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Design and synthesis of (*E*)-4-((3-ethyl-2,4,4-trimethylcyclohex-2-enylidene)methyl)benzoic acid

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ABSTRACT

(*E*)-4-((3-Ethyl-2,4,4-trimethylcyclohex-2-enylidene)methyl)benzoic acid, **6**, was synthesized in 87% starting from β-cyclocitral. The target compound **6** was synthesized starting from **1** via a Grignard reaction to form alcohol **2**. Compound **2** was converted to Wittig salt **3** by treatment with aldehyde **4** in butyllithium and hexane at −78 °C to form ester **5**. Ester **5** was saponified and, following acidification, acid **6** was isolated as white solid yield 87%.

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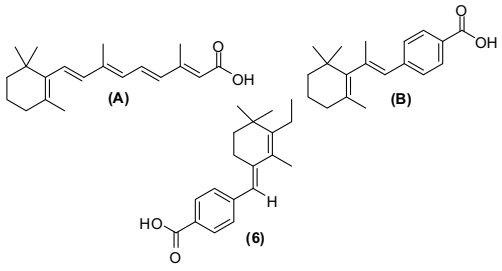
Our long-term goal is to develop novel diagnostic and therapeutic agents for retinoic acid receptors antagonist, agonist and related signaling pathways, and to identify new gene targets of these pathways. For this purpose, we have prepared a variety of retinoic acid analogues and evaluated their bio-activity using developing zebra fish embryos.

All-trans-retinoic acid (ATRA), the biologically most active metabolite of vitamin A, plays a major role in the regulation of gene expression, in cellular differentiation and proliferation of epithelial cells.[1] Differentiating agents redirect cells toward their normal phenotype and therefore may reverse or suppress evolving malignant lesions or prevent cancer; they represent an attractive target for medicinal intervention. ATRA is being used in differentiation therapy of cancer, in cancer chemoprevention, and for the treatment of dermatological diseases, including, acne, psoriasis, and ichthyosis.[2] Recently, ATRA has proven useful in cancer chemotherapy.[3] One of the most impressive effects of ATRA is on acute promyelocytic leukemia. Treatment of acute promyelocytic leukemia patients with high doses of ATRA resulted in complete remission.[4,5] In spite of these encouraging results, the effects of prolonged ATRA therapy on human cancers in the clinic have been disappointing, but treatment of dermatological diseases has been far more promising.

It has been suggested that the therapeutic effects of ATRA are undermined by its rapid in vivo metabolism and catabolism by cytochrome P450 enzymes.[6] An important consideration is that two cellular retinoic acid-binding proteins (referred to as CRABP-I and CRABP-II) are believed to be involved in the presentation of ATRA to metabolizing CYP enzymes and its channeling to the RAR, receptors.[7,8] One of the strategies for preventing in vivo catabolism of ATRA is to inhibit the P450 enzymes responsible for this process. This may yield effective agents for the chemoprevention and/or treatment of cancers and dermatological diseases.[9] Major emphasis has been given to liarozole, the most studied and first Retinoic Acid Metabolism Blocking Agents (RAMBAs) to undergo clinical investigation and different small molecules for example 4-azolyl retinoid, benzeneacetic acid derivatives, and 2,6-disubstituted naphthalenes.[10]

Though major emphasis has been given to RAMBAs, we envisioned the synthesis of analogues of ATRA (**A**) in Scheme 1 which entails changing the flexible alkene backbone to a more rigid



Scheme 1.

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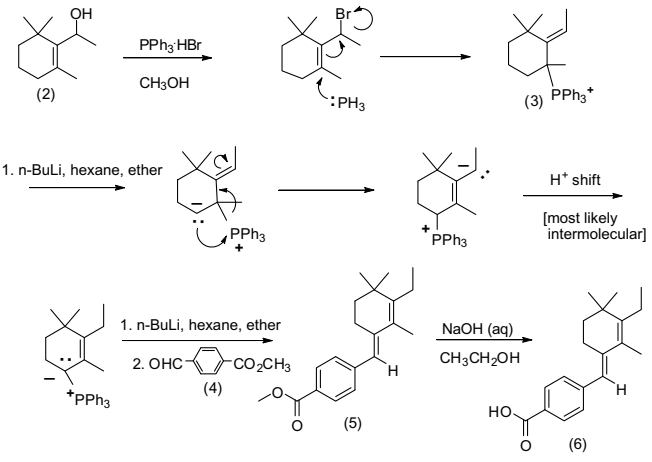
phenyl ring, **B** could act as RAMBA itself. During our investigation, we discovered an unusual reaction which produced **6**, in Scheme 1.

