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A Highly Abbreviated Synthesis of Dibenzo[*def,p*]chrysene and Its 12-Methoxy Derivative, a Key Precursor for the Synthesis of the Proximate and Ultimate Carcinogens of Dibenzo[*def,p*]chrysene

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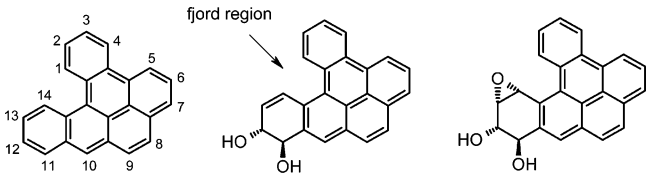
Abstract: Dibenzo[*def*,*p*]chrysene (DBC) (**1**), is by far the most mutagenic and toxic polycyclic aromatic hydrocarbon identified. Its metabolic activation leads to *trans*-11,12-dihydroxy-11,12-dihydro-DBC (**2**), which is further metabolized to the ultimate metabolite, *anti-trans*-11,12-dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DBC (**3**), that binds to DNA causing mutations and ultimately tumor induction. We report a facile route for the syntheses of DBC (**1**) and its 12-methoxy derivative (12-methoxy-DBC) (**13**), a key intermediate for the synthesis of **2** and **3**, using a Suzuki cross-coupling approach.

Dibenzo[*def*,*p*]chrysene (DBC) (**1**) (commonly known as dibenzo[*a*,*l*]pyrene), a peri-condensed hexacyclic polycyclic aromatic hydrocarbon (PAH), possesses a bay and a fjord region and is the most carcinogenic PAH compound known to date.[1] It has been identified in cigarette smoke condensate,[2] coal combustion emissions,[3] and in soil and sediments.[4] DBC is a potent tumorigen on mouse skin, in mammary glands,[5] and in lungs.[6] Because of its potency as a carcinogen, DBC has attracted the increasing attention of chemists and biologists. A metabolism study by Cavalieri and co-workers[7] has identified *trans*-8,9-dihydroxy-8,9-dihydro-DBC, *trans*-11,12-dihydroxy-11,12-dihydro-DBC (**2**), and 7-hydroxy-DBC as its major metabolites. Furthermore, Baird et al.[8] have reported that DBC activation in cultures of the human mammary carcinoma cell line (MCF-7) led to fjord-region *anti*- and *syn*-11,12-dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DBC, which bind extensively to deoxyadenosine (dA) in DNA.[9] Both of these fjord region diol epoxides have been shown to be far more potent than any of the previously investigated diol epoxides in four *His* strains of *Salmonella typhimurium* as well as in Chinese hamster V79 cells.[10] In addition, the *anti-trans*-11,12-dihydroxy-13,14-epoxy-11,12,13,14-tetrahydro-DBC (**3**) was found to be a potent carcinogen in newborn mice[11] and in the rat mammary gland,[12] besides being moderately carcinogenic on mouse skin.[13]



1 **2** **3**

Previous syntheses of DBC (**1**)[10,13,14] and its dihydrodiol **2** with a fjord region double bond[10,13,15,16] have been reported in the literature. However, the methods either involve many steps or cannot be adapted to the large-scale synthesis of **2** and **3** because of reaction limitations in the synthesis of their key precursor, i.e., appropriately substituted methoxy derivatives of DBC.[10,13,15,16] As part of our overall program to synthesize dA and deoxyguanosine (dG) adducts of DBC and corresponding phosphoramidites for the preparation of specifically adducted oligomers, we have developed an abbreviated, high-yield synthesis of DBC and its 12-methoxy derivative (Scheme 1), an intermediate for the synthesis of **2** and **3**, involving the Suzuki cross-coupling reaction. The palladium-catalyzed cross-coupling reaction of aryl halides with boronic acid is one the most versatile and widely used procedures for selective construction of carbon−carbon bonds.[17] The method is easy, gives high yields, and can

