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STEREOSELECTIVE SYNTHESIS OF 9-METHYLENE-13-DEMETHYL ANALOGS OF NATURAL RETINOIDS

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STEREOSELECTIVE SYNTHESIS OF 9-METHYLENE-13-DEMETHYL ANALOGS OF NATURAL RETINOIDS

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ABSTRACT

9-Methylene-13-demethyl analogs of retinol, retinal and retinoic acid, methyl ester were synthesised *via* new synthons β -methylenealdehydes.

Retinoids have various biological activities, including cellular differentiation, apoptosis and also act as modulators of inflammatory and immunological events.^{1,2} Although retinoids are thought to have great therapeutic potential, the wide range of toxic effects has often limited their clinical use.³

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We recently reported the synthesis of a novel class of synthons, β -methylenealdehydes, and their use in the synthesis of 13 Z retinoic acids.⁴ Noteworthy, only a few examples of synthesis and use of β -methylenealdehydes in organic chemistry were reported.⁵⁻¹¹

Nevertheless, the stereochemistry of C-9 (9-methylene) could be preserved and we report here the syntheses of 9-methylene-13-demethyl analogs of retinols, retinals and methyl retinoate *via* the β -methylenealdehydes **1a** and **1b** (Figure 1).



These new synthons 1(a, b) were respectively synthesised from β -ionone 2a and α -ionone 2b. Formylation (CH₃ONa, HCOOCH₃, pentane) and acetalisation of the sodium salts of hydroxymethylenic compounds 3 (a, b) (CH₃OH, H₂SO₄) furnished the β -ketoacetals 4 (a, b). Witting reaction (*t-But*OK, (C₆H₅)₃P⁺-CH₃ Br⁻, cyclohexane) and mild acidic hydrolysis of the β -methyleneacetals 5 (a, b) (HCOOH, pentane), produce the β -methylenealdehydes 1 (35% from 2a and 30% from 2b)⁴ (Scheme 1).

Reaction of compounds 1 with 4-(diethoxyphosphoryl)-but-2-enoic acid, methyl ester (NaH, DME, -60° C), affords the 9-methylene derivatives **6a** (40%) and **6b** (45%), with no detectable conjugated isomers. Thus, this Horner-Emmons synthesis of compounds 1 with 4-(diethoxyphosphoryl)-but-<u>2E</u>-enoic acid, methyl ester, led stereoselectively ($\geq 99\%$) to the new 7E, 11E, 13E-9-methylene-13-demethyl analogs of retinoic acid, methyl esters.¹²

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The retinol analogs 7 (7a, 65%, 7b, 70%) could be easily obtained from these latter by reduction (DIBAL-H, -5° C, then rt, 30 min), and the retinal analogs 8 (8a, 60%, 8b, 70%) by MnO₂ oxidation of alcohols 7 (MnO₂, pentane, rt, 12 h) (Scheme 2).

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- 6a: Yellow oil (40%). Anal. Calc. pour C₂₀H₂₈O₂: C, 79.96; H, 9.39; O, 10.65. Found: C, 79.83; H, 9.43; O, 10.74. IR (film): 1721, 1644 cm⁻¹.

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¹H NMR (400 Mz, C₆D₆): 7.55 (dd, 1H, J = 15.5, J = 10.8, C₁₃-H); 6.24 (s, 2H, C₇-H and C₈-H); 6.06 (dd, 1H, J = 15.2, J = 10.8, C₁₂-H); 5.96 (d, 1H, J = 15.5, C₁₄-H); 5.94 (dt, 1H, J = 15.2, J = 6.5, C₁₁-H); 5.09 and 4.94 (2s, 2H, C₉-CH₂); 3.54 (s, 3H, CO₂<u>CH₃</u>); 2.94 (d, 2H, J = 6.5, C₁₀-H); 2.02 (t, 2H, J = 6.3, C₃-H); 1.81 (s, 3H, C₂-CH₃); 1.67 (m, 2H, C₄-H); 1.54 (m, 2H, C₅-H); 1.16 (s, 6H, C₆-CH₃). ¹³C NMR (100 Mz, CDCl₃); 167.5 (C₁₅); 144.8, 141.7, 134.0, 129.5, 128.1 and 119.2 (C₇, C₈, C₁₁, C₁₂, C₁₃ and C₁₄); 143.5, 137.2 and 129.1 (C₁, C₂ and C₉); 115.6 (C₉-CH₂); 51.3 (CO₂<u>CH₃</u>); 39.3, 35.8, 32.7 and 19.1 (C₃, C₄, C₅ and C₁₀); 34.0 (C₆); 28.7 and 21.5 (C₂-CH₃ and C₆-CH₃).

