New Synthesis of (±)-5-Hydroxymarmesin, Biogenetic Precursor of the Skin Photosensitizing Agent Bergapten (5-MOP)

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A convenient synthesis is described of (±)-5-hydroxymarmesin, 4-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-7*H*-furo[3,2-*g*][1]benzopyran-7-one, a physiological intermediate in the biogenetic pathway of 5-*O*-alkylfurocoumarins. The synthesis was achieved by a regiospecific 6-C isoprenylation of 5,7-diacetoxycoumarin; the 6-C isoprenylated derivative is then submitted to an oxidative cyclization obtaining mainly the title compound together with its angular isomer.

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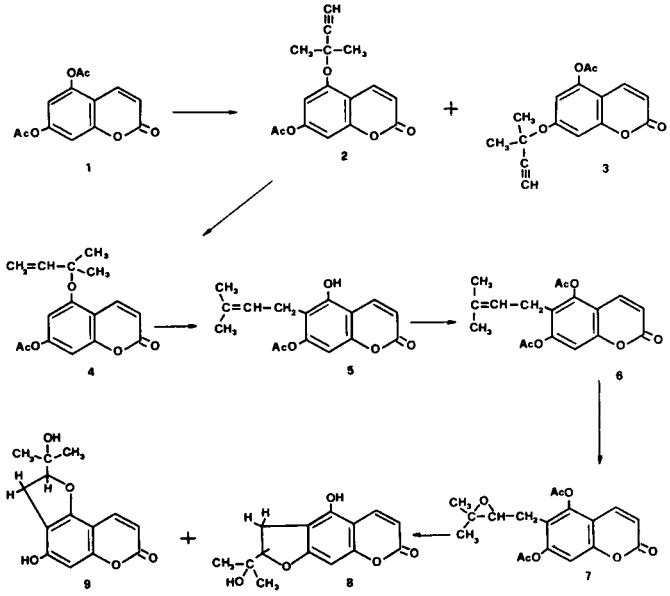
Recently, with the intent of clarifying certain aspects of linear furocoumarin biogenesis, we prepared (1) the previously unknown (±)-5-hydroxymarmesin, 4-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**8**), a 5-hydroxylated linear dihydrofurocoumarin, for which the role of a physiological precursor in the biogenetic pathway of 5-*O*-alkylfurocoumarins was suggested (2). Linear furocoumarins, or psoralens, are a group of naturally occurring compounds, showing marked photosensitizing properties on human skin and on several other biological systems (3,4). These substances are the cause of some phytophotodermatitis, produced by contact of the skin with the plant containing the furocoumarin and successive exposure to sunlight.

The capacity of these substances to photosensitize the skin has long been used for the treatment of vitiligo and more recently for the photochemotherapy of psoriasis and of other skin diseases (5,6,7); for this therapy, xanthotoxin (8-methoxypsoralen, 8-MOP) is the most used, although recently bergapten (5-methoxypsoralen, 5-MOP) is becoming important (8).

In the previously described synthesis, the key intermediate was 5,7-diacetoxy-8-(3'-methylbut-2'-enyl)-coumarin, from which, by an oxidative cyclization, (±)-5-hydroxycolumbianetin (9), 5-hydroxy-8-(1-hydroxy-1-methylethyl)-8,9-dihydro-2*H*-furo[2,3-*h*][1]benzopyran-2-one, was obtained. This compound by treatment with strong alkali followed by acidification, undergoes relactonization giving (±)-5-hydroxymarmesin together with the starting product.

The results obtained in preliminary biogenetic experiments on *Ficus carica* and *Ruta graveolens* with (±)-5-hydroxymarmesin (10) indicated the role of a biogenetic precursor for this substance. Consequently, the necessity to dispose of larger amounts of (±)-5-hydroxymarmesin in order to extend the biogenetic experiments on various plants, encouraged us to ameliorate the previously described synthetic pathway, which is very expensive



(eleven steps) and results in a low overall yield (about 0.9%). In this connection, the possibility of obtaining the 5-hydroxymarmesin through a 6-C regioselective isoprenylation, which was previously discarded (1), has been reconsidered and successfully employed, after discovering improved conditions for the 5-*O*-monopropargylation of 5,7-diacetoxycoumarin.

