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STABILIZATION OF A PROSTAGLANDIN TERTIARY ALLYLIC ALCOHOL SYSTEM BY FLUORINE: SYNTHESIS, ACID STABILITY STUDIES AND PHARMACOLOGY OF A 16-FLUOROMETHYL ANALOG OF SC-46275.

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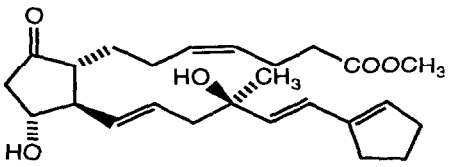
Abstract: The synthesis of a 16-fluoromethyl analog of SC-46275, a potent, long-acting and selective analog of enisoprost, is described. Introduction of a fluorine atom to the C-16 methyl group of SC-46275 conveys a remarkable increase in stability toward acid induced epimerization, dehydration and allylic rearrangement while having minimal influence on the pharmacological profile.

Introduction

SC-46275 (**1**), an ω-chain cyclopentenyl analog of enisoprost, is a potent, long-acting gastric antisecretory mucosal protective prostaglandin with minimal diarrheagenic side effects.[1-3] Other properties of SC-46275 which made it an attractive developmental candidate were its high affinity for parietal cell prostaglandin receptors (EP_3)[4] and the lack of detectable plasma levels following oral administration of effective antisecretory doses to dogs.[2]



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One of the problems encountered in the development of SC-46275 was the acid instability of the ω-chain tertiary allylic alcohol system.[1] SC-46275 not only undergoes acid catalyzed epimerization at C-16 to generate a mixture of isomers, it also is highly susceptible to dehydration and allylic rearrangement decomposition under acid conditions (Figure 1). In an attempt to minimize these acid driven events, we decided to add a fluorine atom to the C-16 methyl group to suppress carbonium ion formation at the tertiary center.

Synthesis

The target compound **2** (Figure 2) was prepared by conjugate addition of the racemic cuprate reagent **5** to resolved enone **4**[5], mild hydrolysis of protecting groups, and chromatographic purification. As with other Δ^{17} analogs[1], the C-16 epimers **2** and **3** were easily separable by chromatography. As previously done[1], configurations of **2** and **3** were assigned on the basis of elution sequence and biological activity.

Figure 1

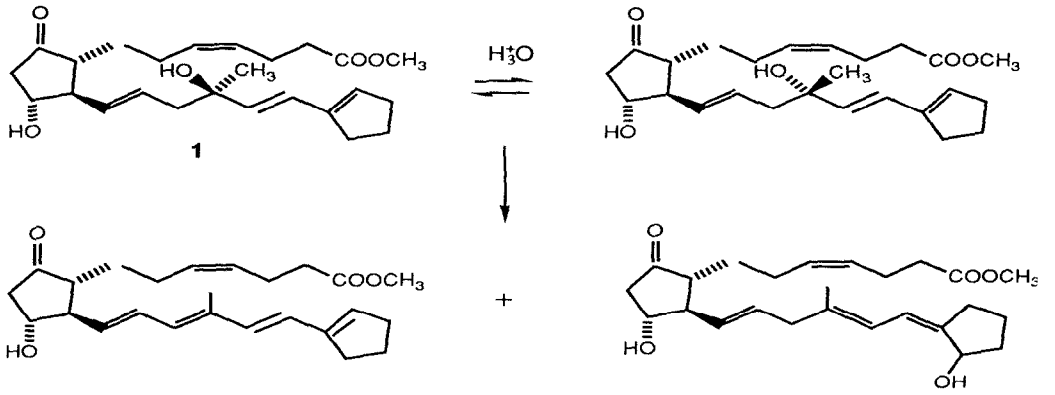
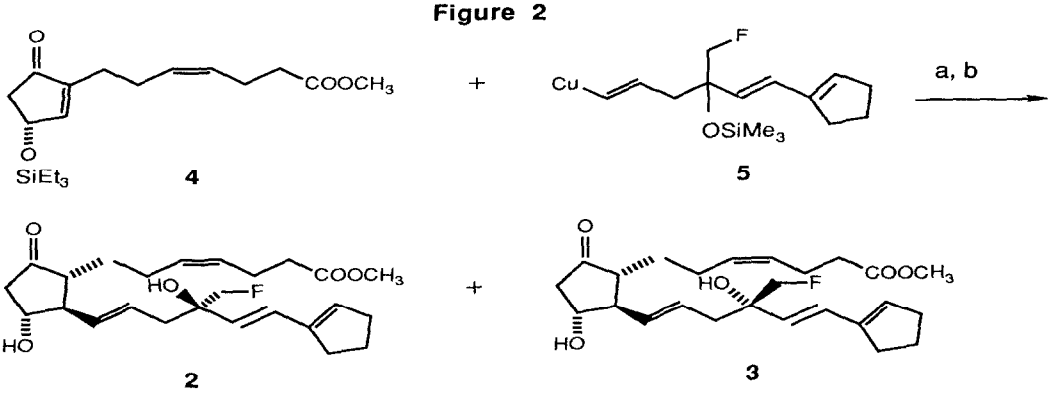


