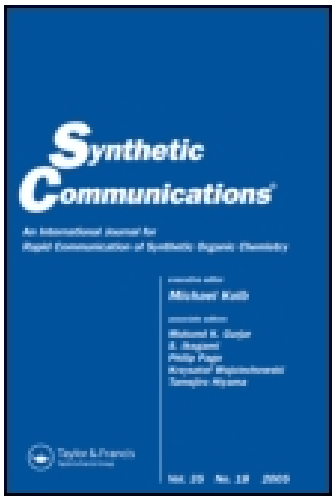

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STEREOSELECTIVE SYNTHESIS OF 9-METHYLENE-13-DEMETHYL ANALOGS OF NATURAL RETINOIDS

Alain Valla [a] , Virginie Prat [a] , Alain Laurent [a] , Zo Andriamialisoa [a] , Dominique Cartier [a] , Roger Labia [a] & Pierre Potier [b]

[a] rue de l'Université , Chimie et Biologie des Substances Naturelles, FRE 2125 CNRS 6, Quimper, 29000, France

[b] Institut de Chimie des Substances Naturelles , UPR 2301 CNRS Avenue de la Terrasse, Gif-sur-Yvette, Cedex, 91198, France

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

Alain Valla,[1,*] Virginie Prat,[1] Alain Laurent,[1] Zo Andriamialisoa,[1] Dominique Cartier,[1] Roger Labia,[1] and Pierre Potier[2]

[1]Chimie et Biologie des Substances Naturelles
FRE 2125 CNRS 6, rue de 1'Université –
29000 Quimper, France
[2]Institut de Chimie des Substances Naturelles,
UPR 2301 CNRS Avenue de la Terrasse 91198
Gif-sur-Yvette Cedex, France

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]

*Corresponding author. Fax: (33) 2 98908048; E-mail: Valla@iutquimp.univ-brest.fr

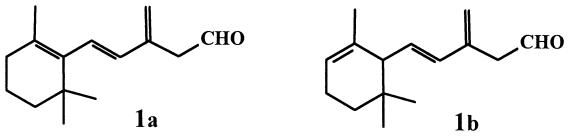
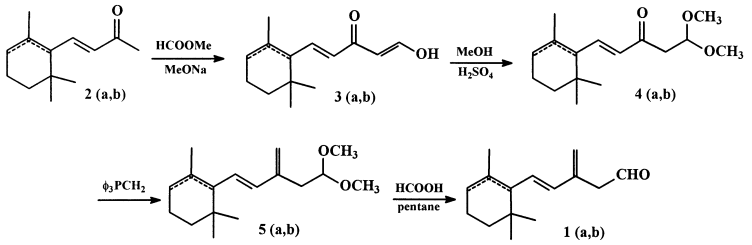


Figure 1.

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).



Scheme 1.

These new synthons **1**(**a**, **b**) were respectively synthesised from β-ionone **2a** and α-ionone **2b**. Formylation (CH_3ONa, $HCOOCH_3$, pentane) and acetalisation of the sodium salts of hydroxymethylenic compounds **3** (**a**, **b**) (CH_3OH, H_2SO_4) furnished the β-ketoacetals **4** (**a**, **b**). Witting reaction (*t-But*OK, $(C_6H_5)_3P^+$-CH_3 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-2*E*-enoic acid, methyl ester, led stereoselectively (≥ 99%) to the new 7*E*, 11*E*, 13*E*-9-methylene-13-demethyl analogs of retinoic acid, methyl esters.[12]

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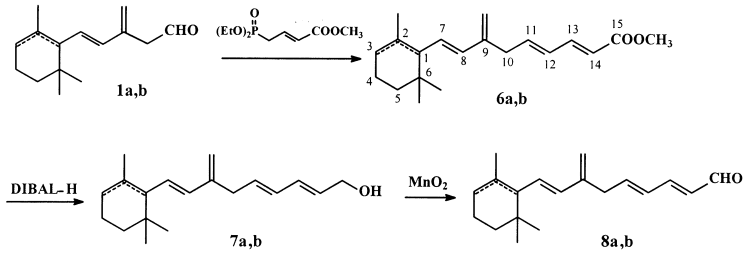

Scheme 2.

