1.46–2.11 (11H, m), 2.39–2.56 (1H, m), 3.50–3.57 (1H, m), 3.84–3.92 and 3.94–4.02 (total 1H, each m), 4.32–4.39 and 4.43–4.48 (total 1H, each m), 4.70–4.74 and 4.88–4.92 (total 1H, each m); Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 9.00. Found: C, 69.35; H, 8.94.

(1R,2S,4S,5S,6S)-5-Methoxy-4-methylbicyclo[4.1.0]heptan-2-ol (15) and (1R,2S,4S,5R,6S)-5-methoxy-4-methylbicyclo[4.1.0]heptan-2-ol (16)

***Via* L-Selectride® reduction:** To a solution of **12** (8.6 g, 38 mmol) in THF (300 mL) was added L-Selectride® (76.7 mL of 1 M solution in THF, 77 mmol) under nitrogen atmosphere at –78°C. After being stirred at the same temperature for 30 min, the solution was allowed to warm to 0°C over 2 hr and water (5 mL), 3N aqueous sodium hydroxide (25 mL), and 35% aqueous hydrogen peroxide (25 mL) was added at 0°C. After being stirred at room temperature for 1 hr, water (250 mL) was added and the mixture was extracted with ethyl acetate (2 x 300 mL). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (300 g) eluted with *n*-hexane/ethyl acetate (6:1–2:1) to give **13** (8.7 g, quantitative) as an inseparable mixture of four diastereomers (**13** and their diastereomers due to the THP group), which were employed in the next step without further purification; colorless oil; $[\alpha]_D^{20}$ –66.1°(*c* 0.11, $CHCl_3$); IR (film) ν_{max} 3443, 2939, 1454, 1384, 1260, 1201, 1183, 1137, 1111, 1076, 1023, 999, 867, 810 cm^{-1}; ^{1}H-NMR [300 MHz, $CDCl_3$, major two isomers (*ca.* 1:1) could be assigned] δ 0.42 and 0.57–0.69 (total 2H, q and m, *J*= 5.4 Hz), 0.91 and 0.92 (total 3H, each d, *J*= 6.6 and 6.3 Hz), 1.12–1.90 (12H, m), 3.46–3.54 (1H, m), 3.84–3.91 and 3.95–4.04 (total 2H, each m), 4.26–4.32 and 4.38–4.42 (total 1H, each m), 4.65–4.68 and 4.87–4.90 (total 1H, each m); Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.98; H, 9.82. Found: C, 68.55; H, 9.71.

To a suspension of sodium hydride (4.20 g of 60% dispersion in mineral oil was washed with *n*-hexane, 105 mmol) in THF (180 mL) under nitrogen atmosphere were added **13** (8.00 g, 35 mmol), iodomethane (13.0 mL, 209 mmol), and tetrabutylammonium iodide (80 mg, 0.2 mmol). After being stirred at 60°C for 4 hr, the mixture was cooled to 0°C, poured into cold water (200 mL) carefully, and extracted with ethyl acetate (3 x 200 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (200 g) eluted with *n*-hexane/ethyl acetate (30:1–10:1) to give **14** (8.23 g, 97%, colorless oil) as an inseparable mixture of four diastereomers, which were employed in the next step without further purification; colorless oil; $[\alpha]_D^{23}$ –142°(*c* 0.90, $CHCl_3$); IR (film) ν_{max} 2937, 1737, 1455, 1385, 1201, 1183, 1135, 1109, 1022, 993, 941, 906, 869, 814 cm^{-1}; ^{1}H-NMR [300 MHz, $CDCl_3$, major two isomers (*ca.* 1:1) could be assigned] δ 0.33 and 0.46 (total 1H, each q, *J*= each 5.5 Hz), 0.57–0.65 (1H, m), 0.88 and 0.89 (total 3H, each d, *J*= 7.0 and 6.0 Hz), 1.01–1.89 (11H, m), 3.32–3.37 (1H, m), 3.41 and 3.39 (total 3H, each s), 3.44–3.51 (1H, m), 3.82–3.89 and 3.94–4.01 (total 1H, each m), 4.23–4.29 and 4.36–4.41 (total 1H, each m), 4.65 and 4.86 (total 1H, each br t, *J*= 4.3 and 3.6 Hz); Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.08. Found: C, 70.11; H, 10.03.

To a solution of **14** (8.00 g, 33 mmol) in methanol (100 mL) at 0°C was added 1 N aqueous hydrochloric acid (200 mL) over 30 min. After being stirred for 1 hr at the same temperature, the solution was neutralized with powdered sodium bicarbonate (18 g) and extracted with dichloromethane (5 x 200 mL). The combined organic

phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*, and the residue was chromatographed on silica gel (250 g) eluted with *n*-hexane/ethyl acetate (5:1–2:1) to give **15** (4.80 g, 92%) as a less polar component and **16** (0.37 g, 7%). Compound **15**; colorless oil; $[\alpha]_D^{21}$ –258° (*c* 0.26, $CHCl_3$); IR (film) ν_{max} 3390, 2929, 1644, 1462, 1363, 1330, 1302, 1255, 1214, 1160, 1090, 1033, 1003, 960, 940, 906 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.39 (1H, q, *J*= 5.4 Hz), 0.61 (1H, dt, *J*= 5.4, 9.2 Hz), 0.91 (3H, d, *J*= 6.5 Hz), 1.04 (1H, ddd, *J*= 2.2, 5.0, 13.3 Hz), 1.30–1.46 (3H, m), 1.55–1.74 (2H, m), 3.19 (1H, dd, *J*= 1.7, 2.8 Hz), 3.42 (3H, s), 4.41 (1H, dt, *J*= 6.8, 5.0 Hz); Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 68.89; H, 10.29. Compound **16**; colorless oil; $[\alpha]_D^{21}$ –79.6° (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3400, 2929, 1651, 1463, 1363, 1329, 1302, 1256, 1184, 1084, 1033, 984, 970, 930 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.56 (1H, dt, *J*= 5.4, 8.8 Hz), 0.71 (1H, q, *J*= 5.4 Hz), 0.94 (3H, d, *J*= 6.8 Hz), 1.25–1.68 (6H, m), 3.29 (1H, dd, *J*= 7.1, 12.4 Hz), 3.40 (3H, s), 4.31 (1H, br q, *J*= 5.9 Hz); Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 68.70; H, 10.35.

***Via* NaBH4 reduction:** To a solution of **12** (200 mg, 0.89 mmol) in absolute ethanol (5 mL) at 0°C was added sodium borohydride (38 mg, 1.00 mmol) over 5 min. After being stirred for 2hr, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (6:1–2:1) to give **13** (178 mg, 88%). Etherification (94%) followed by deprotection (91%) was performed as described above to give **15** and **16** (1:4).

(1R,4S,5S,6S)-5-Methoxy-4-methylbicyclo[4.1.0]heptan-2-one (17)

To a solution of **15** (4.68 g, 30 mmol) in dichloromethane (250 mL) at 0°C was added Dess-Martin periodinane[7c] (14.00 g, 33 mmol) over 5 min. After being stirred at the same temperature for 1.5 hr, 10% aqueous sodium thiosulfate (150 ml) and saturated aqueous sodium bicarbonate (150 mL) were added. The mixture was stirred at room tempareture for 1 hr and extracted with dichloromethane (2 x 300 mL). The combined organic phase was washed with brine (300 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (250 g) eluted with *n*-hexane/ethyl acetate (10:1) to give **17** (3.92 g, 85%); colorless oil; $[\alpha]_D^{22}$ –97.7° (*c* 1.41, $CHCl_3$); IR (film) ν_{max} 3020, 2823, 1693, 1459, 1355, 1338, 1283, 1247, 1193, 1092, 1031, 968, 947, 924, 906 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, *J*= 6.6 Hz), 1.13 (1H, q, *J*= 5.9 Hz), 1.19 (1H, ddd, *J*= 5.9, 8.4, 9.7 Hz), 1.81 (1H, ddd, *J*= 5.9, 7.1, 9.7 Hz), 1.88–2.04 (2H, m), 2.06 (1H, dd, *J*= 7.1, 18.3 Hz), 2.14 (1H, dd, *J*= 7.3, 18.3 Hz), 3.47 (3H, s), 3.63 (1H, t, *J*= 2.6 Hz); Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.17. Found: C, 69.83; H, 9.12.

(1R,4S,5R,6S)-5-Methoxy-4-methylbicyclo[4.1.0]heptan-2-one (18)

The oxidation of **16** (300 mg, 1.9 mmol) was performed as described above for **17** to give **18** (266 mg, 90%); colorless oil; $[\alpha]_D^{21}$ +90.0° (*c* 0.43, $CHCl_3$); IR (film) ν_{max} 2932, 2823, 1694, 1455, 1359, 1285, 1253, 1174, 1093, 985, 946, 905, 851 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.99 (3H, d, *J*= 6.5 Hz), 1.17 (1H, ddd, *J*= 5.4, 8.4, 9.5 Hz), 1.33 (1H, q, *J*= 5.4 Hz), 1.84–2.01 (3H, m), 1.85 (1H, dd, *J*= 9.2, 16.7 Hz), 2.41 (1H, dd, *J*= 4.3, 16.7 Hz), 3.47 (3H, s), 3.48 (1H, dd, *J*= 4.8, 7.2 Hz); Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.17. Found: C, 70.09; H, 9.08.

