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Synthesis of (±)-Heritol, a Sesquiterpene Lactone belonging to the Aromatic Cadinane Group

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A synthesis of (±)-heritol, a sesquiterpene lactone, was accomplished starting from methyl 3-methoxy-4-methylbenzoate using an intramolecular Wittig reaction as a key reaction for constructing the butenolide ring.

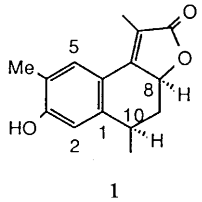
Keywords heritol; sesquiterpene lactone; intramolecular Wadsworth–Emmons reaction; butenolide; α-hydroxyketone; Arndt–Eistert reaction

Heritol (**1**), a sesquiterpene lactone, was isolated from the root of *Heritiera littoralis* (mangrove plant) as an ichthyotoxic substance by Miles and his co-workers, and was shown to be a sesquiterpene lactone belonging to the aromatic cadinane group.1) Recently, Katsumura *et al.* reported the synthesis of (±)-jolkinolides A and B by an application of the intramolecular Wittig reaction to construct the butenolide ring in the two natural products.2) As a part of our continuing studies on the synthesis of natural products,3) we describe here a synthesis of (±)-heritol using the intramolecular Wittig reaction (Wadsworth–Emmons, W–E reaction) for constructing the butenolide ring.

First, we aimed at the synthesis of (±)-dihydroactinidiolide (**2**) starting from 2,2,6-trimethylcyclohexanone (**3**). Treatment of **3** with trimethylsilyltriflate (TMSOTf) and triethylamine in methylene chloride followed by *m*-chloroperbenzoic acid (mCPBA) afforded the unstable epoxide (**4**), desilylation of which, with tetrabutylammonium fluoride (TBAF), gave the α-hydroxyketone (**5**) in 82% yield. Acylation of **5** with dimethylphosphonoacetyl chloride gave the phosphonate (**6**) in 75% yield. The phosphonate was subjected to the intramolecular W–E reaction with sodium hydride in benzene at room temperature for 30 min, furnishing (±)-dihydroactinidiolide (**2**) in 80% yield. The spectroscopic properties of the synthetic compound showed good agreement with reported data,4) indicating the availability of the W–E reaction for constructing the butenolide ring.

Reduction of methyl 3-methoxy-4-methylbenzoate (**7**) with lithium aluminum hydride gave the alcohol (**8**), which was smoothly oxidized to the aldehyde (**9**) with manganese dioxide. Condensation of **9** and dimethyl malonate in the usual manner gave the benzalmalonate (**10**). Addition reaction of lithium dimethyl cuprate on **10** in ether gave the 1,4-addition product (**11**) which was transformed to the carboxylic acid (**12**) by the reaction sequence of alkaline hydrolysis and decarboxylation at 150—170 °C. The acid (**12**) was submitted to an Arndt–Eistert homologation reaction under the improved condition of Newman and Beal III5) to give the homoester (**13**). Treatment of the acid (**14**), obtained by alkaline hydrolysis of **13**, with oxalyl chloride followed by aluminum chloride in methylene chloride gave the tetralone (**15**) in good yield. Although the synthesis of the tetralone (**15**) required a long sequence of reactions, each reaction carried out as above showed acceptable yields and the overall yield of **15** from the methyl benzoate (**7**) in eight steps was more than 35%.

When the reaction sequence (silylation, oxidation, and desilylation) used for the preparation of the α-hydroxyketone (**5**) was applied, the tetralone (**15**) gave the α-hydroxyketone (**16**) as a major product in 64% yield. On the other hand, oxidation of **15** with iodosobenzene diacetate (IBDA) gave the stereoisomeric α-hydroxyketone (**17**) in 67% yield. Stereostructures of these α-hydroxyke-



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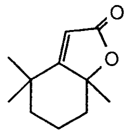

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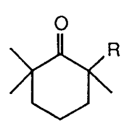

3 : R=H
5 : R=OH
6 : R=OCOCH$_2$P(O)(OMe)$_2$

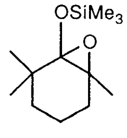

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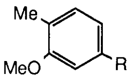
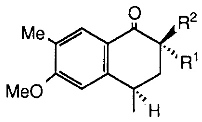
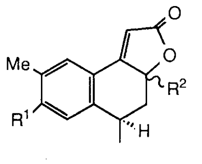
Chart 1



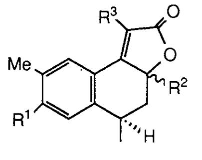
7 : R=COOMe
8 : R=CH$_2$OH
9 : R=CHO
10 : R=CH=C(COOMe)$_2$
11 : R=CH(CH$_3$)CH(COOMe)$_2$
12 : R=CH(CH$_3$)CH$_2$COOH
13 : R=CH(CH$_3$)CH$_2$CH$_2$COOMe
14 : R=CH(CH$_3$)CH$_2$CH$_2$COOH



15 : R^1=R^2=H
16 : R^1=OH; R^2=H
17 : R^1=H; R^2=OH
18 : R^1=OCOCH$_2$P(O)(OMe)$_2$; R^2=H
19 : R^1=H; R^2=OCOCH$_2$P(O)(OMe)$_2$
26 : R^1=OCOCHP(O)(OMe)$_2$ (Me); R^2=H
27 : R^1=H; R^2=OCOCHP(O)(OMe)$_2$ (Me)



