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STEREOSELECTIVE SYNTHESIS OF DISUBSTITUTED NAPHTHALENE-1,2-OXIDES

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Abstract: Spiroepoxy naphthalenones, obtained from the stereoselective oxidation of 2-hydroxyalkyl-1-naphthols with sodium periodate, were converted to naphthalene-1,2-oxides by reaction with methyllithium followed by Payne rearrangement.

The formation of arene oxides as the primary mammalian metabolites of substituted and unsubstituted aromatic hydrocarbons is well documented.[1] In order to study the genotoxicity of arene oxides, many synthetic methods have been developed for the synthesis of K-region and non-K-region arene oxides. Most of the reported synthetic routes lead to racemic arene oxides. The thermal instability and the greater chemical reactivity of the non-K-region arene oxides has precluded the use of most of the synthetic methods reported for the K-region arene oxides. Naphthalene oxides **1a-c** were reported to be stable only in solution.[2] The present investigation describes a mild and efficient method for the stereoselective synthesis of stable, disubstituted naphthalene 1,2-oxides.

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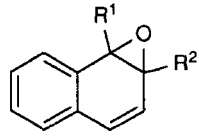
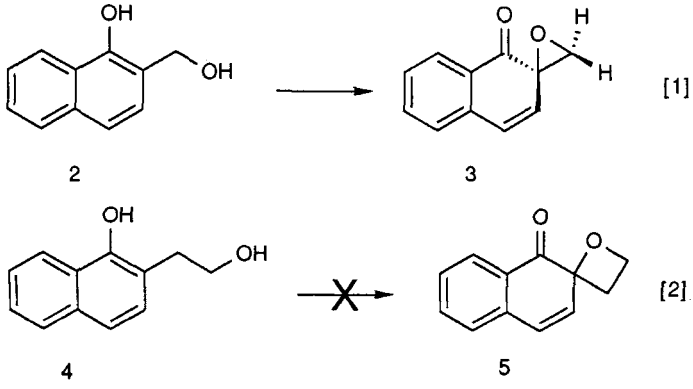
The oxidation of salicyl alcohols with sodium periodate is well known,[3] however this method has apparently not been applied to other aromatic systems. Reduction of 1-hydroxy-2-



1a $R^1 = R^2 = H$
1b $R^1 = H, R^2 = Me$
1c $R^1 = Me, R^2 = H$

naphthoic acid with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) at 0 °C furnished **2**. Oxidation of **2** with 0.3 M aqueous sodium periodate in THF (ca. 1/1, v/v) for 5 h provided **3** in 63% yield (eq 1). Under similar conditions homolog **4** failed to provide **5** (eq 2).

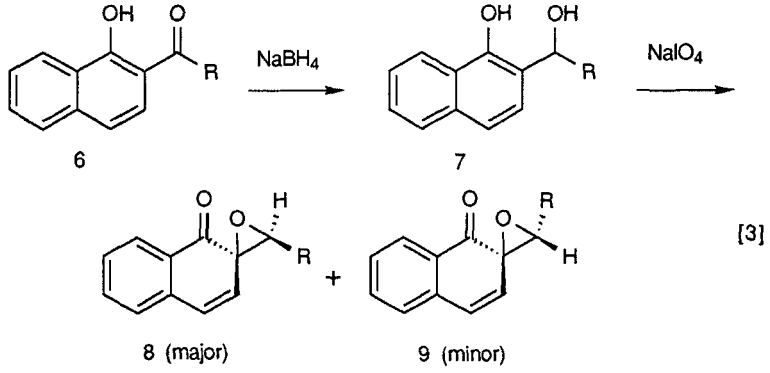


[1]

[2]

The effect of substitution at the benzylic carbon on the stereochemistry of the products was examined. Naphthyl ketones **6a**, **6b** and **6d** were prepared (eq 3) from 1-hydroxy-2-naphthoic acid by addition of the appropriate alkyllithium.[4] Fries rearrangement[5] of 1-naphthyl isobutyrate ($AlCl_3$, 100-