Thus, (±)-5-hydroxymarmesin was prepared in six steps as shown in Figure 1 in 9.3% overall yield. It is well known that partial methylation or isoprenylation (11-13) of 5,7-diacetoxycoumarin in acetone solution occurs giving a slight excess of the 5-*O*-alkylated derivatives. Moreover, if dimethoxyethane is used as the solvent (1,14,15), alkylation in the 5-*O*-position becomes more selective.

Synthesis was then initiated by condensing 5,7-diacetoxycoumarin (16) with 3-chloro-3-methylbut-1-yne in the presence of anhydrous potassium carbonate in dimethoxyethane solution. By working up the reaction mixture by silica gel chromatography, the pure 5-*O*-dimethyl-

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Table

Compound No.		Molecular weight	Calculated		Found	
			C	H	C	H
1	$C_{13}H_{10}O_6$	262.21	59.54	3.84	59.33	3.81
2	$C_{16}H_{14}O_5$	286.26	67.12	4.93	66.98	4.89
3	$C_{16}H_{14}O_5$	286.27	67.12	4.93	66.95	4.94
4	$C_{16}H_{16}O_5$	288.29	66.66	5.59	66.61	5.50
5	$C_{16}H_{16}O_5$	288.29	66.66	5.59	66.51	5.53
6	$C_{18}H_{18}O_6$	330.32	65.74	5.49	65.65	5.43
7	$C_{18}H_{18}O_7$	346.32	62.42	5.24	62.27	5.21
8	$C_{14}H_{14}O_5$	262.25	64.11	5.38	64.01	5.35

propargylated derivative, *i.e.*, 5-(1′,1′-dimethylprop-2′-ynyloxy)-7-acetoxycoumarin (**2**) (15), was isolated, together with a small amount of the 7-*O*-dimethylpropargyl ether isomer **3**.

The 5-*O*-dimethylpropargylated compound **2** was then hydrogenated to give 5-(1′,1′-dimethylallyloxy)-7-acetoxycoumarin (**4**), which on heating at 100° under reduced pressure, rearranged to 5-hydroxy-6-(3′-methylbut-2′-enyl)-7-acetoxycoumarin (**5**). High resolution ^{1}H-nmr spectroscopy of **5** showed a long range coupling between the 4-C and 8-C protons (1), indicating the rearrangement of the migrating group to the 6-position.

Compound **5** was acetylated and then epoxidized, and the epoxy derivative **7** was cyclized by treatment with sodium bicarbonate in methanolic solution. Both the *ortho* 5- and 7-*O*-acetylated positions may be involved in the cyclization. Practically speaking under the mildly alkaline conditions employed, the 7-position was preferred giving as the major product the desired linear dihydrofurocoumarin (**8**), which was identical to the previously synthesized material.

In addition, by silica gel chromatography of the mother liquors, a small amount of the previously unknown angular isomer, 4-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-7*H*-furo[2,3-*f*][1]benzopyran-7-one (**9**) was isolated.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Büchi-Tottoli SPM-20 capillary melting point apparatus. Analytical thin-layer chromatography (tlc) was performed on pre-coated silica gel 60 F-254 plates (Merck; 0.25 mm.), developing with an ethyl acetate-cyclohexane mixture (35:65), unless otherwise indicated.

^{1}H-nmr spectra were recorded on a Hitachi-Perkin-Elmer R-24 A or a Varian FT-80 A spectrometer with tetramethylsylane (TMS) as internal standard and deuteriochloroform as solvent, unless otherwise stated. Coupling constants are given in Hz. The relative peak areas and the decoupling experiments were in agreement with all the assignments. In the case of multiplets, chemical shifts quoted were measured from the approximate center. Uv spectra were measured in methanolic solution on a Perkin-Elmer 554 spectrophotometer.

Elemental analysis were performed by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the University of Padua. All evaporations were carried out at reduced pressure with a rotary evaporator.

5-(1′,1′-Dimethylprop-2′-ynyloxy)-7-acetoxycoumarin (**2**).

