A New Approach to *dl*-Cannabichromene

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Natural *dl*-cannabichromene was synthesized in 6 steps from methyl 5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-acetate prepared by the cyclization of 2-hydroxy-6-methoxy-4-pentylbenzaldehyde with dimethyl isopropylidenemalonate.

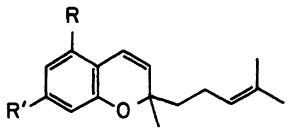
In our previous study we found a new one-step preparation of 2-methyl-2*H*-chromen-2-acetates from salicylaldehyde and isopropylidenemalonate.[1] Recently, we have also found an enantioselective hydrolysis of 2-methyl-2*H*-chromen-2-acetate.[2] Thus, 2-methyl-2*H*-chromen-2-acetates were expected as new chiral synthons for some natural 2,2-dimethyl-2*H*-chromenes having a long side chain in one of the C-2 methyl groups. We now describe a new approach to natural cannabichromene (**1c**) for checking 2-methyl-2*H*-chromen-2-acetates as synthons. *dl*-Cannabichromene (**1c**) was first isolated from extracts of Cannabis sativa L.[3] Some syntheses of **1c** have already been reported; their key steps are base-catalyzed condensations of olivetol (5-pentylresorcinol)[4] or 5-pentyl-1,3-cyclohenanedione[5] with citral and oxidative cyclizations of 2-geranylolivetol using choranile[6] or DDQ.[7] However, these are all procedures for racemic chromenes. Our new procedure might be the only one available for chiral chromenes.

dl-Cannabichromene (**1c**) is a 2,2-dimethyl-2*H*-chromene derivative, and has a C_5 side chain in one of the C-2 methyl groups (Chart 1). Thus, by using methyl 2-methyl-2*H*-chromen-2-acetate (**4a**) the side-chain conversion was first studied. Chromen-2-acetate (**4a**), readily prepared from salicylaldehyde and dimethyl isopropylidenemalonate,[1] was reduced by treating it with lithium aluminium hydride (LAH) in refluxing ether to give 2-(2-methyl-2*H*-chromen-2-yl)ethanol (**5a**) in 94% yield (Chart 2). The conversion of **5a** to the corresponding chloro derivative (**6a**) was most effective (94% yield) by adding a benzene solution of **5a** and pyridine to thionyl chloride followed by refluxing the mixture for 1 h. A treatment of **6a** with magnesium metal did not give the corresponding Grignard reagent (**9**), but did give a mixture of a cyclopropane derivative (**10**) and a dimer (**11**) (Chart 3).[8] Chloro derivative (**6a**) was then treated with sodium cyanide in refluxing DMF for 30 min to give a nitrile derivative (**7a**) (90%), which was reduced to an aldehyde derivative (**8a**) (45%) by treating with diisobutylaluminium hydride (DIBALH) in dry ether at −78 °C for 3 h. A Wittig reaction of an aldehyde derivative (**8a**) with isopropylidenetriphenylphosphorane gave the desired 2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene (**1a**) in 39% yield. Although Crombie et al. reported a photocyclization of cannabichromeme (**1c**) to cannabicyclol (**2c**) in acetone,[9] our similar photocyclization of **1a** to **2a** was effective in benzene.[10]

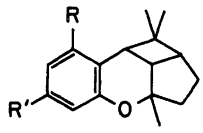
2-Hydroxy-6-methoxy-4-pentylbenzaldehyde (**3b**), a salicylaldehyde for natural cannabichromene, was prepared by the demethylation of 2,6-dimethoxy-4-pentylbenzaldehyde[11] with magnesium iodide etherate. A similar cyclization of **2b** with dimethyl isopropylidenemalonate gave methyl 5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-acetate (**4b**) in 54% yield by treating it with potassium carbonate at 130 °C in DMF for 8 h. Chromen-2-acetate **4b** was similarly converted to the corresponding aldehyde derivative (**8b**) via a reduction with LAH (**5b**: 88%), chlorination with thionyl chloride (**6b**: 68%), cyanation with sodium cyanide (**7b**: 77%), and reduction with DIBALH (**8b**: 44%). A Wittig reaction of **8b** with isopropylidenetriphenylphosphorane gave *O*-methylcannabichromene (**1b**) in 69% yield, which was then demethylated to cannabichromene (**1c**) in 55% yield by treating it with sodium ethanethiolate in refluxing dry DMF. The spectral data of *O*-methylcannabichromene (**1b**) and cannabichromene (**1c**) thus obtained were identical with those of natural ones.[3] Chiral (but unnatural) cannabichromene will be obtained by a similar procedure starting from chiral methyl 5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-acetate; this procedure might be the only available procedure for chiral 2,2-dimethyl-2*H*-chromene derivatives having a side-chain in one of the C-2 methyl groups.

