

Synthesis and Characterization of Hydroxyl-Pinacolone Retinoate

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Abstract. All-trans retinoic acid (10) was synthesized by β -ionone (5) through knoevenagel condensation, reduction and hydrolysis reaction. Then, hydroxyl- pinacolone retinoate (11) was prepared by the esterification with 1-hydroxy- 3, 3-dimethylbutan-2-one. This route not only reduces the synthesis steps but also helps to increase the yield. The structure of the product was characterized by ^1H NMR and ^{13}C NMR.

1. Introduction

Vitamin A also known as retinol, vitamin A in a broad sense also includes retinol derivatives (Figure 1) such as retinene (1) retinoic acid (2) retinyl acetate (3) and retinyl palmitate (4) [1-4]. The structures are interconvertible [5,6] They have a wide range of physiological functions [7], including in vision [8], immune function [9] and tumor suppression [10]. Vitamin A or vitamin A derivatives have been explored extensively. The long electron-rich conjugated polyene chains of the vitamin A molecule are highly unstable, it can be easily destroyed [11,14]. To avoid inactivation, vitamin A is often converted into vitamin A derivatives. It has been found that vitamin A ester derivatives have all the physiological functions of vitamin A, with higher stability and a wider range of applications [15-18]. Hydroxyl-pinacolone retinoate (12), one of the important derivatives of retinoic acid, could regulate the metabolism of the stratum corneum, which has been widely used in cosmetics fields, so the searches for efficient synthetic routes to these compounds are becoming increasingly important. The main synthetic routes for retinoic acid are C14+C6 represented by Roche [19] and C15+C5 represented by BAST [20]. In addition, the synthesis of retinoic acid was made by transition metal-catalyzed cross-coupling [21]. However, the method has major drawbacks. For example, the residue of transition metals is difficult to be separated. We have attempted to design a route with simple steps and mild conditions by adopting the knoevenagel condensation method.

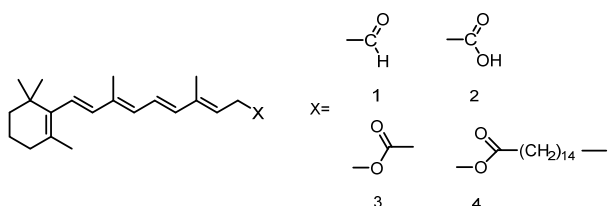


Figure 1. The molecular formula of vitamin A derivatives

2. Results and discussion

2.1 Chemical synthesis

The C15+C6-C1 route was applied to the syntheses of all-trans retinoic acid. Starting from commercial β -ionone (5), the synthesis of C15 nitrile was made by the condensation with cyanoacetic acid and further decarboxylation, and the reduction of C15 nitrile to C15 aldehyde with DIBAL-H in toluene into. A knoevenagel condensation of C15 aldehydes with 3-methyl-2-butenate in methanol led to retinoic acid methyl ester (8). Hydrolysis under alkaline conditions gave retinoic acid (9). Subsequent chlorination with PCl_3 and finally esterification with 1-hydroxy-3, 3-dimethylbutan-2-one provided hydroxyl-pinacolone retinoate (12).

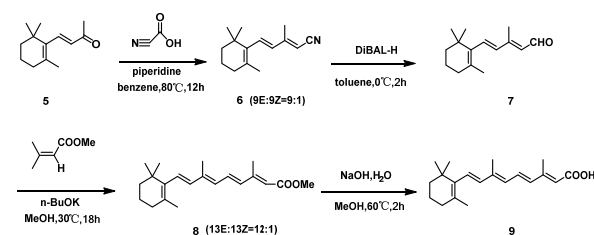


Figure 2. Synthesis route of all-trans retinoic acid

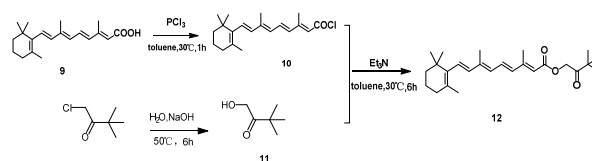


Figure 3: Synthesis route of hydroxyl-pinacolone retinoate

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Table 1 Influence of the PCl_3 dosage on the synthesis of compound(10)

n(retinoic acid):n(PCl_3)	Quality /g	Yield/%
1:0.5	14.6	65.7
1:0.6	19.18	86.0
1:0.7	20.5	92.0
1:0.8	18.5	91.2

