(45 mg, 0.4 mmol, 30 μL), and **2** (63 mg, 0.4 mmol) in 1.5 mL of *t*-BuOH. The reaction was heated at 70 °C for 8 h.

Preparation of Indoles 12 and 13 by Reaction of 1a + 4-Oxohexanoic Acid. This reaction was carried out in the same manner as the indole formation above, using **1a** (0.2 g, 0.75 mmol), trifluoroacetic acid (86 mg, 0.75 mmol, 57 μL), and 4-oxohexanoic acid (Aldrich, 0.1 g, 0.75 mmol) in 2 mL of *t*-BuOH. The reaction was heated at 80 °C for 23.75 h. ^{13}C NMR (25.2 MHz, *t*-BuOH) data are reported in Table III.

Acknowledgment. We acknowledge Ms. L. DiMichele for NMR spectra, Mr. J. Smith for the mass spectral data, and Dr. D. L. Hughes for helpful discussions. We also thank Ms. M. Spears for preparation of this manuscript.

Registry No. **1a**, 103252-87-5; **1b**, 125687-04-9; **1c**, 125687-05-0; **1d**, 103252-74-0; **2**, 15118-53-3; **3a**, 125687-06-1; **3a** ethyl ester, 125687-07-2; **3c**, 125687-08-3; **4a**, 125687-09-4; **4b**, 125687-10-7; **4c**, 125687-11-8; **5d**, 125687-12-9; **12**, 103252-86-4; **13**, 125687-13-0; **15**, 125687-14-1; $H_3CCH_2CO(CH_2)_2CO_2H$, 1117-74-4; phenylhydrazine hydrochloride, 59-88-1; 4-chlorobenzyl chloride, 104-83-6; ethyl isobutyrate, 97-62-1; epoxybutane, 106-88-7; 2,2-dimethyl-4-hydroxyhexanoic acid γ-lactone, 54491-23-5; 4-chlorobenzylamine hydrochloride, 42365-43-5; aniline, 62-53-3; [2-^{15}N]phenylhydrazine hydrochloride, 125687-15-2; 4-chlorobenzylamine trifluoroacetate, 125687-16-3; [^{15}N]ammonium trifluoroacetate, 125687-17-4; ethyl 2,2-dimethyl-4-oxohexanoate, 89509-76-2; perdeuteriophenylhydrazine hydrochloride, 125687-18-5.

Syntheses of 1- and 2-Naphthol Analogues of DL-Tyrosine. Potential Fluorescent Probes of Peptide Structure and Dynamics in Complex Environments

Marco A. Vela, Frank R. Fronczek, Gregory W. Horn, and Mark L. McLaughlin*

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803-1804

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The racemic 1- and 2-naphthol analogues of tyrosine, (±)-2-amino-3-(4-hydroxy-1-naphthyl)propanoic acid hydrochloride, **1**, and (±)-2-amino-3-(6-hydroxy-2-naphthyl)propanoic acid hydrobromide, **2**, have been synthesized in gram quantities from 4-hydroxy-1-naphthaldehyde and 6-methoxy-2-naphthaldehyde in overall yields of 29 and 41%, respectively. The naphthaldehydes were condensed with hippuric acid to form the (*Z*)-oxazolones stereoselectively and oxazolone ring opening to the (*Z*)-propenoic acid derivatives with ethoxide or hydroxide was stereospecific. Hydrogenation over 10% Pd/C and deprotection gave the products **1** and **2**. Single-crystal X-ray structures of ethyl (*Z*)-2-(*N*-benzoylamino)-3-(4-hydroxy-1-naphthyl)propenoate, **1c**, (*Z*)-2-(*N*-benzoylamino)-3-(4-hydroxy-1-naphthyl)propenoic acid, **1f**, and ethyl (±)-2-(*N*-benzoylamino)-3-(4-hydroxy-1-naphthyl)propenoate, **1d**, verified the *Z* double bond stereochemistry or were proof of structure. NOE ^1H NMR measurements were used to demonstrate the double bond stereochemistry for **1f** and the analogous (*Z*)-2-(*N*-benzoylamino)-3-(6-methoxy-2-naphthyl)propenoic acid, **2h**.

Two types of fluorescent probes have been used to report structure and dynamics of peptides and proteins: extrinsic probes, e.g. fluorescein[1] or dansyl,[2] and intrinsic probes, e.g. tryptophan or tyrosine.[3] Intrinsic fluorescent probes are inherently more reliable reporters of peptide or protein structure and dynamics because the native characteristics are not perturbed. However, intrinsic fluorescent probes suffer from hopelessly complex spectral overlap problems when several natural fluorophores occur in the native peptide or protein. Hybrids of extrinsic and intrinsic fluorescent probes are needed in order to determine the conformation(s) of flexible peptide hormone analogues during the lifetime of complexes with membrane-bound receptors. Otherwise, spectral overlap from similar fluorophores in the membrane-bound receptors will make the selective monitoring of the structure and dynamics of the bound peptide hormone very complex. This fundamental information may allow a completely rational rather than partly empirical approach to the design of peptide hormone analogues. The synthesis of hybrid fluorescent probes that structurally mimic the tyrosine residue of superpotent peptide hormone analogues of somatostatin are reported in this paper.[4]

Tyrosine analogues which have 1- and 2-naphthol fluorophores in place of the 4-hydroxyphenyl fluorophore of tyrosine absorb and emit at longer wavelengths than native amino acid fluorophores and may be substituted for the tyrosine residues of somatostatin analogues with minimal perturbation of peptide hormone structure and dynamics.

Results and Discussion

Synthesis of the 1-Naphthol Tyrosine Analogue. The synthesis of the 1-naphthol tyrosine analogue began with a Gatterman condensation of 1-naphthol, and subsequent imine hydrolysis afforded **1a**.[5] Condensation of **1a** with hippuric acid in a heated slurry of sodium acetate and acetic anhydride gave the acetylated oxazolone **1b** in a 53% yield (Scheme I). Decreased yields of **1b** were observed if the reagents were not anhydrous. Concomitant ring opening and deacetylation of **1b** with sodium ethoxide gave **1c** in 90% yield. We expected exclusive formation of the (*Z*)-oxazolone and stereospecific ring opening to the (*Z*)-dehydro amido carboxylic acid derivative under these conditions.[6] We verified the double bond stereochemistry at this point with a single crystal X-ray structure of **1c** and **1f** (Figures 1 and 2). **1f** was obtained by reaction of the oxazolone with refluxing 1% NaOH in 86% yield. See the discussion of NMR experiments later.

