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A High Yield and Pilot-Scale Process for the Preparation of Adapalene

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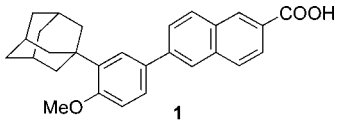
Abstract:

Strategies that were adopted during the process development of adapalene to achieve a cost-effective commercial-scale synthesis are described herein. These included (1) the use of $AcOH/H_2SO_4$ to afford 2-(1-adamantyl)-4-bromophenol in quantitative yield; (2) the dimethyl sulfate methylation to enhance the yield of methylation to 95%; (3) direct conversion of the Grignard reagent into methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate by the catalysis of both $PdCl_2(PPh_3)_2$ and $ZnCl_2$ in high yield; (4) the use of EDTA-disodium salt dihydrate to ensure the heavy metal's content within acceptable limits; (5) the use of toluene to simplify the original chromatographic purification to recrystallization. The pilot-scale synthesis of adapalene is described in detail in the Experimental Section.

Introduction

Retinoids are natural and synthetic analogues of the hormone retinoic acid. Retinoids are currently being investigated clinically as drugs in several areas, including dermatology and oncology. However, their therapeutic efficacy is limited because they cause a number of toxic side effects such as teratogenicity and mucocutaneous toxicity.[1] To decrease the number of side effects associated with retinoid treatment, medical chemists have recently developed ligands which are specific for a particular receptor subtype.[2,3] Adapalene **1** (Figure 1) is a member of this new generation of synthetic, receptor-selective retinoids, and it is specific for RARβ and RARγ receptors.[3] It is topically effective in the treatment of acne, psoriasis, and photoaging.[4] This naphthoic acid derivative has been developed by CIRD Galderma that patented[5] its preparation and use as a topical drug (Differin) and has been on the market since 1996. Structurally, **1** is composed of two units that are a large lipophilic 2-(1-adamantyl)anisole moiety and a naphthoic acid moiety, connected with a single bond. From a synthetic point of view the preparation of this compound shows some difficulties. Although 2-(1-adamantyl)-4-bromoanisole **5** and 6-bromo-2-naphthoic acid methyl ester **6** are easily available, the construction of functionally substituted benzene–naphthalene structure is not readily achievable on an industrial scale.



Adapalene (Differin)

Figure 1. **Chemical structure of adapalene.**

The reported synthetic approach[5] of **1** is based on the Negishi coupling of **5** with **6**. First, a Friedel–Crafts alkylation of 1-adamantanol **2** with 4-bromophenol **3** in the presence of 98% H_2SO_4 led to 2-(1-adamantyl)-4-bromophenol **4**. Compound **4** was submitted to methylation with CH_3I and NaH to give compound **5**. Compound **5** was converted into zincate derivative and then condensed to compound **6** by a nickel-catalyzed Negishi cross-coupling. Adapalene **1** was obtained through saponification of **7**. These methods suffer different disadvantages. The transformation of the alcohol **2** and the phenol **3** to **4** suffers from oxidation of phenols and formation of the unwanted phenyl sulfates due to the strong acidity and oxidation potential of 98% H_2SO_4. The preparation of **5** needed the handling and the extensive employment of CH_3I and of hazardous reagent NaH. Moreover, the yield is only 68%. The Negishi coupling of **5** and **6** with use of stoichiometric amounts of zincate derivative of **5** can result in a number of processing problems (particularly upon scale-up). In addition, the reported chromatographic purification procedure of compound **7** is unsuitable for the pilot-plant scale-up with its poor solubility in most organic solvents at room temperature.

A patent report[6] has described preparations of **5** and **7** from the commercially available 4-bromoanisole and methyl 6-(4-methoxyphenyl)-2-naphthoate by Friedel–Crafts alkylation with 1-acetoxyadamantane, respectively. Although 4-bromoanisole and methyl 6-(4-methoxyphenyl)-2-naphthoate can be considered as the potential raw materials of **1**, the yields (69% for **5** and 68% for **7**) of Friedel–Crafts alkylation were unsatisfactory because the activities of their anisole structures were inferior to those of the phenol **3**. These would directly result in the decline of the overall yield. Accordingly, these two approaches were not adopted. Therefore, a practical synthesis, using a suitable procedure, was needed for **1**.