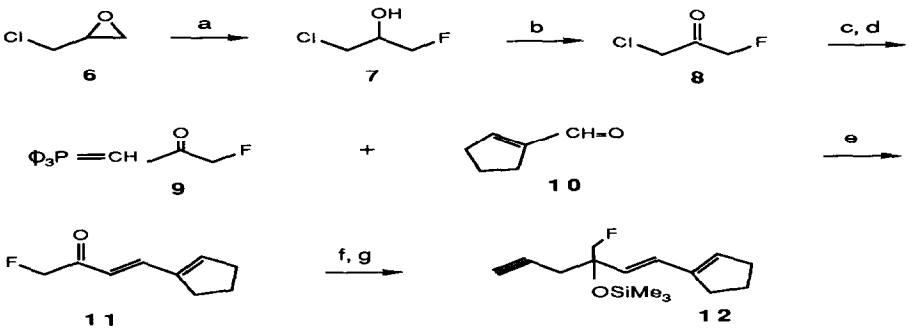
Figure 2



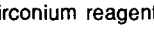
a) -60°C; b) PPTS, r.t., 1h.

The key intermediate in the preparation of the fluorinated ω-chain precursor **12** (Figure 3) was 1-chloro-3-fluoroacetone **8**. The synthesis of **8** has been described[6] but in very low yield so we employed a slightly different approach. Thus, epichlorohydrin **6** was treated with triethylamine/hydrogen fluoride complex[7] to generate **7** which was oxidized with Jones reagent to give **8**. Conversion of **8** to the Wittig reagent **9**[8] and subsequent reaction with 1-cyclopentene-1-carboxaldehyde **10**[1] proceeded smoothly and provided the fluoromethylketone **11**. Propargyl magnesium bromide addition to **11** at low temperature followed by silylation produced the protected alcohol **12**.

Figure 3



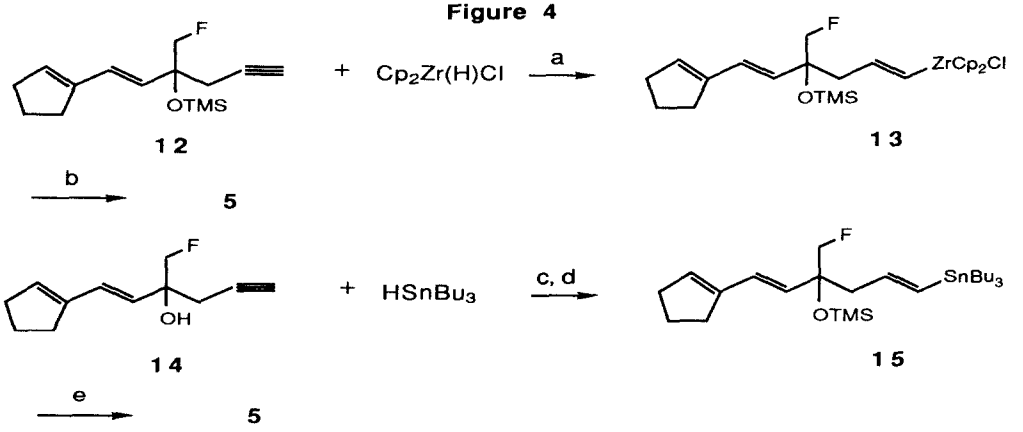
a) $Et_3N \cdot 3HF$, 100°C, 4h; b) CrO_3, H_2SO_4, acetone; c) Φ_3P, Δ

d) Na_2CO_3; e) toluene, Δ; f) 

, -78°C; g) TMSCl, DMF, imidazole

The initial approach for conversion of **12** to a cuprate reagent (Figure 4) and subsequent prostaglandin formation was the one-pot procedure[9] consisting of hydrozirconation, alkyl lithium-metal exchange, formation of a mixed cuprate by addition of cuprous cyanide and enone addition. Although this procedure worked quite well for the preparation of SC-46275, it provided very poor yields (10-20%) of prostaglandin in the present case. Further analysis of this procedure implicated the hydrozirconation step as the problem. We found that one equivalent of the zirconium reagent only partially consumed the alkyne while two equivalents effected complete reaction. However, while the one equivalent reaction produced low yields of prostaglandin, the two equivalent reaction provided no prostaglandin whatsoever. Presumably, the zirconium hydride is attacking the conjugated diene system in competition with alkyne reaction. The resulting dienyl zirconium adduct cannot produce prostaglandin itself and, when one equivalent of zirconium hydride is employed, this undesired product likely interferes to some degree with the formation of the desired cuprate species **5**. When two equivalents of zirconium hydride are used, both positions of the side chain are derivatized resulting in complete failure of the cuprate reaction. While the integrity of the zirconium hydride reagent is often a problem and may be questioned in this case, assurance of its purity was established by reaction with a simple alkyne and subsequent prostaglandin formation in good yield.

