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**Research Article**

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# Content variation of disubstituted adamantane in a synthetic procedure to adapalene

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**ABSTRACT**

*Content variation of disubstituted adamatane was reported. Disubstituted adamatane was formed through an unusual Friedel-Crafts reaction of adamantanol with 4-bromoanisole. The structure of it was identified by means of an X-ray crystal structure determination.*

**Keywords:** Adapalene, disubstituted adamantane, friedel-crafts alkylation.

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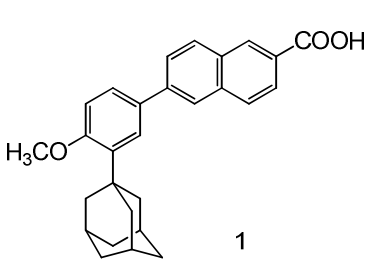
## INTRODUCTION

Retinoids, natural and synthetic analogues of retinoic acid, an active metabolite of vitamin A, play a major role in controlling cell proliferation, differentiation and morphogenesis [1-2]. These properties offer this class of substances a high potential for their chemopreventive and therapeutic application in the areas of oncology and dermatology [3-5]. Some synthetic retinoids, such as **compound 1** (adapalene) have been proven to be clinically useful in the treatment of acne and psoriasis [6-9] and since 1996 it has been used as a topical drug under the trade name of Differin [10-12].

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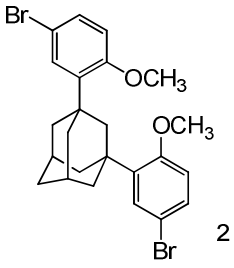


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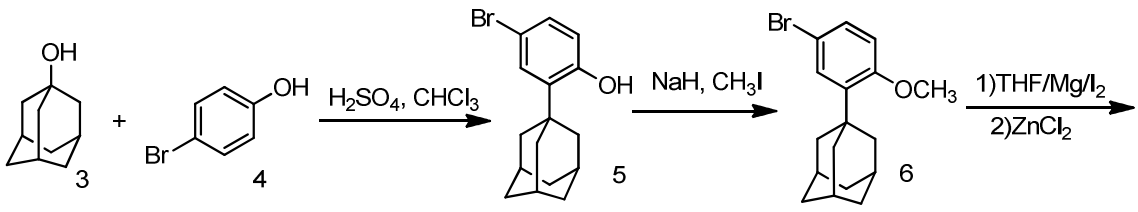
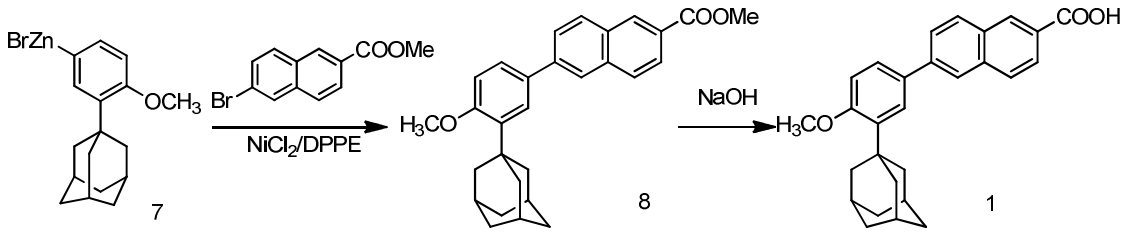
**Recently, we were involved in the optimization of the synthesis sequence of adapalene, according to the procedures (Scheme 1) [13-14].**

**Scheme 1**




3 4 5 6




The known synthetic methods capable of producing **compound 1** employ 1-adamantanol as the starting material. It generates monosubstituted adamantane (**5**) as main product through Friedel-Crafts Alkylation. We found this process also generated disubstituted adamantine (**9**) as by-product. Synthesis of disubstituted adamantane is outlined in **Scheme 2**. First, a Friedel-Crafts alkylation with 1-adamantanol (**3)** and 4-bromophenol (**4)** led to **compounds 5** and **9**. Then, **compounds 5** and **9** were converted into **compounds 6** and **2** through methylation by iodomethane or dimethyl sulfate. Finally, **compound 2** was isolated and characterized by NMR and X-ray crystal structure determination (**Figure 1**). After fine-tuning the process, the disubstitute adamantane become the major product.

