New, Regioselective, One-Pot Synthesis of (all-*E*)-Retinoic Acid and Analogues from Enaminodiester Synthons

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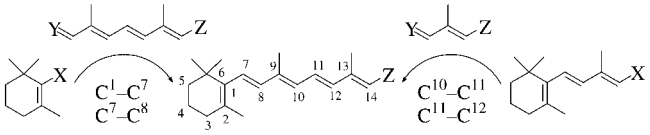
A one-pot synthesis of (all-*E*)-retinoic acid and related compounds from new enamino diester synthons is described. The enamino diesters was produced nearly quantitatively from methyl propylidene- and isopropylidenemalonate and DMF–DMA. This easy process allowed retinoic acid to be produced in 1 d and appeared advantageous to current industrial syntheses.

Natural retinoids have been found to be active in the regulation and differentiation of many cell types, the best effects having been achieved with retinol, retinaldehyde, (13*Z*)-retinoic acid and (all-*E*)-retinoic acid.[1,2] This last has selective biological activity for normal growth and epithelial differentiation. Retinoic acid receptors (RARs) have a high affinity both for (all-*E*)-retinoic acid and its (9*Z*) isomer, the latter being the natural ligand of the retinoid X receptors (5RXRs).[3] These transcription factors (RARα, RARβ, RARγ and RXRα, RXRβ, RXRγ) activate transcription by interaction with their target genes through specific DNA-binding domains. It was recently found that retinoic acid induced apoptosis in leukaemia cells was mediated by paracrine action of a tumour necrosis factor related apoptosis-inducing ligand.[4]

These important biological activities have prompted an intensive search to obtain the required stereochemistry of the ethylenic linkage.

The industrial synthetic routes were based on the procedures of Wittig[5] (BASF AG), Julia[6] (Aventis) and Isler[7] (Hoffmann−La Roche). A range of recent examples, using tricarbonyliron complexes[8] and palladium-catalysed cross-coupling reactions such as the Negishi reaction,[9] Suzuki coupling,[10] Stille reaction,[11] Heck reaction[12] and Sonogashira coupling[13] etc. have been investigated.

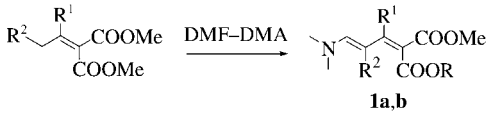
The major strategies are illustrated in Scheme 1.[14] Each pathway has been achieved by two approaches. For the construction of the $C^{10}-C^{11}$ or $C^{11}-C^{12}$ bonds, BASF AG and Aventis joined a C_{15} component with an added C_5 unit, and Hoffmann−La Roche a C_{14} constituent with a further C_6 unit. For the construction of the C^1-C^7 or C^7-C^8 bonds, Aventis coupled a C_9 unit with a C_{11} component while Sumitomo combined two C_{10} synthons.



Scheme 1

For these regioselective syntheses, ethylenic partners with the required stereochemistry were needed and, furthermore, large numbers of steps or purifications were necessary.

With the intention of synthesising the economically most important retinoids by a single pathway, we recently prepared enamino diesters synthons **1a** and **1b**, which could be easily obtained and directly coupled with β-ionone. Thus, condensation of methyl alkylidenemalonates and *N*,*N*-dimethylformamide dimethyl acetal (DMF−DMA) directly afforded the desired intermediates **1a** and **1b** in excellent yields (Scheme 2).



1a,**b**

Scheme 2. **a**: R^1 = Me, R^2 = H; **b**: R^1 = H, R^2 = Me

In series **a**, the synthon **1a** allowed a one-pot synthesis of (all-*E*)-retinoic acid.[15] The step-by-step sequence of the synthesis is described in Scheme 3. The lithium enolate of β-ionone was treated with the enamino diester **1a** to give the addition product **4a** [(all-*E*)/(12*Z*)= 80:20; 65%] via an