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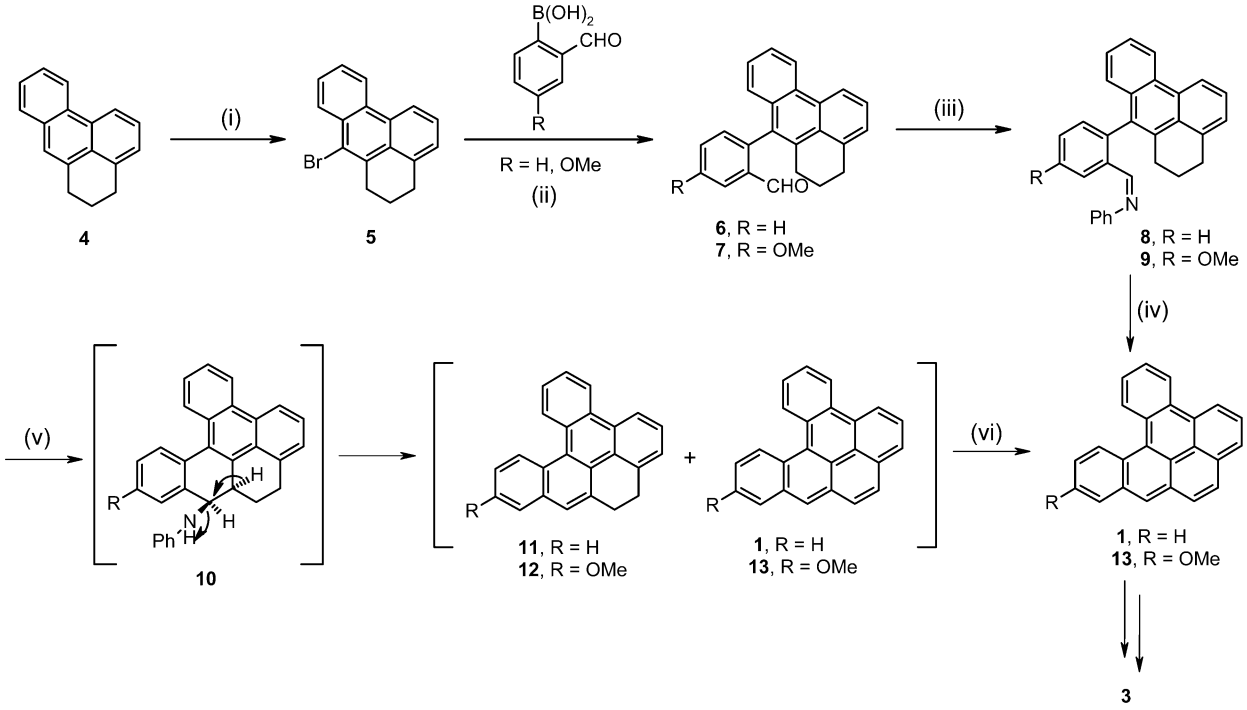
SCHEME 1[a]



[a] Reagents and conditions. (i) Br_2, CCl_4. (ii) CsF, $Pd(PPh_3)_4$, DME, reflux. (iii) Ph-NH_2, toluene, reflux. (iv) *t*-BuOK, DMF. (v) KOH, DMF, 100 °C. (vi) DDQ, PhH, reflux, 30 min.

be adapted to large-scale synthesis. Therefore, it is used not only in research laboratories but also on an industrial scale.[18] The Suzuki reaction has recently been applied to the synthesis of PAH ring systems.[19−23] In our laboratory, we have utilized this approach for the synthesis of benzo[*c*]phenanthrene,[19c] benzo[*g*]chrysene,[19c] naphtho-[1,2-*a*]pyrene,[19c,20] naphtho[1,2-*e*]pyrene,[19c,21] 5-methylchrysene,[19a] benzo[*c*]chrysene,[23] 7,12-dimethylbenz[*a*]anthracene,[23] and their metabolites.[20−23]

