Retinoids and Related Compounds; 18:[1] A Convenient Synthesis of Retinoic Acid Analogs Having an Anthraquinone Ring

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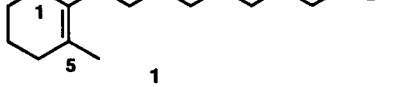
Received 24 October 1994, revised 3 March 1995

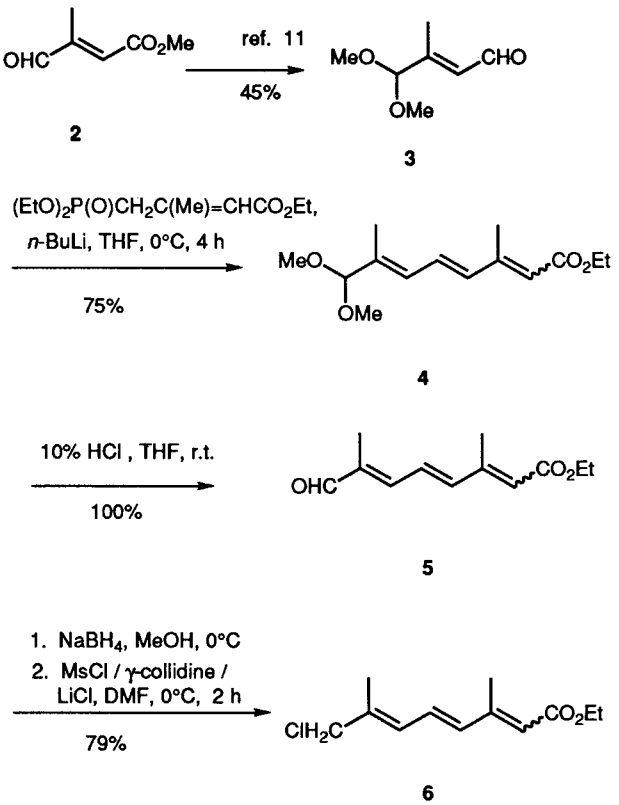
Synthesis of retinoic acid analogs involving an anthraquinone ring is described. The reaction of *p*-toluenesulfonylmethylanthraquinones **8** with ethyl 8-chloro-3,7-dimethyl-2,4,6-octatrienoate **(6)** and subsequent desulfonylation afforded the esters **10** and **11** as a mixture of terminal double bond isomers. After separation of these isomers, basic hydrolysis using 10% potassium hydroxide gave the corresponding acids **12** and **13**, respectively, without isomerization of the terminal double bond in excellent yields.

Retinoic acid **(1)** is a very important compound in the vital cells because it indicates differentiation by binding to a nuclear receptor and subsequent transcription of specific genes,[2] and is known to suppress tumorigenesis as well as antipromotor activity.[3] On the other hand, several naturally occurring compounds having substituted anthraquinone moieties are widely used in cancer chemotherapy,[4] and, also, many naturally occurring anthraquinones exhibit a variety of biological activities.[5] This led to the synthesis of a number of retinoic acid analogs[6] in order to develop new potent compounds with retinoidal activities. In this paper, we wish to report the synthesis of novel retinoic acid analogs, in which the 2,6,6-trimethylcyclohexenyl group in **1** is replaced by the anthraquinone ring.



