Quantitative conversion of **4** into **7** via **6** was also observed when **4** was treated with 0.5 N DCl–D_2O–CD_3OD at room temperature for 2 h (by ^1H NMR). The isolated yield of **7** from **4** by this latter method was 85%. It is interesting to note that **6** is hydrolyzed with exclusive ring retention under such mild conditions as described above since it is known that compounds **8** and **9** are hydrolyzed rapidly with 70% and nearly 100% ring opening, respectively, and that compounds **10** and **11** are hydrolyzed as slowly as their acyclic analogues.[4a]

In summary, we have described a facile synthesis of **6** by spontaneous or silica gel catalyzed cyclization of **5** and the synthesis of **7** by spontaneous or acid-catalyzed hydrolysis of **6**.

Experimental Section

The melting point was determined on a Yanagimoto micromelting point apparatus and is uncorrected. ^1H and ^{13}C NMR spectra of **7** were determined on a Jeol FX-100 spectrophotometer. All other ^1H NMR spectra were determined on a Hitachi R-24 spectrophotometer. Infrared spectra were obtained on a 215 Hitachi grating infrared spectrophotometer. Mass spectra were obtained on a Jeol JMS-OISG spectrometer. Elemental analyses were obtained on a Yanaco CHN Corder MT-2 instrument. Merck precoated silica gel $60F_{254}$ plates were used for TLC and visualization was performed by I_2 for all compounds and the molybdenum blue reagent[5] for **6** and **7**. Silica gel, 60–80 mesh, used for column chromatography, was a product of Kanto Chemical Co., Inc., Tokyo.

Di-*n*-butyl 3-(2-Tetrahydropyranyloxy)-1-propynylphosphonate (2). A solution of **1** (42 g, 0.3 mol) in THF (120 mL) was added dropwise to a stirred solution of EtMgBr (0.3 mol) in THF (240 mL) at 0–5 °C under N_2 and the mixture was stirred at room temperature for 30 min. To this mixture was added a solution of $ClPO(OBu\text{-}n)_2$[2] (68.6 g, 0.3 mol) in benzene (360 mL) dropwise, keeping the temperature below 40 °C. After being stirred at room temperature for a further 3 h, the mixture was worked up in the usual manner. The crude product was chromatographed (silica gel, 200 g; Et_2O–hexane, 1:1) to afford **2** (49.7 g, 50%) as an oil: IR (neat) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ ~3.6 (2 H, m, OCH_2 of THP), 4.05 (4 H, dt, $^3J_{PH}$ = 7 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.31 (2 H, d, $^4J_{PH}$ = 4 Hz, 3-H), 4.74 (1 H, m, acetal H).

Di-*n*-butyl 3-Hydroxy-1-propynylphosphonate (3). A solution of **2** (20 g, 60 mmol) and TsOH (100 mg) in MeOH (300 mL) was heated at 55 °C for 1 h. MeOH was removed at room temperature and the residue was dissolved in Et_2O (200 mL), washed with 5% $NaHCO_3$ solution followed by brine, and dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed (silica gel, 200 g; MeOH–Et_2O, 1:49) to afford **3** (11.5 g, 77%) as an oil: IR (neat) 3380, 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (4 H, dt, $^3J_{PH}$ = 7.5 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.23 (2 H, d, $^4J_{PH}$ = 4 Hz, 3-H).

Di-*n*-butyl *cis*-3-(2-Tetrahydropyranyloxy)-1-propenylphosphonate (4). Compound **2** (6.64 g, 20 mmol) was hydrogenated in the same manner as described for the preparation of **5** from **3** (see below). The crude product was chromatographed (silica gel, 120 g; Et_2O–hexane, 2:1) to afford **4** (6.21 g, 93%) as an oil: IR (neat) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ ~3.6 (2 H, m, OCH_2 of THP), 4.02 (4 H, br q, $^3J_{PH} \simeq {}^3J_{HH} \simeq$ 6 Hz, OCH_2 of *n*-Bu), 4.58 (3 H, m, acetal H and 3-H), 5.63 (1 H, ddt, $^3J_{PH}$ = 19 Hz, $^3J_{HH}$ = 14 Hz, $^4J_{HH}$ = 1.5 Hz, 1-H), 6.60 (1 H, ddt, $^3J_{PH}$ = 50 Hz, $^3J_{HH_1}$ = 14 Hz, $^4J_{HH_3}$ = 5.5 Hz, 2-H).