Experimental

The boiling points (1 mmHg=133.322 Pa) are uncorrected. The IR spectra were measured on a Hitachi EPI-S2 spectrophotometer in liquid films, and the UV spectra were measured on a Hitachi 220A spectrophotometer in ethanol (Table 1). The ^{1}H NMR spectra were recorded on a JEOL



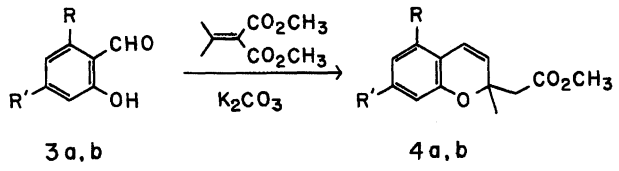
1a, b, c



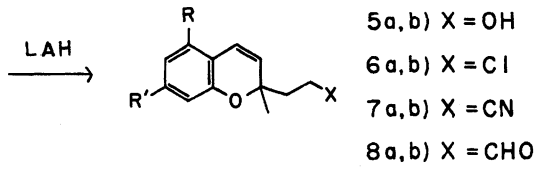
2a, c

a) R = R' = H, b) R = OCH_3 R' = n-C_5H_{11}, c) R = OH R' = n-C_5H_{11}

Chart 1.

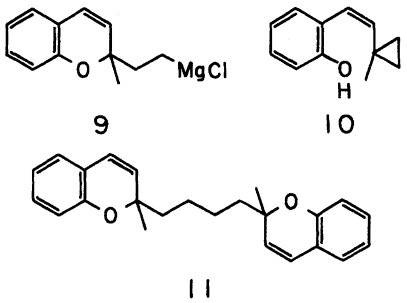


3a, b 4a, b



5a, b) X = OH
6a, b) X = Cl
7a, b) X = CN
8a, b) X = CHO

Chart 2.



9 10 11

Chart 3.

PMX-60Si spectrometer or a JEOL JNM-FX90Q FT NMR spectrometer in $CDCl_3$ (Table 2). The mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

Preparation of 3b. To a benzene solution of magnesium iodide etherate,[12] prepared from magnesium metal (1.31 g, 53.8 mmol) and crystalline iodine (11.1 g, 43.8 mmol) in dry ether (65 mL) and dry benzene (100 mL), was added a solution of 2,6-dimethoxy-4-pentylbenzaldehyde[11] (8.54 g, 36.1 mmol) in dry benzene (180 mL); the mixture was then refluxed for 1.5 h. After cooling, the mixture was treated with 10% hydrochloric acid and extracted with ether. The extracts were washed with sodium hydrogensulfite to remove iodine, and dried over anhydrous sodium sulfate. After removing the solvent, the residual oil was distilled under reduced pressure to give 2-hydroxy-6-methoxy-4-pentylbenzaldehyde (**3b**) (5.03 g, 63%) as fractions boiling at 140—142 °C; IR ν 1650 cm^{-1}; ^1H NMR δ=0.9 (3H, t, J=5 Hz, CH_3 in propenyl), 1.2—1.9 (6H, m, $-CH_2-$ ×3 in propenyl), 2.5 (2H, t, J=7 Hz, Ar–CH_2–), 3.8 (3H, s, O–CH_3), 6.1 (1H, s, Ar-H), 6.3 (1H, s, Ar-H), 10.2 (1H, s, CHO), 11.9 (1H, s, OH); MS m/z 222 (M^+), 180, 166. Found: C, 70.11; H, 8.21%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

Cyclization of 3b with Dimethyl Isopropylidenemalonate. According to a procedure reported in our previous paper,[1] a solution of **3b** (5.03 g, 22.6 mmol) and dimethyl isopropylidenemalonate (4.03 g, 23.4 mmol) in dry DMF (60 mL) was treated with anhydrous potassium carbonate (9.39 g, 67.9 mmol) at 130 °C for 8 h. After a similar working-up the crude oil was chromatographed on a silica-gel column to give methyl 5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-acetate (**4b**) (3.89 g, 54%) as fractions eluted with cyclohexane–benzene (1 : 1).