20 : R^1=MeO; R^2=◀H
21 : R^1=MeO; R^2=···H
22 : R^1=HO; R^2=◀H
23 : R^1=HO; R^2=···H



28 : R^1=MeO; R^2=◀H; R^3=Me
29 : R^1=MeO; R^2=···H; R^3=Me
30 : R^1=MeO; R^2=∿Me; R^3=H
31 : R^1=AcO; R^2=···H; R^3=Me
32 : R^1=AcO; R^2=◀H; R^3=Me
33 : R^1=HO; R^2=◀H; R^3=Me

Chart 2

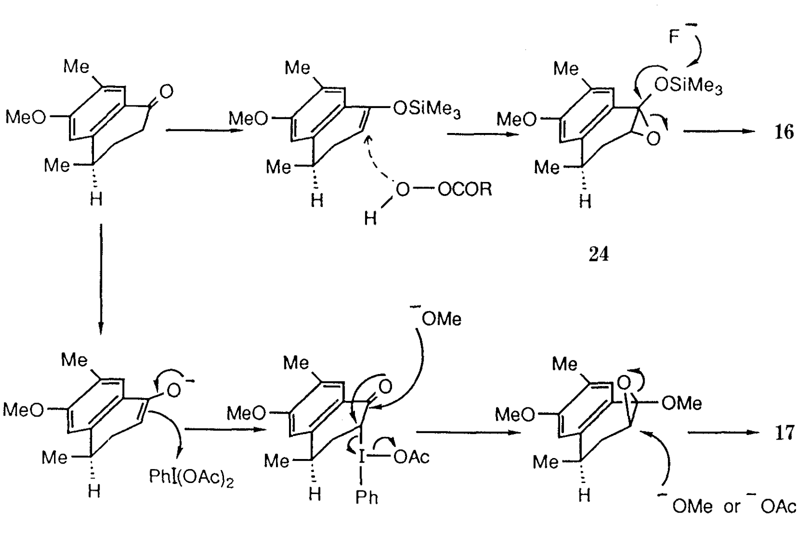


Chart 3

tones were not readily elucidated at this stage, because the signals of the protons on the carbon bearing the hydroxyl group of both compounds (**16** and **17**) showed similar patterns in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. Acylation of both α-hydroxyketones (**16** and **17**) with dimethylphosphonoacetyl chloride gave the phosphonates (**18** and **19**) respectively, which were smoothly cyclized in a few minutes to the respective butenolides (**20** and **21**) by treatment with sodium hydride in tetrahydrofuran (THF) under ice cooling in 80% yield. In a nuclear Overhauser effect (NOE) experiment in the ^{1}H-NMR spectrum of one (**21**) of these butenolides, 8% enhancement at the signal of the proton on the carbon (C_8) bearing oxygen was observed upon irradiating the proton on the carbon (C_{10}) bearing the secondary methyl group, confirming the *cis*-relationship of these protons in **21** and in turn the stereostructures of the α-hydroxyketones (**16** and **17**).

In the case of preparation of the α-hydroxyketone (**16**) by mCPBA oxidation, mCPBA would approach the double bond of an enol ether from the less hindered side, affording the oxide (**24**), which was converted to the α-hydroxyketone (**16**) by treatment with TBAF (Chart 3). On the other hand, when IBDA was used as an oxidation reagent, the stereoisomeric oxide (**25′**) would be formed by the participation of carbonyl oxygen as shown in the intermediate (**25**), which was produced by approach of IBDA from the less hindered side. The oxide ring of **25′** would be opened by nucleophilic attack of acetate or methoxide ion, affording the isomer (**17**).

Treatment of each butenolide (**20** and **21**) with boron trichloride in methylene chloride at 0 °C for 10 d gave the phenolic compounds (**22** and **23**) in 45% and 27% yields, respectively, accompanied with 45% recovery of the starting materials. During the course of the synthesis, we observed that the compounds having a *cis*-relationship between C_8-H and C_{10}-H exhibited the signals assigned to an aromatic proton at the *ortho*-position to the methoxy group at lower field (approximately 0.17 ppm) than the corresponding signals of the *trans*-isomers. This observation provided a convenient means to distinguish the stereostructures of the series of compounds and to evaluate the ratio of the two isomeric compounds in mixtures obtained from various reactions.

Next, our attention was focused on the synthesis of (±)-heritol. Treatment of the *trans*-α-hydroxyketones (**16**) with α-(dimethylphosphono)propionyl chloride6) (DMPP chloride) in the same way as mentioned above gave the phosphonates (**26**) in good yield. Each phosphonate is thought to be a mixture of two diastereoisomers concerning the stereochemistry of the newly introduced acyl group, but no attempt was made to isolate each isomer in pure form, because the α-carbon of the acyl moiety is converted to an sp^2 carbon in the next step. The hydroxyketone (**17**) gave the same type of a mixture in good yield.

Intramolecular W–E reaction of these phosphonates with several kinds of bases (sodium hydride, potassium hydride, potassium hydroxide, and some organic bases) in several kinds of solvents was sluggish and both phosphonates afforded the same inseparable mixture consisting of the *trans*- and *cis*-butenolides (**28** and **29**) in the same ratio (*trans* : *cis*, 10 : 1) in very low yield (1.4%). This result might be attributable to a subtle *peri*-effect but can not be clearly explained at present.

