2-Anthracenonyl Acetic Acids as 5-Lipoxygenase Inhibitors

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Summary

The synthesis of 2-substituted anthracenonyl acetic acid (2-AA) derivatives is described. The key step is the Marschalk reaction of 1-hydroxy-8-methoxy-anthracenedione with glycolic acid. After protection of the resulting 2-anthracenonyl acetic acid derivative, the 2-monoalkylated derivatives are selectively obtained by direct alkylation. The methodology proves quite general and allows for the introduction of various substituents onto the 2-position of the carboxylic side chain. Reduction of the anthracenediones proceeds with concomitant protecting group removal and provides final 2-AA products in good yields. The results of initial biological studies demonstrate enhanced 5-lipoxygenase inhibition compared to anthralin.

Introduction

Anthracenone derivatives have an important place in the clinical management of psoriasis[1, 2]. However, these agents produce side effects such as inflammation and staining of the skin, and sometimes successful courses of treatment must be even halted. Accordingly, analogues of the antipsoriatic anthralin, 1,8-dihydroxy-9(10*H*)-anthracenone, with lower irritancy and optimal efficacy at low dose are widely sought[3]. In the search of analogues with improved therapeutic indices, the primary structural changes introduced into the 9(10*H*)-anthracenone chemotype have been esterification of the oxygen functions and substitution at the 10-position, but these compounds were less efficient than anthralin[1]. While the preparation of 10-substituted compounds can be performed on the anthracenone stage[4, 5], introduction of substituents into the 2-position requires the anthracenediones as precursors. Nonetheless, this latter approach has led to compounds endowed with very potent 5-lipoxygenase inhibitory action[6].

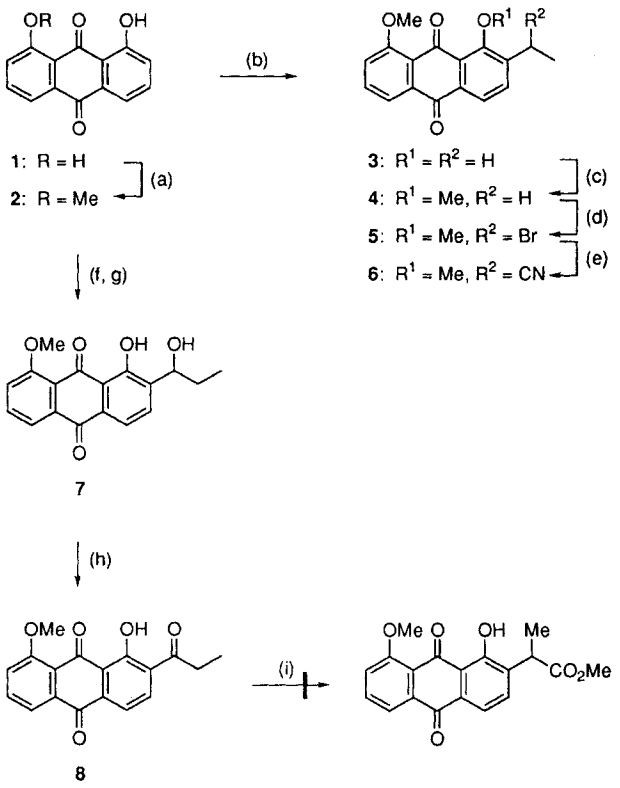
Since 2-aryl propionic acids are one of the largest class of non-steroidal antiinflammatory agents[7], we reasoned that a structural pattern, consisting of the anthracenone pharmacophore attached to a 2-propionic acid side chain, would provide an antipsoriatic agent with improved antiinflammatory efficacy.

In this paper, we describe experiments directed toward the synthesis of 2-substituted anthracenon-2-yl acetic acids (2-AA) and the results of preliminary biological studies (5-lipoxygenase inhibition).

Chemistry

In view of the chemical instability of hydroxyanthracenones, introduction of side chains onto the anthracenone nucleus has to be accomplished by a stepwise procedure *via* the anthracenedione stage. However, hydroxyanthracenediones are completely resistant to Friedel-Crafts type reactions, because of the deactivation of the aromatic rings by the quinone carbonyl groups[8]. Accordingly, preparation of 2-substituted anthracenediones by Marschalk reaction[6, 8, 9] appears to be a reasonably efficient and concise process for the preparation of the desired anthracenones.

