Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 273–276.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1235

JLCR

Short Research Article

Stable isotopic labelling of heterocyclic compounds†

ANDREW J. BURTON* and ALAN H. WADSWORTH
GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

Received 23 August 2006; Revised 18 December 2006; Accepted 18 December 2006

Abstract: Stable isotopically labelled (SIL) versions of Glimepiride **1** (10 steps, 11% overall yield), a blood glucose lowering drug, and Melagatran **13** (9 steps, 17% overall yield), an anticoagulant with similar uses to warfarin, were synthesized as internal standards for LCMS assays. Modifications of known routes (Weyer *et al.*, US Patent 4379785, Hocchst, 1983; Antonsson *et al.*, PCT International Application W09429336, 1994) to these compounds are examples of the introduction of stable isotopes *via* heterocyclic intermediates. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: Glimepiride; Melagatran; isotope labelling; pyrrolidinone; oxadiazolinone

Introduction

Marketed compounds Glimepiride, a blood glucose lowering agent for use in the treatment of diabetes, and Melagatran, an anticoagulant, were required in stable isotopically labelled form by GSK as reference standards for comparison work. Both syntheses are variations of the published synthetic routes and involve the stable labelling of heterocyclic precursors; a pyrrolidinone and an oxadiazolinone in the case of Glimepiride and Melagatran, respectively.

Results and discussion

$^2H_5$-Glimepiride

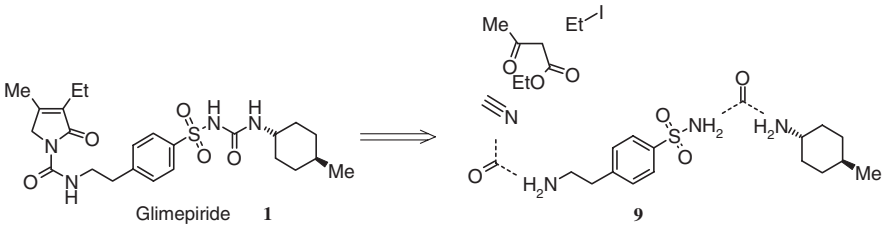
The Retrosynthesis of Glimepiride **1** is shown (Scheme 1). In contrast to the published route,[1] which employs a coupling with phenylethyl isocyanate followed by a chlorosulfonylation, commercially available 4-(2-aminoethyl)benzenesulfonamide **9** was selected as a more suitable, alternative starting material

Readily available $^2H_5$-ethyl iodide seemed the most appropriate isotopically labelled starting material and therefore the success of the synthesis hinged upon construction of labelled pyrrolidinone **7**. Fortunately, a synthesis of the unlabelled pyrrolidinone had already been developed by Rapoport.[3] However, the synthesis was low yielding and required the use of Raney nickel for reduction of the cyanohydrin **4**.

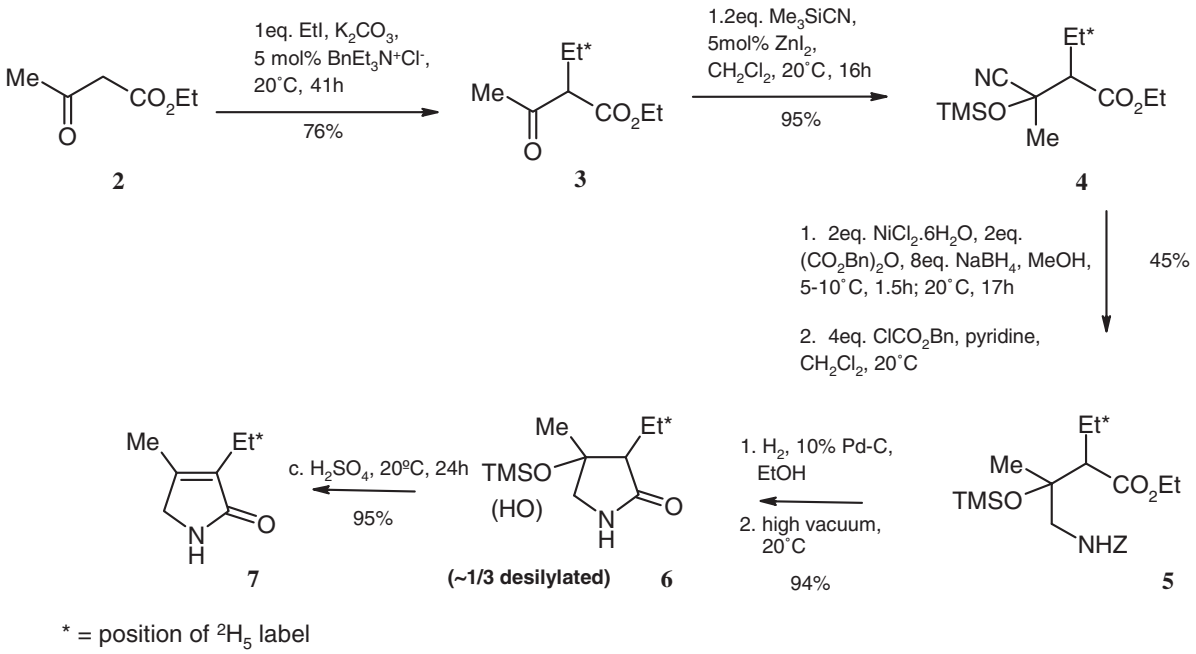
Thus, $^2H_5$-ethyl iodide alkylation of ethyl acetoacetate under phase transfer conditions gave the monoalkylated β-ketoester in 76% yield. In contrast to Rapoport's reported conditions, no problem was observed with over alkylation. The silyl cyanohydrin **4** was formed under standard conditions and reduced with nickel hydride, generated *in situ* using Caddick's conditions.[4] Here dibenzyl-dicarbonate was used as the trap for the resulting primary amine. The residual amine was protected with benzyl chorofor-mate, giving an overall yield of 45% for the transformation. Catalytic hydrogenation of compound **5** and spontaneous cyclisation, followed by acid induced elimination gave the required labelled pyrrolidinone **7** (Scheme 2).