**Scheme 2**

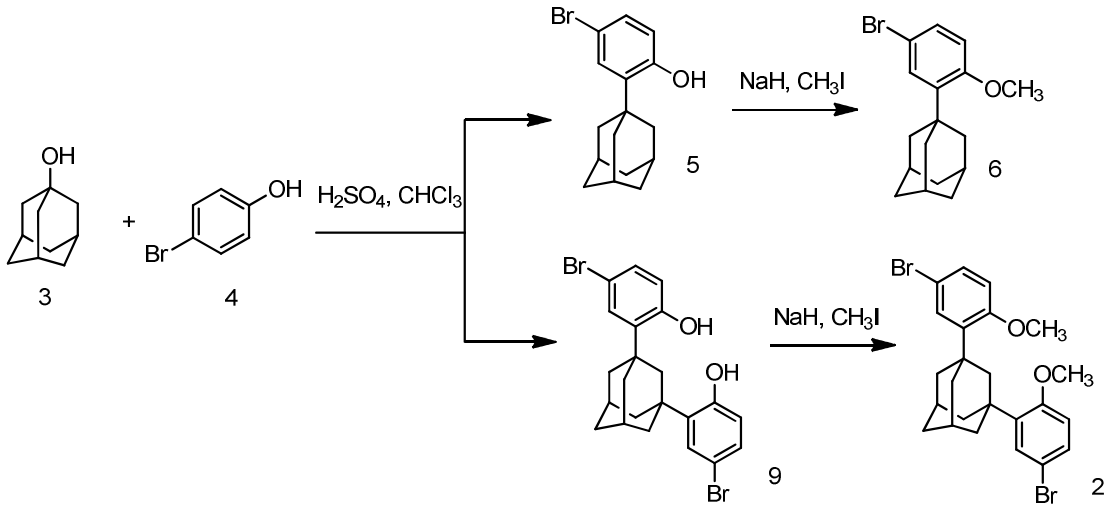
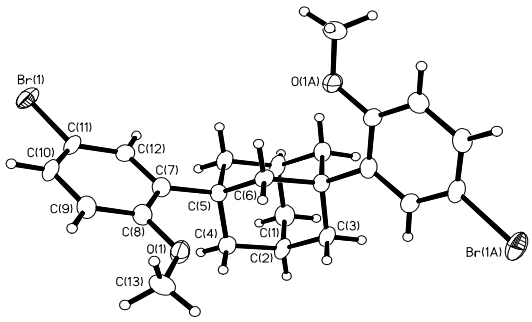



**Figure 1 Perspective view of the X-ray structure of compound 2**




We were very surprised by the results and a search in the literatures showed that **compound 2** has been isolated as an unexpected impurity by E. Brenna in 2007 [15]. But the percentage of **compound 2** versus **compound 6** in the crude product and the influence factors of their content variations had not been reported, which were strictly related to the purity of **compound 6**. In this paper, the content variations of **compound 2** in different conditions and the suggested mechanism had been discussed.

## EXPERIMENTAL SECTION

2.1 X-ray Crystallographic Analysis

A crystal of the **compound 2** (colorless, plate-shaped, size 0.20 x 0.10 x 0.06 mm) was mounted on a glass fiber

with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphite-monochromated Mo K radiation (λ = 0.71073 Å), operating at 50 kV and 30 mA over 2 ranges of 3.90 ~ 49.96º. No significant decay was observed during the data collection. Data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package [16].

2.2 $^1$HNMR spectroscopy

$^1$HNMR spectra were acquired on a Bruker DMX 300 instrument at 305 K. The hydrogen chemical shifts is referred to the internal tetramethylsilane(TMS). The coupling constants are expressed in Hertz.

2.3 HPLC

HPLC analyses were performed on an Agilent 1100 liquid chromatograph instrument, using a Agilent C18 column (4.6 mm ×150 mm).

