A Highly Efficient Synthesis of 3-Methylcholanthrene

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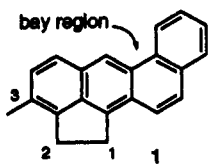
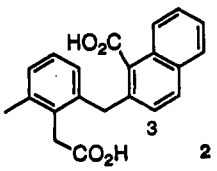
A five-step synthesis of 3-methylcholanthrene (1) has been achieved starting from 5-methylhomophthalic anhydride and *N,N*-diethyl-1-naphthamide in 55% overall yield. Treatment of a solution of the preformed lithium enolate of 5-methylhomophthalic anhydride (3) with an equimolar solution of 2-lithio-1-naphthamide (4), followed by acid hydrolysis, provides cleanly the spirobislactone 5 in 80% overall yield. In addition, the synthesis features a unique, highly selective double Friedel–Crafts cyclization of the aryl diacid 2 with PPA to give rise, after acetylation, to keto acetate 6.

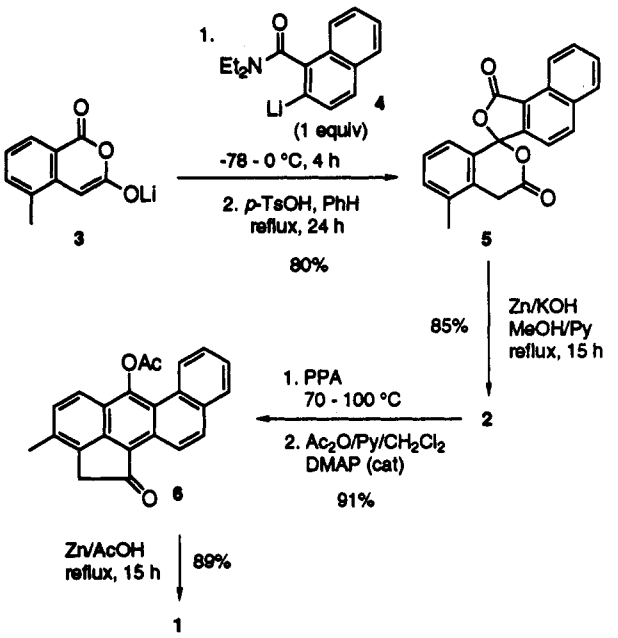
3-Methylcholanthrene (3-MC; 1) occupies a unique position among a large number of carcinogenic and/or mutagenic polycyclic aromatic hydrocarbons (PAHs) due to the highly intricate mode of metabolic activation necessary for the expression of its biological activity.[1] It has been amply demonstrated that the initial metabolic activation involves hydroxylation primarily at C-1 and/or C-2 sites.[2] Nevertheless, there is a wealth of observation pointing to the notion that some of these primary metabolites undergo further activation in the bay region to the ultimate carcinogen diol epoxides.[3] In addition, 3-MC is widely employed as a cytochrome P-450 inducer in experimental animals.[4] It is, therefore, not surprising that this highly potent hydrocarbon has attracted considerable attention for many years.[1]





The first synthesis of 3-MC was achieved by Fieser and Seligman in the mid-1930s[5] and a modification of this synthesis was reported by Tang and Maggiulli in 1981, which was aimed at the establishment of operational simplicity and large-scale production capability.[6] In 1982, Harvey disclosed a potentially versatile synthesis of 3-MC beginning with the reaction of 4-methyl-1-indanone and 2-lithio-*N,N*-diethyl-1-naphthamide.[7] In an effort to suppress the otherwise highly problematic enolization of the indanone carbonyl group during the addition reaction, the 2,2-dideuterio derivative of the indanone was employed, resulting in the formation of the desired adduct in 50% yield. In a similar study by Newman and Sujeeth on the synthesis of 3-MC derivatives, it was pointed out that the low-yielding nucleophile addition to 4-methyl-1-indanone, utilized as the first step in the synthesis, was further complicated by dehydration of the formed adduct.[8]

Scheme I



In conjunction with our interest in the synthesis of cyclopenta-fused PAHs through the use of the double Friedel–Crafts cyclization reaction,[9] a study aimed at a more efficient synthesis of 3-MC was undertaken. It was envisaged that the aryl diacid 2 should be employable for such an approach. In this report, a novel, highly-efficient five-step synthesis of 3-MC is described which features the use of the double Friedel–Crafts cyclization of the aryl diacid 2. In addition, the preformed lithium enolate of 5-methylhomophthalic anhydride (3)[10] was employed as a convenient means for both preventing the enolization of the homophthalic anhydride and for driving the nucleophilic addition toward the aromatic carbonyl of the homophthalic anhydride during the nucleophilic addition step.