(1S,2S,3S,5S,6R)-3-Methylbicyclo[4.1.0]heptane-2,5-diol (19) and (1S,2R,3S,5S,6R)-3-methylbicyclo[4.1.0]-heptane-2,5-diol (20)

To a solution of **13** (98 mg, 0.43 mmol, obtained by L-Selectride® reduction) in methanol (10 mL) was added *p*-toluenesulfonic acid monohydrate (1 mg). After being stirred at room temperature for 6 hr, powdered sodium bicarbonate (5 mg) was added and the mixture was concentrated *in vacuo*. The residue was diluted with

diethyl ether (20 mL) and anhydrous magnesium sulfate was added. The mixture was stirred for 30 mim, filtered through Celite® pad and concentrated *in vacuo*. The crude oil was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (10:1–1:1) to give **19** (44 mg, 71%, white solid) as a less polar component and **20** (3 mg, 5%). Compound **19** (after recrystallization from *n*-hexane/ethyl acetate); colorless needles; mp 105–106°C; $[\alpha]_D^{21}$ –515° (*c* 0.09, $CHCl_3$); IR (nujol) ν_{max} 3288, 1310, 1261, 1051, 1025, 1009, 971 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.50 (1H, q, *J*= 5.4 Hz), 0.60 (1H, dt, *J*= 5.4, 9.2 Hz), 0.93 (3H, d, *J*= 6.3 Hz), 1.07–1.18 (1H, m), 1.29–1.63 (6H, m), 3.99 (1H, br s), 4.40–4.48 (1H, m); Anal. Calcd for $C_8H_{14}O_2$: C, 66.62; H, 9.94. Found: C, 67.11; H, 9.82. Compound **20**; colorless oil; $[\alpha]_D^{23}$ –24.1° (*c* 0.08, $CHCl_3$); IR (film) ν_{max} 3360, 3012, 2927, 1726, 1462, 1255, 1141, 1107, 1036, 982, 927, 845, 746 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.53 (1H, dt, *J*= 5.3, 8.9 Hz), 0.76 (1H, q, *J*= 5.3 Hz), 0.97 (3H, d, *J*= 6.3 Hz), 1.22 (1H, ddd, *J*= 4.8, 11.9, 14.3 Hz), 1.34–1.68 (6H, m), 3.64 (1H, dd, *J*= 5.6, 8.4 Hz), 4.33 (1H, ddd, *J*= 3.0, 4.8, 7.6 Hz); Anal. Calcd for $C_9H_{14}O_2$: C, 66.62; H, 9.94. Found: C, 66.13; H, 9.80.

Single crystal X-ray diffraction analysis of 19: Recrystallizaton of **19** again from diethyl ether/chloroform gave colorless prisms for X-ray analysis; $C_8H_{14}O_2$, *M*r=142.20, monoclinic, space group $P4_3$, *a*=10.580(4) Å, *c*=7.236(4) Å, *V* = 810.0(6) Å^3, *Z*=4, *D*x= 1.166 g/cm^3, *F*(000)=312, and μ(Mo*K*α)=0.84 cm^{-1}, crystal size 0.2 x 0.2 x 1.0 mm. All data were obtained on Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo *K*α radiation. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. The intensities were measured using $\omega/2\theta$ scan up to 45°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors. Absorption corrections were applied (Transmission factor = 0.8 to 1.0). Of the 663 independent reflections which were collected, 424 reflections with $I > 3.0\ \sigma(I)$ were used for structure determination and refinement. The structure was solved by direct method using TEXSAN crystallographic software package (Molecular Structure Corporation). All non-H atoms were found in the Fourier map. All H atoms were calculated at geometrical positions and refined isotropically. The refinement of atomic parameters was carried out by the full matrix least-squares refinement, using anisotropically temperature factors for all non-H atoms. The final refinement converged with *R* = 0.070 and *R*w = 0.075 for 90 parameters. The minimum and maximum peaks in the final difference Fourier map were –0.23 and 0.27 eÅ^{-3}. The supplementary data has been deposited at Cambridge Crystallographic Data Center.

(2R,3R)-2,3-Epoxypentan-1-ol (21)

The epoxy alcohol **21** was prepared from the corresponding allyl alcohol by Sharpless' asymmetric epoxidation.[8] To a solution of (–)-diethyl tartrate (13.0 g, 63 mmol) and (*E*)-2-pentenol[23] (20.7 g, 240 mmol) in dichlorometane (500 mL) in the presence of powdered 3A-molecular seives (14.4 g, activated in a vacuum oven at 160°C and 1 mmHg pressure for 12 hr) at –20°C was added titanium(IV) isopropoxide (13.0 g, 46 mmol). After being stirred for 30 min, *tert*-butyl hydroperoxide (96 mL of 5 M solution in decane, 480 mmol) was added over 15 min. The reaction mixture was stirred for 3 hr at the same temperature and quenched by the addition of sodium thiosulfate pentahydrate (60 g) and water (30 mL). After being stirred at room temperature for 3 hr, the mixture was diluted with diethyl ether (1 L) and filtered through Celite® pad. The filtrate was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (500 g) eluted with *n*-hexane/ethyl acetate (1:1) to give an inseparable mixture of **21** and (–)-diethyl tartrate. The mixture was distilled (84–85°C/20 mmHg, lit. 77–78°C/2266 Pa [8c]) to give **21** (14.8 g, 60%, 93% ee) as a colorless oil. The optical purity was determined by GC analysis (PEG-20M, 0.25 mm I. D. x 60 m L.) of its Mosher ester according to the literature.[8b]

(2R,3R)-2,3-Epoxypentyl benzoate (22)

To a solution of **21** (4.1 g, 40 mmol), triethylamine (12.2 g, 121 mmol), and 4-dimethylaminopyridine (49 mg, 0.4 mmol) in dichloromethane (50 mL) at 0°C was added benzoyl chloride (6.7 g, 48 mmol). After 30 min, methanol (1 mL) was added. Stirring was continued for additional 30 min and water (50 mL) was added. The mixture was extracted with diethyl ether (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (500 g) eluted with *n*-hexane/ethyl acetate (15:1–5:1) to give **22** (8.1 g, quantitative); colorless oil; $[\alpha]_D^{23}$ +21.5°(*c* 1.03, $CHCl_3$); IR (film) ν_{max} 2970, 1724, 1602, 1452, 1385, 1315, 1274, 1177, 1107, 1070, 1026, 972, 892, 713 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, t, *J*= 7.5 Hz), 1.56–1.72 (2H, m), 2.93 (1H, dt, *J*= 2.8, 5.7 Hz), 3.12 (1H, ddd, *J*= 2.8, 3.3, 6.2 Hz), 4.18 (1H, dd, *J*= 6.2, 12.3 Hz), 4.62 (1H, dd, *J*= 3.3, 12.3 Hz), 7.44 (2H, t, *J*= 7.5 Hz), 7.57 (1H, t, *J*= 7.5 Hz), 8.06 (2H, d, *J*= 7.5 Hz); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.86. Found: C, 69.84; H, 6.85.

(2S,3R)-6-tert-Butyldimethylsilyloxy-3-ethyl-2-hydroxy-4-hexynyl benzoate (23)

To a solution of propargyl alcohol *tert*-butyldimethylsilyl ether (6.1 g, 36 mmol) in diethyl ether (300 mL) under nitrogen atmosphere at –78°C was added *n*-butyllithium (23 mL of 1.66 M solution in *n*-hexane, 38 mmol) over 20 min. After 1 hr, trimethylaluminum (36 mL of 1.01 M solution in *n*-hexane, 36 mmol) was added over 50 min. After 1 hr, **22** (6.1 g, 30 mmol) in diethyl ether (30 mL) was added over 15 min. After 20 min, boron trifluoride diethyl etherate (5.1 g, 36 mmol) in diethyl ether (15 mL) was added over 15 min and stirring was continued for 1 hr. The mixture was quenched with methanol (30 mL) and allowed to warm to 0°C over 2 hr. Saturated aqueous sodium bicarbonate (300 mL) was added and the mixture was extracted with diethyl ether (3 x 300 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (1 kg) eluted with *n*-hexane/ethyl acetate (10:1–5:1) to give **23** (4.9 g, 43%) along with a less polar impurity (3.2 g, not identified); colorless oil; $[\alpha]_D^{21}$ +27.3°(*c* 1.14, $CHCl_3$); IR (film) ν_{max} 3472, 2957, 2930, 2858, 1724, 1603, 1584, 1453, 1373, 1316, 1276, 1093, 1027, 1002, 837, 779, 712 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.90 (9H, s), 1.07 (3H, t, *J*= 7.4 Hz), 1.55 (1H, ddq, *J*= 9.5, 11.7, 7.4 Hz), 1.79 (1H, ddq, *J*= 4.3, 11.7, 7.4 Hz), 2.41 (1H, d, *J*= 5.6 Hz), 2.55–2.65 (1H, m), 3.88–3.97 (1H, m), 4.32 (2H, d, *J*= 1.9 Hz), 4.45 (1H, dd, *J*= 6.9, 11.7 Hz), 4.64 (1H, dd, *J*= 2.9, 11.7 Hz), 7.45 (2H, t, *J*= 7.5 Hz), 7.58 (1H, t, *J*= 7.5 Hz), 8.06 (2H, t, *J*= 7.5 Hz); Anal. Calcd for $C_{21}H_{32}O_4Si$: C, 66.97; H, 8.58. Found: C, 67.20; H, 8.72.

