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DIHYDROXYLATION OF FUNCTIONALIZED COUMARIN DERIVATIVES†

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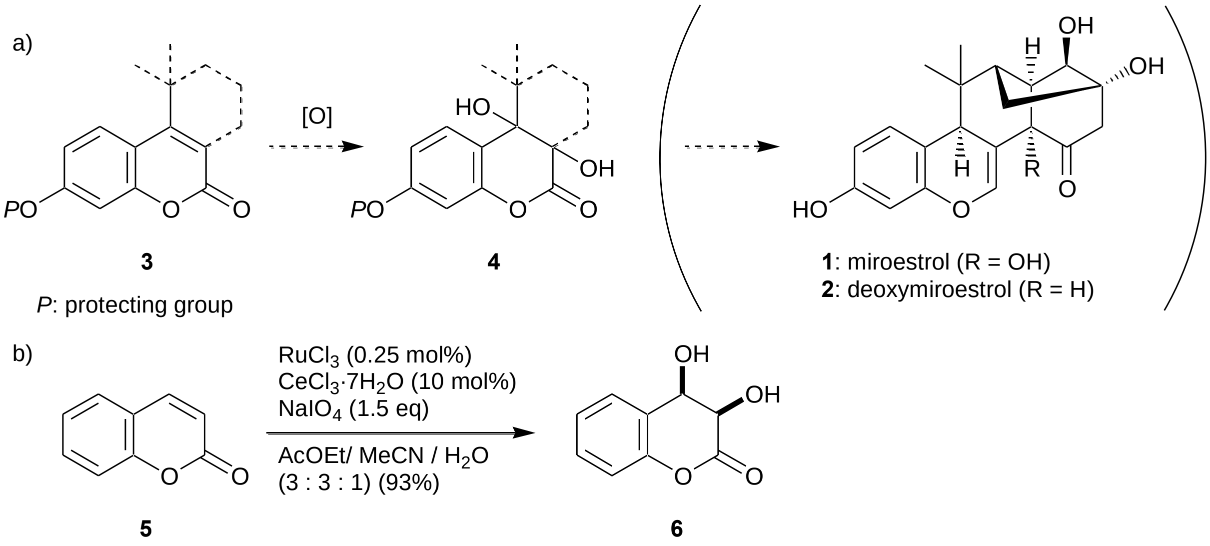
Abstract – 7-Acetoxy- and 7-tosyloxycoumarins were successfully dihydroxylated in $RuCl_3/NaIO_4/CeCl_3$ system to give the corresponding glycol derivatives in excellent yields. Tricyclic coumarin with tetrasubstituted olefin function also gave the desired diol in good yield. Introduction of electron-deficient protecting group to coumarin skeleton is critical for the successful dihydroxylation.

Coumarins are one of the most popular constituents in medicinal plants and also have been used as substrates for the synthesis of natural products.[1] In our synthetic approaches[2] towards phytoestrogenic miroestrol (**1**)[3,4] and the deoxy isomer deoxymiroestrol (**2**),[5] we planned the dihydroxylation of 7-hydroxy-4-substituted coumarin derivatives **3** to the corresponding diols **4** (Scheme 1a).

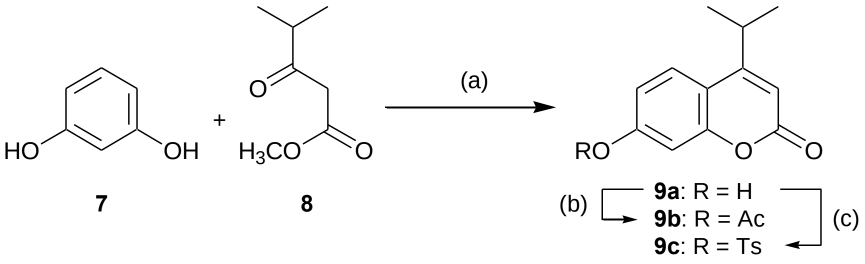


Scheme 1. a) Synthetic plan of miroestrols **1-2** via dihydroxylation of coumarin **3**. b) Reported example for the dihydroxylation of coumarin itself (**5**).

