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A Stereocontrolled, Enantiomerically Specific Total Synthesis of Thienamycin

T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard and B. G. Christensen

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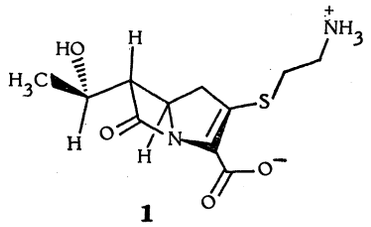
A stereocontrolled, enantiomerically specific total synthesis of thienamycin

By T. N. Salzmann, R. W. Ratcliffe, F. A. Bouffard and B. G. Christensen
Merck Sharp and Dohme Research Laboratories, P.O. Box 2000, *Rahway, New Jersey* 07065, *U.S.A.*

A versatile stereocontrolled total synthesis of thienamycin starting from L-aspartic acid is reported. Stereocontrol is achieved by potassium tri-*sec*-butylborohydride reduction of a thermodynamically formed 3α-acetylazetidinone intermediate. The key [3.2.0] bicyclic ring system is prepared by a metal catalyzed carbene insertion reaction.

Thienamycin (**1**) is an antibiotic of exceptional potency and breadth of antibacterial spectrum. Of unusual interest is its stability to β-lactamases and activity against *Pseudomonas* sp. (Kropp *et al.* 1976). These unparalleled biological properties alone make it and related analogues worthy targets for synthesis. The unique structure (Albers-Schonberg *et al.* 1978) of thienamycin makes that goal doubly attractive. It differs from the 'classical' β-lactam antibiotics (Cama & Christensen 1978*a*) in several important respects. The basic 1-carbapenem† ring system differs from the nuclei found in penicillins and cephalosporins by virtue of the lack of sulphur‡ as well as the high degree of ring strain associated with the bicyclo[3.2.0]heptene system. The ring substituents of thienamycin are also 'non-classical' in nature. While penicillins and cephalosporins almost invariably have β-amide side chains at C-6(7), thienamycin has a hydroxyethyl group at position 6. Furthermore, the hydroxyethyl group of thienamycin has the α orientation, a situation which invariably renders penicillins and cephalosporins devoid of antibacterial activity (Johnson & Maria 1969). Finally, the exocyclic cysteamine residue is unique among naturally occurring β-lactam antibiotics.



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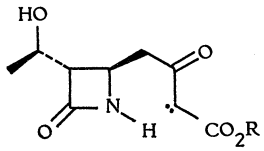
Any analysis of potential synthetic routes to thienamycin invariably must consider two major synthetic problems: (1) synthesis of the three contiguous chiral centres (5*R*, 6*S*, 8*R*), and (2) construction of the novel 1-carbapenem nucleus. Although thienamycin has been previously synthesized (Johnston *et al.* 1978), that synthesis was deliberately designed to achieve most readily the synthesis of all stereoisomers of thienamycin. Since that objective has now been

† It is proposed that the nucleus of thienamycin be named 1-carbapenem to conform to the penam–cephem nomenclature commonly used in β-lactam chemistry.

‡ Replacement of sulphur by carbon has been previously shown to be consistent with good biological activity in the 1-carbacephalosporins (Guthikonda *et al.* 1974).

accomplished, any new synthesis of thienamycin must address itself to the problem of stereocontrol and chirality.

Similarly, while the 1-carbapenem system had been synthesized by two different routes in the first total synthesis (Johnston *et al.* 1978) as well as in the total synthesis of the nucleus itself (Cama & Christensen 1978*b*), a third method of construction based upon previous work (Cama & Christensen 1978*c*; Salzmann *et al.* 1978) seemed an attractive alternative. The key reaction involves generation of a carbenoid intermediate **2** which inserts into the free N—H bond of the azetidinone to provide the bicyclo keto ester **3**.



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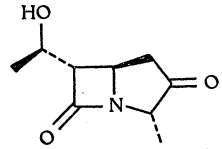

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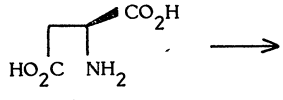
Finally, since **3** lacks the cysteamine residue found in thienamycin, a method for incorporating this moiety must be devised. We should like to report the first stereocontrolled, enantiomerically specific total synthesis of thienamycin.

Synthesis of a suitable azetidinone precursor

Consideration of several inexpensive, chiral starting materials, most notably sugars, amino acids and other natural products, led to the choice of L-aspartic acid as a suitable precursor. It is written (**4**) to emphasize its relationship to thienamycin (**1**). Although several methods (Isaacs 1976) are available for cyclizing β-amino acids to azetidinones, the Grignard mediated closure of an *N*-silyl ester derivative (Birkofer & Schramm 1975) appeared particularly suitable in this case. Conversion of dibenzyl aspartate *p*-toluenesulphonate (**5**) (Ferris *et al.* 1957) to its trimethylsilyl derivative **6** was readily accomplished by neutralization with potassium carbonate and treatment with trimethylsilyl chloride. Treatment of **6** *in situ* with t-butylmagnesium chloride followed by acid hydrolysis gave the azetidinone, **7**. Hydrogenolytic ester cleavage of **7** followed by acid hydrolysis to optically pure L-aspartic acid demonstrated the stereochemical integrity of **7**. Sodium borohydride reduction of **7** yielded **8**. Conversion of **8** via the mesylate **9*a*** to the chiral iodide **9*b*** was accomplished in excellent overall yield.