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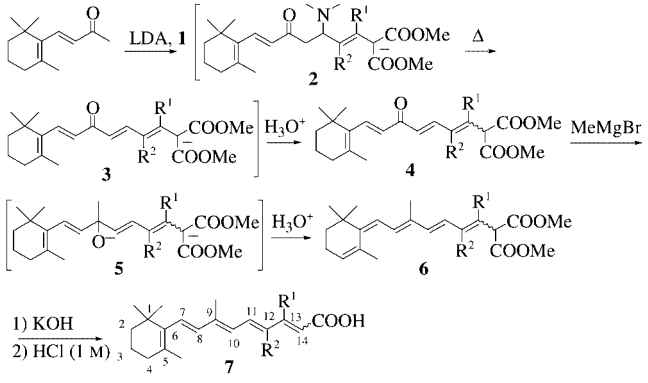
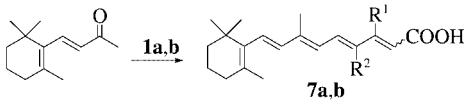
intermediate unstable compound **2a**, which spontaneously underwent elimination of dimethylamine to provide **3a**, which was further protonated. The Grignard reaction between MeMgBr and compound **4a** required an excess of reagent, 1 equiv. serving to regenerate the anion **3a**. The presence of this delocalized negative charge between the two ester groups should protect them from being attacked by MeMgBr. The Grignard reagent therefore reacted only with the ketone to give intermediate **5a** and, after protonation and dehydration, the (methoxycarbonyl)-*retro*-retinoate **6a** [(12*E*)/(12*Z*) = 75:25; 69%]. This, after saponification and concomitant decarboxylation, afforded mainly the (all-*E*)-retinoic acid (**7a**) [(all-*E*)/(13*Z*) = 83:17; 80%]. The (all-*E*) isomer was purified by rapid column chromatography with CH_2Cl_2/MeOH (98:2) as eluent, followed by crystallisation from acetonitrile (Scheme 3). Compounds of series **b** were obtained by the same route, via enamino diester **1b** [**4b**: (all-*E*)/(12*Z*) = 80:20; 57%; **6b**: (all-*E*)/(12*Z*) = 80:20; 48%; **7b**: (all-*E*)/(12*Z*) = 80:20; 50%].



Scheme 3

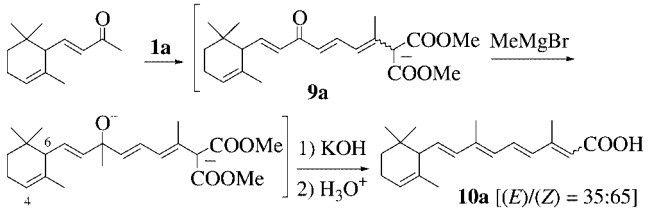
A one-pot procedure for the synthesis of retinoic acid (**7a**), depicted in Scheme 3, was desirable from both an economic and an ecological point of view. It was feasible because the reaction conditions for each successive step are compatible (i. LDA, **1a**; ii. MeMgBr; iii. KOH/EtOH/H_2O). The intermediary malonic acid corresponding to compound **5** in Scheme 3 was thus spontaneously decarboxylated, and coupling of the obtained monoacid preferentially afforded the (all-*E*) isomer. This one-pot process was accomplished in 1 d and (all-*E*)-retinoic acid was obtained with an increased overall yield [(all-*E*)/(13*Z*) = 87:13; 70%].

The other compound **7b** [(all-*E*)/(13*Z*) = 85:15; 55%] was also obtained by the same one-pot route (Scheme 4).



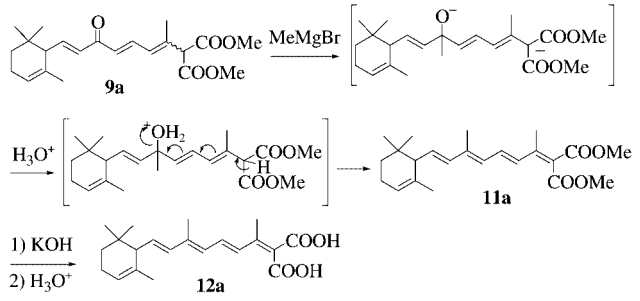
Scheme 4. **a**: R^1 = Me, R^2 = H; **b**: R^1 = H, R^2 = Me

A possible alternate mechanism: Surprisingly, when starting with α-ionone and synthon **1a**, the one-pot synthesis gave the retinoic acid **10a** with, in this case, favourable (13*Z*) regioselectivity [(all-*E*)/(13*Z*) = 35:65] but *without any detectable amounts of the expected isomer* **7a** (Scheme 5).