(2S,3R,4Z)-6-tert-Butyldimethylsilyloxy-3-ethyl-2-hydroxy-4-hexenyl benzoate (24)

To a solution of **23** (4.0 g, 11 mmol) in methanol (50 mL) was added Lindlar catalyst (0.2 g, Aldrich Chemical Co.). The mixture was stirred vigorously under hydrogen atmosphere (1 atm) at room temperature for 3 hr, filtered through Celite® pad and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) eluted with *n*-hexane/ethyl acetate (10:1) to give **24** (4.0 g, quantitative); colorless oil; $[\alpha]_D^{26}$ +4.31°(*c* 0.19, $CHCl_3$); IR (film) ν_{max} 3479, 2956, 2857, 1723, 1603, 1584, 1453, 1379, 1362, 1316, 1275, 1177, 1093, 1027, 837, 776, 712, 687 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.88 (9H, s), 0.90 (3H, t, *J*= 7.4 Hz), 1.31 (1H, ddq, *J*= 9.9, 13.5, 7.4 Hz), 1.80 (1H, ddq, *J*= 3.7, 13.5, 7.4 Hz), 2.52–2.56 (1H, m), 2.59 (1H, d, *J*= 5.8 Hz), 3.80–3.87 (1H, m), 4.21 (1H, dd, *J*= 6.8, 11.6 Hz), 4.22 (2H, dd, *J*= 1.5, 6.2 Hz), 4.46 (1H, dd, *J*= 2.9, 11.6 Hz), 5.23 (1H, tt, *J*= 1.5, 10.9 Hz), 5.79 (1H, dt, *J*= 10.9, 6.2 Hz), 7.44 (2H, t, *J*= 7.5 Hz), 7.57 (1H, t, *J*= 7.5 Hz), 8.05 (2H, d, *J*= 7.5 Hz); Anal. Calcd for $C_{21}H_{34}O_4Si$: C, 66.61; H, 9.07. Found: C, 66.45; H, 9.05.

(2S,3R,4Z)-2,6-Bis-tert-butyldimethylsilyloxy-3-ethyl-4-hexenyl benzoate (25)

To a solution of **24** (290 mg, 0.77 mmol) and 2,6-lutidine (312 mg, 2.91 mmol) in dichloromethane (15 mL) under nitrogen atmosphere at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.32 mL, 1.39 mmol) over 10 min. After being stirred for 1 hr, brine (20 mL) was added and the mixture was extracted with dichloromethane (2 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (20:1) to give **25** (378 mg, quantitative), which was employed in the next step without further purification; colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.05 (3H, s), 0.07 (3H, s), 0.85 (9H, s), 0.86 (3H, t, *J*= 7.4 Hz), 0.87 (9H, s), 1.23 (1H, ddq, *J*= 10.9, 13.4, 7.4 Hz), 1.75 (1H, ddq, *J*= 3.5, 13.4, 7.4 Hz), 2.46 (1H, ddt, *J*=3.5, 5.3, 10.9 Hz), 3.83 (1H, dt, *J*= 4.1, 5.3 Hz), 4.15 (1H, ddd, *J*= 1.6, 5.9, 13.3 Hz), 4.20 (1H, dd, *J*= 5.3, 11.4 Hz), 4.25 (1H, ddd, *J*= 1.6, 6.7, 13.3 Hz), 4.36 (1H, dd, *J*= 4.1, 11.4 Hz), 5.23 (1H, tt, *J*= 1.6, 10.9 Hz), 5.67 (1H, br dt, *J*= 10.9, 5.9, 6.7 Hz), 7.44 (2H, t, *J*= 7.5 Hz), 7.57 (1H, t, *J*= 7.5 Hz), 8.05 (2H, d, *J*= 7.5 Hz).

(2S,3R,4Z)-2,6-Bis-tert-butyldimethylsilyloxy-3-ethyl-4-hexen-1-ol (26)

To a solution of **25** (237 mg, 0.48 mmol) in THF (10 mL) under nitrogen atmosphere at –78°C was added methyllithium (1.0 mL of 1 M solution in diethyl ether, 1.0 mmol) over 10 min. After being stirred for 30 min, the mixture was quenched with water (0.1 mL), warmed to room temperature, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (30:1) to give **26** (159 mg, 85%), which was employed in the next step without further purification; colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.08 (6H, s), 0.82 (3H, t, *J*= 7.4 Hz), 0.90 (9H, s), 0.91 (9H, s), 0.97–1.13 (1H, m), 1.72–1.85 (1H, m), 2.30 (1H, br t, *J*= 6.6 Hz), 2.51 (1H, ddt, *J*=3.5, 8.3, 10.9 Hz), 3.44 (1H, dt, *J*= 8.3, 3.5 Hz), 3.50–3.61 (2H, m), 4.16 (1H, ddd, *J*= 1.5, 6.1, 12.7 Hz), 4.29 (1H, ddd, *J*= 1.5, 6.8, 12.7 Hz), 5.15 (1H, tt, *J*= 1.5, 10.9 Hz), 5.69 (1H, br dt, *J*= 10.9, 6.1, 6.8 Hz).

(2S,3R,4Z)-2,6-Bis-tert-butyldimethylsilyloxy-3-ethyl-4-hexenyl trifluoromethanesulfonate (27)

To a solution of **26** (100 mg, 0.26 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (264 mg, 1.29 mmol) in dichloromethane (10 mL) under nitrogen atmosphere at –78°C was added trifluoromethanesulfonic anhydride (56 μL, 0.33 mmol) over 10 min. After being stirred for 30 min, the mixture was quenched with water (0.1 mL) and warmed to room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with diethyl ether (3 x 30 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (50:1) to give **27** (134 mg, quantitative), which was employed in the next step without further purification; colorless oil;.^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.08 (3H, s), 0.09 (3H, s), 0.85 (3H, t, *J*= 7.4), 0.90 (9H, s), 0.91 (9H, s), 1.13 (1H, ddq, *J*= 10.9, 14.9, 7.4 Hz), 1.72 (1H, ddq, *J*= 3.5, 14.9, 7.4 Hz), 2.39 (1H, ddt, *J*= 3.5, 7.1, 10.9 Hz), 3.74 (1H, ddd, *J*= 2.9, 6.1, 7.1 Hz), 4.20 (2H, dd, *J*= 1.6, 5.8 Hz), 4.31 (1H, dd, *J*= 6.1, 10.1 Hz), 4.50 (1H, dd, *J*= 2.9, 10.1 Hz), 5.10 (1H, tt, *J*= 1.6, 10.9 Hz), 5.73 (1H, dt, *J*= 10.9, 5.8 Hz).

(2S,3R,4Z)-6-tert-Butyldimethylsilyloxy-3-ethylhex-4-ene-1,2-diol (28)

To a solution of **24** (2.00 g, 5.28 mmol) in methanol (50 mL) at room temperature was added potassium carbonate (50 mg, 0.36 mmol). After being stirred for 3 hr, water (100 mL) was added and the mixture was extracted with diethyl ether (5 x 100 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl

acetate (5:1–2:1) to give **28** (1.44 g, 99%); colorless oil; $[\alpha]_D^{24}$ +89.9° (*c* 0.21, $CHCl_3$); IR (film) ν_{max} 3391, 2957, 2930, 2858, 1463, 1362, 1255, 1081, 940, 837, 777, 717, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.85 (3H, t, *J*= 7.4 Hz), 0.91 (9H, s), 1.15–1.29 (1H, m), 1.78–1.92 (1H, m), 2.29 (2H, br s), 2.47–2.59 (1H, m), 3.39–3.45 (1H, m), 3.55–3.66 (2H, m), 4.06 (1H, dd, *J*= 6.3, 12.1 Hz), 4.28 (1H, ddd, *J*= 1.4, 8.0, 12.1 Hz), 5.27 (1H, br t, *J*= 10.9 Hz), 5.79 (1H, ddd, *J*= 6.3, 8.0, 10.9 Hz); Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.25; H, 11.04. Found: C, 60.87; H, 11.08.