Figure 4



a) THF, r.t.; b) 2MeLi, CuCN, MeLi, -30° - 78°C; c) hv;

d) TMSCl, DMF, imidazole; e) n-BuLi; CuC ≡CC_3H_5•2P(NMe_2)$_3$, -60°C

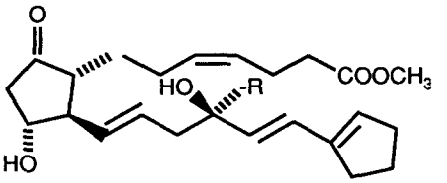
With the failure of the one-pot hydrozirconation approach, we returned to the more traditional hydrostannation, lithium-metal exchange, copper pentyne procedure. Hydrostannation of the ω-chain of SC-46275 and similar dienyl acetylenes is sluggish and poor yielding[1,10] presumably due to free radical quenching by the conjugated diene and addition of tin hydride to the diene. However, we felt that the presence of the fluorine atom might favorably alter the reactivity of the system toward free radical chemistry. Indeed, light catalyzed hydrostannation[1] of the free alcohol **14** was a facile reaction and provided **15** in good yield following silylation of the alcohol. Treatment of **15** with n-BuLi at -60°C followed successively by a copper pentyne/hexamethylphosphorus triamide solution and the enone **4** gave the desired prostaglandin products[11] in good (-60% from **4**) yield.

Acid Stability

SC-46275 **1** and its fluoromethyl analog **2** were compared for rates of acid catalyzed epimerization and formation of dehydration and allylic rearrangement products in aqueous HCl/THF. Thus, 1 mg of each compound was dissolved in 1 ml of THF, treated with 2 drops of 0.1 N HCl, and allowed to stand at room temperature. Aliquots from both solutions were withdrawn at 1, 2, 4 and 8 hours and examined by both TLC and HPLC. SC-46275 showed some epimerization and dehydration of the 16-hydroxy group at 2 hours and pronounced epimerization, dehydration and allylic rearrangement after 8 hours. In contrast, **2** was remarkably stable showing no detectable reaction after 8 hours. In a second experiment, both compounds were studied in a 3:1 THF:H_2O solution containing 0.3 N HCl. SC-46275 underwent rapid and substantial

epimerization, dehydration and allylic rearrangement while its fluoromethyl counterpart showed no detectable dehydration or allylic rearrangement products at 8 hours. Epimerization did occur but very slowly. At 1 hour, traces of the C-16 epimer were observed but 6 hours were required to reach a 3:1 mixture (50% reaction) and 24 hours to reach a 1:1 mixture.

Table. Comparative Gastric Antisecretory and Diarrheal Activities



Compound	R	ED_{50}, μg/kg	
		Gastric Antisecretory Activity in Dogs[a]	Diarrheal Effects in Rats[b]
SC-46275 (1)	H	0.01[c]	>3160[d]
2	F	0.05[c] (0.02-0.14)[e]	>3160

[a]Determined in food-stimulated Pavlov pouch dogs by intrapouch administration.

[b]Determined in adult male rats by intragastric administration.

[c]See reference 2 for dose-response data and ED_{50} determination; ED_{50} value is dose required to reduce 4 hour total acid output by 50%.

[d]See reference 3 for dose-response data.

[e]95% confidence limits.

Pharmacology

The fluoromethyl analog **2** was compared to SC-46275 for gastric antisecretory activity in Pavlov pouch dogs[2] and diarrheagenic activity in rats.[3] As seen in the Table, **2** is approximately one-fifth as active as SC-46275 as an antisecretory agent while showing similarly weak diarrheagenic effects. This small reduction in antisecretory potency is a relatively modest tradeoff for the substantial improvement in stability. Thus, **2** is a candidate for more detailed pharmacological assessment. These studies are currently in progress.

As a follow-up to this work, we also prepared the di- and trifluoro analogs. These compounds, while showing the same impressive acid stability as **2**, exhibited disappointingly weak gastric antisecretory activity.

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11. ^{1}H NMR ($CDCl_3$) data for **2**: δ 2.02 (dtd, 1H, 8H); 2.22 (dd, 1H, 10αH); 2.50 (ddd, 1H, 15H); 2.73 (dd, 1H, 10βH); 3.67 (s, 3H, OCH_3); 4.03 (q, 1H, 11H); 4.30 (d, J=47.8 Hz, 2H, CH_2F); 5.32 (m, 2H, 4,5 H's); 5.48 (dd, 1H, 13H); 5.48 (d, 1H, 17H); 5.69 (ddd, 1H, 14H); 6.58 (d, 1H, 18H).