A New Stereoselective Synthesis of Acitretin (= *Soriatane*®, *Neotigason*®)

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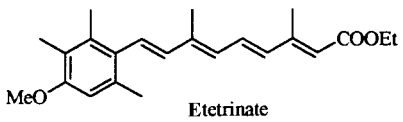
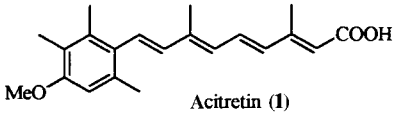
A new synthesis of acitretin *via* a $C_{15} + C_5$ route is reported. The C_{15} unit is the key step, involving a procedure that provides the required (all-*E*)-C_{15}-aldehyde with high stereoselectivity.

Introduction. – 'Etretinate' (*Tigason*®), an aromatic analogue of ethyl retinoate, is currently used for the treatment and prevention of skin malignancies. Because of its favorable pharmacokinetic profile, its corresponding acid 'acitretin' (= *Neotigason*®, *Soriatane*®) actually tends to replace it for the treatment and prevention of a range of cutaneous diseases such as psoriasis (for reviews, see [1]) [2–5].



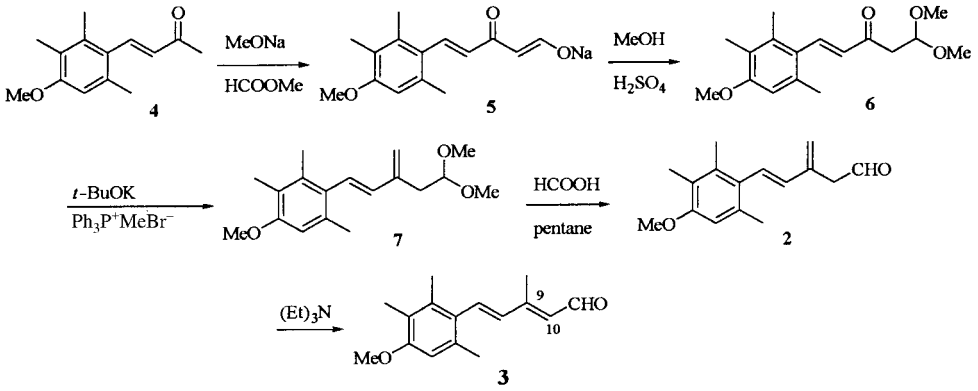
Etetrinate



Acitretin (**1**)

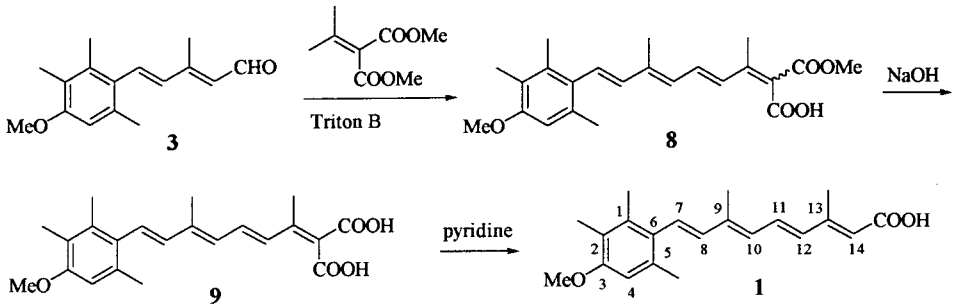
Results and Discussion. – The most usual process of preparation of retinoids is the $C_{15} + C_5$ route, and several reports related to the syntheses of the C_{15} aldehyde synthons have been published (for a book, see [6]). We report herein a new route to the intermediate synthon required for the synthesis of acitretin (**1**). This key-step intermediate was synthesized from a 'β-methylidene aldehyde' compound **2** [7], avoiding the problems linked to the configuration of the C=C bonds, according to usual procedures [8–11]. A convenient reconjugation of **2** led selectively to the (*E*,*E*)-α,β-unsaturated aldehyde **3** ((*E*,*E*)/(*E*,*Z*) 97:3). Thus, a *Stobbe*-like condensation with dimethyl isopropylidenemalonate and concomitant hydrolysis of the intermediary acid-ester obtained led to the new 14-carboxy retinoid, which was regioselectively monodecarboxylated to acitretin (**1**). Formylation of the unsaturated ketone **4** [7] ($MeONa/HCO_2Me$, room temp. 3 h) and acetalization of the sodium salt of the hydroxymethylidene compound **5** ($MeOH/H_2SO_4$, room temp. 12 h) furnished the β-keto acetal **6**. A *Wittig* reaction led to the corresponding methylidene derivative (*t*-BuOK/$Ph_3P^+MeBr^-$, Et_2O, reflux, 1 h then **6**, Et_2O, 0° to room temp., 12 h), which, after acidic hydrolysis of the β-methylidene acetal **7** obtained (HCOOH/pentane, r.t., 3 h), gave the β-methylidene aldehyde **2** (60% from **4**) [12][13]. Catalytic reconjugation (Et_3N, 0.2 equiv., room temp., 24 h) provided quantitatively the (*E*,*E*)-α,β-unsaturated aldehyde **3** ((*E*,*E*)/(*E*,*Z*) 97:3) (*Scheme 1*).

