A SYNTHETIC SCHEME FOR THE PREPARATION OF CARBON LABELLED FURAN COMPOUNDS

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SUMMARY

A facile synthesis for the efficient incorporation of ^{14}C or ^{13}C into trisubstituted furan compounds has been elaborated. 3-Methyl-4,5,6,7-tetrahydrobenzofuran was prepared in five steps from methyl- and ethyl-2-oxo-1 cyclohexanecarboxylate with overall yield of 65%. Radioactive label was nearly quantitatively incorporated. One new compound, 7, has been prepared in elaborating the synthetic sequence.

Key Words: Carbon-14 or 13, Trisubstituted Furans, 3-Methyl-4,5,6,7-tetrahydrobenzofuran, Synthesis.

INTRODUCTION

Furanosesquiterpenes have been shown to be toxic constituents of the plant *Tetradymia glabrata* (1). Other furan compounds such as furosemide (2), ipomeanol, (3) and aflatoxins (4) are also known to possess physiological toxicity. In several cases metabolism by the hepatic system increases the toxicity of these compounds (5). In order to identify the products of metabolism, it was necessary to synthesize model furan compounds with ^{13}C or ^{14}C labels in appropriate positions. In this article the facile synthesis of radiolabelled 3-methyl-4,5,6,7-tetrahydrobenzofuran, 5, is reported.

Numerous schemes for the synthesis of trisubstituted furan compounds like menthofuran have been reported since 1937. None of these were satisfactory for our purposes because the yields were 30% or less and most were initiated from pulegone or isopulegone (6). Wenkert (7) initiated the synthesis at an

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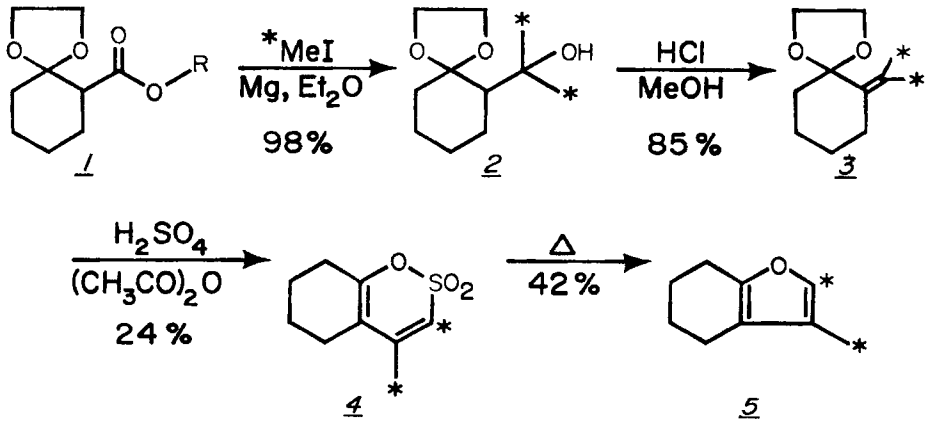
appropriate stage, but yields were unsatisfactory. Takeda (8) described an elegant synthesis for menthofuran with high yields (75%) but it was less suitable for producing labelled compounds.

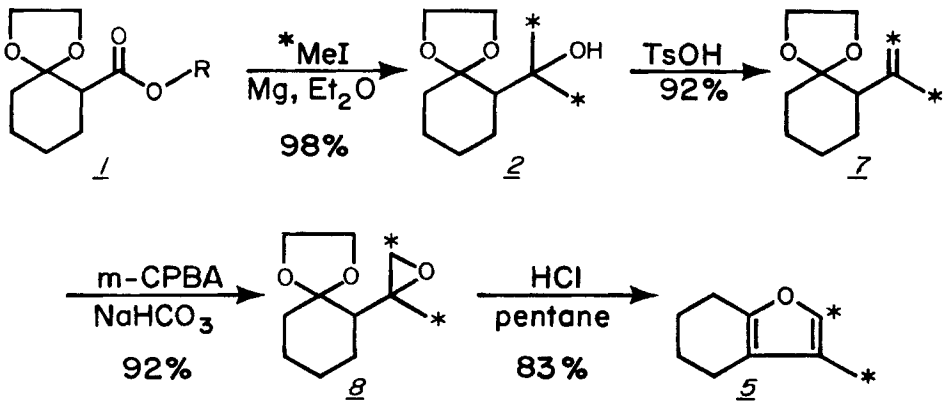
Two synthetic sequences are reported herein and shown as Schemes 1 and 2.

Scheme 1



In the first sequence unlabelled 5 was prepared in 42% yield. The early synthetic steps are very efficient but the final steps, those preparing the sulfonate and its subsequent thermal decomposition (9) are very inefficient. The better reaction sequence for our labelling requirements (Scheme 2) utilized an epoxide intermediate to form the furan moiety in excellent yields (10).

Scheme 2



This five step procedure not only provides a reasonable yield of trisubstituted furan (65%) but also accommodates an efficient method for either ^{14}C or ^{13}C incorporation. The Grignard reaction was nearly quantitative (98%) and subsequent steps had a 70% overall yield.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on a Bruker WM 250 MHz spectrometer. Mass spectra were obtained from a Varian Mat CH-5 spectrometer. A Beckman LS-100 scintillation counter was used. Elemental analyses were performed by the University of Idaho. 2-Oxo-1-cyclohexanecarboxylate was obtained from Aldrich as a mixture of ethyl and methyl esters (60:40, respectively).

