Notes

An Efficient Preparation and Selected Birch Reduction−Alkylations of 3,4-Dihydro-4,5-dialkyl-2-benzopyran-1-ones

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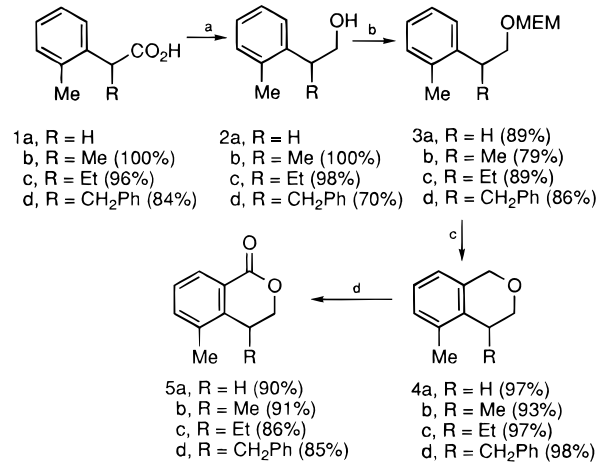
In connection with a study of the Birch reduction−alkylation of chiral 3,4-dihydroisoquinolin-1-ones[1] and related heterocyclic systems, we needed convenient access to 3,4-dihydro-4,5-dialkyl-2-benzopyran-1-ones (also called 3,4-dihydroisocoumarins); *e.g.*, **5a**−**d**. Dihydroisocoumarins occur widely in plants,[2] and certain 3,4-dihydro-8-hydroxyisocoumarins are used as trail marking pheromones by ants.[3] Although several methods for synthesis of 3,4-dihydroisocoumarins are available,[4] we desired a reasonably general procedure that would accommodate alkyl substitution at C(4) and C(5). We have developed and now report a synthesis of 3,4-dihydro-4,5-dialkyl-2-benzopyran-1-ones **5a**−**d** starting with readily available *o*-tolylacetic acid (**1a**) (Scheme 1). Selected Birch reduction−alkylations of **5b** and **5d** leading to bridged and fused tetracyclic lactones (Scheme 2) demonstrate the potential utility of chiral 3,4-dihydro-4,5-dialkyl-2-benzopyran-1-ones in organic synthesis.

Alkylation of the dianion of *o*-tolylacetic acid (**1a**) provided the α-substituted carboxylic acids **1b**−**d**.[5] Reduction of carboxylic acids **1a**−**d** with $LiAlH_4$ provided alcohols **2a**−**d**. Alcohols **2a**−**d** were converted to the 2-(methoxyethoxy)methyl (MEM) ethers **3a**−**d**, which were cyclized in the presence of $TiCl_4$[6] to give benzopyrans **4a**−**d**.

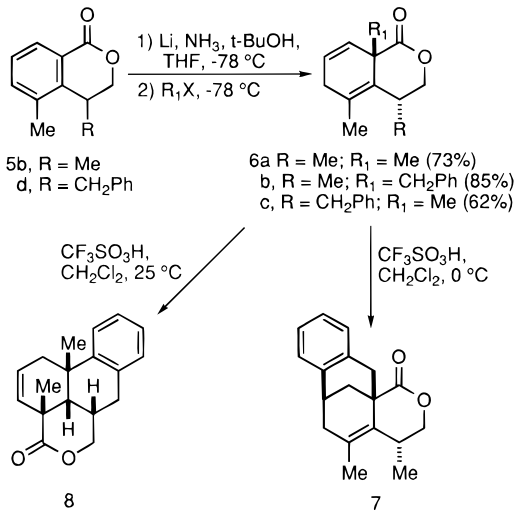
There are several methods available for the oxidation of methylene groups adjacent to aromatic rings and/or ether oxygen atoms.[7] Some[7a,d,f] were found to be suitable for oxidation of the benzopyrans **4a**−**d**, but the preferred reagent system consisting of potassium permanganate absorbed on alumina[8] gave the desired 3,4-dihydroisocoumarins in excellent yields by simple filtration of the reaction mixture and evaporation of solvent. This method of oxidation is ideally suited to large-scale laboratory synthesis because the use of more toxic and expensive oxidants and aqueous extraction procedures are avoided.

Scheme 1[a]



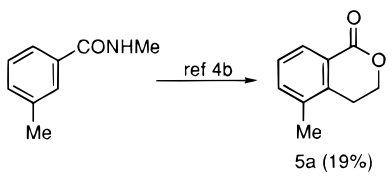
[a] Reaction conditions: (a) $LiAlH_4$, THF, reflux; (b) MEMCl, DIPEA, CH_2Cl_2; (c) $TiCl_4$, CH_2Cl_2, 0 °C; (d) $KMnO_4$, alumina, CH_2Cl_2, 25 °C.

