Studies on the Total Synthesis of Triptolide. 1

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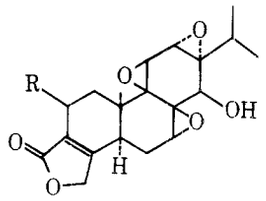
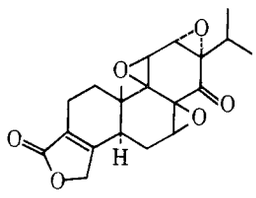
A convenient sequence for the conversion of 6-methoxy-1-tetralone (**5**) to **16** in nine steps is described. Robinson annelation of **16** affords **17** in overall yield of 33% from **5**. Tricyclic enone **17** is converted in five steps to **22** that on oxidation with periodate affords **23** and thus provides a convenient entry to the stereospecific synthesis of the C-ring functionality in triptolide (**1**).

The isolation of triptolide (**1**), tripdiolide (**2**), and triptonide (**3**) by Kupchan and co-workers provided the first recognized diterpenoid triepoxides.[1] More recently a related diterpenoid bisepoxide, stemolide (**4**), has been isolated.[2] Of particular interest is the antileukemic activity of **1** and **2** and



1, R = H
2, R = OH



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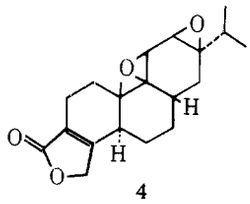

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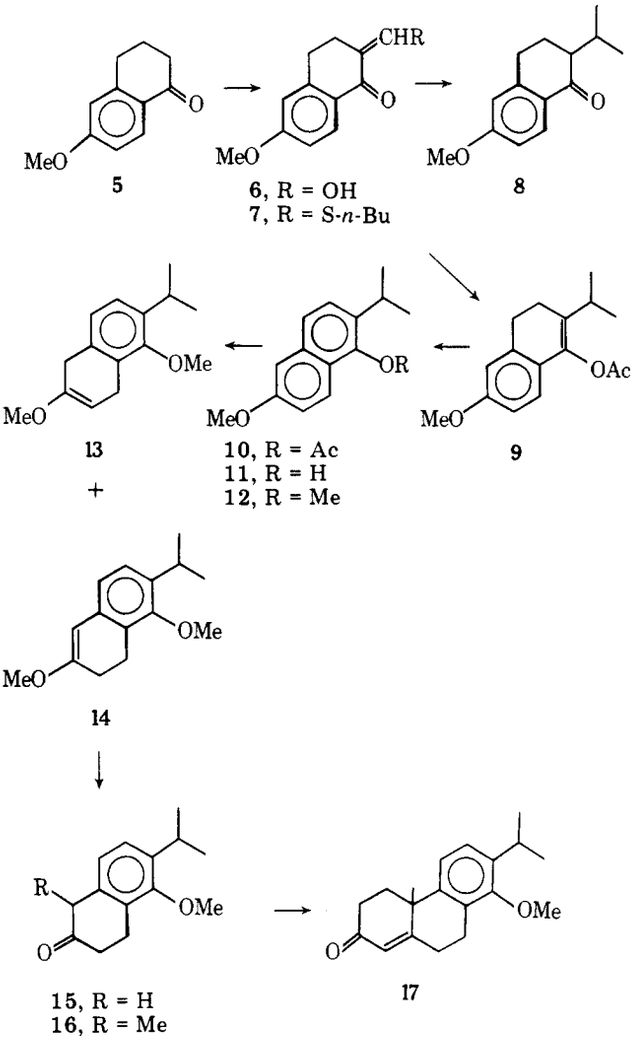
the hypothesis that the hydroxyl-assisted addition of nucleophiles to the 9,11-epoxide of **1** and **2** may mimic the mechanism by which they exert their antileukemic activity.[1]

In connection with efforts toward the total synthesis of **1**, a convenient synthesis of 6-isopropyl-5-methoxy-1-methyl-3,4-dihydro-2(*H*)-naphthalenone (**16**) was desired to provide a starting material that could be obtained in reasonable quantity for an annelation reaction (such as **16** → **17**) as an entry to an appropriately substituted tricyclic skeleton. In addition it was desired to convert **17** to **22** to determine whether the model system **22** followed the usual reaction course of substituted *o*-hydroxymethylphenols with periodate[3] to afford the corresponding epoxy cyclohexadienone (**23**) as an entry to the C-ring functionality in **1**.

A convenient starting material for the synthesis of **16** (Scheme I) was 6-methoxy-1-tetralone (**5**). Although monoalkylation of **5** to afford **8** was effected to an extent of 55% on treatment with 1 equiv of lithium diisopropylamide in 1,2-dimethoxyethane in the presence of excess isopropyl iodide at 50 °C for 23 h, no further conversion was effected by prolonged heating; and, although alkylation with 2 equiv of base increased the conversion to 65%, it resulted in substantially more side products. Since separation of **8** from unalkylated **5** required a tedious distillation that resulted in reduced yields, a more satisfactory preparation of pure **8** was developed. Formylation of **5** with excess ethyl formate and base at room temperature afforded **6**[4,5] in nearly quantitative yield, and subsequent reaction of **6** with *n*-butanethiol in the presence of *p*-toluenesulfonic acid catalyst with removal of water according to the general procedure of Ireland and Marshall[6] gave crystalline **7** in 72% yield. Application of the Coate's procedure[7] for bis-conjugative alkylation of *n*-butylthio-

Scheme I



5 — 6, R = OH; 7, R = S-*n*-Bu — 8

9 — 10, R = Ac; 11, R = H; 12, R = Me — 13 + 14

15, R = H
16, R = Me

17

methylene ketones with lithium dimethylcuprate afforded, after aqueous workup, tetralone **8** in 93% yield from **7**.

Attempts to dehydrogenate **8** to the corresponding naphthol with quinone reagents were not successful.[8,9] Consequently the enolate generated in the reaction of **7** with lithium dimethyl cuprate was quenched with acetic anhydride to give **9** (92%). Dehydrogenation of **9** with sulfur at 250 °C afforded **10** in 68% yield. Acetate **10** was hydrolyzed to naphthol **11** in quantitative yield with 10% aqueous sulfuric acid in methanol at reflux, and **11** smoothly underwent quantitative methylation with dimethyl sulfate and barium hydroxide in dimethylformamide to afford **12**.

