Tetrahedron 70 (2014) 5082–5092

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Studies on the synthesis of orthogonally protected azalanthionines, and of routes towards β-methyl azalanthionines, by ring opening of *N*-activated aziridine-2-carboxylates

Keith O'Brien, Keith ó Proinsias, Fintan Kelleher *

Molecular Design and Synthesis Group, Centre of Applied Science for Health, Institute of Technology Tallaght, Dublin 24, Ireland

ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 19 May 2014
Accepted 2 June 2014
Available online 9 June 2014

Keywords:
1,2-Diaminopropanoic acids (DAPs)
Lanthionine
Aziridine-2-carboxylates
Ring-opening
Azalanthionines
β-Methyl azalanthionines

ABSTRACT

Orthogonally protected azalanthionines were successfully synthesised by the ring-opening of *N*-activated aziridine-2-carboxylates with protected diaminopropanoic acids (DAPs). The required DAPs were also prepared by ring-opening of *N*-activated aziridine-2-carboxylates with *para*-methoxybenzylamine, but it was found that the choice of aziridine protecting groups dictated both the success of the reaction as well as the regioselectivity of the isolated products. Attempts to extend the methodology to the preparation of the more sterically demanding β-methyl azalanthionines have, so far, been unsuccessful.

1. Introduction

The incorporation of amino acid cross-linkers into peptide structures, which leads to the formation of cyclic peptides, is an important way that nature uses to give defined peptide and protein conformations with high biological activity. Importantly the stability of the peptides can also be increased due to their increased resistance to proteolytic cleavage.[1] There are many such cross-linkers in nature including lysinoalanine and histidinoalanine,[2] while the lanthipeptides contain the lanthionine or β-methyl-lanthionine cross-linking amino acids (Fig. 1).[3] Nisin is one of the most studied lanthipeptides and is a highly active antimicrobial peptide, which has been used worldwide for decades as a food preservative (E234). The chemical synthesis of orthogonally protected lanthionines and β-methyllanthionines has been studied extensively.[4] Vederas has also reported on the replacement of the thioether bridge of lanthionines and β-methyllanthionines with both carbon chain and oxygen bridged analogues.[5]

We recently reported on our preliminary studies on extending the range of lanthionine thioether bridge replacements that are available by preparing orthogonally protected azalanthionines, which have an amine linker, which should have quite different physicochemical properties to any of the other analogues (lanthionines, oxalanthionines or carbalanthionines), including water solubility at physiological pH.[6] To date this is the only reported method for the preparation of orthogonally protected azalanthionines though a small number of reports on the synthesis of

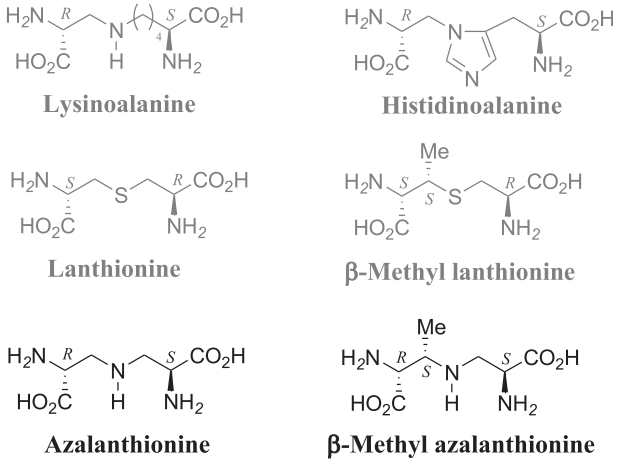


Fig. 1. Structures of some cross-linking amino acids.[2,3]

* Corresponding author. Department of Science, Institute of Technology Tallaght, Tallaght, Dublin 24, Ireland. Tel.: +353 1 404 2869; fax: +353 1 404 2700; e-mail address: fintan.kelleher@ittdublin.ie (F. Kelleher).

http://dx.doi.org/10.1016/j.tet.2014.06.011
0040-4020/

azalanthionines are known, but none gave orthogonally protected compounds, which would be suitable for use in solid-phase peptide synthesis.[7] The presence of a nitrogen atom in the cross-linker would also provide a very useful handle for further derivatisation, or conjugation, where required.

Thus, the goals of the current study were firstly to extend the range of orthogonally protected azalanthionines using our previously developed aziridine ring-opening methodology. Our initial report demonstrated the viability of the methodology but only one azalanthionine analogue was prepared with the correct stereochemistry, when compared to stereochemistry of natural lanthionine containing peptides. For the future incorporation of azalanthionines, in order to prepare lantibiotic analogues, a number of differentially protected analogues would be required with the desired stereochemistry. Since many lanthipeptides also contain the β-methyllanthionine moiety, the second goal of this study was the extension of the methodology to prepare a range of β-methyl azalanthionines, again with the correct stereochemistry at each stereocentre.

2. Results and discussion

2.1. Synthesis of orthogonally protected azalanthionines

The retrosynthetic analysis of the orthogonally protected azalanthionines shows that they could be prepared by ring-opening of *N*-activated aziridine-2-carboxylates with protected diaminopropionic acids (DAPs) (Fig. 2). In turn the DAPs could be obtained by ring-opening of differently protected aziridines with *p*-methoxybenzylamine.