1

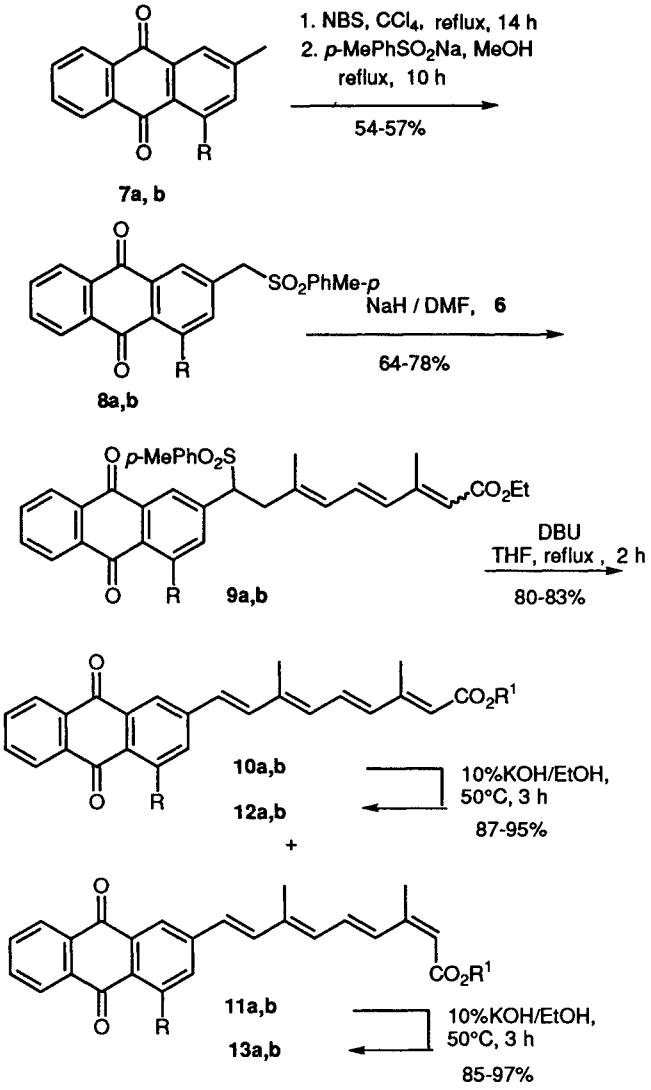
Although most retinoid analogs are synthesized by the step-wise construction of the side chain due to the sensitivity of the conjugated double bond system,[7] there are only few reports dealing with the methodology connecting the ring and the side chains directly ($C_{10} + C_{10}$ method). These studies can be categorized into two classes. The first involves a Wittig reaction[8] and the other an intermediate sulfone for the alkenylation.[9] The significance of these methods has not been sufficiently shown due to lack of examples. We have adopted the latter method because quinones are not suitable for the Wittig reaction. The preparation of side chain part is shown in Scheme 1. The stereoselective synthesis of all-*E*-isomer of the formyl ester **5**[10] has already been reported, however, we used an isomeric mixture of **5** in order to clarify the structure–activity relationship of retinoic acid analogs. The Emmons–Horner reaction of acetal aldehyde **3**[11] prepared from the formyl ester **2** with C_5-phosphonate afforded the acetal ester **4** as an *E*/*Z* isomeric mixture of the C-2 double bond in 75% yield. After deprotection of acetal, the aldehyde group in **5** was reduced with sodium borohydride and the resulting alcohol was converted to the corresponding chloride **6** by treatment with mesyl chloride and collidine in the presence of lithium chloride in 79% yield. *p*-Toluenesulfonylmethylanthraquinone **8a** was easily prepared from the methylanthraquinone **7a** by the sequence of bromination and substitution with sodium *p*-toluenesulfinate. In the same manner, 1-ethoxy derivative **8b** was obtained from 1-ethoxy-3-methylanthraquinone **(7b)** prepared by the alkylation of 1-hydroxy-3-methylanthraquinone.[12]



Scheme 1

Condensation of anthraquinones **8** with the side chain part **6** was accomplished using sodium hydride as a base to give the sulfonyl esters **9** in satisfactory yields. Treatment of these esters with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran under reflux caused desulfonylation to afford the esters **10** and **11** as an *E*/*Z* isomeric mixture of the terminal double bond (3:2), which were separated by preparative TLC in pure form. The ^{1}H NMR spectra of these esters confirm their structures. Thus, the stereochemistry of the newly produced double bond was determined as *E* from the coupling constants, and the *Z* geometry of the terminal double bond was decided from the combination of significant downfield

shift of the olefinic proton and upfield shift of methyl protons (δ = 7.85, 2.10 for **11a**, δ = 7.92, 2.10 for **11b**) in comparison with those of the *E* isomers (δ = 6.46, 2.39 for **10a**, δ = 6.42, 2.37 for **10b**). Finally, basic hydrolysis of **10** and **11** in ethanol at 50 °C afforded the corresponding acids **12** and **13**, respectively, without isomerization of the terminal double bond in high yields (Scheme 2) (Table). The biological activity of **12** and **13** are now under investigation.



7-9	R
a	H
b	OEt

10,11	R	R^1
a	H	Et
b	OEt	Et

12,13	R	R^1
a	H	H
b	OEt	H

Scheme 2

In conclusion, the condensation of *p*-toluenesulfonylmethylanthraquinones **8** with the chloroolefin **6** and subsequent desulfonylation described here provides a new and facile route for the synthesis of retinoic acid analogs having an anthraquinone ring. This methodology could be widely applicable to the preparation of retinoic acid analogs possessing other ring systems.