Cleavage reaction of the aromatic methoxy group of the mixture with boron trichloride also gave a mixture consisting of phenolic *trans*- and *cis*-compounds in the same ratio as the starting material. The *cis*–*trans* ratios of the mixtures were determined from the diagnostic signals at δ 6.88 and 6.68 in the ^{1}H-NMR spectra. However, treatment of the butenolides (**20** and **21**) with lithium diisopropylamide (LDA) in THF followed by methyl iodide gave the *cis*-butenolide ((±)-*O*-methylheritol) (**29**) as a major product (15%) along with the γ-alkylation product (**30**) (25%) and a minute amount of the *trans*-isomer (**28**): the ratio of *cis*- and *trans*-isomers was revealed to be 8 : 1 by the analysis of the diagnostic signals in the ^{1}H-NMR. Treatment of *O*-methylheritol (**29**) with boron trichloride in the same manner as mentioned above gave (±)-heritol in 59% yield. ^{1}H-NMR spectroscopic data of the synthetic compound and its acetate were identical with those of heritol and its acetate kindly provided by Professor D. H. Miles

(University of Central Florida), confirming the successful synthesis of this sesquiterpene lactone. The synthetic compounds showed weak toxicity to guppies.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Shimadzu IR-408 spectrometer. ^{1}H-NMR and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on JEOL PMX-60, JEOL FX 90Q and JNM-GX 400 NMR spectrometers with tetramethylsilane as an internal standard and chemical shifts are given in δ (ppm). Mass spectra (MS) were recorded with a JEOL JMS-DX303 instrument. Column chromatography was performed with Kieselgel 60 (70—230 mesh) and flash column chromatography was performed with Kieselgel 60G (Art 7731). Thin layer chromatography (TLC) and preparative thin layer chromatography (preparative TLC) were carried out on Kieselgel 60F254 (Merck) with appropriate solvents. Homogeneities of the oily compounds cited in this report were confirmed by ^{1}H-NMR spectroscopy and TLC.

Methyl 3-Methoxy-4-methylbenzoate (7) A solution of excess diazomethane in ether (100 ml) was added to a solution of 3-methoxy-4-methylbenzoic acid (5 g, 30.1 mmol) in ether (50 ml). A few drops of acetic acid were added to the reaction mixture, which was diluted with ether (300 ml), and the ethereal solution was washed with aqueous 3% Na$_2$CO$_3$ and water, dried (MgSO$_4$), and evaporated *in vacuo* to afford a residue. The residue was recrystallized from *n*-hexane–ether to give methyl 3-methoxy-4-methylbenzoate (7) as colorless crystals (4.93 g, 91%). mp 42—43 °C. IR (CHCl$_3$): 1710 cm^{-1}. ^{1}H-NMR (60 MHz, CDCl$_3$): 2.33 (3H, s), 3.97 (3H, s), 4.03 (3H, s) 7.10 (1H, dd, *J*=7.2, 3.0 Hz), 7.83 (1H, s), 7.88 (1H, dd, *J*=7.2, 2.0 Hz). *Anal.* Calcd for C$_{10}$H$_{12}$O$_3$: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.64.

3-Methoxy-4-methylbenzyl Alcohol (8) A solution of the methylester (7) (4.93 g, 27.4 mmol) in ether (100 ml) was added dropwise to a stirred, ice-cooled suspension of lithium aluminum hydride (LiAlH$_4$) (1.04 g, 27.4 mmol) in ether (100 ml). The whole was heated under reflux with stirring for 2.5 h, and the usual work-up gave the alcohol (8) as a yellow oil (3.65 g, 88%). IR (CHCl$_3$): 3520 cm^{-1}. ^{1}H-NMR (60 MHz, CDCl$_3$): 2.27 (3H, s), 2.57 (1H, s,), 3.97 (3H, s), 4.77 (2H, s), 6.97 (1H, d, *J*=7.8 Hz), 7.07 (1H, s), 7.34 (1H, d, *J*=7.8 Hz). MS *m/z*: 152 (M$^+$).

3-Methoxy-4-methylbenzaldehyde (9) A mixture of active MnO$_2$ (51.7 g) and the alcohol (8) (5.17 g, 34.0 mmol) in methylene chloride (400 ml) was heated under reflux for 2 h and filtered. The filtrate was diluted with methylene chloride (400 ml) and the methylene chloride solution was washed with aqueous 2% Na$_2$CO$_3$ and water, dried (MgSO$_4$), and evaporated *in vacuo* to afford a residue. The residue was recrystallized from *n*-hexane–ether to give the aldehyde (9) as colorless crystals (4.60 g, 90%), mp 39—40 °C. IR (CHCl$_3$): 1695, 1685 cm^{-1}. ^{1}H-NMR (60 MHz, CDCl$_3$): 2.30 (3H, s), 3.97 (3H, s), 7.60 (3H, s), 10.2 (1H, s). *Anal.* Calcd for C$_9$H$_{10}$O$_2$: C, 71.98; H, 6.71. Found: C, 71.84; H, 6.71.

