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New Access to dl-Paniculide A Using α-Phenylthio-β-Vinylbutenolide as Synthetic Block

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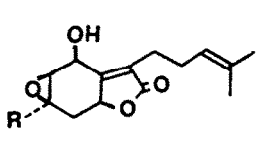
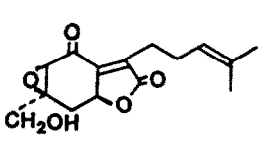
Abstract - A new synthetic approach to dl-paniculide A (1) based on the annulation of 2-formylpropionate with α-phenylthio-β-vinylbutenolide **4** is described. The annulation products **6a-6c** was dehydrated to give **7**, and the sulfoxide of **7** was submitted to sulfoxide-sulfinate rearrangement in aqueous media to yield **8a** and **8b**. The latter was converted to the former by configurational inversion of its hydroxyl group. Saturated lactone **11a** obtained from **8a** was homoprenylated, and after desilylation, the product **12b** was selenenylated to give **13a**. Alkaline hydrolysis followed by oxidative elimination of the selenenyl group provided **14a**, which was then acetylated and oxidized with lead tetraacetate to yield **15a** and **16a-16c**. dl-Paniculide A was derived from **15a** and **16a** via **18a**.

Paniculide A (1) was isolated from cullus culture derived from hypocotyl and stem tissues of Andrographis paniculata Nees along with paniculide B (2) and C (3).[1] This sesquiterpene lactone is a highly oxygenated bisabolene, and its characteristic and fundamental structure is 2,4,5,6,-7,7a-hexahydro-4-hydroxy-benzofuran-2-one which has seldom be found in natural products. As a



1: R=CH_3 (paniculide A)
2: R=CH_2OH (paniculide B)

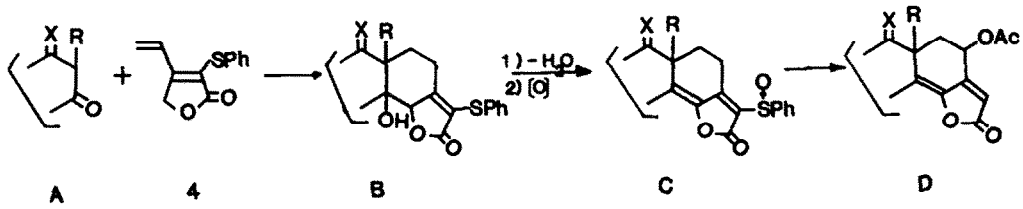


3 (paniculide C)

convenient construction for such a structure, we recently described a novel lactone annulation reaction of active methylene compounds with α-phenylthio-β-vinylbutenolide **4**,[2] i.e. under mild basic conditions, active methylene compound **A** reacted with **4** to provide lactone-annulated product **B** in consequence of 1,6-conjugate addition followed by concurrent aldolic cyclization of the adduct (Scheme 1). The annulation product obtained was dehydrated to give a butenolide, which was then oxidized to the corresponding sulfoxide **C**. Sulfoxide-sulfinate rearrangement of **C** afforded acetate **D** when the reaction was conducted in acetic anhydride-pyridine mixture.

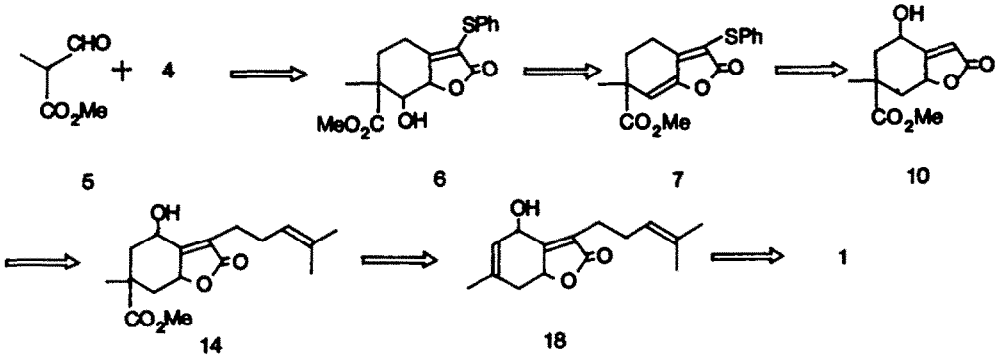
To illustrate the efficiency of this reaction in the synthesis of natural products involving such oxygenated perhydrobenzofuranone structures in molecules, we describe here details of our total synthesis of dl-paniculide A (1).[3,4]

Our access to **1** was planned to start with **7**, which was previously derived on dehydration of