The generation of the *ortho*-lithiated naphthamide 4[11] was effected by reverse addition of an *N,N*-diethyl-1-naphthamide solution to a *s*-BuLi/TMEDA solution in diethyl ether at a temperature between −105 and −100 °C.

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(9) Gimisis, T.; Kampf, J. W.; Koreeda, M. *J. Org. Chem.* In press.

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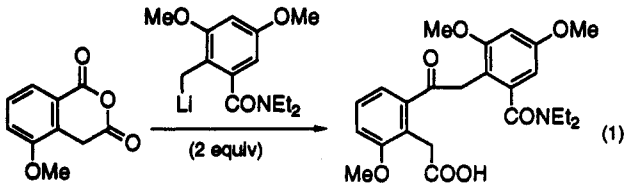
Previous reports utilized the addition of *s*-BuLi to a solution of *N,N*-diethyl-1-naphthamide at higher temperatures (e.g., −78 °C).[7,8] However, it was found crucial to carry out the reverse addition at these low temperatures in order to achieve cleaner *ortho*-lithiation than the similar reactions reported in the literature.[7,8]

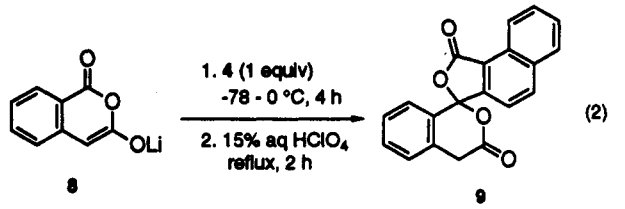
The nucleophilic addition to a group of carbonyl-bearing compounds such as homophthalic anhydrides which can undergo competitive enolate formation is often problematic. Watanabe circumvented this problem by generating the enolate in situ through the use of 2 equiv of the nucleophile (see eq 1).[12] However, it was felt that the use



7 (1)

of an additional equivalent of the lithiated naphthamide 4 may both be uneconomical and make the isolation of the desired product unnecessarily cumbersome. In addition, the protonated naphthamide molcule represents a potentially competing electrophile. Therefore, the lithium enolate of 5-methylhomophthalic anhydride (3) was generated at −95 °C with *t*-BuLi prior to the addition of the lithiated naphthamide 4.

Addition of an equimolar solution of 4 in diethyl ether to a solution of lithium enolate 3 in THF provided an adduct which was directly converted into the spirophthalide 5 in 80% overall yield from 3 by refluxing the adduct in benzene in the presence of *p*-toluenesulfonic acid. The aromatic methyl group ortho to the carboxymethyl group is likely to direct the conformation of the carboxyl group toward the diaryl ketone carbonyl group to form the hemiketal, which in turn should provide the necessary anchimeric assistance for the intramolecular hydrolysis of the amide group. The notation that this methyl group plays a significant role was further reinforced by the results of the same sequence of the reactions of homophthalic anhydride lithium enolate (8) and 4. Thus, although the overall yield of the reaction (73%) was comparable to that of the formation of 5, hydrolysis of the amide of the initial addition product 10 from 8 and 4 was found to require the use of considerably more vigorous (reflux in 15% $HClO_4$) conditions (see eq 2). An additional point that bears



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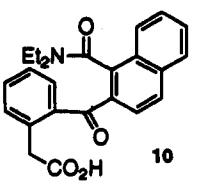
comment concerns the fact that the use of a 1:1 molar ratio of 3 (or 8) and 4 was quite beneficial in suppressing the potential second addition of the latter to the initial addition product which could regenerate the carbonyl group in situ. Reductive cleavage of the spirophthalide 5 with activated zinc in KOH smoothly furnished the desired aryl diacid 2 in 85% yield.