Di-*n*-butyl *cis*-3-Hydroxy-1-propenylphosphonate (5). A mixture of **3** (12.82 g, 51.7 mmol), 5% Pd–$BaSO_4$ (0.4 g), quinoline (0.4 g), and MeOH (100 mL) was shaken under H_2 at room temperature and at atmospheric pressure until 1 equiv of H_2 was absorbed. The mixture was filtered and evaporated to give crude **5** as an oil (ca. 95% pure by ^1H NMR): IR (neat) 3400, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (4 H, dt, $^3J_{PH}$ = 7 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.48 (2 H, m, 3-H), 5.57 (1 H, ddt, $^2J_{PH}$ = 17 Hz, $^3J_{HH}$ = 14 Hz, $^4J_{HH}$ = 1.5 Hz, 1-H), 6.70 (1 H, ddt, $^3J_{PH}$ = 53 Hz, $^3J_{HH_1}$ = 14 Hz, $^3J_{HH_3}$ = 5.5 Hz, 2-H).

2-*n*-Butyloxy-2-oxo-1,2-oxaphosphol-3-ene (6). Crude **5** obtained from **3** (1.24 g, 5 mmol) as above was percolated through a silica gel (30 g) column using MeOH–Et_2O (1:49) as an eluent to afford pure **6** (0.73 g, 83% from **3**) as an oil: TLC R_f 0.70 (BuOH–AcOH–H_2O, 3:1:1); IR (neat) 3080, 1590 cm^{-1}; mass spectrum *m/e* 176 (M^+); ^1H NMR ($CDCl_3$) δ 3.95 (2 H, dt, $^3J_{PH}$ = 9 Hz, $^3J_{HH}$ = 6.5 Hz, OCH_2 of *n*-Bu), 4.75 (2 H, d of br t, $^3J_{PH}$ = 6.5 Hz, $^3J_{HH} = {}^4J_{HH}$ = 2 Hz, 5-H),[7] 6.10 (1 H, ddt, $^2J_{PH}$ = 34 Hz, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$ = 2.5 Hz, 3-H), 7.15 (1 H, ddt, $^3J_{PH}$ = 47 Hz, $^3J_{HH_3}$ = 9 Hz, $^3J_{HH_5}$ = 1.5 Hz, 4-H). Anal.[8] Calcd for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 46.96; H, 7.46.

2-Hydroxy-2-oxo-1,2-oxaphosphol-3-ene (7). (A) Compound **6** (0.242 g, 1.38 mmol) was kept in a vial as a ca. 1 mm thick film at room temperature under air for 48 h. Crystals separated were washed with Et_2O–hexane (2:1) to afford pure **7** (0.166 g, 95%): mp 110–111 °C; TLC R_f 0.07 (BuOH–AcOH–H_2O, 3:1:1); IR (Nujol) 3500–2000, 3100, 1590, 1250–1200, 1010 cm^{-1}; mass spectrum *m/e* 120 (M^+); ^1H NMR ($Me_2SO\text{-}d_6$)[9,10] δ 4.67 (2 H, d of br t, $^3J_{PH}$ = 5.9 Hz, $^3J_{HH} \simeq {}^4J_{HH} \simeq$ 2 Hz, 5-H),[11] 6.30 (ddt, $^2J_{PH}$ = 34.8 Hz, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.4 Hz, 3-H), 7.14 (ddt, $^3J_{PH}$ = 45.6 Hz, $^3J_{HH_3}$ = 8.5 Hz, $^3J_{HH_5}$ = 1.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$)[10] δ 147.5 ($^2J_{PC}$ = 15.9 Hz, 4-C), 118.2 ($^1J_{PC}$ = 157.5 Hz, 3-C), 70.2 ($^2J_{PC}$ = 13.4 Hz, 5-C). Anal. Calcd for $C_3H_5O_3P$: C, 30.01; H, 4.20. Found: C, 30.05; H, 4.20. Recrystallization from $CHCl_3$ did not alter the physical constants.

