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The Synthesis of 2- and 3-Fluorokhellin

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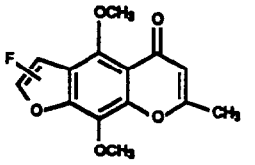
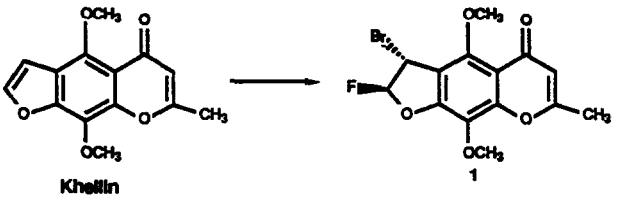
ABSTRACT: The bromofluorination of khellin is described. The unique influence of fluorine is demonstrated in various substitution and elimination reactions leading ultimately to the preparation of both 2- and 3-fluorokhellin.

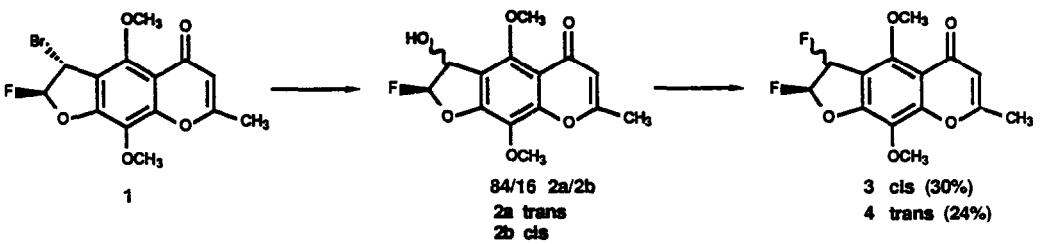
Khellin, a medicinal agent known to man for 3000 years,[1] has been used for a variety of pharmacological indications including hypertension, renal and biliary colic, and stomach disorders. The recent discovery of khellin's lipid-altering activity in man and antiatherosclerotic activity in animal models has renewed interest in khellin analogues.[2] During the course of our analogue program, we recognized the liability associated with the furan ring in khellin, since molecules containing a furan ring often covalently bind to cellular macromolecules.[3] In such cases, the furan ring is thought to undergo oxidative metabolic activation with subsequent covalent binding to various macromolecules.[3] We were interested in preparing 2- and 3-fluorokhellin to see if fluorine substitution would render the olefin less susceptible to metabolic oxidation while not altering the topology and thus the pharmacological profile of the molecule.



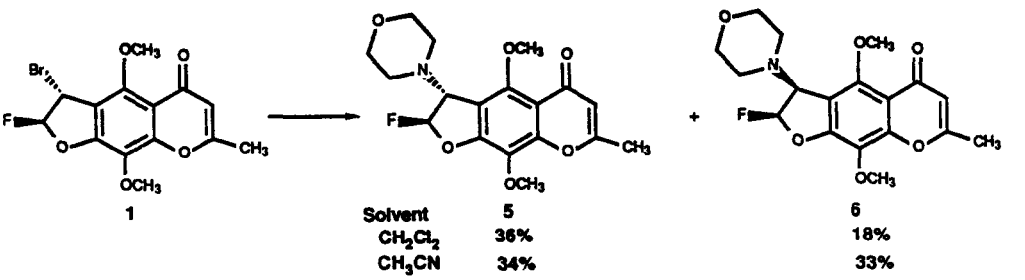
With regard to the fluorination of benzofurans, Barton has reported that treatment of benzofuran with CF_3OF in freon at -78°C lead to a mixture of fluorinated products[4] and that under similar conditions, khellin afforded a quinone,[5] the product of oxidative demethylation. In order to circumvent the problem of oxidative demethylation experienced by Barton we investigated the bromofluorination of khellin in hopes of finding reaction conditions which would not involve the generation of the powerful oxidizing agent F^+. We found that treatment of khellin with BrF (HF/dibromantin/THF/CH_2Cl_2/4°C [84%] or Poly HF/NBS/CH_2Cl_2/0°C [82%]) afforded trans-3-bromo-2-fluoro-2,3-dihydrokhellin 1 (mp, 127-129°C) in excellent yield and thus established a sound method for the introduction of fluorine into the furochromone nucleus. Several avenues were then investigated for the transformation of 1 to the desired 2- and 3-fluoro analogues.



