Preparation of Potential Anti-Inflammatory Agents from Dehydroabietic Acid

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Abstract □ Methyl 16-nor-16-carboxydehydroabietate (**22**), 16-nor-16-carboxydehydroabietinol acetate (**23**), methyl 7-keto-16-nor-16-carboxydehydroabietate (**29**), 16-nor-16-carboxydehydroabietic acid (**30**), 16-nor-16-carboxydehydroabietinol (**31**), 7-keto-16-nor-16-carboxydehydroabietic acid (**32**), methyl 7-hydroxy-16-nor-16-carboxydehydroabietate (**33**), and 7-hydroxy-16-nor-16-carboxydehydroabietic acid (**34**) were prepared from dehydroabietic acid. Only **22** and **32** had weak anti-inflammatory activity.

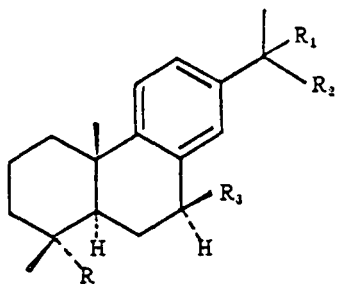
Although the isolation of natural products from plants or animals may aid in the discovery of a useful drug, semisynthetic modification of natural products is a more economical approach to the search for a biologically active compound. Dehydroabietic acid (**1**) is readily available from many sources. Although considerable work has been done on this resin acid, no practical application has yet been achieved for any form of **1**. Chemical modification of this acid to produce substances with particular pharmacologic activities is a worthy endeavor. The presence of an isopropyl side chain at position 13 in the structure of **1** suggests that if a carboxylic group was introduced in this side chain, it would have an α-arylpropionic function like that of ibuprofen, a potent nonsteroidal anti-inflammatory agent. On the basis of this idea, a series of distant analogues of ibuprofen were prepared from **1** by modification of the isopropyl side chain, as well as positions 4 and 7, and potential anti-inflammatory activity was examined.

Results and Discussion

Compound **1** was isolated from the resin by chromatography. The yield of the expected acid was low, and most of it was in a mixture with other unidentified acids. The acid mixture was esterified with diazomethane to form a methyl ester mixture from which methyl dehydroabietate (**2**) was isolated in 25% yield from the resin.

Compound **2** was first oxidized with chromic acid in acetic acid and acetic anhydride[1] to yield a mixture from which **3**, **4**, and **5** were isolated by chromatography. Because the yield of the desired acetoxy compound (**3**) from chromic acid oxidation was poor, an alternative oxidation reagent was sought. *N*-Bromosuccinimide (NBS) is well documented as a good reagent for benzylic oxidation.[2] Benzylic oxidation of **2** led to the expected product **6** in 79% yield and another side product, **5**. NBS oxidations were also carried out for dehydroabietinol acetate (**7**) to yield **9** and **10**. Similarly, dehydroabietane gave a mixture from which **11** and impure 7-ketodehydroabietane were obtained with chromatographic separation. No further characterization was attempted for this impure side product.

Once the 15-hydroxy compound was obtained, the next step was the dehydration of **6**, **9**, and **11** in benzene with a trace of *p*-toluenesulfonic acid to afford **12**, **13**, and **14**, respectively, in high yield.



	R	R_1	R_2	R_3
1	COOH	H	CH_3	H
2	CO_2CH_3	H	CH_3	H
7	CH_2OAc	H	CH_3	H
8	CH_3	H	CH_3	H
17	CH_2OAc	OH	CH_2OH	OAc
18	CO_2CH_3	H	CH_2OH	H
19	CO_2CH_3	OH	CH_2OH	H
20	CH_2OAc	H	CH_2OH	H
21	CH_2OAc	OH	CH_2OH	H
22	CO_2CH_3	H	COOH	H
23	CH_2OAc	H	COOH	H
25	CH_2OH	H	CH_3	H
27	CHO	H	CH_3	H
28	CO_2CH_3	H	CH_2OH	OH
30	COOH	H	COOH	H
31	CH_2OH	H	COOH	H
33	CO_2CH_3	H	COOH	OH
34	COOH	H	COOH	OH

Treatment of **12** and **15** with a catalytic amount osmium tetroxide and *N*-methylmorpholine-*N*-oxide in *tert*-butyl alcohol, acetone, and water, followed by reductive workup, yielded the expected diols, **16** and **17**, respectively, in high yield.[3]

The next step, according to the preparation plan, was to remove the 15-tertiary hydroxyl group of **16** by hydrogenolysis with 10% palladium on carbon in absolute ethanol. At a very early stage of the reaction, a spot appeared on the thin-layer chromatogram that had a retardation factor that was lower than that of the starting material; this spot was suspected to be due to a triol resulting from reduction of the 7-keto group. No attempt was made to isolate this suspected triol. As the hydrogenolysis proceeded, the 7-keto group was removed to give the 15,16-dihydroxyl compound **19**, and then the tertiary hydroxyl group in the side chain was removed by hydrogenolysis. Unexpectedly, as the amount of the desired product [the 16-monohydroxyl compound (**18**)] increased, quantities of another product corresponding to **2** also increased. This undesired product apparently resulted from the concurrent removal of both the 15- and 16-hydroxyl groups from the side chain by an unknown mechanism. The removal of the tertiary alcohol by

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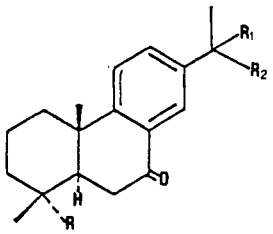
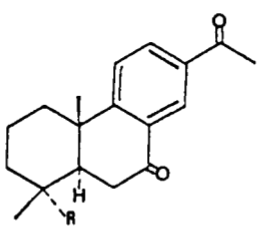
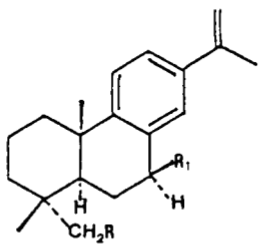
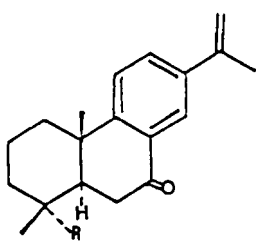


	R	R_1	R_2
3	CO_2CH_3	OAc	CH_3
5	CO_2CH_3	H	CH_3
6	CO_2CH_3	OH	CH_3
9	CH_2OAc	OH	CH_3
10	CH_2OAc	H	CH_3
11	CH_3	OH	CH_3
16	CO_2CH_3	OH	CH_2OH
29	CO_2CH_3	H	COOH
32	COOH	H	COOH





4	R = CO_2CH_3	15	R = R_1 = OAc
24	R = CH_2OAc	26	R = R_1 = OH



12	R = CO_2CH_3
13	R = CH_2OAc
14	R = CH_3

hydrogenolysis was unexpectedly difficult; probably because it is sterically hindered.

Hydrogenolysis was also carried out for 17 with the same conditions as those used for 16 to yield a mixture of 20, 21, and 7. The yield for the major compound, 20, was 55%, which is comparable to that of 18.

With 18 in hand, the subsequent step was the crucial oxidation of its primary alcohol to a carboxylic acid. Compound 18 has two benzylic positions in addition to the primary alcohol functionality. Suitable oxidation conditions should be applied to avoid the simultaneous oxidation of the vulnerable benzylic positions. The oxidation reagent of first choice was the Jones reagent,[4] which had been used successfully to oxidize alcohols to carboxylic acids or ketones. However, thin-layer chromatography (TLC) of the oxidation reaction mixture showed a complicated mixture of products. It was thus necessary to search for alternative conditions. This tricky oxidation was finally accomplished with a mixture of chromic acid and sulfuric acid in aqueous acetone.[5] Upon workup and purification of the crude product by chromatography, a major product (22, 62% yield), along with a minor one (4), was isolated. Compound 20 was also oxidized under the same condition as that used for 18 to give the desired product (23) and a side product (24). The yield of 23 was somewhat lower than that of 22; the reason for this difference is not clear.

