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Synthesis of a Series of Novel 3,9-Disubstituted Phenanthrenes as Analogues of Known N-Methyl-D-aspartate Receptor Allosteric Modulators

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Abstract 9-Substituted phenanthrene-3-carboxylic acids have been reported to have allosteric modulatory activity at the N-methyl-D-aspartate (NMDA) receptor. This receptor is activated by the excitatory neurotransmitter L-glutamate and has been implicated in a range of neurological disorders such as schizophrenia, epilepsy and chronic pain, and in neurodegenerative disorders such as Alzheimer’s disease. Herein, the convenient synthesis of a wide range of novel 3,9-disubstituted phenanthrene derivatives starting from a few common intermediates is described. These new phenanthrene derivatives will help to clarify the structural requirements for allosteric modulation of the NMDA receptor.

Key words phenanthrenes, NMDA receptor, allosteric modulators, palladium coupling, Wittig reaction

Phenanthrene is a naturally occurring polycyclic aromatic ring system that is found in a number of biologically active compounds.1 Recently, we reported that phenanthrene derivatives such as 1, 2 and 3 (Figure 1) are allosteric modulators of the N-methyl-D-aspartate (NMDA) family of ionotropic glutamate receptors (i-GluRs).2 NMDA receptors are tetrameric ligand-gated ion channels comprised of GluN1 and GluN2A-D subunits.2 NMDA receptors have been implicated in a range of neurological disorders such as epilepsy, schizophrenia and chronic pain, and neurodegenerative disorders such as ischaemia, Alzheimer’s disease and Parkinson’s disease.2 Allosteric modulators have the potential to be used in the treatment of these disorders because they are less likely to interfere with the physiological roles of NMDA receptors compared with competitive antagonists or channel blockers.3 A convenient synthetic route to 3-carboxy-phenanthrenes with a wide range of hydrophobic and hydrophilic substituents at the 9-position was required to conduct a structure-activity relationship (SAR) study on allosteric modulators 1–3.

Figure 1 NMDA receptor allosteric modulators

With the exception of the 9-bromo, 9-chloro and 9-carboxy derivatives, no 9-substituted 3-carboxyphenanthrenes have previously been reported.4,5 Herein, we report the synthesis of 1–3 and a novel series of their derivatives starting from a few common intermediates.

Initial studies suggested that 9-iodophenanthrene-3-carboxylic acid (1) had an interesting pharmacological profile4 and so we investigated suitable methods for larger scale production of this compound. We recently reported a two-step route to 1 in which an aromatic Finkelstein reaction6 was utilised to convert 3-acetyl-9-bromophenanthrene (4) into its corresponding 9-iodo analogue 9 (Scheme 1).7 A haloform reaction was then employed to oxidise the acetyl group and give the desired acid. However, although our initial experiments led to complete conversion, subsequent attempts to synthesise 9 led only to inseparable mixtures of 4 and 9. Despite extensive investigation...
(e.g., different amine ligands, alternative solvents, purification of copper (I) iodide catalyst), no satisfactory reason for the non-reproducibility of the aromatic Finkelstein reaction could be established. With the halogen conversion route proving unreliable, an alternative and more robust pathway to 1 was sought. Unfortunately, attempts to iodinate the 9-position of phenanthrene-3-carboxylic acid (5) directly using either iodine monochloride or sodium iodide and sodium hypochlorite (Scheme 2) led only to the recovery of unreacted starting material. As a consequence, we decided to focus on developing an alternative route to ketone 9. The most obvious route to this compound is through Friedel–Crafts acylation. However, whilst Friedel–Crafts acylation can be used to synthesise the 3-acetyl derivatives of both 9-bromo and 9-chlorophenanthrene, we found that employing the same reaction conditions on 9-iodophenanthrene (6) led only to the isolation of a black tar (Scheme 2). Attempts to modify the reaction conditions by using aluminium iodide instead of aluminium chloride, or acetic anhydride instead of acetyl chloride, led to the same outcome. With all previous routes proving unsuccessful, we investigated the use of lithiation as a possible way of introducing the iodo substituent (Scheme 1). After protecting ketone 4 as the acetal 7, lithiation at the 9-position followed by quenching with \((n\text{-Bu})_3\text{SnCl}\) afforded stannane 8. The 9-iodo group was then readily introduced by stirring with a saturated solution of iodine in dichloromethane at 0 °C. Subsequent deprotection gave ketone 9, which was then easily converted into 1 by using the haloform reaction described previously. In theory, the iodo group could have been introduced by quenching the lithiated species with iodine. However, we were concerned that employing this route would lead to the formation of side products that could not be easily separated from the desired product. Although it added an additional step, utilising stannane 8 allowed 1 to be synthesised both cleanly and in high yield.
Scheme 3  Reagents and conditions: **Part A** (a) Methyl acrylate, (o-tolyl)₃P, Et₃N, Pd(OAc)₂, DMF, 100 °C, 18 h; ii. Mel, K₂CO₃, DMF, r.t., 18 h; (b) i. OsO₄, TMAO, t-BuOH/H₂O, r.t., 2 d; ii. NaIO₄; (c) MeOH, H₂SO₄, reflux, 48 h. **Part B** (a) RCH₂PPh₃X, KHMDS, THF, 4 h, r.t.; (b) alkene, (o-tolyl)₃P, Et₃N, Pd(OAc)₂, DMF, 100 °C, 18 h; (c) (n-Bu)₃SnCH=CH₂, Pd(PPh₃)₄, toluene, reflux, 4 h; (d) H₂, 10% Pd/C, EtOAc, r.t., 18 h; (e) i. NaOH or KOH (aq), THF, reflux or dioxane, 75 °C; ii. 1 M HCl (aq); (f) 17a. CH₂N₂, Et₂Zn, CH₃Cl₂, 0 °C, 18 h; (g) LiOH (aq), dioxane, r.t.; (h) 1 M HCl (aq); (i) 3-thienylboronic acid, K₂CO₃, Pd(dppe)Cl₂·CH₂Cl₂, DME, 80 °C, 24 h; (i) i. NaOH (aq), dioxane, 75 °C; ii. 1 M HCl (aq); iii. crystallisation (AcOH).
Our attention then turned to the synthesis of a structurally diverse series of 3-carboxyphenanthrenes bearing hydrophobic substituents at the 9-position as analogues of compounds 1–3. Amongst the initial group of compounds generated was thioether 12, which was synthesised by using an identical strategy to that described for 1 with the exception that after being lithiated, acetal 7 was quenched with dimethyl disulfide (Scheme 1). Deprotection subsequently afforded acetyl 11, which was then readily converted into carboxylic acid 12 by using the haloform reaction.

In addition to thioethers, compounds bearing alkyl substituents at the 9-position were synthesised. Initial attempts to generate these derivatives by reacting alkyl aldehydes with lithiated acetal 7 gave only a complex mixture of products. Consequently, an alternative route was devised to allow a range of alkyl chains to be introduced using common intermediates, which could be prepared both quickly and in high yield. With this in mind, the 9-formyl (15) and 9-bromo (16) substituted phenanthrenes were chosen because both functional groups could be easily manipulated by using either Wittig or palladium coupling chemistry to afford a large variety of 9-alkyphenanthrenes from commercially available reagents. Both 15 and 16 were conveniently prepared from 9-bromo acid 13 (Scheme 3, A). Heck coupling of 13 with methyl acrylate followed by esterification with methyl iodide afforded diester 14. Oxidation of alkene 14 with osmium tetroxide and cleavage of the resultant 1,2-diol with sodium periodate afforded 9-formyl derivative 15. Methyl ester 16 was generated in good yield by Fisher esterification of acid 13.

Conducting either Wittig or Heck chemistry on 15 and 16 proceeded smoothly and led to the synthesis of alkene intermediates 17a–i, which, in the majority of cases, were hydrogenated immediately to their corresponding alkyl counterparts 18a–i (Scheme 3, B). Base-mediated hydrolysis subsequently afforded the desired 9-alkyl-3-carboxyphenanthrenes (3, 19a–d, 19f–h, and 19j). The 9-cyclopropyl derivative 2 was synthesised from vinyl 17a in two steps. First, the cyclopropyl ring was formed through a Simmons–Smith reaction to give 20. Base-mediated hydrolysis of the ester subsequently afforded the desired acid 2. Initially, alkene 17a was prepared from 15 through Wittig chemistry. Although this route proved to be successful, we found that the compound was more conveniently prepared through Stille coupling between 16 and (tri-n-butyl)vinyl tin (Scheme 3, B).

