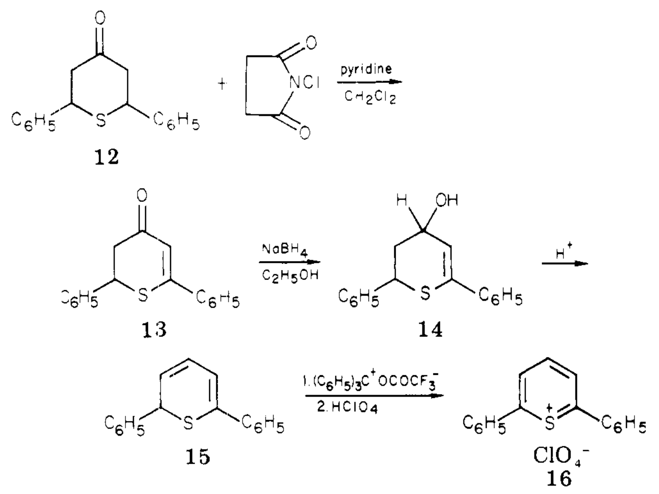
Scheme I



lium salt, and the compound formed in the largest yield was given structure **10**. When a solution of **4** in pyridine was heated on a steam bath, **3** was not formed. The dimer **3** can be prepared from the phosphonium salt **1** and hot pyridine, but this method offers no advantages.

The starting pyrylium salts are conveniently prepared by the method of Dorofeenko and Mezheritskii[6] by adding perchloric acid to a methyl aryl ketone in excess triethyl orthoformate. For the preparation of larger amounts of the pyrylium salt, where the use of large quantities of perchloric acid could be hazardous, anhydrous fluoroboric acid in acetic acid gave the pyrylium fluoroborate salts in good yield. The preparation of 2,6-diphenylthiopyrylium perchlorate is outlined in Scheme I.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The dimers **3**, **5**, and **7** were prepared by published procedures and showed infrared spectra identical with those of the compounds prepared in this paper. The other dimers gave satisfactory elemental analyses. The mass spectra of all the dimers gave an M^+. We had trouble determining the NMR spectra because of the poor solubility of the dimers.

General Method for the Preparation of Dimers. A mixture of 10 mmol of the pyrylium or thiopyrylium salt, 10 wt % of triphenylphosphine, and 15 mL of pyridine was heated on a steam bath for 2 h and chilled. The solid was collected and recrystallized from pyridine.

Reaction of Benzo[*b*]thiopyrylium Perchlorate. A mixture of 1.0 g of benzo[*b*]thiopyrylium perchlorate, 0.1 g of triphenylphosphine, and 5 mL of pyridine was heated on a steam bath for 1 h and chilled. The red solid was collected and recrystallized from pyridine to yield 0.095 g of **11**: mass spectrum, *m/e* 292, 260, 259, 258, 178, 146, 93.

The mother liquors were diluted with methyl alcohol, and the solid was collected and recrystallized twice from a mixture of pyridine and methyl alcohol. The mass spectrum of this material (**10**) gives mostly *m/e* 292 (M^+), but small amounts of *m/e* 438 and 582 were present. The infrared spectra of **10** and **11** were different.

2,6-Diphenylpyrylium Fluoroborate. To 100 mL of acetic anhydride at −10 °C was added 33.3 g of 48% fluoroboric acid, keeping the temperature at 5–15 °C. This solution was added dropwise over 30 min at ambient temperature to a mixture of 23 mL of acetophenone and 100 mL of triethyl orthoformate. The mixture was stirred for 2 h and allowed to stand overnight. The yellow solid was collected and washed with ether: yield 20.2 g; mp 210–212 °C. Anal. Calcd for $C_{17}H_{13}BF_4O$: C, 63.8; H, 4.1. Found: C, 63.6; H, 3.8.

