Synthesis of Pygmaeocine E, a Linear Abietane Diterpene from *Pygmaeopremna herbacea* (ROXB.) MOLDENKE

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Received January 25, 1996; accepted March 22, 1996

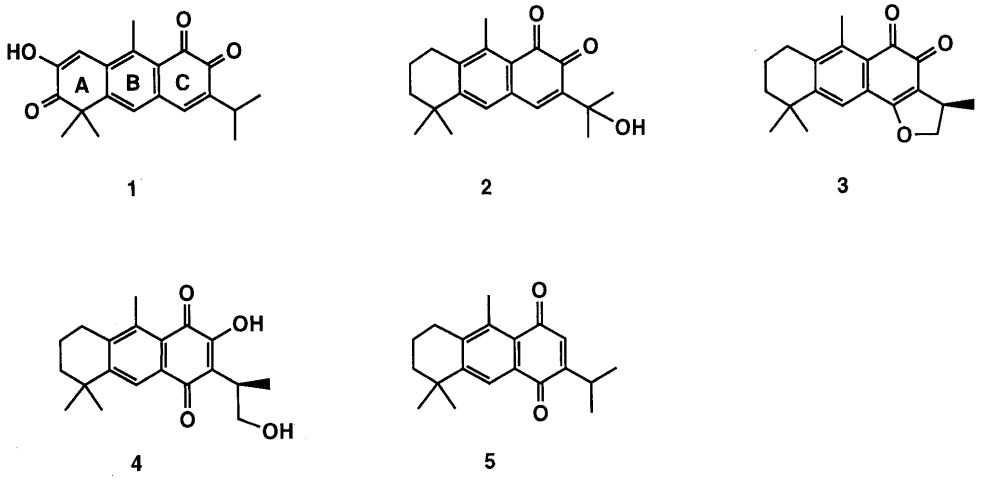
Methyl 12-methoxy-7-oxo-8,11,13-abietatrien-18-oate (10), prepared from (+)-dehydroabietic acid (9), was rearranged into methyl 7-isopropyl-6-methoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (13) *via* a series of reactions: dehydrogenation with selenium(IV) oxide, sodium borohydride reduction, and dehydration with boron trifluoride etherate. Reduction of 13 with lithium aluminum hydride afforded an alcohol (14), which was further rearranged into 2-isopropyl-3-methoxy-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene (16) by treatment with methanesulfonyl chloride in pyridine. The alcohol 14 was then converted into 7-isopropyl-5,6-dimethoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene (22) by means of the following reactions: pyridinium chlorochromate oxidation, Huang–Minlon reduction, demethylation, oxidation with Fremy's salt, catalytic hydrogenation, and methylation. Compound 22 was also prepared from methyl 11,12-dimethoxy-7-oxo-8,11,13-abietatrien-18-oate (23) *via* methyl 7-isopropyl-5,6-dimethoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (26). Treatment of 22 with DDQ produced an enone (29), which was converted into a diosphenol derivative (31) *via* a series of reactions: catalytic hydrogenation, and oxidations with Jones reagent and then with oxygen in the presence of potassium *tert*-butoxide. Demethylation of 31 with ethanethiol and anhydrous aluminum chloride afforded pygmaeocine E (1) and 3,6-dihydroxy-7-isopropyl-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (32).

Key words synthesis; pygmaeocine E; diterpene; *Pygmaeopremna herbaceae*

Pygmaeocine E[1] (**1**), a rare natural diterpene ortho-quinone possessing a rearranged linear abietane skeleton, was isolated from the roots of *Pygmaeopremna herbaceae* (ROXB.) MOLDENKE (Verbenaceae), which is used as a folk remedy in China to reduce inflammation and to cure malaria. Recently, similar natural diterpenes such as umbrosone[2] (**2**), aegyptinones[3] A (**3**) and B (**4**), and 12,16-dideoxy-aegyptinone B[4] (**5**) have also been isolated from the roots of medicinal plants, *Hyptis umbrosa* SALZM (Lamiaceae),[2] *Salvia aegyptiaca* L. (Lamiaceae),[3] and *Zhumeria majdae* ROCH. (Labiatae).[4] Among these natural diterpene quinones, pygmaeocine E (**1**) has an unique structural feature, possessing a diosphenol moiety in the ring A (Fig. 1).

In a previous paper,[5] we reported on a novel skeletal rearrangement of a hydrophenanthrene into a hydroanthracene. That is, the enone (**6**) possessing a hydrophenanthrene skeleton was reduced with sodium borohydride in the presence of cerium(III) chloride heptahydrate and the resulting 7-hydroxy compound (**7**) was treated with boron trifluoride etherate to give an optically active rearranged ester (**8**) possessing a hydroanthracene skeleton. We planned to apply this novel rearrangement to the syntheses of biologically active linear abietane diterpenes. This paper describes the first synthesis of **1** starting from (+)-dehydroabietic acid (**9**), which is readily available from pine rosin.

Methyl 12-methoxy-7-oxo-8,11,13-abietatrien-18-oate (**10**), prepared from **9** by a known procedure,[6] was refluxed with selenium(IV) oxide in aqueous acetic acid to give an enone (**11**) in 82% yield. Reduction of **11** with sodium borohydride in the presence of cerium(III) chloride



1 2 3 4 5

Fig. 1. Natural Linear Abietane Diterpenes

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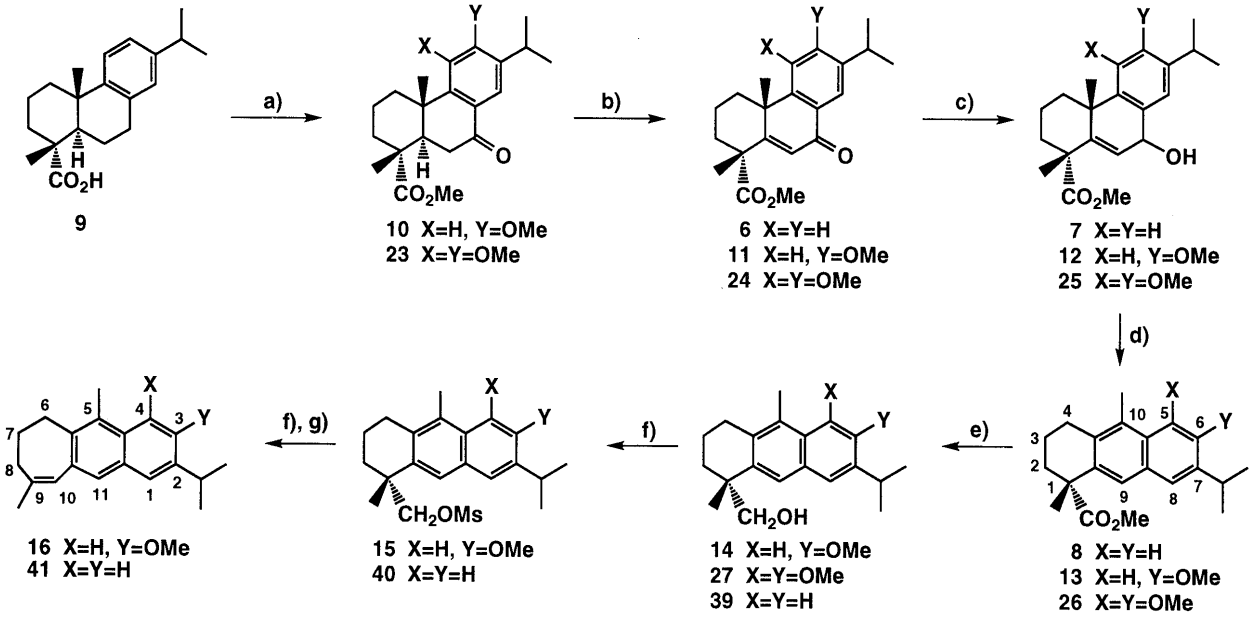


Reagents a) Ref. 6,7 b) SeO_2 c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$ d) $BF_3 \cdot OEt_2$ e) $LiAlH_4$ f) MsCl, pyridine g) 80-83°C

