# Directed, DDQ-Promoted Benzylic Oxygenations of Tetrahydronaphthalenes

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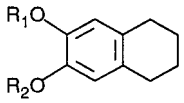
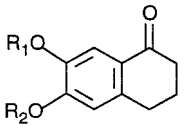
Positional preferences for para benzylic oxygenation of tetrahydronaphthalenes by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)−aqueous dioxane were investigated by comparing the tetralone products from 6-hydroxy-7-methoxy- and 6-acetoxy-7-methoxy-1,2,3,4-tetrahydronaphthalene. The directing influence by an aromatic substituent on para benzylic oxygenation was in the order OH > OMe > OAc. Consistent with this finding were results obtained from lignan analogues. Treatment of (+)-$\beta$-conidendryl alcohol with DDQ in dry dioxane resulted in the intramolecular bridging by one of two primary hydroxy groups to the benzylic position, giving an oxabicyclo[3.2.1]octane. Similar treatment of (+)-dimethyl-$\beta$-conidendryl alcohol resulted in bridging by the alternate primary hydroxyl group to the benzhydrylic carbon giving an isomeric oxabicyclo[3.2.1]octane.

We have been interested in developing methods for introducing oxygen selectively and efficiently at the benzylic positions of 1,2,3,4-tetrahydronaphthalenes (THN), including a number of lignans incorporating this particular structural feature. Direct benzylic oxygenations of simple 6-hydroxy- and 6-methoxytetrahydronaphthalenes have been achieved using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of water or methanol.[1] We observe that treatment of the dissymmetrically substituted THN, **1**,[2] with DDQ−water results in a 70% yield of known tetralone **2**.[3] This conversion demonstrated the preference for oxygenation occurring at the methylene carbon para to the hydroxy group, rather than para to the methoxy group, and marks the terminal carbon involved in intermediate quinone methide formation.[4−6] However, the preferred position for oxygenation can be switched to the methylene para to the methoxy group. This change was achieved by acetylating the hydroxy group of **1**, prior to DDQ−water treatment, for the purpose of deactivating the hydroxy group.[7] Thus, **3** yielded acetoxytetralone **4** in 62% yield. Competitive formation of 2-acetoxy-3-methoxynaphthalene (23%) was anticipated on the basis of known dehydrogenations by other chlorine-substituted 1,4-benzoquinones.[8] Acetoxytetralone **4** was hydrolyzed, and the resulting hydroxytetralone **5**[3] exhibited physical properties agreeing with the assigned structure and contrasting with those of its positional isomer **2**.



**1**: $R_1 = CH_3$; $R_2 = H$
**3**: $R_1 = CH_3$; $R_2 = CH_3CO$



**2**: $R_1 = CH_3$; $R_2 = H$
**4**: $R_1 = CH_3CO$; $R_2 = CH_3$
**5**: $R_1 = H$; $R_2 = CH_3$

In contrast to the simple THN **1**, its lignan analogue (−)-$\beta$-conidendrin[9] (Figure 1) gave the naphthalene dehydroconidendrin in 44% yield as the only isolable product from DDQ−water treatment. Similarly, dimethyl-$\beta$-conidendrin[10] gave dimethyldehydroconidendrin in 53% yield.[10] However, dehydrogenation as the principal outcome was replaced by an intramolecular mode of oxygenation through treatment of (+)-$\beta$-conidendryl alcohol (**6**, Scheme 1) in anhydrous dioxane with DDQ. Oxymethylene bridging to the benzylic carbon of **6** occurred giving **7** (59%). The structure was consistent with the physical data including the HMBC. Oxymethylene bridging switched from the benzyl to the benzhydrylic position when the phenolic hydroxy groups of **6** were replaced by methoxy groups, as demonstrated by the conversion of **8**[10] to **9** (70%) using DDQ in $CH_2Cl_2$. Persistence of some competitive dehydrogenation was evident in the formation of the naphthalene **10** (2%). Compound **9** was an inseparable

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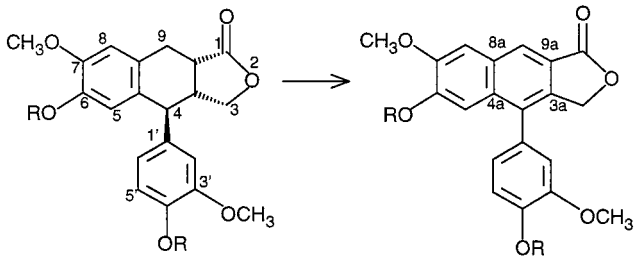
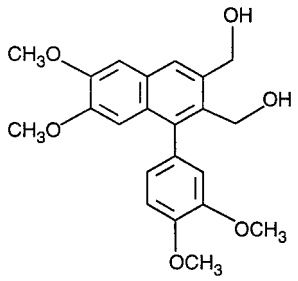


**Figure 1.** Tetrahydronaphthalene lignans $\beta$-conidendrin (R = H) and dimethyl-$\beta$-conidendrin (R = $CH_3$) undergoing dehydrogenation with DDQ in dioxane−5% water to dehydroconidendrin and dimethyldehydroconidendrin, respectively.

mixture of near-equimolar amounts of rotational diastereomers, as evidenced by pairs of signals in the $^{13}C$ NMR.