2,6-Diphenylthiopyrylium Perchlorate (16). A mixture of 13.2 g (0.05 mol) of 2,6-diphenyl-2,3-dihydro-4*H*-thiopyran-4-one (**13**),[7] 200 mL of ethanol, and 2 g of $NaBH_4$ was stirred for 1 h and then diluted with water, and the gummy solid was collected. The solid was dissolved in ether, washed with water, and dried ($MgSO_4$), and the solvent was removed, giving 12 g of **14**. Anal. Calcd for $C_{17}H_{16}OS$: C, 76.1; H, 6.0; S, 11.9. Found: C, 75.8; H, 5.8; S, 11.9.

A mixture of 20 g of **14**, 1 g of *p*-toluenesulfonic acid, and 250 mL of toluene was refluxed for 1 h, and the toluene was removed on a rotary evaporator. The residue was dissolved in ether and passed through a short column of alumina. Evaporation of the solvent gave 14 g of **15**.

A mixture of 5.8 g (0.023 mol) of **15**, 6 g (0.023 mol) of triphenylmethanol, and 20 mL of trifluoroacetic acid was refluxed for 2 h, and the solvent was removed under vacuum. The residue was dissolved in ether and ethanol, and 3.5 mL of 70% perchloric acid was added. The mixture was chilled, and the solid was collected. The solid was stirred with 75 mL of boiling benzene and filtered hot. This was repeated twice, giving 6.1 g (83%) of **16**, mp 185–186 °C (lit.[8] mp 185–186 °C).

Registry No. 3, 42506-57-0; **5**, 42506-60-5; **6**, 71750-02-2; **7**, 59155-88-3; **8**, 4388-05-0; **9**, 71750-03-3; **10**, 71750-04-4; **11**, 71785-23-4; **13**, 60839-95-4; **14**, 71750-05-5; **15**, 71750-06-6; **16**, 13586-29-3; benzo[*b*]thiopyrylium perchlorate, 3220-72-2; triphenylphosphine, 603-35-0; 2,6-diphenylpyrylium fluoroborate, 15696-48-7; acetophenone, 98-86-2; triethyl orthoformate, 122-51-0; 2,6-di-*p*-tolylpyrylium perchlorate, 55665-98-0; 2,6-bis(*p*-chlorophenyl)pyrylium perchlorate, 55666-00-7.

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Synthesis of 7,8-Epoxy-7,8-dihydroretinoids

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Of the various retinoid epoxides, only those in which the 5,6 double bond has been oxidized are well documented.[1-3] Recent assertions that retinol undergoes Co(II)-mediated autoxidation to give the 11,12-epoxide[4] or peracetic acid oxidation to give the 11,12-epoxy aldehyde[5] do not seem to be adequately documented and are inconsistent with subsequent experiments.[6] In connection with a project which is directed toward the preparation of possible retinoid metabolites, it is desirable to have samples of the various epoxides. Thus, we have resorted to total synthesis. In this Note we report the synthesis of 7,8-epoxy-7,8-dihydroretinoids **1**–**4**. We have also characterized the 13*Z* isomer of methyl 7,8-epoxy-7,8-dihydroretinoate (**5**).

Reaction of vinylmagnesium bromide with methyl (*E*)-3-formylbut-2-enoate[7] affords alcohol **7** in 83% yield. This

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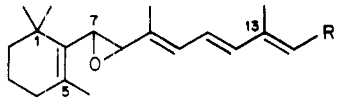
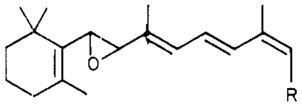
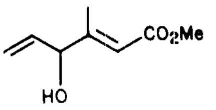


1, R = CO_2H
2, R = CO_2CH_3
3, R = CH_2OH
4, R = CHO



5, R = CO_2CH_3
6, R = CHO



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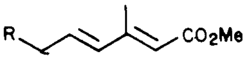
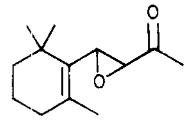


