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First Synthesis of 9-Demethyl-14-Carboxyretinoic Acid

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Abstract: *A short synthesis of 9-demethyl-14-carboxyretinoic acid from β-ionone via 9-demethyl-β-ionylideneacetaldehyde is reported (48% overall yield).*

In a recent paper, we described [1] a new preparation of the β-C_{18} ketone **1**, a key intermediate for Vitamin A **2** synthesis (fig.1).

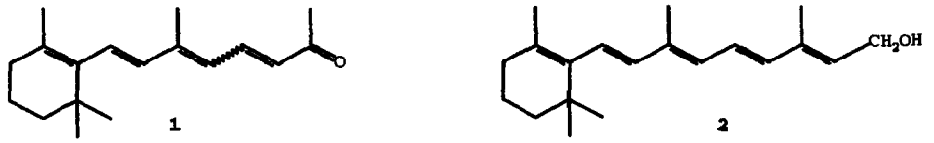
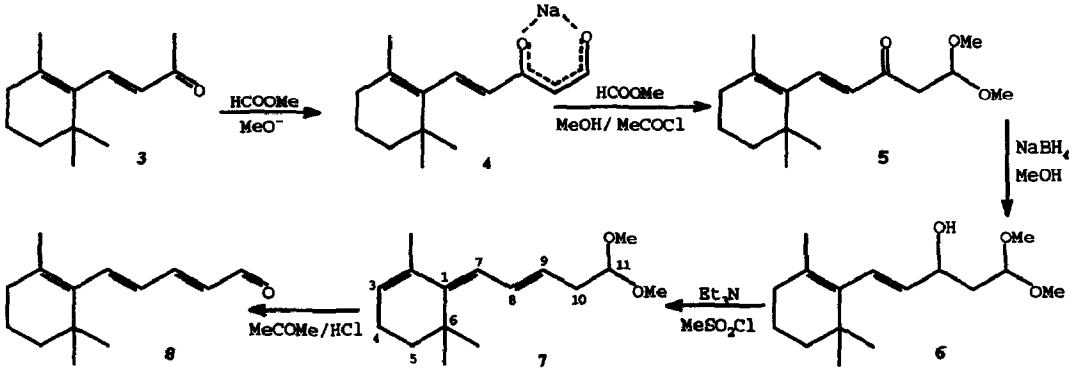


fig.1

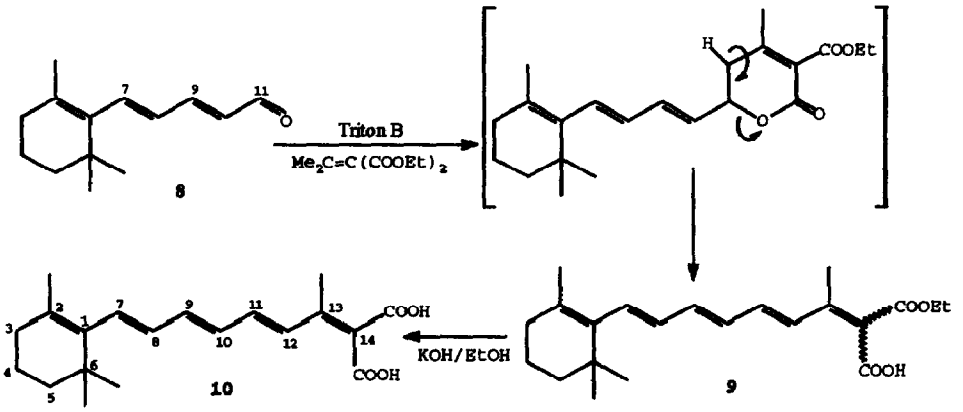
In connection with our investigations in this field, we report herein a convenient synthesis of 9-demethyl-14-carboxyretinoic acid **10** from 9-demethyl-β-ionylideneacetaldehyde **8**. This aldehyde was prepared by a new five steps procedure (62% overall yield) from β-ionone **3** as outlined in scheme 1. A six steps preparation of this compound (24% overall yield) - from the same starting material - was previously published [2].



scheme 1

Formylation of β-ionone **3** (HCOOMe/MeONa/cyclohexane) afforded sodium salt **4** (90%) [3], which was subsequently converted (MeCOCl/HCOOMe/MeOH) into β-ketoacetal **5** (98%) [4, 5]. 1, 2 sodium borohydride reduction of **5** in the absence of Ce^{+++} provided the β-hydroxyacetal **6** (~100%) [6] which was further dehydrated ($Et_3N/MeSO_2Cl$) to "retroacetal" **7** (~100%) [7]. Similar deconjugation of Δ^7 bond by dehydration of this type of compounds has already been observed [4,8]. Acidic cleavage of **7** with concomitant reconjugation (1N HCl/MeCOMe) led to 9-demethyl-β-ionylideneacetaldehyde **8** (70%) [9] whose all *E* configuration was deduced from ^1H NMR data ($J_{7,8} = J_{9,10}$=16Hz). Aldehyde **8** was also directly obtained by dehydration and hydrolysis of **6** without isolation of intermediate **7** (1N HCl/MeCOMe, 75%)[10].