With the preparation of two target analogues from 2 and 7, attention was turned to the modification of position 4 to obtain a series of analogues for comparative evaluation of biological activity.

Reductions of 2 and 12 to alcohols 25 and 26, respectively, were accomplished smoothly in high yield by using lithium aluminum hydride.[6] Both 25 and 26 were acetylated with acetic anhydride and a small amount of dimethylaminopyridine in pyridine to give monoacetate 7 and diacetate 15, respectively, in high yield.[7] The diacetate 15 was converted to the desired acid analogue (23) by successive reactions of hydroxylation, hydrogenolysis, and oxidation, as described previously.

Further modification of position 4 was accomplished by oxidation of 25 with pyridinium chlorochromate to give the aldehyde 27,[8] which was, in turn, reduced under Huang Minlon reduction conditions[9] to dehydroabietane (8).

Although the route from 12 through 16 and 18 satisfactorily led to the desired α-arylpropionic acid analogue, the low yield of the alcohol 18 from hydrogenolysis was limiting. As a possible alternative route to the target compound, hydroboration of the 7-keto olefin 12 to a 7,16-diol not only might provide another way to the acid analogues, but also might furnish a feasible way to modify position 7.

Hydroboration of 12 with a BH_3–tetrahydrofuran complex followed by an oxidative workup[10] produced a 7,16-diol (28) and a small amount of unidentified product with a TLC retardation factor lower than that of 28. Compound 28 was oxidized under the same conditions used for 18 to afford the 7-keto acid (29) and a side product (4), as described previously.

With the three α-arylpropionic acid analogues (22, 23, and 29) prepared, further modifications at positions 4 and 7 would yield differently substituted acid analogues. Compounds 22, 23, and 29 were hydrolyzed with NaOH to give 30, 31, and 32, respectively.

The 7-keto groups in 29 and 32 were reduced to the α-oriented hydroxyl groups of 33 and 34, respectively, with sodium borohydride in methanol.[11] The reduction surprisingly took place only in the presence of a large amount of the reducing agent. Resistance to reduction was assumed to be due to the presence of the carboxyl group(s).

The final products, α-arylpropionic acid analogues, were tested for anti-inflammatory activity and submitted for routine qualitative antimicrobial screening. All compounds were assayed for anti-inflammatory activity at a concentration of 300 μM. Results, expressed as percentage of the label converted to prostaglandins, are as follows: ethanol (87%), ibuprofen (30 μM, 62%) indomethacin (10 μM, 37%), 22 (80%), 30 (91%), 29 (87%), 23 (91%), 33 (92%), 31 (93%), 32 (83%), and 34 (93%). Thus, none of the compounds showed significant activity at 300 μM, except for the very weak activity of 22 and 32. However, neither 22 or 32 showed promising activity against the microorganisms tested.

Experimental Section

General Experimental Procedure—Melting points were determined on a Fisher-Johns digital melting analyzer model 355 and were not corrected. IR spectra were taken on a Perkin-Elmer 281 B spectrometer. Specific rotations were obtained on a Perkin-Elmer 141 automatic polarimeter. Low-resolution mass spectra (MS) were obtained on a Finnigan model 3200 (70 eV ionization potential) with the INCOS data system or Hewlett Packard model 5985. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded either on a Varian EM-390 (90 MHz) or a Varian VXR-300 (300 MHz). The ^{13}C NMR spectra, attached proton test (APT), and distortionless

enhancement by polarization transfer–grand luxe (DEPTGL) were performed on a Varian VXR-300. Column chromatography was carried out on silica gel 60 (Macherey–Nagel; 70–270 mesh). Analysis by TLC was performed on precoated plates (Macherey–Nagel), and detection of compounds was done by spraying with a *p*-anisaldehyde spray reagent. Solvents used for measuring specific rotation and IR spectra were spectroscopic grade, and those used for chromatography were analytical reagent grade.

Material—The raw material, resin from which **1** was isolated, was purchased from Hercules Company Incorporated.

Biological Screening Procedures—The final products were tested for anti-inflammatory activity by a prostaglandin (PG) synthetase assay, with ibuprofen as standard. The enzyme, prepared from sheep seminal vesicles, catalyzed the conversion of arachidonic acid to PGE_2 and $PGE_{2\alpha}$. The [^{14}C]arachidonic acid and PGs were separated by TLC after extraction, and the conversion was quantitated by scraping the plates and determining radioactivity with liquid scintillation counting (LSC). Results are expressed as percentage of the label converted to PGs.

The procedures described by Hufford et al.,[12] as modified by Clark et al.,[13] were used for qualitative antibacterial screening. The target compounds were tested for activity against the following microorganisms: *Escherichia coli* (ATCC 10536), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 15442), *Bacillus subtilis* (ATCC 6633), *Mycobacterium smegmatis* (ATCC 607), *Cryptococcus neoformans* (ATCC 32264), *Saccharomyces cerevisiae* (ATCC 9763), *Aspergillus flavus* (ATCC 9170), *Aspergillus fumigatus* (ATCC 26934), and *Trichophyton mentagraphytes* (ATCC 9972).

Dehydroabietic Acid (1)—The resin (50 g) was chromatographed over silica gel 60 (500 g) and eluted with $CHCl_3$:*n*-hexane (1:1). Fractions containing the acid were combined on the basis of TLC and gas chromatographic analyses of the methyl ester.

Fraction 4 (1.75 g) was pure **1** from gas chromatographic analysis of its methyl ester. It was crystallized from hot methanol with a few drops of water to give prisms: mp 167–169 °C, $[\alpha]_D$ +57.3 (*c*, 1.04, $CHCl_3$); IR (KBr): υ3500–2400, 1695, 1615, 1495, 1055, 885, and 820 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, s), 1.27 (6H, d, J = 7.0 Hz, H-16 and H-17), 1.30 (3H, s), 1.43–2.03 (7H, complex pattern), 2.23–2.43 (2H, complex pattern), 2.70–3.07 (3H, complex pattern, H-7 and H-15), 7.00 (1H, s, H-14), 7.10 (1H, br d, J = 8.0 Hz, H-12), 7.30 (1H, d, J = 8.0 Hz, H-11), and 10.60 (1H, br s, COOH); ^{13}C NMR ($CDCl_3$): δ 38.0 (t, C-1), 18.6 (t, C-2), 36.8 (t, C-3), 47.5 (s, C-4), 44.6 (d, C-5), 21.8 (t, C-6), 30.0 (t, C-7), 134.7 (s, C-8), 146.8 (s, C-9), 36.9 (s, C-10), 124.1 (d, C-11), 123.9 (d, C-12), 145.8 (s, C-13), 126.9 (d, C-14), 33.5 (d, C-15), 24.0 (q, C-16), 24.0 (q, C-17), 185.5 (s, C-18), 16.2 (q, C-19), and 25.2 (q, C-20); MS: *m/z* (relative abundance) 300 (M^+, 28), 285 (86), and 239 (base peak).

Methyl Dehydroabietate (2)—Diazomethane was prepared by the general procedure provided by Aldrich Company, and the acid (8.0 g) was added directly to the first receiver to afford the crude methyl ester (8.14 g). The methyl ester was a mixture of two compounds, on the basis of TLC analysis on a silica gel plate with *n*-hexane saturated with acetonitrile as the developing solvent system. The methyl ester mixture was chromatographed over a silica gel column (300 g), with *n*-hexane saturated with acetonitrile as the eluting solvent, to yield **2** (3.82 g), which was recrystallized from hot methanol and water to give colorless prisms: mp 64–65 °C, $[\alpha]_D$ +50.6 (*c*, 0.9, $CHCl_3$); IR (KBr): υ1720, 1495, 1180, 880, and 830 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, s), 1.27 (6H, d, J = 6.0 Hz, H-16 and H-17), 1.30 (3H, s), 1.43–2.03 (7H, complex pattern), 2.30–2.47 (2H, complex pattern), 2.73–3.07 (3H, m, H-7 and H-15), 3.72 (3H, s, CO_2CH_3), 7.00 (1H, s, H-14), 7.10 (1H, br d, J = 9.5 Hz, H-12), and 7.33 (1H, d, J = 9.5 Hz, H-11); ^{13}C NMR ($CDCl_3$): δ 38.0 (t, C-1), 18.6 (t, C-2), 36.7 (t, C-3), 47.7 (s, C-4), 44.9 (d, C-5), 21.7 (t, C-6), 30.0 (t, C-7), 134.7 (s, C-8), 146.9 (s, C-9), 37.0 (s, C-10), 124.1 (d, C-11), 123.9 (d, C-12), 145.7 (s, C-13), 126.9 (d, C-14), 33.5 (d, C-15), 24.0 (q, C-16), 24.0 (q, C-17), 179.1 (s, C-18), 16.5 (q, C-19), 25.1 (q, C-20), and 51.9 (q, OCH_3); MS: *m/z* (relative abundance) 314 (M^+, 15), 299 (22), 255 (13), and 239 (base peak).