We first found that treatment of 1 with DBU (DMSO/RT/2d) effected a very smooth cis elimination of HF to yield 3-bromokhellin (mp, 215-216°C) in 72% yield.[7] To extend that methodology to the synthesis of 3-fluorokhellin we viewed the cis-2,3-difluoro analogue as an appropriate target. Two routes to the cis difluoro adduct were developed in an effort to maximize the formation of the cis isomer. The solvolytic and nucleophilic displacement chemistry of 1 proved very interesting. Solvolysis of 1 in 70% aqueous CH_3CN afforded in 99% yield an 84/16 mixture of trans/cis-3-hydroxy-2-fluoro-2,3-dihydrokhellin 2a/b. The trans isomer was obtained pure via recrystallization (acetone, mp, 219-221°C). Treatment of trans 2a with mesyl fluoride and tetrabutylammonium fluoride afforded cis-2,3-difluoro-2,3-dihydrokhellin 3 (mp, 179°C) in 30% yield along with the trans isomer 4 (mp, 141-142°C) in 24% yield.

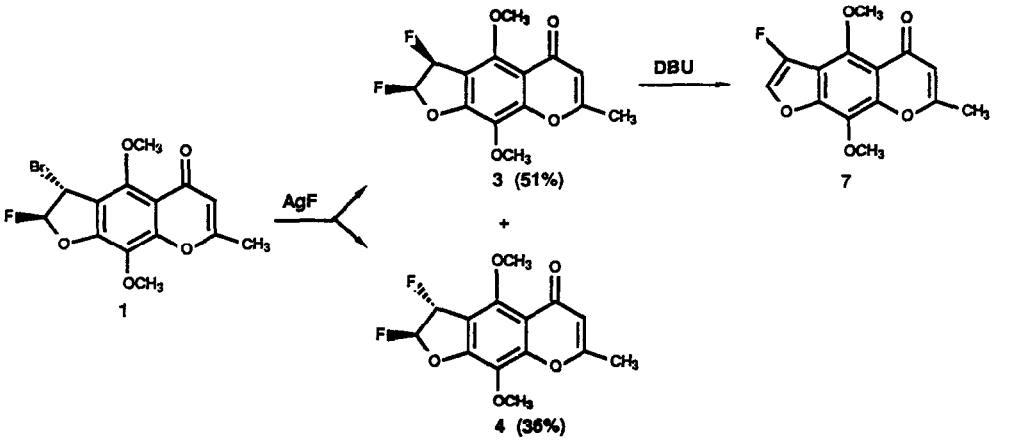


In general, we found that addition of nucleophiles to 1 afforded cis/trans mixtures in which the trans adduct predominated. In some cases, as illustrated by the addition of morpholine to 1, the product distribution was influenced to some extent by solvent. Attempts to epimerize 3, 4, 5 and

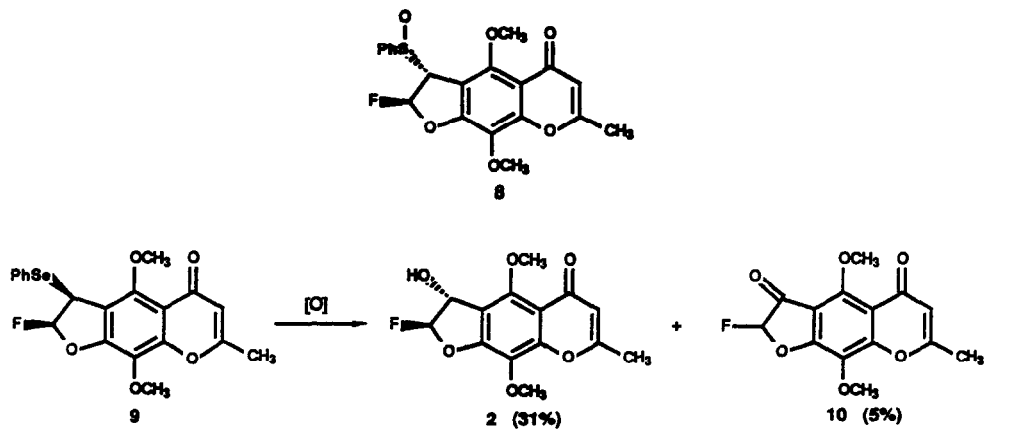


6, failed, implying the distribution of the cis and trans adducts was kinetically controlled and thus suggested that the reaction proceeded via an SN_1 type mechanism in which fluorine was having a substantial directing effect on the incoming nucleophile. The best cis/trans ratio of difluoro compounds (3 [51%] / 4 [36%]) was obtained by treating 1 with AgF (1.1 equiv./10%

$CH_3CN/PhCH_3/RT$).[9] Treatment of **3** with DBU in DMSO at 100°C for two days afforded the desired 3-fluorokhellin **7** (mp, 194-195°C) in 55% yield. The trans difluoro isomer also underwent elimination under forcing conditions (six days) in low yield (10%).

