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NEW STRATEGY FOR THE CONSTRUCTION OF CARBAPENEMS. TOTAL SYNTHESIS OF 6-*epi* PS-5 AND PS-5.

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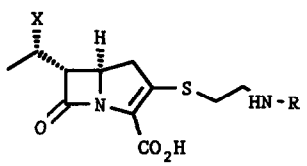
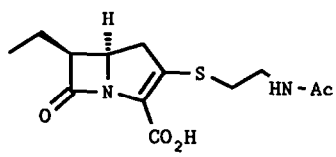
Summary: *A strategically novel approach to carbapenems has been developed. The pyrrolidine ring is first constructed, appended with the required side chains, and the β-lactam ring is then annealed. We have demonstrated the utility of the approach to the asymmetric synthesis of antibiotics 6-epi PS-5 and PS-5.*

Carbapenem antibiotics have gained considerable synthetic attention due to their broad antibacterial spectrum, covering both Gram(+) and Gram(-) bacteria.[1] Thienamycin (**1**) is a member of this class of compounds, and its formimido derivative, imipenem, is currently marketed in several countries in a formulation containing a β-lactamase inhibitor. Side-chain deoxygenated members, such as PS-5 (**2**) and PS-6 (**3**), are of interest, since they are active also against a number of β-lactamase producing bacteria. The antibacterial efficacy of the 6-*epi* series (6-*epi* PS-5, **4**) usually exceeds that of the natural series. However, synthetic efforts leading to these potentially important compounds are limited. Herein we report a novel chirospecific synthesis of the carbapenem antibiotics 6-*epi* PS-5 and PS-5.





1 X = OH R = H Thienamycin
2 X = H R = Ac PS-5
3 X = CH_3 R = Ac PS-6

4 6-*epi* PS-5

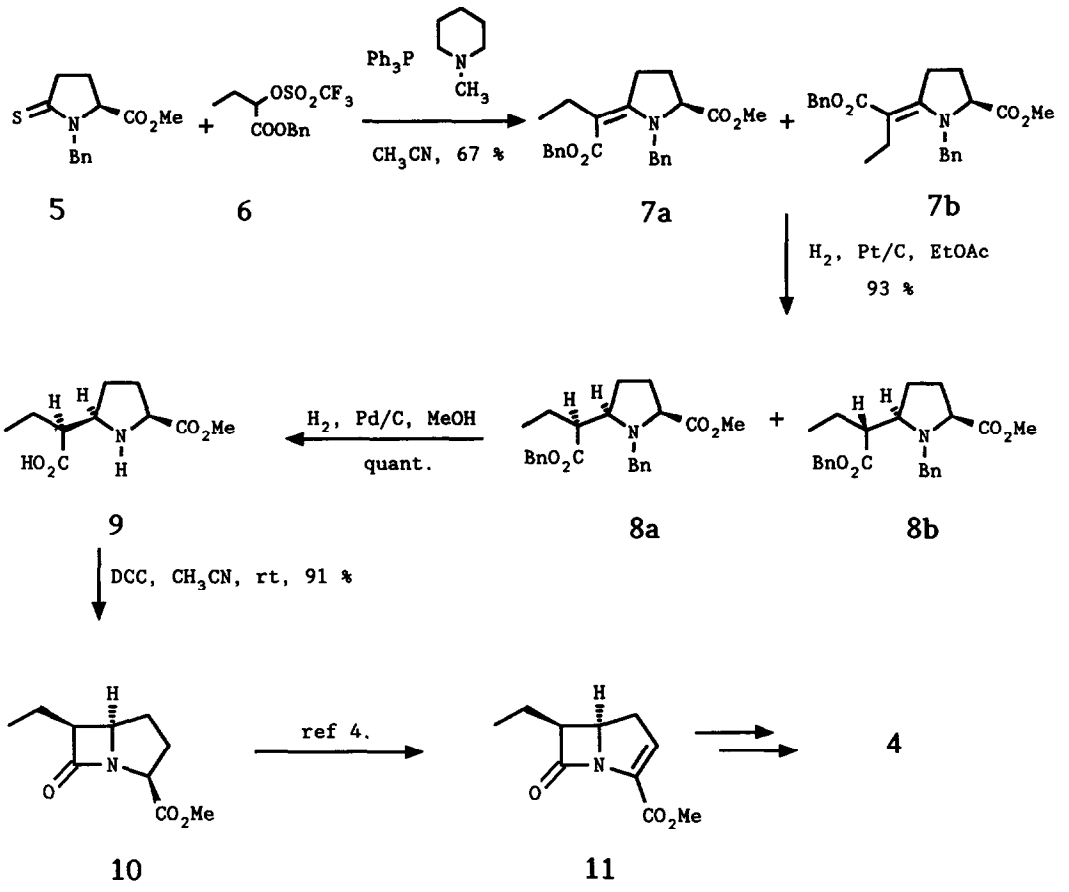
PS-5 has been synthesized in both racemic[2] and optically active[3] form using a strategy relying on the initial construction of the β-lactam ring, followed by elaboration of the pyrrolidine ring and adjustment of the oxidation level. The only exception is the recent communication by Izawa *et al.*, who utilized electrochemical oxidation to functionalize proline prior to β-lactam closure.[4] The *cis*-carbapenem antibiotic 6-*epi* PS-5 has been synthesized in a racemic form,[5] using the β-lactam → pyrrolidine strategy. We envisaged that the alternative ring construction mode (pyrrolidine → β-lactam) could provide a powerful novel strategy for the synthesis of these compounds.