Methods for the preparation of 2-aryl propionic acids have been extensively described, and a large number of different routes to the aliphatic side chains have been reported[7]. The approach of Scheme 1 envisaged a synthesis from a nitrile precursor and begins with Marschalk alkylation of 1-hydroxy-8-methoxy-anthracenedione (**2**). The selective protection of one of the hydroxyls of 1,8-dihydroxyanthracenedione (**1**) usually requires a tedious procedure involving selective acetylation through the intermediacy of a bis(diacetoxy)boron chelate, followed by methylation and hydrolysis of the



Scheme 1. Reagents: (a) Me_2SO_4, K_2CO_3, acetone, 55 °C; $BF_3 \bullet Et_2O$, toluene, 112 °C, 12 h; (b) acetaldehyde, NaOH, $Na_2S_2O_4$, 90 °C, N_2; (c) Me_2SO_4, K_2CO_3, acetone, 55 °C; (d) DBH, benzoyl peroxide, CCl_4, 77 °C; (e) Et_4NCN, DMSO, 40 °C; (f) propionaldehyde, KOH–MeOH, $Na_2S_2O_4$, 0–5 °C, N_2; (g) air, 45 min; (h) PDC, DMF, room temperature; (i) K-10, $Tl(NO_3)$, MeOH, trimethyl orthoformate, CH_2Cl_2.

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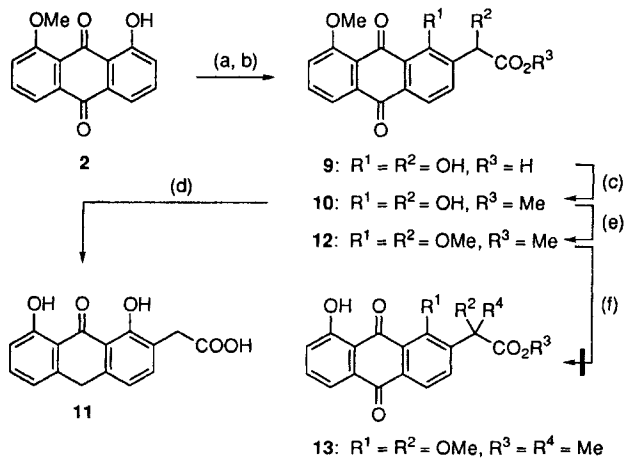
acetate[10, 11]. Therefore, an alternative method was developed for large-scale preparation. When **1** was dimethylated and then treated with boron trifluoride–diethyl ether as described for microscale preparations[12], the desired selective deprotection took place, giving rise to **2** in 90% yield. Alkylation of **2** with acetaldehyde provided **3**, which was protected as the methyl ether **4**. Benzylic bromination of **4** was achieved with *N,N*-dibromo-5,5-dimethylhydantoin (DBH)[11]. Although the cyanide ion was complexed as a quaternary ammonium salt[13], treatment of the bromide **5** with cyanide gave only poor yields of the nitrile **6**, which limit the present synthetic usefulness of this procedure.

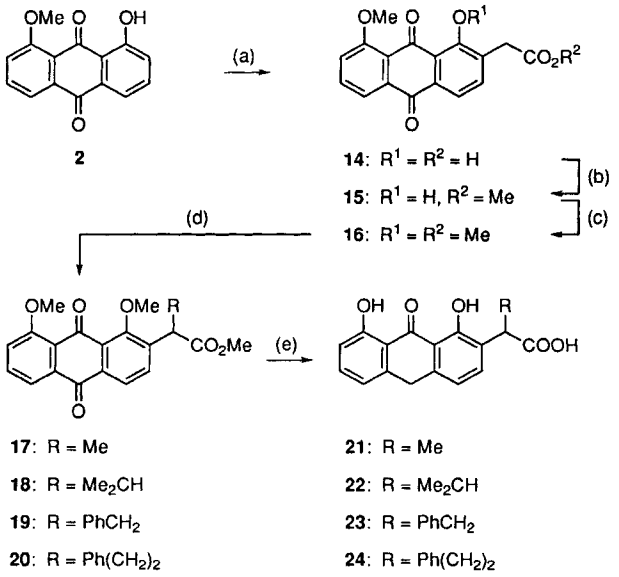
Our next attempt at the synthesis of 2-AA involved Marschalk reaction of **2** with pyruvic acid, since examples of intramolecular addition of ketones to anthracenediones under the conditions of the Marschalk reactions have been reported[8]. However, the desired product could not be detected, even after prolonged reaction and addition of excess sodium dithionite.