A number of examples of dihydroxylation of simple olefins have been investigated;[6] however, the successful results for the olefin units in coumarin skeletons are so limited. Plietker *et al.*[7] reported that the addition of cerium chloride ($CeCl_3$) was effective for dihydroxylation of electron-deficient olefins including coumarin itself (**5**) in $RuCl_3$/ $NaIO_4$ system, in which oxidative cleavage of carbon-carbon double bond was avoided (Scheme 1b). We applied this reaction condition to the dihydroxylation of functionalized coumarins.

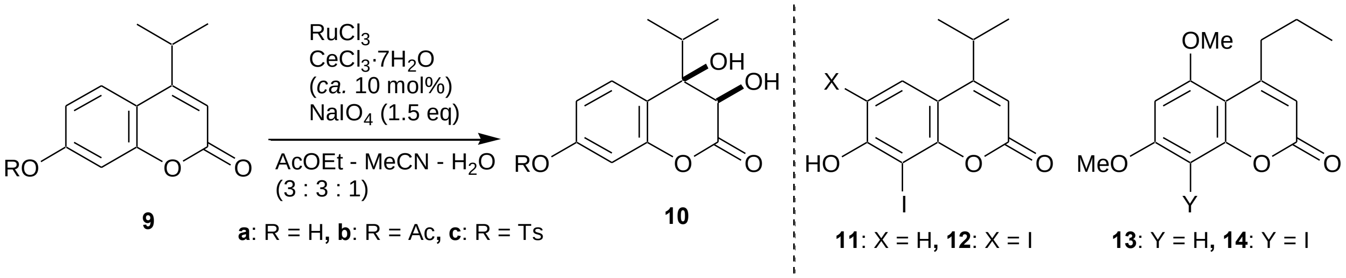
7-Hydroxycoumarin with isopropyl group at position 4 was synthesized by conventional Pechman condensation[8] of resorcinol (**7**) and β-ketoester **8** in the presence of concentrated sulfuric acid in 76% yield. The corresponding acetate **9b** and tosylate **9c** were prepared from **9a** (Scheme 2).

Trial for the dihydroxylation of the non-protected hydroxycoumarin **9a** in the presence of 10 mol% of Ru species gave no desired product **10a,** instead iodocoumarins **11** and **12** in low yields (run 1, Table 1). Electron-rich coumarin **13**[9] gave the corresponding 8-iodo derivative **14** under the same reaction



Scheme 2. Preparation of 4-isopropyl-7-hydroxycoumarin derivatives **9**. Reagents and conditions: (a) conc. H_2SO_4, rt, 1 h (73%). (b) Ac_2O, pyridine, rt, 2 h (80%). (c) TsCl, K_2CO_3, acetone, reflux, 2 h (92%).

Table 1. Dihydroxylation of coumarins **9** and **13**.

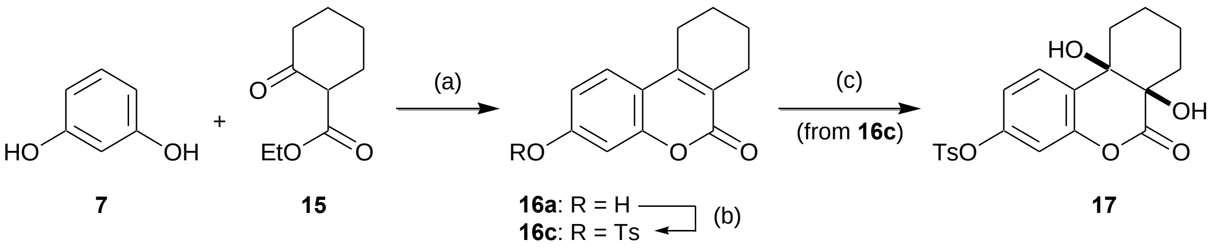


run	coumarin	$RuCl_3$ (mol%)	conditions	results
1	**9a**	10	0 °C to rt, 10 h	**11** (10%), **12** (14%)
2	**13**	17	0 °C to rt, 19 h	**14** (15%)[a]
3	**9b**	10	0 °C, 30 min	**10b** (88%)
4	**9b**	0.27	0 °C, 2 h	**10b** (88%)
5	**9c**	0.25	0 °C, 4 h	**10c** (95%)