(2S,3R,4Z)-6-tert-Butyldimethylsilyloxy-3-ethyl-1-p-toluenesulfonyloxy-4-hexen-2-ol (29)

To a solution of **28** (0.92 g, 3.4 mmol), triethylamine (1.70 g, 16.8 mmol), and 4-dimethylaminopyridine (10 mg) in dichloromethane (50 mL) under nitrogen atmosphere at 0°C was added *p*-toluenesulfonyl chloride (0.83 g, 4.4 mmol). After being stirred for 3 hr, water (100 mL) was added and the mixture was extracted with diethyl ether (2 x 100 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl acetate (10:1–7:1) to give **29** (1.10 g, 76%); colorless oil; $[\alpha]_D^{24}$ +3.87° (*c* 0.51, $CHCl_3$); IR (film) ν_{max} 3444, 2956, 2857, 1734, 1599, 1463, 1361, 1255, 1189, 1177, 1096, 974, 902, 836, 776 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.83 (3H, t, *J*= 7.5 Hz), 0.88 (9H, s), 1.14–1.28 (1H, m), 1.66–1.80 (1H, m), 2.32–2.43 (1H, m), 2.44 (3H, s), 2.51 (1H, d, *J*= 5.5 Hz), 3.63–3.72 (1H, m), 3.86 (1H, dd, *J*= 7.4, 10.4 Hz), 4.12 (1H, dd, *J*= 2.9, 10.4 Hz), 4.14 (2H, dd, *J*= 1.2, 6.3 Hz), 5.10 (1H, tt, *J*= 1.2, 10.9 Hz), 5.71 (1H, dt, *J*= 10.9, 6.3 Hz), 7.33 (2H, d, *J*= 8.2 Hz), 7.78 (2H, d, *J*= 8.2 Hz); Anal. Calcd for $C_{21}H_{36}O_5SSi$: C, 58.83; H, 8.48. Found: C, 58.72; H, 8.53.

(2S,3R,4Z)-2,6-Bis-tert-butyldimethylsilyloxy-3-ethyl-4-hexenyl p-toluenesulfonate (30)

To a solution of **29** (97 mg, 0.23 mmol) and 2,6-lutidine (0.10 mL, 0.86 mmol) in dichloromethane (5 mL) under nitrogen atmosphere at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (94 μL, 0.41mmol) over 10 min. After being stirred for 1 hr, brine (20 mL) was added and the mixture was extracted with dichloromethane (2 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (10 g) eluted with *n*-hexane/ethyl acetate (10:1) to give **30** (124 mg, quantitative), which was employed in the next step without further purification; colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.03 (3H, s), 0.05 (6H, s), 0.78 (3H, t, *J*= 7.4 Hz), 0.84 (9H, s), 0.89 (9H, s), 1.11 (1H, ddq, *J*= 10.9, 18.4, 7.4 Hz), 1.50–1.64 (1H, m), 2.28 (1H, ddt, *J*= 1.8, 6.4, 10.9 Hz), 2.45 (3H, s), 3.67 (1H, dt, *J*= 3.6, 6.4 Hz), 3.80 (1H, dd, *J*= 6.4, 9.8 Hz), 4.01 (1H, dd, *J*= 3.6, 9.8 Hz), 4.13 (1H, ddd, *J*= 1.6, 5.8, 13.2 Hz), 4.19 (1H, ddd, *J*= 1.6, 5.8, 13.2 Hz), 5.06 (1H, tt, *J*= 1.6, 10.9 Hz), 5.62 (1H, dt, *J*= 10.9, 5.8 Hz), 7.33 (2H, d, *J*= 8.3 Hz), 7.77 (2H, d, *J*= 8.3 Hz).

(2S,3R,4Z)-2,6-Bis-tert-butyldimethylsilyloxy-3-ethyl-1-iodo-4-hexene (31)

A mixture of **30** (100 mg, 0.18 mmol), sodium iodide (83 mg, 0.55 mmol), sodium bicarbonate (46 mg, 0.55 mmol) in DMF (10 mL) under nitrogen atmosphere was stirred at 90°C for 12hr. After cooling, the mixture was poured into cold water (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (100:1–50:1) to give **31** (76 mg, 83%), which was employed in the next step without further purification; colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (6H, s), 0.09 (3H, s), 0.84 (3H, t, *J*= 7.5 Hz), 0.92 (9H, s), 0.94 (9H, s), 1.13 (1H, ddq, *J*= 10.9, 14.6, 7.5 Hz), 1.72 (1H, ddq, *J*= 3.4, 14.6, 7.5 Hz), 2.45 (1H, ddt, *J*= 3.4, 7.0, 10.9 Hz), 3.12 (1H, ddd, *J*= 3.1, 5.1, 7.0 Hz), 3.24 (1H, dd, *J*= 5.1, 10.1 Hz), 3.29 (1H, dd, *J*= 3.1, 10.1 Hz), 4.30 (1H, ddd, *J*= 1.7, 6.0, 13.1 Hz), 4.40 (1H, ddd, *J*= 1.7, 6.0, 13.1 Hz), 5.02 (1H, tt, *J*= 1.7, 10.9 Hz), 5.66 (1H, dt, *J*= 10.9, 6.0 Hz).

(2S,3R,4Z)-6-tert-Butyldimethylsilyloxy-3-ethyl-1,2-epoxy-4-hexene (32)

To a solution of **29** (1.00 g, 2.3 mmol) in methanol (30 mL) at room temperature was added potassium carbonate (0.39 g, 2.8 mmol). After being stirred for 1 hr, water (100 mL) was added and the mixture was extracted with diethyl ether (3 x 100 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) eluted with *n*-hexane/ethyl acetate (30:1) to give **32** (0.53 g, 89%); colorless oil; $[\alpha]_D^{26}$ −11.2° (*c* 0.52, $CHCl_3$); IR (film) ν_{max} 2958, 2930, 2857, 2463, 1408, 1362, 1255, 1091, 838, 777 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 0.91 (3H, t, *J*= 7.5 Hz), 1.38 (1H, ddq, *J*= 7.4, 12.5, 7.5 Hz), 1.71 (1H, ddq, *J*= 4.9, 12.5, 7.5 Hz), 2.05–2.15 (1H, m), 2.47 (1H, dd, *J*= 2.6, 4.9 Hz), 2.69 (1H, t, *J*= 4.9 Hz), 2.80(1H, ddd, *J*= 2.6, 4.9, 6.9 Hz), 4.18 (2H, dd, *J*= 1.3, 6.0 Hz), 5.22 (1H, tt, *J*= 1.3, 10.7 Hz), 5.68 (1H, dt, *J*= 10.7, 6.0 Hz); Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.55; H, 11.03. Found: C, 65.97; H, 11.04.

(3S,5S)-4-Methoxy-3,5-dimethylcyclohexanone (34)

To liquid ammonia (*ca.* 30 mL) under nitrogen atmosphere at −78°C was added lithium (*ca.* 22 mg). After 15 min, a solution of **17** (100 mg, 0.65 mmol) in THF (5 mL) was added over 5 min to the dark-blue solution and the mixture was stirred for additional 30 min. Ammonium chloride (50 mg) was added and the white suspension was allowed to warm to room temperature. After evaporation of ammonia was complete, diethyl ether (30 mL) and anhydrous sodium sulfate was added to the residual white solid. The mixture was stirred vigorously for 1 hr and filtered through Celite® pad. The filter cake was washed with diethyl ether and the combined filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (10:1–5:1) to give **34** (76 mg, 75%). Birch reduction of **18** (100 mg) was performed as described above to give **34** (79 mg, 78%); colorless oil; $[\alpha]_D^{26}$ −14.0° (*c* 0.51, $CHCl_3$); IR (film) ν_{max} 2960, 2824, 1714, 1455, 1382, 1279, 1245, 1194, 1140, 1101, 1039, 987, 945, 920 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, d, *J*= 7.0 Hz), 0.99 (3H, d, *J*= 6.3 Hz), 1.99 (1H, ddd, *J*= 1.3, 5.6, 14.0 Hz), 2.18–2.48 (4H, m), 2.58 (1H, dd, *J*= 5.8, 14.0 Hz), 3.09 (1H, dd, *J*= 2.4, 5.2 Hz), 3.42 (3H, s); Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 69.33; H, 10.26.

(1R,3R,4S,5R,6S)-3-Hydroxy-5-methoxy-4-methylbicyclo[4.1.0]heptan-2-one (39) and (1R,3S,4S,5R,6S)-3-hydroxy-5-methoxy-4-methylbicyclo[4.1.0]heptan-2-one (40)

Oxidation of silyl enol ether of 17 with osmium tetroxide: To a solution of **17** (4.30 g, 28 mmol) and triethylamine (8.50 g, 84 mmol) in dichloromethane (100 mL) under nitrogen atmosphere at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (7.7 mL, 34 mmol) over 10 min. After being stirred for 30 min, the mixture was poured into cold *n*-pentane (300 mL). The organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. In order to remove polar impurities, the residue was chromatographed on silica gel (15 g) eluted with *n*-pentane/diethyl ether (5:1) to give a colorless oil (7.79g).