The lower part of Scheme 1 arose out of an attempt to use the oxidative rearrangement of propiophenone to methyl 2-phenylpropionate with thallium(III) nitrate adsorbed on montmorillonite clay, according to the method of Taylor et al.[14]. Conducting the Marschalk reaction of **2** with propionaldehyde at 0–5 °C, to avoid thermal elimination of the hydroxyl group[8], and employing reoxidation with air afforded the secondary alcohol **7**. Oxidation of **7** with PDC in DMF gave the propiophenone **8**. Following the method of Taylor et al.[14], however, formation of the rearranged product was not observed.

While studying the reduction of the anthracenedione **10**, prepared from **2** by Marschalk reaction with glycolic acid at low temperature and esterification of the α-hydroxy acid **9**, to the anthracenone **11**, we have observed a clean concomitant reduction of the benzylic hydroxyl group (Scheme 2). Since dialkylated side products are obtained in the direct methylation of aryl acetic acids[7], we considered that **10** would be a versatile intermediate for the synthesis of 2-AA, in that reaction of **12**, fully protected with dimethyl sulfate, would allow selective monoalkylation. Reduction of a



Scheme 2. Reagents: (a) glycolic acid, KOH–MeOH, $Na_2S_2O_4$, 0–5 °C, N_2; (b) air, 45 min; (c) MeOH, conc. H_2SO_4; (d) $SnCl_2$, HCl, HOAc, 118 °C; (e) Me_2SO_4, K_2CO_3, acetone, 55 °C; (f) MeI, NaH, THF.



Scheme 3. Reagents: (a) glycolic acid, $NaHCO_3$, $Na_2S_2O_4$, 90 °C, N_2; (b) MeOH, conc. H_2SO_4; (c) Me_2SO_4, K_2CO_3, acetone, 55 °C; (d) **17**: MeI, NaH, THF, **18–20**: isopropyl, benzyl, or phenylethyl bromide, NaH, DMSO; (e) $SnCl_2$, HCl, HOAc, 118 °C.

monoalkylated **13** was anticipated to proceed with concomitant ether cleavage to the desired anthracenone. However, attempted methylations of **12** were unsuccessful, in spite of varying the base, only starting material was isolated.

Finally, the successful synthesis of 2-AA also utilized **2** as a starting point (Scheme 3). Marschalk alkylation with glycolic acid under standard conditions led to compound **14**, which was then esterified to give **15** and protected as the methyl ether **16**. Alkylation with methyl iodide in THF provided the anthracenedione **17**. Surprisingly, even after prolonged reaction no dialkylated product was obtained.

Exchanging THF for DMSO, the benzylic carbanion of **16** also reacted with isopropyl, benzyl and phenylethyl bromide to give advanced intermediates **18–20** in good yields. Reduction of the anthracenediones **17–20** with stannous chloride in acetic acid–hydrochloric acid[15] proceeded with concomitant protecting group removal and provided final 2-AA products **21–24**.

Results and Discussion

The novel 2-AA are derivatives of the antipsoriatic anthralin and were therefore evaluated for their antiinflammatory activity in preliminary screens. Since lipoxygenase products of arachidonic acid metabolism are important mediators of inflammation in psoriatic lesions[16], the compounds were tested for their inhibitory activity against 5-lipoxygenase in polymorphonuclear leukocytes. Table 1 shows that the novel anthracenones were all more potent enzyme inhibitors than anthralin. Enhanced inhibitory activity is clearly attributed to the presence of a terminal phenyl ring in the branched chain alkyl spacer linking the anthracenone and the carboxylic acid group (**23**, **24**) or a bulky isobutyl spacer (**22**), whereas the ethyl linker (**21**) leads only to a twofold increase in activity as compared to anthralin, which is a moderate enzyme inhibitor.

Table 1: 5-Lipoxygenase inhibition by 2-AA and their reactivity against DPPH.

Entry	5-LO, IC_{50} (μM)[a]	k_{DPPH} (M^{-1} s^{-1})[b]
Anthralin	37	24.2
11	22	22.2
21	17	23.7
22	2	ND
23	1	22.9
24	2	23.2

[a] Inhibition of 5-HETE and LTB_4 biosynthesis in bovine PMNL; $n = 3$ or more, inhibition was significantly different with respect to control, $P < 0.01$. Lonapalene was used as the standard ($IC_{50} = 0.5$ μM)[4]. [b] Reducing activity against 2,2-diphenyl-1-picrylhydrazyl in acetone/phosphate-buffered saline, pH 7.4, with an equimolar amount of the test compound ($n = 3$ or more, SD < 10%)[17].

