with ethyl acetate and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent removal gave crude 5-nonyl-5-hexenoic acid, which was esterified with diazomethane. Medium-pressure column chromatography over silica gel with 10% ethyl acetate/hexane followed by Kugelrhor distillation [94–96 °C (0.03 mmHg)] gave 1.4 g (5.5 mmol, 78.6%) of methyl 5-nonyl-5-hexenoate (11): IR (film) 3070, 2920, 2850, 1745, 1650, 1465, 1460, 1440, 1370, 1150, 890 cm^{-1}; ^1H NMR ($CDCl_3$) 4.71 (d, 2 H, J = 8.8 Hz), 3.67 (s, 3 H), 2.30 (t, 2 H, J = 7.5 Hz), 2.01 (quintet, 4 H, J = 8.0 Hz), 1.77 (quintet, 2 H, J = 7.0 Hz), 1.27 (s, 14 H), 0.88 ppm (t, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) 173.9, 148.8, 109.4, 51.3, 35.9, 35.4, 33.5, 31.9, 29.6, 29.4, 27.8, 23.0, 22.7, 14.0 ppm. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.67; H, 11.79.

Methyl 2-Methyl-5-nonyl-5-hexenoate (12). A solution of 25 mL of anhydrous THF, 25 mL of anhydrous HMPA, and 1.33 g (13.1 mmol) of diisopropylamine was cooled to −78 °C in dry ice/acetone bath and treated with 10 mL (13.1 mmol, 1.34 M) of n-BuLi. After the mixture was stirred for 1 h, 2.67 g (10.5 mmol) of methyl 5-nonyl-5-hexenoate (11) was added dropwise. After 1 h methyl iodide (12 g, 84 mmol) was added, and the solution was stirred for 5 h at −50 °C. The mixture was acidiifed and the product isolated with ether, dried over $MgSO_4$ solution, and concentrated. Medium-pressure column chromatography over silica gel with 10% ethyl acetate/hexane followed by Kugelrhor distillation [80–82 °C (0.05 mmHg)] afforded 2.60 g (9.69 mmol, 92.3%) of methyl 2-methyl-5-nonyl-5-hexenoate (12): IR (film) 3060, 2910, 2840, 1735, 1645, 1460, 1430, 1380, 1260, 1200, 1160, 1100, 1020, 890, 800 cm^{-1}; ^1H NMR ($CDCl_3$) 4.70 (d, 2 H, J = 6.7 Hz), 3.67 (s, 3 H), 2.45 (sextet, 1 H, J = 6.9 Hz), 1.99 (m, 4 H), 1.83 (m, 1 H), 1.56 (m, 1 H), 1.26 (s, 14 H), 1.16 (d, 3 H, J = 7.0 Hz), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 177.1, 149.1, 1090.1, 51.4, 39.0, 36.0, 33.5, 31.9, 29.6, 29.4, 27.8, 22.7, 17.0, 14.1. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.13; H, 11.98.

Methyl 2-Methyl-5-hydroxy-5-(hydroxymethyl)tetradecanoate. A solution of 0.75 g (5.5 mmol) of N-methylmorpholine N-oxide, 2.5 mL of water, 2.5 mL of *tert*-butyl alcohol, 0.05 g of osmium tetraoxide, and 1.34 g (5.0 mmol) of methyl 2-methyl-5-nonyl-5-hexenoate (13) was stirred under argon at room temperature for 44 h. Sodium bisulfite (0.6 g), Celite (1.0 g), and water (2 mL) were added to the solution. The slurry was stirred 15 min and filtered and the filtrate acidified to pH 2. The crude diol was isolated with ethyl acetate. Medium-pressure column chromatography over silica gel with 50% ethyl acetate/hexane followed by Kugelrhor distillation [100–103 °C (0.01 mmHg)] afforded 1.40 g (4.63 mmol, 92.5%) of methyl 2-methyl-5-hydroxy-5-(hydroxymethyl)tetradecenoate as a mixture of diastereomers: IR (film) 3440 (br), 2970, 2940, 2860, 1745, 1470, 1460, 1440, 1420, 1385, 1265, 1120 (br), 800 (br) cm^{-1}; ^1H NMR ($CDCl_3$) 3.67 (s, 3 H), 3.46 (s, 2 H), 2.55 (m, 2 H), 2.10–1.45 (m, 5 H), 1.27 (s, 16 H), 1.17 (dd, 3 H, J = 7.0 1.7 Hz), 0.88 ppm (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 177.2, 175.5, 74.5, 67.9, 67.7, 51.6, 39.7, 35.9, 35.7, 35.2, 33.1, 31.9, 30.3, 30.0, 29.6, 29.3, 27.4, 27.2, 25.5, 23.3, 22.7, 17.3, 17.1, 14.1 ppm. Anal. Calcd for $C_{17}H_{34}O_4$: C, 67.51; H, 11.33. Found: C, 67.54; H, 11.49.