Dimethyl 3-Methoxy-4-methylbenzylidenemalonate (10) A mixture of the aldehyde (9) (7.56 g, 50.0 mmol), dimethyl malonate (8.65 g, 65.0 mmol), benzoic acid (1.0 g), and piperidine (0.80 ml) in benzene (200 ml) was refluxed overnight in an argon atmosphere with a Dean–Stark apparatus. The reaction mixture was diluted with benzene (250 ml). The benzene solution (450 ml) was washed with aqueous 2% NaOH, aqueous 2% HCl and water, dried (MgSO$_4$), and evaporated under reduced pressure to leave a residue. The residue was recrystallized from *n*-hexane–ether to give the benzylidenemalonate (10) as colorless crystals (12.1 g, 91%). mp 84—86 °C. IR (CHCl$_3$): 1725 cm^{-1}. ^{1}H-NMR (60 MHz, CDCl$_3$): 2.30 (3H, s), 3.97 (3H, s), 4.00 (6H, s), 7.17 (1H, d, *J*=2.0 Hz), 7.20 (1H, d, *J*=2.0 Hz), 7.36 (1H, s), 8.05 (1H, s). *Anal.* Calcd for C$_{14}$H$_{16}$O$_5$: C, 63.62; H, 6.10. Found: C, 63.62; H, 6.04.

Methyl 3-(3-Methoxy-4-methylphenyl)-2-methoxycarbonylbutanoate (11) A solution of MeLi (72.3 ml, 1.19 mmol in ether) was added dropwise to a stirred suspension of CuI (7.70 g, 40.0 mmol) in ether (100 ml) at −78 °C under argon and stirred for 30 min. The benzylidenemalonate (10) (5.35 g, 20.0 mmol) in ether (100 ml) was added dropwise to the solution. The resulting mixture was stirred at the same temperature for 2 h, allowed to warm to room temperature, quenched with aqueous 3% NH$_4$Cl and extracted with ether (100 ml). The combined ethereal layer (300 ml) was washed with aqueous 2% Na$_2$CO$_3$, aqueous 2% HCl and water, dried (MgSO$_4$), and concentrated to dryness to afford the 1,4-addition product (11) as a pale yellow oil (5.44 g, 96%). IR (CHCl$_3$): 1750, 1730 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.31 (3H, d, *J*=6.6 Hz), 2.16 (3H, s), 3.49 (3H, s), 3.60 (2H, m), 3.76 (3H, s), 3.80 (3H, s), 6.60 (1H, d, *J*=1.8 Hz), 6.66 (1H, dd, *J*=7.5, 1.8 Hz), 7.03 (1H,dd, *J*=7.5, 0.9 Hz). MS *m/z*: 280 (M$^+$). The foregoing diester (11) (5.42 g, 19.0 mmol) gave the acid (12) as an oil on alkaline hydrolysis with KOH in aqueous EtOH followed by heating at 150—170 °C, in 86% yield. IR (CHCl$_3$): 3500—2700, 1710 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.31 (3H, d, *J*=7.0 Hz), 2.17 (3H, s), 2.56 (1H, d, *J*=3.3 Hz), 2.64 (1H, d, *J*=1.5 Hz), 3.24 (1H, m), 3.80 (3H, s), 6.67 (1H, s), 6.71 (1H, dd, *J*=7.3, 1.7 Hz), 7.05 (1H, dd, *J*=7.3, 0.63 Hz), 10.6 (1H, br s). MS *m/z*: 208 (M$^+$).

Methyl 4-(3-Methoxy-4-methylphenyl)pentanonate (13) A solution of the acid (12) (4.02 g, 19.0 mmol) and oxalyl chloride (7 ml) in benzene (50 ml) was stirred overnight at room temperature, and evaporated to dryness to give a residue. An ethereal solution of the residue was treated with excess diazomethane in ether and then the reaction mixture was stirred at 0 °C for 2 h, and evaporated to dryness to give a residue, which was dissolved in anhydrous MeOH (80 ml). To this solution, triethylamine (12 ml) and silver benzoate (1.6 g) were added portionwise with stirring under ice-cooling, and the whole was stirred at room temperature for 3 h, then filtered. The filtrate was evaporated to dryness to afford a residue. The residue was taken up in ether (300 ml), and the ethereal solution was washed with aqueous 2% HCl, aqueous 2% Na$_2$CO$_3$ and water, dried (MgSO$_4$), and evaporated to give the homoester (13) as a yellow oil (4.48 g, 98%). IR (CHCl$_3$): 1730 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.25 (3H, d, *J*=6.8 Hz), 1.92 (2H, m), 2.20 (2H, m), 2.17 (3H, s), 2.68 (1H, m), 3.60 (3H, s), 3.80 (3H, s), 6.61 (1H, s), 6.66 (1H, dd, *J*=7.2, 1.8 Hz), 7.02 (1H, dd, *J*=7.2, 0.66 Hz). MS *m/z*: 236 (M$^+$). The ester (13) gave the corresponding acid (14) as an oil on alkaline hydrolysis with KOH in aqueous EtOH in 92% yield. IR (CHCl$_3$): 3500—2700, 1705 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.26 (3H, d, *J*=6.8 Hz), 1.86 (2H, m), 2.17 (3H, s), 2.25 (2H, m), 2.68 (1H, m), 3.81 (3H, s), 6.62 (1H, s), 6.66 (1H, dd, *J*=7.5, 1.8 Hz), 7.04 (1H, dd, *J*=7.5, 0.65 Hz). MS *m/z*: 222 (M$^+$).