To investigate the introduction of a heteroaromatic moiety, Suzuki coupling was employed to react 16 and 3-thienyl boronic acid (Scheme 3, B). Unfortunately, this reaction did not go to completion and led to the isolation of a mixture of product 21 and starting material 16 (ca. 75:25 ratio based on 1H NMR spectroscopic analysis). Despite an investigation of different solvent systems, it was not possible to separate the individual esters by silica gel chromatography. Consequently, the mixture was taken forward and hydrolysed by using a base. By conducting multiple recrystallisations from glacial acetic acid, we were able to separate the mixture of acids and obtain a pure sample of 22 (Scheme 3, B).

### Scheme 4

**Reagents and conditions:**
(a) CuI, NaI, MeMgCl, TMSCl, CH₂Cl₂/Me₂S, –78 °C then r.t., 3 h; (b) KHMDS, THF, 2-tosyl-3-phenyloxaziridine, –78 °C then r.t., 2 h; (c) i. LiBH₄, THF, 0 °C, 30 min then r.t., 4 h; ii. t-BuOH–H₂O (4:1), NaIO₄, r.t., 30 min; (d) NaBH₄, THF, r.t., 4 h; (e) i. MsCl, Et₃N, 0 °C, 1 h then r.t., 3 h; ii. NaOH, acetone, reflux, 24 h; iii. H₂, Et₃N, 10% Pd/C, r.t., 18 h; (f) i. NaOH (aq), dioxane, 75 °C; ii. 1 M HCl (aq).
Synthesis of the branched 9-isopropyl derivative 30 required a different strategy to that described above (Scheme 4). This strategy had the added advantage of generating two intermediates (24 and 28) that could be pharmacologically characterised. Starting from diester 14, 1,4-conjugate addition of methyl magnesium chloride afforded 23 in reasonable yield. Whilst a small amount of this compound was hydrolysed with base to diacid 24, the majority was reacted with 2-tosyl-3-phenyloxaziridine 8 to generate alcohol 25 (Scheme 4). Reduction of the alkyl ester with lithium borohydride and cleavage of the resultant 1,2-diol with sodium periodate, led to the synthesis of aldehyde 26.

Reduction of the aldehyde with sodium borohydride gave alcohol 27 in good yield. A small amount of this ester was hydrolysed to the corresponding acid 28 by using a base (Scheme 4). Alcohol 27 was then converted into the corresponding mesylate by reaction with methanesulfonyl chloride. The mesylate was, in turn, converted into the corresponding iodo derivative through a Finkelstein reaction. Subsequent hydrogenation led to dehalogenation and yielded the 9-isopropyl derivative 29, which was readily hydrolysed to the desired acid 30 (Scheme 4).

In addition to its use in the previously described Wittig chemistry, aldehyde 15 was utilised as a starting point for the synthesis of 9-methyl derivative 35 (Scheme 5). Reduction of the aldehyde by using sodium borohydride afforded 9-hydroxymethyl derivative 31. A small portion of this compound was hydrolysed to yield acid 32 for pharmacological characterisation, whereas the majority was taken forward and reacted with phosphorus tribromide to afford 9-bromomethyl 33. Hydrogenation subsequently afforded 9-methyl derivative 34, which was readily hydrolysed to the corresponding acid 35 (Scheme 5).

Although the introduction of hydrophobic substituents was our primary focus, we wanted to synthesise some compounds with more polar groups at the 9-position to gather additional data on the requirements for biological activity. For example, aldehyde 15 was reacted with isopropylamine through reductive amination to afford ester 36, which was subsequently hydrolysed to acid 37 (Scheme 5). Similarly, alkene 14 was hydrogenated to afford alkyl diester 38, which was then hydrolysed to diacid 39 (Scheme 6).

To identify the optimal 3-position substituent for biological activity, the 3-carboxy group in 1 was subjected to chemical modification (Scheme 7). Interestingly, attempts to reduce this moiety by using lithium aluminium hydride led not only to reduction of the desired group but also to dehalogenation. Consequently, a pathway was devised in which the acid chloride of 1 was generated through reac-
tion with thionyl chloride and then reduced under mild conditions using sodium borohydride (Scheme 7). This route was successful and led to the synthesis of 3-hydroxymethyl 40 in good yield. Reaction of 40 with phosphorus tribromide afforded 3-bromomethyl 41, which was, in turn, converted into the corresponding nitrile 42 by reaction with sodium cyanide under phase-transfer conditions. Hydrolysis of the nitrile under acidic conditions gave 3-acetic acid derivative 43 (Scheme 7).9

Scheme 7  Reagents and conditions: (a) i. SOCl₂, dioxane, reflux, 12 h; ii. NaBH₄, THF, 0 °C, 0.5 h, then r.t., 12 h; (b) Br₃P, CH₂Cl₂, 0 °C then r.t., 1 h; (c) NaCN, TBAB, H₂O/CH₂Cl₂ (1:1), r.t., 5 d; (d) AcOH, H₂SO₄, H₂O, 118 °C, 3 h.

In a further modification to the 3-position, the acid chloride of 1 was reacted with benzylamine, phenethylamine and the tert-butyl ester of glycine to afford amides 44a, 44b and 45 (Scheme 8). Deprotection of the tert-butyl ester to afford acid 46 was achieved readily and in good yield by reaction with TFA (Scheme 8).

Table 1  Activity of Selected 3,9-Disubstituted Phenanthrene Derivatives at Recombinant NMDA Receptor Subtypes

<table>
<thead>
<tr>
<th>NMDAR (n=4)⁴</th>
<th>GluN2A</th>
<th>GluN2B</th>
<th>GluN2C</th>
<th>GluN2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.6 ± 4.8</td>
<td>0.9 ± 0.1</td>
<td>-34.1 ± 8.3</td>
<td>-52.3 ± 3.0</td>
</tr>
<tr>
<td>2</td>
<td>36.0 ± 7.4</td>
<td>51.2 ± 13.2</td>
<td>-7.3 ± 0.4</td>
<td>5.6 ± 4.7</td>
</tr>
<tr>
<td>3</td>
<td>31.5 ± 10.0</td>
<td>34.0 ± 8.5</td>
<td>21.8 ± 8.1</td>
<td>24.3 ± 3.6</td>
</tr>
<tr>
<td>35</td>
<td>-4.8 ± 4.6</td>
<td>-3.2 ± 0.3</td>
<td>-15.1 ± 0.3</td>
<td>-4.1 ± 0.9</td>
</tr>
<tr>
<td>19b</td>
<td>6.6 ± 1.2</td>
<td>30.0 ± 1.8</td>
<td>5.2 ± 4.0</td>
<td>7.8 ± 1.8</td>
</tr>
<tr>
<td>19d</td>
<td>42.6 ± 9.6</td>
<td>42.1 ± 14.3</td>
<td>26.4 ± 5.4d</td>
<td>20.3 ± 5.3</td>
</tr>
<tr>
<td>19f</td>
<td>28.2 ± 11.4</td>
<td>20.5 ± 7.5</td>
<td>19.6 ± 3.0</td>
<td>24.6 ± 7.3</td>
</tr>
<tr>
<td>22</td>
<td>10.7 ± 6.4</td>
<td>3.9 ± 12.6</td>
<td>-52.7 ± 9.1</td>
<td>-45.2 ± 8.7</td>
</tr>
<tr>
<td>37</td>
<td>-21.9 ± 9.2</td>
<td>-0.3 ± 1.8</td>
<td>-13.0 ± 2.5</td>
<td>-2.6 ± 0.8</td>
</tr>
<tr>
<td>39</td>
<td>-48.1 ± 6.5</td>
<td>-51.1 ± 3.4</td>
<td>-17.8 ± 2.7</td>
<td>-15.1 ± 0.7</td>
</tr>
<tr>
<td>43</td>
<td>-23.5 ± 3.9</td>
<td>-30.9 ± 3.8</td>
<td>-46.7 ± 4.3</td>
<td>-66.6 ± 4.1</td>
</tr>
</tbody>
</table>

⁴ All compounds tested at a concentration of 100 μM.
⁵ Percent inhibition (negative number) or potentiation (positive number) of the responses of recombinant rat NMDA receptors (GluN1 expressed with the indicated GluN2 subunit) expressed in Xenopus oocytes (mean ± s.e.m.).
⁶ All of the compounds were made up as stocks solutions in DMSO and were soluble up to a concentration of 100 μM in the buffer used in these assays.
⁷ 19d inhibited 22% in one experiment; this value was not included in the average shown.

