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SYNTHESIS OF ARNEBINOL, AN ANSA-TYPE PRENYLATED PHENOL WITH EFFECTS INHIBITORY TO PROSTAGLANDIN BIOSYNTHESIS

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Abstract--Arnebinol, a new ansa-type prenylated phenol, was synthesized in 12 steps from geraniol and p-benzoquinone in 5.1 % overall yield.

In 1983 Sankawa and his co-workers reported the isolation of arnebinol **1a** from the root of Arnebia euchroma (Royle) Johnst. (Japanese name: Nan-shikon).[1] Its unique ansa-type structure **1a** as revealed by the X-ray analysis together with its bioactivity as an inhibitor of prostaglandin biosynthesis[1] prompted us to synthesize it in an amount sufficient for its further biological evaluation. Herein we describe a detailed account of our synthesis.[2]

As shown in Fig 1, our retrosynthetic analysis of arnebinol was straightforward. We could visualize an intermediate **A** by disconnecting the bond a of **1a**. As the precursors leading to **A**, we selected **B** and **C** by disconnecting the bond b of **A**. These two building blocks were to be coupled by the method of Maruyama and Naruta.[3] Geraniol **D** was chosen as the starting material for **B**. The final macrocyclization reaction (**A**→**1a**) was the crucial one and most of our efforts were devoted to it. The overall yield of **1a** as achieved by the present improved route was 5.1 % from geraniol and about 9 times higher than that reported in our preliminary communication.[2]

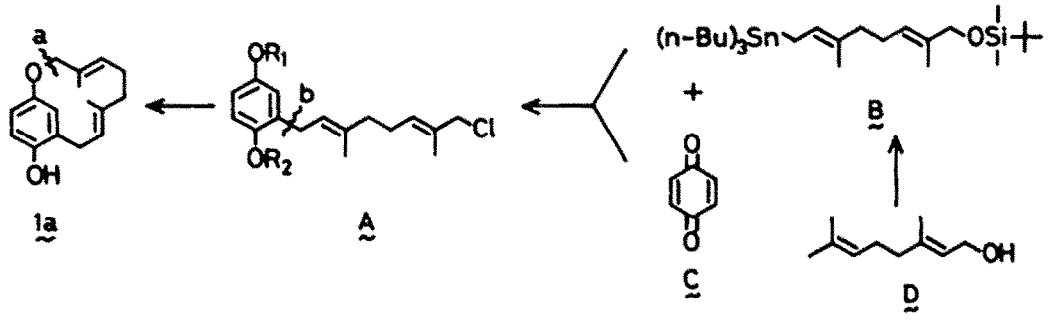

Fig.1. Retrosynthetic analysis of arnebinol.

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Geraniol D was converted to **2** (Fig 2) in 49 % yield by our method.[4] Silylation of **2** with t-$BuMe_2SiCl$ in the presence of Et_3N and 4-N,N-dimethylaminopyridine (DMAP)[5] gave an acetoxy silyl ether **3a** in 94 % yield, which was hydrolyzed with K_2CO_3 in aq MeOH to give a diol monosilyl ether **3b** in 98 % yield. Treatment of **3b** with MsCl and LiCl in s-collidine-DMF[6] yielded a chloride **4** in 96 % yield. Stannylation of **4** with $(n\text{-}Bu)_3SnLi$[7] furnished an allylstannane **5** (*B) in 91 % yield. Reductive prenylation of p-benzoquinone with 2 eq of **5** in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2[3] gave a prenylated hydroquinone **6a** in 91 % yield (45.5 % based on **5**). The use of 2 eq of **5** was essential in realizing the efficient conversion of **5** and p-benzoquinoe to **6a**. When 1.15 eq of **5** was used, the yield of **6a** dropped to 40.2 % (34.6 % based on **5**). Removal of the silyl protective group of **6a** was effected with aq HF in MeCN[8] to give **6b** in 97 % yield. Treatment of **6b** with Ph_3P and CCl_4 yielded **7a** in quantitative yield.

