Skeletal Rearrangement of the Dehydroabietic Acid Derivative

Takashi Matsumoto,* Yoshio Takeda, Kimiko Soh,
Mitsuo Sakamoto, and Sachihiko Imai†

Faculty of Integrated Arts and Sciences, The University of Tokushima, Minamijosanjima, Tokushima 770
†Suzugamine Women's College, Inokuchi, Nishi-ku, Hiroshima 733

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Methyl 7-oxo-5,8,11,13-abietatetraen-18-oate was reduced with sodium borohydride in the presence of cerium(III) chloride heptahydrate to give the corresponding 7-hydroxy compound, which was rearranged into methyl 7-isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (**14**) possessing a rearranged linear abietane skeleton, by a treatment with boron trifluoride etherate. The reduction of **14** with lithium aluminum hydride afforded 7-isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-methanol (**15**). This was further converted into 7-isopropyl-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene. The mesylate of 15 was also rearranged into 2-isopropyl-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene, possessing a seven-membered A ring.

Recently, unusual natural diterpene quinones, such as pygmaeocine E[1] (**1**), umbrosone[2] (**2**), and aegyptinones[3] A (**3**) and B (**4**) have been isolated from the roots of medicinal plants, Pygmaeopremna herbaceae (Roxb.) Moldenke (Verbenaceae),[1] Hyptis umbrosa Salzm (Lamiaceae),[2] and Salvia aegyptiaca L. (Lamiaceae).[3] These natural diterpenes showed significant antimicrobial[2,3] and antiinflammatory[1] activities, and have a rare structural feature, possessing a rearranged linear abietane skeleton, which was named the skeleton pygmaeocane E by Meng et al.[1] (Fig. 1).

In a previous paper[4] we reported on a rearrangement of the angular methyl group in dehydroabietic acid derivatives. That is, the alcohol **6** derived from methyl 7-oxo-5,8,11,13-abietatetraen-18-oate (**5**) was rearranged into methyl 5*β*-methyl-10-norabieta-1(10),6,8,11,13-pentaen-18-oate (**8**) with an intact C(4)–C(5) bond via a C-10 carbonium ion intermediate (**7**) by a treatment with *p*-toluenesulfonic acid monohydrate in benzene. Also, a similar acidic treatment of the alcohol **10** derived from 5,8,11,13-abietatetraen-7-one (**9**) caused a cleavage of the C(4)–C(5) bond and produced 4,5-seco-5,10-friedo-abieta-3,5(10),6,8,11,13-hexaene (**12**) via a C-10 carbonium ion intermediate (**11**) (Scheme 1)

In order to devise an efficient synthetic route to the pygmaecane *E*-type diterpenes, we further conducted some preliminary experiments on a rearrangement of the abietane skeleton. This paper describes a new skeletal rearrangement of the dehydroabietic acid derivative.

The enone **5**[5] prepared from (+)-dehydroabietic acid (**13**) was reduced with sodium borohydride in the presence of cerium(III) chloride heptahydrate[6] at room temperature; the resulting 7-hydroxy compound **6**[4] was then treated with boron trifluoride etherate in dichloromethane at 2 °C for 20 min to give a mixture of two optically-active rearranged esters, **8** (59.0% yield from **5**), $[\alpha]_D$ −347° ($CHCl_3$) and **14** (18.0% yield from **5**), $[\alpha]_D$ −27.3° ($CHCl_3$). On the other hand, a treatment of the 7-hydroxy compound **6** with boron trifluoride etherate at room temperature for 1 h produced only the ester **14** (74.2% yield from **5**), which was also obtained from the rearranged ester **8** by a similar treatment with boron trifluoride etherate at room temperature in 70.0% yield. The structure of ester **8** was assigned as methyl 5*β*-methyl-10-norabieta-1(10),6,8,11,13-pentaen-18-oate by direct comparisons of its physical and spectral data with those of an authentic sample.[4] The mass spectrum of another ester **14** gave a molecular ion peak at m/z 310.1925 (M^+), corresponding to the formula $C_{21}H_{26}O_2$. In the ^1H NMR spectrum, ester **14** exhibited the presence of an isopropyl group at $\delta=1.32$ (6H, d, $J=6.8$ Hz) and 3.03 (1H, m, $J=6.8$ Hz), a tertiary methyl group at $\delta=1.65$ (3H, s), a methyl group on an aryl ring at $\delta=2.55$ (3H, s), a methoxycarbonyl group at $\delta=3.65$ (3H, s), and four aromatic protons at $\delta=7.34$ (1H, dd, $J=2.0$ and 8.8 Hz), 7.53 (2H, br.s), and 7.93 (1H, d, $J=8.8$Hz). The differential nuclear Overhauser effects (NOE's) of **14** were observed between an aryl methyl signal at $\delta=2.55$ and an ortho-coupling aromatic proton signal at $\delta=7.93$ and a methylene signal at $\delta=2.91$ (2H, m), and between a methyl signal at $\delta=1.65$ and an aromatic proton signal at $\delta=7.53$, as shown in Fig. 2. Since ester **14** showed optical activity, the stereochemistry of the C-1 position in **14** was

