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AN UNEXPECTED PERICYCLIC REACTION BETWEEN PROPIOLIC ESTER AND A 2-VINYL BENZOFURAN[#]

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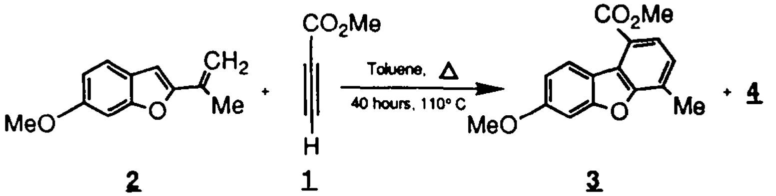
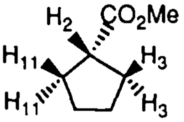
Abstract:
A 2:1 adduct of hitherto unknown structure results from heating methyl propiolate 1 and 2-isopropenyl-6-methoxybenzofuran 2. We describe a series of chemical and NMR spectroscopic studies which elucidate the structure of this material, and propose a mechanism for its formation.

Several years ago, the thermal reaction of methyl propiolate 1 and 2-isopropenyl-6-methoxybenzofuran 2 ($C_{12}H_{12}O_2$) was reported[2]. In addition to the expected dibenzofuran 3, ($C_{16}H_{16}O_4$) there was obtained a high-melting crystalline solid 4, ($C_{20}H_{20}O_6$) whose spectral and analytical data suggested a 2:1 adduct between the reagents. An improved synthesis[3], modelled after Ref. 4 proceeded in greater than 50% yield, and allowed further spectroscopic analysis of this adduct to be performed.



Scheme 1



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This earlier work demonstrated that 4 possessed the intact aromatic ring present in 2, three *O*-methyl groups, an isolated *C*-methyl group, and five additional protons whose chemical shifts and coupling pattern were suggestive of a substituted cyclopentane (fragment 5). However, no convincing structure was proposed.

The present work entails a combination of isotopic labelling studies and two dimensional nmr and cmr experiments which define the structure of this 2:1 adduct 4 as that shown below, and proposes a mechanism for its formation. From the 300 MHz ^1H nmr spectrum, Fig. 1, there is a methine proton H_2 whose downfield (δ 3.48) chemical shift suggests that it is α to an ester carbonyl group. This proton also appears to be coupled vicinally to the less-shielded (but not the more-shielded) proton in each of two adjacent methylene groups, supporting substructure 5. This assignment is reinforced by the 2-D (^1H-^1H) and (^1H-^{13}C) correlation spectra, as well as being fully consistent with the interpretation of a series of nuclear Overhauser enhancement experiments (data not shown). Chemical shift information is summarized in Table 1.

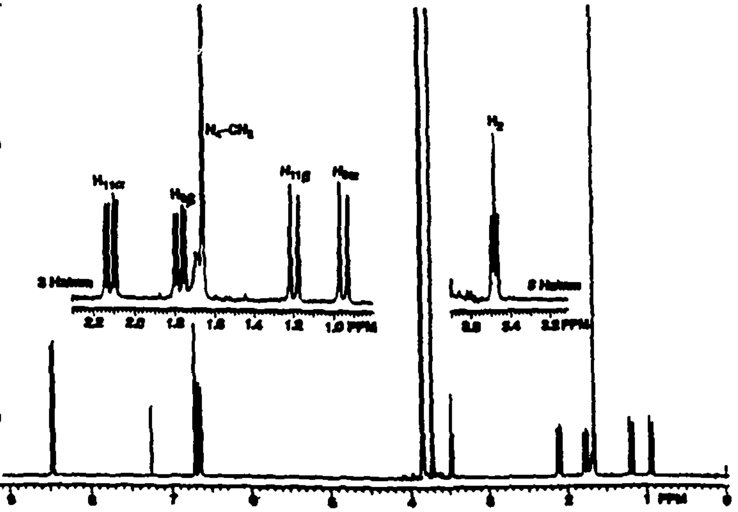
[#] This paper is dedicated to Prof. E. Grunwald on the occasion of his retirement.

Table 1. Assignments* of ^{1}H and ^{13}C NMR Chemical Shifts†

Carbon No.^{13}	C Shift	^{1}H Shift
1	116.2	
1-CO_2Me	165.3	
2	31.8	3.48 (*t*, 4.7)
3	34.2	0.94 (*d*, 11.2) 1.77 (*dd*, 11.2, 4.7)
4	32.7	
4a	80.1	
4-CH_3	9.9	1.66 (*s*)
5a	163.7	
6	96.0	6.72 (*d*, 2.0)
7	166.5	
8	109.9	6.66 (*dd*, 8.0, 2.0)
9	128.8	8.48 (*d*, 8.0)
9a	115.2	
9b	142.5	
10	35.9	
10-CO_2Me	169.5	
11	29.9	1.19 (*d*, 12.6) 2.11 (*dd*, 12.6, 4.7)
OCH_3	51.4	3.83 (*s*)
	51.8	3.71 (*s*)
	55.7	3.86 (*s*)

* Assignments were made on the basis of APT, 2D (^{1}H-^{1}H) and 2D (^{13}C-^{1}H) techniques. † Chemical shifts are in ppm (δ) with reference to internal standard TMS.