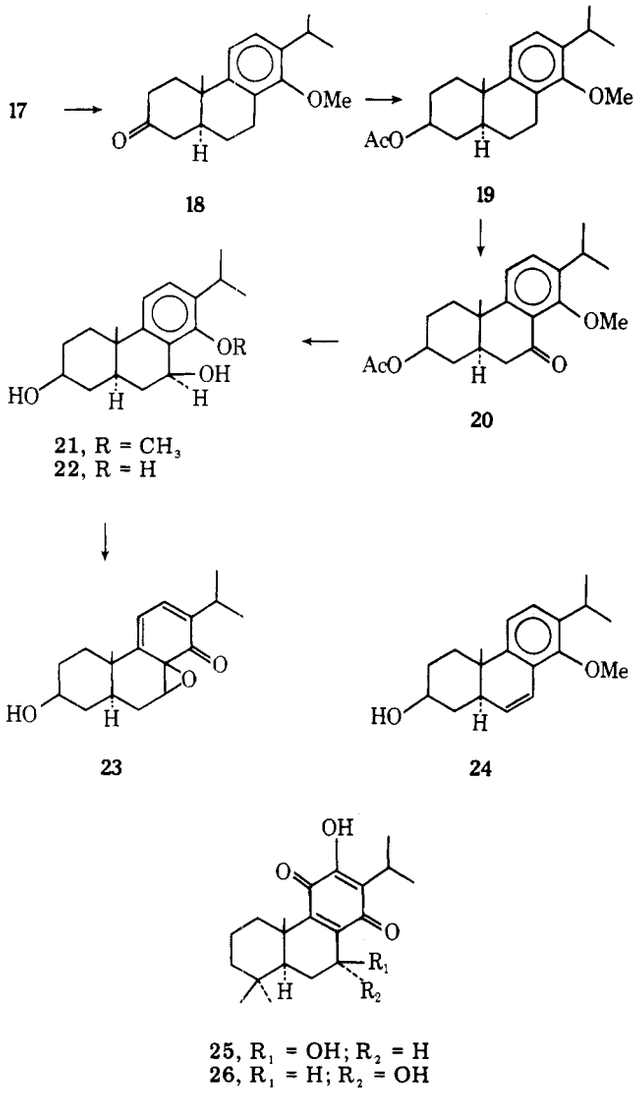
Under Birch conditions (Na/NH_3/THF/EtOH) **12** gave enol ether **13** as the sole product (94%). Reduction of **12** with sodium in ethanol under reflux according to the general procedure of Conforth and Robinson[10] proved to be preparatively

superior and afforded in nearly quantitative yield a 2:1 mixture of 13 and 14 (see Experimetal Section). The enol ether mixture was hydrolyzed with oxalic acid in aqueous methanol under reflux to give tetralone 15 (92%) that was conveniently isolated and purified as the air-stable bisulfite adduct.

Mild conversion of 15 to the pyrrolidine enamine was effected by stirring a benzene solution of 15 with pyrrolidine over 3A molecular sieves at room temperature, and methylation of the enamine with excess methyl iodide in refluxing dioxane afforded, after hydrolysis, 16 in 98% yield from 15.[11] Robinson annelation of 16 with methyl vinyl ketone in aqueous methanolic potassium hydroxide gave tricyclic enone 17 in 81% yield; the overall yield of 17 from 5 is 33%.

Reduction of 17 (Scheme II) with lithium in ammonia[12] provided trans-fused ring ketone 18 that was obtained in 81%

Scheme II



yield on small scale after purification by column chromatography on alumina and on large scale could be isolated by recrystallization in 66% yield. Conversion of 18 to the 3β-acetoxy derivative 19 in 78% yield was accomplished by lithium tri-*tert*-butoxyaluminum hydride reduction to the 3β alcohol, according to the known stereochemical course of reductions of 3-keto steroids,[13] followed by acetylation with acetic anhydride in pyridine.

Attempts to effect benzylic oxidation of 19 with selenium dioxide in refluxing acetic acid or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[14] in refluxing methanol were not successful, but chromium trioxide oxidation in aqueous acetic acid afforded ketone 20 in 42% yield after dry column chromatography on alumina. Reduction of the ketone function of 20 with sodium borohydride followed by workup with aqueous acid effected stereoselective reduction of the ketone function to the β alcohol with cleavage of the acetoxy group to afford 21 in 94% yield. The NMR spectrum of the product indicated that it was 97% β alcohol and 3% α alcohol. As expected, reduction of ketone 20 with lithium tri-*tert*-butoxyaluminum hydride gave slightly more α alcohol (94% β:6% α), and reduction with potassium tri-*sec*-butylborohydride (K-Selectride), the reagent of choice for selective reduction of cyclohexanones to axial alcohols,[15] gave considerably more α alcohol (60% β:40% α). Further support for the stereochemical assignment in 21 is obtained from the NMR spectrum where the α benzylic carbinol hydrogen appears at δ 5.16 as a triplet with an apparent coupling constant of 8 Hz and a half-band width of 15 Hz as expected for the coupling of this axial proton with the adjacent methylene group. A similar pattern is observed for the axial 7α hydrogen in the NMR spectrum of taxoquinone (25), which appears as a broad triplet with an apparent coupling constant of 7 Hz, whereas the corresponding absorption for the 7β hydrogen in horminone (26) is a broad signal with a half-band width of 8 Hz as expected for an equatorial β hydrogen.[16]

Cleavage of the *O*-methyl ether of 21 was effected with boron tribromide in methylene chloride at room temperature but always resulted in substantial dehydration of the benzylic alcohol to olefin 24. Quantitative demethylation of 21 to 22 was effected with sodium *n*-propanethiolate in dimethylformamide at 40 °C for 30 h. At 100 °C considerable dehydration of the benzylic alcohol was observed.

Reaction of 22 with sodium metaperiodate in aqueous methanol afforded 23 in 66% yield as a pale yellow solid, the spectral data of which allow unambiguous assignment of structure (see Experimental Section). The periodate reaction with *o*-hydroxymethylphenols thus appears to be a convenient entry to an attractive intermediate for the stereospecific construction of the C-ring functionality in triptolide and related substances.

