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A SHORT AND EFFICIENT SYNTHESIS OF 4-[2,2-DIMETHYL-4(TOL-4-YL)BENZOCHROM-3-EN-7-YL]BENZOIC ACID - A POTENT RETINOIC ACID RECEPTOR ANTAGONIST

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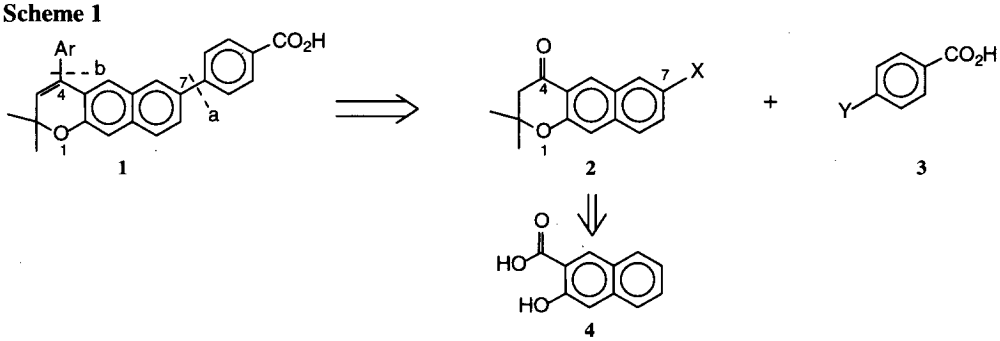
Abstract: An efficient synthesis of a potent RAR antagonist is described starting from disubstituted β-naphthol. The functional groups on 2 and 3 positions of the β-naphthol **5** were elaborated into benzochromanone **8**. The title compound was prepared by Suzuki coupling of the left and right hand pieces. © 1999 Elsevier Science Ltd. All rights reserved.

Retinoids play a crucial role in epithelial cell growth and differentiation by regulating gene transcription through nuclear retinoic acid receptors (RARs). As a consequence, retinoic acid and some synthetic analogs (e.g. isotretinoin, etretinate, adapalene, tazarotene) are used for the treatment of dermatological diseases.[1] In addition, synthetic and natural retinoids are being evaluated for their possible beneficial effects in several cancers.[2] However, these compounds have undesirable side effects associated with hypervitaminosis A syndrome which limit their therapeutic utility. One way to obviate some of these toxicities is to use RAR antagonists on non target tissues in conjunction with the retinoid agonists.

Recently, we disclosed the syntheses of a series of tricyclic RAR antagonists.[3] The syntheses were based on a strategy which was suitable only for small scale preparation. Here, we report an alternate synthesis of the benzochromene class of RAR antagonists which is amenable to large scale preparation.

Scheme 1



Retrosynthetic analysis of the target molecule **1** (Scheme 1) suggested dissection at bonds 'a' and 'b' giving rise to the benzochromanone derivative **2** and benzoic acid derivative **3**. The benzochromanone **2** can be obtained from commercially available β-naphthol derivative **4**. An appropriate functional group at the 7 position of compound **2** would serve as the reaction site for coupling with **3**.

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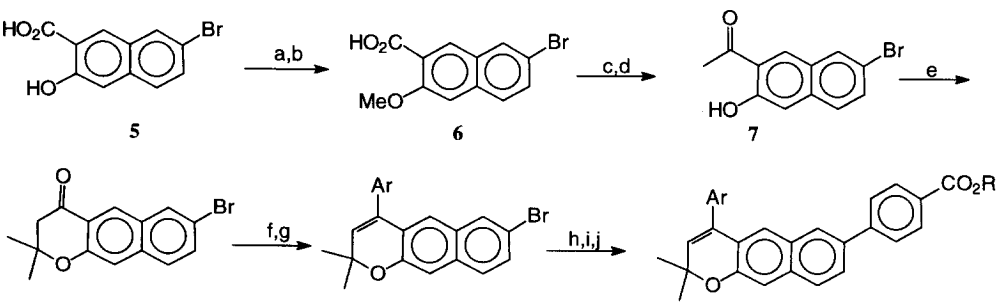
The synthesis was implemented as shown in Scheme 2. Compound **5**[4] was reacted with dimethylsulfate to give the dimethylated compound, which on alkaline hydrolysis gave **6**. Addition of methyllithium followed by demethylation with BBr_3 gave compound **7**. Condensation of **7** with acetone gave the required tricyclic ketone **8**. Addition of tolyl lithium to the ketone gave the tertiary alcohol, which was treated with pTSA to give the dehydrated compound **9**. Compound **9** was coupled with ethyl-4-iodo benzoate under Suzuki[5] coupling conditions. Thus bromine in **9** was converted to the corresponding boronic acid and reacted with ethyl-4-iodobenzoate in the presence of Pd(0) to give ester **10**. Alkaline hydrolysis then gave the target compound **1**. Some of the noteworthy points in this sequence are: overall yield of 7.5%; 10 step sequence with the products from the first four steps being purified by recrystallization; the Ar group may include any aryl or heteroaryl group.

Scheme 2



(a) Me_2SO_4, K_2CO_3, acetone, 70°C, 16h (b) KOH, H_20, MeOH, 80°C, 3h, 90% (2 steps) (c) MeLi in ether, THF, 20°C, 3h, 60% (d) BBr_3 - CH_2Cl_2, -78°C – 0°C, 2h, 95% (e) Acetone, Piperidiumtrifluoroacetate, benzene, 100°C, 48h, 40% (f) 4-Tolyl lithium, THF, -78°C – O°C, 2h, 50% (g) pTSA, MeOH, 20°C, 16h, 90% (h) *t*-BuLi, THF, -78°C – O°C, 2h, then $B(OMe)_3$, O°C, 1h (i) Ethyl-4-iodobenzoate, $Pd(PPh_3)_4$, K_2CO_3, Toluene, MeOH, 90°C, 16h, 75% (2 steps) (j) KOH, H_20, MeOH, 20°C, 16h, 90%.

In conclusion, we have synthesized the target molecule by a short and efficient synthetic sequence. This route is amenable to large scale preparation of this benzochromene class of retinoids.

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