Chart 1

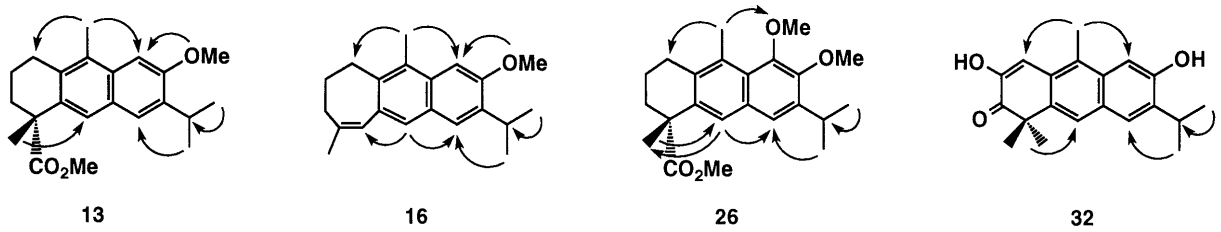
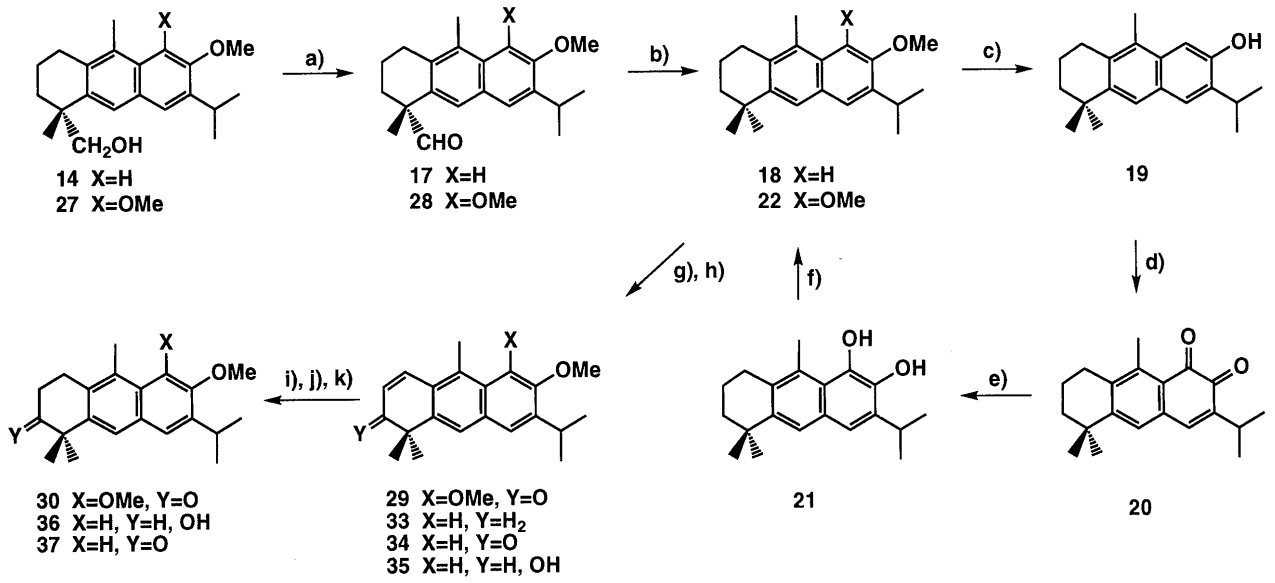


Fig. 2. NOE of Rearranged Compounds, **13**, **16**, **26**, and **32**

heptahydrate in a mixture of tetrahydrofuran and methanol (1 : 1) at 0—5 °C afforded a 7-hydroxy compound (**12**), which was treated with boron trifluoride etherate in dichloromethane at room temperature for 1 h without purification to give an optically active ester (**13**), $[\alpha]_D$ −15.6° ($CHCl_3$), in 62% yield from **11**. The high-resolution mass spectrum of **13** gave a molecular ion peak at *m/z* 340.2053 (M^+), corresponding to the formula $C_{22}H_{28}O_3$. In the ^{1}H-NMR spectrum, the ester **13** showed the presence of an isopropyl group at δ 1.28 (6H, d, J=6.8 Hz) and 3.38 (1H, m, J=6.8 Hz), a tertiary methyl group at δ 1.65 (3H, s), a methyl group on an aryl ring at δ 2.51 (3H, s), a methoxycarbonyl group at δ 3.65 (3H, s), a methoxyl group on an aryl ring at δ 3.95 (3H, s), and three aromatic protons at δ 7.15 (1H, s), 7.49 (1H, s), and 7.50 (1H, s). Differential nuclear Overhauser effects (NOE's) were observed between an aryl methyl signal at δ 2.51 and an aromatic proton signal at δ 7.15 and a methylene signal at δ 2.85—2.98 (2H, m), between a methyl signal at δ 1.65 and an aromatic proton signal at δ 7.49, between a methoxyl signal at δ 3.95 and an aromatic proton signal at δ 7.15, and between an isopropyl methyl signal at δ 1.28 and an isopropyl methine signal at δ 3.38 and an aromatic proton signal at δ 7.50, as shown in Fig. 2. Since **13** showed optical activity, the stereochemistry of the C-1 position was assigned to be the same as that of the C-4 position in the starting compound **10**. Thus, the structure of **13** was assigned as methyl 7-isopropyl-6-methoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate.

Subsequently, conversion of a methoxycarbonyl group in **13** into a methyl group was carried out as follows. The ester **13** was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to give an alcohol **14** (99% yield), which was then treated with methanesulfonyl chloride in pyridine at room temperature. However, the product was not the desired mesylate (**15**), but a new crystalline compound **16**, which was obtained in 76% yield from **14**. The high-resolution mass spectrum of **16** gave a molecular ion peak at *m/z* 294.1975 (M^+), corresponding to the formula $C_{21}H_{26}O$. The ^{1}H-NMR spectrum of **16** showed the presence of an isopropyl group at δ 1.29 (6H, d, J=6.8 Hz) and 3.38 (1H, m, J=6.8 Hz), a methyl group on an olefinic bond at δ 1.98 (3H, s), a methyl group on an aryl ring at δ 2.60 (3H, s), three methylene groups at δ 2.02 (2H, m), 2.15 (2H, t, J=6.8 Hz), and 2.91 (2H, t, J=6.1 Hz), an olefinic proton at δ 6.48 (1H, s), and three aromatic protons at δ 7.18 (1H, s), 7.35 (1H, s), and 7.50 (1H, s). The differential NOE's of **16** were observed between an isopropyl methyl signal at δ 1.29 and signals at δ 3.38 and 7.50, between an aryl methyl signal at δ 2.60 and signals at δ 2.91 and 7.18, between a methoxyl signal at δ 3.96 and a signal at δ 7.18, and between an aromatic proton signal at δ 7.35 and signals at δ 6.48 and 7.50 (Fig. 2). Thus, the structure of **16** was assigned as 2-



Reagents a) pyridinium chlorochromate b) $NH_2NH_2 \cdot H_2O$; NaOH c) EtSH, $AlCl_3$ d) Fremy's salt, KH_2PO_4 e) H_2, PtO_2 f) Me_2SO_4, NaOH; MeI, K_2CO_3 g) DDQ h) $NaBH_4$ i) H_2, PtO_2; Jones reagent j) H_2, 10%Pt-C k) Jones reagent

Chart 2

isopropyl-3-methoxy-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene. It is of interest that the alcohol **14** was easily rearranged to the cyclohepta[*b*]naphthalene derivative (**16**) by treatment with methanesulfonyl chloride in pyridine. Since conversion of the hydroxymethyl group in **14** into a methyl group *via* a mesylate was unsuccessful, another route was examined. Oxidation of **14** with pyridinium chlorochromate in dichloromethane at room temperature, followed by a Huang–Minlon reduction of the resulting formyl compound **17** (96% yield), afforded the desired *gem*-dimethyl compound (**18**) in 83% yield. The high- resolution mass spectrum of **18** gave a molecular ion peak at *m/z* 296.2140 (M^+), corresponding to the formula $C_{21}H_{28}O$. To introduce an oxygen function at the C-5 position, compound **18** was demethylated with anhydrous aluminum chloride and ethanethiol in dichloromethane. The resulting phenol **19** (84% yield) was oxidized with Fremy's salt and potassium dihydrogenphosphate in aqueous *N,N*-dimethylformamide to give an orthoquinone **20** in 85% yield. Catalytic hydrogenation of **20** over platinum(IV) oxide in methanol, followed by methylation of the resulting dihydroxy compound (**21**) *in situ* (under hydrogen) with dimethyl sulfate and aqueous sodium hydroxide produced a 5,6-dimethoxy compound **22** in 88% yield from **20**.

