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Synthesis of 5,6-Methylenedioxy-1-tetralone. An Aryl Grignard Approach from Guaiacol.

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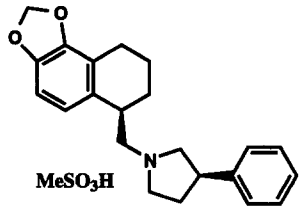
Abstract: A convenient synthesis of 5,6-methylenedioxy-1-tetralone (**1**) is described. The main features of this synthesis are the formation of **6** via a Grignard reaction using succinic anhydride followed by selective reduction and Friedel-Crafts cyclization to generate the desired tetralone **1**.

A novel polycylic compound, (±)-(1'R*,3R*)-3-phenyl-1-[1',2',3',4'-tetrahydro-5',6'-methylenedioxy-1'-naphthalenyl-methyl]-pyrrolidine methane-sulfonate (ABT-200, **2**), is an *alpha*-2 antagonist and possesses the additional property of norepinephrine uptake inhibition.[1] Having this profile of combined activities, this compound has potential utility in the treatment of depression.[1]



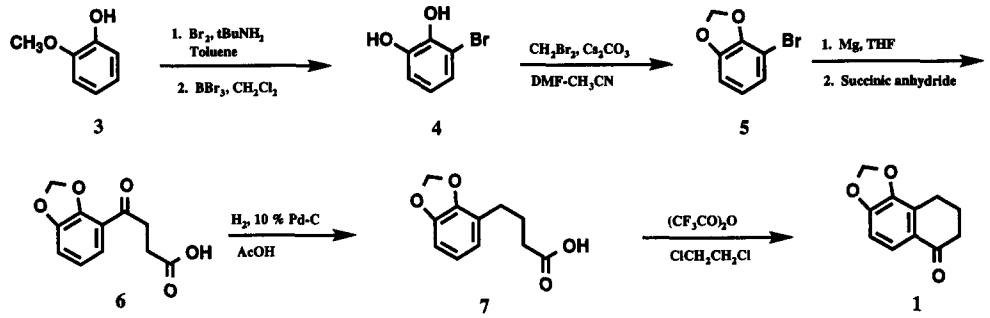
2

One of the key intermediates in the synthesis of ABT-200 is 5,6-methylenedioxy-1-tetralone (**1**). Although 5,6-dihydroxy-1-tetralone has been converted to **1**,[2] obtaining this catechol by demethylation of 5,6-dimethoxy-1-tetralone had the potential of generating oxidative impurities at a late stage in the synthesis. In addition, the reported syntheses of 5,6-dimethoxy-1-tetralone[3] are too costly and unamenable to large-scale production; therefore, alternate routes were investigated. The use of succinic anhydride for the preparation of α-tetralones has also been well-documented in the literature.[4] However, for aromatic compounds containing ortho-para-directing groups, acylation with succinic anhydride gives mainly or exclusively the para products, leading to the 4,5-substituted α-tetralones. In order to obtain the desired regioisomer, we sought to direct the initial acylation to afford an intermediate which would give the 5,6-substituted α-tetralone. We report herein a new, simple, inexpensive, and practical approach to the preparation of 5,6-methylenedioxy-1-tetralone (**1**) using readily available starting materials: guaiacol and succinic anhydride.

We initiated the synthesis by preparing 4-bromo-1,3-benzodioxole (**5**). Following the literature procedure,[5] guaiacol (**3**) was ortho-brominated to afford 2-bromo-6-methoxyphenol in a 60% yield. Using an excess of guaiacol (2.0 mole equivalents) minimized the formation of polybrominated products, which were otherwise difficult to separate during the distillation of the final product. Trace amounts of the para-brominated product, 3-bromo-6-methoxyphenol, were occasionally observed upon scale-up, but the related impurities were easily removed during the purification of **6**. Demethylation of 2-bromo-6-methoxyphenol went cleanly in three hours using 1.1 equivalents of 1.0 M boron tribromide in methylene chloride. The resulting 3-bromocatechol (**4**), without further purification, was converted to 4-bromo-1,3-benzodioxole (**5**) in a 87% yield using dibromomethane (2.0 mole equivalents) and cesium carbonate (2.0 mole equivalents).[2] The reaction was conducted in acetonitrile and dimethylformamide (9:1) at 80 °C for 1.5 hours. This reaction can also be carried out in dimethylformide (DMF) using potassium carbonate as the base with similar results; however, minimizing the amount of DMF in the reaction mixture simplified the isolation of **5**.

After synthesizing the bromide **5**, we turned our attention to the preparation of γ-oxo-1,3-benzodioxole-4-butanoic acid (**6**) via Grignard reaction. It has been reported that phenylmagnesium bromide adds to succinic anhydride at -78 °C affording 3-benzoylpropionic acid in good yield.[6] Only trace amounts of by-products resulting from over addition were observed. To use this approach in our synthesis, it is important that the generation of the Grignard reagent from **5** takes place under less extreme conditions.

Scheme 1



3 **4** **5** **6** **7** **1**

We found that the generation of the Grignard reagent from **5** went cleanly and efficiently at 20-25 °C. The formation of the Grignard reagent appeared to be quantitative based on the amount of unreacted bromide. The freshly generated Grignard reagent was added to a solution of succinic anhydride (1 mole equivalents) in THF at 5 °C. After stirring at room temperature overnight, γ-oxo-1,3-benzodioxole-4-butanoic acid (**6**) was isolated in 51% yield after base extraction.[7] The γ-keto acid **6** can be recrystallized from ethyl acetate and hexane. Selective reduction of the ketone in the γ-keto acid **6** was accomplished under catalytic hydrogenation conditions using 10% Pd-C at 40 psi of hydrogen. The reaction was run in acetic acid at 60 °C to afford 1,3-benzodioxole-4-butanoic acid (**7**) as a white solid in a 94% yield.[8] Friedel-Crafts acylation of **7** using trifluoroacetic anhydride (2.0 mole equivalents) in dichloroethane afforded the desired 5,6-methylenedioxy-1-tetralone (**1**) in an 86% yield after 1.5 hours. The tetralone was recrystallized from ethyl acetate and hexane to afford white crystals, mp. 136-137 °C.

In conclusion, we have developed a new, convenient and inexpensive synthesis of 5,6-methylenedioxy-tetralone (**1**). The synthesis was efficient, requiring only six steps and resulted in an overall yield of 22%. Also noteworthy was the direct incorporation of the functionalized, four-carbon appendage necessary for constructing the tetralone ring system.

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7. γ-Oxo-1,3-benzodioxole-4-butanoic acid (**6**): mp 144.5-146 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 12.16 (s, 1 H), 7.29 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.16 (dd, *J* = 7.6, 1.3 Hz, 1 H), 6.94 (dd, *J* = 8.3, 7.6 Hz, 1 H), 6.19 (s, 2 H), 3.17 (t, *J* = 6.4 Hz, 2 H), 2.57 (t, *J* = 6.4 Hz, 2 H). Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.84; H, 4.51.
8. 1,3-Benzodioxole-4-butanoic acid (**7**): mp 83.5-85.0 °C; ^{1} H NMR ($CDCl_3$) δ 11.02 (br s, 1 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.69 (dd, *J* = 7.5, 1.7 Hz, 1 H), 6.65 (dd, *J* = 7.5, 1.7 Hz, 1 H), 5.92 (s, 2 H), 2.65 (t, *J* = 7.5 Hz, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 1.97 (q, *J* = 7.5 Hz, 2 H). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.14; H, 5.86.

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