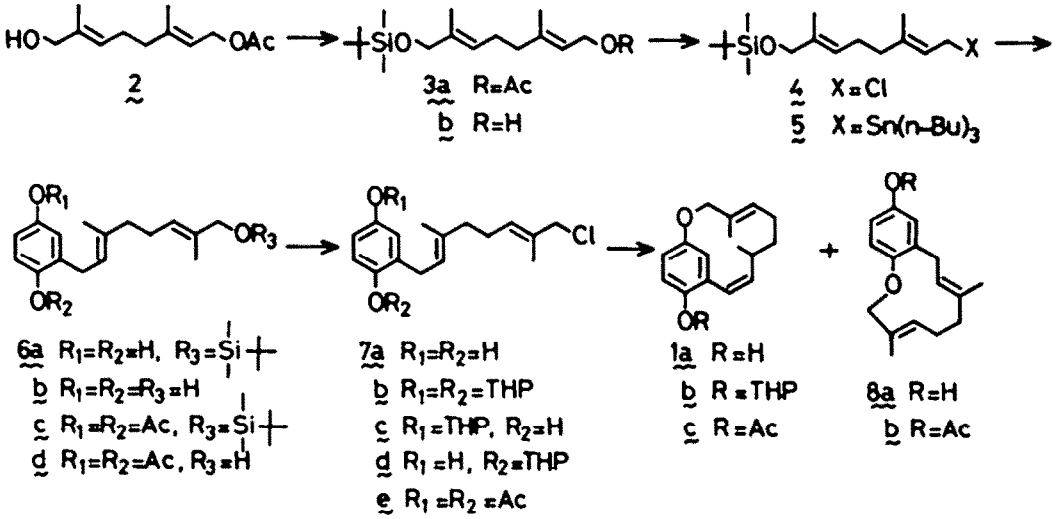

Fig.2. Synthesis of arnebinol and isoarnebinol.

With the desired key-intermediate **7a** in hand, we attempted the cyclization of **7a** or its derivatives under various conditions. Firstly, direct cyclization of **7a** with K_2CO_3 in acetone-DMF was found to give arnebinol **1a** in 11 % yield together with a regioisomeric cyclization product **8a** named isoarnebinol (13 % yield). To improve the yield, many kinds of combinations of a base and solvents were examined. With aq NaOH as the base, use of DMF, DMF-ether or DMF-C_6H_6 as the solvents resulted in the formation of resinous materials. When aq DMF was used as the solvent, ca 20 % yield of a mixture of **1a** and **8a** was obtained. The use of $Ba(OH)_2$ in acetone generated only isoarnebinol **8a** besides polymeric materials. K_2CO_3 in acetone or aq acetone produced a mixture of **1a** and **8a** in 35~40 % yield only if the reaction was carried out in a micro-scale. The reaction was not always reproducible under a large-scale condition. When K_2CO_3 was used in C_6H_6 in the presence of either 18-crown-6 or $(n\text{-}Oct)_3N^+MeCl^-$, the products were isoarnebinol **8a** and less polar unidentified material, and no arnebinol **1a** was obtained. These unpromising results forced us to examine the second approach. Treatment of **7a** with 12 eq of dihydropyran in CH_2Cl_2 in the presence of p-TsOH yielded **7b** (12 % yield), **7c** (19 %), **7d** (20 %) and the recovered **7a** (47 %) after chromatographic purification. The mono THP ether **7d** was treated with aq NaOH in DMF to give arnebinol THP ether **1b**. Removal of the THP group of **1b** with p-TsO-C_5H_5NH (PPTS) in MeOH yielded arnebinol **1a** in 48 % yield from **7d**. Although the yield of the cyclization (**7d**→**1b**) was fair, this approach had to be abandoned due to the low yield of **7d** from **7a** and also to the instability of **7d**. Indeed even in the course of its chromatographic purification over SiO_2, **7d** deteriorated to give a mixture of **7a**, **7b**, **7c** and **7d**. Attempts to prepare a monoacetate (**7d**, Ac instead of THP) were not successful, either.