To a dimethoxyethane (100 ml.) solution of 5,7-diacetoxycoumarin (**1**) (5.0 g., 19.1 mmoles), 3-chloro-3-methylbut-1-yne (4.22 ml., 37.1 mmoles) and anhydrous potassium carbonate (5.2 g.) were added and the mixture was refluxed with stirring for 3 hours. The mixture was chilled and the solid was filtered and washed with acetone. The combined filtrate and acetone washings were evaporated and the uncrystallizable oily residue was chromatographed on a silica gel column (silica gel Merck 60, 0.063-0.200 mm) by eluting with chloroform. Fractions containing products with R*f* 0.4-0.5 by tlc were collected, evaporated and rechromatographed on a silica gel column (silica gel Merck 60; under 0.063 mm) under pressure (nitrogen, 4 atmospheres) giving 5-(1′,1′-dimethylprop-2′-ynyloxy)-7-acetoxycoumarin (**2**) (1.423 g., 26%), m.p. 107° (from ethyl acetate/cyclohexane); ^{1}H-nmr: δ 7.97 (1H, d, J = 9.6, 4-H), 7.16 (1H, d, J = 2, 6-H), 6.77 (1H, d, J = 2, 8-H), 6.28 (1H, d, J = 9.6, 3-H), 2.69 (1H, s, 3′-H), 2.32 (3H, s, 7-OAc) and 1.75 (6H, s, 1′-gem methyls). We also obtained 5-acetoxy-7-(1′,1′-dimethylprop-2′-ynyloxy)-coumarin (**3**) (0.262 g., 4.8%), m.p. 130-131° (from ethyl acetate/cyclohexane); ^{1}H-nmr: δ 7.65 (1H, d, J = 9.6, 4-H), 7.17 (1H, d, J = 2, 6-H), 6.89 (1H, d, J = 2, 8-H, 6.26 (1H, d, J = 9.6, 3-H), 2.70 (1H, s, 3′-H), 2.37 (3H, s, 5-OAc) and 1.71 (6H, s, 1′-gem methyls).

5-(1′,1′-Dimethylprop-2′-enyloxy)-7-acetoxycoumarin (**4**).

5-(1′,1′-Dimethylprop-2′-ynyloxy)-7-acetoxycoumarin (**2**) (1.3 g., 4.54 mmoles) was dissolved in ethyl acetate (100 ml.) and hydrogenated in the presence of 10% palladium on calcium carbonate (0.2 g.) until 1 equivalent of hydrogen was consumed. The catalyst was filtered off, the solvent evaporated at low temperature and the residue crystallized from an ethyl acetate/*n*-hexane mixture giving 5-(1′,1′-dimethylprop-2′-enyloxy)-7-acetoxycoumarin (**4**) (1.11 g., 85%), m.p. 101°; ^{1}H-nmr: δ 7.98 (1H, d, J = 9.6, 4-H), 6.70 (2H, broadening singlet, 6-H and 8-H), 6.25 (1H, d, J = 9.6, 3-H), 6.15 and 5.28 (3H, centers of a vinyl ABX system, 2′- and 3′-protons), 2.29 (3H, s, 7-OAc) and 1.57 (6 H, s, 1′-gem methyls).

5-Hydroxy-6-(3′-methylbut-2′-enyl)-7-acetoxycoumarin (**5**).

5-(1′,1′-Dimethylprop-2′-enyloxy)-7-acetoxycoumarin (**4**) (1.4 g., 4.86 mmoles) was heated at 100-105° for 0.5 hour under reduced pressure. After chilling, the solid was chromatographed on a silica gel column (silica gel Merck 60, under 0.063 mm) by eluting with ethyl acetate/cyclohexane mixture (20:80) under 4 atmospheres of pressure. From the pooled fractions containing a single product with R*f* 0.29 by tlc, the solvent was removed and the residue was crystallized from ethyl acetate/*n*-hexane giving 5-hydroxy-6-(3′-methylbut-2′-enyl)-7-acetoxycoumarin (**5**) (1.04 g., 74%); m.p. 165-166°; ^{1}H-nmr: δ 8.03 (1H, d, J = 9.6 and J = 0.7, 4-H), 6.65 (1H, s, displayed by deuterium oxide addition, 5-OH), 6.61 (1H, d, J = 0.7, 8-H), 6.28 (1H, d, J = 9.6, 3-H), 5.23 (1H, t, J = 7.5, 2′-H), 3.31 (2H, d, J = 7.5, 1′-H), 2.35 (3H, s, 7-OAc) and 1.81 (6H, broadening singlet, 3′-gem methyls).

5,7-Diacetoxy-6-(3'-methylbut-2'-enyl)coumarin (**6**).