Chromic Acid Oxidation of 2—The procedure of Wenkert et al.[1] was followed. Chromic acid (300 mg) was added over a 6-h period to a solution of **2** (200 mg) in acetic acid (2.0 mL) and acetic anhydride (1.6 mL) at room temperature. The reaction mixture was stirred for another 2 h, poured onto ice (6.0 g), and stirred for 5 min. This workup was followed by addition of cold water (10 mL) and extraction with ether (3 × 30 mL). The combined ethereal solution was washed with water (2 × 30 mL) and dried over magnesium sulfate, and the solvent was evaporated to give 172 mg of residue. The residue was chromatographed on silica gel (5 g) with 10% chloroform in *n*-hexane as eluant to provide **3** (32% yield), **4**, and **5**.

Methyl 7-Keto-15-acetoxydehydroabietate (3)—This compound was crystallized from ether–*n*-hexane to give prisms: mp 132.5–134.5 °C, $[\alpha]_D$ +19.9 (*c*, 1.08, $CHCl_3$); IR (KBr): υ1730, 1715, 1680, 1605, 1490, and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, s), 1.37 (3H, s), 1.80 (6H, s, H-16 and H-17), 2.07 (3H, s, acetate), 2.13–2.83 (3H, complex pattern), 1.53–1.90 (6H, complex pattern coincident with the singlet at δ 1.80), 3.73 (3H, s, CO_2CH_3), 7.45 (1H, d, J = 9.0 Hz, H-11), 7.67 (1H, dd, J = 9.0 Hz, 3.0, H-12), 8.13 (1H, d, J = 3.0 Hz, H-14); MS: *m/z* (relative abundance) 386 (M^+, 13), 344 (46.0), 343 (87.8), and 327 (base peak).

Methyl 7-Keto-13-acetyldeisopropyldehydroabietate (4)—This compound was crystallized from ether–*n*-hexane, to give prisms: mp 141–142 °C, $[\alpha]_D$ +26.9 (*c*, 0.58, $CHCl_3$); IR (KBr): υ1725, 1685, 1605, and 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (3H, s), 1.40 (3H, s), 1.50–2.07 (6H, complex pattern), 2.07–2.90 (3H, complex pattern, coincident with the singlet at δ 2.67), 2.67 (3H, s, $COCH_3$), 3.73 (3H, s, $COOCH_3$), 7.63 (1H, d, J = 9.0 Hz, H-11), 8.28 (1H, dd, J = 9.0 Hz, 2.0, H-12), 8.68 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 328 (M^+, 19.7), 253 (39.0), and 43 (base peak).

Methyl 7-Ketodehydroabietate (5)—This compound was isolated as an oily substance: $[\alpha]_D$ +13.0 (*c*, 0.7, $CHCl_3$); IR ($CHCl_3$): υ1725, 1675, and 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (6H, d, J = 6.0 Hz, H-16 and H-17), 1.30 (3H, s), 1.36 (3H, s), 1.60–2.84 (9H, complex pattern), 3.00 (1H, septet, H-15), 3.70 (3H, s, $COCH_3$), 7.40 (1H, d, J = 9.0 Hz, H-11), 7.53 (1H, br d, J = 9.0 Hz, H-12), and 8.00 (1H, br s, H-14); MS: *m/z* (relative abundance) 328 (M^+, 36.5), 269 (13.3), and 253 (base peak).

Oxidation with NBS—The compound (10 mmol) was dissolved in dioxane (120 mL), and water (25 mL) and calcium carbonate (4 g, 40 mmol) were added. The mixture was refluxed by light (1000-watt, tungsten lamp) with stirring, and NBS [10.62 g (60 mmol) in 80 mL of dioxane] was added in a dropwise manner over a period of 20 min. The reaction mixture was refluxed and stirred for another 20 min. The reaction mixture was cooled to room temperature, filtered, and evaporated to remove the solvent. The residue was extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (150 mL), dried over anhydrous sodium sulfate, and filtered, and the solvent was removed to give a residue, which was chromatographed on silica gel, with *n*-hexane–ethyl acetate as the eluting solvent, to obtain the product.

Methyl 7-Keto-15-hydroxydehydroabietate (6)—Compound **2** was oxidized with NBS to produce **6** (79%) and **5**. Compound **6** was crystallized from ether to give prisms: mp 83–86 °C, $[\alpha]_D$ +9.4 (*c*, 0.6, $CHCl_3$); IR (KBr): υ 3460, 1725, 1680, 1605, 1492, and 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.28 (3H, s), 1.37 (3H, s), 1.60 (6H, s, H-16 and H-17), 1.80 (4H, br s), 2.03–2.83 (6H, complex pattern), 3.70 (3H, s, $COOCH_3$), 7.43 (1H, d, J = 9.0 Hz, H-11), 7.83 (1H, dd, J = 9.0 Hz, 2.0, H-12), and 8.20 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 344 (M^+, 4.0), 330 (20.6), and 329 (base peak).

7-Keto-15-hydroxydehydroabietinol Acetate (9)—Compound **7** was oxidized with NBS to produce **9** (76%) and **10**. Compound **9** was a viscous substance that could not be induced to crystallize: $[\alpha]_D$ +121.3 (*c*, 0.4; $CHCl_3$); IR ($CHCl_3$): υ3600, 3465, 1725, 1675, 1605, 1240, and 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, s, H-19), 1.33 (3H, s, H-20), 1.63 (6H, s, H-16 and H-17), 2.05 (3H, s, acetate), 1.17–2.57 (7H, complex pattern), 2.33 (1H, br s, exchangeable proton), 2.67 (1H, s), 2.77 (1H, br s), 3.77 (1H, d, J = 10.0 Hz, CH_2OAc), 3.93 (1H, d, J = 10.0 Hz, CH_2OAc), 7.50 (1H, d, J = 8.0 Hz, H-11), 7.88, (1H, dd, J = 8.0 Hz, 2.0, H-12), and 8.20 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 358 (M^+, 10.7), 343 (base peak), 340 (57.7), 283 (65.6), 265 (44.9), and 187 (91.1).

7-Ketodehydroabietinol Acetate (10)—This compound was isolated as an oily substance: $[\alpha]_D$ +22.9 (*c*, 1.03, $CHCl_3$); IR ($CHCl_3$): υ1725, 1675, 1605, 1490, 1255, and 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, s), 1.27 (6H, d, J = 6.0 Hz, H-16 and H-17); 1.30 (3H, s), 2.03 (3H, s, acetate), 0.9–2.53 (7H, complex pattern), 2.67 (1H, s), 2.77 (1H, d, J = 2.0 Hz), 2.97 (1H, septet, J = 6.0 Hz, H-15), 3.77 (1H, d, J = 12.0 Hz, CH_2OAc), 3.93 (1H, d, J = 12.0 Hz, CH_2OAc), 7.42 (1H, d, J = 8.0 Hz, H-11) 7.53 (1H, dd, J = 8.0 Hz, 2.0, H-12), 8.00 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 342 (M^+, 23.7), 282 (52.2), 267 (base peak), 225 (31.4), and 187 (97.3).