To overcome the drawbacks of 98% H_2SO_4, an improved Friedel–Crafts alkylation reaction[6,7] was adopted (Scheme

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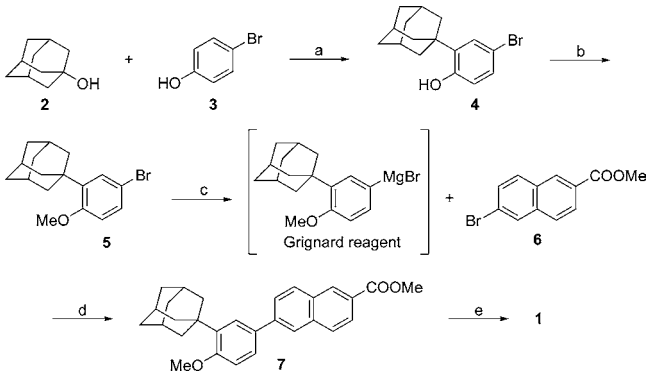
Scheme 1. **Synthesis of adapalene (1)**[a]



[a] Reagents and conditions: (a) AcOH/H_2SO_4 (5:1,v/v), rt, 2 days (quantitative yield); (b) dimethyl sulfate, K_2CO_3, acetone, reflux, 8 h (95% yield); (c) Mg/THF, 40 °C, 1 h; (d) $PdCl_2(PPh_3)_2$ (2% mol), $ZnCl_2$ (5% mol), 55 °C, 45 min (86% yield); (e) (i) NaOH, MeOH, reflux, 8 h; (ii) aqueous HCl, (85% yield).

1). Compound **4** was obtained from **2** and **3** by the catalysis of the mixture of H_2SO_4 and AcOH. The dimethyl sulfate−K_2CO_3 method,[8] a cheaper and more efficient method for methylation, was sought to substitute for the CH_3I−NaH method. We also employed a recently reported novel Pd−Zn double metal catalyzed coupling[9] to avoid the preparation of stoichiometric amounts of zincate derivative. The suitable purification process of **7** has also been sought. This paper describes the improvements that were necessary to achieve a practical pilot-plant synthesis that could be scaled up for the commercial manufacture of **1**.

Results and Discussion

As mentioned above, we first examined the Friedel−Crafts reaction of **2** and **3**. The original Friedel−Crafts reaction of **2** and **3** was carried out with 98% H_2SO_4 in CH_2Cl_2.[5] However, amounts of phenyl sulfates were obtained as the major byproducts in ∼20% yield. The color of the product remained yellow after recrystallization in isooctane due to the oxidation of phenols. To prevent the occurrence of these unwanted reactions, we first opted to reduce the oxidation of phenols by cooling the reaction temperature to 0 °C. However, the result was unsatisfactory, and significant amounts of phenyl sulfates were still obtained. Previously, a process patent[6] reported the synthesis of **4** from **3** and 1-acetoxyadamantane in good yield and high purity. The 1-acetoxyadamantane was obtained by esterification of **2** with Ac_2O in the presence of 98% H_2SO_4. It is uneconomical for commercial manufacturing because of the number of the steps involved. On the basis of the literature,[6,7] we then adopted AcOH to dilute 98% H_2SO_4 so as to weaken its strong acidity. As the literature[6] mentioned, 1-acetoxyadamantane was considered as the active intermediate of this improved process. At first, the intermediate 1-acetoxyadamantane was formed by the condensation of **2** and AcOH in the presence of 98% H_2SO_4. Then, 1-acetoxyadamantane was directly reacted with **3** to give compound **4** in the presence of 98% H_2SO_4. This improved process has the major advantage of keeping the formation of byproducts to a minimum and even eliminating them entirely. By adjusting the AcOH to 98% H_2SO_4 ratio, we found out that the yield was almost 100% when the reaction was carried out with AcOH/98% H_2SO_4 (5/1, v/v) as the catalyst in CH_2Cl_2 at ambient temperature for 2 days. Neutralizing with sodium bicarbonate and washing with water removed the waste acids. Compound **4** was obtained as a white crystal and in high purity (99%) and quantitative yield (Lit.:[5] 86%) after recrystallization in isooctane.

