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A New Route To Steroidal Vinyl Fluorides[1]

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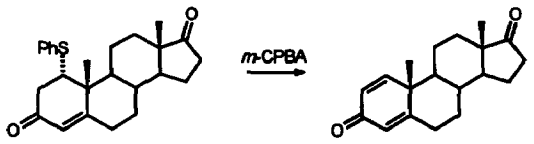
Abstract: Steroidal β-fluoro-α,β-unsaturated ketones are prepared by reaction of the corresponding phenyl vinyl sulfides with N-bromosuccinimide / HF or N-bromosuccinimide / DAST in dichloromethane in 50 - 70% yield.

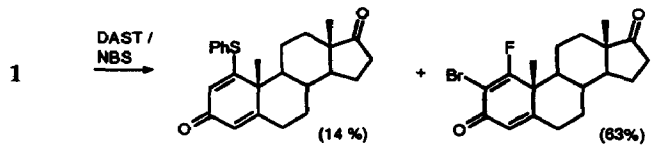
In connection with our search for fluorinated substrate analogues as inhibitors of aromatase,[2,3] we have discovered an interesting new route to steroidal vinyl fluorides. Fluorination at the saturated β-carbon of a ketone is complicated by facile loss of hydrogen fluoride. The attempted application of the fluoro-Pummerer rearrangement[4] to the steroidal case fails due to rapid formation of the 3-keto-$\Delta^{1,4}$-steroid **2** after the inital oxidation of steroidal 3-keto-1-sulfide **1** with *meta*-chloroperbenzoic acid (Scheme 1).



1 **2**

Scheme 1: Attempted Fluoro-Pummerer rearrangement

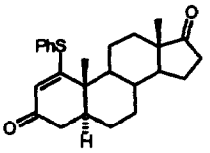
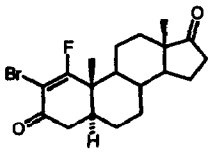
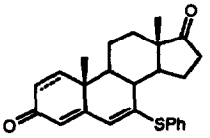
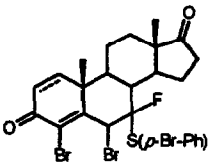
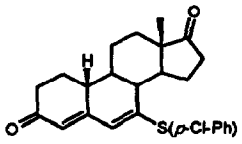
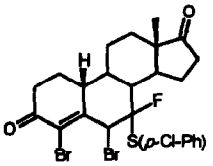
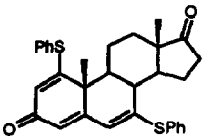
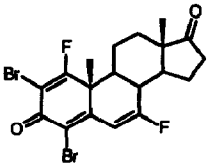
The efficient conversion of phenyl thioglycosides to glycosyl fluorides with N-bromosuccinimide (NBS) and diethylaminosulfur trifluoride (DAST)[5] prompted us to examine the reaction of sulfide **1** with that reagent in spite the risk of elimination. This procedure gives surprisingly 1-fluoroandrosta-1,4-diene-3,17-dione (**4**) from phenyl sulfide **1** in 63% yield (Scheme 2). Monitoring of the reaction by TLC reveals the primary formation of phenyl vinyl sulfide **3** followed by the 1-fluorosteroid **4**. The optimum yield of **4** is achieved after 4.5 h at 0 °C when **3** is still present.



3 **4**

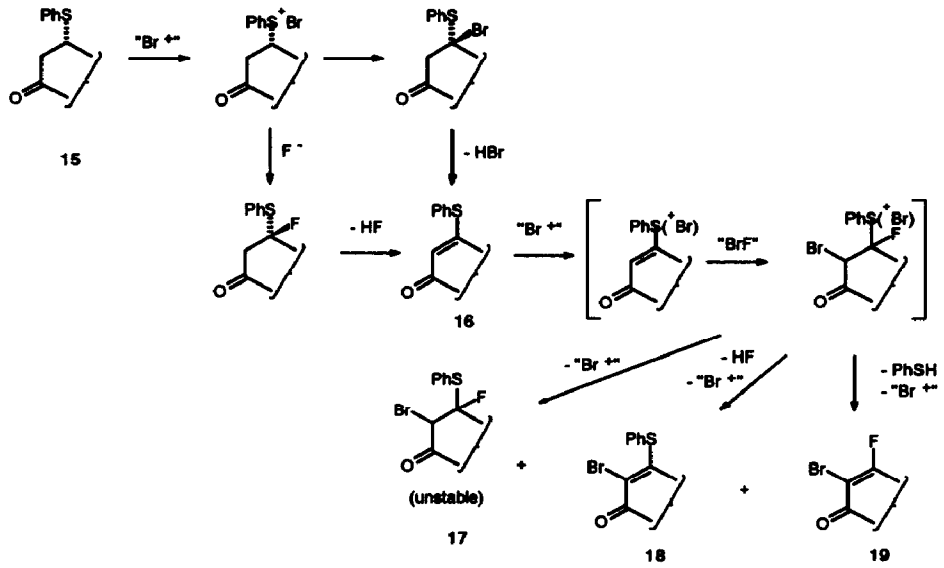
Scheme 2: Bromofluorination of 1α-thiophenylandrostenedione **1**