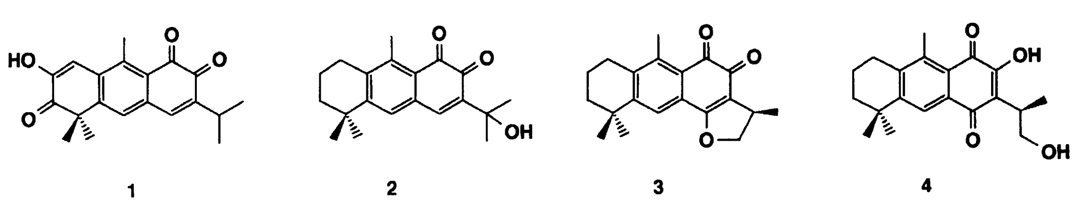
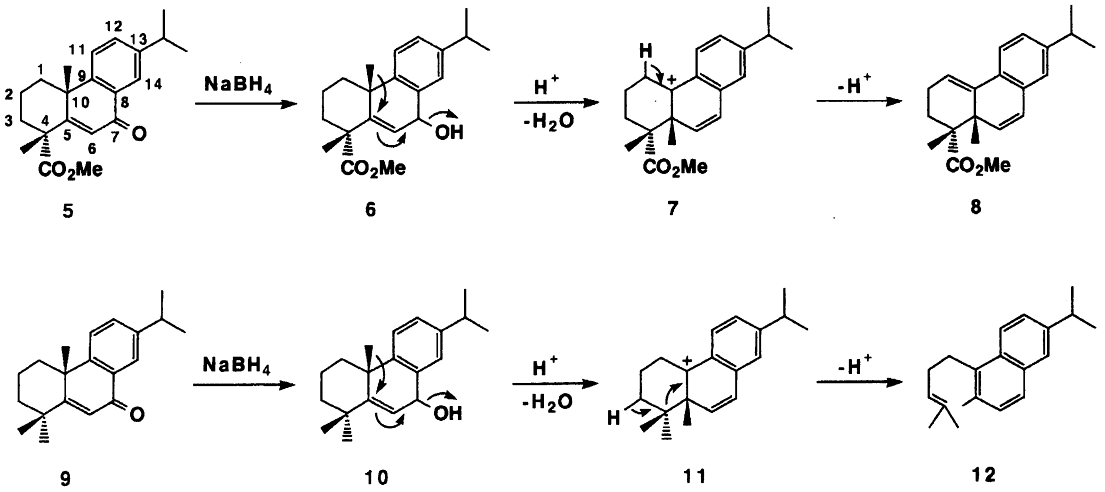


Fig. 1.



Scheme 1.