Hydrogenation of **1c** over Pd/C gave racemic **1d** in 75% yield. The single-crystal X-ray structure of **1d** was proof

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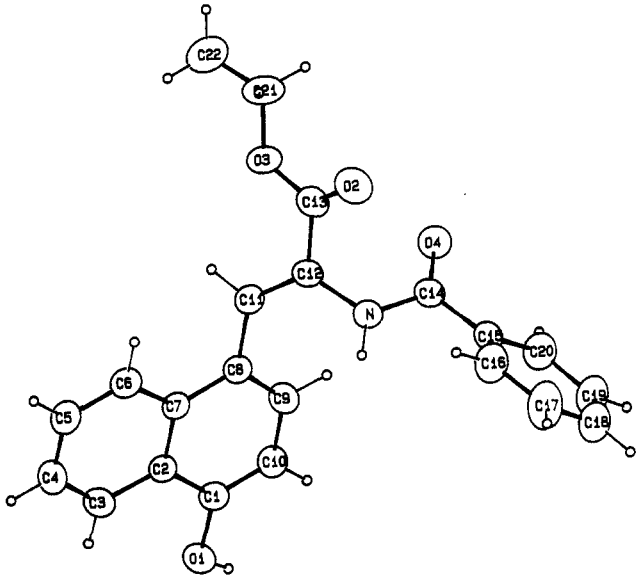

Figure 1. ORTEP drawing of **1c**. Selected bond distances and bond angles for **1c**: C8–C11, 1.478 (3); C11–C12, 1.324 (3); C12–N, 1.415 (3); and C12–C13, 1.493 (3) Å; C8–C11–C12, 128.0 (2); N–C11–C12, 123.3 (2); and C11–C12–C13, 122.9 (2)°.

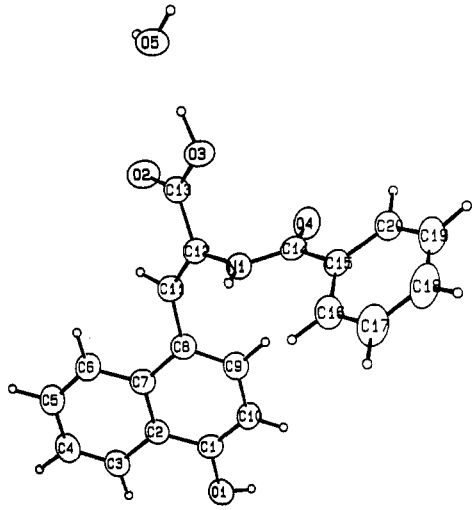

Figure 2. ORTEP drawing of **1f**. Selected bond distances and bond angles for **1f**: C8–C11, 1.462 (2); C11–C12, 1.334 (2); C12–N, 1.427 (2); and C12–C13, 1.486 (2) Å; C8–C11–C128 130.1 (1); N–C11–C12, 123.6 (1); C11–C12–C13, 118.9 (1)°.

of structure (Figure 3). Saponification of the ester function provided a 92% yield of **1e**, a compound that recrystallized with difficulty. If the saponification was carried out under reflux, an oil resulted. Hydrolysis of the benzoyl group with refluxing 6 N hydrochloric acid in dioxane from **1d** and **1e** furnished the hydrochloride of 2-amino-3-(4-hydroxy-1-naphthyl)propanoic acid (**1**) in 81 and 92% yield, respectively. The overall yield from **1b** via **1d** was 55%. Attempts to remove the benzoyl group from **1e** and **1d** with the HF–pyridine complex were unsuccessful.

Synthesis of the 2-Naphthol Tyrosine Analogue. We made the 2-naphthol analogue as shown in Scheme II. An appropriate 2-naphthaldehyde precursor had been prepared by a three-step procedure. Dibromination of 2-naphthol and selective debromination gave 6-bromo-2-naphthol in excellent yield.[7] O-Methylation of the naphthol in basic solution with dimethyl sulfate provided 6-bromo-2-methoxynaphthalene;[8] Grignard reaction with dimethylformamide gave **2c**[9] in a 43% overall yield.

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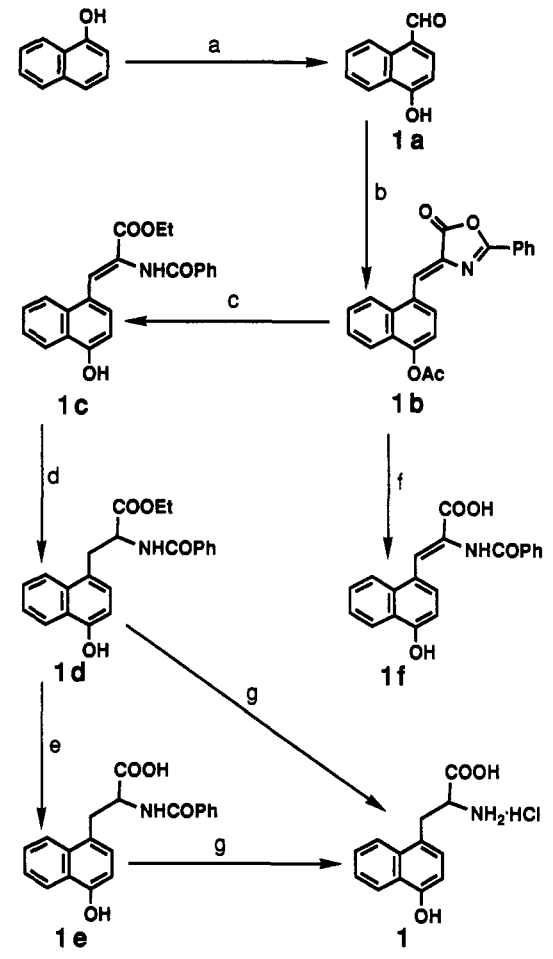
Scheme I[a]



[a] (a) $Zn(CN)_2$, $HCl_{(g)}$, ethyl ether, than aq. EtOH, Δ; b) Hippuric acid, anh. NaOAc, Ac_2O, Δ; c) EtONa, EtOH, 0–5 °C; d) H_2, Pd/C; e) 2M KOH, 30°C; f) 1% NaOH, aq. EtOH, Δ; g) 6N HCl, dioxane, Δ.