The activated mixed urea **8** could be formed on treatment of **7** with 1,1′-carbonyldiimidazole and could then be reacted with the commercially available 4-(2-aminoethyl) benzenesulfonamide **9** to give urea **10**. The formation of the sulfonyl urea was then readily achieved by activation with methyl chloroformate to give **11** and then reaction with *trans*-4-methycyclohexylamine **12**. Thus the overall synthesis of [M+5] glimepiride had been completed in 10 steps, 11% overall yield (Scheme 3).

*Correspondence to: Andrew J. Burton, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK.
E-mail: andrew.j.burton@gsk.com
†Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



Scheme 1



Scheme 2

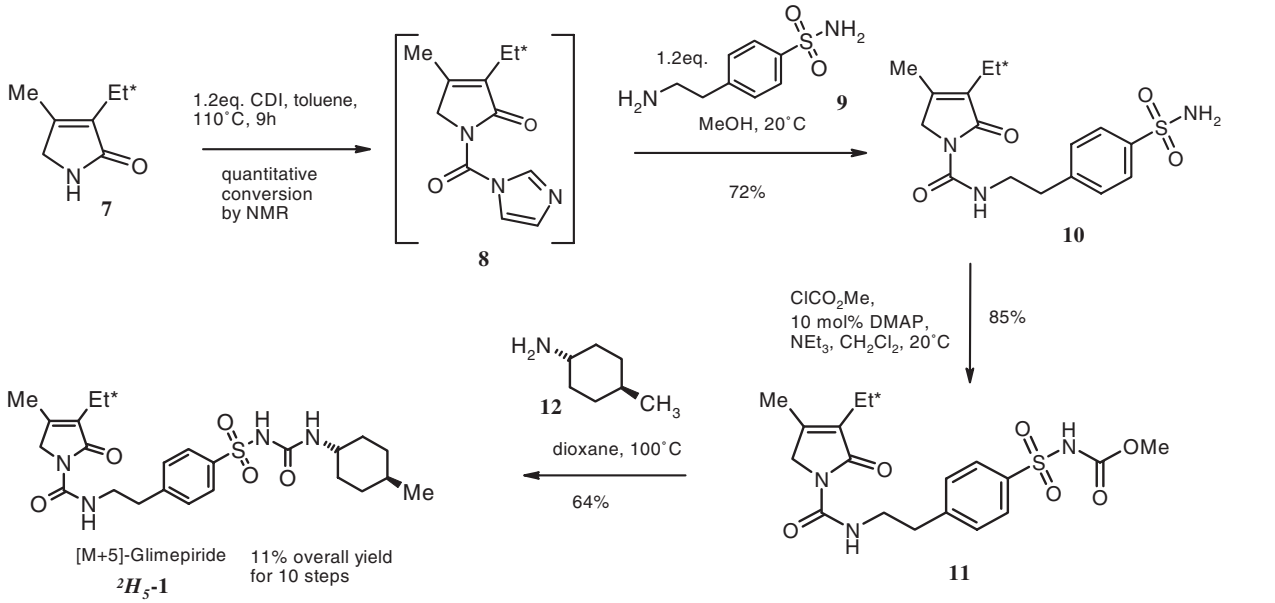
$^{13}C_1$,$^{15}N_3$-Melagatran

The commercial synthesis of Melagatran[2] **13** involves the coupling of dipeptide **14** with protected 4-aminomethyl benzamidine **15** and glycolic acid **16**. Previous work published by GSK[5] demonstrated that the desired amidine could be obtained from mild hydrogenolysis of oxadiazolinones, themselves easily synthesised and compatible with the proposed labelling strategy (Scheme 4)