The synthesis of DBC and the 12-methoxy-DBC is outlined in Scheme 1. 5,6-Dihydro-4*H*-benz[*de*]anthracene (**4**) was prepared from benzanthrone in 74% yield according to the reported procedure.[24] Bromination of **4** using Br_2 in CCl_4 led exclusively to the formation of the 7-bromo derivative **5**. Palladium-catalyzed Suzuki coupling reaction of 2-formylphenylboronic acid with 7-bromo-5,6-dihydro-4*H*-benz[*de*]anthracene (**5**) gave the aldehyde **6**. Intramolecular cyclization of **6** to **11** was investigated by applying synthetic strategy analogous to the widely used Siegrist reaction for the synthesis of stilbenes.[25] Thus, the treatment of **6** with aniline in CH_2Cl_2 in the presence of molecular sieves (4 Å) furnished the imine **8**. An attempt to purify imine **8** by column chromatography led to decomposition so that about 50% of it reverted to aldehyde **6**. However, the crude **8** was nearly pure and was used as such for cyclization reaction. Heating of the imine **8** in DMF in the presence of KOH gave a mixture of 8,9-dihydro-DBC (**11**) (∼90%) and DBC (**1**) (∼10%) as determined by ^{1}H NMR. Mechanistically, this transformation involves the formation of benzylic anion by KOH, followed by the cyclization and base-assisted elimination of aniline to give **11**. The elimination of aniline from intermediate **10** requires trans arrangement of the anilino group and the vicinal hydrogen, and such elimination of arylamines has been observed by us earlier in the synthesis of substituted pyrimidinones.[26]

The formation of about 10% of DBC is attributed to the KOH-assisted tandem aromatization. This percentage could not be improved, even by heating the reaction for 24 h. Though this mixture was column-separable, for our purpose, we treated it as such with DDQ in refluxing benzene to afford DBC (**1**) in excellent yield. The structure was confirmed by ^{1}H NMR, MS, and mp, all of which were comparable to values reported in the literature.[10,13]

There are examples of aromatization of PAHs using strong bases such as *n*-BuLi.[27] The formation of about 10% of DBC on treatment of imine **8** with KOH indicated that a stronger base might lead to complete formation of DBC from the imine in one step. In view of this, we

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treated imine **8** with *t*-BuOK in DMF at room temperature. As expected, this gave DBC in 83% yield. While this shortcut did not change the overall yield of the total synthesis it definitely reduced one step.

To demonstrate the scope of this new method, we applied the described reaction sequence to the synthesis of 12-methoxy-DBC, the key intermediate for the synthesis of *trans*-dihydrodiol **2** and *anti*-diol epoxide **3** of DBC.[13,15] The palladium-catalyzed Suzuki coupling reaction of 2-formyl-4-methoxyphenylboronic acid[28] with **5** gave the aldehyde **7** which, on treatment with aniline in CH_2Cl_2 in the presence of 4 Å molecular sieves, afforded the imine **9**. Unlike imine **8**, the methoxy-substituted imine **9** was found to be stable to silica gel column chromatography and thus was column purified without any loss due to decomposition. It was then easily converted to 12-methoxy-DBC (**13**) by treatment with *t*-BuOK in DMF or by heating in DMF in the presence of KOH, followed by treatment with DDQ in refluxing benzene. The structure of **13** was assigned on the basis of ^{1}H NMR, MS, and mp, which were comparable to those reported in the literature.[13]

In conclusion, the synthesis involving the Suzuki cross-coupling reaction proved to be an excellent method for preparing large quantities of DBC and its 12-methoxy derivative in fewer steps with a high overall yield (∼33%) from easily accessible reagents. The availability of a high-yielding synthesis of 12-methoxy-DBC will allow us to obtain **2** and **3** in practical quantities for the synthesis of site-specific adducted oligonucleotides that will enable the elucidation of molecular mechanisms by which DBC induces its carcinogenic activity. The synthesis of these site-specific adducted oligonucleotides has not yet been attempted largely because of the lack of an efficient and convenient method for the synthesis of **2** and **3**.