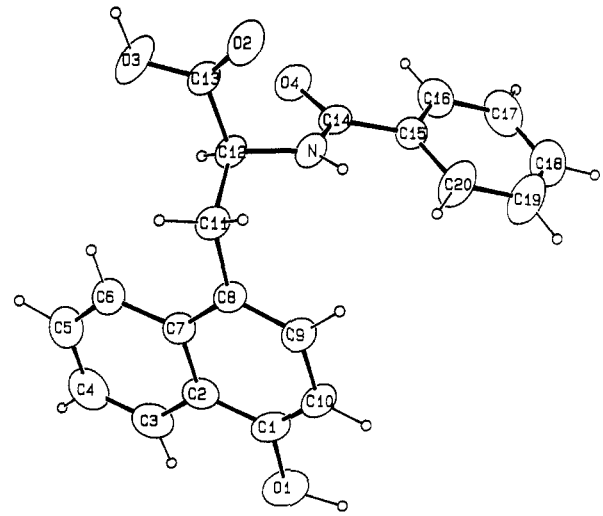


Figure 3. ORTEP drawing of **1d**. Selected bond distances and bond angles for **1d**: C8–C11, 1.505 (1); C11–C12, 1.541 (1); C12–N, 1.44. (1); and C12–C13, 1.513 (1) Å; C8–C11–C12, 112.76 (7); N–C11–C12, 110.04 (7); and C11–C12–C13, 107.85 (7)°.

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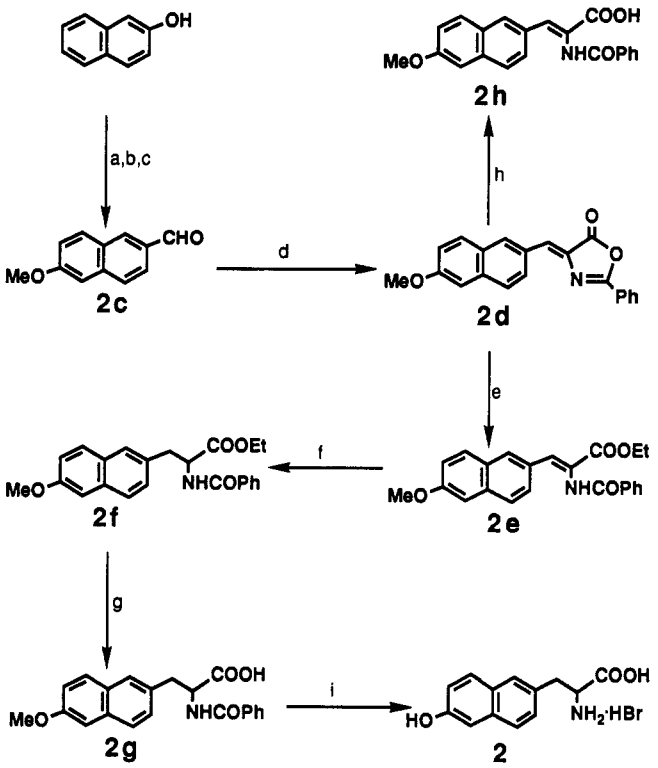
Scheme II[a]

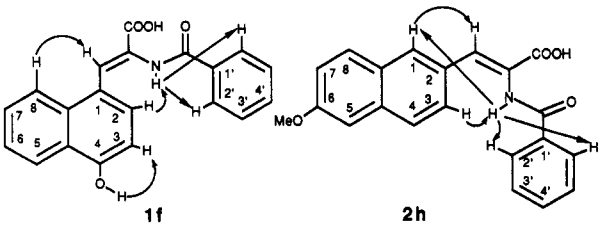


[a] (a) Br_2, HOAc, then Sn, Δ; b) Me_2SO_4, aq. NaOH; c) Mg, THF, then DMF; d) Hippuric acid, NaOAc, Ac_2O, Δ; e) EtONa, EtOH, 0–5°C; f) H_2, Pd/C; g) 2M NaOH; h) 1% NaOH, aq. EtOH; i) 48% HBr, Δ.

Condensation of **2c** with hippuric acid in a hot slurry of anhydrous sodium acetate and acetic anhydride provided oxazolone **2d** in 70% yield. Opening of the oxazolone ring with sodium ethoxide gave **2e** in 71% yield. Hydrogenation of **2e** gave **2f** in 96% yield. Saponification as above gave **2g** in almost quantitative yield. Ring opening of the oxazolone with 1% NaOH gave the dehydro amino acid in 89% yield with a *Z* double bond stereochemistry according to NMR experiments discussed later. Concomitant deprotection of the methyl ether and benzoyl groups with refluxing 48% HBr gave the racemic hydrobromide of 2-amino-3-(6-hydroxy-2-naphthyl)propanoic acid, **2**, in 86% yield. The overall yield from **2c** was 41%. Attempts to make **2** from **2f** by removing the ethyl, methyl, and benzoyl groups produced a resinous material.

NMR Assignments and Structure Analysis. The aromatic region NMR assignments of **1f** and **2h** were made by means of COSY, NOE, and selective irradiation experiments. These measurements were carried out in DMSO-d_6 and in C_6D_6 containing 10% DMSO-d_6. Irradiation of the amide hydrogen of **1f** affected the absorption of H-2, H-2′, and H-6′; the vinylic proton remained unaffected. Saturation of the vinylic proton clearly showed an effect on H-8 but not on H-2. These NMR observations lead us to conclude that the propenoic acid chain prefers a conformation that is similar in the solid state and in solution. These observations independently confirmed that the configuration of the double bond is *Z*.

Irradiation of the amide hydrogen of **2h** affected the absorption of the hydrogens H-1, H-3, and the ortho hydrogens of the benzoyl protecting group, but the vinylic proton was unaffected. Saturation of the vinyl proton



showed a weak effect on the protons of H-1 and H-3 and no effect on the amide hydrogen. These observations confirmed that the configuration of the double bond is *Z* and also led us to conclude that in solution the propenoic acid chain prefers an orientation perpendicular to the plane of the naphthalene ring.

Absorption and Emission of 1 and 2. Tryptophan has the lowest energy absorption and emission of the naturally occurring amino acids, exhibiting a relative absorption maxima at 270 that extends to 300 nm and emission from 335–350 nm.[3] The fluorescence behavior of **1** and **2** will be unique when incorporated into peptides since the relative maxima absorption and emission bands of the naphthol chromophores are at 320 and 400 nm, respectively.[10,11] In addition, **1** and **2** undergo a two-state excited-state proton transfer like 1- and 2-naphthol which is also unique compared to native amino acids.[11]

Conclusion

Good yields of gram quantities of the 1- and 2-naphthol analogues of racemic tyrosine are reported. It is clear from preliminary fluorescence studies, that these tyrosine analogues can provide unique fluorophores even when complexed with large proteinaceous materials. We will test how well these tyrosine analogues perform as isomorphic replacements for native tyrosine residues of somatostatin and bombesin when the pure enantiomers are prepared by testing the biological activity of these analogues.