Scheme 5

Conversely, by the step-by-step procedure, starting with α-ionone and synthon **1a**, very poor yields of diester **11a** were obtained (18%, compared with 69% in the case of diester **6a**, Scheme 6).



Scheme 6

This suggested an alternate mechanism for α-ionone in the one-pot procedure, but this mechanism is also credible in the one-pot procedure for β-ionone, as illustrated in Scheme 6. We may note that this mechanism does not involve a (methoxycarbonyl)-*retro*-retinoate **6a**, which can be isolated in the case of β-ionone, but not with α-ionone. On the other hand, the first mechanism implies a vacant proton for the dehydration process in position 4 or 6. In the α-ionone series, the proton at C^4 is ethylenic and the proton at C^6 poorly accessible due to steric hindrance.

This procedure offers an alternative, inexpensive method for the production of other important related products such as vitamin A[17,18] and β-carotene[19] via a single synthon **1a** and β-ionone. Syntheses of these compounds could be completed in 2−3 d from (all-*E*)-retinoic acid (obtained in 61% overall yield from β-ionone) by established procedures.

Experimental Section

General: All experiments were carried out under argon. All starting products were purchased from Sigma−Aldrich. Melting points were measured with a Leitz 350 heated-stage microscope and are not corrected. IR spectra were recorded with a Bruker IFS 55 spectrometer. ^{1}H and ^{13}C NMR spectra were determined with a Bruker Avance DPX 400 spectrometer (^{1}H: 400 MHz; ^{13}C: 100 MHz). Chemical shifts (δ) are expressed in ppm downfield from internal TMS. *J* values are given in Hz. The traditional retinoid numbering system[20] is used for identification and spectroscopic data (Scheme 3). Chemical Abstracts nomenclature is used below.

Dimethyl 2-[(2*E*)-3-(Dimethylamino)-1-methyl-2-propenylidene]malonate (1a): A mixture of dimethyl isopropylidenemalonate (43 g, 250 mmol) and DMF−DMA (40 mL, 1.2 equiv.) was heated at 95 °C for 18 h with removal of the MeOH (Dean−Stark) and then heated at reflux for 2 h. After elimination of the excess of DMF−DMA under reduced pressure, the enamino ester was crystallized from pentane/diethyl ether. Yellow crystals, m.p. 113 °C (54 g, 95%). IR (KBr): $\tilde{\nu}$ = 1716, 1686, 1619, 1539, 1433, 1399, 1330, 1191, 1115, 1068, 995, 959 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.93 (d, *J* = 13.2 Hz, 1 H, 4-H), 6.07 (d, *J* = 13.2 Hz, 1 H, 5-H), 3.71 (s, 6 H, $COOCH_3$), 2.91 [s, 6 H, $N(CH_3)_2$], 2.10 (s, 3 H, 3-CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.5, 167.3 (CO); 148.8, 97.4 (CH); 52.0, 51.9, 41.0, 16.7 (CH_3) ppm. $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 58.02, H 7.58, N 6.28.

Dimethyl 2-[(2*E*)-3-(Dimethylamino)-2-methyl-2-propenylidene]malonate (1b): This compound was obtained by the same procedure, from dimethyl propylidenemalonate (34.4 g, 200 mmol). Orange crystals, m.p. 91−93 °C (33.5 g, 77%). IR (KBr): $\tilde{\nu}$ = 1724, 1678, 1619, 1536, 1426, 1390, 1371, 1233, 1169, 1126, 1082, 1023, 918, 881, 761, 726 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.31 (s, 1 H, 5-H), 6.79 (s, 1 H, 3-H), 3.82 and 3.75 (2 s, 6 H, $N(CH)_3$], 3.08 (s, 6 H, OCH_3), 1.83 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.3, 166.9 (CO); 155.0, 154.1 (CH); 51.8, 51.5, 43.3, 13.5 (CH_3) ppm. $C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 58.03, H 7.64, N 6.13.