Since the cyclization of the mono THP ether **7d** proceeded in an acceptable yield, we suspected that the presence of the two free phenolic OH groups in **7a** might have been the origin of the poor yield observed in cyclizing **7a**. For this reason we decided to employ the diacetate **7e** as the substrate for cyclization. Treatment of **7e** with a base would first lead to the preferential hydrolysis of the less hindered OAc group and the resulting phenolate anion would then participate in the cyclization reaction to give arnebinol acetate **1c**. The required substrate **7e** was obtained by acetylation of **7a** with Ac_2O-C_5H_5N in 83 % yield from **6b**. An alternative route to **7e** was also explored starting from **6a**. Thus acetylation of **6a** with Ac_2O C_5H_5N-DMAP gave **6c**, which was desilylated with aq AcOH-THF to **6d**. Treatment of **6d** with N-chlorosuccinimide (NCS) and Me_2S in CH_2Cl_2[10] gave **7e**. However, the overall yield of **7e** from **6a** via this route was only 22 %. The cyclization of **7e** was first tried with aq NaOH in DMF. To our disappointment, isoarnebinol **8a** was the only identified product with a large amount of unidentified and less polar materials. The second and successful trial to achieve the cyclization was to treat **7e** with K_2CO_3 in acetone. Hydrolysis of the crude product yielded arnebinol **1a** (12~21 % yield) and isoarnebinol **8a** (11~32 % yield). Unfortunately arnebinol **1a** was the minor product. The reaction condition was therefore further modified to establish a more successful procedure employing the following one-pot process. A dilute soln (0.1 % w/v) of **7e** in DMF was treated with an excess of 0.4 N K_2CO_3 aq for 1 day at room temp to give a mixture of **1c** and **8a** as the major products. The very minor products were **1a** and **8b**. Without isolating the products, the reaction mixture containing **1a**, **1c**, **8a**, **8b** and K_2CO_3 was diluted with MeOH. This caused the removal of the Ac groups of **1c** and **8b** to give a mixture of **1a** and **8a**. These two were separable by SiO_2 chromatography. Arnebinol **1a**, m.p. 161.5~163.0° (lit.[1] m.p. 163.5~164.0°), was obtained as the major product in 35 % yield from **7e**. Its 400 MHz ^{1}H-NMR spectrum was completely identical with the authentic spectrum kindly provided by Prof. C. Sankawa. The unwanted regioisomer **8a** (isoarnebinol) was obtained as a minor product in 23.5 % yield from **7e**. The overall yield of arnebinol **1a** was 10.5 % in 9 steps from **2** or 5.1 % in 12 steps from geraniol **D**.

In summary, our time-consuming effort to improve the efficiency of the cyclization resulted in the preparation of **1a** in an amount sufficient for its further biological evaluation in Prof. Sankawa's laboratory.

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated.

2,6-Dimethyl-2,6-octadiene-1,8-diol 1-t-butyldimethylsilyl ether 8-acetate **3a**. A soln of **2** (21.2 g, 0.1 mol) in dry CH_2Cl_2 (35 ml) was added dropwise to a stirred and ice-cooled soln of t-$BuMe_2SiCl$ (15.1 g, 0.1 mol), Et_3N (16 ml, 0.16 mol) and DMAP (488 mg, 4 mmol) in dry CH_2Cl_2 (120 ml) under Ar. The mixture was stirred at room temp for 1 day. It was then diluted with CH_2Cl_2 (150 ml), washed with sat NH_4Cl soln, water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residual crude oil (45.0 g) was chromatographed over SiO_2 (Merck, Art 7734, 200 g). Elution with n-hexane and n-hexane-ether (100:1) gave 16.2 g of **3a** (94.2 % based on the consumed **2**; 10.0 g of **2** was recovered by further elution). A portion of **3a** was distilled to give an analytical sample of **3a**, b.p. 119~138°/0.3 mm; n_D^{20} 1.4587; ν_{max} 1740 (s), 1230 (s), 1065 (s), 810 (s) cm^{-1}; δ(CDCl$_3$) 0.05 (6H, s), 0.90 (9H, s), 1.59 (3H, br.s), 1.69 (3H, br.s), 2.03 (3H, s), 2.09 (4H, br.s), 3.99 (2H, br.s), 4.56 (2H, d, J=7 Hz), 5.36 (2H, br.t, J=7 Hz). (Found: C, 66.10; H, 10.70. Calc for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.51 %). In another run 85.5 g of **2** gave 94.3 g (86.4 % based on the consumed **2**; 14.5 g of **2** was recovered) of **3a**.

2,6-Dimethyl-2,6-octadiene-1,8-diol 1-t-butyldimethylsilyl ether **3b**. A soln of K_2CO_3 (13.8 g, 0.1 mol) in water (20 ml) was added to a stirred soln of **3a** (15.2 g, 46.6 mmol) in MeOH (100 ml). After stirring for 1 h at room temp, the mixture was concentrated in vacuo to remove MeOH. The residue was partitioned between ether and brine. The ether soln was dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled to give 12.9 g (97.7 %) of **3b** as a slightly pale yellow oil, b.p. 119~124°/0.25 mm; n_D^{20} 1.4671; ν_{max} 3330 (br.s), 1660 (w), 1250 (m), 1105 (m), 1060 (s), 1000 (m), 830 (s), 770 (m) cm^{-1}; δ(CDCl$_3$) 0.06 (6H, s), 0.90 (9H, s), 1.57 (3H, br.s), 1.65 (3H, br.s), 1.70 (1H, br, OH), 2.06

(4H, br.s), 3.95 (2H, br.s), 4.06 (2H, d, J=7 Hz), 5.05 (2H, br.t, J= 7 Hz). (Found: C, 67.20; H, 11.50. Calc for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34 %).