Experimental Section

7-Bromo-5,6-dihydro-4*H*-benz[*de*]anthracene (5). A well-stirred solution of **4**[24] (4.36 g, 20 mmol) in CCl_4 (40 mL) was heated to gentle reflux, and to this was added bromine (3.83 g, 1.23 mL, 24 mmol) in CCl_4 (20 mL) dropwise over a period of 1 h. The mixture was refluxed for an additional 2 h, cooled, and poured into ice-cold water. It was then extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by a silica gel column chromatography (hexanes) to give **5** (5.1 g, 86%) as a white crystalline solid. mp 117−118 °C. ^{1}H NMR: δ 2.11 (m, 2H), 3.12 (t, 2H, J = 6.2 Hz), 3.33 (t, 2H, J = 6.2), 7.40 (d, 1H, J = 6.9 Hz), 7.57 (dd, 1H, J = 8.2 and 7.2 Hz), 7.60−7.70 (m, 2H), 8.45 (dd, 1H, J = 9.5 and 2.0 Hz), 8.53 (d, 1H, J = 8.5 Hz), 8.64 (dd, 1H, J = 9.5 and 2.0 Hz). HRMS calcd for $C_{17}H_{13}Br$, 296.0195; found, 296.0197.

7-(2-Formylphenyl)-5,6-dihydro-4*H*-benz[*de*]anthracene (6). A mixture of 7-Bromo-5,6-dihydro-4*H*-benz[*de*]anthracene (**5**) (1.48 g, 5.0 mmol), 2-formylphenyl boronic acid (0.82 g, 5.5 mmol), cesium fluoride (1.67 g, 11.0 mmol), and $Pd(PPh_3)_4$ (0.23 g, 0.20 mmol) in anhydrous DME (40 mL) was refluxed for 24 h. The mixture was cooled to room temperature, and the reaction was quenched with ice-cold H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Concentration in vacuo provided a residue that was purified by silica gel column chromatography (EtOAc/hexanes 3:97) to give **6** (0.98 g, 61%) as a pale yellow crystalline solid. mp 206−208 °C. ^{1}H NMR: δ 1.99 (m, 2H), 2.60−2.80 (m, 2H), 3.15 (t, 2H, J = 6.2 Hz), 7.20 (dd, 1H, J = 8.2 and 0.7 Hz), 7.36 (dd, 1H, J = 7.6 and 1.0 Hz), 7.41−7.46 (m, 2H), 7.57−7.65 (m, 3H), 7.76 (dt, 1H, J = 7.6 and 1.3 Hz), 8.17 (dd, 1H, J = 7.9 and 1.0 Hz), 8.64 (d, 1H, J = 8.5 Hz), 8.74 (d, 1H, J = 7.9 Hz), 9.61 (s, 1H). HRMS calcd for $C_{24}H_{18}O$, 322.1352; found, 322.1357.