Experimental Section

General. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were determined either with a Perkin-Elmer Model 237-B or Model 567 grating spectrophotometer. ^{1}H NMR spectra were determined with either a 60-MHz Varian Model T-60 spectrometer or, where noted, with a 90-MHz Hitachi Model R-22 spectrometer. Chemical shift data are reported in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E spectrometer with an ionizing potential of 70 eV and are expressed in percent relative to the most intense peak. Except for the high-mass region only the *m/e*'s of greater than 20% relative intensity are listed. High-resolution mass spectra were run on a CEC-21-110B spectrometer.[17] Ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. Gas chromatographic analyses and isolation of compounds were performed on a Varian Aerograph Series 2100 (flame ionization) chromatograph with 6 ft × 2 or 3.5 mm i.d. glass columns packed with specified liquid phase and inert support (glass injection port and glass effluent splitter). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

2-Hydroxymethylene-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (6). The procedures of Akhrem and Zavel'skaya[4] and of Banerjee, Chatterjee, Pillai, and Bhatt[5] were modified as follows. To a stirred mixture of 105 mL (96.9 g, 1.314 mol) of ethyl formate, 43.2 g (0.801 mol) of sodium methoxide, and 450 mL of reagent benzene in a three-neck 2-L round-bottom flask under nitrogen at 0 °C was added dropwise over a 45-min period a solution of 75.0 g (0.426 mol) of 5 (Aldrich) in 300 mL of reagent benzene. The ice bath was removed, and stirring was continued for an additional 1.75 h. The mixture was quenched, with cooling, with 600 mL of 5% aqueous sulfuric acid. The benzene layer was washed with two portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo

to give 86.5 g (100%) of **6** as a tan solid (>95% pure by NMR and GLC), mp 63–68 °C (lit.[4] mp 66.5–67.5 °C, lit.[5] mp 67–68 °C).

2-*n*-Butylthiomethylene-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (7). A solution of 57.10 g (0.280 mol) of **6**, 35 mL (0.325 mol) of *n*-butanethiol, 48 mg (0.25 mmol) of *p*-toluenesulfonic acid monohydrate, and 200 mL of reagent benzene was stirred under reflux in a nitrogen atmosphere for 21 h with removal of water in a Dean-Stark trap (4.25 mL, 85% theory). The mixture was cooled to room temperature and quenched with 150 mL of saturated sodium bicarbonate solution. The benzene layer was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a dark oil which crystallized after trituration with petroleum ether (30–60 °C). The crude material was recrystallized from 700 mL of hexanes. In the initial stages of crystallization the filtrate was decanted from an oil and dark solid which had formed, and the recrystallization was allowed to continue to give 55.72 g (72%) of **7** as tan prisms, mp 60–64 °C. An analytically pure sample was prepared by recrystallization from pentane to give large, pale green-yellow prisms: mp 63.5–64.5 °C; IR (CCl_4) 2960, 2940, 1655, 1600, 1560, 1555, and 880 cm^{-1}; NMR ($CDCl_3$) δ 0.77–1.13 (3 H, m), 1.20–1.93 (4 H, m), 2.60–3.04 (6 H, m), 3.87 (3 H, s), 6.60 (1 H, m, obscured by other aromatic proton absorption), 6.74 (1 H, d of d, J = 8, 2 Hz), 7.65 (1 H, br s), and 7.97 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 277 (3), 276 (M^+, 13), 243 (12), 219 (60).

Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.52; H, 7.29; S, 11.60. Found: C, 69.59; H, 7.33; S, 11.61.

2-Isopropyl-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (8). A dry three-neck 1-L round-bottom flask equipped with nitrogen inlet and magnetic stirring bar was charged with 40.00 g (0.210 mol) of purified cuprous iodide and, under nitrogen, with 100 mL of dry ethyl ether. To the mixture at 0 °C under nitrogen was added over a 15-min period 247 mL (0.420 mol) of 1.7 M methyllithium in ether (Alfa). Solid **7** (27.60 g, 0.100 mol) was added to the cooled mixture in small portions over a 30-min period from an Erlenmeyer flask through Gooch tubing. The mixture was stirred in the cold for 30 min and then quenched at 0 °C with a slow dropwise addition of 20 mL of water. The mixture was diluted with an additional 50 mL of water and filtered through a medium pore sintered-glass funnel. The copper salts were washed with ethyl ether. The combined ethereal extracts were washed with water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 20.16 g (93%) of **8** as an amber liquid. The product (>95% pure by NMR and GLC) was used without further purification but could be distilled at 120–123 °C (0.35 Torr) to give a pale yellow oil. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 180 °C) to give a colorless oil: IR (CCl_4) 2960, 2940, 1760, 1600, 1490, 1465, 1370, 1350, 1270, 1260, 1250, and 1230 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 1.7–3.1 (6 H, m), 3.85 (3 H, s), 6.65 (1 H, m, obscured by other aromatic proton absorption), 6.76 (1 H, d of d, J = 8, 2 Hz), and 7.98 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 218 (M^+, 7), 203 (11), 176 (7), 175 (100).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.87; H, 8.25.

1-Acetoxy-2-isopropyl-6-methoxy-3,4-dihydronaphthalene (9). To a 5-L three-neck round-bottom flask, equipped with a mechanical stirrer and attached with Gooch tubing to an Erlenmeyer flask containing starting material **7**, was charged with 285.66 g (1.50 mol) of reagent cuprous iodide and, under nitrogen, with 600 mL of dry ethyl ether. The system was flushed thoroughly with nitrogen and cooled to −20 °C (dry ice/CCl_4). The contents of three 1-mol bottles of 1.8 M methyllithium in ether (Alfa) were added via cannula at a rapid rate over a 20-min period to the stirred mixture followed by the addition of 198 g (0.718 mol) of solid **7** over a 30-min period. During the addition the temperature of the bath was maintained below −5 °C. Stirring was continued at the cold temperature for an additional 30 min followed by the slow addition of 375 mL of acetic anhydride via syringe. (Caution! exothermic. Bath temperature was maintained below −10 °C.) The mixture was stirred at room temperature for 3 h and then carefully quenched with 225 mL of water via syringe. The ethereal layer was decanted from the precipitate which was washed with an additional 400 mL of ethyl ether. Concentration of the combined ethereal solutions gave some wet solid product. The precipitate in the flask was washed with 800 mL of chloroform. The suspension was transferred to a medium pore sintered-glass funnel and filtered under suction. The salts were washed with an additional 800 and 600 mL of chloroform. The combined solution of crude product and chloroform filtrates was filtered through Celite in a medium pore sintered-glass funnel, washed with saturated brine, dried (Na_2SO_4), filtered again through Celite, and evaporated in vacuo to give a wet solid. Volatiles were removed under high vacuum to give a solid which was washed with several portions of pentane totaling 500 mL to give, after air drying, 171.6 g (92%) of **9** as a pale yellow, crystalline solid, mp 112–120 °C. The product (≫95% pure by NMR and GLC) was used without further purification. A 0.479-mol scale gave 93% yield of **9**. An analytically pure sample was prepared by three recrystallizations from pentane to give very pale yellow, fine plates: mp 122.5–123 °C; IR (CCl_4) 2960, 2940, 2840, 1770, 1610, 1465, 1430, 1370, 1310, 1280, 1255, 1230, 1215, 1135, 1125, 1075, 1050, and 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (6 H, d, J = 7 Hz), 2.07–3.08 (5 H, m), 2.28 (3 H, s), 3.75 (3 H, s), and 6.47–7.00 ppm (3 H, m; br s at 6.67, d at 6.92, J = 9 Hz); MS *m/e* (rel intensity) 261 (4), 260 (M^+, 19), 258 (3), 219 (6), 218 (35), 203 (70), 43 (100).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.78; H, 7.84.