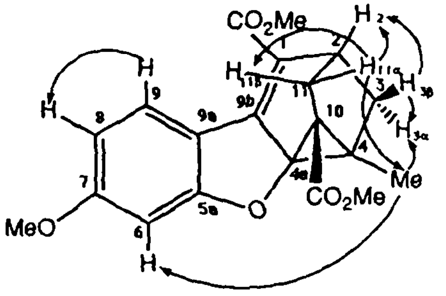
Fig. 1. 300 MHz ^{1}H NMR Spectrum of **1** in $CDCl_3$



An APT experiment identified the quaternary carbons separating the assignable aromatic positions from the upfield aliphatic part of the molecule, so a series of selective INEPT[5] experiments was performed in order to glean the two- and three-bond connectivities of these carbons relative to the upfield aliphatic protons. The results of those studies are summarized in Table 2. Due to the geometric constraint imposed by the tricyclo[3.2.1.0^{2,7}]octane ring system on the dihedral angles in the molecule, it is noteworthy that each geminal proton is transferring polarization to a different set of quaternary carbons. Analysis showed connectivity of all five cyclopentyl protons to vinyl carbon 1. There are additional two-bond polarization transfers for all the aliphatic protons. The anomalous chemical shift of $\underline{H}_2$ (δ 3.48 ppm) is due to that bridgehead proton being locked in the deshielding cones of the conjugated Δ_{9b-1} olefin and ester carbonyl.

Table 2. Summary of Selective INEPT Experiments*

Carbon No.	^{13}C Shift	$H_{3\alpha}$	$H_{11\beta}$	$H_{4\text{-}Me}$	$H_{3\beta}$	$H_{11\alpha}$	H_2
1	116.2	++	++		++	++	++
1-$\underline{C}O_2$	165.3						++
2	31.8	+			+	+	
3	34.2		+	+			
4	32.7	+	++	++	+		+
4-$\underline{C}H_3$	9.9				+		
4a	80.1	+	+	++	++	++	
9b	142.5						++
10	35.9	++	++	++		+	+
11	29.9	+					



Nuclear Overhauser Effects; Arrows indicate positive NOE's

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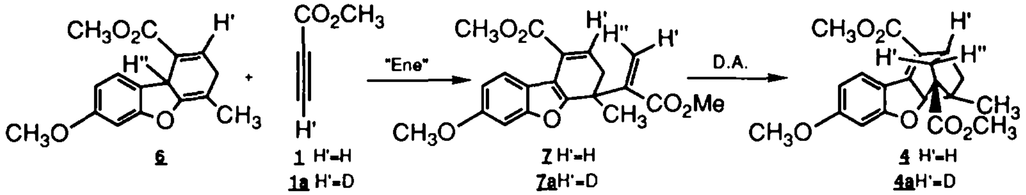
Final corroboration of the structural assignment was made by a 100 MHz 2-D carbon-carbon correlation (INADEQUATE)[6] experiment involving 1.3 grams of compound **4**, and 70 hours of acquisition time. Analysis of the results so obtained (data not shown) allows only the structure shown above for **4**, one which is fully consistent with all the data. This structure, dimethyl 3,4-dihydro-7-methoxy-4-methyl-2$\underline{H}$-2,4,4a-ethanyl-ylidine dibenzofuran-1,10-dicarboxylate, comprises a new ring system. Regarding the mechanism for its formation, the presence of a cyclopropane suggests a di-π methane or arene-olefin process. However, the most plausible mechanism (shown in Scheme 2) is that the transiently formed 1,4-diene intermediate **6** is intercepted by excess **1** *via* an "ene" reaction to generate the 1,3-diene **7**. This latter then undergoes an intramolecular Diels-Alder reaction to yield the observed byproduct **4**.



Scheme 2

This postulate predicts that ^{13}C specifically incorporated into the methylene group of starting material **2** will appear exclusively at carbon 3 in the product **4**, and that large one bond couplings will be seen for protons $\underline{H}_{3\alpha}$ and $\underline{H}_{3\beta}$ (0.94 and 1.77 ppm), with small three bond couplings to $\underline{H}_{11\beta}$ (1.19 ppm) and to the methyl group protons $\underline{H}_{4\text{-}CH_3}$ (1.66 ppm). $^{13}CH_2P(C_6H_5)_3$, prepared from the commercially available phosphonium salt, was reacted with 2-acetyl-6-methoxybenzofuran to give **2** isotopically labeled in the methylene position. Reaction with excess **1** and isolation of labeled **4** gave the predicted coupling pattern[7], and supports the conclusions derived from the selective INEPT studies.

