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# SYNTHESIS OF β-IONONE<sup>#</sup>

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#### SYNTHETIC COMMUNICATIONS, 31(2), 219-224 (2001)

### SYNTHESIS OF $\beta$ -IONONE<sup>#</sup>

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#### ABSTRACT

Preparation of  $\beta$ -ionone by a reaction sequence starting from acetone is described.

We were interested to find a convenient synthetic route to prepare  $\beta$ -ionone, which is an important building block in our approach towards vitamin-A and (RS)abscisic acid syntheses. Many patented reports for the synthesis of  $\beta$ -ionone, along with a few published reports regarding synthesis of  $\beta$ -ionone through  $\Psi$ -ionone, are available in the literature (1).  $\beta$ -Ionone has received considerable attention because of its wide use in cosmetics (7), food flavoring (8), as a bactericide (9), and an antagonist (10). In this report we present a convenient and practical synthesis of the title compound (Scheme 1).

Acetone is reacted with sodium acetylide at  $-50^{\circ}$ C to form the acetylenic alcohol **1** in 87.9% yield. The resulting acetylenic alcohol underwent partial reduction using Lindlars catalyst at room temperature to afford the substituted allyl alcohol **2**. The allylic rearrangement of compound **2** is carried out using either HCl

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<sup>&</sup>lt;sup>#</sup> IICT communication number 4541.

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*Reagents and conditions:* (a) Acetylene,  $NH_3$ ,  $NaNH_2$  or Acetylene, Na, THF or Acetylene,  $NaNH_2$ , THF at  $-50^{\circ}$ C, 5 h; (b) H<sub>2</sub>/Lindlar, Hexane, rt, 10 h, atm. pressure; (c) 37% HCl,  $0^{\circ}$ C, 1 h; (d) 48% HBr,  $0^{\circ}$ C, 0.5 h; (e) CH<sub>3</sub>COONa, TEBA, 4.5 h; (f) 10% NaOH, reflux, 2.5 h; (g) MnO<sub>2</sub>, Petroleum ether, rt, 17 h; (h) 200°C/40atm, 1.5 h or (i) LiCl, Toluene, Hydroquinone, reflux, after work up (ii) 1,2-dichlorobenzene, LiCl, 135°C; (i) Acetone, NaOMe,  $-10-(-5)^{\circ}$ C, 1h; (j) H<sub>2</sub>SO<sub>4</sub>, Hexane-Acetone.

#### Scheme 1.

or HBr at 0°C for 1 h to obtain **3a** and **3b**, respectively. The allyl chloride **3a** underwent nucleophilic substitution with sodium acetate in presence of TEBA as PTC for 4.5 h to afford the acetate **4** in 96.4% yield. Our procedure for this conversion is more efficient compared to the earlier reports. Hydrolysis of acetate **4** with 10% sodium hydroxide solution under refluxing conditions for 2.5 h gave allyl alcohol **5** in 95% yield, which was subjected to allylic oxidation with MnO<sub>2</sub> in petroleum ether at RT for 17 h, resulting the  $\alpha$ , $\beta$ -unsaturated aldehyde **6**. Allylic alcohol **5** and the aldehyde **6** were reacted using LiCl catalyst to form citral **7** according to literature procedure, which involved Claisen followed by Cope rearrangements. Citral **7** underwent condensation reaction with acetone to form the alcohol **8**. Finally, compound **8** was subjected to smooth cyclization in H<sub>2</sub>SO<sub>4</sub> to give  $\beta$ -ionone (**9**) in 75% yield. Synthesis of  $\beta$ -ionone has been achieved from acetone in nine steps via citral.