Inspection of the structures **1-4** provided several clues which might provide a strategically novel approach to carbapenems. Firstly, the pyrrolidine ring is 2,5-*cis*-disubstituted. We reasoned that this structural feature could be controlled by catalytic hydrogenation of a suitable 5-alkylidene proline derivative.[6] This would also allow a convenient handle for the introduction of the desired absolute stereochemistry, since that at C-2 corresponds to the natural amino acid stereochemistry. The requisite pyrrolidine precursor would be thiopyroglutamate **5**, which can be easily prepared from L-glutamic acid. The side chain on the pyrrolidine should be a 2-carboxypropyl one. This would suit perfectly with our chosen strategy, since the electron withdrawing substituent (alkoxycarbonyl) would be needed for the ensuing sulfide contraction step.

Stereochemistry at the side chain asymmetric center (C-6) would remain a hitherto unaddressed problem. We reasoned that the (*E*)-vinylogous carbamate **7a** (leading to **4**) should be formed preferentially over the (*Z*)-isomer **7b** (precursor of **3**) due to less steric crowding. Catalytic hydrogenation of this functionality under carefully controlled conditions should lead to the correct (5*R*,6*S*)-stereochemistry for **4** at both of the two new chiral centers C-5 and C-6. Subsequent reactions would consist of demolition of the protections, closure of the β-lactam and further adjustments within the pyrrolidine ring to attain the correct substitution and oxidation pattern.

Thiolactam **5** (mp. 61-2 °C) was readily prepared in four steps from L-glutamic acid through N-benzylation (PhCHO, $NaBH_4$), ring closure (rfx in H_2O), esterification (MeOH, HCl) and thionation (P_4S_{10}, THF, rt) in 77 % overall yield.[7]

The triflate **6** was prepared from benzyl 2-hydroxybutanoate (82 %), and used to alkylate the thiolactam **5** (CH_3CN, rt, overnight, then Ph_3P, N-methylpiperidine, rt, 6 h, 67 %) to give the vinylogous carbamate **7a,b** as a mixture of *Z*/*E*-isomers (4.5:1 by NMR). The isomers were not separated



at this stage, since we conceived that the separation of isomers can be deferred to a later stage.

Hydrogenation of the double bond without effecting debenzylation could be carried out in a highly stereocontrolled manner using a Pt/C catalyst (EtOAc, 3 atm. H_2, rt, overnight). The stereoisomers **8a,b** could be conveniently separated at this stage by flash chromatography[8] to furnish a 70 % isolated yield of the desired (5*R*,6*S*)-isomer **8a**.

Cleavage of the benzyl protecting groups was effected by a further catalytic hydrogenation over Pd/C catalyst (MeOH, 4 atm. H_2, overnight), to give the cyclization precursor amino acid **9** in quantitative yield.

Formation of the β-lactam ring was conducted using dicyclohexyl carbodiimide in acetonitrile to give the bicycle **10** (91 %). Our material exhibited a signal at δ 3.88 due to H-3, indicative of the 3,5-*cis* relationship.[4,9] The H-6 resonates at δ 3.13 (dddd, $J_{5,6}$=5.1 Hz, $J_{5,1}$=1.2 Hz), establishing the 5,6-*cis* relationship.[9] Since compound **10** has been

converted to 6-*epi* PS-5 previously,[4] our synthesis constitutes a new synthesis of the antibiotic. Similarly, the minor isomer **8b** was converted to the known[4] intermediate of the synthesis of PS-5.[10]

We have demonstrated that the reversal of the ring construction steps in the synthesis of carbapenems is feasible, and enables a powerful new synthetic protocol for these structures. We are currently investigating alternative methods to control the stereochemistry at the two new chiral centers (C-5, C-6), as well as possibilities for extending the method to the synthesis of more highly substituted analogues.

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