Experimental Section

Melting points are uncorrected. NMR spectra and COSY experiments were recorded on a Bruker AC200 spectrometer at 200 MHz for ^1H and at 50 MHz for ^{13}C and a Bruker AM 400 at 400 MHz for ^1H and at 100 MHz for ^{13}C and are specified. Chemical shifts are reported in ppm downfield from tetramethylsilane. NOE, INAPT, and selective irradiation experiments were run on a Bruker AM400. FT-IR spectra were recorded with either a Nicolet IR 44 or a MIDAC spectrometer. UV–vis spectra were recorded with a Hewlett-Packard 8451A spectrometer; the solvents used were spectroscopic grade. MS and FAB-MS spectra were recorded on a Finnigan TSQ 70 mass spectrometer. Exact-mass determinations were performed at the Midwest Center for Mass Spectrometry of the University of Nebraska—Lincoln. Elemental analyses were performed by either Desert Analytics (Tucson, AR) or Oneida Research Services, Inc. (Whiteboro, NY).

Materials and Methods. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. Ethyl ether was distilled from liquified sodium–potassium alloy. Tetrahydrofuran (THF) was distilled from potassium. Other solvents were distilled and used immediately.

4-Hydroxy-1-naphthaldehyde (1a). This compound was prepared according to Adams and Levine;[5] decolorization and recrystallization from ethanol–water (7:3) gave 67% of **1a** as a brown solid: mp 182–184 °C (lit.[5] mp 178 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 10.08 (s, 1 H, CHO), 9.19 (dd, 1 H, Ar H), 8.25 (dd, 1 H, Ar H), 7.98 (d, 1 H, ArH), 7.69 (ddd, 1 H, Ar H), 7.56 (ddd, 1 H, Ar H), 7.03 (d, 1 H, ArH); ^{13}C NMR (DMSO-d_6,

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50 MHz, ppm) 192.4, 160.0, 140.7, 132.0, 129.6, 125.9, 124.5, 124.3, 123.0, 122.8, 107.7.

(Z)-2-Phenyl-4-((4-acetoxy-1-naphthyl)methylene)-5-oxazolone (1b). **1a** (8.6 g, 50 mmol), hippuric acid (9.5 g, 50 mmol), anhydrous NaOAc (4.1 g, 50 mmol), and anhydrous Ac_2O (20 mL, 0.211 mol) were boiled for 2 min with constant stirring, cooled, and treated with 95% ethanol (100 mL). The suspension was cooled in an ice bath, the resulting precipitate was crushed, filtered, and successively washed with cold water and cold ethanol. The residue was dried and recrystallized from hot benzene as fine yellow needles of **1b** (9.5 g, 53.2%): mp 201–203 °C; UV (2-propanol) 204 (ε 39 700), 298 (ε 9500), 402 (ε 23 200) nm; IR (KBr pellet) 3065, 1798, 1759, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.07 (d, 1 H, H2), 8.32 (d, 1 H, H8), 8.19 (dd, 2 H, H2′, H6′), 8.07 (s, 1 H, CH=), 7.98 (dd, 1 H, H5), 7.51–7.67 (m, 5 H, H6, H7, H3′, H4′, H5′), 7.44 (d, 1 H, H3), 2.50 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 168.9, 167.6, 164.0, 149.0, 133.9, 133.7, 133.4, 131.9 (C2), 128.9 (C2′, C6′), 128.4 (C3′, C5′), 127.9, 127.5, 126.9, 126.7, 126.0 (CH=), 125.6, 123.1 (C8), 122.1 (C5), 118.3 (C3), 21.0 (CH_3); MS *m/z* (relative intensity) 357 (M^+), 315, 105 (100), 77. Anal. Calcd for $C_{22}H_{15}NO_4$ (357.4): C, 73.87; H, 4.23; N, 3.92. Found: C, 73.85; H, 3.99; N, 3.79.

Ethyl (Z)-2-(N-Benzoylamino)-3-(4-hydroxy-1-naphthyl)propenoate (1c). Sodium (0.51 g, 0.022 g-atom) was dissolved in absolute ethanol (200 mL) under argon. The solution was cooled to 0–5 °C, and **1b** (7.2 g, 20.0 mmol) was added slowly to the solution and stirred for 3 h at 0–5 °C. The solution was poured onto cold water (250 mL) and slowly acidified to pH 4 using cold 10% HCl. The precipitate was filtered, washed with water, and dried, and **1c** recrystallized as off-white crystals from hot 2-propanol (7.22 g, 90%); mp 182–183 °C. X-ray quality crystals were grown by slow evaporation from 2-propanol: UV (MeOH) 204 (ε 39 900), 240 (e 32 400), 348 (ε 14 700) nm; IR (KBr pellet) 3300 (broad), 1716, 1645 cm^{-1}. ^1H NMR (THF-d_8, 400 MHz) δ 9.38 (s, 1 H), 8.98 (s, 1 H), 8.26 (d, 1 H, H8), 7.98 (d, 1 H, H5), 7.87 (s, 1 H, CH=), 7.86 (d, 2 H, H2′, H6′), 7.62 (d, 1 H, H2), 7.36–7.52 (m, 5 H, H6, H7, H3′, H4′, H5′), 6.76 (d, 1 H, H3), 4.26 (q, 2 H, CH_2O), 1.29 (t, 3 H, CH_3); ^{13}C NMR (THF-d_8, 100 MHz, ppm) 167.1 (CO), 165.8 (CO), 155.7 (C4), 135.5, 134.1, 131.9, 129.9 (CH=), 128.9, 128.8, 128.7, 128.5, 127.5, 126.0, 125.3, 124.6, 123.7 (C5), 122.9 (C8), 108.4 (C3), 61.4 (OCH_2), 14.2 (CH_3); MS *m/z* (relative intensity) 361 (M^+), 240, 183, 182, 154, 128, 127, 105, 77 (100). Anal. Calcd for $C_{22}H_{19}NO_4$ (361.4): C, 73.12; H, 5.30; N, 3.88. Found: C, 73.26; H, 5.34; N, 3.82.

