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Synthesis of new ethyl 9-methylene-13*E* and 13*Z*-retinoates via the Julia olefination reaction

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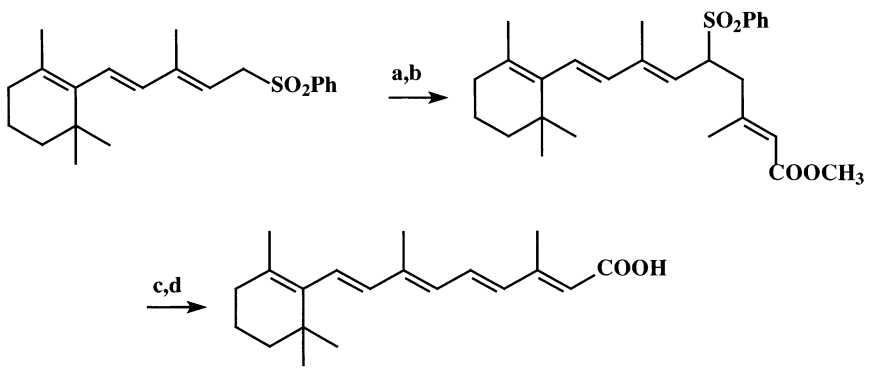
Abstract—Synthesis of new ethyl 9-methylene-13*E* and 13*Z*-retinoates via the 9-methylene C-15 sulphone **5** is reported. The Julia olefination strategy was used for building the C-20 skeleton.

Retinoids are metabolites, derivatives and synthetic analogues of vitamin A which exert biological effects by binding to and activating nuclear retinoid receptors. The therapeutic actions of retinoids are due to their ability to regulate cellular processes such as cellular differentiation, proliferation and modulation of apoptosis.[1–3] The search for new analogues which minimise the wide range of toxic effects is therefore of current interest and prompted us to synthesise the 9 and 13-methylenic analogues of retinal,[4] using β-methylenealdehyde as synthon.[5,6]

It is noteworthy that a few synthetic retinoids possess an *exo*-methylenic sub-structure on the polyene chain.[7–10]

The Julia reaction is by far the most important type of sulphone elimination process and the synthetic significance of this reaction is reflected by its widespread use in the total synthesis of natural products such as retinoic acid[11] (Scheme 1).

We report herein on a synthesis of new 13*Z* and 13*E* ethyl 9-methylene retinoates via a new 9-methylene C-15 sulphone **5**. The required sulphone was prepared as follows: *O*-silylation of the lithium enolate of β-ionone **1** with Me_3SiCl gave the trimethylsilylenol ether **2**. Catalytic condensation ($ZnBr_2$) of enol **2** with chloromethyl phenyl sulphide led to the β-ketosulphide **3**. Peterson olefination of **3** furnished the methylenic sulphide **4**. Oxidation of crude **4**, using bis (trimethylsilyl) peroxide[12] afforded the 9 methylene-C-15 sulphone **5** without any detectable oxidation of the C=C double bonds (Scheme 2).



Scheme 1. (a) EtONa; (b) methyl (2*E*)-4-bromo-3-methyl-2-butenoate; (c) KOH/EtOH; (d) H_3O^+.

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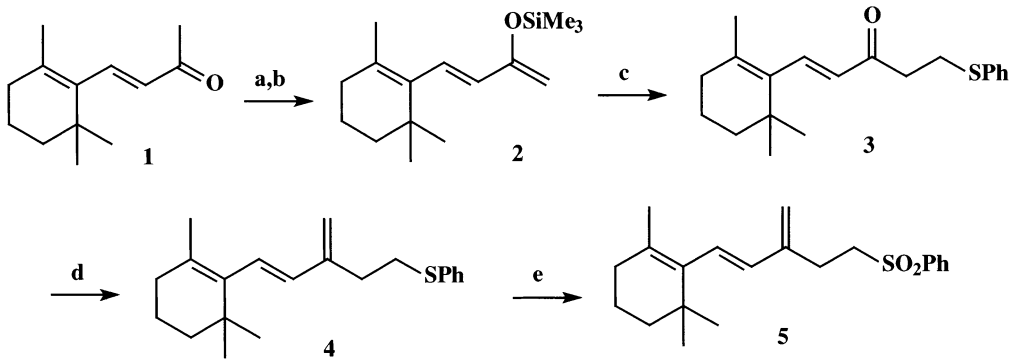
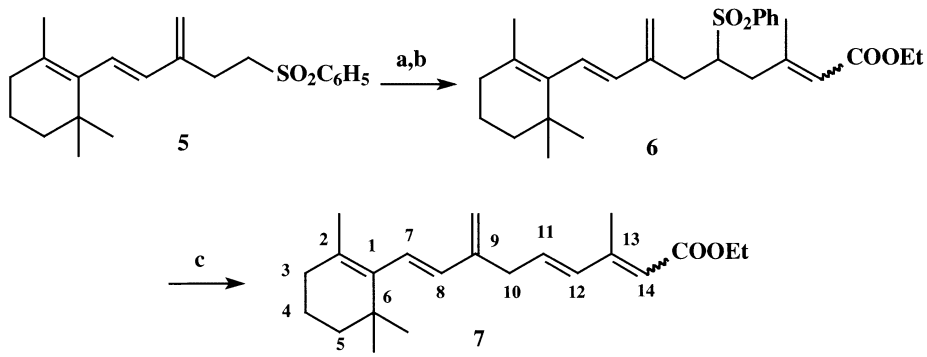