To obtain another example of the novel skeletal rearrangement of a hydrophenanthrene into a hydroanthracene, an alternative synthetic route for the dimethoxy compound **22** was also developed as follows. Methyl 11,12-dimethoxy-7-oxo-8,11,13-abietatrien-18-oate[7,8] (**23**), prepared from (+)-dehydroabietic acid (**9**) according to our previous method,[7] was treated with selenium(IV) oxide in refluxing aqueous acetic acid to give an enone (**24**) in 84% yield. Reduction of **24** with sodium borohydride in the presence of cerium(III) chloride heptahydrate, followed by treatment of the resulting 7-hydroxy compound (**25**) with boron trifluoride etherate at room temperature for 5.5 h produced a rearranged ester (**26**), $[\alpha]_D$ −14.3° ($CHCl_3$), in 59% yield from **24**. The high-resolution mass spectrum of **26** gave a molecular ion peak at *m/z* 370.2162 (M^+), corresponding to the formula $C_{23}H_{30}O_4$. The ^{1}H-NMR spectrum and the differential NOE's (Fig. 2) suggested the structure of **26** to be methyl 7-isopropyl-5,6-dimethoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate. The rearranged ester **26** was then converted into **22** (87% yield) *via* an alcohol (**27**, 98% yield) and a formyl compound (**28**, 87% yield) *via* a series of reactions: lithium aluminum hydride reduction, pyridinium chlorochromate oxidation, and Huang–Minlon reduction. Treatment of **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 3 molar eq.) in refluxing 1,4-dioxane afforded an enone (**29**, 47% yield), whose IR spectrum showed an absorption band at 1655 cm^{-1} due to an α,β-unsaturated carbonyl group. The enone **29** in methanol was then submitted to catalytic hydrogenation over platinum(IV) oxide at room temperature. Since the crude product contained a small amount of a 2-hydroxy compound, it was oxidized with Jones reagent in acetone at 0—3 °C to give a pure 2-oxo compound (**30**, 61% yield). Oxidation of **30** in *tert*-butyl alcohol with oxygen in the presence of potassium *tert*-butoxide at room temperature afforded a diosphenol derivative (**31**) in 77% yield. The IR spectrum of **31** showed absorption bands at 3440, 3250, 1655, and 1635 cm^{-1} corresponding to a diosphenol moiety. Compound **31** was demethylated with ethanethiol and anhydrous aluminum chloride in dichloromethane to give a phenolic compound (**32**, 66% yield) and an orthoquinone (**1**, 26% yield). The high-resolution mass spectrum of **1** gave a molecular ion peak at *m/z* 324.1354 (M^+), corresponding to the formula $C_{20}H_{20}O_4$. The

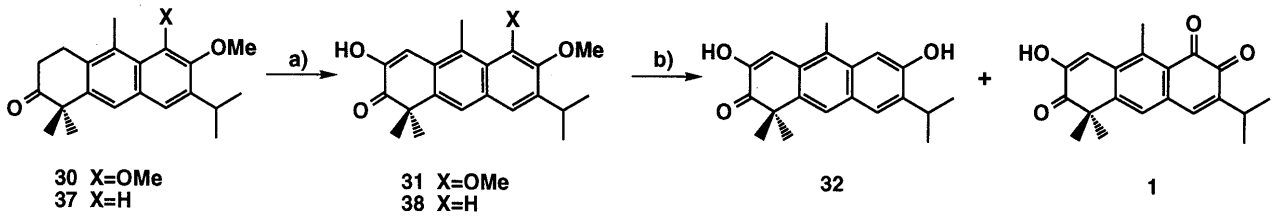


Chart 3

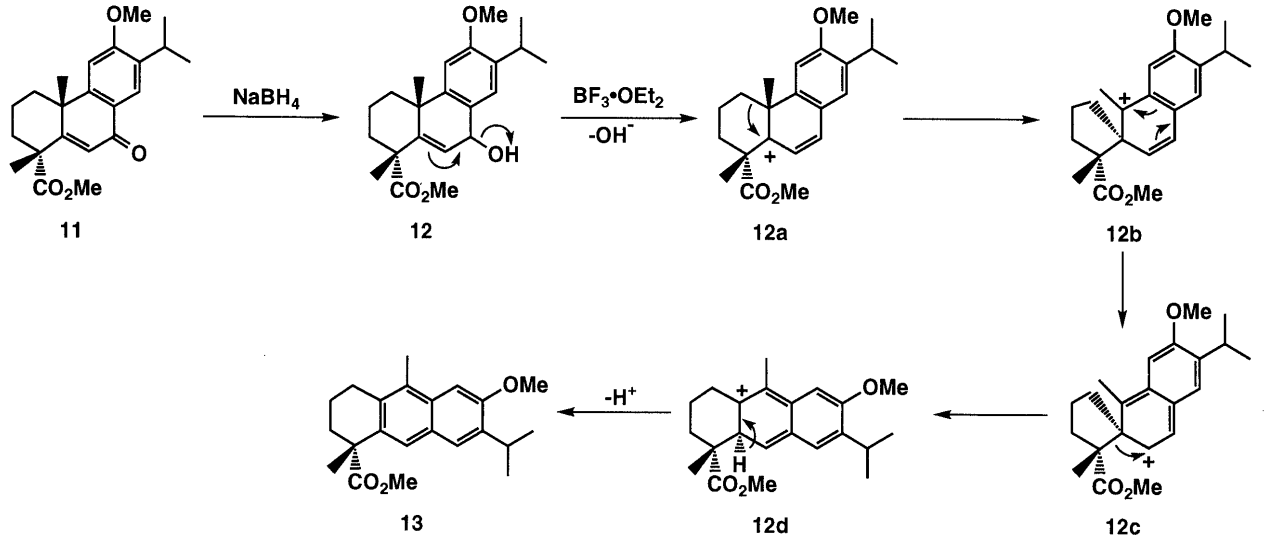


Chart 4

^{1}H-NMR spectrum of **1** showed signals at δ 1.19 (6H, d, J=6.8 Hz) and 3.06 (1H, m, J=6.8 Hz) due to an isopropyl group, at δ 1.56 (6H, s) due to a *gem*-dimethyl group, at δ 2.78 (3H, s) due to a methyl group on an aryl ring, at δ 6.53 (1H, s) due to a hydroxyl group, at δ 7.14 (1H, s) and 7.32 (1H, s) due to two olefinic protons, and at δ 7.17 (1H, s) due to an aromatic proton. From these spectral data, the structure of **1** was assigned as 3-hydroxy-7-isopropyl-1,1,10-trimethyl-1,2-dihydroanthracene-2,5,6-trione. The synthetic **1** was shown to be identical with natural pygmaeocine E by spectral comparisons. On the other hand, the high-resolution mass spectrum of **32** gave a molecular ion peak at m/z 310.1580 (M^+), corresponding to the formula $C_{20}H_{22}O_3$. In the ^{1}H-NMR spectrum, compound **32** showed the presence of an isopropyl group at δ 1.36 (6H, d, J=6.8 Hz) and 3.35 (1H, m, J=6.8 Hz), a *gem*-dimethyl group at δ 1.59 (6H, s), a methyl group on an aryl ring at δ 2.65 (3H, s), two hydroxyl groups at δ 5.21 (1H, s) and 6.42 (1H, s) (disappeared on deuteration), three aromatic protons at δ 7.28 (1H, s), 7.58 (1H, s), and 7.61 (1H, s), and an olefinic proton at δ 7.44 (1H, s). The differential NOE's of **32** were observed between an isopropyl methyl signal at δ 1.36 and signals at δ 3.35 and 7.58, between a *gem*-dimethyl signal at δ 1.59 and a signal at δ 7.61, and between an aryl methyl signal at δ 2.65 and signals at δ 7.28 and 7.44 (Fig. 2). These spectral data suggested the structure of **32** to be 3,6-dihydroxy-7-isopropyl-1,1,10-trimethyl-1,2-dihydroanthracen-2-one.