Malyngolide (14). A solution of 0.32 g (1.05 mmol) of methyl 2-methyl-5-hydroxy-5-(hydroxymethyl)tetradecanoate, 0.09 g (1.59 mmol) of potassium hydroxide, and 5.0 mL of absolute ethanol was heated to reflux under argon for 38 h. After the solution was cooled, ethanol was removed, and 5 mL of water was added; the mixture was cooled to −5 °C and acidified to pH 5 with 2 M sulfuric acid. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent removal gave the crude acid. The crude acid, 10 mL of chloroform, and one drop of concentrated HCl were stirred for 4 h. The mixture was poured into 10% $NaHCO_3$ and isolated with $CHCl_3$. Medium-pressure column chromatography over silica gel with 50% ethyl acetate/hexane followed by Kugelrhor distillation [108–110 °C (0.5 mmHg)] gave 0.18 g (0.66 mmol, 62.9%) of malyngolide (14): R_f 0.41 (50% EtOAc/hexane). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.14; H, 11.23.

The remaining material from the chromatography consisted of epimalyngolide (15), which was Kugelrohr distilled [148–150 °C (0.06 mmHg)] to give 0.10 g (0.37 mmol, 35.2%): R_f 0.27 (50% EtOAc/hexane). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.14; H, 11.23. Both malyngolide and epimalyngolide had spectroscopic characteristics identical with those reported in the literature.[8]

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Synthesis of 2,7-Dibromopyrene

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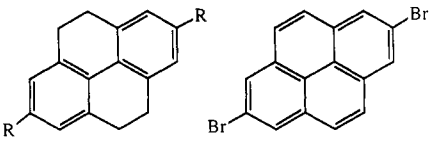
In connection with a program to prepare the active metabolites of polycyclic aromatic hydrocarbons for carcinogenesis research, we required 2,7-dibromopyrene (2) as a starting compound. Pyrene is known to undergo electrophilic substitution preferentially in the 1,6- and 1,8-positions.[1,2] The most convenient synthetic strategy for the introduction of groups into the 2- and 7-positions involves conversion of pyrene to a biphenyl aromatic ring system by regiospecific catalytic hydrogenation in the 4,5- and 9,10-positions.[3] Electrophilic reactions of 4,5,9,10-tetrahydropyrene (1a) are known to take place predominantly in the 2- and 7-positions.[2,4] However, direct bromination of 1a reportedly failed to afford 2-bromo-4,5,9,10-tetrahydropyrene, and 2-bromopyrene has been prepared only in low yield from 2-aminopyrene by means of the Sandmeyer reaction.[5] As far as we are aware, 2 has not been previously prepared.



1a: R = H
b: R = Br

2

We now report convenient synthesis of 2 involving bromination of 1a to yield 2,7-dibromo-4,5,9,10-tetrahydropyrene (1b)[6] followed by dehydrogenation by an unusual method. Bromination of 1a with 2 equiv of bromine in an aqueous medium in the presence of $FeCl_3$ as a catalyst took place smoothly at room temperature to afford 1b in quantitative yield. Analogous reaction of 1a with 1 equiv of bromine gave a mixture of mono and dibromo compounds along with unreacted 1a. The 500-MHz NMR spectrum of 1b was in good agreement with the assigned structure, exhibiting a benzylic singlet at δ 2.82 and an aromatic singlet at δ 7.20 in a 2:1 ratio. Attempted dehydrogenation of 1b with DDQ afforded mixtures of

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partially debrominated products. However, dehydrogenation to **2** was effected smoothly and quantitatively by treatment of **1b** with bromine in CS_2 for 3 h at room temperature. This unusual method of dehydrogenation is based on the observation that attempted monobromination of **1a** with bromine in CS_2 gave pyrene as a major product. The mechanism of this transformation apparently involves bromination on a benzylic site followed by dehydrobromination. This method of dehydrogenation has not previously been reported;[7] it may potentially be extended to other hydroaromatic compounds.

Experimental Section

2,7-Dibromo-4,5,9,10-tetrahydropyrene (1b). To a suspension of **1a** (618 mg, 3 mmol) and $FeCl_3 \cdot H_2O$ (10 mg) in water (60 mL) was added dropwise a solution of Br_2 (0.31 mL, 6 mmol) in H_2O (32 mL) over 4 h at ambient temperature. After addition was complete, the suspension was stirred overnight. During this period the solution completely decolorized. The white precipitate was filtered and dried and identified as **1b** (1.09 g, 99%) virtually pure by NMR. Crystallization from benzene gave the analytical sample of **1b** as white needles, mp 218–219 °C: NMR (500 MHz, $CDCl_3$) δ 2.82 (8, s, benzylic), 7.20 (4, s, aromatic).

Anal. Calcd for $C_{16}H_{12}Br_2$: C, 52.78; H, 3.32; Br, 43.90. Found: C, 52.65; H, 3.36; Br, 43.88.