The proposed synthesis of **B** involved straightforward reactions but, unexpectedly, generated **6** rather than **B**. The structure of **6** was confirmed by the NMR (^{1}H, ^{13}C, NOE) experiments and HRMS. From ^{1}H NMR δ 2.19 (q, 2H) and ^{13}C δ 22.3 is the characteristic peak for methylene peak at 4-position of cyclohexene ring system. NOE experiment clearly indicates phenyl ring at trans position. Compound **6** (1H–1H NOes: 6.46 ppm→7.38 ppm-4%, 6.46 ppm→1.85 ppm-18%, 7.39 ppm→7.90 ppm-7%, 7.39 ppm >6.46 ppm-4%, 7.39 ppm → 2.55 ppm −1%.

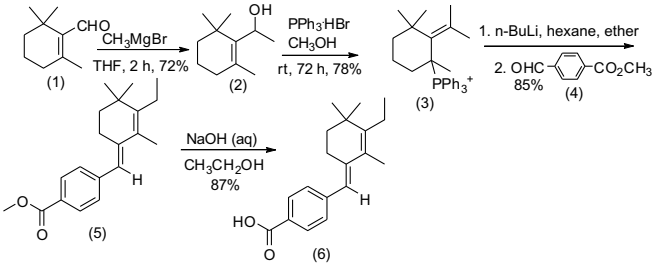
The synthesis of **6** involves the reaction with methyl magnesium bromide with β-cyclocitral in THF to give alcohol **2** as a yellow oil (Scheme 2).[11] The alcohol gave satisfactory spectral data and was directly converted to **3** by treatment with triphenylphosphine hydrobromide in methanol. Recrystallization of **3** from methanol/ether (1:6) gave a yellow crystalline solid.[12] Formation of the Wittig reagent from **3** in ether was accomplished with *n*-butyllithium in hexane at room temperature (dark-red color), then the Wittig reagent was treated with methyl 4-formylbenzoate **4** in ether at −78 °C for 10–15 min and then stirred at room temperature under a nitrogen atmosphere for 30 h. After work up, crude ester **5** was purified by flash column chromatography (hexane/ethyl acetate: 98/2) to give a brown oil in 85% yield.[13] The ester was saponified to generate a white solid which was filtered, washed with water, and dried. The product was recrystallized from hot ethanol and washed with dry hexane to give acid **6** as white crystals (87%) yield.[14] The structure was confirmed by ^{1}H, ^{13}C NMR and NOE experiment, HMBC, and HRMS.

Although a detailed study has not yet been completed, the formation of **6** could arise as outlined in the following scheme.



Compound **2** when treated with triphenyl phosphine hydrogen bromide in methanol, forms the expected allylic bromide. Nucleophilic attack of the triphenylphosphine at the β-carbon of the allylic bromide results in the formation of **3**. Addition of butyllithium results in deprotonation at the carbon adjacent to the phosphonium ion. An intermolecular, proton shift then generates the ylide that reacts in a Wittig reaction to generate the observed product, **5**. Saponification and acidification then generates **6**.

In summary, we report here the synthesis of a novel analogue of ATRA generated by replacing the acyclic alkene backbone with a phenyl ring. The biological activity of **6** and its derivatives is currently underway and will submitted for publication in the near future. The formation of **6** involved an unusual triphenylphospine substitution reaction which may comprise a new method for converting allylic tertiary alcohols to dienes. The generality of the new reaction is currently being investigated.



Scheme 2.

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Supplementary data

Supplementary data (^{1}H, ^{13}C NMR, NOE and HRMS) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.136.

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14. *A detailed experimental procedure follows: Compound* (**6**)—ester **5** (1.08 g, 3.61 mmol) was dissolved in ethanol (17 mL), while maintaining at a N_2 atmosphere. An aqueous solution of NaOH (0.83 g, 21 mmol in 36 mL H_2O) was added. The reaction mixture was heated at reflux under N_2 for 5 h during which, the mixture became a clear yellow solution. After cooling to near room temperature, the solution was acidified with concentrated aqueous HCl. A white solid formed and was filtered, washed with water. The solid was dried and recrystallized from hot ethanol. After washing with dry hexane, **6** was obtained as white crystals (0.89 g, 87%), mp 187 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.0–12.6 (br s, 1H), 7.90–7.82 (d, J = 8.0 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 6.47 (s, 1H), 2.55 (m, 2H), 2.19 (q, 2H), 1.86 (s, 3H), 1.44 (m, 2H), 1.05 (s, 6H) and 1.03 (t, *J* = 8 Hz, 3H) ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.1, 142.8, 141.2, 129.03, 127.8, 126.6, 120.5, 67.1, 38.1, 35.4, 27.3, 23.7, 22.3 and 14.6. HR FT-ICR MS: calcd for $C_{19}H_{24}O_2$ ([M+H]$^+$) 285.1848; found: 285.1856.