Also, we determined the reducing capability of the compounds against the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH)[17]. As compared to anthralin, their reactivity against DPPH remained unchanged and did not correlate with their improved 5-lipoxygenase inhibitory action. This suggests that a nonspecific redox effect, such as scavenging of intermediate radicals that are formed within the active site of the enzyme, does not explain the activity of the compounds.

Experimental Part

Melting points: Büchi 510 (uncorrected).– ^1H NMR: Varian EM 390 (90 MHz) or Bruker WM 250 (250 MHz), TMS as internal standard.– Fourier-transform IR (KBr): Nicolet 510M.– Thin layer chromatography (TLC): Merck Kieselgel 60 F_{254}.– Column chromatography: Merck silica gel (70–230 mesh), CH_2Cl_2 as eluant, unless otherwise stated.– Elemental analyses: Microanalytical Laboratories at the University of Regensburg.

*1-Hydroxy-8-methoxy-9,10-anthracenedione (**2**)*

To a suspension of 1,8-dihydroxy-9,10-anthracenedione (**1**, 96.0 g, 0.40 mol) and K_2CO_3 (450 g, 2.39 mol) in dry acetone (2.50 L) heated to reflux was added dropwise Me_2SO_4 (200 g, 1.58 mol), and the mixture was refluxed for 48 h (TLC control). Then it was poured into a mixture of ice (2 kg) and 37% HCl (300 mL), the precipitate was filtered by suction and washed with water (2 × 1 L). The residue thus obtained was refluxed in toluene (1 L) at a Dean-Stark trap. The solution was then cooled to room temperature, $BF_3 \cdot Et_2O$ (113.5 g, 0.80 mol) was added dropwise, and the mixture was refluxed for 12 h. Then it was cooled in an ice-bath for 1 h. The red-crystalline precipitate was filtered by suction and washed with hexane (1 L), then suspended in methanol (1 L) and stirred for 20 min at 40 °C. Water (50 mL) was added, and the mixture was stirred for an additional 2 h. Then it was filtered, dried under vacuum at 90 °C, and the residue purified by chromatography to provide a yellow powder: 90% yield; mp 187 °C (ref.[11] 185–186 °C).

General Procedure for the Marschalk Reaction.
*2-Ethyl-1-hydroxy-8-methoxy-9,10-anthracenedione (**3**)*

To a solution of NaOH (6 g) in water (300 mL) was added **2** (5.0 g, 19.68 mmol). The solution was stirred at 40 °C and a solution of $Na_2S_2O_4$ (5.0 g, 28.72 mmol) in water (25 mL) was added in one portion under N_2. Acetaldehyde (13.2 g, 300 mmol) was added, and the temperature was raised to 90 °C. The solution was stirred for 12 h under N_2. Then it was cooled to room temperature, aerated for 15 min and then poured into water (250 mL), acidified with 20% HCl, and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phase was washed with water (4 × 200 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue purified by chromatography to provide an orange powder: 41% yield; mp 209 °C.– FTIR: 1663, 1634 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 13.37 (s, 1 H, OH), 8.02–7.27 (m, 5 H, aromatic H), 4.07 (s, 3 H, OMe), 2.08 (q, $J = 7.5$ Hz, 2 H, CH_2Me), 1.25 (t, $J = 7.5$ Hz, 3 H, CH_2*Me*).– Anal. ($C_{17}H_{14}O_4$).

*2-Ethyl-1,8-dimethoxy-9,10-anthracenedione (**4**)*

To a suspension of **3** (2.0 g, 7.08 mmol) and K_2CO_3 (9.8 g, 71.0 mmol) in dry acetone (200 mL) heated to reflux was added dropwise Me_2SO_4 (4.47 g, 35.44 mmol). The mixture was refluxed until all starting material was consumed (TLC control). Then it was filtered by suction, poured into water (1 L), and extracted with ether (3 × 100 mL). The combined organic phase was washed with water (2 × 150 mL) and dried over Na_2SO_4. The solvent was evaporated the residue purified by chromatography to provide yellow crystals: 76% yield; mp 131 °C.– FTIR: 1679 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.01–7.23 (m, 5 H, aromatic H), 3.97 (s, 6 H, OMe), 2.80 (q, J = 6 Hz, 2 H, CH_2Me), 1.23 (t, $J = 6$ Hz, 3 H, CH_2*Me*).– Anal. ($C_{18}H_{16}O_4$).