8, R = Br
9, R = PO_3Et_2

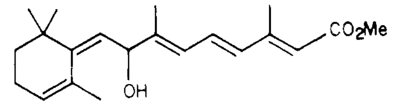


10

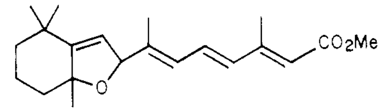
substance is converted by anhydrous HBr in ether into crystalline *E,E* bromo ester **8** (54%). Compound **8** reacts with triethyl phosphite at 130–140 °C to provide phosphonate **9** in quantitative yield. The anion of **9** reacts with the known β-ionone epoxide **10**,[8] furnishing a 55:45 mixture of esters **2** and **5** in 82% yield. The absence of 9*Z* stereoisomers is intriguing, since formation of retinoids by Wittig formation of the C_9–C_{10} bond normally produces larger amounts of the 9*Z* isomer.[9] Pure samples of the two isomers may be obtained by high-pressure liquid chromatography. Stereostructures were assigned to **2** and **5** on the basis of a comparison of their ^{1}H NMR spectra with those of methyl retinoate and methyl (13*Z*)-retinoate. Particularly compelling evidence in favor of the 13*Z* stereochemistry in **5** is the characteristic downfield shift of the C_{12} vinyl proton resonance (7.70 ppm) and upfield shift of the C_{13} methyl resonance (2.04 ppm) relative to the corresponding resonances in **2** (6.35 and 2.34 ppm, respectively). The assigned structures are supported by the ^{13}C NMR spectra (see Table I), especially in the resonances for C-12 and the C-13 methyl group, which occur at 135.7 and 13.7 ppm for the all-trans ester **2** and at 130.2 and 18.0 ppm for the 13-cis ester **5**. The observed shifts are perfectly analogous to those reported for methyl retinoate and methyl (13*Z*)-retinoate by Englert.[10]

Hydrolysis of ester **2** (methanolic NaOH) provides 7,8-epoxy-7,8-dihydroretinoic acid (**1**) in 23% yield. Reduction of **2** using diisobutylaluminum hydride affords the retinol epoxide **3** (85% yield), which may be oxidized by manganese dioxide to yield aldehyde **4**, along with its 13*Z* diastereomer **6**.

Epoxy ester **2** is very acid labile. It reacts instantaneously with HCl in chloroform, giving a complex mixture of products from which alcohol **11** may be isolated in 15% yield. Surprisingly, the 5,8-epoxy-5,8-dihydro isomer **12**[2] is not produced, although it is almost the sole product formed when the 5,6-epoxide is subjected to the same treatment!



11



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Compounds **1**, **2**, and **5** were assayed in the Sporn tracheal organ culture.[11] Results are summarized in Table II, along with comparison data for the corresponding retinoids lacking the 7,8-oxido bridge. It is clear that epoxidation of the 7,8 double bond greatly reduced the activity of retinoic acid. It is somewhat suprising that ester **2** appears to be more active than its parent acid, since the reverse is usually found to be the case.

Experimental Section

All boiling points are uncorrected. IR spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined by using a Varian Model T-60 or EM 390 NMR spectrometer. The chemical shift values are expressed in δ values relative to tetramethylsilane as an internal standard. Significant ^{1}H NMR data are tabulated in parentheses in the following order: number of protons, multiplicity, proton assignments. ^{13}C NMR spectra were determined on a Nicolet TT-23 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Mass spectra were obtained with Varian MS-12 and Consolidated 21-110B mass spectrometers. Mass spectra are given as *m/e* with relative intensities (percent of total ion current) in parentheses. Gas–liquid partition chromatograph (GLC) analyses were performed on a Varian Aerograph 920 analytical gas chromatograph. Preparative high-pressure liquid chromatography(LC) was conducted on a Waters Prep LC/System 500 using Porasil columns. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