Dimethyl 2-[(1*E*,3*E*,6*E*)-1-Methyl-5-oxo-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,6-heptatrienyl]malonate (4a): A solution of BuLi (1.6 M in hexanes, 13.2 mL, 21 mmol) was added at −25 °C to *i*Pr_2NH (3.1 mL, 22 mmol) in DME (20 mL), and β-ionone (3.85 g, 20 mmol) in DME (20 mL) was then slowly added at −30/−40 °C. After the mixture had been kept at −30 °C for 20 min, **1a** (4.77 g, 1.05 equiv.) in DME (50 mL) was quickly added. The refrigerated bath was then removed and the mixture was allowed to warm to room temperature. After 10 min, the crude mixture was heated at reflux for 2 h (until the evolution of Me_2NH had ceased). The solution was quenched at 0 °C with HCl in water (1 M) and extracted with diethyl ether. After conventional workup, the crude product was purified by column chromatography (SiO_2; CH_2Cl_2) to yield a yellow oil [4.86 g, 65%; (all-*E*)/(12*Z*) = 80:20). IR (film): $\tilde{\nu}$ = 2954, 2931, 2866, 1739, 1653, 1627, 1598, 1435, 1364, 1310, 1263, 1201, 1153, 1080, 1029, 983 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.49 (dd, *J* = 15.1, *J* = 11.4 Hz, 1 H, 11-H), 7.35 (d, *J* = 16.1 Hz, 1 H, 7-H), 6.44 (d, *J* = 15.1 Hz, 1 H, 10-H), 6.28 (d, *J* = 16.1 Hz, 1 H, 8-H), 6.18 (d, *J* = 11.4 Hz, 1 H, 12-H), 4.14 (s, 1 H, 14-H), 3.68 (s, 6 H, OMe), 1.99 (m, 2 H, 4-CH_2), 1.98 (s, 3 H, 13-CH_3), 1.69 (s, 3 H, 5-CH_3), 1.55 (m, 2 H, 3-CH_2), 1.40 (m, 2 H, 2-CH_2), 1.00 (s, 6 H, 1-CH_3) ppm. ^{13}C NMR: δ = 189.2, 167.6 (CO); 143.3, 137.4, 130.2, 130.2, 130.0 (CH); 40.1, 34.0, 19.2 (CH_2); 60.9, 53.1, 29.2, 22.2, 16.6 (CH_3) ppm. $C_{22}H_{30}O_5$ (374.47): calcd. C 70.56, H 8.07; found C 70.41, H 8.26.

Dimethyl 2-[(1*E*,3*E*,6*E*)-2-Methyl-5-oxo-7-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,6-heptatrienyl]malonate (4b): This compound was obtained by the same procedure, from **1b** and β-ionone (0.96 g, 5 mmol). Yellow oil, purified by column chromatography (SiO_2; CH_2Cl_2); yield 1.07 g [57%; (all-*E*)/(12*Z*) = 80:20]. IR (film): $\tilde{\nu}$ = 2976, 2940, 1752, 1635, 1703, 1436, 1320, 1262, 1220, 1196 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 16.0 Hz, 1 H, 11-H), 7.32 (d, *J* = 15.8 Hz, 1 H, 7-H), 6.46 (d, *J* = 16.0 Hz, 1 H, 10-H), 6.46 (d, *J* = 15.8 Hz, 1 H, 8-H), 6.20 (d, *J* = 9.6 Hz, 1 H, 13-H), 4.48 (s, 1 H, 14-H), 3.79 (s, 6 H, OMe), 2.09 (m, 2 H, 4-CH_2), 1.92 (s, 3 H, 12-CH_3), 1.82 (s, 3 H, 5-CH_3), 1.64 (m, 2 H, 3-CH_2), 1.50 (m, 2 H, 2-CH_2), 1.10 (s, 6 H, 1-CH_3) ppm. ^{13}C NMR: δ = 189.3, 167.9 (CO); 145.5, 143.1, 130.1, 128.6, 126.9, 51.8 (CH); 39.8.1, 34.1, 20.4 (CH_2); 53.0, 28.8, 21.9, 12.9 (CH_3) ppm. $C_{22}H_{30}O_5$ (374.47): calcd. C 70.56, H 8.07; found C 70.39, H 8.19.