Knoevenagel condensation of **8** with diethyl isopropylidenemalonate in the presence of Triton B afforded the half-ester **9** [11] as a mixture of stereomers (82%). Isotopically labelled compounds allowed us to establish that a Stobbe-like mechanism, involving a 5, 6-dihydropyran-2-one intermediate, was implied in such a condensation under kinetically controlled conditions [12]. Hence, the primary product formed is a 7 *E*, 9 *E*, 11 *E*, 13 *E* half-ester which under thermodynamically controlled usual conditions is partially isomerized to the 7 *E*, 9 *E*, 11 *E*, 13 *Z* stereomer (scheme 2). Subsequent hydrolysis of the crude isomeric half-esters afforded the 7 *E*, 9 *E*, 11 *E*-9-demethyl-14-carboxyretinoic acid **10** (95%) [13].



scheme 2

Stereospecific decarboxylation of **10** to 13 *E* -or 13 *Z*-9-demethylretinoic acid is currently under investigation.

References and notes:

1. Andriamialisoa Z., Valla A., Zennache S., Giraud M. and Potier P., *Tetrahedron Lett.* **1993**, *34*, 8091-8092.
2. Van Temple P.J. and Huisman H.O., *Tetrahedron* **1966**, *22*, 293-299
3. NMR spectra were recorded at 300 MHz (^{1}H) and 75.47 Mhz (^{13}C) in $CDCl_3$ unless otherwise mentionned. Coupling constants *J* are given in Hz.
   4 IR (KBr) 3400, 2900, 1650, 1600, 1500 cm^{-1}.
   ^{1}H NMR (Na salt in D_2O): 8.95 (d, 1H, *J*=12, C-11-H); 6.85 (d, 1H, *J*=16, C-7-H); 6.10 (m, 1H, C-8-H); 5.20 (d, 1H, *J*=12, C-10-H); 1.87 (m, 2H, C-3-H); 1.65 (m, 2H, C-4-H); 1.57 (s, 3H, C-2-CH_3); 1.35 m, 2H, C-5-H); 0.88 (s, 6H, C-6-CH_3).
   ^{13}C NMR: ($CDCl_3$/MeOH, 90: 10): 184.8 (C-9); 182.4 (C-10); 137.0 (C-1); 135.7 (C-8); 135.1 (C-7); 131.1 (C-2); 101.8 (C-11); 50.5 ($\underline{C}H_3OH$); 39.8 (C-5); 34.2 (C-6); 33.3 (C-3); 28.9 (C-2-$\underline{C}H_3$); 21.7 (C-6-$\underline{C}H_3$); 19.2 (C-4).
4. Nicolaux G.J.M., Gay E.A., Matet J., Mauge R.L.H., Sandevoir C.M.T. and Wasmer A.J.A., *French.Pat.* 1, 243, 824 (1960); *Chem.Abstr.* **1962**, *57*, 16671h.
5. **5** IR (film) 2900, 1690, 1660 cm^{-1}.
   ^{1}H NMR: 7.28 (d, 1H, *J*=16, C-7-H); 6.18 (d, 1H, *J*=16, C-8-H); 4.88 (t, 1H, *J*=5.5, C-11-H); 3.41 (s, 6H, OCH_3); 2.92 (d, 2H, *J*=5.5, C-10-H); 2.08 (m, 2H, C-3-H); 1.79 (s, 3H, C-2-CH_3); 1.75 (m, 2H, C-4-H); 1.40 (m, 2H, C-5-H); 1.09 (s, 6H, C-6-CH_3).
   ^{13}C NMR: 196.5 (C-9); 143.2 (C-8); 136.6 (C-1); 136.1 (C-2); 130.9 (C-7); 102.3 (C-11); 54.0 (OCH_3); 44.2 (C-10); 39.8 (C-5); 33.9 (C-6); 33.6 (C-3); 28.8 (C-2-$\underline{C}H_3$); 21.8 (C-6-$\underline{C}H_3$); 18.7 (C-4).
6. **6** IR (film): 3400, 2900, 1460 cm^{-1}.
   ^{1}H NMR 6.04 (d, 1H, *J*=16, C-7-H); 5.38 (dd, *J*=16, *J'*=6.5, C-8-H); 4.56 (t, 1H, *J*=4.6, C-11-H); 4.22 (m, 1H, C-9-H); 3.32 (s, 6H, OCH_3); 1.93 (m, 2H, C-10-H); 1.84 (m, 2H, C-3-H); 1.61 (s, 3H, C-2-CH_3); 1.49 (m, 2H, C-4-H); 1.39 (m, 2H, C-5-H); 0.93 (s, 6H, C-6-CH_3).
   ^{13}C NMR 136.9 (C-1); 135.7 (C-8); 128.9 (C-2); 128.4 (C-7); 103.4 (C-11); 70.0 (C-9); 53.6, 53.3 (OCH_3); 39.9 (C-10); 39.5 (C-5); 34.1 (C-6); 32.8 (C-3); 28.9 (C-2-$\underline{C}H_3$); 21.6 (C-6-$\underline{C}H_3$); 19.4 (C-4).
7. **7** IR (film): 2900, 1630 cm^{-1}.
   ^{1}H NMR: 6.70 (dd, 1H, *J*=13, *J'*=11, C-8-H); 6.00 (d, 1H, *J*=11, C-7-H); 5.55 (t, 1H, *J*=4, C-3-H); 5.50 (m, 1H, C-9-H); 4.30 (t, 1H, *J*=4.6, C-11-H); 3.30 (s, 6H,OCH_3); 2.45 (m, 2H, C-4-H); 2.00 (m, 2H, C-10-H); 1.80 (s, 3H, C-2-$\underline{C}H_3$); 1.40 (m, 2H, C-5-H); 1.10 (s, 6H, C-6-$\underline{C}H_3$).
   ^{13}C NMR 143.6 (C-1); 133.8 (C-2); 131.2 (C-8); 130.4 (C-7); 128.2 (C-5); 128.8 (C-9); 104.0 (C-11); 52.8 (OCH_3); 40.5 (C-10); 37.0 (C-3); 35.6 (C-6); 29.0 (C-2-$\underline{C}H_3$); 22.8 (C-4); 21.7 (C-6-$\underline{C}H_3$).
8. Smit A., *Rec.Trav.Chim.Pays-Bas* **1961**, *80*, 891-904.