7-Keto-15-hydroxydehydroabietane (11)—Compound **8** was oxidized with NBS to yield **11** (77%). Compound **11** was crystallized from methanol and water to give prisms: mp 134–135 °C, $[\alpha]_D$ +11.5 (*c*,

1.86, $CHCl_3$); IR ($CHCl_3$): ν 3600, 3470, 1675, 1605, and 1495 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97, 1.03 (3H for each, s, H-18 and H-19), 1.27 (3H, s, H-20), 1.63 (6H, s, H-16 and H-17), 1.20–2.10 (6H, complex pattern), 2.33 (1H, br s, exchangeable proton), 2.40 (1H, br d, J = 11.0 Hz, H-5), 2.72 (1H, d, J = 4.0 Hz), 2.80 (1H, s), 7.52 (1H, d, J = 8.0 Hz, H-11), 7.92 (1H, dd, J = 8.0 Hz, 2.5, H-12), and 8.28 (1H, d, J = 2.5 Hz, H-14); MS: *m/z* (relative abundance) 300 (M^+, 18.1), 286 (70.7), and 285 (base peak).

Dehydration—Compounds 6, 9, and 11 (8.0 mmol) were refluxed in benzene (200 mL) for 30 min in the presence of a trace amount of *p*-toluenesulfonic acid. The reaction solution was cooled, and a saturated sodium bicarbonate solution (100 mL) was added. The benzene solution was dried over anhydrous sodium sulfate. Removal of solvent gave a residue, which was chromatographed over silica gel, with *n*-hexane–ethyl acetate as the eluting solvent, to obtain products 12 (85%), 13 (85%), and 14 (85%).

Methyl 7-Keto-15(16)-dehydrodehydroabietate (12)—This compound was isolated as colorless prisms when crystallized from methanol and water: mp 80–82 °C, $[\alpha]_D$ +25.9 (*c*, 0.53, $CHCl_3$); IR (KBr): ν 3090, 1725, 1675, 1628, 1604, 1490, 990, and 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (3H, s), 1.37 (3H, s), 1.80–1.97 (6H, complex pattern), 2.20 (3H, s, H-17), 2.30–2.87 (3H, complex pattern), 3.73 (3H, s, $COOCH_3$), 5.18 (1H, m, H-16), 5.50 (1H, s, H-16), 7.45 (1H, d, J = 9.0 Hz, H-11), 7.78 (1H, dd, J = 9.0 Hz, 2.0, H-12), and 8.30 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 326 (M^+, 42.0) 311 (1.1), 267 (9.6), 252 (19.1), and 251 (base peak).

7-Keto-15(16)-dehydrodehydroabietinol Acetate (13)—This compound was isolated as an oily substance: $[\alpha]_D$ +14.4 (*c*, 0.34, $CHCl_3$); IR ($CHCl_3$): ν3050, 1725, 1680, 1630, 1605, 1495, 1250, 1045, 995, and 905 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (3H, s, H-19), 1.30 (3H, s, H-20), 2.03 (3H, s, acetate), 2.20 (3H, s, H-17), 1.03–2.53 (7H, complex pattern), 2.67 (1H, s), 2.77 (1H, d, J = 2.0 Hz), 3.77, 3.93 (1H for each, d, J = 11.0 Hz, CH_2OAc), 5.17 (1H, br s, H-16), 5.48 (1H, s, H-16), 7.45 (1H, d, J = 8.0 Hz, H-11), 7.77 (1H, dd, J = 8.0 Hz, 2.0, H-12), and 8.23 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 340 (M^+, 76.7), 280 (73.2), 265 (base peak), 223 (52.5), and 197 (60.2).

7-Keto-15(16)-dehydrodehydroabietane (14)—This compound has a mp of 108.0–110 °C: $[\alpha]_D$ +24.9 (*c*, 0.83, $CHCl_3$); IR ($CHCl_3$): ν 1675, 1630, 1605, 1490, 1380, 985, and 905 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97, 1.03 (3H, for each, s, H-18 and H-19), 1.27 (3H, s, H-20), 1.20–2.10 (6H, complex pattern), 2.33 (3H, s, H-17), 2.40 (1H, br d, J = 11.0 Hz), 2.70 (1H, d, J = 4.0 Hz), 2.80 (1H, s), 5.20 (1H, m, H-16), 5.50 (1H, s, H-16), 7.47 (1H, d, J = 8.0 Hz, H-11), 7.80 (1H, dd, J = 8.0 Hz, 2.0, H-12), and 8.25 (1H, d, J = 2.0 Hz, H-14); MS: *m/z* (relative abundance) 282 (M^+, 82.3), 268 (27.6), and 267 (base peak).

Oxidation with Osmium Tetroxide—The sample (13.1 mmol) in 25 mL of *tert*-butyl alcohol was added to a mixture consisting of *N*-methylmorpholine-*N*-oxide (2.133 g, 13.9 mmol) in 25 mL of aqueous acetone solution (H_2O:acetone, 5:2) and osmium tetroxide in *tert*-butyl alcohol (10.48 mg; 0.42 mL of 5% by weight in *tert*-butyl alcohol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 24 h. To the reaction mixture, a slurry (20 mL) of saturated sodium bisulfite was added. After being stirred for an additional 30 min, the reaction mixture was filtered, washed with aqueous acetone solution (20 mL), and salted out with saturated brine, and the product was extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate solution was washed twice with acidic saturated brine (pH 2) and dried over anhydrous sodium sulfate, and the solvent was evaporated to give a residue. The residue was chromatographed on silica gel, with *n*-hexane–ethyl acetate as eluting solvent, to obtain the hydroxylated products. This type of workup was carried out for 12 and 15 to produce 16 and 17, respectively.

Methyl 7-Keto-15,16-dihydroxydehydroabietate (16)—This compound was isolated in 85% yield as plates when crystallized from ether–*n*-hexane: mp, 70–74 °C, $[\alpha]_D$ +12.1 (*c*, 0.51, $CHCl_3$); IR (KBr): ν3450, 1725, 1680, 1605, 1490, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (3H s), 1.35 (3H, s), 1.53 (3H, s, H-17), 1.60–1.93 (5H, complex pattern), 2.17–2.83 (4H, complex pattern), 3.33 (2H, br s, D_2O exchangeable protons), 3.63 (1H, d, J = 6.0 Hz, CH_2OH), 3.72 (3H, s, $COOCH_3$), 3.83 (1H, d, J = 6.0 Hz, CH_2OH), 7.37 (1H, d, J = 8.5 Hz, H-11), 7.80 (1H, dd, J = 8.5 Hz, 2.0, H-12), and 8.13 (1H, d, J = 2.0 Hz, H-14).

7-Acetoxy-15,16-dihydroxydehydroabietinol Acetate (17)—This compound was isolated in 81.4% yield: $[\alpha]_D$ +8.9 (*c*, 0.56, $CHCl_3$); IR ($CHCl_3$): ν 3560, 3450, 1725, 1500, 1380, 1245, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (3H, s), 1.30 (3H, s), 1.50 (3H, s, H-17), 2.05 (3H, s, acetate), 2.13 (3H, s, acetate), 1.17–2.60 (9H, complex pattern), 3.00 (1H, br s, D_2O exchangeable proton), 3.63 (1H, d, J = 9.0 Hz, CH_2OH), 3.70 (1H, br s, exchangeable proton underneath other peak), 3.77 (1H, d, J = 9.0 Hz, CH_2OH), 3.80 (1H, d, J = 12.0 Hz, CH_2OAc), 3.97 (1H, d, J = 12.0 Hz, CH_2OAc), 6.10 (1H, br t, J = 8.0 Hz, H = 7), and 7.40 (3H, br s, aromatic protons); MS: *m/z* (relative abundance) 400 (M^+—H_2O), 327 (87.5), 285 (21.0), and 197 (base peak).

Hydrogenolysis—A solution (100 mL) of absolute ethanol containing compound (10.4 mmol) and palladium on activated-carbon catalyst (2 g, 10% palladium) was subjected to hydrogenolysis under a hydrogen pressure of 50 lb with shaking for 18 h. The resulting reaction mixture was filtered and concentrated under reduced pressure to obtain a residue. The products were separated by chromatography of the residue on silica gel 60, with *n*-hexane–ethyl acetate as eluting solvent. Hydrogenolysis of 16 produced 18, 19, and 5, and hydrogenolysis of 17 produced 20, 21, and 7.