Scheme 2



The efficiency of this procedure for 3,4-dihydroisocoumarin construction is illustrated by comparison of the overall yield for preparation of **5a** from *o*-tolylacetic acid (77% on a 17 g scale) to that for the only other reported synthesis of **5a** (19%).[4b] The literature method involves nuclear metalation of *N*-methyl-*m*-toluamide and alkylation with ethylene epoxide.

Box and Yiannikouros reported the Birch reduction−



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(2) Hill, R. A.; Krebs, H. C.; Verpoorte, R.; Wijnsma, R. *Progress in the Chemistry of Natural Products 49*; Springer: New York, 1986.
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(5) (a) Hauser, C. R.; Chambers, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 4942−4944. (b) Klärner, F.-G.; Band, R.; Glock, V.; König, W. A. *Chem. Ber.* **1992**, *125*, 197−208. (c) Ghosh, S.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1982**, *47*, 4692−4702.
(6) Ahmar, M.; Bloch, R. *Syn. Commun.* **1992**, *22*, 1417−1420.
(7) (a) PDC/t-BuOOH: Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048−5051. (b) $FeCl_3/H_2O$, *hν*: Barbier, M. *Helv. Chim. Acta* **1984**, *67*, 866−869. (c) $PdCl_2$, $CuCl_2$, CO, O_2/acetone (30 atm): Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1994**, 1149−1152. (d) Mn_2O_7/CCl_4−acetone: Trömel, M.; Russ, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1007−1009. (e) Stoichiometric RuO_4: Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205−211. (f) Catalytic RuO_4, $NaIO_4/CH_3CN$, CCl_4, H_2O: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.
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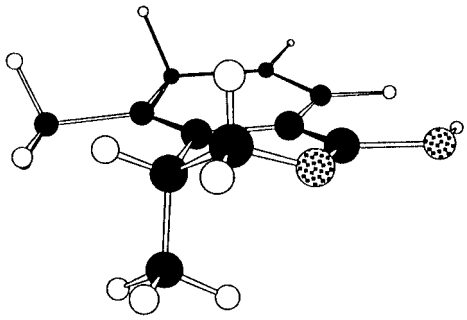

Figure 1. Most stable conformation of the enolate generated by Birch reduction of **5b** (MM2, MacroModel, Version 3.0).

alkylation of phthalides in 1990.[9a] We are aware of no other report of successful Birch reduction of aromatic lactones analogous to **5**. A problem with lactones in general is their susceptibility to ring-opening reactions by NH_3. In fact, **5a** is converted to the corresponding amido alcohol under conditions required for reduction with lithium; a control experiment with **5b** demonstrated complete stability in NH_3/THF solution at −33 °C for 1 h. The greater stability of **5b** toward lactone ring opening is attributed to the peri-effect involving the C(4) and C(5) methyl substituents.

Selected Birch reduction-alkylations of **5b** and **5d** are shown in Scheme 2. The diastereoselectivities for conversions to **6a**−**c** were found to be in excess of 10:1. The high degree of chirality transfer resulting from alkylations of enolates derived from **5b** and **5d** is explained by conformational control resulting from a relief of eclipsing interactions between the C(4) and C(5) substituents as shown in Figure 1. Thus, the methyl substituent at C(5) forces the substituent at C(4) to occupy a pseudoaxial position that very effectively blocks the α-face of the enolate.[9b]

These new procedures for stereoselective reductive alkylation are expected to be useful for the construction of complex carbocyclic frameworks. Two examples are shown in Scheme 2. Treatment of **6b** with CF_3SO_3H[10] gave the bridged tetracyclic lactone **7**. Analogous cyclization of **6c** gave the fused tetracyclic lactone **8** with all cis stereochemistry. Related acid-catalyzed cyclizations of β-arylethylcyclohexanols or the derived cyclohexenes give trans-fused or mixtures of trans- and cis-fused perhydrophenanthrenes.[10] Such cyclizations have found utility in diterpene synthesis; *e.g.*, podocarpic acid.[10f] The availability of technology for the production of optically active α-arylpropanoic acids (the Profen drugs)[11] suggests that the chemistry outlined in this report should be readily adaptable to asymmetric organic synthesis.

