Condensation Reactions of Olivetol Bis(tetrahydropyranyl Ether) Homocuprate with Propargylic Substrates. A Convenient Synthesis of (±)-3,4-*cis*-$\Delta^{1,2}$-Tetrahydrocannabinol and (±)-3,4-*trans*-$\Delta^{1,2}$-Cannabidiol

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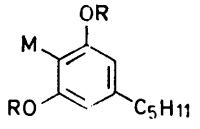
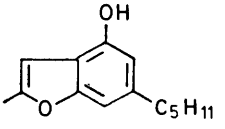
A versatile synthesis of (±)-3,4-*cis*-$\Delta^{1,2}$-tetrahydrocannabinol (12) and two pyrolytic cracking products of 3,4-*trans*-$\Delta^{1,2}$-cannabidiol is described. A modification of a previously described synthesis of (12), by condensation of olivetol with citral, led to a convenient synthesis of (±)-3,4-*trans*-$\Delta^{1,2}$-cannabidiol (3) and (±)-3,4-*trans*-$\Delta^{1,2}$-tetrahydrocannabinol.

RECENTLY organocopper reagents have received considerable interest because of their wide synthetic possibilities. In a previous paper [1] we explored the use of these reagents for the preparation of derivatives of olivetol (1a) specifically substituted at C-2. Since the reactions of organocopper compounds with propargylic substrates have received only limited attention we studied the reaction of olivetol bis(tetrahydropyranyl ether) homocuprate (1c) with some propargylic halides and acetates.

The reaction of organocopper compounds with propargylic substrates may proceed either in an S_N2 manner [2,3] and/or *via* an S_N2' mechanism,[3,4] resulting in the formation of acetylenes and allenes respectively. In the case of (1c) these acetylenic and/or allenic coupling products offer good possibilities for the preparation of heterocyclic derivatives. Thus the reaction of (1c) with an excess of propargyl bromide, followed by acid hydrolysis of the tetrahydropyranyl groups and simultaneous ring closure of the intermediate phenolic product yields

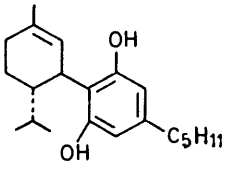


(1)



(2)

a; M = H, R = H
b; M = H, R = THP
c; M = $(CuLi.LiBr)_{1/2}$, R = THP

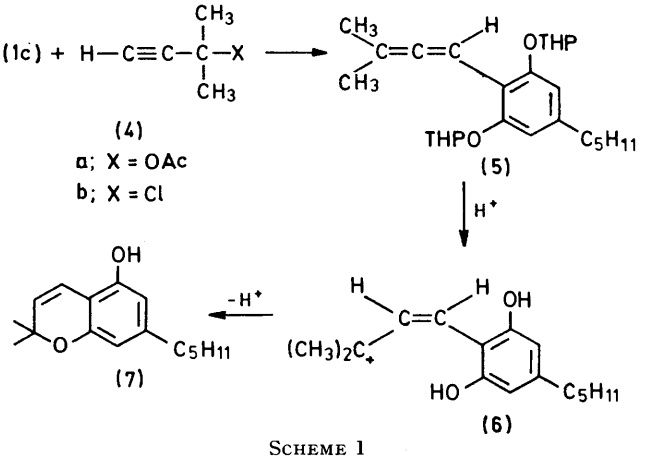


(3)

THP = tetrahydropyranyl

one main product (70% by g.l.c.). The spectroscopic data for this compound are in full agreement with structure (2), 4-hydroxy-2-methyl-6-pentylbenzofuran. Furthermore the mass spectral and g.l.c. data for (2) are identical with those of a pyrolytic cracking product of cannabidiol (CBD) (3) which was earlier tentatively identified by Küppers *et al.*[5] as 5-hydroxy-7-pentyl-2*H*(or 4*H*)-benzopyran.

