A simple and efficient synthesis of 5′-($^2H_3$)olivetol

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Received May 28, 1986

This paper is dedicated to Dr. O. E. (Ted) Edwards

MICHEL GIRARD, DAVID B. MOIR, and JOHN W. APSIMON. Can. J. Chem. **65**, 189 (1987).

The title compound **1** was prepared in 13% overall yield starting from the commercially available and inexpensive 3,5-dimethoxybenzoic acid (**4**). The *n*-pentyl side chain was elaborated from cross-coupling reactions between halides.

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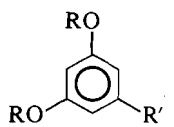
On rapporte la synthèse du composé **1** à partir de l'acide diméthoxy-3,5-benzoïque (**4**) commercial. L'élaboration de la chaîne *n*-pentyle se fait par deux réactions de couplages croisés d'halogénures.

In the course of studies directed towards the synthesis of isotopically substituted cannabinoid standards (for a recent review on cannabinoid synthesis, see ref. 1) we required the preparation of 5′-($^2H_3$)olivetol (**1**). The unlabelled parent compound olivetol (**2**) is generally best prepared by the method of Focella *et al.* (2) (Scheme 1). We reasoned, however, that the applicability of this method for the preparation of **1** suffers from two serious disadvantages: first, the lack of an easy access to the suitably labelled starting material (i.e., hexanal), and secondly, the high cost associated with the introduction of the label in the early stages of the synthetic scheme. Similarly, the only previous synthesis of **1**, reported by Pitt *et al.* (3), uses the relatively expensive 3,5-dimethoxybenzaldehyde (**3**) as starting

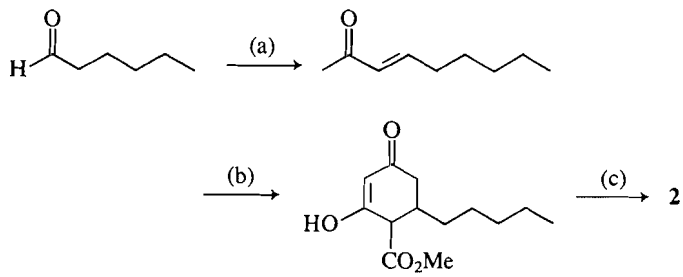


1 R = H, R′ = $(CH_2)_4C^2H_3$
2 R = H, R′ = $(CH_2)_4CH_3$
3 R = CH_3, R′ = CHO

compound. We have therefore devised an efficient synthesis of **1** that makes use of relatively inexpensive starting material and labelling agent and that allows for the introduction of the label in the penultimate step of the synthetic scheme.

We wish to report here the preparation of **1** by a stepwise elaboration of the labelled *n*-pentyl side chain starting from the commercially available 3,5-dimethoxybenzoic acid (**4**) (Scheme 2). Our approach relies on the use of two cross-coupling reactions between alkyl halides and Grignard reagents (for an overview, see ref. 4) to provide the side chain.

The starting acid **4** was first converted to bromide **5** by successive hydride reduction and nucleophilic displacement using phosphorus tribromide. A first cross-coupling reaction was then used to achieve a three-carbon unit chain extension by reacting bromide **5** with allyl magnesium bromide. The best yields of olefin **6** were obtained by using a 1:2 molar ratio of **4** to Grignard reagent. Hydroboration–oxidation at the terminal carbon of olefin **6**, followed by nucleophilic displacement according to the recently reported method of Olah *et al.* (5),



(a) NaOH, acetone; (b) NaOMe, $CH_2(CO_2Me)_2$; (c) Br_2, DMF

SCHEME 1

afforded bromide **7** in good yield. The label was then introduced by means of a second cross-coupling reaction between bromide **7** and deuterated methyl magnesium iodide in the presence of dilithium tetrachlorocuprate as catalyst (6). The labelled dimethoxyolivetol **8** thus obtained was demethylated using trimethylsilyliodide (7) to afford the title compound **1** in 13% overall yield.

Experimental

The ^1H and ^{13}C nmr spectra were recorded on a Varian XL-200 spectrometer. Deuterated chloroform ($CDCl_3$) was used as the standard solvent and tetramethylsilane (TMS) as an internal reference. All chemical shifts are expressed in ppm downfield from TMS. Infrared spectra were measured on a Perkin–Elmer 237-B grating infrared spectrophotometer. Mass spectra were obtained on a VG-7070E instrument.

All reactions were routinely monitored by analytical thin-layer chromatography (tlc) on precoated silica gel plates (Merck-60 PF-254). Silica gel (Davison Chemical Co., grade 923, 100–200 mesh) was used for column chromatography. High-performance liquid chromatography (hplc) was performed using a Waters Prep-500 high performance liquid chromatograph.

Dry solvents were obtained by distillation over lithium aluminum hydride (DME and THF) or sodium (ether and benzene).