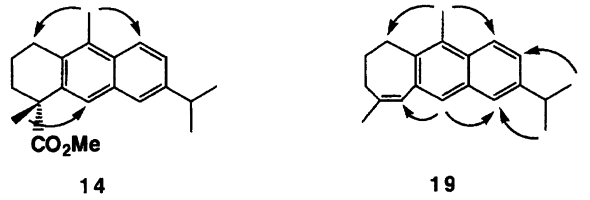


Fig. 2. NOE spectra of rearranged compounds, **14** and **19**.

assigned to be the same as that of the C-4 position in the starting compound **5**. Thus, the structure of **14** was assigned as methyl 7-isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate.

Subsequently, conversion of a methoxycarbonyl group in **14** into a methyl group was carried out as follows. The ester **14** was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to give an alcohol **15** in 98.0% yield. Oxidation of **15** with pyridinium chlorochromate in dichloromethane at room temperature, followed by a Huang–Minlon reduction of the resulting formyl compound **16** (86.9% yield), afforded a gem-dimethyl compound **17** in 83.3% yield. The mass spectrum of **17** gave a molecular ion peak at m/z 266.2046 (M^+) corresponding to the formula $C_{20}H_{26}$. In the ^{1}H NMR spectrum, compound **17** exhibited the presence of two isopropyl methyl groups at $\delta=1.33$ (6H, d, $J=7.3$ Hz), two methyl groups at $\delta=1.39$ (6H, s), a methyl group on an aryl ring at δ=2.52 (3H, s), and four aromatic protons at δ=7.29 (1H, dd, J=1.6 and 8.8 Hz), 7.53 (1H, br.s), 7.68 (1H, s), and 7.92 (1H, d, J=8.8 Hz). These spectral data suggested the structure of **17** to be 7-isopropyl-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene, possessing the pygmaeocane E skeleton. Finally, the alcohol **15** was treated with methanesulfonyl chloride in pyridine at room temperature to give a mesylate **18** in 96.6% yield. This was further converted into a new hydrocarbon compound **19** by heating at 80—83 °C in 94.3% yield. The mass spectrum of **19** gave a molecular ion peak at m/z 264.1897 (M^+), corresponding to the formula $C_{20}H_{24}$. The ^{1}H NMR spectrum of **19** showed the presence of two isopropyl methyl groups at δ=1.32 (6H, d, J=6.8 Hz), a methyl group on olefinic bond at δ=1.98 (3H, d, J=1.5 Hz), a methyl group on an aryl ring at δ=2.63 (3H, s), three methylene groups at δ=2.01 (2H, m), 2.15 (2H, t, J=6.8 Hz), and 2.91 (2H, t, J=5.9 Hz), a methine proton at δ=3.03 (1H, m, J=6.8 Hz), an olefinic proton at δ=6.50 (1H, br.s), and four aromatic protons at δ=7.33 (1H, dd, J=2.0 and 8.8 Hz), 7.39 (1H, s), 7.52 (1H, d, J=2.0 Hz), and 7.92 (1H, d, J=8.8 Hz). The differential NOE's of **19** were observed between an isopropyl methyl signal at δ=1.32 and signals at δ=3.03, 7.33, and 7.52, between an aryl methyl signal at δ=2.63 and signals at δ=2.91 and 7.92, and between an aromatic proton signal at δ=7.39 and signals at δ=6.50 and 7.52 (Fig. 2). Thus, the structure of **19** was assigned as 2-isopropyl-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene (Fig. 3).

A possible mechanism for the conversion of the enone **5** into methyl 7-isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carboxylate (**14**) is depicted in Scheme 2. The enone **5** is first converted into a C-5 carbonium ion intermediate (**6a**) by sodium borohy-