To a mixture of a portion of the above oil (6.60 g), 4-methylmorpholine *N*-oxide (3.40 g, 29 mmol), THF (300 mL) at room temperature was added osmium tetroxide (60 mg, 0.24 mmol). After being stirred for 12 hr, 15% aqueous sodium thiosulfate (500 mL) was added and the mixture was extracted with chloroform (3 x 300 mL). The combined organic phase was washed with brine (300 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl acetate (3:1) to give an inseparable mixture (*ca.* 2:3, determined by integration of ^{1}H-NMR spectrum) of **39** and **40** (4.00 g, quantitative yield from **17**), which were employed in the next step without further purification; colorless oil; $[\alpha]_D^{20}$ −143° (*c* 0.15, $CHCl_3$); IR (film) ν_{max} 3439, 2977, 2939, 2829, 1695, 1454, 1328, 1220, 1190, 1157, 1091, 1026, 986, 920, 893, 844, 825 cm^{-1}; ^{1}H-NMR spectroscopic data of **39** and **40** are described below; Anal. Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.31. Found: C, 63.28; H, 8.27.

Oxidation of silyl enol ether of 17 with *m*-CPBA: To a solution of **17** (170 mg, 1.1 mmol) and triethylamine (390 mg, 3.9 mmol) in dichloromethane (10 mL) at 0°C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.33 mL, 1.4 mmol) over 5 min. After being stirred for 30 min, the mixture was added at 0°C to a solution of *m*-chloroperbenzoic acid (770 mg, 4.5 mmol) in dichloromethane (10 mL). After 1 hr, 1 M aqueous sodium hydroxide (10 mL) was added and the mixture was extracted with chloroform (5 x 30 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was dissolved in acetonitrile (10 mL) and 48% aqueous hydrogen fluoride (200 mg) was added at room temperature. The mixture was stirred at 70°C for 1 hr. After cooling, saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with ethyl acetate (5 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (5:1) to give **39** (122 mg, 65%); pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, *J*= 6.8 Hz), 1.00 (1H, q, *J*= 5.7 Hz), 1.44 (1H, dt, *J*= 5.7, 9.6 Hz), 1.67–1.76 (1H, m), 1.97 (1H, ddd, *J*= 5.7, 7.8, 9.6 Hz), 2.55–2.64 (1H, m), 3.42 (3H, s), 3.60 (1H, d, *J*= 3.5 Hz), 3.75 (1H, dd, *J*= 1.6, 4.6 Hz), 3.96 (1H, t, *J*= 3.5 Hz).

Oxidation of 17 with $Pb(OAc)_4$: A mixture of **17** (259 mg, 1.68 mmol), lead tetraacetate (2.24 g, 5.05 mmol) and benzene (20 mL) was stirred at 80°C for 40 hr. After cooling, 15% aqueous sodium thiosulfate (50 mL) was added and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organic phase was successively washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (10:1–5:1) to give the acetate of **40** (268 mg, 75%) as a colorless oil. To a solution of the acetate (120 mg, 0.57 mmol) in methanol (5 mL) at room temperature was added potassium carbonate (10 mg). After being stirred for 5 hr, diethyl ether (15 mL) and anhydrous magnesium sulfate was added and the mixture was stirred vigorously for 1 hr. The mixture was filtered through Celite® pad and the filter cake was washed with diethyl ether. The combined filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (5:1–3:1) to give **40** (51 mg, 53%); colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (1H, q, *J*= 5.3 Hz), 1.18 (3H, d, *J*= 6.7 Hz), 1.17–1.25 (1H, m), 1.74 (1H, ddq, *J*= 2.2, 12.2, 6.7 Hz), 1.83–1.96 (2H, m), 3.31 (1H, br s), 3.51 (3H, s), 3.71 (1H, t, *J*= 2.2 Hz), 3.84 (1H, d, *J*= 12.2 Hz).

*(2R,3S,4R,5S)-2-Hydroxy-4-methoxy-3,5-dimethylcyclohexanone (**41**) and (2S,3S,4R,5S)-2-hydroxy-4-methoxy-3,5-dimethylcyclohexanone (**42**)*

To a solution of a mixture (*ca.* 2:3) of **39** and **40** (600 mg, 35 mmol, obtained by the osmium tetroxide oxidation of the silyl enol ether of **17**) in THF (30 mL) under nitrogen atmosphere at –78°C was added lithium bis(trimethylsilyl)amide (35 mL of 1 M solution in *n*-hexane, 35 mmol) over 10 min. After being stirred for additional 5 min, the mixture was added through a cannular to a dark-blue solution of lithium (*ca.* 240 mg, 35 mg atom) in liquid ammonia (*ca.* 200 mL) under nitrogen atmosphere at –78°C. After 10 min, ammonium chloride (200 mg) was added and the mixture was allowed to warm to room temperature. After evaporation of ammonia was complete, chloroform (200 mL) and anhydrous magnesium sulfate was added to the residual white solid. The mixture was stirred vigorously for 1 hr and filtered through Celite® pad. The filter cake was washed with chloroform and the combined filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) eluted with *n*-hexane/ethyl acetate (10:1–5:1) to give **42** (190 mg, 31%) as a less polar isomer and **41** (140 mg, 23%, white solid). Compound **41** (after recrystallization from *n*-hexane); colorless plates; mp 67–68°C; $[\alpha]_D^{21}$ +54.7° (*c* 0.24, $CHCl_3$); IR (nujol) ν_{max} 3419, 1716, 1229, 1170, 1096, 1047, 975 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, d, *J*= 7.1 Hz), 1.10 (3H, d, *J*= 5.9 Hz), 1.99–2.14 (2H, m), 2.50 (1H, dd, *J*= 9.2, 12.2 Hz), 2.87 (1H, ddq, *J*= 4.2, 5.7, 7.1 Hz), 3.27 (1H, dd, *J*= 4.2, 9.8 Hz), 3.41 (3H, s), 3.42 (1H, s),

4.23 (1H, d, *J*= 5.7 Hz); Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.38. Found: C, 62.74; H, 9.39. Compound **42**; colorless oil; $[\alpha]_D^{23}$ –90.7° (*c* 0.19, $CHCl_3$); IR (film) ν_{max} 3479, 2965, 2933, 2826, 1714, 1456, 1424, 1386, 1243, 1192, 1160, 1097, 1064, 1005, 926, 804 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, d, *J*= 7.3 Hz), 1.25 (3H, d, *J*= 6.6 Hz), 1.90 (1H, ddq, *J*= 2.6, 11.2, 6.6 Hz), 2.18 (1H, br d, *J*= 13.3 Hz), 2.56–2.67 (1H, m), 2.88 (1H, dd, *J*= 6.2, 13.3 Hz), 3.12 (1H, t, *J*= 2.6 Hz), 3.44 (4H, s), 4.07 (1H, br d, *J*= 11.2 Hz); Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.38. Found: C, 63.08; H, 9.31.

Methyl (3S,4R,5R)-6-oxo-4-methoxy-3,5-dimethylhexanoate (43)

To a solution of **41** (42 mg, 0.24 mmol) in benzene-methanol (v/v= 4:1, 10 mL) at room temperature was added lead tetraacetate (140 mg, 0.32 mmol). After being stirred for 10 min, 15% aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL) was added to the reddish yellow solution. The mixture was stirred for 30 min and extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC developed with benzene/ethyl acetate (4:1) to give **43** (44 mg, 89%). The oxidative cleavage of **42** (48 mg) was performed as described above to give **43** (44 mg, 78%). In larger-scale reaction, the mixture of **41** and **42** (2:3, 2.30 g) was oxidized as described above to give **43** (2.18 g, 81%); colorless oil; $[\alpha]_D^{21}$ –17.5° (*c* 0.34, $CHCl_3$); IR (film) ν_{max} 2976, 2836, 1732, 1438, 1382, 1286, 1174, 1087, 1007 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, *J*= 6.4 Hz), 1.07 (3H, d, *J*= 7.1 Hz), 2.21–2.34 (1H, m), 2.28 (1H, dd, *J*= 7.7, 18.1 Hz), 2.47 (1H, dd, *J*= 9.3, 18.1 Hz), 2.62 (1H, dqui, *J*= 2.7, 7.1 Hz), 3.32 (1H, dd, *J*= 2.8, 7.1 Hz), 3.39 (3H, s), 3.69 (3H, s), 9.78 (1H, d, *J*= 2.7 Hz); Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.99. Found: C, 58.88; H, 8.75.