120 °C, 3 h) furnished **6c** in 60% yield. Reduction of **6a-d** with sodium borohydride in THF/methanol (ca. 1/1) at 0 °C for 5 min afforded the labile alcohols **7a-d** which were immediately oxidized with sodium periodate to provide spiroepoxides **8** and **9** (Table 1). The relative stereochemistry of **8a** was assigned based on the nuclear Overhauser effect between the methyl and olefinic hydrogens. The stereochemistry of **8b** and **8c** were assigned by comparison of the chemical shifts of the methine and olefinic hydrogens. Periodate oxidation of **7d** with aqueous $NaIO_4$ or n-Bu_4NIO_4 in THF was not successful. In other solvents (methanol, dioxane, dichloromethane), the formation of other oxidation products dominated, suggesting that the bulky *t*-butyl group inhibited the desired reaction. This is consistent with the increase in reaction times (**7a**, 12 h; **7b**, 17 h; **7c**, 24 h) and decrease in isolated yield with increase in the size of R.



[3]

(a) R = Me; (b) R = n-Bu; (c) R = i-Pr; (d) R = t-Bu

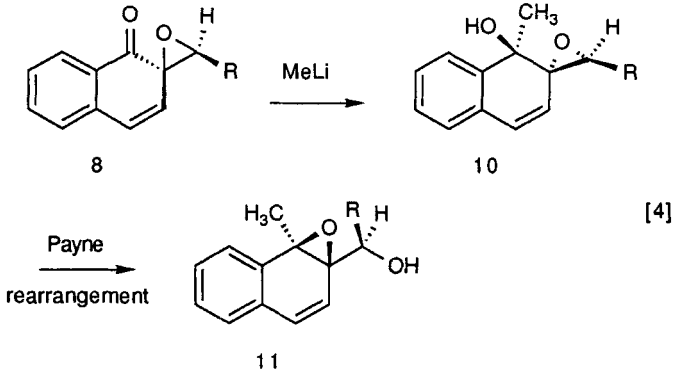
The behavior of spiroepoxy naphthalenones **8a-c** toward methyllithium was examined. Treatment of **8a** with either methylmagnesium bromide or with methyllithium in ether at -78 °C produced erythro epoxy alcohol **10a** as only product to

the limits of detection by ^1H nmr (eq 4). Addition of water to the reaction mixture and stirring at 0 °C for 12 h led to the formation of **11a** in 40% yield, along with recovered starting material. At 23 °C the Payne rearrangement leading to **11a** proceeded in 90% yield during 4 h. The rearranged structure of **11a** was confirmed by conversion to the acetate and observing a 1.3 ppm downfield shift in the ^1H nmr spectrum of the appropriate methine signal. Epoxynaphthalenones **8b** and **8c** were converted to naphthalene oxides **11b** and **11c** in the same manner (Table 1).[6]

Table 1

	Yield[a] (ratio of 8/9)	Yield **10**[b]	Yield **11**[b]
7a	67% (25/1)	91%	90%
7b	64% (5/1)	91%	82%
7c	49% (2/1)	93%	73%
7d	0%		

[a]Products were purified by flash column chromatography on neutral alumina.[b] Products were purified by flash column chromatography on silica gel.

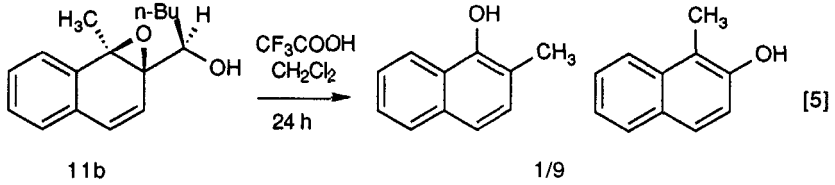


[4]

The rearrangement of **11b** with trifluoroacetic acid in dichloromethane at 23 °C for 24 h afforded 2-methyl-1-

naphthol and 1-methyl-2-naphthol (ca. 1/9) in 80% yield (eq 5). Both products are the result of acid mediated epoxide ring opening with loss of valeraldehyde, the minor product arising from migration of the methyl group.[2,7]

In summary, a versatile synthesis of disubstituted naphthalene 1,2-oxides has been described. The availability of methods for the enantioselective reduction[8] of aryl alkyl ketones suggests that this work will be suitable for the preparation of optically active materials.