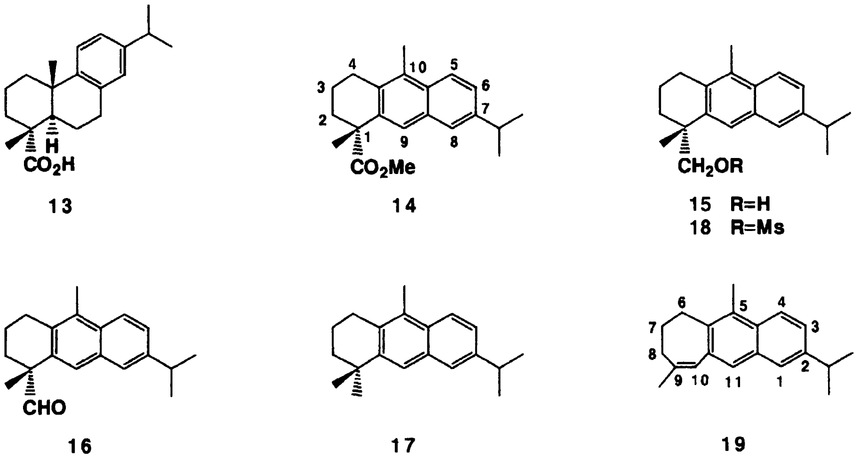
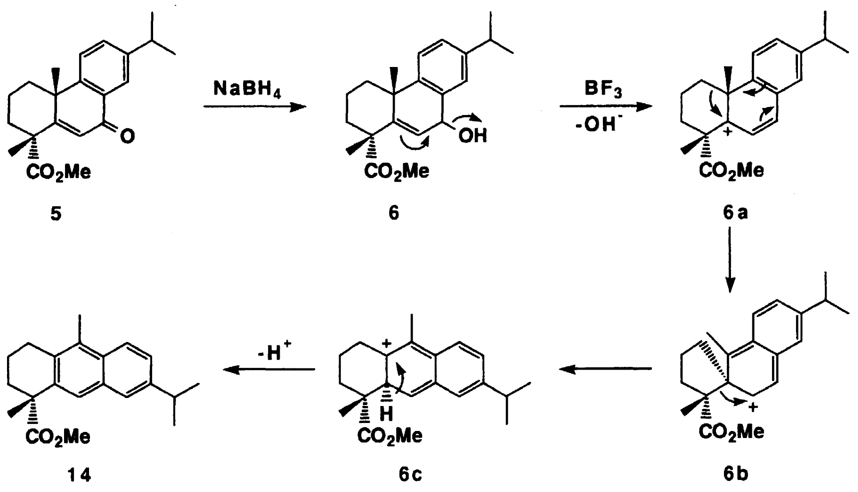


Fig. 3.



Scheme 2.

dride reduction and a subsequent treatment of the resulting alcohol (**6**) with boron trifluoride etherate. The migration of the C(1)–C(10) bond in **6a** into the C-5 position provides a C-10 carbonium ion intermediate, which is isomerized to a spiro intermediate (**6b**). Subsequent migration of the C(4)–C(5) bond in **6b** to the C-6 position results in the formation of a new carbonium ion intermediate (**6c**), which is then transformed into the optically-active ester **14** by deprotonation.

A possible mechanism for the conversion of the mesylate **18** into the dihydrocyclohepta[b]naphthalene derivative **19** is also depicted in Scheme 3. Elimination of a mesyloxyl group in **18** provides a cyclopropane intermediate **18a**, whose cyclopropane ring is cleaved to give a carbonium ion intermediate **18b**. This intermediate **18b** is then deprotonated to give compound **19**.

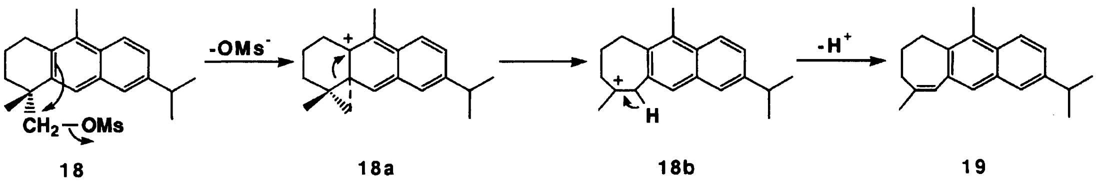
From the present study it is clear that (+)-dehydroabietic acid (**13**) is a useful relay compound for the synthesis of pygmaeocane E diterpenes, such as pygmaeocine E (**1**) and umbrosone (**2**).

