Synthesis and spectroscopic characterization of some chromanochalcones and their dihydro derivatives

M. Srinivasa Rao,*[a,b] J. Kotesh,[a] R. Narukulla,[c] and H. Duddeck[d]

[a] *Department of Chemistry, Kakatiya University, Warangal, A. P., India*
[b] *Department of Biomedical Sciences, University of Rhode Island, Kingston, RI 02881, USA*
[c] *Department of Chemistry, The Open University, Walton Hall, Milton Keynes MK7 6AA, England, UK*
[d] *Hannover University, Institute of Organic Chemistry, Schneiderberg 1B, D-30167 Hannover, Germany*
E-mail: srmeneni@mail.uri.edu

This paper is dedicated to Professor P. Srinivasa Rao on the occasion of 65th birthday

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Abstract

Synthesis of naturally occurring 6-(α,β-dihydrocinnamoyl)-3,4-dihydro-2*H*-chromanes has been carried out by the reaction of 6-acetyl-3,4-dihydro-2*H*-chromanes with methoxybenzaldehydes followed by hydrogenation of the resulting 6-cinnamoyl-3,4-dihydro-2*H*-chromanes.

Keywords: Chromanochalcones, chromano dihydrochalcones, hydrogenation, NMR spectroscopy

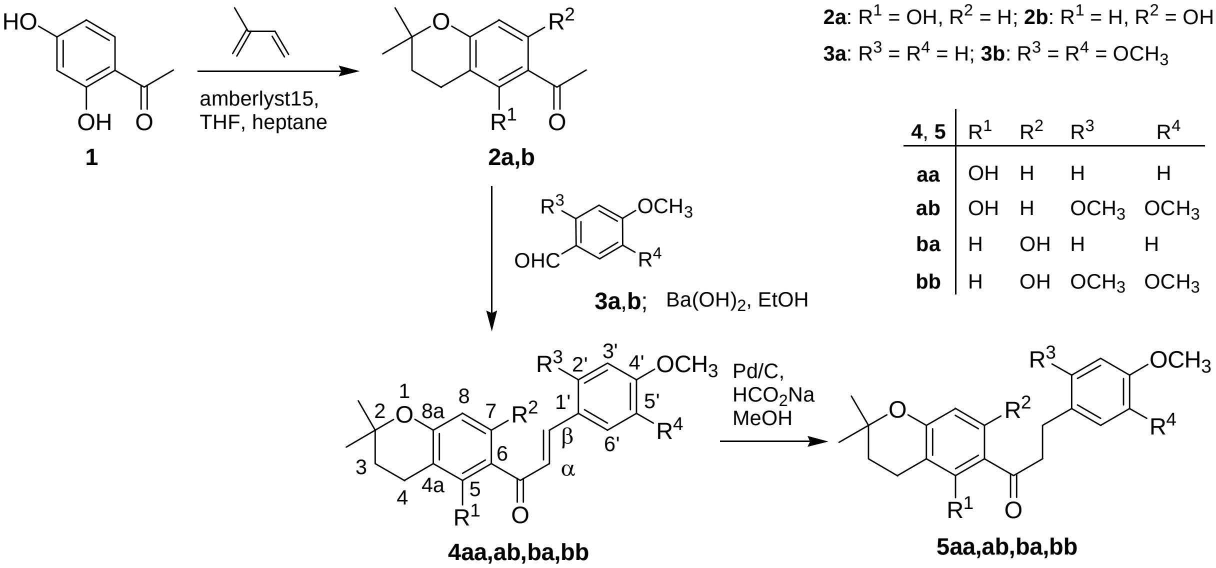
Introduction

Flavonoids are phenol derivatives present in substantial amounts (0.5–1.5%) in plants[1] in which they carry out important functions for their biochemistry and physiology.[2] These compounds contribute to color, flavor and processing characteristics important in many foods (vegetables, fruits) and in drinks (tea, wine). Food from common plants contain from traces up to several grams per kg fresh weight of flavanoids.[3] Biological properties of flavonoids and their pharmaceutical potencies have been widely investigated and extensively reviewed during the past 30 years.[4] Dihydrochalcones comprise a small group of compounds chemically and biochemically very closely related to chalcones. The utilization of certain dihydrochalcone derivatives and related compounds as sweetening agents has been reported.[5]

Previously, we have isolated chalcones **5aa**, **5ab**, **5ba**, and **5bb** (Scheme 1) in our laboratory from the Indian medicinal plant species *crotalaria*. Here we have undertaken the synthesis of these dihydrochalcones. The aim of the current synthetic study was to provide clear and easy access to prenylated dihydrochalcones with the saturation and unsaturation in α- and β- positions and also in the chromane part. Our strategy was the construction of 6-acetylchromanes **2a** and **2b** by condensation of 2,4-dihydroxyacetophenone (**1**) with isoprene in presence of Amberlyst 15, followed by the condensation with methoxybenzaldehydes **3a**,**b** to afford the target chromanochalcones.[6,7]

Results and Discussion

2,4-Dihydroxyacetophenone (**1**) can be obtained from commercially available resorcinol by reaction with acetyl chloride and zinc chloride. It was reacted with 2-methylbuta-1,3-diene in the presence of sulfonic acid cation exchange resin Amberlyst 15 in THF to give two regioisomeric acetylchromanes, 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)ethanone (**2a**) and 1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)ethanone (**2b**) (Scheme 1).



