Synthesis of 3β-Hydroxytaxodione and Coleons S and T

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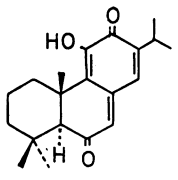
Hinokiol diacetate was converted into 3β-acetoxyabieta-8,11,13-triene-6β,12-diol *via* 3β,12-diacetoxyabieta-8,11,13-trien-7-one and 3β,12-diacetoxyabieta-6,8,11,13-tetraene. Oxidation of the 6β,12-diol with benzoyl peroxide produced 3β-acetoxy-12-benzoyloxyabieta-8,11,13-triene-6β,11-diol, which was converted into 3β,11,12-triacetoxyabieta-8,11,13-trien-6-one by lithium aluminium hydride reduction, acetylation, and Jones oxidation. Acidic hydrolysis of the triacetoxy ketone, followed by column chromatography on silica gel, afforded 3β-hydroxytaxodione. Oxidation of the 6β,11-diol with *m*-chloroperbenzoic acid afforded 3β-acetoxy-12-benzoyloxy-6β-hydroxyabieta-8,12-diene-11,14-dione. This was further converted into 3β,11,14-triacetoxy-12-benzoyloxyabieta-8,11,13-triene-6,7-dione by a series of reactions: Jones oxidation, reduction with zinc powder and dilute hydrochloric acid, acetylation, and Jones oxidation. Alkaline hydrolysis of the 6,7-dioxo compound afforded coleon T, which was isomerized to coleon S by refluxing with concentrated hydrochloric acid in methanol.

In the previous papers,[1-3] we reported the synthesis of taxodione (**1**), a tumor-inhibitory diterpene quinonemethide isolated from *Taxodium distichum* Rich by Kupchan *et al.*[4] We have now synthesized the analogous quinonemethide compound in order to compare their tumor-inhibiting activity with that of **1**.

Recently, coleon S and coleon T, highly-oxygenated tricyclic diterpenes possessing an abietane skeleton, were isolated from leaf-glands of *Plectranthus caninus* Roth (Labiatae) by Eugster *et al.*[5] On the basis of chemical and spectroscopic studies, they deduced the structures of these coleons, S and T, to be 3β,6,11,12,14-pentahydroxyabieta-5,8,11,13-tetraen-7-one (**2**) and 3β,11,12,-14-tetrahydroxyabieta-8,11,13-triene-6,7-dione (**3**), respectively. As a part of our synthetic studies on the naturally-occurring terpenes, we have attempted the syntheses of these highly-oxygenated tricyclic diterpenes. This paper will describe the syntheses of 3β-hydroxytaxodione (**4**) [3β,11-dihydroxyabieta-7,9(11),13-triene-6,12-dione] and coleons S (**2**) and T (**3**), starting from the optically active hinokiol diacetate (**5**), which has been synthesized[6] from (+)-dehydroabietic acid.

Oxidation of **5** with Jones reagent afforded 3β,12-diacetoxyabieta-8,11,13-trien-7-one (**6**), together with a small amount of 12-acetoxyabieta-8,11,13-triene-3,7-dione (**7**). The diacetoxy ketone **6** was reduced with sodium borohydride in methanol and the resulting mixture of epimeric 7-hydroxy compounds (**8**) was immediately subjected to dehydration with dilute hydrochloric acid in refluxing methanol. Under these conditions, the acetoxyl groups were partially hydrolyzed. Therefore, the crude product was acetylated with acetic anhydride in pyridine and then purified by column chromatography on silica gel to give 3β,12-diacetoxyabieta-6,8,11,13-tetraene (**9**). The 3,7-dioxo compound **7** was also transformed to **9** by a series of reactions: reduction with lithium aluminium hydride in ether, dehydration with dilute hydrochloric acid in refluxing methanol, and acetylation with acetic anhydride in pyridine. The tetraene **9** was subjected to epoxidation at room temperature with *m*-chloroperbenzoic acid in dichloromethane. The resulting epoxide (**10**), without purification, was refluxed with dilute hydrochloric acid in methanol and then acetylated with acetic anhydride in pyridine. Purification of the crude product by column chromatography on silica gel yielded 3β,12-diacetoxyabieta-8,11,13-trien-6-one (**11**) as a major product and 3β,6α,12-triacetoxyabieta-8,11,13-trien-7-one (**12**) as a minor one. The α-configuration of the acetoxyl group at C-6 in **12** was supported by its ^{1}H NMR spectrum, which showed a doublet due to the C-6 proton at δ 5.82 with a coupling constant of 13 Hz, suggesting the presence of a β hydrogen. The minor ketone **12** was easily converted to the major ketone **11** by reduction with lithium aluminium hydride in ether, followed by dehydration with dilute hydrochloric acid in refluxing methanol and acetylation with acetic anhydride. Reduction of **11** with lithium aluminium hydride in refluxing tetrahydrofuran produced abieta-8,11,13-triene-3β,6β,12-triol (**13**), which was partially acetylated at room temperature with acetic anhydride in pyridine to give 3β,12-diacetoxyabieta-8,11,13-trien-6β-ol (**14**) and a small amount of 12-acetoxyabieta-8,11,13-triene-3β,6β-diol (**15**). Similar acetylation of **15** gave **14**. The diacetoxy alcohol **14** was partially hydrolyzed with sodium hydrogencarbonate in refluxing aqueous methanol to yield 3β-acetoxyabieta-