8-Chloro-2,6-dimethyl-2,6-octadien-1-ol t-butyldimethylsilyl ether 4. A soln of dry LiCl (5.1 g, 0.12 mol) in dry DMF (150 ml) was added dropwise to a stirred mixture of 3b (28.4 g, 0.1 mol) and s-collidine (14.5 g, 0.12 mol) under Ar. To the stirred and cooled (ice-salt) mixture was added MsCl (13.7 g, 0.12 mol) at 0°. After the addition, the stirring was continued for 3 h at 0°. The mixture was poured into ice-water and the org layer was separated. The aq layer was extracted with ether-n-pentane (1:1). The combined org layer was washed with $Cu(NO_3)_2$ soln and water, dried (Na_2SO_4) and concentrated in vacuo at 20° to give 29.0 g (95.9 %) of 4, ν max 1250 (m), 1065 (m), 835 (s), 770 (m) cm^{-1}; δ(CCl_4) 0.03 (6H, s), 0.90 (9H, s), 1.58 (3H, br.s), 1.72 (3H, s), 2.10 (4H, br), 3.92 (2H, s), 4.00 (2H, d, J=8 Hz), 5.30 (1H, t, J=6 Hz), 5.42 (1H, t, J= 8 Hz). This was employed in the next step without further purification.

8-Tri-n-butylstannyl-2,6-dimethyl-2,6-octadien-1-ol t-butyldimethylsilyl ether 5. A soln of $LiN(i\text{-}Pr)_2$ was prepared by the dropwise addition of a soln of n-BuLi in n-hexane (1.5 M, 120 ml, 180 mmol) over 10 min to a stirred and cooled (ice-salt) soln of $(i\text{-}Pr)_2NH$ (27.5 ml, 196 mmol) in dry THF (360 ml) at -6~0° under Ar. After stirring for 25 min at -6~0°, $(n\text{-}Bu)_3SnH$ (44 ml=47.6 g, 164 mmol) was added dropwise over 20 min. The stirring was continued for 30 min and then the cooling-bath was changed to a dry ice-acetone bath. A soln of 4 (50.0 g, 165 mmol) in dry THF (100 ml) was added dropwise over 40 min to the stirred and cooled mixture at -68~-65°. The stirring was continued for 1 h at -68~-65°. Then the temp was allowed to rise to 0° over 20 min. The mixture was diluted with n-hexane (1 l). The hexane soln was washed with water (1 l x 2), dried ($MgSO_4$) and concentrated in vacuo to give 103.0 g of a crude oil. This was chromatographed over SiO_2 (500 g) mixed with finely powdered dry K_2CO_3 (15 g). Elution with n-hexane gave 81.3 g (90.5 %) of 5, ν max 2980 (s), 2950 (s), 2880 (s), 1660 (w), 1465 (s), 1255 (s), 1115 (s), 1070 (vs), 860 (s), 840 (vs), 775 (s) cm^{-1}; δ(CCl_4) 0.03 (6H, s), 0.89 (9H, s), 0.80~1.90 (29H, m), 1.56 (6H, s), 2.00 (4H, br.s), 3.92 (2H, br.s), 5.28 (2H, t, J=8 Hz). This was employed in the next step without further purification.

8-(2',5'-Dihydroxyphenyl)-2,6-dimethyl-2,6-octadien-1-ol t-butyldimethylsilyl ether 6a. A soln of p-benzoquinone (54 mg, 0.5 mmol) and $BF_3 \cdot Et_2O$ (71 mg, 61.5 μl, 0.5 mmol) in dry CH_2Cl_2 (10 ml) was stirred for 30 min at room temp under Ar. This was then cooled with a dry ice-acetone bath. To the stirred and cooled soln was added a soln of 5 (575 mg, 1.0 mmol) in dry CH_2Cl_2 (2 ml) at -70°. The stirring was continued at -70° for 30 min and then the temp was allowed to rise to room temp over 1 h. After stirring for 1 h, the reaction was quenched with 2 N HCl. The mixture was extracted with ether. The ether soln was washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residual orange syrup (573 mg) was chromatographed over SiO_2 (Merck Art 9385, 60 g). Elution with $CHCl_3$ (200 ml) and $CHCl_3$-EtOH (19:1, 500 ml) gave 171 mg (91.0 %) of 6a, ν max 3400 (s), 1515 (m), 1460 (m), 1260 (m), 1200 (s), 1075 (m), 840 (s), 780 (m) cm^{-1}; δ($CDCl_3$) 0.09 (6H, s), 0.92 (9H, s), 1.55 (3H, br.s), 1.63 (3H, br.s), 2.12 (4H, m), 3.22 (2H, d, J=8 Hz), 4.03 (2H, br.s), 5.10~5.55 (3H, m, 1OH), 6.26 (1H, br.s, OH), 6.60 (3H, s); MS (m/z): 376 (M^+), 319 (M^+-t-Bu), 244 (M^+-t-BuMe$_2$SiOH), 229 (M^+-t-BuMe$_2$SiOH-Me). (Found: C, 69.56; H, 9.74. Calc for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.64 %). In another run 6.50 g (60.1 mmol) of p-benzoquinone and 7.3 ml (59.4 mmol) of $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 (1200 ml) was treated with a soln of 39.0 g (69.9 mmol) of 5 in dry CH_2Cl_2 (150 ml) to give 9.10 g (40.2 % based on p-benzoquinone and 34.6 % based on 5) of 6a. In this case 0.52 g of 6b was also obtained as a by-product.