2,7-Dibromopyrene (2). To a solution of **1b** (4.41 g, 12.1 mmol) in CS_2 (300 mL) was added dropwise Br_2 (4.26 g, 26.6 mmol) in CS_2 (300 mL) over 3 h. The reaction mixture which contained a white precipitate was stirred an additional hour. Evaporation of the solvent under reduced pressure gave virtually pure **2** (4.3 g, 99%) by HPLC on a DuPont Zorbax Sil column (4.6 mm × 15 cm) eluted with hexane (3 mL/min). Crystallization from chlorobenzene yielded 3.17 g of **2** as short white needles, mp >230 °C; NMR (500 MHz, $CDCl_3$) δ 7.98 (4, s, $H_{4,5,9,10}$), 8.28 (4, s, $H_{1,3,6,8}$).

Anal. Calcd for $C_{16}H_8Br_2$: C, 53.38; H, 2.23; Br, 44.39. Found: C, 53.63; H, 2.34; Br, 44.64.

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Registry No. **1a**, 781-17-9; **1b**, 17533-36-7; **2**, 102587-98-4.

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N^4-(Malonyl-D-cysteinyl)-L-2,4-diaminobutyrate: The End-Group-Modified Retro-Inverso Isomer of Glutathione

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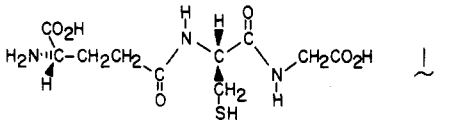
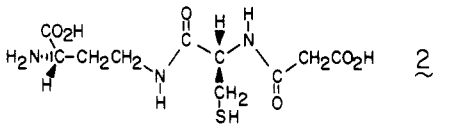
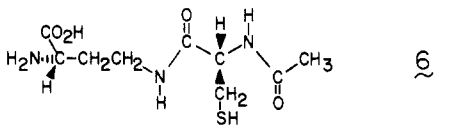
The tripeptide glutathione, **1** (GSH), is an important and ubiquitous cofactor in biological systems. It is a substrate or product for more than a dozen enzymes in conjuction with its role as a redox buffer and its involvement in amino acid transport and in the detoxication of electrophiles.[1] Most enzymes which catalyze chemistry at the sulfhydryl group of the peptide are very specific for GSH. For instance, the only known alternative substrate for GSH with the glutathione *S*-transferase is homoglutathione.[2] In this paper we report the preparation of the end-group-modified retro-inverso isomer[3] of GSH, **2** (rGSH), and a related *retro*-peptide, **6**, and the observation that **2** and **6** are substrates for several enzymes that participate in the biochemistry of the sulfhydryl group of GSH.







Synthesis of **2** is straightforward commencing with the ethyl chloroformate mediated condensation of N^2-tosyl-L-2,4-diaminobutyrate benzyl ester with *N*-*t*-BOC-*S*-benzyl-D-cysteine to give the protected dipeptide **3**. Removal of the *t*-BOC group with anhydrous CF_3CO_2H and coupling of the resulting dipeptide **4** with monobenzyl malonate in the presence of dicyclohexylcarbodiimide gave the fully protected tripeptide **5** in 66% overall isolated yield from D-cysteine. Complete deprotection of **5** in CF_3CO_2H with 1 M CF_3SO_3H and 2.6 M thioanisole gave a 65% isolated yield of **2** with <10% of the decarboxylated product **6**, after aqueous workup and purification by preparative HPLC. Decarboxylated peptide **6** was isolated in 40–50% yield as the exclusive sulfhydryl-containing peptide upon removal of CF_3CO_2H and thioanisole under vacuum, before workup. Oxidation of **2** with diamide gave the disulfide rGSSGr, **7**, in quantitative yield.

Structures of peptides **2**, **6**, and **7** were confirmed by ^1H and ^{13}C NMR and circular dichroism spectroscopy. Of particular interest was the exchange behavior of the malonyl methylene protons of **2** and **7**. The carboxy-terminal methylene protons of **2** [δ 3.42 (s, 2 H)] exchanged in D_2O (pD ~1.7, 23 °C) with a $t_{1/2}$ of 1–2 h with concomitant collapse of the singlet ^{13}C resonance at 42.6 ppm in the ^1H-decoupled spectrum to a 1:2:2:1 quartet at 42.3 ppm ($^1J_{^2H,^{13}C}$ = 21 Hz). Similar behavior is observed for the two malonyl residues of **7**, where the two pairs of diastereotopic methylene protons [H_A, δ 3.09 (d, 2 H, ^2J = 15.9 Hz); H_B, δ 3.23 (d, 2 H, ^2J = 15.5 Hz)] exchange with significantly different rate constants, $k^{H_A} = 3.4 \times 10^{-4}$ s^{-1} and $k^{H_B} = 7.7 \times 10^{-5}$ s^{-1}, at pH 4.1 and 21 °C. Both **2** and **7** are unstable at low pH. Prolonged storage of either at pH <2 results in substantial decarboxylation.

Circular dichroic transitions of the peptide backbones (190–200 nm) of the *retro*-peptides **2** and **7** (Figure 1) are of opposite sign to those of **1** and its disulfide **8** as might be expected for molecules with mirror-image peptide backbones. The reason for the large difference in absolute magnitude of the transitions at 200 nm of **1** and **2** is not clear but may be due to contributions from the distal chiral center of the two molecules or population of different conformational states.

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