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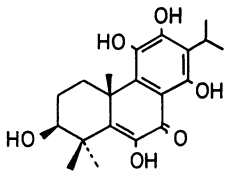

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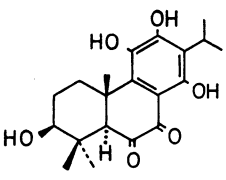

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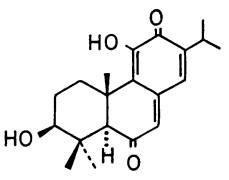

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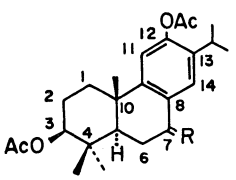
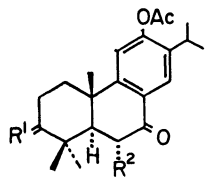
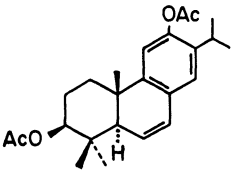
8,11,13-triene-6β,12-diol (**16**). Oxidation of **16** with benzoyl peroxide in chloroform at room temperature afforded a phenol (**17**), along with three dienones (**18**, **19**, and **20**) as minor products. The structures of these products (**17**—**20**) were assigned on the basis of the following evidence. The phenol **17** responded positively to the Gibbs test,[7] which suggested the presence of an aromatic proton para to a phenolic hydroxyl group. Oxidation of **17** with *m*-chloroperbenzoic acid in dichloromethane at room temperature afforded a benzoyloxy-*p*-benzoquinone (**21**). The ^{1}H NMR spectrum of **17** showed a singlet signal at δ 6.60 due to the C-14 proton, while for that of **21** no corresponding signal was observed. Thus, the structure of **17** was assigned to be 3β-acetoxy-12-benzoyloxyabieta-8,11,13-triene-6β,11-diol. The ^{1}H NMR spectrum of **18** showed a signal at δ 1.06 due to the equivalent methyls of the isopropyl group. On the other hand, the spectra of **19** and **20** showed two nonequivalent secondary methyl group signals, at δ 0.96 and 1.15 and at δ 0.88 and 1.13, respectively. From these spectral data and those of the IR spectra (see Experimental section), it is obvious that **18** is a para-substituted dienone,[2,8] while **19** and **20** are ortho-substituted dienones.[2,8] Hydrolysis of **18** with potassium carbonate in refluxing aqueous methanol afforded the corresponding trihydroxy ketone (**22**). In the ^{1}H NMR spectrum of **22**, the downfield shift of the signal (δ 1.64) due to the methyl group at C-10 relative to the corresponding signal (δ 1.43) for **18** suggested a 1,3-diaxial-*cis*-relationship between the methyl group and the hydroxyl group at C-8. Thus, the structure of **18** was assigned to be 3β-acetoxy-8β-benzoyloxy-6β-hydroxyabieta-9(11),13-dien-12-one. In order to determine the stereochemistry at C-13 in the ortho-dienones **19** and **20**, the following thermal rearrangements were carried out. A solution of **19** in toluene was refluxed for 4 h to give **17** (6.7%) together with the starting substance (**19**: 93.0%). However, a similar treatment of **20** gave **17** (63.8%) and **18** (26.0%) along with some recovered **20** (10.0%). From the rearrangement of **20** into **18**, the stereochemistry of the benzoyloxyl group in **20** was assigned to be the β-configuration, and therefore, that in **19** to be the α-configuration. Conversion of **17** into 3β-hydroxytaxodione was successfully carried out as follows. In order to change the benzoyloxyl group in **17** into an acetoxyl group which should be easily hydrolyzed under acidic conditions, **17** was reduced with lithium aluminium hydride in ether. The resulting tetrahydroxy compound (**23**), for the protection of the hydroxyl groups at C-3, C-11, and C-12, was partially acetylated with acetic anhydride in pyridine at room temperature to give 3β,11,12-triacetoxyabieta-8,11,13-trien-6β-ol (**24**). The triacetoxy alcohol **24** was oxidized with Jones reagent at 0 °C to afford 3β,11,12-triacetoxyabieta-8,11,13-trien-6-one (**25**), which was easily converted into 3β,11,12-trihydroxyabieta-8,11,13-trien-6-one (**26**) by refluxing with concentrated hydrochloric acid in ethanol under an atmosphere of nitrogen. Column chromatography of **26** on silica gel afforded a quinonemethide compound; its structure was assigned to be that of the desired 3β-hydroxytaxodione by the IR and ^{1}H NMR spectra.