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 (60MHz) or a JEOL JNM EX-400 (400MHz) spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated. 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).

Rearrangement of Methyl 7-Oxo-5,8,11,13-abietatetraen-18-oate (5). a) Sodium borohydride (75 mg) was added to a stirred mixture of **5** (620 mg) and cerium(III) chloride heptahydrate (739 mg) in methanol and tetrahydrofuran (1:1, 6.2 ml) at room temperature for 5 min. The mixture was further stirred at room temperature for 10 min, diluted with ether, washed with brine, dried over sodium sulfate, and evaporated in vacuo to give a crude alcohol (**6**) (640 mg).

A mixture of the above crude alcohol **6** (640 mg) and boron trifluoride etherate (1.2 ml) in dichloromethane (30 ml) was stirred at 2 °C for 20 min. The mixture was diluted



Scheme 3.

with ether, washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was repeatedly chromatographed on silica gel (50—100 times the sample weight in each case), using hexane–chloroform (1 : 1) as an eluent, to give an ester **14** (106 mg, 18.0% yield from **5**), mp 102—103 °C (from methanol), $[\alpha]_D$ −27.3° ($\mathrm{CHCl_3}$, *c* 0.31). IR 1720 cm^{-1}. ^{1}H NMR (400 MHz) δ=1.32 (6H, d, *J*=6.8 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 1.65 (3H, s, $-\mathrm{CH_3}$), 1.77 and 2.35 (each 1H, m, $-\mathrm{CH_2}-$), 1.89 and 1.98 (each 1H, m, $-\mathrm{CH_2}-$), 2.91 (2H, m, $-\mathrm{CH_2}-$), 2.55 (3H, s, $-\mathrm{CH_3}$), 3.03 (1H, m, *J*=6.8 Hz, $-\mathrm{C\underline{H}(CH_3)_2}$), 3.65 (3H, s, $-\mathrm{CO_2CH_3}$), 7.34 (1H, dd, *J*=2.0 and 8.8 Hz), 7.53 (2H, br.s), and 7.93 (1H, d, *J*=8.8 Hz) (aromatic protons). HRMS. Found: *m/z* 310.1925 (M$^+$). Calcd for $\mathrm{C_{21}H_{26}O_2}$: M, 310.1933. Further elution with hexane–chloroform (1 : 1) afforded an ester **8** (348 mg, 59.0% yield from **5**), mp 57—59 °C (from methanol), $[\alpha]_D$ −347° ($\mathrm{CHCl_3}$, c 0.84). The IR and ^{1}H NMR spectra of **8** were identical with those of methyl 5β-methyl-10-norabieta-1(10),6,8,11,13-pentaen-18-oate.[4)]

b) A mixture of **5** (1.497 g) and cerium(III) chloride heptahydrate (1.796 g) in methanol and tetrahydrofuran (1 : 1, 15 ml) was reduced with sodium borohydride (182 mg) to give a crude alcohol **6** (1.508 g).

A mixture of the above crude alcohol **6** (1.508 g) and boron trifluoride etherate (1.5 ml) in dichloromethane (30 ml) was stirred at room temperature for 1 h. The mixture was treated as described in a). The crude product was chromatographed on silica gel (150 g), using hexane–chloroform (1 : 1) as an eluent, to give an ester **14** (1.057 g, 74.2% yield from **5**), mp 102—103 °C (from methanol), $[\alpha]_D$ −27.7° ($\mathrm{CHCl_3}$, *c* 2.60). The IR and ^{1}H NMR spectra were identical with those of an authentic sample.

Rearrangement of Methyl 5β-Methyl-10-norabieta-1(10),6,8,11,13-pentaen-18-oate (8). A mixture of **8** (347 mg) and boron trifluoride etherate (0.65 ml) in dichloromethane (15.6 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 (50 g), using hexane–chloroform (1 : 1) as an eluent, to give **14** (243 mg, 70.0% yield), mp 102—103 °C (from methanol), $[\alpha]_D$ −27.6° ($\mathrm{CHCl_3}$, *c* 2.69). The IR and ^{1}H NMR spectra were identical with those of an authentic sample.