Methyl 14-(Methoxycarbonyl)-*retro*-retinoate (6a): A solution of MeMgBr (3 M in THF, 7.5 mL, 2.8 equiv.) was added at −10 °C to **4a** (2.98 g, 8 mmol) in THF (30 mL). The chilled bath was removed and, 30 min later, the crude mixture was quenched with a satd. solution of NH_4Cl and extracted with diethyl ether. After conventional workup, the crude, oily product was purified by column chromatography (SiO_2; CH_2Cl_2). Yellow oil [2.05 g, 69%; (all-*E*)/(12*Z*) = 75:25]. IR (film): $\tilde{\nu}$ = 2955, 2915, 2847, 1736, 1436, 1306, 1279, 1204, 1142, 1020, 958, 877, 733 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.75 (d, *J* = 12.30 Hz, 1 H, 10-H), 6.41−6.22 (m, 3 H, 7-H + 11-H + 12-H), 6.22 (d, *J* = 6.2 Hz, 1 H, 8-H), 5.79 (t, *J* = 5.50 Hz, 1 H, 4-H), 4.73 (s, 1 H, 14-H), 3.77 (s, 3 H, OCH_3), 2.22 (m, 2 H, 2-CH_2), 1.96, 1.91, 1.91, (3 s, 9 H, 5-CH_3, 9-CH_3, 13-CH_3), 1.51 (m, 2 H, 3-CH_2), 1.29 (s, 6 H, 1-CH_3) ppm. ^{13}C NMR: δ = 168.3, 168.1 (CO); 139.6, 134.2, 132.0, 128.6, 122.5, 119.7 (CH); 40.5, 22.8 (CH_2); 53.5, 52.4, 28.8, 21.4, 21.3, 11.9 (CH_3) ppm. $C_{23}H_{32}O_4$ (372.50): calcd. C 74.16, H 8.66; found C 74.01, H 8.76.

Dimethyl 2-[(1*E*,3*E*,5*E*,7*Z*)-2,5-Dimethyl-7-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-1,3,5-heptatrienyl]malonate (6b): This compound was obtained as a yellow oil by the same method, from 8 mmol of **4b** (column chromatography: SiO_2; CH_2Cl_2); yield 1.43 g [48%; (all-*E*)/(12*Z*) = 80:20]. IR (film): $\tilde{\nu}$ = 2956, 2936, 2868, 1736, 1661, 1436, 1313, 1272, 1197, 1149, 1020, 911, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.77 (d, *J* = 12.30 Hz, 1 H, 10-H), 6.37−6.35 (m, 2 H, 7-H + 11-H), 5.79−5.75 (m, 2 H, 4-H + 13-H), 4.44 (d, 1 H, 13-H), 3.75 (s, 3 H, OCH_3), 2.10 (m, 2 H, 2-CH_2), 1.90, 1.90, 1.89, (3 s, 9 H, 5-CH_3, 9-CH_3, 12-CH_3), 1.50 (m, 2 H, 3-CH_2), 1.30 (s, 6 H, 1-CH_3) ppm. ^{13}C NMR: δ = 168.6 (CO); 130.5, 130.3, 128.2, 121.2, 119.9, 51.5 (CH); 35.6, 34.2 (CH_2); 53.7, 28.9, 27.9, 21.7, 13.1 (CH_3) ppm. $C_{23}H_{32}O_4$ (372.50): calcd. C 74.16, H 8.66; found C 73.99, H 8.81.

Retinoic Acid (7a): A solution of *retro*-retinoate **6a** (10.38 g, 25 mmol) in ethanol (250 mL) was saponified with an aqueous ethanolic solution of KOH (8.4 g, 6 equiv.) in water (150 mL) at 40 °C for 45 min. The solvents were distilled under reduced pressure and the crude mixture was acidified with cold HCl (2 M). After extraction with ethyl acetate and conventional workup, the oily product was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) to yield 5 g of (all-*E*)- and 1.05 g of (13*Z*)-retinoic acid. The physicochemical properties were identical to those of a reference product (SIGMA).