6-Methoxy-4,7-dimethyltetral-1-one (15) A solution of oxalyl chloride (5 ml) and the acid (14) (3.85 g, 17.0 mmol) in benzene (50 ml) was stirred at room temperature overnight, and evaporated to dryness to give a residue, which was dissolved in methylene chloride (300 ml). To this solution, AlCl$_3$ (2.7 g) was added under ice-cooling. The reaction mixture was stirred at room temperature for 1 h, and washed with aqueous 2% HCl, aqueous 2% NaOH and brine, dried (MgSO$_4$), and evaporated to afford a residue. The residue was recrystallized from *n*-hexane–ether to give the tetralone (15) as colorless crystals (2.80 g, 79%), mp 107—109 °C. IR (CHCl$_3$): 1660 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.39 (3H, d, *J*=6.8 Hz), 1.91 (2H, m), 2.19 (3H, s), 2.63 (2H, m), 3.01 (1H, m), 3.89 (3H, s), 6.67 (1H, s), 7.81 (1H, s). *Anal.* Calcd for C$_{13}$H$_{16}$O$_2$: C, 76.44; H, 7.90. Found: C, 76.45; H, 7.90.

***trans*-2-Hydroxy-6-methoxy-4,7-dimethyltetral-1-one (16)** Triethylamine (742 mg) was added to a solution of TMSOTf (653 mg, 2.94 mmol) and tetralone (15) (300 mg, 1.47 mmol) in methylene chloride (10 ml) at 0 °C with stirring under argon and the reaction mixture was stirred at room temperature overnight, then diluted with methylene chloride (30 ml). The methylene chloride solution was washed with aqueous 2% NaHCO$_3$, dried (MgSO$_4$) and evaporated to dryness to leave a residue, which was dissolved in methylene chloride (5 ml). mCPBA (380 mg, 2.21 mmol) was added to the above solution, and the reaction mixture was stirred at room temperature for 4 h, diluted with ether (40 ml), washed with aqueous 3% Na$_2$CO$_3$ and water, dried (MgSO$_4$) and evaporated to leave a residue which was dissolved in THF. The solution thus obtained was treated with TBAF (769 mg, 2.94 mmol) and the resulting mixture was stirred at room temperature for 0.5 h, and diluted with ether (40 ml). The ethereal solution was washed with aqueous 2% HCl, aqueous 2% Na$_2$CO$_3$ and water, dried (MgSO$_4$), and evaporated to leave a residue which was chromatographed on silica gel in *n*-hexane–ether (2 : 1). Elution with the same solvent gave the recovered tetralone (15) (80 mg, 27%). Further elution with the same solvent gave the *trans*-α-hydroxyketone (16) (207 mg, 64%), which was recrystallized from *n*-hexane–ether as colorless crystals, mp 78—80 °C. IR (CHCl$_3$): 3450, 1670 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.47 (3H, d, *J*=7.3 Hz), 2.19 (3H, s), 2.31 (2H, m), 3.23 (1H, m), 3.89 (1H, s), 3.89 (3H, s), 4.58 (1H, dd, *J*=12.6, 6.4 Hz), 6.60 (1H, s), 7.77 (1H, s). *Anal.* Calcd for C$_{13}$H$_{16}$O$_3$: C, 70.89; H, 7.32. Found: C, 70.74; H, 7.25.

***cis*-2-Hydroxy-6-methoxy-4,7-dimethyltetral-1-one (17)** A solution of the tetralone (15) (500 mg, 2.45 mmol) and KOH (2.1 g, 36.8 mmol) in MeOH (20 ml) was stirred for 10 min under cooling (ice-salt bath) and IBDA (947 mg, 2.94 mmol) was added. The whole was stirred at the same temperature for 1 h and then at room temperature overnight. The reaction mixture was concentrated under reduced pressure to leave a residue, which was dissolved in ether (70 ml), and the ethereal solution was washed with aqueous 3% NaHCO$_3$ and water, and evaporated to dryness to give the *cis*-α-hydroxyketone (**17**) as colorless prisms (361 mg, 67%), mp 103 °C (from *n*-hexane–ether). IR (CHCl$_3$): 3450, 1670 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.46 (3H, d, J=6.8 Hz), 1.74 (1H, m), 2.21 (3H, s), 2.49 (1H, ddd, J=12.6, 5.4, 4.2 Hz), 3.10 (1H, m), 3.91 (1H, s), 3.91 (3H, s), 4.33 (1H, ddd, J=12.6, 5.4, 1.3 Hz), 6.77 (1H, s), 7.83 (1H, s). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.67; H, 7.28.

***trans*-2-Dimethylphosphonoacetyloxy-6-methoxy-4,7-dimethyltetral-1-one (18)** A solution of dimethylphosphonoacetyl chloride (219 mg, 0.71 mmol) in methylene chloride (3 ml) was added to a solution of the *trans*-α-hydroxyketone (**16**) (156 mg, 0.71 mmol) and pyridine (0.7 ml) in methylene chloride (5 ml) with stirring under an argon atmosphere with cooling (ice-salt bath). The reaction mixture was stirred for 1 h at the same temperature and diluted with ether (30 ml). The ethereal solution was washed with aqueous 2% NaHCO$_3$, aqueous 2% HCl and water, dried (MgSO$_4$) and evaporated to leave a residue, which was chromatographed on silica gel in *n*-hexane–ether (2 : 1). Elution with the same solvent gave the *trans*-phosphate (**18**) which was recrystallized from *n*-hexane–ether as colorless prisms (190 mg, 72%), mp 102—103 °C. IR (CHCl$_3$): 1740, 1685, 1260 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.49 (3H, d, J=7.5 Hz), 2.19 (3H, s), 2.38 (2H, m), 3.15 (2H, d, J=21.3 Hz), 3.27 (1H, br s), 3.85 (6H, d, J=10.1 Hz), 3.89 (3H, s), 5.77 (1H, dd, J=12.6, 5.7 Hz), 6.59 (1H, s), 7.77 (1H, s). *Anal.* Calcd for $C_{17}H_{23}O_7P$: C, 55.13; H, 6.26. Found: C, 54.97; H, 6.30.