Reaction of (1c) with 3-acetoxy-3-methylbut-1-yne (4a) followed by the usual acidic work-up results in the

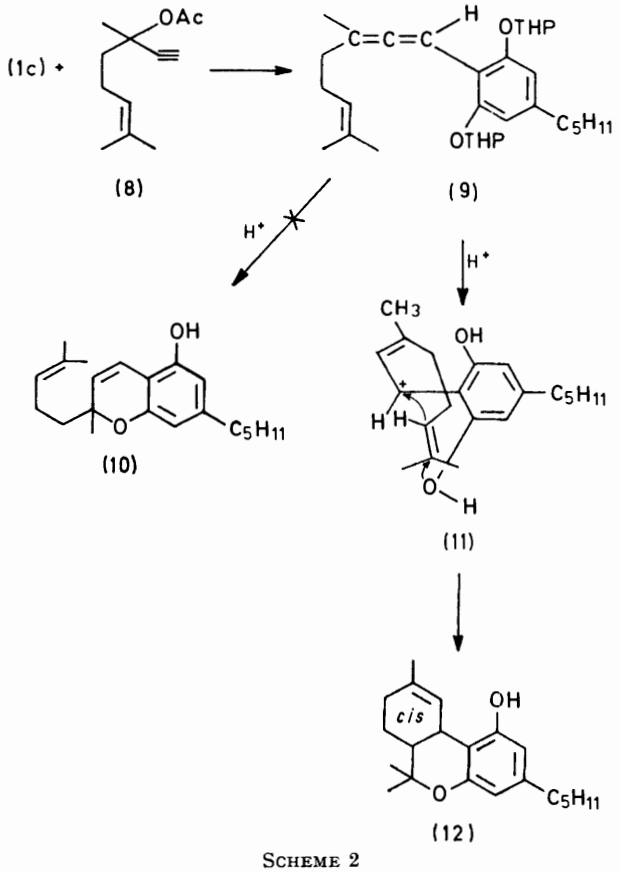


SCHEME 1

formation of 5-hydroxy-2,2-dimethyl-7-pentylchromen (7) in 70—80% yield (g.l.c.). This reaction probably proceeds *via* a 1,2-addition yielding the allene (5). Subsequent acidic treatment of (5) will result in ring closure of the intermediate allylic cation (6) to form (7) (Scheme 1). A similar ring closure was earlier described by Jacobs *et al.*[6] Our original synthesis [1] of (7) was low in yield and the chromatographic separation of (7) from the isomeric 7-hydroxy-2,2-dimethyl-5-pentylchromen was difficult. As a consequence, the procedure described here is the method of choice for the preparation of (7). Comparable results are obtained when the corresponding chloride (4b) is used instead of the acetate (4a).

It was expected that, by analogy with the reaction described above, reaction of (1c) with dehydrolinaloöl acetate (8) would yield cannabichromen (CBC) (10). However, in addition to unchanged olivetol one main product is obtained, whose spectroscopic data, after isolation by column chromatography (overall yield 20%), prove to be identical with those of 3,4-*cis*-$\Delta^{1,2}$-tetrahydrocannabinol [(±)-*cis*-THC] (12).[7,8] The formation of (±)-*cis*-THC can be explained if we again assume the

formation of an intermediate allylic cation (11), followed by *trans*-addition to the isopropylidene group as shown in Scheme 2. Since the retention time and mass spectrum of our product differ significantly from the data given by Vree *et al.*,[9] a reference sample of (±)-*cis*-THC was prepared by a known procedure,[10] starting from olivetol and citral. The (±)-*cis*-THC thus obtained is identical with our product. It must thus be concluded that Vree *et al.* were in error; as a consequence this finding throws serious doubts on the constant ratio (1.85) of the retention times of *cis*- and *trans*-cannabinoids proposed by these authors. A major advantage of this new synthetic route to (±)-*cis*-THC is the simplicity of the chromatographic isolation since no isomeric THCs are formed in contrast to procedures used previously.



SCHEME 2

During one of our efforts to optimize the synthesis of (12) from olivetol and citral using boron trifluoride as catalyst, as described by Mechoulam *et al.*,[10] we made an interesting observation. If a two-fold excess of citral is used and the boron trifluoride concentration is lowered to 0.05%, after 1 h at room temperature only two products are obtained (*ca.* 50% each by g.l.c.), which after isolation by column chromatography (overall yields *ca.* 25% each), prove to be identical in all respects to (±)-3,4-*trans*-CBD (3) and (±)-3,4-*trans*-THC. In view of the good yield and the ready availability of citral this is the simplest method presently at our disposal for the preparation of racemic cannabidiol.

