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AN EFFICIENT SYNTHESIS OF BERGAPTEN

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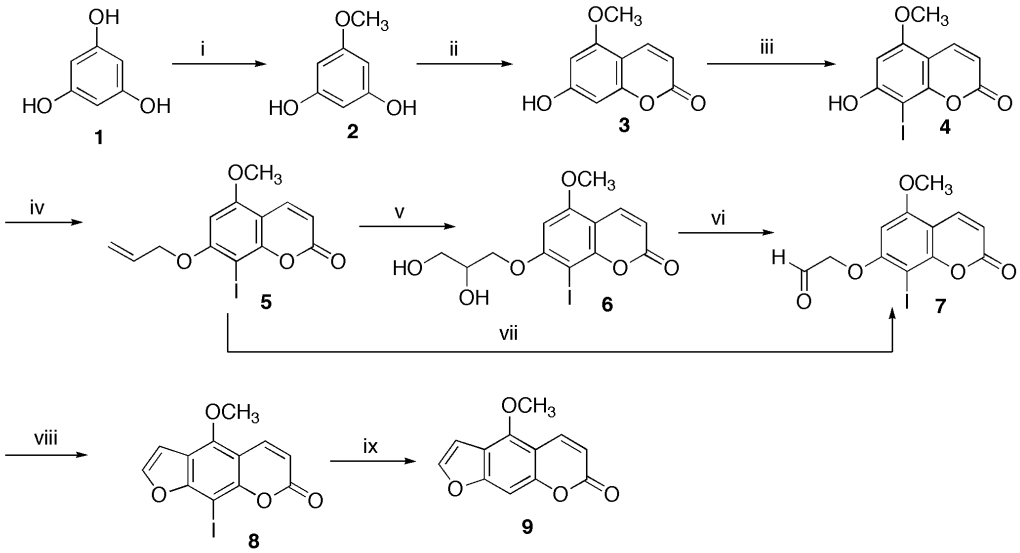
Abstract — An efficient synthesis of the linear furanocoumarin, bergapten, is reported. In order to avoid the formation of the angular furanocoumarin, we have adopted iodine as protecting group at the 8 position of the coumarin ring.

Furanocoumarins are natural products showing a wide range of biological properties,[1] the most prominent of which are photobiological effects that can occur upon irradiation with long-wavelength UV light.[2] Thus, many furanocoumarins are potent photosensitizers of human skin with valuable applications in medicine for the treatment of skin deseases.[3] In the field of molecular biology, furanocoumarins have been used as photochemical reagents for the investigation of nucleic acid structures and functions.[4] Recently, it was found that components isolated from grapefruit juice have furanocoumarin dimer structures showing extremely high affinities for a form of cytochrome P450 (CYP3A4).[5]

Most approaches to the synthesis of linear furanocoumarins have involved the stepwise elaboration of the two heterocyclic rings beginning from a central aromatic core unit.[6] These are often associated with difficulty in controlling the regiochemical problems. The biological properties of the furanocoumarins and moderate yields in which they are obtained prompted us to work on alternative routes for synthesis of bergapten. To insure regiochemical integrity and convergence, we adopted iodine as an easily introducable and removable group. Herein we report an efficient route for the synthesis of the linear furanocoumarin, bergapten.

The synthetic route used by our group to obtain bergapten is outlined in Scheme 1. The commercially available phloroglucinol (**1**) was monomethylated using a previously published procedure,[7] producing the corresponding anisole derivatives (**2**). The reaction of **2** and ethyl propiolate in the presence of $ZnCl_2$ gave 7-hydroxy-5-methoxycoumarin (**3**) in 68% yield.[8] In order to avoid the formation of the angular furanocoumarin, the 8-position of **3** was protected by iodine according to the reported procedure.[9] The allylation of **4** afforded the *O*-allyl derivative (**5**), which was oxidatively cleaved to the aldehyde (**7**) *via* the diol (**6**), using osmium tetraoxide and sodium metaperiodate in moderate yield.[10] Recently Jin *et al*. reported an improved procedure for the oxidative cleavage of olefins by OsO_4-$NaIO_4$.[11] The addition of 2,6-lutidine resulted in suppression of the side reaction and improvement in the yield of the oxdation process (69%→ 92%). Next, the construction of the furan ring was performed by cyclization of aldehyde (**7**) with $BF_3{\cdot}Et_2O$ in the presence of tetra-*n*-butylammonium bromide. Ahluwalia *et al*. already reported