***cis*-Dimethylphosphonoacetoxy-6-methoxy-4,7-dimethyltetral-1-one (19)** By use of the same procedure as described for the preparation of the *trans*-phosphonate (**18**), the *cis*-α-hydroxyketone (**17**) (1.03 g, 4.67 mmol) was transformed to the *cis*-phosphonate (**19**), which was recrystallized from *n*-hexane–ether as colorless crystals (0.90 g, 52%), mp 83—84 °C. IR (CHCl$_3$): 1740, 1690, 1255 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.47 (3H, d, J=6.8 Hz), 1.98 (1H, m), 2.20 (3H, s), 2.41 (1H, m), 3.16 (2H, d, J=22.0 Hz), 3.20 (1H, m), 3.86 (6H, d, J=11.2 Hz), 3.92 (3H, s), 5.55 (1H, dd, J=13.5, 5.1 Hz), 6.75 (1H, s), 7.81 (1H, s). *Anal.* Calcd for $C_{17}H_{23}O_7P$: C, 55.13; H, 6.26. Found: C, 54.81; H, 6.18.

12-Demethyl-8-*epi*-heritol Methyl Ether (20) A solution of the *trans*-phosphonate (**18**) (190 mg, 0.51 mmol) in benzene (10 ml) was added dropwise to a suspension of sodium hydride (60% in oil, 25 mg, 0.61 mmol) in benzene (10 ml) under an argon atmosphere with stirring and cooling (ice-salt bath). The reaction mixture was stirred at the same temperature for 15 min. After addition of a few drops of acetic acid, the solution was diluted with benzene (20 ml). The benzene solution was washed with aqueous 2% Na$_2$CO$_3$, aqueous 2% HCl and water, dried (MgSO$_4$), and evaporated under reduced pressure to give a residue, which was chromatographed on silica gel in chloroform. Elution with the same solvent gave 12-demethyl-8-*epi*-heritol methyl ether (**20**), which was recrystallized from *n*-hexane–ether as colorless prisms (104 mg, 83%), mp 157—158 °C. IR (CHCl$_3$): 1735 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.44 (3H, d, J=7.5 Hz), 1.93 (1H, m), 2.22 (3H, s), 2.41 (1H, m), 3.29 (1H, m), 3.87 (3H, s), 5.25 (1H, ddd, J=12.6, 5.4, 1.5 Hz), 5.93 (1H, dd, J=1.8, 0.88 Hz), 6.63 (1H, s), 7.33 (1H, s). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.65. Found: C, 73.66; H, 6.65.

12-Demethylheritol Methyl Ether (21) The *cis*-phosphonate (**19**) (798 mg, 2.16 mmol) was treated in the same manner as described above to give 12-demethylheritol methyl ether (**21**), which was recrystallized from *n*-hexane–ether as colorless prisms (411 mg, 78%), mp 153 °C. IR (CHCl$_3$): 1735 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.36 (1H, m), 1.46 (3H, d, J=6.7 Hz), 2.22 (3H, s), 2.63 (1H, ddd, J=11.7, 4.5, 4.1 Hz), 3.10 (1H, m), 3.88 (3H, s), 5.04 (1H, ddd, J=13.5, 4.5, 1.8 Hz), 5.93 (1H, d, J=0.9 Hz), 6.81 (1H, s), 7.36 (1H, s). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.65. Found: C, 73.40; H, 6.55.

12-Demethyl-8-*epi*-heritol (22) Excess boron trichloride was added to a solution of 12-demethyl-8-*epi*-heritol methyl ether (**20**) (24 mg, 0.098 mmol) in anhydrous methylene chloride (5 ml) at −78 °C with stirring. The whole was stirred at 0 °C for 10 d, and evaporated under reduced pressure to leave a residue, which was taken up in ether (30 ml). The ethereal solution was washed with aqueous 3% NaHCO$_3$, aqueous 3% NH$_4$Cl and water, dried (MgSO$_4$) and evaporated to leave a residue, which was separated by preparative TLC (*n*-hexane–ether, 1 : 1) to give 12-demethyl-8-*epi*-heritol (**22**). The product was recrystallized from ether as colorless prisms (6 mg, 27%), mp 196—197 °C. IR (CHCl$_3$): 3250, 1730 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.39 (3H, d, J=7.5 Hz), 2.18 (2H, m), 2.26 (3H, s), 3.23 (1H, m), 5.26 (1H, ddd, J=13.6, 5.5, 1.6 Hz), 5.93 (1H, d, J=0.88 Hz), 6.24 (1H, br s), 6.68 (1H, s), 7.34 (1H, s). MS m/z: 230 (M$^+$). HR-MS m/z: Calcd for $C_{14}H_{14}O_3$: 230.094. Found: 230.096. A part of the starting material (**20**) (14 mg, 58%) was recovered.

12-Demethylheritol (23) By use of the same procedure as described above, 12-demethylheritol methyl ether (**21**) (12 mg, 0.049 mmol) gave 12-demethylheritol (**23**) (4 mg, 35%), which was recrystallized from ether as colorless prisms, mp 188—190 °C. IR (CHCl$_3$): 3200, 1735 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.37 (1H, m), 1.41 (3H, d, J=6.8 Hz), 2.56 (1H, m), 3.04 (1H, m), 5.94 (1H, d, J=1.1 Hz), 6.03 (1H, br s), 6.84 (1H, s), 7.34 (1H, s). MS m/z: 230 (M$^+$). HR-MS m/z: Calcd for $C_{14}H_{14}O_3$: 230.094. Found: 230.097 and recovery of (**21**) (6 mg, 50%).

