New Methods of Synthesis of 4-Methylangelicin

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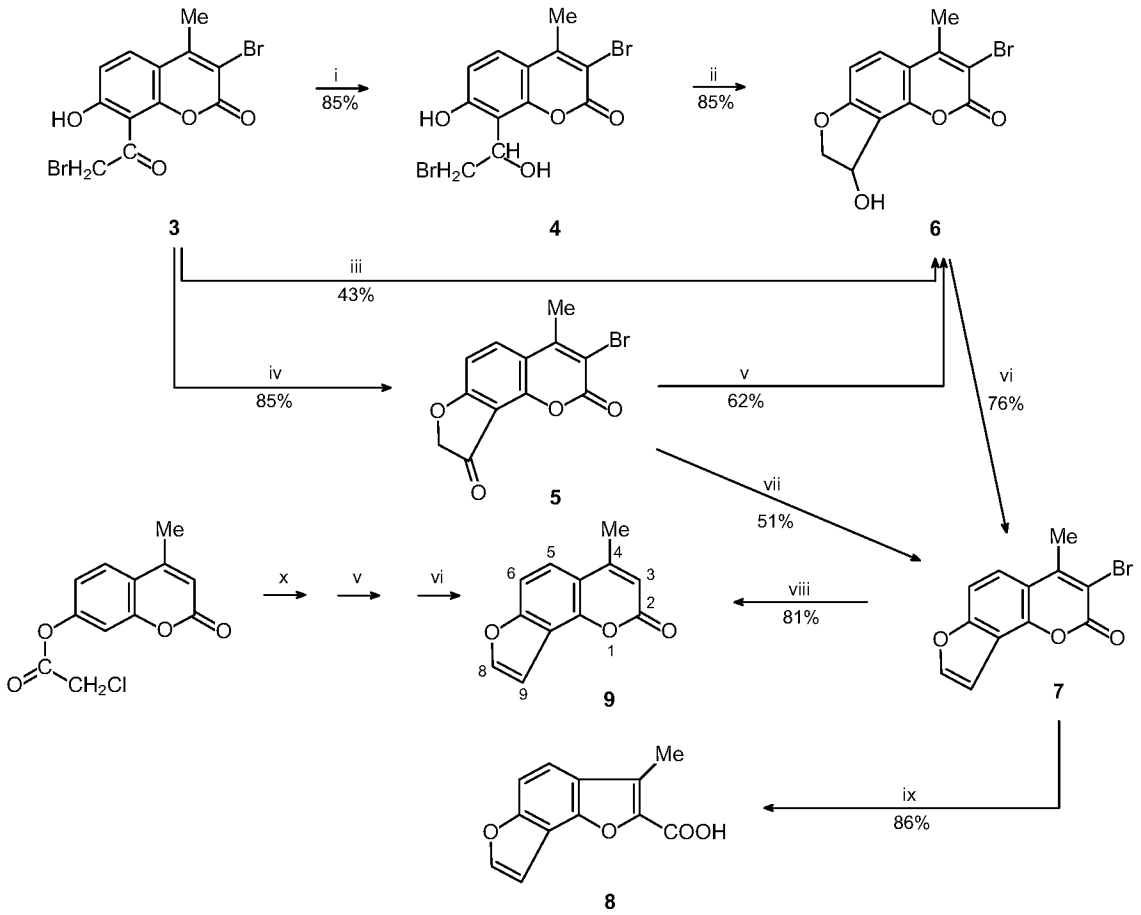
New methods for the preparation of 4-methylangelicin have been developed *via* transformations of 7-hydroxy-8-halogenoacetyl-4-methylcoumarins.

The phototherapeutic effect of some natural furocoumarins is based on their ability to undergo [2 + 2]cycloadditions with the pyrimidine bases of microorganism DNA.[1,2] Angelicin and its derivatives show this effect as well. Several methods of angelicin preparation are known;[3–9] some of them involve too many steps,[3,7,8] while others are based on a decarboxylation step which proceeds in rather a low yield.[6,8] We have developed new methods of angelicin preparation which are characterised by a low number of steps and high yields. The preparation of 4-methylangelicin is given below as an example.