Methyl (*E*)-4-Hydroxy-2,5-hexadienoate (7). To a rapidly stirring solution of methyl (*E*)-3-formylbut-2-enoate[7] (2.56 g, 0.02 mol) in 40 mL of ether under a nitrogen atmosphere at −10 to −15 °C is added a solution of vinylmagnesium bromide in THF (14 mL, 1.5 M) over a period of 1 h. After the addition is complete, the mixture is stirred for 10 min and is then diluted with 20 mL of ether and poured over 20 g of crushed ice. The pH of the solution is adjusted to 5–6, and the ether layer is separated and washed with water (30 mL) and brine (30 mL) and then dried over Na_2SO_4. Removal of solvent under reduced pressure affords alcohol **7** as a pale yellow liquid (2.6 g, 83%), which is sufficiently pure to use in the next step. An analytical sample was obtained by chromatography on silica gel using hexane/ether (70:30) as eluant. ^{1}H NMR (CCl_4) δ 5.03–6.03 (4 H, m), 4.50 (1 H, d), 3.70 (3 H, s); IR (neat) ν_{max} 3450, 1720, 1660 cm^{-1}; MS, *m/e* (rel intensity) 156 (0.11), 138 (5.46), 125 (16.30). Anal. Calcd for $C_8H_{12}O_3$: C, 61.53; H, 7.69. Found: C, 61.73; H, 7.70.

Methyl (*E,E*)-6-Bromo-3-methyl-2,4-hexadienoate (8). Anhydrous HBr is bubbled into 20 mL of anhydrous ether and cooled to −20 °C until a saturated solution results (about 10 g of HBr is required). A solution of 1.56 g (0.01 mol) of alcohol **7** in 10 mL of ether is slowly dropped into the ethereal HBr solution. The reaction temperature is allowed to rise to −10 °C, and the mixture is stirred at this temperature for 2 h. The cooling bath is then removed and the mixture allowed to warm to room temperature. After 30 min, the dark brown mixture is poured onto a mixture of 20 mL of water, 10 g of crushed ice, and 20 mL of ether. The ether layer is separated and washed with water (20 mL), saturated

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Table I. ^{13}C NMR Chemical Shifts of 7,8-Epoxy-7,8-dihydroretinoids

	compd			
	2	5	3	4
C-1	34.5	34.4	34.4	34.5
C-2	40.4	40.3	40.3	40.4
C-3	19.2	19.1	19.1	19.2
C-4	32.7	32.6	32.7	32.8
C-5	131.3	131.1	131.0	131.6
C-6	133.4	133.3	136.3	132.7
C-7	58.4	58.0	59.3	58.6
C-8	62.7	62.7	63.1	62.6
C-9	138.5	138.7	137.4	140.5
C-10	126.9	128.0	128.0	129.5
C-11	129.7	130.8 (130.2)[a]	130.7	131.1
C-12	135.7	130.2 (130.8)[a]	136.8	135.2
C-13	152.4	150.8	130.5	153.0
C-14	118.8	116.9	123.9	126.8
C-15	167.3	116.4	58.0	191.0
C-1 CH_3	28.2 (28.5)[a]	28.4 (28.2)[a]	28.5 (28.3)[a]	28.5 (28.3)[a]
C-1′ CH_3	28.5 (28.2)[a]	28.2 (28.4)[a]	28.3 (28.5)[a]	28.3 (28.5)[a]
C-5 CH_3	19.8	19.7	19.7	19.8
C-9 CH_3	11.9	11.6	11.4	12.2
C-13 CH_3	13.7	18.0	12.4	13.0
ester CH_3	50.8	50.7		

[a] This pair of assignments may be reversed.