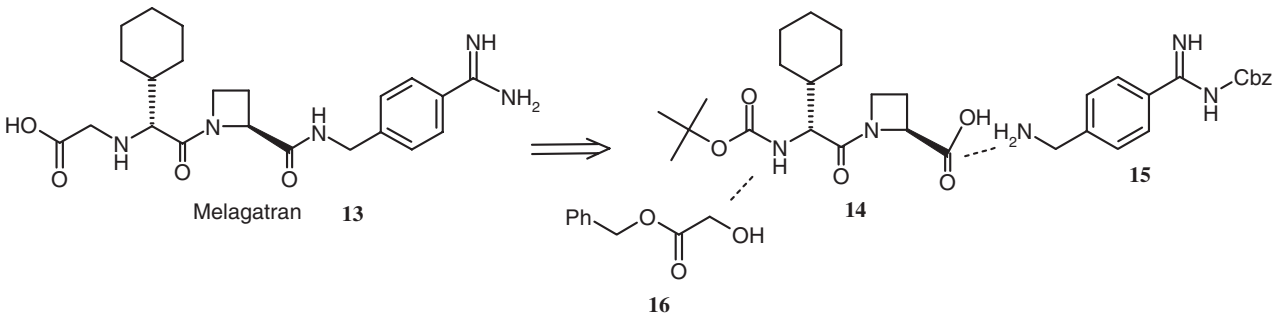
Amidation of 4-iodophenyl acetic acid **17** with $^{15}NH_3$ gave the corresponding primary amide **18**. Next cyanation using Buchwald's conditions[6] allowed introduction of a doubly labelled nitrile group to give $^{13}C_1$,$^{15}N_2$-benzonitrile **19**. In addition the coupling reaction produced two major impurities: the dehalogenated amide and a dimer formed from a Buchwald coupling of the amide and iodide. The final labelled atom was introduced *via* reaction of the nitrile with ^{15}N labelled hydroxylamine. The resultant amidoxime **20** was then converted to the oxadiazolinone **21** *via* condensation with 1,1′-carbonyldiimidazole. Hoffmann rearrangement of **21** with Koser's reagent **22** gave $^{13}C_1$,$^{15}N_3$-benzylamine **23** as its tosylate salt (Scheme 5).

Peptide coupling of benzylamine **23** and N-protected dipeptide **14** followed by Boc deprotection gave amine **24**. Alkylation with the *p*-nosylate derivative of glycolic acid lead to over-alkylation. Instead, reductive amidation using benzyl glyoxylate yielded the direct precursor to [M+4] Melagatran. Hydrogenolysis cleaved both the benzyl protection and oxadiazolinone to complete the synthesis in 9 steps and 17% overall yield (Scheme 6).