Melting points are uncorrected. UV spectra were recorded on a JASCO Ubest-55 instrument and IR spectra on a Shimadzu IR-27G spectrometer. ^{1}H NMR spectra were obtained on a Varian XL-200 or VXR-500 NMR spectrometer. Mass spectra were determined on a Hitachi M-80 or M-4100 instrument.

Ethyl (2*E*)- and (2*Z*)-8,8-Dimethoxy-3,7-dimethyl-2,4,6-octatrienoate (4):
To a solution of triethyl 3-methyl-4-phosphonocrotonate[13] (*E*/*Z* = 3:2) (6.7 g, 26 mmol) in THF (30 mL) was added BuLi (1.65 M hexane solution, 16 mL, 26.4 mmol) at 0 °C. After stirring for an additional 30 min, a solution of the aldehyde **3**[11] (2.4 g, 17 mmol) in THF (10 mL) was added at 0 °C and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. NH_4Cl (30 mL) and the mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel using Et_2O/hexane (20:80) as eluent to give the ester **4** as a yellow oil; yield: 3.2 g (75%).

all-*E*-isomer **4**:

IR ($CHCl_3$): ν = 1715, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.84 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 3.31 (s, 6 H, 2 × OCH_3), 4.20 (q, 2 H, *J* = 7 Hz, OCH_2), 4.63 (s, 1 H, OCH), 5.81 (s, 1 H, =CH), 6.33 (d, 1 H, *J* = 11.5 Hz, =CH), 6.35 (d, 1 H, *J* = 15.5 Hz, =CH), 6.87 (dd, 1 H, *J* = 11.5, 15.5 Hz, =CH).

Ethyl (2*E*)- and (2*Z*)-7-Formyl-3-methyl-2,4,6-octatrienoate (5):
To a solution of the ester **4** (3.2 g, 12.6 mmol) in THF (20 mL) was added a solution of 10% H_2SO_4 (10 mL) at r.t. After stirring for 30 min, sat. aq $NaHCO_3$ solution (30 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel using Et_2O/hexane (30:70) as eluent to give **5** as a yellow oil; yield: 2.68 g (100%).

all-*E*-isomer **5**:

IR ($CHCl_3$): ν = 1700, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 2.00 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 4.28 (q, 2 H, *J* = 7 Hz, OCH_2), 6.01 (s, 1 H, =CH), 6.7–7.3 (m, 3 H, =CH × 3), 9.53 (s, 1 H, CHO).

Ethyl (2*E*)- and (2*Z*)-8-Chloro-3,7-dimethyl-2,4,6-octatrienoate (6):
To a solution of $NaBH_4$ (700 mg, 18 mmol) in MeOH (10 mL) was added a solution of **5** (1.7 g, 8.2 mmol) in MeOH (5 mL) at 0 °C. After stirring for 1 h, MeOH was removed under reduced pressure. To the residue was added water (20 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. To a stirred solution of the intermediate hydroxy ester thus obtained (1.71 g, 8.1 mmol), γ-collidine (1.9 g, 16 mmol) and LiCl (690 mg, 16 mmol) in DMF (15 mL) was added MsCl (1.87 g, 16 mmol) at 0 °C. After stirring for 1 h, the resulting mixture was poured into ice water (30 mL), and extracted with Et_2O (3 × 30 mL). The combined extracts were successively washed with 5% HCl (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL), and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel using Et_2O/hexane (15:85) as eluent to give **6** as a yellow oil; yield: 1.47 g (79%).

all-*E*-isomer **6**:

IR ($CHCl_3$): ν = 1700, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.97 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 4.14 (s, 2 H, CH_2Cl), 4.23 (q, 2 H, *J* = 7 Hz, OCH_2), 5.83 (s, 1 H, =CH), 6.27 (d, 1 H, *J* = 11 Hz, =CH), 6.35 (d, 1 H, *J* = 15 Hz, =CH), 6.83 (dd, 1 H, *J* = 11, 15 Hz, =CH).

