Synthesis of the selective estrogen receptor modulator STX and of a precursor for the radio labelling of STX with radioactive methyl iodide

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Introduction

In the brain, rapid estrogen responses through non genomic pathways have been found. Those responses are not caused by estrogen receptor mediated gene transcription. Recently, a molecule was reported, which does not bind to nuclear estrogen receptors (ER) but showed estrogen like effects. This non-genomic response is induced by rapidly inhibiting G-Protein-coupled inwardly rectifying potassium channels (GIRK) activation in hypothalamic γ-amino butyric acid and proopio-melanocortin neurons.

This estrogen-like effect suggests that a novel estrogen receptor exists, which is different from nuclear ER. To image the distribution and concentration of these receptors in the brain, the compound STX had to be synthesized and labelled with [^{11}C-methyl iodide].

Experimental

Our synthesis of a reference compound (STX itself) and a labeling precursor lacking a methyl group were guided by the original literature report. However, during the course of the synthesis we examined several of the transformations in detail and in many cases optimized the literature procedure to increase yield and/or to improve the scalability of the synthesis.

The first step in the synthesis of STX was a titanocene-mediated alkylation of an alkyne that was quenched with bromine to selectively yield the E-Olefin (A). The isolated bromoalkene was then used in a Negishi-type reaction for the tetrakis-(triphenyl-phosphine)-Pd (0) catalyzed cross coupling of the organozinc intermediate with the tertbutoxybromo-benzene to give the phenyl-4-tert-butoxy-phenyl-trimethylsilylbutene (B). The trimethylsilyl-group was replaced through treatment of (B) with a bromine solution in anhydrous dichloromethane to yield the vinyl bromide (C).

At this stage of the synthesis two inseparable stereoisomers were formed in the ratio 2:1 favouring the Z isomer. The mixture of the two stereo isomers was then transmetalated with BuLi and a dry stream of carbon dioxide was conveyed through the reaction mixture to yield the carboxylic acids (D).

In a nucleophilic substitution of the 2-(dimethylamino) ethyl chloride by the Boc-protected 4-aminophenol and subsequent removal of the protecting group the para substituted Aniline (E) was obtained. The E/Z mixture of the enoic acid was then coupled with HBTU and DMAP to the para-substituted aniline (E) to obtain a mixture of amides. Hydrolyses of the 4-terbutylether resulted in the compounds ST-X and ST-Y. Direct N-demethylation of ST-X failed so the precursor synthesis starts from compound E to yield the monomethylated version of the ST-X, that can be labelled with ^{11}C-methyl iodide. (Figure 2).

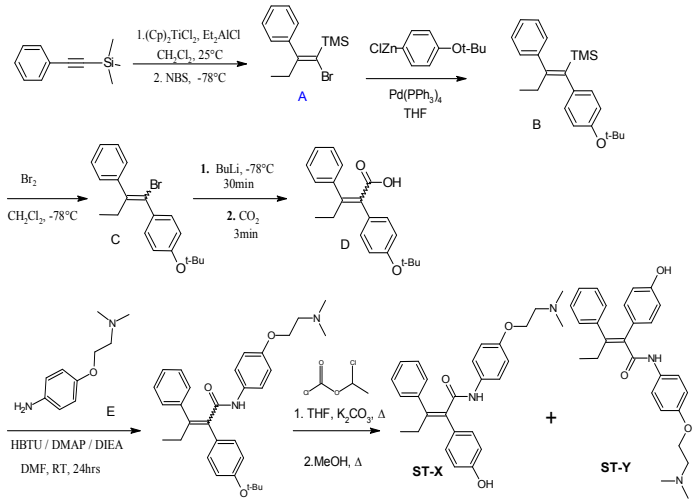

Figure 1. Synthesis of the reference compound ST-X

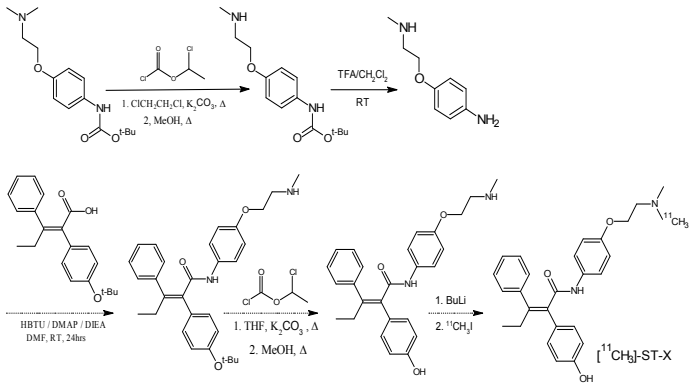

Figure 2. Precursor synthesis and radio labelling with [$^{11}CH_3$-I].

Results: The desired molecule ST-X could be successfully synthesized but not separated from co-forming stereoisomer ST-Y. At the time of writing no ^{11}C-labelled ST-X had yet been obtained.

References

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