Table II. Activity of Retinoids in Tracheal Organ Culture[a]

compd	10^{-9} M	10^{-10} M
1	1/7	0/5
2	3/5	3/7
5	3/6	0/4
retinoic acid[b]	419/474	134/256
methyl retinoate[b]	26/28	3/16
ethyl (13*Z*)-retinoate[b]	6/6	

[a] Results are expressed in terms of the fraction of cultures in which the compound effectively reversed keratinization under defined in vitro conditions (see ref 12). [b] Data of D. L. Newton, W. R. Henderson, and M. B. Sporn, private communication.

$NaHCO_3$ (10 mL), and water (20 mL), and is then dried over Na_2SO_4. Removal of solvent affords a brown oil which is immediately purified by chromatography on silica gel, eluting with hexane/ether (80:20). Bromide **8** is obtained as a pale yellow oil (1.54 g, 70%). Further purification may be accomplished by high-pressure LC. In this manner, we obtained 1.19 g (54%) of very pure **8**: mp 37–39 °C; ^{1}H NMR (CCl_4) δ 6.16 (2 H, m), 5.63 (1 H, s), 3.90 (2 H, m), 3.60 (3 H, s), 2.16 (3 H, s); IR (neat) ν_{max} 1710, 1610 cm^{-1}; MS, *m/e* (rel intensity) 220, 218 (4.36), 189, 187 (5.96), 139 (65.62). Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.83; H, 5.02; Br, 36.52. Found: C, 43.66; H, 5.05; Br, 36.50.

Methyl (*E*,*E*)-6-(Diethylphosphono)-3-methyl-2,4-hexadienoate (9). A mixture of triethyl phosphite (0.996 g, 6.0 mmol) and bromo ester **8** (0.876 g, 4.0 mmol) is heated at 130–140 °C under a slow stream of nitrogen for 30 min. The excess triethyl phosphite is removed under reduced pressure, leaving 1.10 g of yellow oil which is purified by chromatography on silica gel, eluting with chloroform/methanol (99:1). Pure **9** is obtained as a colorless oil (1.08 g, 100%). ^{1}H NMR (CCl_4) δ 5.53–6.26 (3 H, m), 3.93 (4 H, m), 3.56 (3 H, s), 2.50 (2 H, dd), 2.26 (3 H, s), 1.23 (6 H, t); IR (neat) ν_{max} 1710, 1620, 1610, 1030, 1010 cm^{-1}; MS, *m/e* (rel intensity) 276 (23.81). Anal. Calcd for $C_{12}H_{21}O_5P$: C, 52.17; H, 7.60; P, 11.03. Found: C, 51.24; H, 7.73; P, 11.02.

7,8-Epoxy-7,8-dihydro-β-ionone (10). To a rapidly stirring solution of β-ionone (9.6 g, 50 mmol) and 8 mL of 30% H_2O_2 in 60 mL of methanol at 30–35 °C is added 3 mL of 6 N aqueous NaOH over a period of 3 h (syringe pump). After the addition is complete, 200 mL of water and 150 mL of ether are added. The ether layer is separated, washed with more water (2 × 100 mL) and dried over Na_2SO_4. Evaporation of solvent affords the crude epoxide. Purification by preparative high-pressure LC provided 5.92 g (57%) of analytically pure material: ^{1}H NMR (CCl_4) δ 3.53 (1 H, br s), 3.13 (1 H, d), 2.03 (3 H, s), 1.63 (3 H, s), 1.20 (3 H, s), 1.03 (3 H, s); IR (neat) ν_{max} 1710, 1670 cm^{-1}; MS, *m/e* (rel intensity) 208 (23.80), 193 (15.49), 190 (9.87). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.67. Found: C, 74.78; H, 9.45.