Scheme 1



A *Stobbe*-like condensation of **3** with dimethylisopropylidene malonate (*Triton B*, room temp., 3 h), followed by hydrolysis of the intermediary malonic acid mono-ester **8** (NaOH/MeOH, room temp., 24 h) afforded the corresponding (all-*E*)-14-carboxyacitretin (**9**; 65%). A monodecarboxylation of the pyridinium salt of **9** (pyridine, 2 equiv., room temp., 24 h) yielded stereoselectively the (13*E*)-isomer, *i.e.*, acitretin (**1**; 85%; *Scheme 2*). Acitretin (**1**) was obtained in 33.15% yield from ketone **4**.

Scheme 2



Experimental Part

General. IR Spectra: *Bruker IFS-55* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance DPX-400* spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz); chemical shifts (δ) in ppm downfield from internal TMS, *J* values in Hz. The traditional retinoid numbering system is used for assignment of spectroscopic data.

1-Methoxy-2,3,5-trimethylbenzene. To a stirred suspension of NaH (60% in oil, 7.6 g, 190 mmol) in DMSO (70 ml) was added dropwise a soln. of 2,3,5-trimethylphenol (13.6 g, 100 mmol) and MeI (6.23 ml, 100 mmol) in DMSO (70 ml). The mixture was stirred for 12 h at 30–40° and hydrolyzed with H_2O (700 ml). The aq. layer was extracted with Et_2O, and the org. layers were washed with H_2O and dried ($MgSO_4$). The residue was purified by column chromatography (CC) (silica gel; petroleum/Et_2O 93:7) to provide *1-methoxy-2,3,5-trimethylbenzene* as a yellow oil (13.5 g, 90%). IR (film): 2900, 1600. ^{1}H-NMR: 6.77 (*s*, H–C(6)); 6.69 (*s*, H–C(4)); 3.94 (*s*, MeO); 2.45, 2.38, 2.27 (3*s*, 3 Me). ^{13}C-NMR: 157.7 (C(1)); 137.5, 135.4, 121.8 (C(2), C(3), C(5)); 122.9 (C(4)); 108.9 (C(6)); 55.4 (MeO), 21.3, 19.9, 11.2 (3 Me).

4-Methoxy-2,3,6-trimethylbenzaldehyde. To DMF (22.5 ml) at 0° was slowly added $POCl_3$ (8.9 ml, 95 mmol), and the soln. was stirred for 1 h. A soln. of 1-methoxy-2,3,5-trimethylbenzene (13.5 g, 95 mmol) in

DMF (30 ml) was added, and the soln. was stirred for 30 min at 0° and 24 h at r.t. The mixture was poured onto ice (100 g) and neutralized to pH 6 with 5M NaOH. The aq. layer was extracted with AcOEt, and the org. layer was washed with H_2O and dried ($MgSO_4$). The crude product was purified by CC (silica gel; petroleum/CH_2Cl_2 75:25) to give 10 g (63%) of *4-methoxy-2,3,6-trimethylbenzaldehyde* as yellow needles. M.p. 60–65° (pentane). IR (film): 2900, 1680, 1600. ^{1}H-NMR: 10.55 (*s*, CHO); 6.58 (*s*, H–C(4)); 3.90 (*s*, MeO); 2.62, 2.55, 2.17 (3*s*, 3 Me). ^{13}C-NMR: 192.7 (CO); 160.6 (C(4)); 141.4 (C(1)); 141.1, 126.2, 123.8 (C(2), C(3), C(6)); 110.7 (C(5)); 55.4 (MeO); 21.2, 15.6, 11.1 (3 Me). Anal. calc. for $C_{11}H_{14}O_2$: C 74.13, H 7.92, O 17.95; found: C 74.02, H 7.94, O 18.04.