(B) A solution of **4** (3.34 g, 10 mmol) in 0.5 N HCl in H_2O–MeOH (1:4, 15 mL) was stirred for 2 h at room temperature. The solvent was evaporated at room temperature and the residue was recrystallized from $CHCl_3$ to afford **7** (1.02 g, 85%). The physical constants were the same as given above.

Acknowledgment. We thank Dr. T. Suzuki and Miss K. Koizumi for taking the ^1H and ^{13}C NMR spectra of **7**, Mrs. T. Yamashiro for mass spectral measurements, and Miss Y. Nakajo for elemental analyses.

Registry No.—**1**, 6089-04-9; **2**, 68492-50-2; **3**, 68492-51-3; **4**, 68492-52-4; **5**, 68492-53-5; **6**, 68492-54-6; **7**, 68492-55-7; phosphorochloridic acid dibutyl ester, 819-43-2.

References and Notes

(1) (a) R. S. Macomber, *J. Org. Chem.*, **36**, 2714 (1971); (b) R. S. Macomber and E. R. Kennedy, *ibid.*, **41**, 3191 (1976).
(2) G. M. Steinberg, *J. Org. Chem.*, **15**, 637 (1950).
(3) No change was observed in the sample of **6** kept at room temperature under N_2 for 16 months.
(4) (a) F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968). For other excellent reviews on the hydrolysis of cyclic phosphoryl derivatives, see (b) C. A. Bunton, *Acc. Chem. Res.*, **3**, 257 (1970); (c) P. Gilespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem., Int. Ed. Engl.*, **12**, 91 (1973); (d) E. Cherbuliez in "Organic Phosphorus Compounds", Vol. 6, G. M. Kosolapoff and L. Maier, Ed., Weily-Interscience, New York, 1973, p 330.
(5) The reagent prepared according to R. J. Maile *et al.*[6] and originally used for cellulose TLC was found to be useful also for silica gel TLC.
(6) R. J. Maile, G. J. Fisher, and M. M. Anderson, *J. Chromatogr.*, **132**, 366 (1977).
(7) The two protons seem to have identical chemical shifts with each other since the signal shape is the same as that of the corresponding protons in **7**. The appearance of the signal as a double triplet is attributed to the inadequate resolution.
(8) The slight difference between the calculated and experimental values may be due to some hydrolysis of **6** by moisture during handling of the sample.
(9) For the predicted ^1H NMR values, see ref 1b.
(10) The assignment was confirmed by ^1H–^1H and ^1H–^{13}C decoupling experiments.
(11) The signal failed to give a double quartet because of inadequate resolution.

Synthesis of 12-Fluoro-7-methylbenz[*a*]anthracene and 7-Fluoro-12-methylbenz[*a*]anthracene

Melvin S. Newman* and J. M. Khanna[2]