2-*p*-Toluenesulfonylmethylanthraquinones 8; General Procedure:
A mixture of methylanthraquinone (5 mmol), NBS (5.5 mmol) and AIBN (0.2 mmol) in CCl_4 (80 mL) was heated under reflux for 16 h. After cooling, the precipitate was removed by filtration, and the

Table. Physical and Spectral Data of Retinoic Acid Derivatives **10–13**

Product[a]	Yield (%)	mp (°C) (solvent)	UV (EtOH) λ (nm)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
10a	80[b]	174–176 (CH_2Cl_2/hexane)	425 (sh), 367, 252	1700, 1680, 1590	8.4–8.3 (m, 4H), 7.9–7.8 ,(m, 3H), 7.19 (d, 1H, J = 16), 7.05 (dd, 1H, 11.5, 15.5), 6.81 (d, 1H, J = 16), 6.49 (d, 1H, J = 16), 6.46 (d, 1H, J = 15.5), 5.90 (s, 1H), 4.23 (q, 2H, J = 7), 2.39 (s, 3H), 2.12 (s, 3H), 1.32 (t, 3H, J = 7)
11a	80[b]	167–178 (CH_2Cl_2/hexane)	424 (sh), 367.5, 252	1685, 1670, 1590	8.4–8.3 (m, 4H), 7.9–7.8 (m, 3H), 7.85 (d, 1H, J = 15.5), 7.15 (d, 1H, J = 16), 7.00 (dd, 1H, J = 11, 15.5), 6.77 (d, 1H, J = 16), 6.55 (d, 1H, J = 11), 5.72 (s, 1H), 4.20 (q, 2H, J = 7), 2.10 (s, 6H), 1.32 (t, 3H, J = 7)
10b	83[c]	165–167 (CH_2Cl_2/hexane)	431, 364,5, 251,5	1690, 1660, 1590	8.3–8.2 (m, 2H), 8.04 (s, 1H), 7.8–7.7 (m, 2H), 7.28 (1H, s), 7.12 (d, 1H, J = 16), 7.01 (dd, 1H, J = 11, 16), 6.69 (d, 1H, J = 16), 6.46 (d, 1H, J = 11), 6.42 (d, 1H, J = 16), 5.86 (s, 1H), 4.30 (q, 2H, J = 7), 4.19 (q, 2H, J = 7), 2.37 (s, 3H), 2.10 (s, 3H), 1.62 (t, 3H, J = 7), 1.31 (t, 3H, J = 7)
11b	83[c]	144–146 (CH_2Cl_2/hexane)	429.5, 366, 253	1700, 1665, 1590	8.3–8.2 (m, 2H), 8.03 (s, 1H), 7.92 (d, 1H, J = 16), 7.8–7.7 (m, 2H), 7.32 (1H, s), 7.13 (d, 1H, J = 16), 7.00 (dd, 1H, J = 11, 16), 6.71 (d, 1H, J = 16), 6.57 (d, 1H, J = 11), 5.73 (s, 1H), 4.31 (q, 2H, J = 7), 4.20 (q, 2H, J = 7), 2.10 (s, 6H), 1.62 (t, 3H, J = 7), 1.31 (t, 3H, J = 7)
12a	95	219–222 (CH_2Cl_2)	436 (sh), 365, 252	1690, 1675, 1590	12.15 (br s, 1H), 8.3–7.9 (m, 7H), 7.34 (d, 1H, J = 16), 7.09 (dd, 1H, J = 11.5, 15), 6.96 (d, 1H, J = 16), 6.61 (d, 1H, J = 11.5), 6.51 (d, 1H, J = 15), 5.90 (s, 1H), 2.32 (s, 3H), 2.10 (s, 3H)
13a	97	207–208 (CH_2Cl_2)	435 (sh), 365.5, 253	1690, 1675, 1590	12.19 (br s, 1H), 8.3–7.8 (m, 7H), 7.86 (d, 1H J = 15.5), 7.29 (d, 1H, J = 16), 7.01 (dd, 1H, J = 12, 15,5), 6.85 (d, 1H, J = 16), 6.60 (d, 1H, J = 12), 5.69 (s, 1H), 2.10 (s, 6H)
12b	87	212–212 (CH_2Cl_2)	432, 362.5, 251	1700, 1675, 1590	12.14 (br s, 1H), 8.3–8.0 (m, 2H), 7.90 (s, 1H), 7.9–7.8 (m, 2H), 7.63 (1H, s), 7.34 (d, 1H, J = 16), 7.08 (dd, 1H, J = 12, 16), 6.88 (d, 1H, J = 16), 6.60 (d, 1H, J = 12), 6.52 (d, 1H, J = 16), 5.88 (s, 1H), 4.27 (q, 2H, J = 7), 2.30 (s, 3H), 2.08 (s, 3H), 1.46 (t, 3H, J = 7)
13b	85	205.5–208 (CH_2Cl_2)	434.5, 362.5, 252	1700, 1675, 1600	12.18 (br s, 1H), 8.2–8.0 (m, 2H), 7.90 (s, 1H), 7.9–7.8 (m, 3H), 7.63 (1H, s), 7.41 (d, 1H, J = 16.5), 7.06 (dd, 1H, J = 11.5, 16), 6.87 (d, 1H, J = 11.5, 16), 6.87 (d, 1H, J = 16.5), 6.67 (d, 1H, J = 11.5), 5.71 (s, 1H), 4.27 (q, 2H, J = 7), 2.08 (s, 6H), 1.47 (t, 3H, J = 7)

