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Synthesis and Assignment of the Relative Stereochemistry of a Putative Biosynthetic Precursor of Tabtoxinine β-Lactam.

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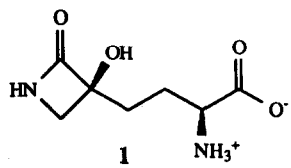
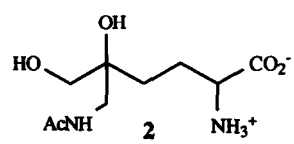
Abstract: The synthesis and assignment of the relative stereochemistry of a recently isolated amino acid is reported. This synthesis utilises the S_H2' coupling of an allylic stannane to a protected β-iodoalanine.

We have been interested in tabtoxinine β-lactam **1**,[1] the causative agent of wildfire disease in tobacco plants, and related compounds for some time.[2] Consequently our attention was drawn to a recent report by Durbin *et al.* on the isolation of a putative biosynthetic intermediate **2**[3] from a genetically blocked mutant of *Pseudomonas syringae* pv. *tabaci*, Fig. 1.



1

Tabtoxinine β-lactam

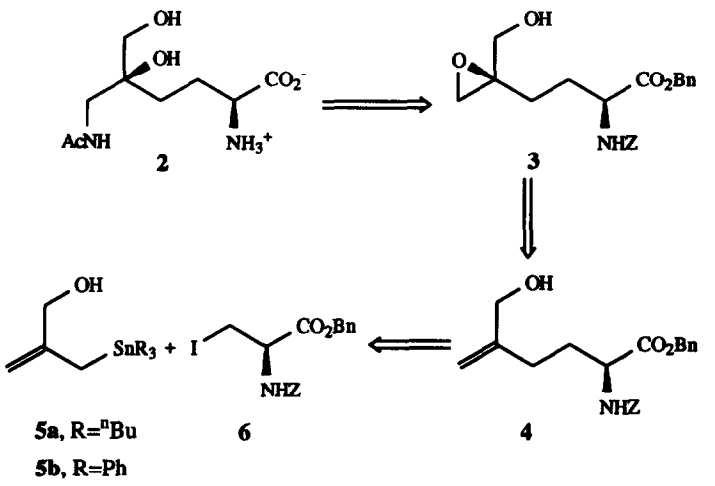


2

Fig. 1

The molecular formula and connectivity of **2** were established by a combination of ^1H and ^{13}C nmr and mass spectrometric methods. We felt that synthesis of **2** would be able to confirm the proposed structure and establish the stereochemistry. By comparison to tabtoxinine-ß-lactam it would appear that the stereochemistry of **2** is most likely to be as shown in Scheme 1.

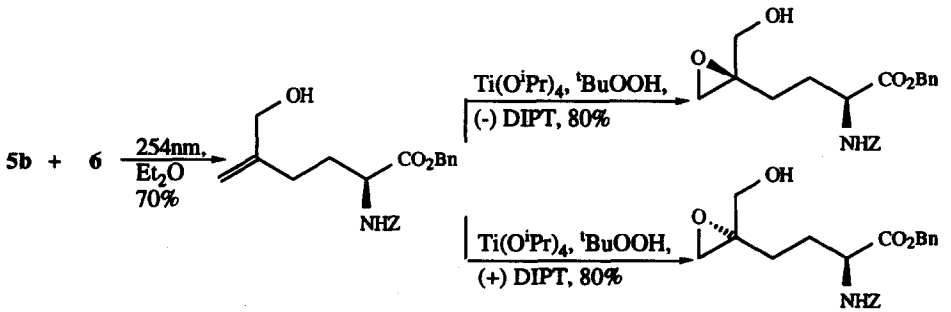
For preference, however, the synthetic route should allow preparation of any desired stereoisomer. It appeared that the most direct approach to the acetamido-diol fragment would be from epoxyalcohol **3**, which in turn could be established in either epimeric form *via* a Sharpless asymmetric epoxidation.[4] It was anticipated that the required δ-alkenyl amino acid **4** could be made using our previously reported radical coupling methodology, as the required stannane **5** had the necessary degeneracy to rearrangement under radical conditions.[5]



Scheme 1

Initially we prepared the stannane **5a** in 43% yield using a procedure adapted from Trost *et al.* for the trimethylsilyl analogue.[6] This compound proved difficult to purify, requiring the use of base washed silica,[7] and in addition was found to undergo slow decomposition on storage. Since it is known that simple allyltriphenylstannanes are frequently crystalline,[8] we next prepared **5b** in an analogous manner in 58% yield. This was found to be a white crystalline solid (m.p. 81°C) and stable to storage for several months at room temperature. Additionally it was found to be more stable towards protodestannylation than **5a**, permitting chromatography on flash silica.[9] The diprotected iodoalanine **6** was prepared by known methods.[10]