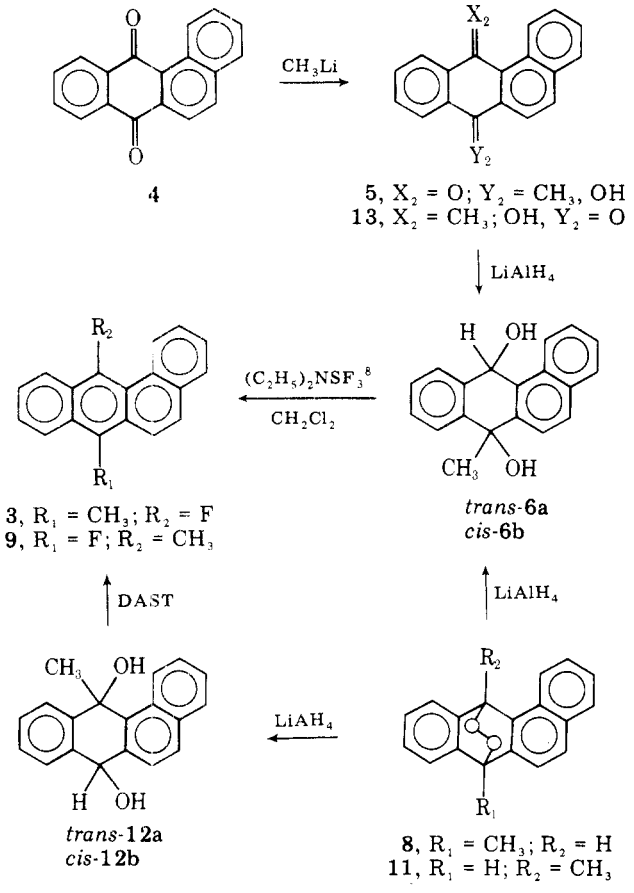
Department of Chemistry, Ohio State University, Columbus, Ohio 43210

Received August 14, 1978

7-Methylbenz[*a*]anthracene (**1**) has long been recognized to be the most carcinogenic monomethylbenz[*a*]anthracene.[3] The substitution of a methyl group at position 12 of **1** to produce 7,12-dimethylbenz[*a*]anthracene (DMBA) (**2**) leads to the most carcinogenic dimethylbenz[*a*]anthracene hydrocarbon known. For some time[4] we have been concerned with understanding why the methyl group at 12 should increase the activity of **1**. Three explanations may be considered: 1, the methyl at 12 is metabolized to give a more potent carcinogen; 2, the methyl at 12 blocks a detoxification mechanism which occurs at position 12; and 3, the steric effect of the 12-methyl group causes sufficient intramolecular overcrowding that the noncoplanar[5] DMBA is more easily metabolized to the ultimate carcinogen.

0022-3263/79/1944-0866$01.00/0

Scheme I



We wished to obtain a sufficient amount of the key compound, 12-fluoro-7-methylbenz[*a*]anthracene (**3**), that extensive biological experiments could be carried out. For one thing, **3** represents the last of the monofluoro-7-methylbenz[*a*]anthracenes to be tested.[6] Furthermore, the testing of **3** is considered particularly important because the 12-fluoro group should not only prevent any metabolism at the 12-position (explanations 1 and 2 above) but the steric effect of the fluorine at 12 is considerably less than that of a methyl group.[7] Our first synthesis of **3** is outlined in Scheme I.

The reaction of **4** with Grignard reagents has previously been carried out almost entirely with excess methylmagnesium halide[9] or methyllithium[10] to yield the dimethyldiols. When the amount of methyllithium was held to 2 equiv a mixture of products was obtained from which a 30% yield of **5**[11] could be isolated. Reduction of **5** to a mixture of **6a** and **6b** proceeded well and treatment of **6** (either pure **6b** or a mixture of **6a** and **6b**) with DAST[8] afforded **3**, mp 96–97 °C, in 48% yield. A small amount of 7-methylbenz[*a*]anthracene (**1**), was also isolated from the reaction mixture. When **6** was treated with anhydrous HF 42% yield of **1** was obtained. This surprizing result has no analogy that we have seen.

Because of the poor yield of **5** via the reaction of CH_3Li with **4** and the difficulty in isolation of **5** we sought improved methods for the preparation of **5** and of **6**. When the cyclic peroxide, **8**[12], of **1** was treated with alcoholic KOH an 83% yield of **5** was obtained.[13] The preparation of **6b** was accomplished almost quantitatively by $LiAlH_4$ reduction of **8** so that the preferred synthesis of **3** involves the steps **1** → **8** → **6** → **3**. When **5** was reduced with $LiAlH_4$ an almost quantitative yield of diol **6**, mainly **6a**, was produced. However, when the peroxide **8** was reduced only **6b** was produced. Either **6a**, **6b**, or a mixture of the two afforded **3** in about the same yield (45–48%).