Scheme 1

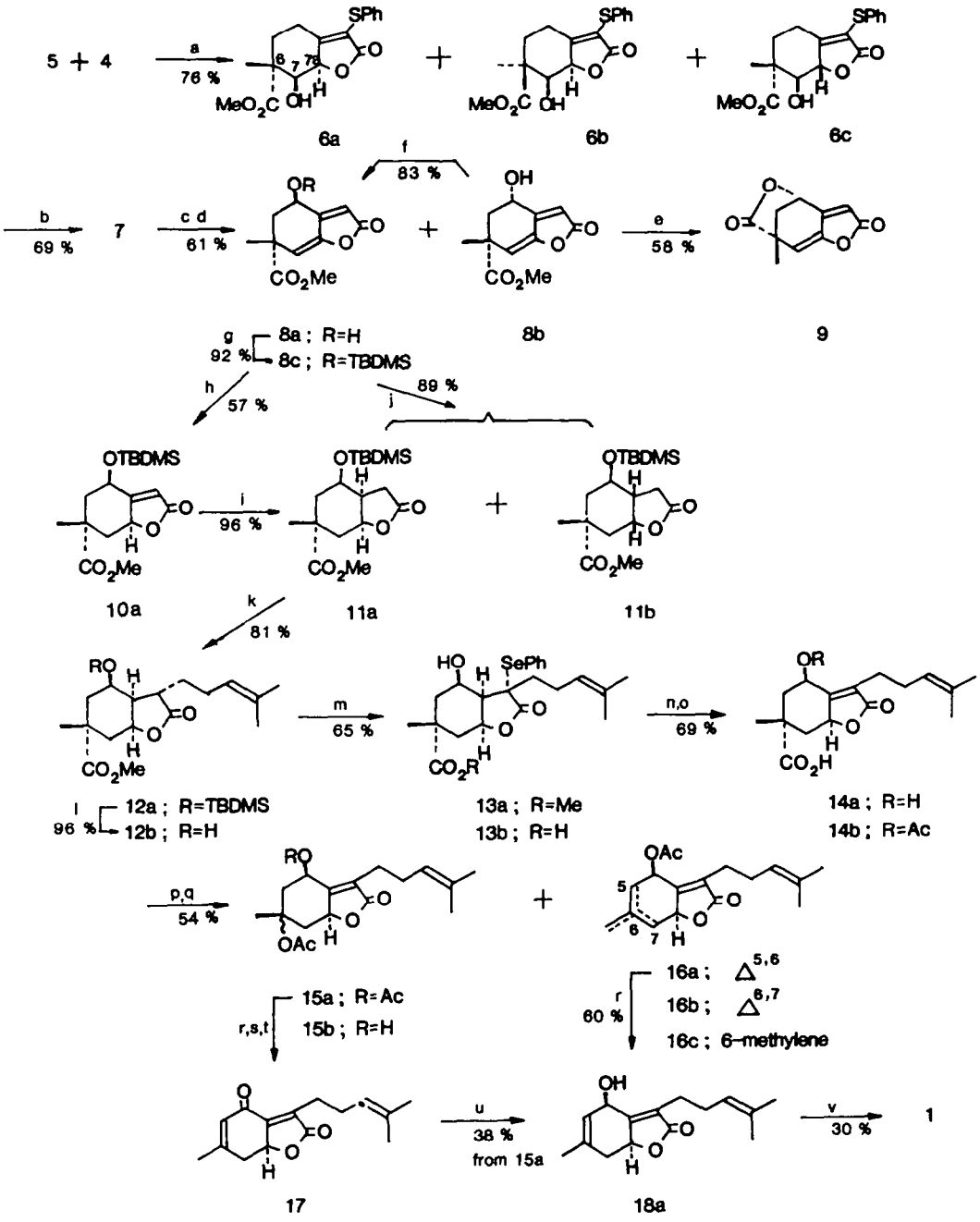
the annulation product 6 obtained from methyl 2-formylpropionate (5) and 4 (Scheme 2).[2] It was readily presumed that introduction of a hydroxyl group on the cyclohexane ring of 7 would be feasible on sulfoxide-sulfinate rearrangement of the sulfoxide corresponding to 7 under aqueous conditions.[5] After the enol lactone double bond in 7 had been selectively saturated to lead to 10, introduction of the homoprenyl side chain into the lactone ring of 10 may derive 14 which possesses the fundamental carbon framework of 1. Further elaboration is introduction of a double bond at the desired position (see 18) by eliminative demethoxycarbonylation of 14, followed by stereoselective epoxidation of the resulting olefin 18. In the light of this protocol, it was necessary to secure the relative stereochemistry of 10 in which the hydroxyl group is syn to the lactonic ether oxygen.



Scheme 2

In the reported manner, the starting sulfide (7) was prepared from 5 (Scheme 3). The annulation reaction of 5 with 4 was conducted with potassium fluoride as catalyst in dimethyl sulfoxide-1,2-dimethoxyethane (DME) mixture, giving a mixture (69:22:9) of three separable diastereomers in good combined yield. In the ^{1}H NMR spectra of both the major (6a) and middle products (6b), couplings with 4 Hz were observed for protons at C(7) and C(7a), showing that these coupled protons were syn and that these two products would therefore be diastereomeric with respect to the C(6) position. On the other hand, the minor product (6c) showed a larger coupling (9 Hz) for protons at the same positions, this demonstrating an anti disposition of these protons. In addition, a large nuclear Overhauser effect was observed between the tertiary methyl and C(7a) protons of 6c, and this compound isomerized to the more stable isomer 6a on silica gel thin layer chromatography. Although another diastereomer of 6c was not isolated, the above interrelation allowed us to assign their stereostructures as depicted.

