General Preparation of 7-Substituted 4-Chromanones: Synthesis of a Potent Aldose Reductase Inhibitor

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Benzopyrans are an important structural class[1] which have valuable and diverse biological properties. Synthetic benzopyran derivatives including the K^+ channel opener cromakalim[2] (1), the LTB_4 antagonist Ro 25-3562[3] (2), the Class III antiarrhythmic RP-58866[4] (3), and the aldose reductase inhibitor sorbinil[5] (4), exemplify the pharmacological importance of this heterocyclic substructure. In addition, benzopyrans are commonly found in many natural products, in particular, the flavonoids and the cannabinoids.[6]

Current synthetic protocols are not acceptable for the synthesis of many structurally relevant benzopyrans.[7] Most methods require severe conditions, are low-yielding, and lack generality for sensitive substituent patterns. One important entry into this structural type is through the synthesis of functionalized 4-chromanones.[8] The definitive step in this classical 4-chromanone syntheses involves the intramolecular acylation of β-phenoxypropionic acids in the presence of Lewis or anhydrous strong acids.[9] Alternately, direct Friedel–Crafts acylation or Fries rearrangement followed by intramolecular cyclization have been used with moderate success.[10] More recently, γ-bromoprop-2-ynyl aryl ethers undergo thermal transformations or mercury(II)-mediated cyclizations affording good yields of 4-chromanones.[11] While these methods enjoy some generality, they are often difficult to perform on large scale and suffer in the cases of unsymmetrical substrates. Regiochemical isomer mixtures are usually observed, affording low yields and requiring tedious chromatographic separations. These general difficulties are exacerbated in the preparation of C-2 unsubstituted 4-chromanones because of polymerization and in situ oxidation to the stable chromone product.

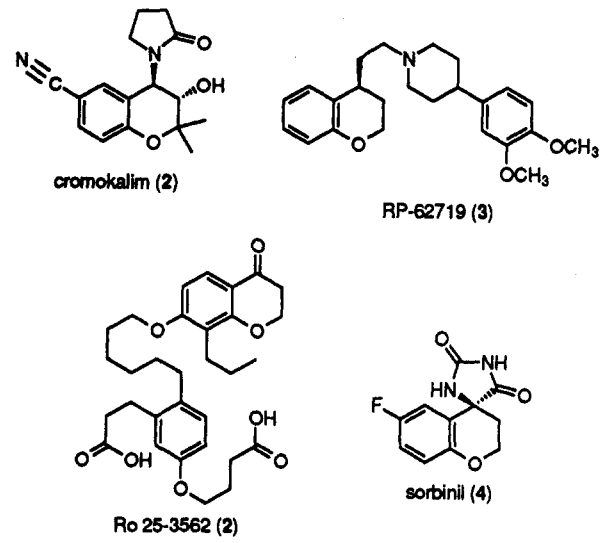

Figure 1.

A straightforward, general, and scalable synthesis of a wide assortment of 7-substituted 4-chromanones would be of value for the synthesis of biologically active materials. In particular, we required a convergent preparation of 7-substituted analogs of the aldose reductase inhibitor sorbinil, to facilitate the study of structure–activity relationships. This mechanistic class is of potential value in the therapy of chronic complications of diabetes mellitus by inhibiting the conversion of glucose to the undesirable sorbitol.[12] A number of 6- or 8-aryl-substituted sorbinil analogues had been previously synthesized by classic methods which showed promising *in vivo* and *in vitro* activities.[20] However, due to synthetic difficulties, few 7-substituted hydantoins have been prepared.

The key intermediate 7 should be readily obtainable from resorcinol and the appropriate three-carbon synthon followed by trifluoromethanesulfonylation of the resulting phenol. Introduction of diverse functionality could be accomplished by taking advantage of the recent findings regarding the reactivity of aryl and vinyl halides and trifluoromethanesulfonates (triflates) in palladium-mediated reactions.[13] Using this novel synthetic sequence, an array of substituents could be introduced into the 7 position of the chromanone skeleton. A survey of the literature revealed that 7-hydroxy-4-chromanone had been prepared by the reaction of resorcinol and 3-chloropropionic acid in neat HF at 50 °C in a steel bomb followed by basic intramolecular cyclization in 37% overall yield.[14] Since this method was unacceptable to us for the multigram preparation of our required intermediate, we undertook a study of the reactivity of resorcinol with a variety of anhydrous acids and acylating agents.