[a] **13** (41%) was recovered.

conditions (run 2).[10,11] It was supposed that molecular iodine (I_2) generated by the reduction of periodinate[12] by low-valent Ru species would react with electron-rich coumarins such as **9a** and **13**. Thus, electron-deficient group-substituted hydroxycoumarins were targeted. Dihydroxylation of acetate **9b** proceeded smoothly to give the corresponding 1,2-diol **10b** in 88% yield (run 3). The reduced amount of $RuCl_3$ did not affected to the yield (run 4). Tosylate **9c** also afforded the corresponding diol **10c** in excellent yield (run 5).

Application to tricyclic coumarin with tetrasubstituted olefin function was examined (Scheme 3). Tricyclic coumarin **16c**, prepared by Pechman condensation of **7** and β-ketoester **15** followed by tosylation, was dihydroxylated in the same manner as those for **9c** to give the corresponding diol **17** in 76% yield (Scheme 3).



Scheme 3. Synthesis and dihydroxylation of coumarin **16c**. Reagents and conditions: (a) conc. H_2SO_4, 0 °C to rt, 1 h (quant). (b) TsCl, K_2CO_3, acetone, reflux, 1 h (71%). (c) $RuCl_3$ (0.26 mol%), $CeCl_3 \cdot 7H_2O$ (14 mol%), $NaIO_4$ (1.7 eq), AcOEt - MeCN - H_2O (3 : 3 : 1), 0 °C to rt, 1 h (76%).

In conclusion, dihydroxylation of functionalized coumarins was succeeded with $RuCl_3/NaIO_4/CeCl_3$ system. Introduction of electron-deficient protecting group on 7-hydroxy group is important for this reaction. Tricyclic coumarin derivative with tetrasubstituted olefin function was also subjected to the dihydroxylation conditions to give the corresponding diol in good yield. Further trials for the synthetic studies towards miroestrols are now under investigation.

EXPERIMENTAL

General: All melting points were measured on Yanagimoto MPSI melting point apparatus and are uncorrected. IR spectra were recorded with Attenuated Total Reflectance (ATR) system on a JASCO FT / IR-300E spectrophotometer. ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a JEOL JNM-GSX-400α or JEOL JNM-ECP-400. MS spectra were measured on JEOL JNM MS-GCMATE for EIMS, and JEOL JMS-HX110 or JEOL JMS-AX505 for FABMS. For column chromatography was used Kanto Chemical silica gel 60 spherical. For TLC were used Merck Art 5715 DC-Fertigplatten Kieselgel 60 F_{254}.

7-Hydroxy-4-isopropylcoumarin (9a)

To a mixture of resorcinol (**7**, 1.08 g, 9.84 mmol) and β-ketoester **8** (1.84 g, 12.4 mmol), conc. H_2SO_4 (2.0 mL) was added under ice cooling and the whole was stirred at rt for 1 h. Ice (*ca.* 40 mL) was added and the whole was stirred at rt for 6 h. The precipitate was filtered off, washed with cold H_2O, and dried to give pale brown solids, which was recrystallized from $CHCl_3$ to give **9a** (1.46 g, 73%).

Colorless plates. mp 133.5-136 °C (lit.,[13] 129.4-130.8 °C). IR (cm^{-1}): 3145 (OH), 1675 (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.21 (6H, d, J = 6.8 Hz, 2 x Me), 3.29 (1H, sep, J = 6.8 Hz, CH), 6.06 (1H, s, 3-H), 6.70 (1H, d, J = 2.4 Hz, 8-H), 6.80 (1H, dd, J = 8.8, 2.4 Hz, 6-H), 7.68 (1H, d, J = 8.8 Hz, 5-H), 10.52 (1H, s, OH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ (ppm): 21.56, 27.90, 102.51, 106.45, 110.59, 112.94, 125.98, 155.13, 160.77, 160.89, 162.60.

