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ORIGINAL PAPER

Stereoselective total synthesis of protected sulfamisterin and its analogues

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The stereoselective synthesis of sulfamisterin *I* and its unnatural analogues *II* and *V* in their protected form was achieved through a common strategy. The Wittig reaction of aldehydes *VIII* and *IX* with the C_{14} hydrophobic side-chain *X* served as the key C—C connecting transformation. Subsequent functional group inter-conversions in the coupling products *XI* and *XX* completed the total synthesis.

Keywords: sulfamisterin, total synthesis, stereoselective, α-substituted α-amino acid, Wittig reaction, serine palmitoyltransferase

Introduction

(+)-Sulfamisterin *I*, (2*S*,3*R*)-2-amino-(2-hydroxymethyl)-12-oxo-3-(sulphooxy)octadecanoic acid (Fig. 1), is a new, natural, antifungal product that has been isolated from the culture broths of *Pycnidiella* sp. AB5366 (Sato et al., 2005; Yamaji-Hasegawa et al., 2005). This compound is reported to be responsible for both in vivo and in vitro inhibitory activity (Sato et al., 2005; Yamaji-Hasegawa et al., 2005) towards serine palmitoyltransferase (Hanada, 2003), an enzyme playing a crucial role in the sphingolipid biosynthesis.

The structure-elucidation study (Sato et al., 2005; see also references herein) revealed that *I* is an unusual α-substituted α-amino acid derivative possessing a C_{18} straight carbon chain with the C═O group at C-12, two stereogenic centres which are (2*S*,3*R*)-configured and C-3 alcohol function bearing a sulphate moiety. The inhibitory profile of *I* and related compounds depends on the stereochemistry at the C-2 quaternary centre and the 2*S* configuration is essential for high activity (Sato et al., 2005; Yamaji-Hasegawa et al., 2005). On the other hand, the stereochemistry of the 3-hydroxy group as well as its sulphation plays no essential role in the biological activity (Sato et al., 2005; Yamaji-Hasegawa et al., 2005). Although *I* and also its analogues *II*, *III*, and *IV* have an interesting β-hydroxy-α-substituted serine motif (Kang et al., 2005; Ohfune & Shinada, 2005; Byun et al., 2006) and exhibit remarkable bioactivity, only one total synthesis of *I* and its structurally-related derivatives has been reported to date (Sato et al., 2005). Prompted by these facts, and pursuing our interest in the construction of structures containing a densely functionalised quaternary centre (Gonda et al., 2006; Martinková et al., 2006, 2008, 2010, 2012a, 2012b), we focused on the synthesis of *I* and its desulphated congeners *II* and *V* (Sato et al., 2005) in their protected form.

Experimental

All commercial reagents were used with the highest available purity from Aldrich, Fluka, Merck or Acros Organics, without further purification. Solvents were dried and purified prior to use following standard procedures. Kieselgel 60 (0.040–0.063 mm, Merck) was used for flash column chromatography. Solvents

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