8-(2',5'-Dihydroxyphenyl)-2,6-dimethyl-2,6-octadien-1-ol 6b. 15 % HF aq (1.5 ml) was added to a stirred soln of 6a (2.49 g, 6.61 mmol) in MeCN (50 ml). After stirring for 30 min at room temp, the mixture was poured into water (100 ml) and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 2.66 g of a crude oil. This was chromatographed over SiO_2 (30 g). Elution with n-hexane-EtOAc (3:1) gave 1.68 g (96.8 %) of 6b, ν max 3350 (br.s), 2940 (s), 1705 (w), 1650 (w), 1610 (w), 1505 (m), 1450 (s), 1380 (m), 1195 (s), 1000 (m), 805 (m) cm^{-1}; δ($CDCl_3$) 1.62 (6H, s), 2.10~2.30 (4H, m), 3.24 (2H, d, J=8 Hz), 4.03 (2H, s), 4.66 (3H, s, 3OH), 5.00~5.60 (2H, m), 6.40~6.70 (3H, m). (Found: C, 72.70; H, 8.30. Calc for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45 %).

8-(2',5'-Diacetoxyphenyl)-2,6-dimethyl-2,6-octadien-1-ol t-butyldimethylsilyl ether 6c. Ac_2O (0.5 ml, 5.3 mmol) and DMAP (1 mg) were added to a soln of 6a (171 mg, 0.455 mmol) in dry C_5H_5N (3 ml), and the mixture was stirred for 16 h at room temp. It was then poured into dil HCl and extracted with ether. The ether soln was washed with dil HCl, water, $CuSO_4$ soln, water, $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residual pale yellow syrup (172 mg) was chromatographed over SiO_2 (Merck Art 7734, 20 g). Elution with n-pentane-$CHCl_3$ (1:1~3:2) gave 120 mg (57.4 %) of 6c, ν max 1770 (s), 1205 (s), 1170 (s) cm^{-1}; δ($CDCl_3$) 0.06 (6H, s), 0.89 (9H, s), 1.56 (3H, s), 1.66 (3H, br.s), 2.06 (4H, m), 2.24 (6H, s), 3.18 (2H, d, J=8 Hz), 3.94 (2H, s), 4.60 (1H, m), 5.30 (1H, m), 6.90 (3H, s); MS (m/z): 460 (M^+=$C_{26}H_{40}O_5Si$), 403 (M^+-t-Bu), 361 (M^+-t-Bu-CH_2CO), 319 (M^+-t-Bu-2CH_2CO).

8-(2',5'-Diacetoxyphenyl)-2,6-dimethyl-2,6-octadien-1-ol 6d. A soln of 6c (438 mg; crude, prepd from 448 mg (1.16 mmol) of 6a) in AcOH-H_2O-THF (3:1:1, 10 ml) was stirred for 47 h at room temp under Ar. The soln was poured into $NaHCO_3$ soln and extracted with ether. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 214 mg (53.3 % from 6a) of 6d, ν max 3450 (br.s), 1770 (s), 1620 (w), 1210 (s), 1190 (s), 1170 (s) cm^{-1}; δ ($CDCl_3$) 1.61 (6H, br.s), 2.05 (4H, m), 2.17 (6H, s), 3.12 (2H, d, J=7 Hz), 3.73 (2H, s), 4.30 (1H, br, OH), 5.05~5.60 (2H, m), 6.85 (3H, s); MS (m/z): 346 (M^+=$C_{20}H_{26}O_5$), 328 (M^+-H_2O), 304 (M^+-CH_2CO), 286 (M^+-CH_2CO-H_2O), 271, 269, 268, 267, 262, 260, 246, 245, 244, 243.