Reductions of 4a and 4b to Alcohol 5a and 5b. To a solution of lithium aluminium hydride (152 mg, 4 mmol) in dry ether (20 mL) was added a solution of methyl 2*H*-chromen-2-acetate (**4a** or **4b**) (ca. 3 mmol). After the mixture was refluxed for 30 min and cooled it was treated with 10% hydrochloric acid and extracted with ether. The ether extracts were washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatographed on a silica-gel column to give 2-(2-methyl-2*H*-chromen-2-yl)-ethanol (**5a**) (94%) or 2-(5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-yl)ethanol (**5b**) (88%) as fractions eluted with benzene.

Chlorination of Alcohol 5a and 5b. To a solution of thionyl chloride (0.50 mL, 6.98 mmol) in dry benzene (20 mL) was added a solution of **5a** or **5b** (ca. 3.5 mmol) and pyridine (0.60 mL, 7.42 mmol) in dry benzene (15 mL); the mixture was then refluxed for 1 h. After cooling the mixture, it was treated with 10% hydrochloric acid and extracted with benzene. The benzene layer was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After removing the benzene, the residual oil was chromatographed on a silica-gel column to give 2-(2-chloroethyl)-2-methyl-2*H*-chromene (**6a**) (91%) or 2-(2-chloroethyl)-5-methoxy-2-methyl-7-pentyl-2*H*-chromene (**6b**) (68%) as fractions eluted with cyclohexane–benzene (9 : 1).

Cyanation of Chloride 6a and 6b. To a solution of **6a** or **6b** (ca. 2 mmol) in dry DMF (25 mL) was added sodium cyanide (311 mg, 6.35 mmol); the mixture was then refluxed for 30 min. After removing most of the DMF, the mixture was diluted with water and extracted with ether. The ether layer was washed with a 5% sodium hydroxide solution and a saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatographed on a silica-

Table 1. The Data of New Chromene Derivatives

Compound No.	Boiling Point θ/°C (mmHg)	IR ν/cm^{-1}	Mass M^+; m/z	Found (%) C	H	N	Calcd (%) C	H	N	
4b	ca. 148 (3.5)	1730	318	71.96	8.38		71.67	8.23		($C_{19}H_{26}O$)
5a	120—150 (17)	3300	190	75.55	7.29		75.76	7.42		($C_{12}H_{14}O_2$)
5b	ca. 166 (3)	3360	290	74.24	8.92		74.44	9.03		($C_{18}H_{26}O_3$)
6a	105—110 (15)	690	208	69.34	6.43		69.07	6.28		($C_{12}H_{13}ClO_2$)
6b	ca. 148 (4)	710	308	70.06	8.19		70.00	8.16		($C_{18}H_{25}ClO_2$)
7a	ca. 190 (20)	2250	199	78.55	6.74	6.97	78.36	6.58	7.03	($C_{13}H_{13}NO$)
7b	ca. 190 (3)	2250	299	76.49	8.44	4.70	76.22	8.42	4.68	($C_{19}H_{25}NO_2$)
8a	85—95 (3)	1720	202	76.98	7.10		77.20	6.98		($C_{13}H_{14}O_2$)
8b	ca. 163 (4)	1720	302	75.64	8.53		75.46	8.67		($C_{19}H_{26}O_3$)
1a	100—110 (16)	—	228	84.15	8.95		84.16	8.83		($C_{16}H_{20}O$)
1b	ca. 183 (20)	—	328	80.46	9.78		80.44	9.83		($C_{22}H_{32}O_2$)

Table 2. ^{1}H NMR Data of New Chromenes [δ/ppm (J/Hz)]