2a: $R^1 = OH$, $R^2 = H$; **2b**: $R^1 = H$, $R^2 = OH$

3a: $R^3 = R^4 = H$; **3b**: $R^3 = R^4 = OCH_3$

4, 5	R^1	R^2	R^3	R^4
aa	OH	H	H	H
ab	OH	H	OCH_3	OCH_3
ba	H	OH	H	H
bb	H	OH	OCH_3	OCH_3

Scheme 1

Treatment of the 6-acetylchromanes **2a**,**b** with methoxybenzaldehydes **3a** ($R^3 = R^4 = H$) and **3b** ($R^3 = R^4 = OMe$) in basic media [$Ba(OH)_2$ in EtOH] afforded the corresponding chromanochalcones **4aa, 4ab** and **4ba, 4bb**, respectively. Except **4ab**, all chalcones have been described before.[8] Finally, the respective dihydrochalcones **5** were synthesized by reduction of chalcones **4** with sodium formate in Pd/C. Only **5ba** has been reported in the literature.[8]

The structures of all compounds were determined by electron-impact mass spectrometry and by 1D and 2D NMR spectroscopy (DEPT, $^1H,^1H$-COSY, HMBC, HMQC). Thereby, all ^1H and ^{13}C signals could be assigned, and the atomic connectivities were established unambiguously (Tables 1 and 2). The easiest way to differentiate the regioisomers of products **4** and **5** was the inspection of the two aromatic protons 7,8-H (**aa**, **ab**) and 5,8-H (**ba**, **bb**), respectively, which are either in *ortho*- or in *para*-position with respect to each other; accordingly, these signals appeared as doublets (J = 8–9 Hz) or as singlets (J < 1 Hz), respectively.

The ^{1}H NMR spectra of the chalcones show a signal for a chelated aromatic hydroxyl group in between δ 13.0 and 14.0, and in addition signals of aromatic methoxyl groups and aromatic protons. The two sharp doublets between δ 7.0–8.0 with J = 15.3 Hz are characteristic of the trans double bond of chalcones **4**. All NMR data are compiled in Tables 1and 2.

Table 1. ^{1}H Chemical shifts and ^{1}H,^{1}H coupling constants J [Hz] of compounds **2**, **4**, and **5**; in CDCl$_3$ at 400.1 MHz. For atom numbering see structure **4** in Scheme 1

Atom Pos.	**2a**	**2b**	**4aa**	**4ab**	**5aa**	**5ab**	**4ba**	**4bb**	**5ba**	**5bb**
2,2-(CH$_3$)$_2$	1.34 s	1.35 s	1.36 s	1.37 s	1.34s	1.34 s	1.37 s	1.36 s	1.34 s	1.34 s
3	2.68 t	1.82 t	2.73 t	2.73 t	1.81t	1.80 t	1.84 t	1.83 t	1.81 t	1.80 t
4	1.81 t	2.75 t	1.83 t	1.82 t	2.68t	2.69 t	2.78 t	1.83 t	2.68 t	2.69 t
5	–	7.44 s	–	–	–	–	7.63 s	7.62 s	7.42 s	7.45 s
5-OH	13.11 s	–	13.96 s	14.08 s	13.18s	13.18 s	–	–	–	–
6-CH$_3$CO	2.54 s	2.55 s	–	–	–	–	–	–	–	–
7	7.49 d $J_{7,8}$ = 8.9	–	7.69 d $J_{7,8}$ = 9	7.70 d $J_{7,8}$ = 9	7.49 d $J_{7,8}$ = 8	7.50 d $J_{7,8}$ = 9	–	–	–	–
7-OH	–	12.34 s	–	–	–	–	13.10 s	13.23 s	12.38 s	12.49 s
8	6.33 d	6.31 s	6.38 d	6.38 d	6.31 d	6.31 d	6.37 s	6.36 s	6.31 s	6.31 s
α	–	–	7.48 d J = 15.3	7.54 d J = 15.4	3.18 d	3.12 dd	7.47 d J = 15.4	7.49 d = 15.4	3.18 dd	3.12 dd
β	–	–	7.86 d	8.17 d	2.98 dd	2.95 dd	7.83d	8.16 d	2.98 dd	2.95 dd
2’	–	–	7.60	–	7.16	–	7.63	–	7.16	–
3’	–	–	6.93	6.53 s	6.83	6.51 s	6.94	6.52 s	6.84	6.51 s
5’	–	–	6.93	–	6.83	–	6.94	–	6.84	–
6’	–	–	7.60	7.12 s	7.16	6.75 s	7.63	7.13 s	7.16	6.75 s
2’-OCH$_3$	–	–	–	3.91 s	–	3.82 s	–	3.91 s	–	3.82 s
4’-OCH$_3$	–	–	3.86 s	3.96 s	3.78 s	3.88 s	3.81 s	3.95 s	3.79 s	3.88 s
5’-OCH$_3$	–	–	–	3.91 s	–	3.81 s	–	3.92 s	–	3.81 s