8-(2',5'-Dihydroxyphenyl)-2,6-dimethyl-2,6-octadienyl chloride 7a. Ph_3P (2.96 g, 11.3 mmol) was added to a soln of 6b (2.63 g, 10.0 mmol) in DMF (20 ml) and CCl_4 (70 ml). The mixture was stirred and heated under reflux for 1 h. An additional amount of Ph_3P (1.04 g, 3.97 mmol) was added to the mixture and the stirring and heating were continued for 30 min. After cooling, the mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (70 g). Elution with C_6H_6-EtOAc (10:1)

gave 2.81 g (quantitative) of 7a, νmax 3400 (s), 1705 (w), 1660 (w), 1605 (w), 1500 (m), 1445 (m), 1190 (s) cm^{-1}; δ($CDCl_3$) 1.66 (6H, s), 2.04 (4H, br.s), 3.21 (2H, d, J=8 Hz), 3.94 (2H, s), 5.05~5.60 (2H, m), 5.95 (2H, s, 2OH), 6.30~6.70 (3H, m). This was unstable at room temp and readily decomposed to give isoarnebinol and some unidentified less polar materials. This was therefore employed in the next step without further purification.

Preparation of the THP ethers 7b, 7c and 7d. To a stirred soln of 7a (128 mg, 0.46 mmol) and p-TsOH (2 mg) in dry CH_2Cl_2 (40 ml) was added slowly a soln of dihydropyran (50 mg, 0.59 mmol) in dry CH_2Cl_2 (1 ml) at room temp. After 20 min 200 mg (2.36 mmol) of dihydropyran was added to the mixture. Subsequently 40 min after the second addition another 200 mg portion (2.36 mmol) of dihydropyran was added. The mixture was stirred for 30 min after the third addition. It was then poured into sat $NaHCO_3$ soln. The org layer was separated, dried ($MgSO_4$) and concentrated in vacuo to remove the solvent and low b.p. impurities originating from dihydropyran. The residue was chromatographed over SiO_2 (Merck Art 7734, 20 g). Elution with C_6H_6 gave 25 mg (12 %) of 7b, 31 mg (19 %) of 7c, 33 mg (20 %) of 7d and 60 mg (47 %) of the recovered 7a. The spectral data of 7b: ν max 1665 (m), 1605 (w), 1590 (w), 1495 (s), 1200 (s), 1035 (s), 970 (s) cm^{-1}; δ(CCl_4) 1.70 (6H, s), 1.20~2.80 (16H, m), 3.10~4.00 (6H, m), 3.90 (2H, s), 5.00~5.70 (4H, m), 6.30~7.10 (3H, m). The spectral data of 7c: ν max 3400 (m), 1665 (w), 1610 (w), 1500 (s), 1200 (s) cm^{-1}; δ(CCl_4) 1.30 2.80 (10H, m), 1.68 (6H, s), 3.10~4.00 (4H, m), 3.88 (2H, s), 5.00~5.60 (4H, m), 6.50~7.10 (3H, m). The spectral data of 7d: νmax 3400 (m), 1665 (w), 1600 (w), 1500 (s), 1200 (s) cm^{-1}; δ (CCl_4) 1.67 (6H, s), 1.30~2.70 (10H, m), 3.00~4.00 (4H, m), 3.88 (2H, s), 5.00~5.60 (3H, m), 6.30~7.20 (3H, m), 6.22 (1H, br.m, OH).

8-(2',5'-Diacetoxyphenyl)-2,6-dimethyl-2,6-octadienyl chloride 7e. (a) From 6b: Ph_3P (998 mg, 3.80 mmol) was added to a soln of 6b (412 mg, 1.57 mmol) in DMF (4 ml) and CCl_4 (10 ml). The mixture was stirred and heated under reflux for 2.5 h. It was then poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residual 7e was dissolved in ether (5 ml) and C_5H_5N (3.5 ml). To this was added Ac_2O (1.08 g, 10.6 mmol) and the soln was stirred overnight at room temp. It was then poured into water and extracted with ether. The ether soln was washed with 2 N HCl and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with C_6H_6 gave 475 mg (82.9 %) of 7e, νmax 1775 (s), 1210 (s), 1170 (s) cm^{-1}; δ($CDCl_3$) 1.65 (3H, s), 1.70 (3H, s), 2.07 (4H, m), 2.24 (6H, s), 3.17 (2H, d, J=7 Hz), 3.95 (2H, s), 4.50~5.60 (2H, m), 6.93 (3H, s); MS (m/z): 366, 364 (M^+-$C_{20}H_{25}O_4Cl$), 328 (M^+-HCl), 324, 322 (M^+-CH_2CO), 285, 282, 280 (M^+-$2CH_2CO$), 244 (M^+-HCl-$2CH_2CO$).