As this mechanism further requires that specific deuteration at the β-position of starting material **1** will incorporate two labels, replacing $\underline{H}_2$ and $\underline{H}_{11\beta}$ (3.48 and 1.19 ppm), deuterated methyl propiolate, **1a**, was prepared from the carbanion of **1** following the protocol in Ref. 8, and was reacted with **2**. The resultant **4a**, obtained with about 65% isotopic substitution at the propiolate-derived positions, shows a marked diminution of these two signals in the ^1H nmr spectrum, as well as simplification of the multiplicities of the protons to which they are coupled. Deuterium nmr shows incorporation exclusively at these two positions, and APT shows sign reversal of the two carbon signals at $\underline{C}_2$(δ 31.8) and $\underline{C}_{11}$(δ 29.9) (data not shown). These observations are in accordance with the anticipated suprafacial "ene" reaction generating **7a** with deuterium *cis* to the ester moiety, followed by the intramolecular Diels-Alder proceeding by the sterically constrained *endo* mode.

Experimental Section[9]

2-Isopropenyl-6-methoxybenzofuran, **2**—By slightly modifying the method of Ref. 4, equimolar amounts of 4-methoxysalicylaldehyde and chloroacetone were heated at reflux with excess potassium carbonate in acetone for 48 hours, after which time the volatiles were removed and the residue was extracted with ether versus water. The organic layer was dried with $MgSO_4$, and the ether was removed to give a pale yellow solid. This was dissolved in dry THF and added via syringe to a solution of an equivalent of methylenetriphenylphosphorane in dry THF cooled to -78° C. The reaction was allowed to warm to room temperature, quenched with aqueous ammonium chloride solution and extracted with ether. The volatiles were removed and the residue was chromatographed on silica gel, eluting with 20% ether in hexanes, to give the title compound as a pale oil which solidified upon standing, and whose spectroscopic properties were identical to those previously described[2].

Methyl 7-methoxy-4-methyl-dibenzofuran-1-carboxylate, **3**—The material from the above reaction, **2**, and a >5-fold excess of methyl propiolate **1**, were heated in refluxing toluene as previously described[2], and the progress of the reaction was followed by tlc on silica gel, eluting with 20% ether in hexanes. After 48 hours, the volatiles were removed and the residue was chromatographed on silica gel using the same solvent to give the title compound as a pale solid, whose spectroscopic properties were identical to those previously described[2].

Dimethyl 3,4-dihydro-7-methoxy-4-methyl-2H-2,4,4a-ethanylylidine dibenzofuran-1,10-dicarboxylate, **5**—Further elution of the above reaction mixture provided the title compound as a pale solid, and whose spectroscopic properties were identical to those previously described[2].

Methyl 3-deuteriopropiolate, **1a**—Following the protocol of Ref. 8, a solution of methyl propiolate in a 4:1:1 mixture of THF, ether, and pentane was cooled to -120° C. An equivalent of n-butyl lithium in hexane was added dropwise via syringe over 15 minutes, and the reaction was stirred an additional 10 minutes at this temperature before being quenched with an excess of deuterioacetic acid. After warming to room temperature, the reaction mixture was partitioned between toluene and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with further fresh aliquots of toluene. The combined organic layers were dried with $MgSO_4$, and this solution was used directly in the thermal reaction with **2**. Product analysis of this subsequent reaction indicated that isotopic incorporation was about 65%.

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[7] $\underline{H}_{3\alpha}$(δ 0.94): $^1J_{C\text{-}H}$ =126 Hz.; $\underline{H}_{3\beta}$(δ 1.77): $^1J_{C\text{-}H}$ =126 Hz.; $\underline{H}_{11\beta}$(δ 1.19): $^3J_{C\text{-}H}$ = 6.5 Hz.; $\underline{H}_{4\text{-}Me}$($\delta$ 1.66): $^3J_{C\text{-}H}$ = 3.0 Hz.

[8] Midland, M.M., Tramontano, A., and Cable, J.R.: *J. Org. Chem.* **1980**, *45*, 28-29.

[9] General Methods: Starting materials and solvents were obtained commercially and were used as received, with the exception of THF which was distilled from sodium benzophenone ketyl before use. Reactions were run under a nitrogen atmosphere. ^1H NMR 1-D and 2-D experiments were performed on Varian XL-200, 300, or 400 MHz instruments. ^{13}C-^{13}C INADEQUATE spectroscopy was performed on a Varian XL-400 operating at 100.8 MHz.