11b 1/9 [5]

Experimental

Dichloromethane was distilled from phosphorous pentoxide. Ether and THF were distilled from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (Oxford magnet) NMR spectrometer. Chemical shifts were measured in parts per million (ppm) relative to the residual protio chloroform in deuterated chloroform (7.26 ppm) as an internal standard. Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Broad signals are designated br. High resolution EI mass spectra were recorded on a VG-70SE instrument. Flash column chromatography was performed on Brinkmann silica gel (0.040-0.063 mm). Infrared spectra were recorded on a Perkin-Elmer 1430 double beam instrument. Solid samples were recorded in solution and oils were recorded neat.

Spiroepoxy naphthalenone 3. To a solution of 165 mg (0.94 mmol) of 1-hydroxy-2-hydroxymethylnaphthalene **2** in 2 mL THF was added dropwise 4.7 mL (1.4 mmol) of a 0.3 M aqueous solution of $NaIO_4$. The reaction mixture was stirred for 5 h, then partitioned between dichloromethane and water. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography on neutral alumina, eluting with 10% ethyl acetate in hexanes to produce 103 mg (63% yield) of spiroepoxide **3** (oil): IR (CCl_4) 3060, 2980, 1695, 1600, 1550, 1335, 1265, 1220, 1005, 975, 920 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.06 (d, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.73 (d, J = 7.8 Hz, 1 H), 6.29 (d, J = 9.9 Hz, 1 H), 5.42 (d, J = 9.6 Hz, 1 H), 3.17 (d, J = 7.8 Hz, 1 H), 2.44 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 192.49, 137.58, 134.64, 131.68, 131.10, 129.82, 128.37, 128.12, 126.75, 57.48, 55.48; mass spectrum *m/e* 173 (M^++1, 18%), 172 (M^+, 89%), 171 (69%), 156 (M^+-O, 7%), 143 (10%), 130 (12%), 115 (57%), 102 (9%), 84 (100%); calcd for $C_{11}H_8O_2$ 172.0524, found 172.0526.

The procedures described below for the preparation of **8a**, **9a**, **10a** and **11a** are representative for the entire series.

Spiroepoxy naphthalenone 8a. A solution of 1.018 g (5.47 mmol) of **6a** in 10 mL of methanol at 0 °C was treated with 228 mg (6.02 mmol) of sodium borohydride. After 5 min 3 mL of aqueous sodium dihydrogen phosphate was added and most of the methanol removed at reduced pressure. The residue was partitioned between ether and water, and the ether layer was concentrated to ca. 2 mL. The labile hydroxynaphthol **7a** was dissolved in 50 mL THF at 23 °C and 18.2 mL of a 0.3 M aqueous solution of $NaIO_4$ (5.47 mmol) was added at a rate of 6.1 mL every 2 h. Following stirring for 12 h, the reaction mixture was extracted with dichloromethane. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography on neutral alumina, eluting with 5% ethyl

acetate in hexanes, to produce 654 mg (64% yield) of **8a** and 26 mg (3% yield) of the more mobile isomer **9a**. **8a** (oil): IR (neat) 1685, 1600, 1400, 1305, 920, 875 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.11 (d, J = 7.8 Hz, 1 H), 7.04 (dt, J = 7.5, 1.2 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.74 (d, J = 7.5 Hz, 1 H), 6.36 (d, J = 9.9 Hz, 1 H), 5.65 (d, J = 9.9 Hz, 1 H), 3.50 (q, J = 5.4 Hz, 1 H), 0.92 (d, J = 5.4 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 193.1, 137.3, 134.5, 131.7, 129.5, 128.5, 128.4, 128.1, 126.7, 66.3, 60.2, 14.3; mass spectrum *m/e* 186 (M^+, 68%), 171 (M^+-CH_3, 100%), 159 (10%), 143 (6%), 131 (15%), 114 (28%), 102 (8%), 84 (75%), 78 (72%); calcd for $C_{12}H_{10}O_2$ 186.0691, found 186.0694. **9a** (oil): ^1H NMR (300 MHz, C_6D_6) δ 8.10 (d, J = 6.6 Hz, 1 H), 7.03 (t, J = 7.5 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.45 (d, J = 7.5 Hz, 1 H), 6.26 (d, J = 9.9 Hz, 1 H), 5.51 (d, J = 9.9 Hz, 1 H), 2.94 (q, J = 5.1 Hz, 1 H), 1.23 (d, J = 5.1 Hz, 1 H).