7-Acetoxy-4-isopropylcoumarin (9b)

A mixture of **9a** (5.00 g, 24.5 mmol), pyridine (4.0 mL, 49.0 mmol), and acetic anhydride (2.5 mL, 26.9 mmol) was stirred at rt for 2 h. Ice (*ca.* 5 mL) was added and the whole was stirred at rt for 3 h and then filtered. The precipitate was washed with cold H_2O, dried and recrystallized from hexane - AcOEt (10 : 1) to give **9b** (4.84 g, 80%).

Colorless pillars. mp 88-89 °C. Anal. Calcd for $C_{14}H_{14}O_4$: C: 68.28, H: 5.73. Found: C: 67.98, H: 5.67. IR (cm^{-1}): 1733 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.33 (6H, d, J = 6.8 Hz, 2 x Me), 2.35 (3H, s, Ac), 3.27 (1H, sep, J = 6.8 Hz, CH), 6.30 (1H, s, 3-H), 7.08 (1H, dd, J = 8.6, 2.2 Hz, 6-H), 7.13 (1H, d, J = 2.2 Hz, 8-H), 7.69 (1H, d, J = 8.6 Hz, 5-H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.06, 21.67, 28.69, 110.67, 110.74, 116.64, 117.95, 124.88, 152.72, 154.45, 161.11, 161.40, 168.69. EIMS *m/z* 246 (M^+, 12.5), 204 (100), 161 (65.9).

4-Isopropyl-2-oxo-2*H*-chromen-7-yl *p*-toluenesulfonate (9c)

A mixture of **9a** (3.00 g, 14.7 mmol), K_2CO_3 (5.08 g, 36.7 mmol), and TsCl (3.17 g, 16.3 mmol) in acetone (25 mL) was refluxed for 2 h. After cooling, the solvent was evaporated. H_2O (70 mL) was added to the residue and the whole was extracted with AcOEt (3 x 100 mL). The combined organic layer was washed with H_2O (3 x 80 mL) and brine (1 x 100 mL) and was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was recrystallized from hexane - AcOEt (7 : 1) to give **9c** (4.83 g, 92%).

Colorless pillars. mp 117.5-119 °C. Anal. Calcd for $C_{19}H_{18}O_5S$: C: 63.67, H: 5.06. Found: C: 63.76, H: 5.06. IR (cm^{-1}): 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (6H, d, J = 6.8 Hz, 2 x Me), 2.48 (3H, s, Me), 3.23 (1H, sep, J = 6.8 Hz, CH), 6.30 (1H, s, 3-H), 6.84 (1H, d, J = 2.4 Hz, 8-H), 7.12 (1H, dd, J = 8.8, 2.4 Hz, 6-H), 7.35 (2H, d, J = 8.4 Hz, Ts-meta), 7.65 (1H, d, J = 8.8 Hz, 5-H), 7.75 (2H, d, J = 8.4 Hz, Ts-ortho). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.40, 21.49, 28.47, 110.90, 110.99, 117.46, 118.35, 125.19, 128.15, 129.83, 131.66, 145.83, 150.99, 153.92, 160.41, 161.04. EIMS *m/z* 358 (M^+, 23.5), 207 (73.7), 155 (72.2), 91 (100).

Trials for dihydroxylation of hydroxycoumarin 9a. Generation of 8-iodo- (11) and 6,8-diiodo- (12) coumarins (run 1 in Table 1)

A mixture of $CeCl_3·7H_2O$ (13.1 mg, 35 μM) and $NaIO_4$ (81 mg, 0.38 mmol) in distilled H_2O (0.1 mL) was stirred for *ca.* 10 min until the color of the suspension turned to yellow. Under ice-cooling, AcOEt (0.1 mL) and MeCN (0.3 mL) was added and the whole was stirred at rt for 2 min. 0.1 M aq. $RuCl_3$ (0.25 mL, 0.025 mmol, 10 mol%) was added and the whole was stirred at rt for 2 min. A solution of **9a** (50 mg, 0.24 mmol) in AcOEt (0.2 mL) was added and the whole was stirred at 0 °C for 3 h and at rt for 7 h. AcOEt (3 mL) and Na_2SO_4 (ca. 200 mg) were added and the whole was filtered off. The precipitate was washed with AcOEt. The filtrate and the washing were combined and the whole was washed with sat. aq. Na_2SO_3 (1 x 10 mL) and was dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (CC, hexane - AcOEt = 5 : 1) to give less polar **12** (15 mg, 14%) and more polar **11** (8 mg, 10%).