#### **EXPERIMENTAL**

#### Preparation of 3-Methyl-1-butyn-3-ol (1)

In a 5-L, three-necked, round-bottom flask fitted with a cold finger, dropping funnel, and a gas bubbler NaNH $_2$  (273 g, 7 mol) and ammonia (3 L) is collected

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at  $-50^{\circ}$ C. Acetylene gas is passed for 30 min. To this mixture was added acetone (530 mL) during 3 h at the same temperature. After completion of this addition, the cooling bath was removed and the mixture kept at room temperature overnight. Stirring of the mixture continued for 30 min at  $25^{\circ}$ C, then it was quenched with 10% H<sub>2</sub>SO<sub>4</sub> (500 mL), and 35% H<sub>2</sub>SO<sub>4</sub> (1300 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>; the organic layer was concentrated under reduced pressure and purified by distillation at 104–105°C. Yield: 87.9% (516.9 g). IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 3302 <sup>1</sup>H NMR (400 MHz/CDCl<sub>3</sub>) ppm: δ 1.55 (s, 6H); 1.95 (brs, 1H); 2.40 (s, 1H). MS-EI (m/e): 84 (M<sup>+</sup>); 69 (M<sup>+</sup>-CH<sub>3</sub>); 67 (M<sup>+</sup>-OH).

#### Preparation of 3-Methyl-1-butene-3-ol (2)

#### Procedure I

Compound 1 (70 g, 0.833 mol), Lindlar catalyst (7 g), and hexane (210 mL) are taken in a 1-L round-bottom flask and maintained at room temperature for 10 h under H<sub>2</sub> atmosphere. Filtered and purified by distillation over a column packed with glass beads, pure fraction was collected at 97°C. Yield: 91.1% (65.3 g). IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 3540 <sup>1</sup>H NMR (400 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.30 (s, 3H); 1.50 (s, 3H); 2.50 (brs, 1H); 4.95 (d, J = 7.4 Hz, 1H); 5.15 (d, J = 14.8 Hz, 1H); 5.95 (dd, J = 14.8, 7.4 Hz, 1H). MS-EI (m/e): 86  $(M^+)$ ; 71  $(M^+-CH_3)$ ; 69  $(M^+-OH)$ .

#### Procedure II

The above procedure was followed using Compound 1 (52 g, 0.619 mol), Lindlar catalyst (4.6 g), quinoline (2.6 g) and petroleum ether (75 mL) to afford compound 2. Yield: 99% (53.46 g).

#### Preparation of 1-Chloro-3-methyl-2-butene (3a)

Compound 2 (13 g, 0.1511 mol) in a 100-mL round-bottom flask was mixed with 37% aq. HCl (44.2 mL, 0.44 mol) at 0°C and stirred at the same temperature for 1 h. The organic layer was separated, washed with water  $(2 \times 20 \text{ mL})$ , dried over anhy. Na<sub>2</sub>SO<sub>4</sub> and distilled at 109°C to obtain product **3a**. Yield: 96.3% (15.2 g). <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.75 (s, 3H); 1.80 (s, 3H); 4.05 (d, J = 7.78 Hz, 2H), 5.45 (t, J = 7.78 Hz, 1H). MS-EI (m/e): 104, 105 (M<sup>+</sup>).

#### Preparation of 1-Bromo-3-methyl-2-butene (3b)

Vinyl alcohol 2 (13.49 g, 0.1568 mol) was placed in a 250-mL round-bottom flask and cooled to  $0^{\circ}$ C. Then 48% aq. HBr (62.7 mL) was slowly introduced



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into the reaction flask and the resulting mixture stirred for 30 min at the same temperature. The organic layer was separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer and extracts were dried over anhy. Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and distilled off at 59°–60°C. Yield: 90% (21.03 g). R<sub>f</sub> = 0.8 (Petroleum ether) <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.70 (s, 3H); 1.75 (s, 3H); 3.95 (d, J = 6.74 Hz, 2H); 5.50 (t, J = 6.74 Hz, 1H). MS-EI (m/e): 148, 150 (M<sup>+</sup>).

#### Preparation of 1-Acetoxy-3-methyl-2-butene (4)

Compound **3a** (4.27 g, 0.0408 mol), NaOAc (3.868 g, 0.0471 mol), TEBA (0.1044 g, 0.00045 mol) were heated in a 50-mL round-bottom flask for 4.5 h at 95°–105°C, then extracted with DCM (3 × 10 mL) and concentrated under vacuum. Yield: 96.4% (5.04 g)  $R_f = 0.75$  (Ethyl acetate-Petroleum ether, 1:4) b.p.: 160°C/10 mm IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 3300, 1720. <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.75 (s, 3H); 1.80 (s, 3H); 2.05 (s, 3H); 4.55 (d, J = 6.9 Hz, 2H); 5.35 (t, J = 6.9 Hz, 1H). MS-EI (m/e): 128 (M<sup>+</sup>); 113 (M<sup>+</sup>-CH<sub>3</sub>).