As can be seen from Table 1, the yield gradually increased as the dosage of PCl_3 increased, and when n(retinoic acid):n(PCl_3) = 1:0.7, the product quality was 20.5g, yield 92%, and the dosage continued to increase with a slight decrease in yield. Therefore, the optimum amount of PCl_3 is n(retinoic acid):n(PCl_3) = 1:0.7.

Table 2 Influence of the Triethylamine dosage on the synthesis of compound(12)

n(Compound10): n (Et_3N)	Quality /g	Yield/%
1:1.0	15.6	65.3
1:1.2	19.8	82.8
1:1.5	16.5	79.0

As can be seen from Table 2, the yield gradually increased with the increase of triethylamine dosage, when n(retinyl chloride): n(triethylamine) = 1:1.2, the product quality was 19.8g, yield 82.8%. Therefore, the optimum amount of triethylamine is n(retinyl chloride):n(Et_3N) = 1:1.2.

Table 3 Influence of the dropping time of compound(11) on the synthesis of compound(12)

Time/min	Quality/g	Yield/%
10	15.6	65.3
20	17.5	73.2
30	19.8	82.8
40	18.9	81.5

As can be seen from Table 3, the yield gradually increased with the extension of the titration time, and the product quality was 19.5g with a yield of 82.8% at a titration time of 30min, and the yield decreased slightly with further extension. Therefore, the optimum titration time is 30 min.

Table 4 Influence of the time on the synthesis of compound(12)

Time/h	Quality/g	Yield/%
2	14.6	61.1
4	19.8	82.8
5	19.5	81.8
6	19.1	81.3

As can be seen from Table 4, the reaction yield increases with the increase of reaction time, when the reaction time is 4h the yield is the largest, 82.8% continue to increase the reaction time yield increase is not obvious, because with the increase of time by-products increase, the yield decreases. Therefore, the optimum reaction time is 4h.

Table 5 Influence of the temperature on the synthesis of compound(12)

Temp/ $^{\circ}\text{C}$	Quality/g	Yield/%
10	15.6	65.3
20	17.5	73.2
30	19.8	82.8
40	18.6	77.8

As can be seen from Table 5, with the increase of temperature, the yield gradually increased, and the product quality was 19.8g with a yield of 82.85% at a temperature of 30 $^{\circ}\text{C}$. The yield decreased slightly when the reaction temperature continued to increase. Because the reaction temperature is too high to produce more by-products, so the yield is reduced, therefore, the best reaction temperature is 30 $^{\circ}\text{C}$.

3. Experimental section

3.1 General

All chemicals are purchased from commercial sources and do not require further purification. (^1H & ^{13}C) spectrum were recorded in $\text{CDCl}_3/\text{DMSO-d}_6$ on a Bruker Avance 500 MHz. Samples are analyzed by high performance liquid chromatograph P230 (Dalian Elite Corporation) and gas chromatograph GC-6890 (Jinglu Weiye Corporation)

3.2 Synthesis of 3-methyl-5-(2, 6, 6-trimethyl-1-cyclohexen-1-yl)-2, 4-Pentadienenitrile (6)

β -ionone (5) (20g,10mmol) was suspended in benzene(100ml) and a solution of cyanoacetic acid(13.2g,15mmol) was added. Subsequent addition of piperidine (15ml), holding reaction at 80 $^{\circ}\text{C}$ for 12 h. At the end of the reaction water was added. Mixture extracted with ethyl acetate. Organic phase is concentrated. Purification by silica column chromatography eluting with 1% ethyl acetate/petroleum ether to gave the compound 6 (17.5g, 78%, E/Z=9:1). ^1H NMR (500 MHz, CDCl_3) δ 6.50 (d, J=16.1 Hz, 1H), 6.11 (d, J=16.1Hz, 1H), 4.62 (s, 1H), 2.44(s,3H), 1.92 (t, 2H), 1.71(s,3H), 1.61(m,2H), 1.32(m,2H), 1.01(s,6H); ^{13}C NMR (126 MHz, CDCl_3) δ 208.16, 136.5, 126.3, 42.2, 31.0, 23.6, 22.5, 17.6, 16.8.