Scheme 1



Reagents, conditions, and yields: i, sat. HCl / MeOH, dioxane, 70°C, 12 h, 89%; ii, $ZnCl_2$, ethyl propiolate, 90°C, 1.5 h, 68%; iii, I_2, 5% KI, 20% NH_4OH, 0°C, 50 min, 82%; iv, ally lbromide, K_2CO_3, DMF reflux, 15 min, 86%; v, OsO_4,NMO, THF / H_2O. rt 75 h, 86%; vi, $NaIO_4$, THF / H_2O, rt 72 h, 80%; vii, 2,6-lutidine, OsO_4,$NaIO_4$, dioxane / H_2O, rt 72 h, 92%; viii, BF_3 Et_2O, tetra-*n*-butylammonium bromide, $CHCl_3$ reflux, 30 min, 71%; ix, $Pd(OAc)_2$, HCOOH, Et_3N, PPh_3, DMF 80°C 11 h, 90%.

that attempts to prepare **8** *via* Claisen migration of **5** were unsuccessful.[12] Finally, the iodine was removed by $Pd(OAc)_2$ to afford bergapten (**9**). Bergapten was isolated in 90% yield as colorless needles, mp 180-182°C, with spectroscopic properties identical to these of an authentic sample of the natural product.[13]

In summary, we have reported an efficient route for synthesis of the linear furanocoumarin, bergapten. Bergapten is also an applicable intermediate for the synthesis of more complex natural products. Work is currently underway to prepare various furanocoumarin dimers that have an inhibitory effect on human CYP3A4.

EXPERIMENTAL

All melting points were determined using a Yamato melting point apparatus (model MP-21) and are uncorrected. IR spectra were recorded using a JASCO A-102 spectrophotometer. NMR spectra were obtained using JEOL JNM LA300 and JEOL JNM EX-400 spectrometers. The chemical shifts are reported in ppm (□) relative to TMS (0.0 ppm) as the internal standard. MS spectra (MS, HRMS) were obtained using a Shimadzu GC MS 9100-MK gas chromatograph-mass spectrometer. Column chromatography was conducted using silica gel (Merck, Kieselgel 60, 70-230 mesh).

5-Methoxybenzene-1,3-diol (2)

Phloroglucinol·$2H_2O$ (3.5 g, 27.8 mmol) in dioxane (10 mL) and methanol (40 mL, saturated with dry HCl at 0°C) were heated at 70°C in a sealed-pressure glass bottle. After evaporation, the residue was purified by column chromatography using hexane–AcOEt (2:1, v/v) to give **2** as pale yellow oil. Yield 3.45 g (89%). The spectral data of this product were identical to those reported in ref. 7.

7-Hydroxy-5-methoxychromen-2-one (3)

A mixture of **2** (2.23 g, 15.9 mmol), $ZnCl_2$ (2.18 g, 16 mmol), and ethyl propiolate (2.35 g, 24 mmol) was heated at 90 °C for 1.5 h. After cooling, the reaction mixture was treated with 1M HCl solution. The precipitates were collected on a filter funnel. Colorless needles (from methanol),

yield 2.08 g (68%), mp 244-247 °C (lit.,[14] mp 244-245 °C).