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 MnO_2 oxidation of alcohols **7** (MnO_2, pentane, rt, 12 h) (Scheme 2).

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11. Cardillo, G.; Contento, M.; Sandri, S. Tetrahedron Lett. **1974**, 2215.
12. **6a**: Yellow oil (40%). Anal. Calc. pour $C_{20}H_{28}O_2$: 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}.

^{1}H NMR (400 Mz, C_6D_6): 7.55 (dd, 1H, $J=15.5$, $J=10.8$, C_{13}-H); 6.24 (s, 2H, C_7-H and C_8-H); 6.06 (dd, 1H, $J=15.2$, $J=10.8$, C_{12}-H); 5.96 (d, 1H, $J=15.5$, C_{14}-H); 5.94 (dt, 1H, $J=15.2$, $J=6.5$, C_{11}-H); 5.09 and 4.94 (2s, 2H, C_9-CH_2); 3.54 (s, 3H, $CO_2\underline{CH_3}$); 2.94 (d, 2H, $J=6.5$, C_{10}-H); 2.02 (t, 2H, $J=6.3$, C_3-H); 1.81 (s, 3H, C_2-CH_3); 1.67 (m, 2H, C_4-H); 1.54 (m, 2H, C_5-H); 1.16 (s, 6H, C_6-CH_3). ^{13}C NMR (100 Mz, $CDCl_3$); 167.5 (C_{15}); 144.8, 141.7, 134.0, 129.5, 128.1 and 119.2 (C_7, C_8, C_{11}, C_{12}, C_{13} and C_{14}); 143.5, 137.2 and 129.1 (C_1, C_2 and C_9); 115.6 (C_9-CH_2); 51.3 ($CO_2\underline{CH_3}$); 39.3, 35.8, 32.7 and 19.1 (C_3, C_4, C_5 and C_{10}); 34.0 (C_6); 28.7 and 21.5 (C_2-CH_3 and C_6-CH_3).

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}. ^{1}H NMR (C_6D_6): 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, C_9-CH_2); 3.54 (s, 3H, $CO_2\underline{CH_3}$); 2.86 (d, 2H, $J=6.3$, C_{10}-H); 2.20 (d, 1H, $J=9.5$, C_1-H); 2.07 (m, 2H, C_4-H); 1.73 (s, 3H, C_2-CH_3); 1.51 (dt, 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, C_6-CH_3). ^{13}C NMR ($CDCl_3$): 167.5 (C_{15}); 144.8, 141.6, 132.4, 132.2. 129.5, 120.9 and 119.1 (C_3, C_7, C_8, C_{11}, C_{12}, C_{13} and C_{14}); 143.2 and 133.9 (C_2 and C_9); 115.1 (C_9-CH_2); 54.5 and 51.4 (C_1 and $CO_2\underline{CH_3}$); 35.9, 31.7 and 22.9 (C_4, C_5 and C_{10}); 32.3 (C_6); 27.3, 26.9 and 22.8 (C_2-CH_3 and C_6CH_3).

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}. ^{1}H NMR: ($CDCl_3$): 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-CH_2); 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-CH_3); 1.62 (m, 2H, C_4-H); 1.47 (m, 2H, C_5-H); 1.01 (s, 6H, C_6-CH_3). ^{13}C NMR ($CDCl_3$); 144.6, 137.4 and 128.9 (C_1, C_2 and C_9); 134.4, 132.5, 131.5, 130.8, 130.0 and 127.7 (C_7, C_8, C_{11}, C_{12}, C_{13} and C_{14}); 114.9 (C_9-CH_2); 63.2 (C_{15}); 39.3, 35.4, 32.7 and 19.1 (C_3, C_4, C_5, and C_{10}); 34.1 (C_6); 28.7 and 21.5 (C_2-CH_3 and C_6-CH_3).