Methyl (3S,4R,5R)-5-(1,3-dioxolan-2-yl)-4-methoxy-3-methylhexanoate (44)

A mixture of **43** (2.10 g, 10.4 mmol), ethylene glycol (13.0 g, 209 mmol), *p*-toluenesulfonic acid monohydrate (50 mg), and benzene (100 mL) was heated and refluxed for 30 min with azeotropic removal of water by passing a condensed liquid through a column of 4A-molecular seives. After cooling, the mixture was poured into cold saturated aqueous sodium bicarbonate (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (150 g) eluted with *n*-hexane/ethyl acetate (5:1) to give **44** (2.51 g, 98%); colorless oil; $[\alpha]_D^{24}$ –20.4° (*c* 0.31, $CHCl_3$); IR (film) ν_{max} 2976, 2885, 1739, 1437, 1365, 1283, 1165, 1087, 1045, 1009, 943 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, *J*= 6.9 Hz), 0.88 (3H, d, *J*= 6.6 Hz), 2.00 (1H, ddq, *J*= 2.4, 9.6, 6.6 Hz), 2.19–2.30 (1H, m), 2.33 (1H, dd, *J*= 7.8, 14.7 Hz), 2.45 (1H, dd, *J*= 6.1, 14.7 Hz), 3.07 (1H, dd, *J*= 2.2, 9.6 Hz), 3.41 (3H, s), 3.68 (3H, s), 3.82–3.99 (4H, m), 5.04 (1H, d, *J*= 2.4 Hz); Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.50; H, 9.02. Found: C, 58.63; H, 9.01.

(3S,4R,5R)-5-(1,3-Dioxolan-2-yl)-4-methoxy-3-methylhexanal (45)

To a solution of **44** (2.50 g, 10.1 mmol) in dichloromethane (100 mL) under nitrogen atmosphere at –78°C was added dropwise diisobutylaluminum hydride (12.0 mL of 0.94 M solution in *n*-hexane, 11.3 mmol) over 30 min. After being stirred for 30 min, the reaction mixture was quenched with methanol (1.5 mL) and allowed to warm to room temperature over 1 hr. Saturated aqueous ammonium chloride (1.5 mL) was added and stirring was continued for 1 hr. The mixture was dried over anhydrous magnesium sulfate and filtered through Celite® pad. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl acetate (10:1) to give **45** (2.02 g, 91%); colorless oil; $[\alpha]_D^{24}$ +2.59° (*c* 0.31, $CHCl_3$); IR (film) ν_{max} 2885, 1724, 1455, 1392, 1090, 1045, 942 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*=

6.8 Hz), 0.95 (3H, d, *J*= 6.5 Hz), 2.03 (1H, ddq, *J*= 2.5, 9.3, 6.5 Hz), 2.30–2.41 (1H, m), 2.43 (1H, ddd, *J*= 2.0, 4.8, 16.4 Hz), 2.55 (1H, ddd, *J*= 2.0, 5.6, 16.4 Hz), 3.06 (1H, dd, *J*= 2.4, 9.3 Hz), 3.39 (3H, s), 3.84–4.00 (4H, m), 5.03 (1H, d, *J*= 2.5 Hz), 9.79 (1H, t, *J*= 2.0 Hz); Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.07; H, 9.34. Found: C, 60.86; H, 9.23.

(2R,3R,4S,6E)-2-(1,3-Dioxolan-2-yl)-3-methoxy-4-methyl-6-octene (46)

To a mixture of chromium(II) chloride (1.27 g, 10.3 mmol) and THF (30 mL) under dark and nitrogen atmosphere at room temperature was added a solution of **45** (280 mg, 1.29 mmol) and 1,1-diiodoethane[24] (726 mg, 2.58 mmol) in THF (5 mL) in one portion. After being stirred for 3 hr, water (50 mL) was added and the mixture was extracted with diethyl ether (2 x 50 mL). The combined organic phase was washed with brine (30 mL), washed with saturated aqueous sodium bicarbonate (30 mL), washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) eluted with *n*-hexane/ethyl acetate (20:1) to give **46** (236 mg, 80%); colorless oil; $[\alpha]_D^{25}$ +53.5° (*c* 0.10, $CHCl_3$); IR (film) ν_{max} 2970, 2935, 2883, 1454, 1380, 1161, 1097, 1043, 967, 941 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.80 (3H, d, *J*= 7.4 Hz), 0.83 (3H, d, *J*= 7.3 Hz), 1.61–1.73 (1H, m), 1.66 (3H, d, *J*= 5.0 Hz), 1.94–2.07 (2H, m), 2.10–2.18 (1H, m), 3.08 (1H, dd, *J*= 2.5, 9.4 Hz), 3.43 (3H, s), 3.83–4.00 (4H, m), 5.05 (1H, d, *J*= 2.3 Hz), 5.40 (1H, dt, *J*= 15.1, 5.7 Hz), 5.46 (1H, dq, *J*= 15.1, 5.0 Hz); Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.37; H, 10.61. Found: C, 68.05; H, 10.49. In larger scale, **45** (1.90 g) was converted to **46** (1.37 g, 69%) and 17% of **45** was recovered.

(2R,3R,4S,6E)-2-(1,3-Dithian-2-yl)-3-methoxy-4-methyl-6-octene (47)

To a solution of **46** (1.67g, 7.3 mmol) and 1,3-propanedithiol (1.19 g, 11.0 mmol) in dichloromethane (70 mL) under nitrogen atmosphere at –78°C was added boron trifluoride diethyl etherate (2.3 mL, 18.2 mmol) over 10 min. The mixture was stirred for 30 min, allowed to warm to 0°C over 2 hr, poured into cold saturated aqueous sodium bicarbonate (200 mL), and extracted with diethyl ether (2 x 100 mL). The combined organic phase was successively washed with 1N aqueous sodium hydroxide (2 x 100 mL) and brine (2 x 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/diethyl ether (50:1–30:1) to give **47** (1.94 g, 97%) as a white solid. Recrystallization from methanol gave an analytical sample; colorless needles; mp 76–77°C; $[\alpha]_D^{25}$ –8.89° (*c* 0.14, $CHCl_3$); IR (nujol) ν_{max} 1308, 1276, 1202, 1127, 1084, 1035, 968, 948, 912 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, d, *J*= 6.4 Hz), 0.98 (3H, d, *J*= 7.0 Hz), 1.59–1.70 (1H, m), 1.67 (3H, d, *J*= 5.1 Hz), 1.76–1.92 (1H, m), 1.95–2.06 (2H, m), 2.08–2.19 (2H, m), 2.83–2.90 (3H, m), 3.03 (1H, ddd, *J*= 2.4, 12.5, 13.9 Hz), 3.23 (1H, dd, *J*= 2.0, 9.9 Hz), 3.54 (3H, s), 4.52 (1H, d, *J*= 2.4 Hz), 5.40 (1H, dt, *J*= 14.1, 5.5 Hz), 5.47 (1H, dq, *J*= 14.1, 5.1 Hz); Anal. Calcd for $C_{14}H_{26}OS_2$: C, 61.25; H, 9.57. Found: C, 61.56; H, 9.59.

2-[(2R,3R,4Z)-6-tert-Butyldimethylsilyloxy-3-ethyl-2-hydroxy-4-hexenyl]-2-[(1R,2R,3S,5E)-2-methoxy-1,3-dimethyl-5-heptenyl]-1,3-dithiane (48)

To a solution of **47** (630 mg, 2.29 mmol) in HMPA-THF (v/v= 1:10, 20 mL) under nitrogen atmosphere at 0°C was added *n*-butyllithium (1.8 mL of 1.53 M solution in *n*-hexane, 2.75 mmol) over 3 min. The reddish-yellow solution was stirred for 5 min and a solution of **32** (383 mg, 1.49 mmol) in HMPA-THF (v/v= 1:10, 2 mL) was added over 3 min. After being stirred for 30 min, water (30 mL) was added and the mixture was extracted with diethyl ether (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g). By eluting with *n*-hexane/ethyl acetate (100:1–80:1) the dithiane **47** (283 mg) was recovered. Further elution with *n*-hexane/ethyl acetate (–30:1) gave **48** (610 mg, 91% based on consumed **47** and 77% from **32**); colorless

oil; $[\alpha]_D^{22}$ −11.3°(*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3439, 2929, 2856, 1463, 1379, 1254, 1089, 967, 837, 776 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.76 (6H, s), 0.86 (3H, t, *J*= 7.4 Hz), 0.89 (3H, d, *J*= 6.5 Hz), 0.90 (9H, s), 1.15–1.30 (1H, m), 1.20 (3H, d, *J*= 7.0 Hz), 1.56–1.66 (1H, m), 1.67 (3H, d, *J*= 4.6 Hz), 1.73–2.06 (4H, m), 2.09–2.32 (4H, m), 2.52 (1H, qui, *J*= 6.5 Hz), 2.70–2.82 (2H, m), 2.93 (1H, ddd, *J*= 3.2, 9.9, 14.4 Hz), 3.03 (1H, ddd, *J*= 3.1, 10.1, 14.4 Hz), 3.37 (3H, s), 3.41 (1H, br d, *J*= 6.5 Hz), 3.73 (1H, br s), 3.90–3.98 (1H, m), 4.23 (2H, dd, *J*= 1.1, 6.0 Hz), 5.23 (1H, tt, *J*= 1.1, 10.9 Hz), 5.34–5.50 (2H, m), 5.70 (1H, dt, *J*= 10.9, 6.0 Hz); Anal. Calcd for $C_{28}H_{54}O_3S_2Si$: C, 63.33; H, 10.27. Found: C, 63.70; H, 10.23.