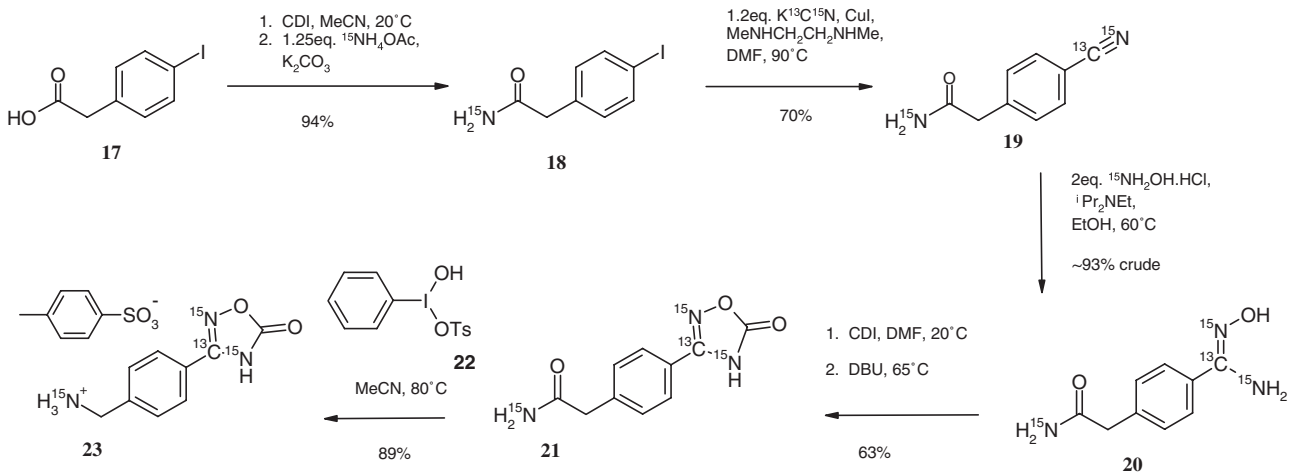
DOI: 10.1002.jlcr



Scheme 3

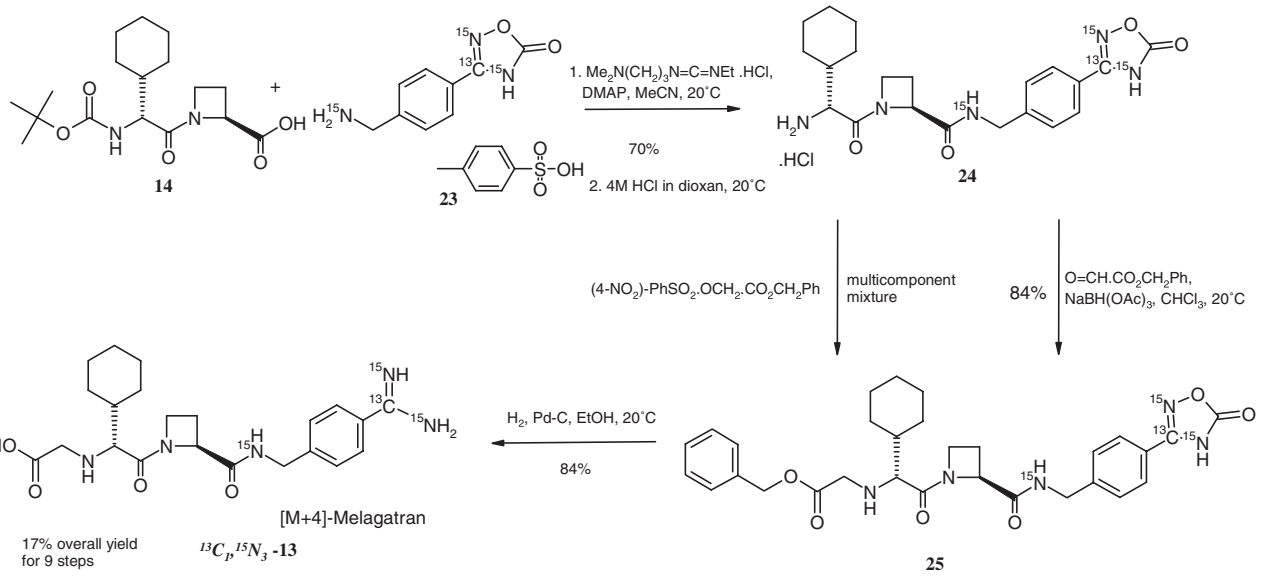


Scheme 4



Scheme 5

DOI: 10.1002.jlcr



Scheme 6

Conclusion

Modification of known routes to Glimepiride and Melagatran have been investigated and have allowed the introduction of stable isotopes into compounds *via* heterocyclic intermediates. These compounds have been used successfully within GSK as reference standards in therapeutic studies.

Acknowledgements

We are grateful for support and helpful suggestions from other members of the GSK Isotope group in Stevenage, UK.

REFERENCES

1. Weyer R, Hitzel V, Geisen K, Regitz G. US Patent 4379785 Hoechst, 1983.
2. Antonsson KT, Bylund RE, Gustafsson ND, Nilson NOI. PCT International Application WO9429336 Astra AB, 1994.
3. Bishop JE, Nagy JO, O'Connell JF, Rapoport H. *J Am Chem Soc* 1991; **113**: 8024–8035.
4. Caddick S, Haynes AKdeK, Judd DB and Williams MRV. *Tetrahedron Lett* 2000; **41**: 3513–3516. DOI:10.1016/S0040–4039(00)00410–X
5. Bolton RE, Coote SJ, Finch H, Lowdon A, Pegg N, Vinader MV. *Tetrahedron Lett* 1995; **36**: 4471–4474. DOI:10.1016/0040-4039(95)00755-2
6. Zanon J, Klapars A, Buchwald SL. *J Am Chem Soc* 2003; **125**: 2890–2891. DOI: 10.1021/ja0299708