2.4 Chemistry

*A typical synthetic procedure of **compound 9**:*

**3** (3.05 g, 0.020 mol) and **4** (3.46 g, 0.020 mol) were dissolved in $CH_2Cl_2$ (18 mL). To the resulting solution was slowly added the concentrated $H_2SO_4$ (1.07 mL 0.020 mol) with internal temperature at around 25-30 °C. The resulting mixture was stirred at around 30 °C for 3 hours, poured into water (100 ml), neutralized to pH 6 with saturated sodium carbonate solution, extracted with $CH_2Cl_2$ (3×100 mL). The organic phase was washed with water (2 x 100 ml), dried over anhydrous sodium sulfate, filtered. HPLC showed the solution contained about 30% **compound 9**, 70% **compound 5**. The solution was evaporated to dryness. The solid was purified by flash chromatography, eluted with the mixture of $CH_2Cl_2$ and methanol (95 : 5) to give 3.62 g pure light yellow solid **compound 9** (99.5 % HPLC). Yield: 37.5%. The compound also can be obtained by recrystalling the crude solid in chloroform and isooctane. The recovery was lower. $^1$H NMR (CDCl3, 400 MHz): 7.33 (s, 1H), 7.18 (d, 1H), 6.55 (d, 1H), 4.81 (s, 1H), 2.42 (s, 1H), 2.30 (s, 1H), 2.19 (d, 2H), 2.05 (d, 2H), 1.79 (s, 1H).

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*A typical synthetic procedure of **compound 2**:*

Dimethyl sulfate (2.0 mL, 0.021 mol) was added to a suspension of **compound 9** (4.78 g, 0.010 mol) and anhydrous potassium carbonate (6.61 g, 0.063 mol) in dry acetone (100 mL). The mixture was reflux overnight, poured into water (200 ml), extracted with $CH_2Cl_2$ (2 × 100 mL). The organic layer was washed with 1 M NaOH (2×100 mL) and brine (2×100 mL), dried over anhydrous sodium sulfate, filtered. To the filtrate was added heptane (200 mL) and concentrated. Off-white solid came out during concentration. The solid was filtered, washed with heptane to give 4.35 g **compound 10** (98.5 % HPLC). Yield: 86%. $^1$H NMR (DMSO-d6, 400 MHz): 7.35 (d, 1H), 7.20 (s, 1H), 6.95 (d, 1H), 3.79 (s, 3H), 2.27 (s, 1H), 2.20 (s, 1H), 2.15 (d, 2H), 1.87 (d, 2H), 1.70 (s, 1H).

## RESULTS AND DISCUSSION

The formation of **compound 9** was not reported in the original synthesis of **compound 1 [**13-14]. It was possibly because **compound 9** and **5** have similar polarity and close NMR spectrum. By following the exact procedure in the reference **[**13], about 5 % **compound 9** was detected in the reaction by carefully developed HPLC and TLC methods. The recrystallization of the crude in isooctane cannot remove **compound 9**. On the contrary the solid came out from the solution enriched **compound 9** due to its poorer solubility in isooctane. The percentage of **compound 9** versus **compound 5** in the crude product was increased with increased reaction temperature (5, 10, 20, 30 °C) while using either $CH_2Cl_2$ or $CHCl_3$ as solvents. But when using chloroform as solvent the percentage of **compound 9** versus **compound 5** was decreased with elevated addition temperature (40, 50, 60 °C) of sulfuric acid (**Table 1**).