Scheme 2. *Reagents and conditions*: (a) LDA, −70°C/THF, 30 min; (b) Me_3SiCl/−70°C, 30 min to 0°C, 1 h (95%); (c) $C_6H_5SCH_2SCl/CH_2Cl_2/ZnBr_2$ (0.1 equiv), rt, 12 h (55%); (d) Me_3SiCH_2MgCl/ether, 0°C, 30 min then rt, 1 h (85%); (e) bis (trimethylsilyl) peroxide/C_6H_6 80°C, 18 h (70%).



Scheme 3. *Reagents and conditions*: (a) BuLi/THF, −70°C, 30 min; (b) ethyl 4-bromo-3-methyl-2-butenoate (2*E*/2*Z*: 50/50)/THF, −70°C, 90 min (75%); (c) EtONa (5 equiv.)/cyclohexane, 90 min, rt (95%).

The Julia strategy permitted to build the C-20 skeleton with no detectable amounts of conjugated isomers. Thus, anionisation of the sulphone **5** using BuLi, followed by treatment with ethyl 4-bromo-3-methyl-2-butenoate (2*E*/2*Z*: 50/50) led to the sulphone-ester **6**, as a mixture of *E* and *Z* isomers (*E*/*Z*: 50/50). Elimination of the sulfonyl residue to form ethyl 9-methylene-retinoates **7** was performed by treating the crude ester **6** mixture with EtONa in cyclohexane, to form **7** as a mixture of 13*E* and 13*Z* isomers (*E*/*Z*: 50/50) (Scheme 3). Pure analytical samples of compounds **7** (13*E*) and **7** (13*Z*) were obtained by analytical chromatography performed on Merck silica gel (60 F_{254}) plates, using CH_2Cl_2 as eluent.[13]

Acknowledgements

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13. Compound **2**: yellow oil. IR (film): 1610. ^1H NMR (400 MHz, $CDCl_3$): 6.42 and 5.89 (2d, 2H, $J=15.8$, C_7-H and C_8-H); 4.34 and 4.32 (2s, 2H, C_{10}-H); 2.02 (t, 2H, $J=6.2$, C_3-H); 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); 0.27 (s, 9H, $Si(Me)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 155.2, 136.7 and 129.6 (C_9, C_2 and C_1); 129.9 and 128.1 (C_8 and C_7); 95.3 (C_{10}); 39.5 (C_5); 34.0 (C_6); 32.9 (C_3); 28.7 (C_6-CH_3); 22.0 (C_2-CH_3); 19.1 (C_4); 0.0 ($Si(Me)_3$).

Compound **3**: yellow oil. IR (film): 1665; 1604; 1585. ^1H NMR ($CDCl_3$): 7.39–7.20 (m, 6H, Ph and C_7-H); 6.10 (d, 1H, $J=16.3$, C_8-H); 3.25 (t, 2H, $J=7.6$, C_{11}-H); 2.94 (t, 2H, $J=7.6$, C_{10}-H); 2.10 (t, 2H, $J=6.2$, C_3-H); 1.77 (s, 3H, C_2-CH_3); 1.63 (m, 2H, C_4-H); 1.49 (m, 2H, C_5-H); 1.07 (s, 6H, C_6-CH_3). ^{13}C NMR ($CDCl_3$): 198.9 (C_9); 143.2, 130.4, 129.8, 129.4 and 126.6 (C_8, C_7 and Ph); 137.4, 136.3 and 136.2 (C_2, C_1 and q Ph); 40.3 and 40.1 (C_{11} and C_{10}); 34.5 (C_6); 34.0 (C_5); 29.2 (C_6-CH_3); 28.4 (C_3); 22.2 (C_2-CH_3); 19.2 (C_4).