7-Hydroxy-6,8-diiodo-4-isopropylcoumarin (12)

Yellow solids. mp 137-146 °C. IR (cm^{-1}): 3259 (OH), 1695 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (6H, d, *J* = 6.7 Hz, 2 x Me), 3.21 (1H, sep, *J* = 6.7 Hz, CH), 6.19 (1H, s, 3-H), 8.01 (1H, s, 5-H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.84, 28.67, 74.38, 77.20, 109.36, 115.09, 134.16, 154.51, 156.52, 160.47, 160.74. HREIMS *m/z* 455.8734 (Calcd for $C_{12}H_{10}I_2O_3$: 455.8720).

7-Hydroxy-8-iodo-4-isopropylcoumarin (11)

Colorless solids. mp 133-140 °C. IR (cm^{-1}): 3282 (OH), 1691 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (6H, d, *J* = 6.8 Hz, 2 x Me), 3.26 (1H, sep, *J* = 6.8 Hz, CH), 6.20 (1H, s, 3-H), 7.00 (1H, d, *J* = 8.8 Hz, 5-H), 7.58 (1H, d, *J* = 8.6 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.86, 28.75, 77.20, 104.48, 113.12, 125.52, 154.17, 158.42, 161.20, 162.03 (one carbon lacked, provably because of overlap with the peak of $CDCl_3$). HREIMS *m/z* 329.9753 (Calcd for $C_{12}H_{11}IO_3$: 329.9753).

8-Iodo-5,7-dimethoxy-4-propylcoumarin (14) (run 2 in Table 1)

Identical procedure for the synthesis of **11** and **12** was applied with **13**[9] (50 mg, 0.20 mmol), $CeCl_3·7H_2O$ (8.1 mg, 22 μmol), $NaIO_4$ (65 mg, 0.31 mmol), and 0.1 M aq. $RuCl_3$ (0.15 mL, 15 μM) in AcOEt - MeCN - H_2O (3 : 3 : 1, 0.7 mL) to give **14** (11 mg, 15%) with recovery of **13** (20 mg, 41%) after the purification by CC (hexane - AcOEt = 4 : 1 to 2 : 1).

Colorless solids. mp 111-116 °C. IR (cm^{-1}): 1711 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.01 (3H, t, *J* = 7.5 Hz, Me), 1.61 (2H, diffused sep, *J* = 7.5 Hz, Me$\underline{H_2}$), 2.87 (2H, t, *J* = 7.5 Hz, C$\underline{H_2}$Ar), 3.96, 3.99 (each 3H, s, 2 x OMe), 6.00 (1H, s, 3-H), 6.36 (1H, s, 6-H). ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.00, 22.76, 38.41, 56.00, 56.66, 66.38, 91.22, 105.11, 111.45, 155.51, 157.69, 159.45, 160.35, 161.25. HREIMS *m/z* 374.0013 (Calcd for $C_{14}H_{15}IO_4$: 374.0015).

(3*R,4*R**)-7-Acetoxy-3,4-dihydroxy-4-isopropylchroman-2-one (10b) (Run 4 in Table 1)**

