Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 526–527.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1240

JLCR

Short Research Article

Labelling of S-0139 with [M+4]-fumaric acid†

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

Keywords: carbon-13; fumarate; selective hydrolysis

Introduction

Shionogi's S-0139 **1** is a highly selective endothelin-A receptor antagonist that was developed in a joint venture with GSK. A stable isotope labelled version **12** was requested for use as a mass labelled internal standard.

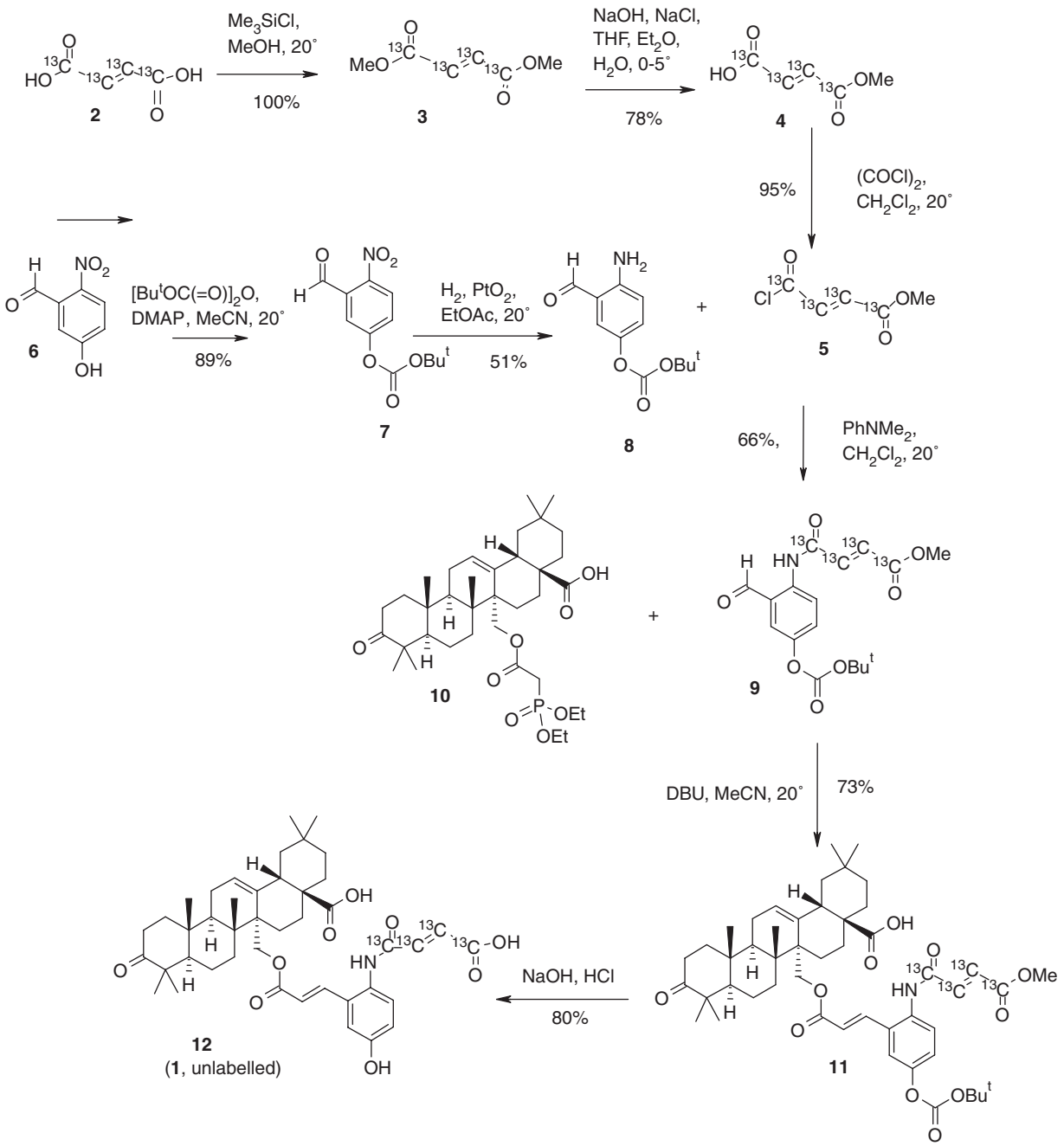
Results and discussion

Selective saponification of dimethyl fumarate to its half-acid methyl ester is reported by Niwayama[1] in 79% yield, by portionwise addition of sodium hydroxide in aqueous THF at 0°C. The authors suggest that the high selectivity of this reaction is due to effects at the interface of the biphasic reaction medium. In our hands the yield was only 50% and the reaction became homogeneous towards the end. We found that addition of ether and sodium chloride maintained the two phases. As a result, we were able to obtain reproducibly a yield of >75% half-ester **4** albeit containing ca. 20% diacid **2**. Hydroxynitroaldehyde **6** was O-protected with a Boc group in order to avoid selectivity problems during the subsequent anilide formation.[2] The catalytic reduction of nitroaldehyde **7** needed to be carefully controlled to minimize the reduction of the aldehyde group. The Wittig–Horner–Emmons reaction of ketal-phosphonate **10** with aldehyde **9** to give the protected S-0139 **11** was carried out with DBU as base. De-protection required alkaline hydrolysis to saponify the methyl ester group and strong acid hydrolysis to cleave the ketal and O-Boc groups, followed by chromatographic purification. Compound **12** was found to contain no detectable level of unlabelled material.

Conclusion

A synthesis of [M + 4] S-0139 **12** has been demonstrated in eight steps with an overall yield of 28%, using an efficient preparation of the half-ester half-acid chloride of [$^{13}C_4$] fumaric acid.

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



REFERENCES

1. (a) Niwayama S. *Tetrahedron Lett* 2000; **41**: 10163–10166; (b) Niwayama S. *J Org Chem* 2000; **65**: 5834–5836.

2. Konoike T, Araki Y, Hayashi T, Sakurai K, Tozyo T. European Patent 628569A1 Shionogi, 1994.

DOI: 10.1002.jlcr