Dehydration of the diastereomeric mixture of 6a-6c with thionyl chloride provided 7 in good yield, while under the same conditions, that of the major annulation product 6a gave the same product in almost quantitative yield. The phenylthio group of 7 was oxidized with peracid to give the corresponding sulfoxide, which was then warmed in aqueous pyridine[5] to afford rearranged products 8a and 8b in a ratio of 56:44. The relative stereochemistry of the hydroxyl and ester groups of this compound was unambiguously assigned on observation that the minor product 8b gave dilactone 9 on heating with p-toluenesulfonic acid in benzene. While keeping in mind that the rearranged products 8a and 8b would be interconvertible by the configurational inversion of their



Scheme 3

Reagents: a) KF, Me_2SO-DME; b) $SOCl_2$, pyr; c) m-CPBA, CH_2Cl_2; d) aq. pyr; e) p-TsOH, PhH; f) Ph_3P, $N_2(CO_2Et)_2$, AcOH-THF, then aq. HCl, dioxane; g) t-$BuMe_2SiCl$, imidazole, DMF; h) $NaBH_4$, K_2CO_3, DME-MeOH; i) $NaBH_4$, $NiCl_2$, MeOH; j) H_2, Pd-$SrCO_3$, EtOH; k) LDA, $Me_2C{=}CH(CH_2)_2I$, THF; l) Bu_4NF, THF; m) LDA, PhSeCl, THF-HMPT; n) KOH, EtOH; o) H_2O_2, THF-HOAc; p) Ac_2O, DMAP, $CHCl_3$; q) $Pb(OAc)_4$, $Cu(OAc)_2$, PhH-pyr; r) K_2CO_3, MeOH; s) CrO_3-pyr_2, CH_2Cl_2; t) Et_3N, CH_2Cl_2; u) $NaBH_4$, MeOH; v) t-BuO_2H, MoO(acac)$_2$, PhH.

hydroxyl groups, we first employed the major product **8a** for further transformation.

To explore the direct introduction of the homoprenyl side chain into the α position of the butenolide ring of **8a**, silylated derivative **8c** was treated with sodium borohydride in aqueous methanol-DME under basic conditions to give **10a**, and the depicted stereochemistry could be assigned on the basis of coupling patterns in the ^{1}H NMR spectrum (see Experimental). As we could secure, at this stage, the reduction product **10a** whose siloxyl group and lactonic ether oxygen were syn, the hydroxyl group of **8b** was inverted according to Mitsunobu's procedure[7] giving **8a** in good yield.

Unfortunately many attempts of homoprenylation of **10a** with homoprenyl iodide were fruitless, resulting in formation of intractable mixtures. We thus turned our attention to homoprenylation of a butyrolactone derivative obtainable on reduction of **10a**. Reduction of **10a** with sodium borohydride in the presence of nickel (II) chloride[8] yielded butyrolactone (**11a**) quantitatively, while catalytic hydrogenation of **8c** provided a separable mixture of **11a** and its diastereomer **11b** in the 74:26 ratio. In practice, the latter procedure was superior to the former for deriving **11a** from **8c** (66% vs. 55% in isolation yield). The desired homoprenylation product **12a** was obtained by the reaction of the enolate of **11a** generated with lithium diisopropylamide and homoprenyl iodide in tetrahydrofuran-hexamethylphosphoric triamide mixture in good yield. The product was stereochemically homogeneous and the alkenyl side chain was introduced from the convex α-face of **11a** as revealed by analysis of its ^{1}H NMR spectrum (see Experimental). To derive butenolide structure, the next step was to introduce a double bond into the butyrolactone ring by selenenylation followed by oxidative elimination. The selenenylation was expected to take place similarly at the less hindered face of the butyrolactone ring as proven in the above-mentioned results of homoprenylation and the anticipated stereochemistry was convenient for leading to the desired butenolide. Since selenenylation of **12a** with benzeneselenenyl chloride was sluggish to proceed probably due to the bulky protective group of hydroxyl, **12a** was desilylated and the resulting alcohol **12b** was submitted to this reaction, which smoothly gave **13a** in acceptable yield. Although any direct evidence was not obtainable to confirm the stereochemistry of the benzeneselenenyl group in this product, the depicted structure was tentatively assigned on the basis of the discussion described above.

Since some attempts were unsuccessful in selective hydrolysis of its ester group, the selenenylated lactone **13a** was hydrolyzed with an excess of potassium hydroxide in aqueous ethanol and the reaction mixture was then treated with hydrochloric acid to give lactonic acid **13b**. It was suspected, however, that the lactone ring was also hydrolyzed under the above conditions and that relactonization with acid might have provided a diastereomer of **13b** regarding the α position of lactone. Since methylation of the hydrolysis product with diazomethane, fortunately, reproduced only the original methyl ester **13a**, this result allowed us to assign the depicted stereostructure **13b** to this acid. Hydrogen peroxide oxidation of **13b** yielded butenolide **14a** as expected, and no isomeric olefin was not detected. The product **14a** was then acetylated to give **14b** for protection of its hydroxyl group against oxidative conditions in the next step.