**10**

The demonstrated influence of a C-6 aromatic substituent on para benzylic oxygenation of a THN is in the order OH > $OCH_3$ > OAc. This finding allows for selectivity in DDQ-promoted oxygenations of benzylic positions through appropriate, prior blocking of a para phenolic hydroxy group. This was demonstrated by the simple disubstituted THNs and the more complex (+)-$\beta$-conidendryl and dimethyl-$\beta$-conidendryl alcohols.

## Experimental Section

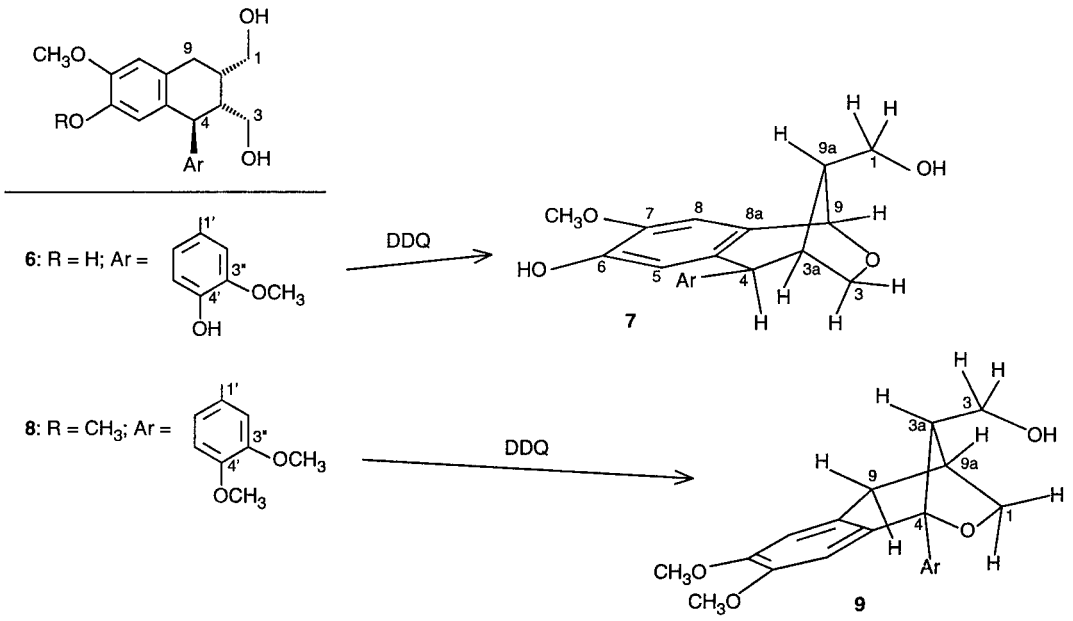
**Reaction Procedures**. All reactions with DDQ were conducted under $N_2$ at 25 °C. **(a) Reactions of THNs 1 and 3**. DDQ in anhydrous dioxane (<0.01% $H_2O$) was added dropwise to the THN in ~5% aqueous dioxane. Processing the reaction mixture involved the following steps in succession: filtration if required through sintered glass, evaporation of the solvent from the filtrate, and partitioning of the residue between EtOAc and 5% aqueous $NaHCO_3$. The EtOAc layer was washed with proportional amounts of 5% aqueous $NaHCO_3$, $H_2O$, and brine. The residue obtained on removal of the EtOAc at reduced pressure was chromatographed. **(b) Reaction of (+)-$\beta$-Conidendryl Alcohol, 6**. The reaction procedure and processing were the same as described in part a**,** except **6** was dissolved in anhydrous dioxane. **(c) Reaction of (+)-Dimethyl-$\beta$-conidendryl Alcohol, 8**. DDQ in $CH_2Cl_2$ was added dropwise to **8** in $CH_2Cl_2$. Processing solvent $Et_2O$ replaced EtOAc.

