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A NEW ROUTE TO 3a,8a-DIHYDROFURO[2,3-b]BENZOFURANS †

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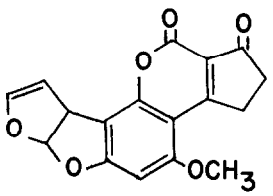
The 3a,8a-dihydrofuro[2,3-b]benzofuran function occurs in several mold toxins, namely, the aflatoxins, sterigmatocystin, and versicolorin A[1]. The toxic and carcinogenic properties of aflatoxin B_1 (1) are markedly dependent on the integrity of this function[2]. Buchi and co-workers[3] have devised a proficient synthesis for a 3a,8a-dihydrofuro[2,3-b]benzofuran (2b) as an intermediate in their ingenious construction of aflatoxin B_1. Since the system 2a and substituted



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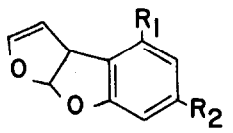


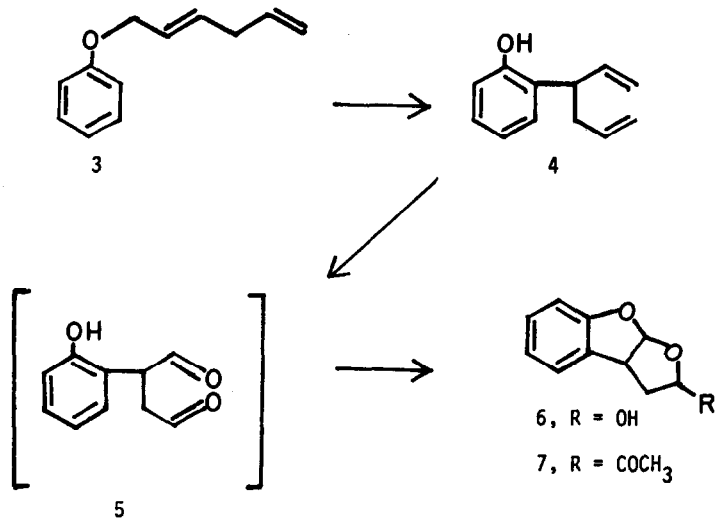
2a, $R_1 = R_2 = H$

2b, $R_1 = OCOCH_3$; $R_2 = OCH_3$

forms are desired for biological testing, we investigated an alternate route to 2a.

Alkylation of phenol in glyme with 1-bromo-2,5-hexadiene[4] in the presence of potassium carbonate gave the primary ether 3. Fortunately, 3-bromo-1,5-hexadiene with phenol under the identical conditions yields the same ether, avoiding the necessity of separating the secondary bromide which accompanies its allylic isomers. When a mixture containing 19% of the secondary

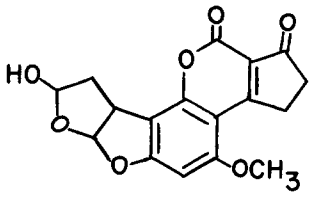
bromide is used, the ether produced contains less than one percent of its secondary isomer. The isomeric secondary ether can be preferentially formed by heating the phenol with neat secondary bromide.



Borontrichloride catalyzed Claisen rearrangement[5] of the cold ether 3 leads to 4, o-(3-hexa-1,5-dienyl)phenol, in 49% yield. The only side product from the rearrangement is the expected ether cleavage product, phenol. The traditional conditions for the Claisen rearrangement, heating (200° C) neat or in N,N-dimethylaniline, gave several unidentified products. Among these is probably a Cope rearranged product of 4 and the abnormal Claisen rearrangement product[6].

Oxidative cleavage of the two double bonds in 4 with osmium tetroxide-sodium periodate yields the hemiacetal 6, (ir(KBr pellet) 3470, 2940, 1601, 1489, 1257, 1222, 1190, 752, 744 cm^{-1}; λ max (EtOH) 278(2290), 273(2280), 115(6230); nmr ($CDCl_3$, δ) 7.16(4H, m), 6.45(1H,d,J=6H_3), 5.70 (1H, m), 4.15(1H, m), 2.50(2H, m; 1H, OH); mass spectrum 178(parent, 7%), 160(31), 147(30), 132(25) 131(100), 123(28), 103(29), 91(40), 89(27), 77(51), 51(31), 39(31). Hemiacetal 6 is easily converted to its more stable acetate 7.

Concomitant formation of 6 from 5 is expected. 2-Allylphenol when cleaved by osimum tetroxide-sodium periodate spontaniously forms 2,3-dihydro-2-hydroxybenzofuran, which is easily converted to benzofuran by the action of phosphoric acid. Buchi[3b] theorized that 9 was formed upon basic treatment of the hemiacetal of aflatoxin B_1, 8, as evidenced by a bathochromic shift typical of a phenoxide in the ultraviolet spectra and by racemization of the natural material. Acidification of



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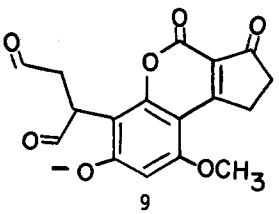

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9 regenerated optically inactive 8. Also treatment of 1 with aqueous acid, conditions which should establish a preferred equilibrium form among acetals and hemiacetal, produces 8[3,7].

Final confirmation of the structure of 6 and 7 is attained via synthesis by an alternate route, the procedure used by Buchi[3] in his construction of 2b during his synthesis of Aflatoxin B_1, 1. Pyrolysis of 7 according to Buchi[3] yields 2a.

Acknowledgment

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