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Short Research Article

Synthesis of (4-^{14}C)fluasterone†

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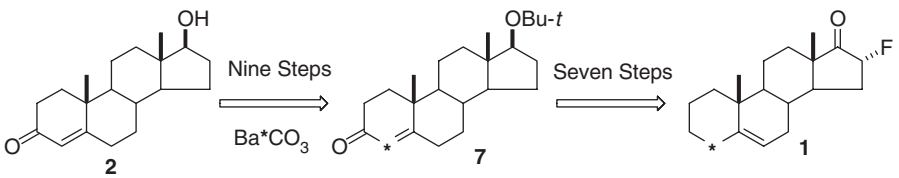
Introduction

Fluasterone (**1**), (16α)-16-fluoro-androst-5-en-17-one, is a synthetically stable adrenocortical steroid analog of dehydroepiandrosterone (DHEA). Fluasterone has demonstrated efficacy in a variety of anti-autoimmune, anti-proliferative and anti-diabetic models. The National Cancer Institute (NCI) is evaluating fluasterone as a cancer-preventative agent. Preventive efficacy has been demonstrated in numerous preclinical models, including tumors of the breast, liver, colon, prostate, skin and lymphatic tissue. Fluasterone suppresses inflammation and is effective in preclinical models of chronic inflammatory disease including psoriasis, asthma, rheumatoid arthritis, multiple sclerosis and lupus erythematosus.

To facilitate further research on this novel DHEA-analog, we have synthesized [4-^{14}C]fluasterone, starting from testosterone Scheme 1.



Scheme 1

Carbon-14 is introduced into the 4-position of testosterone (**2**) in nine steps, via $^{14}CH_3MgI$, generated from barium [^{14}C]carbonate, through [^{14}C]methanol and [^{14}C]iodomethane. High-purity [4-^{14}C]fluasterone (**1**) (chemical purity >98.1%, radiochemical purity = 98.9%, optical purity = 99.3%, specific activity 58.3 mCi/mmol) is subsequently produced in seven steps, with an overall radioactive yield of approximately 13% from [^{14}C]iodomethane. The overall synthetic strategy for preparation of fluasterone is derived from the original synthesis reported by Lewbart *et al.* in 1988.[1]

Results and discussion

The *t*-butyl-protected carbon-14-labeled testosterone (**7**) was synthesized according to a published method,[2] from testosterone (**2**) as starting material in 57% chemical/65% radiochemical yield. The carbon-14 was introduced into the lactone (**5**) framework at step-4, via $^{14}CH_3MgI$, generated from barium [^{14}C]carbonate, through [^{14}C]methanol and [^{14}C]iodomethane.

Treatment of **6** with ethanolic sodium hydroxide at room temperature overnight gave enone **7**. Acetylation of enone **7** was accomplished in refluxing acetyl chloride and acetyl anhydride. This was followed by reduction with $NaBH_4$, iodination using I_2/PPh_3, and subsequent dehalogenation with Zn in refluxing acetic acid, to produce the acetyl-protected **11** in 60% yield. If the duration of reflux is less than 4 h, the product is a

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mixture of the compounds: **11**, R = *t*-butyl and R = H. The value of exchanging the protecting group from *t*-butyl to acetyl is that the base hydrolysis in step 10 is easier and of higher yield than the corresponding acid hydrolysis that would be necessitated if R = *t*-butyl.

Jones oxidation of the alcohol (**12**) affords ketone **13**, which is then silylated using trimethylsilyl trifluoromethanesulfonate to afford **14**, *in situ*, which is then immediately used in the next reaction. The desired product [4-^{14}C]-16α-fluoro-5-androsten-17-one (**1**) was obtained from **14** by reaction with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate) (SelectFluor^{TM}) in 48% yield (overall from **13**).

The total chemical and radiochemical yield from testosterone **2** and [^{14}C]iodomethane are 12 and 13%, respectively. The purity of the final target compound (**1**) was: chemical purity >98.1%, radiochemical purity = 98.9%, optical purity = 99.3%, specific activity 58.3 mCi/mmol).[3,4]

Acknowledgements

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REFERENCES

1. Schwartz AG, Lewbart ML, Pashko LL. *Cancer Res* 1988; **48**: 4817.
2. Han M, Hayes BA, Prendergast PT, Gupta S. *J Label Compd Radiopharm* 2000; **43**: 1149.
3. Column: Alltech Altima C18, 5 μm particle size, 250 mm × 4.6 mm ID; Mobile phase: (A) 20% acetonitrile in water, (B) acetonitrile; program: 45% B for 20 min, to 100% B in 15 min, hold 10 min; Detector: UV (λ = 212 nm; β-RAM Model B3.
4. Chiral column: Regis (*R*, *R*) Whelk-01; 5 μm particle size, 250 mm × 4.6 mm ID; Mobile phase: (A) 20% acetonitrile in water, (B) acetonitrile; Program: isocratic, 90% A, 10% Bo 100% B; Detector: UV (λ = 212 nm).

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