5 R = H_2
6 R = O
8 R = <H, OH



7 R^1 = O, R^2 = H
12 R^1 = α-H, β-OAc; R^2 = OAc



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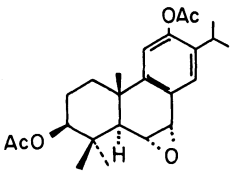

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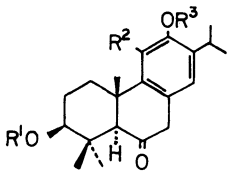
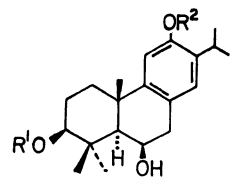
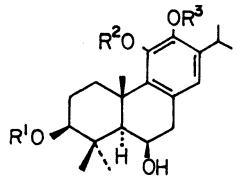


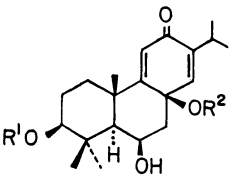
11 R^1 = R^3 = Ac, R^2 = H
25 R^1 = R^3 = Ac, R^2 = OAc
26 R^1 = R^3 = H, R^2 = OH



13 R^1 = R^2 = H
14 R^1 = R^2 = Ac
15 R^1 = H, R^2 = Ac
16 R^1 = Ac, R^2 = H

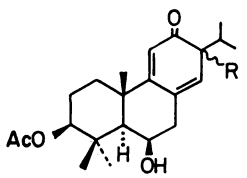


17 R^1 = Ac, R^2 = H, R^3 = Bz
23 R^1 = R^2 = R^3 = H
24 R^1 = R^2 = R^3 = Ac

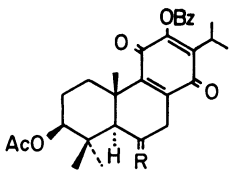


18 R^1 = Ac, R^2 = Bz
22 R^1 = R^2 = H

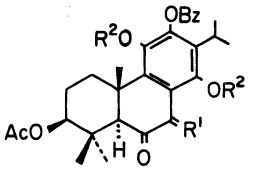
Our next effort was directed toward the syntheses of coleons S and T. Oxidation of **21** with Jones reagent at 0 °C afforded 3β-acetoxy-12-benzoyloxyabieta-8,12-diene-6,11,14-trione (**27**) which, without purification, was used in the next reaction. For the protection of the unstable C ring, the trione **27** was reduced with a mixture of zinc powder and dilute hydrochloric acid in refluxing benzene. The resulting crude phenol (**28**) was acetylated at 85—90 °C with acetic anhydride in pyridine to give 3β,11,14-triacetoxy-12-benzoyloxyabieta-8,11,13-trien-6-one (**29**). Subsequently, oxidation of the C-7 position in **29** was carried out with Jones reagent at room temperature. The crude 6,7-dioxo compound (**30**) was immediately hydrolyzed with aqueous sodium carbonate in refluxing methanol under an atmosphere of nitrogen to give coleon T (**3**), which was further converted into coleon S pentaacetate (**31**) by treatment with acetic anhydride in pyridine. The



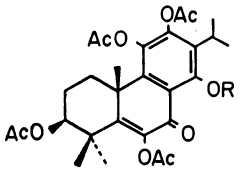
19 R = α-OBz
20 R = β-OBz



21 R = α-H, β-OH
27 R = O



28 R' = H$_2$, R^2 = H
29 R' = H$_2$, R^2 = Ac
30 R' = O, R^2 = Ac



31 R = Ac
32 R = H

synthetic coleon T was finally isomerized with concentrated hydrochloric acid in refluxing methanol to give coleon S (**2**) which was also converted into the pentaacetate (**31**).

Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the ^{1}H NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, bd: broad doublet, dd: double doublet, bt: broad triplet, m: multiplet. Column chromatography was performed using Merck silica gel (0.063 mm).

Oxidation of Hinokiol Diacetate (5). Jones reagent (2.5 M (1 M = 1 mol dm^{-3}): 13.6 ml) was added dropwise to a stirred solution of hinokiol diacetate[6] (**5**) (4.289 g) in acetone (80 ml) with cooling in an ice–water bath for 15 min. The mixture was stirred at this temperature for 15 min and at room temperature for 6 h. The mixture was then 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 (150 g), using ether–benzene (3 : 97) as the eluent, to give the recovered **5** (1.051 g: 24.5%). Subsequent elution with ether–benzene (5 : 95) afforded 3β,12-diacetoxyabieta-8,11,13-trien-7-one (**6**) (2.284 g: 51.4%), which was recrystallized from methanol; mp 178—179.5 °C; $[\alpha]_D$ +52.5°; IR: 1755, 1725, 1675, 1610 cm^{-1}; ^{1}H NMR 0.95 and 1.03 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.23 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.29 (3H, s, $C_{10}-CH_3$), 2.01 and 2.29 (each 3H and s, 2-OCO$C\underline{H}_3$), 2.63 (2H, d, J=8 Hz, $-CH_2CO-$), 2.99 (1H, m, $-C\underline{H}(CH_3)_2$), 4.51 (1H, bt, $W_{1/2}$=16 Hz, C_3–H), 6.90 (1H, s, C_{11}–H), 7.90 (1H, s, C_{14}–H). Found: C, 71.87; H, 8.25%. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05%.

Further elution with ether–benzene (1 : 9) afforded 12-acetoxyabieta-8,11,13-triene-3,7-dione (**7**) (0.213 g: 5.4%) as an oil; $[\alpha]_D$ +12.4°; IR: 1755, 1705, 1675, 1610 cm^{-1}; ^{1}H NMR: 1.12, 1.20, and 1.47 (each 3H and s, $-\dot{C}(CH_3)_2$ and $C_{10}-CH_3$), 1.25 (6H, d, J=6 Hz, $-CH(C\underline{H}_3)_2$), 2.31 (3H, s, $-OCOCH_3$), 6.95 (1H, s, C_{11}–H), 7.91 (1H, s, C_{14}–H). Found: C, 74.03; H, 8.10%. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92%.