*(2Z,4R,5R,8R,9R,10S,12E)-tert-Butyldimethylsilyloxy-4-ethyl-5-hydroxy-9-methoxy-8,10-dimethyl-2,12-tetradecadien-7-one (**49**)*

To a mixture of **48** (1.70 g, 3.2 mmol), calcium carbonate (500 mg, 5.0 mmol), and THF (200 mL) at room temperature was added mercury(II) perchlorate (167 mL of 0.025 M solution in water). After being stirred for 30 min, the white suspension was diluted with diethyl ether (300 mL) and filtered through Celite® pad. Aqueous phase was separated and extracted with diethyl ether (2 x 100 mL). The combined organic phase was successively washed with saturated aqueous sodium bicarbonate (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl acetate (20:1) to give **49** (1.17 g, 83%); colorless oil; $[\alpha]_D^{24}$ +5.93° (*c* 0.18, $CHCl_3$); IR (film) ν_{max} 3443, 2931, 2857, 1709, 1462, 1378, 1255, 1201, 1089, 967, 838, 776 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.84 (3H, t, *J*= 7.4 Hz), 0.84(3H, d, *J*= 6.7 Hz), 0.90 (9H, s), 0.91 (3H, d, *J*= 7.0 Hz), 1.10–1.25 (1H, m), 1.53–1.65 (1H, m), 1.67 (3H, d, *J*= 5.4 Hz), 1.77–1.90 (1H, m), 1.91–2.01 (1H, m), 2.07–2.17 (1H, m), 2.22–2.33 (1H, m), 2.52 (1H, dd, *J*= 10.1, 16.8 Hz), 2.71 (1H, dd, *J*= 1.9, 16.8 Hz), 2.85 (1H, dq, *J*= 9.7, 7.0 Hz), 3.30 (3H, s), 3.36 (1H, dd, *J*= 2.0, 9.7 Hz), 3.48 (1H, d, *J*= 2.9 Hz), 3.78–3.86 (1H, m), 4.16–4.29 (2H, m), 5.11 (1H, t, *J*= 10.9 Hz), 5.37 (1H, dt, *J*= 15.3, 5.8 Hz), 5.46 (1H, dq, *J*= 15.3, 5.4 Hz), 5.70 (1H, dt, *J*= 10.9, 5.8 Hz); Anal. Calcd for $C_{25}H_{48}O_4Si$: C, 68.11; H, 11.00. Found: C, 68.02; H, 10.96.

*(2Z,12E,4R,5R,7R,8S,9R,10S)-1-tert-Butyldimethylsilyloxy-4-ethyl-9-methoxy-8,10-dimethyl-2,12-tetradecadiene-5,7-diol (**50**) and (2Z,4R,5R,7S,8S,9R,10S,12E)-1-tert-butyldimethylsilyloxy-4-ethyl-9-methoxy-8,10-dimethyl-2,12-tetradecadiene-5,7-diol (**51**)*

Table 3, entry 6: To a solution of **49** (550 mg, 1.25 mmol) in diethyl ether (50 mL) under nitrogen atmosphere at room temperature was added lithium iodide (840 mg, 6.28 mmol). After lithium iodide was completely dissolved (*ca.* 5 min), the solution was cooled to –78°C and stirred for 15 min. Lithium tri-*tert*-butoxyaluminum hydride (1.59 g, 6.25 mmol) was added in one portion. The mixture was allowed to warm slowly to 0°C over 2 hr and stirred at the same temperature for additional 1 hr. Saturated potassium sodium tartrate (50 mL) was added and the mixture was stirred at room temperature for 2 hr. The mixture was extracted with diethyl ether (2 x 100 mL) and the combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) eluted with *n*-hexane/ethyl acetate (10:1) to give **51** (50 mg, 9%, colorless oil) as a less polar isomer and **50** (502 mg, 91%, white solid). Compound **50** (after recrystallization from *n*-hexane); colorless needles; mp 96–97°C; $[\alpha]_D^{22}$ +11.6° (*c* 0.10, $CHCl_3$); IR (nujol) ν_{max} 3433, 1252, 1185, 1144, 1101, 1045, 1020, 997, 971, 945, 917, 839 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.86 (3H, t, *J*= 7.5 Hz), 0.90 (9H, s), 0.93 (3H, d, *J*= 6.4 Hz), 0.94 (3H, d, *J*= 7.2 Hz), 1.10–1.30 (2H, m), 1.66 (3H, d, *J*= 5.3 Hz), 1.68–1.90 (5H, m), 2.06–2.13 (1H, m), 2.35–2.46 (1H, m), 2.63 (1H, d, *J*= 6.7 Hz), 3.00 (1H, t, *J*= 5.4 Hz), 3.47 (3H, s), 3.48 (1H, d, *J*= 2.7 Hz), 3.68–3.78 (1H, m), 4.14–4.28 (3H, m), 5.18 (1H, t, *J*= 10.9 Hz), 5.35 (1H, dt, *J*= 15.4, 5.7 Hz), 5.43 (1H, dq, *J*= 15.4, 5.3 Hz), 5.71 (1H, dt, *J*= 10.9, 6.2 Hz); Anal. Calcd for $C_{25}H_{50}O_4Si$: C,

67.80; H, 11.40. Found: C, 68.25; H, 11.44. Compound **51**; colorless oil; $[\alpha]_D^{26}$ −22.4°(*c* 0.12, $CHCl_3$); IR (film) ν_{max} 3389, 2959, 2857, 1463, 1379, 1361, 1255, 1194, 1091, 966, 838 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.76 (3H, d, *J*= 7.0 Hz), 0.85 (3H, t, *J*= 7.5 Hz), 0.86 (3H, d, *J*= 7.1 Hz), 0.90 (9H, s), 1.15–1.34 (2H, m), 1.58–1.81 (5H, m), 1.67 (3H, d, *J*= 5.7 Hz), 1.92–2.05 (1H, m), 2.05–2.17 (1H, m), 2.27 (1H, ddt, *J*= 3.4, 6.9, 10.9 Hz), 2.98 (1H, dd, *J*= 2.4, 8.6 Hz), 3.46 (3H, s), 3.62–3.69 (1H, m), 3.82–3.89 (1H, m), 4.18–4.28 (2H, m), 4.39 (1H, br s), 5.18 (1H, t, *J*= 10.9 Hz), 5.37 (1H, dt, *J*= 15.3, 5.5 Hz), 5.46 (1H, dq, *J*= 15.3, 5.7 Hz), 5.70 (1H, dt, *J*= 10.9, 5.5 Hz); Anal. Calcd for $C_{25}H_{50}O_4Si$: C, 67.80; H, 11.40. Found: C, 68.14; H, 11.42.

(2Z,4R,5R,7R,8S,9R,10S,12E)-4-Ethyl-9-methoxy-8,10-dimethyl-2,12-tetradecadiene-1,5,7-triol (52)

To a solution of **50** (490 mg, 1.11 mmol) in THF (20 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.44 mL of 1 M solution in THF, 1.44 mmol). After being stirred for 1 hr, water (50 mL) was added and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) eluted with *n*-hexane/ethyl acetate (2:1–1:1) to give **52** (365 mg, quantitative) as a white solid. Recrystallization from *n*-hexane gave an analytical sample; colorless needles; mp 101°C; $[\alpha]_D^{24}$ +21.2° (*c* 0.15, $CHCl_3$); IR (nujol) ν_{max} 3416, 1193, 1099, 1045, 1029, 1013, 983, 967, 824 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, t, *J*= 7.4 Hz), 0.89 (3H, d, *J*= 7.1 Hz), 0.92 (3H, d, *J*= 7.5 Hz), 1.12–1.28 (1H, m), 1.36 (1H, ddd, *J*= 2.3, 7.3, 14.2 Hz), 1.59–1.93 (7H, m), 1.66 (3H, d, *J*= 5.2 Hz), 2.05–2.14 (1H, m), 2.52–2.63 (1H, m), 3.04 (1H, t, *J*= 3.2 Hz), 3.50 (3H, s), 3.51 (1H, d, *J*= 3.0 Hz), 3.83 (1H, dt, *J*= 3.0, 7.2 Hz), 4.02 (1H, ddd, *J*= 0.9, 6.0, 12.3 Hz), 4.17–4.22 (1H, m), 4.26 (1H, ddd, *J*= 0.9, 8.3, 12.3 Hz), 5.22 (1H, tt, *J*= 0.9, 10.9 Hz), 5.36 (1H, dt, *J*= 15.4, 5.4 Hz), 5.44 (1H, dq, *J*= 15.4, 5.2 Hz), 5.85 (1H, ddd, *J*= 6.0, 8.3, 10.9 Hz); Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.45; H, 11.07. Found: C, 69.13; H, 11.07.