**Conversion of 6-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene (1)[2] to Tetralone 2**. DDQ (231 mg, 1.02 mmol) in 2 mL of dry dioxane and **1** (89 mg, 0.5 mmol) in 0.5 mL of aqueous dioxane gave after 3 h and MPLC (EtOAc/hexane 1:1) compound **2** (68 mg, 71%): mp 117−119 °C (lit.[3] mp 115−118 °C); IR (film, NaCl disk, $cm^{-1}$) 3338, 1664; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.07 (m, 2), 2.57 (t, $J$ = 6.53 Hz, 2), 2.83 (t, $J$ = 6.11 Hz, 2), 3.88 (s, 3), 6.44 (s, 1, OH), 6.73 (s, 1), 7.51 (s, 1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 23.5, 29.2, 38.5, 56.1, 108.5, 113.8, 125.6, 140.1, 145.7, 150.8, 197.3; MS 192 [$M^+$].

**Conversion of 6-Acetoxy-7-methoxy-1,2,3,4-tetrahydronaphthalene (3) to Tetralone 4 and 2-Acetoxy-3-methoxynaphthalene**. DDQ (454 mg, 2 mmol) in 4 mL of dry dioxane and **3** (220 mg, 1 mmol) in 1 mL of aqueous dioxane gave after 20 h and MPLC (EtOAc/hexanes 3:5) **4** (146 mg, 62%) and 2-acetoxy-3-methoxynaphthalene (50 mg, 23%). **4**: mp 118.5−119.5 °C; IR (film, NaCl disk, $cm^{-1}$) 1675, 1769; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.11 (m, 2), 2.28 (s, 3), 2.57 (t, $J$ = 6.53 Hz, 2), 2.91 (t, $J$ = 6.08 Hz, 2), 3.86 (s, 3), 6.74 (s, 1), 7.69 (s, 1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.4, 23.2, 29.7, 38.4, 56.0, 111.3, 121.5, 126.1, 138.7, 144.5, 155.2, 168.8, 196.2; MS 234 [$M^+$]. 2-Acetoxy-3-methoxynaphthalene: mp 114−116 °C; IR 1764; $^1H$ NMR $\delta$ 2.38 (s, 3), 3.95 (s, 3), 7.22 (s, 1), 7.36 (ddd, $J$ = 8.14, 7.51, 1.24 Hz, 1), 7.44 (ddd, $J$ = 8.23, 7.55, 1.34 Hz, 1), 7.50 (s, 1), 7.73 (dd, $J$ = 7.43, 1.1 Hz, 1), 7.75 (dd, $J$ = 8.13, 1.0 Hz, 1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 20.6, 55.8, 107.3, 120.3, 124.2, 126.1, 126.5, 127.2, 128.3, 132.5, 140.3, 150.2, 169.2; HRMS calcd for $C_{13}H_{12}O_3$ 216.0786 [$M^+$], found 216.0783.

**Conversion of 6-Methoxy-7-acetoxy-1-tetralone (4) to Tetralone 5**. To **4** (117 mg, 0.5 mmol) in 7 mL of methanol was added 3.5 mL of water and then 3.5 mL of saturated aqueous $NaHCO_3$. The resulting solution was stirred under $N_2$ at 25 °C for 17 h, acidified with aqueous HCl (1 M), and extracted with $CH_2Cl_2$ (5 × 6 mL). The combined $CH_2Cl_2$

**Scheme 1**



extracts were washed with brine and dried ($MgSO_4$). Removal of $CH_2Cl_2$ at reduced pressure gave **5** (94 mg, 98%): mp 151−152 °C (lit.[3] mp 148−152 °C); IR (film, NaCl disk, $cm^{-1}$) 3369, 1665; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.09 (m, 2H), 2.57 (t, $J$ = 6.54 Hz, 2), 2.86 (t, $J$ = 6.11 Hz, 2), 3.93 (s, 3), 5.68 (s, 1), 6.65 (s, 1), 7.55 (s, 1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 23.6, 29.5, 38.6, 56.0, 109.7, 112.3, 126.6, 138.4, 144.5, 151.2, 197.2; MS 192 [$M^+$].