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}. ^{1}H NMR ($CDCl_3$): 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-CH_2);

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4.14 (d, 2H, $J=6.0$, C_{15}-H); 3.00 (d, 2H, $J=6.7$, C_{10}-H); 2.16 (d, 1H, $J=9.5$, C_1-H); 2.02 (m, 2H, C_4-H); 1.59 (s, 3H, C_2-CH_3); 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, C_6-CH_3). ^{13}C NMR ($CDCl_3$): 144.8 and 134.6 (C_2 and C_9); 133.3, 132.8, 132.3, 131.9, 131.4, 130.5 and 121.4 (C_3, C_7, C_8, C_{11}, C_{12}, C_{13}, and C_{14}); 114.9 (C_9-CH_2); 63.6 (C_{15}); 55.1 (C_1); 36.1, 32.3 and 23.5 (C_4, C_5 and C_{10}); 32.8 (C_6); 27.8, 27.5 and 23.4 (C_2-CH_3 and C_6-CH_3).

8a: Yellow oil (60%). Anal. Calc. pour $C_{19}H_{26}O$: 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}. ^{1}H NMR (C_6D_6): 9.48 (d, 1H, $J=7.8$, C_{15}-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, $J=15.4$, $J=7.8$, C_{14}-H); 5.95 (m, 2H, C_{11}-H and C_{12}-H); 5.12 and 4.92 (2s, 2H, C_9-CH_2); 2.95 (d, 2H, $J=5.3$, C_{10}-H); 2.03 (t, 2H, $J=6.2$, C_3-H); 1.82 (s, 3H, C_2-CH_3); 1.67 (m, 2H, C_4-H); 1.56 (m, 2H, C_5-H); 1.17 (s, 6H, C_6-CH_3). ^{13}H NMR ($CDCl_3$): 193.8 (C_{15}); 152.2, 144.2, 133.9, 130.4, 129.7 and 128.3 (C_7, C_8, C_{11}, C_{12}, C_{13} and C_{14}); 143.2, 137.1 and 129.3 (C_1, C_2 and C_9); 115.9 (C_9-CH_2); 39.3, 36.0, 32.7 and 19.1 (C_3, C_4, C_5 and C_{10}); 34.7 (C_6); 28.7 and 21.5 (C_2-CH_3 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}. ^{1}H NMR (C_6D_6): 9.46 (d, 1H, $J=7.9$, C_{15}-H); 6.56 (dd 1H, $J=15.5$, $J=10.0$, C_{13}-H); 6.16 (d, 1H, $J=15.5$, C_8-H); 6.00 (dd, 1H, $J=15.2$, $J=7.9$, C_{14}-H); 5.95 (m, 2H, C_{11}-H and C_{12}-H); 5.57 (dd, 1H, $J=15.5$, $J=9.5$, C_7-H); 5.52 (m, 1H, C_3-H); 5.08 and 4.92 (2s, 2H, C_9-CH_2); 2.88 (d, 2H, $J=5.2$, C_{10}-H); 2.21 (d, 1H, $J=9.5$, C_1-H); 2.07 (m, 2H, C_4-H); 1.72 (s, 3H, C_2-CH_3); 1.51 (dt, 1H, $J=13.0$, $J=8.0$, C_5-H); 1.23 (dt, 1H, $J=13.0$, $J=4.8$. C_5-H); 1.01 and 0.92 (2s, 6H, C_6-CH_3). ^{13}C NMR ($CDCl_3$): 193.8 (C_{15}); 152.2, 144.1, 132.4, 132.2, 130.3, 129.7 and 121.0 (C_3, C_7, C_8, C_{11}, C_{12}, C_{13}, and C_{14}); 142.8 and 133.8 (C_2 and C_9); 115.5 (C_9-CH_2); 54.5 (C_1); 36.2, 31.7 and 22.9 (C_4, C_5 and C_{10}); 32.3 (C_6); 27.3, 26.9 and 22.8 (C_2-CH_3 and C_6-CH_3).

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