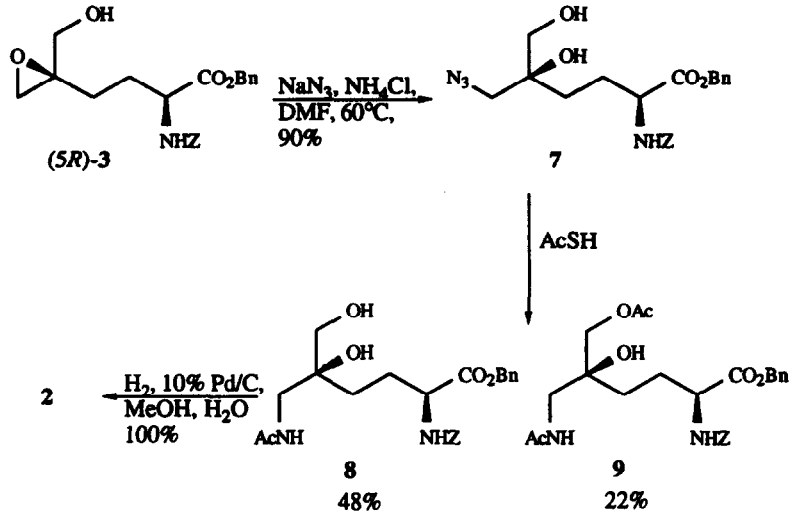
The radical coupling reaction could be initiated thermally using AIBN but the best yield[11] (70%) was obtained by irradiation of a 3:1 mixture of **5b** and **6** in ether with a medium pressure Hg lamp. Subsequent Sharpless epoxidation with either enantiomer of diisopropyl tartrate (DIPT) proceeded smoothly in 80% yield to give the corresponding epoxides, diastereomerically pure in each case as judged by 500 MHz ^{1}H nmr, (Scheme 2).



Scheme 2

Optimised conditions for introduction of the azido group were found to be $NaN_3/NH_4Cl/DMF/60°C$, affording the crude azide **7** in 90% yield as a single regioisomer. We were not able to prepare an analytically pure sample and so the material was carried through to the next step directly. Any possibility that a Payne rearrangement had accompanied epoxide opening was ruled out by comparison of the ^{13}C nmr spectra of the diastereomeric azides : two clearly resolved signals for the CH_2N_3 carbon were seen in a mixed sample.

Reductive acetylation of the azide **7** to acetamide **8** was achieved directly in 48% yield by treatment with neat thiolacetic acid[12] for 2 days,with 22% of diacetyl compound **9** being isolated. Shorter reaction times reduced the amount of desired product, however. Hydrogenation over 10% Pd/C in MeOH/H_2O gave the amino acid in quantitative yield as a fluffy white powder (Scheme 3).



Scheme 3

The (5*R*) diastereomer of **2** was also synthesised, from the corresponding (5*S*) epoxide, and comparison of the ^1H nmr (500MHz) of the two diastereomeric amino acids revealed a difference in the resonances associated with the γ-CH_2 protons, Fig. 2. This was sufficient to allow assignment of the relative stereochemistry of the natural product as shown in Scheme 1. In the absence of optical data it was not possible to assign the absolute stereochemistry, although on biosynthetic grounds it is highly likely to be as shown.

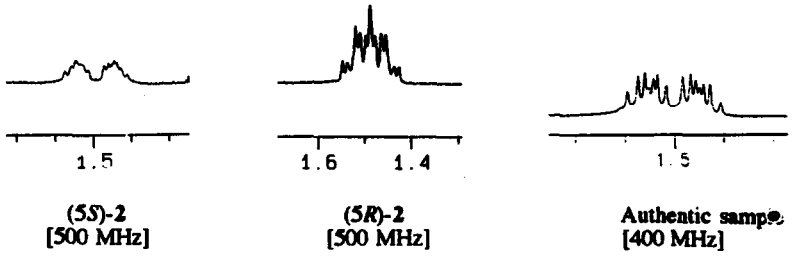


Fig. 2

In summary we have described a short asymmetric synthesis of a recently isolated amino acid, and in so doing have confirmed the proposed connectivity and assigned its relative stereochemistry.

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