Synthesis of Potential Metabolites of Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate

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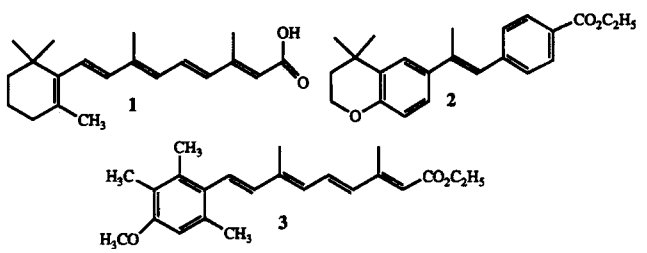
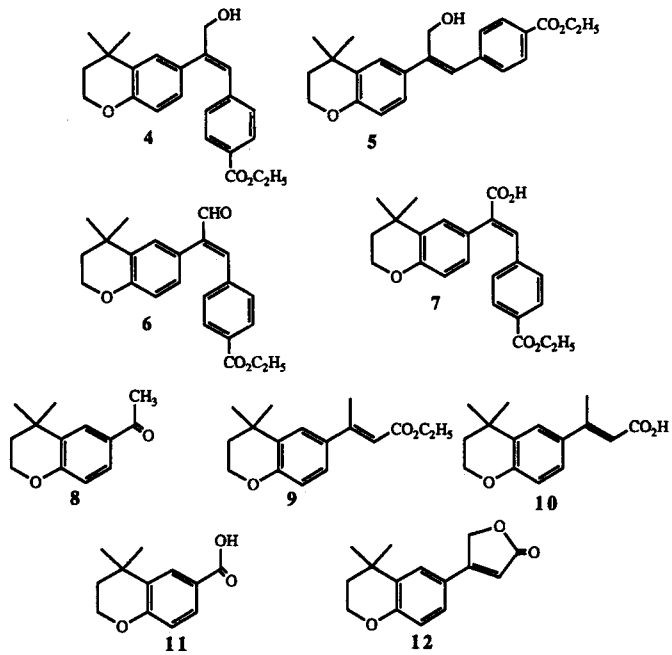
Abstract □ Potential metabolites of ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate were synthesized. The new compounds include ethyl 3-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonate, 3-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonic acid, 3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-carboxylic acid, 4-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]Δ^2-butenolide, ethyl (*E*)-4-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoate, ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenal]benzoate, and ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenoic acid]benzoate. Stereospecific oxidizing reagents and/or conditions were developed for these sensitive systems and include the use of SeO_2, Clorox bleach, activated MnO_2, and $NaClO_2$ in the presence of resorcinol as a chlorine scavenger.

The utility of retinoids in cell differentiation, proliferation, and the treatment of some skin disorders is well documented in the literature.[1–3] In recent years, a number of structurally modified retinoids have been synthesized and evaluated for pharmacological activity.[4–6] One such heteroaretinoid that has shown good activity compared with the standard *trans*-retinoic acid (**1**) is ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate (**2**).[4–10] In this paper we describe the synthesis of some potential metabolites of **2**. The metabolism of all *trans*-retinoic acid **1** in rats occurs primarily by oxidation of the carbocyclic ring or by the oxidative cleavage of the polyene side chain.[11,12] Hanni and co-workers[13] have done metabolic studies in humans and rats with etretinate (**3**), a clinically used synthetic arotinoid. Metabolites from humans given **3** arise primarily from cleavage of the side chain, leaving the aromatic ring intact.[13] The structures of compounds synthesized as the potential metabolites of **2** are, to some degree, reminiscent of those observed from all *trans*-retinoic acid (**1**) and etretinate (**3**). Our target molecules (potentially obtainable from **2**) may be classified into two groups: those from oxidation of allylic methyl group (as in **4–7**) and those in which the side chain underwent oxidative cleavage (such as in **8–12**). Intermediate **9** would not be an expected metabolite.





