to a 500-mL graduate cylinder inverted in a breaker of water. The reaction flask was immersed in an oil bath at 100 °C. Gas evolution ceased after 1 h, and the system was left for 1 h to reach ambient temperature (24 °C). Volume of gas: found 250 mL; calcd 263 mL; yield 95%; GC/MS of a sample from the collected gas $m/z$ 28 ($M^+$).

**1-(Formyloxy)-1-phenyl-1-heptene.** 1-Phenyl-1-heptyne (2.25 g) and formic acid (6.1 g) were heated at 100 °C for 4 h. Two liquid phases were present throughout the reaction. Workup of the reaction solution as described above for 1-octyne gave a brown liquid which was subjected to GC/MS and $^1H$ NMR analyses (for results, see text).

A sample of the above mixture (1.0 g) and formic acid (5 g) were heated for 4 h at 100 °C to give quantitatively (GC analysis with 1-methylnaphthalene as an internal standard) a single product identified as heptanophenone by GC (mixed injection with an authentic sample). MS $m/z$ 190 ($M^+$).

## Metal–Halogen Exchange Reactions of 1,5-Diiodonaphthalene. Synthesis of 1,5-Disubstituted Naphthalene Derivatives

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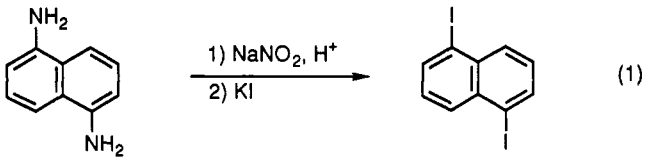
In connection with other investigations, we had need of 1,5-difunctionalized naphthalene derivatives such as carboxylic acids **4** and **6a**. Because these compounds and derivatives thereof were unavailable commercially, our attention turned to synthetic approaches. We felt that 1,5-diiodonaphthalene (**2**)[1] would be ideally suited for our purposes, since it was potentially a precursor both of organometallic reagents and of compounds derived from nucleophilic substitution. Also, **2** could be prepared readily from commercially available 1,5-diaminonaphthalene (**1**) by diazotization/KI.[2] This paper describes our efforts in the preparation of 1,5-disubstituted naphthalenes derived from **2**.

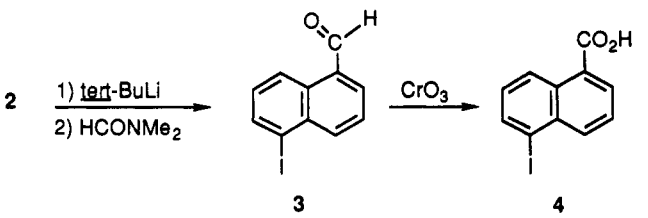



(1)

**1** **2**

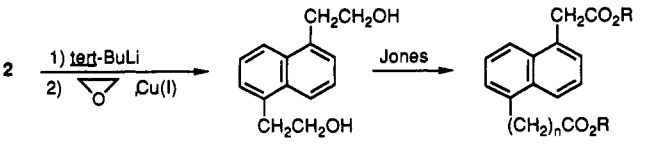
Depending upon reaction conditions, 1,5-diiodonaphthalene could be converted to either a monolithio- or dilithio derivative. A monolithio compound has previously been prepared from 1,8-diiodonaphthalene,[3] but to our knowledge, metal–halogen exchange reactions of **2** have not been reported previously. The difficulties in regioselectively dimetallating naphthalene by hydrogen–metal exchange has been summarized recently.[4] Treatment of **2** with *tert*-butyllithium in a 1:2 molar ratio under equilibrating conditions produced a solution of 1-lithio-5-iodonaphthalene as evidenced by the formation of only monodeuteroiodonaphthalene when the reaction mixture was quenched with methanol-$d_4$. Treatment of 1-lithio-5-iodonaphthalene with dimethylformamide gave 5-iodonaphthaldehyde **3** in 55% yield. Oxidation of **3** with Jones reagent furnished 5-iodonaphthoic acid **4**[5] (Scheme I).

**Scheme I**



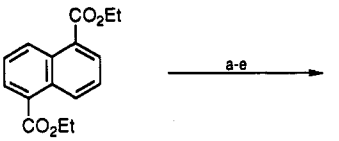

**3** **4**

**Scheme II**




**5**

**6a**, n=1, R = H
**6b**, n=1, R = Et
**7a**, n=0, R = H
**7b**, n=0, R = Et




**6b**

[a] $LiAlH_4$, then $H_3O^+$.[9,12] [b] $MeSO_2Cl$, $Me_3N$. [c] KCN.[10] [d] KOH then $H_3O^+$. [e] EtOH, heat.

