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INTRAMOLECULAR 2+2 ADDITION OF A DIFLUOROVINYL ETHER ALDEHYDE YIELDS [3.2.0] AND NO [3.1.1] PRODUCTS

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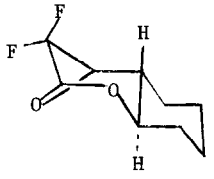
Summary: Irradiation of the difluorovinyl ether aldehyde 6 yields the tricyclic products 7 and 8 and the bicyclic dioxepene 9. There was no evidence for the formation of the isomeric [3.1.1] structure 1 containing the ring system of thromboxane A_2.

Recently, we described synthetic routes leading to the 2,6-dioxabicyclo [3.1.1] heptane ring system present in thromboxane A_2, in which two fluorines are substituted for hydrogen at C-7, α to the acetalic carbon,[1] as exemplified by structure 1. The intent of the work was to increase the stability of the highly unstable oxetane ring of TXA_2 towards hydro-

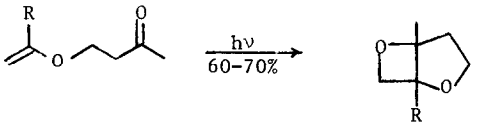


1

lytic cleavage. This objective was fully realized as demonstrated by the 10^8 fold decrease of the bimolecular rate constant of hydrolysis for a difluorooxetane as compared to that for TXA_2 and for simple nonfluorinated oxetane acetals.[2]

An alternative pathway leading to 1 employing a photochemical cycloaddition reaction appeared extremely promising, since Schroeter and Orlando[3] had been able to prepare 2- and 3-alkoxyoxetanes from aldehydes or ketones and vinyl ethers. However, attempts by Carless and Haywood[4] to employ such a reaction for the construction of the 2,6-dioxabicyclo

[3.1.1] system yielded only the isomeric [3.2.0] 2. A more recent publication by this group[5] reports success in a homologous case leading to the 2,7-dioxabicyclo [4.1.1] heptane system 3.



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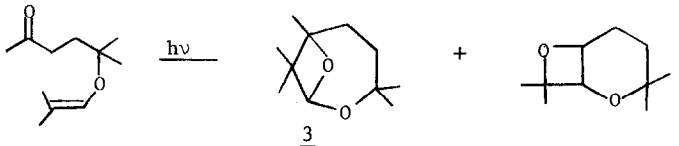
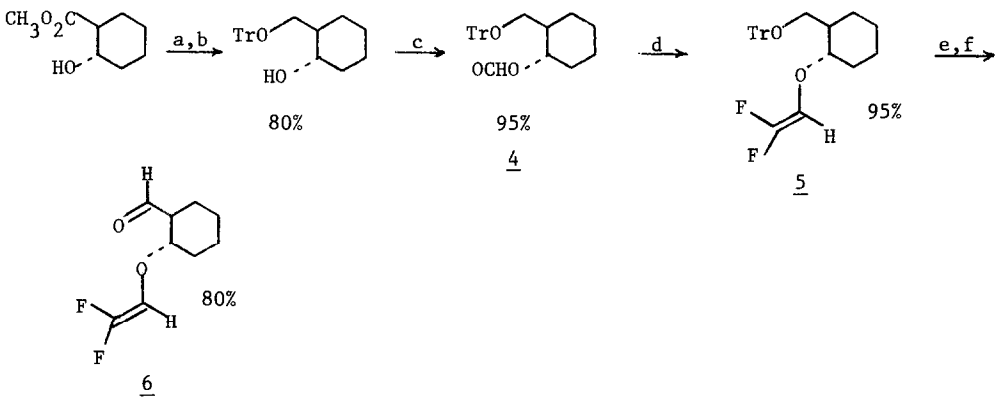
The synthesis of 1 required as a precursor the difluorovinyl aldehyde 6, which was pre-



3 11% 54%

pared in excellent yield from trans-2-carbomethoxycyclohexan-1-ol as shown in Scheme 1.

Scheme 1



80% 95% 95% 80%

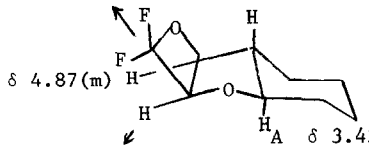
4 5 6

a, $LiAlH_4$, Et_2O, 25°; b, TrCl 2 equiv., pyridine, 25°, 12 h; c, $OCHOCOCH_3$, pyridine:CH_2Cl_2 1:5, 12 h; d, $(NMe_2)_3P$, CF_2Br_2, triglyme[6], 85°, TLC; e, 90% acetic acid, 25°, 12 h; f, $(COCl)_2$, DMSO, Et_3N.