According to Kochi's procedure,[9] the carboxylic acid **14b** was decarboxylated with lead tetraacetate in the presence of cupric sulfate in benzene, giving diacetate **15a** and three olefins **16a**-**16c** (38:25:15:23) in moderate combined yield. After chromatographic separation, the structure of each product was assigned by coupling patterns in the ^{1}H NMR spectrum (see Experimental). Under mild conditions, the desired olefin **16a** was hydrolyzed with potassium carbonate to give allylic alcohol **18a**, which was also derived from the diacetate **15a** by a sequence of reactions, partial hydrolysis with potassium carbonate giving **15b**, Collins oxidation followed by treatment with triethylamine leading to **17**, and reduction with sodium borohydride.[10]

When epoxidation of **18a**, the final step, was performed with t-butyl hydroperoxide using bis(acetoacetonato)oxovanadium (IV)[11] as catalyst, the oxidation product obtained was **17**. By replacing the vanadium catalyst with bis(acetoacetonato)oxomolybdenum (IV),[12] **18a** afforded paniculide A (**1**) as identified by direct comparison of spectral data and of behavior on thin layer chromatography with those of an authentic sample.

Experimental

Melting points are uncorrected. IR spectra were obtained with a JASCO A-3 spectrophotometer in $CHCl_3$, unless otherwise described. ^1H NMR spectra were recorded on a JEOL PS-100 (100 MHz) spectrometer, except where noted, in $CDCl_3$. Chemical shift are reported as δ values relative to tetramethylsilane as internal standard, and coupling constants (J) are given in herz. A JEOL JMS-01SG-2 high resolution mass spectrometer was used for accurate mass measurements. Column chromatography was performed by using silica gel (Merck, kieselgel 60, 70-230 mesh), and kieselgel GF_{254} was employed for preparative thin-layer chromatography (TLC) as an absorbent. Solvent systems used are shown in parentheses. Anhydrous $MgSO_4$ was employed to dry extracts.

2,4,5,6,7,7aα-Hexahydro-7β-hydroxy-6α-methoxycarbonyl-6β-methyl-3-phenylthio-1-benzofuran-2-one (6a) and Its 6- and 7a-Epimers (6b and 6c). A solution of methyl propionate (13.2 g, 0.15 mol) in THF (50 mL) was added dropwise to a solution of LDA, which was prepared from a hexane solution of BuLi (0.17 mol) and a THF solution (100 mL) of diisopropylamine (18.2 g, 0.18 mol), at -78 °C. After stirring had been continued for an additional 1 h, ethyl formate (16.65 g, 0.225 mol) in THF (30 mL) was added and stirred for 1 h at the same temperature. The mixture was diluted with water and extracted with ether, and the aqueous layer was acidified with dilute HCl at 0°C. The product was extracted with CH_2Cl_2, and the extract was washed with brine and dried. Removal of the solvent afforded an oil, which was distilled (bp 66-69°C at 40 mmHg) to give **5** (6.9 g, 40%) as a tautomeric mixture; IR 3600-2500, 1750, 1710, 1672 1615 cm^{-1}; ^1H NMR 1.33 (d, 1H, J=8), 1.67 (br s, 2H), 3.43 (q, 0.33H, J=8), 3.75 (br s, 3H), 6.94 (br s, 0.66H), 9.75 (s, 0.33H), 7.05 (br s, 0.66H).

KF (35 mg, 1.1 mmol) was added to a stirred solution of **5** (116 mg, 1 mmol) in a mixture of DMSO-DME (2:1)(4 mL) at 0 °C, and a solution of **4**[2] (109 mg, 0.5 mmol) in the same mixed solvent (2 mL) was then added. After being stirred for 2 h, the mixture was poured into ice-dilute HCl, and the product was extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$, water and brine, and dried. Concentration gave crystals, which was separated by TLC (CH_2Cl_2, 10:1) to afford **6a** (87 mg, 52%), **6b** (28 mg, 17%), and **6c** (12 mg, 7%) slightly contaminated with **6a** as shown by ^1H NMR. **6a**: mp 161-162 °C (recrystallized from CH_2Cl_2-hexane); IR 3600, 3310, 1758, 1730, 1638, 1585 cm^{-1}; ^1H NMR 1.33 (s, 3H), 3.16 (d, 1H, J=4), 3.75 (s, 3H), 4.01 (t, 1H, J=4), 4.99 (d, 1H, J=4), 7.1-7.4 (m, 5H). Anal. Calcd for C, 61.06; H, 5.43; S, 9.59. Found: C, 60.79; H, 5.36; S, 9.43. **6b**: mp 138 °C (recrystallized from ether-hexane); IR 3600, 3420, 1762, 1738, 1640, 1585 cm^{-1}; ^1H NMR 1.35 (s, 3H), 3.70 (s, 3H), 4.50 (d, 1H, J=4), 4.98 (d, 1H, J=4), 7.0-7.5 (m, 5H). **6c**: mp 110 °C (recrystallized from CH_2Cl_2-hexane); IR 3590, 3380, 1775, 1760, 1735, 1635, 1585 cm^{-1}; ^1H NMR 1.38 (s, 3H), 3.70 (s, 3H), 3.89 (dd, 1H, J=9 and 3), 4.84 (d, 1H, J=9) 7.2-7.5 (m, 5H). For **6c**, a NOE (16%) was observed between signals at δ 1.38 and 3.89 on irradiation of the former. A sample sufficiently purified on recrystallization showed again a spot of **6a** on silica gel thin-layer chromatography.