Table 2. ^{13}C Chemical shifts of compounds **2**, **4**, and **5**; in $CDCl_3$ at 100.6 MHz. For atom numbering see structure **4** in Scheme 1

Atom Pos.	**2a**	**2b**	**4aa**	**4ab**	**5aa**	**5ab**	**4ba**	**4bb**	**5ba**	**5bb**
2	75.8	75.8	75.7	75.7	75.7	76.1	75.9	75.8	75.8	76.1
2,2-$(CH_3)_2$	26.7	26.9	26.7	26.7	26.7	27.4	27.6	26.9	26.9	27.4
3	31.8	32.7	31.8	31.9	31.8	33.2	32.8	32.7	21.7	33.2
4	16.2	21.7	16.3	16.4	16.3	22.2	21.8	21.8	32.7	22.2
4a	109.0	112.7	109.3	109.3	109.1	109.1	112.6	112,4	112.6	114.9
5	162.6	132.2	164.0	164.0	162.8	162.8	131.0	131.0	131.4	132.2
6	112.6	113.9	112.8	113.0	112.1	112.1	114.2	114.3	113.5	113.3
7	129.5	162.8	128.4	128.4	128.7	128.7	164.1	164.0	163.0	162.0
8	109.1	104.6	109.0	108.9	109.1	109.1	104.9	104.8	104.7	105.0
8a	160.7	161.3	160.7	160.5	160.6	160.6	161.3	161.0	161.2	161.0
6-$\underline{C}H_3CO$	26.0	26.2	–	–	–	–	–	–	–	–
6-C=O	202.5	202.3	191.8	192.3	203.5	202.5	191.7	192.1	203.4	204.1
α	–	–	118.1	118.4	39.8	39.8	118.0	118.2	39.9	39.3
β	–	–	143.6	139.2	29.7	26.4	143.8	139.3	29.6	26.4
1’	–	–	127.6	115.6	133.0	121.0	127.7	115.5	133.1	121.0
2’	–	–	130.2	154.8	129.3	151.8	130.3	154.7	129.3	151.8
3’	–	–	114.4	96.9	114.0	98.0	114.4	96.8	114.0	98.0
4’	–	–	161.6	152.6	158.0	148.5	161.7	152.6	158.1	148.5
5’	–	–	114.4	143.3	114.0	143.3	114.4	143.2	114.0	143.3
6’	–	–	130.2	111.7	129.3	114.9	130.3	111.7	129.3	114.9
2’-OCH_3	–	–	–	56.6	–	56.9	–	56.7	–	56.9
4’-OCH_3	–	–	55.4	56.1	55.3	56.9	55.4	56.0	55.3	56.9
5’-OCH_3	–	–	–	56.3	–	56.9	–	56.3	–	56.9

Experimental Section

General Procedures. The NMR spectra of $CDCl_3$ solutions were recorded using a Bruker DPX-400 spectrometer (^{1}H: 400.1 MHz; ^{13}C: 100.6 MHz). Standard Bruker software was employed for all one- and two-dimensional experiments. ^{1}H and ^{13}C NMR spectroscopic data are compiled in Tables 1 and 2. Electron impact mass spectra (70 eV) were obtained from a Finnigan MAT-312 instrument. All solvents were purified and distilled prior to use. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). Thin-layer chromatography was performed using pre-coated aluminum TLC plates of silica gel (60 F_{254}).

1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)ethanone (2a) and **1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)ethanone (2b).** To a stirred solution of Amberlyst-15 (6.2 g) and 1-(2,4-dihydroxyphenyl)ethanone **1** (4.56 g, 30 mmol) in THF (10 mL) at 65–70 °C isoprene (3.2 mL, 47 mmol) in heptane (10 mL) was added dropwise over a period of 2 h. The reaction mixture was filtered and washed with hot acetone (2 x 50 mL) and separated by column chromatography using as eluants hexane/ethyl acetate (8:2 and 6:4) thus affording **2a** (2.8 g, 43%) and **2b** (0.95 g, 15%).