3β,12-Diacetoxyabieta-6,8,11,13-tetraene (9). *From 6*: Sodium borohydride (125 mg) was added at *ca.* 15 °C to a stirred solution of **6** (871 mg) in methanol (35 ml). The mixture was stirred at room temperature for 1.5 h, acidified with dilute hydrochloric acid (10%: 2.0 ml), and refluxed for 1 h. The methanol was evaporated *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated. The residual oil was acetylated at 78—80 °C with acetic anhydride (2.0 ml) in pyridine (6.0 ml) for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (15 g), using benzene as the eluent, to give **9** (804 mg: 96.2% from **6**) as an oil; $[\alpha]_D$ −7.1°; IR: 1750, 1725 cm^{-1}; ^{1}H NMR: 0.97 (3H, s) and 1.07 (6H, s) ($-\dot{C}(CH_3)_2$ and $C_{10}-CH_3$), 1.18 and 1.21 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.01 and 2.24 (each 3H and s, 2-OCO$C\underline{H}_3$), 2.93 (1H, m, $-C\underline{H}(CH_3)_2$), 4.50 (1H, m, C_3–H), 5.90 (1H, dd, J=2.5 and 10 Hz, C_6–H), 6.54 (1H, dd, J=2.5 and 10 Hz, C_7–H), 6.68 and 6.95 (each 1H and s, C_{11}–H and C_{14}–H). Found: C, 74.79; H, 8.68%. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39%.

From 7: A mixture of **7** (361 mg), lithium aluminium hydride (125 mg), and dry ether (10 ml) was stirred at room temperature for 1 h. The mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give a crude triol (333 mg); IR: 3605, 3320 cm^{-1}.

A mixture of the crude triol (333 mg) and 10% hydrochloric acid (1.0 ml) in methanol (10 ml) was refluxed for 1 h, and then evaporated *in vacuo*. The residue was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to give an oil (328 mg).

The above oil (328 mg) was immediately acetylated at 81—84 °C with acetic anhydride (2.0 ml) in pyridine (4.0 ml) for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (20 g), using benzene as the eluent, to give an oil (290 mg: 74.4% from **7**), whose IR and ^{1}H NMR spectra were identical with those of **9**.

Epoxidation of 9. A solution of **9** (2.763 g) and *m*-chloroperbenzoic acid (85%: 2.150 g) in dichloromethane (50 ml) was allowed to stand at room temperature for 9 h. The solution was diluted with ether and then washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and water. After being dried over sodium sulfate, the solution was evaporated *in vacuo* to give a crude epoxide (**10**) (2.783 g); IR: 1750, 1723 cm^{-1}; ^{1}H NMR: 1.99 and 2.23 (each 3H and s, 2-OCOCH_3), 6.68 and 7.37 (each 1H and s, C_{11}–H and C_{14}–H). The crude epoxide was immediately subjected to the next reaction.

3β,12-Diacetoxyabieta-8,11,13-trien-6-one (11). *From 10*: A solution of the crude epoxide (**10**) (2.783 g) and 10% hydrochloric acid (10 ml) in methanol (60 ml) was refluxed for 1 h. The solution was concentrated *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated. The oily residue was acetylated with acetic anhydride (5.0 ml) in pyridine (7.0 ml) at 80—82 °C for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (100 g), using ether–benzene (3 : 97) as the eluent, to give **11** (2.037 g: 70.8% from **9**), which was recrystallized from acetone–hexane; mp 183—187 °C; $[\alpha]_D$ +107°; IR: 1750, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.10, 1.20, and 1.37 (each 3H and s, $-\dot{C}(CH_3)_2$ and $C_{10}-CH_3$), 1.19 (6H, d, J=7

Hz, -CH(C$\underline{H}_3$)$_2$), 2.08 and 2.32 (each 3H and s, 2-OCOC$\underline{H}_3$), 2.53 (1H, s, C_5-H), 3.62 (2H, s, -COC$\underline{H}_2$-), 4.45 (1H, m, C_3-H), 6.91 and 7.00 (each 1H and s, C_{11}-H and C_{14}-H). Found: C, 72.08; H, 8.23%. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05%.

Further elution with ether–benzene (1:9) afforded 3β,6α,-12-triacetoxyabieta-8,11,13-trien-7-one (**12**) (300 mg: 9.1% from **9**) as an oil; $[\alpha]_D$ +71.5°; IR: 1750, 1735, 1690, 1613 cm^{-1}; ^{1}H NMR: 1.05, 1.08, and 1.45 (each 3H and s, -C(C$\underline{H}_3$)$_2$ and C_{10}-C$\underline{H}_3$), 1.21 (6H, d, J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 2.01, 2.16, and 2.28 (each 3H and s, 3-OCOC$\underline{H}_3$), 2.29 (1H, d, J=13 Hz, C_5-H), 2.97 (1H, m, -C$\underline{H}$(CH$_3$)$_2$), 4.44 (1H, m, C_3-H), 5.82 (1H, d, J=13 Hz, C_6-H), 6.92 (1H, s, C_{11}-H), 7.90 (1H, s, C_{14}-H).