Dilithiation of **2** was accomplished by use of 4 equiv of *tert*-butyllithium. Treatment of the dilithio compound with an excess of ethylene oxide under copper catalysis[6] furnished diol **5** (56%). Direct conversion of **5** to 1,5-naphthalenediacetic acid **6a**[7] was complicated by competitive oxidation at the benzylic carbons.[8] Under the best conditions found, a mixture of **6a** and **7a** could be obtained in a 74% yield in a ratio of ca. 5:1, respectively. Diacids **6a** and **7a** were separated and characterized as their ethyl esters **6b** and **7b** (Scheme II). Diester **6b** could also be prepared by homologation of naphthalene-1,5-dicarboxylic acid by standard reactions requiring five steps.

An attempt to prepare diacid **6a** by treatment of **2** with sodiomalonic ester under copper catalysis[11] gave only the monoalkylated product **8** (38 or 50% on the basis of recovered **2**) after hydrolysis and decarboxylation.

## Experimental Section

All moisture- or oxygen-sensitive reactions were conducted under a $N_2$ atmosphere. Melting points were taken on a Thomas

(1) Suzuki, H.; Kondo, A.; Inouye, M.; Ogawa, T. *Synthesis* **1986**, 121.
(2) Hedgson, H. H. *J. Chem. Soc.* **1947**, 80.
(3) Sugihara, Y.; Yamamoto, H.; Mizone, K.; Murata, I. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1247. Katz, H. E. *Organometallics* **1986**, *5*, 2308.
(4) Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633.
(5) This acid was prepared previously via the Sandmeyer reaction of 5-aminonaphthoic acid: Seer, C.; Scholl, R. *Ann.* **1913**, *398*, 92.
(6) Huynh, C.; Dergurni-Bonmechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
(7) This acid has previously been reported as a product of the reaction of naphthalene with chloroacetic acid in the presence of ferric oxide–potassium bromide: Ogata, Y.; Ishiguro, J.; Kitamura, Y. *J. Org. Chem.* **1951**, *16*, 239.
(8) Similar problems in the oxidation of β-phenylethanol derivatives have been reported: Plaue, S.; Heissler, D. *Tetrahedron Lett.* **1987**, *28*, 1401.
(9) This diol was previously made from 1,5-(dichloromethyl)-naphthalene via the diacetoxy derivative: Lock, G.; Schneider, R. *Ber. Dtsch. Chem. Ges.* **1951**, *84*, 636.
(10) Muruhashi, S.; Matsukawa, H. *Bull. Inst. Phys. Chem. Research, Tokyo* **1942**, *21*, 509; *Chem. Abstr.* **1952**, *46*, 8072h.
(11) Setsune, J. I.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367.
(12) Lock, G. *Monatsh. Chem.* **1950**, *81*, 850.

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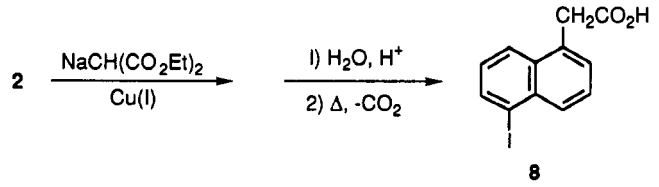


8

Hoover apparatus and are uncorrected. NMR spectra were recorded ($\delta$) by use of a Magnachem-200 or a GN-300 spectrometer with TMS as an internal reference in $CDCl_3$ unless otherwise noted. Mass spectra were obtained on a MAT CH-5-DF(FAB), a FINNIGAN 8230 B(EI), a KRATOS MS-80 (HR EI), and a MAT CH-7(CI) mass spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording IR spectrophotometer. Dimethylformamide (Fisher), THF (Fisher), ether (Fisher), methylene chloride (Fisher), CuI, ethyl malonate, and *tert*-butyllithium (Aldrich) were all used as received from commercial suppliers.