Methyl 16-Hydroxydehydroabietate (18)—This compound was obtained as needles when crystallized from ether–*n*-hexane in a yield of 58%: mp 70–72 °C, $[\alpha]_D$ +54.2 (*c*, 0.37, $CHCl_3$); IR (KBr): ν3380, 1720, 1495, 1255, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (3H, s), 1.30 (3H, s) 1.26 (3H, d, J = 6.0 Hz, H-17, overlapped with singlets at 1.23 and 1.30), 1.20–2.10 (8H, complex pattern, including a signal for one exchangeable proton at δ 1.67), 2.20–2.43 (2H, complex pattern), 2.77–3.01 (3H, m), 3.77 (3H, s, $COOCH_3$), 3.77 (2H, d, J = 6.0 Hz, H-16), 7.00 (1H, br s, H-14), 7.07 (1H, br d, J = 9.0 Hz, H-12), and 7.32 (1H, d, J = 9.0 Hz, H-11); MS: *m/z* (relative abundance) 330 (M^+, 17.1), 315 (22.2), 299 (28.4), 256 (19.7), and 255 (base peak).

Methyl 15,16-Dihydroxydehydroabietate (19)—This compound was crystallized from ether–*n*-hexane to afford plates: mp 101–103.5 °C, $[\alpha]_D$ +33.9 (*c*, 0.54, $CHCl_3$); IR (KBr): ν3420, 1715, 1500, 1385, 1250, 1180, and 1135 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (3H, s), 1.30 (3H, s), 1.55 (3H, s, H-17), 1.40–2.47 (11H, complex pattern), 2.87 (2H, m), 3.72 (3H, s, $COOCH_3$), 3.81 (1H, d, J = 10.5 Hz, CH_2OH), 3.63 (1H, d, J = 10.5 Hz, CH_2OH), 7.20 (1H, br s, aromatic proton), 7.30 (1H, br s, aromatic proton), and 7.37 (1H, br s, aromatic proton); MS: *m/z* (relative abundance); 346 (M^+, 0.1), 315 (16.9), 59 (9.7), and 43 (base peak).

16-Hydroxydehydroabietinol Acetate (20)—This compound was isolated as an oily substance in a yield of 55%: $[\alpha]_D$ +60.9 (*c*, 0.56, $CHCl_3$); IR ($CHCl_3$): ν 3600, 3440, 1730, 1495, 1380, 1250, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (3H, s, H-19), 1.23 (3H, s, H-20), 1.28 (3H, d, J = 7.0 Hz, H-17), 1.35–1.97 (9H, complex pattern), 2.07 (3H, s, acetate), 2.33 (1H, br d, J = 11.0 Hz), 2.90 (3H, m), 3.73 (2H, d, J = 7.0 Hz, CH_2OH), 3.78 (1H, d, J = 10.0 Hz, CH_2OAc), 4.08 (1H, d, J = 10.0 Hz, CH_2OAc), 7.00 (1H, br s, H-14), 7.10 (1H, br s, J = 8.0 Hz, H-12), and 7.33 (1H, d, J = 8.0 Hz, H-11); MS: *m/z* (relative abundance) 344 (M^+, 38.2), 313 (67.2), 269 (base peak), and 131 (51.1).

15,16-Dihydroxydehydroabietinol Acetate (21)—This compound was isolated as a viscous substance: $[\alpha]_D$ +48.2 (*c*, 0.6, $CHCl_3$); IR ($CHCl_3$): ν 3560, 3445, 1720, 1495, 1380, 1250, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (3H, s, H-19), 1.23 (3H, s, H-20), 1.53 (3H, s, H-17), 1.10–1.97 (8H, complex pattern), 2.07 (3H, s, acetate), 2.25 (2H, m, include one D_2O exchangeable proton), 2.87 (3H, m, complex pattern), 3.63 (1H, d, J = 11.0 Hz, CH_2OH), 3.73 (1H, d, J = 11.0 Hz, CH_2OAc), 3.83 (1H, d, J = 11.0 Hz, CH_2OH), and 4.07 (1H, d, J = 11.0 Hz, CH_2OAc), and 7.20–7.57 (3H, complex pattern, aromatic protons); MS: *m/z* (relative abundance) 360 (M^+, 2.6), 330 (90.0), 269 (32.3), 187 (56.4), and 173 (base peak).

Dehydroabietinol Acetate (7)—This compound was isolated as an oily substance: $[\alpha]_D$ +50.5 (*c*, 1.05, $CHCl_3$); IR ($CHCl_3$): ν1720, 1495, 1380, 1250, 1040, and 835 cm^{-1}; ^1H NMR ($CDCl_3$): 0.95 (3H, s, H-19), 1.22 (3H, S, H-20), 1.23 (6H, d, J = 7.0 Hz, H-16, 17), 1.10–1.90 (8H, complex pattern), 2.03 (3H, s), 2.33 (1H, br d, J = 11.0 Hz), 2.87 (3H, m), 3.75 (1H, d, J = 10.0 Hz, CH_2OAc), 4.07 (1H, d, J = 10.0 Hz, CH_2OAc), 7.00 (1H, br s, H-14), 7.10 (1H, br d, J = 9.0 Hz, H-12), and 7.30 (1H, d, J = 9.0 Hz, H-11); MS: *m/z* (relative abundance) 328 (M^+, 47.6), 313 (12.9), 268 (21.9), 254 (base peak), and 211 (30.2).

Oxidation with Chromic Acid—A solution of compound (4.43 mmol) in acetone (30 mL) was added in one portion to a constantly stirred and well-cooled mixture of CrO_3 (1.33 g, 13.3 mmol) and concentrated H_2SO_4 (1.12 mL) in aqueous acetone (9 mL; H_2O:acetone, 2:1). The reaction mixture was stirred for 15 min at 10–15 °C. The reaction mixture was passed through a pad of infusorial earth (Celite) on a sintered glass funnel, and the filter cake was washed with two 10-mL portions of acetone. After removal of organic

solvent under reduced pressure without heating, the aqueous solution was extracted thoroughly with ether. The combined ethereal solutions were dried over anhydrous sodium sulfate and concentrated to yield a residue, which was chromatographed on silica gel, with *n*-hexane–ethyl acetate–0.25% acetic acid acid as the eluting solvent, to obtain pure acid. Compound 18 was oxidized in this way to produce 22 and 4; compound 20, to produce 23 and 24; and compound 28, to produce 29.

Methyl 16-nor-16-Carboxydehydroabietate (22)—This compound (62% yield) was recovered as prisms when crystallized from ether–*n*-hexane: mp 122–124 °C, $[\alpha]_D$ +36.4 (*c*, 0.64, $CHCl_3$); IR (KBr): ν 3400–2540, 1725, 1705, 1495, 1245, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20 (3H, s, H-19), 1.30 (3H, s, H-20), 1.47 (3H, d, J = 7.0 Hz, H-17), 1.10–2.43 (9H, complex pattern), 2.87 (2H, m, H-7), 3.67 (1H, q, J = 7.0 Hz, H-15), 3.70 (3H, s, CO_2CH_3), 7.04 (1H, br s, H-14), 7.13 (1H, br d, J = 9.0 Hz, H-12), 7.28 (1H, d, J = 9.0 Hz, H-11), and 9.00 (1H, br s, D_2O exchangeable proton, COO*H*); ^{13}C NMR ($CDCl_3$): δ 38.1 (t, C-1), 18.7 (t, C-2), 36.8 (t, C-3), 47.7 (s, C-4), 44.9 and 44.8 (d, C-5, C-15), 21.7 (t, C-6), 30.0 (t, C-7), 135.2, 136.7 (s, C-8 C-9), 37.2 (s, C-10), 124.9 and 124.5 (d, C-11, C-12), 148.6 (s, C-13), 128.1 (d, C-14), 180.2 (s, C-16), 18.2 (q, C-17), 178.9 (s, C-18), 16.7 (q, C-19), 25.2 (q, C-20), and 52.0 (q, OCH_3); MS: *m/z* (relative abundance) 344 (M^+, 14.5), 329 (17.5), and 269 (base peak); high-resolution mass spectrum (HRMS): found, 344.1930; calc., 344.1937.