From **12**: A mixture of **12** (338 mg), lithium aluminium hydride (150 mg), and dry ether (8.0 ml) was refluxed for 1 h. The mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*.

The oily residue (277 mg) was dissolved in methanol (5.0 ml) containing 10% hydrochloric acid (0.5 ml), and then refluxed for 1 h. The methanol was evaporated *in vacuo* and the residue was extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated. The oily residue (250 mg) was acetylated at 80—84 °C with acetic anhydride (2.0 ml) in pyridine (3.0 ml) for 1 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (10 g), using ether–benzene (3 : 97) as the eluent, to give an oil (195 mg; 66.1%), whose IR and ^{1}H NMR spectra were identical with those of **11**.

*3β,12-Diacetoxyabieta-8,11,13-trien-6β-ol (**14**).* A solution of **11** (1.401 g) in dry tetrahydrofuran (45 ml) was added to a stirred suspension of lithium aluminium hydride (700 mg) in dry tetrahydrofuran (150 ml) with cooling in an ice–water bath. The mixture was refluxed for 4 h, cooled, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give the crude abieta-8,11,13-triene-3β,6β,12-triol (**13**) as a solid which, without purification, was used in the next reaction.

The above crude **13** was acetylated at 18—19 °C for 4 h with acetic anhydride (8.0 ml) in pyridine (15 ml). After the usual work-up, the crude product was chromatographed on silica gel (50 g), using ether–benzene (3 : 97) as the eluent, to give **14** (1.026 g: 72.8% from **11**), which was recrystallized from acetone–hexane; mp 135.5—136.5 °C; $[\alpha]_D$ +45.4°; IR: 3614, 3500, 1750, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.04 and 1.32 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.20 (6H, d, J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 1.60 (3H, s, C_{10}-C$\underline{H}_3$), 2.09 and 2.32 (each 3H and s, 2-OCOC$\underline{H}_3$), 4.3—4.8 (2H, m, C_3-H and C_6-H), 6.90 and 6.98 (each 1H and s, C_{11}-H and C_{14}-H). Found: C, 71.32; H, 8.74%. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51%.

Further elution with ether–benzene (6 : 94) afforded 12-acetoxyabieta-8,11,13-triene-3β,6β-diol (**15**) (133 mg: 10.6% from **11**), which was recrystallized from acetone–hexane; mp 188—189.5 °C; $[\alpha]_D$ +29.7°; IR: 3618, 3444, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.15 and 1.25 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.20 (6H, d, J=6 Hz, -CH(C$\underline{H}_3$)$_2$), 1.56 (3H, s, C_{10}-C$\underline{H}_3$), 2.32 (3H, s, -OCOC$\underline{H}_3$), 4.70 (1H, m, $W_{1/2}$=8 Hz, C_6-H), 6.89 and 6.98 (each 1H and s, C_{11}-H and C_{14}-H). Found: C, 73.04; H, 9.06%. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95%.

The monoacetate **15** (133 mg) was further acetylated with acetic anhydride (1.5 ml) in pyridine (2.0 ml) at 17—19 °C for 4 h. Chromatographic purification of the crude product yielded **14** (110 mg: 74.3%) and the recovered **15** (27 mg: 20.3%).

*3β-Acetoxyabieta-8,11,13-triene-6β,12-diol (**16**).* A stirred mixture of **14** (993 mg), sodium hydrogencarbonate (420 mg), methanol (25 ml), and water (3.0 ml) was refluxed for 15 min. The mixture was concentrated *in vacuo*, 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 recrystallized from benzene to give **16** (601 mg); mp 220—221.5 °C; $[\alpha]_D$ +31.8°; IR: 3610, 3400, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.03 and 1.32 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.23 (6H, d, J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 1.56 (3H, s, C_{10}-C$\underline{H}_3$), 2.13 (3H, s, -OCOC$\underline{H}_3$), 6.65 and 6.82 (each 1H and s, C_{11}-H and C_{14}-H). Found: C, 73.41; H, 9.16%. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95%. The mother liquor of recrystallization was evaporated *in vacuo* and the residue was chromatographed on silica gel (10 g), using ether–benzene (5 : 95) as the eluent, to give an additional **16** (224 mg). The total yield was 92.7%.

*Oxidation of **16** with Benzoyl Peroxide.* A solution of **16** (863 mg) and benzoyl peroxide (2.939 g) in chloroform (10 ml) was allowed to stand at room temperature for 80 h. The chloroform solution was diluted with ether. This ether solution, after addition of acetic acid (9.0 ml) and aqueous potassium iodide (30%: 30 ml), was stirred at room temperature for 3 h. The mixture was washed successively with water, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and water. After being dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was purified by repeated column chromatography on silica gel, using ether–benzene (3 : 97) as the eluent, to give four products (**17**—**20**).

a): 3β-Acetoxy-12-benzoyloxyabieta-8,11,13-triene-6β,11,-diol (**17**) (609 mg: 52.9%), which responded positively to the Gibbs test;[7] mp 224—225.5 °C (from methanol); $[\alpha]_D$ +52.2°; IR: 3575, 3430, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.05 and 1.31 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.18 (6H, d, J=7 Hz, -CH-(C$\underline{H}_3$)$_2$), 1.72 (3H, s, C_{10}-C$\underline{H}_3$), 1.88 (3H, s, -OCOC$\underline{H}_3$), 4.2—4.7 (2H, m, C_3-H and C_6-H), 6.18 (1H, s, -OH), 6.60 (1H, s, C_{14}-H), 7.3—8.4 (5H, m, -C_6H_5). Found: C, 72.81; H, 7.67%. Calcd for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55%.