Results and Discussion

The synthetic scheme for **4–7** originated from the parent compound **2**. First, the oxidation of **2** with SeO_2 converted the methyl group [C(12)] into a hydroxymethyl group. Interestingly, the major product **4** isolated has the two aromatic rings *cis* to each other. Small quantities of allylic alcohol **5** (*trans* isomer) and the aldehyde **6** were also detected and isolated from this same oxidation. Oxidation of **2** was carried out using three equivalents of SeO_2 in boiling 95% alcohol for 24 h. Although some of the starting material was recovered and the allylic alcohol **4** was obtained in fair yields, increasing the reaction times or the number of equivalents of SeO_2 used did not change the yield significantly. Whereas **4** appears to be a vulnerable precursor of **6**, the best yield (76%) of the latter was obtained by treatment of **4** with activated MnO_2. This reaction was done in CH_2Cl_2 with 20 equivalents of activated MnO_2 at room temperature. After the removal of excess MnO_2 by filtration, the solution was concentrated to yield aldehyde **6** as a yellow solid. Carboxylic acid **7** was realized by further oxidation of aldehyde **6** with special conditions using NaH_2PO_4 and $NaClO_2$ in *t*-butanol. Because ClO_2 (which is the oxidant generated in this reaction) and Cl^- are formed in situ, resorcinol was added as a scavenger to limit further oxidation. Control of pH in the reaction was accomplished with a phosphate buffer. Confirmation of all products was established by UV, ^1H NMR, and ^{13}C NMR spectral analyses.[14]

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The other class of the potential metabolites (**9–12**) was synthesized from the methyl ketone **8**. Reaction of ketone **8** with triethyl phosphonoacetate under Wadsworth–Emmons conditions gave α,β-unsaturated ester **9**. In this reaction, NaH proved an effective base along with 15-crown-5. Saponification of ester **9** was performed with 35% alcoholic KOH and, after neutralization, led to acid **10**. Carboxylic acid **11** was obtained by subjecting methyl ketone **8** to the haloform reaction with commercially available bleach (Clorox) containing 5.25% NaOCl. The Δ^2-butenolide derivative **12** was isolated from a one-pot reaction of α,β-unsaturated ester **9** with SeO_2 in boiling benzene. The Δ^2-butenolide derivative **12** is probably formed from initial oxidation by SeO_2 of the methyl group [C(12)] in **9** to a hydroxymethyl group, followed by a lactonization. After workup, **12** was obtained as a yellow oil which solidified.

Experimental Section

General—Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra of all compounds were recorded on a Perkin-Elmer 681 as KBr pellets or as films. UV data are obtained on a Varian DMS 200 UV-visible spectrophotometer (equipped with a Epson Lx-800 professional computer printer). The NMR spectra were recorded on either a Varian XL-300 BB spectrometer (^1H and ^{13}C at 299.94 and 75.43 MHz, respectively) or an XL-400 MHz unit (^1H and ^{13}C at 399.9 and 100.6 MHz, respectively) using $DCCl_3$ solutions. Data are reported as follows: chemical shift (in δ values or ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constant (in Hz), and assignment. Mass spectral data were recorded on a VG analytical instrument model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The Chromatotron (model 7924T) was obtained from Harrison Research, Palo Alto, CA.

Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoate (4)—To the suspension of 1.29 g (11.6 mmol) of SeO_2[15] in 95% alcohol (30 mL) was added 1.35 g (3.85 mmol) of **2**.[7–10] The reaction mixture was boiled for 24 h. The mixture was then cooled to room temperature, and black elemental Se was separated by filtration. The residue was washed with 95% alcohol (10 mL). Evaporation of the alcohol gave a residue that was dissolved in ether (50 mL). The ether layer was washed with water (1 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), and finally with brine (1 × 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to a light brown oil. Purification of this oil was accomplished by chromatography with the Chromatotron with a 4-mm silica gel plate. Gradient elution was effected with 100 mL of hexanes:ethyl acetate (9.5:0.5), 100 mL of hexanes:ethyl acetate (9.0:1.0), 100 mL of hexanes:ethyl acetate (8.0:2.0), and finally with 250 mL of hexanes:ethyl acetate (7.5:2.5). Different fractions (1 to 20) of 20 mL each were collected. Fractions 16, 17, and 18 were combined, and the solvent was evaporated to afford 0.44 g (31.2%) of a thick, very light tan-colored oil of ester **4**; IR (neat): 3650–3120 and 1720 cm^{-1}; UV (EtOH): λ_{max} 284.2 nm (ε 1.16 × 10^4); ^1H NMR ($DCCl_3$): δ 1.15 [s, 6 H, H(9,10)], 1.35 [t, 3 H, H(22)], 1.61 [s, 1 H, H(OH)], 1.80 [m, 2 H, H(3)], 4.18 [m, 2 H, H(2)], 4.30 [q, 2 H, H(21)], 4.47 [s, 2 H, H(12)], 6.67 [s, 1 H, H(12)], 6.75–7.85 [m, 7 H (aromatic-H)]; ^{13}C NMR ($DCCl_3$): ppm 14.2 [C(22)], 30.4 [C(4)], 30.4 [C(9,10)], 37.3 [C(3)], 60.7 [C(21)], 63.1 [C(2)], 63.1 [C(12)]; Ar-C and vinylic-C; 117.3, 124.6, 127.9, 128.2, 128.9, 129.1, 129.2, 132.0, 141.7, 143.8, 153.4; 166.4 [C(20)]. Unfortunately, **4** retained traces of water even after drying under reduced pressure.