We next turned to the synthesis of 7-fluoro-12-methylbenz[*a*]anthracene (**9**) as we wished to know if this compound would prove to be about as carcinogenic as DMBA. This finding would also cast light on the mechanism by which DMBA produces cancer, because a fluorine at position 7 would block a detoxification pathway and would make impossible a carcinogenic mechanism which involves metabolism at the 7-methyl group of DMBA.

Photochemical oxidation of 12-methylbenz[*a*]anthracene (**10**) afforded the 7,12-peroxide **11**.[12] On reduction of **11**, *cis*-7,12-dihydroxy-12-methyl-7,12-dihydrobenz[*a*]anthracene (**12b**) was obtained in high yield. On treatment with alcoholic KOH[13] **11** yielded 12-hydroxy-12-methylbenz[*a*]anthracen-7(12H)-one (**13**),[11] which on reduction yielded a mixture of *cis*- and *trans*-diols **12**. A 9% yield of **13** was also obtained from the reaction of CH_3Li with **4** (see above). Treatment of *cis*-**12** or a mixture of *cis*- and *trans*-**12** with DAST afforded 53% yields of **9**. In these reactions a small amount of **10** was also produced.

Experimental Section[14]

7-Hydroxy-7-methylbenz[a]anthracen-12(7*H*)-one (5). In the best of several experiments 52 mL of 1.6 M CH_3Li (Alpha Products Ventron) was added to a cooled stirred solution of 10.0 g (0.039 mol) of **4** in 300 mL of dry THF. After 2 h at room temperature the mixture was treated with a little water and the THF removed on a rotary evaporator. The product was extracted into ether in the usual way[14] and the ether removed in vacuo. The residue was recrystallized from benzene to yield 2.5 g (22%) of 7,12-dihydroxy-7,12-dimethyl-7,12-dihydrobenz[*a*]anthracene (**7**), mp 183–185 °C, cis form.[12] The material in the filtrate was subjected to dry column chromatography using silica gel/benzene to yield 3.2 g (30%) of **5**, mp 119–122 °C, after crystallization from benzene–petroleum ether, 9% of **13**, mp 140–142 °C (lit.[11] mp 139–140 °C), 9% of a mixture of **5** and **13**, and 20% of **4**. The mp of **5** given in ref 11 is 127–128 °C. Our purest **5**, obtained as above or in 90% yield by treating a solution of 100 mg of **8** and 200 mg of KOH in 10 mL of ethanol at room temperature for 15 min, always melted at 119–122 °C.

12-Hydroxy-12-methylbenz[*a*]anthracen-7(12*H*)-one (13). Treatment of the peroxide **11** with alcoholic KOH as described above for **8** afforded **13**, mp 142–144 °C,[11,15] in 83% yield after recrystallization from benzene–petroleum ether.