2,4,5,6-Tetrahydro-6-methoxycarbonyl-6-methyl-3-phenylthio-1-benzofuran-2-one (7). To a stirred solution of a mixture of **6a-6c** (87 mg, 0.26 mmol) in pyridine (2 mL) was added $SOCl_2$ (0.05 mL) at 0 °C, and the mixture was stirred for 1 h. The reaction mixture was poured into ice-dilute HCl. The product was extracted with CH_2Cl_2, and the extract was successively washed with dilute HCl, $NaHCO_3$, water, and brine, and dried. The oily residue obtained by evaporation was purified by TLC (CH_2Cl_2) to yield **7** (57 mg, 69%) as an oil; IR 1780, 1732, 1662, 1600 cm^{-1}; ^1H NMR 1.38 (s, 3H), 3.66 (s, 3H), 5.88 (s, 1H), 7.18-7.45 (m, 5H). Anal. Calcd for $C_{17}H_{16}O_4S$; C, 64.54; H, 5.0; S, 10.14. Found: C, 64.72; H, 4.84; S, 10.03.

On the other hand, **6a** (302 mg) yielded **7** (274 mg, 96%) under the same conditions.

2,4,5,6-Tetrahydro-4β-hydroxy-6α-methoxycarbonyl-6β-methyl-1-benzofuran-2-one (8a) and Its 4-Epimer (8b). A solution of m-chloroperbenzoic acid (1.05 g, 4.85 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a solution of **7** (1.46 g, 4.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After being stirred at the same temperature for 30 min, the mixture was filtered, and the filtrate was washed with $NaHCO_3$, water and then brine, and dried. The crude sulfoxide obtained by evaporation was dissolved in a mixture of pyridine (18 mL) and water (3.6 mL) and heated at 35-37 °C for 1.5 h. The resulting mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed with dilute HCl, water and brine, and dried. The removal of the solvent afforded an oil, which was separated by silica gel column chromatography. Elution with CH_2Cl_2-ether (2:1) gave **8a** (354 mg, 34%) and **8b** (283 mg, 27%), mp 76-77 °C (recrystallized from ether-hexane). **8a**: IR 3450, 3140, 1778, 1755, 1730, 1672, 1620 cm^{-1}; ^1H NMR 1.48 (s, 3H), 1.71 (t, 1H, J=12), 2.64 (q, 1H, J=12.5), 3.70 (s, 3H), 5.01 (br m, 1H), 5.75 (br s, 1H), 6.14 (t, 1H, J=2). Exact mass: (**8a**) Calcd for $C_{11}H_{12}O_5$, 224.0684. Found, 224.0687. **8b**: IR 3425, 3120, 1790, 1740, 1672, 1620 cm^{-1}; ^1H NMR 1.49 (s, 3H), 2.1-2.8 (m, 2H), 3.83 (s, 3H), 4.00 (br m, 1H), 5.03 (dd, 1H, J=12 and 6), 6.03 (d, 1H, J=2), 6.13 (t, 1H, J=2). Anal. Calcd for $C_{11}H_{12}O_5$: C,58.92; H,5.40. Found: C,59.12; H,5.43.

2,4,5,6-Tetrahydro-6β-methyl-1-benzofuran-2-one-6α,4α-carbolactone (9). A solution of **8b** (108 mg, 0.48 mmol) and a catalytic amount of p-toluenesulfonic acid in benzene (3 mL) was refluxed for 2.5 h. The resulting mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$, water and brine, and dried. Recrystallization of the evaporation residue from methanol afforded **9** (54 mg, 58 %) as faint yellow crystals, mp 176-177 °C; IR (KBr) 1795, 1762, 1660, 1622 cm^{-1}; ^1H NMR (C_5D_5N) 1.43 (s, 3H), 2.30 (d, 1H, J=11), 2.49 (dd, 1H, J=11 and 5), 5.85 (d, 1H, J=5) 6.34 (m, 1H). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H,4.20. Found: C, 62.19; H, 4.15.

Conversion of 8b into 8a. To a stirred solution of **8b** (140 mg, 0.63 mmol), triphenylphosphine (246 mg, 0.94 mmol) and acetic acid (57 mg, 0.94 mmol) in THF (2 mL) was added a solution of diethyl azodicarboxylate (164 mg, 0.94 mmol) in THF (1 mL) at room temperature. After being stirred at the same temperature for 15 h, the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, water and saturated brine, and dried. Removal

of the solvent afforded an oil (622 mg), which was purified by TLC to give an oil (126 mg, 76%). A solution of the product (100 mg, 0.376 mmol) and 6M HCl (0.7 mL) in dioxane (1.5 mL) was stirred for 20 h at 30 °C. After dilution with water, the product was extracted with CH_2Cl_2, and washed with $NaHCO_3$, water and brine, and dried. Evaporation of the solvent afforded an oil, which was purified by TLC (CH_2Cl_2-ether, 2:1) to provide an oil (70 mg, 83 %). The product was identified as **8a** spectroscopically.

2,4,5,6-Tetrahydro-4β-t-butyldimethylsiloxy-6α-methoxycarbonyl-6β-methyl-1-benzofuran-2-one (8c). A mixture of **8a** (400 mg, 1.8 mmol), t-butyldimethylsilyl chloride (400 mg, 2.6 mmol) and imidazole (360 mg, 5.3 mmol) in DMF (8 mL) was stirred at room temperature for 2.5 h. The resulting mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water and brine, and dried. After concentration, purification of the residue by silica gel column chromatography (CH_2Cl_2) afforded **8c** (558 mg, 92%) as crystals, mp 62-63 °C (recrystallized from ether); IR 1780, 1732, 1670, 1622 cm^{-1}; ^1H NMR 0.16 (s, 3H), 0.95 (s, 3H), 1.28 (s, 3H), 1.73 (t, 1H, J=12), 2.56 (dd, 1H, J=12 and 6), 3.67 (s, 3H), 4.98 (ddd, 1H, J=12.6 and 2), 5.70 (br s, 1H), 5.97 (t, 1H, J=2). Anal. Calcd for $C_{17}H_{26}O_5Si$: C, 60.33; H, 7.74. Found: C, 60.75; H, 8.05.