The structure of **32** was finally confirmed by the following synthesis. Treatment of a monomethoxy compound (**18**) with DDQ (1.2 molar eq) in refluxing methanol afforded a dehydrogenated compound (**33**, 97% yield), which was further refluxed with DDQ (3 molar eq) in methanol to give an enone (**34**) in 63% yield. Reduction of **34** with sodium borohydride in methanol afforded an allylic alcohol (**35**) in 79% yield. This was submitted to catalytic hydrogenation over platinum on carbon in methanol, and the resulting 2-hydroxy compound **36** (83% yield) was oxidized with Jones reagent in acetone to give a 2-oxo compound (**37**) in 79% yield. Oxidation of **37** in *tert*-butyl alcohol with oxygen in the presence of potassium *tert*-butoxide at room temperature afforded the corresponding diosphenol derivative (**38**) in 85% yield. This was demethylated with ethanethiol and anhydrous aluminum chloride in dichloromethane to give a phenolic compound (86% yield), which was shown to be identical with **32** by spectral comparisons. Thus, it is clear that an unusual reductive deoxygenation occurred at the *peri*-position in the dimethoxy compound (**31**) during the demethylation with ethanethiol and anhydrous aluminum chloride in dichloromethane. Similar reductive deoxygenation of oxygenated polyarenes has already been reported in detail by Node *et al.*[9]

A possible mechanism for the skeletal rearrangement of the enone **11** into the ester **13** is depicted in Chart 4. The enone **11** is first transformed into a C-5 carbocation intermediate (**12a**) by sodium borohydride reduction and subsequent treatment of the resulting 7-hydroxy compound (**12**) with boron trifluoride etherate. The migration

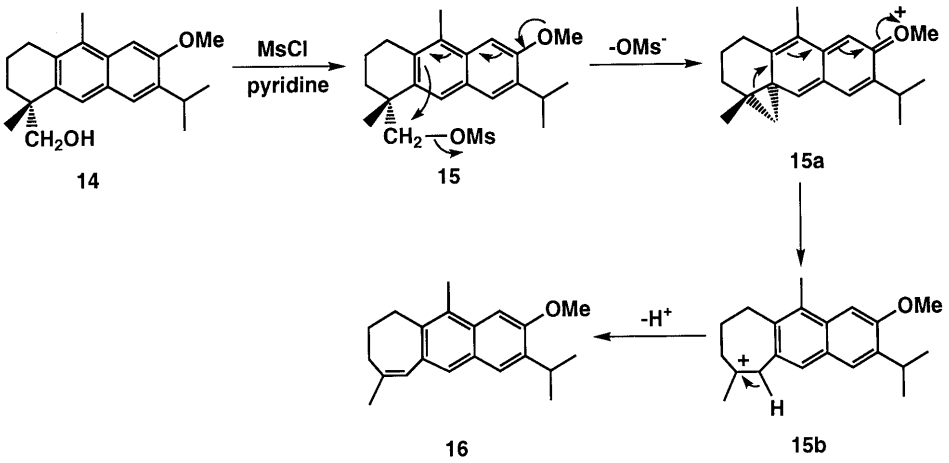


Chart 5

of the C(1)–C(10) bond in **12a** to the C-5 position provides a spiro intermediate (**12b**), which is isomerized to a C-6 carbocation intermediate (**12c**). Subsequent migration of the C(4)–C(5) bond in **12c** to the C-6 position results in the formation of a new carbocation intermediate (**12d**), which is then transformed into the optically active ester **13** by deprotonation.

In a previous paper,[5] we reported that the treatment of 7-isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-methanol (**39**) with methanesulfonyl chloride in pyridine at room temperature afforded a mesylate (**40**), which was rearranged into 2-isopropyl-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene (**41**) by heating at 80—83 °C. However, when the alcohol **14** possessing a methoxyl group at the C-6 position was treated with methanesulfonyl chloride in pyridine at room temperature, the corresponding mesylate (**15**) could not be isolated but the cyclohepta[*b*]naphthalene derivative (**16**) was directly obtained. Therefore, it is clear that the rearrangement of **14** into **16** proceeded more easily than that of **39** into **41**.

A possible mechanism for the conversion of the alcohol **14** into the dihydrocyclohepta[*b*]naphthalene derivative **16** is depicted in Chart 5. Treatment of **14** with methanesulfonyl chloride in pyridine provides a mesylate (**15**), whose mesyloxyl group is eliminated to give a cyclopropane intermediate (**15a**). Cleavage of the cyclopropane ring of **15a** yields a carbocation intermediate **15b**, which is then deprotonated to give compound **16**.

From the present study, it is clear that (+)-dehydroabietic acid (**9**) is a useful relay compound for the synthesis of linear abietane diterpenes such as pygmaeocine E (**1**).

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured on a Shimadzu IR-400 spectrometer in chloroform, and the optical rotations were measured with a JASCO DIP-360 digital polarimeter. The mass spectra were recorded on a JEOL JMS-SX102A spectrometer. The ^{1}H-NMR spectra were recorded with a Hitachi R-1500 (60 MHz) or a JEOL JNM EX-400 (400 MHz) spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated, and the following abbreviations are used: s=singlet, d=doublet, dd=double doublet, t=triplet, m=multiplet, br=broad. Column chromatography was performed using Merck silica gel (0.063—0.200 mm).

Methyl 12-Methoxy-7-oxo-5,8,11,13-abietatetraen-18-oate (11) A stirred mixture of methyl 12-methoxy-7-oxo-8,11,13-abietatrien-18-oate[6] (**10**) (6.377 g, 17.8 mmol) and selenium(IV) oxide (95%, 31.885 g, 273 mmol) in acetic acid (128 ml) and water (64 ml) was refluxed for 10 h. The cooled mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was extracted with ether. The ether solution was washed successively with aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (120 g), using ether–benzene (5:95) as an eluent, to give **11** (5.193 g, 82% yield). This was recrystallized from a mixture of acetone and hexane, mp 117—118 °C, $[\alpha]_D$ +92.5° ($CHCl_3$, c=2.13). IR: 1720, 1645 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.22 and 1.25 (each 3H, d, J=6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.55 (3H, s) and 1.64 (3H, s) (C4-CH_3 and C10-CH_3), 3.30 (1H, m, $-C\underline{H}(CH_3)_2$), 3.72 (3H, s, $-CO_2CH_3$), 3.91 (3H, s, $-OCH_3$), 6.11 (1H, s, C6-H), 6.86 (1H, s, C11-H), 7.98 (1H, s, C14-H). HRMS *m/z*: Calcd for $C_{22}H_{28}O_4$ (M^+): 356.1988. Found: 356.1993.

Rearrangement of 11 into Methyl 7-Isopropyl-6-methoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (13) Sodium borohydride (114 mg, 3.01 mmol) was added to a stirred mixture of **11** (1.024 g, 2.87 mmol) and cerium(III) chloride heptahydrate (1.121 g, 3.01 mmol) in methanol and tetrahydrofuran (1:1, 15 ml) at 0—3 °C over a 3-min period. The mixture was further stirred at this temperature for 10 min, diluted with ether, washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude alcohol (**12**, 1.047 g). IR: 3600, 3400, 1720 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.21 and 1.23 (each 3H, d, J=7.0 Hz, $-CH(C\underline{H}_3)_2$), 1.27 (6H, s, C4-CH_3, and C10-CH_3), 3.29 (1H, m, $-C\underline{H}(CH_3)_2$), 3.66 (3H, s, $-CO_2CH_3$), 3.83 (3H, s, $-OCH_3$), 4.96 (1H, br d, J=8.5 Hz, C7-H), 5.70 (1H, d, J=2.1 Hz, C6-H), 6.80 (1H, s) and 7.49 (1H, s) (C11-H and C14-H).