Methyl 7,8-Epoxy-7,8-dihydroretinoates 2 and 5. To a suspension of 94 mg (2.2 mmol, 57% dispersion, washed with pentane) of sodium hydride in 2 mL of THF under a nitrogen atmosphere is added a solution of phosphonate **9** (608 mg, 2.2 mmol) in 2 mL of THF. After being stirred at room temperature for 5 min, the mixture is cooled in an ice bath, and a solution of ketone **10** (416 mg, 2.0 mmol) in 2 mL of THF is added dropwise. The resulting mixture is stirred at 0 °C for 2 h and is then diluted with 40 mL of ether. The organic phase is washed with water (4 × 20 mL) and brine (20 mL) and then dried over Na_2SO_4. Removal of solvent affords 540 mg (82%) of a pale yellow oil which is chromatographed on Woelm activity V alumina, eluting with ether/hexane (20:80). In one such run, 505 mg (76%) of colorless oil was obtained and was demonstrated by analytical high-pressure LC (μ-Porasil, 98:2 hexane/ether, 2.5 mL min^{-1}) to be a 45:55 mixture of 13*Z* and 13*E* diastereomers. This material was separated by preparative high-pressure LC (Porasil, 98:2 hexane/ether) to furnish 140 mg of pure **2**, 50 mg of pure **5**, and 250 mg of a mixture of the two isomers. The mixed fraction was rechromatographed to obtain a further 60 mg of **2** and 44 mg of **5**. Thus, in this experiment, the yield of pure **2** (mp 75–76 °C) was 44%, while the yield of **5** (oil) was 18%.

Epoxy ester 2: ^{1}H NMR (CCl_4) δ 6.80 (1 H, dd, *J* = 9, 15 Hz), 6.24 (3 H, m), 5.66 (1 H, s), 3.6 (3 H, s), 3.3 (1 H, br s), 3.03 (1 H, d, *J* = 1 Hz), 2.30 (3 H, s), 1.73 (3 H, s), 1.62 (3 H, s), 1.16 (3 H, s), 1.03 (3 H, s); IR (CCl_4) ν_{max} 1720, 1605 cm^{-1}; UV (EtOH) λ_{max} 324 nm (ϵ 16 000); MS, *m/e* (rel intensity) 330 (16.19), 315 (9.43). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.29; H, 9.24.

Epoxy ester 5: ^{1}H NMR (CCl_4) δ 7.70 (1 H, d, J = 14Hz), 6.13–6.90 (2 H, m), 5.53 (1 H, s), 3.60 (3 H, s), 3.30 (1 H, br s), 3.06 (1 H, d, J = 1Hz), 2.07 (3 H, s), 1.73 (3 H, s), 1.63 (3 H, s), 1.20 (3 H, s), 1.06 (3 H, s); IR (CCl_4) ν_{max} 1720, 1605 cm^{-1}; UV (EtOH) λ_{max} 315 (ϵ 10 900); MS, *m/e* (rel intensity) 330 (2.77), 315 (2.02). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.11; H. 9.30.

7,8-Epoxy-7,8-dihydroretinoic Acid (1). A solution of crystalline epoxy ester **2** (140 mg, 0.42 mmol) in 1.5 mL of 1 N methanolic NaOH is heated to reflux for 2 h. The solution is then cooled in an ice bath and extracted with 10 mL of petroleum ether. The methanol layer is separated, diluted with 10 mL of ether, and then stirred rapidly at 0 °C while aqueous 0.1 N HCl is slowly added. When the pH reaches about 7, 2 mL of pH 4 buffer solution is added, and the ether layer is separated. The aqueous layer is extracted with a further 10 mL of ether. The combined ether extracts are washed with 15 mL of water, dried over Na_2SO_4, and evaporated to yield an oil. Trituration of this oil with 5 mL of cold hexane affords 70 mg (53%) of crude acid 1. Recrystallization from hexane furnishes 30 mg of pure 1 as pale yellow crystals: mp 153–154 °C; ^{1}H NMR (CDCl$_3$) δ 6.93 (1 H, t), 6.33 (1 H, s), 6.16 (1 H, d), 5.76 (1 H, s), 3.36 (1 H, br s), 3.16 (1 H, d), 2.33 (3 H, s), 1.76 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.06 (3 H, s); IR (CH$_2$Cl$_2$) ν_{max} 1680, 1600 cm^{-1}; UV (EtOH) λ_{max} 302 (ε 50 000); MS, *m/e* (rel intensity) 316 (10.36). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.91. Found: C, 75.58; H, 9.13.

