Preliminary Note

Preparation of a fluorinated shikimic acid*

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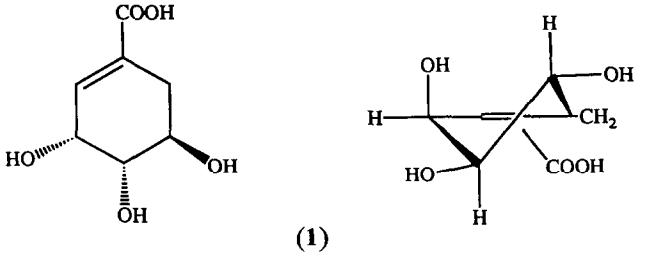
Abstract

The reaction of dialkylaminosulfur trifluoride with shikimic acid (**1**) gives a single isomer of a product **2** in which two hydroxy groups have been replaced by fluorine.

Introduction

Shikimic acid (**1**) is a key intermediate in the biosynthesis of aromatic amino acids [1]. Compounds which can interrupt such metabolic paths function as safe, selective herbicides [2].

The largest selling compound in this class is Glyphosate, $^{-}O_3PCH_2NH_2{}^{+}CH_2COO^{-}$, Monsanto's Roundup®, which interferes with enol phosphate formation. Hall determined the ^1H NMR spectrum of shikimic acid [3]. Its structure is shown below as two representations (**1**). The key link between the NMR spectrum and the structure is the 8.4 Hz coupling between H-4 and H-5.



(**1**)

Introducing fluorine strategically into metabolic intermediates can lead to interesting biological activity [4]. Fluorine can be introduced into shikimic acid in several different ways. The method of total synthesis begins with simple precursors, getting all the stereochemistry right and introducing the fluorine into a specific, designed location [5, 6]. Alternatively, the process can begin with a preformed sugar or shikimic acid itself and replacing one or more atoms or groups by fluorine. The fluorinated product can have either one or more hydrogen or hydroxy groups replaced by fluorine. Our approach was to try to replace a hydroxy group in shikimic acid by fluorine.

DAST, bis-dialkylaminosulfur trifluoride, is an easy to use, versatile fluorinating agent [7]. It replaces hydroxy by fluorine with inversion of configuration under mild conditions. Some sugars have been selectively fluorinated with no protection–deprotection steps [8]. DAST reacts with a shikimic acid epoxide to prepare a fluorinated shikimic acid [9].

Results

We treated a suspension of shikimic acid (or its derivative with the carboxy group protected as an Me_3Si derivative) in CH_2Cl_2 with DAST at −50 °C and allowed the mixture to warm to room temperature. The crude, proton-decoupled ^{19}F NMR spectrum showed two major resonances in the chemical shift region expected for CHF groups. Assuming that the fluorination had been non-specific, we attempted to separate the putative products by HPLC. All fractions showing fluorine NMR signals still exhibited the same two resonances found in the crude product. The ratio of the integrals of the two resonances in all fractions was one-to-one within the limits of routine integration procedures.

A GC–MS analysis of the pertrimethylsilylated derivative of the crude product showed that the latter was not the expected monofluoride. The single fluorine-containing product was a *difluoride* with the empirical formula $C_{13}H_{24}F_2O_3Si_2$ (Calc., 322.1231. Obs., 322.1226). The fragmentation pattern did not provide any further information about the structure.

With this added insight, we can complete the structural assignment from the ^1H and ^{19}F NMR data. The ^{19}F NMR spectrum showed two resonances at −191 ppm and −198 ppm from two, non-equivalent fluorines in the same molecule. At high resolution, it was possible to resolve a 2.0-Hz coupling between these fluorines. Each undecoupled resonance was a 49-Hz doublet due to coupling with its geminal proton. In addition, the upfield fluorine was also a quartet, $J=27$ Hz. Each half of the low-field doublet was very broad, but no individual couplings could be resolved.

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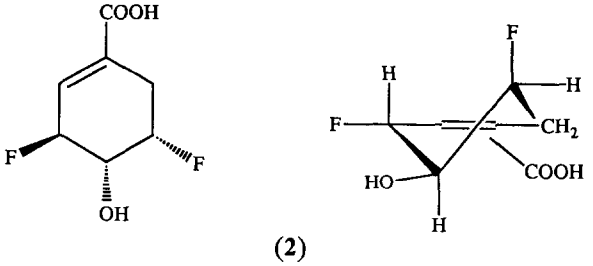
The proton spectrum showed the following resonances in acetone-d_6. The chemical shifts of the CH_2 protons (H-6) were accidentally equivalent at 2.75 ppm, but the expected AB pattern ($J_{AB}=17$ Hz) was visible in $CDCl_3$. The remaining C*H*OH (H-4) appeared at 4.02 ppm. The two new C*H*F resonances were at 5.01 and 5.22 ppm and the =C*H* (H-2) resonance was at 6.80 ppm. These data are also consistent with a difluoride structure.