7-(2-Formyl-4-methoxy)phenyl-5,6-dihydro-4*H*-benz[*de*]-anthracene (7). A mixture of 7-bromo-5,6-dihydro-4*H*-benz[*de*]-anthracene (**5**) (2.67 g, 9.0 mmol), 2-formyl-(4-methoxyphenyl)-boronic acid (1.78 g, 9.9 mmol), cesium fluoride (3.0 g, 19.8 mmol), and $Pd(PPh_3)_4$ (0.42 g, 19.8 mmol) in anhydrous DME (70 mL) was refluxed for 24 h. A similar workup as described for **6** gave the crude product, which was purified by silica gel column chromatography (EtOAc/hexanes 3:97) as eluent to yield **7** (2.05 g, 65%) as a pale yellow crystalline solid. mp 213-214 °C. ^{1}H NMR: δ 1.98 (m, 2H), 2.61−2.80 (m, 2H), 3.14 (t, 2H, J = 6.2), 3.97 (s, 3H), 7.22−7.27 (m, 2H), 7.33 (dd, 1H, J = 8.2 and 2.9 Hz), 7.41−7.46 (m, 2H), 7.56−7.62 (m, 2H), 7.55 (d, 1H, J = 2.9 Hz), 8.63 (d, 1H, J = 8.2 Hz), 8.73 (d, 1H, J = 8.2 Hz), 9.55 (s, 1H). HRMS calcd for $C_{25}H_{20}O_2$, 352.1458; found, 352.1467.

***N*-[2-(5,6-Dihydro-4*H*-benz[*de*]anthracen-7-yl)benzylidene]aniline (8).** To a solution of aniline (0.23 g, 0.23 mL, 2.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added the molecular sieves (4 Å, 1.0 g), and a solution of **6** (0.80 g, 2.5 mmol) in CH_2Cl_2 (10 mL) was introduced dropwise. The reaction mixture was stirred for 4 h, filtered, and concentrated to give 0.95 g (96%) of the imine **8**, which was used as such for cyclization. It was recrystallized from a mixture of ether and hexanes. mp 162−163 °C. ^{1}H NMR: δ 1.93−2.03 (m, 2H), 2.65−2.85 (m, 2H), 3.15 (t, 2H, J = 6.2 Hz), 6.82−6.84 (m, 2H), 7.03−7.07 (m, 1H), 7.14−7.18 (m, 2H), 7.29−7.31 (m, 2H), 7.41−7.46 (m, 2H), 7.57−7.64 (m, 4H), 8.02 (s, 1H), 8.51 (d, 1H, J = 6.9 Hz), 8.64 (d, 1H, J = 8.2 Hz), 8.74 (d, 1H, J = 8.2 Hz). HRMS calcd for $C_{30}H_{23}N$, 397.1825; found, 397.1835.

***N*-[2-(5,6-Dihydro-4*H*-benz[*de*]anthracen-7-yl)-5-methoxybenzylidene]aniline (9).** To a solution of aniline (0.46 g, 0.45 mL, 5.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added the molecular sieves (4 Å, 2 g), and a solution of **7** (1.76 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was introduced dropwise. The reaction mixture was stirred for 4 h, filtered, and concentrated to give a nearly pure imine, which was purified by column chromatography (EtOAc/hexanes 2:98) to give 2.0 g (94%) of the imine **9** as a pale yellow solid. mp 145−146 °C. ^{1}H NMR: δ 1.93−2.03 (m, 2H), 2.67−2.86 (m, 2H), 3.14 (t, 2H, J = 6.2), 4.02 (s, 3H), 6.68−6.71 (m, 2H), 7.03−7.07 (m, 1H), 7.14−7.20 (m, 4H), 7.34 (dd, 1H, J = 8.2 and 1.0 Hz), 7.36 (dd, 1H, J = 7.6 and 1.0 Hz), 7.42−7.46 (m, 2H), 7.56−7.62 (m, 2H), 7.97 (s, 1H) 7.99 (d, 1H, J = 2.3 Hz), 8.63 (d, 1H, J = 8.2 Hz), 8.73 (d, 1H, J = 8.2 Hz). HRMS calcd for $C_{31}H_{25}NO$, 427.1931; found, 427.1938.