1-Acetoxy-2-isopropyl-6-methoxynaphthalene (10). A 500-mL Claisen flask was charged with a mixture of 52.0 g (0.20 mol) of **9** and 6.40 g (0.20 mol) of sulfur (Merck sublimed). While nitrogen was swept through the system and through a trap containing 200 mL of 2 N sodium hydroxide, the flask was immersed in a silicone oil bath preheated to 230 °C. After 5 min a vigorous exothermic reaction ensued. Oil-bath temperature was maintained at 250 °C for an additional 75 min. Trituration of cooled crude product with three 100-mL portions of pentane left a dark solid which was sublimed (100 °C, 0.05 Torr) to initially give a yellow, oily impurity which was rinsed from the cold finger. Further sublimation gave 35.2 g (68%) of **10** as pale yellow prisms, mp 123–127 °C. A 0.352-mol scale reaction afforded 64% yield of sublimed material. An analytically pure sample was obtained by an additional sublimation (115–120 °C, 0.05 Torr) to give pale yellow prisms: mp 126.5–128 °C; IR (CCl_4) 2965, 1770, 1610, 1485, 1420, 1370, 1270, 1240, 1205, 1175, 1170, 1035, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (6 H, d, J = 7 Hz), 2.44 (3 H, s), 3.14 (1 H, septet, J = 7 Hz), 3.80 (3 H, s), and 6.95–7.73 ppm (5 H, m); MS *m/e* (rel intensity) 259 (4), 258 (M^+, 20), 216 (78), 201 (84), 43 (100).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.50; H, 7.01.

2-Isopropyl-6-methoxy-1-naphthol (11). A mixture of 52.25 g (0.202 mol) of **10**, 400 mL of reagent methanol, and 100 mL of 10% aqueous sulfuric acid was deoxygenated with nitrogen and stirred under reflux in the dark for 43 h. Most of the methanol was evaporated in vacuo, and product was extracted with two portions (500 and 100 mL) of ethyl ether. The ether solution was washed with three 200-mL portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 42.88 g (98%) of **11** as a pale yellow solid, mp (sublimed 67 °C) 75–83 °C. The air-sensitive product was usually used immediately in the next reaction, but can be stored safely under nitrogen in a refrigerator. The reaction was successfully run on a 0.55-mol scale to give 100% yield of **11**. An analytically pure sample was prepared by two recrystallizations from petroleum ether (bp 30–60 °C) to give colorless needles: mp 85–86.5 °C; IR ($CHCl_3$) 3600, 3370, 2960, 2940, 1630, 1605, 1580, 1480, 1460, 1425, 1390, 1380, 1370, 1340, 1280, 1265, 1255, 1185, 1165, 1155, 1140, 1075, 1030, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (6 H, d, J = 7 Hz), 3.22 (1 H, septet, J = 7 Hz), 3.86 (3 H, s), 5.17 (1 H, s, exchanges with D_2O), 7.06–7.30 (4 H, m), and 8.00 ppm (1 H, m); MS *m/e* (rel intensity) 217 (9), 216 (M^+, 58), 201 (100).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.74; H, 7.41.

1,6-Dimethoxy-2-isopropylnaphthalene (12). In a 2-L three-neck round-bottom flask a solution of 42.88 g (0.187 mol) of **11** in 500 mL of reagent DMF was thoroughly deoxygenated with nitrogen and cooled under a nitrogen atmosphere with an ice-bath. The system was opened to the atmosphere just long enough to add 78.7 g (0.249 mol) of barium hydroxide octahydrate to the stirred solution. After 5 min 55 mL (73.1 g, 0.58 mol) of dimethyl sulfate (Aldrich) was added at a moderately rapid rate to the cooled mixture via addition funnel. Stirring was continued at room temperature under nitrogen overnight. Sodium hydroxide (500 mL, 2 N) was added followed by stirring for an additional 1 h. The mixture was extracted with two portions (500 and 200 mL) of chloroform. The chloroform solution was washed with three 500-mL portions of water and with 300 mL of saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil. Residual DMF was removed under high vacuum to give 45.57 g (100%) of **12** as an almost colorless solid, mp 84–86 °C. The product was sufficiently pure to use directly in the next reaction. The reaction was successfully run on a 0.547-mol scale to give 99% yield of **12**. An analytically pure sample was prepared by two recrystallizations from pentane to give fine, colorless plates: mp 85–86 °C; IR (CCl_4) 2960, 2940, 1630, 1605, 1485, 1460, 1445, 1410, 1370, 1340, 1315, 1265, 1245, 1235, 1195, 1165, 1160, 1085, 1035, 995, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (6 H, d, J = 7 Hz), 3.54 (1 H, septet, J = 7 Hz), 3.85 (3 H, s), 3.88 (3 H, s), 7.05–7.55

(4 H, m), and 7.89–8.05 ppm (1 H, m); MS *m/e* (rel intensity) 231 (14), 230 (M^+, 88), 215 (100), 128 (34), 115 (30).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.18; H, 7.93.

2,5-Dimethoxy-6-isopropyl-1,4-dihydronaphthalene (13) and 2,5-Dimethoxy-6-isopropyl-3,4-dihydronaphthalene (14) by Sodium–Ethanol Reduction of 12. A 2-L three-neck round-bottom flask equipped with mechanical stirrer and two condensers was charged with 80.5 g (0.35 mol) of **12** and 600 mL of absolute ethanol. One wide-diameter condenser for sodium addition was attached to a nitrogen inlet tube, while the other was attached to an outlet tube leading to a bubbler. The mixture was heated under a slow nitrogen flow to near reflux. When all solid had dissolved, 58.9 g (2.56 mol) of sodium was added in thin pieces over a 90-min period causing gentle refluxing of the mixture. Reflux was maintained until all of the sodium had reacted. The solution was diluted with 100 mL of absolute ethanol, allowed to cool to room temperature, and then diluted cautiously with 300 mL of water. Evaporation of ethanol in vacuo was followed by extraction with two portions (500 and 200 mL) of ethyl ether. The ether solution was washed with two 200-mL portions of water and with two portions of saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 80.9 g (100%) of **13** and **14** as a somewhat air-sensitive oil which was used without further purification. The product can be safely stored under nitrogen in a refrigerator. The NMR spectrum indicated a 64:36 mixture of enol ethers **13** and **14**, respectively, according to integration of the corresponding vinyl absorptions: 4.79 ppm (m) for **13** and 5.50 ppm (s) for **14**. A sample of pure 1,4-dihydro compound **13** was prepared by Birch reduction as described in the following experiment.