Methyl 13-Acetyldeisopropyldehydroabietate (4)—Overoxidation product 4 was in the form of prisms when crystallized from methanol: mp 92–94 °C, $[\alpha]_D$ +66.1 (*c*, 0.41, $CHCl_3$); IR (KBr): ν 1735, 1680, 1605, 1565, 1280, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (3H, s), 1.30 (3H, s), 1.40–2.40 (9H, complex pattern), 2.57 (3H, s, Ar-$COCH_3$), 2.93 (2H, m, H-7), 3.70 (3H, s, CO_2CH_3), 7.40 (1H, d, J = 9.0 Hz, H-11), 7.73 (1H, br s, H-14), and 7.78 (1H, br d, J = 9.0 Hz, H-12); MS: *m/z* (relative abundance) 314 (M^+, 24.7), 239 (98.9), and 43 (base peak).

16-nor-16-Carboxydehydroabietinol Acetate (23)—This compound was isolated as a viscous substance in a yield of 52%: $[\alpha]_D$ +39.9 (*c*, 0.68, $CHCl_3$); IR (KBr): ν 3600–2500, 1735, 1705, 1495, 1380, 1240, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (3H, s, H-19), 1.20 (3H, s, H-20), 1.47 (3H, d, J = 7.0 Hz, H-16), 1.20–1.90 (8H, complex pattern), 2.03 (3H, s, acetate), 2.33 (1H, br d, H-5), 2.93 (2H, m, H-7), 3.70 (1H, q, J = 7.0 Hz, H-15), 3.73 (1H, d, J = 10.0 Hz, CH_2OAc), 4.07 (1H, d, J = 10.0 Hz, CH_2OHc), 7.10 (1H, br s, H-14), 7.17 (1H, br d, J = 9.0 Hz, H-12), 7.37 (1H, d, J = 9.0 Hz, H-11), and 10.40 (1H, br s, exchangeable pattern, COO*H*); ^{13}C NMR ($CDCl_3$): δ 17.5 (q), 18.0 (q), 18.5 (t), 18.9 (t), 21.0 (q), 25.3 (q), 30.1 (t), 35.5 (t), 36.8 (s), 37.6 (s), 38.2 (t), 44.0 (d), 44.9 (d), 72.4 (t), 124.8 (d), 124.9 (125.0, d, twin), 128.08, (128.15, d, twin), 128.2 (s), 135.4 (s), 136.6 (s), 148.9 (s), 171.5 (s), and 180.7 (s); MS: *m/z* (relative abundance) 358 (M^+, 5.8), 284 (20.8), and 283 (base peak).

13-Acetyldeisopropyldehydroabietinol Acetate (24)—This overoxidation product was in the form of prisms when crystallized from ether–*n*-hexane: mp 65–67 °C, $[\alpha]_D$ +46.3 (*c*, 0.46, $CHCl_3$); IR (KBr): ν 1735, 1680, 1600, 1565, 1240, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (3H, s, H-19), 1.23 (3H, s, H-20), 1.33–1.97 (8H, complex pattern), 2.03 (3H, s, acetate), 2.35 (1H, br d, J = 12.0 Hz), 2.57 (3H, s, Ar$COCH_3$-13), 2.97 (2H, m), 3.77 (1H, d, J = 10.0 Hz, CH_2OAc), 4.07 (1H, d, J = 10.0 Hz, CH_2OAc), 7.43 (1H, d, J = 9.0 Hz, H-11), 7.77 (1H, br s, H-14), and 7.83 (1H, br d, J = 9.0 Hz, H-12); MS: *m/z* (relative abundance) 328 (M^+, 28.8), 268 (85.0), and 253 (base peak).

Methyl 7-Keto-16-nor-16-carboxydehydroabietate (29)—This compound (49% yield) was in the form of plates when crystallized from methanol–water: mp 140–142 °C, $[\alpha]_D$ +9.7 (*c*, 0.38, $CHCl_3$); IR (KBr): ν 3550–2500, 1725, 1705, 1680, 1605, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (3H, s), 1.37 (3H, s), 1.53 (3H, d, J = 7.0 Hz, H-17), 1.80 (4H, br s), 2.23–2.83 (5H, complex pattern), 3.70 (3H, s, OCH_3-19), 3.83 (1H, q, J = 7.0 Hz, H-15), 7.44 (1H, d, J = 8.0 Hz, H-11), 7.63 (1H, dd, J = 8.0 Hz, 2.0, H-12), 8.07 (1H, d, J = 2.0 Hz, H-14), and 8.17 (1H, br s, exchangeable proton); ^{13}C NMR ($CDCl_3$): δ 16.4 (q), 17.9 (q), 18.1 (t), 23.6 (q), 36.5 (t), 37.0 (t), 37.4 (s), 37.7 (t), 43.6 (d), 44.8 (d), 46.7 (s), 52.3 (q), 124.1 (d), 126.5 (126.6, d, twin), 130.9 (s), 133.4 (133.5, d, twin), 138.1 (s), 154.4 (s), 177.8 (s), 179.80 (179.84, s, twin), and 198.25 (198.28, s, twin); MS: *m/z* (relative abundance) 358 (M^+, 24.1), 299 (16.3), and 283 (base peak); HRMS: found, 358.1794; calc., 358.1780.

Dehydroabietinol (25)—A mixture of lithium aluminum hydride (0.62 g, 16.24 mmol) and tetrahydrofuran (THF, 100 mL) was stirred under reflux for a few minutes, and 2 (6.8 g, 21.66 mmol) in THF (30 mL) was added slowly through a dropping funnel with vigorous stirring. The whole mixture was stirred at the reflux temperature for 1.5 h. Ethyl acetate (10 mL) was added, and the reaction mixture was stirred and refluxed for another 5 min. After the reaction mixture was cooled to room temperature, 50 mL of cooled sulfuric acid solution (4 N) was added slowly. The reaction mixture was extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate solutions were washed with ammonium hydroxide solution (10%, 100 mL), dried over anhydrous sodium sulfate, and evaporated to give a residue (6.54 g), which was purified by chromatography on silica gel (120 g), with ethyl acetate:*n*-hexane (1:4) as the eluting solvent, to obtain the pure alcohol 25 (6.2 g, 97% yield) as an oily substance: $[\alpha]_D$ +51.9 (*c*, 0.45, $CHCl_3$); IR ($CHCl_3$): ν3620, 3460, 1495, 1045, and 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, s, H-19), 1.23 (3H, s, H-20), 1.23 (6H, d, J = 6.0 Hz, H-16 and H-17), 1.03–1.87 (9H, complex pattern including one exchangeable proton), 2.27 (1H, m), 2.83 (3H, m), 3.23 (1H, d, J = 11.0 Hz, H-18), 3.53 (1H, d, J = 11.0 Hz, H-18), 7.00 (1H, br s, H-14), 7.08 (1H, br d, J = 8.0 Hz, H-12), and 7.30 (1H, d, J = 8.0 Hz, H-11).

7-Hydroxy-15(16)-dehydrodehydroabietinol (26)—Lithium aluminum hydride (0.7 g, 18.5 mmol) reduction of 12 (4.02 g, 12.3 mmol), as described earlier, furnished 26 in a yield of 79% as a powder from ether–*n*-hexane: mp 143–145.5 °C, $[\alpha]_D$ +94.7 (*c*, 0.47, $CHCl_3$); IR (KBr): ν 3260, 1625, 1495, 1200, 1075, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (3H, s, H-19), 1.30 (3H, s, H-20), 1.10–2.40 (11H, complex pattern containing two exchangeable protons), 2.17 (3H, s, H-17), 3.17 (1H, d, J = 10.0 Hz, CH_2OH), 3.50 (1H, d, J = 10.0 Hz, CH_2OH), 4.87 (1H, t, J = 8.0 Hz, H-7), 5.10 (1H, br s, H-16), 5.43 (1H, br s, H-16), 7.27 (1H, d, J = 8.0 Hz, H-11), 7.43 (1H, dd, J = 8.0 Hz, 2.0, H-12), and 7.73 (1H, br s); MS: *m/z* (relative abundance) 300 (M^+, 46.9), 249 (63.5), and 160 (base peak).