Dibenzo[*def,p*]chrysene (1). Method 1. To a solution of **8** (0.60 g, 1.5 mmol) in DMF (6 mL) was added powdered KOH (0.25 g, 4.5 mmol), and the reaction mixture was heated at 100 °C for 1 h. The reaction mixture was cooled, and water was added, extracted with CH_2Cl_2, and dried over $MgSO_4$. After removal of solvent, the crude product obtained was purified by silica gel column chromatography (EtOAc/hexane 2:98) to give a mixture of DBC (**1**) and **11** in ∼ 1:9 ratio (as determined by ^{1}H NMR). To a solution of this mixture in C_6H_6 was added DDQ (1.02 g, 4.5 mmol), and the reaction was refluxed for 30 min. The mixture was cooled, filtered, and concentrated. Purification of the crude residue on silica gel column (EtOAc/hexanes 2:98) gave **1** (0.40 g, 88%) as a pale yellow solid.

Method 2. To a solution of imine **8** (0.16 g, 0.4 mmol) in DMF (4 mL) was added *t*-BuOK (0.13 g, 1.2 mmol), and the reaction mixture was stirred at room temperature for 6 h. Water was then added to the reaction mixture, and it was extracted with EtOAc and dried over $MgSO_4$. Removal of the solvent gave the crude mixture, which was purified by silica gel column chromatography (EtOAc/hexanes 2:98) to give **1** (0.1 g, 83%) as a pale yellow solid. mp 161−162 °C (ref 10: mp 159−160 °C; ref 14: 162−163 °C). ^{1}H NMR: δ 7.66−7.79 (m, 4H), 7.84 (d, 1H, J = 9.2 Hz), 7.95 (d, 1H, J = 9.2 Hz), 7.99 (dd, 1H, J = 7.8 and 7.6 Hz), 8.07 (d, 1H, J = 7.6 Hz), 8.26−8.29 (m, 1H), 8.49 (s, 1H), 8.88−8.91 (m, 2H), 9.10 (d, 1H, J = 7.8 Hz), 9.20−9.23 (m, 1H).

12-Methoxydibenzo[*def,p*]chrysene (13). Method 1. To a solution of **9** (0.85 g, 2.0 mmol) in DMF (9 mL) was added

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powdered KOH (0.34 g, 6.0 mmol); the reaction mixture was heated at 100 °C for 1 h. The crude product, obtained after following a similar workup as mentioned above for **1**/**11**, was purified by silica gel column chromatography (EtOAc/hexanes 2:98) to give a mixture of **12** and **13** in ~ 9:1 ratio (as determined by ^{1}H NMR). To a solution of this mixture in C_6H_6 was added DDQ (1.36 g, 6.0 mmol), and this reaction was refluxed for 30 min. The mixture was then cooled, filtered, and concentrated. Purification of the crude residue by silica gel column chromatography (EtOAc/hexanes 2:98) gave 12-methoxy-DBC (**13**) (0.51 g, 84%) as a pale yellow solid.

Method 2. To a solution of **9** (0.94 g, 2.2 mmol) in DMF (15 mL) was added *t*-BuOK (0.74 g, 6.6 mmol), and the reaction mixture was stirred at room temperature for 6 h. A similar workup as mentioned above (Method 2 for **1**) gave the crude mixture, which was purified by silica gel column chromatography (EtOAc/hexanes 2:98) to give **13** (0.60 g, 81%) as pale yellow solid; mp 193−194 °C (ref 13: 192−193 °C). ^{1}H NMR: δ 4.06 (s, 3H), 7.37 (dd, 1H, J = 9.5 and 2.6 Hz), 7.53 (d, 1H, J = 2.6 Hz), 7.69−7.78 (m, 2H), 7.85 (d, 1H, J = 9.2 Hz), 7.94 (d, 1H, J = 9.2 Hz), 7.98 (dd, 1H, J = 8.0 and 7.6 Hz), 8.07 (d, 1H, J = 7.6 Hz), 8.39 (s, 1H), 8.88−8.91 (m, 2H), 9.03 (d, 1H, J = 8.0 Hz), 9.11 (d, 1H, J = 9.5 Hz).

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**, **5**, **6**, **7**, **8**, **9**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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