Table 1: Bromofluorination of Steroidal Vinylsulfides

entry[a]	vinylsulfide	reagent[b]	bromofluorosteroid	yield[c],%
1	**3**	DAST / NBS	**4**	76 (68 with HF)
2	 **5**	HF / NBS	 **6**	50 (8 with DAST)
3	 **7, 8: Δ^1**	HF / NBS	 **9, 10: Δ^1**	48 (11 with DAST)
4				44 (Δ^1)
5	 **11**	DAST / NBS	 **12**	42 (14 with HF)
6	 **13**	DAST / NBS	 **14**	77 (53 with HF)

[a]The reactions were generally performed on a 5-20 mmole scale in CH_2Cl_2. [b]Two equivalents of NBS were used, the reactions were monitored by TLC, quenched with saturated $NaHCO_3$ solution after 0.25 to 7 h at temperatures varying from -30 °C to 0 °C, extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. [c]Yields were obtained after chromatography (silica gel, hexane / ethyl acetate). All compounds gave satisfactory analytical data (^{1}H- and ^{13}C-NMR, microanalysis).[6]

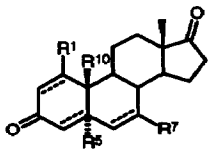
With 3-keto-$\Delta^{1,4}$-steroid **3** as starting material the yield of **4** is improved to 76%. Phenyl sulfides **1** or **15** require 3 equivalents of NBS for completion. Possible pathways for the new fluorination (Scheme 3) of **15** are the introduction of the double bond by oxidative halogenation / elimination to **16**, activation of vinyl sulfide **16** by NBS, addition of "BrF" and loss of thiophenol or hydrogen fluoride to give the isolated products **17**, **18** and **19**. Formation of the phenyl vinyl sulfide **16** from **15** is possible by reaction of NBS alone.



Scheme 3: Possible pathways for the new fluorination

As the possible intermediate vinyl sulfide **16** is stable, we looked into the reactions of several other steroidal vinyl sulfides with NBS / DAST or NBS / $(HF)_n$-pyridine. The results are summarized in Table 1. This transformation requires only 2 equivalents of NBS, because the introduction of the double bond is separated from the main reaction.

Tabelle 2: Reduction of Bromofluorosteroids with Bu_3SnH / AIBN

	entry	product no.	R^1	R^5	R^7	R^{10}	Δ	yield,%
	1	**21**	F	-	H	Me	1,4	66
	2	**22**	F	H	H	Me	1	58
	3	**23**	H	-	F	Me	4,6	53
	4	**24**	H	-	F	Me	1,4,6	34
	5	**25**	H	-	F	H	4,6	21
	6	**26**	F	-	F	Me	4,6	10

All examples were checked with both reagents (DAST or $(HF)_n$-pyridine). The more efficient reagent is given in Table 1. Identified side products shown in figure 1 include 1-fluoro-1-thiophenyl-androst-4-ene-3,17-dione (**27**, entry 1), 2-bromo-1-thiophenyl-androst-1-ene-3,17-dione (**28**, entry 2), 1,1,3,3-tertrafluoro-androstane-17-one (**29**, entry 2), 4,6-dibromo-7,7-difluoroandrost-4-ene-3,17-dione (**30**, entry 3), 4,6-dibromo-7-fluoro-7-thiophenyl-androst-4-ene-3,17-dione (**31**, entry 4) and 6-bromo-7-thio-(4-chlorophenyl)-estra-4,6-diene-3,17-dione (**32**, entry 5). Due to this diverse spectrum of side products it is recommended to test at least DAST and $(HF)_n$-pyridine in every new case of this bromofluorination for optimum yield.