*(±)-2-[1-(1-Bromoethyl)]-1,8-dimethoxy-9,10-anthracenedione (**5**)*

To a suspension of **4** (1.0 g, 3.37 mmol) in dry CCl_4 (50 mL) heated to reflux was added DBH (0.57 g, 2.00 mmol) and benzoyl peroxide (0.24 g, 1.00 mmol). The addition was repeated after 30 min. The mixture was then heated under reflux, until all starting material was consumed (TLC control). Carbon tetrachloride was evaporated, the residue was treated with water (200 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phase was washed with water (200 mL) and dried over Na_2SO_4. The solvent was evaporated the residue purified by chromatography to provide yellow crystals: 43% yield; mp 115 °C.– FTIR: 1671 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.12–7.25 (m, 5 H, aromatic H), 5.78 (q, $J = 6$ Hz, 1 H, C*H*Me), 4.07 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 2.02 (d, $J = 6$ Hz, 3 H, CH*Me*).– Anal. ($C_{18}H_{15}O_4Br$).

*(±)-2-(9,10-Dihydro-1,8-dimethoxy-9,10-dioxo-2-anthracene)propionitrile (**6**)*

To a solution of **5** (0.45 g, 1.20 mmol) in dry DMSO (25 mL) was added tetraethylammonium cyanide (0.75 g, 4.8 mmol). The mixture was stirred at 40–50 °C for 18 h under N_2. Then it was cooled to room temperature, poured into water (500 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with water (2 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue purified by chromatography to provide yellow crystals: 12% yield; mp 149 °C.– FTIR: 2238, 1675 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.16–7.26 (m, 5 H, aromatic H), 4.43 (q, J = 6 Hz, 1 H, C*H*Me), 4.02 (s, 6 H, OMe), 1.66 (d, $J = 6$ Hz, 3 H, CH*Me*).– Anal. ($C_{19}H_{15}NO_4$) calcd C, 71.02; H, 4.71; N, 4.36; found C, 71.26; H, 5.29; N, 3.86.

General Procedure for the Marschalk Reaction at Low Temperature.
*(±)-1-Hydroxy-2-[1-(1-hydroxypropyl)]-8-methoxy-9,10-anthracenedione (**7**)*

To a suspension of **2** (5.0 g, 19.68 mmol) and KOH (15.0 g) in methanol (500 mL) under N_2 was added dropwise a solution $Na_2S_2O_4$ (4.35 g, 24.98 mmol) in water (30 mL), and the mixture was cooled to 0–5 °C. Propionaldehyde (11.62 g, 200 mmol) was added dropwise, and the mixture was stirred at 0–5 °C for 12 h under N_2. Then air was bubbled through it for 45 min, the mixture was acidified with 7% HCl until it turned orange and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phase was washed with water (3 × 300 mL), dried over Na_2SO_4, evaporated, and purified by column chromatography using CH_2Cl_2–methanol (99+1) to provide orange crystals: 21% yield; mp 160 °C.– FTIR: 3506, 1665, 1634 cm^{-1}.– ^1H NMR (250 MHz, $CDCl_3$): δ = 13.41 (s, 1 H, OH), 7.95–7.27 (m, 5 H, aromatic H), 5.04–4.95 (m, 1 H, C*H*OH), 4.07 (s, 3 H, OMe), 2.65 (d, $J = 5.55$ Hz, 1 H, CHO*H*), 2.00–1.73 (m, 2 H, CH_2Me), 1.00 (t, $J = 7.34$ Hz, 3 H, CH_2*Me*).– Anal. ($C_{18}H_{16}O_5$) calcd C, 69.22; H, 5.16; found C, 68.41; H, 5.42.

*1-Hydroxy-8-methoxy-2-[1-(1-oxopropyl)]-9,10-anthracenedione (**8**)*

A solution of **7** (1.00 g, 3.20 mmol) in dry DMF (20 mL) and PDC (4.0 g, 12.80 mmol) was stirred at room temperature for 3 h. The solution was poured into water (500 mL) and the product extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phase was washed with water (4 × 100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography to provide orange crystals: 41% yield; mp 191 °C.– FTIR: 1667, 1636 cm^{-1}.– ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 13.90 (s, 1 H, OH), 8.00–7.65 (m, 5 H, aromatic H), 4.01 (s, 3 H, OMe), 3.08 (q, *J* = 7.13 Hz, 2 H, C*H*$_2$Me), 1.10 (t, *J* = 7.22 Hz, 3 H, CH$_2$*Me*).– Anal. ($C_{18}H_{14}O_5$).