A previously described electrophysiological assay on GluN1 and GluN2A-D subunits individually expressed in Xenopus oocytes³ was used to pharmacologically characterise a selection of the synthesised phenanthrenes. The compounds were tested at a concentration of 100 μM for their effects on GluN1/GluN2A-D receptor responses and percentage antagonism or potentiation of responses to glutamate (10 μM) and glycine (10 μM) was determined (Table 1). Although only preliminary, these data suggest that:
(a) an alkyl substituent at the 9-position promotes NMDA receptor potentiating activity; (b) as the length and/or size of the alkyl chain increases so does NMDA receptor potentiation (compare activity of 35 vs. 2, 3, 19b, 19d and 19f); (c) introduction of a polar group into the alkyl side chain promotes NMDA receptor antagonist over potentiation (37 and 39); (d) the 9-iodo group can be replaced by a 3-thienyl ring without adversely affecting activity (compare activity of 1 vs. 22), and (e) moving the carboxyl group away from the phenanthrene ring is beneficial for NMDA receptor antagonism (compare activity of 1 vs. 43).

In conclusion, we have developed an alternative and robust synthetic pathway to 9-iodophenanthrene-3-carboxylic acid (1), a novel allosteric NMDA receptor modulator. Starting from a few common intermediates, we have synthesised a series of novel phenanthrene derivatives with a variety of substituents at the 3- and 9-positions of the phenanthrene ring. It is hoped that these compounds will lead to a better understanding of the structural requirements for allosteric modulation of the NMDA receptor. The preliminary pharmacological data described here suggests that the new compounds have interesting profiles of activity on NMDA receptor subtypes. Further pharmacological characterisation of these newly synthesised compounds is ongoing and will be reported in due course.

Reagents were purchased from commercial suppliers and purified by standard techniques when necessary. All anhydrous solvents were obtained from either Acros or Sigma–Aldrich and used without further drying. All anhydrous reactions were conducted under an inert atmosphere. Melting points were determined with an Electrothermal IA9100 capillary apparatus and are uncorrected. 1H NMR spectra were measured with either a Jeol spectrometer at 270.18 MHz, a Jeol JNM-LA300 spectrometer at 300.53 MHz, or a Jeol JNM-ECP400 spectrometer at 400.18 MHz. A Varian 400MR spectrometer at 400.52 MHz, a Jeol JNM-ECP400 spectrometer at 399.77 MHz, or a Varian 400MR spectrometer at 300.53 MHz. 13C NMR (75 MHz, CDCl3) δ = 26.7, 102.4, 122.7, 123.8, 126.1, 127.9, 128.1, 128.4, 129.8, 130.7, 132.4, 133.5, 135.1, 137.5, 137.9, 197.8.

Tributyl-[3-(2-methyl[1,3]dioxolan-2-yl)phenanthren-9-yl]stannane (8)

To a solution of 7 (22.2 g, 65 mmol) in anhydrous THF (350 mL) at –78 °C was added carefully and dropwise a solution of n-BuLi (2.5 M in hexane, 31 mL, 78 mmol). The resultant mixture was stirred for 1 h at –78 °C, then the reaction was quenched with n-Bu3SnCl (23 mL, 84.5 mmol). After complete addition, the solution was warmed to r.t., the reaction mixture was diluted with Et2O (500 mL) and the organic layer was washed with NaHCO3 (50 mL) and dried over MgSO4 and concentrated in vacuo. The resultant residue was purified by flash chromatography (EtOAc–hexane, 2%) to afford 8 (31.9 g, 89%), which was utilised in the next step without further analysis.

3-Acetyl-9-iodophenanthrene (9)

Compound 8 (31.9 g, 57.7 mmol) was dissolved in CH2Cl2 (150 mL) and a saturated iodine solution in CH2Cl2 was added slowly at 0 °C until the colour of the last drop of iodine did not disappear within 30 s. The organic solution was then washed with sat. NaHSO3 (50 mL), H2O (50 mL), dried over MgSO4, and concentrated in vacuo. The resultant residue was dissolved in acetone (200 mL) and aq. 2 M HCl (4 mL) was added dropwise. The ketone precipitated out of solution almost immediately and, after stirring for 30 min, 9 was collected by filtration. Yield: 17.0 g (85%); white solid; mp 149–151 °C (Lit. 148–150 °C).

HRMS (CI): m/z [M + H]+ calculated for C24H13O5Br: 343.0334; found: 343.0338.

3-(2-Methylsulfonylphenanthrene-3-yl)-1,3-dioxolane (10)

To a stirring solution of 7 (1.72 g, 5.00 mmol) in anhydrous THF (50 mL) at –78 °C was added dropwise a solution of n-BuLi (2.5 M in hexane, 2.4 mL, 6.00 mmol). After complete addition, the solution was stirred for 1 h, then the reaction was quenched by the dropwise addition of dimethyl disulfide (0.59 mL, 6.50 mmol). The mixture was then warmed to r.t. before being diluted with Et2O (50 mL). The organic layer was washed, dried with H2O (50 mL), and concentrated in vacuo. The resultant residue was purified by flash chromatography (EtOAc–hexane, 2%) to afford 10, which was utilised in the next step without further analysis.

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M. W. Irvine et al.
1-[9-(Methylsulfanyl)phenanthren-3-yl]ethanone (11)

Concentrated HCl (0.4 mL) was added dropwise to a stirred solution of 10 in acetone (100 mL). The resultant solution was stirred for 1 h, during which a precipitate formed. This solid was filtered off and washed with cold acetone (20 mL). Recrystallisation from acetone afforded 11.

Yield: 954 mg (72%); off-white solid; mp 135–137 °C.

1H NMR (400 MHz, CDCl3): δ = 6.09 (s, 3 H), 7.28 (s, 3 H), 7.50 (s, 1 H), 7.67–7.78 (m, 2 H), 8.07 (d, J = 8.4 Hz, 1 H), 8.19–8.25 (m, 1 H), 8.37 (m, 1 H), 8.46 (d, J = 8.0 Hz, 1 H), 8.71–8.75 (m, 1 H), 9.32 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 14.1, 120.3, 123.4, 123.9, 124.4, 127.0, 127.0, 127.6, 127.6, 127.9, 129.4, 130.8, 131.0, 134.1, 134.2, 134.7, 135.9, 142.2, 167.1, 167.2, 167.3, 172.7.

HRMS (CI): m/z [M + H]+ calcd for C17H12O3: 266.0766; found: 266.0765.

Yield: 9.06 g (87%); pale-yellow solid; mp 151–153 °C (Lit.4 155–155.5 °C).

Methyl 9-Formylphenanthrene-3-carboxylic Acid (12)

A stirred suspension of 11 (400 mg, 1.50 mmol) in dioxane (50 mL) was heated at 40 °C until complete dissolution of the solid. At the same time, a solution of sodium hypobromite was prepared by the dropwise addition of bromine (0.38 mL, 7.50 mmol) to an ice-cooled solution of sodium hydroxide (1.05 g, 26.3 mmol) dissolved in H2O (50 mL). The sodium hypobromite solution was then added dropwise to the dioxane solution (complete addition took around 10 min) and stirring was continued until TLC analysis indicated complete conversion. The mixture was then cooled to r.t. and a saturated sodium sulfite solution (10 mL) was added to quench excess hypobromite. The mixture was then cooled to r.t. and a saturated sodium sulfite solution (10 mL) was added to quench excess hypobromite. The mixture was then cooled to r.t. and a saturated sodium sulfite solution (10 mL) was added to quench excess hypobromite. The mixture was then cooled to r.t. and a saturated sodium sulfite solution (10 mL) was added to quench excess hypobromite. The mixture was then cooled to r.t. and a saturated sodium sulfite solution (10 mL) was added to quench excess hypobromite.

Yield: 5.17 g (98%); pale-yellow solid; mp 180–182 °C.