12-Methyl-13-demethylretinoic Acid (7b): This compound was obtained by the same route from **6b** (5 mmol) and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 99:1) to produce (all-*E*)-**7b** (0.76 g, 51%). Yellow crystals, m.p. 97 °C (pentane/ether). IR (film): $\tilde{\nu}$ = 3447, 2970, 2943, 2875, 1708, 1675, 1446, 1381, 1265, 1170, 1061, 972, 733 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.50 (d, *J* = 15.50 Hz, 1 H, 13-H), 6.93, (d, *J* = 12.0 Hz, 1 H, 11-H), 6.71 (d, *J* = 15.8 Hz, 1 H, 7-H), 6.36 (d, *J* = 15.8 Hz, 2 H, 8-H), 6.30 (d, *J* = 12.0 Hz, 1 H, 10-H), 5.83 (d, *J* = 15.5 Hz, 1 H, 14-H), 2.08 (s, 3 H, 12-CH_3), 1.94 (s, 3 H, 9-CH_3), 1.86 (m, 2 H, 4-CH_2), 1.76 (s, 3 H, 2-CH_3), 1.66 (m, 2 H, 3-CH_2), 1.50 (m, 2 H, 2-CH_2), 1.16 (s, 3 H, 1-CH_3) ppm. ^{13}C NMR: δ = 175.0 (CO); 151.6, 141.4, 137.6, 132.7, 125.4, 114.6 (CH); 39.5, 34.2, 19.1 (CH_2); 30.9, 28.9, 21.7, 12.7, 12.3 (CH_3) ppm. $C_{20}H_{28}O_2$ (300.44): calcd. C 79.96, H 9.39; found C 79.81, H 9.56.

One-Pot Procedure. Retinoic Acid (7a): Butyllithium (1.6 M in hexanes, 100 mL, 160 mmol) was added at −25 °C to diisopropylamine

(23 mL, 1.1 equiv.) in DME (120 mL). β-Ionone (30.5 mL, 150 mmol) in DME (120 mL) was then slowly added at −30 to −40 °C. The mixture was stirred at this temp. for 20 min, and enamino ester **1a** (35.8 g, 1.05 equiv.) in DME (350 mL) was then added. The refrigerating bath was removed and, after 10 min, the solution was refluxed for 1 h. The temp. was allowed to rise to −10 to 0 °C, and methylmagnesium bromide (3 M in THF, 115 mL, 2.3 equiv.) was added. The refrigerating bath was removed and, after 30 min, ethanol (150 mL) and then KOH (50.5 g, 6 equiv.) in water (450 mL) were added at 0 °C. After 30 min, the solution was heated at 40 °C for 45 min. The solvents were distilled under reduced pressure and the crude mixture was acidified with cold HCl (2 M). The oily product was extracted and purified as reported above; yield 27.6 g (61%) of the (all-*E*) isomer and 5.6 g (12%) of the (13*Z*) isomer.

12-Methyl-13-demethylretinoic Acid (7b): This compound was obtained by the same procedure, from 15 mmol (2.88 g) of β-ionone; yield 2.1 g (47%).

Dimethyl 2-[(1*E*,3*E*,6*E*)-1-Methyl-5-oxo-7-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1,3,6-heptatrienyl]malonate (9a): This compound was obtained as a yellow oil, purified by column chromatography (SiO_2; CH_2Cl_2); yield 4.87 g [65%; (all-*E*)/(12*Z*) = 80:20] by the same method as used for **4a** [from 20 mmol (3.85 g) of α-ionone]. IR (film): $\tilde{\nu}$ = 2956, 2915, 2868, 1736, 1661, 1627, 1586, 1436, 1365, 1286, 1211, 1150, 1040, 979 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.51 (dd, *J* = 15.1, *J* = 11.0 Hz, 1 H, 11-H), 6.72 (dd, *J* = 15.6, *J* = 9.8 Hz, 1 H, 7-H), 6.48 (d, *J* = 15.1 Hz, 1 H, 10-H), 6.25 (d, *J* = 15.6 Hz, 1 H, 8-H), 6.21 (d, *J* = 12.05 Hz, 1 H, 12-H), 5.49 (m, 1 H, 4-H), 4.17 (s, 1 H, 14-H), 3.75 (s, 6 H, OMe), 2.30 (d, *J* = 9.8 Hz, 1 H, 6-H), 2.03 (s, 3 H, 13-CH_3), 2.02 (m, 2 H, 3-CH_2), 1.48 (s, 3 H, 5-CH_3), 1.43 and 1.20 (2 s, 6 H, 1-CH_3) ppm.^{13}C NMR: δ = 189.1, 167.6 (CO); 148.9, 139.2, 131.9, 129.5, 128.9, 122.5, 60.6, 52.1 (CH); 32.5, 22.7 (CH_2); 53.4, 53.3, 27.8, 26.7, 22.9, 16.2 (CH_3) ppm. $C_{22}H_{30}O_5$ (374.47): calcd. C 70.56, H 8.07; found C 70.37, H 8.19.