Experimental Section

Preparation of α-Alkylbenzeneacetic Acids: α,2-Dimethylbenzeneacetic acid (1b). To a solution of **1a** (5.0 g, 0.033 mol) in THF (100 mL) at −78 °C under N_2 was added *n*-butyllithium (32 mL, 0.08 mol in hexanes) over 15 min. After 20 min, methyl iodide (8.3 mL, 0.13 mol) was added in one portion. The cold bath was left in place, and the reaction was allowed to warm to room temperature (~3 h) and then stirred overnight at room temperature. The solution was acidified with 10% aqueous HCl, diluted with water (100 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with sodium thiosulfate, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide **1b**[5] as a white solid (5.4 g, 100%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 7.1 Hz, 1 H), 7.17−7.22 (m, 3 H), 4.00 (q, J = 7.1 Hz, 1 H), 2.40 (s, 3 H), 1.50 (d, J = 7.0 Hz, 3 H).

α-Ethyl-2-methylbenzeneacetic Acid (1c). Reaction of **1a** with ethyl bromide on a 1.0 g scale provided **1c** (1.14 g, 96%) as a crystalline solid (mp 102−104 °C): ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 7.3 Hz, 1 H), 7.15−7.20 (m, 3 H), 3.76 (t, J = 7.5 Hz, 1 H), 2.39 (s, 3 H), 2.10−2.15 (m, 1 H), 1.76−1.81 (m, 1 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.45, 136.90, 136.43, 130.47, 127.12, 126.78, 126.39, 48.36, 25.79, 19.84, 12.11; IR (film) 3500−2700 (br), 1700 cm^{-1}; CIMS m/z (relative intensity) 179 (M^+ + 1, 100), 161 (10), 133 (75).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.27; H, 7.97.

α-(2-Methylphenyl)benzenepropionic Acid (1d). Reaction of **1a** with benzyl bromide on a 5.0 g scale provided **1d** (7.40 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, J = 7.5, 1.2 Hz, 1 H), 7.08−7.24 (m, 8 H), 4.12−4.15 (m, 1 H), 3.42 (dd, J = 13.7, 8.0 Hz, 1 H), 2.98 (dd, J = 13.7, 6.9 Hz, 1 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.90, 138.89, 136.57, 136.35, 130.35, 128.89, 128.34, 127.36, 126.89, 126.47, 126.42, 48.68, 38.90, 19.65; IR (film) 3000−2800 (br), 1705 cm^{-1}; CIMS m/z (relative intensity) 241 (M^+ + 1, 100), 195 (16).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 78.93; H, 6.76.

Preparation of β-Alkylbenzeneethanols: β,2-Dimethylbenzeneethanol (2b). 1b (5.12 g, 0.03 mol) dissolved in THF (30 mL) was added to a stirred slurry of $LiAlH_4$ (1.50 g, 0.04 mol) in THF (100 mL). The resulting solution was stirred at reflux for 2 h, cooled to room temperature, and then quenched with 10% aqueous KOH and heated until a white precipitate formed. The clear solution was filtered, and the white precipitate was refluxed (10 min) with another 100 mL of THF. The combined filtered organic phases were subjected to rotary evaporation to provide an oil that was diluted with CH_2Cl_2 (150 mL), washed with brine (50 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation gave **2b** (4.69 g, 100%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.13−7.22 (m, 4 H), 3.74 (overlapping dd, J = 10.7, 7.1 Hz, 1 H), 3.68 (overlapping dd, J = 10.8, 6.6 Hz, 1 H), 3.26 (q, J = 7.0 Hz, 1 H), 2.38 (s, 3 H), 1.25 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.75, 136.38, 130.51, 126.32, 126.22, 125.40, 67.94, 37.13, 19.56, 17.46; IR (CH_2Cl_2) 2970, 1490, 1465, 1385, 1080 cm^{-1}; CIMS m/z (relative intensity) 150 (M^+ + 1, 10), 133 (100).

β-Ethyl-2-methylbenzeneethanol (2c). Reduction of **1c** (4.9 g) provided **2c** (4.42 g, 98%). Chromatographic purification was unnecessary: ^{1}H NMR ($CDCl_3$) δ 7.17−7.22 (m, 3 H), 7.11−7.14 (m, 1 H), 3.72−3.79 (m, 2 H), 3.06−3.11 (m, 1 H), 2.36 (s, 3 H), 1.76−1.81 (m, 1 H), 1.56−1.62 (m, 1 H), 0.84 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.43, 137.30, 130.45, 126.31, 126.15, 125.70, 66.94, 44.56, 44.53, 25.10, 19.97, 19.90, 11.80; IR (film) 3350, 2940 cm^{-1}; CIMS m/z (relative intensity) 164 (20), 147 (100), 133 (50).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 80.44; H, 9.82. Found: C, 80.16; H, 9.77.