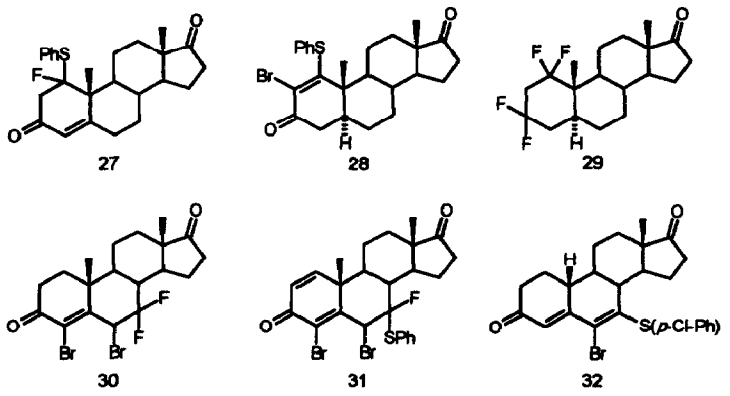


Figure 1: Side products isolated from reactions described in Table 1

The obtained bromofluorosteroids were selectivly reduced by treatment with tributyltin hydride (Bu_3SnH) / azobisisobutyronitrile (AIBN) to the debrominated vinyl fluorides (Table 2). The low yields in the cases with $\Delta^{4,6}$ or $\Delta^{1,4,6}$ (entries 3 - 6) are due to the high stability of the 4-bromo intermediates towards reduction. After prolonged reaction times (3 to 7 h , 90 °C) for the 4-bromosteroids with Bu_3SnH / AIBN a small yield of the debromination product is obtained.

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References and Notes

1. This work was partially reported at the 10th Europ. Symp. Fluorine Chem., Padua, Italy, September **1992**.
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3. M. G. Rowlands, A. B. Foster, J. Mann, B. Pietrzak, J. Wilkinson and R. C. Coombes, *Steroids* **49**, 371 (1987).
4. G. Krishnan and P. Sampson, *Tetrahedron Lett.* **31**, 5609 (1990).
5. K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis and J. L. Randall, *J. Am. Chem. Soc.* **106**, 4189 (1984).
6. All new fluorinated compounds were characterised by IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis. Selected data ^{1}H-NMR at (300 MHz in $CDCl_3$, ^{13}C-NMR at 75 MHz in $CDCl_3$): (**21**) m. p. 119 °C, $[\alpha]_D^{22}$ = +62.2° (c = 0.5% in $CHCl_3$), ^{1}H-NMR δ 6.07 (1H, s, 4-H), 5.92 (1H, dd, J = 2 and 16 Hz, 2-H), 2.5 (3H, m), 1.43 (3H, s, 19-H), 0.93 (3H, s, 18-H), ^{13}C-NMR δ 14.4 (18-C), 16.2 (19-C, d, $J_{C\text{-}F}$ = 2.9 Hz), 22.7 (15-C), 23.9 (11-C, d, $J_{C\text{-}F}$ = 8.6 Hz), 31.8 (7-C, d, $J_{C\text{-}F}$ = 1.2 Hz), 32.2 (6-C, d, $J_{C\text{-}F}$ = 3.5 Hz), 33.2 (12-C), 35.8 (8-C), 36.2 (16-C), 46.8 (10-C, d, $J_{C\text{-}F}$ = 18.0 Hz), 47.9 (13-C), 51.0 (14-C), 54.3 (9-C, d, $J_{C\text{-}F}$ = 3.8 Hz), 110.1 (2-C, d, $J_{C\text{-}F}$ = 13.5 Hz), 124.0 (4-C), 164.4 (5-C, d, $J_{C\text{-}F}$ = 4.9 Hz), 182.8 (1-C, d, $J_{C\text{-}F}$ = 287.4 Hz), 188.2 (3-C, d, $J_{C\text{-}F}$ = 17.5 Hz), 220.4 (17-C); (**25**) m. p. 199-201 °C, $[\alpha]_D^{22}$ = +114.9° (c = 0.5% in $CHCl_3$), ^{13}C-NMR δ 13.9 (18-C), 23.9 (15-C, d, $J_{C\text{-}F}$ = 7.8 Hz), 24.5 (11-C, d, $J_{C\text{-}F}$ = 2.2 Hz), 26.6 (1-C), 31.0 (12-C), 35.3 (2-C, d, $J_{C\text{-}F}$ = 2.0 Hz), 37.2 (16-C), 39.7 (10-C), 41.2 (8-C , d, $J_{C\text{-}F}$ = 18.2 Hz), 46.7 (9-C, d, $J_{C\text{-}F}$ = 7.7 Hz, 14-C), 48.7 (13-C), 108.3 (6-C, d, $J_{C\text{-}F}$ = 21.2 Hz), 124.1 (4-C, d, $J_{C\text{-}F}$ = 10.3 Hz), 157.3 (5-C, d, $J_{C\text{-}F}$ = 11.8 Hz), 170.2 (7-C, d, $J_{C\text{-}F}$ = 283.1 Hz), 198.6 (3-C), 219.0 (17-C).

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