1H NMR (300 MHz, CDCl3): δ = 4.04 (s, 3 H), 7.71–7.80 (m, 2 H), 8.03 (d, J = 8.8 Hz, 1 H), 8.20–8.24 (m, 2 H), 8.74–8.77 (m, 1 H), 9.29–9.34 (m, 2 H), 10.38 (s, 1 H).

13C NMR (75 MHz, CDCl3): δ = 52.7, 123.0, 125.2, 126.1, 127.2, 128.2, 128.4, 128.8, 130.5, 130.5, 132.2, 132.4, 132.8, 139.7, 146.9, 193.5.

MS (CI): m/z (%): [M + H]+ = 265 (100) [M + H]+.


Methyl 9-Bromophenanthrene-3-carboxylate (16)

A flask containing 13 (10.0 g, 33.2 mmol) was briefly evacuated and backfilled with argon. Anhydrous MeOH (300 mL) was then added to the flask by using a cannula followed by a catalytic amount of concentrated H2SO4 (3 mL). The resultant mixture was heated to reflux for 4 h, then cooled to r.t. before being concentrated in vacuo. The resultant dark-orange solid was dissolved in CH2Cl2 (250 mL) and washed with sat. aq NaHCO3 (3 × 50 mL), H2O (50 mL) and brine (50 mL). The organic layer was dried over MgSO4 and concentrated in vacuo to afford 16.

Yield: 9.06 g (87%); orange solid; mp 151–153 °C (Lit.4 155–155.5 °C).

1H NMR (400 MHz, CDCl3): δ = 4.03 (s, 3 H), 7.69–7.77 (m, 2 H), 7.78 (d, J = 8.4 Hz, 1 H), 8.07 (s, 1 H), 8.17 (dd, J = 8.4, 1.6 Hz, 1 H), 8.33–8.37 (m, 1 H), 8.71–8.75 (m, 1 H), 9.32 (s, 1 H).

13C NMR (100 MHz, CDCl3): δ = 52.4, 123.0, 124.6, 125.2, 127.1, 127.8, 128.0, 128.0, 128.2, 128.2, 129.1, 129.9, 130.5, 130.7, 131.0, 133.4, 133.7, 133.9, 135.9, 142.2, 167.1, 167.2, 167.3, 172.7.


Anal Calcd for C19H12O3·0.25 H2O: C, 70.43; H, 4.53. Found: C, 70.43; H, 4.53.

Methyl 9-(3-Methoxy-3-oxoprop-1-en-1-yl)phenanthrene-3-carboxylate (14)

A flask was charged with 13 (30.1 g, 0.1 mol), palladium acetate (0.24 g, 0.1 mmol) and tri-o-tolylphosphine (1.28 g, 0.04 mmol). The flask was then briefly evacuated and backfilled with argon three times. A degassed solution of Et3N (40 mL, 0.26 mol) and methyl acrylate (12 mL, 0.13 mol) in DMF (300 mL) was then added to the flask by using a cannula and the resultant mixture was heated at 100 °C for 18 h. After cooling to r.t., any remaining volatile compounds were removed in vacuo. Na2CO3 (10.6 g, 0.1 mol) was then added followed by methyl iodide (12.5 mL, 0.2 mol), and the reaction mixture was stirred at r.t. overnight. The mixture was then diluted with Et2O (500 mL) and the organic layer was isolated, washed with H2O (2 × 200 mL) and dried over MgSO4. Concentration in vacuo gave 14 as a 1:1 mixture of cis and trans isomers.

Yield: 29.5 g (92%); pale-yellow solid; mp 186–188 °C.
Methyl 9-Vinylphenanthrene-3-carboxylate (17a)
By following General Procedure A, methyltriphenylphosphonium iodide (1.38 g) afforded 17a as a light-yellow oil (793 mg, 2.71 mmol) as a light-yellow oil (793 mg, 91%).

General Procedure B; Heck Reaction
A flask was charged with 16 (1.00 g, 3.17 mmol), palladium acetate (1.00 g, 3.17 mmol), tri-o-tolylphosphine (39 mmg, 4 mol%), and (if a solid) the appropriate alkene (3.96 mmol). The flask was then briefly evacuated and backfilled with argon three times. Degassed anhydrous DMF (7.2 mg, 1 mol%) and the appropriate alkene (3.96 mmol). The resultant solution was hydrogenated under 3 bar of hydrogen in the presence of 10 wt% palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered through a Celite pad before being concentrated in vacuo. Purification of the resultant residue by flash chromatography (EtOAc–hexane, 5 → 10%) afforded the individual alky phenanthrenes.

Methyl 9-Prop-1-en-1-ylphenanthrene-3-carboxylate (17b)
By following General Procedure A, ethyltriphenylphosphonium bromide (1.38 g) afforded 17b as a light-yellow oil (729 mg, 88%).

Methyl 9-(2-Phenylethenyl)phenanthrene-3-carboxylate (17h)
By following General Procedure B, styrene (0.45 mL) afforded 17h (924 mg, 91%) as a dark-orange oil.

Methyl 9-Pent-1-en-1-ylphenanthrene-3-carboxylate (17d)
By following General Procedure B, 1-pentene (0.43 mL) afforded 17d (850 mg, 2.62 mmol) as a dark-orange oil. Yield: 685 mg (94%); clear oil.

1H NMR (400 MHz, CDCl₃): δ = 1.09 (t, J = 7.8 Hz, 3 H), 1.81 (m, J = 7.8 Hz, 2 H), 2.98 (t, J = 7.8 Hz, 2 H), 3.23 (s, 3 H), 7.43 (s, 1 H), 7.57–7.66 (m, 2 H), 7.71 (d, J = 9.0 Hz, 1 H), 8.01–8.05 (m, 1 H), 8.14 (d, J = 9.0 Hz, 1 H), 8.72–8.75 (m, 1 H), 9.32 (s, 1 H).
13C NMR (75 MHz, CDCl₃): δ = 14.4, 22.9, 52.2, 123.4, 124.4, 125.0, 125.4, 126.5, 126.7, 127.0, 127.1, 128.1, 129.0, 130.8, 131.4, 134.9, 141.2, 167.5.
HRMS (CI): m/z [M + H]+ calcd for C₁₉H₁₈O₂: 279.1380; found: 279.1373.

Methyl 9-(4-Methylpent-1-en-1-yl)phenanthrene-3-carboxylate (17e)
By following General Procedure C, 2-ethylphenylacetic acid (176 mg, 0.90 mmol) afforded 17e (850 mg, 91%); clear oil.

1H NMR (300 MHz, CDCl₃): δ = 1.04 (t, J = 7.8 Hz, 3 H), 1.50–1.59 (m, 3 H), 1.79–1.87 (m, 2 H), 3.12 (t, J = 7.8 Hz, 2 H), 4.05 (s, 3 H), 5.78–5.79 (m, 1 H), 7.67–7.74 (m, 2 H), 7.82–7.86 (m, 2 H), 8.12–8.15 (m, 1 H), 8.20 (d, J = 8.0 Hz, 1 H), 8.82–8.85 (m, 1 H), 9.14 (s, 1 H).
13C NMR (100 MHz, CDCl₃): δ = 14.2, 23.1, 32.4, 33.4, 52.3, 123.5, 124.7, 125.1, 125.5, 126.6, 126.8, 127.1, 127.2, 128.2, 129.1, 131.0, 131.6, 135.0, 140.1, 167.6.
HRMS (CI): m/z [M + H]+ calcd for C₂₉H₂₉O₂: 293.1542; found: 293.1553.

Methyl 9-(2-Methylprop-1-en-1-yl)phenanthrene-3-carboxylate (17f)
By following General Procedure C, 2-methylpropionic acid (176 mg, 0.90 mmol) afforded 17f (950 mg, 94%); clear oil.