*(3*E*)-4-(4-methoxy-2,3,6-trimethylphenyl)but-3-en-2-one* (**4**). To a soln. of 4-methoxy-2,3,6-trimethylbenzaldehyde (10 g, 56 mmol) in acetone (200 ml) was added a soln. of NaOH (1.6 g, 40 mmol) in H_2O (16 ml). The soln. was stirred for 24 h and then quenched with 10% HCl. The solvent was evaporated, and the residue was extracted with Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). The crude product was purified by CC (silica gel, CH_2Cl_2) to afford 9 g (75%) of **4**. Yellow oil. IR (film): 2900, 1665, 1600. ^{1}H-NMR: 7.73 (*d*, *J* = 16, H–C(8)); 6.63 (*s*, H–C(4)); 6.27 (*d*, *J* = 16, H–C(7)); 3.85 (*s*, MeO); 2.42 (*s*, Me(10)); 2.37, 2.29, 2.18 (3*s*, 3 Me). ^{13}C-NMR: 198.5 (C(9)); 157.3 (C(3)); 143.1 (C(8)); 136.5, 126.5, 123.1, 118.2 (C(1), C(2), C(5), C(6)); 134.8 (C(7)); 101.1 (C(4)); 55.3 (MeO); 27.3 (C(10)); 21.5, 17.4, 11.7 (Me). Anal. calc. for $C_{14}H_{18}O_2$: C 77.03, H 8.31, O 14.66; found: C 77.14, H 8.20, O 14.68.

*(1*E*)-5,5-Dimethoxy-1-(4-methoxy-2,3,6-trimethylphenyl)pent-1-en-3-one* (**6**). To a suspension of MeONa (1.62 g, 30 mmol) in Et_2O (30 ml) was added dropwise at 0° a soln. of **4** (6.54 g, 30 mmol) and HCO_2Me (3.8 ml, 60 mmol) in Et_2O (30 ml). The mixture was stirred for 2 h at r.t. and filtered off. The precipitate was then dissolved with MeOH (70 ml), and acidified at 0° with 12% H_2SO_4 in MeOH (16 ml). After stirring for 12 h at r.t., the mixture was neutralized with a MeOH soln. of 3M KOH, and the salts were filtered off. The solvent was evaporated, and the residue was extracted with Et_2O. The org. layer was washed with H_2O and brine, and the crude product purified by CC (silica gel; benzene/CH_2Cl_2 50:50) to give 7.38 g (90%) of **6**. Orange oil. IR (film): 2900, 1665, 1600. ^{1}H-NMR: 7.78 (*d*, *J* = 16, H–C(8)); 6.63 (*s*, H–C(4)); 6.30 (*d*, *J* = 16, H–C(7)); 4.92 (*t*, *J* = 6, H–C(11)); 3.85, 3.44 (2*s*, 2 MeO); 3.02 (*d*, *J* = 6, 2 H–C(10)); 2.36, 2.28, 2.17 (3*s*, 3 Me). ^{13}C-NMR: 196.7 (C(9)); 157.4, 136.7, 135.0, 126.6, 123.1 (C(1), C(2), C(3), C(5), C(6)); 143.0 (C(8)); 131.6 (C(9)); 110.1 (C(4)); 102.1 (C(11)); 54.0, 53.4 (MeO); 44.4 (C(10)); 21.5, 17.4, 11.3 (3 Me).

*2-[(1*E*)-3-(2,2-dimethoxyethyl)buta-1,3-dienyl]-5-methoxy-1,3,4-trimethylbenzene* (**7**). To a suspension of *t*-BuOK (3.3 g, 29.4 mmol) in cyclohexane (50 ml) was added $Ph_3P^+MeBr^-$ (11.6 g, 32.6 mmol). The mixture was refluxed for 90 min, cooled to r.t., and, then, a soln. of **6** (5.32 g, 20 mmol) in cyclohexane (20 ml) was added at 0°. The mixture was stirred for 1 h at r.t. and Ph_3PO was filtered off. The filtrate was washed with H_2O, dried ($MgSO_4$), and the residue was purified by CC (silica gel; cyclohexane/CH_2Cl_2 50:50) to provide 4.35 g (75%) of **7**. Orange oil. IR (film): 2900, 1600. ^{1}H-NMR: 6.64 (*d*, *J* = 16, H–C(8)); 6.62 (*s*, H–C(4)); 6.20 (*d*, *J* = 16, H–C(7)); 4.86, 4.81 (2*s*, CH_2=C(9)); 4.56 (*t*, *J* = 6, H–C(11)); 3.40, 3.35 (2*s*, 2 MeO); 2.70 (*d*, *J* = 6, H–C(10)); 2.33, 2.30, 2.16 (3*s*, 3 Me). ^{13}C-NMR: 156.0, 141.3, 141.1, 135.7, 133.7, 122.5 (C(1), C(2), C(3), C(5), C(9)); 135.8 (C(8)); 129.7 (C(7)); 117.2 (*C*H_2=C(9)); 109.7 (C(4)); 103.1 (C(10)); 53.3, 53.1, 52.5 (3 MeO); 40.8 (C(10)); 22.7, 17.2, 11.7 (3 Me). Anal. calc. for $C_{16}H_{20}O_2$: C 78.65, H 8.25, O 14.70; found: C 78.30, H 8.10, O 13.60.