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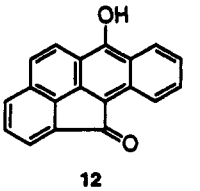

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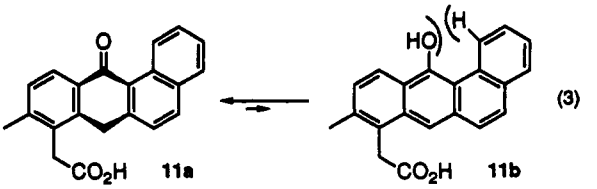
Brief treatment (15 min) of diacid 2 with deoxygenated polyphosphoric acid (PPA) under a nitrogen atmosphere, between 70 to 100 °C, followed by acetylation of the crude mixture resulted in the formation of 3-methyl-6-acetoxybenz[*j*]aceanthrenone (6) in 91% yield. There was initial concern that the benzylic acyl cation might undergo an alternate cyclization onto the naphthyl group at C-3 (see 2). However, the double Friedel–Crafts cyclization was highly selective with 6 being the only product observed. Interestingly, cyclization of the diacid 2 under liquid HF (−78 °C to rt) or 80% aqueous H_2SO_4 (85 °C, 15 min) conditions did not proceed beyond the first cyclization and gave rise to 11, which was shown to exist in its 12-benz[*a*]anthrone tautomeric form (11a), as judged from



11a 11b (3)

the presence of a methylene signal at δ 4.62 in the ^1H NMR spectrum in $CDCl_3$.[13] This observation is in marked contrast to that encountered in the synthesis of 12 where the phenol form was found to be more favored.[9] Evidently, it may be viewed that in the present case, the strain induced by the angular benzo ring on the bay-region oxygen atom at the C-12 position is partially relieved in the nonplanar keto tautomer. The higher stability of the benz[*a*]anthrone over the benz[*a*]anthrol tautomer may explain the inability of the monocyclized product 11 to undergo the second cyclization in liquid HF or aqueous 80% H_2SO_4. This observation highlights the importance of the PPA reagent and its ability to effect readily the second cyclization step, presumbably by facilitating the benz[*a*]anthrone–benz[*a*]anthrol tautomerization and/or, possibly, stabilizing the anthrol tautomer. Although the mechanistic details of this unique reaction remain to be elucidated,[14] the use of PPA has proven instrumental for the success of the double Friedel–Crafts cyclization method in this system. The completion of the synthesis of 3-MC was accomplished by the exhaustive deoxygenation of the keto acetate 6 with activated zinc in acetic acid in 89% yield. The first step of this exhaustive deoxygenation reaction seems to involve the reductive cleavage of the 6-acetoxy group which is facilitated by the presence of the electron-withdrawing effect of the ketone at C-1. The intermediate 3-methylbenz[*j*]aceanthren-1-one, which could be isolated after shorter reaction times, was further deoxygenated under the same reaction conditions.

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In summary, 3-MC has been synthesized from 5-methylhomophthalic anhydride and *N,N*-diethyl-1-naphthamide in five steps and in 55% overall yield, featuring in situ protection of the former by deprotonation with *s*-BuLi prior to the addition of 2-lithio-1-naphthamide (4), and a highly selective double Friedel–Crafts cyclization of the aryl diacid 5 promoted by the use of PPA. The synthesis described above compares favorably with those previously reported in its brevity and overall efficiency.

