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Research Article

Synthesis of radiolabelled photolabile fusidic acid analogues

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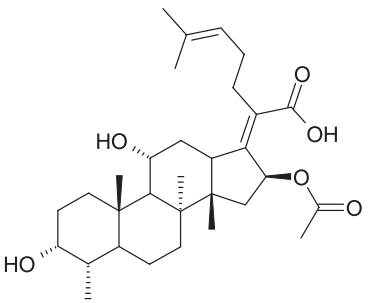
Abstract: Two analogues of the antibiotic fusidic acid with photolabile groups, 4-azidophenyl and 4-benzoylphenyl, were successfully labelled with tritium via Pd/C catalysed tritiation of unsaturated precursors. Specific activities of 36 and 44 Ci/mmol were obtained. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: tritium; photolabile groups; fusidic acid analogues; Pd/C catalysed tritiation

Introduction

Fusidic acid is a unique antibiotic with a potent activity against *Staphylococcus aureus*. Fusidic acid inhibits the bacterial protein synthesis by interference with the elongation factor G (EF-G)/ribosome complex.[1] In an attempt to clarify the mechanism of action of fusidic acid, two radioactive, photolabile-labelled compounds ([24,25-$^3H_2$]**5** and [24,25-$^3H_2$]**8**) were prepared. Tritium was introduced via a Pd/C-catalysed tritiation.



Fusidic Acid

Results and discussion

Compounds **1** and **2** (24-*E*/*Z*; 1:3 mixture) were prepared according to a described method.[1] [24,25-$^3H_2$]**3** was prepared by treating **1** and **2** with $^3H_2$ gas in MeOH for 70 min in the presence of Pd/C affording 600 mCi crude product. [24,25-$^3H_2$]**3** was transformed into the azide [24,25-$^3H_2$]**4** by a procedure reported by Liu and Tor[2] by treating the amine with triflyl azide and triethylamine in the presence of $CuSO_4$ as catalyst. The protective group was removed by treating [24,25-$^3H_2$]**4** with K_2CO_3 in MeOH at room temperature for 1.5 h. Final purification was achieved by prep-HPLC (RP-18, THF:H_2O:CH_3COOH (50:50:1)) affording [24,25-$^3H_2$]**5** (37.8 mCi) with a specific activity of 36 Ci/mmol in 6.3% overall radiochemical yield. Because of an unexpected formation of 3-formyl-[24,25-$^3H_2$]**5** when THF:H_2O:HCOOH (50:50:1) was used as eluent in the HPLC purification, a reduced yield was obtained. By replacing formic acid with acetic acid in the HPLC eluent no esterification of [24,25-$^3H_2$]**5** took place (Scheme 1).

Compounds **6** and **7** (24-*E*/*Z*; 1:3 mixture), prepared as described in the literature,[1] were treated with $^3H_2$ gas in the presence of Pd/C in MeOH for 12 min affording 638 mCi of crude [24,25-$^3H_2$]**8**. The crude product was filtered through silica gel to remove remains of catalyst followed by prep-HPLC purification (RP-18, THF:H_2O:CH_3COOH (37:63:0.5)) affording [24,25-$^3H_2$]**8** (161 mCi) with a specific activity of 44 Ci/mmol in 25% overall radiochemical yield. Owing to difficulties in the HPLC separation of unreacted *E*-isomer (**6**) from [24,25-$^3H_2$]**8**, not all [24,25-$^3H_2$]**8** was isolated from the reaction mixture (Scheme 2).

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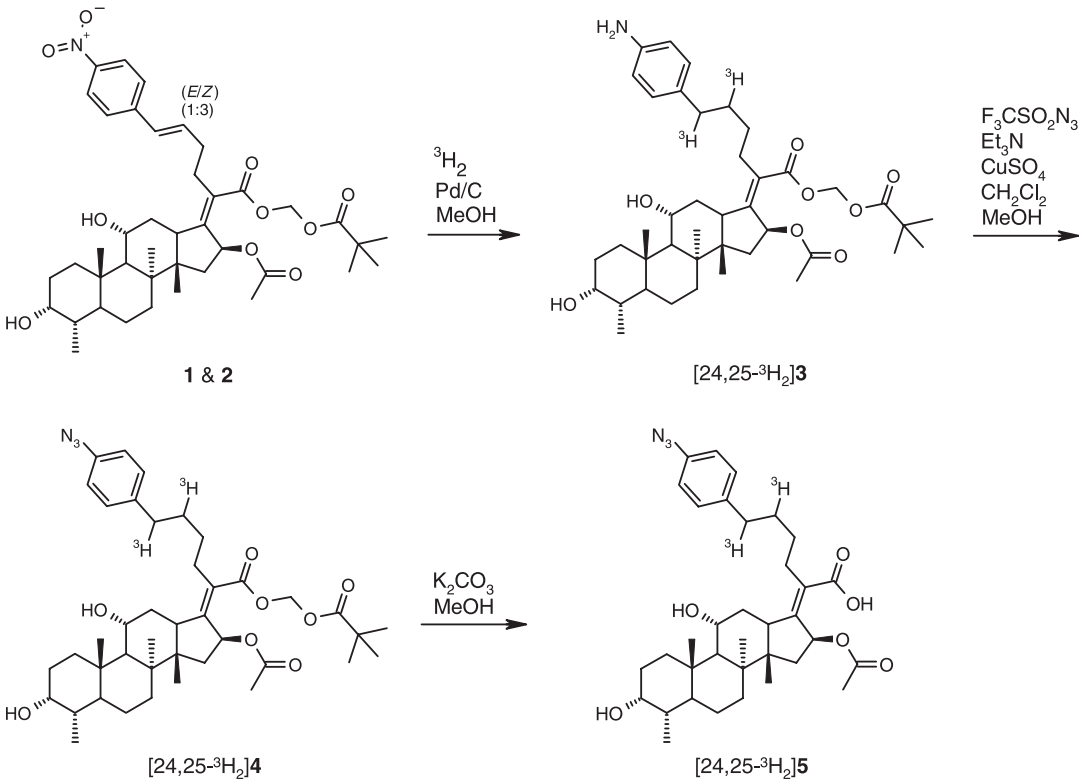
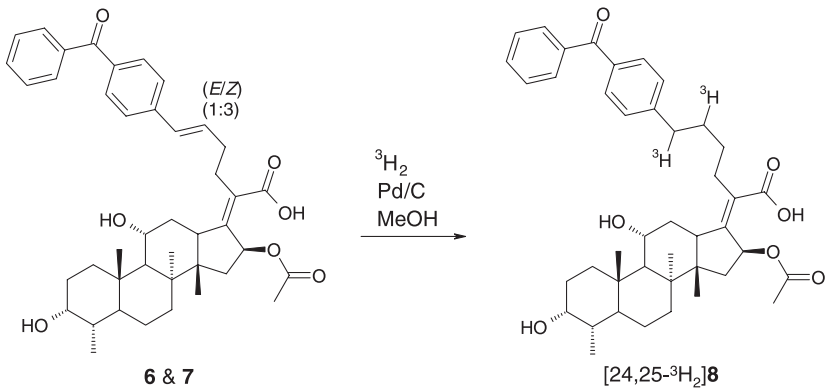


Scheme 1



Scheme 2

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