

Short Research Article

Labelling of GW796406X with (M+4)-methylcopper[†]

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Received 29 August 2006; Revised 14 December 2006; Accepted 14 December 2006

Keywords: carbon-13; [¹³C, ²H₃]methyl copper; oxazolidinone; GW796406

Introduction

A stable isotope labelled (SIL) version of GW796406X¹ **1** was required as a mass labelled internal standard and a carbon-14 version **12** for ADME studies.

Results and discussion

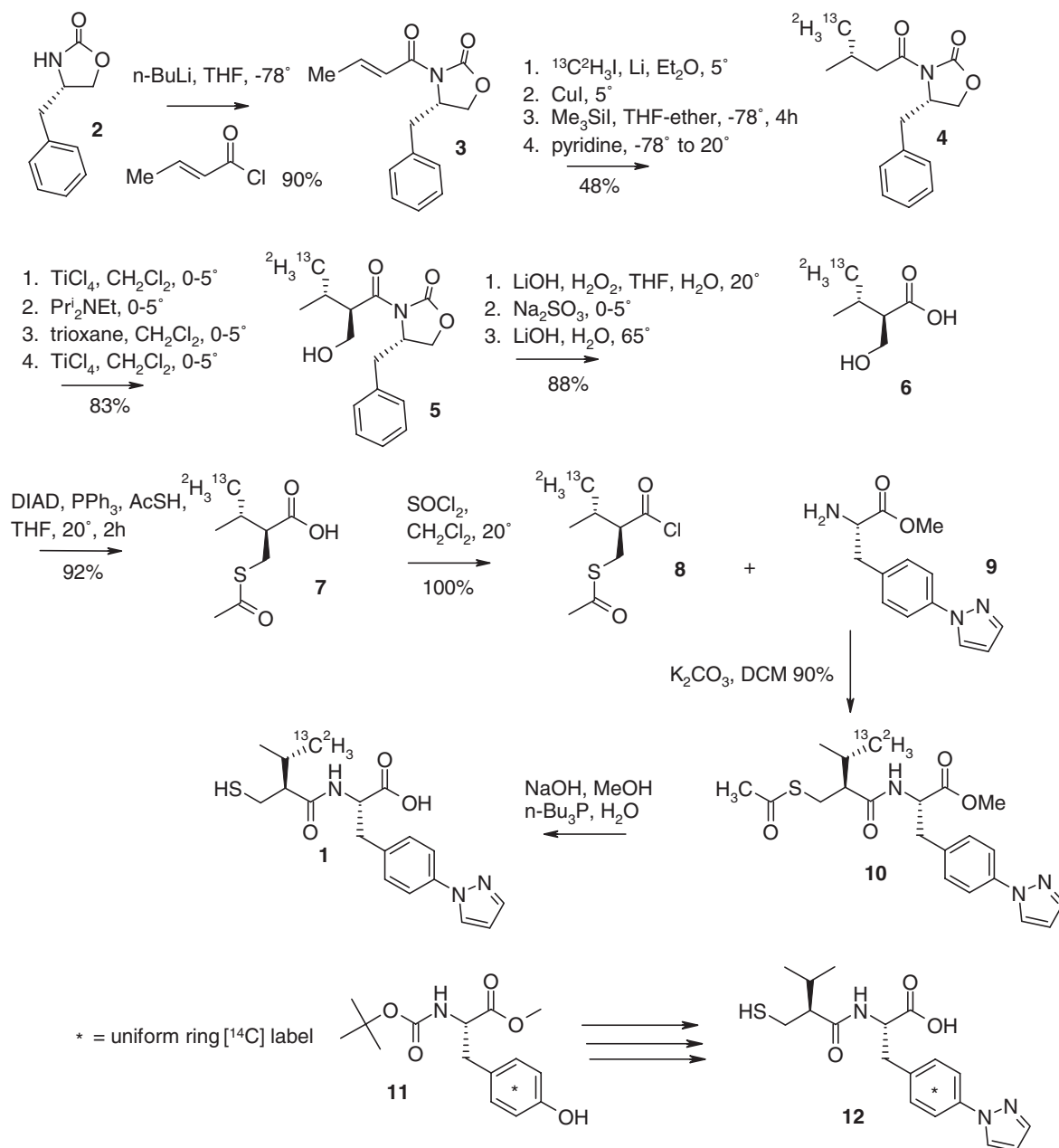
Addition of 2 equivalents of [²H₃, ¹³C]methylcopper to the chiral N-(*E*)-crotonyl oxazolidinone² **3** gave clean conversion to the required **4**. The highly stereoselective chelation-controlled aldol reaction of the titanium enolate of imide (**4**) with formaldehyde trimer gave essentially one diastereoisomer **5**. Trace amounts of the other C-2 diastereoisomer were removed during the purification. Hydrolytic cleavage gave the acid **6** cleanly. Mitsunobu reaction of alcohol **6** with thiolac-

etic acid gave the adduct **7**. Treatment with thionyl chloride gave acid chloride **8**.

Compound **9** was prepared from N-Boc tyrosine methyl ester by derivatisation of the phenolic OH group to triflate, palladium-catalysed boronic ester formation, and periodate-assisted hydrolysis gave a boronic acid. As **9** would eventually contain a carbon-14 label, we optimized the coupling of the boronic acid and pyrazole with equivalent amounts of each. Chiral HPLC confirmed that **9** had not racemized. Condensation of **8** with amine **9** was readily carried out using Schotten-Baumann conditions. The purified (*S,S*) product **10** was shown (chiral HPLC, NMR) to contain insignificant amounts of the undesired (*R,S*) and (*S,R*) diastereoisomers. Alkaline hydrolysis gave the SIL-GW796406 **1** after a simple work-up. The carbon-14 labelled version **12** of GW796406 was prepared similarly from N-Boc [¹⁴C]tyrosine methyl ester **11**.

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



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