(b) From 6d: Me_2S (88 μl, 1.2 mmol) was added to a stirred and ice-cooled soln of NCS (147 mg, 1.1 mmol) in dry CH_2Cl_2 (10 ml) at 0° under Ar. To the resulting mixture was added slowly a soln of 6d (346 mg, 1.0 mmol) in dry CH_2Cl_2 (2.5 ml). The mixture was stirred for 1 h at 0°. It was then poured into water. After mixing thoroughly, the org layer was separated and the aq layer was extracted with ether. The combined org soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Art 7734, 20 g). Elution with n-hexane-$CHCl_3$ (7:3) gave 144 mg (71.6 % based on the consumed 6d) of 7e, whose spectral properties were identical with those described above. The starting 6d (155 mg) was recovered in the later fractions.

Arnebinol 1a and isoarnebinol 8a. (a) From 7a: To a stirred and heated soln of K_2CO_3 (19.6 g, 142 mmol) in acetone (3000 ml)-DMF (150 ml)-water (300 ml) was added dropwise over 1 h a soln of 7a (3.85 g, 13.7 mmol) in acetone (50 ml) under reflux. The color of the mixture changed from pale green to dark brown. The mixture was stirred and heated under reflux at 59° for 22 h. It was then concentrated in vacuo. The residue was acidified with 2 N HCl (500 ml) and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (8.72 g) was chromatographed over SiO_2 (Merck Art 7734, 40 g). Elution with C_6H_6-ether (1:1) gave a mixture of 1a and 8a. This was rechromatographed over SiO_2. Elution with C_6H_6 gave 362 mg (10.8 %) of 1a and 423 mg (12.9 %) of 8a. Our synthetic arnebinol 1a showed the following properties: prisms from C_6H_6, m.p. 161.5~163.0°(lit.[1] 163.5~164.0°; lit.[2] 159.0~160.0°); νmax 3440 (s), 3050 (w), 3000 (w), 2950 (s), 2930 (s), 2890 (sh), 2850 (s), 1822 (w), 1658 (w), 1602 (m), 1505 (vs), 1458 (s), 1440 (s), 1420 (s), 1390 (m), 1340 (s), 1310 (m), 1270 (m), 1250 (s), 1190 (vs), 1140 (s), 1102 (w), 1085 (m), 1062 (w), 1040 (w), 1020 (w), 985 (s), 970 (s), 935 (m), 910 (m), 890 (m), 860 (m), 845 (s), 830 (m), 802 (s), 795 (s), 708 (w), 695 (s), 638 (m), 607 (w), 575 (m), 540 (w), 500 (w), 470 (m), 450 (w) cm^{-1}; λmax 203 nm (log ε=4.36); δ(400 MHz, $CDCl_3$) 1.24 (3H, s), 1.50 (3H, s), 2.14 (1H, br.s), 2.34 (2H, t, J=7 Hz), 2.49 (1H, br.s), 3.07 (1H, br.s), 3.30 (1H, br.s), 4.35 (1H, s), 4.52 (2H, br.s), 5.51 (1H, t, J=7 Hz), 5.67 (1H, t, J=7 Hz), 6.55 (1H, dd, J=3, 8.5 Hz), 6.59 (1H, d, J=8.5 Hz), 7.44 (1H, d, J=3 Hz); MS (m/z): 244.1463 (M^+=$C_{16}H_{20}O_2$=244.1464). (Found: C, 78.93; H, 8.07. Calc for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25 %). The 400 MHz ^{1}H-NMR spectrum of synthetic 1a was identical with that of the natural product. Isoarnebinol 8a showed the following properties: prisms from C_6H_6-n-hexane, m.p. 160.5~162.5°(lit.[2] m.p. 163.0~165.0°); ν max 3400 (s), 3030 (w), 2990 (s), 2930 (s), 2900 (s), 2850 (s), 1840 (w), 1665 (w), 1615 (w), 1585 (m), 1498 (vs), 1460 (s), 1435 (s), 1383 (m), 1360 (w), 1325 (s), 1290 (w), 1265 (m), 1232 (vs), 1192 (vs), 1165 (m), 1145 (m), 1100 (m), 1075 (m), 1030 (m), 960 (m), 940 (vs), 920 (m), 910 (m), 880 (s), 858 (s), 830 (w), 815 (s), 800 (s), 770 (m), 760 (m), 738 (w), 720 (w), 670 (w), 630 (m), 603 (m), 560 (m), 530 (w), 502 (m) cm^{-1}; λmax 203.5 nm (log ε=4.49); δ(400 MHz, $CDCl_3$) 1.57 (3H, s), 1.59 (3H, s), 2.15 (4H, m), 3.19 (2H, d, J=6 Hz), 4.39 (2H, s), 4.47 (1H, s), 4.83 (1H, t, J=6 Hz), 5.08 (1H, t, J=8 Hz), 6.60 (1H, d, J=3 Hz), 6.64 (1H, dd, J=3, 8 Hz), 6.85 (1H, d, J=8 Hz); MS (m/z): 244.1438 (M^+=$C_{16}H_{20}O_2$=244.1464). (Found: C, 78.32; H, 8.19. Calc for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25 %).