Anal.—Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15; calcd for $C_{23}H_{26}O_4 \cdot \frac{1}{4}H_2O$: C, 74.49; H, 7.15. Found: C, 74.10; H, 7.29. Mass spectral data calculated for $C_{23}H_{26}O_4$ m/e (M^+): 366.1831; Found: 366.1831. Very small amounts of ester **5** were isolated from which it was only possible to obtain a proton NMR spectrum after very long acquisition times. The signal for H(12) [vinyl H] on the slightly crude sample was clearly discernible at δ 6.85. This is in agreement with the observation that this proton in a (*Z*)-isomer is always at lower field than the corresponding proton in the (*E*)-isomer.[6,14] The nomenclature for (*Z*)- and (*E*)-isomers differs in **4** and **5** because of the priority given to the CH_2OH group relative to a methyl group, the aromatic ring, or to hydrogen. Effectively, this means that the isomer with both aryl rings in a *cis* arrangement [our (*E*)-isomer **4**] has the vinyl proton at the higher field compared with the isomer with the aryl rings trans [our (*Z*)-isomer **5**] as has been noted previously.[14]

Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenal]benzoate (6)—To 0.04 g (0.11 mmol) of ethyl (*E*)-4-[2-(4,4-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoate (**4**) in 15 mL of CH_2Cl_2 was added 0.15 g (2.2 mmol) of activated MnO_2.[16] The reaction mixture was stirred at room temperature for 24 h and then filtered. The residue was washed with 10 mL of $CHCl_2$. The combined filtrate and washing were concentrated to yield 0.03 g (76%) of a yellow-colored solid. The solid was crystallized [95% alcohol] to give yellow-colored crystals of ester **6**, mp 157–158 °C; IR (KBr): 1725 and 1680 cm^{-1}; UV (EtOH): λ_{max} 286.8 nm (ε 1.48 × 10^4); ^1H NMR ($DCCl_3$): δ 1.15 [s, 6 H, H(9,10)], 1.3 [t, 3 H, H(22)], 1.8 [m, 2 H, H(3)], 4.15 [m, 2 H, H(2)], 4.30 [1, 2,H, H(21)], 6.72–7.85 [m, 8 H, H (aromatic & vinylic)], 9.7 [s, 1 H, H(12)]; ^{13}C NMR ($DCCl_3$): ppm 14.2 [C(23)], 30.5 [C(4)], 30.8 [C(9, 10)], 37.3 [C(3)], 61.1 [C(21)], 63.1 [C(2)]; Ar-C and vinylic-C: 117.4, 124.0, 128.1, 128.4, 129.4, 130.2, 131.0, 132.0, 138.7, 143.0, 154.0; 165.8 [C(20)], 194.0 [C(21)].

Anal.—Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64; Found: C, 75.64; H, 6.72. Mass spectral data calculated for $C_{23}H_{24}O_4$ *m/e* (M^+): 364.1668; found: 364.1662.

Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenoic acid]benzoate (7)—To 0.035 g (0.096 mmol) of ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propen]-benzoate (**5**) and 0.012 g of resorcinol in *t*-butanol (5 mL) was added a solution of 0.079 g (0.87 mmol) of $NaClO_2$ and 0.093 g (0.672 mmol) of NaH_2PO_4 in water (10 mL).[17] The reaction mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave a residue to which was added water (25 mL), and the new solution was cooled (ice bath). This cold solution was acidified with 6 M HCl (1 mL) to pH 1 (litmus). The aqueous solution was extracted with ether (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated to give 0.03 g (82%) of a yellow-colored oil. Crystallization was induced by scratching to give a solid. Recrystallization (absolute alcohol) of the solid gave yellow crystals of ester **6**, mp 197–198 °C; IR (KBr): 3600–2850, 1740, and 1680 cm^{-1}; UV (EtOH): λ_{max} 286.2 nm (ε 1.28 × 10^4); ^1H NMR ($DCCl_3$): δ 1.18 [s, 2 H, H(9,10)], 1.36 [t, 3 H, H(22)], 1.82 [m, 2 H, H(3)], 4.21 [m, 2 H, H(2)], 4.33 [q, 2 H, H(21)], 6.79–7.89 [m, 8 H, H(aromatic & vinylic)]; ^{13}C NMR ($DCCl_3$): ppm 14.2 [C(22)], 30.5 [C(4)], 30.8 [C(9,10)], 37.4 [C(3)], 61.0 [C(21)], 63.1 [C(2)]; Ar-C and vinylic-C: 117.3, 126.0, 128.5, 128.9, 129.3, 130.3, 130.4, 131.9, 133.8, 139.2, 140.3, 153.7; 166.0 [C(20)], 172.7 [C(12)].

