Pergamon

Tetrahedron Letters 41 (2000) 7221–7224

TETRAHEDRON LETTERS

Syntheses of new 9- and 13-methylene isomers of retinal

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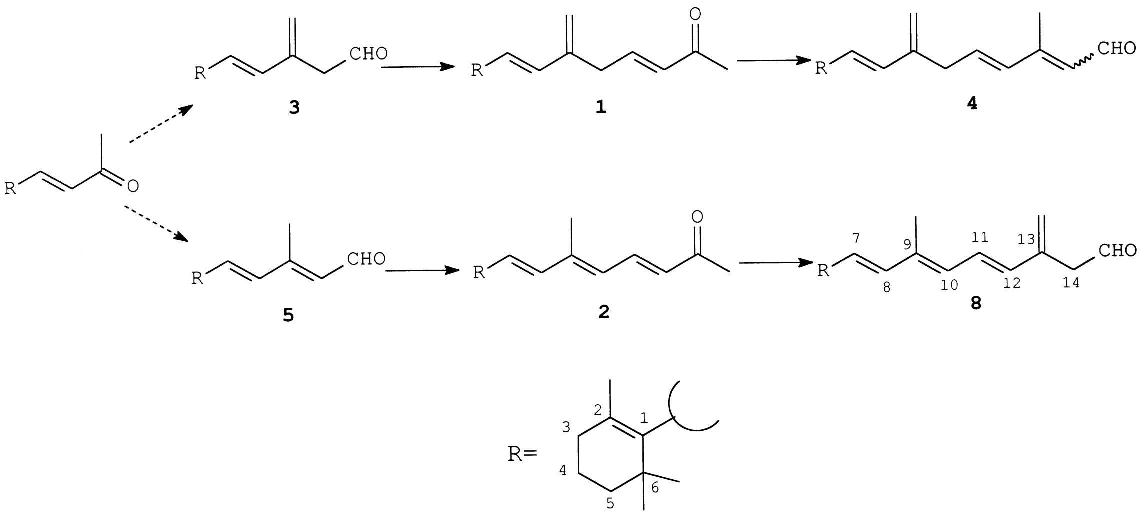
Received 23 June 2000; accepted 21 July 2000

Abstract

Syntheses of new 9- and 13-methylene isomers of retinal via the '9-methylene-C-18 ketone' **1** or 'C-18 ketone' **2** are reported. © 2000 Published by Elsevier Science Ltd.

To our knowledge, only one methylene derivative of retinoids has been reviewed as 13-methylene isomer of retinoic acid[1]. Herein, we describe the syntheses of new isomers of retinal, 9- and 13-methylene using the new C-18 (9-methylene) ketone **1** and the well-known C-18 ketone **2**[2] (Scheme 1).



Scheme 1.

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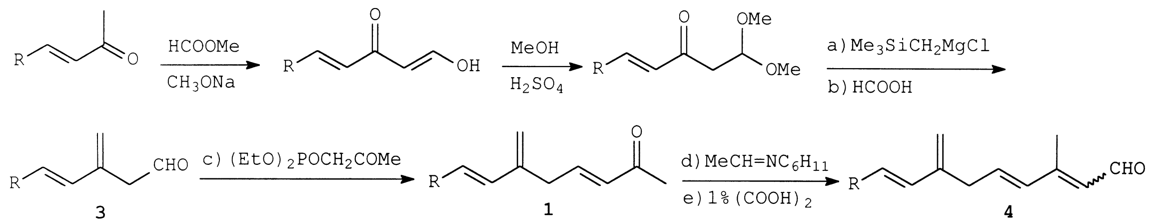
PII: S0040-4039(00)01240-5