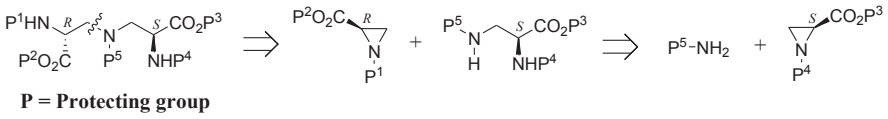


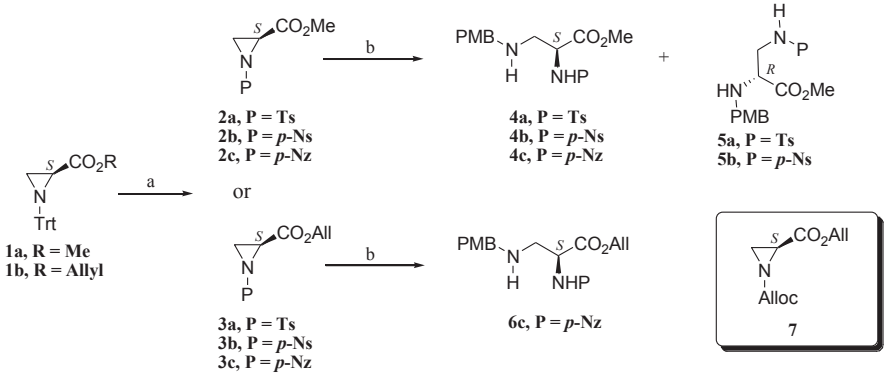
Fig. 2. Retrosynthetic analysis of orthogonally protected azalanthionines.

In order to prepare a range of different orthogonally protected azalanthionines suitable for solid-phase peptide synthesis the precursor *N*-activated aziridine-2-carboxylates were first prepared to explore the optimal substitution patterns for the synthesis of the required DAPs (Scheme 1). Starting with the known *N*-trityl aziridine-2-carboxylates, **1a** and **1b**,[8] replacement of the trityl group with a number of electron-withdrawing groups gave the required *N*-activated aziridines (**2a**–**c**, **3a**–**c** and **7**). The regioselectivity of the ring-opening reaction, on treatment of the *N*-activated aziridines with *p*-methoxybenzylamine, was highly dependent on both the nature of the *N*-substituent and the ester group in the 2-position, as well as the temperature of the reaction.[9] In all cases two molar equivalents of *p*-methoxybenzylamine was used.

Aziridine **2a** gave a mixture of **4a** and **5a** in a 70:23 ratio at room temperature (Table 1, entry 1). However, the selectivity was reversed to give **4a** and **5a** in a 32:41 ratio, when the reaction was conducted at 80 °C (entry 2). Further reactions in this series were conducted at room temperature to maximise the yield of the product obtained from attack at the aziridine β-position. It was found that the *p*-Ns aziridine **2b** gave **4b** and **5b** in a 63:21 ratio (entry 3). However, the *p*-Nz substituted aziridine **2c** only gave **4c**, the product of attack at the less hindered β-carbon of the aziridine in a 66% yield (entry 4). For the *N*-activated aziridine allyl esters **3a**–**c** (entries 5–7), only the *N*-*p*-Nz substituted derivative **3c** underwent reaction with *p*-methoxybenzylamine, with **6c** being obtained in a 66% yield, as the sole product. The *N*-alloc activated aziridine **7** gave no product from attack by *p*-methoxybenzylamine (entry 10). For the unsuccessful reactions, use of Lewis acid catalysis (boron trifluoride etherate) and/or heating to 80 °C, did not lead to any of the desired products. An examination of the results of the ring-opening reactions shows that the regioselective outcome is not predictable.[9]

Having prepared a number of the required DAPs they were then used to prepare orthogonally protected azalanthionines by ring-opening of the protected *N*-activated aziridines (Scheme 2). In these cases, it was found that there was no reaction observed at 25 °C, in the presence of 2 M equivalents of the DAP. When the reactions were heated to 80 °C, only products from attack at the less sterically hindered aziridine β-position were obtained. It is most likely that this is due to the increased steric bulk of the secondary amine nucleophile of the DAP compared to the primary amino group of the *p*-methoxybenzylamine. Thus far a range of six diastereoisomeric azalanthionines (**8**–**12**, **17**) have been prepared using this methodology, with the stereochemistry of the diastereoisomer depending on whether L- or D-serine was used as the starting material for the precursor *N*-activated aziridines (Scheme 2 and Table 2).

The isolated yields of the azalanthionines, after aqueous workup, were 27–51%, which are comparable with those obtained for similar aziridine ring-opening reactions with protected cysteine



Reagents and conditions; (a) See Supporting Information; (b) *p*-methoxybenzylamine (2 molar equiv.), MeCN, rt, 24 h.

Scheme 1. Synthesis of 1,2-diaminopropanoic acid derivatives (4–6).