3,5-Dimethoxybenzyl bromide (5)

To a suspension of lithium aluminum hydride (3.8 g, 0.10 mol) in 100 mL of anhydrous ether was added acid **3** (18.2 g, 0.10 mol) dissolved in 60 mL of ether at such a rate that a gentle reflux was maintained. The reaction was stirred for 16 h at room temperature, then worked up by the slow addition of 5 mL of water, 5 mL of 15% aqueous NaOH, and a further 15 mL of water. The suspension was filtered through a pad of Celite, which was washed with ether. The combined ether washings were concentrated under reduced pressure and the residual oil was immediately dissolved in 50 mL of anhydrous dichloromethane. After cooling the mixture to 0°C, phosphorus tribromide (27.1 g, 0.10 mol) was added dropwise and the reaction was allowed to warm to room temperature, then stirred for 1 h. The mixture

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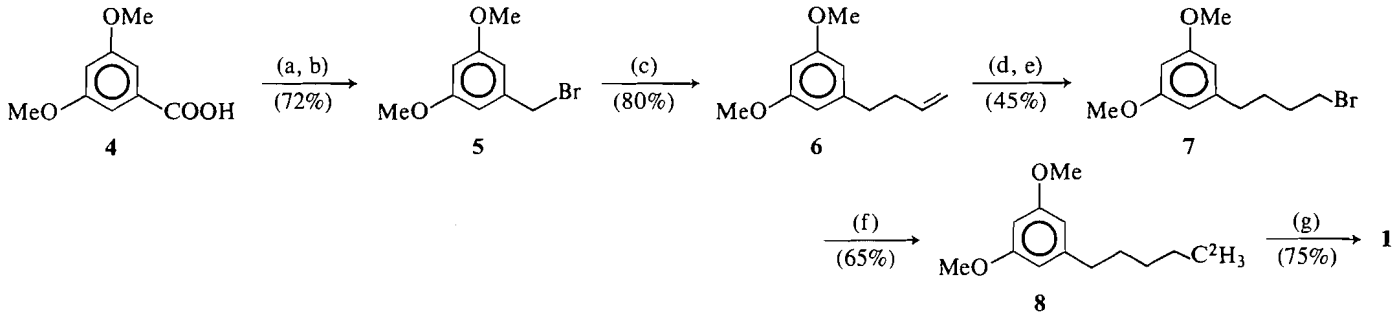

(a) LAH, ether; (b) PBr_3, CH_2Cl_2; (c) $H_2C{=}CHCH_2MgBr$, ether; (d) $BH_3{\cdot}Me_2S$, then $H_2O_2/NaOH$; (e) TMSCl, LiBr, MeCN; (f) $^2H_3CMgI$, Li_2CuCl_4, THF; (g) TMSI, $CHCl_3$

SCHEME 2

was poured into ice-water and the organic layer was collected. The aqueous phase was extracted with dichloromethane (75 mL) and the combined organic phases were washed with water (100 mL), saturated $NaHCO_3$ (100 mL), and saturated NaCl (100 mL), then dried over magnesium sulfate. Concentration gave 22 g (78%) of bromide **5** as a colorless solid; ^1H nmr: 3.8 (6H, s, OMe), 4.3 (2H, s, benzylic), 6.2–6.6 (3H, m, aromatic).

4-(3,5-Dimethoxyphenyl)-1-butene (6)

To a cooled solution of allyl magnesium bromide (286 mL of 1 *M* ether solution, 0.286 mol) was added dropwise bromide **5** (33.0 g, 0.14 mol) in ether (200 mL). The reaction was allowed to warm to room temperature and then stirred for 30 h. The reaction mixture was quenched by addition of a saturated ammonium chloride solution, followed by water (250 mL). The organic layer was separated and the aqueous layer was extracted with ether (200 mL). The resulting emulsion was passed through glass wool and the organic layers were combined and dried over magnesium sulfate. Solvent evaporation and purification by hplc (10% ethyl acetate in hexane) afforded olefin **6** (22.0 g, 80%); ir (neat): 1640 (C=C); 920 (C=CH_2) cm^{-1}; ^1H nmr: 2.2–2.8 (4H, m, CH_2's), 3.75 (6H, s, OMe), 4.8–5.3 and 5.5–6.1 (3H, m, CH=CH_2), 6.35 (3H, s, aromatics); ms *m/e* (relative intensity): 192 (M^+, 62), 177 (15), 151 (100). High resolution ms: M^+ calcd. for $C_{12}H_{16}O_2$: 192.1150; found: 192.1157.