After a short survey of common Lewis acids and solvents,[15] we found that the reaction of resorcinol with 3-chloropropionic acid in neat trifluoromethanesulfonic

(1) (a) Ellis, G. P.; Lockhart, I. M. *Chromans and Tocopherols*; Wiley: New York, 1981; (b) Harborne, J. B.; Marby, H. J.; Marby, H. *The Flavonoids*; Academic Press: New York, 1975.
(2) Prous, J. R. *Drugs Future* **1991**, *16*, 264 (Prous Science Pub.: Barcelona, Spain).
(3) Cook, C. S.; Gaginella, T. S.; Fretland, D., Jr.: Tsai, B. S.; Djuric, S. W.; Shone, R. L. *Drugs Future* **1990**, *15*, 695 (Prous Science Pub.: Barcelona, Spain).
(4) Mestre, M.; Escande, D.; Cavero, I. *Eur. J. Pharmacol.* **1990**, *183*, 1239.
(5) Sarges, R.; Bordner, J.; Dominy, B. W.; Peterson, M. J.; Whipple, E. B. *J. Med. Chem.* **1985**, *28*, 1716.
(6) Middleton, E., Jr.; Kandaswami, C. *Biochem. Pharmacol.* **1992**, *43*, 1167.
(7) (a) Ellis, G. P. *Chromenes, Chromanones and Chromones*; Wiley: New York, 1977. (b) Robertson, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, *33*, 1529.
(8) Kabbe, H. J.; Widdig, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 247.
(9) (a) Camps, F.; Coll, J.; Messeguer, A.; Pericas, M. A.; Ricart, S.; Bowers, W. S.; Soderlund, D. M. *Synthesis* **1980**, 725. (b) Offe, H. A.; Barkow, W. *Chem. Ber.* **1947**, *80*, 458.
(10) (a) Sato, K.; Lin, Y. S.; Amakasu, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2600. (b) Baker, W.; Floyd, J. F.; McOmie, F. W.; Pope, G.; Weaving, A. S.; Wild, J. H. H. *J. Chem. Soc.* **1956**, 2010.
(11) (a) Subramanian, R. S.; Balasubramanian, K. K. *J. Chem. Soc. Chem. Commun.* **1990**, 1469. (b) Ariamala, G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 3487. (c) Gapalsamy, A.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1988**, *34*.
(12) Lipinski, C. A.; Hutson, N. J. *Annu. Rep. Med. Chem.* **1984**, *17*, 169.
(13) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.
(14) Dann, V. O.; Volz, G.; Haber, O. *Liebigs Ann. Chem.* **1954**, *587*, 16.
(15) Naylor, P.; Ramage, G. R.; Schofield, F. *J. Chem. Soc.* **1958**, 1190. A number of variations of solvent (methylene chloride, nitrobenzene), acid (PPA, $AlCl_3$, H_2SO_4), and acylating agent (3-chloropropionic acid, 3-chloropropionyl chloride) were attempted resulting in low yields of the desired product.

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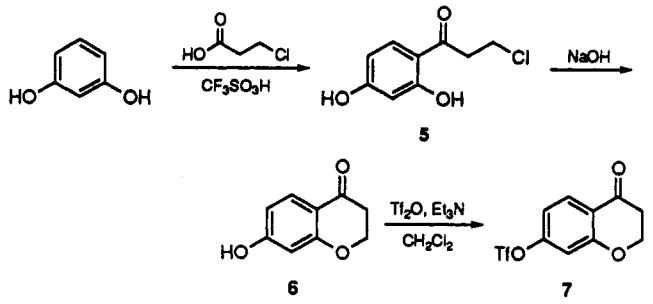
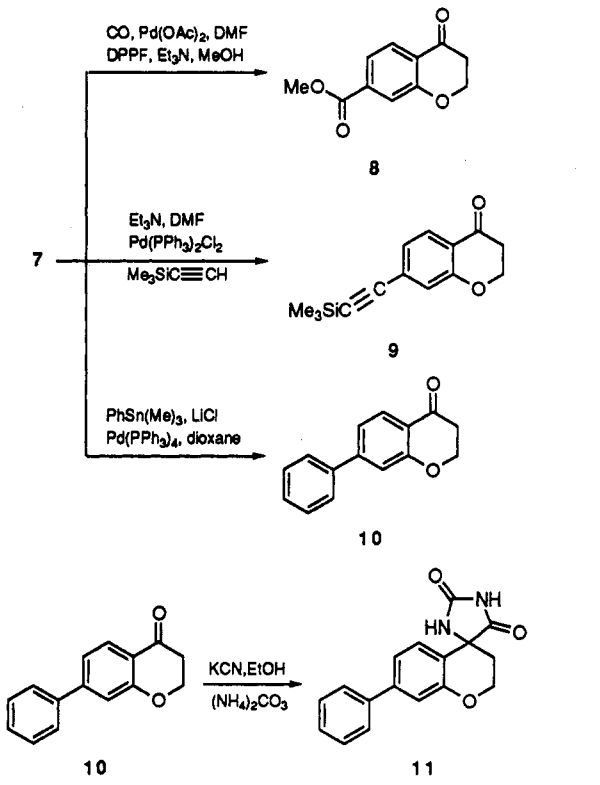
Scheme 1