Experimental Section

1′,3′-Dihydrospiro[5-methylisochroman-1,3′-naphtho[1,2-*c*]furan]-3,1′-dione (5). To a cooled (between −105 and −100 °C) solution of 1.13 M *sec*-butyllithium in cyclohexane (12.8 mL, 14.5 mmol) and TMEDA (1.95 mL, 13.0 mmol) in 150 mL of dry ether was added, under an argon atmosphere with stirring, *N,N*-diethyl-1-naphthamide (2.99 g, 13.1 mmol) in 25 mL of dry ether over a 30-min period, and the resulting clear bright yellow mixture was stirred for an additional 45 min at −76 °C. While the above ethereal solution was stirred, to a cooled (−95 °C) solution of 5-methylhomophthalic anhydride[11] (2.30 g, 13.0 mmol) in 80 mL of dry THF was added dropwise, under an argon atmosphere with stirring, 1.45 M *tert*-butyllithium in hexanes (9.0 mL, 13.0 mmol). The ethereal solution containing 2-lithio-1-naphthamide (4) was then transferred to the solution of the lithium enolate of 5-methylhomophthalic anhydride via a cannula. The initial bright yellow color of the solution changed during the transfer to yellow-green and finally to deep green. The reaction mixture was stirred for 4 h, during which time the temperature was allowed to gradually rise to 10 °C. The solution was then recooled to −60 °C and treated with acetic acid (5.0 mL, 87 mmol), and the resulting mixture was allowed to warm to 0 °C, at which point it was treated successively with H_2O (20 mL), saturated aqueous NH_4Cl (40 mL), and finally 5% aqueous HCl (20 mL). The organic layer was washed with 5% aqueous HCl (50 mL) and was extracted with 3M aqueous NaOH (3 × 50 mL). The combined basic extracts were washed with ether (50 mL) and then acidified with concd HCl while cooling in an ice bath. The resulting acidic aqueous solution was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was then washed with H_2O (2 × 20 mL) and was dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a slightly colored foam (4.20 g, 80%), a part of which (2.00 g, 4.96 mmol) was dissolved in dry benzene (50 mL), and the solution was refluxed in the presence of *p*-toluenesulfonic acid monohydrate (0.96 g, 5.05 mmol) in a 100-mL, round-bottomed flask equipped with a Dean–Stark apparatus. After 24 h or when TLC (10% MeOH/$CHCl_3$) showed the disappearance of the starting material, the solvent was evaporated under reduced pressure, and the resulting solid residue was dissolved in ethyl acetate (50 mL). This solution was washed successively with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), and brine (30 mL) and was then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure followed by trituration of the residue with ether (5 mL) gave white precipitates which were collected by filtration and were washed with ether (2 mL) to furnish 4.59 g (93%) of the spirophthalide 5 as a colorless crystalline solid. Purification of the neutral extracts of the first workup by silica gel flash column chromatography (50% ethyl acetate/hexanes) provided an additional 0.49 g of 5, thus bringing its overall yield up to 80%. For 5: mp 241–241 °C (EtOH); ^1H NMR (360 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.08 and 4.12 (AB q, 2H, J_{AB} = 19.5 Hz), 6.65 (d, 1H, *J* = 7.7 Hz), 7.11 (dd, 1H, *J* = 7.7, 7.6 Hz), 7.32 (d, 1H, *J* = 7.6 Hz), 7.60 (d, 1H, *J* = 8.4 Hz), 7.74 (ddd, 1H, *J* = 8.2, 7.0, 1.3 Hz), 7.81 (ddd, 1H, *J* = 8.3, 7.0, 1.4 Hz), 8.06 (d, 1H, *J* = 8.2 Hz), 8.29 (d, 1H, *J* = 8.4 Hz), 8.98 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 18.80 (q), 32.62 (t), 106.36 (s), 119.88 (d), 121.87 (s), 122.83 (d), 123.94 (d), 127.25 (d), 128.53 (d), 128.68 (s), 128.76 (d), 129.84 (d), 129.95 (s), 130.12 (s), 132.43 (d) 134.67 (s), 136.02 (s), 136.62 (d), 145.56 (s), 166.99 (s), 168.24 (s); IR (KBr) 1781, 1189, 1122, 935, 913 cm^{-1}. Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.35; H, 4.27. Found: C, 76.21; H, 4.33.

2-[(2-(Carboxymethyl)-3-methylphenyl)methyl]naphthoic Acid (2). To a stirred suspension of Zn (10 g) [activated by successive washings with 10% aqueous HCl (10 mL), H_2O (10 mL), 5% aqueous $CuSO_4$ (20 mL), H_2O (10 mL), and MeOH (10 mL)] in methanol (15 mL), were added KOH (1.50 g, 25.7 mmol) in H_2O (7.5 mL) and the spirobislactone 5 (960 mg, 2.87 mmol) in pyridine (15 mL). The resulting green suspension was refluxed for 15 h, at which point it was diluted with 1M aqueous NaOH (10 mL) and filtered through Celite. The filtrate was washed with chloroform (10 mL), acidified with concd HCl in an ice bath, and was then extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed successively with H_2O (2 × 40 mL) and brine (40 mL) and were then dried ($MgSO_4$). Removal of the solvent by rotary evaporation followed by trituration with CH_2Cl_2 and evaporation under reduced pressure furnished 990 mg of an off-white solid. Recrystallization from ethyl acetate/hexanes afforded 852 mg (85%) of the diacid 2 as colorless needles: mp 264–266 °C dec; ^1H NMR (360 MHz, acetone-d_6) δ 2.35 (s, 3H), 3.77 (s, 2H), 4.34 (s, 2H), 6.97 (m, 1H), 7.07–7.12 (m, 2H), 7.16 (d, 1H, *J* = 8.6 Hz), 7.53 (ddd, 1H, *J* = 8.0, 6.9, 1.2 Hz), 7.59 (ddd, 1H, *J* = 8.4, 6.9, 1.5 Hz), 7.86 (d, 1H, *J* = 8.6 Hz), 7.92 (d, 1H, *J* = 8.0 Hz), 8.00 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (90.5 MHz, acetone-d_6) δ 20.42 (q), 35.17 (t), 37.45 (t), 125.86 (d), 126.74 (d), 127.72 (d), 127.86 (d), 128.18 (d), 128.95 (d), 129.37 (d), 129.41 (d), 129.88 (s), 130.16 (d), 130.57 (s), 132.89 (s), 133.55 (s), 136.08 (s), 140.04 (s), 170.64 (s), 172.46 (s); IR (KBr) 3434, 3049, 1691, 1232, 761 cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.42. Found: C, 75.53; H, 5.30.