7-Acetoxy-4-methylcoumarin readily undergoes the Fries rearrangement with 8-acetyl-7-hydroxy-4-methylcoumarin **1** formation in very good yield.[10] Bromination of **1** by 1 mol of bromine in acetic acid gives 8-acetyl-3-bromo-7-hydroxy-4-methylcoumarin **2**. Use of 2 mol bromine under the same conditions results in 3-bromo-8-bromoacetyl-7-hydroxy-4-methylcoumarin **3**.† Compound **3** yields 3-bromo-8-(2′-bromo-1′-hydroxyethyl)-7-hydroxy-4-methylcoumarin **4** *via* reduction with $NaBH_4$ in dioxane. Treatment of compound **4** with K_2CO_3 in DMSO results in 3-bromo-9-hydroxy-4-methyldihydrofuro[2,3-*h*]coumarin **6**. Compound **6** has been prepared without isolation of the coumarin **4** as an intermediate product, simply by treatment of **3** with $NaBH_4$ (under TLC control) and then with K_2CO_3.

Dihydrofurocoumarin **6** is also available through intermediate formation of compound **5**. 3-Bromo-4-methyldihydrofuro[2,3-*h*]coumarin-9-one **5** is a product of coumarin **3** cyclization in the presence of K_2CO_3. Dehydration of the compound **6** in a solution of 74% H_2SO_4 gives 3-bromo-4-methylangelicin **7** in good yield. Compound **7** has also been prepared by reduction of compound **5** (similar to compound **6** preparation, but with longer heating time).

3-Bromo-4-methylangelicin has properties which are specific to 3-halogenocoumarins – debromination with transformation of the pyrone ring to the furan ring and subsequent debromination which leaves the pyrone ring untouched.[11] Treatment of compound **7** with 30% aqueous NaOH gives 3-methylfuro[2,3-*g*]benzofuran-2-carboxylic acid



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, dioxane, 20 °C, 1 h; ii, K_2CO_3, DMSO, 20 °C, 1 h; iii, (1) $NaBH_4$, dioxane, 110 °C, 20 min; (2) K_2CO_3, 110 °C, 3 h; iv, K_2CO_3, DMSO, 40–50 °C, 20 min; v, $NaBH_4$, dioxane, 30–40 °C, 15 min; vi, 74% H_2SO_4, 100 °C, 3 h; vii, $NaBH_4$, dioxane, 30–40 °C, 2 h; viii, Zn, EtOH, 78 °C, 14 h; ix, 30% NaOH, 100 °C, 3 h; x, $AlCl_3$, 120 °C, 45 min.

† We have introduced a bromine atom into the acetyl group (keeping position 3 untouched with 7-hydroxy group protection only) by means of 7-acetoxy-8-acetyl-4-methylcoumarin bromination.

8. Smooth debromination of compound **7** to the final product, 4-methylangelicin **9**, was achieved with zinc dust in alcohol.

Angelicin **9** has also been obtained by an even shorter method, without halogenation and dehalogenation steps. The Fries rearrangement of 7-chloroacetoxy-4-methylcoumarin proceeds rather unusually, giving 4-methyldihydrofuro-[2,3-*h*]coumarin-9-one as the main product in a satisfactory yield. Reduction of the latter compound with $NaBH_4$ followed by dehydration gives 4-methylangelicin.

All transformations studied are presented in Scheme 1. Melting points and spectral data of new compounds are listed below.‡

‡ **2**: m.p. 214–215 °C; ^{1}H NMR (200 MHz, $CDCl_3$, *J*/Hz), δ: 2.62 (s, 3H, 4Me), 2.96 [s, 3H, C(O)Me], 6.95 (d, 1H, 6-H, $J_{6,5}$ 9.2), 7.73 (d, 1H, 5H, $J_{5,6}$ 9.2), 13.54 (s, 1H, OH); IR (KBr), ν_{max}/cm^{-1}: 3420 (br.), 1720, 1620, 1600, 1380, 1310, 1250, 1230, 1100, 870, 850, 755.

3: m.p. 200–201 °C; ^{1}H NMR (200 MHz, $CDC1_3$, *J*/Hz), δ: 2.63 (s, 3H, 4Me), 4.91 (s, 2H, CH_2Br), 6.99 (d, 1H, 6-H, $J_{6,5}$ 9.1), 7.79 (d, 1H, 5-H, $J_{5,6}$ 9.1), 12.84 (s, 1H, OH); IR (KBr), ν_{max}/cm^{-1}: 3420 (br.), 1720, 1630, 1580, 1380, 1310, 1260, 1250, 1180, 1100, 1020, 690; MS, *m*/*z*: 374/376/378 (M^+).