Compound No.	2-CH_3	2-CH_2	CH_2-X	3-H	4-H	Ar-H	Others		
4b	1.5 (s)	2.6 (d,14) 2.8 (d,14)	—	5.6 (d,10)	6.6 (d,10)	6.1 (d,2) 6.2 (d,2)	0.9 (t,5) 3.6 (s)	1.2—1.7 (m) 3.8 (s)	2.5 (t,6)
5a	1.4 (s)	1.9 (t,6)	3.8 (t,6)	5.6 (d,10)	6.3 (d,10)	6.6—7.2 (m)	2.0 (br s)		
5b	1.4 (s)	2.0 (t,6)	3.9 (t,6)	5.4 (d,10)	6.7 (d,10)	6.3 (s)	0.9 (t,5) 2.1 (br s)	1.2—1.8 (m) 3.8 (s)	2.8 (t,6)
6a	1.4 (s)	2.2 (t,8)	3.7 (t,8)	5.5 (d,10)	6.4 (d,10)	6.6—7.3 (m)			
6b	1.4 (s)	2.0—2.3 (m)	3.6 (dd,9&7)	5.4 (d,10)	6.6 (d,10)	6.1 (d,2) 6.2 (d,2)	0.9 (t,5) 3.8 (s)	1.1—1.7 (m)	2.5 (t,7)
7a	1.4 (s)	1.8—2.2 (m)	2.3—2.6 (m)	5.5 (d,10)	6.4 (d,10)	6.6—7.2 (m)			
7b	1.4 (s)	1.8—2.2 (m)	2.3—2.7[a] (m)	5.4 (d,10)	6.8 (d,10)	6.3 (s)	0.9 (t,6) 3.8 (s)	1.2—1.7 (m)	2.3—2.7 (m)[a]
8a	1.4 (s)	1.8—2.2 (m)	2.4—2.7 (m)	5.4 (d,10)	6.3 (d,10)	6.5—7.2 (m)	9.7 (t,2)		
8b	1.4 (s)	1.8—2.2 (m)	2.4—2.8[a] (m)	5.4 (d,10)	6.7 (d,10)	6.2 (s)	0.9 (t,5) 3.8 (s)	1.1—1.8 (m) 9.8 (t,2)	2.4—2.8 (m)[a]
1a	1.3 (s)	1.4—1.8 (m)	1.9—2.4 (m)	5.4 (d,10)	6.3 (d,10)	6.5—7.3 (m)	1.5 (s)	1.6 (s)	5.1 (br t,7)
1b	1.3 (s)	1.1—1.7[a] (m)	2.0 (br q,6)	5.3 (d,10)	6.6 (d,10)	6.1 (d,2) 6.2 (d,2)	0.9 (t,5) 1.6 (s)	1.1—1.7 (m)[a] 1.7 (s) 5.1 (br t,6)	2.5 (t,6) 3.8 (s)

a) The signals overlapped together.

gel column to give 3-(2-methyl-2*H*-chromen-2-yl)propanenitrile (**7a**) (90%) or 3-(5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-yl)propanenitrile (**7b**) (77%) as fractions eluted with cyclohexane–benzene (1 : 1).

Reduction of Nitrile 7a and 7b to Aldehyde 8a and 8b. To a solution of **7a** or **7b** (ca. 4 mmol) in dry ether was added 1.0 M DIBALH cyclohexane-solution (4.5 mL, 4.5 mmol) by a syringe at −78 °C under an argon atmosphere; the mixture was stirred first at −78 °C for 30 min and then at room temperature for 3 h. After working-up with methanol, a saturated ammonium chloride solution, and 10% hydrochloric acid, the mixture was extracted with ether. The ether layer was washed with a saturated sodium hydrogencarbonate solution and a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After removing the ether the residual oil was chromatographed on a silica-gel column to give 3-(2-methyl-2*H*-chromen-2-yl)-propanal (**8a**) (71%) or 3-(5-methoxy-2-methyl-7-pentyl-2*H*-chromen-2-yl)propanal (**8b**) (44%) as fractions eluted with benzene.

Wittig Reactions of 8a and 8b. To 2-isopropyltriphenylphosphonium bromide (1.88 g, 4.87 mmol) in dry ether was added a 1.6 M butyllithium hexane-solution (3.0 mL, 4.8 mmol) by a syringe under an argon atmosphere (1 M=1 mol dm^{-3}); the mixture was then stirred for 2 h. To the thus-prepared ylide solution was added a solution of **8a** or **8b** (ca. 3 mmol) in dry ether (10 mL); the mixture was then stirred for 1 h and refluxed for 4 h. After cooling, it was poured onto ice-water and extracted with ether. The ether layer was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatographed on a silica-gel column to give 2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene (**1a**) (39%) or 5-methoxy-2-methyl-2-(4-methyl-

3-pentenyl)-7-pentyl-2*H*-chromene (**1b**) (69%) as fractions eluted with cyclohexane–benzene (9:1).