A mixture of the above crude alcohol **12** (1.047 g) and boron trifluoride etherate (1.0 ml, 8.13 mmol) in dichloromethane (21 ml) was stirred at room temperature for 1 h. The mixture was diluted with ether, washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using hexane–benzene (2:3) as an eluent, to give a rearranged ester **13** (609 mg, 62% yield from **11**). This was recrystallized from hexane or methanol, mp 100—100.5 °C, $[\alpha]_D$ −15.6° ($CHCl_3$, c=1.04). IR: 1715, 1635 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.28 (6H, d, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.65 (3H, s, C1-CH_3), 1.73—1.79 (1H, m) and 2.32—2.38 (1H, m) (C2-H_2), 1.82—1.93 (1H, m) and 1.93—2.04 (1H, m) (C3-H_2), 2.51 (3H, s, C10-CH_3), 2.85—2.98 (2H, m, C4-H_2), 3.38 (1H, m, J=6.8 Hz, $-C\underline{H}(CH_3)_2$), 3.65 (3H, s, $-CO_2CH_3$), 3.95 (3H, s, $-OCH_3$), 7.15 (1H, s, C5-H), 7.49 (1H, s, C9-H), 7.50 (1H, s, C8-H). HRMS *m/z*: Calcd for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2053.

7-Isopropyl-6-methoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-methanol (14) Lithium aluminum hydride (135 mg, 3.56 mmol) was added to a stirred solution of **13** (1.211 g, 3.56 mmol) in dry tetrahydrofuran (12 ml) with cooling in a water bath over a 15-min period. The mixture was gently refluxed for 2 h, cooled, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using ether–benzene (15:85) as an eluent, to give **14** (1.096 g, 99% yield). This was recrystallized from hexane, mp 98—99 °C, $[\alpha]_D$ −24.1° ($CHCl_3$,

$c=3.22$). IR: 3600, 3450, 1600 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.29 (6H, d, $J=6.7$ Hz, $-CH(C\underline{H}_3)_2$), 1.35 (3H, s, C1-CH_3), 1.53—2.08 (4H, m, C2-H_2 and C3-H_2), 2.51 (3H, s, C10-CH_3), 2.87 (2H, br t, $J=5.6$ Hz, C4-H_2), 3.41 (1H, m, $J=6.7$ Hz, $-C\underline{H}(CH_3)_2$), 3.55 (1H, d, $J=11$ Hz) and 3.88 (1H, d, $J=11$ Hz) ($-C\underline{H}_2OH$), 3.95 (3H, s, $-OCH_3$), 7.17 (1H, s), 7.53 (1H, s), and 7.59 (1H, s) (C5-H, C8-H, and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{28}O_2$ (M^+): 312.2089. Found: 312.2094.

Rearrangement of 14 into 2-Isopropyl-3-methoxy-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene (16) A mixture of **14** (95 mg, 0.30 mmol) and methanesulfonyl chloride (0.1 ml, 1.29 mmol) in pyridine (1.5 ml) was allowed to stand at room temperature for 22 h. The mixture was poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using hexane–chloroform (4 : 1) as an eluent, to give **16** (68 mg, 76% yield). This was recrystallized from hexane, mp 101—102 °C. ^{1}H-NMR (400 MHz) δ: 1.29 (6H, d, $J=6.8$ Hz, $-CH(C\underline{H}_3)_2$), 1.98 (3H, s, C9-CH_3), 2.02 (2H, m, C7-H_2), 2.15 (2H, t, $J=6.8$ Hz, C8-H_2), 2.60 (3H, s, C5-CH_3), 2.91 (2H, t, $J=6.1$ Hz, C6-H_2), 3.38 (1H, m, $J=6.8$ Hz, $-C\underline{H}(CH_3)_2$), 3.96 (3H, s, $-OCH_3$), 6.48 (1H, s, C10-H), 7.18 (1H, s, C4-H), 7.35 (1H, s, C11-H), 7.50 (1H, s, C1-H). HRMS m/z: Calcd for $C_{21}H_{26}O$ (M^+): 294.1984. Found: 294.1975.

7-Isopropyl-6-methoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carbaldehyde (17) A mixture of **14** (1.740 g, 5.57 mmol) and pyridinium chlorochromate (2.401 g, 11.14 mmol) in dichloromethane (70 ml) was stirred at room temperature for 3 h. The mixture was diluted with ether and aqueous sodium hydrogen carbonate, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using chloroform as an eluent, to give **17** (1.653 g, 96% yield), $[\alpha]_D$ −12.4° ($CHCl_3$, $c=2.70$). IR: 2720, 1720, 1635, 1600 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.28 (6H, d, $J=6.7$ Hz, $-CH(C\underline{H}_3)_2$), 1.50 (3H, s, C1-CH_3), 1.75—2.23 (4H, m, C2-H_2 and C3-H_2), 2.52 (3H, s, C10-CH_3), 2.91 (2H, dd, $J=6.2$, 5.3 Hz, C4-H_2), 3.39 (1H, m, $J=6.7$ Hz, $-C\underline{H}(CH_3)_2$), 3.96 (3H, s, $-OCH_3$), 7.18 (1H, s, C5-H), 7.33 (1H, s) and 7.52 (1H, s) (C8-H and C9-H), 9.53 (1H, s, –CHO). HRMS *m/z*: Calcd for $C_{21}H_{26}O_2$ (M^+): 310.1933. Found: 310.1932.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene (18) A mixture of **17** (4.922 g, 15.86 mmol) and hydrazine monohydrate (24.6 ml, 0.507 mol) in diethylene glycol (123 ml) was refluxed for 2 h, then powdered sodium hydroxide (24.6 g, 0.615 mol) was added. The mixture was heated at 180—185 °C (bath temperature) for 2 h, cooled, diluted with water, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using hexane–chloroform (4 : 1) as an eluent, to give **18** (3.922 g, 83% yield). This was recrystallized from methanol, mp 65—67 °C. IR: 1635, 1600 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.29 (6H, d, $J=6.7$ Hz, $-CH(C\underline{H}_3)_2$), 1.38 (6H, s, C1-$(CH_3)_2$), 1.60—2.10 (4H, m, C2-H_2 and C3-H_2), 2.50 (3H, s, C10-CH_3), 2.89 (2H, br t, $J=6.0$ Hz, C4-H_2), 3.39 (1H, m, $J=6.7$ Hz, $-C\underline{H}(CH_3)_2$), 3.94 (3H, s, $-OCH_3$), 7.16 (1H, s, C5-H), 7.52 (1H, s) and 7.63 (1H, s) (C8-H and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{28}O$ (M^+): 296.2140. Found: 296.2140.

7-Isopropyl-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracen-6-ol (19) Anhydrous aluminum chloride (14.347 g, 0.107 mol) was added to a stirred solution of **18** (3.988 g, 13.45 mmol) and ethanethiol (8.05 ml) in dichloromethane (40 ml) with cooling in an ice-water bath over a 10-min period. After having been stirred at room temperature for 5 h, the mixture was poured into ice-dilute hydrochloric acid and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (300 g), using hexane–chloroform (3 : 7) as an eluent, to give the starting **18** (494 mg). Further elution with the same solvent afforded **19** as an oil (3.179 g, 84% yield). IR: 3610, 3320, 1635, 1600 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.32 (6H, d, $J=6.7$ Hz, $-CH(C\underline{H}_3)_2$), 1.37 (6H, s, C1-$(CH_3)_2$), 1.54—2.21 (4H, m, C2-H_2 and C3-H_2), 2.41 (3H, s, C10-CH_3), 2.85 (2H, br t, $J=6.0$ Hz, C4-H_2), 3.32 (1H, m, $J=6.7$ Hz, $-C\underline{H}(CH_3)_2$), 5.13 (1H, br s, –OH), 7.17 (1H, s, C5-H), 7.53 (1H, s) and 7.62 (1H, s) (C8-H and C9-H). HRMS *m/z*: Calcd for $C_{20}H_{26}O$ (M^+): 282.1984. Found: 282.1978.