2,4,5,6,7,7aα-Hexahydro-4β-t-butyldimethylsiloxy-6α-methoxycarbonyl-6β-methyl-1-benzofuran-2-one (10a). To a stirred solution of K_2CO_3 (810 mg, 5.9 mmol) and $NaBH_4$ (180 mg, 4.8 mmol) in a mixture of water (7 mL) and methanol (2 mL) was added a solution of **8c** (390 mg, 1.15 mmol) in DME (4 mL) at room temperature. After being stirred for 1 h, the mixture was acidified with dilute HCl at 0 °C and CH_2Cl_2 was then added. The mixture was stirred at the same temperature for an additional 10 min. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with saturated brine, and dried. Evaporation of the solvent left an oil, which was separated by TLC (CH_2Cl_2) to afford recovered **8c** (94 mg) and **10a** (168 mg, 43%; 57% based on consumed **8c**), mp 83-84 °C (recrystallized from ether-hexane); IR 1785, 1748, 1735, 1660 cm^{-1}; ^1H NMR 0.12 (s, 6H), 0.95 (s, 9H), 1.32 (s, 3H), 2.58 (ddd, 1H, J=13.6 and 2), 2.90 (ddd, 1H, J=13.6 and 2), 3.74 (s, 3H), 4.59 (ddd, 1H, J=12.6 and 2), 4.87 (ddd, 1H, J=12.6 and 2), 5.88 (t, 1H, J=2). Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 59.97; H, 8.29. Found: C, 60.17; H, 8.51.

2,3,3aα,4,5,6,7,7a-Octahydro-4β-t-butyldimethylsiloxy-6α-methoxycarbonyl-6β-methyl-1-benzofuran-2-one (11a) and its 3a(7a)-Epimer (11b). a) $NaBH_4$ (88 mg, 2.27 mmol) was added portionwise to a stirred solution of **10a** (153 mg, 0.45 mmol) and $NiCl_2$ hexahydrate (27 mg, 0.11 mmol) in methanol (1.5 mL) at 0 °C. After being stirred at the same temperature for an additional 2 h, the mixture was acidified with dilute HCl at 0 °C, and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$, water and brine, and dried. Evaporation of the solvent gave an oil, which was purified by TLC (CH_2Cl_2-ether 20:1) to afford **11a** (153 mg, 100 %), mp 115-116 °C (recrystallized from ether); IR 1770, 1730 cm^{-1}; ^1H NMR 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.26 (s, 3H), 3.69 (s, 3H), 3.90 (dt, 1H, J=11 and 5.5), 4.76 (dt, 1H, J=10 and 6). Anal. Calcd for $C_{17}H_{30}O_5Si$: C, 59.62; H, 8.83. Found: C, 59.81; H, 9.81.

b) A solution of **8c** (403 mg, 1.2 mmol) in ethanol (15 mL) was hydrogenated over 5% Pd-$SrCO_3$ under atmospheric pressure at room temperature until uptake of hydrogen ceased. Filtration followed by evaporation of the reaction mixture afforded an oil, which was separated by TLC (CH_2Cl_2-ether, 20:1) to give **11a** (269 mg, 66%) and **11b** (94 mg, 23.1%), mp 110-111 °C (recrystallized from ether); IR 1768, 1725 cm^{-1}; ^1H NMR 0.12 (s, 3H), 0.15 (s, 3H), 0.87 (s, 9H), 1.26 (s, 3H), 3.65 (s, 3H), 3.76 (ddd, 1H, J=11.9 and 4), 4.55 (br dd, 1H, J=10 and 4). Anal. Calcd for $C_{17}H_{30}O_5Si$: C, 59.62; H, 8.83. Found: C, 59.45; H, 8.55.

2,3,3aα,4,5,6,7,7aα-4β-t-Butyldimethylsiloxy-6α-methoxycarbonyl-6β-methyl-3α-(4-methyl-3-pentenyl)-1-benzofuran-2-one (12a). A solution of **11a** (410 mg, 1.2 mmol) in THF (2 mL) was added dropwise to a solution of LDA, prepared from BuLi (3 mmol) and diisopropylamine (0.5 mL) in THF (2 mL), at -78 °C. The mixture was allowed to warm up to -20 °C over 1.5 h, and HMPT (0.2 mL) and 1-iodo-4-methyl-3-pentene[13] (1 mL, 5 mmol) was added. After being gradually warmed up to 0 °C over 1.5 h, the mixture was treated with saturated NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water and brine, and then dried. Removal of the solvent provided an oil, which was purified by TLC (CH_2Cl_2) to give **12a** (410 mg, 81%), mp 78 °C (recrystallized from hexane-ether); IR 1765, 1728 cm^{-1}; ^1H NMR 0.07 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.25 (s, 3H), 1.59 (br s, 3H), 1.66 (br s, 3H), 3.67 (s, 3H), 3.88 (dt, 1H, J=11 and 4.55), 4.65 (dt, 1H, J=11 and 7), 5.03 (br t, 1H, J=6). Exact mass: Calcd for $C_{23}H_{40}O_5Si$, 424.2643. Found 424.2598.