7,12-Dihydroxy-7-methyl-7,12-dihydrobenz[*a*]anthracene* (6a, 6b). A solution of 3.2 g of **5** in 150 mL of dry ether was added dropwise to a stirred suspension at 0 °C of 1.5 g of $LiAlH_4$ in 50 mL of ether. After 2 h at room temperature a conventional workup yielded 2.2 g (69%) of **6a**, trans, mp 186–188 °C after crystallization from benzene: NMR (Me_2SO-d_6, Me_4Si) δ 1.68 (s, 3, 7-Me), 5.68 (d, 1, 12-OH, exchangeable with D), 5.85 (s, 1, 7-OH), 6.30 (d, 1, 12-H singlet after D exchanged), 7–8 (m, 9, ArH), 8.40 (m, 1, 1-H). From the filtrate 1.0 g (30%) of a mixture of **6a** and **6b** in about equal ratio was obtained. Similar reduction of 200 mg of **8** in ether–$LiAlH_4$ afforded pure **6b**, cis, mp 158–160 °C after crystallization from benzene, in 87% yield: NMR δ 1.53 (s, 3, 7-Me), 5.75 (s, 1, 7-OH exchangeable), 5.65 (d, 1, 12-OH, exchangeable), 6.10 (d, 1, 12-H singlet after D exchange), 8.60 (m, 1, 1-H), 7–8 (m, 9, ArH) [8.6 (m, 1, 1-H)]. Crystallization of either diol from alcohol affords lower less sharp melting samples. However, such material on recrystallization from benzene yields colorless **6a**, mp 186–188 °C, or **6b**, mp 158–160 °C.

7,12-Dihydroxy-12-methyl-7,12-dihydrobenz[*a*]anthracene* (12a, 12b). Reduction of **13** as described above for reduction of **5** afforded in almost quantitative yield a mixture of **12a** and **12b** from which only pure **12b**, mp 201–203 °C, was isolated in 79% yield: NMR δ 1.65 (s, 3, 12-Me), 5.45 (d, 1, 7-CH singlet after D exchange), 6.05 (s, 1, 12-OH, exchangeable), 6.45 (d, 1, 7-OH exchangeable), 7.2–8.2 (m, 9, ArH), 9.5 (m, 1, 1-H). The cis form, **12b**, was also best obtained in high yield by reduction of peroxide **11** in ether–$LiAlH_4$. These diols are also best crystallized from benzene. Since mixtures of **12a** and **12b** gave as good a yield of **9** (see below) as that obtained when pure **12b** was used, separation of the isomeric diols is unnecessary when the synthesis of **9** is the goal. No pure **12a** was isolated.

12-Fluoro-7-methylbenz[*a*]anthracene* (3). A solution of 1.0 g of **6a, 6b,** or a mixture of the two, in 250 mL of CH_2Cl_2, was added dropwise to a solution of 1.3 g of DAST[8] in 10 mL of CH_2Cl_2 at room temperature. After 2 h the reaction mixture was worked up as usual and the product was chromatographed over silica gel using low-boiling petroleum ether. Crystallization of the material in the first ten 75-mL fractions of eluate yielded 450 mg (48%) of pale yellow thin prisms of

3,[6] mp 96–97 °C. Recrystallization from 95% gave a colorless polymorphic form, mp 94–5 °C. Both samples had identical IR and TLC patterns. From the next ten fractions of eluate was isolated 125 mg (14%) of **1**, mp and mmp 135–137 °C (lit,[16] mp 140.2–140.8 °C, corr) and TLC identity.

7-Fluoro-12-methylbenz[*a*]anthracene* (9). As described above for the synthesis of **3** from **6**, 200 mg of **12a** and/or **12b** yielded 100 mg (53%) of **9**, mp 80–82.5 °C, as pale yellow crystals from aqueous alcohol. In addition 20 mg (11%) of **10**, mp 136.0–137.5 °C (lit.[17] mp 138.6–139.6 °C), was obtained.

Pyrolysis of 12-Methyl-7,12-peroxy-7,12-dihydrobenz[*a*]anthracene (11). On pyrolysis of **11** at 105 °C for 1 min in a melting point tube TLC showed that **10** was the main product produced.

Registry No.—**1**, 2541-69-7; **3**, 23683-71-8; **4**, 2498-66-0; **5**, 17513-43-8; **6a**, 68781-42-0; **6b**, 68781-43-1; **7**, 55125-19-4; **8**, 68781-44-2; **9**, 68781-45-3; **10**, 2422-79-9; **11**, 68781-46-4; **12a**, 68781-47-5; **12b**, 68781-48-6; **13**, 17513-39-2.