β-(2-Methylphenyl)benzenepropanol (2d). Reduction of **1d** (7.40 g) provided **2d** (5.26 g, 70%, two steps) after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.07 (m, 9 H), 3.81 (d, J = 6.6 Hz, 2 H), 3.43 (m, J = 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 3.02 (dd, J = 13.4, 7.3 Hz, 1 H), 2.85 (dd, J = 13.4, 7.3 Hz, 1 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.03, 137.03, 130.52, 128.99, 128.21, 126.39, 126.29, 126.00, 125.98, 65.87, 44.81, 38.90, 19.64 (three missing/overlapping peaks); IR (film) 3370 (br), 3040, 2950, 1040 cm^{-1}; CIMS m/z (relative intensity) 209 (35), 131 (60), 117 (100).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.65; H, 8.06.

Preparation of MEM Ethers: [1-[(2-Methoxyethoxy)-methoxy]-2-methylethyl]benzene (3b). To a stirred solution

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(11) (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163. (b) Manimaran, T.; Stahly, G. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1949−1954.

of **2b** (2.18 g, 0.016 mol) in CH_2Cl_2 (50 mL) was added *N*,*N*-diisopropylethylamine (DIPEA, 3.60 mL, 0.02 mol) and (2-methoxyethoxy)methyl chloride (2.2 mL, 19 mmol). The reaction was stirred at room temperature for 8 h, diluted with CH_2Cl_2 (50 mL), washed with aqueous HCl, dried, filtered, and evaporated. Flash chromatography (hexane−ethyl acetate, 4:1) provided **3b** (2.84 g, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.08−7.22 (m, 4 H), 4.68−4.71 (m, 2 H), 3.71 (dd, J = 7.8, 6.5 Hz, 1 H), 3.56−3.64 (m, 3 H), 3.49−3.53 (m, 2 H), 3.39 (s, 3 H), 3.27−3.34 (m, 1 H), 2.37 (s, 3 H), 1.28 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.32, 135.77, 130.24, 126.04, 125.97, 125.46, 95.37, 72.85, 71.67, 66.58, 58.91, 34.84, 19.43, 18.05; IR (CH_2Cl_2) 2925, 2880, 1110, 1045 cm^{-1}; CIMS m/z (relative intensity) 239 (M^+ + 1, 20), 163 (100), 133(35).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.53; H, 9.51.

[1-[(2-Methoxyethoxy)methoxy]-2-methylpropyl]benzene (3c). 2c (4.0 g) provided **3c** (5.5 g, 89%) after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.13−7.17 (m, 3 H), 7.07−7.11 (m, 1 H), 4.67 (d, J = 6.9 Hz, 1 H), 4.64 (d, J = 6.9 Hz, 1 H), 3.66−3.69 (m, 2 H), 3.47−3.60 (m, 4 H), 3.37 (s, 3 H), 3.08−3.14 (m, 1 H), 2.34 (s, 3 H), 1.82−1.88 (m, 1 H), 1.57−1.63 (m, 1 H), 0.82 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.05, 136.57, 130.13, 125.95, 125.84, 125.83, 95.37, 71.92, 71.68, 66.53, 58.91, 42.04, 25.45, 19.83, 11.69; IR (film) 2930, 1450, 1050 cm^{-1}; CIMS m/z (relative intensity) 253 (M^+ + 1, 10), 177 (100), 147 (30).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.57.

[3-[(2-Methoxyethoxy)methoxy]-2-(2-methylphenyl)]propyl]benzene (3d). 2d (1.37 g) provided **3d** (1.64 g, 86%) as a clear, colorless oil after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.00−7.30 (m, 9 H), 4.66 (m, 2 H), 3.71 (d, J = 6.6 Hz, 2 H), 3.53−3.56 (m, 2 H), 3.44−3.49 (m, 3 H), 3.36 (s, 3 H), 3.09 (dd, J = 13.7, 6.6 Hz, 1 H), 2.85 (dd, J = 13.7, 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 140.64, 140.05, 136.33, 130.12, 129.00, 128.03, 126.21, 126.02, 125.88, 125.84, 95.44, 71.64, 70.85, 66.61, 58.89, 42.41, 39.15, 19.56; IR (film) 2940, 1450, 1050 cm^{-1}; CIMS m/z (relative intensity) 315 (M^+ + 1, 5), 239 (85), 221 (100).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.12; H, 8.26.