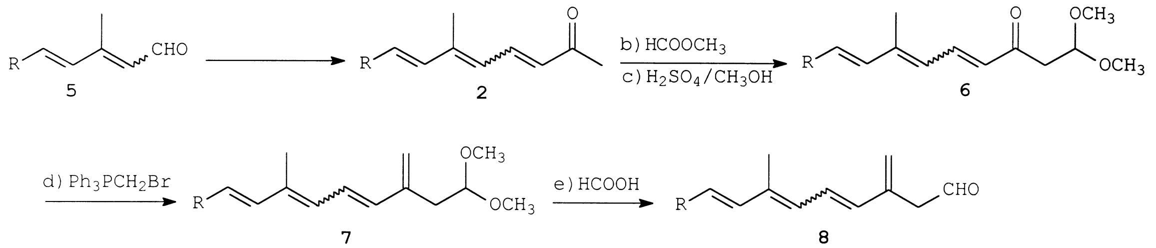
The synthesis of methylene-ketone **1** (11 $E > 99\%$) was achieved by condensation of the β-methylenealdehyde **3** with diethyl (2-oxopropyl) phosphonate: (1) NaH/DME/phosphonate, 0°C; (2) **3**/DME, –10°C, 51%, affording **1**. The aldehyde **3** was synthesised by a Peterson's reaction with the β-ketoacetal, followed by acidic hydrolyse, giving the β-methylenealdehyde **3**. This procedure increased the yield obtained by Wittig's procedure:[3] (1) Me_3SiCH_2MgCl/ether/acetal/0°C then rt, 1 h; (2) HCOOH/cyclohexane, rt, 1 h, 60%. Condensation of ketone **1** with the anion derived of *N*-ethylidenecyclohexylamine:[4] (1) LDA/*N*-ethylidenecyclohexylamine/–78°C /**1**/THF; (2) $(COOH)_2$ 1%/THF, 0°C, 10 min then 65°C, 12 h, 40% affords the 9-methylene retinals **4**[5] (13 *E*: 80/13 *Z*: 20) (Scheme 2).



Scheme 2. (a) Me_3SiCH_2MgCl, ether, 0°C then addition of β-ketocetal, 0°C to rt, 1 h. (b) HCOOH, cyclohexane, rt, 90 min (60%). (c) $(EtO)_2POCH_2COMe$, DME, NaH, 0°C, 1 h then addition of **3**, DME, –10°C to rt, 15 min (55%). (d) LDA, $MeCH{=}NC_6H_{11}$, THF, –30°C to 0°C, 1 h then addition of **8**, THF, –78°C, 1 h. (e) 1% $(COOH)_2$, H_2O, THF, 0°C, 10 min then reflux 12 h (40%)

Synthesis of ketones **2** (9*E*: 80/9*Z*: 20) was performed by condensation of β-ionylidene-acetaldehydes **5** (9*E*: 80/9*Z*: 20) with acetone.[6,7] Formylation of ketones **2** ($HCOOCH_3/CH_3ONa$/pentane) and concomitant ketalisation (H_2SO_4/CH_3OH, 75%) afforded the β-ketoacetals **6** (9*E*: 80/9*Z*: 20). Wittig reaction (*t*-BuOK/$(C_6H_5)_3P^+CH_3$ Br^-/cyclohexane) followed by acidic hydrolysis of the β-methyleneketals **7** (HCOOH/cyclohexane) produced the 9*E* and the 9*Z*-13-methylene retinals **8** separated by column chromatography[8] (SiO_2/CH_2Cl_2 9*E*: 80/9*Z*: 20) (Scheme 3).

These procedures avoid the conjugation of aldehydes **4** and **8** to their α,β-unsaturated analogs.



Scheme 3. (a) Refs. 6 and 7. (b) MeONa, pentane, 0°C then addition of **2**, 0°C to rt, 2 h. (c) MeOH, H_2SO_4, 0°C then rt, 12 h. (d) *t*-BuOK, cyclohexane, $(C_6H_5)_3P^+CH_3$, Br^-, reflux 1 h then addition of **6**, 10°C to rt. (e) HCOOH, H_2O (60:40), rt, 10 min