(2Z,4R,5R,7S,8S,9R,10S,12E)-4-Ethyl-9-methoxy-8,10-dimethyl-2,12-tetradecadiene-1,5,7-triol (53)

The desilylation of **51** (50 mg, 0.11 mmol) was performed as described above for **52** to give **53** (37 mg, quantitative) as a colorless oil; $[\alpha]_D^{26}$ −10.1° (*c* 0.10, $CHCl_3$); IR (film) ν_{max} 3350, 2964, 2931, 1455, 1379, 1136, 1070, 967, 847 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, d, *J*= 6.9 Hz), 0.86 (3H, d, *J*= 7.2 Hz), 0.88 (3H, t, *J*= 7.6 Hz), 1.17–1.38 (2H, m), 1.45–1.59 (1H, m), 1.61–1.75 (3H, m), 1.67 (3H, d, *J*= 5.7 Hz), 1.93–2.02 (1H, m), 2.06–2.16 (1H, m), 2.56–2.66 (1H, m), 3.01 (1H, dd, *J*= 2.6, 8.5 Hz), 3.09 (3H, br s), 3.49 (3H, s), 3.79–3.88 (2H, m), 3.92 (1H, dd, *J*= 6.6, 12.0 Hz), 4.22 (1H, dd, *J*= 8.2, 12.0 Hz), 5.36 (1H, t, *J*= 10.8 Hz), 5.37 (1H, dt, *J*= 15.3, 6.3 Hz), 5.47 (1H, dq, *J*= 15.3, 5.7 Hz), 6.00 (1H, ddd, *J*= 6.6, 8.2, 10.8 Hz); Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.45; H, 11.07. Found: C, 69.16; H, 10.95.

(2Z,4R,5R,7R,8S,9R,10S,12E)-4-Ethyl-7-hydroxy-9-methoxy-8,10-dimethyl-2,12-tetradecadien-5-olide (pironetin 1)

To a solution of **52** (30 mg, 0.09 mmol) in benzene (6 mL) at room temperature was added manganese dioxide (159 mg, 1.83 mmol, Junsei Chemical Co., Ltd.). The mixture was stirred for 5 hr and filtered through Celite® pad. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (5 g) eluted with *n*-hexane/diethyl ether (1:3) to give a white solid (28 mg), which was recrystallized from *n*-hexane to give **1** (26 mg, 88%); colorless needles; mp 77°C; lit. mp 78–79°C;[1a,2a] $[\alpha]_D^{25}$ −150° (*c* 0.52, $CHCl_3$); lit. $[\alpha]_D^{20}$ −136.6° (*c* 1.0, $CHCl_3$),[1a] $[\alpha]_D^{27}$ −143.7° (*c* 0.5, $CHCl_3$);[4a] IR (KBr) ν_{max} 3509, 2965, 2933, 2882, 1727, 1464, 1410, 1386, 1317, 1287, 1270, 1144, 1095, 1076, 988, 964, 938, 892 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, *J*= 7.3 Hz), 0.96 (3H, d, *J*= 6.7 Hz), 1.00 (3H, d, *J*= 7.0 Hz), 1.45–1.54 (1H, m),

1.64–1.74 (3H, m), 1.66 (3H, d, *J*= 5.8 Hz), 1.75–1.81 (1H, m), 1.83–1.90 (2H, m), 2.06–2.13 (1H, m), 2.26–2.31 (1H, m), 2.98 (1H, dd, *J*= 4.6, 5.8 Hz), 3.47 (3H, s), 3.48 (1H, d, J= 2.6 Hz), 4.20 (1H, br d, *J*= 9.2 Hz), 4.73 (1H, dt, *J*= 9.2, 3.5 Hz), 5.37 (1H, dt, *J*= 15.3, 5.9 Hz), 5.44 (1H, dq, *J*= 15.3, 5.8 Hz), 6.02 (1H, d, *J*= 9.8 Hz), 7.01 (1H, dd, *J*= 6.1, 9.8 Hz); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 11.0, 12.2, 15.2, 18.0, 20.8, 36.1, 36.7, 37.2, 38.9, 39.1, 61.6, 67.4, 77.7, 91.9, 120.8, 126.9, 128.7, 150.7, 164.7; Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.32; H, 9.96. Found: C, 70.27; H, 9.94.

*(2Z,4R,5R,7S,8S,9R,10S,12E)-4-Ethyl-7-hydroxy-9-methoxy-8,10-dimethyl-2,12-tetradecadien-5-olide (**54**)*

The oxidative lactonization of **53** (30 mg, 0.09 mmol) was performed as described above for **1** to give **54** (23 mg, 79%); colorless oil; $[\alpha]_D^{24}$ –166° (*c* 0.30, $CHCl_3$); IR (film) ν_{max} 3458, 2966, 2934, 1714, 1462, 1386, 1255, 1093, 1023, 966 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*= 6.8 Hz), 0.88 (3H, d, *J*= 6.8 Hz), 0.98 (3H, t, *J*= 7.5 Hz), 1.44–1.60 (1H, m), 1.61–1.88 (4H, m), 1.67 (3H, d, *J*= 5.6 Hz), 1.93 (2H, t, *J*= 7.2 Hz), 1.95–2.04 (1H, m), 2.08–2.17 (1H, m), 2.35–2.44 (1H, m), 3.04 (1H, dd, *J*= 2.4, 8.4 Hz), 3.47 (3H, s), 3.74 (1H, dt, *J*= 5.3, 7.2 Hz), 4.80 (1H, dt, *J*= 2.2, 7.2 Hz), 5.38 (1H, dt, *J*= 15.3, 6.3 Hz); 5.48 (1H, dq, *J*= 15.3, 5.6 Hz), 6.03 (1H, d, *J*= 9.8 Hz), 7.05 (1H, dd, *J*= 6.2, 9.8 Hz); Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.32; H, 9.96. Found: C, 70.26; H, 9.89.

*(2Z,4R,5R,7R,8S,9R,10S,12E)-4-Ethyl-7,10-dihydroxy-8,10-dimethyl-2,12-tetradecadien-5-olide (**2**)*

To a solution of **1** (13 mg, 0.04 mmol) in dichloromethane (2 mL) under nitrogen atmosphere at –78°C was added 0.77 mL of 0.3 M solution (0.23 mmol) of 15-crown-5 saturated with sodium iodide in dichloromethane, which was freshly prepared before use. Boron tribromide (0.12 mL of 1 M solution in dichloromethane, 0.12 mmol) was added. The mixture was allowed to warm to 0°C over 3 hr and stirred at the temperature for additional 3 hr. The mixture was diluted with diethyl ether (10 mL). Saturated aqueous sodium bicarbonate (5 mL) and 15% aqueous sodium thiosulfate (5 mL) were added and the mixture was extracted with diethyl ether (2 x 20 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was dissolved in diethyl ether (20 mL) and stirred at room temperature for 12 hr together with silica gel (1 g). The mixture was filtered through glass filter and washed with ethyl acetate (50 mL). The filtrate was washed with 15% aqueous sodium thiosulfate (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC developed with *n*-hexane/ethyl acetate (1:1) to give a white solid (11 mg), which was recrystallized from *n*-hexane to give **2** (10 mg, 80%); colorless needles; mp 77–78°C; lit. mp 77–78°C;[1d] $[\alpha]_D^{22}$ –133° (*c* 0.20, $CHCl_3$); lit. $[\alpha]_D^{20}$ –123.0° (*c* 1.0, $CHCl_3$);[1d] IR (KBr) ν_{max} 3417, 2965, 1721, 1461, 1381, 1254, 1094, 1066, 1026, 963 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*= 7.1 Hz), 0.88 (3H, d, *J*= 6.8 Hz), 0.97 (3H, t, *J*= 7.5 Hz), 1.43–2.13 (8H, m), 1.67 (3H, d, *J*= 5.6 Hz), 2.25–2.34 (1H, m), 2.29 (1H, br s), 3.15 (1H, br s), 3.57 (1H, dd, *J*= 3.3, 8.4 Hz), 4.16 (1H, br d, *J*= 10.5 Hz), 4.79 (1H, dt, *J*= 10.0, 3.1 Hz), 5.42 (1H, dt, *J*= 15.3, 6.5 Hz), 5.50 (1H, dq, *J*= 15.3, 5.6 Hz), 6.03 (1H, d, *J*= 9.5 Hz), 7.03 (1H, dd, *J*= 6.1, 9.5 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 11.0, 12.2, 12.3, 17.9, 20.9, 34.8, 35.4, 37.5, 39.1, 39.8, 69.7, 77.2, 77.4, 120.7, 127.0, 129.3, 150.7, 164.7; Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.63; H, 9.76. Found: C, 69.48; H, 9.70.

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