3.3 Synthesis of 3-Methyl-5-(2, 6, 6 - trimethylcyclohex-1-enyl) penta -2, 4-dienal (7)

Compound 6 (18g, 83.7mmol) was added to dry toluene(120ml), cooled to 0 $^{\circ}\text{C}$ and DIBAL-H (1M in toluene, 83.7ml) is added to hold the reaction for 2 h. A refrigerated solution of 1M H_2SO_4 was added. Mixture extracted with ether, Organic phase is concentrated. Purification by silica column chromatography eluting with 10% Et_2O /hexane to gave the compound 7 (14.5g, 74.4%). ^1H NMR (500Hz, CDCl_3) δ 10.06 (d, J=8.1Hz, 1H), 6.52 (d, J=16.2Hz, 1H), 6.18 (d, J=15.6Hz, 1H), 5.84

(d, J=8.13Hz, 1H), 2.3 (s, 3H), 2.01 (m, 2H), 1.65 (s, 3H), 1.60 (m, 2H), 1.45 (m, 2H), 1.12 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 136.2, 132.5, 128.8, 46.5, 36.5, 30.6, 23.2, 18.6, 11.4.

3.4 Synthesis of all-trans retinoic acid methyl ester (8)

A slurry of n-BuOK (5.6g, 49.6mmol) was in MeOH (80ml) at 0 °C. Methyl 3-methyl-2-butenate (7.9g, 33mmol) was added. After stirring for 30 min. Compound 7 (7.4 g, 49.5 mmol) was added react for 18 h at 30 °C. The solvent methanol is removed in a vacuum and then water is added. Mixture extracted with methyl tert-butyl ether, Organic phase is concentrated. Purification by silica column chromatography eluting with 5% EtOAc/hexane to give the compound 8 (6.4g, 62%, E/Z=12:1). ¹H NMR (500 MHz, DMSO) δ 7.07 (dd, J = 15.0, 11.6 Hz, 1H), 6.42 (d, J = 15.1 Hz, 1H), 6.23 (dt, J = 36.5, 16.1 Hz, 3H), 5.85 (s, 1H), 3.62 (s, 3H), 2.30 (s, 3H), 2.04-1.95 (m, 5H), 1.69 (s, 3H), 1.62-1.52 (m, 2H), 1.48-1.38 (m, 2H), 1.01 (s, 6H); ¹³C NMR (126 MHz, DMSO) δ 166.62, 152.74, 139.38, 137.21, 136.89, 135.02, 131.49, 129.75, 129.51, 128.01, 117.74, 50.73, 33.82, 32.57, 28.76, 21.47, 18.67, 13.49, 12.59.

3.5 Synthesis of all-trans retinoic acid (9)

Compound 8 (5g, 16mmol) was added to MeOH (60ml), followed by NaOH (2M 20ml) and the temperature was raised to 60 °C for 2 h, neutralized with 1M HCl and extracted with dichloroethane. Organic phase is concentrated. Recrystallisation with methanol to give compound 9 (4.0g, 82.4%). ¹H NMR (500 MHz, DMSO) δ 12.03 (s, 1H), 7.02 (s, 1H), 6.40 (d, J = 15.1 Hz, 1H), 6.19 (t, J = 24.8 Hz, 3H), 5.77 (s, 1H), 2.28 (s, 3H), 2.01 (dd, J = 14.7, 8.8 Hz, 2H), 1.98 (s, 3H), 1.69 (s, 3H), 1.59 (s, 2H), 1.43 (s, 2H), 1.04 (d, J = 27.5 Hz, 6H); ¹³C NMR (126 MHz, DMSO) δ 167.76, 151.61, 138.89, 137.22, 136.92, 135.40, 130.80, 129.84, 129.42, 127.78, 119.41, 33.82, 32.57, 28.77, 21.48, 18.68, 13.37, 12.57.