Ethyl (±)-2-(N-Benzoylamino)-3-(4-hydroxy-1-naphthyl)propanoate (1d). A Parr hydrogenation bottle was charged with **1c** (3.0 g, 14 mmol), 10% Pd/C (0.5 g), absolute ethanol (150 mL), and 45 psi of hydrogen pressure for 8 h. The mixture was filtered through a Celite pad, and the pad was washed with absolute ethanol (10 mL) three times. The combined filtrate and washings were evaporated under reduced pressure. The resulting dark brown oil was purified by flash chromatography on a silica gel column (H_2CCl_2–ethanol, 95:5) to give **1d** as a pale yellow oil which crystallized from hot 2-propanol as colorless crystals (3.8 g, 75%): mp 159–162 °C; UV (MeOH) 210 (ε 47 400), 236 (ε 43 500), 326 (ε 9400); IR (KBr pellet) 3500–2900 (broad), 1722, 1643 cm^{-1}; ^1H NMR (THF-d_8, 200 MHz) δ 8.85 (s, 1 H), 8.25 (d, 1 H, H8), 8.12 (d, 1 H, H5), 7.71–7.79 (m, 1 H, H3′, H4′, H5′), 7.31–7.52 (m, 4 H, H6, H7, H2′, H6′), 7.16 (d, 1 H, H2), 6.67 (d, 1 H, H3), 4.96 (q, 1 H, CH_α), 4.00–4.12 (m, 2 H, OCH_2), 3.49–3.60 (m, 2 H, $ArCH_2$), 1.11 (t, 3 H, CH_3); ^{13}C NMR (THF-d_8, 50 MHz, ppm) 172.7 (CO), 167.2 (CO), 153.8 (C4), 135.8, 134.3, 131.7, 128.8, 128.4 (C2), 128.2, 126.9, 126.5, 124.9, 124.8, 124.3 (C5), 123.8 (C8), 107.9 (C3), 61.3 (CH_2O), 54.8 (CH_α), 35.3 ($ArCH_2$), 14.4 (CH_3); MS *m/z* (relative intensity) 363 (M^+), 242 (100), 207, 169, 161, 157, 128, 105, 77. Anal. Calcd for $C_{22}H_{21}NO_4$ (363.4): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.68; H, 5.71; N, 3.78.

(±)-2-(N-Benzoylamino)-3-(4-hydroxy-1-naphthyl)propanoic Acid (1e). **1d** (2.0 g, 5.51 mmol) was dissolved in 2 M KOH (25 mL) and stirred under argon at 30 °C for 24 h. The solution was decolorized, filtered, and slowly neutralized with cold 10% HCl until a yellowish solid formed, which was filtered, washed with water, and dried. This solid was redissolved in a saturated solution of $NaHCO_3$, and any solids were removed by filtration. The filtrate was neutralized with 10% HCl, and a solid was formed. Crystallization from ethanol–water provided yellowish crystals of **1e** (1.70 g, 92%): mp 222–225 °C (dec); UV (MeOH) 212 (ε 40 600), 236 (ε 34 600), 304 (ε 8200) nm; IR (KBr pellet) 3600–3300 (broad), 1726, 1713 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.79 (s, 1 H), 9.96 (s, 1 H), 8.15 (d, 1 H, H8), 8.06 (d, 1 H, H5), 7.76 (dd, 2 H, H2′, H6′), 7.26–7.74 (m, 5 H, H6, H7, H3′, H4′, H5′), 7.29 (d, 1 H, H2), 6.74 (d, 1 H, H3), 4.61–4.73 (m, 1 H, CH_α), 3.26–3.66 (m, 2 H, $ArCH_2$); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) 173.4 (CO), 166.3 (CO), 152.2 (C4), 133.9, 132.4, 131.3, 128.2 (C2), 127.8, 127.3, 126.3, 124.9, 124.9, 124.2, 123.9, 123.1, 122.7 (C8), 107.3 (C3), 53.6 (CH_α), 33.3 ($ArCH_2$); MS (*m/z*, relative intensity) 335 (M^+), 289, 214, 169, 157, 128, 105, 77 (100). Anal. Calcd for $C_{20}H_{17}NO_4$ (335.4): C, 71.63; H, 5.11; N, 4.17. Found: C, 71.33; H, 5.17; N, 4.11.

(Z)-2-(N-Benzoylamino)-3-(4-hydroxy-1-naphthyl)propenoic Acid (1f). **1b** (3.00 g, 8.4 mmol) was suspended in a 1% NaOH solution made up in 70% ethanol (100 mL) and vigorously refluxed with stirring for 15 min. The flask was cooled in an ice bath, the deep red solution was slowly acidified with cold concentrated HCl to pH 1, and then water (50 mL) was added. The solution was cooled overnight; the precipitate was filtered, washed with water, and dried. Crystallization from ethanol–water afforded **1f** as yellow crystals (2.40, 86%): mp 214–216 °C; UV (MeOH) 204 (ε 34 000), 240 (ε 32 000), 336 (ε 13 000); IR (KBr pellet) 1674, 1641 cm^{-1}; ^1H NMR (C_6D_6–DMSO-d_6, 9:1, 400 MHz) δ 8.18 (d, 1 H, H8), 8.07 (d, 1 H, H5), 7.55 (t, 1 H, H6), 7.46 (t, 1 H, H7), 7.20 (d, 1 H, H2), 6.87 (d, 1 H, H3), 3.33–3.62 (m, 3 H, $ArCH_2$, CH_α); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 170.4 (CO), 153.1 (C4), 132.4, 128.7 (C2), 126.5, 125.1, 124.3 (C5), 123.3 (C8), 122.8, 120.9, 107.6 (C3), 52.9 (CH_α), 33.2 (CH_2) MS (*m/z*, relative intensity) 289 ($M - CO_2 - H_2O$), 184, 168, 154, 105, 77, 44 (100). Anal. Calcd for $C_{20}H_{15}NO_4 \cdot H_2O$ (351.33): C, 68.37; H, 4.87; N, 3.98. Found: C, 68.17; H, 4.76; N, 3.85.

X-ray Crystallographic Analysis of Compounds 1c, 1f, and 1d. Data collection was carried out on Enraf-Nonius CAD-4 diffractometers with either Mo Kα, (0.710 73 Å) or Cu Kα (1.541 84 Å) radiation using ω – 2θ scans. Data reduction included corrections for background, Lorentz, polarization, and absorption by φ scans for **1c** and **1f**. Structures were solved by direct methods and refined by full-matrix least-squares using data with $I > 3\sigma(I)$. Non-hydrogen atoms were refined anisotropically; hydrogen atoms were located by ΔF and were refined isotropically. Crystal data and collection parameters are shown in Table I. Selected bond distances and bond angles of **1c**, **1f**, and **1d** are in the captions of Figures 1, 2, and 3.