Identical procedure for the synthesis of **11** and **12** was applied with **9b** (901 mg, 3.66 mmol), $CeCl_3 \cdot 7H_2O$ (139 mg, 0.37 mmol), $NaIO_4$ (1.17 g, 5.48 mmol), and 0.1 M aq. $RuCl_3$ (0.10 mL, 10 μM) in AcOEt - MeCN - H_2O (3 :3 : 1, 12.6 mL) to give **10b** (906 mg, 88%) after the purification by CC (hexane - AcOEt = 3 :1 to 1 :1). An aliquot was recrystallized from hexane - acetone (15 : 1) to give an authentic sample. Colorless prisms. mp 132.5-134 °C. Anal. Calcd for $C_{14}H_{16}O_6$: C: 59.99, H: 5.75. Found: C: 59.61, H: 5.73. IR (cm^{-1}): 3464 (OH), 1759 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.07, 1.11 (each 3H, d, *J* = 7.1 Hz, 2 x Me), 2.31 (3H, s, Ac), 2.33 (1H, sep, *J* = 7.1 Hz, CH), 2.78, 3.26 (each 1H, s, 2 x OH, exchangeable with D_2O), 4.53 (1H, s, 3-H), 6.89 (1H, d, *J* = 2.4 Hz, 8-H), 6.98 (1H, dd, *J* = 8.6, 2.4 Hz, 6-H), 7.56 (1H, d, *J* = 8.6 Hz, 5-H). ^{13}C-NMR (100 MHz) δ (ppm): 16.72, 16.91, 21.00, 34.02, 71.06, 75.42, 110.44, 117.92, 123.35, 128.17, 149.78, 141.12, 168.53, 169.35. EIMS *m/z* 281 [$(M+1)^+$, 13%], 262 (11%), 207 (100%).

(3*R,4*R**)-3,4-Dihydroxy-4-propyl-2-oxo-2*H*-chromen-7-yl *p*-toluenesulfonate (10c) (Run 5 in Table 1)**

Identical procedure for the synthesis of **11** and **12** was applied with **9c** (1.00 g, 2.80 mmol), $CeCl_3 \cdot 7H_2O$ (108 mg, 0.29 mmol), $NaIO_4$ (896 mg, 4.19 mmol), and 0.1 M aq. $RuCl_3$ (70 μL, 7.0 μM) in AcOEt - MeCN - H_2O (3 : 3 : 1, 14 mL) to give **10c** (1.04 g, 95%) after the purification by CC (hexane - AcOEt 3 : 1 to 1 :1). An aliquot was recrystallized from benzene to give an authentic sample.

Colorless prisms. mp 145-146.5 °C. Anal. Calcd for $C_{19}H_{20}O_7S$: C: 58.15, H: 5.14. Found: C: 58.19, H: 5.20. IR (cm^{-1}) 3543, 3469 (OH), 1745 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.03, 1.06 (each 3H, d, *J* = 7.0 Hz, 2 x Me), 2.25 (1H, sep, *J* = 7.0 Hz, CH), 2.47 (3H, s, Me), 2.79 (1H, s, OH, exchangeable with D_2O), 3.24 (1H, d, *J* = 3.3 Hz, OH, exchangeable with D_2O), 4.50 [1H, d (s with D_2O), *J* = 3.3 Hz, 3-H], 6.72 (1H, d, *J* = 2.4 Hz, 8-H), 6.94 (1H, dd, *J* = 8.6, 2.4 Hz, 6-H), 7.34 (2H, d, *J* = 8.1 Hz, Ts-meta), 7.50 (1H, d, *J* = 8.6 Hz, 5-H), 7.75 (2H, d, *J* = 8.1 Hz, Ts-ortho). ^{13}C-NMR (100 MHz) δ (ppm): 16.70, 17.06, 21.72, 33.95, 70.93, 75.31, 111.17, 118.74, 124.43, 128.36, 128.40, 129.94, 132.05, 145.85, 149.87, 150.00, 168.26. EIMS *m/z* 392 (M^+, 20%), 374 (12%), 349 (25%), 219 (32%), 155 (89%), 91 (100%).

3-Hydroxy-7,8,9,10-tetrahydrobenzo[*c*]chromen-6-one (16a)

Identical procedure for the synthesis of **9a** was applied with **7** (1.00 g, 9.12 mmol), **15** (2.01 g, 10.3 mmol) and conc. H_2SO_4 (2.0 mL) to give **16a** (2.02 g, quant).

