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# A concise synthesis of 1-substituted-2-tetralones by selective diol dehydration leading to ketone transposition[1]

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**Abstract**

Dehydration of 1-substituted-1,2-tetralindiols with zinc iodide afforded the corresponding 2-tetralones in excellent yields. This procedure was found to be superior to the more conventional $BF_3$-catalyzed rearrangement of 1-substituted-1,2-epoxytetralins. 

*Keywords:* ketones; rearrangements; epoxides; diols.

The tetralone family serves as an important source of synthetic precursors for a wide range of compounds, including steroids,[2] heterocycles,[3] and pharmaceuticals.[4] While the 1-tetralones are inexpensive, easily prepared and commercially available, the 2-tetralones are often very expensive[5] and much more difficult to synthesize. This is especially true of the 1-substituted-2-tetralones. The literature describes but two routes for their preparation, neither of which is convenient and/or high yielding. Alkylation of the metal enolate of 2-tetralone suffers from polyalkylation and poor yield.[6] The enamine alkylation developed in our laboratory is an excellent method; however, it is limited by the availability of the 2-tetralone and requires multiple steps.[7] Prompted by a recent report by Meyers and co-workers,[8] who demonstrated that epoxides derived from 1-tetralones can rearrange in good yield to afford 2-tetralones, we report herein a complementary method leading to the title compounds.

Epoxides have long been known for their ability to undergo acid-catalyzed rearrangement by 1,2-oxygen shift affording ketones.[9] Over the years, numerous catalysts have been investigated for epoxide isomerization, including $BF_3$, $H_2SO_4$, and transition metal complexes.[10] During the syntheses of tetralin-containing heterocyclics, we studied the feasibility of using an epoxide isomerization step in the formation of 1-alkyl-, 1-aryl-, and 1-arlyalkyl-2-tetralones. Our study showed that three different, yet complementary, intermediates could be obtained—any one of which would give the desired rearrangement product. Furthermore, the scheme is simple, uses

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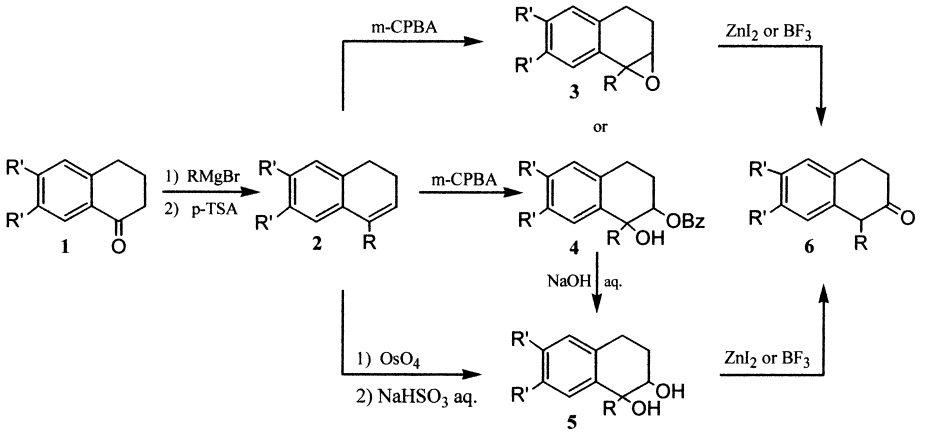
inexpensive reagents, affords the title compounds in high yield, and can be done in only four steps (Scheme 1).




Scheme 1.

In our initial study we chose to study the acid-catalyzed isomerization of 1-benzyl-1,2-epoxytetralin (**3c**). The requisite alkene **2c** was prepared in a two-step sequence involving Grignard addition of benzylmagnesium bromide to 1-tetralone (R′ = H). The resulting alcohol, without purification, was dehydrated by *p*-toluenesulfonic acid in refluxing toluene for 1 h to give 1-benzyl-3,4-$\Delta^1$-tetralin (**2c**) in 90% yield. This alkene was then treated with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride for 1.5 h to furnish the corresponding epoxide **3c** in 96% yield. Upon rearrangement with either boron trifluoride etherate or zinc iodide, 1-benzyl-1,2-epoxytetralin (**3c**) gave 1-benzyl-2-tetralone (**6c**) in 98–99% yield. This four-step sequence gave the desired product in 85% overall yield without resorting to expensive reagents or tedious work-up procedures. Encouraged by these results we next turned our attention to the 1-aryl- and 1-alkyl-2-tetralones. These compounds, however, gave us some unexpected results.