Naphthalene oxides 10a and 11a. A solution of 29 mg (0.16 mmol) of **8a** in 3 mL of ether at -78 °C was treated with 160 μL (0.24 mmol) of a 1.47 M solution of methyllithium in ether. After 10 min the reaction was quenched with water and was stirred at 23 °C for 4 h. The reaction mixture was partitioned between ether and water and the ether layer was washed with brine and dried over $MgSO_4$. Solvent evaporation and flash column chromatography (silica gel, 15% ethyl acetate in hexanes containing 1% triethylamine) produced 28 mg (90% yield) of **11a** as an oil: IR (neat) 3420, 3040, 2980, 2920, 2840, 1490, 1450, 1380, 1280, 1250, 1080, 1060, 910, 880, 830 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.46 (d, J = 6.9 Hz, 1 H), 7.08-7.00 (m, 3 H), 6.56 (d, J = 9.9 Hz, 1 H), 6.24 (d, J = 9.9 Hz, 1 H), 3.95 (q, J = 6.6 Hz, 1 H), 2.36 (s, 1 H), 1.73 (s, 3 H), 1.31 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.5, 132.6, 131.9, 129.1, 128.5, 127.8, 127.3, 125.7, 67.5, 67.2, 64.2, 18.9, 15.8; mass spectrum m/e 200 (M^+-2, 1.6%), 158 (M^+-C_2H_4O, 22%), 78 (100%). In an effort to secure a derivative with more persistent fragment ions, **11a** was converted to the acetate which had a strong fragment ion at *m/e* 158, corresponding to

loss of $C_4H_6O_2$. Exact mass calcd for $C_{11}H_{10}O$ 158.0732, found 158.0729. When the reaction mixture was worked up immediately after quenching, naphthalene oxide **10a** was isolated as the sole product in 91% yield following flash column chromatography. **10a** (oil): IR (neat) 3460, 2990, 2940, 1455, 1365, 1160, 1075, 1000, 895, 795, 760 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.75 (d, J = 7.5 Hz, 1 H), 7.08 (t, J = 7.5 Hz, 1 H), 6.99 (t, J = 7.5 Hz, 1 H), 6.81 (d, J = 7.5 Hz, 1 H), 6.31 (d, J = 10.2 Hz, 1 H), 5.54 (d, J = 10.2 Hz, 1 H), 3.59 (q, J = 5.7 Hz, 1 H), 1.96 (s, 1 H; exchanges with D_2O), 1.53 (s, 3 H), 0.91 (d, J = 5.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.82, 131.82, 131.22, 128.47, 128.04, 127.58, 126.69, 123.67, 72.62, 67.58, 57.24, 27.06, 14.11; mass spectrum *m/e* 202 (M^+, 2%), 184 (M^+-H_2O, 5%), 169 (M^+-H_2O -CH_3, 9%), 158(M^+-CH_3CHO, 100%), 141 (19%), 129 (34%), 115 (27%), 102 (5%), 78 (87%), 63 (11%); calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0991.

Listed below are spectroscopic data for **8-11b** and **8-11c**.