7-Hydroxy-8-iodo-5-methoxychromen-2-one (4)

Aqueous NH_4OH (20%, 11 mL) was added to a solution of **3** (427 mg, 2.2 mmol) in dioxane (5 mL). A solution of iodine (620 mg, 2.44 mmol) in 36 mL of aqueous KI (5% w/v) was then added dropwise with stirring and cooling in an iced water bath. After maintaining the agitation for 50 min, the mixture was acidified with 2.5 M H_2SO_4. The precipitates were collected on a filter funnel. Pale yellow needles (from ethanol), yield 580 mg (82%), mp 226-229 °C (lit.,[9] mp 224-225 °C), ^{1}H-NMR (300 MHz, $CDCl_3$) □ 3.87 (3H, s), 6.15(1H, d, *J*=9.8 Hz), 6.54 (1H, s), 7.94 (1H, d, *J*=9.8 Hz), 11.40 (1H, s). MS *m*/*z* 318 (M^+). The spectral data of this product were identical to those reported in ref. 9.

8-Iodo-5-methoxy-7-prop-2-enyloxychromen-2-one (5)

To a solution of **4** (540 mg, 1.7 mmol) and allyl bromide (620 mg, 5.1 mmol) in DMF (25 mL) was added K_2CO_3 (700 mg 5.1 mmol), and the mixture was heated at 80 °C for 15 min. After filtration, the solvent was removed *in vacuo* to give the crude **5**. Pale yellow needles (from ethanol), yield 511 mg (86%), mp 196-200 °C (lit.,[12] mp 210-212 °C), ^{1}H-NMR (500 MHz, DMSO-d_6) □ 3.92 (3H, s), 4.70 (2H, d, *J*=4.6 Hz), 5.36 (1H, d, *J*=9.7 Hz), 5.57 (1H, d, *J*=16.6 Hz), 6.05(1H, m), 6.14 (1H, d, *J*=9.7 Hz), 6.69 (1H, s), 7.95 (1H, d, *J*=9.7 Hz). ^{13}C-NMR (125 MHz, DMSO-d_6) □ 57.2, 66.1, 70.4, 93.9, 104.7, 111.8, 111.8, 133.3, 139.3, 155.3, 158.0, 160.6, 161.5. MS *m*/*z* 358 (M^+). The spectral data of this product were identical to those reported in ref. 12.

7-(2,3-Dihydroxypropoxy)-8-iodo-5-methoxychromen-2-one (6)

A mixture of *N*-methylmorpholine *N*-oxide (270 mg, 2.0 mmol) and 2 mL of 0.02 M OsO_4 in *tert*-BuOH (2 mL) were added to a solution of **5** (358 mg, 1 mmol) in 2:1 (v/v) of THF and H_2O (30 mL). The resulting solution was stirred for 60 h at rt, treated with 1 mL of saturated $Na_2S_2O_3$ solution, and stirred for 5 min. The reaction mixture diluted with AcOEt was washed with water and brine, then dried over anhydrous Na_2SO_4. After filtration, the solvent was removed *in vacuo* to give the crude **6**. Pale yellow needles (from methanol), yield 337 mg (86%), mp 195-199 °C, ^{1}H-NMR (300 MHz, DMSO-d_6) □ 3.50-3.61 (2H, m), 3.83-3.87 (1H, m), 3.96 (3H, s), 4.11-4.22 (2H, m), 4.73 (1H, t, *J*=5.7 Hz), 5.03 (1H, t, *J*=4.8 Hz), 6.18 (1H, d, *J*=9.5 Hz), 6.69 (1H, s), 7.94 (1H, d, *J*=9.5 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6) □ 56.6, 62.5, 65.5, 69.8, 71.1, 93.0, 103.9, 111.0, 138.7, 154.7, 157.5, 160.0, 161.6. MS *m*/*z* 392 (M^+). *Anal*. Calcd for $C_{13}H_{13}O_6I$: C, 39.82; H, 3.34; I, 32.36. Found: C, 39.91; H, 3.24; I, 32.26.

