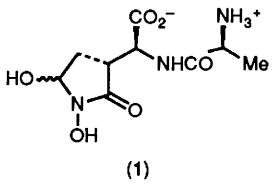
Enantiospecific Synthesis of Dealanylalahopcin

Jack E. Baldwin,* Robert M. Adlington, David W. Gollins, and Christopher J. Schofield

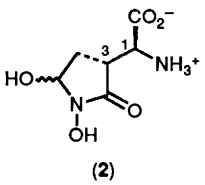
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

The first synthesis of the novel α-amino acid dealanylalahopcin from (L)-aspartic acid in thirteen steps is described.

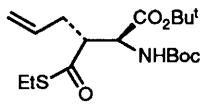
The dipeptide antibiotic alahopcin (B-52653) (**1**), isolated by Higashide *et al.* from a culture of *Streptomyces albulus*, was found to be active against a wide range of both Gram-positive and Gram-negative bacteria.[1] From the same fermentation studies a new α-amino acid (**2**) was also discovered. This amino acid had low antibacterial activity [~1% *cf.* alahopcin (**1**)] but showed similar prolyl collagen hydroxylase and bacterial α-amylase inhibition to (**1**).[2] Enzymatic hydrolysis (using α-amino acid hydrolase) of alahopcin (**1**) also yielded this new α-amino acid (**2**) and (L)-alanine; thus (**2**) was named dealanylalahopcin (B-52653-C).[2] A degradative study was performed from which the structures of alahopcin (**1**) and dealanylalahopcin (**2**) were deduced;[3] however to date, no synthetic route to these compounds has been published to confirm their structures and configurations.



(**1**)

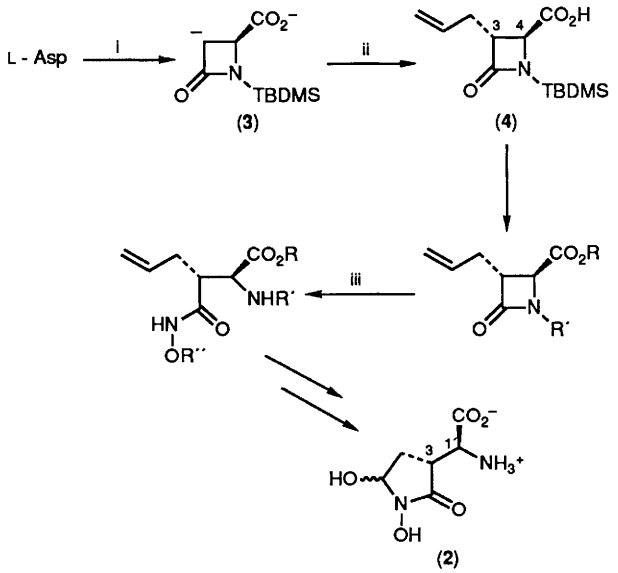


(**2**)



(**8**)

Boc = t-butoxycarbonyl



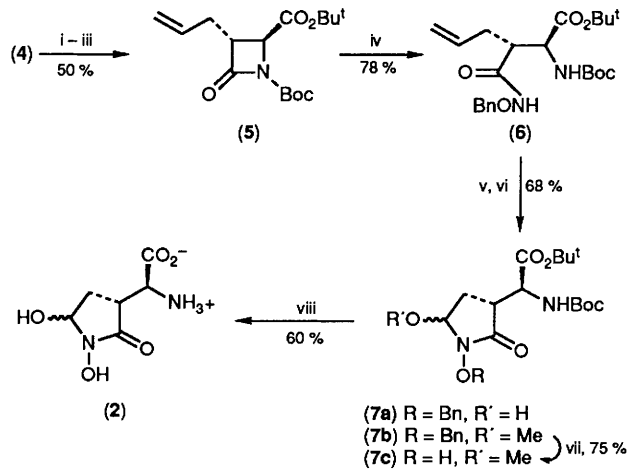
TBDMS = Bu^tMe_2Si

Scheme 1. *Reagents*: i, see ref. 5(c); ii, allyl bromide then H_3O^+; iii, NH_2–OR″.

Previously, we demonstrated that a β-lactam derived from (L)-serine could be used as a homochiral synthon for β-functionalised α-amino acid synthesis.[4] As an extension of this principle a stereospecific synthesis of dealanylalahopcin (**2**), from a β-lactam precursor derived from (L)-aspartic acid, is now reported.

Retrosynthetic analysis of dealanylalahopcin (**2**) reveals its structure to be derived from a ring closed form of a stereospecifically β-functionalised (L)-aspartic acid derivative. The required 3*R*, 1′*S*-relative stereochemistry of (**2**) should in principle be available from a *trans*-alkylation,[5] with allyl bromide, of the β-lactam dianion (**3**).[5c] Subsequent β-lactam opening by a hydroxylamino nucleophile would then provide the key structural requirement of (**2**) (Scheme 1).

