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A new one-pot synthesis of *all E*-retinoic acid via a new enaminodiester synthon

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Abstract—A 'one-pot' synthesis of *all E*-retinoic acid from a new enaminodiester was described. The enaminodiester was easily produced from methyl isopropylidenemalonate and DMF-DMA.

All E-retinoic acid (RA) and some of its isomers inhibit some cancer cell growth in culture and in animal models.[1] *All E*-RA and its 9*Z* and 13*Z* isomers have some efficacy against certain human leukemia and several skin cancers.[2] Retinoids have been shown to affect multiple signal transduction pathways, including regulation and differentiation and the best effects were achieved with retinol, retinaldehyde, 13*Z*-RA and *all E*-RA.[3,4] It has been shown that retinoic acid receptors (RARs) have a high affinity for both RA-retinoic acid and its 9*Z* isomer, the latter was the natural ligand of the retinoid X receptors (5RXRs).[5] It was found recently that the retinoic acid-induced apoptosis in leukemia cells was mediated by the paracrine action of tumor-selective death ligand trail (tumor necrosis factor-related apoptosis-inducing ligand).[6]

The traditional and industrial synthetic routes of retinoids have been so far based on three procedures: Wittig[7] (BASF), Julia[8] (Aventis: ex. Rhône-Poulenc) and Isler[9] (Hoffmann-La Roche). All make use of β-ionone as the starting material. More recently, new stereoselective approaches have been exhaustively explored using palladium-catalyzed cross-coupling reactions such as: the Negishi reaction,[10] the Suzuki coupling,[11] the Stille reaction,[12] the Heck reaction,[13] and the Sonogashira coupling.[14]

In order to obtain stereoselective syntheses, these strategies implied the use of polyethylenic partners with the required stereochemistry, which increased the purification problems and/or the number of steps.

With a new concise route in mind for the synthesis of *all E* retinoic acid,[15] we recently synthesized a new C-6 enaminodiester **1**, which could be easily obtained and directly condensed with β-ionone. Thus, dimethyl isopropylidenemalonate and dimethylformamide dimethylacetal (DMF-DMA) directly provided this compound, in nearly quantitative yield (Dean–Stark, 90°C, 18 h then reflux, 2 h) (Scheme 1).

The 'one-pot' procedure is illustrated in Scheme 2. The lithium enolate of β-ionone was reacted with enaminodiester **1** to give the ketoester **3** via an intermediate **2** which, by heating, underwent elimination of dimethylamine (LDA, DME, −25°C, then β-ionone in DME, 20 min, −25°C then **1**, DME, −25°C to rt then reflux, 1 h). Addition of the methyl Grignard reagent led to compound **4** (MeMgBr, THF, −20°C then rt) which, after saponification and further decarboxylation ((1) KOH, 5 equiv., EtOH, H_2O, 40°C, 45 min, (2) HCl 2 M), afforded regioselectively the *all E* retinoic acid **5** (*all E*/13*Z*: 87/13, 70%). The physicochemical properties were identical to those of a standard purchased from Sigma (Scheme 2).

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Scheme 1.

Keywords: *all E* retinoic acid; enaminodiester.
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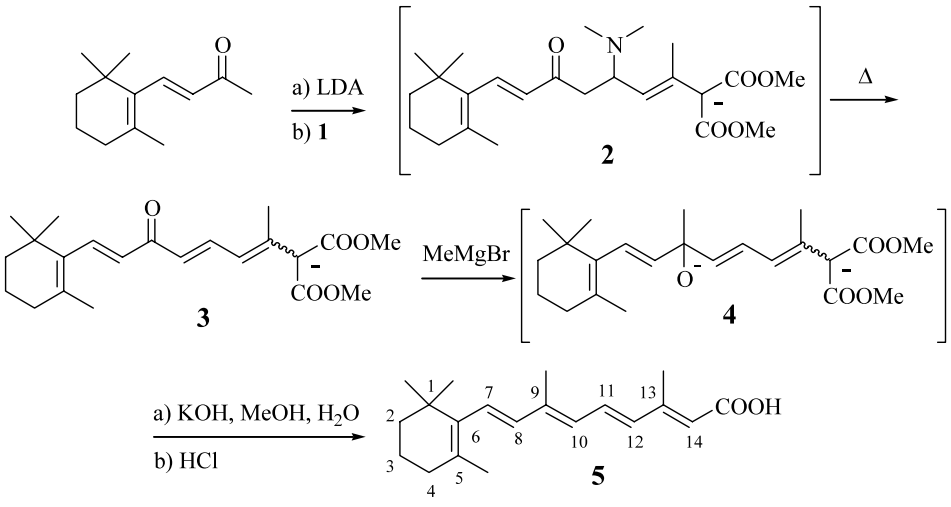

Scheme 2.

The one-pot route was needed from both economical and ecological points of view. This process was viable because the reaction conditions of the successive steps were compatible: thus the Grignard reagent could react with the ketone because the negative charge of **3** was stabilized by the two esters at the C_{14} position. After hydrolysis of the esters and acidification, the malonic acid obtained spontaneously decarboxylates, regioselectively to *all E* retinoic acid. This synthesis was concluded in 1 day with more than 70% yield from β-ionone on a 100 g scale.[16]

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16. **1**. Beige crystals, mp = 113°C. IR (KBr): 1716; 1686; 1619; 1539; 1433; 1399; 1330; 1191; 1115; 1068; 995; 959. ^{1}H NMR ($CDCl_3$): 6.93 (d, 1H, J = 13.2, H_4); 6.07 (d, 1H, J = 13.2, H_5); 3.71 (s, 6H, $COOCH_3$); 2.91 (s, 6H, N-$(CH_3)_2$); 2.10 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$) (CO): 167.3 (CH); 148.8; 97.4 (CH_3); 52.0; 51.9; 41.0; 16.7.