***trans*-2-(α-Dimethylphosphono)propionyloxy-6-methoxy-4,7-dimethyltetral-1-one (26)** A solution of DMPP chloride (213 mg, 1.07 mmol) in anhydrous methylene chloride (3 ml) was added to a solution of pyridine (0.5 ml) and the *trans*-α-hydroxyketone (**16**) (168 mg, 0.764 mmol) in anhydrous methylene chloride (5 ml) with stirring under an argon atmosphere, with cooling (ice-salt bath), and the mixture was stirred at the same temperature for 1 h, then diluted with ether (30 ml). The ethereal solution was washed with aqueous 2% NaHCO$_3$, aqueous 2% HCl and water, dried (MgSO$_4$) and evaporated to leave a residue, which was chromatographed on silica gel in chloroform–ethyl acetate (1 : 1) to give a mixture of the diastereoisomers of the *trans*-phosphate (**26**) as a yellow oil (193 mg, 66%). IR (CHCl$_3$): 1735, 1685 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.66 (3H, d, J=7.5 Hz), 2.24 (3H, s), 2.37 (1H, m), 2.38 (1H, m), 2.95 (3H, dd, J=7.3, 2.9 Hz), 3.12 (2H, m), 3.83 (6H, d, J=11.0 Hz), 3.89 (3H, s), 5.78 (1H, ddd, J=12.6, 6.3, 3.2 Hz), 6.60 (1H, s), 7.77 (1H, s). MS m/z: 384 (M$^+$).

***cis*-2-(α-Dimethylphosphono)propionyloxy-6-methoxy-4,7-dimethyltetral-1-one (27)** In the same manner as mentioned above, the *cis*-α-hydroxyketone (**17**) (289 mg, 1.31 mmol) gave the same type of mixture of the *cis*-phosphonate (**27**) as a yellow oil (272 mg, 54%). IR (CHCl$_3$): 1735, 1690 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.47 (3H, d, J=6.7 Hz), 1.66 (3H, d, J=7.5 Hz), 2.00 (1H, m), 2.20 (3H, s), 2.24 (1H, m), 3.28 (2H, m), 3.84 (6H, d, J=12.0 Hz), 3.91 (3H, s), 5.55 (1H, ddd, J=12.6, 5.4, 4.0 Hz), 6.75 (1H, s), 7.80 (1H, s). MS m/z: 384 (M$^+$).

Intramolecular W–E Reaction of the *trans*-Phosphonate (26) A solution of the *trans*-phosphonate (**26**) (211 mg, 0.53 mmol) in anhydrous THF (4 ml) was added dropwise to a stirred suspension of sodium hydride (60% in oil, 26 mg, 0.64 mmol) in anhydrous THF (3 ml) under an argon atmosphere with cooling (ice-salt bath), and the whole was stirred at the same temperature for 15 min. After adding a few drops of acetic acid, the solution was diluted with ether (20 ml). The ethereal solution was washed with aqueous 2% Na$_2$CO$_3$, aqueous 2% HCl and water, dried (MgSO$_4$), and evaporated to give a mixture of (±)-heritol methyl ether (**29**) and (±)-8-*epi*-heritol methyl ether (**28**) (2 mg, 1.4%) (**29** : **28** = 1 : 10). The ratio was calculated from the ^{1}H-NMR spectrum, but the isomers were not isolated in pure forms at this stage.

Intramolecular W–E Reaction of the *cis*-Phosphate (27) Under the foregoing conditions, the *cis*-phosphonate (**27**) (250 mg, 0.63 mmol) gave a similar mixture consisting of (±)-heritol methyl ether (**29**) and (±)-8-*epi*-heritol methyl ether (**28**) (22 mg, 13%) (**29** : **28** = 1 : 10) (calculated from the ^{1}H-NMR spectrum).

(±)-Heritol Methyl Ether (29) 1) *n*-BuLi (0.52 ml, 1.49 M in *n*-hexane) was added dropwise to a solution of diisopropylamine (0.13 ml, 0.82 mmol) in anhydrous THF (2 ml) at −78 °C under argon and the mixture was stirred at the same temperature for 30 min, at 0 °C for 30 min, and then at room temperature for 30 min. Next, a solution of 12-demethyl-8-*epi*-heritol methyl ether (**20**) (100 mg, 0.41 mmol) in anhydrous THF (3 ml) was added with stirring at −78 °C, and the resulting mixture was stirred at the same temperature for 1 h. Methyl iodide (0.1 ml, 0.62 mmol) was then added dropwise to the reaction mixture with stirring at −78 °C. Stirring was continued at the same temperature for 30 min and at room temperature for 1 h, then aqueous 3% NH$_4$Cl was added to the reaction mixture and the whole was extracted with ether (30 ml). The combined organic layer was washed with aqueous 3% NH$_4$Cl and water, dried (MgSO$_4$) and evaporated to leave a residue, which was submitted to preparative TLC (*n*-hexane–ether, 1 : 1). The faster-running portion gave a mixture (14 mg, 15%) consisting of (±)-heritol methyl ether (**29**) and (±)-8-*epi*-heritol methyl ether (**28**). The ratio of the two isomers was calculated from the ^{1}H-NMR spectrum using the diagnostic signals (**29** : **28** = 8 : 1). The 8-*epi* isomer (**28**) was easily crystallized from *n*-hexane–ether. mp 166—167 °C. IR (CHCl$_3$): 1735 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl$_3$): 1.44 (3H, d, J=7.2 Hz), 2.12 (3H, d, J=1.8 Hz), 2.24 (3H, s), 3.87 (3H, s), 5.01 (1H, m), 6.67 (1H, s), 7.40 (1H, s). MS m/z: 258 (M$^+$). HR-MS m/z: Calcd for $C_{16}H_{18}O_3$: 258.126. Found: 258.131. After removal of the crystalline 8-*epi* isomer (**28**) by filtration, the mother liquor was concentrated to dryness and the resulting residue was submitted to demethylation without further purification. The slower-running portion obtained from the above preparative TLC gave the γ-alkylation product