1,2-Dihydro-3-methyl-6-acetoxybenz[*a*]aceanthrylen-1-one (6). Polyphosphoric acid (PPA) (5 mL) was heated to 70 °C under a nitrogen atmosphere with stirring. The acid was then deoxygenated by repeated cycles consisting of careful application of vacuum, followed by flushing with nitrogen. This PPA was then treated with the diacid 2 (100 mg, 0.30 mmol, neat) and the resulting mixture was stirred vigorously to form a homogeneous solution. The solution thus obtained was heated to 100 °C under vigorous stirring with occasional applications of the above vacuum-nitrogen flushing sequence. After 15 min at 100 °C, the solution was cooled to 10 °C with the use of an ice bath and was then quenched with H_2O (10 mL). The resulting mixture was partitioned between ice–water (100 mL) and ethyl acetate (50 mL) by vigorously stirring for 10 min. The two phases were then filtered through Celite and separated, the organic layer was washed successively with H_2O (25 mL) and brine (25 mL) and was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. A 50-mL, round-bottomed flask was charged with this crude product (91 mg, 0.30 mmol) and pyridine (1.0 mL) in dry CH_2Cl_2 (10 mL), and the solution was cooled to −14 °C and treated with acetic anhydride (0.07 mL, 0.75 mmol) and DMAP (5 mg, 0.04 mmol). The mixture was then allowed to warm up to 20 °C and stirred at that temperature for 2 h, at which time the reaction was quenched with H_2O (5 mL) at 0 °C. The organic solvent was evaporated under reduced pressure, and the resulting residue was partitioned between ethyl acetate (25 mL) and H_2O (25 mL). The organic layer was washed successively with H_2O (10 mL), saturated aqueous NH_4Cl (10 mL), H_2O (10 mL), and brine (10 mL) and then was dried (Na_2SO_4). Evaporation of the solvent under reduced pressure followed by purification of the crude product by silica gel flash chromatography (80% $CHCl_3$/hexanes) afforded 90 mg (88%) of the benz[*a*]aceanthrenone 6 as a yellow solid: mp 270–272 °C dec (CH_2Cl_2/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ, 2.53 (s, 3H), 2.69 (s, 3H), 3.85 (s, 2H), 7.48 (d, 1H, *J* = 8.8 Hz), 7.68 (m, 2H), 7.77 (d, 1H, *J* = 8.8 Hz), 7.88 (d, 1H, *J* = 9.1 Hz), 7.93 (dd, 1H, *J* = 7.2, 2.1 Hz), 9.13 (d, 1H, *J* = 9.1 Hz), 9.24 [d with an additional small (*J* < 0.8 Hz) long-range coupling, 1H, *J* = 8.0 Hz]; ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 19.06 (q), 21.61 (q), 41.71 (t), 119.27 (d), 121.72 (s), 122.40 (d), 125.40 (s), 126.58 (d), 127.42 (d), 127.56 (d) 129.31 (s), 129.42 (d), 130.88 (s), 131.04 (s), 131.38 (d), 131.67 (d), 132.82 (s), 144.09 (s), 148.84 (s), 168.46 (s), 202.30 (s); IR (KBr) 2924, 1760, 1700, 1184, 1115 cm^{-1}. Anal. Calcd for $C_{23}H_{16}O_3 \cdot 1/4CH_2Cl_2$: C, 77.22; H, 4.60. Found: C, 77.31; H, 4.52.