Anal.—Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36; found: C, 72.36; H, 6.64. Mass spectral data calculated for $C_{23}H_{24}O_5$ *m/e* (M^+): 380.1623; found: 380.1625.

Ethyl 3-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonate (9)—To 0.212 g (5.39 mmol) of NaH in dry tetrahydrofuran (THF, 10 mL) was added in dropwise manner a mixture of 1.0 g (4.9 mmol) of 4,4-dimethylchroman-6-yl methyl ketone (**8**),[18] 1.21 g (5.39 mmol) of triethyl phosphonoacetate, and 0.10 g (0.454 mmol) of 15-crown-5 in THF (10 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 24 h. It was then boiled for 2 h and allowed to cool to room temperature over a period of 24 h. The reaction mixture was acidified with glacial acetic acid (1 mL). Then, a saturated solution of NaCl (50 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 30 mL), and the combined extracts and the organic layer were washed with water (3 × 30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give 1.03 g of reddish-brown oil. The oil was purified by chromatography with a 4-mm silica gel Chomatotron plate with 50 mL of hexanes:ethyl acetate (9.5:0.5) and 200 mL of hexanes:ethyl acetate (9.0:1.0). The ester **9** was obtained as a thick oil (0.52 g, 38.7%); IR (neat): 1720 cm^{-1}; UV (EtOH): λ_{max} 298.2 nm (ε 1.39 × 10^4); ^1H NMR ($DCCl_3$): δ 1.32 [t, 3 H, H(16)], 1.35 [s, 6 H, $(CH_3)_2$], 1.84 [m, 2 H, H(3)], 2.55 [s, 3 H, H(12)], 4.19 [q, 2 H, H(15)], 4.20 [m, 2 H, H(2)], 6.08 [s, 1 H, H(13)], 6.76 [d, J = 8.50 Hz, 1 H, H(8)], 7.21 [dd, J = 8.47 Hz, J = 2.38 Hz, 1 H, H(7)], 7.40 [d, J = 2.33 Hz, 1 H, H(5)]; ^{13}C NMR: ppm 14.3 [C(16)], 17.7 [C(12)], 30.6 [C(14)], 30.9 [C(9,10)], 37.4 [C(3)], 59.6 [C(15)], 63.6 [C(2)], 114.9 [C(8)], 116.9 [C(13)], 125.0 [C(5)], 125.3 [C(7)], 131.4 [C(6)], 134.0 [C(4a)], 154.6 [C(11)], 155.4 [C(8a)], 167.0 [C(14)].

Anal.—Calcd for $C_{17}H_{22}O_3$: C, 74.43; H, 8.08; found: C, 74.46; H, 8.00. Mass spectral data calculated for $C_{17}H_{22}O_3$ *m/e* (M^+): 274.1569;

found: 274.1566.

3-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonic Acid (10)—To 52 mg (0.19 mmol) of ethyl 3-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonate (**9**) in 2 mL of absolute ethanol was added 5 mL of H_2O and 1 mL of 35% (w/v) KOH. The solution was boiled for 5 h, then allowed to cool to the room temperature, further cooled in an ice bath, and neutralized with 6 M HCl (2 mL). The white solid which formed was collected by filtration and washed with cold water. This solid was crystallized [absolute alcohol:water (1:1)] to afford 35 mg (74.8%) of the acid **10**, mp 126–128 °C; IR (KBr): 3500–3010 and 1670 cm^{-1}; UV (EtOH): λ_{max} 291.6 nm (ε 1.30 × 10^4); ^1H NMR ($DCCl_3$): δ 1.2 [s, 6 H, H(9,10)], 1.7 [m, 2 H, H(3)], 2.4 [s, 3 H, H(12)], 5.9 [s, 1 H, H(13)], 6.6-7.3 [m, 3 H, H(aromatic)]; ^{13}C NMR ($DCCl_3$): ppm 18.1 [C(12)], 30.6.[C(4)], 36.9 [C(9,10)], 37.3 [C(3)], 63.2 [C(2)], 114.1 [C(8)], 117.1 [C(13)], 125.2 [C(5)], 125.5 [C(7)], 131.5 [C(6)], 133.8 [C(4a)], 155.0 [C(11)], 158.4 [C(8a)], 172.3 [C(14)]. Unfortunately, acid **10** retained traces of water even after drying under reduced pressure.