1H NMR (400 MHz, CDCl₃): δ = 1.06 (t, J = 7.8 Hz, 3 H), 1.50–1.59 (m, 3 H), 1.79–1.87 (m, 2 H), 3.12 (t, J = 7.8 Hz, 2 H), 4.05 (s, 3 H), 5.78–5.79 (m, 1 H), 7.67–7.74 (m, 2 H), 7.82–7.86 (m, 1 H), 8.12–8.15 (m, 1 H), 8.20 (d, J = 8.0 Hz, 1 H), 8.82–8.85 (m, 1 H), 9.14 (s, 1 H).
13C NMR (100 MHz, CDCl₃): δ = 14.2, 23.1, 32.4, 33.4, 52.3, 123.5, 124.7, 125.1, 125.5, 126.6, 126.8, 127.1, 127.2, 128.2, 129.1, 131.0, 131.6, 135.0, 140.1, 167.6.
HRMS (CI): m/z [M + H]+ calcd for C₂₉H₂₉O₂: 293.1542; found: 293.1553.
Methyl 9-n-Pentylphenanthrene-3-carboxylate (18d)
By following General Procedure C, 17d (850 mg, 2.79 mmol) afforded 18d.
Yield: 815 mg (95%); viscous yellow oil.

\[ \text{HRMS (CI): } m/z [M + H]^{+} \text{ calc for C}_{29}H_{30}O_{2}: 370.1698; \text{ found: 370.1697.} \]

Methyl 9-(4-Methylpent-1-yl)phenanthrene-3-carboxylate (18e)
By following General Procedure C, 17e (924 mg, 2.90 mmol) afforded 18e.
Yield: 886 mg (95%); viscous yellow oil.

\[ \text{HRMS (CI): } m/z [M + H]^{+} \text{ calc for C}_{30}H_{32}O: 382.2357; \text{ found: 382.2357.} \]

Methyl 9-hexylphenanthrene-3-carboxylate (18f)
By following General Procedure C, 17f (950 mg, 2.98 mmol) afforded 18f.
Yield: 899 mg (94%); viscous yellow oil.

\[ \text{HRMS (CI): } m/z [M + H]^{+} \text{ calc for C}_{30}H_{32}O: 382.2357; \text{ found: 382.2357.} \]

Methyl 9-heptylphenanthrene-3-carboxylate (18g)
By following General Procedure C, 17g (760 mg, 2.29 mmol) afforded 18g.
Yield: 500 mg (65%); viscous pale-yellow oil.

\[ \text{HRMS (CI): } m/z [M + Na]^{+} \text{ calc for C}_{31}H_{34}O_{2}: 387.1831; \text{ found: 387.1822.} \]

9-ethylphenanthrene-3-carboxylic Acid (19a)
By following General Procedure D, 18a (550 mg, 2.08 mmol), NaOH (250 mg, 6.24 mmol) and dioxane afforded 19a.
Yield: 495 mg (95%); white solid; mp 425–429 °C (dec).
HRMS (ESI): m/z [M – H]– calcd for C$_{19}$H$_{18}$O$_2$: 277.1232; found: 277.1232.

Yield: 221 mg (34%); white solid; mp 196–199 °C.

1H NMR (400 MHz, DMSO-d$_6$): δ = 0.85 (t, J = 7.2 Hz, 3 H), 1.22–1.37 (m, 4 H), 1.43 (quint, J = 7.2 Hz, 2 H), 1.73 (quint, J = 7.2 Hz, 2 H), 3.12 (t, J = 7.2 Hz, 2 H), 7.71–7.79 (m, 3 H), 8.01 (d, J = 8.0 Hz, 1 H), 8.11 (dd, J = 8.0, 1.2 Hz, 1 H), 8.16–8.21 (m, 1 H), 8.85–8.90 (m, 9 H), 9.32 (s, 1 H), 13.08 (br s, 1 H).

13C NMR (100 MHz, DMSO-d$_6$): δ = 13.8, 22.2, 31.9, 32.3, 123.3, 124.3, 124.6, 125.2, 126.5, 127.1, 127.3, 128.0, 128.2, 130.0, 130.8, 134.1, 139.4, 167.5.

HRMS (ESI): m/z [M – H]– calcd for C$_{19}$H$_{18}$O$_2$: 277.1234; found: 277.1232.

Anal. Calcld for C$_{19}$H$_{18}$O$_2$: C, 81.85; H, 6.41.

9-n-Butylphenanthrene-3-carboxylic Acid (19c)

By following General Procedure D, 18c (550 mg, 2.22 mmol), NaOH (266 mg, 6.66 mmol) and dioxane afforded 19c as a white solid which was recrystallised from a mixture of toluene and EToH.

Yield: 248 mg (40%); white solid; mp 208–211 °C.

1H NMR (400 MHz, DMSO-d$_6$): δ = 0.98 (t, J = 7.6 Hz, 3 H), 1.45 (m, 4 H), 1.73 (quint, J = 7.6 Hz, 2 H), 3.12 (t, J = 7.2 Hz, 2 H), 7.71–7.79 (m, 3 H), 8.01 (d, J = 8.0 Hz, 1 H), 8.11 (dd, J = 8.0, 1.2 Hz, 1 H), 8.16–8.21 (m, 1 H), 8.85–8.90 (m, 9 H), 9.32 (s, 1 H), 13.08 (br s, 1 H).

13C NMR (100 MHz, DMSO-d$_6$): δ = 13.8, 22.2, 31.9, 32.3, 123.3, 124.3, 124.6, 125.2, 126.5, 127.1, 127.3, 128.0, 128.2, 130.0, 130.8, 134.1, 139.4, 167.5.

HRMS (ESI): m/z [M – H]– calcd for C$_{19}$H$_{18}$O$_2$: 277.1234; found: 277.1232.

Anal. Calcld for C$_{19}$H$_{18}$O$_2$: C, 81.99; H, 6.52. Found: C, 81.85; H, 6.41.

9-n-Pentylphenanthrene-3-carboxylic Acid (19d)

By following General Procedure D, 18d (573 mg, 1.88 mmol), NaOH (226 mg, 5.64 mmol) and dioxane afforded 19d as a white solid, which was recrystallised from toluene.

Yield: 141 mg (26%); white solid; mp 194–197 °C.

1H NMR (400 MHz, DMSO-d$_6$): δ = 0.87 (t, J = 7.2 Hz, 3 H), 1.29–1.47 (m, 4 H), 1.74 (quint, J = 7.2 Hz, 2 H), 3.10 (t, J = 7.2 Hz, 2 H), 7.70–7.79 (m, 3 H), 8.00 (d, J = 8.4 Hz, 1 H), 8.12 (dd, J = 8.4, 1.6 Hz, 1 H), 8.15–8.20 (m, 1 H), 8.84–8.92 (m, 9 H), 9.33 (s, 1 H), 13.13 (br s, 1 H).

13C NMR (100 MHz, DMSO-d$_6$): δ = 14.5, 22.6, 30.0, 31.9, 33.2, 123.9, 124.9, 125.1, 125.8, 127.2, 127.6, 127.9, 128.6, 128.9, 130.7, 131.4, 134.7, 140.0, 168.2.

MS (ESI): m/z (%) = 291 (100) [M – H]–, 247 (46).

Anal. Calcld for C$_{20}$H$_{20}$O$_2$: C, 82.16; H, 6.89. Found: C, 82.00; H, 6.82.

9-(4-Methylpent-1-yl)phenanthrene-3-carboxylic Acid (3)

By following General Procedure D, 18e (675 mg, 2.11 mmol), NaOH (253 mg, 6.33 mmol) and dioxane afforded 3 as a white solid, which was recrystallised from toluene.

Yield: 264 mg (41%); white solid; mp 193–196 °C.
9-[(4-Carboxyphenyl)ethyl]phenanthrene-3-carboxylic Acid (19j)

By following General Procedure D, 18i (400 mg, 1.00 mmol), KOH (337 mg, 6.00 mmol) and THF afforded 19j.

Yield: 216 mg (58%); off-white solid; mp >250 °C.

1H NMR (400 MHz, DMSO-d6): δ = 3.15 (t, J = 8.0 Hz, 2 H), 3.45 (t, J = 8.0 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.75–7.81 (m, 3 H), 7.88 (d, J = 8.4 Hz, 2 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.11 (dd, J = 8.0, 1.6 Hz, 1 H), 8.27–8.32 (m, 1 H), 8.87–8.93 (m, 1 H), 9.34 (s, 1 H), 12.97 (br s, 1 H), 13.15 (br s, 1 H).

13C NMR (100 MHz, DMSO-d6): δ = 34.1, 35.6, 123.3, 124.3, 124.6, 125.5, 126.6, 127.2, 127.5, 128.2, 128.3, 128.4, 128.5, 128.6, 129.4, 130.1, 130.6, 134.0, 138.2, 146.7, 167.2, 167.5.


Flash chromatography (EtOAc–hexane, 5%) afforded Compound 20.

Yield: 216 mg (58%); off-white solid; mp >250 °C.