Acetylation—To a mixture of 25 (5.9866 g, 20.93 mmol), acetic anhydride (30 mL), and pyridine (30 mL) at room temperature was added, in one portion, 4-dimethylaminopyridine (73.2 mg, 0.6 mmol). The mixture was stirred under nitrogen atmosphere for 4 h, poured into ice water (150 mL), and extracted with chloroform (3 × 150 mL). The combined chloroform solutions were washed with HCl solution (10%) until the water layer remained acidic. The chloroform solution was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford 6.211 g of acetate 7 in a yield of 90.5%. Compound 26 was also acetylated; 2.88 g of 26 (9.6 mmol), 20 mL of acetic acid, 20 mL of pyridine, and 73.2 mg of 4-dimethylaminopyridine (0.6 mmol) were used, and the yield of the product 15 was 93%.

7-Acetoxy-15(16)-dehydrodehydroabietinol Acetate (15)—This compound was isolated as an oily substance: $[\alpha]_D$ +10.5 (*c*, 0.49, $CHCl_3$); IR ($CHCl_3$): ν1725, 1380, 1245, 1050, and 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (3H, s, H-19), 1.33 (3H, s, H-20), 1.23–2.50 (9H, complex pattern), 2.07 (6H, s, acetate), 2.17 (3H, s, H-17), 3.80 (1H, d, J = 10.0 Hz, CH_2OAc), 4.00 (1H, d, J = 10.0 Hz, CH_2OAc), 5.13 (1H, br s, H-16), 5.40 (1H, br s, H-16), 6.13 (1H, br t, J = 8.0 Hz, H-7), 7.30–7.60 (3H, complex pattern, aromatic protons); MS: *m/z* (relative abundance) 384 (M^+, 5.9), 342 (98.7), and 43 (base peak).

Dehydroabietinal (27)—To a suspension of pyridinium chlorochromate (9.6 g, 44.7 mmol) in methylene chloride (100 mL), 25 (8.52 g, 29.8 mmol) in methylene chloride (30 mL) was added in one portion. The mixture was stirred at room temperature. As the reaction progressed, the reaction mixture became dark. After 2 h, 300 mL of anhydrous ether was added to the reaction mixture, and the solvent was decanted and passed through a Celite bed on a Buchner funnel. The black solid remaining in the reaction flask was washed with ether (2 × 150 mL). The combined ether solutions were evaporated to leave a dark residue (9.7 g), which was chromatographed on a silica gel column (100 g) and eluted with *n*-hexane:chloroform (1:5) to obtain the pure aldehyde 27 (6.87 g, 81%). Compound 27 was crystallized from hot methanol to afford needles: mp 86–88 °C, $[\alpha]_D$ +55.8 (*c*, 0.95, $CHCl_3$); IR (KBr): ν2830, 2710, 1725, 1500, 1380, 1365, and 830 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (3H, s), 1.27 (3H, s) 1.20 (6H, d, J = 7.0 Hz, H-16, 17), 1.33–2.03 (8H, complex pattern), 2.40 (1H, m), 2.87 (3H, m), 7.00 (1H, br s, H-14), 7.08 (1H, br d, J = 8.0 Hz, H-12) 7.30 (1H, d, J = 8.0 Hz, H-11), and 9.40 (1H, s, CHO); MS: *m/z* (relative abundance) 284 (M^+, 90.7) and 269 (base peak).

Dehydroabietane (8)—A mixture of 27 (6.67 g, 23.3 mmol), hydrazine hydrate (2.24 g), and diethylene glycol (100 mL) was refluxed at 110 °C with stirring for 1 h. A few drops of hydrazine were added during the time the temperature was being raised to ~100 °C, which caused the appearance of some solid. The reaction mixture was cooled to room temperature, and potassium hydroxide (5.22 g) was added. The whole mixture was heated to 210 °C and then refluxed for

4 h. After being cooled, water (200 mL) was added to the reaction mixture, and the mixture was extracted with ether (3 × 200 mL). The combined ethereal solutions were washed with dilute HCl (5%, 200 mL), followed with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated to obtain the crude product (6.04 g), which was chromatographed on silica gel (120 g) and eluted with 5% ethyl acetate in *n*-hexane to afford **8** in 79% yield as prisms when crystallized from ether–*n*-hexane: mp 44–46 °C, $[\alpha]_D$ +53.4 (*c*, 1.79, $CHCl_3$); IR ($CHCl_3$): υ 1610, 1495, 1460, 1390, 1380, 1365, 890, and 830 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (6H, s, H-18, 19), 1.20 (6H, s, H-16, 17), 1.30 (3H, s, H-20), 1.13–2.00 (8H, complex pattern), 2.33 (1H, br d, J = 11.0 Hz, H-5), 2.73–3.07 (3H, complex pattern), 7.03 (1H, br s, H-14), 7.10 (1H, br d, J = 8.0 Hz, H-12), and 7.33 (1H, d, J = 8.0 Hz, H-11); MS: *m/z* (relative abundance) 270 (M^+, 29.1) and 255 (base peak).

Methyl 7,16-Dihydroxydehydroabietate (28)—Compound **12** (1 mmol) was dissolved in THF (20 mL) in a two-necked flask, and the solution was cooled in an ice bath. Borane–THF complex (1.5 mL of a 1 M solution) was added via a syringe. After being stirred under a nitrogen atmosphere for 2.5 h, the reaction mixture was cooled and added to a solution of ethanol (5 mL), hydrogen peroxide (30%, 5 mL), and aqueous NaOH (6 N, 4 mL). The resultant reaction mixture was brought to 55 °C in a water bath and continuously stirred for 1 h. After removal of the solvent, the concentrated solution was extracted with ether, and the combined ethereal layers were dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel to yield **28** (72% yield) as a viscous substance: $[\alpha]_D$ +50.7 (*c*, 0.73, $CHCl_3$); IR ($CHCl_3$): υ 3590, 3420, 1705, 1495, 1255, 1130, 1040, and 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (3H, d, J = 7.0 Hz, H-17), 1.30 (3H, s), 1.33 (3H, s), 1.47–2.00 (7H, complex pattern), 2.28 (2H, m), 2.90 (3H, m, containing exchangeable protons), 3.63 (2H, m, CH_2OH-16), 3.70 (3H, s, OCH_3), 4.87 (1H, t, J = 9.0 Hz, H-7), 7.13 (1H, d, J = 8.0 Hz, H-11) 7.27 (1H, br d, J = 8.0 Hz, H-12), and 7.47 (1H, br s, H-14); MS: *m/z* (relative abundance) 346 (M^+, 7.3), 315 (42.5), 253 (56.3), and 31 (base peak).

Hydrolysis—To the compound (1.66 mmol) was added 3 N methanolic NaOH (20 mL). The mixture was refluxed in an oil bath at 90 °C for 3 h, diluted with water (50 mL), acidified with concentrated HCl to pH 2, and extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate solutions were dried over anhydrous sodium sulfate, filtered, and evaporated to obtain a residue, which was purified by chromatography on silica gel 60 and eluted with *n*-hexane:ethyl acetate (7:3) and 0.25% glacial acetic acid.

Hydrolysis was carried out on **22** to produce **30** (71% yield), on **23** to produce **31** (79% yield), and on **29** to produce **32** (81% yield).

