

A Simple Method for the Synthesis of Exaltolide

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Synopsis. Copper-catalyzed reaction of β -propiolactone with 12-methoxydodecylmagnesium bromide, derived from 1,12-dodecanediol, gives 15-methoxypentadecanoic acid in a high yield, which is easily converted into exaltolide.

15-Pentadecanolide (exaltolide, **1**) is a component of the root oil of *Archangelica officinalis* Syn., which is known as a perfume of the most strong and elegant musk-like fragrance in the series of macrocyclic lactones. Among the numerous synthetic methods for exaltolide so far reported, the most common one is the cyclization of 15-hydroxy- or 15-bromopentadecanoic acid. These acids have been usually prepared from long-chain carboxylic acids arising from several plant oils, such as (*Z*)-13-docosenoic acid (erucic acid)¹⁾ from rapeseed oil, 9,10,16-trihydroxyhexadecanoic acid (aleuritic acid)²⁾ from the resin of schellac, or 10-undecenoic acid from castor oil.³⁾ Recently cyclododecanone has been frequently used as a useful starting material of C_{12} unit because of easy availability from butadiene trimer, and various routes to exaltolide have been elaborated by C_3 extension of cyclododecanone.⁴⁾ A short-step synthesis of exaltolide (**1**) via 15-bromopentadecanoic acid (**4**) was investigated from easily available starting materials of β -propiolactone (**2**) and 1,12-dodecanediol (**3**).

In this route, the regioselective reaction of β -propiolactone with a Grignard reagent⁵⁾ containing an oxygen functionality was applied as a key step for the synthesis of exaltolide, i.e., the three carbon homologation terminating in a carboxyl function was easily achieved by the copper catalyzed reaction of 12-methoxydodecylmagnesium bromide (**6**) with the lactone **2** to furnish 15-methoxypentadecanoic acid (**5**) which was smoothly converted into **4**. Thus, to a mixture of

(**1**) in 78% yield.

The Grignard reagent **6** of C_{12} unit was easily derived from the diol **3**. Chipped sodium was slowly added to an excess of **3** at 100 °C and then dimethyl sulfate was added dropwise. After stirring for 2 h at 120 °C, 12-methoxy-1-dodecanol (**7**) was obtained quantitatively. Bromination of **7** with phosphorus tribromide and pyridine at room temperature for 2 d gave 1-bromo-12-methoxydodecane (**8**) in a yield of 65%, which was easily transformed into the Grignard reagent **6** by the reaction with magnesium metal in refluxing ether.

As mentioned above, by the use of the regioselective reaction of the Grignard reagent of an oxygen functionality with β -propiolactone in the presence of a copper(I) catalyst, exaltolide was conveniently synthesized from the easily available materials.

Experimental

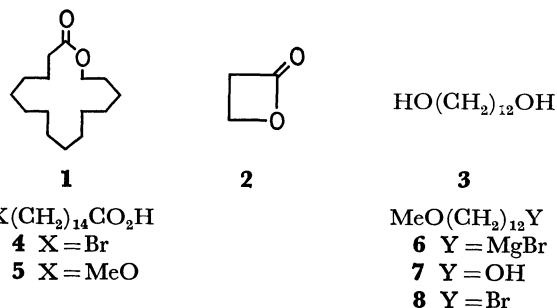
The IR spectra were recorded on a Hitachi EPI-G2 spectrometer. The NMR spectra were taken with a Varian A-60 spectrometer using TMS as an internal standard. All boiling points and melting points are uncorrected.

12-Methoxy-1-dodecanol (7). Chipped sodium (0.744 g, 31 mg atom) was slowly added to 1,12-dodecanediol (25 g, 124 mmol) at 100 °C. After the sodium was dissolved, dimethyl sulfate (3.9 g, 31 mmol) was added dropwise at 120 °C and the mixture was stirred for 2 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with chloroform. The extracts were dried over anhydrous $MgSO_4$. The solvent was removed and the residue was extracted with hexane. Distillation of the hexane solution gave **7** (6.9 g, quant.): bp 120–124 °C/0.8 mmHg; IR (KBr) 3300 (OH) and 1120 cm^{-1} (C–O); NMR (CCl_4) δ 1.10–1.78 (20H, broad), 3.12–3.60 (5H, m), and 3.20 (3H, s).