7-Isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-methanol (15). Lithium aluminum hydride (88 mg) was added to a stirred solution of **14** (360 mg) in dry tetrahydrofuran (10 ml) with cooling in an ice-water bath over a 5-min period. The mixture was refluxed for 1 h, cooled, poured into ice-dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (15 g), using chloroform as an eluent, to give an alcohol **15** (321 mg, 98.0% yield), mp 79—81 °C (from hexane), $[\alpha]_D$ −26.2° ($\mathrm{CHCl_3}$, *c* 0.48). IR 3590 and 3440 cm^{-1}. ^{1}H NMR (60 MHz) δ=1.33 (6H, d, *J*=6.7 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 1.34 (3H, s, $-\mathrm{CH_3}$), 1.69—2.16 (4H, m, $-\mathrm{(CH_2)_2}-$), 2.52 (3H, s, $-\mathrm{CH_3}$), 2.77—3.28 (3H, m, $-\mathrm{CH_2}-$ and $-\mathrm{C\underline{H}(CH_3)_2}$), 3.55 and 3.89 (each 1H, d, *J*=11 Hz, $-\mathrm{C\underline{H}_2OH}$), 7.33 (1H, dd, *J*=1.8 and 8.8 Hz), 7.54 (1H, br.s), 7.63 (1H, s), and 7.94 (1H, d, *J*=8.8 Hz) (aromatic protons). HRMS. Found: *m/z* 282.1984 (M$^+$). Calcd for $\mathrm{C_{20}H_{26}O}$: M, 282.1984.

7-Isopropyl-1,10-dimethyl-1,2,3,4-tetrahydroanthracene-1-carbaldehyde (16). A mixture of **15** (146 mg) and pyridinium chlorochromate (190 mg) in dichloromethane (5.8 ml) was stirred at room temperature for 3.5 h. The mixture was diluted with ether, washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (15 g), using hexane–chloroform (1 : 9) as an eluent, to give an aldehyde **16** (126 mg, 86.9% yield), $[\alpha]_D$ −36.3° ($\mathrm{CHCl_3}$, *c* 0.71). IR 2720 and 1720 cm^{-1}. ^{1}H NMR (60 MHz) δ=1.32 (6H, d, *J*=7.0 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 1.51 (3H, s, $-\mathrm{CH_3}$), 1.76—2.10 (4H, m, $-\mathrm{(CH_2)_2}-$), 2.56 (3H, s, $-\mathrm{CH_3}$), 2.81—3.16 (3H, m, $-\mathrm{CH_2}-$ and $-\mathrm{C\underline{H}(CH_3)_2}$), 7.36 (1H, dd, *J*=1.9 and 8.8 Hz), 7.38 (1H, s), 7.54 (1H, s), and 7.96 (1H, d, *J*=8.8 Hz) (aromatic protons), and 9.54 (1H, s, $-\mathrm{CHO}$). HRMS. Found: *m/z* 280.1816 (M$^+$). Calcd for $\mathrm{C_{20}H_{24}O}$: M, 280.1827.

7-Isopropyl-1,1,10-trimethyl-1,2,3,4-tetrahydroanthracene (17). After a mixture of **16** (110 mg) and hydrazine hydrate (0.55 ml) in diethylene glycol (2.8 ml) was refluxed for 2 h, powdered sodium hydroxide (550 mg) was added. The mixture was heated at 180—185 °C for 2h, cooled, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (15 g), using hexane–chloroform (8 : 2) as an eluent, to give **17** (87 mg, 83.3% yield). ^{1}H NMR (60 MHz) δ=1.33 (6H, d, *J*=7.3 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 1.39 (6H, s, $-\mathrm{C(CH_3)_2}-$), 1.55—2.05 (4H, m, $-\mathrm{(CH_2)_2}-$), 2.52 (3H, s, $-\mathrm{CH_3}$), 2.78—3.15 (3H, m, $-\mathrm{CH_2}-$ and $-\mathrm{C\underline{H}(CH_3)_2}$), 7.29 (1H, dd, *J*=1.6 and 8.8 Hz), 7.53 (1H, br.s), 7.68 (1H, s), and 7.92 (1H, d, *J*=8.8 Hz) (aromatic protons). HRMS. Found: *m/z* 266.2046 (M$^+$). Calcd for $\mathrm{C_{20}H_{26}}$: M, 266.2035.