1-[[(2-Methoxyethoxy)methoxy]ethyl]-2-methylbenzene (3a). 2a[12] (18.0 g, 0.133 mol) provided **3a** (26.5 g, 89%) as a clear, colorless oil after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.12−7.16 (m, 4 H), 4.72 (s, 2 H), 3.76 (t, J = 7.3 Hz, 2 H), 3.62 (m, 2 H), 3.50 (m, 2 H), 3.38 (s, 3 H), 2.91 (t, J = 7.3 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.82, 136.30, 130.11, 129.32, 126.33, 125.87, 95.29, 71.69, 67.45, 66.63, 58.92, 33.40, 19.33; IR (film) 2870, 1100 cm^{-1}; CIMS m/z (relative intensity) 225 (M^+ + 1, 100), 165 (90), 149 (50), 118 (24).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.47; H, 8.93.

Preparation of 3,4-Dihydro-2(1*H*)-benzopyrans: 3,4-Dihydro-4,5-dimethyl-2(1*H*)-benzopyran (4b). To a flame-dried flask were added **3b** (3.80 g, 0.016 mol) and CH_2Cl_2 (100 mL). The stirred solution was cooled to 0 °C, and $TiCl_4$ (2.10 mL, 19 mmol) in CH_2Cl_2 (20 mL) was added via addition funnel. The yellow solution was stirred for an additional 2 h at 0 °C, whereupon the reaction was quenched with the slow addition of water (30 mL). The two-phase system was warmed to room temperature and allowed to stir until the organic layer was clear. The organic phase was collected, and the aqueous layer was washed with CH_2Cl_2 (50 mL). The combined organic layers were dried, filtered, and evaporated to provide **4b**[6] (2.42 g, 93%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.08 (t, J = 7.6 Hz, 1 H), 7.04 (m, 1 H), 6.82 (d, J = 7.3 Hz, 1 H), 4.83 (d, J = 15.2 Hz, 1 H), 4.75 (d, J = 15.2 Hz, 1 H), 3.93 (d, J = 11.0 Hz, 1 H), 3.81 (dd, J = 11.0, 2.8 Hz, 1 H), 2.81−2.83 (m, 1 H), 2.32 (s, 3 H), 1.33 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.12, 135.74, 133.86, 128.28, 125.77, 121.92, 71.02, 68.02, 30.08, 19.09, 18.01; IR ($CDCl_3$) 2970, 1450, 1125, 920 cm^{-1}; CIMS m/z (relative intensity) 163 (M^+ + 1, 100).

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3,4-Dihydro-4-ethyl-5-methyl-2(1*H*)-benzopyran (4c). 3c (5.0 g) provided **4c** (3.4 g, 97%) as a pale-yellow oil. Chromatographic purification was unnecessary: ^{1}H NMR ($CDCl_3$) δ 7.04−7.10 (m, 2 H), 6.81 (d, J = 7.4 Hz, 1 H), 4.81 (d, J = 14.9 Hz, 1 H), 4.76 (d, J = 14.9 Hz, 1 H), 4.16 (d, J = 11.5 Hz, 1 H), 3.67−3.70 (dd, J = 11.3, 2.7 Hz, 1 H), 2.46 (m, 1 H), 2.30 (s, 3 H), 1.76−1.83 (m, 1 H), 1.51−1.58 (m, 1 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.93, 135.86, 133.95, 128.33, 125.78, 121.80, 67.99, 66.52, 37.28, 25.33, 18.04, 12.36; IR (film) 2950, 1460, 1120 cm^{-1}; CIMS m/z (relative intensity) 177 (M^+ + 1, 100), 159 (10), 147 (12).

3,4-Dihydro-5-methyl-4-(phenylmethyl)-2(1*H*)-benzopyran (4d). 3d (1.88 g) provided **4d** (1.38 g, 98%) as a white solid (mp 72−73 °C). Chromatographic purification was unnecessary: ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 4 H), 7.24−7.30 (m, 1 H), 7.08−7.18 (m, 2 H), 6.88 (d, J = 7.3 Hz, 1 H), 4.92 (d, J = 15.0 Hz, 1 H), 4.81 (d, J = 15.0 Hz, 1 H), 3.97 (d, J = 11.5 Hz, 1 H), 3.58 (dm, J = 11.2 Hz, 1 H), 2.85−3.01 (m, 3 H), 2.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.59, 136.08, 135.75, 134.33, 129.34, 128.51, 126.19, 126.18, 122.07, 68.11, 65.90, 38.31, 37.69, 18.22; IR (film) 2850, 1450, 1110 cm^{-1}; CIMS m/z (relative intensity) 239 (M^+ + 1, 95), 221 (100), 146 (10).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.79; H, 7.65.