2,3,3aα,4,5,6,7,7aα-Octahydro-4β-hydroxy-6α-methoxycarbonyl-6β-methyl-3α-(4-methyl-3-pentenyl)-1-benzofuran-2-one (12b). After a mixture of **12a** (212 mg, 0.5 mmol), Bu_4NF (1.5 mmol), and THF (2.5 mL) had been stirred at room temperature for 1 h, the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed with water and saturated brine, and dried. Removal of the solvent left an oil, which was purified by TLC (CH_2Cl_2-ether, 10:1) to afford **12b** (149 mg, 96 %), mp 90-91 °C (recrystallized from hexane-ether); IR 3610, 3500, 1765, 1725 cm^{-1}; ^1H NMR 1.27 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 3.67 (s, 3H), 3.98 (m, 1H), 4.67 (dt, 1H, J=10 and 7), 5.08 (br t, 1H, J=7). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.75; H, 8.44. Found: C, 65.71; H, 8.84.

2,3,3aα,4,5,6,7,7aα-Octahydro-4β-hydroxy-6α-methoxycarbonyl-6β-methyl-3β-(4-methyl-3-pentenyl)-3-phenylselenenyl-1-benzofuran-2-one (13a). To a solution of LDA, prepared from BuLi (4.46 mmol) and diisopropylamine (0.7 mL) in THF (2.5 mL), was added dropwise a solution of **12b** (360 mg, 1.16 mmol) in THF (1.3 mL) containing HMPT (0.8 mL) at -78 °C. After being warmed up to -20 °C over 1.5 h, the mixture was cooled to -55 °C, and the resulting enolate solution was quenched by the addition of benzeneselenenyl chloride (1 g, 5.2 mmol) in THF (2 mL). The temperature was raised again to -30 °C, the mixture was treated with aqueous NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water and saturated brine, and dried. Evaporation left an oil, which was purified by TLC (CH_2Cl_2-ether, 10:1) to give recovered **12b** (86 mg, 24 %) and **13a** (267 mg, 50%; 65% based on consumed **12b**), mp 134-135 °C (recrystallized from ether); IR 3610, 3500, 1755, 1728 cm^{-1}; ^1H NMR 1.30 (s, 3H), 1.64 (br s, 3H), 1.67 (br s, 3H), 3.68 (s, 3H), 4.26 (br m, 1H), 5.01

(m, 1H), 7.2-7.7 (m, 5H). Anal. Calcd for $C_{22}H_{30}O_5Se$: C, 59.35; H, 6.50. Found: C, 59.60; H, 6.29.

2,4,5,6,7,7aα-Hexahydro-6α-carboxy-4β-hydroxy-6β-methyl-3-(4-methyl-3-pentenyl)-1-benzofuran-2-one (14a). A solution of **13a** (464 mg, 1 mmol) in 10% ethanolic KOH (10 mL) was refluxed for 3 h. After cooling in an ice bath, the reaction mixture was diluted with water and then acidified with dilute HCl at 0 °C. After being stirred at the same temperature for 30 min, the product was extracted with CH_2Cl_2, and the extract was washed with water and saturated brine, and dried. Evaporation left crude **13b** (473 mg) as an oil. A small amount of **13b** in methanol was treated with a slight excess of ethereal diazomethane, and the product isolated in usual manner was shown to be homogeneous on silica gel thin-layer chromatography and identified to be **13a** by spectral comparison.

H_2O_2 (30%, 0.6 mL) was added dropwise to a solution of the above crude **13b** (473 mg) in THF (6 mL) containing acetic acid (2 drops) at 0 °C. After being stirred at room temperature for 30 min, aqueous $NaHCO_3$ was added to the mixture, and the product was extracted with CH_2Cl_2. The extract was washed with saturated brine and dried. Removal of the solvent left an oil, which was purified by TLC (CH_2Cl_2-ether, 1:1) to give oily **14a** (203 mg, 69% from **13a**); IR 3450, 1740, 1700, 1620 cm^{-1}; ^1H NMR 1.38 (s, 3H), 1.60 (br s, 3H), 4.77 (m, 2H), 5.20 (br t, 1H, J=8), 6.30 (br, 1H).