4,5-Didehydro-5,6-dihydroretinoic Acid (α-Retinoic Acid) (10a): This compound was obtained by the same method as used for the one-pot route [from 1.92 g (10 mmol) of α-ionone]. Yellow oil purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 99:1); yield 0.53 g of (all-*E*), 0.98 g of (13*Z*) (together 50%). **(all-*E*) Isomer:** Yellow crystals, m.p. 161 °C (pentane/ether). IR (film): $\tilde{\nu}$ = 2963, 2915, 2861, 1680, 1586, 1443, 1252, 1190, 965, 904, 727 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.99 (dd, *J* = 15.0, *J* = 11.4 Hz, 1 H, 11-H), 6.28, (d, *J* = 15.0 Hz, 1 H, 12-H), 6.11 (2d, 2 H, *J* = 15.5, *J* = 11.4, 10-H + 8-H), 5.77 (s, 1 H, 14-H), 5.64 (dd, *J* = 15.5, *J* = 9.5 Hz, 1 H, 7-H), 5.4 (s, 1 H, 4-H), 2.35 (s, 3 H, 13-CH_3), 2.18 (d, *J* = 9.5 Hz, 1 H, 6-H), 2.00 (m, 2 H, 3-CH_2), 1.93 (s, 3 H, 9-CH_3), 1.56 (s, 3 H, 5-CH_3), 1.43 and 1.21 (2 m, 2 H, 2-CH_2), 0.89 and 0.80 (2 s, 3 H, 1-CH_3) ppm. ^{13}C NMR: δ = 172.0 (CO); 135.6, 134.8, 133.2, 131.6, 128.9, 121.0, 117.8, 55.1 (CH); 30.7, 30.2, 26.9 (CH_2); 27.5, 26.9, 23.3, 13.9, 13.1 (CH_3) ppm. $C_{20}H_{28}O_2$ (300.44): calcd. C 79.96, H 9.39; found C 79.79, H 9.54. **(13*Z*) Isomer:** Yellow crystals, m.p. 149 °C (pentane/ether). IR (film): $\tilde{\nu}$ = 2961, 2920, 2864, 1673, 1590, 1445, 1251, 1182, 967, 822, 725. ^1H NMR ($CDCl_3$): δ = 7.75 (d, *J* = 15.3 Hz, 1 H, 12-H), 7.11, (dd, *J* = 15.3, *J* = 11.4 Hz, 1 H, 11-H), 6.25 (d, *J* = 11.4 Hz, 1 H, 10-H), 6.15 (d, *J* = 15.4 Hz, 1 H, 8-H), 5.65 (dd, *J* = 15.4, *J* = 9.3 Hz, 1 H5, 7-H), 5.42 (s, 1 H, 4-H), 2.20 (d, *J* = 9.35 Hz, 1 H, 6-H), 2.08 (s, 3 H, 13-CH_3), 2.02 (m, 2 H, 3-CH_2), 1.94 (s, 3 H, 9-CH_3), 1.58 (s, 3 H, 5-CH_3), 1.45 and 1.19 (2 m, 2 H, 2-CH_2), 0.92 and 0.83 (2 s, 3 H, 1-CH_3) ppm. ^{13}C NMR: δ = 171.8 (CO); 135.9, 133.2, 132.9, 129.8, 129.2, 121.4, 115.9, 54.9 (CH); 30.9, 23.5, 19.1 (CH_2); 27.7, 27.0, 23.0, 21.2, 13.3 (CH_3) ppm. $C_{20}H_{28}O_2$ (300.44): calcd. C 79.96, H 9.39; found C 79.77, H 9.57.

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