Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 500–501.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1223

JLCR

Short Research Article

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

ALAN H. WADSWORTH and KENNETH W. M. LAWRIE*
GlaxoSmithKline, Isotope Chemistry, Medicines Research Centre Gunnels Wood Road Stevenage SG1 2NY, UK

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

Keywords: carbon-13; [^{13}C,$^{2}H_3$]methyl copper; oxazolidinone; GW796406

Introduction

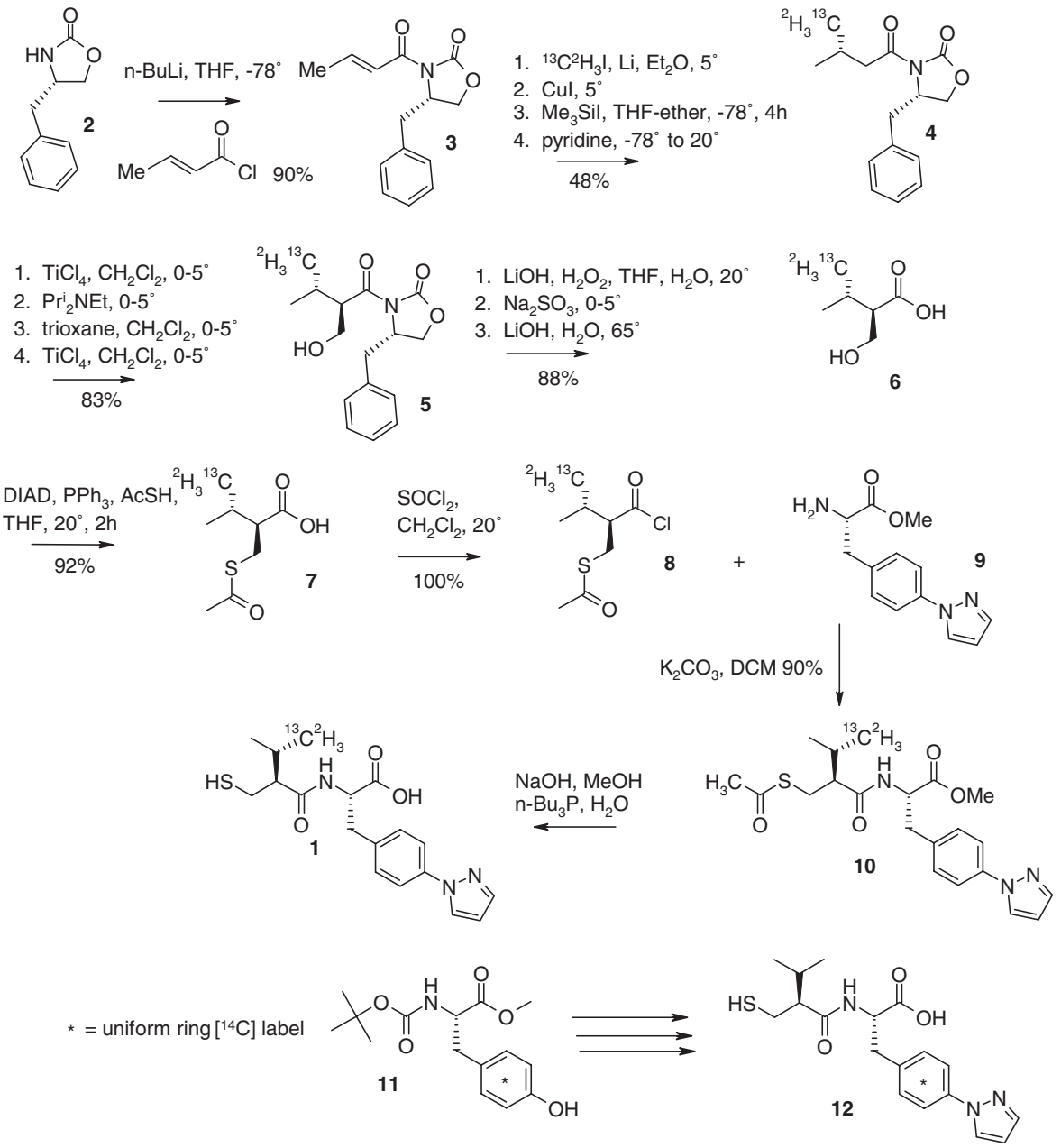
A stable isotope labelled (SIL) version of GW796406X[1] **1** was required as a mass labelled internal standard and a carbon-14 version **12** for ADME studies.

Results and discussion

Addition of 2 equivalents of [$^{2}H_3$,^{13}C]methylcopper to the chiral N-(*E*)-crotonyl oxazolidinone[2] **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 thiolactic 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 [U-^{14}C]tyrosine methyl ester **11**.

*Correspondence to: Kenneth W. M. Lawrie, GlaxoSmithKline, Isotope Chemistry, Medicines Research Centre Gunnels Wood Road Stevenage SG1 2NY, UK. E-mail: ken.w.lawrie@gsk.com
†Proceedings of the Ninth Inernational Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



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DOI: 10.1002.jlcr