b): 3β-Acetoxy-8β-benzoyloxy-6β-hydroxyabieta-9(11),13-dien-12-one (**18**) (22 mg: 1.9%); $[\alpha]_D$ −20.1°; IR: 3605, 1725, 1668, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.01 and 1.31 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.06 (6H, d, J=6.5 Hz, -CH-(C$\underline{H}_3$)$_2$), 1.43 (3H, s, C_{10}-C$\underline{H}_3$), 2.06 (3H, s, -OCOC$\underline{H}_3$), 4.3—4.7 (2H, m, C_3-H and C_6-H), 6.27 and 6.42 (each 1H and s, C_{11}-H and C_{14}-H), 7.3—8.1 (5H, m, -C_6H_5).

c): 3β-Acetoxy-13α-benzoyloxy-6β-hydroxyabieta-8(14),-9(11)-dien-12-one (**19**) (96 mg: 8.4%), which was recrystallized from benzene; mp 184—185 °C; $[\alpha]_D$ +240°; IR: 3500, 1720, 1660, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.96 and 1.15 (each 3H, d, and J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 1.02 and 1.31 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.57 (3H, s, C_{10}-C$\underline{H}_3$), 2.10 (3H, s, -OCOC$\underline{H}_3$), 4.3—4.7 (2H, m, C_3-H and C_6-H), 5.95 (1H, s, C_{14}-H), 6.15 (1H, s, C_{11}-H), 7.3—8.2 (5H, m, -C_6H_5). Found: C, 72.73; H, 7.66%. Calcd for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55%.

d): 3β-Acetoxy-13β-benzoyloxy-6β-hydroxyabieta-8(14),-9(11)-dien-12-one (**20**) (70 mg: 6.1%), which was recrystallized from ether–hexane; mp 180—180.5 °C; $[\alpha]_D$ −145°; IR: 3525, 1720, 1665, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): 0.88 and 1.13 (each 3H, d, and J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 1.07 and 1.33 (each 3H and s, -C(C$\underline{H}_3$)$_2$), 1.59 (3H, s, C_{10}-C$\underline{H}_3$), 2.10 (3H, s, -OCOC$\underline{H}_3$), 4.3—4.7 (2H, m, C_3-H and C_6-H), 5.95 (1H, s, C_{14}-H), 6.13 (1H, s, C_{11}-H), 7.3—8.2 (5H, m, -C_6H_5). Found: C, 72.73; H, 7.78%. Calcd for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55%.

3β-Acetoxy-12-benzoyloxy-6β-hydroxyabieta-8,12-diene-11,14-

dione (21). A solution of **17** (441 mg) and *m*-chloroperbenzoic acid (85%: 280 mg) in dichloromethane (10 ml) was allowed to stand at room temperature for 36 h, and then diluted with ether. The solution was washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and water. After drying over sodium sulfate, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography on silica gel (40 g), using ether–benzene (1 : 99) as the eluent, to give **21** (338 mg: 74.4%), which was recrystallized from benzene; mp 260.5—261.5 °C; $[\alpha]_D$ +24.2°; IR: 3610, 3535, 1725, 1660, 1607 cm^{-1}; ^1H NMR ($CDCl_3$): 1.01 and 1.31 (each 3H and s, $-C(CH_3)_2$), 1.25 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.68 (3H, s, $C_{10}-CH_3$), 2.08 (3H, s, $-OCOCH_3$), 4.3—4.8 (2H, m, C_3–H and C_6–H), 7.45—8.30 (5H, m, $-C_6H_5$). Found: C, 70.70; H, 7.04%. Calcd for $C_{29}H_{34}O_7$: C, 70.42; H, 6.93%.

Further elution with ether–benzene (3 : 97) afforded the recovered **17** (52 mg: 11.7%).

3β,6β,8β-Trihydroxyabieta-9(11),13-dien-12-one (22). A mixture of **18** (18.0 mg), potassium carbonate (54 mg), methanol (2.0 ml), and water (0.5 ml) was refluxed for 75 min. After the methanol had been evaporated *in vacuo*, the residue was extracted with ether. The ether extract was washed with brine, dried over sodium sulafte, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (5.0 g), using ether–benzene (25 : 75) as the eluent, to give **22** (7.0 mg); IR: 3359, 1661, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.04 and 1.08 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.11 and 1.27 (each 3H and s, $-C(CH_3)_2$), 1.64 (3H, s, $C_{10}-CH_3$), 2.44 (2H, dd, J=4 and 14 Hz, $-CH(OH)-C\underline{H}_2-$), 4.55 (1H, m, C_6–H), 6.05 and 6.42 (each 1H and s, C_{11}–H and C_{14}–H).