**5-Iodo-1-naphthaldehyde (3).** 1,5-Diiodonaphthalene[1,2] (1.14 g, 3.1 mmol) in 15 mL of ether was cooled to −78 °C and treated with 6.3 mmol of *tert*-butyllithium. The resulting pinkish solution was stirred for 6.5 h while being warmed to 5 °C. The now-brown solution was recooled to −78 °C, and 0.45 mL (3.0 mmol) of tetramethylethylenediamine was added. After 10 min, 0.30 mL (3.0 mmol) of dimethylformamide was added and the mixture was stirred for 17 h as it warmed to room temperature. The organic layer was washed with saturated aqueous $NH_4Cl$, dried ($MgSO_4$), and concentrated to give 0.77 g of crude product. Purification by column chromatography (silica gel, 1:10 ether–hexane, $R_f$ 0.25) yielded 0.47 g (55%) of **3**: mp 115–117 °C; $^1H$ NMR (200 MHz) $\delta$ 7.34 (t, $J$ = 8 Hz, 1 H), 7.68 (t, $J$ = 8 Hz, 1 H), 8.00 (d, $J$ = 8 Hz, 1 H), 8.18 (d, $J$ = 8 Hz, 1 H), 8.40 (d, $J$ = 8 Hz, 1 H), 9.28 (d, $J$ = 8 Hz, 1 H), 10.38 (s, 1 H); IR (KBr) 1685 (C=O) $cm^{-1}$; HRMS (EI) for $C_{11}H_7IO$ calcd 281.9543, found 281.9547.

**5-Iodo-1-naphthoic acid (4).** To a solution of 0.61 g (2.17 mmol) of **3** in 30 mL of acetone was added 1.62 mL (4.43 mmol) of Jones reagent. The mixture was stirred for 17 min, filtered, and concentrated in vacuo. The residue was dissolved in 30 mL of 4 N NaOH and filtered. The filtrate was acidified with 2.5 mL of concd $H_2SO_4$ and cooled to 0 °C. The precipitate was collected by filtration and dried to give 0.73 g (113%) of **4** as a slightly pink solid: mp 250–252 °C (lit.[5] mp 251–252 °C); IR (KBr) 2960–2800, 1615 (C=O) $cm^{-1}$; HRMS (EI) for $C_{11}H_7IO_2$ calcd 297.9493, found 297.9498.

**1,5-Naphthalenediethanol (5).** A suspension of 1,5-diiodonaphthalene[1,2] (2.50 g, 6.58 mmol) in 40 mL of ether was cooled to −78 °C, and 16.2 mL of a solution of *tert*-butyllithium (1.7 M in pentane, 26.7 mmol) was added. The light pink suspension was stirred for 1 h, 300 mg (3.30 mmol) of cuprous cyanide was added, and stirring was continued for 45 min at −55 to −65 °C. During this period, the suspension turned yellow. Ethylene oxide (8 mL, 164 mmol) was added all at once, and the mixture was stirred overnight as it gradually warmed to 25 °C. In a good hood the mixture was poured into 100 mL of 10% sulfuric acid (caution: HCN evolved!),[13] filtered, and extracted with $CH_2Cl_2$ (3 × 50 mL). The extracts were dried ($Na_2SO_4$) and evaporated to give a crude solid that was triturated with ether to give 0.80 g (56%) of **5** as a white solid: mp 105 °C; $^1H$ NMR (DMSO-$d_6$, 200 MHz) $\delta$ 3.39 (t, $J$ = 8 Hz, 2 H), 3.86 (t, $J$ = 8 Hz, 2 H), 7.38 (m, 4 H), 7.98 (d, $J$ = 8 Hz, 2 H); IR (KBr) 3350 (br, OH) $cm^{-1}$; HRMS (EI) for $C_{14}H_{16}O_2$ calcd 216.1150, found 216.1156. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.57.

**Oxidation of 1,5-Naphthalenediethanol (5).** A solution of 335 mg (1.5 mmol) of **5** in 8 mL of acetone was treated with 1.62 mL (4.16 mmol) of Jones reagent for 15 min at 25 °C. The solvent was evaporated, and the residue was dissolved in 25 mL of 4 N sodium hydroxide. The solution was filtered and acidified ($H_2SO_4$), and the precipitate was collected and dried to give 280 mg (74% on the basis of **6a**) of the diacids **6a**[7] and **7a**. The diacids were esterified ($SOCl_2$, EtOH) under standard conditions to give 392 mg of diesters **6b** and **7b** (ca. 5:1 by $^1H$ NMR). This mixture was chromatographed on silica gel (1:2 ether–hexane) to give 100 mg of diethyl 1,5-naphthalenediacetate (**6b**) $R_f$ 0.59: mp 82–84 °C; $^1H$ NMR (200 MHz) $\delta$ 1.25 (t, $J$ = 8 Hz, 6 H), 4.10 (s, 4 H), 4.20 (q, $J$ = 8 Hz, 4 H), 7.49 (m, 4 H), 7.99 (d, $J$ = 8 Hz, 2 H); IR (film) 1720 (CO) $cm^{-1}$; HRMS (EI) for $C_{18}H_{20}O_4$ calcd 300.1361, found 300.1368.

