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Aromatic Annulation: Two New Methods for the Synthesis of Chiral Bicyclic Phenols

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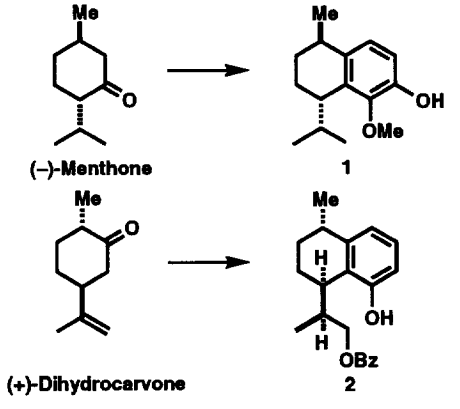
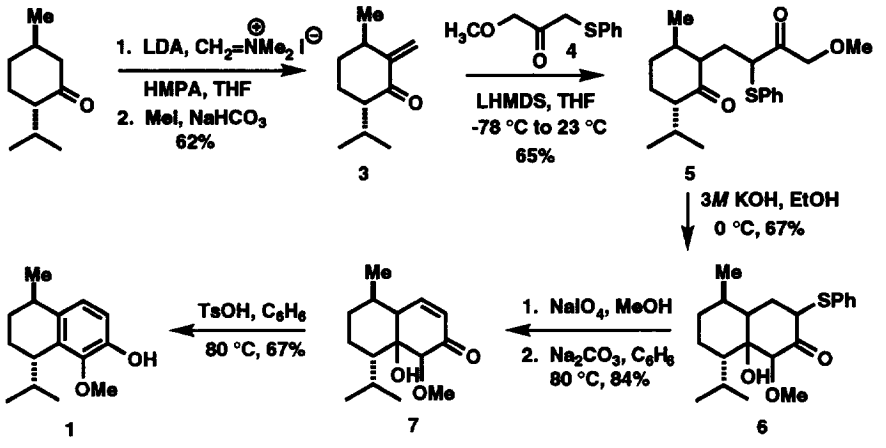
Summary: Two selective and mild aromatic annulation procedures are described for the synthesis of chiral substituted tetrahydronaphthalene derivatives from (–)-menthone and (+)-dihydrocarvone.

There have been recent developments in the methodology for the construction of chiral substituted tetrahydronaphthalene derivatives,[1] a type of structure found in various terpenoid natural products.[2] In general, there are two possible approaches for the synthesis of such fused ring structures. The most common strategy involves starting with an aromatic ring, attaching a carbon chain and cyclizing to form the hydroaromatic ring. The second approach, which consists of adding an aromatic ring to a non-aromatic chiral cyclic precursor,[3] is limited by a paucity of methods for aromatic annulation, most of which are applicable only to simple substituted cycloalkanones since epimerization of stereocenters represents a major problem. Herein, we report two effective methods for the synthesis of chiral substituted bicyclic phenols by aromatic annulation, one starting from (–)-menthone and the other from (+)-dihydrocarvone, as shown below.

We began our studies with the synthesis of fused catechol **1**, whose structure is closely related to the cadinane family of sesquiterpenes. This compound is not accessible through the use of the Takaki annulation method which leads to 7- or 8-substituted tetrahydronaphthalenes.[4] Our approach to the synthesis of the 5,6-disubstituted tetrahydronaphthalene system of **1** is shown in Scheme I. Methylenation of menthone was accomplished by treatment of the lithium enolate with Eschenmoser's salt followed by reaction of crude amine with MeI and elimination using 10% aqueous $NaHCO_3$ to give the α,β-unsaturated ketone **3** in 62% yield.[5] The ketone **4** was readily prepared in 88% yield by reaction of methyl methoxyacetate with phenylthiomethyllithium in