In the previous process,[5] the CH_3I−NaH method was used in the methylation of **4**, and **5** was obtained in only 68% yield. We then decided to adopt a more efficient method to enhance the yield of **5**. After investigation of several methods for the methylation, the method of dimethyl sulfate−K_2CO_3 in acetone[8] was found to give the best result. At first, large excesses of dimethyl sulfate (3−5 equiv) and K_2CO_3 (7−9 equiv) were used to enhance the yield of methylation. The highest yield was 96%. However, it was discovered that excessive amounts of these two were fully unnecessary. In fact, we have observed that the yield of methylation was already 92% above when the dosage of dimethyl sulfate was ∼1 equiv and the dosage of K_2CO_3 was 2−4 equiv. Under optimal conditions, the following methylation was accomplished by reflux of an acetone solution of **4**, 1.05 equiv of dimethyl sulfate, and 3 equiv of K_2CO_3 for 8 h. No traces of autocondensation products of acetone were observed (HPLC analysis). Aqueous NaOH (5% solution in water) was used to treat the residual dimethyl sulfate. Ethyl acetate was used for the extractive workup. After workup, white crystalline **5** was obtained in good yield (95%) and purity (99.5%) by simple concentration of the organic solution and recrystallization in ethyl acetate. The recycled acetone could subsequently be used again without further purification in a scale-up process.

The original synthesis of **7** utilized a nickel-catalyzed Negishi cross-coupling.[5] The preparation and use of stoichiometric amounts of ArZnBr, however, resulted in a number of processing issues. Formation of the zincate of **5** via transmetalation of the corresponding Grignard reagent with $ZnCl_2$ usually produces a thick suspension of ArZnBr and $MgCl_2$, which is difficult to stir or pump unless substantially diluted. The handling of large amounts of extremely hygroscopic $ZnCl_2$ can also prove very difficult when operating on increased scale. To overcome these disadvantages, a recently reported method[9] was adopted to achieve the synthesis of **7** directly from the Grignard reagent and **6** by employing $ZnCl_2$ in catalytic quantities (Scheme 1). Accordingly, the reaction was carried out by the addition of Grignard reagent of **5** to a solution of **6**, $PdCl_2(PPh_3)_2$ (2% mol), and $ZnCl_2$ (5% mol) in THF at 55 °C, followed by stirring for 30 min. After evaporation of THF and addition of aqueous HCl (5% solution in water), the suspension was washed thoroughly with water. After washing, crude product **7** was collected by suction filtration. This procedure not only avoids the preparation of stoichiometric amounts of ArZnBr but is also favorable in regards to the removal of residual metals. However, we observed that compound **7** was not soluble in most organic solvents at room temperature and

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would precipitate during the workup, making separation from the catalysts and impurities extremely difficult. Thus, the reported chromatographic purification[5] is not workable on an industrial scale. It was possible to recrystallize the crude product to high purity. Due to the poor solubility of **7** in most solvents at room temperature, several solvents with high boiling points were investigated for the recrystallization of **7**, and toluene was found to be most suitable.

As was mentioned previously, the residual metals were problematic due to the poor physical characteristics of the solid. Although **7** was not the final drug substance, it was decided to control the heavy metal content at this point since we wished to avoid extensive purification in the last step, if possible. To ensure low heavy metal content (<20 ppm in the final drug substance), the following strategy was adopted. After the filtration of the water solution of **7**, the residue was washed with a solution of EDTA-disodium salt dihydrate (0.5% in water) so as to remove the last traces of metals, and the suspension was filtered. The isolated product was further purified by crystallization twice in toluene. The desired product **7** was obtained in good yield (86%) and high purity (98.8%). The heavy metal content was under 20 ppm. However, the heavy metal content was 300 ppm above before the washing of the crude product **7** with a solution of EDTA-disodium salt dihydrate.

According to the method of the literature,[5] adapalene **1** was obtained in 85% yield and 99% purity by the saponification of **7**. The heavy metal content was within acceptable limits (<20 ppm) without further purification.