As before, methylmagnesium bromide and phenylmagnesium bromide reacted with 1-tetralones and underwent subsequent dehydration to furnish 1-methyl- or 1-phenyl-$\Delta^1$-tetralin (**2a**, **2b**) in 75–90% yield. However, all attempts to isolate the epoxides after oxidation with *m*-chloroperbenzoic acid failed. We discovered that epoxide ring opening had occurred under acidic conditions resulting in the formation of the α-hydroxy benzoate esters **4**. The regiochemistry of epoxide opening was proven by the substantial resonance deshielding (5.38 ppm) of the C-2 proton of the *m*-chlorobenzoate ester **4a**, whereas the C-2 proton in the diol **5a** appeared at 3.83 ppm.[11] The problem of epoxide opening was easily overcome by performing this reaction in a heterogeneous water/methylene chloride medium, where the *m*-CPBA was converted into its sodium salt by the addition of sodium bicarbonate. The desired compounds **3a**–**b** were isolated in 86–90% yield. Here too, acid-catalyzed isomerization with $BF_3$ or $ZnI_2$ dehydration gave the desired 1-substituted-2-tetralones **6a**–**b** in 94–99% yield.

The unexpected isolation of α-hydroxy benzoate esters during the course of our work prompted us to examine their chemistry as an alternate route to the title compounds. Upon base hydrolysis, the esters were converted to 1-methyl- and 1-phenyl-1,2-tetralindiol (**5a**–**b**). We then decided to examine their behavior toward acid conditions. When treated with $ZnI_2$ or $BF_3$, yields of **6a**–**b** ranging from 93–97% were realized. The ramifications of these results demonstrated that an *epoxide*

*intermediate was not necessary* in order to accomplish the desired 1,2-carbonyl transposition. In order to demonstrate this fact, the 1-substituted-$\Delta^1$-tetralins **2** were dihydroxylated with 2.5% osmium tetraoxide in aqueous *t*-butyl alcohol containing pyridine and using trimethylamine *N*-oxide as a co-oxidant affording the corresponding 1,2-tetralindiols **5** in 88–91% yield. Spectral comparison showed them to be identical with the diols formed by oxidation with *m*-chloroperbenzoic acid. Subsequent acid-catalyzed isomerization with zinc iodide or boron trifluoride gave the 1-substituted-2-tetralones **6a–b** in 93 to 97% yields.

We were able to extend this study to tetralone rings possessing electron-donating methoxyl groups. The 6,7-dimethoxytetralin series proved to be extremely sensitive to epoxidation by *m*-chloroperbenzoic acid, affording low yields of the epoxides and numerous by-products. Unlike their unsubstituted analogs, diols **5d–e** were found to dehydrate most smoothly in a benzene solution containing a catalytic amount of zinc iodide;[12] see the results shown in Tables 1 and 2. The dehydration method provided high yields of the 2-tetralones with no decomposition or colored by-products. The complete four-step sequence via the tetralindiols **5d–e** afforded the desired 2-tetralones **6d–e** in overall yields of 79–85%.[13]

Table 1
1- > 2-Tetralone transposition via epoxide method

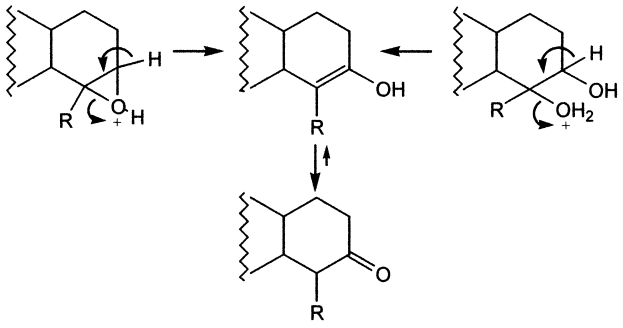
| Entry | R | R' | Yield(%) 2->3 | Method $BF_3$ Yield(%) 6 | $ZnI_2$ |
|---|---|---|---|---|---|
| a | H | Me | 90 | 97 | 99 |
| b | H | Ph | 86 | 94 | 95 |
| c | H | Bn | 96 | 98 | 99 |