4-(3,5-Dimethoxyphenyl)-1-bromobutane (7)

Olefin **6** (20.0 g, 0.104 mol) was dissolved in dichloromethane (35 mL) and cooled to 0°C. Borane–dimethyl sulfide complex (3.8 mL of 10.2 *M* BH_3, 38 mmol) was then added dropwise. The temperature was maintained at 0°C for 25 min, then allowed to rise to room temperature. The reaction was stirred for 3 h, then concentrated under reduced pressure. Dichloromethane (35 mL) and ethanol (35 mL) were added, followed by 12.8 mL of 3 *N* NaOH (38.5 mmol). The mixture was cooled to 0°C and an equivalent volume of 30% aqueous hydrogen peroxide was added. The reaction was refluxed for 1 h, cooled, and poured into 500 mL of ice-water. The mixture was extracted with ether (3 × 100 mL) and the combined organics were washed with water (200 mL) and brine (200 mL) and dried over magnesium sulfate. Concentration and purification by hplc afforded 14.2 g (65%) of 4-(3,5-dimethoxyphenyl)-1-butanol as an oil; ^1H nmr: 1.3–2.0 (4H, br m, CH_2's), 2.55 (2H, t, benzylic), 3.75 (6H, s, OMe), 3.5–3.7 (2H, m, CH_2OH), 6.3 (3H, br s, aromatics).

Lithium bromide (8.30 g, 0.095 mol) was suspended in 250 mL of acetonitrile. Trimethylsilyl chloride (12.93 g, 0.119 mol) was added, followed by the addition of a solution of the previously prepared alcohol (10.00 g, 0.048 mol) in acetonitrile (120 mL). The reaction was refluxed for 12 h. The solution was then poured into ice-water and extracted with ether (3 × 200 mL). The combined organic phases were washed with saturated sodium bicarbonate solution, then with brine, and dried over anhydrous magnesium sulfate. Purification by flash chromatography afforded 8.5 g of pure title compound (70% yield); ^1H nmr: 1.7–2.0 (4H, br m, CH_2's), 2.6 (2H, t, benzylics), 3.55 (2H, t, CH_2Br), 3.80 (6H, s, OMe), 6.4 (3H, br s, aromatics).

5'-($^2H_3$)-Olivetol dimethyl ether (8)

Bromide **7** (11.00 g, 0.040 mol) was dissolved in dry THF (30 mL) and cooled to 0°C. The Grignard reagent, prepared by the addition of ($^2H_3$)-iodomethane (7.60 g, 0.052 mol, MSD Isotopes >99.5%) in dry ether (15 mL) to magnesium (1.37 g, 0.056 mol) in ether (10 mL), was then added dropwise to the bromide **7** solution via stainless steel cannula. Li_2CuCl_4 (2.02 mL of a 0.1 *M* solution in THF, 0.2 mmol) (6) was added with a syringe. The reaction was allowed to warm to room temperature and stirred for 16 h. Sulfuric acid (1.8 *M*) was added slowly until all the precipitate had dissolved. The mixture was extracted with ether (3 × 150 mL). The combined organic layers were washed with saturated sodium bicarbonate solution, then with brine, and dried over $MgSO_4$. Concentration and purification by hplc (5% ethyl acetate in hexane) provided 6.55 g (60%) of the title compound as a viscous oil; bp 79–82°C (0.05 Torr; 1 Torr = 133.3 Pa); ^1H nmr: 2.3–2.6 (2H, t, benzylics), 3.8 (6H, s, OMe), 6.3 (3H, s, arom.); ^{13}C nmr: 14–15 ppm (septuplet, C^2H_3), 22.3, 31.05, 31.5, 36.3, 55.2 (OMe), 97.5, 106.5, 145.4, 160.7; ms *m/e* (relative intensity): 211 (M^+, 30), 192 (2.5), 169 (12), 165 (10), 152 (100). High resolution ms: M^+ calcd. for $C_{13}H_{17}{}^2H_3O_2$: 211.1665; found: 211.1671. The percentage of incorporation was determined by mass spectrometry and was found to be: $^2H_3$ = 98.7%; $^2H_2$ = 0.1%; $^2H_1$ = 0.1%; $^2H_0$ = 1.1%.

5'-($^2H_3$)-Olivetol (1)

The labelled dimethyl ether **8** (6.55 g, 0.031 mol) was dissolved in chloroform (30 mL) and treated with trimethylsilyl iodide (18.60 g, 0.093 mol). The mixture was heated to 40°C until no more starting material was detected by tlc (48 h). The reaction was cooled, poured into 150 mL of methanol, and evaporated *in vacuo*. Ether (100 mL) was added and the solution was washed with aqueous sodium bisulfite (100 mL), sodium bicarbonate, brine, and dried over magnesium sulfate. Concentration under reduced pressure and purification afforded the title compound (4.25 g, 75%); mp 38–39°C; ir ($CDCl_3$): 3400 (OH) cm^{-1}; ^1H nmr: 2.55 (2H, t, benzylics), 6.4 (3H, br s, arom.).

Acknowledgements

This work was supported in part by operating grants from the Natural Sciences and Engineering Research Council of Canada. We thank Carleton University for scholarships to M.G. and D.B.M.

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