1-Bromo-12-methoxydodecane (8). To a mixture of phosphorus tribromide (3.10 g, 11.4 mmol) and pyridine (0.048 g, 0.61 mmol) in dry ether (5 ml) was added dropwise **7** (7.45 g, 34.4 mmol) in pyridine (0.160 g, 2.02 mmol) at –20 °C. The reaction mixture was stirred at room temperature for 2 d. Hydrochloric acid (1 M) was added and the mixture was extracted with ether. The extracts were washed with 5% sodium hydrogencarbonate solution and dried over anhydrous $MgSO_4$. After removal of the solvent, distillation afforded **8** (6.24 g, 65%): bp 114–119 °C/0.5 mmHg; IR (KBr) 1120 (C–O), 645 and 560 cm^{-1} (C–Br); NMR (CCl_4) δ 1.3 (20H, m) and 3.12–3.60 (4H, m), 3.20 (3H, s).

15-Methoxypentadecanoic Acid (5). 12-Methoxydodecylmagnesium bromide (**6**) was prepared from magnesium (1.17 g, 48 mmol) and **8** (6.19 g, 22 mmol) in ether (24 ml), which was titrated by Eastham's method⁶⁾ (0.547 M, 74%).

To a THF (4 ml) solution of copper(I) iodide (3.8 mg, 0.02 mmol), dimethyl sulfide (0.5 ml) and β -propiolactone (72.2 mg, 1.00 mmol) was added the Grignard reagent **6** (0.55 ml, 1.01 mmol) at 0 °C. The reaction mixture was



the lactone **2** (1 equiv) and copper(I) iodide (0.02 equiv) in THF– Me_2S (8:1) was added **6** (1 equiv) at 0 °C. After the reaction mixture was stirred at 0 °C for 3 h, the desired acid **5** was obtained in a yield of 99%. Treatment of **5** with excess boron tribromide in CH_2Cl_2 at –25 °C for 4 d gave 15-bromopentadecanoic acid (**4**) in 78% yield. Then, according to the method of Mandolini *et al.*,⁶⁾ the ω -bromo acid was treated with potassium carbonate in dimethyl sulfoxide at 75 °C to furnish exaltolide

stirred for 3 h, quenched with water and then made basic with 3 M aqueous sodium hydroxide solution. The white precipitate was filtered and the filtrate was washed with ether. The water layer was acidified with 6 M hydrochloric acid. The solid was dissolved in this acidic solution, which was extracted with ether. The extracts were dried over anhydrous MgSO_4 and the solvent was evaporated to afford **5** (268 mg, 99%): mp 47–48 °C; IR (KBr) 3300–2500, 1700 (CO_2H), and 1125 cm^{-1} (C–O); NMR (CCl_4) δ 1.10–1.72 (24H, m), 2.20 (2H, t, $J=7$ Hz), 3.20 (3H, s), 3.23 (2H, t, $J=7$ Hz), 9.20 (1H, s).

15-Bromopentadecanoic Acid (4). To a solution of **5** (0.234 g, 0.86 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise boron tribromide (0.870 g, 3.47 mmol) in dry CH_2Cl_2 at –78 °C and the reaction mixture was stirred for 30 min. The solution was warmed to –25 °C and allowed to stand for 4 d. Sodium hydrogencarbonate (2.60 g, 3.09 mmol) was added at –25 °C. The mixture was then acidified with 3 M hydrochloric acid and extracted with ether. The extracts were dried over anhydrous MgSO_4 . Removal of the solvent gave **4** (0.215 g, 78%): mp 66–67 °C (lit.⁸) 66 °C; IR (KBr) 3500–2400, 1700 (CO_2H) and 650 cm^{-1} (C–Br); NMR (CCl_4) δ 1.20–2.00 (24H, m), 2.30 (2H, t, $J=7$ Hz), and 9.50 (1H, s).

Exaltolide (1). To a suspension of powdered potassium carbonate (0.563 g, 4.08 mmol) in dimethyl sulfoxide (11 ml) was added dropwise **4** (0.321 g, 1.00 mmol) in dimethyl sulfoxide (5 ml) at 75 °C in 4 h under vigorous stirring. After the mixture was cooled to room temperature, cold water (10 ml) was added and resulting mixture was extracted with hexane. The extracts were dried over anhydrous MgSO_4 and the solvent was evaporated. The crude

product was purified by TLC on silica gel (hexane:ether=8:1) to afford **1** (0.189 g, 78%): mp 32 °C (lit.¹) 32 °C; IR (KBr) 1735 cm^{-1} (C=O); NMR (CCl_4) δ 1.00–2.00 (26H, m), 2.17 (2H, t, $J=7$ Hz), and 3.93 (2H, t, $J=5$ Hz). The spectral data were identical with those of an authentic sample.

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