Conclusions

In summary, a highly efficient four-step synthesis of the retinoid adapalene **1** was developed and demonstrated on a commercial scale in 68% overall yield. Each step does not use chromatographic purification. The most important features are the following: (1) the use of AcOH/98% H_2SO_4 to overcome the drawbacks of 98% H_2SO_4 to afford **4** in quantitative yield; (2) the highly efficient dimethyl sulfate−K_2CO_3 method to enhance the yield of methylation to 95%; (3) the novel Pd−Zn double metal catalyzed coupling to avoid the preparation of stoichiometric amounts of ArZnBr and give **7** in good yield; (4) the use of EDTA-disodium salt dihydrate to ensure the metal content within acceptable limits; (5) the use of toluene to simplify the original chromatographic purification to recrystallization and give **7** in high purity. These make this process a very practical alternative to the existing methods. It can be easily adapted to a multikilogram scale.

Experimental Section

Materials and Instruments. All solvents and reagents were purchased from the suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 at room temperature on a Varian INOVA-400 spectrometer (400 MHz ^{1}H). The chemical-shift scale is based on internal TMS. Melting points were measured on a RY-1 melting-point apparatus, and are uncorrected. TLC analyses were performed on Merck silica gel 60 F_{254} plates.

HPLC analyses were performed on an Angilent Series 1100 HPLC system according to the following conditions: column, Zorbax Eclipse XDB-C_{18} (125 mm × 4.0 mm, 5 μm); eluent, 900:100:1 methanol/water/phosphoric acid; flow rate 1.0 mL/min; temperature, 30 °C; wavelength 254 nm.

2-(1-Adamantyl)-4-bromophenol (4). 3 (1730 g, 10 mol) and **2** (1520 g, 10 mol) were dissolved in CH_2Cl_2 (5 L). To the resulting solution was slowly added the mixture of 98% H_2SO_4 (0.55 L) and AcOH (2.75 L). The resulting mixture was stirred for 2 days at room temperature, poured into water (2.5 L), neutralized to pH 6 with saturated sodium bicarbonate solution, extracted with CH_2Cl_2 (3 × 5 L). The organic phase was washed with water (2 × 10 L), dried over anhydrous sodium sulfate, filtrated through Celite, and evaporated in vacuo. The recycled CH_2Cl_2 could subsequently be used again after anhydration with anhydrous calcium chloride. After recrystallization in isooctane (3078 g/35 L), **4** was obtained as a pure white (99% HPLC) solid (3050 g, 99%), mp 147−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1 H, d, J = 2.0 Hz, 3-phenyl H), 7.14 (1 H, dd, J = 8.4 Hz, J = 2.0 Hz, 5-phenyl H), 6.52 (1 H, d, J = 8.4 Hz, 6-phenyl H), 4.80 (1 H, s, -OH), 2.06 (9 H, s, H on 1-adamantyl), 1.76 (6 H, s, H on 1-adamantyl).

2-(1-Adamatyl)-4-bromoanisole (5). Dimethyl sulfate (100 mL, 1.05 mol) was added to a suspension of **4** (307 g, 1 mol) and anhydrous potassium carbonate (415 g, 3 mol) in dry acetone (9 L). The mixture was refluxed for 8 h. After cooling, the solid was removed by suction filtration. The solvent was recycled in vacuo, and the residue was washed with 5% aqueous sodium hydroxide (5 L). Then the mixture was extracted with ethyl ether (3 × 2.5 L). The organic layer was successively washed with water (3 × 2.5 L) and brine (2.5 L), dried with anhydrous sodium sulfate, filtrated through Celite, and concentrated in vacuo. The resultant (314 g) was recrystallized from ethyl acetate (1.5 L) to give the pure (99.5% HPLC) white solid **5** (305 g, 95%), mp 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1 H, d, J = 2.0 Hz, 3-phenyl H), 7.25 (1 H, dd, J = 8.4 Hz, J = 2.0 Hz, 5-phenyl H), 6.72 (1 H, d, J = 8.4 Hz, 6-phenyl H), 3.80 (3 H, s, -OCH_3), 2.05 (9 H, s, H on 1-adamantyl), 1.76 (6 H, s, H on 1-adamantyl).

Methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate (7). A solution of **5** (965 g, 3 mol) in THF (5 L) was added under nitrogen to a stirred mixture of Mg (96 g, 4 mol), cut in small pieces, and a small crystal of iodine in THF (0.5 L). The reaction mixture was stirred at 40 °C for 1 h. The solution of Grignard reagent was then added directly to a stirred solution of **6** (660 g, 2.5 mol), $PdCl_2(PPh_3)_2$ (36 g, 0.05 mol) and fused $ZnCl_2$ (17 g, 0.125 mol) in THF (5 L) at 55 °C over the course of 30 min. After the addition of the Grignard reagent was complete, the reaction was stirred at 55 °C for an additional 15 min. After evaporation of THF (8 L) under reduced pressure, the reaction was quenched in 5% aqueous HCl (2 L). The suspension was filtrated through Celite. The residue was thoroughly washed with water (3 × 5 L) and a solution of EDTA-disodium salt dihydrate (0.5% in water, 3 × 5 L) by using a stirrer in a big beaker, and purified by crystallization twice in toluene (1100 g/10 L/time)

to give pure (98.8% HPLC) **7** (915 g, 86%), mp 221−222 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (6 H, s, H on 1-adamantyl), 2.10 (3 H, s, H on 1-adamantyl), 2.18 (6 H, s, H on 1-adamantyl), 3.91 (3 H, s, H on $ArOCH_3$), 3.99 (3 H, s, H on $COOCH_3$), 7.00 (1 H, d, J = 8.4 Hz, 5-phenyl H), 7.55 (1 H, dd, J = 8.4 Hz, J = 2.0 Hz, 6-phenyl H), 7.60 (1 H, d, J = 2.0 Hz, 2-phenyl H), 7.80 (1 H, d, J = 8.8 Hz, 7-naphthyl H), 7.92 (1 H, d, J = 8.8 Hz, 4-naphthyl H), 7.99 (1 H, d, J = 8.8 Hz, 8-naphthyl H), 8.01 (1 H, s, 5-naphthyl H), 8.08 (1 H, d, J = 8.8 Hz, 3-naphthyl H), 8.62 (1 H, s, 1-naphthyl H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.07, 37.10, 37.18, 40.56, 52.23, 55.16, 112.05, 124.73, 125.55, 125.72, 125.98, 126.48, 126.87, 128.22, 129.70, 130.83, 131.21, 132.52, 135.92, 138.97, 141.37, 158.89, 167.35.

6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphthoic Acid (Adapalene, 1). Compound **7** (213 g, 0.5 mol) was treated with 2 N NaOH solution (8 L) in methanol under reflux for 8 h. After evaporation of methanol (7 L) and addition of water (1.5 L), the mixture was acidified until pH 1 with 6 N HCl and filtrated through Celite. The residue was washed with water (3 × 5 L), and recrystallized twice in THF (194 g/2 L/time) to give pure (99% HPLC) **1** (177 g, 85%), mp 320−322 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77 (6 H, s, H on 1-adamantyl), 2.07 (3 H, s, H on 1-adamantyl), 2.14 (6 H, s, H on 1-adamantyl), 3.87 (3 H, s, H on $ArOCH_3$), 7.12 (1 H, d, J = 8.4 Hz, 5-phenyl H), 7.58 (1 H, d, J = 2.0 Hz, 2-phenyl H), 7.65 (1 H, dd, J = 8.4 Hz, J = 2.0 Hz, 6-phenyl H), 7.89 (1 H, d, J = 8.8 Hz, 7-naphthyl H), 7.98 (1 H, d, J = 8.8 Hz, 4-naphthyl H), 8.08 (1 H, d, J = 8.8 Hz, 8-naphthyl H), 8.15 (1 H, d, J = 8.8 Hz, 3-naphthyl H), 8.22 (1 H, s, 5-naphthyl H), 8.60 (1 H, s, 1-naphthyl H), 13.05 (1 H, s, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.32, 36.47, 40.09, 55.28, 112.68, 123.99, 124.99, 125.38, 125.68, 125.85, 127.55, 128.25, 129.72, 130.13, 130.83, 131.46, 135.38, 138.00, 140.13, 158.53, 167.34.

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