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5. **1** (11 ***E***). Oil, IR (film): 1699, 1674 cm^{-1}. ^{1}H NMR [400 MHz] (DMSO D-6): 6.91 (dt, 1H, *J* = 16.0, *J* = 6.4, C_{11}–H); 6.12 and 6.05 (2d, 2H, *J* = 16.3, C_7–H and C_8–H); 6.08 (d, 1H, *J* = 16.0, C_{12}–H); 5.12 and 5.03 (2s, 2H, C_9–CH_2); 3.22 (d, 2H, *J* = 6.4, C_{10}–H); 2.19 (s, 3H, C_{14}–H); 1.97 (t, 2H, *J* = 6.0, C_3–H); 1.64 (s, 3H, C_2–CH_3); 1.56 (m, 2H, C_4–H); 1.42 (m, 2H, C_5–H); 0.95 (s, 6H, C_6–CH_3). ^{13}CNMR [100 MHz] ($CDCl_3$): 198.3 (C_{13}); 145.9 (C_{11}); 142.7, 137.1 and 129.4 (C_1, C_2 and C_9); 133.8 and 128.4 (C_7 and C_8); 132.2 (C_{12}); 116.1 (C_9–CH_2); 39.3 (C_5); 35.3 (C_{10}); 34.7 (C_6); 32.7 (C_3); 28.7 (C_6–CH_3); 26.8 (C_{14}); 21.5 (C_2–CH_3); 19.1 (C_4). **1** (11 ***Z***). Oil, IR (film): 1694 cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.25 (d, 1H, *J* = 11.4, C_{12}–H); 6.14 (dt, 1H, *J* = 11.4, *J* = 6.7, C_{11}–H); 6.07 (m, 2H, C_7–H and C_8–H); 5.01 and 4.98 (2s, 2H, C_9–CH_2); 3.64 (d, 2H, *J* = 6.7, C_{10}–H); 2.25 (s, 3H, C_{14}–H); 2.00 (t, 2H, *J* = 6.3, C_3–H); 1.69 (s, 3H, C_2–CH_3); 1.62 (m, 2H, C_4–H); 1.46 (m, 2H, C_5–H); 0.99 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 199.2 (C_{13}); 146.6, 134.2, 128.3 and 126.8 (C_7, C_8, C_{11} and C_{12}); 144.5, 137.3 and 129.1 (C_1, C_2 and C_9); 115.1 (C_9–CH_2); 39.3, 32.7, 32.6 and 19.1 (C_3, C_4, C_5 and C_{10}); 34.0 (C_6); 31.6, 28.7 and 21.5 (C_2–CH_3, C_6–CH_3 and C_{14}). **4** (11 ***E***, 13 *E*). Oil, IR (film): 1668 cm^{-1}. ^{1}H NMR ($CDCl_3$): 10.13 (d, 1H, *J* = 8.0, C_{15}–H); 6.40 (dt, *J* = 15.7, *J* = 6.4, C_{11}–H); 6.30 (d, 1H, *J* = 15.7, C_{12}–H); 6.14 and 6.07 (2d, 2H, *J* = 16.3, C_7–H and C_8–H); 5.92 (d, 1H, *J* = 8.0, C_{14}–H); 5.06 and 4.98 (2s, 2H, C_9–CH_2); 3.20 (d, 2H, *J* = 6.4, C_{10}–H); 2.28 (s, 3H, C_{13}–CH_3); 2.00 (m, 2H, C_3–H); 1.70 (s, 3H, C_2–CH_3); 1.62 (m, 2H, C_4–H); 1.46 (m, 2H, C_5–H); 0.99 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 191.4 (C_{15}); 154.4, 143.6, 137.1 and 129,2 (C_1, C_2, C_9 and C_{13}); 136.9 (C_{11}); 134.5 (C_{12}); 134.0 and 128.3 (C_7 and C_8); 128.6 (C_{14}); 115.6 (C_9–CH_2); 39.3 (C_5); 36.0 (C_{10}); 34.1 (C_6); 32.7 (C_3); 28.7 (C_6–CH_3); 21.5 (C_2–CH_3); 19.1 (C_4); 12.9 (C_{13}–CH_3). **4** (11 ***E***, 13 *Z*). Oil, IR (film): 1669 cm^{-1}. ^{1}H NMR ($CDCl_3$): 10.19 (d, 1H, *J* = 8.1, C_{15}–H); 7.18 (d, 1H, *J* = 15.5, C_{12}–H); 6.30 (dt, *J* = 15.5, *J* = 6.6, C_{11}–H); 6.15 and 6.08 (2d, 2H, *J* = 16.3, C_7–H and C_8–H); 5.85 (d, 1H, *J* = 8.1, C_{14}–H); 5.08 and 5.00 (2s, 2H, C_9–CH_2); 3.24 (d, 2H, *J* = 6.6, C_{10}–H); 2.09 (s, 3H, C_{13}–CH_3); 2.01 (m, 2H, C_3–H); 1.70 (s, 3H, C_2–CH_3); 1.62 (m, 2H, C_4–H); 1.46 (m, 2H, C_5–H); 0.99 (s, 6H, C_6–CH_3). ^{13}CNMR ($CDCl_3$): 190.1 (C_{15}); 154.5, 143.6, 137.1 and 129.3 (C_1, C_2, C_9 and C_{13}); 137.9 (C_{11}); 133.9 and 128.3 (C_7 and C_8); 127.6 (C_{14}); 126.4 (C_{12}); 115.7 (C_9–CH_2); 39.2 (C_5); 36.2 (C_{10}); 34.1 (C_6); 32.7 (C_3); 28.7 (C_6–CH_3); 21.4 (C_2–CH_3); 21.2 (C_{13}–CH_3); 19.1 (C_4).
