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Short Research Article

Synthesis of ^{13}C- and ^{2}H-labelled AZD4619: a selective PPARα agonist†

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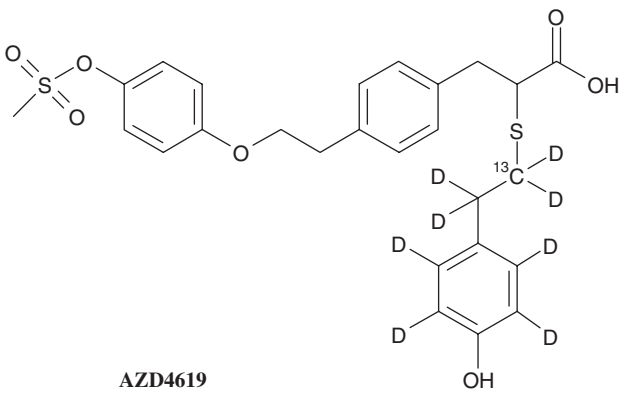
Introduction

PPARα (peroxisome proliferator-activated receptor alpha) is a member in the nuclear receptor superfamily and is a regulator of genes in lipid and fatty acid metabolism. A disorder in these genes can cause IRS (insulin resistance syndrome) with dyslipidemia and type II diabetes. Our approach to the PPARα is to correct dyslipidemia in IRS and hyperglycemia of type II diabetes that will reduce cardiovascular morbidity and mortality. To support our research program, a stable isotope-labelled compound **(AZD4619)** was needed for quantitative mass bio-analytical studies.



AZD4619

Results and discussion

Commercially available *p*-cresole-d_8 was protected with methyl iodide to give **(1)** which was reacted with N-bromosuccinimide in carbon tetrachloride under photoirradiation.[1] The resulting **(2)** was directly treated with $K^{13}CN$ in the presence of 18-crown-6 in acetonitrile[2] giving the desired ^{13}C-labelled precursor **(3)**. NaOD was carefully made from Na and D_2O and used for the hydrolysis of nitrile **(3)** to acid **(4)**. Deprotection to **(5)** was performed using microwave heating with deuterium bromide.Esterification of the carboxylic acid **(5)** with benzyl chloride to **(6)** was done with microwaves, followed by reduction to the alcohol **(7)** with lithium aluminum deuteride. The complex was quenched with deuterium oxide and deuterium chloride. A new protection of the phenol was performed using benzyl chloride to give **(8)**, whereupon **(8)** was treated with mesyl chloride to give mesylate **(9)**, which was reacted with thioacetic acid in presence of cesium carbonate to give thioester **(10)**.**(10)** was deprotected with sodium methanethiolate in methanol and DMF to give the free thiol, which was alkylated with alkyl chloride **(11)** to give **(12)**. Deprotection to the phenol **(13)** was done with boron trifluoride diethyl etherate and dimethyl sulfide in DCM. The ester hydrolysis to reach **AZD4619** was done with LiOD carefully made from Li and D_2O.

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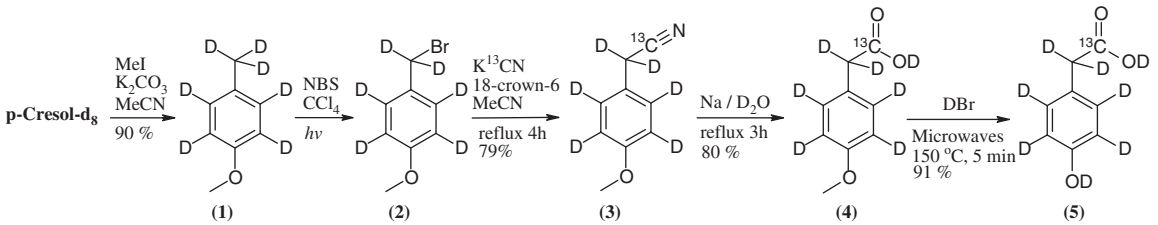
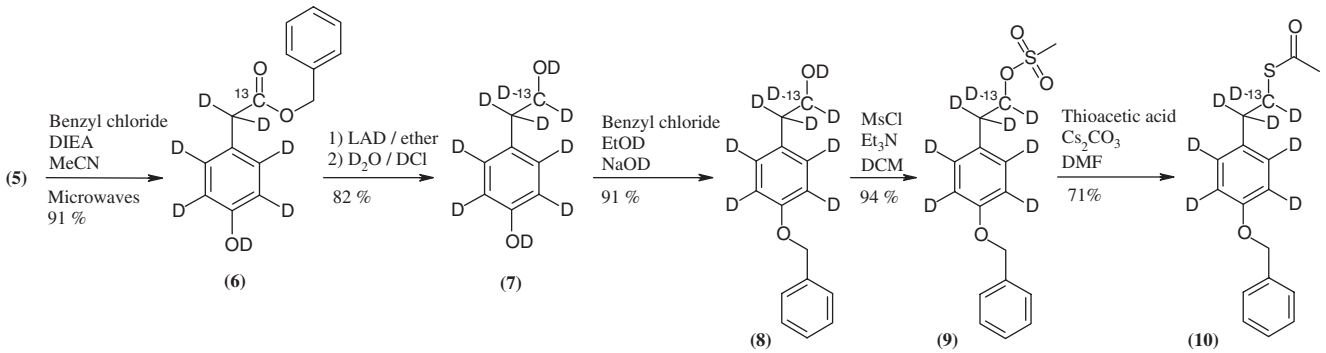
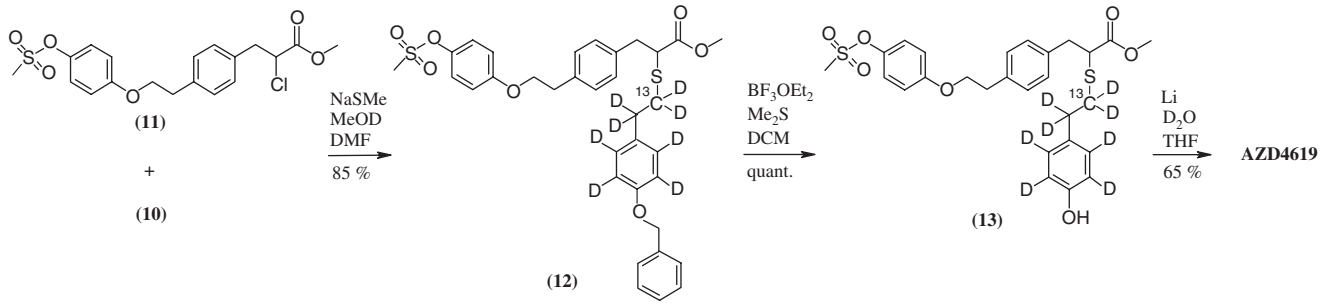
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



Scheme 1



Scheme 2



Scheme 3

Conclusions

The synthesis of AZD4619 included 14 steps with an overall yield of 13%. To reach the requirements of an increase in molecular weight by at least nine, both ^{13}C and ^{2}H had to be incorporated. According to our previous experiences the loss of deuterium in acidic positions necessitates the use of deuterated solvents and reagents.

REFERENCES

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