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LETTERS

## Use of trityl thiol for stereoselective thioester synthesis: a new preparation of (*S*)-thiolactic acid

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### Abstract

Trityl thiol is found to be a convenient reagent for the enantioselective preparation of (*S*)-thiolactic acid and a muramic acid thioester. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* thiols; thioesters; enzyme reactions.

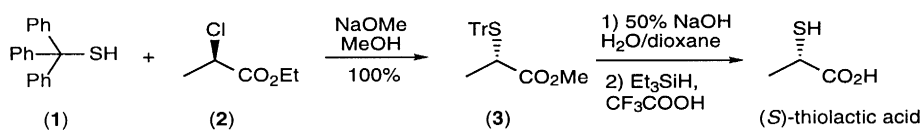
Peptide thioesters are convenient reagents for the assay of a wide range of protease and peptidase enzymes, via release of a thiol equivalent and reaction with a chromogenic thiol reagent such as 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB).<sup>1</sup> For *endo*-peptidases which require an oligopeptide substrate containing a central thioester linkage, such thioester substrates must incorporate a functionalised thiol component, which may contain one or more chiral centres. Few methods are available for the stereoselective introduction of sulphur, the most widely used reagent being thioacetic acid, a noxious liquid whose acyl protecting group is prone to hydrolysis under basic conditions.<sup>2</sup>

(*S*)-Thiolactic acid, a useful starting material for synthesis of *anti*-platelet activating factor agents,<sup>3</sup> has previously been prepared using thioacetic acid via a selective enzymatic deprotection method.<sup>4</sup> In the course of the preparation of peptide thioester substrates for the enzyme *N*-acetyl-muramyl-L-alanine amidase,<sup>5</sup> we have developed a method for the convenient introduction of sulphur in a stereoselective fashion using trityl (triphenylmethyl) thiol, a reagent which has not previously been used for stereoselective synthesis.<sup>6</sup> We report here its application for the synthesis of (*S*)-thiolactic acid and its incorporation into a complex thioester.

Trityl thiol (**1**) was prepared by the method of Balfe et al. via reaction of triphenylmethanol with hydrogen sulfide in acidic solution, in quantitative yield.<sup>7</sup> Reaction of trityl thiol with (*R*)-ethyl chloropropionate (**2**) in the presence of sodium methoxide proceeded cleanly to give the protected thioether (**3**) (Scheme 1). A sample of (**3**) was deprotected by treatment with 0.5 M aqueous sodium hydroxide:1,4-dioxane (1:1),<sup>8</sup> then trifluoroacetic acid/triethylsilane to give (*S*)-thiolactic acid, which was found to be

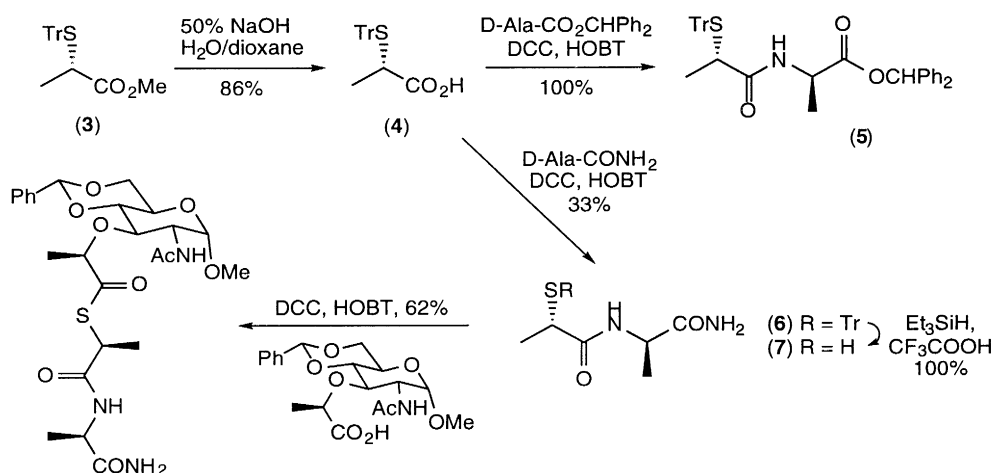
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enantiomerically pure upon treatment with chiral shift reagent  $\text{Eu}(\text{hfc})_3$ , compared with a sample of racemic thiolactic acid.



Scheme 1.

The absolute configuration of **(3)** was confirmed by synthetic conversion to the dipeptide derivative **(5)**. The methyl ester of **(3)** was deprotected by treatment with 0.5 M aqueous sodium hydroxide:1,4-dioxane (1:1)<sup>8</sup> to give acid **(4)** (Scheme 2). DCC coupling with either D-alanine diphenylmethyl ester or D-alanine amide gave the dipeptide analogues **(5)** or **(6)**, respectively. Crystals of dipeptide ester **(5)** grown by vapour diffusion from isopropanol/water were suitable for X-ray diffraction, and determination of the X-ray crystal structure confirmed that the thiolactyl chiral centre has the *S* configuration. Analysis of the <sup>1</sup>H NMR spectrum of dipeptide amide **(6)** showed no evidence of epimerisation at the sulphur centre. The lack of racemisation upon hydrolysis is noteworthy, and is preceded for trityl-protected cysteine derivatives.<sup>8</sup>



Scheme 2.

Deprotection of the trityl thioether was achieved by treatment of **(6)** with trifluoroacetic acid in the presence of triethylsilane (2 equiv.), which gave the deprotected thiol **(7)** in quantitative yield. Coupling with a protected muramic acid derivative then formed the thioester linkage in 62% yield.<sup>9</sup>

Thus, trityl thiol can be used for the clean  $\text{S}_{\text{N}}2$  displacement of a secondary halide, which proceeds with inversion of configuration. The trityl thioether product can be deprotected selectively at sulphur under acidic conditions, or at a carboxyl terminus under basic conditions. Trityl thiol offers practical advantages over reagents such as thioacetic acid, being an odourless crystalline solid which can be prepared in quantitative yield and is easily stored. It is of sufficient reactivity to be of use for the preparation of a variety of complex sulphides and thioesters. The preparation and biological evaluation of peptide thioester substrates for *N*-acetyl-muramyl-L-alanine amidase will be reported in due course.

## Acknowledgements

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