*Attempted Rearrangement of **8***

The thallium(III) nitrate/K-10 reagent was prepared according to the method of Taylor et al.[14]. Propiophenone **8** (0.31 g, 1.00 mmol) was suspended in dry CH_2Cl_2 (50 mL), and the TNN/K-10 reagent (1.90 g, 1.50 mmol $Tl(NO_3)_3$) was added. The mixture was stirred at room temperature. After 5 h only starting material was detected.

*Methyl (9,10-Dihydro-1-hydroxy-8-methoxy-9,10-dioxo-2-anthracene)hydroxyacetate (**10**)*

This was prepared from **2** (5.0 g, 19.68 mmol) and glycolic acid monohydrate (3.83 g, 41.60 mmol) in water (50 mL) and a saturated solution of $NaHCO_3$ (50 mL) as described for **7**. The mixture was stirred at 0–5 °C for 6 h under N_2. Then air was bubbled through it for 45 min, and the mixture was acidified with 7% HCl until it turned orange. The precipitate thus obtained was filtered by suction and the residue refluxed in toluene at a Dean-Stark trap. The crude acid **9** was suspended in methanol (500 mL) and 96% H_2SO_4 (5 mL) and refluxed until all starting material was consumed (TLC control). Then it was cooled to 0–5 °C, filtered by suction, washed with water (100 mL) and petroleum ether (100 mL), dried, and purified by chromatography using CH_2Cl_2–methanol (99+1) to provide orange crystals: 47% yield; mp 208 °C.– FTIR: 3506, 1762, 1669, 1627 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 13.43 (s, 1 H, OH), 7.92–7.47 (m, 5 H, aromatic H), 6.42 (d, *J* = 6 Hz, 1 H, CHO*H*), 5.50 (d, *J* = 6 Hz, 1 H, C*H*OH), 3.92 (s, 3 H, 8-OMe), 3.65 (s, 3 H, CO_2Me).– Anal. ($C_{18}H_{14}O_7$).

*(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)acetic Acid (**11**)*

This was prepared from **10** (0.31 g, 0.92 mmol) as described for **21** and gave pale-yellow crystals: 82% yield; mp 220 °C (dec, ref.[18] 220 °C, dec).

*(±)-Methyl (9,10-Dihydro-1,8-dimethoxy-9,10-dioxo-2-anthracene)methoxyacetate (**12**)*

This was prepared from **10** (2.0 g, 5.84 mmol) as described for **4** and gave yellow crystals: 74% yield; mp 146 °C.– FTIR: 2831, 1752, 1669 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.08–7.23 (m, 5 H, aromatic H), 5.28 (s, 1 H, CH), 4.03 (s, 6 H, 1,8-OMe), 3.72 (s, 3 H, CHO*Me*), 3.43 (s, 3 H, CO_2Me).– Anal. ($C_{20}H_{18}O_7$).

*(9,10-Dihydro-1-hydroxy-8-methoxy-9,10-dioxo-2-anthracene)acetic Acid (**14**)*

This was prepared from **2** (10.0 g, 39.33 mmol) and glycolic acid monohydrate (4.60 g, 49.97 mmol) in water (100 mL) and a saturated solution of $NaHCO_3$ (50 mL) as described for **3**. The solution was stirred for 2 h at 90 °C under N_2. Then it was cooled to room temperature, aerated for 15 min, poured into water (250 mL), acidified with 20% HCl, and the precipitate thus obtained was filtered by suction. The residue was refluxed in toluene at a Dean-Stark trap to afford a yellow crystalline powder: 92% yield; mp 258 °C (dec, ref.[18] 258 °C, dec).

*Methyl (9,10-Dihydro-1-hydroxy-8-methoxy-2-anthracene)acetate (**15**)*

This was prepared by esterification of **14** (11.0 g, 35.23 mmol) as described for **10** and afforded orange needles: 73% yield; mp 159 °C.– FTIR: 1733, 1671, 1636 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 13.32 (s, 1 H, OH), 8.00–7.23 (m, 5 H, aromatic H), 4.03 (s, 3 H, OMe), 3.77 (s, 2 H, CH_2), 3.70 (s, 3 H, CO_2Me).– Anal. ($C_{18}H_{14}O_6$).