Thus, allylation of (**3**) [allyl bromide (2.2 equiv.), tetrahydrofuran (THF), 0 °C, 2 h] gave, after acidic work-up, the acid (**4**) (95%) as the sole allylated product† for which a *trans*-stereochemistry was established from the observed coupling constant J_{3H-4H} of 3 Hz.[5b,c] As the hydroxylamino nucleophile, subsequently required for β-lactam opening, might have reacted with unhindered esters and in order to activate the β-lactam towards such nucleophilic attack,[6] the acid (**4**) was transformed to the *N*-(t-butoxycarbonyl) t-butyl ester (**5**) [50% from (**4**)]. Initially, (**5**) proved resistant to ring opening by *O*-benzylhydroxylamine (THF, reflux), but with the addition of sodium ethanethiolate (10 mol%)[7] coupled with the slow addition of potassium t-butoxide (80 mol%) over



Bn = $PhCH_2$

Scheme 2. *Reagents*: i, *O*-(t-butyl)trichloroacetimidate, catalytic $BF_3{\cdot}Et_2O$, dichloromethane:cyclohexane, 0 °C (ref. 8); ii, CsF, MeOH; iii, Boc_2O, catalytic dimethylaminopyridine, MeCN; iv, NH_2OBn, $Na^+{}^-SEt$(10 mol%), $K^+{}^-OBu^t$(80 mol%), THF, reflux; v, catalytic OsO_4, $NaIO_4$, H_2O: 1,4-dioxan; vi, MeOH, catalytic TFA; vii, H_2, 10% Pd/C, MeOH; viii, 1 M HCl: 1,4-dioxan (1:1).

† ^1H NMR analysis (200 MHz): i, of the total crude from (**3**) revealed (**4**) as the only detectable allylated product (>95%); ii, of the crude from (**5**) revealed (**6**) as the only detectable stereoisomer (>95%).

6 h, the ring opening of (**5**) by *O*-benzylhydroxylamine to (**6**) was realised in 78% yield.† Oxidative cleavage of the alkene (catalytic OsO_4, $NaIO_4$) gave an aldehyde [in equilibrium with the ring closed form (**7a**)] which was directly protected [MeOH, catalytic trifluoroacetic acid (TFA)] as the ring closed methoxylactam (**7b**) [68% from (**6**), as a 6 : 1 epimeric mixture]. Hydrogenolysis (H_2, 10% Pd/C, MeOH) followed by aqueous acid hydrolysis [1,4-dioxan: 1 M HCl (1 : 1), 18 h] and cationic ion exchange chromatography gave dealanylalahopcin (**2**) (45%) (Scheme 2).‡

In summary, the first synthesis of dealanylalahopcin (**2**) has been achieved confirming the original structural assignment based upon a degradative study.[3] Noteworthy points of the synthetic approach are the stereospecific '*trans*' allylation (>95%) of the β-lactam dianion (**3**) and the use of the so-formed stereospecifically functionalised β-lactam as a stereospecifically β-alkylated (L)-aspartic acid synthon. The conditions required for the β-lactam ring opening also merit comment. Presumably the thiolate rapidly ring opened the β-lactam (**5**) to the thioester (**8**)[4a] (itself isolable from crude reaction mixtures) and this sterically more accessible form could then be transformed to the hydroxamate (**6**). The potassium t-butoxide was probably required to deprotonate the hydroxamate (**6**) which may otherwise have interfered with the reaction by protonation of the *O*-benzylhydroxylamine. Synthesis of the parent dipeptide alahopcin (**1**) is a current objective.

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‡ *Analytical data* for (**2**): MS *m/z* 191 (FAB^+); $[\alpha]_D^{20}$ +45.6° (*c* 0.88, H_2O), $[\alpha]_D^{20}$ +56.2° (*c* 0.4, 0.1 M HCl); {lit.,[2] $[\alpha]_D^{20}$ +50.8° (*c* 0.5, H_2O), $[\alpha]_D^{20}$ +55.6° (*c* 1, 0.1 M HCl)}; δ_H (500 MHz, D_2O, internally referenced to 1,4-dioxan @ δ 3.63) 1.53—1.59 and 2.55—2.61 (2H, 2 × m, 4-H, minor epimer), 2.00—2.05 and 2.09—2.15 (2H, 2 × m, 4-H, major epimer), 2.88—2.92 (1H, m, 3-H, minor epimer), 3.06—3.11 (1H, m, 3-H, major epimer), 3.95—3.98 (2H, m, 1′H, both epimers), 5.14 (1H, dd, *J* 5, 7 Hz, 5-H, minor epimer), 5.19 (1H, d, *J* 7 Hz, 5-H, major epimer); δ_C (125.8 MHz, D_2O, internally referenced to 1,4-dioxan) 28.6 and 28.7 (4-C), 38.5 and 39.1 (3-C), 54.7 (1′-C), 81.7 and 82.1 (5-C), and 169.1, 170.0, and 170.7, (2 × C=O), (^1H and ^{13}C NMR data consistent with that reported previously[2,3]).

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