Thermal Rearrangement of Dienones (19 and 20). *a*): A solution of **19** (125 mg) in dry toluene (9.0 ml) was refluxed for 4 h and the crude product, after evaporation of the solvent, was purified by column chromatography on silica gel (10 g), using ether–benzene (3 : 97) as the eluent, to give **17** (8.4 mg: 6.7%). Further elution with ether–benzene (1 : 9) afforded the recovered **19** (116 mg: 93.0%).

b): A solution of **20** (60.0 mg) in dry toluene (5.0 ml) was refluxed for 4 h. The crude product was chromatographed on silica gel (10 g), using ether–benzene (3 : 97) as the eluent, to give **17** (38.3 mg: 63.8%) and **18** (15.6 mg: 26.0%). Further elution with ether–benzene (1 : 9) afforded the recovered **20** (6.0 mg: 10.0%).

3β,11,12-Triacetoxyabieta-8,11,13-trien-6β-ol (24). Lithium aluminium hydride (372 mg) was added to a stirred solution of **17** (1.180 g) in dry ether (30 ml) with cooling in an ice–water bath. The mixture was refluxed for 2 h, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude tetrol (**23**) which, without purification, was used in the next reaction.

The above crude **23** was acetylated at room temperature for 3.5 h with acetic anhydride (3.2 ml) in pyridine (5.0 ml). After the usual work-up, the crude product was chromatographed on silica gel (30 g), using ether–benzene (6 : 94) as the eluent, to give **24** (832 mg: 73.6% from **17**), which was recrystallized from acetone–hexane; mp 186—187.5 °C; $[\alpha]_D$ 38.1°; IR: 3613, 1762, 1724 cm^{-1}; ^1H NMR: 0.96 and 1.25 (each 3H and s, $-C(CH_3)_2$), 1.15 and 1.19 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.53 (3H, s, $C_{10}-CH_3$), 1.98 (3H, s) and 2.19 (6H, s) (3-$OCOCH_3$), 4.2—4.65 (2H, m, C_3–H and C_6–H), 6.78 (1H, s, C_{14}–H). Found: C, 67.74; H, 7.97%. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88%.

3β,11,12-Triacetoxyabieta-8,11,13-trien-6-one (25). A solution of **24** (842 mg) in acetone (4.0 ml) was oxidized at 0—5 °C for 3 min with Jones reagent (2.5 M: 1.2 ml). The mixture was 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 (25 g), using ether–benzene (3 : 97) as the eluent, to give **25** (703 mg: 83.8%), which was recrystallized from acetone–hexane; mp 121—122.5 °C; $[\alpha]_D$ +113°; IR: 1770, 1719 cm^{-1}; ^1H NMR: 1.02 and 1.21 (each 3H and s, $-C(CH_3)_2$), 1.16 and 1.20 (each 3H, d, and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.35 (3H, s, $C_{10}-CH_3$), 2.00 (3H, s) and 2.24 (6H, s) (3-$OCOCH_3$), 2.73 (1H, s, C_5–H), 3.58 (2H, bs, $-COCH_2-$), 4.40 (1H, m, C_3–H), 6.82 (1H, s, C_{14}–H). Found: C, 68.00; H, 7.55%. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47%.

3β-Hydroxytaxodione (4). A solution of **25** (86.0 mg) in ethanol (5.0 ml) was refluxed for 2 h with concentrated hydrochloric acid (1.5 ml) in a stream of nitrogen. The mixture was concentrated *in vacuo*, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude 3β,11,12-trihydroxyabieta-8,11,13-trien-6-one (**26**).

The crude **26** was subjected to repeated column chromatography on silica gel (10 g and then 8 g), using ether–benzene (8 : 92) as the eluent, to give **4** (46.4 mg: 74.9% from **25**), which was recrystallized from acetone–petroleum benzine; mp 183.5—184.5 °C; $[\alpha]_D$ +69.0°; IR: 3616, 3340, 1674, 1644, 1628, 1616, 1602 cm^{-1}; ^1H NMR ($CDCl_3$): 1.17 (6H, bd, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.28 (9H, s, $-C(CH_3)_2$ and $C_{10}-CH_3$), 2.60 (1H, s, C_5–H), 6.22 and 6.90 (each 1H and s, C_7–H and C_{14}–H), 7.61 (1H, s, C_{11}–OH). Found: C, 72.57; H, 8.02%. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%.

3β,11,14-Triacetoxy-12-benzoyloxyabieta-8,11,13-trien-6-one (29). A solution of **21** (590 mg) in acetone (30 ml) was oxidized with Jones reagent (2.5 M: 0.8 ml) at 0—5 °C for 2.5 min. The mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to give the crude 3β-acetoxy-12-benzoyloxyabieta-8,12-diene-6,11,14-trione (**27**) (585 mg); IR: 1720, 1660 cm^{-1}.

A stirred solution of the above crude **27** (585 mg) in benzene (12 ml) was refluxed for 20 min with a mixture of zinc powder (1.2 g) and 10% hydrochloric acid (12 ml). After cooling, the mixture was extracted with ether. The extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude phenol (**28**); IR: 3575, 3425, 1720 cm^{-1}.