Demethylation of *O*-Methylcannabichromene (1b). To a suspension of a 60% oily sodium hydride (121 mg, 3.03 mmol) in dry DMF (8.4 mL) was added ethanethiol (0.25 mL, 3.4 mmol) by a syringe, then a solution of **1b** (365 mg, 1.11 mmol) in dry DMF (3.0 mL); the mixture was refluxed for 1.5 h. After cooling the mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with ether. The ether was washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatographed on a silica-gel column to give 2-methyl-2-(4-methyl-3-pentenyl)-7-pentyl-2*H*-chromen-5-ol (Cannabichromene) (**1c**) (192 mg, 55%) as fractions eluted with cyclohexane–benzene (9:1). **1c**; IR ν 3370 cm^{-1}; UV λ_{max} 228, 279, 290sh nm; ^1H NMR δ=0.9 (3H, t, J=6 Hz, CH_3 in propenyl), 1.1—1.8 (8H, m, $-CH_2-$ ×4), 1.3 (3H, s, 2-CH_3), 1.6 (3H, s, CH_3–C=C), 1.7 (3H, s, CH_3–C=C), 1.9—2.6 (2H, m, CH_2–C=C), 2.4 (2H, t, J=7 Hz, Ar–CH_2–), 4.6 (1H, br s, OH), 5.1 (1H, br t, J=6 Hz, C=C–H), 5.4 (1H, d, J=10 Hz, 3-H), 6.0 (1H, d, J=1 Hz, Ar-H), 6.1 (1H, d, J=1 Hz, Ar-H), 6.5 (1H, d, J=10 Hz, 4-H); Mass m/z 314 (M^+), 231 ($M^+ - C_6H_{11}$). Found: C, 80.27; H, 9.38%. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%.

Photocyclization of 1a. To a solution of **1a** (332 mg, 1.45 mmol) in benzene (250 mL) was added benzophonone (267 mg, 1.47 mmol); the solution was then irradiated for 4 h under an argon atmosphere using a 100 W high-pressure mercury lamp. After removing the benzene the residual oil was chromatographed on a silica-gel column to give 2,2,6-trimethyl-7-oxobenzo[*h*]tricyclo[4.3.1.$0^{3,10}$]decane (**2a**) (84 mg, 25%) as fractions eluted with cyclohexane–benzene (3:1). **2a**; bp 95—115 °C (3 mmHg); ^1H NMR δ=0.7 (3H, s, 6-CH_3), 1.4 (6H, s, 2-CH_3 ×2), 1.5—1.8 (4H, m, $-CH_2-$ ×2), 2.4 (1H, ddd, J=8, 7, and 2.5 Hz, 3-H), 2.6 (1H, dd, J=9 and 8 Hz, 10-H), 3.1 (1H, br d, J=9 Hz, 1-H), 6.9 (3H, m, Ar-H ×3), 7.1 (1H, m, ArH ×1); Mass m/z 228 (M^+). Found: C, 83.93; H, 8.90%. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83%.

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2) Treating **4a** with pig liver esterase in acetone-0.1 M phosphate buffer solution gave (−)-acid and (+)-ester. Details of the hydrolysis will be reported soon.

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8) Treatment of **6a** (0.75 g, 3.6 mmol) with magnesium metal (0.13 g, 5.5 mmol) in refluxing ether for 20 h gave *o*-[*cis*-2-(1-methylcyclopropyl)vinyl]phenol (**10**) (248 mg, 40%) and 1,4-bis(2-methyl-2*H*-chromen-2-yl)butane (**11**) (47 mg, 3.4%).

10; bp ca. 120 °C (22 mmHg); IR 3400 cm^{-1}; ^1H NMR δ=0.5 (4H, s, $-CH_2-$ ×2), 1.0 (3H, s, CH_3), 5.1 (1H, br s, OH), 5.6 (1H, d, J=11 Hz, C=CH), 6.2 (1H, d, J=11 Hz, C=CH), 6.6—7.2 (4H, m, Ar-H ×4); High Mass Found: m/z 174.105. Calcd for $C_{12}H_{14}O$: M, 174.105.

11; bp 180—185 °C (4 mmHg); ^1H NMR δ=1.3 (6H, s, CH_3 ×2), 1.2—2.0 (8H, m, $-CH_2-$ ×4), 5.4 (2H, d, J=10 Hz, C=CH), 6.3 (2H, d, J=10 Hz, C=CH), 6.6—7.1 (8H, m, Ar-H ×8); Mass m/z 346 (M^+). Found: C, 83.41; H, 7.62%. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56%. The conversion of chloro derivative (**6a**) to Grignard reagent (**9**) might be too slow to cause secondary nucleophilic attacks intramolecularly to **10** or intermolecularly to **11**.

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