6b: Yellow oil (45%). Anal. Calc. pour $C_{20}H_{28}O_2$: C, 79.96; H, 9.39; O, 10.65. Found: C, 79.78; H, 9.45; O, 10.77. IR (film): 1721, 1644 cm⁻¹. ¹H NMR (C₆D₆): 7.50 (dd, 1H, J=15.6, J=10.8, C_{13} -H); 6.15 and 5.93 (2d, 2H, J=15.6, C_8 -H and C_{14} -H); 6.00 (dd, 1H, J=15.2, J=10.8, C_{12} -H); 5.89 (dt, 1H, J=15.2, J=6.3, C_{11} -H); 5.56 (dd, 1H, J=15.6, J=9.5, C_7 -H); 5.51 (m, 1H, C_3 -H); 5.06 and 4.89 (2s, 2H, C₉-CH₂); 3.54 (s, 3H, CO₂<u>CH</u>₃); 2.86 (d, 2H, J=6.3, C_{10} -H); 2.20 (d, 1H, J=13.2, J=8.0, C_5 -H); 1.22 (dt, 1H, J=13.2, J=5.0, C_5 -H); 1.00 and 0.92 (2s, 6H, C₆-CH₃). ¹³CNMR (CDCl₃): 167.5 (C₁₅); 144.8, 141.6, 132.4, 132.2. 129.5, 120.9 and 119.1 (C₃, C₇, C₈, C₁₁, C₁₂, C₁₃ and C₁₄); 143.2 and 133.9 (C₂ and C₉); 115.1 (C₉-CH₂); 54.5 and 51.4 (C₁ and CO₂<u>CH₃</u>); 35.9, 31.7 and 22.9 (C₄, C₅ and C₁₀); 32.3 (C₆); 27.3, 26.9 and 22.8 (C₂-CH₃ and C₆CH₃).

7a: Yellow oil (65%). Anal. Calc. pour $C_{19}H_{28}O$: C, 83.77; H, 10.36; O, 5.87. Found: C, 83.59; H, 10.52; O, 5.89. IR (film): 3334 cm⁻¹. ¹H NMR: (CDCl₃): 6.27 and 6.14 (2dd, 2H, J = 15.0, J = 10.6, C_{12} -H and C_{13} -H); 6.15 and 6.06 (2d, 2H, J = 16.0, C_7 -H and C_8 -H); 5.81 (dt, 1H, J = 15.0, J = 6.7, C_{11} -H); 5.75 (dt, 1H, J = 15.0, J = 6.0, C_{14} -H); 5.00 and 4.95 (2s, 2H, C_9 -CH₂); 4.17(d, 2H, J = 6.0, C_{15} -H); 3.07 (d, 2H, J = 6.7, C_{10} -H); 2.01 (t, 2H, J = 6.2, C_3 -H); 1.70 (s, 3H, C_2 -CH₃); 1.62 (m, 2H, C_4 -H); 1.47 (m, 2H, C_5 -H); 1.01 (s, 6H, C_6 -CH₃). ¹³C NMR (CDCl₃); 144.6, 137.4 and 128.9 (C₁, C₂ and C₉); 134.4, 132.5, 131.5, 130.8, 130.0 and 127.7 (C₇, C_8 , C_{11} , C_{12} , C_{13} and C_{14}); 14.9 (C₉-CH₂); 63.2 (C₁₅); 39.3, 35.4, 32.7 and 19.1 (C₃, C₄, C₅, and C_{10}); 34.1 (C₆); 28.7 and 21.5 (C₂-CH₃ and C₆-CH₃).

7b: Yellow oil (70%). Anal. Calc. pour $C_{19}H_{28}O$: C, 83.77; H, 10.36; O, 5.87. Found: C, 83.62; H, 10.51; O, 5.87. IR (film): 3331 cm⁻¹. ¹H NMR (CDCl₃): 6.23 and 6.09 (2dd, 2H, J = 15.0, J = 10.5, C_{12} -H and C_{13} -H); 6.07 (d, 1H, J = 15.6, C_8 -H); 5.76 (dt, 1H, J = 15.0, J = 6.7, C_{11} -H); 5.72 (dt, 1H, J = 15.0, J = 6.0, C_{14} -H); 5.52 (dd, 1H, J = 15.6, J = 9.5, C_7 -H); 5.42 (m, 1H, C_3 -H); 4.98 and 4.90 (2s, 2H, C_9 -CH₂);