Scintillation experiments. The scintillation solution consisted of 2,5-diphenyloxazole (1.9962g) and 1,4-bis-2-(5-phenyloxazolyl)benzene (0.0250g) diluted to 500 ml in toluene. Sample (1μl) was injected into 15 ml scintillation solution for counting. Counts were corrected to a standard sample.

Preparation of Ketal 1. A solution of methyl- and ethyl-2-oxo-1-cyclohexanecarboxylate (19.40g, 118 mmol, 40% methyl ester), ethylene glycol (8.50g, 137 mmol) and p-toluenesulfonic acid in 80ml benzene was refluxed with a Dean-Stark water trap until no more water separated. The reaction mixture was neutralized with sodium ethoxide, washed with water and brine and then dried over $MgSO_4$. Benzene was removed by rotary evaporation. The resulting yellow liquid was distilled giving 22.18g (90%) of 1: bp 80-90° (1mm) [lit (11) bp 120-124° (8mm)].

Preparation of Alcohol 2. For ^{14}C incorporation 0.71mg (250 μCi) of $^{14}CH_3I$ was combined with 20.95g of cold CH_3I and dissolved in 60 ml of ether. To this solution 3.5 g (0.144 mol) of Mg turnings were added and the mixture refluxed for 30 minutes. Subsequently, 15.20 g (0.073 mol) of ketal-ester 1 in ether was added dropwise with stirring over a period of 30 minutes at room temperature. This solution remained as such for an additional 3 hours at which time 14g of NH_4Cl in 40 ml of ice water was added. The ether layer was separated and the aqueous solution was washed 3 times (25 ml) with fresh ether. The combined ether

fractions were dried with Na_2SO_4, filtered and the solvent removed by rotoevaporation. Distillation of this yellow oil afforded 14.1g (96.6% yield) of a colorless liquid: bp 135-137°C (16mm) [lit.(11) bp 160-162°(20mm)]. IR(neat) 3450cm^{-1}; ^{1}H NMR (CCl_4)ppm 4.25(1H,s), 3.95(4H,s) 2.15-2.35(1H,m), 1.30-2.00(8H,m), 1.15(3H,s), 1.05(3H,s); Mass spectrum M^+ 200 m/e. Activity 19.68 μCi/g.

Preparation of Alkene 7. A solution of 2 (5.01 g, 25.1 mmol) and 0.215 g p-toluenesulfonic acid was refluxed with a Dean-Stark water trap until no more water separated (≅8 hrs). The reaction mixture was washed with 20 ml 5% $NaHCO_3$ solution and brine and dried over $MgSO_4$. Removal of solvent gave a yellow oil which was chromatographed on 40 g silica gel [eluent was hexane-ether (20:1)] yielding 4.25 g of 7 (92%) as a colorless liquid: bp 94-95° (11 mm); IR (neat) 3020,1650,1445,1155,1090,1045 cm^{-1}; ^{1}H NMR ($CDCl_3$)ppm 1.8 (3H,s), 1.2-2.5 (9H,m), 3.8 (4H,s), 4.8 (2H,s); ^{13}C NMR ($CDCl_3$)ppm 146.1, 113.4, 111.1, 65.1, 65.0, 52.5, 37.0, 30.2, 25.9, 24.3, 23.7; mass spectrum M^+ 186 m/e; Anal. calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95, found C, 72.56; H, 10.04.

Epoxidation of Alkene 7. m-Chloroperbenzoic acid [4.03g, 20 mmol (80-90% peracid)] was added to 100 ml CH_2Cl_2 with stirring. After dissolution of the peracid, $NaHCO_3$ (2.0 g) was added and the solution was cooled to 0°. A solution of 7 (1.94 g, 10.4 mmol) in 10 ml of CH_2Cl_2 was added dropwise. The reaction mixture was stirred at 0° for 1 hr. The solution was washed with 10% $Na_2S_2O_3$ (20 ml), 5% NaOH (40 ml) and brine and then dried over $MgSO_4$. After solvent was removed, the yellow oil was chromatographed on 5 g silica gel [eluted with hexane-ether (10:1)] yielding 1.86 g 8 (92%) as a colorless liquid: IR (neat) 1720, 1160, 1095, 1045, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$)ppm 3.95 (4H,s), 2.3-2.9 (2H,m); ^{13}C NMR ($CDCl_3$)ppm 109.7 64.3, 64.0, 55.9, 53.2; mass spectrum M^+ 198 m/e.

Cyclization of 8 to 3-methyl-4,5,6,7-tetrahydrobenzofuran 5. Epoxide 8 (3.45 g, 17.4 mmol) was dissolved in 50 ml pentane and 25 ml aqueous HCl (2M) was added. The resulting mixture was stirred vigorously for 2.5 hrs. The layers were separated and the aqueous layer was extracted four times with 20 ml pentane fractions. The combined pentane layers were washed with 5% $NaHCO_3$ (25 ml

portions) and brine, and then were dried over $MgSO_4$. After removal of solvent, the yellow oil was distilled to yield 1.97 g (83%) of furan 5, a colorless liquid: bp 69-71° (10mm) [lit. (8) bp 110° (13mm)]; IR and ^1H NMR data were identical to those reported in the literature (9); ^{13}C NMR ($CDCl_3$) ppm 151.0, 136.8, 119.9, 117.95, 34.8, 23.4, 23.1, 20.6, 8.1; mass spectrum, M^+ 136m/e. Activity was 20.26 μCi/g.

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