3,4-Dihydro-5-methyl-2(1*H*)-benzopyran (4a). 3a (11.8 g, 53 mmol) provided **4a** (7.6 g, 97%). Chromatographic purification was unnecessary: ^{1}H NMR ($CDCl_3$) δ 7.08 (m, 2 H), 7.05 (dd, J = 7.3, 0.7 Hz, 1 H), 4.77 (s, 2 H), 4.02 (t, J = 5.7 Hz, 2 H), 2.72 (d, J = 5.7 Hz, 2 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.44, 134.74, 131.68, 127.65, 125.60, 121.97, 68.27, 65.49, 26.07, 18.78; IR (film) 2930, 2850, 1120 cm^{-1}; CIMS m/z (relative intensity) 163 (M^+ + 15, 50), 149 (M^+ + 1, 100), 119 (6).

Oxidation of 3,4-Dihydro-2(1*H*)-benzopyrans: 3,4-Dihydro-4,5-dimethyl 2(1*H*)-benzopyran-1-one (5b). A solution of **4b** (100 mg, 0.6 mmol) in methylene chloride (5 mL) was stirred with $KMnO_4/Al_2O_3$ (5 equiv) at room temperature for 6 h. The solvent was filtered through Celite, dried, filtered, and evaporated to provide lactone **5b** (99 mg, 91%) as a colorless oil that solidified upon standing. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.29 (t, J = 7.8 Hz, 1 H), 4.54 (dd, J = 11.0, 3.1 Hz, 1 H), 4.40 (d, J = 11.2 Hz, 1 H), 3.09−3.12 (m, 1 H), 2.37 (s, 3 H), 1.36 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.34, 143.20, 135.43, 134.30, 128.32, 127.06, 124.12, 72.18, 29.48, 17.95, 17.18; IR (CH_2Cl_2) 2980, 1715, 1140, 1020 cm^{-1}; CIMS m/z (relative intensity) 177 (M^+ + 1, 100).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.93; H, 6.82.

3,4-Dihydro-4-ethyl-5-methyl-2(1*H*)-benzopyran-1-one (5c): yield 86% (mp 68−70 °C); ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.26−7.29 (m, 1 H), 4.59 (dd, J = 11.3, 1.3 Hz, 1 H), 4.44 (dd, J = 11.2, 2.9 Hz, 1 H), 2.79−2.82 (m, 1 H), 2.35 (s, 3 H), 1.71−1.77 (m, 1 H), 1.59−1.63 (m, 1 H), 1.08 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.56, 142.66, 135.45, 134.43, 128.25, 127.07, 124.46, 68.54, 36.24, 24.21, 18.21, 12.12; IR (KBr) 2950, 1700, 1270 cm^{-1}; CIMS m/z (relative intensity) 191 (M^+ + 1, 100).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.86; H, 7.45.

3,4-Dihydro-5-methyl-4-(phenylmethyl)-2(1*H*)-benzopyran-1-one (5d): yield 85% (mp 101−104 °C); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 7.9 Hz, 1 H), 7.43 (d, J = 7.6 Hz, 1 H), 7.31−7.37 (m, 3 H), 7.23-7.29 (m, 3 H), 4.33−4.40 (m, 2 H), 3.08−3.14 (m, 1 H), 2.86−2.90 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.43, 141.73, 138.52, 135.58, 134.61, 129.16, 128.73, 128.51, 127.43, 126.77, 124.59, 68.22, 37.20, 37.06, 18.06 (two missing/overlapping peaks); IR (KBr) 2910, 1710, 1280 cm^{-1}; CIMS m/z (relative intensity) 253 (M^+ + 1, 100).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.86; H, 6.33.

3,4-Dihydro-5-methyl-2(1*H*)-benzopyran-1-one (5a):[4b] 90% yield on a 16.68 g scale (mp 68−70 °C); ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 7.8 Hz, 1 H), 7.40 (d, J = 7.3 Hz, 1 H), 7.29 (t, J = 7.5 Hz, 1 H), 4.53 (t, J = 6.0 Hz, 2 H), 2.98 (t, J = 6.0 Hz, 2 H), 2.33 (s, 3 H).