7-Isopropyl-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene-5,6-dione (20) A stirred solution of **19** (460 mg, 1.63 mmol) in *N,N*-dimethylformamide (55.2 ml) was protected from light with aluminum foil. After the addition of a solution of Fremy's salt (potassium nitrosodisulfonate, 2.186 g, 8.15 mmol) and potassium dihydrogenphosphate (842 mg, 6.19 mmol) in water (84.2 ml), the mixture was stirred at room temperature under a stream of nitrogen for 3 h. The mixture was poured into dilute hydrochloric acid and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using chloroform as an eluent, to give an orthoquinone **20** (409 mg, 85% yield). This was recrystallized from hexane to give red crystals, mp 124—126 °C. IR: 1680, 1660 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.17 (6H, d, $J=7.0$ Hz, $-CH(C\underline{H}_3)_2$), 1.32 (6H, s, C1-$(CH_3)_2$), 1.51—2.08 (4H, m, C2-H_2 and C3-H_2), 2.58 (3H, s, C10-CH_3), 2.69 (2H, br t, $J=6.2$ Hz, overlap, C4-H_2), 3.04 (1H, m, $J=7.0$ Hz, $-C\underline{H}(CH_3)_2$), 7.10 (2H, br s, C8-H and C9-H). HRMS *m/z*: Calcd for $C_{20}H_{24}O_2$ (M^+): 296.1776. Found: 296.1743.

7-Isopropyl-5,6-dimethoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene (22) a) A solution of **20** (100 mg, 0.337 mmol) in methanol (5.0 ml) was stirred with platinum(IV) oxide catalyst (20 mg) at room temperature under an atmosphere of hydrogen for *ca.* 10 min. When the red solution had become colorless, dimethyl sulfate (0.5 ml) and aqueous sodium hydroxide (30%, 1.0 ml) were added, still with exclusion of air. The mixture was stirred at room temperature for 7 h and then more dimethyl sulfate (0.5 ml) and aqueous sodium hydroxide (30%, 1.0 ml) were added. After stirring for 17 h (total 24 h), the mixture was filtered to remove the catalyst, which was washed with water and ether. The filtrate was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give crude **22** (110 mg) containing a small amount of phenolic compound.

A mixture of the above crude **22** (110 mg), methyl iodide (0.5 ml, 8.03 mmol) and anhydrous potassium carbonate (700 mg, 5.06 mmol) in ethyl methyl ketone (2.0 ml) was refluxed for 8 h. The mixture was diluted with ether, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using hexane–benzene (1 : 1) as an eluent, to give pure **22** (97 mg, 88% yield). ^{1}H-NMR (60 MHz) δ: 1.30 (6H, d, $J=7.0$ Hz, $-CH(C\underline{H}_3)_2$), 1.37 (6H, s, C1-$(CH_3)_2$), 2.79 (3H, s, C10-CH_3), 3.36 (1H, m, $J=7.0$ Hz, $-C\underline{H}(CH_3)_2$), 3.84 (3H, s, C5-OCH_3), 3.94 (3H, s, C6-OCH_3), 7.32 (1H, s, C8-H), 7.59 (1H, s, C9-H). HRMS *m/z*: Calcd for $C_{22}H_{30}O_2$ (M^+): 326.2246. Found: 326.2249.

b) A mixture of **28** (591 mg, 1.74 mmol) and hydrazine monohydrate (3.0 ml, 61.8 mmol) in diethylene glycol (15 ml) was refluxed for 2 h, then powdered sodium hydroxide (3.0 g, 7.50 mmol) was added. The mixture was heated at 160—170 °C for 30 min and at 170—180 °C (bath temperature) for 1 h, cooled, diluted with water, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using hexane–benzene (1 : 1) as an eluent, to give **22** (493 mg, 87% yield). The IR and ^{1}H-NMR spectra of **22** were identical with those of the authentic sample obtained in a).

Methyl 11,12-Dimethoxy-7-oxo-5,8,11,13-abietatetraen-18-oate (24) A stirred mixture of methyl 11,12-dimethoxy-7-oxo-8,11,13-abietatrien-18-oate[7,8] (**23**) (4.373 g, 11.26 mmol) and selenium(IV) oxide (95%, 21.90 g, 187 mmol), acetic acid (88 ml), and water (44 ml) was refluxed for 19 h. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in ether and the solution washed successively with water, aqueous sodium hydrogen carbonate, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g), using ether–benzene (5 : 95) as an eluent, to give **24** (3.634 g, 84% yield). IR: 1725, 1650 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.23 and 1.27 (each 3H, d, $J=6.7$ Hz, $-CH(C\underline{H}_3)_2$), 1.64 (6H, s, C4-CH_3 and C10-CH_3), 3.20 (1H, m, $-C\underline{H}(CH_3)_2$), 3.71 (3H, s, $-CO_2CH_3$), 3.84 and 3.92 (each 3H, s, 2-OCH_3), 6.16 (1H, s, C6-H), 7.87 (1H, s, C14-H). HRMS *m/z*: Calcd for $C_{23}H_{30}O_5$ (M^+): 386.2093. Found: 386.2112.

Rearrangement of 24 into Methyl 7-Isopropyl-5,6-dimethoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (26) Sodium borohydride (291 mg, 7.69 mmol) was added to a stirred solution of **24** (2.720 g, 7.04 mmol) and cerium(III) chloride heptahydrate (2.739 g, 7.35 mmol) in a mixture of methanol and tetrahydrofuran (1 : 1, 40 ml) with cooling in an ice-water bath over an 8-min period. The mixture was stirred at this temperature for 12 min, diluted with ether, and washed with brine. The dried solution was evaporated *in vacuo* to give a crude alcohol **25** (2.800 g). IR: 3450, 3230, 1720 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.21 and 1.25 (each 3H, d, $J=6.8$ Hz, $-CH(C\underline{H}_3)_2$), 1.43 and 1.55 (each 3H, s, C4-CH_3 and C10-CH_3), 3.69 (3H, s, $-CO_2CH_3$), 3.78 and 3.87 (each 3H, s, 2-OCH_3), 4.92 (1H, br d, $J=9.4$ Hz, C7-H), 5.63 (1H, d,

J=2.3 Hz, C6-H), 7.27 (1H, s, C14-H).

Boron trifluoride etherate (4.4 ml, 35.78 mmol) was added all at once to a stirred solution of the above crude alcohol **25** (2.800 g) in dichloromethane (58 ml) at room temperature. The mixture was stirred at room temperature for 5.5 h, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (75 g), using benzene as an eluent, to give **26** (1.529 g, 59% yield from **24**), $[\alpha]_D$ −14.3° ($CHCl_3$, c=3.41). IR: 1710 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.29 (6H, d, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.64 (3H, s, C1-CH_3), 1.75 (1H, m) and 2.34 (1H, m) (C2-H_2), 1.88 (1H, m) and 1.96 (1H, m) (C3-H_2), 2.80 (3H, s, C10-CH_3), 2.88 (2H, m, C4-H_2), 3.35 (1H, m, J=6.8 Hz, $-C\underline{H}(CH_3)_2$), 3.66 (3H, s, $-CO_2CH_3$), 3.84 (3H, s, C5-OCH_3), 3.94 (3H, s, C6-OCH_3), 7.31 (1H, s, C8-H), 7.45 (1H, s, C9-H). Differential NOE's were observed between a signal at δ 1.29 and signals at δ 3.35, 7.31, between a signal at δ 1.64 and a signal at δ 7.45, between a signal at δ 2.80 and signals at δ 2.88, 3.84, and between a signal at δ 7.45 and signals at δ 1.64, 7.31 (Fig. 2). HRMS m/z: Calcd for $C_{23}H_{30}O_4$ (M^+): 370.2144. Found: 370.2162.

