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SYNTHESIS OF β-IONONE[#]

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ABSTRACT

Preparation of β-ionone by a reaction sequence starting from acetone is described.

We were interested to find a convenient synthetic route to prepare β-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 β-ionone, along with a few published reports regarding synthesis of β-ionone through Ψ-ionone, are available in the literature (1). β-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°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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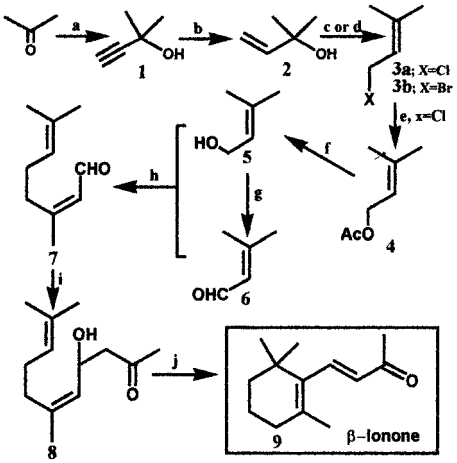

Reagents and conditions: **(a)** Acetylene, NH_3, $NaNH_2$ or Acetylene, Na, THF or Acetylene, $NaNH_2$, THF at -50°C, 5 h; **(b)** H_2/Lindlar, Hexane, rt, 10 h, atm. pressure; **(c)** 37% HCl, 0°C, 1 h; **(d)** 48% HBr, 0°C, 0.5 h; **(e)** CH_3COONa, TEBA, 4.5 h; **(f)** 10% NaOH, reflux, 2.5 h; **(g)** MnO_2, 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_2SO_4, 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_2 in petroleum ether at RT for 17 h, resulting the α,β-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_2SO_4 to give β-ionone (**9**) in 75% yield. Synthesis of β-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°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°C, then it was quenched with 10% H_2SO_4 (500 mL), and 35% H_2SO_4 (1300 mL). The aqueous layer was extracted with CH_2Cl_2; the organic layer was concentrated under reduced pressure and purified by distillation at 104–105°C. Yield: 87.9% (516.9 g). IR (Neat, ν_{max}) cm^{-1}: 3302 ^1H NMR (400 MHz/$CDCl_3$) ppm: δ 1.55 (s, 6H); 1.95 (brs, 1H); 2.40 (s, 1H). MS-EI (m/e): 84 (M^+); 69 (M^+-CH_3); 67 (M^+-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_2 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, ν_{max}) cm^{-1}: 3540 ^1H NMR (400 MHz/$CDCl_3$) ppm: δ 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 × 20 mL), dried over anhy. Na_2SO_4 and distilled at 109°C to obtain product **3a**. Yield: 96.3% (15.2 g). ^1H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+).

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°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_2Cl_2. The combined organic layer and extracts were dried over anhy. Na_2SO_4, concentrated under reduced pressure, and distilled off at 59°–60°C. Yield: 90% (21.03 g). $R_f = 0.8$ (Petroleum ether) ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+).

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, ν_{max}) cm^{-1}: 3300, 1720. ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+); 113 (M^+-CH_3).

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_2SO_4), and concentrated under reduced pressure. Distillation at 137°C gave pure compound **5**. Yield: 95% (8.6 g). IR (Neat, ν_{max}) cm^{-1}: 3332. ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+); 71 (M^+-CH_3).

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

Compound **5** (28.2 g, 0.327 mol) and MnO_2 (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, ν_{max}) cm^{-1}: 1682. ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+), 69 (M^+-CH_3).

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°C. To this was added NaOMe

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(0.8862 g, 0.0164 mol), slowly maintaining the temperature below −5°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) ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+); 193 (M^+-OH).

Preparation of β-Ionone **9**

Hexane (3.6 mL) and H_2SO_4 (5.16 mL) were taken in a round-bottom flask and the contents were cooled to −10°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°C. The reaction mixture was extracted with DCM (2 × 25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield: 75% (2.325 g) $R_f = 0.53$ (Ethyl acetate-Petroleum ether, 1:9) b.p.: 138°–140°C/10 mm IR (Neat, ν_{max}) cm^{-1}: 1693, 1673. ^{1}H NMR (200 MHz/$CDCl_3$) ppm: δ 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^+); 177 (M^+-CH_3); 123 (M^+-C_4H_5O).

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