*(4*E*)-5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylidenepent-4-enal* (**2**). To a soln. of **7** (5 g, 17 mmol) in cyclopentane (20 ml) was added HCO_2H (10 ml). The soln. was stirred for 90 min at r.t. H_2O (50 ml) was added, and the aq. layer was extracted with cyclopentane. The org. layer was washed with H_2O and brine, and dried ($MgSO_4$). The residue was purified by CC (silica gel; CH_2Cl_2) to furnish 3.65 g (88%) of **2**. IR (film): 3400, 2950, 1710. ^{1}H-NMR: 9.74 (*t*, *J* = 2.5, H–C(11)); 6.62 (*s*, H–C(4)); 6.51 (*d*, *J* = 16, H–C(8)); 6.28 (*d*, *J* = 16, H–C(7)); 5.34, 5.22 (2*s*, C*H*$_2$=C(9)); 3.84 (*s*, 3 MeO); 3.45 (*d*, *J* = 2.5, H–C(10)); 2.28, 2.22, 2.16 (3*s*, 3 Me). ^{13}C-NMR: 200.4 (C(11)); 156.1, 137.5, 135.8, 133.8, 129.0, 122.6 (C(1), C(2), C(3), C(5), C(9)); (C(4)); 134.9 (C(8)); 129.4 (C(7)); 119.6 (*C*H_2=C(9)); 109.8 (C(4)); 55.4 (MeO); 47.5 (C(10)); 21.2, 17.3, 15.0 (3 Me).

*(2*E*,4*E*)- and (2*Z*,4*E*)-5-(4-Methoxy-2,3,6-trimethyl)-3-methylpenta-2,4-dienal* (**3**). To a soln. of **2** (3.65 g, 15 mmol) in Et_2O (75 ml) was added Et_3N (0.3 ml, 3 mmol). The soln. was stirred for 24 h at r.t. After acidification with a soln. of 10% HCl and extraction with Et_2O, **3** was obtained as a mixture of isomers (3.65 g, 100%, (*E*)/(*Z*) 97:3). The (2*Z*)- and (2*E*)-isomers were separated by CC (silica gel, cyclopentane/Et_2O 90:10).

*Data of (2*E*)-Isomer:* Orange oil. IR (film): 2950, 1680, 1600. ^{1}H-NMR: 10.19 (*d*, *J* = 8, H–C(11)); 7.20 (*d*, *J* = 16, H–C(8)); 6.64 (*s*, H–C(4)); 6.35 (*d*, *J* = 16, H–C(7)); 6.02 (*d*, *J* = 8, H–C(10)); 3.84 (*s*, MeO); 2.44, 2.30, 2.22, 2.17 (4*s*, 4 Me). ^{13}C-NMR: 191.2 (C(11)); 156.8, 154.5, 135.9, 134.1, 128.3, 122.9 (C(1), C(2), C(3), C(5), C(6), C(9)); 136.4, 135.2 (C(8), C(10)); 129.2 (C(7)); 110.0 (C(4)); 55.4 (MeO); 21.3, 17.4, 12.9, 11.7 (Me). Anal. calc. for $C_{16}H_{20}O_2$: C 78.65, H 8.25, O 13.10; found: C 78.60, H 8.30, O 13.10.

Data of (2Z)-Isomer: Orange oil. IR (film): 2950, 1680, 1600. ^{1}H-NMR: 10.19 (*d*, *J* = 8, H–C(11)); 7.27 (*d*, *J* = 16, H–C(8)); 7.11 (*d*, *J* = 16, H–C(7)); 6.66 (*s*, H–C(4)); 5.97 (*d*, *J* = 8, H–C(10)); 3.86 (*s*, MeO); 2.41, 2.30, 2.28, 2.16 (4*s*, 4 Me). ^{13}C-NMR: 189.8 (C(11)); 156.8, 154.6, 135.9, 134.1, 128.3, 128.2, 122.8 (C(1), C(2), C(3), C(5), C(6), C(9)); 136.3 (C(10)); 128.5, 128.3 (C(7), C(8)); 110.0 (C(4)); 55.3 (MeO); 21.4, 21.0, 17.4, 11.7 (4 Me).