There was also obtained 18 mg of **ethyl 5-carbethoxy-1-naphthylacetate (7b)** ($R_f$ 0.63) as an oil that solidified on standing: mp 45–46 °C; $^1H$ NMR (200 MHz) $\delta$ 1.21 (t, $J$ = 7 Hz, 3 H), 1.46 (t, $J$ = 6 Hz, 3 H), 4.07 (s, 2 H), 4.14 (q, $J$ = 8 Hz, 2 H), 4.58 (q, $J$ = 8 Hz, 2 H), 7.48 (t, $J$ = 8 Hz, 1 H), 7.55 (t, $J$ = 8 Hz, 1 H), 7.53 (d, $J$ = 8 Hz, 1 H), 8.14 (d, $J$ = 8 Hz, 1 H), 8.21 (d, $J$ = 8 Hz, 1 H), 8.82 (d, $J$ = 8 Hz, 1 H); HRMS (EI) for $C_{17}H_{18}O_4$ calcd 286.1205, found 286.1209. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.07; H, 6.55.

**5-Iodonaphthylacetic Acid (8).** According to Setsune's general procedure,[11] ethyl malonate (1.92 g, 12.0 mmol), sodium hydride (380 mg, 12.5 mmol), CuI (2.29 g, 12.0 mmol), and 1,5-diiodonaphthalene (1.14 g, 3.00 mmol) were combined in 20 mL of dioxane. The mixture was heated at 101 °C for 25 h, cooled to 23 °C, partitioned between chloroform (60 mL) and water (40 mL), and filtered to remove the insoluble solid. The chloroform portion of the filtrate was washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo to give an oil. The crude product was purified by column chromatography (silica gel, ether–hexane (1:2)) to give 277 mg (24%) of 1,5-diiodonaphthalene ($R_f$ 0.8 in 2:1 $CHCl_3$–ether) and 469 mg of an alkylated product. The malonate-containing portion was heated at reflux in $H_2O$ containing NaOH (771 mg, 19.3 mmol) and NaCl (8.0 g) for 24 h. To the cooled reaction mixture was added concd HCl (3 mL, 30.4 mmol), and the mixture was heated at reflux for 8 h. The crude product was isolated by filtration to give 356 mg (38 or 50% on the basis of recovered **2**) of **8** as a white solid: mp > 290 °C; $^1H$ NMR (DMSO-$d_6$) $\delta$ 4.10 (s, 2 H), 7.30 (t, $J$ = 8 Hz, 1 H), 7.55 (d, $J$ = 8 Hz, 1 H), 7.65 (t, $J$ = 8 Hz, 1 H), 7.96 (d, $J$ = 8 Hz, 1 H), 8.05 (d, $J$ = 8 Hz, 1 H), 8.20 (d, $J$ = 8 Hz, 1 H); HRMS (EI) for $C_{12}H_9IO_2$ calcd 311.9649, found 311.9672.

**Acknowledgment.** We thank the Upjohn Co. for support of this research.

**Supplementary Material Available:** $^1H$ NMR spectra for compounds **3**, **4**, **6b**, and **8** and $^{13}C$ NMR spectra for compound **8** (5 pages). Ordering information is given on any current masthead page.

(13) A reviewer suggested that a better workup would use an $NH_4Cl$–$NH_4OH$ solution as described in: Behling, J. R.; Ng, J. S.; Babiak, K. A.; Campbell, A. L.; Ellsworth, E.; Lipshutz, B. H. *Tetrahedron Lett.* **1989**, *30*, 27.

## Synthesis of (±)-Aspidospermidine

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Some time ago there was introduced a short, direct method of construction of the pentacyclic skeleton of the Aspidosperma alkaloids from indoleacetic anhydride[2] and 3-acetyl-1,4,5,6-tetrahydropyridine[3] (i.e., the preparation of lactam **1** in Scheme I).[4] It lacked only the placement

(1) CNRS-URA 1310.
(2) Hart, J. C.; Matheson, E. M.; Hutzinger, O. *Can. J. Chem.* **1970**, *48*, 177.
(3) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G. *J. Org. Chem.* **1968**, *33*, 747.
(4) Wenkert, E.; Bindra, J. S.; Chauncy, B. *Synth. Commun.* **1972**, *2*, 285. Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesch, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719.

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