Table I. Crystal Data and Collection Parameters

	1c	1f	1d
formula	$C_{22}H_{19}NO_4$	$C_{20}H_{15}NO_4 \cdot H_2O$	$C_{20}H_{17}NO_4$
M_r, g mol^{-1}	361.4	351.6	335.4
system	orthorhombic	triclinic	monoclinic
space group	$P2_12_12_1$	$P\bar{1}$	$P2_1/c$
a, Å	10.8918 (12)	7.9122 (5)	11.5611 (9)
b, Å	13.1460 (14)	9.1873 (6)	16.0730 (7)
c, Å	12.989 (3)	13.6465 (9)	9.5390 (12)
α, deg	–	108.785 (6)	–
β, deg	–	92.481 (6)	105.161 (9)
γ, deg	–	114.213 (6)	–
V, $Å^3$	1859.8 (5)	838.7 (1)	1710.9 (5)
Z	4	2	4
D_c, g cm^{-3}	1.291	1.391	1.302
cryst size, mm	0.30 × 0.35 × 0.48	0.08 × 0.18 × 0.35	0.23 × 0.35 × 0.40
radiation	Mo Kα	Cu Kα	Cu Kα
μ, cm^{-1}	0.83	7.93	7.09
temp, K	292	296	299
collection range, deg	2θ = 2–50	2θ = 4–150	2θ = 4–150
no. of unique data	1870	3456	3506
no. of observed data	1497	2684	2858
no. of variables	253	304	295
R	0.038	0.038	0.042
R_w	0.044	0.056	0.055
goodness of fit	2.34	2.06	2.82
extinction	7.8 (5) × 10^{-7}	3.5 (7) × 10^{-6}	2.41 (14) × 10^{-6}
resid e density, e $Å^{-3}$	0.33	0.20	0.21

(±)-2-Amino-3-(4-hydroxy-1-naphthyl)propanoic Acid Hydrochloride (1·HCl) from 1d. **1d** (3.0 g, 8.26 mmol) was refluxed in 6 N HCl (40 mL) and dioxane (10 mL) with stirring under argon for 20 h. The solution was cooled, water (50 mL) was added, the precipitate was filtered, and the filtrate was extracted with ethyl ether (5 × 100 mL). The aqueous solution was evaporated under vacuum at 25–50 °C (0.2–0.5 mmHg); additional water (50 mL) was added and evaporated again. The residue was triturated several times with ethyl ether until a nonhygroscopic solid was obtained. The residue was dried under vacuum at room temperature to afford 1·HCl as a brown powdery solid (1.8 g, 81%): mp 189–194 °C (dec, sealed tube); UV (MeOH) 212 (ε 29 000), 236 (ε 24 500), 302 (ε 4900) nm; IR (KBr pellet) 3600–2500 (broad), 1730 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.18 (d, 1 H, H8), 8.07 (d, 1 H, H5), 7.55 (t, 1 H, H6), 7.46 (t, 1 H, H7), 7.20 (d, 1 H, H2), 6.87 (d, 1 H, H3), 3.33–3.62 (m, 3 H, $ArCH_2$, CH_α); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 170.4 (CO), 153.1 (C4), 132.4, 128.7 (C2), 126.5, 125.1, 124.3 (C5), 123.3 (C8), 122.8, 120.9, 107.6 (C3), 52.9 (CH_α), 33.2 (CH_2); MS (FAB/MS/MS) *m/z* 232, (M − Cl), 215, 186, 173, 145. Anal. Calcd for $C_{13}H_{13}NO_3$·HCl·H_2O (285.7): C, 54.65; H, 5.65; N, 4.90. Found: C, 54.94; H, 5.30; N, 5.06.

1·HCl from 1e. **1e** (1.50 g, 4.47 mmol) was refluxed in 6 N HCl (30 mL) and dioxane (10 mL) with stirring under argon for 20 h, and 1·HCl, 1.10 g (92%), was isolated according to the workup procedure described for the reaction from **1d**.

6-Bromo-2-naphthol (2a). This compound was prepared according to the procedure reported by Koelsch;[6] a 96% yield of **2a** was obtained after crystallization from acetic acid–water (1:2): mp 124–129 °C (lit.[6] mp 127–129 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 9.93 (s, 1 H), 8.01 (d, 1 H, Ar H), 7.74 (d, 1 H, Ar H), 7.64 (d, 1 H, Ar H), 7.46 (dd, 1 H, Ar H), 7.09–7.14 (m, 2 H, Ar H); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) 155.8, 133.2, 129.4, 128.8 128.7, 128.3, 119.8, 115.3, 108.8, missing one ^{13}C resonance.

6-Bromo-2-methoxynaphthalene (2b). This compound was prepared by the procedure reported by Kern and Sears;[7] after sublimation, colorless crystals of **2b** were obtained in 70% yield: mp 105–107 °C (lit.[7] mp 102–107 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.89 (d, 1 H, Ar H), 7.59 (m, 2 H, Ar H), 7.47 (dd, 1 H, Ar H), 7.146 (dd, 1 H, Ar H), 7.06 (d, 1 H, Ar H), 3.89 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 157.9, 133.0, 130.0, 129.6, 128.5, 128.4, 119.7, 117.0, 105.8, 55.3 (CH_3), missing one ^{13}C resonance.

6-Methoxy-2-naphthaldehyde (2c). The Grignard reaction reported by Eriguchi and Takegoshi[8] was initiated with a few drops of 1,2-dibromoethane. The product, after crystallization from chloroform–hexane, gave yellowish crystals of **2c** (64%): mp 75–77 °C (lit.[8] mp 81–82 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 10.05 (s, 1 H, CHO), 8.45 (s, 1 H, Ar H), 8.03 (d, 1 H, Ar H), 7.81–7.94 (m, 2 H, Ar H), 7.42 (d, 1 H, Ar H), 7.27 (dd, 1 H, Ar H), 3.9 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) 192.5 (CHO), 159.9, 137.9, 134.3, 132.0, 131.2, 127.7, 127.6, 123.1, 119.8, 106.5, 55.5 (CH_3).

(*Z*)-2-Phenyl-4-((6-methoxy-2-naphthyl)methylene)-5-oxazolone (2d). **2c** (9.30 g, 50 mmol), hippuric acid (9.50 g, 50 mmol), anhydrous sodium acetate (4.10 g, 50 mmol), and anhydrous acetic anhydride (20 mL, 0.211 mol) was heated to 100 °C for 2 min with constant stirring and cooled, and 95% ethanol (100 mL) was added slowly. The suspension was cooled in an ice bath; the yellow precipitate was crushed, filtered, and washed successively with cold water and cold ethanol. The solid was dried and crystallized from hot benzene to afford 11.40 g of **2d** as yellow needles (70.5%): mp 216–217 °C; UV (2-propanol) 224 (ε 340 000), 254 (ε 167 500), 298 (ε 105 700), 416 (ε 361 000) nm; IR (KBr pellet) 1788, 1772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.48 (dd, 1 H, H3), 8.43 (s, 1 H, H1), 8.22 (dd, 2 H, H2′, H6′), 7.84 (d, 1 H, H8), 7.62–7.53 (m, 3 H, H3′, H4′, H5′), 7.39 (s, 1 H, CH=), 7.19 (dd, 1 H, H7), 7.15 (d, 1 H, H5), 3.95 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 167.8, 163.0, 159.7 (C6), 136.2, 134.0, 133.1, 132.5, 132.3, 130.8, 129.4, 128.9, 128.7, 128.3, 127.5, 125.9, 119.5 (C7), 106.1 (C5), 55.5 (OCH_3); MS *m/z* (relative intensity) 329 (M^+), 314, 196, 153, 106, 105 (100), 77. Anal. Calcd for $C_{21}H_{15}NO_3$ (329.3): C, 76.58; H, 4.59; N, 4.25. Found: C, 76.62; H, 4.61; N, 4.23.