4: m.p. 205–206 °C; ^{1}H NMR (200 MHz, [$^2H_6$]acetone, *J*/Hz), δ: 2.61 (s, 3H, 4Me), 3.81 (dd, 1H, $2'_A$-H, J_{gem} 10.7, $J_{2'_A,1'}$ 7.0), 3.90 (dd, 1H, $2'_B$-H, J_{gem} 10.7, $J_{2'_B,1'}$ 4.2), 5.74 (ddd, 1H, 1′-H, $J_{1',2'_A}$ 7.0, $J_{1',OH}$ 5.3, $J_{1',2'_B}$ 4.2), 6.33 (d, 1H, OH, $J_{OH,1'}$ 5.3), 6.86 (d, 1H, 6-H, $J_{6,5}$ 8.7), 7.70 (d, 1H, 5-H, $J_{5,6}$ 8.7), 9.90 (s, 1H, 7-OH); IR (KBr), ν_{max}/cm^{-1}: 3210 (br.), 1690, 1620, 1600, 1380, 1280, 1240, 1090, 1070, 840, 680.

5: m.p. 269–270 °C; ^{1}H NMR (200 MHz, [$^2H_6$]acetone, *J*/Hz), δ: 2.59 (s, 3H, 4Me), 4.83 (s, 2H, CH_2), 7.18 (d, 1H, 6-H, $J_{6,5}$ 9.1), 8.18 (d, 1H, 5-H, $J_{5,6}$ 9.1); IR (KBr), ν_{max}/cm^{-1}: 1720, 1620, 1595, 1330, 1275, 1190, 1090, 1000, 845, 760, 600; MS, *m*/*z*: 294/296 (M^+).

6: m.p. 190–192 °C; ^{1}H NMR (200 MHz, [$^2H_6$]acetone, *J*/Hz), δ: 2.64 (s, 3H, 4Me), 4.55 (dd, 1H, 8_A-H, J_{gem} 11.0, $J_{8_A,9}$ 2.4), 4.73 (dd, 1H, 8_B-H, J_{gem} 11.0, $J_{8_B,9}$ 6.5), 5.00 (d, 1H, 9-OH, $J_{OH,9}$ 5.8), 5.70 (ddd, 1H, 9-H, $J_{9,8_B}$ 6.5, $J_{9,OH}$ 5.8, $J_{9,8_A}$ 2.4), 6.88 (d, 1H, 6-H, $J_{6,5}$ 8.9), 7.78 (d, 1H, 5-H, $J_{5,6}$ 8.9); IR (KBr), ν_{max}/cm^{-1}: 3420, 1690, 1620, 1600, 1345, 1280, 1240, 1090, 960, 830, 760; MS, *m*/*z*: 296/298 (M^+).

7: m.p. 213–214 °C; ^{1}H NMR (200 MHz, [$^2H_6$]acetone, *J*/Hz), δ: 2.75 (s, 3H, 4Me), 7.22 (dd, 1H, 8-H, $J_{8,9}$ 2.2, $J_{8,6}$ 1.1), 7.60 (dd, 1H, 6-H, $J_{6,5}$ 9.1, $J_{6,8}$ 1.1), 7.83 (d, 1H, 5-H, $J_{5,6}$ 9.1), 8.05 (d, 1H, 9-H, $J_{9,8}$ 2.2); IR (KBr), ν_{max}/cm^{-1}: 3110, 1720, 1620, 1600, 1385, 1350, 1150, 1085, 775; MS, *m*/*z*: 278/280 (M^+).

8: m.p. 160 °C (decomp.); ^{1}H NMR (200 MHz, [$^2H_6$]acetone, *J*/Hz), δ: 2.66 (s, 3H, 3Me), 7.22 (dd, 1H, 7-H, $J_{7,8}$ 2.4, $J_{7,5}$ 0.9), 7.60 (dd, 1H, 5-H, $J_{5,4}$ 8.5, $J_{5,7}$ 0.9), 7.68 (d, 1H, 4-H, $J_{4,5}$ 8.5), 8.00 (d, 1H, 8-H, $J_{8,7}$ 2.4); IR (KBr), ν_{max}/cm^{-1}: 3090 (br.), 2900, 2600, 1670, 1580, 1440, 1300, 1190, 1160, 810, 760.

9: m.p. 189 °C (lit.,[8] m.p. 189 °C).

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Received: Moscow, 12th July 1994
Cambridge, 6th October 1994; Com. 4/04475D