**Conversion of (+)-*β*-Conidendryl Alcohol (6) to Oxabicyclooctane 7**. DDQ (150 mg, 0.66 mmol) in 8.5 mL of dioxane and **6** (200 mg, 0.56 mmol) in 45 mL of dioxane gave **7** (117 mg, 59%) after a 5 h reaction period, processing, and preparative TLC (EtOAc). **7:** mp 167−169 °C; $[\alpha]^{25}_D = -30.95°$ (*c* 1.58, acetone); IR 3370 (film, NaCl disk, $cm^{-1}$); $^1H$ NMR (300 MHz, MeOH-$d_4$) $\delta$ 2.54 (m, 2), 3.38 (dd, $J$ = 10.92, 6.20 Hz, 1), 3.59 (dd, $J$ = 10.73, 9.17 Hz, 1), 3.75 (d, $J$ = 8.57 Hz, 1), 3.83 (s, 3), 3.94 (s, 3), 4.10 (dd, $J$ = 8.58, 5.94 Hz, 1), 4.18 (d, $J$ = 1.65 Hz, 1), 4.84 (brs, 4), 6.50 (dd, $J$ = 8.14, 1.88 Hz, 1), 6.54 (s, 1), 6.72 (d, $J$ = 1.87 Hz, 1), 6.78 (d, $J$ = 8.12 Hz, 1), 6.88 (s, 1); $^{13}C$ (75 MHz, $CDCl_3$) $\delta$ 45.5, 46.6, 53.7, 56.4, 56.5, 62.8, 71.8, 79.4, 112.8, 113.8, 115.9, 118.7, 122.5, 130.3, 133.2, 138.2, 146.1, 147.7, 147.8, 148.8; HRMS calcd for $C_{20}H_{22}O_6$ 358.1416, found 358.1417.

**Conversion of (+)-Dimethy-*β*-conidendryl Alcohol (8)[10] to Oxabicyclooctane 9 and Naphthalene 10**. DDQ (2.32 g, 10.22 mmol) in 118 mL of $CH_2Cl_2$ and **8** (3.5 g, 9.18 mmol) in 60 mL of $CH_2Cl_2$ gave **9** (2.48 g, 70%) after a 5.5 h reaction period, processing, and MPLC ($CH_2Cl_2$/EtOAc 1:1). **9**: mp 121−122 °C; $[\alpha]^{22}_D = -6.7°$ (*c* 1.93, acetone); IR 3450 (film, NaCl disk, $cm^{-1}$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.43 (br s, 2H), 2.55 (t, $J$ = 6.28 Hz, 2), 2.89 (m, 4), 3.22 (m, 1), 3.29 (m, 3), 3.43 (m, 2), 3.51 (s, 3), 3.52 (s, 3), 3.741 (s, 3), 3.745 (d, $J$ = 8.51 Hz, 2), 3.826 (s, 3), 3.833 (s, 3), 3.89 (s, 3), 3.90 (s, 3), 3.92 (s, 3), 4.22 (m, 2), 6.12 (s, 1), 6.16 (s, 1), 6.56 (d, $J$ = 1.76 Hz, 1), 6.66 (dd, $J$ = 1.95, 8.36 Hz, 1), 6.65 (s, 1), 6.67 (s, 1), 6.86 (d, $J$ = 8.39 Hz, 1), 6.90 (d, $J$ = 8.31 Hz, 1), 7.32 (dd, $J$ = 8.31, 1.81 Hz, 1), 7.36 (d, $J$ = 1.59 Hz, 1); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 37.73, 37.74, 38.15, 38.19, 52.94, 53.14, 55.73, 55.79, 55.92, 55.94, 56.06, 62.56, 62.58, 71.43, 71.48, 86.05, 86.14, 110.33, 110.41, 110.47, 110.63, 111.00, 111.97, 112.03, 119.29, 119.77, 126.94, 127.17, 131.62, 132.23, 135.09, 135.36, 146.90, 146.97, 147.70, 148.38, 148.54, 148.69; HRMS calcd for $C_{22}H_{26}O_6$ 386.1729, found 386.1732. Also obtained by MPLC was **10** (63 mg, 2%): mp 193−194 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.71 (s, 3), 3.85 (s, 3), 3.98 (s, 3), 3.99 (s, 3), 4.60 (d, $J$ = 11.93 Hz, 1), 4.64 (d, $J$ = 11.96 Hz, 1), 4.91 (s, 2), 6.77 (s, 1), 6.89 (m, 2), 7.00 (dd, $J$ = 6.78, 1.90 Hz, 1), 7.13 (s, 1), 7.70 (s, 1); $^{13}C$ NMR (75 MHz) $\delta$ 55.65, 55.89, 55.92, 55.97, 60.82, 65.4, 106.1, 106.3, 111.2, 113.6, 122.5, 127.2, 128.6, 128.8, 131.4, 133.2, 135.7, 139.2, 148.3, 148.8, 149.7, 149.8; HRMS calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.15601.

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**Supporting Information Available:** Experimental procedures, compound characterization, and selected interpretations of HMBC are provided for **3,** dehydroconidendrin**,** dimethyldehydroconidendrin, **6**, **7**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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