Methyl 9-Cyclopropylphenanthrene-3-carboxylate (20)

A flame-dried flask was successively charged with 16 (1.00 g, 3.17 mmol), 3-thienylboronic acid (573 mg, 4.48 mmol), K2CO3 (1.31 g, 9.51 mmol) and Pd(dppf)Cl2·CH2Cl2 (261 mg, 0.32 mmol). After each addition, the flask was briefly evacuated and backfilled with argon. Degassed anhydrous DME (75 mL) was then added into the flask by using a cannula and the resultant mixture was stirred at 80 °C for 24 h. After cooling to r.t., the reaction mixture was diluted with EtOAc (2 × 25 mL) and then brine (2 × 25 mL). After drying over MgSO4, concentration in vacuo afforded a dark-brown/black residue, which was partially purified by flash chromatography (EtOAc–hexane, 10%) to give a pale-yellow solid (618 mg, 61%), which 1H NMR analysis showed was a mixture of 21 and 16 (ca. 75:25). The mixture was taken forward to the next step without further purification.

Yield: 216 mg (58%); mp >250 °C.
Methyl 9-(3-Hydroxy-2-methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylate (25)

To a stirring solution of 23 (2.74 g, 8.15 mmol) in anhydrous THF (40 mL) at −78 °C, was added dropwise KHMS (0.5 M in toluene, 17.3 mL, 8.65 mmol) followed by a solution of 2-tert-phenyllaziridine (3.2 g, 12.25 mmol) in THF (20 mL). After complete addition, the mixture was warmed to r.t. and stirred for approximately 2 h. H2O (30 mL) and Et2O (60 mL) were then added and the organic layer was isolated and washed with sat. sodium sulfite solution (20 mL),aq 1M HCl (20 mL), and brine (20 mL). Concentration in vacuo afforded 25 as an oil, which was utilised in the next step without further purification or analysis.

Methyl 9-(1-Oxo-propan-2-yl)phenanthrene-3-carboxylate (26)

A stirred solution of 25 in anhydrous THF (20 mL) was cooled to 0 °C and LiBH4 (227 mg, 12.3 mmol) was added portionwise over a period of 10 min. After complete addition, the mixture was stirred for 30 min at 0 °C and then at r.t. until TLC analysis indicated complete conversion. The reaction was then quenched by the addition of aq 1 M HCl (5 mL) and extracted with Et2O (2 × 30 mL). The organic layers were pooled, dried over MgSO4 and concentrated in vacuo to obtain the crude 1,2-diol as an orange oil. This intermediate was dissolved in a mixture of r-BuOH and H2O (30 mL, 4:1), and NaOH (5.13 g, 24 mmol) was added to the solution. The resultant mixture was stirred at r.t. for 30 min before the reaction was quenched by the addition of H2O (20 mL). The aqueous mixture was then extracted with Et2O (2 × 30 mL) and the organic layers were pooled, dried over MgSO4, and concentrated in vacuo. Purification of the resultant residue by flash chromatography (EtOAc–hexane, 5%) afforded 26.

Yield: 1.55 g (65%); viscous light–orange oil.

9-(4-Methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylic Acid (24)

By following General Procedure D, 23 (508 mg, 1.51 mmol), NaOH (362 mg, 9.06 mmol) and dioxane afforded 24.

Yield: 377 mg (81%); white solid; mp>250 °C.

1H NMR (300 MHz, CDC13); δ = 1.67 (d, J = 8.8 Hz, 3 H), 2.07 (dd, J = 7.8, 12.0 Hz, 1 H), 2.87 (dd, J = 7.8, 12.0 Hz, 1 H), 4.07 (m, J = 7.8 Hz, 1 H), 7.77–7.80 (m, 2 H), 8.06 (dd, J = 8.7 Hz, 1 H), 8.13 (d, J = 8.7 Hz, 1 H), 8.27–8.30 (m, 1 H), 8.90–8.93 (m, 1 H), 9.33 (s, 1 H).

13C NMR (75 MHz, CDCl3); δ = 21.7, 31.0, 41.6, 54.3, 56.7, 122.8, 124.0, 124.3, 124.7, 127.0, 127.6, 128.0, 128.7, 128.9, 130.1, 130.6, 130.7, 133.1, 143.3, 168.0, 173.8.


9-(4-Methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylate (25)

To a stirred solution of 23 (2.74 g, 8.15 mmol) in anhydrous THF (40 mL) at −78 °C, was added dropwise KHMS (0.5 M in toluene, 17.3 mL, 8.65 mmol) followed by a solution of 2-tert-phenyllaziridine (3.2 g, 12.25 mmol) in THF (20 mL). After complete addition, the mixture was warmed to r.t. and stirred for approximately 2 h. H2O (30 mL) and Et2O (60 mL) were then added and the organic layer was isolated and washed with sat. sodium sulfite solution (20 mL),aq 1M HCl (20 mL), and brine (20 mL). Concentration in vacuo afforded 25 as an oil, which was utilised in the next step without further purification or analysis.

Methyl 9-(3-Hydroxy-2-methoxy-4-oxobutan-2-yl)phenanthrene-3-carboxylate (25)

To a stirring solution of 23 (2.74 g, 8.15 mmol) in anhydrous THF (40 mL) at −78 °C, was added dropwise KHMS (0.5 M in toluene, 17.3 mL, 8.65 mmol) followed by a solution of 2-tert-phenyllaziridine (3.2 g, 12.25 mmol) in THF (20 mL). After complete addition, the mixture was warmed to r.t. and stirred for approximately 2 h. H2O (30 mL) and Et2O (60 mL) were then added and the organic layer was isolated and washed with sat. sodium sulfite solution (20 mL),aq 1M HCl (20 mL), and brine (20 mL). Concentration in vacuo afforded 25 as an oil, which was utilised in the next step without further purification or analysis.
9-(Propan-2-yl)phenanthrene-3-carboxylic Acid (30)

By following General Procedure D, 29 (205 mg, 0.74 mmol), NaOH (89 mg, 2.22 mmol) and dioxane afforded 30.
Yield: 166 mg (85%); white solid; mp 226–230 °C.

1H NMR (400 MHz, DMSO-d6): δ = 1.42 (d, J = 6.8 Hz, 6 H), 3.78 (sept, J = 6.8 Hz, 1 H), 7.72–7.79 (m, 2 H), 7.83 (s, 1 H), 8.06 (d, J = 8.4 Hz, 1 H), 8.12 (dd, J = 8.4, 1.6 Hz, 1 H), 8.24–8.31 (m, 1 H), 8.86–8.92 (m, 1 H), 9.33 (s, 1 H), 13.06 (br s, 1 H).

13C NMR (100 MHz, DMSO-d6): δ = 12.0, 23.2, 28.8, 52.2, 121.7, 123.5, 124.1, 124.9, 126.5, 126.6, 127.0, 127.1, 128.3, 128.8, 131.0, 134.9, 145.5, 167.5.


Methyl 9-(Hydroxymethyl)phenanthrene-3-carboxylate (31)

To a stirred solution of 15 (1.10 g, 4.16 mmol) in anhydrous THF (150 mL) was added slowly and portionwise NaBH4 (472 mg, 12.48 mmol). i-PrOH (2 mL) was then added and the resultant suspension was stirred at rt until TLC analysis indicated complete reduction. Excess NaBH4 was destroyed by the dropwise addition of H2O. Concentration in vacuo afforded a solid, which was dissolved in a mixture of EtOAc (50 mL) and H2O (50 mL). The organic layer was isolated and the aqueous layer was further extracted with EtOAc (2 × 25 mL). The organic layers were pooled, washed with H2O (25 mL) and brine (25 mL), dried over MgSO4 and concentrated in vacuo to afford 31.
Yield: 1.05 g (95%); pale-yellow solid; mp 179–182 °C.

1H NMR (400 MHz, DMSO-d6): δ = 6.85 (s, 3 H), 5.05 (d, J = 5.6 Hz, 2 H), 5.52 (t, J = 5.6 Hz, 1 H), 7.69–7.81 (m, 2 H), 7.96 (s, 1 H), 8.07–8.18 (m, 3 H), 8.85–8.91 (m, 1 H), 9.34 (s, 1 H).

13C NMR (100 MHz, DMSO-d6): δ = 12.0, 23.2, 28.8, 52.2, 121.7, 123.5, 124.1, 124.9, 126.5, 126.6, 127.0, 127.1, 128.3, 128.8, 131.0, 134.9, 145.5, 167.5.