Table 2
1- > 2-Tetralone transposition via diol method

| Entry | R | R' | Yield(%) 2->5 | Method $BF_3$ Yield(%) 6 | $ZnI_2$ |
|---|---|---|---|---|---|
| a | H | Me | 91 | 93 | 95 |
| b | H | Ph | 91 | 95 | 97 |
| c | H | Bn | 88 | 97 | 97 |
| d | OMe | Me | 90 | -- | 89 |
| e | OMe | Ph | 92 | -- | 97 |
| f | OMe | Bn | 91 | -- | 91 |

In conclusion, two efficient high-yielding methods for the preparation of 1-substituted-2-tetralones have been developed using well-known reactions. The 'epoxide' method was shown to be highly efficient but restricted to the synthesis of 1-benzyl-2-tetralone and 1-methyl-2-tetralone. On the other hand, the 'diol' method was universally more convenient for the preparation of all types of 2-tetralones, including the more sensitive 6,7-dimethoxytetralone series. Zinc iodide was uniquely suited for the selective dehydration of diols **5a–c** providing high yields of the desired 2-tetralones with neither decomposition nor colored by-products. In each case, the four-step sequences described here afforded the desired products in greater than 85% overall yields without

resorting to expensive reagents or tedious workup procedures. Mechanistically, it appears that diol dehydration and epoxide isomerization proceed through a common enol intermediate leading to the 2-tetralone (Scheme 2).




Scheme 2.

## Acknowledgements

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13. Representative procedures. **Epoxide method**: Solid zinc iodide (100 mg, 0.30 mmol) was heated under aspirator pressure at 120°C for a period of 1 h. After cooling, a solution of epoxide **3c** (210 mg, 0.89 mmol) in benzene (5 mL) was added to the zinc iodide. The mixture was stirred under reflux for 1 h, cooled to room temperature, and washed with water. After drying over magnesium sulfate, the solvent was removed affording **6c** (208 mg, 99%).

**Diol method**: Boron trifluoride etherate (2 drops) was added to a solution of diol **5c** (333 mg, 1.31 mmol) in ether (3 mL). The solution was stirred at 30°C for 20 min, washed with water and dried over magnesium sulfate. Evaporation of the solvent afforded a colorless oil which distilled at 127°C (750 mm) giving **6c** (301 mg, 97%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.40–2.54 (m, H-3, 2H), 2.62 (m, H-4, 1H), 2.83 (m, H′-4, 1H), 3.21 (ddd, J = 14.9, 10.1, 6.2 Hz, H-Bn, 2H), 3.74 (t, J = 6.2 Hz, H-1, 1H), 6.85–6.96 (m, Ar-H, 3H), 7.13–7.22 (m, Ar-H, 6H); $^{13}$C NMR (75 Hz, $CDCl_3$) $\delta$ 27.48, 38.51, 39.27, 55.19, 126.67, 126.89, 127.04, 127.91, 128.37, 128.80, 129.63, 136.61, 137.10, 138.39, 212.59; MS (*m*/*z*) 236 (M+); IR (neat) 1717 cm$^{-1}$ (C=O). Semicarbazone: mp 199–200°C. Anal. calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53. Found: C, 73.43; H, 6.57. Similarly, **6f** was produced in 91% yield by the diol method using zinc iodide: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.46 (ddd, J = 17.3, 9.2, 6.2 Hz, H-3, 1H), 2.59 (dt, J = 17.3, 4.2 Hz, H′-3, 1H), 2.65 (ddd, J = 15.6, 9.6, 4.9 Hz, H-4, 1H), 2.78 (ddd, J = 15.6, 6.4, 4.2 Hz, H′-4, 1H), 3.06 (dd, J = 13.2, 8.3 Hz, H-Bn, 1H), 3.20 (dd, J = 13.2, 4.9 Hz, H-Bn, 1H), 3.61 (dd, J = 8.3, 4.9 Hz, H-1, 1H), 3.63 (s, OMe, 3H), 3.88 (s, OMe, 3H), 6.21 (s, H-5, 1H), 6.63 (s, H-8, 1H), 6.88 (m, Ar-H, 2H), 7.17 (m, Ar-H, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 27.20, 38.80, 40.05, 54.86, 55.99, 56.10, 110.98, 112.09, 126.65, 128.24, 128.83, 129.80, 138.44, 147.60, 147.78, 212.92; MS (*m*/*z*) 296 (M+); IR (neat) 1700 cm$^{-1}$ (C=O). Semicarbazone: mp 189–191°C (dec). Anal. calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56. Found: C, 67.46; H, 6.65.