EXPERIMENTAL

G.l.c.–mass spectral analysis was carried out on a JEOL JMS07 instrument equipped with a double stage jet separator. G.l.c. was performed on a glass column (2 m × 2 mm) packed with 3% OV17 on Chromosorb WHP 80—100 mesh, using nitrogen as carrier gas (15 ml min^{-1}). 3,4-*trans*-CBD (3) was used as reference to calculate the relative retention times [R_x (CBD) ≡ 1.00].

Olivetol Bis(tetrahydropyranyl Ether) (1b).—To a mixture of olivetol (9.15 g) and dihydropyran (10.7 g) phosphoric acid (85%; 3 drops) was added. Heat was evolved and the mixture was stirred for 4 h at room temperature. Ether was added and the solution was extracted with aqueous sodium hydroxide (2N). The ethereal solution was dried (Na_2SO_4) and the solvent and excess of dihydropyran were evaporated under reduced pressure (0.1 mmHg), yielding the bis(tetrahydropyranyl ether) (1b) (18 g, 97%), an oil, which was unstable under the g.l.c. conditions used; $\nu_{max.}$ (neat) 2 930, 2 850, 2 870, 1 590, 1 450, 1 200, 1 155, 1 150, 1 015, and 900 cm^{-1}; δ(90 MHz; CCl_4) 6.48 (1 H, t, *J* 2.5 Hz, ArH), 6.40 (2 H, d, *J* 2.5 Hz, 2 × ArH), 5.33br (2 H, s, 2 × CH), 3.3—4.1 (4 H, m, 2 × OCH_2), 2.49 (2 H, t, *J* 7 Hz, benzylic CH_2), 1.0—2.2 (18 H, m), and 0.88 (3 H, t, *J* 6 Hz, ω-Me).

4-Hydroxy-2-methyl-6-pentylbenzofuran (2). *General Procedure for Condensations with Olivetol Bis(tetrahydropyranyl Ether) Homocuprate* (1c).—Olivetol bistetrahydropyranyl ether (1b) (1.3 g, 3.7 mmol) was dissolved in dry THF (15 ml) under nitrogen. The solution was cooled (−10 °C) and n-butyl-lithium (2N, 2.7 ml) was added. After stirring for 4 h the flask was chilled (−10 °C) and copper(I) bromide (275 mg, 1.9 mmol) was added. The temperature was raised until copper(I) bromide had dissolved; then the mixture was cooled (−30 °C) and propargyl bromide (650 mg, 5.5 mmol) was added. The temperature was allowed to rise to room temperature and the mixture was stirred for an additional 12 h. After addition of aqueous hydrochloric acid (2N, 40 ml) the organic layer was separated and the solvent evaporated. Oxalic acid (1 g), water (10 ml), and ethanol (30 ml) were added and the mixture was refluxed for 1—2 h. After evaporation of the ethanol the water layer was extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated, yielding crude (2) [70% by g.l.c.; R_x 0.28, R_x(olivetol) 0.20]. The residue was chromatographed on silica gel using gradient elution with hexane–ether to give the benzofuran (2) (625 mg) as an oil; $\nu_{max.}$ (CCl_4) 3 605, 3 380, 2 960, 2 930, 2 860, 1 635, 1 600, 1 430, 1 220, 1 160, and 1 050 cm^{-1}; δ(90 MHz; CCl_4) 6.72 (1 H, s, 3-H), 6.30 (2 H, s, 2 × ArH), 6.1br (1 H, s, OH), 2.53 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 2.37 (3 H, s, 2-Me), 1.0—1.8 (6 H, m, $[CH_2]_3$), and 0.86 (3 H, t, *J* 6 Hz, ω-Me); *m/e* 219 (3%), 218 (34,M^+), 175 (6), 163 (4), 162 (41), 161 (100), and 147 (4).

3,4-cis-Δ^{1,2}-Tetrahydrocannabinol (12).—Dehydrolinaloöl acetate (8), b.p. 78 °C at 1 mmHg, was prepared in almost quantitative yield from dehydrolinaloöl with excess of acetic acid anhydride and phosphoric acid.[11] It was condensed with (1c) and worked up as described above. 3,4-*cis*-Δ^{1,2}-Tetrahydrocannabinol (12) was obtained as an oil (20%); R_x 1.23; R_F 0.43, R_F (CBD) 0.44 on silica gel (Merck) eluting with hexane–ether (4 : 1). Mass, n.m.r., and

i.r. spectral data are identical with those in the literature [11] and with those of a reference sample prepared by a known procedure.

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