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Generation and Intramolecular Cycloaddition of *o*-Quinonemethides in Protic Solvent. An Efficient Synthesis of (–)-*trans*-Hexahydrocannabinol

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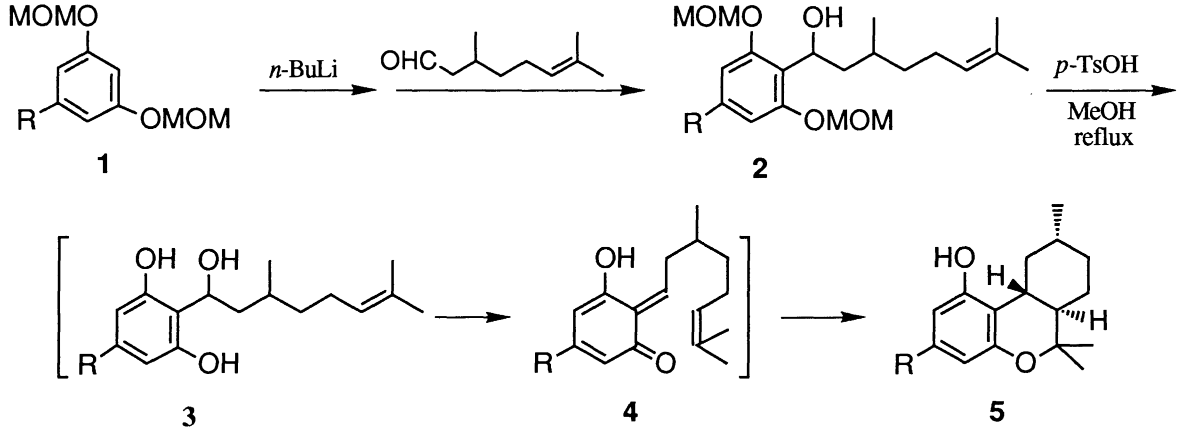
A very facile and efficient synthesis of (–)-*trans*-hexahydrocannabinol was achieved through the intramolecular Diels-Alder reaction of an *o*-quinonemethide derived from 2-(1-hydroxycitronellyl)olivetol 1,3-bismethoxymethyl ether in methanol.

o-Quinonemethides[1)] are reactive intermediates useful in organic synthesis, and they undergo di- or trimerization, [1,5] or [1,7] hydrogen shifts to give chromenes under heating conditions, inter- and intramolecular Diels-Alder reaction to furnish chromans, and very easy Michael addition of protic compounds such as methanol.[2)] Therefore most reactions of *o*-quinonemethides have been conducted in aprotic solvents. Recently we reported[3)] a generation of *o*-quinonemethides from *o*-[1-(alkylthio)alkyl]phenols in THF or benzene under mild conditions and applied the reaction to the three-step synthesis of (±)-*trans*-hexahydrocannabinol (HHC) (**5b**).

We wish to report here a facile preparation of *o*-quinonemethides from protected phenols, their selective intramolecular cycloaddition reaction in methanol, and application of the reaction to the short synthesis of (–)-*trans*-HHC (**5c**).[4)]

In a preliminary experiment, substituted resorcinol **2a**, prepared from resorcinol 1,3-bismethoxymethyl ether (**1a**) by the published method[5)] in 78% yield, was heated in methanol at reflux for 18 h in the presence of *p*-toluenesulfonic acid (0.1 equiv.) to afford chroman **5a** as a single stereoisomer in 80% yield.

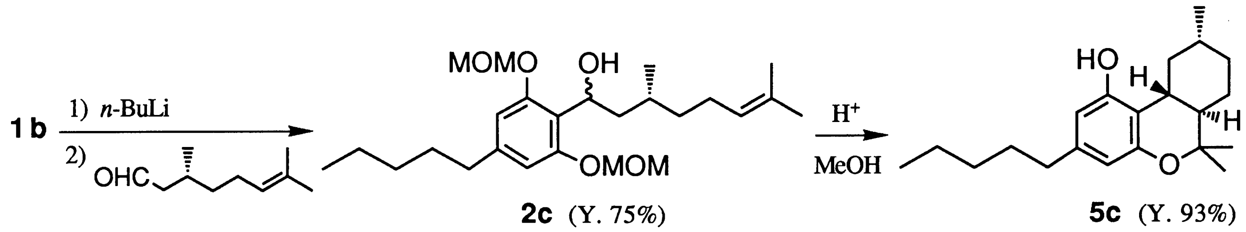


a: R = H
b: R = n-C_5H_{11}

It is noteworthy that deprotection,6) a sequence of dehydration, and intramolecular cycloaddition took place cleanly in one flask and addition of methanol to the *o*-quinonemethide **4a** was never detected.

In comparison, saligenine (2-hydroxymethylphenol) was treated with styrene (44 equiv.) in methanol in the presence of *p*-toluenesulfonic acid at reflux for 3 h to give 2-phenylchroman (17% yield) and 2-methoxymethylphenol (61% yield), indicating the preferential addition of methanol to the *o*-quinonemethide.

We then applied the above reaction to the synthesis of **5c** from olivetol 1,3-bismethoxymethyl ether (**1b**).7) **1b** was reacted with butyllithium in hexane in the presence of *N,N,N',N'*-tetramethylethylenediamine (2 equiv.) to afford **2c**7) in 75% yield8) after condensation with (+)-citronellal.9) The treatment of **2c** with *p*-toluenesulfonic acid (0.5 equiv.) in methanol at reflux for 6 h afforded **5c** $[\alpha]_D$ −98.6° (*c* 0.45, $CHCl_3$)10) in 93% yield.



In conclusion, a facile preparation and selective *intra*molecular cycloaddition of *o*-quinonemethides has been achieved by starting from *o*-substituted phenol methoxymethyl ethers in methanol at reflux.

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References

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4) For the total synthesis of optically active HHC, see: a) L,-F. Tietze, G. von Kiedrowski, and B. Berger, *Angew. Chem., Int. Ed. Engl.*, **21**, 221 (1982); b) J. P. Marino and S. L. Dax, *J. Org. Chem.*, **49**, 3671 (1984); c) G. Casiraghi, M. Cornia, G. Casnati, G. G. Fava and M. F. Belicchi, *J. Chem. Soc., Chem. Commun.*, **1986**, 271.
5) J. J. Talley, *J. Org. Chem.*, **50**, 1695 (1985).
6) Talley was unsuccessful in direct deprotection of **2a** with a number of acidic and basic reagents (Ref. 5).
7) All the new compounds were characterized by IR and ^{1}H-NMR spectroscopy.
8) When *N,N,N',N'*-tetramethylethylenediamine was not used the yield was very low: the reaction of **1b** with butyllithium in ether followed by addition of (±)-citronellal afforded **2b** in 36% yield.
9) (+)-Citronellal, $[\alpha]_D$ +14.1° (*c* 1.04, $CHCl_3$), was obtained via the oxidation of (+)-citronellol (98% e.e.).
10) The reported specific rotation values are: $[\alpha]_D$ −93.6° (*c* 0.7, $CHCl_3$) (Ref. 4a); $[\alpha]_D$ −73.9° (*c* 0.014) (Ref. 4b); $[\alpha]_D$ −73.2° (*c* 1, $CHCl_3$) (Ref. 4c).

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