Ethyl (*Z*)-2-(*N*-Benzoylamino)-3-(6-methoxy-2-naphthyl)propenoate (2e). Sodium (1.00 g, 0.0435, g-atom) was dissolved in absolute ethanol (200 mL) under argon. The solution was cooled to 0–5 °C and the oxazolone **2d** (12.20 g, 40 mmol) was added in small portions, after complete addition the mixture was stirred at 0–5 °C for 4 h. The mixture was poured onto cold water (250 mL) and slowly neutralized to neutral pH using cold 10% HCl, and the resulting milky solution was extracted with chloroform (3 × 100 mL); the extract dried over anhydrous Na_2SO_4, and solvent was evaporated under reduced pressure. The resulting brown oil solidified upon standing; this solid crystallized from benzene–isooctane to afford 10.7 g (71%) of **2e** as yellow needles: mp 112–115 °C; UV (MeOH) 202 (ε 24 900), 222 (ε 36 800), 272 (ε 27 100) nm; IR (KBr pellet) 3273, 1709 cm^{-1}; ^1H NMR (THF-d_8, 400 MHz) δ 8.01 (s, 1 H, CH=), 7.98 (d, 2 H, H2′, H6′), 7.75 (d, 1 H, H3), 7.69 (d, 1 H, H8), 7.68 (d, 1 H, H4), 7.44–7.52 (m, 4 H, H1, H3′, H4′, H5′), 7.18 (d, 1 H, H5), 7.10 (dd, 1 H, H7), 4.24 (q, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 1.28 (t, 3 H, CH_3); ^{13}C NMR (THF-d_8, 100 MHz, ppm) 165.8, 159.8, 158.2, 135.9, 132.9, 132.1, 131.1, 130.7, 129.7, 129.1, 128.5, 127.8, 127.6, 127.0, 126.7, 123.7, 122.6, 119.9 (C7), 106.5 (C5), 61.5 (OCH_2), 55.5 (OCH_3), 14.6 (CH_3); MS *m/z* (relative intensity) 375 (M^+, 100), 329, 303, 270, 224, 197, 153, 105 (100), 77; MS *m/z* (M^+) calcd 375.1471, obsd 375.1470.

Ethyl (±)-2-(Benzoylamino)-3-(6-methoxy-2-naphthyl)propanoate (2f). A Parr hydrogenation bottle charged with **2e** (4.1 g, 11 mmol), 10% Pd/C (0.5 g), absolute ethanol (200 mL), 45 psi of hydrogen pressure was shaken until no more hydrogen uptake was observed (16–20 h). The mixture was filtered through a Celite pad, and this pad was washed three times with absolute ethanol (20 mL). The combined filtrate and washings were evaporated to a small volume under reduced pressure and cooled to 10 °C for 2 h, and 4.0 g (96%) of **2f** crystallized as a white solid: mp 129–130 °C; UV (MeOH) 202 (ε 15 600), 230 (ε 70 900) nm; IR (KBr pellet) 3333, 1753, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 1 H, H2′, H5′), 7.65 (d, 1 H, H8), 7.63 (d, 1 H, H4), 7.53 (s, 1 H, H5), 7.47–7.51 (m, 1 H, H4′), 7.38–7.42 (m, 2 H, H3′, H5′), 7.24 (dd, 1 H, H7), 7.10–7.14 (m, 2 H, H1, H3), 6.63 (d, 1 H, NH), 5.13 (m, 1 H, CH_α), 4.21 (q, 2 H, OCH_2), 3.90 (s, 3 H, OCH_3), 3.39 (m, 2 H, $ArCH_2$), 1.26 (t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 171.7 (CO), 166.9 (CO), 157.6 (C6), 134.0, 133.6, 131.7, 131.1, 129.0, 128.9, 128.6, 128.0, 127.1, 127.0, 119.0 (C7), 105.7 (C5), 61.7 (OCH_2), 55.3 (CH_α), 53.7 (OCH_3), 37.9 ($ArCH_2$), 14.2 (CH_3); MS *m/z* (relative intensity) 377 (M^+), 256 (100), 212, 171, 128, 105, 74. Anal. Calcd for $C_{23}H_{23}NO_4$ (377.4): C, 73.20; H, 6.14; N, 3.71. Found: C, 73.05; H, 6.14; N, 3.65.

(±)-2-(*N*-Benzoylamino)-3-(6-methoxy-2-naphthyl)propanoic Acid (2g). **2f** (2.50 g, 6.66 mmol) was stirred at room temperature for 3 h with 2 N NaOH (40 mL) and absolute ethanol (40 mL) and filtered. The filtrate was neutralized slowly with 10% HCl, the resulting white precipitate was filtered, thoroughly washed with water, and dried, and **2g** crystallized from hot ethanol as colorless crystals (2.30 g, 99%): mp 174–175 °C; UV (MeOH) 230 (ε 110 000) nm; IR (KBr pellet) 3500–2750 (broad), 1743, 1615, cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.76 (s, 1 H), 8.76 (d, 1 H, NH), 7.69–7.89 (m, 5 H, Ar H), 7.38–7.50 (m, 4 H, Ar H), 7.24 (d, 1 H, H5), 7.09 (dd, 1 H, H7), 4.64–4.75 (m, 1 H, CH_α), 3.82 (s, 3 H, OCH_3), 3.13–3.37 (m, 2 H, $ArCH_2$); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) 173.1 (CO), 160.2 (CO), 156.9 (C6), 133.9, 133.3, 133.0, 131.3, 128.8, 128.4, 128.2, 128.0, 127.3, 127.2, 126.5, 118.5 (C7), 105.7 (C5), 55.1 (CH_3,o), 54.3 (CH_α), 36.3 ($ArCH_2$); MS *m/z* (relative intensity) 349 (M^+), 303, 228, 184, 171 (100), 156, 128, 105, 77. Anal. Calcd for $C_{21}H_{19}NO_4$ (349.4): C, 72.19; H, 5.48; N, 4.01. Found: C, 72.12; H, 5.48; N, 4.00.