1′,3′-Dihydrospiro[isochroman-1,3′-naphtho[1,2-*c*]furan]-3,1′-dione (9). The procedure used for the synthesis of 5 was also employed for compound 9 using the following quantities of reagents/solvents and compounds: 2.27 g of *N,N*-diethyl-1-naphthamide (10.0 mmol) in 10 mL of dry ether for the *ortho*-lithiation with 8.46 mL of 1.30 M *sec*-butyllithium in cyclohexane

(11.0 mmol) and 1.65 mL of TMEDA (11.0 mmol) in 90 mL of dry ether; 1.78 g of homophthalic anhydride (11.0 mmol) in 40 mL of dry THF and 6.47 mL of 1.70 M *tert*-butyllithium (11.0 mmol) for the lithium enolate formation of homophthalic anhydride. Workup and removal of the solvent gave the amide acid **10** as a slightly colored foam (3.10 g, 81%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz), 3.15 and 3.17 (AB q, 2H, J_{AB} = 14.3 Hz; each of these proton peaks are further split into q with J = 7.2 Hz), 3.55 and 3.69 (AB q, 2H, J_{AB} = 14.3 Hz; each of these proton peaks are further split into q with J = 7.2 Hz), 3.79 and 4.20 (br AB q, 2H, J_{AB} = 16.6 Hz), 7.32–7.53 (m, 4H), 7.56 (d, 1H, J = 8.6 Hz), 7.67 (m, 2H), 7.94–7.97 (m, 2H), 8.02 (m, 1H); ^{13}C NMR (90.5 MHz, acetone-d_6) δ 12.72 (q), 13.63 (q), 39.10 (t), 39.19 (t), 43.89 (t), 127.06 (d), 127.25 (d), 127.45 (d), 128.23 (d), 128.44 (d), 128.96 (d), 129.13 (d), 129.81 (s), 131.49 (d), 132.01 (d), 132.64 (d), 134.27 (s), 135.47 (s), 135.93 (s), 137.83 (s) 139.48 (s), 169.10 (s), 172.90 (s), 199.14 (s).

To this crude product **10** was added 15% aqueous $HClO_4$ (50 mL). The resulting suspension was heated at 100 °C for 2 h, or until the initial oil became an insoluble solid. This mixture was then poured into ice (100 mL) and the resulting precipitate (2.50 g) was collected by filtration, which was recrystallized from $CHCl_3$/hexanes to afford 2.27 g (90%) of **9** as white prisms: mp 281–282 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 and 4.36 (AB q, 2H, J_{AB} = 19.0 Hz), 6.82 (d, 1H, J = 7.7 Hz), 7.23 (dd, 1H, J = 7.7, 7.5 Hz), 7.38 (d, 1H, J = 7.5 Hz), 7.48 (dd, 1H, J = 7.5, 7.5, 1.1 Hz), 7.61 (d, 1H, J = 8.4 Hz), 7.75 (ddd, 1H, J = 8.1, 6.9, 1.3 Hz), 7.83 (ddd, 1H, J = 8.3, 6.9, 1.3 Hz), 8.07 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 8.4 Hz), 8.99 (d, 1H, J = 8.1 Hz); ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 34.20 (t), 99.48 (s), 120.15 (d), 122.85 (d), 123.97 (s), 125.15 (d), 127.70 (d), 128.10 (d), 128.64 (d), 128.86 (s), 129.34 (d), 130.21 (d), 130.32 (s), 130.99 (d), 131.89 (s), 134.39 (s), 137.58 (d), 146.09 (s), 166.68 (s), 167.60 (s); IR (KBr) 1774, 1765, 1188, 1129, 925 cm^{-1}. Anal. Calcd for $C_{20}H_{12}O_4$: C, 75.94; H, 3.82. Found: C, 75.98; H, 3.73.

3-Methylcholanthrene (3-MC; 1). Zinc (1.23 g) [activated by successive washings with 5% aqueous HCl (5 mL), H_2O (5 mL), 5% aqueous $CuSO_4$ (5 mL), H_2O (5 mL), MeOH (5 mL), and Et_2O (5 mL), followed by drying under vacuum] was mixed with glacial acetic acid (10 mL). The resulting zinc suspension was heated to reflux, to which was added dropwise a solution of the keto acetate **6** (16 mg, 0.05 mmol) in acetic acid (6 mL). The reaction mixture was refluxed for an additional 15 h and then was cooled to rt and poured into ice–water with vigorous stirring. The resulting mixture was filtered through Celite. The solid remaining on the top of the Celite was washed with ethyl acetate (20 mL), and the two phases of the resulting filtrate were separated. The organic layer was washed successively with H_2O (2 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL) and was dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product (13 mg) was purified by flash chromatography using silica gel deactivated with 1% Et_3N (hexanes) to afford 12 mg (89%) of the 3-methylcholanthrene (**1**) as a light green-yellow crystalline solid: mp 179–180 °C (cyclohexane) (lit[6] mp 178.5–179.5 °C).

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