Anal.—Calcd for $C_{15}H_{18}O_3$: C, 73.15, H, 7.37; calcd for $C_{15}H_{18}O_3 \cdot 1/8H_2O$: C, 72.51, H, 7.35; found: C, 72.42; H, 7.43. Mass spectral data calculated for $C_{15}H_{18}O_3$: *m/e* (M^+): 246.1256; found: 246.1260.

3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-carboxylic acid (11)—To 15 mL of commercially available Clorox solution containing 5.25% NaOCl was added 0.3 g (1.47 mmol) of 4,4-dimethylchroman-6-yl methyl ketone (**8**) in 95% alcohol (5 mL). The reaction mixture was stirred well and boiled for 1.5 h and then cooled to the room temperature. This mixture was first neutralized with a 25% solution of sodium metabisulfite (25 mL) and then with concentrated HCl (2 mL). A white solid was filtered and then washed with cold water (50 mL) until the filtrate was free of acid. Recrystallization [95% alcohol] of the product afforded 0.2 g (67%) of a white crystalline solid **11**,[19] mp 227–229 °C; IR (KBr): 3400–2950 and 1680 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.37 [s, 6 H, H(9,10)], 1.85 [m, 2 H, H(3)], 4.27 [m, 2 H, H(2)], 6.83 [d, J = 8.62 Hz, 1 H, H(8)], 7.84 [dd, J = 8.67 Hz, J = 2.85 Hz, 1 H, H(7)], 8.07 [d, J = 2.12 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$): ppm 30.59 [C(4)], 30.75 [C(9,10)], 36.97 [C(3)], 63.49 [C(2)]; Ar-C 117.1, 121.7, 129.5, 129.9, 131.5, 158.5; 171.89 [C(11)].

Anal.—Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.84; found: C, 69.79, H, 667. Mass spectral data calculated for $C_{12}H_{14}O_3$ *m/e* (M^+): 206.0943; found: 206.0943.

4-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]Δ^2-butenolide (12)—To 0.2 g (0.75 mmol) of **9** in dry benzene (25 mL) was added 0.41 g (3.70 mmol) of SeO_2.[20] The reaction mixture was boiled for 20 h. After cooling the mixture to room temperature, the deposited metallic Se was separated by gravity filtration. Water (25 mL) was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 25 mL), and then the combined extracts and organic layer were dried (Na_2SO_4), filtered, and concentrated to a thick yellow oil. Crystallization was then induced by scratching to give 0.18 g (98.2%) of a yellowish, orange solid. The solid was recrystallized [95% alcohol] to give yellow crystals of **12**, mp 133–134 °C; IR (KBr): 1780 and 1740 cm^{-1}; UV (EtOH): λ_{max} 308.1 nm (ε 2.52 × 10^4); ^1H NMR ($DCCl_3$): δ 1.36 [s, 6H, H(9,10)] 1.86 (m, 2H, H(3)], 4.26 [m, 2 H, H(2)], 5.19 [s, 2 H, H(12)], 6.22 [s, 1 H, H(15)], 6.82 [d, J = 8.52 Hz, 1 H, H(8)], 7.22 [dd, J = 8.46 Hz, J = 2.28 Hz, 1 H, H(7)], 7.39 [d, J = 2.28 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$): ppm 30.5 [C(4)], 30.7 [C(9,10)], 36.9 [C(3)], 63.4 [C(2)], 70.9 [C(12)], 110.1 [C(15)], 118.0 [C(11)], Ar-C: 121.9, 125.3, 125.7, 132.5, 156.8; 164.0 [C(14)].

Anal.—Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; found: C, 73.57; H, 6.65. Mass spectral data calculated for $C_{15}H_{16}O_3$ *m/e* (M^+): 244.1099; found: 244.1099.

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19. Compound **11** has been cited in a Belgium patent not available to us (see Shrout, B.; Eustache, J.; Bernardon, J. M.; Belg BE 903, 254, 1986; *Chem. Abstr.* **1986**, *105*, 19098). No properties of **11** are given in the abstract.
20. A highly modified approach of this type of oxidation appeared many years ago in one rare, isolated example in the field of steroids: Danieli, N.; Mazur, Y.; Sondheimer, F. *Tetrahedron* **1966**, *22*, 3189–3193.

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