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8. **6** (9 ***E***, 11 ***E***). Oil, IR (film): 1655 cm^{-1}. ^{1}H NMR [400 MHz] ($CDCl_3$): 7.65 (dd, 1H, J_1 = 15.1, J_2 = 11.9, C_{11}–H); 6.45 and 6.19 (2d, 2H, *J* = 16.0, C_8–H and C_7–H); 6.22 (d, 1H, *J* = 15.1, C_{12}–H); 6.18 (d, 1H, *J* = 11.9, C_{10}–H); 4.88 (t, 1H, *J* = 5.6, C_{15}–H); 3.40 (s, 6H, O–CH_3); 2.91 (d, 2H, *J* = 5.6, C_{14}–H); 2.08 (s, 3H, C_9–CH_3); 2.05 (t, 2H, *J* = 5.7, C_3–H); 1.73 (s, 3H, C_2–CH_3); 1.63 (m, 2H, C_4–H); 1.49 (m, 2H, C_5–H); 1.05 (s, 6H, C_6–CH_3). ^{13}C NMR [100 MHz]($CDCl_3$): 196.7 (C_{13}); 146.1, 137.3 and 131.0 (C_9, C_2 and C_1); 139.4, 136.6, 131.4, 128.5 and 127.6 (C_{12}, C_{11}, C_{10}, C_8 and C_7); 102.2 (C_{15}); 54.0 (O–CH_3); 44.7 (C_{14}); 39.5 (C_5); 34.1 (C_6); 33.0 (C_3); 28.8 (C_6–CH_3); 21.7 (C_2–CH_3); 19.0 (C_4); 13.0 (C_9–CH_3). **6** (9 ***E***, 11 *Z*). Oil, IR (film): 1651 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.73 (dd, J_1 = 15.0, J_2 = 11.9, C_{11}–H); 6.74 and 6.42 (2d, 2H, *J* = 15.9, C_8–H and C_7–H); 6.16 (d, 1H, *J* = 15.0, C_{12}–H); 6.10 (d, 1H, *J* = 11.9, C_{10}–H); 4.87 (t, 1H, *J* = 5.56, C_{15}–H); 3.41 (s, 6H, O–CH_3); 2.90 (d, 2H, *J* = 5.56, C_{14}–H); 2.06 (s, 3H, C_9–CH_3); 2.05 (t, 2H, *J* = 5.2, C_3–H); 1.74 (s, 3H, C_2–CH_3); 1.66 (m, 2H, C_4–H); 1.49 (m, 2H, C_5–H); 1.05 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 196.8 (C_{13}); 145.0, 137.6 and 130.8 (C_9, C_2 and C_1); 138.2, 132.4, 129.1, 127.9 and 126.1 ($C_{12,}$ C_{11}, C_{10}, C_8 and C_7); 102.3 (C_{15}); 54.0 (O–CH_3); 44.8 (C_{14}); 39.3 (C_5); 34.1 (C_6); 32.9 (C_3); 28.8 (C_6–CH_3); 21.7 and 21.0 (C_6–CH_3 and C_2–CH_3); 19.0 (C_4). **7** (9 ***E***, 11 *E*). Oil, IR (film): 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.68 (dd, 1H, J_1 = 15.3, J_2 = 11.2, C_{11}–H); 6.32 (d, 1H, *J* = 15.3, C_{12}–H); 6.20 and 6.12 (2d, 2H, *J* = 16.2, C_8–H and C_7–H); 6.10 (d, 1H, *J* = 11.2, C_{10}–H); 5.16 and 5.11 (2s, 2H, H_2C=); 4.60 (t, 2H, *J* = 5.5, C_{14}–H); 3.38 (s, 6H, O–CH_3); 2.62 (d, 1H, *J* = 5.5, C_{14}–H); 2.03 (t, 2H, *J* = 6.2, C_3–H); 1.97 (s, 3H, C_9–CH_3); 1.72 (s, 3H, C_2–CH_3); 1.63 (m, 2H, C_4–H); 1.48 (m, 2H, C_5–H); 1.04 (m, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 141.6, 137.7, 136.5 and 129.2 (C_{13}, C_9, C_2 and C_1); 137.5, 134.2, 129.8, 126.9 and 125.4 (C_{12}, C_{11}, C_{10}, C_8 and C_7); 117.6 (H_2C=); 103.4 (C_{15}); 53.1 (O–CH_3); 39.5 (C_5); 35.9 (C_{14}); 34.1 (C_6); 32.9 (C_3); 28.8 (C_6–CH_3); 21.6 (C_2–CH_3); 19.1 (C_4); 12.6 (C_9–CH_3). **7** (9 ***E***, 11 *Z*)**.** Oil, IR (film): 1633 cm^{-1}. ^{1}H NMR ($CDCl_3$): 6.78 (dd, 1H, J_1 = 15.3, J_2 = 11.3, C_{11}–H); 6.65 and 6.21 (2d, 2H, *J* = 16.0, C_7–H and C_8–H); 6.25 (d, 1H, *J* = 15.3, C_{12}–H);