**Table 1**

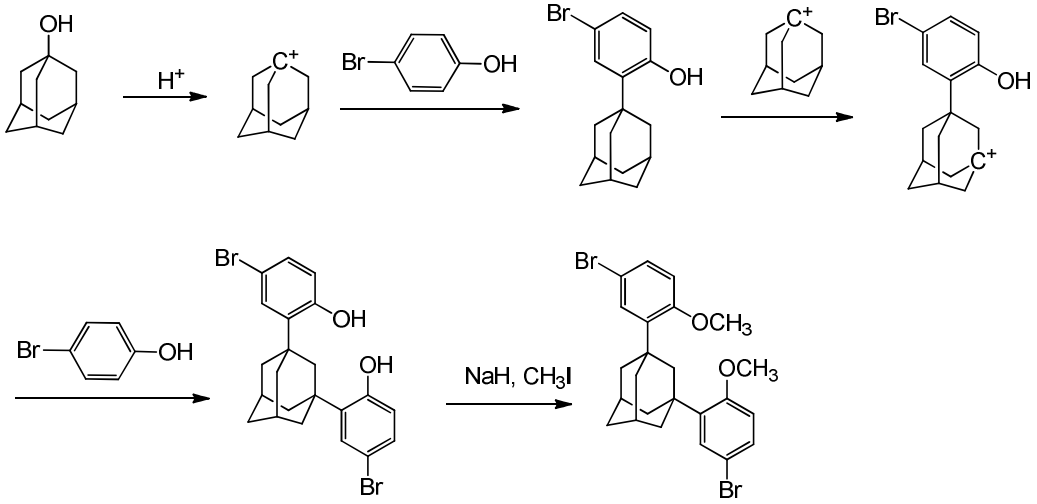
| Substrate: **Comp. 3** versus **Comp. 4** | Temperature (°C) | Solvent | Yield of Comp. **9** (%) | Yield of **Comp. 5** (%) | Resultant: **Comp. 9** versus **Comp. 5** |
|---|---|---|---|---|---|
| 1:1 | 5 | $CH_2Cl_2$ | 5.4 | 57.9 | 0.093 |
| 1:1 | 10 | $CH_2Cl_2$ | 18.8 | 31.2 | 0.60 |
| 1:1 | 20 | $CH_2Cl_2$ | 22.7 | 23.4 | 0.97 |
| 1:1 | 30 | $CH_2Cl_2$ | 32.2 | 4.3 | 7.49 |
| 1:1 | 40 | $CHCl_3$ | 25.6 | 17.6 | 1.45 |
| 1:1 | 50 | $CHCl_3$ | 20.2 | 18.4 | 1.10 |
| 1:1 | 60 | $CHCl_3$ | 17.9 | 19.6 | 0.91 |

Liu et al reported an improved method for the synthesis of adapalene **[**14]. They reported quantitative yield for synthesis of **compound 5** by adding solution of concentrated sulfuric acid in glacial acetic acid. We found that this method also generated **compound 9**. At 5 °C, the crude compound continued about 3 % **compound 9**. It was

increased to about 5 % at 25 °C.

Mechanism for the formation of **compound 9** is not difficult to understand according to the early studies of solvolysis inductive, hyperconjugative effects for 1-adamantyl cation by Sunko and Grob [17-19]. Adamantanol forms stable adamantyl cation (**scheme-3**) and reacts with 4-bromophenol to give mono-substituted **compound 5** (**scheme-3**). This compound is the major product at low temperature. Due to the inductive effect of phenol, **compound 5** can regain the charge from another adamantyl cation. This cation is more stable than the original adamantyl cation. This new cation can further react with 4-bromophenol and forms disubstituted **compound 9**. Due to its poor solubility, **compound 9** precipitated out from reaction. No trisunstituted or tetrasubstituted compound was observed. This mechanism was supported by the observation of adamantane in the reaction detected by GC and relatively low yield. The yield of disubstituted compound was increased between reaction temperature of 5 to 30 °C. This may attribute to the increased exchange rate of **product 5** and adamantyl cation. But the yield started to decrease with even higher temperature may indicate faster reaction rate of adamantyl cation and 4-bromophenol versus cation exchange rate.

**Scheme 3**




## CONCLUSION

**Compound 9** was formed during Friedel-Crafts step employed to prepare intermediate **5**. The structure of its methylated derivative, **compound 2**, was identified by means of an X-ray crystal structure determination. The percentage of **compound 9** versus **compound 5** in the crude product and the influence factors of their content variations had been reported, which were strictly related to the purity of **compound 5**. Furthermore, the suggested mechanism had been discussed.

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[16] Crystal data for 2 at 180 K. C24H26Br2O2, M 506.27. Monoclinic, space group C2, a 21.157(4), b 7.4207(14), c 6.6781(13) Å, β=99.052(2)˚, V 1035.4(3)Å3, F(000) 512, Dc(Z=2) 1.624gcm$^{-1}$, μ(Mo Kα) 0.95 cm$^{-1}$, crystal dimension 0.20x0.10x0.06 mm, 2θmax 50˚, wR(all 4823 data) 0.0832, conventional R (1761 data with I>2σ(I)) 0.0409. Complete crystallographic data, as a CIF file, has been deposited with the Cambridge Crystallographic Data Centre (CCDC No.638605 ). Copies can be obtained free of charge from: The director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk)
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