Mesylation of 15. A mixture of **15** (69 mg) and methanesulfonyl chloride (0.1 ml) in pyridine (1.2 ml) was allowed to stand at room temperature for 20 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 immediately chromatographed on silica gel (10 g), using chloroform as an eluent, to give a mesylate **18** (85 mg, 96.6% yield), $[\alpha]_D$ −40.3° ($\mathrm{CHCl_3}$, *c* 0.84). ^{1}H NMR (60 MHz) δ=1.33 (6H, d, J=6.7 Hz, –CH(C$\underline{H}_3$)$_2$), 1.48 (3H, s, –CH$_3$), 1.71—2.09 (4H, m, –(CH$_2$)$_2$–), 2.53 (3H, s, –CH$_3$), ca. 2.8—3.2 (3H, m, overlap, –CH$_2$– and –C$\underline{H}$(CH$_3$)$_2$), 2.87 (3H, s, –OSO$_2$CH$_3$), 4.31 (2H, s, –CH$_2$O–), 7.35 (1H, dd, J=1.8 and 8.8 Hz), 7.54 (1H, s), 7.63 (1H, s), and 7.94 (1H, d, J=8.8 Hz) (aromatic protons). HRMS. Found: m/z 360.1770 (M$^+$). Calcd for $C_{21}H_{28}O_3S$: M, 360.1759.

Rearrangement of 15. a) The mesylate **18** (55 mg) was heated at 80—83 °C for 15 min. The product was chromatographed on silica gel (10 g), using hexane–chloroform (9 : 1) as an eluent, to give 2-isopropyl-5,9-dimethyl-7,8-dihydro-6*H*-cyclohepta[*b*]naphthalene (**19**) (38 mg, 94.3% yield), mp 66—68 °C (from hexane). IR 1630 cm^{-1}. ^{1}H NMR (400 MHz) δ=1.32 (6H, d, J=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 1.98 (3H, d, J=1.5 Hz, –CH$_3$), 2.01 (2H, m, –CH$_2$–), 2.15 (2H, t, J=6.8 Hz, –CH$_2$–), 2.63 (3H, s, –CH$_3$), 2.91 (2H, t, J=5.9 Hz, –CH$_2$–), 3.03 (1H, m, J=6.8 Hz, –C$\underline{H}$(CH$_3$)$_2$), 6.50 (1H, br.s, =CH–), 7.33 (1H, dd, J=2.0 and 8.8 Hz), 7.39 (1H, s), 7.52 (1H, d, J=2.0 Hz), and 7.92 (1H, d, J=8.8 Hz) (aromatic protons). HRMS. Found: m/z 264.1897 (M$^+$). Calcd for $C_{20}H_{24}$: M, 264.1878.

b) The alcohol **15** (270 mg) was mesylated with methanesulfonyl chloride (0.3 ml) in pyridine (2.7 ml) at room temperature for 24 h. After the work-up described above, the crude product was allowed to stand at room temperature for 48 h, and was then chromatographed on silica gel (15 g), using hexane–chloroform (4 : 1) as an eluent, to give **19** (183 mg, 72.4% yield from **15**), mp 66—68 °C (from hexane). The IR and ^{1}H NMR spectra were identical with those of an authentic sample. Further elution with chloroform afforded the mesylate **18** (24 mg, 7.0% yield), whose IR and ^{1}H NMR spectra were identical with those of an authentic sample.

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