3.6 Synthesis of 3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexen-1-yl) nona -2, 4, 6, 8- tetraenoyl chloride (10)

Compound 9 (4 g, 14 mmol) was added to toluene (20 mL) and PCl₃ (1.38 g, 10 mmol) was added dropwise at 0°C, then the temperature was raised to 30°C for 1 h. At the end of the reaction, the reaction was partitioned and the phosphite was separated to give compound 10 (3.92g, 92%). (Note: Compound 10 is used directly in the next step without treatment).

3.7 Synthesis of 1-hydroxy- 3,3-dimethylbutan-2- ketone (11)

To the flask was added a 1-chloro-3,3-dimethylbutan-2-one (2.7g 20 mmol), 72 g of water, stirred well and then warmed up to 50°C in a water bath. 45.2 g of aqueous sodium hydroxide solution with a mass fraction of 20%

was added dropwise and the reaction was held for 6 hours after the dropwise addition, and the end point was detected by gas chromatography. The organic phase was extracted with ethyl acetate three times, the solvent was evaporated under reduced pressure, and the organic phase was combined and washed with 10% aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and the filtrate was distilled under reduced pressure to obtain compound 11 (1.95g, 84%). ¹H NMR (500 MHz, DMSO) δ 4.82 (s, 1H), 4.56 (d, J = 6.0 Hz, 2H), 1.19 (s, 9H); ¹³C NMR (126 MHz, DMSO) δ 213.0, 64.2, 41.5, 26.5.

3.8 Synthesis of hydroxyl-pinacolone retinoate (12)

Under Ar. To a solution of 1-hydroxy-3,3-dimethyl-2-butanone (3.5g, 30mmol) in toluene (40ml) was added dry Et₃N (2.4g, 23.3mol). Add compound 10 (6.7g, 20mmol) dropwise at 0°C. Reacted at 30 °C for 6 h. The salts were filtered off and then concentrated. The residue was added to anhydrous ethanol and a yellow solid was precipitated to obtain compound 12 (6.5g, 82%). ¹H NMR (500 MHz, DMSO) δ 7.12 (dd, J = 15.1, 11.5 Hz, 1H), 6.49 (d, J = 15.1 Hz, 1H), 6.30 (t, J = 16.0 Hz, 2H), 6.20 (d, J = 16.1 Hz, 1H), 5.95 (s, 1H), 5.05 (s, 2H), 2.40 – 2.23 (m, 3H), 2.10 – 1.94 (m, 5H), 1.73 (d, J = 17.9 Hz, 3H), 1.59 (d, J = 6.0 Hz, 2H), 1.47 (dd, J = 7.5, 3.9 Hz, 2H), 1.16 (s, 9H), 1.04 (s, 6H); ¹³C NMR (126 MHz, DMSO) δ 208.16, 167.51, 156.58, 139.98, 137.64, 137.24, 135.16, 132.01, 130.21, 130.04, 128.54, 119.13, 64.62, 42.54, 34.15, 32.97, 29.18, 26.03, 21.87, 19.07, 13.97, 12.95. Infrared spectra are shown in Figure 4.

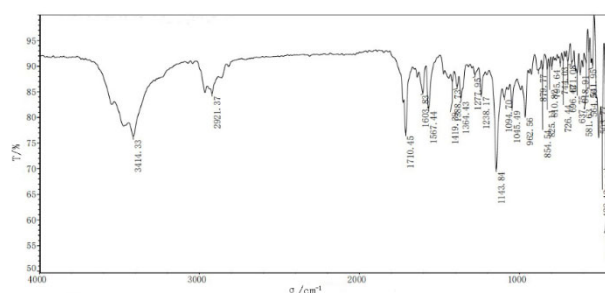


Figure 4. IR of the compound 12

4. Conclusion

The intermediate retinoic acid was synthesised through a series of reactions using β-ionone as the starting material and further synthesised as hydroxyl-pinacolone retinoate. In the process of synthesizing retinoic acid, methyl 3-methyl-2-butenate was used as C6 module to reduce the synthesis steps and helps to increase the yield.

Acknowledgments

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