Scheme 2



acid (3 equiv) at 80 °C for 30 min gave the Friedel–Crafts product **5** (Scheme 1). After aqueous workup, the crude product was stirred in 2.0 M NaOH to afford chromanone **6** in 61% overall yield on a >100 g scale without the need for rigorous chromatography. Treatment of this phenol with trifluoromethanesulfonic anhydride and triethylamine in methylene chloride at −78 °C gave a good yield of the desired aryl triflate **7**.

With our key intermediate in hand for the synthesis of 7-substituted chromanones, we examined the reactivity of this novel electron-deficient aryl triflate.[16] Introduction of a one-carbon unit via palladium-catalyzed CO insertion and alcohol or amine trapping of the aryl palladium intermediate is a powerful method for the functionalization of aromatic moieties. Carbomethoxylation[17] of triflate **7** with palladium catalysis using 1,1′-bis(diphenylphosphino)ferrocene as the ligand in DMF and MeOH under 1 atm of CO afforded chromanone **8** in 94% yield (Scheme 2). Previously, this compound had been prepared in five steps and in 4% overall yield.[18] Introduction of acetylene as a useful two-carbon synthon could be readily accomplished[19] via the reaction of (trimethylsilyl)acetylene with aryl triflate **7** under palladium catalysis in DMF affording chromanone **9** in 96% yield.

The reaction of aryl triflates with functionalized organostannanes has emerged as a powerful and versatile method for carbon-carbon bond formation.[21] Reaction of **7** with phenyltrimethyltin in the presence of tetrakis(triphenylphosphine)palladium(0) and lithium chloride in 1,4-dioxane gave the previously unknown coupled product **10** in 87% yield. The reaction of compound **10** using Bucherer–Bergs conditions[22] afforded the desired hydantoin product **11** in a straightforward manner. This compound was found to have equal potency to racemic sorbinil in the aldose reductase inhibition assay.[20]

In conclusion, we have described the preparation of a number of 7-substituted-4-chromanones in a direct and regioselective manner. These intermediates can be used to prepare important biologically active compounds as exemplified by the novel aldose reductase inhibitor **11**. The ready availability and reactivity of phenols coupled with the versatility of palladium-mediated reactions involving their triflate derivatives is a powerful protocol for the preparation of polysubstituted aromatic structures.

Experimental Section

General. ^{1}H-NMR spectra were determined at 300 MHz. Unless otherwise specified, all NMR spectra were recorded in $CDCl_3$ and chemical shifts are expressed in ppm downfield from tetramethylsilane. Data are presented in order of number of hydrogens, multiplicity, coupling constant. IR values are in inverse centimeters. All substrates and reagents were obtained from Aldrich Chemical Co. and were used as received.

2′,4′-Dihydroxy-3-chloropropiophenone (5).[14] To a stirred mixture of resorcinol (20.0 g, 182 mmol) and 3-chloropropionic acid (20.0 g, 184 mmol) was added trifluoromethanesulfonic acid (100 g) in one portion. The solution was warmed to 80 °C for 30 min, cooled to room temperature over 15 min, and poured into chloroform (400 mL). The solution was slowly poured into water (400 mL), and the layers were separated. The aqueous layer was extracted with 2 × 200 mL of $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Concentration in vacuo gave 24.1 g of a orange semisolid which was used crude in the next step: ^{1}H-NMR δ 12.56 (1H, s), 7.63 (1H, d, J = 7.6 Hz), 6.37–6.46 (2H, m), 3.92 (2H, t, J = 6.3 Hz), 3.41 (2H, t, J = 6.3 Hz).