The next step is to assign the regiochemistry. The fluorine at −198 ppm is adjacent to the CH_2 group (F-5) because it shows large, vicinal coupling to *three* protons. The C*H*OH must be *between* the two CHF groups because it shows large couplings to both fluorines. The vinyl proton shows an 11-Hz coupling to one fluorine. This evidence establishes the regiochemistry as 3,5-difluoro-4-hydroxy.

Next, we assign the stereochemistry. To do this we must assign the two C*H*F resonances to their proper protons. A selective, heteronuclear decoupling experiment provided the necessary information. Decoupling the −191 ppm fluorine resonance (F-3) collapsed the following couplings in the proton spectrum: the 11-Hz coupling to =CH, the 49-Hz, two-bond, coupling to the proton at 5.2 and one of the small 2-Hz couplings to the proton at 5.0 ppm. Since the fluorine resonance at −191 ppm represents the allylic fluorine F-3, we assign the 5.2-ppm resonance to the allylic proton H-3. The remaining resonance at 5.0 ppm represents the C*H*F proton next to the CH_2 group (H-5).

Proper assignment of the proton–proton couplings now completes the assignment. Only one 7-Hz, vicinal, proton–proton coupling involves the C*H*OH proton. This *trans* coupling involves H-3 and H-4. The corresponding coupling between H-4 and H-5 is less than 4 Hz, which means the protons are *cis* to each other. The structure of the product thus deduced is **2**. Each DAST replacement of a hydroxy group by fluorine occurs with inversion.



(2)

Why is the difluoride obtained exclusively? The low solubility of shikimic acid or its TMS derivative in CH_2Cl_2 solvent at the low temperature used for the reaction may be the key factor. Even with a bulk ratio of DAST/substrate less than unity, the actual concentrations of the two reactants in solution may be reversed. The small amount of shikimic acid in solution may always be in the vicinity of a large excess of DAST. The rate of the second fluorination step appears to be faster than the dissolution of shikimic acid or its derivative.

Experimental

General remarks

^{19}F NMR spectra in $CDCl_3$ were recorded on a Nicolet NT-220 spectrometer at 188.2 MHz and 23 °C. ^1H NMR spectra were recorded on a Bruker instrument at 300 MHz. Fluorine chemical shifts are in ppm from $CFCl_3$; negative shifts are upfield. Proton chemical shifts are ppm downfield from Me_4Si.

Fluorination of shikimic acid

A suspension consisting of 0.35 g (2 mmol) shikimic acid and 10 ml CH_2Cl_2 was cooled to 0 °C and treated with 0.83 ml (6 mmol) triethylamine and 0.65 g (6 mmol) trimethylsilyl chloride. The suspension was stirred at room temperature for 1 h, cooled to −78 °C and 1.3 ml dimethylaminosulfur trifluoride added. The reaction mixture was warmed gradually to room temperature. After stirring over the weekend, the mixture was poured onto aqueous $NaHCO_3$ and the resulting two-phase system stirred for 1 h. The aqueous solution was acidified with 10% HCl and further extracted with ethyl acetate. The organic layers were dried and the solvent removed. The crude, proton-decoupled, ^{19}F NMR spectrum showed two peaks of equal intensity. Additional purification by HPLC gave difluoroshikimic acid on which the following spectroscopy results were obtained. ^{19}F NMR δ: −191 (1F, d, 49; broad); −198 (1F, d, 49; q, 27) ppm. ^1H NMR δ: 6.80 (1H, d, 11; d, 1.5); 5.22 (1H, d, 49; d, 15; d, 2; d, 2); 5.01 (1H, d, 49; d, 2; d, 4; d, 8); 4.02 (1H, d, 28; d, 15; d, 7; d, 2); 2.75 (2H, d, 25; m) ppm.

A number of different procedures including adding less than 1 equiv. DAST was tried. In no case was any monofluoroshikimic acid detected by ^{19}F NMR spectroscopy.

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