7-Isopropyl-5,6-dimethoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-methanol (27) Lithium aluminum hydride (185 mg, 4.86 mmol) was added to a stirred solution of **26** (1.800 g, 4.86 mmol) in dry tetrahydrofuran (18 ml) with cooling in an ice-water bath over a 7-min period. The mixture was gently refluxed for 2 h, cooled, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using chloroform as an eluent, to give **27** (1.622 g, 98% yield), $[\alpha]_D$ −17.8° ($CHCl_3$, c=1.62). IR: 3590, 3470 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.30 (6H, d, J=6.4 Hz, $-CH(C\underline{H}_3)_2$), 1.35 (3H, s, C1-CH_3), 2.79 (3H, s, C10-CH_3), 3.14—3.64 (3H, m, $-C\underline{H}(CH_3)_2$ and $-C\underline{H}_2OH$), 3.84 (3H, s, C5-OCH_3), 3.95 (3H, s, C6-OCH_3), 7.32 (1H, s) and 7.56 (1H, s) (C8-H and C9-H). HRMS m/z: Calcd for $C_{22}H_{30}O_3$ (M^+): 342.2195. Found: 342.2194.

7-Isopropyl-5,6-dimethoxy-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carbaldehyde (28) A mixture of **27** (811 mg, 2.37 mmol) and pyridinium chlorochromate (1.021 g, 4.74 mmol) in dichloromethane (32 ml) was stirred at room temperature for 2 h. The mixture was diluted with ether and aqueous sodium hydrogen carbonate, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using chloroform as an eluent, to give **28** as an oil (703 mg, 87% yield), $[\alpha]_D$ −12.2° ($CHCl_3$, c=5.38). IR: 2720, 1720 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.29 (6H, d, J=6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.49 (3H, s, C1-CH_3), 2.81 (3H, s, C10-CH_3), 3.36 (1H, m, J=6.7 Hz, $-C\underline{H}(CH_3)_2$), 3.85 (3H, s, C5-OCH_3), 3.95 (3H, s, C6-OCH_3), 7.31 (2H, s, C8-H and C9-H), 9.52 (1H, s, -CHO). HRMS m/z: Calcd for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2048.

7-Isopropyl-5,6-dimethoxy-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (29) A mixture of **22** (330 mg, 1.01 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (689 mg, 3.03 mmol) in 1,4-dioxane (10 ml) was refluxed for 6 h. The mixture was passed through an aluminum oxide 90 (Merck, 70 g) column and the column was washed with benzene (210 ml). The eluate was evaporated *in vacuo* to give a crude enone. This was further chromatographed on silica gel (20 g), using benzene as an eluent, to give **29** as a red oil (161 mg, 47% yield). IR: 1655, 1610 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.33 (6H, d, J=6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.54 (6H, s, C1-$(C\underline{H}_3)_2$), 3.05 (3H, s, C10-CH_3), 3.41 (1H, m, J=6.7 Hz, $-C\underline{H}(CH_3)_2$), 3.88 (3H, s, C5-OCH_3), 3.97 (3H, s, C6-OCH_3), 6.20 (1H, d, J=10.4 Hz, C3-H), 7.37 (1H, s, C8-H), 7.63 (1H, s, C9-H), 8.10 (1H, d, J=10.4 Hz, C4-H). HRMS m/z: Calcd for $C_{22}H_{26}O_3$ (M^+): 338.1882. Found: 338.1893.

7-Isopropyl-5,6-dimethoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracen-2-one (30) A mixture of **29** (100 mg, 0.295 mmol) and platinum(IV) oxide (50 mg, 0.22 mmol) in methanol (15 ml) was stirred at room temperature under an atmosphere of hydrogen for 70 min. The mixture was filtered to remove the catalyst and the filtrate was evaporated *in vacuo*. The residue was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give a crude product (105 mg) containing a small amount of the 2-hydroxy compound.

A solution of the above crude product (105 mg) in acetone (1.5 ml) was oxidized with Jones reagent (1 mol dm^{-3}, 0.3 ml) at 0—3 °C for 10 min. The mixture was diluted with ether, washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (15 g), using benzene and ether–benzene (3 : 97) as eluents, to give pure **30** as a colorless oil (61 mg, 61% yield). IR: 1710, 1605 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.32 (6H, d, J=6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.51 (6H, s, C1-$(CH_3)_2$), 2.59—2.89 (2H, m, overlap, C3-H_2), 2.89 (3H, s, C10-CH_3), 3.16—3.51 (3H, m, $-C\underline{H}(CH_3)_2$ and C4-H_2), 3.87 (3H, s, C5-OCH_3), 3.97 (3H, s, C6-OCH_3), 7.38 (1H, s, C8-H), 7.60 (1H, s, C9-H). HRMS m/z: Calcd for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2035.

3-Hydroxy-7-isopropyl-5,6-dimethoxy-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (31) A mixture of **30** (35 mg, 0.10 mmol) and a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1 mol dm^{-3}, 4.3 ml, 4.33 mmol) was stirred at room temperature under an atmosphere of oxygen for 1 h. The mixture was diluted with ether, acidified with dilute hydrochloric acid, and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using benzene as an eluent, to give **31** (28 mg, 77% yield), mp 141—143 °C (from hexane). IR: 3440, 3250, 1655, 1635 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.32 (6H, d, J=7.0 Hz, $-CH(C\underline{H}_3)_2$), 1.58 (6H, s, C1-$(CH_3)_2$), 2.99 (3H, s, C10-CH_3), 3.40 (1H, m, $-C\underline{H}(CH_3)_2$), 3.87 (3H, s, C5-OCH_3), 3.97 (3H, s, C6-OCH_3), 6.38 (1H, s, -OH), 7.36 (1H, s, C8-H), 7.55 (2H, s, C4-H and C9-H). HRMS m/z: Calcd for $C_{22}H_{26}O_4$ (M^+): 354.1831. Found: 354.1821.

Pygmaeocine E (1) and 3,6-Dihydroxy-7-isopropyl-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (32) a) Anhydrous aluminum chloride (228 mg, 1.71 mmol) was added to a stirred solution of **31** (76 mg, 0.21 mmol) and ethanethiol (0.13 ml, 1.71 mmol) in dichloromethane (6.0 ml) with cooling in an ice-water bath over a 2-min period. The mixture was stirred at this temperature for 10 min and then at room temperature for 4 h, diluted with ether, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using ether–benzene (5 : 95) as an eluent, to give a phenolic compound **32** (46 mg, 66% yield). This was recrystallized from a mixture of acetone and hexane, mp 197—199 °C. IR: 3600, 3430, 1660, 1635, 1605 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.36 (6H, d, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.59 (6H, s, C1-$(CH_3)_2$), 2.65 (3H, s, C10-CH_3), 3.35 (1H, m, J=6.8 Hz, $-C\underline{H}(CH_3)_2$), 5.21 (1H, s, C6-OH) and 6.42 (1H, s, C3-OH) (disappeared on deuteration), 7.28 (1H, s, C5-H), 7.44 (1H, s, C4-H), 7.58 (1H, s, C8-H), 7.61 (1H, s, C9-H). HRMS m/z: Calcd for $C_{20}H_{22}O_3$ (M^+): 310.1569. Found: 310.1580.