7-Hydroxy-4-chromanone (6).[14] To a stirred solution of 2 M NaOH (1.0 L) at 5 °C was added **5** (24.1 g) in one portion. The solution was warmed to room temperature over 2 h and then recooled to 5 °C, and the pH was adjusted to ca. 2 with 6 M H_2SO_4 (ca. 100 mL). The mixture was extracted with 3 × 200 mL of EtOAc, washed with brine, dried over Na_2SO_4, and filtered. Concentration in vacuo gave a tan solid. Trituration with hexanes, filtration, and then recrystallization from water gave 18.4 g (61%) yield of colorless needles: mp 143 °C (lit.[14] mp 145 °C); ^{1}H-NMR δ 7.84 (1H, d, J = 9.4 Hz), 6.73 (1H, brd s), 6.55 (1H, dd, J = 9.4, 1.8 Hz), 6.43 (1H, d, J = 1.8 Hz), 4.54 (2H, t, J = 6.5 Hz), 2.78 (2H, t, J = 6.5 Hz); IR ($CHCl_3$) 3160, 1660, 1596, 1451, 1370, 1254.

7-[[(Trifluoromethyl)sulfonyl]oxy]-4-chromanone (7). To a stirred solution of **6** (17.4 g, 105 mmol) in methylene chloride (300 mL) at −78 °C were added Et_3N (32.0 g, 116 mmol) and DMAP (250 mg, cat.). After complete dissolution had occurred, trifluoromethanesulfonic anhydride (32.7 g, 116 mmol) was added dropwise over 5 min, and the solution stirred at −78 °C for 30 min and then warmed to room temperature over 2 h. The reaction

(16) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, *85*.
(17) (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931. (b) Dolle, R. E.; Schmidt, S. J.; Krase, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904.
(18) Hirsch, J. A.; Schwartzkopf, G. *J. Org. Chem.* **1973**, *38*, 3534.
(19) Chen, Q. Y.; Yang, Z. Y. *Tetrahedron Lett.* **1986**, *27*, 1171.
(20) Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1987**, *31*, 230.
(21) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
(22) Bucherer, H. T.; Fischbeck, H. T. *J. Prakt. Chem.* **1934**, *140*, 69.

mixture was poured into saturated NH_4Cl solution (250 mL), the layers were separated, and the aqueous layer was extracted with 2 × 100 mL of methylene chloride. The combined organic fractions were washed with water, dried over $MgSO_4$, and filtered. Concentration in vacuo gave a red oil which was passed through a short pad of silica gel (100 g) eluting with hexane/ethyl acetate (8:1). Solvent removal in vacuo gave 22.4 g (71% yield) of an oil which solidified on standing: mp 43–44 °C; ^{1}H-NMR δ 7.98 (1H, d, J = 9.4 Hz), 6.91–6.93 (2H, m), 4.59 (2H, t, J = 6.5 Hz), 2.84 (2H, t, J = 6.5 Hz); IR ($CHCl_3$) 3010, 1682, 1596, 1510, 1461, 1408, MS m/e 296.1 (M^+). Anal. Calcd for $C_{10}H_7F_3O_5S$: C, 40.55; H, 2.38. Found: C, 40.41; H, 2.54.

7-Carbomethoxy-4-chromanone (8).[18] To a stirred solution of 7 (7.89 g, 26.6 mmol) in dry DMF (54 mL) were added methanol (21.6 mL), palladium acetate (110 mg, 0.533 mmol), 1,1′-bis-(diphenylphosphino)ferrocene (0.590 mg, 1.07 mmol), and Et_3N (7.5 mL, 53.3 mmol). Carbon monoxide gas was bubbled through the solution for 5 min and then the mixture was stirred at 50 °C for 3 h under 1 atm of CO. After cooling, the mixture was poured into 120 mL of 1 M HCl and extracted with 2 × 75 mL of ethyl acetate. The combined organic fractions were washed with brine, dried over $MgSO_4$, and then filtered. Solvent evaporation in vacuo and chromatography (silica gel, 1:1 hexane:ether) gave 5.19 g (94% yield) of 8 as a white solid: mp 109 °C (lit.[18] mp = 108–109 °C); ^{1}H NMR δ 7.96 (1H, d, J = 9.2 Hz), 7.60–7.65 (2 H, m), 4.60 (2 H, t, J = 6.7 Hz), 3.93 (3 H, s), 2.88 (2 H, t, J = 6.7 Hz); IR ($CHCl_3$) 1733, 1704, 1627, 1579, 1476, 1433; MS m/e 206.1 (M^+), 178, 147, 119, 91. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.35; H, 5.06.