(**30**) as a colorless oil (28 mg, 25%). IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.40 (3H, d, J=6.5 Hz), 1.44 (1H, s), 2.22 (3H, s), 2.33 (2H, m), 3.09 (1H, m), 3.88 (3H, s), 5.85 (1H, s), 6.80 (1H, s), 7.30 (1H, s). MS m/z: 258 (M^+).

2) In the same way, the 12-demethylheritol methyl ether (**21**) (100 mg, 0.41 mmol) gave a mixture (14 mg, 15%) of (±)-heritol methyl ether (**29**), (±)-8-*epi*-heritol methyl ether (**28**) (**29**:**28**=8:1) and the γ-alkylation product (**30**) (28 mg, 25%) as a colorless oil.

(±)-Heritol (1) The *O*-methyl ether (**29**) (43 mg) (slightly contaminated with **28**) was subjected to the ether cleavage reaction in the same manner as the case described for 12-demethyl-8-*epi*-heritol (**22**) to give (±)-heritol (**1**) as colorless crystals (20 mg, 59%), mp 245—246 °C. IR (KBr): 3250, 1745, 1705 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (3H, d, J=7.0 Hz), 1.46 (1H, m), 2.13 (3H, d, J=1.5 Hz), 2.29 (3H, s), 2.62 (1H, m), 3.08 (1H, m), 4.91 (1H, ddd, J=12.0, 4.0, 1.8 Hz), 5.23 (1H, s), 6.86 (1H, s), 7.42 (1H, s). HR-MS m/z: Calcd for $C_{15}H_{16}O_3$: 244.110. Found: 244.115.

(±)-Heritol Acetate (31) Acetyl chloride (14.1 mg, 0.18 mmol) was added dropwise to a solution of (±)-heritol (**1**) (30 mg, 0.12 mmol) in pyridine (2 ml) and the mixture was stirred at room temperature for 40 min. A few drops of water were added to the mixture at 0 °C with stirring and the resulting mixture was diluted with ethyl acetate (25 ml), and washed with aqueous 2% $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated to leave a residue, which was submitted to preparative TLC and repeatedly developed with the solvent system (*n*-hexane–ether, 2:1). The faster-running portion gave (±)-heritol acetate (**32**) (15 mg) as colorless crystals (from *n*-hexane–ether), mp 135—136 °C. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (3H, d, J=6.6 Hz), 1.47 (1H, m), 2.15 (3H, d, J=1.8 Hz), 2.23 (3H, s), 2.35 (3H, s), 2.64 (1H, ddd, J=12.4, 5.2, 4.7 Hz), 3.12 (1H, m), 4.93 (1H, ddd, J=12.0, 4.0, 1.8 Hz), 7.09 (1H, s), 7.50 (1H, s). ^{13}C-NMR (400 MHz, $CDCl_3$): 141.9 (C_1), 121.1 (C_2), 151.0 (C_3), 126.5 (C_4), 130.2 (C_5), 129.1 (C_6), 155.7 (C_7), 78.2 (C_8), 31.6 (C_9), 38.6 (C_{10}), 175.1 (C_{11}), 118.5 (C_{12}), 20.8 (C_{13}), 10.0 (C_{14}), 16.0 (C_{15}). HR-MS m/z: Calcd for $C_{17}H_{18}O_4$: 286.121. Found: 286.123. When (±)-heritol slightly contaminated with the 8-*epi*-compound (**33**) was used in the acetylation reaction, (±)-8-*epi*-heritol acetate (**32**) was isolated by preparative TLC in a minute amount, mp 170—171 °C (from *n*-hexane–ether). IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.41 (3H, d, J=7.7 Hz), 1.89 (1H, m), 1.89 (2H, m), 2.14 (3H, d, J=1.8 Hz), 2.26 (3H, s), 2.35 (3H, s), 2.41 (1H, ddd, J=12.4, 4.0, 1.5 Hz), 5.12 (1H, ddd, J=12.4, 4.8, 1.8 Hz), 6.96 (1H, s), 7.49 (1H, s). ^{13}C-NMR (400 MHz, $CDCl_3$): 142.4 (C_1), 122.8 (C_2), 150.8 (C_3), 125.9 (C_4), 130.2 (C_5), 129.1 (C_6), 155.4 (C_7), 75.5 (C_8), 32.7 (C_9), 36.2 (C_{10}), 175.1 (C_{11}), 119.1 (C_{12}), 20.8 (C_{13}), 10.0 (C_{14}), 16.1 (C_{15}). HR-MS m/z: Calcd for $C_{17}H_{18}O_4$: 286.121. Found: 286.121.

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