Compound **5**: yellow oil. IR (film): 1603, 1586, 1151. ^1H NMR ($CDCl_3$): 7.97–7.58 (m, 5H, Ph); 5.96 (s, 2H, C_7-H and C_8-H); 4.98 and 4.92 (2s, 2H, H_2C=); 3.30 (m, 2H, C_{11}-H); 2.68 (m, 2H, C_{10}-H); 1.99 (t, 2H, $J=6.3$, C_3-H); 1.65 (s, 3H, C_2-CH_3); 1.60 (m, 2H, C_4-H); 1.45 (m, 2H, C_5-H); 0.96 (s, 6H, C_6-CH_3). ^{13}C NMR ($CDCl_3$): 142.1, 138.8, 136.9 and 129.6 (C_9, C_2, C_1 and q Ph); 133.7, 133.2, 129.3, 128.0 and 127.7 (C_8, C_7 and Ph); 115.6 (H_2C=); 55.3 (C_{11}); 39.3 (C_5); 34.0 (C_6); 32.7 (C_3); 28.8 (C_6-CH_3); 25.3 (C_{10}); 21.5 (C_2-CH_3); 19.0 (C_4).

Compound **7**: (13*Z*) yellow oil. UV (EtOH) λ_{max}: 264 nm. IR (film): 1708; 1613. ^1H NMR (DMSO-d_6): 6.30 (d, 1H, $J=15.7$, C_{12}-H); 6.22 (dt, 1H, $J_1=15.7$, $J_2=6.2$, C_{11}-H); 6.14 and 6.04 (2d, 2H, $J=16.4$, C_7-H and C_8-H); 5.74 (s, 1H, C_{14}-H); 5.07 and 4.99 (2s, 2H, H_2C=); 4.08 (q, 2H, $J=7.1$, CO_2-$\underline{CH_2}$-CH_3); 3.15 (d, 2H, $J=6.2$, C_{10}-H); 2.20 (s, 3H, C_{13}-$\overline{CH_3}$); 1.97 (m, 2H, C_3-H); 1.64 (s, 3H, C_2-CH_3); 1.56 (m, 2H, C_4-H); 1.41 (m, 2H, C_5-H); 1.20 (t, 3H, $J=7.1$, CO_2-CH_2-$\underline{CH_3}$); 0.95 (s, 6H, C_6-CH_3). ^{13}C NMR (DMSO-d_6): 166.6 (C_{15}); 152.3, 144.1, 137.4 and 128.9 (C_{13}, C_9, C_2 and C_1); 135.6 (C_{11}); 134.8 (C_{12}); 134.4 and 128.1 (C_8 and C_7); 117.9 (C_{14}); 116.4 (H_2C=); 59.6 (CO_2-$\underline{CH_2}$-CH_3); 39.3 (C_5); 35.7 (C_{10}); 34.1 (C_6); 32.6 (C_3); 28.9 (C_6-CH_3); 21.7 (C_2-CH_3); 19.1 (C_4); 14.5 (CO_2-CH_2-$\underline{CH_3}$); 13.8 (C_{13}-CH_3).

Compound **7**: (13*E*) yellow oil. UV (EtOH) λ_{max}: 264 nm. IR (film): 1714; 1603. ^1H NMR (DMSO-d_6): 7.57 (d, 1H, $J=15.9$, C_{12}-H); 6.25 (dt, 1H, $J_1=15.9$, $J_2=6.6$, C_{11}-H); 6.13 and 6.03 (2d, 2H, $J=16.4$, C_7-H and C_8-H); 5.66 (s, 1H, C_{14}-H); 5.08 and 5.01 (2s, 2H, H_2C=); 4.06 (q, 2H, $J=7.1$, CO_2-$\underline{CH_2}$-CH_3); 3.17 (d, 2H, $J=6.6$, C_{10}-H); 1.98 (m, 5H, C_{13}-$\overline{CH_3}$ and C_3-H); 1.64 (s, 3H, C_2-CH_3); 1.56 (m, 2H, C_4-H); 1.41 (m, 2H, C_5-H); 1.19 (t, 3H, $J=7.1$, CO_2-CH_2-$\underline{CH_3}$); 0.94 (s, 6H, C_6-CH_3). ^{13}C NMR (DMSO-d_6): 165.6 (C_{15}); 150.9, 144.1, 137.4 and 128.8 (C_{13}, C_9, C_2 and C_1); 137.1 (C_{11}); 134.3 and 128.2 (C_8 and C_7); 128.7 (C_{12}); 116.5 (H_2C=); 116.2 (C_{14}); 59.5 (CO_2-$\underline{CH_2}$-CH_3); 39.3 (C_5); 36.2 (C_{10}); 34.1 (C_6); 32.6 (C_3); 28.9 (C_6-CH_3); 21.7 (C_2-CH_3); 20.8 (C_{13}-CH_3); 19.1 (C_4); 14.5 (CO_2-CH_2-$\underline{CH_3}$).