7-[(Trimethylsilyl)ethynyl]-4-chromanone (9). To a stirred solution of 7 (2.96 g, 10.0 mmol) in dry DMF (30 mL) were added Et_3N (6 mL, excess), $Pd(PPh_3)_2Cl_2$ (210 mg, 0.30 mmol), and trimethylsilylacetylene (2.11 mL, 15.0 mmol). The mixture was stirred under N_2 at 70 °C for 1 h, cooled to room temperature, and poured into saturated NH_4Cl solution (100 mL). The mixture was extracted with 3 × 50 mL of EtOAc, and the combined organic fraction was washed with brine, dried over $MgSO_4$, and filtered. Concentration followed by chromatography (silica gel, hexane:ether 10:1) gave 2.36 g (96% yield) of a yellow crystalline solid: mp 85–86 °C; ^{1}H-NMR δ 7.80 (1H, d, J = 7.9 Hz), 7.04–7.07 (2H, m), 4.51 (2H, t, J = 6.6 Hz), 2.81 (2H, t, J = 6.6 Hz), 0.24 (9H, s); IR ($CHCl_3$) 2171, 1703, 1621, 1562; MS m/e 244 (M^+), 229, 201, 173, 157, 129, 117, 100. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 68.81; H, 6.60. Found: C, 68.63; H, 6.56.

7-Phenyl-4-chromanone (10). To a stirred solution of 7 (2.96 g, 10.0 mmol) in 50 mL of dry 1,4-dioxane were added phenyltrimethyltin (2.64 g, 11.0 mmol), LiCl (1.27 g, 30.0 mmol), $Pd(PPh_3)_4$ (230 mg, 0.20 mmol), and 3 crystals of 2,6-di-*tert*-butyl-4-methyphenol. The mixture was heated at reflux for 18 h, cooled to room temperature, and poured into saturated NH_4Cl solution (100 mL). The mixture was extracted with 3 × 75 mL of diethyl ether, washed with brine, dried over $MgSO_4$, and filtered. Concentration in vacuo gave a yellow oil. Chromatography (silica gel, 5:1 hexane:diethyl ether) and then recrystallization from isopropyl ether gave 1.95 g (87% yield) of yellow needles: mp 109 °C; ^{1}H-NMR δ 7.95 (1H, d, J = 8.1 Hz), 7.57–7.61 (2H, m), 7.36–7.48 (3H, m), 7.25 (1H, dd, J = 8.1, 1.7 Hz), 7.18 (1H, d, J = 1.7 Hz), 4.56 (2H, t, J = 6.7 Hz), 2.83 (2H, t, J = 6.7 Hz); IR ($CHCl_3$) 1710, 1620, 1574, 1442; MS m/e 224 (M^+), 196, 168, 139. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.38. Found: C, 80.48; H, 5.34.

7-Phenyl-2,3-dihydrospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (11). A mixture of chromanone 10 (300 mg, 1.34 mmol), EtOH (2 mL), H_2O (5 mL), $(NH_4)_2CO_3$ (386 mg, 4.00 mmol), and KCN (174 mg, 2.67 mmol) was heated in a sealed tube with stirring for 24 h at 60 °C. The reaction mixture was diluted with 10 mL of H_2O, boiled for 15 min, cooled, and then modified to pH 4 with 1 M HCl. The dark mixture was extracted with $CHCl_3$ (3 × 20 mL), washed with brine, dried over $MgSO_4$, and filtered to afford a greenish oil. Chromatography over silica gel (CH_2Cl_2:MeOH 10:1) gave 140 mg (39% yield) of an off-white solid . An analytical sample was prepared by recrystallization from EtOH/hexane to afford white crystals (ethanol solvate): mp 203–204 °C; ^{1}H-NMR δ 8.43 (1H, s), 7.11–7.55 (8H, m), 6.14 (1H, s), 4.67–4.79 (1H, m), 4.19–4.27 (1H, m), 3.69–3.74 (2H, m), 2.40–2.48 (1H, m), 2.22–2.29 (1H, m), 1.24 (3H, t); IR (DMSO) 1660; MS m/e 295 (M + 1) 224, 196, 174. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8,23. Found: C, 66.79; H, 5.95; N, 8.21.

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