(b) From 7d: Four drops of 5 N NaOH aq were added to the stirred soln of 7d (12 mg, 0.033 mmol) in DMF (12 ml). The mixture was stirred for 1 h at room temp and then concentrated in vacuo to remove DMF. The residue was partitioned between ether and water. The ether soln was dried ($MgSO_4$) and concentrated in vacuo. The residue (8 mg) was purified by prep TLC to give 6 mg (55 %) of 1b, ν max 1660 (w), 1610 (m), 1505 (s), 1205 (s) cm^{-1}. This was dissolved in MeOH (2 ml). PPTS (1 mg) was added to the soln and the mixture was stirred for 2 days at room temp. It was then filtered through a small amount (2 g) of SiO_2 and concentrated in vacuo. The residue was purified by prep TLC to give 4 mg (48 % from 1b) of 1a, which was identical in every respect with 1a prepared by other methods.

(c) From 7e with K_2CO_3 in aq DMF: 0.4 N K_2CO_3 aq (60 ml) was added dropwise over 1 h to a stirred and ice-cooled soln of 7e (438 mg, 1.20 mmol) in DMF (438 ml). After the addition, the cooling bath was removed. The stirring was continued for 14 h. In the reaction mixture there still remained 7e upon TLC analysis. Therefore an additional amount (40 ml) of 0.4 N

K_2CO_3 aq was added to the mixture and the stirring was continued for 7 h until the disappearance of 7e. To this mixture was added MeOH (50 ml). The stirring was continued for 18 h at room temp. Then the mixture was concentrated in vacuo at ca 40° to remove MeOH, water and DMF. The residue was mixed with N HCl (500 ml) and extracted with C_6H_6. The C_6H_6 soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck, Art 7734, 15 g). Elution with C_6H_6–ether (100:1) gave 104 mg (35.5 %) of 1a and 69 mg (23.5 %) of 8a. A mixture of 1a and 8a (4 mg, 1.4 %) was also obtained. Arnebinol 1a and isoarnebinol 8a prepared in this way were identical in every respect with those prepared from 7a. In another run arnebinol acetate 1c was isolated. $\delta(CDCl_3)$ 1.18 (3H, s), 1.48 (3H, s), 2.27 (3H, s), 2.20~2.40 (4H, m), 1.06 (2H, d, J=8 Hz), 4.56 (2H, s), 5.40~5.85 (2H, m), 6.65~7.65 (3H, m).

(d) From 7e with K_2CO_3 in acetone: K_2CO_3 (5 g) was added to a soln of 7e (169 mg, 0.46 mmol) in acetone (200 ml) under Ar. The mixture was stirred and heated under reflux for 48 h. NaBr (1 g) was added to the mixture and the stirring was continued for 20 h under reflux. The mixture was concentrated in vacuo. The residue was acidified with dil HCl and extracted with ether. The ether soln was washed with brine, dried and concentrated in vacuo. The residual oil (141 mg) was purified by prep TLC. The least polar fraction was a mixture of 1c and 8b (90 mg, 68.7 % yield or 76.9 % based on the consumed 7e). 7e (20 mg, 11.8 %) was recovered in a small amount. The mixture of 1c and 8b showed the following IR spectrum: ν_{max} 1773 (s), 1660 (w), 1620 (w), 1500 (s), 1210 (s), 1185 (s) cm^{-1}. The mixture (90 mg, 0.31 mmol) was dissolved in MeOH (4 ml). To this was added aq K_2CO_3 (90 mg in 1 ml) and the mixture was stirred for 45 min at room temp. It was then concentrated in vacuo. The residue was acidified with dil HCl and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried (Na_2SO_4) and concentrated in vacuo to give a brown gum (54 mg). This was chromatographed over SiO_2 and the more polar fraction (51 mg) was obtained by elution with $CHCl_3$. 1a was separated from 8a by HPTLC (Merck Art 5628, Silica gel $60F_{254}$, triply developed with $CHCl_3$). Arnebinol 1a (9 mg, 11.7 %) was obtained as the less polar isomer, m.p. 159~160°, whose spectral properties were identical with 1a prepared by other procedures. As the more polar isomer, isoarnebinol 8a (24 mg, 31.2 %), m.p. 163~165°, was obtained, whose spectral properties were identical with 8a prepared by other procedures.

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