8b (oil): IR (neat) 2980, 1690, 1640, 1600, 1450, 1420, 1300 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.15 (d, J = 7.6 Hz, 1 H), 7.04 (t, J = 7.6 Hz, 1 H), 6.88 (t, J = 7.6 Hz, 1 H), 6.75 (d, J = 7.6 Hz, 1 H), 6.39 (d, J = 10.1 Hz, 1 H), 5.75 (d, J = 10.1 Hz, 1 H), 3.56 (t, J = 5.7 Hz, 1 H), 0.70 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.16, 137.14, 134.90, 131.66, 129.28, 129.06, 128.35, 128.00, 126.72, 71.06, 60.51, 28.81, 28.35, 22.29, 13.81; mass spectrum *m/e* 228 (M^+, 37%), 171 (M^+- *n*-Bu, 100%), 160 (17%), 130 (10%), 115 (16%), 102 (6%); calcd for $C_{15}H_{16}O_2$ 228.1151, found 228.1156.

9b (oil): ^1H NMR (300 MHz, C_6D_6) δ 8.12 (d, J = 7.2 Hz, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 6.88 (t, J = 7.2 Hz, 1 H), 6.74 (d, J = 7.2 Hz, 1 H), 6.29 (d, J = 9.7 Hz, 1 H), 5.59 (d, J = 9.7 Hz, 1 H), 3.00 (t, J = 6.0 Hz, 1 H), 0.68 (t, J = 7.2 Hz, 3 H).

10b (oil): IR (neat) 3450 (broad), 2950, 2850, 1480, 1460, 1360, 1210, 1150 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.77 (d, J = 7.5 Hz, 1 H), 7.08 (t, J = 7.2 Hz, 1 H), 6.99 (t, J = 7.2 Hz, 1 H),

6.82 (d, J = 7.5 Hz, 1 H), 6.32 (d, J = 9.9 Hz, 1 H), 5.61 (d, J = 9.9 Hz, 1 H), 3.58 (dd, J = 6.9, 4.8 Hz, 1 H), 1.72 (s, 1 H), 1.55 (s, 3 H), 0.72 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.81, 131.62, 131.19, 128.40, 128.20, 127.50, 126.60, 123.65, 72.58, 67.65, 61.61, 28.41, 28.36, 26.96, 22.29, 13.84; mass spectrum *m/e* 244 (M^+, 8%), 226 (M^+-H_2O, 12%), 198 (13%), 169 (M^+-H_2O -*n*-Bu, 61%), 158 (M^+-*n*-BuCHO, 100%), 157 (30%), 155 (30%), 142 (27%), 141 (34%), 132 (31%), 129 (33%), 115 (18%); calcd for $C_{16}H_{20}O_2$ 244.1464, found 244.1385.

11b (oil): IR (neat) 3440 (broad), 2960, 2930, 2870, 1500, 1470, 1460, 1385, 1065, 1035, 900, 840 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.47 (d, J = 7.5 Hz, 1 H), 7.09-7.01 (m, 3 H), 6.58 (d, J = 9.9 Hz, 1 H), 6.27 (d, J = 9.9 Hz, 1 H), 3.84 (t, J = 6.5 Hz, 1 H), 2.37 (s, 1 H), 1.76 (s, 3 H), 1.74-1.59 (m, 2 H), 1.38-1.25 (m, 4 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.45, 132.43, 131.88, 129.07, 128.42, 127.80, 127.28, 126.10, 71.59, 67.11, 64.54, 33.15, 28.29, 22.69, 15.88, 13.99; mass spectrum *m/e* 244 (M^+, 2%), 226 (M^+-H2O, 2%), 210 (M^+-H_2O -O, 1%), 169 (M^+-H_2O -*n*-Bu, 20%), 158 (M^+- *n*-BuCHO, 100%), 157 (60%), 141 (15%), 140 (15%), 130 (18%), 129 (67%), 128 (36%), 127 (13%), 115 (21%); calcd for $C_{16}H_{20}O_2$ 244.1464, found 244.1364.