2,5-Dimethoxy-6-isopropyl-1,4-dihydronaphthalene (13) by Sodium-Ammonia Reduction. Ammonia (30 mL) was condensed into a solution of 1.15 g (5 mmol) of **12**, 15 mL of dry THF, and 1.17 mL (20 mmol) of absolute ethanol at −65 °C. Sodium (0.46 g, 20 mmol) was added. After 10 min of stirring under nitrogen 0.4 mL of ethanol was added, and stirring was continued for an additional 30 min. After 1 mL of water was carefully added, the ammonia was allowed to evaporate. The mixture was partitioned between water (10 mL) and ethyl ether (50 mL). The ether solution was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 1.09 g (94%) of **13** as an almost colorless oil which darkened upon prolonged exposure to the atmosphere. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 175 °C) to give a colorless solid: mp (sublimed 52 °C) 55–61 °C dec; IR (CCl_4) 2960, 2940, 1645, 1485, 1465, 1450, 1420, 1385, 1325, 1265, 1200, 1180, 1160, 1150, 1080, 1035, and 835 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (6 H, d, J = 7 Hz), 3.2–3.6 (5 H, m), 3.54 (3 H, s), 3.72 (3 H, s), 4.79 (1 H, m), 6.83 (1 H, d, J = 8 Hz), and 7.07 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 234 (3), 233 (19), 232 (M^+, 99), 217 (100).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 77.32; H, 8.80.

6-Isopropyl-5-methoxy-3,4-dihydro-2(1*H*)-naphthalenone (15). A thoroughly deoxygenated mixture of 80.94 g (0.348 mol) of crude enol ether mixture **13** and **14** in 1200 mL of MeOH/H_2O (85:15) was stirred under reflux with 44.20 g (0.35 mol) of oxalic acid dihydrate under nitrogen in the dark for 21 h. After evaporation of the methanol in vacuo, product was extracted with 500 mL of ethyl ether. The ether solution was washed successively with 100 mL of water, 200 mL of saturated sodium bicarbonate solution, 100 mL of water, and saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil which was dissolved in 100 mL of 95% ethanol and shaken in a 2-L Erlenmeyer flask with a solution of 120 g (1.15 mol) of sodium bisulfite in 500 mL of water. The mixture was shaken thoroughly until a solid adduct had completely formed, placed in a refrigerator overnight with occasional shaking, and filtered. The solid was washed with 75 mL of absolute ethanol and with four 50-mL portions of ethyl ether and air dried to give a white solid adduct. Regeneration of oily air-sensitive tetralone **15** from a hot saturated solution of the bisulfite adduct with sodium carbonate followed by ether extraction and usual workup aforded a 92% yield of **15** from the enol ether mixture. An analytically pure sample was prepared by preparative GLC (10% SE-30 on Chromosorb W, 175 °C) to give a colorless oil: IR (CCl_4) 2965, 2940, 2910, 2870, 1725, 1485, 1450, 1445, 1420, 1330, 1305, 1260, 1210, 1170, 1070, 1055 cm^{-1}; NMR δ ($CDCl_3$) 1.25 (6 H, d, J = 7 Hz), 2.35–2.67 (2 H, m), 2.97–3.7 (5 H, m), 3.53 (2 H, s), 3.77 (3 H, s), 6.85 (1 H, d, J = 8 Hz), and 7.13 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 219 (17), 218 (M^+, 100), 203 (88), 176 (34), 175 (60), 161 (28), 131 (24), 128 (20), 117 (21), 115 (26), and 91 (29).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.75; H, 8.47.

6-Isopropyl-5-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (16). Molecular sieves (3A, predried at 300 °C) (78 g) were added to a solution of 83.08 g (0.381 mol) of **15** in 560 mL of reagent benzene. The solution was thoroughly deoxygenated with nitrogen, cooled briefly with an ice bath, and treated with 36.7 mL (31.3 g, 0.44 mol) of pyrrolidine (Aldrich, 99%) added via syringe at a moderate rate. The ice bath was removed, and stirring was continued at room temperature under nitrogen for 4.5 h. Volatile solvents were evaporated in vacuo to give after high vacuum overnight tan solid enamine which was stored under nitrogen.

Dioxane (670 mL) was passed through 100 mL of neutral activated alumina (Woelm) directly into the flask containing the enamine through a no-air stopper while nitrogen was swept through the system. Methyl iodide (556 g) was added, and the solution was stirred under reflux for 48 h during which time a precipitate formed. The mixture was then stirred under reflux with 280 mL of 5% aqueous hydrochloric acid for 3 h and extracted with three portions (600, 300, and 300 mL) of ethyl ether. The combined ethereal extracts were washed with two portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give after high vacuum overnight 86.99 g (98% from **15**) of **16** as an oil. The product was sufficiently pure to use directly in the next reaction. The reaction was successfully carried out on a 0.686-mol scale. A small sample was purified by distillation at 103 °C (0.08 Torr) to give an almost colorless oil. An analytically pure sample was prepared by preparative GLC to give an almost colorless oil: IR (CCl_4) 2964, 2940, 2870, 1720, 1485, 1450, 1420, 1330, 1260, and 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6 H, d, J = 7 Hz), 1.45 (3 H, d, J = 7 Hz), 2.33–2.67 (2 H, m), 2.77–3.64 (4 H, m), 3.75 (3 H, s), 6.95 (1 H, d, J = 8 Hz), and 7.20 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 213 (5), 186 (52), 110 (100), 52 (21).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.68. Found: C, 77.43; H, 8.53.