Preparation of 3,4,6,8a-Tetrahydro-4,5,8a-trialkyl-2(1*H*)-benzopyran-1-ones: (4R*,8aS*)-3,4,6,8a-Tetrahydro-4,5,8a-trimethyl-2(1*H*)-benzopyran-1-one (6a). A solution of **5b** (50 mg, 0.28 mmol) in THF (1.5 mL) was cooled to −78 °C, and

ammonia (30 mL) and *tert*-butyl alcohol (27 μL, 1 equiv) were added. Lithium (5 mg) was added to the stirred solution in small pieces. After 15 min, piperylene (100 μL) and methyl iodide (180 μL, 10 equiv) were added, and the resulting solution was stirred for 30 min at −78 °C. After the addition of NH_4Cl (0.1 g), the ammonia was allowed to evaporate, and water (10 mL) was added. The mixture was extracted with methylene chloride (3 × 10 mL). The combined organic phases were washed successively with 10% aqueous sodium thiosulfate and brine. Drying, solvent evaporation, and flash chromatography (hexane/ethyl acetate, 4:1) provided **6a** (40 mg, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.46 (dd, J = 9.6, 3.2 Hz, 1 H), 5.77 (m, 1 H), 4.67 (dd, J = 11.2, 2.9 Hz, 1 H), 4.14 (dd, J = 11.3, 1.3 Hz, 1 H), 3.00 (m, 1 H), 2.63 (d, J = 21.7 Hz, 1 H), 2.54 (dd, J = 21.7, 4.9 Hz, 1 H), 1.74 (s, 3 H), 1.33 (s, 3 H), 1.10 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.70, 131.70, 131.31, 128.82, 123.74, 70.98, 43.19, 32.31, 31.08, 27.49, 18.98, 18.50; IR (CH_2Cl_2) 2975, 2930, 1730, 1135 cm^{-1}; CIMS m/z (relative intensity) 193 (M^+ + 1, 100), 177 (9), 133 (26). An acceptable analysis could not be obtained; the 6-oxo analogue was prepared as a stable derivative.

(4*R,8a*S**)-6-Oxo-3,4,6,8a-tetrahydro-4,5,8a-trimethyl-2(1*H*)-benzopyran-1-one.** To a solution of **6a** (100 mg, 0.52 mmol) in benzene (7 mL) was added Celite (1 g), PDC (21 mg, 0.1 equiv), and *tert*-butyl hydroperoxide (0.17 mL, 90% solution, 3 equiv). The reaction was stirred at room temperature for 8 h, filtered through Celite, evaporated, and chromatographed on silica gel (hexane−ethyl acetate, 1:1) to provide a small amount of compound (60 mg, 56%) as a pale-yellow oil. Recrystallization from hexane−ethyl acetate provided the analytical sample as white crystals (mp 86−89 °C): ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 10.0 Hz, 1 H), 6.19 (d, J = 10.0 Hz, 1 H), 4.87 (dd, J = 12.0, 3.2 Hz, 1 H), 4.26 (dd, J = 12.0, 0.8 Hz, 1 H), 3.21−3.23 (m, 1 H), 1.91 (s, 3 H), 1.65 (s, 3 H), 1.24 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.75, 169.67, 154.99, 149.34, 132.94, 126.44, 70.52, 46.36, 32.44, 29.62, 18.18, 12.16; IR (KBr) 2980, 2930, 1725, 1650, 1625, 1250, 1135 cm^{-1}; CIMS m/z (relative intensity) 207 (M^+ + 1, 82), 163 (100), 143 (15).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.66; H, 6.77.

(4*R,8a*S**)-4,5-Dimethyl-8a-(phenylmethyl)-3,4,6,8a-tetrahydro-2(1*H*)-benzopyran-1-one (6b).** Reaction of **5b** (50 mg) with benzyl bromide gave **6b** (65 mg, 85%) after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.18−7.30 (m, 3 H), 7.00−7.02 (m, 1 H), 6.29 (dd, J = 9.7, 3.2 Hz, 1 H), 5.76 (ddd, J = 9.7, 5.0, 2.1 Hz, 1 H), 4.85 (dd, J = 11.6, 3.0 Hz, 1 H), 4.22 (dd, J = 11.5, 1.2 Hz, 1 H), 3.06−3.08 (m, 1 H), 2.94 (d, J = 13.2 Hz, 1 H), 2.84 (d, J = 13.2 Hz, 1 H), 2.13 (dd, J = 22.0, 5.0 Hz, 1 H), 1.63 (s, 3 H), 1.41 (dd, J = 22.0, 1.1 Hz, 1 H), 1.16 (d, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.52, 134.94, 132.39, 131.19, 128.22, 128.02, 127.24, 126.64, 126.28, 71.14, 49.29, 45.33, 32.56, 31.38, 19.35, 18.99; IR (film) 2930, 1725, 1255 cm^{-1}; CIMS m/z (relative intensity) 269 (M^+ + 1, 94), 251 (85), 177 (56), 133 (100).