8c (oil): IR (neat) 2950, 1680, 1630, 1595, 1300 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.15 (d, J = 7.5 Hz, 1 H), 7.02 (td, J = 7.5, 1.2 Hz, 1 H), 6.86 (td, J = 7.2, 1.2 Hz, 1 H), 6.73 (d, J = 7.2 Hz, 1 H), 6.37 (d, J = 10.1 Hz, 1 H), 5.74 (d, J = 10.1 Hz, 1 H), 3.37 (d, J = 9.0 Hz, 1 H), 1.39 (m, 1 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.51 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.13, 137.12, 134.94, 131.71, 129.23, 128.88, 128.37, 128.02, 126.78, 76.49, 61.08, 28.98, 20.20, 18.28; mass spectrum *m/e* 214 (M^+, 28%), 198 (M^+-O, 6%), 171 (M^+-*i*-Pr, 100%), 159 (18%), 143 (8%), 130 (12%), 115 (17%), 84 (95%); calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.0992; calcd for $C_{11}H_7O_2$ 171.0446, found 171.0457.

9c (oil): IR (neat) 2960, 1680, 1630, 1600, 1330 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.12 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 7.8 Hz, 1 H), 6.87 (t, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.5 Hz, 1 H), 6.26 (d, J =

9.9 Hz, 1 H), 5.59 (d, J = 9.9 Hz, 1 H), 2.74 (d, J = 8.7 Hz, 1 H), 2.48 (m, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.45 (d, J = 6.6 Hz, 3 H).

10c (oil): IR (neat) 3440 (sharp), 2970, 1450, 1390, 1360, 1220, 1160 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.75 (d, J = 7.5 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 6.81 (d, J = 7.5 Hz, 1 H), 6.30 (d, J = 10.1 Hz, 1 H), 5.60 (d, J = 10.1 Hz, 1 H), 3.30 (d, J = 9.3 Hz, 1 H), 1.61 (s, 1 H), 1.52 (s, 3 H), 1.34 (m, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.54 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.69, 131.77, 131.16, 128.48, 128.04, 127.58, 126.68, 123.62, 72.78, 67.99, 66.87, 28.33, 26.92, 20.09, 17.99; mass spectrum *m/e* 230 (M^+, 3%), 212 (M^+-H_2O, 4%), 196 (M^+-H_2O -O, 1 %),184 (6%), 169 (36%), 158 (M^+-*i*-PrCHO, 100%), 141 (17%), 129 (21%), 115 (12%); calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1345.

11c (oil): IR (neat) 3450 (broad), 2960, 2880, 1635, 1500, 1470, 1450, 1390, 1265, 1035, 940, 900, 830 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.46 (d, J = 7.0 Hz, 1 H), 7.09-7.01 (m, 3 H), 6.55 (d, J = 9.9 Hz, 1 H), 6.26 (d, J = 9.9 Hz, 1 H), 3.45 (dd, J = 8.4, 3.0 Hz, 1 H), 2.34 (s, 1 H), 2.04-1.90 (m, 1 H), 1.70 (s, 3 H), 1.10, 0.99 (two d, J = 6.6 Hz and J = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.81, 132.11, 131.26, 129.06, 128.64, 127.64, 127.32, 125.21, 77.95, 68.94, 65.93, 31.24, 19.49, 18.23, 17.36; mass spectrum *m/e* 230 (M^+, 2%), 214 (M^+-O, 0.4%), 212 (M^+-H_2O, 0.2%), 187 (M^+-*i*-Pr, 0.4%), 171 (M^+-*i*-Pr -O, 2%), 169 (M^+-*i*-Pr -H_2O, 1%), 158 (M^+-*i*-PrCOH, 44%), 141 (4%), 129 (15%), 128 (13%), 115 (6%), 84 (100%); calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1321; calcd for $C_{11}H_{10}O$ 158.0732, found 158.0721.

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4. Methyllithium or *n*-butyllithium were added to 1-hydroxy-2-naphthoic acid in ether at 0 °C to produce **6a** (79% yield) or **6b** (60% yield). t-Butyllithium was added to 1-hydroxy-2-naphthoic acid at -78 °C and the temperature was allowed to rise to 25 °C to furnish **6d** in 42% yield.
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