The synthesis is straightforward with the exception of the Wittig reaction (step d),[8] which had not previously been applied to a formate ester.

The freshly prepared aldehyde 6[9] was irradiated in CH_2Cl_2 under Argon for 11 hours with a 450 W Hanovia mercury lamp using a Corex filter. All other filters or no filter gave either no or flocculent polymeric products. TLC showed the presence of 3 isomeric compounds 7, 8 and 9 in the approximate ratio of 5:4:1, which were isolated by column chromatography using CH_2Cl_2/pentane mixtures as eluants.[10] Their high resolution mass spectra, which

δ 69.0 (dd, J=104.3, 1.3 Hz) 72.4 (dtdd, J=104.6, 10.7, 1.2, 1.2, 3.0 Hz)



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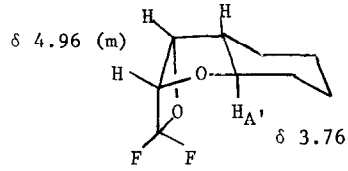
δ 3.42 (dt, J=11.2, 4.0 Hz)

δ 4.66 (dd, J=5.0, 2.0 Hz)

δ 4.94 (m)

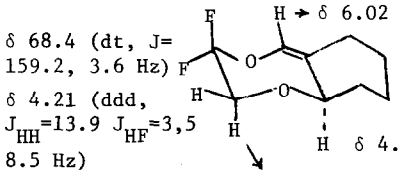


8

δ 3.76 (dt, J=10.1, 3.3 Hz)

δ 66.7 (d, J=107.3, Hz)
73.0 (dd, J=107.6, 10.6 Hz)

δ 70.4 (dddd, J=159.2, 3.1, 7.6, 22.2 Hz)



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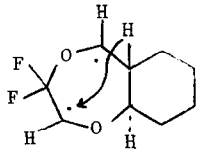
showed molecular ions at m/z 190 and ^{1}H and ^{19}F NMR spectra support the structures shown. The endo-structure 8 is assigned on the basis of the downfield shift of 0.34 δ for H_A, as compared to the signal for H_A in 7, due to the proximity of H_A, to fluorine. Moreover, the NMR spectra of both 7 and 8 show substantial upfield shifts in C_6D_6 for all the protons shown with the exception of the signal for H_A, which remains unchanged. In contrast to all other protons H_A, is not readily accessible for shielding by the solvent due to the presence of the endo ring. The conformation shown for 9 appears to be the most stable one and accounts for the observed coupling constants. The intermediacy of the diradical 10



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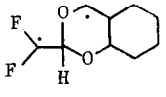

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accounts for all three products of this reaction: 7 and 8 by radical combination, 9 by intramolecular hydrogen shift as shown. The considerably greater stability of the diradical 10 than that of the isomeric 11 appears to be the determining factor in this reaction, although other factors are known to influence the direction of cycloadditions.[11]

Examination of the ^{19}F NMR spectrum of the crude photolysis product showed only signals for 7, 8 and 9, and no evidence for the presence of 1.[1]

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8. To CF_2Br_2 (2.75 ml) in dry(!) triglyme (20 ml) was added $(NMe_2)_3P$ (7.5 ml, chloride free) in triglyme (10 ml) at 0° for 15 min under N_2. After stirring the suspension at 25° for 30 min, 1.0 g of 4 (mp 104-106°) in warm triglyme (5 ml) was added, the mixture stirred for 15 min and warmed to 85°. Reaction time 2 to 4 h determined by TLC. Worked up with hexane. 5: NMR ^1H (500 MHz) $CDCl_3$ δ 5.52 (J_{HF}=16.7, 2.8 Hz), 3.55 (m, 2H), 3.20 (m, 1H); ^{19}F (188.4 MHz) C_6D_6 δ (upfield from $CFCl_3$) 102.84 (dd, J_{FF}=83 Hz, J_{HF}=16.7 Hz), 122.53 (d).
9. NMR ^1H, $CDCl_3$, δ 9.70 (1H, J=1.5 Hz), 5.61 (dd, J_{HF}=16.0, 2.8 Hz), 3.75 (dt, 1H, J=11.1, 4.5 Hz), 2.47 (m, 1H). m/z, 190.0794.
10. All three products were exceedingly volatile, Great care had to be taken when removing solvents.
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