*Methyl (9,10-Dihydroxy-1,8-dimethoxy-9,10-dioxo-2-anthracene)acetate (**16**)*

This was prepared by methylation of **15** (5.0 g, 15.32 mmol) as described for **4**. The mixture was refluxed for 6 h and then filtered by suction. The volume of the solution was reduced, and the product crystallized on addition of small amounts of petroleum ether to provide yellow crystals: 64% yield; mp 134 °C.– FTIR: 1735, 1669 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.10–7.25 (m, 5 H, aromatic H), 4.03 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 3.80 (s, 2 H, CH_2), 3.73 (s, 3 H, CO_2Me).– Anal. ($C_{19}H_{16}O_6$).

*(±)-Methyl 2-(9,10-Dihydro-1,8-dimethoxy-9,10-dioxo-2-anthracene)propionate (**17**)*

A suspension of **16** (2.00 g, 5.88 mmol) in absolute THF (50 mL) and NaH (0.50 g, 20.83 mmol, 80% in paraffin oil) was stirred at room temperature for 20 min. Then MeI (2.50 g, 17.64 mmol) was added dropwise, and the mixture was stirred until all starting material was consumed (TLC control). Then it was poured into a mixture of ice-water (500 g) and 37% HCl (20 mL), and the product was extracted with ether (4 × 100 mL). The combined organic phase was washed with water (3 × 150 mL), dried over Na_2SO_4, and evaporated. The resulting residue was purified by chromatography using ether to give yellow crystals: 61% yield; mp 109 °C.– FTIR: 1743, 1673 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.12–7.25 (m, 5 H, aromatic H), 4.30 (q, *J* = 6 Hz, 1 H, C*H*Me), 4.00 (s, 6 H, OMe), 3.67 (s, 3 H, CO_2Me), 1.53 (d, *J* = 6 Hz, 3 H, CH*Me*).– Anal. ($C_{20}H_{18}O_6$).

*(±)-Methyl 2-(9,10-Dihydro-1,8-dimethoxy-9,10-dioxo-2-anthracene)-3-methylbutanoate (**18**)*

This was prepared from **16** (2.00 g, 5.88 mmol) in dry DMSO (25 mL) and 2-bromopropane (2.17 g, 17.64 mmol) as described for **17** and gave yellow crystals: 64% yield; mp 128 °C.– FTIR: 1733, 1677, 1663 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.12–7.25 (m, 5 H, aromatic H), 4.03 (s, 6 H, OMe, and d, 1 H, C*H*CHMe$_2$), 3.68 (s, 3 H, CO_2Me), 2.52–2.12 (m, 1 H, CHC*H*Me$_2$), 1.10 (d, *J* = 6 Hz, 3 H, CH*Me*), 0.72 (d, *J* = 6 Hz, 3 H, CH*Me*).– Anal. ($C_{22}H_{22}O_6$).

*(±)-Methyl 2-(9,10-Dihydro-1,8-dimethoxy-9-oxo-2-anthracene)-3-phenylpropionate (**19**)*

This was prepared from **16** (2.00 g, 5.88 mmol) in dry DMSO (25 mL) and benzyl bromide (2.01 g, 11.76 mmol) as described for **17** and gave pale-yellow crystals: 51% yield; mp 119 °C.– FTIR: 1733, 1669 cm^{-1}.– ^1H NMR (90 MHz, [D$_6$]DMSO): δ = 8.08–7.03 (m, 10 H, aromatic H), 4.63–4.40 (m, 1 H, C*H*CH$_2$Ph), 4.00 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.62 (s, 3 H, CO_2Me), 3.52–2.87 (m, 2 H, C*H*$_2$Ph).– Anal. ($C_{26}H_{22}O_6$).

*(±)-Methyl 2-(9,10-Dihydro-1,8-dimethoxy-9,10-dioxo-2-anthracene)-4-phenylbutanoate (**20**)*

This was prepared from **16** (2.00 g, 5.88 mmol) in dry DMSO (25 mL) and phenylethyl bromide (2.18 g, 11.76 mmol) as described for **17** and gave yellow crystals: 41% yield; mp 118 °C.– FTIR: 1737, 1675 cm^{-1}.– ^1H NMR (90 MHz, $CDCl_3$): δ = 8.10–6.73 (m, 10 H, aromatic H), 4.28–4.08 (m, 1 H, CH), 4.00 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.67 (s, 3 H, CO_2Me), 2.77–1.85 (m, 4 H, CH_2CH_2).– Anal. ($C_{26}H_{22}O_6$) C, H: calcd, 5.44; found 4.93.