Decarboxylation of 14a with lead tetraacetate. A solution of **14a** (143 mg, 0.49 mmol), acetic anhydride (0.5 mL) and 4-(*N*,*N*-dimethyl)aminopyridine (98 mg, 0.8 mmol) in $CHCl_3$ (2.8 mL) was allowed to stand at room temperature for 15 h. Methanol (0.5 mL) was added at 0 °C and the mixture was then diluted with water. The product was extracted with CH_2Cl_2 and the extract was washed with aqueous HCl, water and saturated brine, and dried. Removal of the solvent afforded **14b** (163 mg) as an oil. A mixture of the acetylation product, $Cu(OAc)_2$ monohydrate (3 mg, 0.015 mmol) and pyridine (2 drops) in benzene (4 mL) was stirred at room temperature for 10 min, and then $Pb(OAc)_4$ (295 mg, 0.66 mmol) was added. After the mixture had been stirred at room temperature for 25 min and then at 85 °C for 30 min, an additional portion of $Pb(OAc)_4$ (140 mg, 0.32 mmol) was added, and stirring was continued at the same temperature for an additional 1 h. The resulting mixture was diluted with ether and passed through a short silica gel column. Removal of the solvent afforded an oily residue, which was separated by TLC (hexane-ether, 25:10) to give **16a** (16 mg, 18%); IR 1750, 1690 cm^{-1}; ^1H NMR 1.58 (s, 3H), 1.68 (s, 3H), 1.77 (s, 3H), 2.16 (s, 3H), 5.09 (br m, 1H), 5.25 (br m, 1H), 5.65 (br s, 1H), 5.85 (dd, 1H, J=9 and 7), **16b** (10 mg, 7%); IR 1750, 1685 cm^{-1}; ^1H NMR 1.58 (s, 3H), 1.68 (s, 3H), 1.82 (s, 3H), 2.16 (s, 3H), 4.92 (dd, 1H, J=10 and 6), 5.08 (br m, 1H), 5.48 (br s, 1H), 6.34 (br s, 1H), **16c** (15 mg, 11%); IR 1748, 1680, 915 cm^{-1}; ^1H NMR 1.57 (s, 3H), 1.68 (s, 3H), 2.16 (s, 3H), 4.58 (dd, 1H, J=11 and 4), 5.11 (m, 3H), 5.62 (dd, 1H, J=12 and 7), and **15a** (30 mg, 18%): IR 1745, 1685cm^{-1}; ^1H NMR 1.67 (s, 3H), 1.70 (s, 3H), 1.77 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 4.88 (dd, 1H, J=12 and 6), 5.14 (br m, 1H), 5.88 (dd, 1H, J= 12 and 6).

2,4,7,7aα-Tetrahydro-4β-hydroxy-6-methyl-3-(4-methyl-3-pentenyl)-1-benzofuran-2-one (18a). (a) To a suspension of K_2CO_3 (8.5 mg, 0.06 mmol) in dry methanol (0.3 mL) was added a solution of **16a** (16 mg, 0.085 mmol) in methanol (1.5 mL) at -10 °C. After being stirred at the same temperature for 1 h, the reaction mixture was neutralized with dilute HCl. After dilution with water, the mixture was extracted with CH_2Cl_2, and the extract was washed with saturated brine and dried. Removal of the solvent afforded an oil, which was purified by TLC (CH_2Cl_2-ether, 10:1) to give **18a** (8 mg, 60%): IR 3555, 3475, 1746, 1678 cm^{-1}: ^1H NMR 1.55 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 4.84 (dd, 1H, J=10 and 7), 5,13 (br m, 1H), 5.50 (br m, 1H). Exact mass: Calcd for $C_{15}H_{20}O_3$ 248.1410; Found 248.1394.

(b) A solution of **15a** (30 mg, 0.086 mmol) in dry methanol (1.3 mL) was added dropwise to a suspension of K_2CO_3 (12 mg, 0.086 mmol) in dry methanol (0.7 mL) at -10 °C. After being stirred for 25 min, the mixture was acidified with dilute HCl and extracted with AcOEt. The extract was washed with saturated brine, dried, and evaporated to give an oil, which was purified by TLC (CH_2Cl_2-ether, 10:1) to give **15b** (20 mg); IR 3480, 1742, 1675; ^1H NMR 1.59 (s, 6H), 1.71 (s, 3H), 2.02 (s, 3H), 4.65 8m, 2H), 5.18 (br t, 1H, J=8).

A mixture of dipyridine-chromium trioxide (84 mg, 0.325 mmol) and **15b** (20 mg, 0.065 mmol) in CH_2Cl_2 (1.2 mL) was stirred at 0 °C for 20 min and diluted with ether. The mixture was passed through a short silica gel column. The eluate was concentrated to give an oil. A solution of the oil in CH_2Cl_2 (1 mL) containing triethylamine (3 drops) was stirred at 0 °C for 30 min. The resulting solution was diluted with CH_2Cl_2 and washed with saturated brine, and dried. Removal of the solvent afforded an oily **17**.

A solution of the crude **17** in methanol (0.5 mL) was added to a solution of $NaBH_4$ (2 mg) in the same solvent (0.5 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was acidified with dilute HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated to afford an oil, which was purified by TLC (CH_2Cl_2-ether, 10:1) to give **18a** (8 mg, 38 % from **15a**) as identified by spectroscopic comparison.

Paniculide A (1). *t*-Butyl hydroperoxide (4 μL) was added dropwise to a solution of **18a** (6 mg, 0.024 mmol) and a catalytic amount of $MoO(acac)_2$ in benzene at room temperature, and the mixture was heated at 70 °C for 1 h. After addition of aqueous $NaHCO_3$, the resulting mixture was diluted with water, and extracted with CH_2Cl_2. The extract was washed with saturated brine, dried, and evaporated. The residue was purified by TLC (ether) to provide crystals (2 mg, 30 %), mp 97 °C (recrystllized from methanol), which was identified as **1** by comparison of its IR and ^1H NMR spectra and of behavior on TLC with those of the natural specimen.

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