(*Z*)-2-(*N*-Benzoylamino)-3-(6-methoxy-2-naphthyl)propenoic Acid (2h). **2d** (3.0 g, 9.11 mmol) was hydrolyzed as with **1f**. Recrystallization from hot 95% ethanol and decolorization yielded (2.80 g, 89%) of **2h** as an off-white product: mp 223–225 °C; UV (MeOH) 204 (ε 24 000), 220 (ε 33 500), 240 (ε 29 800), 320 (ε 23 000); IR (KBr pellet) 1693, 1645 cm^{-1}; ^1H NMR (C_6D_6–DMSO-d_6, 9:1, 400 MHz) δ 8.34 (d, 2 H, H2′, H6′), 7.89–7.94 (m, 3 H, CH=, H1, H3), 7.41–7.46 (m, 2 H, H4, H8), 7.14–7.24 (m, 3 H, H3′, H4′, H5′), 7.03 (dd, 1 H, H7), 6.90 (d, 1 H, H5), 3.95 (s, 3 H, Ar H); ^{13}C NMR (DMSO-d_6, 50 MHz, ppm) 166.4 (CO), 166.0 (CO), 158.3 (C6), 134.6, 133.7, 133.4, 131.7, 130.3, 129.9, 129.1, 12,95, 128.5, 127.7, 126.8, 126.7, 126.6, 119.2 (C7), 105.9 (C5), 55.3 (OCH_3); MS (*m/z*, relative intensity) 347 (M^+), 303, 198, 154, 129, 105 (100), 77. Anal. Calcd for $C_{21}H_{17}NO_4$ (347.37): C, 72.61; H, 4.93; N, 4.03. Found: C, 72.47; H, 4.77; N, 4.00.

(±)-2-Amino-3-(6-hydroxy-2-naphthyl)propanoic Acid Hydrobromide (2·HBr). **2g** (3.00 g, 8.60 mmol) was refluxed in 48% HBr (20 mL) overnight under argon, decolorized over activated charcoal, and filtered through a Celite pad that was washed with warm water (40 mL), and the aqueous solution was cooled to room temperature. The remaining workup as with 1·HCl gave 2·HBr as a pink solid (2.30 g, 86%): mp 248–251 °C (dec, sealed tube); UV (MeOH) 230 (ε 58500) nm; IR (KBr pellet 3600–2400 (broad), 1732 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (d, 1 H, H8), 7.63–7.65 (m, 2 H, H1, H4), 7.28 (dd, 2 H, H3), 7.10 (d, 1 H, H5), 7.08 (dd, 1 H, H7), 4.23 (t, CH_α), 3.21 (d, 2 H, $ArCH_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 170.4 (CO), 155.3 (C6), 133.8 (C10), 129.0 (C8), 128.8 (C2), 128.1, 127.6 (C3), 126.4, 118.8 (C5), 108.5 (C7), 53.2 (CH_α), 35.7 (CH_2); MS (FAB/MS/MS) *m/z* 232 (M - Br), 215, 186, 173, 145. HR-MS (FAB, M - Br + H) calcd 232.0974, obsd 232.0972.

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Registry No. 1·HCl, 126216-15-7; **1a**, 7770-45-8; **1b**, 126190-58-7; **1c**, 126190-60-1; **1d**, 126190-62-3; **1e**, 126190-64-5; **1f**, 126190-66-7; 2·HBr, 126190-57-6; **2c**, 3453-33-6; **2d**, 126190-59-8; **2e**, 126190-61-2; **2f**, 126190-63-4; **2g**, 126190-65-6; **2h**, 126190-67-8; hippuric acid, 495-69-2; 1-naphthol, 90-15-3; 2-naphthol, 135-19-3; 6-bromo-2-naphthol, 15231-91-1; 6-bromo-2-methoxynaphthalene, 5111-65-9.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters, bond distances, and bond angles for **1c**, **1f**, and **1d** (12 pages). Ordering information is given on any current masthead page.

New Syntheses of Cyclopenta[*cd*]pyrene 3,4-Oxide and 4-Pyrenylacetic Acid

Y. Sahali, P. L. Skipper, and S. R. Tannenbaum*

Division of Toxicology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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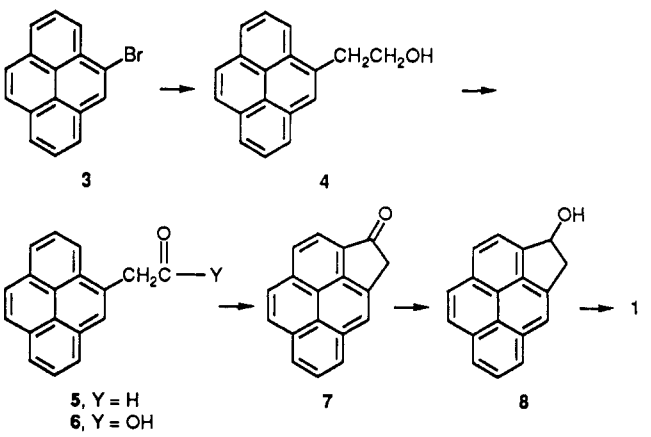
New syntheses of cyclopenta[*cd*]pyrene 3,4-oxide (CPPE) and 4-pyrenylacetic acid, a key intermediate in the synthesis of cyclopenta[*cd*]pyrene and CPPE, are described starting from 1,2,3,6,7,8-hexahydropyrene. 4-Pyrenylacetic acid is prepared from the corresponding alcohol, 2-(4-pyrenyl)ethanol, by applying two mild oxidation reactions. 4-Pyrenylacetaldehyde was obtained by *N*-chlorosuccinimide dimethyl sulfide oxidation, and this was converted smoothly to the desired 4-pyrenylacetic acid by silver oxide oxidation, an approach that has potential for a new route to arylacetic acids from arylethanols. The epoxide CPPE is prepared by cyclization of the 3,4-*trans*-dihydroxycyclopenta[*cd*]pyrene via its monotosylate, prepared in situ, with powdered sodium hydroxide.

Polycyclic aromatic hydrocarbons (PAH), produced during combustion of coal, gasoline, and diesel fuel, are genotoxic environmental pollutants. The biological activity of PAH requires metabolic activation to a variety of oxygenated products, more easily excreted by the organism, in the form of epoxides and/or dihydroxy epoxides.[1,2] Cyclopenta[*cd*]pyrene (CPP), 1, which contains a *cd* fused ring and lacks a bay region, was identified as a component of carbon black[3,4] and automobile exhaust.[5] It was found to be a potent mutagen to bacteria[6] and carcinogenic to mice.[7] Cyclopenta[*cd*]pyrene 3,4-oxide (CPPE, 2) was predicted to be a highly mutagenic metabolite of CPP. Eisenstadt and Gold proposed, on the basis of experimental observation and perturbational molecular orbital calculations, that an electrophilic species is formed by

Scheme I



opening of the epoxide ring at C(3) to give a benzylic carbonium ion capable of reacting with nucleophilic sites of cellular macromplecules such as DNA and proteins.[6]

For further in vivo and in vitro studies on the interaction of CPP and CPPE with DNA and proteins we needed relatively large amounts of CPP and CPPE. A number of syntheses for CPP have been published to date[8-14] and

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