7-Isopropyl-8-methoxy-4a-methyl-4,4a,9,10-tetrahydro-2(3*H*)-phenanthrenone (17). To a deoxygenated solution of 43.20 g (0.655 mol) of 85% potassium hydroxide in 88 mL of water diluted with 1 L of reagent methanol and cooled to 0 °C was added under a nitrogen atmosphere a solution of 132.40 g (0.570 mol) of **16** in 200 mL of reagent methanol. The rapidly stirred solution was cooled to −20° C (dry ice/CCl_4), and 4.7 mL (41 g, 0.577 mol) of 98.5% methyl vinyl ketone (Aldrich) was added slowly over a 15-min period under nitrogen. After 1 h the cooling bath was removed and stirring was continued overnight at room temperature. The mixture was stirred under reflux for 3 h, cooled with an ice bath, and quenched with a solution of 65 mL of concentrated hydrochloric acid which had been diluted to a volume of 250 mL with water. The mixture was diluted with 500 mL of water and extracted with three 1-L portions of ethyl ether. The ether solution was washed with two 1-L portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a yellow solid which was dissolved in 250 mL of hot absolute ethanol and refrigerator cooled to give 130.8 g (81%) of **17** as pale yellow needles, mp (sublimed 94 °C) 100–106 °C. The product was sufficiently pure to use in the next reaction. An analytically pure sample was prepared by two recrystallizations from ethanol to give almost colorless prisms: mp 106–108.5 °C (partially resolidifies and remelts at 116–116.5 °C); IR ($CHCl_3$) 3000, 2970, 2870, 1660, 1625, 1485, 1445, 1410, 1355, 1330, 1260, 1245, and 1030 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (3 H, d, J = 7 Hz), 1.26 (3 H, d, J = 7 Hz), 1.57 (3 H, s), 1.78–3.55 (9 H, m), 3.69 (3 H, s), 5.89 (1 H, s), 7.04 (1 H, d, J = 8 Hz), and 7.15 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 285 (10), 284 (M^+, 46), 270 (20), 269 (100), 227 (16).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.50; H, 8.36.

7-Isopropyl-8-methoxy-4aβ-methyl-3,4,4a,9,10,10aα-hexahydro-2(1*H*)-phenanthrenone (18). The reduction was run in a nitrogen atmosphere under anhydrous conditions with the usual precautions. Into a 2-L three-neck round-bottom flask equipped with dry ice condenser and mechanical stirrer was condensed 500 mL of liquid ammonia. The system was briefly opened to introduce 1.03 g (148 mmol) of lithium wire in about six pieces. After 5 min a solution of 20.0 g (70.5 mmol) of **17** in 500 mL of dry THF was added to the stirring solution via cannula. The dry ice bath was removed, and after stirring for 30 min 0.12 g (17 mmol) of lithium wire was added. After stirring for an additional 1 h 10 mL of water was slowly added via syringe, and the ammonia was allowed to evaporate. The mixture was diluted with 350 mL of water and extracted with two 500-mL portions of ethyl ether. The ether solution was washed with two 250-mL portions of water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give an oil which solidified upon pentane trituration to give 19.82 g of a pale yellow solid containing 10–15% of starting material. The crude product was recrystallized from absolute ethanol to give 13.18 g (66%) of **18** as an almost colorless solid, mp 107–111 °C.

An NMR spectrum indicated about 5% contamination by starting material. On smaller scale crude product was purified by dry column chromatography on alumina (CH_2Cl_2) to give 81% yield of pure **18**. An analytically pure sample was prepared from chromatographed material by recrystallization from pentane to give clusters of very fine colorless needles and thin plates: mp 113.5–115 °C; IR (CCl_4) 2960, 2940, 2870, 1715, 1410, and 1035 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (6 H, d, J = 7 Hz), 1.30 (3 H, s), 1.4–3.2 (11 H, m), 3.29 (1 H, septet, J = 7 Hz), 3.69 (3 H, s), and 7.06 ppm (2 H, s); MS *m/e* (rel intensity) 287 (21), 286 (M^+, 100), 272 (19), 271 (96), 229 (47), and 55 (33).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.67; H, 9.15. Found: C, 79.80; H, 9.20.

2β-Acetoxy-7-isopropyl-8-methoxy-4aβ-methyl-1,2,3,4,4a,-9,10,10aα-octahydrophenanthrene (19). To a solution of 47.62 g (0.182 mol) of lithium tri-*tert*-butoxyaluminum hydride (Alfa) in 500 mL of dry THF cooled to −15 to −20 °C (dry ice/CCl_4) under a nitrogen atmosphere was added via cannula a solution of 40.33 g (0.141 mol) of **18** in 250 mL of dry THF. After 20 min the cooling bath was removed, and stirring was continued at room temperature for 4 h. With ice-bath cooling 200 mL of 10% aqueous hydrochloric acid was added (with caution at first via syringe). The mixture was filtered, and the salts were washed with 100 mL of THF and with 400 mL of ethyl ether. The combined filtrate and washes were diluted with 250 mL of water and extracted with two 500-mL portions of ethyl ether. The ether solution was washed with two 500-mL portions of water and with saturated brine, dried (Na_2SO_4), and concentrated to give a viscous oil which was stirred with 500 mL of acetic anhydride and 30 mL of pyridine at room temperature overnight. The volatiles were removed under high vacuum to give a wet solid which was recrystallized from 200 mL of methanol to give from three crops 36.43 g (78%) of **19** as colorless needles, mp 90–95 °C. An analytically pure sample was prepared by two recrystallizations from methanol to give clusters of beautiful, colorless needles: mp 94.5–96 °C; IR (CCl_4) 2960, 2940, 2870, 1730, 1410, 1360, 1245, and 1035 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.12 (3 H, s), 1.23 (6 H, d, J = 7 Hz), 1.3–2.4 (9 H, m), 2.03 (3 H, s), 2.6–3.1 (2 H, m), 3.28 (1 H, septet, J = 7 Hz), 3.69 (3 H, s), 4.75 (1 H, br m), and 7.04 ppm (2 H, s); MS *m/e* (rel intensity) 331 (12), 330 (M^+, 48), 256 (21), 255 (100), and 43 (63).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.16; H, 9.20.