6.02 (d, 1H, $J=11.3$, C_{10}–H); 5.15 and 5.11 (2s, 2H, H_2C=); 4.60 (t, 2H, $J=5.6$, C_{15}–H); 3.37 (s, 6H, O–CH_3); 2.60 (d, 2H, $J=5.6$, C_{14}–H); 2.06 (t, 3H, $J=6.0$, C_3–H); 1.98 (s, 3H, C_9–CH_3); 1.75 (s, 3H, C_2–CH_3); 1.65 (m, 2H, C_4–H); 1.50 (m, 2H, C_5–H); 1.05 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 141.5, 137.9, 135.2 and 129.5 (C_1, C_2, C_9 and C_{13}); 133.4, 129.7, 128.6, 128.3 and 124.3 (C_{12}, C_{11}, C_{10}, C_8 and C_7); 117.5 (H_2C=); 103.5 (C_{15}); 53.1 (O–CH_3); 39.4 (C_5); 35.8 (C_{14}); 34.1 (C_6); 32.9 (C_3); 28.8 (C_6–CH_3); 21.7 and 20.6 (C_9–CH_3 and C_2–CH_3); 19.1 (C_4). **8** (9 ***E***, 11 *E*)**.** Oil, IR (film): 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): 9.63 (t, 1H, $J=2.5$, CHO); 6.55 (dd, 1H, $J_1=15.3$, $J_2=11.1$, C_{11}–H); 6.39 (d, 1H, $J=15.3$, C_{12}–H); 6.22 and 6.12 (2d, 2H, $J=16.1$, C_8–H and C_7–H); 6.10 (d, 1H, $J=11.1$, C_{10}–H); 5.32 and 5.16 (2s, 2H, H_2C=); 3.34 (d, 2H, $J=2.5$, C_{14}–H); 2.03 (t, 2H, $J=6.2$, C_3–H); 1.95 (s, 3H, C_9–CH_3); 1.72 (s, 3H, C_2–CH_3); 1.62 (m, 2H, C_4–H); 1.48 (m, 2H, C_5–H); 1.03 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 200.2 (CHO); 137.7, 137.6 and 129.4 (C_{13}, C_9, C_2 and C_1); 137.2, 132.9, 129.2, 127.6 and 127.0 (C_{12}, C_{11}, C_{10}, C_8 and C_7); 119.6 (H_2C=); 47.6 (C_{14}); 39.5 (C_5); 34.1 (C_6); 32.9 (C_3); 28.8 (C_6–CH_3); 21.6 (C_2–CH_3); 19.1 (C_4); 12.7 (C_9–CH_3). **8** (9 ***E***, 11 *Z*). Oil, IR (film): 1723 cm^{-1}. ^{1}H NMR ($CDCl_3$): 9.62 (t, 1H, $J=2.5$, CHO); 6.64 (dd, 1H, $J_1=15.3$, $J_2=11.3$, C_{11}–H); 6.59 and 6.23 (2d, 2H, $J=16.0$, C_8–H and C_7–H); 6.33 (d, 1H, $J=15.3$, C_{12}–H); 6.00 (d, 1H, $J=11.3$, C_{10}–H); 5.32 and 5.14 (2s, 2H, H_2C=); 3.32 (d, 2H, $J=2.5$, C_{14}–H); 2.07 (t, 2H, $J=6.3$, C_3–H); 1.98 (s, 3H, C_9–CH_3); 1.77 (s, 3H, C_2–CH_3); 1.65 (m, 2H, C_4–H); 1.50 (m, 2H, C_5–H); 1.05 (s, 6H, C_6–CH_3). ^{13}C NMR ($CDCl_3$): 200.1 (CHO); 137.7, 136.4 and 129.9 (C_{13}, C_9, C_2 and C_1); 132.2, 129.9, 129.4, 127.6 and 125.8 (C_{12}, C_{11}, C_{10}, C_8 and C_7); 47.5 (C_{14}); 39.4 (C_5); 34.1 (C_6); 33.0 (C_3); 28.9 (C_6–CH_3); 21.7 and 20.6 (C_9–CH_3 and C_2–CH_3); 19.6 (C_4).