5-Hydroxy-6-(3'-methylbut-2'-enyl)-7-acetoxycoumarin (**5**) (0.84 g., 2.90 mmoles) and acetic anhydride (20 ml.) were refluxed for 0.5 hour in the presence of anhydrous sodium acetate. Water (100 ml.) was added and the mixture refluxed for an additional 15 minutes. After cooling the mixture was neutralized by adding solid sodium bicarbonate and extracted with ethyl acetate. From the dried (sodium sulphate) organic layer, the solvent was removed and the residue crystallized from ethyl acetate/cyclohexane, giving the 5,7-diacetoxy-6-(3'-methylbut-2'-enyl)coumarin (**6**) (0.814 g., 85%), m.p. 120-121°; ^{1}H-nmr: δ 7.54 (1H, two d, J = 9.6 and J = 0.7, 4-H), 7.04 (1H, d, J = 0.7, 8-H), 6.36 (1H, d, J = 9.6, 3-H), 4.97 (1H, t, J = 7.0, 2'-H), 3.19 (2H, d, J = 7.0, 1'-H), 2.39 and 2.31 (3H each, two s, 5-OAc and 7-OAc) and 1.70 (6H, broadening singlet, 3'-gem methyls).

5,7-Diacetoxy-6-(3'-methyl-2',3'-epoxybutyl)coumarin (**7**).

To 5,7-diacetoxy-6-(3'-methylbut-2'-enyl)coumarin (**6**) (0.45 g., 1.36 mmoles) dissolved in chloroform (100 ml.), a 1% chloroform solution of perbenzoic acid (9.4 ml.) was added. The mixture was kept at room temperature for 3 hours and then washed with saturated sodium bicarbonate solution and water. The chloroform solution was dried (sodium sulphate) and the solvent removed. The semi-solid residue was crystallized from a ethyl acetate/*n*-hexane (1:1) mixture furnishing the 5,7-diacetoxy-6-(3'-methyl-2',3'-epoxybutyl)coumarin (**7**) (0.391 g., 83%), m.p. 133-134°; ^{1}H-nmr: δ 7.56 (1H, broadening doublet, J = 9.6, 4-H), 7.09 (1H, broadening singlet, 8-H), 6.38 (1H, d, J = 9.6, 3-H), 2.75 (3H, broadening singlet, 2' and 1' protons), 2.46 and 2.39 (3H each, two s, 5-OAc and 7-OAc) and 1.36 and 1.29 (3H each, two s, 3'-gem methyls).

(±)-5-Hydroxymarmesin (**8**).

To a methanolic solution (30 ml.) of 5,7-diacetoxy-6-(3'-methyl-2',3'-epoxybutyl)coumarin (**7**) (0.12 g., 0.35 mmole), a 1% (w/v) sodium bicarbonate solution (3 ml.) was added and the mixture was refluxed for 20 minutes. After cooling the mixture was diluted with water (100 ml.), acidified with diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was dried (sodium sulphate) and the solvent was evaporated.

The residue was shown by tlc (chloroform/methanol, 97:3) to contain two products: the main product with an R*f* 0.26 and deep red-orange fluorescence, and the minor product with an R*f* 0.30 and yellow-green fluorescence. By digestion of the residue with ethyl acetate (10 ml.), a white solid was obtained which was (±)-5-hydroxymarmesin (**8**) (0.060 g., 65%), m.p. 275-276° dec. (from acetone); uv (methanol): λ max (nm) (log ε) 335 (4.21), 268 (3.75) (shoulder), 260 (3.86), λ min 284 (2.64); ^{1}H-nmr (hexadeuteroacetone): δ 9.25 (1H, s, displayed by deuterium oxide addition, 5-OH), 8.17 (1H, two d, J = 9.6 and J = 0.7, 4-H), 6.36 (1H, d, J = 0.7, 8-H), 6.16 (1H, d, J = 9.6, 3-H), 4.88 (1H, broadening triplet, J = 9.0, methine proton of the dihydrofuran ring), 3.86 (1H, s, displayed by deuterium oxide addition, 5'-C(CH$_3$)$_2$O*H*), 3.33 (2H, broadening doublet, J = 9.0, methylene protons of the dihydrofuran ring), 1.39 and 1.34 (3H, two s, methyls).