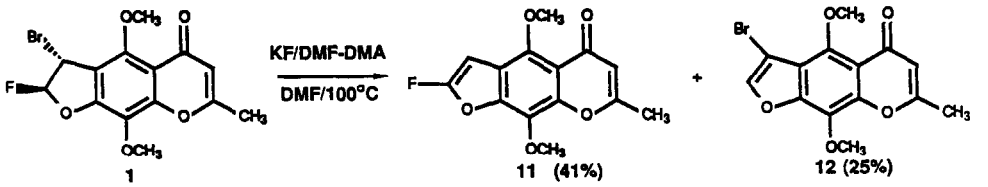


We envisioned the 2-fluoro isomer as arising via a syn elimination on a suitable 3-substituted analogue. However, syn elimination of sulfoxide **8** (a mixture of diastereomers) afforded 2-fluorokhellin in only 4% yield. Attempts to utilize the selenide **9**[10] were also thwarted in that attempts to oxidize that system afforded either the seleno-pummerer product **10** (m-CPBA/CH_2Cl_2) or a mixture of **2** and **10** (H_2O_2/HOAc).[11] It was clear from models that in one of the diastereomeric sulfoxides, the transition state leading to product was extremely unfavorable for steric reasons. It is also reasonable to expect a very unfavorable electronic influence to be exerted by fluorine on the syn elimination process.



Reaction conditions leading to the formation of 2-fluorokhellin evolved from our efforts to prepare the difluoro intermediates **3** and **4**. Surprisingly, we found that treatment of **1** with KF (**3d**) or CsF (**7h**) (1.0 equiv.) in DMF (100°C) afforded the desired 2-fluoroa nalogue **11** (mp, 174°C) in 40%

and 46% yield respectively. In addition, small amounts of 3-bromokhellin (8% and 3%) were also isolated from these reactions. We then found that addition of N,N-dimethylformamide dimethyl acetal (DMF-DMA, 2.0 equiv.) to the KF/DMF reaction dramatically accelerated the reaction (**5h**) to yield **11** in 41% and 3-bromokhellin in 25%. The amount of 3-bromokhellin formed was reduced by running the reaction at 125°C for 45 min. and 100°C for 2.5 h (41% of **11** and 2% of **12**).



1 **11** (41%) **12** (25%)

Thus both 2- and 3-fluorokhellin can be prepared in 2 and 3 steps respectively from khellin. Further examples of the influence of fluorine upon the stereochemistry and the unusual elimination chemistry are forthcoming.

References and Notes

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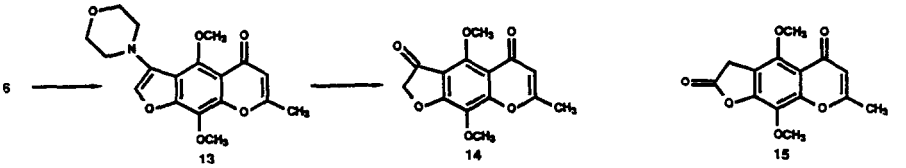
7. Stronger bases opened the pyrone ring and more nucleophillic bases effected substitution at C-3.
8. The regiochemistry of **6** and therefore **1** was established by elimination followed by acid hydrolysis to **14** having a carbonyl absorption in the IR at 1724 cm^{-1} and a methylene absorption in the ^{1}H-NMR at 4.71δ, whereas the previously prepared lactone **15** exhibited absorptions at 1822 cm^{-1} in the IR and 3.84δ in the NMR (Gammill, R.B., Nash, S.A. *J. Org Chem.* **1986**, *51*, 3116).



13 **14** **15**

The trans configuration was assigned on the basis of the lack of coupling (ϕ = 90°) between the C-2 and C-3 hydrogens in the ^{1}H-NMR The cis compound exhibits a coupling constant of 5 Hz.

9. The conversion of alkyl halides to the corresponding fluorides using AgF has been well documented Henne, L.H. *Org. Reactions, Vol 2* **1944**, 49-93, Kornblum, N., Jones, W.J , Hardies, D E *J Amer. Chem. Soc* **1966**, *88*, 1704; Gerstenberger, M.M.C , Haas, A. *Angew Chem. Int. Ed. Engl.* **1981**, *20*, 647, Cohen, T., Solash, J *Tetrahedron Letters* **1973**, 2513; and for a reveiw of the kinetics associated with AgF mediated exchanges see. Rudakov, E.S., Kozhevnikov, I.V , Zamashchikov, V.V *Russian Chemical Reviews* **1974**, *43*, 707
10. Phenylselenide addition to **1** represents the only case we observed where the cis adduct is formed preferentially. A small amount of the trans adduct was isolated in one run and upon oxidation afforded 2% of 2-fluorokhellin, 5% **10**, 31% **2**.
11. The seleno-pummerer reaction has been observed previously upon oxidation and elimination of alpha seleno ketones under acidic conditions. Reich, H J , Renga, J M , Reich, I L. *J. Amer. Chem. Soc.* **1975**, *97*, 5435. A similar reaction is observed upon oxidation of alpha silyl selenides. Reich, H J., Shah, S.K *J. Org Chem.* **1977**, *42*, 1773

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