2β-Acetoxy-7-isopropyl-8-methoxy-4aβ-methyl-2,3,4,4a,10,-10aα-hexahydro-9(1*H*)-phenanthrenone (20). A solution of 13.00 g (130 mmol) of chromium trioxide in 100 mL of acetic acid/water (90:10) was added over a 20-min period to a water bath cooled solution of 21.52 g (65.2 mmol) of **19** in 80 mL of glacial acetic acid. After stirring for 2 h at room temperature an additional 13.00 g (130 mmol) of chromium trioxide in 100 mL of acetic acid/water (90:10) was added. After stirring for an additional 2 h at room temperature 9.80 g (98 mmol) of chromium trioxide in 65 mL of acetic acid/water (90:10) was added following by stirring for 2 h. The solution was then diluted with an equal volume of water and extracted with two 500-mL portions of chloroform. The chloroform solution was washed with two 500-mL portions of water, 250 mL of saturated sodium bicarbonate solution, 500 mL of water, and with two portions of saturated brine, dried ($MgSO_4$), and evaporated in vacuo to give a semisolid. Dry column chromatography of the crude product on alumina ($CHCl_3$, two 2-in. diameter × 30 in. length columns, R_f 0.4) afforded 16.05 g (42%) of **20** as a pale yellow solid, mp 142–147 °C. An analytically pure sample of **20** was obtained by two recrystallizations of chromatographed material from hexanes to give fine, colorless needles: mp 159.5–161.5 °C; IR (CCl_4) 2960, 2930, 2870, 1735, 1685, 1470, 1385, 1365, 1235, and 1030 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.18 (3 H, s), 1.22 (3 H, d, J = 7 Hz), 1.25 (3 H, d, J = 7 Hz), 1.4–2.8 (9 H, m), 2.06 (3 H, s), 3.41 (1 H, septet, J = 7 Hz), 3.79 (3 H, s), 4.73 (1 H, br m), 7.13 (1 H, d, J = 8 Hz), and 7.43 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 345 (9), 344 (M^+, 33), 330 (25), 329 (100), and 43 (49).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.14; H, 8.30.

7-Isopropyl-8-methoxy-4aβ-methyl-1,2,3,4,4a,9,10,10aα-octahydro-2β,9β-phenanthrenediol (21). A mixture of 5.16 g (15 mmol) of **20** in 150 mL of 95% ethanol was warmed until complete solution was obtained, cooled with an ice bath, and treated with 1.13 g (30 mmol) of solid sodium borohydride. The solution was stirred at room temperature for 47 h, cooled, and neutralized with 25% aqueous hydrochloric acid. The mixture was diluted with water and extracted with two portions (350 and 200 mL) of ethyl ether. The ether solution was washed with two 200-mL portions of water, one portion of saturated sodium bicarbonate solution, and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give after high vacuum overnight 4.27 g (94%) of **21** as an almost colorless solid, mp 123–128 °C. Integration of a minor methoxy singlet at 3.86 ppm showed about 3% contamination by the α isomer. An analytical sample of **21** was prepared by two recrystallizations from hot ethyl ether with refrigerator cooling to give clusters of very fine, colorless needles: mp 135–136 °C; IR ($CHCl_3$) 3000, 2965, 2940, 2870, 1335, 1070, 1055, 1025, and 1005 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.20 (3 H, s), 1.21 (3 H, d, J = 7 Hz), 1.28 (3 H, d, J = 7 Hz), 1.3–2.3 (9 H, m), 1.80 (1 H, s, exchanges with D_2O), 3.29 (1 H, septet, J = 7 Hz), 3.66 (1 H, br m), 3.82 (3 H, s), 4.39 (1 H, s, exchanges with D_2O), 5.16 (1 H, br t, J = 8 Hz, half-band width 15 Hz), 7.07 (1 H, d, J = 8 Hz), and 7.18 ppm (1 H, d, J = 8 Hz); MS *m/e* (rel intensity) 306 (3), 305 (22), 304 (M^+, 100), 303 (24), 262 (27), 253 (65), 192 (78), 185 (20), and 177 (78).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.80; H, 9.24.

7-Isopropyl-4aβ-methyl-1,2,3,4,4a,9,10,10aα-octahydro-2β,8,-9β-phenanthrenetriol (22). In a 100-mL round-bottom flask under a nitrogen atmosphere 768 mg (16 mmol) of sodium hydride (50% oil dispersion) was washed with pentane. The pentane was removed via syringe, and 21 mL of dry DMF was added. To the ice-bath cooled mixture was slowly added dropwise via syringe 1.47 mL (16.2 mmol) of propanethiol. After completion of the addition the ice bath was removed, and a solution of 0.96 g (3.16 mmol) of **21** in 16 mL of dry DMF was added. The solution was stirred at 40 °C for 30 h under a nitrogen atmosphere. The cooled solution was then poured into 100 mL of cold 10% ammonium chloride solution and extracted with two 150-mL portions of ethyl ether. The ether solution was washed with water and with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give 0.99 g of **22** as a very pale yellow solid. Trituration of the crude product with benzene left 0.52 g (57%) of **22** as a white solid, mp 82–84 °C (to a wax which liquefied at 140 °C with decomposition). Evaporation of the benzene triturate gave 0.41 g (45%) of crude **22** (about 80% pure). An analytically pure sample was prepared by preparative layer chromatography on silica gel GF (Et_2O, R_f 0.5) to give a white solid which was recrystallized from benzene to give long, fine, colorless needles: mp 83–85 °C (to a waxy solid which liquefies up to 140 °C with decomposition): IR (KBr) 3320, 2950, 2930, 2860, 1450, 1420, 1380, 1335, 1275, 1250, 1105, 1030, 985, and 955 cm^{-1}; NMR (acetone-d_6, 90 MHz) δ 1.15 (3 H, s), 1.20 (3 H, d, J = 7 Hz), 1.22 (3 H, d, J = 7 Hz), 1.3–2.35 (9 H, m), 2.96 (1 H, br s, exchanges with D_2O), 3.31 (1 H, septet, J = 7 Hz), 3.45–3.8 (1 H, br m), 3.72 (1 H, br m, exchanges with D_2O), 5.07 (1 H, br t, half-band width 15 Hz), 5.35 (0.4 H, br m, exchanges with D_2O), 6.79 (1 H, d, J = 8 Hz), 7.06 (1 H, d, J = 8 Hz), and 10.07 ppm (0.6 H, br s, exchanges with D_2O); MS *m/e* (rel intensity) 186 (3), 110 (4), 78 (100), 77 (16), 52 (23), and 51 (21).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: 74.34; H, 8.89.