9-(Hydroxymethyl)phenanthrene-3-carboxylic Acid (32)

By following General Procedure D, 31 (500 mg, 1.88 mmol), NaOH (226 mg, 5.64 mmol) and dioxane afforded 32 as a light-yellow solid which was recrystallised from a mixture of toluene and EtOH.
Yield: 180 mg (38%); mp >250 °C.

1H NMR (400 MHz, DMSO-d6): δ = 5.04 (s, 2 H), 7.67–7.77 (m, 2 H), 7.93 (s, 1 H), 8.06 (d, J = 8.4 Hz, 1 H), 8.13 (dd, J = 8.4, 0.8 Hz, 2 H), 8.85 (d, J = 8.0 Hz, 1 H), 9.32 (s, 1 H).

13C NMR (100 MHz, DMSO-d6): δ = 12.0, 23.2, 28.8, 52.2, 121.7, 123.5, 124.1, 124.9, 126.5, 126.6, 127.0, 127.1, 128.3, 128.8, 131.0, 134.9, 145.5, 167.5.

MS (ESI): m/z (%): 251 (100) [M – H].

Anal. Calcd for C19H18O2·0.25 H2O: C, 74.84; H, 4.91. Found: C, 74.82; H, 4.83.

Methyl 9-(Bromomethyl)phenanthrene-3-carboxylate (33)

A flask containing 31 (1.17 g, 4.39 mmol) was briefly evacuated and backfilled with argon. Anhydrous CH2Cl2 (100 mL) was added to the flask by using a cannula and the resulting solution was cooled to 0 °C. Phosphorus tribromide (1.65 mL, 17.56 mmol) was then added dropwise to the stirring solution. After complete addition, the reaction...
mixture was stirred at 0 °C for 30 min and then at r.t. until TLC analysis confirmed complete conversion. After approximately 2 h, the reaction mixture was again cooled to 0 °C and excess PBr₃ was destroyed by the dropwise addition of saturated NaHCO₃ solution. The organic layer was isolated, dried over MgSO₄ and concentrated in vacuo to afford an off-white solid, which was dissolved in Et₂O (100 mL) and washed successively with H₂O (40 mL) and brine (40 mL). Drying over MgSO₄ followed by concentration in vacuo yielded 33.

Yield: 994 mg (69%); off-white solid; mp 135–139 °C.

1H NMR (300 MHz, CDCl₃): δ = 4.03 (s, 3 H), 5.00 (s, 2 H), 7.73–7.78 (m, 2 H), 7.86 (s, 1 H), 7.90 (d, J = 8.4 Hz, 1 H), 8.20 (dd, J = 8.4, 1.8 Hz, 1 H), 8.22–8.27 (m, 1 H), 8.80–8.87 (m, 1 H), 9.39 (s, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 23.1, 52.4, 123.5, 124.7, 125.1, 126.9, 127.4, 127.5, 128.1, 128.6, 129.8, 130.3, 131.2, 134.0, 134.3, 167.2.

MS (EI⁺): m/z (%): 328/330 (69/67) [M⁺], 249 (100).


**Methyl 9-Methylphenanthrene-3-carboxylate (34)**

Compound 33 (500 mg, 1.52 mmol) and Et₅N (0.21 mL, 1.52 mmol) were dissolved in dioxane (100 mL) and the resultant solution was hydrogenated under 3 bar of hydrogen in the presence of 10 wt% palladium on activated carbon (50 mg) for 18 h. The reaction mixture was then filtered through a Celite pad before being concentrated in vacuo to afford 34.

Yield: 344 mg (91%); off-white solid; mp 152–156 °C.

**9-(Isopropylaminomethyl)phenanthrene-3-carboxylic Acid (35)**

To a stirred mixture of 15 (750 mg, 2.84 mmol) and isopropylamine (0.41 mL, 4.97 mmol) in anhydrous DCE (100 mL) was added sodium triacetoxoyborohydride (843 mg, 3.98 mmol). The resultant suspension was stirred at r.t. for 24 h. At this point TLC analysis indicated incomplete conversion, so 12 drops of glacial acetic acid were added to help catalyse the reaction. Stirring was continued for another 24 h, then excess sodium triacetoxoyborohydride was destroyed through the dropwise addition of sat. aq NaHCO₃ solution. ETOAc (40 mL) was added and the organic phase was isolated, washed with brine (40 mL), dried over MgSO₄ and concentrated in vacuo to give an orange oil. Purification by flash chromatography (EtOAc then MeOH–ETOAc, 20%) afforded 36.

Yield: 779 mg (89%); golden coloured oil.

1H NMR (400 MHz, CDCl₃): δ = 1.21 (d, J = 6.4 Hz, 6 H), 2.98–3.09 (m, 1 H), 4.02 (s, 3 H), 4.27 (s, 2 H), 7.65–7.74 (m, 2 H), 7.77 (s, 1 H), 7.88 (d, J = 8.4 Hz, 1 H), 8.18 (dd, J = 8.4, 1.6 Hz, 1 H), 8.80–8.84 (m, 1 H), 9.38 (s, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 31.8, 52.4, 123.5, 124.7, 125.1, 126.9, 127.4, 127.5, 128.1, 128.6, 129.8, 130.3, 131.2, 134.0, 134.3, 167.4.


**9-(Isopropylaminomethyl)phenanthrene-3-carboxylic Acid (37)**

To a stirring solution of 36 (740 mg, 2.41 mmol) in a mixture of dioxane (80 mL) and H₂O (20 mL) was added dropwise a solution of NaOH (289 mg, 7.23 mmol) dissolved in H₂O (20 mL). The resultant mixture was stirred at 75 °C until TLC analysis indicated complete hydrolysis. After 4 h, the reaction mixture was cooled to r.t. and the dioxane was removed in vacuo. The resultant aqueous solution was topped up with H₂O and acidified to pH 3 by using aq 1 M HCl. No product precipitated from solution, so the pH was readjusted to pH 7 by using aq 1 M NaOH and the solution was concentrated in vacuo to afford a white solid. The crude product was dissolved in a mixture of H₂O and then adsorbed onto AG–50 resin. The column was first eluted with H₂O until the pH of the aqueous fractions was neutral. The product was then eluted with aq 1 M pyridine. Concentration of the aqeous pyridine fractions in vacuo afforded 37 as a white solid, which was azeotroped with water to remove any remaining pyridine and then dried over P₂O₅.

Yield: 496 mg (70%); mp > 250 °C.

1H NMR (400 MHz, D₂O/NaOD, pH 11): δ = 0.99 (d, J = 6.4 Hz, 6 H), 2.67–2.72 (m, 3 H), 3.46 (s, 2 H), 6.99 (s, 1 H), 7.33–7.39 (m, 1 H), 7.42–7.52 (m, 3 H), 7.91 (dd, J = 8.0, 1.2 Hz, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.88 (s, 1 H).

13C NMR (100 MHz, D₂O/NaOD, pH 11): δ = 21.2, 47.1, 47.9, 122.8, 123.1, 123.5, 124.5, 125.6, 126.8, 127.5, 127.6, 127.8, 129.0, 130.5, 131.2, 134.8, 135.5, 167.5.

HRMS (CI⁻): m/z [M – H]⁻ calcd for C₁₉H₁₉NO₂·0.55 H₂O: 305.1572; found: 305.1598.

**Methyl 9-(3-Methoxy-3-oxopropyl)phenanthrene-3-carboxylate (38)**

To a stirred mixture of 14 (1.00 g, 3.12 mmol) was dissolved in ETOAc (150 mL) with the aid of stirring and heating. The resultant solution was hydrogenated under 3 bar of hydrogen in the presence of 10 wt% palladium on activated carbon (100 mg) for 18 h. The reaction mixture was then filtered through a Celite pad before being concentrated in vacuo to afford a viscous pale-yellow oil. Purification by flash column chromatography (EtOAc–hexane, 5 → 30%) afforded 38.

Yield: 536 mg (53%); light-coloured oil that solidified on standing; mp 88–92 °C.