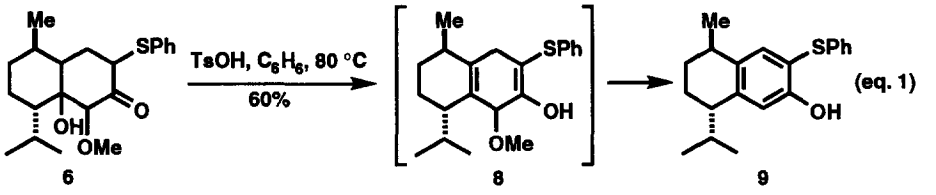




Scheme I. Aromatic annulation of (–)-menthone

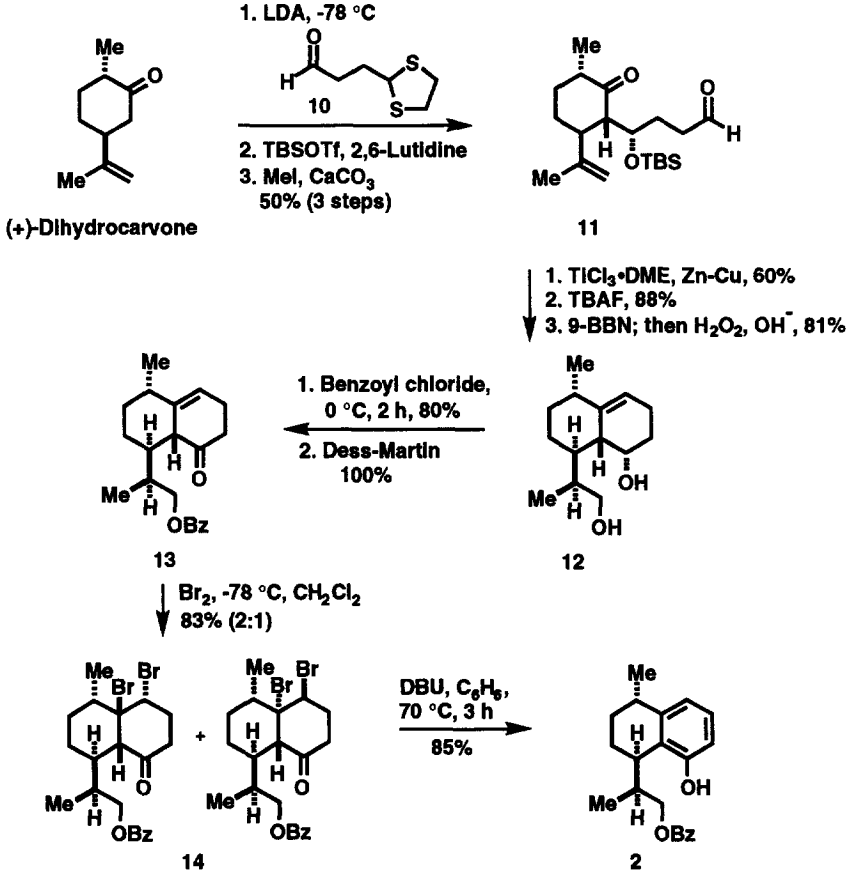
the presence of TMEDA at -78 °C. Treatment of ketone **3** with the lithium enolate of **4** at -78 °C, followed by warming to 23 °C afforded the desired 1,4-addition product **5** in 65% yield (as a separable 1.5 : 1 mixture of diastereomers). Exposure of the diastereomeric mixture **5** to 3*M* ethanolic KOH solution at 0 °C provided the cyclized product **6** in 67% yield. Conversion of **6** to the sulfoxide with $NaIO_4$ in MeOH–H_2O mixture at 23 °C for 24 h and subsequent heating to 80 °C afforded the unsaturated ketone **7** in 84% yield (1.5 : 1 mixture of isomers) which upon treatment with p-toluenesulfonic acid gave the desired tetrahydronaphthol **1** in 67% yield.[9] Interestingly, direct treatment of ketone **6** with p-toluenesulfonic acid in benzene at 80 °C afforded the 6,7-disubstituted tetrahydronaphthol **9** with preservation of the phenylthio substituent. We surmise that this product is formed via intermediate **8** (eq. 1).