7,8-Epoxy-7,8-dihydroretinol (3). To a stirring solution of ester 2 (520 mg, 1.57 mmol) in 6 mL of THF under a nitrogen atmosphere at −78 °C is added 3.5 mL of 1 M diisobutylaluminum hydride in hexane over a period of 20 min. After the addition is complete, the mixture is stirred for 20 min more at −78 °C and is then allowed to warm to −20 °C, at which point 2 mL of water is added. The resulting mixture is warmed to room temperature, and 10 mL of ether is added. The ether phase is separated and washed with water (3 × 10 mL). Removal of solvent under reduced pressure affords alcohol 3 (450 mg, 94%) as a pale yellow oil. Purification may be achieved by chromatography on Woelm activity V alumina, eluting with ether/hexane (30:70). Pure alcohol 3 is a colorless oil (405 mg, 85%): ^{1}H NMR (CDCl$_3$) δ 6.10–6.66 (3 H, m), 5.63 (1 H, t), 4.23 (2 H, d), 3.40 (1 H, m), 3.13 (1 H, d), 1.83 (3 H, s), 1.70 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.06 (3 H, s); IR (neat) ν_{max} 3450, 1690 cm^{-1}; UV (EtOH) λ_{max} 284 (ε 35 000); MS, *m/e* (rel intensity) 302 (1.06). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.99. Found: C, 79.66; H, 9.80.

7,8-Epoxy-7,8-dihydroretinal (4). To a stirring solution of alcohol 3 (130 mg, 0.43 mmol) and three drops of triethylamine in 5 mL of pentane under a nitrogen atmosphere is added 400 mg of γ-MnO$_2$. The reaction course is monitored by thin-layer chromatography (silica gel, 30:70 ether/hexane). After the starting material disappears (about 20 min), 10 mL of ether is added, and the mixture is filtered. Removal of solvent affords 100 mg (77%) of yellow oil which is shown by ^{1}H NMR to be a 80:20 mixture of aldehydes 4 and 6. Preliminary purification may be effected by chromatography on Woelm activity V alumina, eluting with hexane/ether (85:15). In this manner, 40 mg (31%) of a mixture of 4 and 6 was obtained. The two diastereomers are rather difficult to separate, mainly because they are somewhat unstable. We succeeded in obtaining 15 mg of the pale yellow aldehyde 4, of 95% purity, for analytical and biological evaluation: ^{1}H NMR (CDCl$_3$) δ 10.00 (1 H, d), 5.66–6.83 (4 H, m), 3.30 (1 H, m), 3.03 (1 H, d), 2.3 (3 H, s), 1.76 (3 H, s), 1.63 (3 H, s), 1.16 (3 H, s), 1.03 (3 H, s); IR (CCl$_4$) ν_{max} 1660, 1613, 1600 cm^{-1}; UV (EtOH) λ_{max} 337 (ε 27 000); MS, *m/e* (rel intensity) 300 (7.06); high-resolution MS: $C_{20}H_{28}O_2$ requires *m/e* 300.2089. Found: *m/e* 300.2088.

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Registry No. 1, 71685-87-5; 2, 71685-88-6; 3, 71685-89-7; 4, 71685-90-0; 5, 71748-35-1; 6, 71748-36-2; 7, 71685-91-1; 8, 71685-92-2; 9, 71685-93-3; 10, 38448-31-6; methyl (*E*)-3-formylbut-2-enoate, 40835-18-5; triethyl phosphite, 122-52-1; β-ionone, 14901-07-6.