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9-METHYLENE-13-DEMETHYL ANALOGS

4.14 (d, 2H, J = 6.0, C_{15} -H); 3.00 (d, 2H, J = 6.7, C_{10} -H); 2.16 (d, 1H, J=9.5, C₁-H); 2.02 (m, 2H, C₄-H); 1.59 (s, 3H, C₂-CH₃); 1.43 (dt, 1H, $J = 13.0, J = 8.0. C_5$ -H); 1.19 (dt, 1H, $J = 13.0, J = 4.8. C_5$ -H); 0.91 and 0.82 (2s, 6H, C₆-CH₃).¹³C NMR (CDCl₃): 144.8 and 134.6 (C₂ and C₉); 133.3, 132.8, 132.3, 131.9, 131.4, 130.5 and 121.4 (C₃, C₇, C₈, C₁₁, C₁₂, C₁₃, and C₁₄); 114.9 (C₉-CH₂); 63.6 (C₁₅); 55.1 (C₁); 36.1, 32.3 and 23.5 (C₄, C₅ and C₁₀); 32.8 (C₆); 27.8, 27.5 and 23.4 (C₂-CH₃ and C₆-CH₃). 8a: Yellow oil (60%). Anal. Calc. pour C₁₉H₂₆O: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.25; H, 9.77; O, 5.98. IR (film): 1723, 1683, 1638 cm^{-1} . ¹H NMR (C₆D₆): 9.48 (d, 1H, J=7.8, C₁₅-H); 6.51 (dd, 1H, J = 15.4, J = 9.9, C_{13} -H); 6.26 (s, 2H, C_7 -H and C_8 -H); 6.02 (dd, 1H, J = 15.4, J = 7.8, C₁₄-H); 5.95 (m, 2H, C₁₁-H and C₁₂-H); 5.12 and 4.92 (2s, 2H, C₉-CH₂); 2.95 (d, 2H, J = 5.3, C₁₀-H); 2.03 (t, 2H, J = 6.2, C₃-H); 1.82 (s, 3H, C₂-CH₃); 1.67 (m, 2H, C₄-H); 1.56 (m, 2H, C₅-H); 1.17 (s, 6H, C₆-CH₃). ¹³H NMR (CDCl₃): 193.8 (C₁₅); 152.2, 144.2, 133.9, 130.4, 129.7 and 128.3 (C7, C8, C11, C12, C13 and C14); 143.2, 137.1 and 129.3 (C₁, C₂ and C₉); 115.9 (C₉-CH₂); 39.3, 36.0, 32.7 and 19.1 (C3, C4, C5 and C10); 34.7 (C6); 28.7 and 21.5 (C2-CH3 and C_6 - CH_3).

8b: Yellow oil (70%). Anal. Calc. pour $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.33; H, 9.74; O, 5.93. IR (film): 1683, 1640 cm⁻¹. ¹H NMR (C₆D₆): 9.46 (d, 1H, *J*=7.9, C₁₅-H); 6.56 (dd 1H, *J*=15.5, *J*=10.0, C₁₃-H); 6.16 (d, 1H, *J*=15.5, C₈-H); 6.00 (dd, 1H, *J*=15.2, *J*=7.9, C₁₄-H); 5.95 (m, 2H, C₁₁-H and C₁₂-H); 5.57 (dd, 1H, *J*=15.5, *J*=9.5, C₇-H); 5.52 (m, 1H, C₃-H); 5.08 and 4.92 (2s, 2H, C₉-CH₂); 2.88 (d, 2H, *J*=5.2, C₁₀-H); 2.21 (d, 1H, *J*=9.5, C₁-H); 2.07 (m, 2H, C₄-H); 1.72 (s, 3H, C₂-CH₃); 1.51 (dt, 1H, *J*=13.0, *J*=8.0, C₅-H); 1.23 (dt, 1H, *J*=13.0, *J*=4.8. C₅-H); 1.01 and 0.92 (2s, 6H, C₆-CH₃). ¹³C NMR (CDCl₃): 193.8 (C₁₅); 152.2, 144.1, 132.4, 132.2, 130.3, 129.7 and 121.0 (C₃, C₇, C₈, C₁₁, C₁₂, C₁₃, and C₁₄); 142.8 and 133.8 (C₂ and C₉); 115.5 (C₉-CH₂); 54.5 (C₁); 36.2, 31.7 and 22.9 (C₄, C₅ and C₁₀); 32.3 (C₆); 27.3, 26.9 and 22.8 (C₂-CH₃).

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