2a: mp 70 °C. EI-MS: *m/z* (%) 220 (55) [M^+], 205 (19), 177 (21), 165 (100), 147 (14). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.31. Found: C, 70.82; H, 7.29.

2b: 118 °C. EI-MS: *m/z* (%) 220 (43) [M^+], 205 (25), 177 (4), 165 (100), 147 (7). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.31. Found: C, 70.93; H, 7.40.

(2*E*)-1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (4aa), (2*E*)-1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (4ab), (2*E*)-1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (4ba), and **(2*E*)-1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (4bb).**

To a solution of chromanes **2** (150 mg, 0.69 mmol) was added $Ba(OH)_2$ (150mg, 0.9mmol) and a solution of **3a** (204 mg, 1.5 mmol) in ethanol (5 mL), and the mixture was stirred at 35–40 °C for 6 h. After dilution with water (100 mL) and acidification with cold diluted hydrochloric acid (25mL) the resulting solid was filtered off, washed with water and recrystallized from petroleum ether to give yellow needles **4aa** (168 mg, 73%); mp 82–83 °C. EI-MS: *m/z* (%) 338 (5) [M^+], 314 (3), 246 (4), 220 (57), 205 (19), 177 (23), 165 (100), 149 (28), 135 (16), 107 (10), 94 (15), 77 (12). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.51; H, 6.53. Found: C, 74.57; H, 6.58.

Treatment of **2a** with **3b** under the same conditions gave orange needles **4ab** (172 mg, 63%); mp 104–106 °C. EI-MS: *m/z* (%) 398 (54) [M^+], 367 (100), 311 (14), 194 (45), 181 (51), 149 (28). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.35; H, 6.57. Found: C, 69.41; H, 6.66.

Analogously, the reaction of compound **2b** with methoxybenzaldehydes **3a** and **3b** afforded yellow needles **4ba** (160 mg, 69%) and **4bb** (163 mg, 60%), respectively.

4ba. mp 146–147 °C. EI-MS: *m/z* (%) 338 (100) [M^+], 321 (5), 284 (24), 231 (15), 204 (33), 189 (7), 161 (9), 149 (67), 134 (56), 121 (33). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.51; H, 6.53. Found: C, 74.53; H, 6.55.

4bb. mp 168–169 °C. EI-MS: *m/z* (%) 398 (36) [M^+], 367 (100), 311 (7), 206 (10), 194 (25), 181 (37), 165 (13), 149 (16). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.35; H, 6.57. Found: C, 69.39; H, 6.61.

1-(5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)propan-1-one (5aa), 1-(5-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(2,4,5-trimethoxyphenyl)propan-1-one (5ab); 1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)propan-1-one (5ba), and **(2*E*)-1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-chromen-6-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (5bb).** To a solution of chromanochalcone **4aa** (250 mg, 0.74 mmol) and sodium formate (1.0 g, 14.7 mmol) in methanol (25 mL) was added Pd/C (10%, 250 mg, 0.5 mmol), and the mixture was refluxed for 30–45 min. After the catalyst was removed by filtration, the solvent was distilled off, the residue was treated with water, and the product was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and the solvent was removed by evaporation. The residue **5aa** (230 mg, 92%) was essentially pure to get spectral data; mp 102–104 °C. EI-MS: *m/z* (%) 341 [M^++H] (17), 323 (4), 205 (6), 178 (10), 149 (12), 134 (8), 121 (20), 49 (100). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.07; H, 7.09. Found: C, 74.11; H, 7.14.

5ab. The same treatment of compound **4ab** afforded **5ab** (210 mg, 83%); mp 126–128 °C. EI-MS: *m/z* (%) 400 (54) [M^+], 367 (100), 311 (14), 194 (45), 181 (51), 149 (28). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.93; H, 7.04. Found: C, 68.98; H, 7.09.

5ba. Similarly, compound **4ba** yielded **5ba** (220 mg, 87%); mp 117–118 °C. EI-MS: *m/z* (%) = 340 [M^+] (17), 323 (4), 205 (6), 178 (10), 149 (12), 134 (8), 121 (20), 49 (100). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.07; H, 7.09. Found: C, 74.15; H, 7.17.

5bb. Compound **4bb** gave **5bb** (200mg, 79%); mp 138–139 °C. EI-MS: *m/z* (%) 400 (34) [M^+], 205 (24), 181 (100), 151 (12). For ^{1}H and ^{13}C NMR data see Tables 1 and 2. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.93; H, 7.04. Found: C, 68.10; H, 7.06.

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