#### Preparation of Allyl Alcohol 5

Compound **4** (13.4 g, 0.1046 mol) and 10% NaOH solution (4.4 mL) were heated at 100°C for 2.5 h. The organic layer was separated and the aqueous layer extracted with DCM (2 × 250 mL). The extracts were combined with the organic layer, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Distillation at 137°C gave pure compound **5**. Yield: 95% (8.6 g). IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 3332. <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.65 (s, 3H); 1.72 (s, 3H); 1.95 (brs, 1H); 4.05 (d, J = 8 Hz, 2H); 5.35 (t, J = 8 Hz, 1H). MS-EI (m/e): 86 (M<sup>+</sup>); 71 (M<sup>+</sup>-CH<sub>3</sub>).

#### Preparation of 3-Methyl-2-butenal (6)

Compound **5** (28.2 g, 0.327 mol) and MnO<sub>2</sub> (71.2 g, 0.819 mol) were taken in petroleum ether (300 mL) and stirred at room temperature for 7 h, filtered, and the filtrate concentrated to give crude product compound **6**, which was distilled off at 132°–133°C. Yield: 95% (26.12 g) IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 1682. <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.70 (s, 3H); 1.75 (s, 3H); 5.90 (d, J = 9.37 Hz, 1H); 9.95 (d, J = 9.37 Hz, 1H). MS-EI (m/e): 84 (M<sup>+</sup>), 69 (M<sup>+</sup>-CH<sub>3</sub>).

#### Preparation of Compound 8

Compound 7 (7.49 g, 0.0493 mol) and acetone (13 mL, 0.1778 mol) were taken in a round-bottom flask and cooled to  $-10^{\circ}$ C. To this was added NaOMe

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(0.8862 g, 0.0164 mol), slowly maintaining the temperature below  $-5^{\circ}$ C over a period of 30 min, and stirring continued for 30 min at the same temperature. The reaction was quenched with aq. tartaric acid solution (1.107 g of tartaric acid dissolved in 7.38 mL of water), extracted with ethyl acetate (3 × 30 mL), and concentrated to give alcohol **8** Yield: 92% (9.538 g)  $R_f = 0.47$  (Ethyl acetate-Petroleum ether, 1:4) <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.60 (s, 3H); 1.65 (s, 3H); 1.70 (m, 2H); 1.90, 1.95 (s, 3H, two sets); 2.20 (m, 4H); 2.25, 2.30 (s, 3H, two sets); 2.60 (br s, 1H); 5.05 (br s, 1H); 6.05 (m, 2H). MS-EI (m/e): 210 (M<sup>+</sup>); 193 (M<sup>+</sup>-OH).

#### Preparation of $\beta$ -Ionone 9

Hexane (3.6 mL) and H<sub>2</sub>SO<sub>4</sub> (5.16 mL) were taken in a round-bottom flask and the contents were cooled to  $-10^{\circ}$ C and stirred for 10 min. Then compound **8** (3.1 g, 0.0162 mol) in hexane (4 mL) was added within 15 min and stirring continued for 30 min. The reaction mixture was neutralized with 18% NaOH solution until the pH = 7 at  $-10^{\circ}$ C. The reaction mixture was extracted with DCM (2 × 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Yield: 75% (2.325 g) R<sub>f</sub> = 0.53 (Ethyl acetate-Petroleum ether, 1:9) b.p.: 138°-140°C/10 mm IR (Neat,  $\nu_{max}$ ) cm<sup>-1</sup>: 1693, 1673. <sup>1</sup>H NMR (200 MHz/CDCl<sub>3</sub>) ppm:  $\delta$  1.05 (s, 6H); 1.46 (m, 2H); 1.60 (m, 2H); 1.73 (s, 3H); 2.05 (m, 2H); 2.25 (s, 3H); 6.07 (d, J = 16.8 Hz, 1H); 7.20 (d, J = 16.8 Hz, 1H). MS-EI (m/e): 192 (M<sup>+</sup>); 177 (M<sup>+</sup>-CH<sub>3</sub>); 123 (M<sup>+</sup>-C<sub>4</sub>H<sub>5</sub>O).

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