The synthetic route for constructing the 5-substituted tetrahydronaphthalene derivative **2** from (+)-dihydrocarvone is shown in Scheme II. Aldol condensation between the lithium enolate of (+)-dihydrocarvone and aldehyde **10**[6] proceeded diastereoselectively and in 60% yield. The resulting aldol was protected as the *tert*-butyldimethylsilyl (TBS) ether using TBSOTf and 2,6-lutidine (-30 °C, 1 h, 97% yield). Deprotection of the dithioacetal with MeI and $CaCO_3$ in CH_3CN–H_2O at 50 °C for 7 h afforded the keto aldehyde **11** in 77% yield. Addition of **11** in DME to freshly prepared $TiCl_3$•DME, Zn–Cu at reflux temperature, dropwise over a period of 12 h afforded the reductive cyclization product in good yield[7] which upon TBS ether cleavage using $Bu_4N^+F^-$ in THF at reflux temperature for 12 h afforded the corresponding alcohol in 88% yield. Regioselective hydroboration of this product with 9-BBN (3 eq at 0 °C for 2 h) followed by basic hydrogen peroxide work up gave *diastereoselectively* diol **12** in 81% yield.[8] Selective protection of the primary alcohol as the benzoate ester followed by Dess-Martin oxidation (CH_2Cl_2, 23 °C, 1 h) afforded ketone **13** in 80% yield. Addition of Br_2 to a methylene chloride solution of benzoate **13** gave the dibromides **14** in excellent yield as a 2 : 1 mixture of diastereomers. Treatment of the mixture of dibromides with DBU in benzene at 70 °C resulted in



an excellent yield of aromatized product **2**.[9] The mildness of this annulation procedure and the facile construction of diastereomerically pure **2** are noteworthy.

In summary, two new and useful methods for direct benzannulation of (–)-menthone and (+)-dihydrocarvone which produce various enantiomerically pure tetrahydronaphthol derivatives have been developed. These products are valuable intermediates for the synthesis of complex natural products.[10]



Scheme II. Aromatic annulation of (+)-dihydrocarvone

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6. Aldehyde **10** was prepared in 4 steps from γ-butyrolactone according to the following sequence: (a) EtOH, H_2SO_4, 23 °C, 12 h. (b) PCC, NaOAc, 3 h. (c) ethanedithiol, BF_3•OEt_2, -78 °C. (d) DIBAL, CH_2Cl_2, -78 °C (55% overall yield).
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8. The diol **12** was oxidized to the corresponding lactone, the structure of which was established by X-ray crystallographic analysis.
9. The following spectroscopic data were obtained for the final aromatic annulated products.

   Compound 1. R_f 0.44 (20% EtOAc–hexanes); 400-MHz ^{1}H NMR ($CDCl_3$) δ 6.88 (d, J = 8.4 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 5.39 (s, 1 H), 3.74 (s, 3 H), 2.91 (m, 1 H), 2.69 (m, 1 H), 2.14 (m, 1 H), 1.94 (m, 1 H), 1.76 (m, 2 H), 1.27 (m, 1 H), 1.23 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H); 100-MHz ^{13}C NMR ($CDCl_3$) δ 146.5, 144.9, 136.5, 133.9, 122.8, 112.6, 60.6, 39.1, 31.5, 31.4, 29.3, 22.4, 21.4, 21.2, 19.0; IR (neat) cm^{-1} 1294, 1463, 2869, 2929, 3398, 3405, 3435; mass spectrum EI *m/z* (rel. intensity) 234 (25), 216 (25), 191 (100), 161 (40), 115 (25); mass calcd for $C_{15}H_{22}O_2$ 234.2620, found 234.2619.

   Compound 2. R_f 0.28 (20% EtOAc–hexanes); 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.94 (m, 2 H), 7.52 (m, 1 H), 7.41 (m, 2 H), 7.02 (t, J = 7.7 Hz, 1 H), 6.78 (d, J = 7.8 Hz, 1 H), 6.57 (d, J = 7.8 Hz, 1 H), 4.81 (s, 1 H), 4.28 (m, 2 H), 3.18 (m, 1 H), 2.88 (m, 1 H), 2.52 (m, 1 H), 1.88 (m, 3 H), 1.45 (m, 1 H), 1.24 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H); IR (neat) cm^{-1} 3413, 2930, 1718, 1694, 1274; mass spectrum (CI) *m/z* (rel. intensity) 325 (50), 270 (30), 203 (100), 161 (60); mass calcd for $[C_{21}H_{24}O_3+NH_4]^+$ 342.2069, found 342.2054.

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