(4*R,8a*S**)-5,8a-Dimethyl-4-(phenylmethyl)-3,4,6,8a-tetrahydro-2(1*H*)-benzopyran-1-one (6c).** Reaction of **5d** (50 mg) with methyl iodide gave **6c** (33 mg, 62%) as a pale-yellow oil after flash chromatography (hexane/ethyl acetate, 4:1): ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 2 H), 7.22−7.28 (m, 3 H), 6.56 (dd, J = 9.5, 2.9 Hz, 1 H), 5.84 (ddd, J = 9.5, 5.0, 2.2 Hz, 1 H), 4.44 (ddd, J = 11.7, 2.7, 1.0 Hz, 1 H), 4.13 (dd, J = 10.7, 1.5 Hz, 1 H), 3.14 (dm, J = 10.7 Hz, 1 H), 2.55−2.74 (m, 4 H), 1.85 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.82, 138.70, 131.58, 130.93, 129.78, 129.30, 128.59, 126.53, 123.93, 66.20, 43.51, 38.79, 37.37, 32.65, 27.82, 19.16; IR (film) 2930, 1740, 1130 cm^{-1}; CIMS m/z (relative intensity) 269 (M^+ + 1, 100), 251 (16).

(4*R,7*S**,12a*R**)-12*H*-4,5-Dimethyl-7,12a-methano-3,4,6,7-tetrahydro-1*H*-benzo[6,7]cycloocta[c]pyran-1-one (7).** A solution of **6b** (30 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C, trifluoromethanesulfonic acid (5 drops) was added, and the reaction was stirred at this temperature for 50 min. Neutralization with aqueous $NaHCO_3$, followed by CH_2Cl_2 extraction, drying, filtration, evaporation, and flash chromatography (hexane/ethyl acetate, 4:1), provided **7** (19 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 7.10−7.20 (m, 3 H), 7.03 (d, J = 7.0 Hz, 1 H), 4.87 (dd, J = 11.5, 2.9 Hz, 1 H), 4.18 (dd, J = 11.4, 1.3 Hz, 1 H), 3.22−3.25 (m, 1 H), 3.20 (dd, J = 16.6, 1.9 Hz, 1 H), 3.06 (d, J = 16.4 Hz, 1 H), 2.85−2.92 (m, 1 H), 2.59 (dd, J = 17.6, 5.9 Hz, 1 H), 2.31 (dd, J = 12.3, 3.9 Hz, 1 H), 1.95−2.04 (m, 2 H), 1.57 (s, 3 H), 1.18 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.87, 141.27, 131.75, 129.45, 129.41, 128.76, 128.49, 126.45, 126.24, 71.02, 42.10, 42.06, 38.82, 32.81, 31.50, 31.27, 19.63, 18.79; IR (film) 2930, 1735 cm^{-1}; CIMS m/z (relative intensity) 269 (M^+ + 1, 100), 177 (33).

(3a*R,6a*R**,11b*R**,11c*R**)-3a,11b-Dimethyl-3a,6,6a,7,11b,11c-hexahydro-1*H*,4*H*-phenanthro[1,10-*cd*]pyran-4-one (8).** To a solution of **6c** (25 mg, 0.1 mmol) in methylene chloride (2 mL) at room temperature was added trifluoromethanesulfonic acid (3 drops). The solution was stirred at room temperature for 12 h, neutralized with aqueous $NaHCO_3$, and washed with methylene chloride (3 × 15 mL). The combined organic phases were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to provide **8** (10 mg, 40%, unoptimized): ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 7.8 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.09 (dd, J = 7.6, 7.3 Hz, 1 H), 7.03 (d, J = 7.6 Hz, 1 H), 6.11 (dd, J = 9.8, 2.5 Hz, 1 H), 5.73 (ddd, J = 9.8, 6.4, 3.4 Hz, 1 H), 4.50 (dd, J = 11.0, 2.2 Hz, 1 H), 4.39 (dd, J = 11.1, 4.0 Hz, 1 H), 2.85 (dd, J = 16.9, 6.7 Hz, 1 H), 2.75 (dd, J = 16.9, 10.0 Hz, 1 H), 2.68 (dd, J = 16.0, 6.5 Hz, 1 H), 2.59−2.64 (m, 1 H), 2.27 (d, J = 5.8 Hz, 1 H), 2.16 (dm, J = 16.0 Hz, 1 H), 1.51 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.09, 141.87, 135.06, 132.79, 128.60, 126.70, 126.57, 125.94, 125.79, 71.68, 51.13, 43.67, 40.10, 35.73, 32.37, 30.62, 30.44, 28.55.

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Supporting Information Available: ^{1}H NMR spectra of **6a**−**c**, **7**, and **8** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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