8a,9-Epoxy-2β-hydroxy-7-isopropyl-4aβ-methyl-1,2,3,4,4a,-10aα-hexahydro-8(10*H*)-phenanthrenone (23). To a stirred solution of 146 mg (0.504 mmol) of **22** in 3 mL of methanol was added a solution of 120 mg (0.561 mmol) of sodium metaperiodate in 0.75 mL of water. A precipitate formed after 30 s. After being stirred for 5 h at room temperature, the mixture was filtered and partitioned between chloroform and water. The chloroform solution was washed with saturated brine, dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. Preparative layer chromatography on silica gel GF (Et_2O, two developments, R_f after second development ⅔) afforded 96.2 mg (66%) of **23** as a pale yellow solid: mp (sublimed 40°C) 45–48 °C; IR (CCl_4) 3600 (m), 3450 (br), 2960, 2930, 2870, 1660, 1635, and 1040 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.10 (6 H, d, J = 7 Hz), 1.21 (3 H, s), 1.2–2.1 (9 H, m), 1.87 (1 H, s, exchanges with D_2O), 2.92 (1 H, br septet, J = 7 Hz), 3.56 (1 H, br m), 3.96 (1 H, m), 6.33 (1 H, d, J = 7 Hz), and 6.97 ppm (1 H, br d, J = 7 Hz); MS *m/e* (rel intensity) 290 (3), 289 (13), 288 (M^+, 57), 274 (20), 273 (100), 239 (18), 213 (20), 161 (30), 128 (28), 115 (32), 91 (36), 77 (31), 65 (21), 57 (37), 55 (45), 53 (27), 51 (20), 44 (25), 43 (79), 41 (95), 39 (42); UV (95% EtOH) 347.5 nm (ϵ 5600).

High-resolution mass spectrum calcd for $C_{18}H_{24}O_3$: 288.17254. Found: 288.17467 (allowed tolerance: 0.00244).

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Registry No.—**1**, 38748-32-2; **5**, 1078-19-9; **6**, 16252-53-2; **7**, 62416-05-1; **8**, 62416-06-2; **9**, 62416-07-3; **10**, 62416-08-4; **11**, 62416-09-5; **12**, 62416-10-8; **13**, 62416-11-9; **14**, 62416-12-0; **15**, 62416-13-1; **16**, 62460-42-8; **17**, 62416-14-2; **18**, 62416-15-3; **19**, 62416-16-4; **20**, 62416-17-5; **21**, 62416-18-6; **22**, 62416-19-7; **23**, 62416-20-0; ethyl formate, 109-94-4; butanethiol, 109-79-5.

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Base-Catalyzed Reactions of 1,3-Disubstituted Uracils[1]

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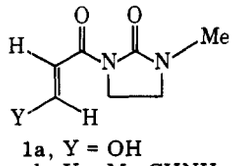
The first step in the base-catalyzed hydrolysis of 1,3-dialkyluracils (**2**) in both aqueous and Me_2SO solutions involves Michael addition to C-6 followed by ring opening between N-1 and C-6 to an enolate (**5**). From aqueous solution, with 1,3-dimethyluracil (**2a**) as substrate, formylacetic acid (**4'**) and *N,N'*-dimethylurea (**3a**) were isolated, but **5** was not observed. On the other hand, in Me_2SO evidence for the very rapid formation of the intermediate enolate was obtained. This enolate, however, was not the stable end product. In the reaction mixture it underwent a complex series of transformations leading finally to the formation of three products. Using **2a** as the disubstituted uracil, these were *N,N'*-dimethylurea (**3a**) and two *pyridine* derivatives: 1-methyl-5-(methylcarbamyl)-2-pyridone (**12a**) and 1-methyl-3-(methylaminomethylene)-2,6-pyridinedione (**13a**). 1-Ethyl-3-methyluracil (**2b**), 3-ethyl-1-methyluracil (**2c**), and 1,3-diethyluracil (**2d**) also yielded analogous, stable end products under the same conditions. A scheme is proposed to rationalize the conversion of **2** to **3**, **12**, and **13** by means of tetramethylammonium hydroxide in Me_2SO solution. The elaboration of this scheme was based on a body of data which included the isolation and characterization of an intermediate, 1,3-dimethyl-5-(methylaminomethylene)-6-(methylcarbamylmethyl)-5,6-dihydrouracil (**10a**), from the reaction of **2a** with TMAH in Me_2SO. It was found that the ethylmethyluracils, **2b** and **2c**, underwent an isomerization reaction in basic Me_2SO in which the positions of the alkyl groups were interchanged. This reaction, as well as the conversion of **2d** to **2a** by means of *N,N'*-dimethylurea in the same medium, provides additional evidence for the reversibility of the transformation of uracil, **2**, to enolate, **5**. The results obtained in this investigation provide alternative mechanisms for H-5 exchange in uracil derivatives and for a number of enzymatic C-methylation reactions. They also suggest a pathway for the biosynthesis of nudiflorine, a naturally occurring 2-pyridone, other than that previously reported.

Although the fact that 1,3-disubstituted uracils are unstable in alkaline solution has been known for more than two decades,[2] it is only recently that an aldehyde has been postulated as an intermediate in the degradation of such compounds.[3] An analogous aldehyde has been postulated as an intermediate in reactions of various substituted 6-hydroxy-5,6-dihydrouracils.[4]

During the course of a study of the reactions of 3-(β-methanesulfonyloxyethyl)-1-methyluracil with bases,[5] an aldehyde was obtained and was identified as N^1-(formylacetyl)-N^3-methylimidazolidone (**1a**). The UV absorption



1a, Y = OH
b, Y = Me_2CHNH

characteristics of Shugar's intermediate[4b] were the same as those of **1a**. Our present experiments elucidate, in detail, the base-catalyzed reactions of 1,3-dialkyluracils in both water and dimethyl sulfoxide (Me_2SO).

The reaction of 1,3-dimethyluracil (**2a**) with sodium hydroxide or tetramethylammonium hydroxide pentahydrate (TMAH) in aqueous solution was followed by means of both UV and ^1H NMR spectroscopy. The spectroscopic changes which were observed corresponded to the formation of 1,3-dimethylurea (**3a**) and the enolate of formyl acetate (**4**) (Scheme I). Unreacted **2a**, **3a**, and anion **4**, as its parent acid (**4'**),[6] were recovered from a reaction mixture by ion exchange chromatography. No intermediates were observed in this degradation even when the reaction conditions were modified. The spectroscopic properties of **4** support the structure assigned to it. The identity of **4'** was confirmed by conversion to its oxime.[7]

The behavior of **2a** in Me_2SO solution containing TMAH was much more complex than in aqueous solution. Scheme I is a representation that is in good agreement with our experimental observations. Compound **2a** was dissolved in Me_2SO containing TMAH. The changes which took place were followed by spectrophotometric observation of the reaction mixture. With a solution 0.1 M in both reactants, it was found that **2a** disappeared and a single new chromophore with λ_{max} 296 nm (**5a**) was produced. The rapidity with which this