*2-[(1*E*,3*E*,5*E*,7*E*)-8-(4-Methoxy-2,3,6-trimethylphenyl)-2,6-dimethylocta-1,3,5,7-tetraenyl]malonic Acid* (**9**). To a mixture of **3** ((2*E*)/(2*Z*) 97:3, 9.82 g, 40.25 mmol) and dimethylisopropylidene malonate (10.6 g, 71.1 mmol) was added a soln. of *Triton B* (40% in MeOH, 42 ml) at 0°. The soln. was stirred for 12 h at r.t. and then hydrolyzed with a soln. of 10% HCl. The aq. layer was extracted with Et_2O and the mono-ester extracted with a soln. of 5% NaOH (2 × 150 ml). The aq. layer was acidified with a soln. of 10% HCl and extracted with Et_2O. The org. layer was washed with H_2O and brine, and dried ($MgSO_4$). The mono-ester was saponified 2 h at r.t. with a soln. of 0.75M NaOH (H_2O/MeOH 60:40, 200 ml). The soln. was acidified with 10% HCl and extracted with Et_2O. The org. layer was washed with H_2O and brine, and dried ($MgSO_4$) to give **9** (13 g, 93%, (9*E*)/(9*Z*) 80:20). The (9*E*)-isomer was easily separated by crystallization in Et_2O (9 g, 65%). M.p. 135°. IR (KBr): 3400, 2950, 1700. ^{1}H-NMR (DMSO): 7.19 (*dd*, *J* = 15, 11, H–C(11)); 7.04 (*d*, *J* = 15, H–C(12)); 6.75, 6.72 (2*d*, *J* = 16, H–C(7), H–C(8)); 6.37 (*s*, H–C(4)); 6.34 (*d*, *J* = 11, H–C(10)); 3.75 (*s*, MeO); 2.50, 2.25, 2.18, 2.10, 2.08 (5*s*, 5 Me). ^{13}C-NMR (DMSO): 167.6, 167.1 (CO_2H); 156.0, 146.2, 140.5, 135.6, 133.3, 129.5, 126.8, 121.9 (C(1), C(2), C(3), C(5), C(6), C(9), C(13), C(14)); 137.9, 133.9 (C(7), C(8)); 131.1 (C(11)); 130.7, 128.9 (C(10), C(12)); 110.4 (C(5)); 55.6 (MeO); 21.5, 17.5, 16.0, 13.1, 12.1 (5 Me). Anal. calc. for $C_{22}H_{26}O_5$: C 71.33, H 7.07, O 21.59; found: C 71.30, H 7.10, O 21.60.

*(3*E*,5*E*,7*E*,9*E*)-10-(4-Methoxy-2,3,6-trimethylphenyl)-4,8-dimethyldeca-3,5,7,9-tetraenoic acid* (*Acitretin*; **1**). A soln. of (9*E*)-**9** (1.8 g, 5.2 mmol) and pyridine (0.84 g, 10.4 mmol) in CH_2Cl_2 (200 ml) was stirred for 24 h at r.t. The solvent was evaporated, and the residue was extracted with Et_2O. The org. layer was washed with a soln. of 10% HCl, H_2O, brine, and dried ($MgSO_4$). After evaporation **1** (1.4 g, 85%) was obtained. M.p. (hexane) 228–230°. IR (KBr): 3400, 2950, 1700. ^{1}H-NMR (DMSO): 7.08 (*dd*, *J* = 15, 11, H–C(11)); 6.72 (2*d*, *J* = 16, H–C(7), H–C(8)); 6.44 (*d*, *J* = 15, H–C(10)); 6.26 (*s* + *d*, *J* = 11, H–C(4), H–C(12)); 5.80 (*s*, H–C(14)); 3.75 (*s*, MeO); 2.50, 2.47, 2.20, 2.08, 2.06 (5*s*, 5 Me). ^{13}C-NMR (DMSO): 168.1 (CO_2H); 156.0, 152.0, 139.2, 135.5, 133.9, 129.5, 121.9 (C(1), C(2), C(3), C(5), C(6), C(9), C(13)); 138.0, 136.1 (C(7), C(8)); 131.1, 130.8 (C(12), C(11)); 128.4 (C(10)); 120.0 (C(14)); 110.4 (C(5)); 55.6 (MeO), 21.5, 17.5, 13.8, 13.0, 12.1 (5 Me). Anal. calc. for $C_{21}H_{26}O_3$: C 77.27, H 8.03, O 14.70; found: C 77.14, H 8.10; O 14.76.

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