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Yield: 156 mg (49%); off-white solid; mp >250 °C. (262 mg, 6.54 mmol) and THF afforded


resulting solution was cooled to 0 °C by using an ice-water bath. The acid chloride was then dissolved in anhydrous THF (100 mL) and THF was put on a stirring plate. The mixture was then stirred at 0 °C for 30 min and then at r.t. until TLC analysis confirmed complete conversion. After 1 h, the reaction mixture was again cooled to 0 °C and excess PBr₃ was destroyed by the dropwise addition of saturated NaHCO₃ solution. The organic layer was isolated, dried over MgSO₄, and concentrated in vacuo to afford a light-yellow solid, which was dissolved in Et₂O (100 mL) and washed successively with H₂O (40 mL) and brine (40 mL). Drying over MgSO₄ followed by concentration in vacuo gave 41.

Yield: 1.87 g (65%); pale-yellow solid; mp 124–128 °C.

1H NMR (500 MHz, CDCl₃): δ = 4.75 (s, 2 H), 7.61 (dd, J = 8.0, 1.5 Hz, 1 H), 7.66–7.72 (m, 2 H), 7.74 (dd, J = 8.0 Hz, 1 H), 8.20–8.23 (m, 1 H), 8.41 (s, 1 H), 8.59–8.62 (m, 1 H), 8.63 (s, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 34.1, 99.7, 122.9, 123.3, 127.8, 128.1, 128.3, 128.4, 130.5, 132.4, 132.8, 133.5, 136.7, 138.2.


(9-Iodophenanthren-3-yl)acetonitrile (42)

A stirred mixture of 43 (9-Iodophenanthren-3-yl)acetic Acid (43) (725 mL) and stirred vigorously with a solution of NaN₃ (136 mg, 2.77 mmol) and tetra-n-butylammonium bromide (TBAB; 89 mg, 0.28 mmol) in H₂O (75 mL). After 5 d, TLC analysis indicated complete conversion. The organic layer was subsequently isolated and the aqueous phase was washed with CH₂Cl₂ (2 × 50 mL). The organic layers were combined, dried over MgSO₄, and concentrated in vacuo to afford a light-brown oil. Purification by flash chromatography (EtOAc–hexane, 10 → 20%) gave 42.

Yield: 492 mg (57%); yellow solid; mp 141–145 °C.

1H NMR (500 MHz, CDCl₃): δ = 4.99 (s, 2 H), 7.50 (dd, J = 8.5, 2.0 Hz, 1 H), 7.68–7.74 (m, 2 H), 7.77 (dd, J = 8.5 Hz, 1 H), 8.20–8.25 (m, 1 H), 8.41 (s, 1 H), 8.59–8.63 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 242, 99.5, 122.1, 122.8, 126.6, 127.8, 128.3, 128.5, 130.7, 130.9, 130.6, 131.5, 133.5, 133.5.


(9-Iodophenanthren-3-yl)acetic Acid (43)

A stirred mixture of 42 (471 mg, 1.37 mmol), glacial acetic acid (15 mL) conc H₂SO₄ (3 mL) and H₂O (3 mL) was heated to reflux until TLC analysis indicated complete consumption of the starting material. After 3 h, the mixture was cooled to r.t. and then diluted with H₂O (100 mL). The aqueous mixture was further extracted with CH₂Cl₂ (2 × 50 mL), and the organic layers were pooled, washed with saturated NaHCO₃ solution, and dried (aq 1 M NaOH (3 × 50 mL)). The alkaline phases were then washed with Ch₂Cl₂ (2 × 50 mL). The organic phases were combined, dried over MgSO₄, and concentrated in vacuo to give 43.

Yield: 355 mg (72%); straw-coloured solid; mp 184–188 °C (dec).

1H NMR (500 MHz, CDCl₃): δ = 3.69 (s, 2 H), 7.58 (dd, J = 8.0, 1.6 Hz, 1 H), 6.76–7.80 (m, 2 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.11–8.16 (m, 1 H), 8.59 (s, 1 H), 8.73 (s, 1 H), 8.78–8.93 (m, 1 H), 12.48 (br s, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 40.9, 98.1, 123.3, 123.6, 127.4, 127.7, 128.2, 129.1, 129.5, 130.1, 131.4, 132.4, 134.6, 137.9, 172.5.


(3-Bromomethyl)-9-iodophenanthrene (41)

A flask containing 40 (2.43 g, 7.27 mmol) was briefly evacuated and backfilled with argon. Anhydrous CH₂Cl₂ (200 mL) was added to the flask by using a cannula and the resulting suspension was cooled to 0 °C. Phosphorus tribromide (2.73 mL, 29.08 mmol) was then added dropwise to the stirred suspension. After complete addition, the solution was stirred at 0 °C for 30 min and then at r.t. until TLC analysis confirmed complete conversion. After 1 h, the reaction mixture was again cooled to 0 °C and excess PBr₃ was destroyed by the dropwise addition of saturated NaHCO₃ solution. The organic layer was isolated, dried over MgSO₄, and concentrated in vacuo to afford a light-yellow solid, which was dissolved in Et₂O (100 mL) and washed successively with H₂O (40 mL) and brine (40 mL). Drying over MgSO₄ followed by concentration in vacuo gave 41.

Yield: 2.45 g (85%); yellow solid; mp 164–168 °C.

1H NMR (400 MHz, DMSO-d₆): δ = 4.77 (s, 2 H), 5.44 (s, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.72–7.81 (m, 2 H), 7.92 (d, J = 8.0 Hz, 1 H), 8.10–8.17 (m, 1 H), 8.59 (s, 1 H), 8.75 (s, 1 H), 8.78–8.83 (m, 1 H).

13C NMR (100 MHz, DMSO-d₆): δ = 63.1, 97.9, 120.0, 123.2, 126.3, 127.5, 127.7, 128.1, 129.4, 130.1, 131.4, 131.5, 132.4, 138.0, 142.1.


9-Iodophenanthrene-3-carboxylic Acid Benzylamide (44a)

A stirred suspension of 1 (1.00 g, 2.87 mmol) and thionyl chloride (5 mL) in anhydrous benzene (45 mL) was heated to reflux for 12 h. The solution was then cooled to r.t. and the solvent was removed in vacuo. The product was dissolved in a second aliquot of anhydrous benzene and again concentrated in vacuo to remove traces of thionyl chloride. The crude acid chloride was then dissolved in anhydrous dioxane (20 mL) and added dropwise to a rapidly stirring solution of benzylamine (0.31 mL, 2.87 mmol) and Et$_3$N (0.48 mL, 3.48 mmol) in anhydrous dioxane (30 mL). After complete addition, the solution was stirred for 3 h at r.t. The solvent was then removed in vacuo and the resultant solid was dissolved in a mixture of CH$_2$Cl$_2$ (100 mL) and H$_2$O (40 mL). The organic layer was layered and washed successively withaq 1 M HCl (2 × 30 mL),aq 1 M NaOH (2 × 30 mL), and H$_2$O (40 mL). Drying over MgSO$_4$, followed by concentration in vacuo afforded 44a.

Yield: 459.2 mg (37%); off-white solid; mp 208–212 °C (dec).

HRMS (ESI):

132.7, 134.0, 137.7, 139.5, 165.8.

126.8, 127.3, 127.7, 128.1, 128.3, 128.6, 129.1, 130.2, 131.6, 132.6, 134.1, 134.5, 137.8, 167.1, 169.5.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{22}$H$_{18}$NOI·0.39 H$_2$O: 460.0169; found: 460.0164.

1H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 6.81 (d, J = 6.0 Hz, 2 H), 7.23–7.24 (m, 1 H), 7.33–7.38 (m, 2 H), 7.38–7.43 (m, 2 H), 7.78–7.87 (m, 2 H), 8.05 (d, J = 8.4 Hz, 1 H), 8.16–8.20 (m, 1 H), 8.17 (dd, J = 8.4, 1.6 Hz, 1 H), 8.68 (s, 1 H), 8.91–8.95 (m, 1 H), 9.38 (s, 1 H), 9.42 (t, J = 6.0 Hz, 1 H).

13C NMR (100 MHz, DMSO-d$_6$): $\delta$ = 28.1, 42.7, 82.7, 101.0, 122.0, 123.6, 126.1, 126.8, 127.3, 127.7, 128.1, 128.3, 129.1, 130.2, 131.6, 132.6, 132.7, 133.4, 137.7, 139.5, 165.8.

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{22}$H$_{18}$NOI: 460.0169; found: 460.0164.

Supporting Information

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Supporting Information

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