[a] Satisfactory HRMS values obtained: $m/z \pm 0.0017$.
[b] Yield of **10a** and **11a**
[c] Yield of **10b** and **11b**

filtrate was condensed under reduced pressure. To this residue were added MeOH (50 mL) and sodium *p*-toluenesulfinate (5 mmol) and the resulting mixture was heated under reflux for 10 h. After removal of the solvent, water (60 mL) was added and the product was extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were washed with brine (200 mL), and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give the sulfone **8** as a yellow solid.

2-p-Toluenesulfonylmethylanthraquinone **(8a)**; yield: 54%; mp 205.5–207°C (EtOH) (Lit.[14] mp 218–219°C).

IR ($CHCl_3$): ν = 3050, 1670, 1600, 1315, 1145 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.32 (d, 2H, J = 8 Hz, ArH), 7.62 (d, 2H, J = 8 Hz, ArH), 7.66 (dd, 1H, J = 8, 2 Hz, ArH), 7.8–7.9 (m, 2H, ArH), 8.01 (d, 1H, J = 2 Hz, ArH), 8.27 (d, 1H, J = 8 Hz, ArH), 8.3–8.4 (m, 2H, ArH).

4-Ethoxy-2-p-toluenesulfonylmethylanthraquinone **(8b)**; yield: 57%; mp 207–210°C (EtOH).

IR ($CHCl_3$): ν = 3050, 1680, 1605, 1325, 1150 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.57 (t, 3H, J = 7 Hz, CH_3), 2.41 (s, 3H, CH_3), 4.19 (q, 2H, J = 7 Hz, OCH_2), 4.40 (s, 2H, CH_2), 7.25 (d, 2H, J = 8 Hz, ArH), 7.26 (s, 1H, ArH), 7.54 (d, 2H, J = 8 Hz, ArH), 7.56 (s, 1H, ArH), 7.7–7.9 (m, 2H, ArH), 8.3–8.4 (m, 2H, ArH).

Ethyl (2*E*)- and (2*Z*)-9-(2-Anthraquinoyl)-3,7-dimethyl-2,4,6,8-nonatetraenoates 10, 11; General Procedure:

To a stirred solution of NaH (2.5 mmol) in anhydr. DMF (20 mL) was added a solution of sulfonylanthraquinone **8** (2.5 mmol) in DMF (10 mL) at 0°C. The mixture was stirred for an additional 15 min at r.t., and to this mixture was added dropwise a solution of **6** (2.5 mmol) in DMF (10 mL). The resulting mixture was stirred for further 3 h. After addition of sat. NH_4Cl (40 mL), the organics were extracted with CH_2Cl_2 (3 × 60 mL), washed with brine, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel using Et_2O/CH_2Cl_2 (2.5:97.5) as eluent to give the sulfonyl ester **9**. A mixture of **9** (2 mmol) and DBU (2 mmol) in THF (60 mL) was refluxed for 15 h. After cooling, sat. aq NH_4Cl (40 mL) was added and the organics were extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were washed with brine, and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel using Et_2O/CH_2Cl_2 (2.5:97.5) as eluent to give the esters **10** and **11** as an isomeric mixture. Isolation of each isomer was carried out by preparative TLC (Et_2O/benzene, 5:95), and pure *Z*-

and *E*-isomers were obtained from the first and second band, respectively (Table).

(2*E*)- and (2*Z*)-9-(2-Anthraquinoyl)-3,7-dimethyl-2,4,6,8-nonatetraenecarboxylic Acids 12 and 13; General Procedure:
A mixture of the ester **10** or **11** (0.5 mmol) and 10% KOH (20 mL) in MeOH (10 mL) was heated at 50 °C for 2 h. After cooling, Et_2O (15 mL) was added and aqueous layer was separated. The aqueous layer was made acidic by 10% HCl (20 mL), and the organics were extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4), and after removal of the solvent, the residue was recrystallized to afford the acid **12** or **13** as a red solid (Table).

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