Pale pink solid. mp 205-208 °C (lit.,[14] 203-204°C). IR (cm^{-1}) 3452 (OH), 1738 (C=O). ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.73-1.79 (4H, m, 8,9-H_2), 2.41 (2H, t, *J* = 6.0 Hz, 10-H_2), 2.76 (2H, t, *J* = 6.0 Hz, 7-H_2), 6.71 (1H, d, J = 2.4 Hz, 4-H), 6.81 (1H, dd, J = 8.6, 2.4 Hz, 2-H), 7.56 (1H, d, J = 8.6 Hz, 1-H), 10.38 (1H, s, OH, D_2O exchangeable). FABMS *m/z* 217 (MH^+).

6-Oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl *p*-toluenesulfonate (16c)

Identical procedure for the synthesis of **9c** was applied with **16a** (200 mg, 0.93 mmol), TsCl (207 mg, 1.06 mmol), K_2CO_3 (325 mg, 2.35 mmol) and acetone (2.0 mL) to give **16c** (244 mg, 71%, after recrystallization from hexane - $CHCl_3$ = 3 : 2).

Colorless prisms. mp 183.5-184.5 °C. Anal. Calcd for $C_{20}H_{18}O_5S$: C: 64.85, H: 4.90. Found: C: 64.72, H: 4.76. IR (cm^{-1}): 1718 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.77-1.89 (4H, m, 8,9-H_2), 2.47 (3H, s, Me), 2.57 (2H, t, J = 5.9 Hz, 7- or 10-H_2), 2.75 (2H, t, J = 6.0 Hz, 10- or 7-H_2), 6.78 (1H, d, J = 2.4 Hz, 4-H), 7.09 (1H, dd, J = 8.8, 2.4 Hz, 2-H), 7.33 (2H, d, J = 8.1 Hz, Ts-meta), 7.53 (1H, d, J = 8.8 Hz, 1-H), 7.72 (2H, d, J = 8.1 Hz, Ts-ortho). ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.14, 21.35, 21.73, 23.96, 25.19, 110.45, 118.60, 119.08, 124.00, 124.26, 128.41, 129.95, 131.83, 145.89, 146.39, 150.30, 152.07, 161.09. EIMS *m/z* 370 (M^+, 100), 215 (74.7), 155 (93.4).

(6a*R,10a*R**)-6a,10a-Dihydroxy-6-Oxo-7,8,9,10-tetrahydrobenzo[*c*]chromen-3-yl**
***p*-toluenesulfonate (17)**

Identical procedure for the synthesis of **11** and **12** was applied with **16c** (51 mg, 0.14 mmol), $CeCl_3 \cdot 7H_2O$ (7 mg, 19 μmol), $NaIO_4$ (49 mg, 0.23 mmol), and 0.1 M aq. $RuCl_3$ (3.5 μL, 0.35 μM) in AcOEt - MeCN - H_2O (3 : 3 : 1, 0.7 mL) to give **17** (46 mg, 83%) after the purification by CC (hexane - AcOEt = 3 : 1 to 1 : 1).

A colorless oil. IR (cm^{-1}) 3464 (OH), 1768 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.27 (1H, diffused t, J = 12.4 Hz, one of CH_2), 1.50 (1H, m, one of CH_2), 1.58-1.78 (4H, m, CH_2), 1.93 (1H, td, J = 13.3, 3.8 Hz, 10-H), 2.30 (1H, br d, J = 13.3 Hz, 10-H), 2.47 (3H, s, Me), 2.89, 3.42 (each 1H, s, 2 x OH, exchangeable with D_2O), 6.73 (1H, d, J = 2.4 Hz, 4-H), 6.97 (1H, dd, J = 8.6, 2.4 Hz, 2-H), 7.35 (2H, d, J = 8.2 Hz, Ts-meta), 7.48 (1H, d, J = 8.6 Hz, 1-H), 7.75 (2H, d, J = 8.2 Hz, Ts-ortho). ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.34, 21.70, 22.17, 31.28, 32.38, 71.86, 74.71, 111.51, 119.01, 123.08, 127.71, 128.39, 129.95, 132.03, 145.86, 150.38, 150.67, 171.78. HREIMS *m/z* 404.0906 (Calcd for $C_{20}H_{18}O_7S$: 404.0930).

REFERENCES AND NOTES

[†] This article is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

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