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A CONVENIENT, PRACTICAL SYNTHESIS OF SUBSTITUTED RESORCINOLS· SYNTHESIS OF DB-2073 AND OLIVETOL* [1]

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Abstract: A wide variety of easily accesible 1,3-cyclohexanediones are readily transformed to substituted dimethyl resorcinols with iodine and methanol

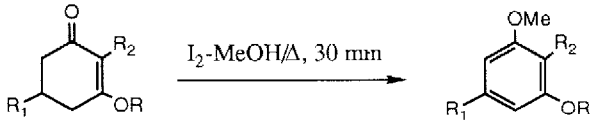
In a recent letter the aromatization of a few Hagemann's esters to p-methoxybenzoates, and to the aryl portion of mitbemycin β_3 using iodine and methanol was described [2] In this article, the protocol is utilized in the synthesis of 2- and 5-substituted resorcinols The substituted resorcinol[3] unit is a basic building block of a large number of valuable naturally occuring polyketide metabolites [4] Five-substituted resorcinols have gained importance in recent years as starting materials/intermediates for the synthesis of cannabinoids[5] and benzochroman derivatives,[6] which possess a wide range of physiological and pharmacological properties Long chain 5-alkyl resorcinols have been successfully utilized by Hecht's group as ideal models for sequence-selective DNA strand scissions [7]

In recent years Danheiser et al have developed an elegant regio-controlled annulation approach to highly substituted resorcinols based on a one step thermal/photochemical combination of alkynyl ethers and vinylketenes derived from either cyclobutenenones[8a-c] or α,β–unsaturated α'-diazo ketone [8d-e] Transition metals have also been used to isomerize 1,3-cyclohexanediones to resorcinols [9]

Our approach to the synthesis of substituted resorcinols involves the use of easy to handle reagents in an *inexpensive, high-yielding*, process, and hence a *practical* synthesis from readily accessible 1,3-cyclo hexanediones The basis of our work is Tamura's approach to highly susbtituted anisoles by aromatization of cyclohexenones using iodine and methanol at reflux [10] In all case, aromatization was completed in 30 minutes instead of the 3 hours required in Tamaru's cases

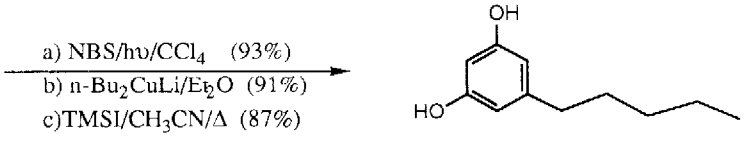
Aromatization of a variety of 1,3-cyclohexanediones gave high yields of 1,3-dimethyl resorcinols which are listed in Table I [11] The products of entries 1 to 4 are also accompanied by trace amounts of the monomethyl resorcinols The formation of dimethyl resorcinols can be rationalized by nucleophilic 1,4-addition-elimination of methanol to the enol form of the cyclohexanedione, thereby replacing the -OH group by -OMe group prior to aromatization The aromatized product (10) is an important building block in the synthesis of leukotriene antagonists [12] The yields of the monomethyl resorcinols can be increased partly by acetylation and completely by silylation of the enolic -OH group, prior to aromatization (see entries 5 and 6) The minor product (11) arises from aromatization of the enol acetate (5) followed by *in situ* hydrolysis of the acetate The requisite precursors for aromatization are all prepared via a tandem Michael- Claisen reaction between the appropriate methyl vinyl ketones and esters using ethanolic sodium ethoxide as a base

Table 1



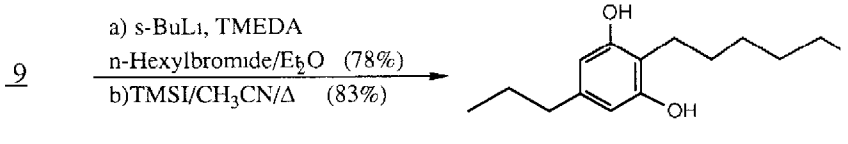
1	R = R_2 = H, R_1 = Me	7	R = R_2 = H, R_1 = Me	87%
2	R = R_2 = H, R_1 = Ph	8	R = R_2 = H, R_1 = Ph	93%
3	R = R_2 = H, R_1 = n-Pr	9	R = R_2 = H, R_1 = n-Pr	86%
4	R = R_1 = H, R_2 = Me	10	R = R_1 = H, R_2 = Me	83%
5	R = Ac, R_1 = Ph, R_2 = H	11	R = R_2 = H, R_1 = Ph (8 + 11 = 7 3)	90%
6	R = TBS, R_1 = Me, R_2 = H	12	R – TBS, R_1 – Me, R_2 = H	84%

Scheme 1



13 Olivetol

Scheme 2



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The aromatized product (7) has been transformed via allylic bromination, cuprate displacement and demethylation to olivetol (13),[13] thereby constituting a formal synthesis of Δ^9-tetrahydrocannabinoids (Scheme1) This three step protocol can be utilized for the convenient synthesis of long chain 5-alkyl resorcinols[7a] and other analogs of olivetol [13f]

Directed metallated alkylations of product (9),[14] followed by TMSI mediated demethylation results in a practical synthesis of the antifungal antibiotic DB-2073 (14) (Scheme 2) [15]

The preparatively useful part of this report lies in the generality and brevity of this approach Additionally, the high yields and the use of easy to handle iodine makes it one of the most efficient and practical syntheses of highly substituted resorcinols The application of this methodology to other natural product synthesis is in progress and will be reported in due course

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* The author would like to dedicate this publication to the memory of a close friend and colleague, Professor Emil R Kofl, who passed away on February 17, 1989

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1 Part of this work was presented at the 199th ACS National Meeting, Boston, ORGN, 459, 22-27 April 1990 Address all correspondence to the author at Bristol Myers Squibb, One Squibb Drive, P O Box 191, New Brunswick, NJ 08903-0191

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15 The author would like to thank Prof R L Danheiser, Department of Chemistry, Massachussetts Institute of Technology for a generous supply of DB-2073 The DB-2073 prepared by us is identical in all respects, ^{1}H NMR, ^{13}CNMR, IR, MS, TLC to the authentic sample

General Procedure for aromatization. To a solution of 2 mmol of the 1,3-cyclohexanedione in 4 mL of methanol were added 4 mmol of iodine beads and stirred until they are dissolved The solution was refluxed under nitrogen for 30 min, and the methanol was removed *in vacuo* The residue was dissolved in benzene and washed with a saturated solution of sodium bicarbonate, sodium thiosulfate, 5% sodium hydroxide, and water before drying over magnesium sulfate The benzene was removed *in vacuo* to give an oily residue which after flash chromatography on silica gel (ether/hexane 1 9) afforded the aromatized product

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