The crude phenol **28** was immediately acetylated at 85—90 °C for 2.5 h with acetic anhydride (4.0 ml) and pyridine (4.0 ml). After the usual work-up, the product was purified by column chromatography on silica gel (30 g), using ether–benzene (5 : 95) as the eluent, to give **29** (480 mg: 69.5% from **21**), which was recrystallized from benzene; mp 284—286 °C; $[\alpha]_D$ +126°; IR: 1765, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): 1.05, 1.27, and 1.37 (each 3H and s, $-C(CH_3)_2$ and $C_{10}-CH_3$), 1.92, 2.04, and 2.38 (each 3H and s, 3-$OCOCH_3$), 2.80 (1H, s, C_5–H), 3.36 (2H, bs, $-COCH_2-$), 4.45 (1H, m, C_3–H), 7.45—8.35 (5H, m, $-C_6H_5$). Found: C, 68.48; H, 6.71%. Calcd for $C_{33}H_{38}O_9$: C, 68.49; H, 6.62%.

3β,11,14-Triacetoxy-12-benzoyloxyabieta-8,11,13-triene-6,7-dione (30). A solution of **29** (195 mg) in acetone (10 ml) was oxidized with Jones reagent (2.5 M: 1.0 ml) at room temperature for 14 h. The mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude **30** (190 mg); ^1H NMR ($CDCl_3$): 1.97, 2.05,

and 2.47 (each 3H and s, 3-$OCOCH_3$), 3.20 (1H, s, C_5–H), 7.45—8.35 (5H, m, $-C_6H_5$). The crude **30** was immediately subjected to the next reaction.

Coleon T (3). A stirred mixture of the crude **30** (190 mg) in methanol (15 ml) and aqueous sodium carbonate (10%: 3.0 ml) was refluxed for 7 h in a stream of nitrogen. The methanol was evaporated *in vacuo*. The residue was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (50 g: Mallinckrodt, Silic AR CC-4), using ether–chloroform (1 : 9) as the eluent, to give **3** (71.2 mg: 58.3% from **29**). Crystallization of **3** from acetone–hexane gave an orange powder; mp 134—137 °C decomp; IR (KBr): 3415, 1725, 1613, 1434, 1381, 1296, 1043, 941 cm^{-1}; ^1H NMR (acetone-d_6): 1.14, 1.36, and 1.42 (each 3H and s, $-\dot{C}(CH_3)_2$ and C_{10}–CH_3), 1.33 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.15 (1H, s, C_5–H), 13.54 (1H, s, C_{14}–OH).

Acetylation of 3. A solution of **3** (54.0 mg) and acetic anhydride (1.0 ml) in pyridine (2.0 ml) was heated at 70—75 °C for 6 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (10 g), using ether–benzene (7 : 93) as the eluent, to give 3β,6,11,-12-tetraacetoxy-14-hydroxyabieta-5,8,11,13-tetraen-7-one (**32**) (22.9 mg: 29.0%), which was recrystallized from ether–hexane; mp 160.5—162.5 °C; IR (KBr): 3418, 1777, 1728, 1632, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): 1.31 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.34 and 1.42 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.74 (3H, s, C_{10}–CH_3), 2.11 (3H, s), 2.30 (6H, s), and 2.35 (3H, s) (4-$OCOCH_3$), 4.83 (1H, m, C_3–H), 13.38 (1H, s, C_{14}–OH). Found: C, 63.62; H, 6.61%. Calcd for $C_{28}H_{34}O_{10}$: C, 63.38; H, 6.46%.

Further elution with ether–benzene (15 : 85) afforded 3β,6,-11,12,14-pentaacetoxyabieta-5,8,11,13-tetraen-7-one (colen S pentaacetate) (**31**) (49.6 mg: 58.1%), which was recrystallized from acetone–hexane; mp 215.5—217.5 °C; $[\alpha]_D$ +79.3°; IR (KBr): 1778, 1764, 1722, 1667, 1632, 1602 cm^{-1}; ^1H NMR ($CDCl_3$): 1.24 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.34 and 1.41 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.75 (3H, s, C_{10}–CH_3), 2.12 (3H, s), 2.35 (9H, s), and 2.41 (3H, s) (5-$OCOCH_3$), 4.83 (1H, m, C_3–H). Found: C, 62.96; H, 6.44%. Calcd for $C_{30}H_{36}O_{11}$: C, 62.92; H, 6.34%. The synthetic **31** was shown to be identical with authentic coleon S pentaacetate by mixed melting point determination and by IR and ^1H NMR spectral comparisons.

Coleon S (2). A solution of **3** (51.0 mg) in methanol (6.0 ml) was refluxed for 30 min with concentrated hydrochloric acid (0.5 ml). The mixture was evaporated *in vacuo*, 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 (10 g: Mallinckrodt, Silic AR CC-4), using ether–chloroform (5 : 95) as the eluent, to give **2** (24.9 mg: 48.8%); IR (KBr): 3383, 1616, 1594, 1561, 1446, 1297, 1259, 1173, 1112, 1061, 1045, 1017, 972, 940, 900, 810, 777 cm^{-1}; ^1H NMR (acetone-d_6, 90 MHz): 1.34 (6H, d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.40 and 1.55 (each 3H and s, $-\dot{C}(CH_3)_2$), 1.75 (3H, s, C_{10}–CH_3), 7.55 (1H, s, C_6–OH), 13.08 (1H, s, C_{14}–OH).

The synthetic **2** was refluxed for 4 h with acetic anhydride in pyridine to give **31**, mp 212.5—214.5 °C (from acetone–hexane), which was shown to be identical with authentic coleon S pentaacetate by mixed melting point determination and by IR and ^1H NMR spectral comparisons.

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