New Synthesis of 5-Methylbenzo[*a*]pyrene and 11-Methylbenzo[*a*]pyrene [1,2]

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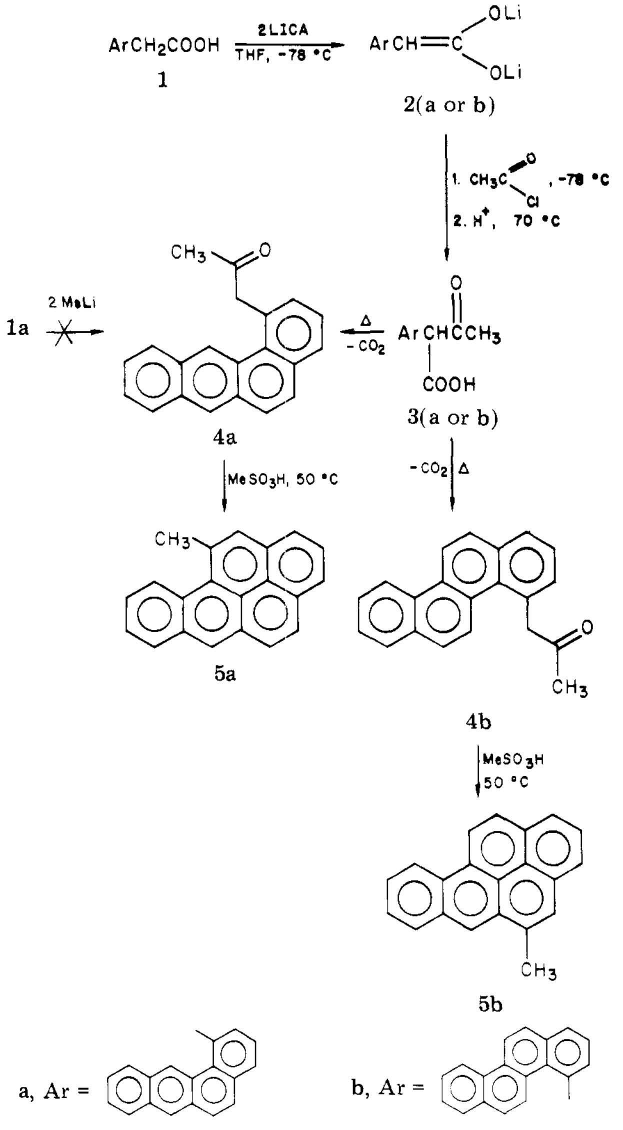
In the course of developing useful syntheses of the potent carcinogen benzo[*a*]pyrene labeled with ^{13}C (90%) at each of the peripheral carbon atoms, we had available the arylacetic acids **1a** and **1b**[3] which are likely intermediates for the preparation of 11-methylbenzo[*a*]pyrene (**5a**) and 5-methylbenzo[*a*]pyrene (**5b**) via the ketones **4a** and **4b**, respectively. Attempts to prepare the ketone **4a** by the addition of 2 equiv of methyllithium to a THF solution of the acid[4] **1a** failed, the only product isolated being the unreacted acid **1a**. Apparently the second equivalent of methyllithium converted the lithium salt of the acid to the dilithium enolate **2a** rather than to the methyl ketone **4a**.



Since the dilithium enolates of carboxylic acids containing at least one α-hydrogen are readily prepared[5] and lithium enolates of esters have been shown to react with acid chlorides to form substituted β-keto esters,[6] we investigated the reaction of the dilithioenolate **2a** with acetyl chloride.[7] Indeed, the reaction of 1-benz[*a*]anthraceneacetic acid (**1a**) with 2 equiv of lithium *N*-isopropylcyclohexylamide (LICA) in THF at −78 °C followed by treatment with acetyl chloride afforded 2-(benz[*a*]anthracen-1-yl)-3-oxobutanoic acid (**3a**) which was decarboxylated at 120–130 °C to give 1-(benz[*a*]anthracen-1-yl)-2-

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