The residue obtained from the ethyl acetate mother liquors was chromatographed on a silica gel column (silica gel Merck 60, under 0.063 mm) eluting with a mixture chloroform/methanol (97:3) giving a further crop of (±)-5-hydroxymarmesin (0.014 g., total yield 81%) and the angular isomer **9** (0.013 g., 14%), uncrystallized; ^{1}H-nmr (hexadeuteroacetone): δ 9.54 (1H, s, displayed by deuterium oxide addition, 7-OH); 7.92 (1H, two d, J = 9.5 and J = 0.7, 4-H), 6.39 (1H, d, J = 0.7, 8-H), 6.15 (1H, d, J = 9.5, 3-H), 5.08 (1H, t, J = 8.9, 5'-H), 3.95 (1H, s, 5'-C(CH$_3$)$_2$O*H*), 3.28 (2H, d, J = 8.9, 4'-H), 1.43 and 1.35 (3H each, two s, 5'-C(C*H*$_3$)$_2$OH).

By refluxing the mixture for a shorter period (5-10 minutes) under the same cyclization conditions and by working up the reaction products in the same manner, (±)-5-acetoxymarmesin was also isolated, m.p. 138-139° (from ethyl acetate/cyclohexane); ^{1}H-nmr: δ 7.58 (1H, broadening doublet, J = 9.6, 4-H), 6.57 (1H, broadening singlet, 8-H), 6.16 (1H, d, J = 9.6, 3-H), 4.73 (1H, t, J = 8.5, 5'-H), 3.07 (2H, d, J = 8.5, 4'-H), 2.37 (3H, s, 5-OAc), 1.32 and 1.22 (3H each, two s, 5'-C(C*H*$_3$)$_2$OH).

REFERENCES AND NOTES

(1) P. Rodighiero, A. Guiotto, G. Pastorini, P. Manzini, F. Dall'Acqua, G. Innocenti and G. Caporale, *Gazz. Chim. Ital.*, **110**, 167 (1980).

(2) F. Dall'Acqua, A. Capozzi, S. Marciani and G. Caporale, *Z. Naturforsch.*, **27b**, 813 (1972).

(3) L. Musajo and G. Rodighiero, in "Photophysiology", Vol. 7, A. C. Giese, Ed., Academic Press, New York, N. Y., 1972, p. 115.

(4) L. Musajo, G. Rodighiero, G. Caporale, F. Dall'Acqua, S. Marciani, F. Bordin, F. Baccichetti and R. Bevilacqua, in "Sunlight and Man", M. A. Pathak, L. C. Harber, M. Seiji, A. Kukita and T. B. Fitzpatrik, Eds., University of Tokyo Press, 1974, p. 369.

(5) T. B. Fitzpatrick, J. A. Parrish and M. A. Pathak, in "Sunlight and Man", M. A. Pathak, L. C. Harber, M. Seiji, A. Kukita and T. B. Fitzpatrick, Eds., University of Tokyo Press, 1974, p. 783.

(6) J. A. Parrish, T. B. Fitzpatrick, L. Tanenbaum and M. A. Pathak, *New Engl. J. Med.*, **291**, 1207 (1974).

(7) A. M. El Mofty, "Vitiligo and Psoralens", Pergamon Press, Oxford, 1968.

(8) H. Hönigsmann, E. Jaschke, F. Gschnait, W. Brenner, P. Fritsch and K. Wolff, *Br. J. Dermatol.*, **101**, 369 (1979).

(9) R. D. H. Murray, M. Sutcliffe and P. H. McCabe, *Tetrahedron*, **27**, 4901 (1971).

(10) F. Dall'Acqua, G. Innocenti, G. Caporale, P. Rodighiero and A. Guiotto, *Z. Naturforsch.*, **34c**, 1278 (1979).

(11) V. K. Ahluwalia, T. R. Seshadri and P. Vankateswarlu, *Indian J. Chem.*, **7**, 115 (1969).

(12) R. D. H. Murray and M. M. Ballantyne, *Tetrahedron*, **26**, 4667 (1970).

(13) R. D. H. Murray, T. C. Hogg, M. M. Ballantyne and P. H. McCabe, *Tetrahedron Letters*, 3317 (1971).

(14) G. Büchi and S. M. Weinreb, *J. Am. Chem. Soc.*, **93**, 746 (1971).

(15) R. D. H. Murray, M. M. Ballantyne, T. C. Hogg and P. H. McCabe, *Tetrahedron*, **31**, 2960 (1975).

(16) L. Crombie and R. Ponsford, *J. Chem. Soc. C*, 788 (1971).