References and Notes

(1) This work was supported by Grant CA-07394 from the National Cancer Institute, Department of Health, Education, and Welfare.
(2) Postdoctoral Research Associate.
(3) For a review of much of the early evidence see J. C. Arcos and M. F. Argus, "Chemical Induction of Cancer", Vol. IIA, Academic Press, New York, 1974, p 31ff.
(4) For an earlier discussion of possible reasons see (a) M. S. Newman and R. F. Cunico, *J. Med. Chem.*, **15**, 323 (1972), and (b) M. S. Newman in "Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism, and Carcinogenesis", Vol. I, R. I. Freudenthal and P. W. Jones, Raven Press, New York, 1976, p 203.
(5) For the latest X-ray structure and discussion of DMBA see D. W. Jones and J. M. Sowden, *Cancer Biochem. Biophys.*, 281 (1976).
(6) By photochemical oxidative cyclization of *trans*-1-(4-fluoro-1-methyl-2-naphthyl)-2-(*o*-iodophenyl)ethylene a compound, mp 81–83 °C, believed to be **3** was obtained by J. Blum, F. Grauer, and E. D. Bergmann, *Tetrahedron*, **25**, 350 (1969). Insufficient material was obtained for biological experimentation. Furthermore, since the mp of pure **3** is 96–97 °C (this paper) the compound reported was somewhat impure or a polymorphic form.
(7) M. S. Newman, R. G. Mentzer, and G. Slomp, *J. Am. Chem. Soc.*, **85**, 4018 (1963).
(8) This compound, DAST, was sent us through the courtesy of Dr. William J. Middleton of the E. I. DuPont de Nemours and Co. See *J. Org. Chem.*, **40**, 574 (1975), for many reactions of DAST. Recently, S. S. Hecht, M. Loy, R. Mazzarese, and D. Hoffmann, *J. Med. Chem.*, **21**, 38 (1978), used DAST on adjacent dihydrodiols to synthesize 6-fluoro-5-methylchrysene and 11-fluoro-5-methylchrysene.
(9) W. E. Bachmann and J. T. Bradbury, *J. Org. Chem.*, **2**, 175 (1937).
(10) See M. S. Newman, L. E. Fikes, M. M. Hashem, R. Kannan, and V. Sankaran, *J. Med. Chem.*, **21**, 1076 (1978), for a review and recent data on the reaction of 7,12-benz[*a*]anthraquinones with organometallic reagents.
(11) J. Fried and D. E. Schumm, *J. Am. Chem. Soc.*, **89**, 5508 (1967), isolated small amounts of **5**, mp 127–128 °C, and **13**, mp 139–140 °C, by oxidation of DMBA and by reaction of **4** with 1 equiv of CH_3MgI but no details or yields in the latter case were given.
(12) J. W. Cook and R. H. Martin, *J. Chem. Soc.*, 1125 (1940).
(13) For a review of this type of reaction first reported by N. Kornblum and H. E. DeLa Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951), see A. G. Davies, "Organic Peroxides", Butterworths, London, 1961, p 183ff.
(14) All temperatures are uncorrected and are in °C. All new compounds are marked with an asterisk and gave analyses within ±0.3% of the theoretical by the Galbraith Microanalytical Laboratories. The term "conventional or usual workup" means that the organic layer containing the product was washed with water and/or alkali and acid and saturated NaCl and filtered through anhydrous $MgSO_4$. The solvent was then removed on a rotary evaporator. All compounds gave IR, mass, and NMR spectra consistent with the structure assigned.
(15) E. Boyland and P. Sims, *Biochem. J.*, **95**, 780 (1965).
(16) L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).
(17) M. S. Newman and R. Gaertner, *J. Am. Chem. Soc.*, **72**, 264 (1950).