2-(8-Iodo-5-methoxy-2-oxochromen-7-yloxy)ethanal (7)

$NaIO_4$ (278 mg, 1.3 mmol) was added to a solution of **6** (392 mg, 1.0 mmol) in 2:1 (v/v) of THF and H_2O (45 mL). The resulting solution was stirred for 72 h at rt and the solvent was removed *in vacuo*. The residue was purified by column chromatography using hexane–AcOEt (2:1, v/v). Pale yellow needles (from hexane-AcOEt), yield 287 mg (80%), mp 220-224 °C, ^{1}H-NMR (300 MHz, DMSO-d_6) □ 3.92 (3H, s), 4.71 (2H, s), 6.18 (1H, s), 6.21 (1H, d, *J*=9. 8 Hz), 7.29 (1H, d, *J*=9.8 Hz), 9.93 (1H, s). MS *m*/*z* 360 (M^+), HRMS *m*/*z* 359.9512 (Calcd for $C_{12}H_9O_5I$: 359.9495). *Anal*. Calcd for $C_{12}H_9O_5I$: C, 40.02; H, 2.52; I, 35.24. Found: C, 40.01; H, 2.44; I, 35.31.

One-step oxidation of 5 to 7

To a solution of **5** (358 mg, 1 mmol) in 3:1 of dioxane and water (10 mL) were added 2,6-lutidine (214 mg, 2 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 200 mg, 0.02 mmol), and $NaIO_4$ (856 mg, 4 mmol). The reaction mixture was stirred at rt for 2 h. After the reaction was completed, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer

was extracted three times by CH_2Cl_2 (10 mL). The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed *in vacuo* to give the crude **7**. Pale yellow needles (from hexane-AcOEt), yield 331 mg (92%). mp 220-224 °C.

9-Iodo-5-methoxyfurano[3,2-*g*]chromen-2-one (8)

To a solution of **7** (180 mg, 0.5 mmol) in $CHCl_3$ (15 mL) were added tetra-*n*-butylammonium bromide (180 mg, 0.55 mmol) and $BF_3{\cdot}Et_2O$ (190 μL, 1.5 mmol). The reaction mixture was refluxed for 30 min. After cooling, a saturated $NaHCO_3$ solution (10 mL) was added. The organic layer was separated and then washed with water and brine then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography using $CHCl_3$–AcOEt (20:1, v/v). Pale yellow needles (from hexane-AcOEt), yield 122 mg (71%), mp 195-196 °C (lit.,[15] mp 197-199 °C), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.28 (3H, s), 6.27 (1H, d, *J*=9.7 Hz), 7.17 (1H, d, *J*=2.4 Hz), 7.68 (1H, d, *J*=2.4 Hz), 8.08 (1H, d, *J*=9.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 56.5, 60.3, 106.2, 107.4, 112.4, 113.0, 139.0, 144.8, 150.2, 152.2, 158.9, 160.5. MS *m/z* 342 (M^+). The spectral data of this product were identical to those reported in ref. 15.

5-Methoxyfurano[3,2-*g*]chromen-2-one (9)

To a solution of **8** (35 mg, 0.1 mmol) in DMF (5 mL) were added $Pd(AcO)_2$ (2 mg), Et_3N (80 μL, 0.6 mmol), and formic acid (15 μL, 0.4 mmol). The reaction was heated at 80°C for 11 h. After cooling, the solvent was removed *in vacuo*. The residue was purified by column chromatography using hexane–AcOEt (2:1, v/v). Colorless needles (from ethanol), yield 20 mg (90%). mp 180-182 °C (lit.,[13] mp 188-189 °C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 4.27 (3H, s), 6.27 (1H, d, *J*=9.7 Hz), 7.02 (1H, d, *J*=2.4 Hz), 7.12 (1H, s), 7.59 (1H, d, *J*=2.4 Hz), 8.15 (1H, d, *J*=9.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 60.1, 93.8, 105.0, 106.4, 112.5, 112.6, 139.2, 144.8, 149.6, 152.7, 158.4, 161.2.

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