16-nor-16-Carboxydehydroabietic Acid (30)—This compound was in the form of prisms when crystallized from methanol–water: mp 218–221 °C, $[\alpha]_D$ +47.3 (*c*, 0.49, $CHCl_3$); IR (KBr): υ 3400–2450, 1705, 1695, 1495, 1280, 1085, and 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (3H, s), 1.30 (3H, s), 1.50 (3H, d, J = 7.0 Hz, H-17), 1.07–2.03 (7H, complex pattern), 2.26 (2H, m), 2.90 (2H, m, H-7), 3.70 (1H, q, J = 7.0 Hz, H-15), 7.07 (1H, br s, H-14), 7.17 (1H, br d, J = 7.5 Hz, H-12), 7.30 (1H, d, J = 7.5 Hz, H-11), and 10.10 (2H, br s, exchangeable protons); ^{13}C NMR ($CDCl_3$): δ 38.0 (t, C-1), 18.6 (t, C-2), 36.8 (t, C-3), 47.5 (s, C-4), 45.0, 44.6 (d, C-5, C-15), 21.7 (t, C-6), 30.0 (t, C-7), 135.5, 136.7 (s, C-8, C-9), 38.0 (s, C-10), 125.1, 124.5 (d, C-11, C-12), 148.4 (s, C-13), 128.2 (d, C-14), 180.6 (s, C-16), 18.2 (q, C-17), 184.8 (s, C-18), 16.4 (q, C-19), and 25.2 (q, C-20); MS: *m/z* (relative abundance) 330 (M^+, 20.1), 315 (39.8), and 269 (base peak); HRMS: found, 330.1826; calc., 330.1831.

16-nor-16-Carboxydehydroabietinol (31)—This compound was isolated as a waxy material with an unclear melting point: $[\alpha]_D$ +32 (*c*, 0.45, $CHCl_3$); IR (KBr): υ 3560–2500, 3420, 1705, 1495, 1380, 1235, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (3H, s, H-19), 1.20 (3H, s, H-20), 1.43 (3H, d, J = 7.0 Hz, H-17), 1.00–1.90 (8H, complex pattern), 2.23 (1H, br d, J = 10.0 Hz), 2.87 (2H, br s), 3.17 (1H, d, J = 10.0 Hz, H-18), 3.43 (1H, d, J = 10.0 Hz, H-18), 3.60 (1H, q, J = 7.0 Hz, H-15), 6.53 (2H, br s, exchangeable protons), 6.95 (1H, br s, H-14), 7.00 (1H, br d, J = 7.5 Hz, H = 12), and 7.20 (1H, d, J = 7.5 Hz, H-11); ^{13}C NMR ($CDCl_3$): δ 17.6 (q), 18.2 (18.3, q, twin), 18.8 (18.9, t, twin), 25.4 (q), 30.1 (t), 35.1 (t), 37.6 (s), 37.9 (t), 38.5 (t), 43.7 (d), 45 (d), 71.8 (t), 124.6 (d), 124.9 (d), 127.9 (128.0, d, twin), 135.3 (s), 136.7 (136.6, s, twin), 148.9 (s), and 179.7 (s); MS: *m/z* (relative abundance) 316 (M^+, 21.2), 301 (66.2), and 283 (base peak); HRMS: found, 316.2033; calc., 316.2038.

7-Keto-16-nor-16-carboxydehydroabietic Acid (32)—This compound was isolated as a waxy substance with an unclear melting point: $[\alpha]_D$ +19.7 (*c*, 0.66, $CHCl_3$); IR (KBr): υ 3540–2500, 1700, 1605, 1490, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (3H, s), 1.37 (3H, s), 1.53 (3H, d, J = 8.0 Hz, H-17), 1.20–1.93 (6H, br s), 2.23–2.87 (3H, complex pattern), 3.83 (1H, q, J = 8.0 Hz, H-15), 7.47 (1H, d, J = 8.0 Hz, H-11), 7.67 (1H, br d, J = 8.0 Hz, H-12), 8.10 (1H, br s, H-14), 10.37 (2H, br s, exchangeable protons, COO*H*); ^{13}C NMR ($CDCl_3$): δ 16.1 (q), 17.9 (q), 18.1 (t), 23.6 (q), 36.5 (t), 36.9 (t), 37.3 (s), 37.6 (t), 43.3 (d), 44.8 (d), 46.4 (s), 124.1 (d), 126.5 (126.7, d, twin), 130.9 (s), 133.5 (133.7, d, twin), 138.1 (s), 154.4 (s), 180.20 (180.23, s, twin), 183.55 (183.57, s, twin), and 198.39 (198.42, s, twin); MS: *m/z* (relative abundance) 344 (M^+, 30.7), 300 (2.8), and 283 (base peak); HRMS: found, 344.1644; calc., 344.1624.

Reduction with Sodium Borohydride—Solutions of compounds (0.79 mmol) in 20 mL of methanol were treated with excess sodium borohydride. The mixture was stirred at room temperature. After 2 h, the reaction solution was carefully neutralized with 10% HCl and then evaporated to remove methanol. The concentrated solution was further acidified to pH 2 with acid and then extracted with ether (3 × 60 mL). The combined ethereal solutions were dried over anhydrous sodium sulfate, filtered, and evaporated to give the crude product, which was purified by chromatography on silica gel 60 and eluted with *n*-hexane:ethyl acetate (7:3) and 0.25% glacial acetic acid.

Very large excesses of sodium borohydride, 23.7 and 47.4 mmol, were used to reduce **29** and **32**, respectively, to produce **33** in 74% yield and **34** in 66% yield, respectively.

Methyl 7-Hydroxy-16-nor-16-carboxyldehydroabietate (33)—This compound was isolated as a waxy substance with an unclear melting point: $[\alpha]_D$ +38.7 (*c*, 0.31, $CHCl_3$); IR (KBr): υ 3560–2500, 1725, 1705, 1495, 1250, 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (3H, s), 1.30 (3H, s), 1.47 (3H, d, J = 7.0 Hz, H-17), 1.13–2.47 (9H, complex pattern), 3.70 (3H, s, CO_2CH_3), 3.73 (1H, q, J = 7.0 Hz, partially coincident with 3.70, H-15), 4.90 (1H, t, J = 9.0 Hz, H-7), 6.98 (2H, br s, exchangeable protons, OH and COOH), 7.30 (2H, br s, aromatic protons), and 7.60 (1H, br s, aromatic protons); ^{13}C NMR ($CDCl_3$): δ 16.6 (q), 18.2 (18.3, q, twin), 18.5 (t), 25.5 (q), 32.4 (t), 36.6 (t), 37.8 (s), 38.0 (t), 43.5 (d), 45.0 (d), 47.4 (s), 52.2 (q), 70.40 (70.44, d, twin), 124.5 (d), 126.7 (d), 137.6 (s), 137.9 (s), 148.2 (s), 178.7 (s), and 179.2 (s); MS: *m/z* (relative abundance) 360 (M^+, 18.5), 285 (16.4), and 267 (base peak); HRMS: found, 360.1932; calc., 360.1937.

7-Hydroxy-16-nor-16-carboxydehydroabietic Acid (34)—This compound was isolated as a waxy substance: mp 217–220 °C, $[\alpha]_D$ +51.1 (*c*, 0.36, dioxane); IR (KBr): υ 3540–2500, 3410, 1705, 1495, 1245, and 1075 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 (6H, br s, H-19, 20), 1.45 (3H, br d, J = 6.0 Hz, H-17), 3.75 (1H, q, J = 7.0 Hz, H-15), 4.90 (1H, t, J = 7.0 Hz, H-7), 7.28 (2H, br s, aromatic protons), 7.60 (1H, br s, aromatic proton), 8.48 (2H, br s, exchangeable protons, COOH); ^{13}C NMR (CD_3OD): δ 18.8 (q), 20.5 (q), 21.2 (t), 27.5 (q), 35.0 (t), 39.5 (t), 40.4 (s), 41.0 (t), 46.6 (d), 48.0 (d), 72.77 (72.80, d, twin), 127.0 (s), 129.14 (129.17, d, twin), 129.3 (d), 141.1 (s), 141.4 (s), 150.9 (s), 179.97 (180.04, s, twin), and 183.7 (s); MS: *m/z* (relative abundance) 346 (M^+, 9.4), 328 (7.9), and 267 (base peak); HRMS: found, 346.1756; calc., 346.1780.

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