General Procedure for the Reduction of Anthracenediones[15].
*(±)-2-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)propionic Acid (**21**)*

To a suspension of **17** (0.30 g, 0.85 mmol) in HOAc (15 mL) heated to reflux was added, dropwise over 30 min, a solution of $SnCl_2$ (2.0 g, 8.86 mmol) in 37% HCl (10 mL). The solution was refluxed for 6 h, then cooled, and the resulting crystals were collected by filtration. Recrystallization from HOAc provided a yellow powder: 81% yield; mp 231 °C.– FTIR: 1702, 1621 cm^{-1}.– ^1H NMR (90 MHz, [D$_6$]DMSO): δ = 12.57 (s, 1 H, OH), 12.03 (s, 1 H, OH), 7.70–6.80 (m, 5 H, aromatic H), 4.40 (s, 2 H, 10-H$_2$), 4.02 (q, *J* = 6 Hz, 1 H, C*H*Me), 1.42 (d, *J* = 6 Hz, 3 H, CH*Me*).– Anal. ($C_{17}H_{14}O_5$).

*(±)-2-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)-3-methylbutanoic Acid (**22**)*

This was prepared from **18** (0.30 g, 0.78 mmol) as described for **21** and gave yellow crystals: 79% yield; mp 224 °C.– FTIR: 1710, 1619 cm^{-1}.– ^1H NMR (90 MHz, [D$_6$]DMSO): δ = 12.63 (s, 1 H, OH), 12.00 (s, 1 H, OH), 7.77–6.77 (m, 5 H, aromatic H), 4.40 (s, 2 H, 10-H$_2$), 3.77 (d, *J* = 6 Hz, 1 H, C*H*CHMe$_2$), 2.43–1.97 (m, 1 H, CHC*H*Me$_2$), 1.05 (d, *J* = 6 Hz, 3 H, CH*Me*), 0.72 (d, *J* = 6 Hz, 3 H, CH*Me*).– Anal. ($C_{19}H_{18}O_5$).

*(±)-2-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)-3-phenylpropionic Acid (**23**)*

This was prepared from **19** (0.30 g, 0.73 mmol) as described for **21** and gave pale-yellow crystals: 72% yield; mp 218 °C.– FTIR: 1706 cm^{-1}.– ^1H NMR (90 MHz, [D$_6$]DMSO): δ = 12.60 (s, 1 H, OH), 12.00 (s, 1 H, OH), 7.66–6.78 (m, 10 H, aromatic H), 4.36 (s, 2 H, 10-H$_2$), 4.46–4.20 (m, 1 H, C*H*CH$_2$Ph), 3.46–2.95 (m, 2 H, CH$_2$Ph).– Anal. ($C_{23}H_{18}O_5$).

*(±)-2-(9,10-Dihydro-1,8-dihydroxy-9-oxo-2-anthracene)-4-phenylbutanoic Acid (**24**)*

This was prepared from **20** (0.30 g, 0.67 mmol) as described for **21** and gave yellow crystals: 80% yield; mp 134 °C.– FTIR: 1708, 1619 cm^{-1}.– ^1H NMR (90 MHz, [D$_6$]DMSO): δ = 12.61 (s, 1 H, OH), 12.05 (s, 1 H, OH), 7.73–6.83 (m, 10 H, aromatic H), 4.43 (s, 2 H, 10-H$_2$), 4.00 (t, *J* = 6 Hz, 1 H, C*H*CH$_2$), 2.72–1.87 (m, 4 H, CH$_2$CH$_2$).– Anal. ($C_{24}H_{20}O_5$).

Bovine PMNL 5-Lipoxygenase Assay

Inhibition of 5-LO was determined using Ca-ionophore-stimulated bovine PMNL (10^7 cells/mL) as described[19,20]. Test compounds were preincubated for 15 min at 37 °C, and the concentrations of LTB_4 and 5-HETE released after 10 min were measured by reversed-phase HPLC analysis.

Determination of the Reducing Activity against 2,2-Diphenyl-1-picrylhydrazyl

The reduction of DPPH (10^{-4} M) by the test compound (10^{-4} M), each in acetone/PBS (1+1), was measured and the second-order rate constants were obtained as described[17].

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