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An Improved Synthesis of Retinoic Acid from β-Ionone

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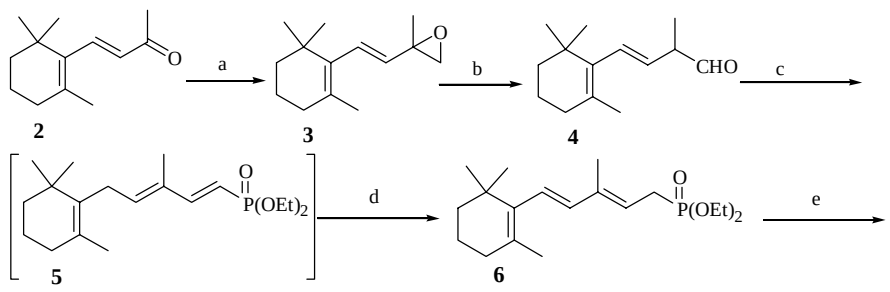
Abstract: A convenient and large-scale preparation of retinoic acid **1** from β-ionone in five steps with 38% overall yield is described. The key steps are the epoxidization of **2** with a new methylated agent and the condensation **4** with tetraethyl methylenediphophonate in one-pot procedure to prepare **6**.

Keywords: Retinoic acid, trimethylsulfonium *p*-tolenesulfonate, allylic phosphonate, Wittig-Horner-Emmons (WHE) reaction, synthesis.

Retinoic acid (Tretinoin **1**) plays a key role in the maintenance and differentiation of epithelial tissue and is very important for the treatment of acne and skin damage by UV-light[1]. In the past years, a number of methods for the synthesis of **1** have appeared[2]. Among these methods, the route from β-ionone seems the most reliable one, which featured Wittig condensation from phosphonium salt and β-formylcrotonic acid ester[3]. Although Wittig condensation provides the high stereoselective polyene chain, this process has the problem of generating triphenylphosphine oxide which is difficult to separation. Recently, a new method for preparation of **1** from allylic phosphonate **6** *via* Wittig-Horner-Emmons (WHE) reaction was reported[4]. However, this procedure suffers from some drawbacks such as use of some expensive, hazardous materials and the tedious separation and purification *etc*. Therefore it is not attractive enough for industrial synthesis of **1**. Herein, we describe an improved synthesis of retinoic acid based on the same C_{15}+C_5 strategy *via* WHE reaction. The synthetic route to **1** is described as shown in **Scheme 1**.

Scheme 1



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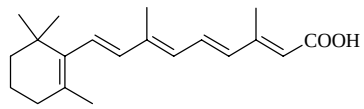

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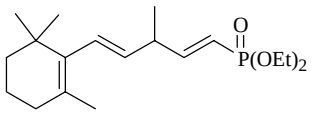
Reagents and conditions: (a) trimethylsulfonium *p*-tolenesulfonate, 50%NaOH, CH_2Cl_2, r.t., 12 h, 90%. (b) $MgBr_2 \cdot Et_2O$, r.t., 1 h, 90%. (c) tetraethyl methylenediphosphonate, EtONa/EtOH, r.t., 12 h, 92%. (d) EtONa/EtOH, reflux, 6 h, 95%. (e) i β-formylcrotonic acid ester, NaOEt/pyridine , r.t, 6 h. ii 25%NaOH, dioxane, 50°C, 6 h; 3 mol/L HCl, 54%.

It was reported that the reaction of β-ionone **2** with trimethylsulfonium agents prepared from various methylated agents such as Me_2SO_4, MeI, MeBr, MeCl could efficiently convert into epoxide **3**[4,5]. These materials are so noxious and environment-unfriendly that set limits to the industrial scale. To avoid these problems, trimethylsulfonium *p*-tolenesulfonate[6] was prepared by stirring methyl sulfide with methyl *p*-tolenesulfonate at room temperature in acetone with a yield of 74%. This new methylated agent provided an easy and convenient procedure for preparing epoxide **3** with high yield (90%). It is mentioned that the byproduct *p*-tolenesulfonic acid could be recycled to prepare the starting material methyl *p*-tolenesulfonate.

Figure 1



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The key intermediate allylic phosphonate **6** was only accessible by addition of the aldehyde **4** to the mixture of tetraethyl methylenediphosphonate and sodium hydride in THF at room temperature to afford 3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,4-pentadienyl-phosphonic acid diethyl ester **7**, followed by isomerizing with t-BuOK in DMSO[4]. However, when EtONa was used as a base in EtOH at room temperature instead of sodium hydride, none of desirable product **7** was obtained. Instead, 3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-pentadieny-phosphonic acid diethyl ester **5**[7] was formed in high yield (92%). It is noted that when the reaction was carried out in reflux temperature, **5** was smoothly isomerized to the desired allylicphophonate **6**[8] in 95% yield. The title compound **1** was prepared from **6** using an improved procedure described by Babler *et al.*[4]. Physical and NMR data for **1** are in agreement with the literature[9].

In conclusion, this procedure is a convenient method for preparing **1** without the use of expensive toxic regents or tedious chromatographic separation. Thus, it can be expected to be more practical method for the preparation of **1** in large scale.

References and Notes

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6. ^{1}HNMR(500MHz, d_6-DMSO): δ 2.29 (s, 3H, CH_3), 2.88 (s, 9H, CH_3), 7.12 (d, 2H, J=8.0, ArH), 7.49 (d, 2H, J=8.0, ArH).
7. Compound **5**: ^{1}HNMR(500MHz,$CDCl_3$): δ 0.96 (s, 6H, $C(CH_3)_2$), 1.33 (m, 6H, CH_3), 1.43 (m, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.58 (m, 2H, CH_2), 1.80 (s, 3H, $CH_3C(3)$), 1.93 (m, 2H, CH_2), 2.88 (d, 2H, J=6.5, H_2C (5)), 4.08 (m, 4H, OCH_2), 5.53 (t, 1H, J=18, H-1), 5.71 (t, 1H, J=6.3, H-4), 7.10(m, 1H, H-2); EI-MS(*m*/*z*): 340 (M^+).
8. Compound **6**:^{1}HNMR(500MHz,$CDCl_3$): δ 1.00 (s, 6H, $C(CH_3)_2$), 1.31 (m, 6H, CH_3), 1.46 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.681 (s, 3H, CH_3), 1.83 (d, 3H, J=3.5, $CH_3C(3)$), 1.99 (m, 2H, CH_2), 2.73 (dd, 2H, $J_{H,H}$=8.0, $J_{P,H}$=22, H-1), 4.11 (m, 4H, OCH_2), 5.43 (m, 1H, H-2), 6.06 (s, 2H, H-4=H-5); EI-MS(*m*/*z*): 340(M^+).
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