Further elution with the same solvent and then ether–benzene (1 : 9) afforded an orthoquinone (**1**) as a solid (18 mg, 26% yield). This was recrystallized from a mixture of acetone and hexane to give brownish-red crystals, mp 196—198 °C. IR: 3425, 1675 sh, 1660, 1630 sh cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.19 (6H, d, J=6.8 Hz, $-CH(C\underline{H}_3)_2$), 1.56 (6H, s, C1-$(CH_3)_2$), 2.78 (3H, s, C10-CH_3), 3.06 (1H, m, J=6.8 Hz, $-C\underline{H}(CH_3)_2$), 6.53 (1H, s, C3-OH), 7.14 (1H, s, C8-H), 7.17 (1H, s, C9-H), 7.32 (1H, s, C4-H). Differential NOE's were observed between a signal at δ 1.19 and signals at δ 3.06, 7.14, between a signal at δ 1.56 and a signal at δ 7.17, and between a signal at δ 2.78 and a signal at δ 7.32. HRMS m/z: Calcd for $C_{20}H_{20}O_4$ (M^+): 324.1362. Found: 324.1354. The synthetic **1** was shown to be identical with natural pygmaeocine E (mp 192—193 °C)[1] by spectral comparisons.

b) Anhydrous aluminum chloride (506 mg, 3.80 mmol) was added to a stirred solution of **38** (164 mg, 0.48 mmol) and ethanethiol (0.28 ml, 3.80 mmol) in dichloromethane (2.0 ml) with cooling in an ice-water bath over a 3-min period. The mixture was stirred at room temperature for 5.5 h, diluted with ether, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether–benzene (3 : 97) as an eluent, to give a phenolic compound (134 mg, 86% yield), mp 197—199 °C (from acetone–hexane), whose IR and ^{1}H-NMR spectra were identical with those of **32** obtained in a). HRMS m/z: Calcd for $C_{20}H_{22}O_3$ (M^+): 310.1569. Found: 310.1579.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2-dihydroanthracene (33) A mixture of **18** (100 mg, 0.34 mmol) and DDQ (91 mg, 1.2 molar eq) in methanol (2.0 ml) was refluxed for 6 h. The mixture was evaporated *in vacuo*. The residue was chromatographed on aluminum oxide 90 (Merck, 15 g), using benzene as an eluent, to give **33** (96 mg, 97% yield), which was recrystallized from hexane, mp 96.5—97 °C. ^{1}H-NMR (60 MHz) δ: 1.29 (6H, d, J=6.7 Hz, $-CH(C\underline{H}_3)_2$), 1.34 (6H, s, C1-$(CH_3)_2$), 2.25 (2H, dd, J=4.4, 1.8 Hz, C2-H_2), 2.61 (3H, s,

C10-CH_3), 3.41 (1H, m, J=6.7 Hz, -C<u>H</u>$(CH_3)_2$), 3.95 (3H, s, -OCH_3), 6.07 (1H, dt, J=10.3, 4.4 Hz, C3-H), 7.00 (1H, br d, J=10.3 Hz, C4-H), 7.20 (1H, s, C5-H), 7.53 (2H, s, C8-H and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{26}O$ (M^+): 294.1984. Found: 294.1970.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (34) A mixture of **33** (834 mg, 2.83 mmol) and DDQ (1.927 g, 3 molar eq) in methanol (70 ml) was refluxed for 6 h. The mixture was evaporated *in vacuo*. The residue was passed through an aluminum oxide 90 (Merck, 100 g) column, using ether–benzene (5 : 95, 300 ml) as an eluent, to give crude **34** (830 mg). This was chromatographed on silica gel (200 g), using ether–benzene (3 : 97) as an eluent, to give pure **34** (550 mg, 63% yield), mp 137—138.5 °C (from hexane). IR: 1650 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.32 (6H, d, J=6.7 Hz, -CH(C<u>H</u>$_3)_2$), 1.55 (6H, s, C1-$(CH_3)_2$), 2.76 (3H, s, C10-CH_3), 3.44 (1H, m, J=6.7 Hz, -C<u>H</u>$(CH_3)_2$), 3.98 (3H, s, -OCH_3), 6.20 (1H, d, J=10.3 Hz, C3-H), 7.26 (1H, s, C5-H), 7.59 (1H, s) and 7.68 (1H, s) (C8-H and C9-H), 8.05 (1H, d, J=10.3 Hz, C4-H). HRMS *m/z*: Calcd for $C_{21}H_{24}O_2$ (M^+): 308.1776. Found: 308.1768.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2-dihydroanthracen-2-ol (35) Sodium borohydride (251 mg, 6.64 mmol) was added to a stirred solution of **34** (513 mg, 1.16 mmol) in methanol (40 ml) with cooling in an ice-water bath. The mixture was stirred at room temperature for 2 h, acidified with dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g), using chloroform as an eluent, to give **35** (416 mg, 79% yield). IR: 3620, 3430 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.30 (6H, d, J=6.7 Hz, -CH(C<u>H</u>$_3)_2$), 1.30 and 1.42 (each 3H, s, C1-$(CH_3)_2$), 2.62 (3H, s, C10-CH_3), 3.42 (1H, m, J=6.7 Hz, -C<u>H</u>$(CH_3)_2$), 3.95 (3H, s, -OCH_3), 4.03 (1H, d, J=4.4 Hz, overlap, C2-H), 6.12 (1H, dd, J=10.0, 4.4 Hz, C3-H), 7.03 (1H, d, J=10.0 Hz, C4-H), 7.20 (1H, s, C5-H), 7.56 (2H, s, C8-H and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{26}O_2$ (M^+): 310.1933. Found: 310.1953.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracen-2-ol (36) A mixture of **35** (292 mg, 0.94 mmol) and 10% Pt-C (146 mg) in methanol (20 ml) was stirred at room temperature under an atmosphere of hydrogen for 5 h. The mixture was filtered to remove the catalyst and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using ether–benzene (3 : 97) as an eluent, to give **36** (244 mg, 83% yield). IR: 3630, 3440 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.30 (6H, d, J=6.7 Hz, -CH(C<u>H</u>$_3)_2$), 1.41 (6H, s, C1-$(CH_3)_2$), 2.51 (3H, s, C10-CH_3), 3.40 (1H, m, J=6.7 Hz, -C<u>H</u>$(CH_3)_2$), 3.96 (3H, s, -OCH_3), 7.19 (1H, s, C5-H), 7.54 and 7.65 (each 1H, s, C8-H and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{28}O_2$ (M^+): 312.2089. Found: 312.2086.

7-Isopropyl-6-methoxy-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracen-2-one (37) A solution of **36** (244 mg, 0.78 mmol) in acetone (3.0 ml) was oxidized with Jones reagent (1 mol dm^{-3}, 0.7 ml) at 0—3 °C for 10 min. The mixture was diluted with ether, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (30 g), using benzene as an eluent, to give **37** (191 mg, 79% yield), mp 134.5—135.5 °C (from hexane). IR: 1710 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.31 (6H, d, J=6.7 Hz, -CH(C<u>H</u>$_3)_2$), 1.52 (6H, s, C1-$(CH_3)_2$), 2.61 (3H, s, C10-CH_3), 2.73 (2H, m, overlap, C3-H_2), 3.31 (3H, m, C4-H_2 and -C<u>H</u>$(CH_3)_2$), 3.98 (3H, s, -OCH_3), 7.22 (1H, s, C5-H), 7.59 and 7.63 (each 1H, s, C8-H and C9-H). HRMS *m/z*: Calcd for $C_{21}H_{26}O_2$ (M^+): 310.1933. Found: 310.1923.

3-Hydroxy-7-isopropyl-6-methoxy-1,1,10-trimethyl-1,2-dihydroanthracen-2-one (38) A mixture of **37** (184 mg, 0.59 mmol) and a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1 mol dm^{-3}, 25 ml, 25 mmol) was stirred at room temperature under an atmosphere of oxygen for 1 h. The mixture was diluted with ether, acidified with dilute hydrochloric acid, and extracted with ether. The ether solution was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using benzene as an eluent, to give **38** (164 mg, 85% yield), mp 177—178 °C (from hexane). IR: 3450, 3280, 1660, 1630 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 1.31 (6H, d, J=6.8 Hz, -CH(C<u>H</u>$_3)_2$), 1.59 (6H, s, C1-$(CH_3)_2$), 2.71 (3H, s, C10-CH_3), 3.42 (1H, m, J=6.8 Hz, -C<u>H</u>$(CH_3)_2$), 3.98 (3H, s, -OCH_3), 6.42 (1H, s, C3-OH), 7.22 (1H, s, C5-H), 7.47 (1H, s, C4-H), 7.56 (1H, s, C8-H), 7.63 (1H, s, C9-H). Differential NOE's were observed between a signal at δ 1.31 and signals at δ 3.42, 7.56, between a signal at δ 1.59 and a signal at δ 7.63, between a signal at δ 2.71 and signals at δ 7.22, 7.47, between a signal at δ 3.98 and a signal at δ 7.22, and between a signal at δ 7.63 and signals at δ 1.59, 7.56. HRMS *m/z*: Calcd for $C_{21}H_{24}O_3$ (M^+): 324.1725. Found: 324.1737.

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