9. **8** IR (film): 2900, 2700, 1690 cm^{-1}.
   ^{1}H NMR *(J obtained by double irradiation experiments)*. 9.50 (d, 1H, *J*=8, C-11-H); 7.15 (dd, 1H, *J*=16, *J'*=11, C-9-H); 6.70 (d, 1H, *J*=16, C-7-H); 6.30 (dd, 1H, *J*=16, *J'*=11, C-8-H); 6.05 (dd, 1H, *J*=16, *J'*=8, C-10-H); 2.05 (m, 2H, C-3-H); 1.70 (s, 3H, C-2-$\underline{C}H_3$); 1.50 (m, 2H, C-4-H); 1.38 (m, 2H, C-5-H); 1.00 (s, 6H, C-6-$\underline{C}H_3$).
   ^{13}C NMR 193.2 (C-11); 153.2 (C-9); 142.4 (C-7); 136.7 (C-1); 134.7 (C-2); 130.2 (C-8); 129.8 (C-10); 39.5 (C-5); 33.9 (C-6); 33.3 (C-3); 28.6 (C-2-$\underline{C}H_3$); 21.6 (C-6-CH_3); 18.7 (C-4).
10. *The same transformation was described by Broek et al using H_3PO_4*: Broek A.D., Muradin-Szeykowska M., Courtin J.M.L. and Lugtenburg J., *J.R. Neth. Chem. Soc.* **1983**, *102*, 46-51 (*Chem.Abstr.***1983**, *98*, 179678a).
11. *Structural analogues of 9 have been prepared using more drastic conditions ($NaNH_2$ in liquid NH_3)*: Shealy Y.F., Krauth C.A., Riordan J.M. and Sani B.P., *J.Med.Chem.* **1988**, *31*, 1124-1130.
12. Rebuffat S., Giraud M. and Molho D., *Bull.Soc.Chim.Fr* **1978**, 457-460.
13. *A solution of 8 (4.4g, 21.6 mM), diethyl isopropylidenemalonate (12.4g, 46 mM in 30mL MeOH, 16.7 mM) and Triton B (27.5 mL of a 40% solution in MeOH) was stirred 1.5 h at room temperature. After usual workup, 6.7g of 9 were obtained (82%). Alkaline hydrolysis of crude 9 (2g in 12 mL EtOH and 6 mL aqueous 3N KOH, 2 h at reflux) gave 1.8g of 10 (95%).*
   10 Orange needles m.p. 161°C (CH_2Cl_2). UV (MeOH): λ_{max} 335nm; ε = 42,100.
   IR (film): 3200, 2900, 1690 cm^{-1}.
   ^{1}H NMR: 7.05 (d, 1H, *J*=15, C-7-H); 6.85 (dd, 1H, *J*=15, *J'*=10, C-11-H); 6.55 (dd, 1H, *J*=15, *J'*=10, C-8-H); 6.45 (m, 1H, C-9-H); 6.30 (d, 1H, *J*=15, C-12-H); 6.20 (dd, 1H, *J*=15, *J'*=10, C-10-H); 2.15 (s, 3H, C-13-$\underline{C}H_3$); 2.10 (s, 3H, C-2-$\underline{C}H_3$); 1.00 (s, 6H, C-6-$\underline{C}H_3$).
   ^{13}C NMR (CD_3COCD_3) 167.0 (COOH); 166.6 (C-14); 153.8 (C-9); 148.3 (C-2); 139.1, 138.2, 134.7, 133.8, 131.6, 130.1 (C-1, C-2, C-7, C-8, C-10, C-12); 137.8 (C-13); 40.1 (C-3); 34.4 (C-6); 33.5 (C-4); 28.9 (C-13-$\underline{C}H_3$); 22.9 (C-2-$\underline{C}H_3$); 21.6 (C-6-CH_3); 19.4 (C-5); 15.6 (C-6-$\underline{C}H_3$).

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