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A Simple Method for the Synthesis of Exaltolide

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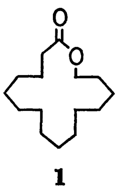
Synopsis. Copper-catalyzed reaction of β-propiolactone with 12-methoxydodecylmagnesium bromide, derived from 1,12-dodecanediol, gives 15-methoxypentadecanoic acid in a high yield, which is easily converted into exaltolide.

15-Pentadecanolide (exaltolide, **1**) is a component of the root oil of *Archangelica officianalis* 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 extention 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 reagent[5] 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 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 (**1**) in 78% yield.



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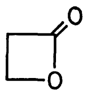

2

$HO(CH_2)_{12}OH$

3

$X(CH_2)_{14}CO_2H$
4 X=Br
5 X=MeO

$MeO(CH_2)_{12}Y$
6 Y=MgBr
7 Y=OH
8 Y=Br

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 method[6] (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 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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