Synthesis of Ubiquinones. 2.[1] An Efficient Preparation of Ubiquinone-10

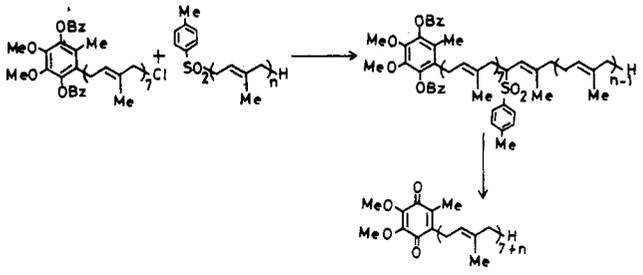
Shinji Terao,* Kaneyoshi Kato, Mitsuru Shiraishi, and Hiroshi Morimoto

Chemical Research Laboratories, Central Research Division, Takeda Chemical Industries, Ltd., Osaka 532, Japan

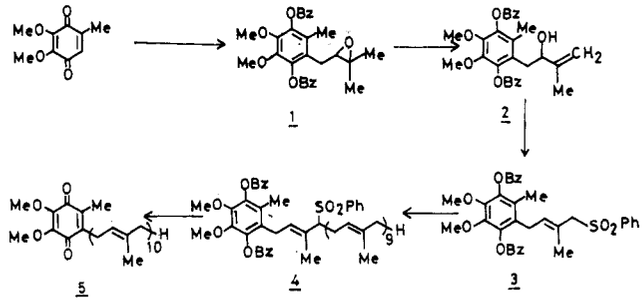
Received September 25, 1978

Since ubiquinone-10 (**5**) has a biological activity such as an electron carrier[2] in mitochondria, clinical effect in human congestive heart failure,[3] and implications in essential hypertension,[4] host defense,[5] and prevention of cardiotoxicity of adriamycin,[6] there is an increasing need for an efficient and stereospecific method of synthesis which is feasible for a large scale production.

Scheme I



Scheme II



Recently,[1] we have developed a new synthetic route for the ubiquinones by (i) the coupling between a sulfonyl component and a halide and (ii) and Benkerser's reductive elimination of the sulfone group followed by the oxidation of the resulting hydroquinone (Scheme I).

In this report, an application of this method in the synthesis of ubiquinone-10 from readily available components is presented (Scheme II).

Epoxide **1** is readily prepared in high yield by acid-catalyzed condensation of 2,3-dimethoxy-5-methyl-1,4-hydroquinone with 2-hydroxy-2-methylbut-3-ene followed by benzylation of the resulting prenylated hydroquinone and by epoxidation of the prenyl double bond with peracetic acid. When epoxide **1** is treated with aluminum isopropoxide in refluxing toluene, allylic alcohol **2** is obtained in good yield. The catalytic reagent has been used for the conversion[7] of cyclic monoterpenoid epoxides into the corresponding allylic alcohols. We found that this conversion could be widely used for the preparation of allylic alcohols from epoxides of (poly)prenylated compounds.[8]

Reaction of allylic alcohol **2** with phenylsulfenyl chloride in the presence of triethylamine and subsequent oxidation of the resulting sulfoxide with peracetic acid leads to the formation of the sulfonyl compound **3** as a single product whose double bond was confirmed to be exclusively trans by TLC and ^1H NMR analyses. The transformation of this type has been reported by Evans and Anderson.[9]

Coupling reaction of sulfonyl compound **3** with solanesyl bromide in the presence of potassium *tert*-butoxide gives coupled compound **4** in 91.3% yield after purification on silica gel. Removal of the benzyl and phenylsulfonyl groups in **4** was efficiently carried out by applying the Benkerser reduction.[10] The resulting hydroquinone is smoothly oxidized with air to give ubiquinone-10 (**5**) in 77.3% after recrystallization from ether–ethanol. The synthesized ubiquinone-10 was confirmed by TLC, LC, ^1H NMR, IR, and MS analyses and identified by the mixed melting point with an authentic sample.[11]

Experimental Section

Melting points were determined on a Yanagimoto Micro Melting Point apparatus and are uncorrected. High-resolution MS spectra

0022-3263/79/1944-0868$01.00/0