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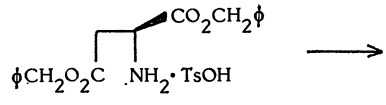

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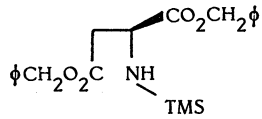

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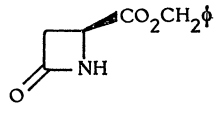

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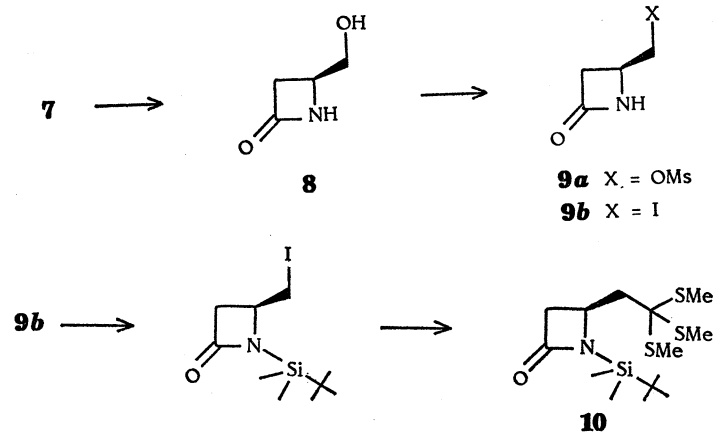
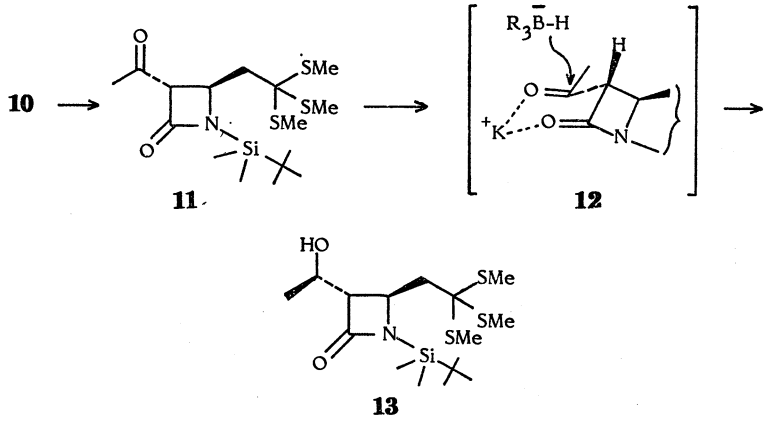
Before elaborating the 6α-(1*R*-hydroxyethyl) side chain, which requires strongly basic conditions, it was necessary to block the azetidinone nitrogen as well as to convert the iodide into a base stable functionality which incorporates a masked oxidized carbon atom. Treatment of **9*b*** with t-butyldimethylsilyl chloride and triethylamine in DMF at 0° followed by treatment

with lithium trimethylorthothioformate at −78 °C afforded the desired azetidinone precursor **10**.



Generation of the three (5*R*, 6*S*, 8*R*) contiguous chiral centres

Previous attempts to acetylate the enolates derived from monocyclic azetidinones have been largely unsuccessful. However, generation of the enolate of **10** with 2.05 equivalents of LDA at −78 °C followed by an inverse quench into *N*-acetylimidazole afforded the desired *trans*-3-acetylazetidinone (**11**). Sodium borohydride reduction of related structures afforded the desired 8*R* stereoisomer as the minor product of a 2:3 *R*:*S* mixture. Reduction of **11** with sodium, lithium and potassium borohydrides was investigated in various solvent mixtures. To increase the proportion of the steric approach control product, sterically hindered hydrides were employed. Reduction of **11** with K-Selectride–KI in THF–ether at room temperature gave an 84:16 ratio of *R*:*S*. The increased stereocontrol may be related to preferential attack from the top face of a complex such as **12**. The desired isomer **13** was directly crystallized at this point. Compound **13** possesses all the requisite chirality of thienamycin.



Alternatively, simple aldol condensation of the enolate derived from **10** with acetaldehyde yielded a mixture of hydroxyethyl isomers, of which the desired product **13** was the major product, formed in more than 50 % yield. The undesired isomers could be recycled by oxidation to the acetylazetidinone **11** (TFAA–DMSO) followed by reduction with K-Selectride–KI in ether.

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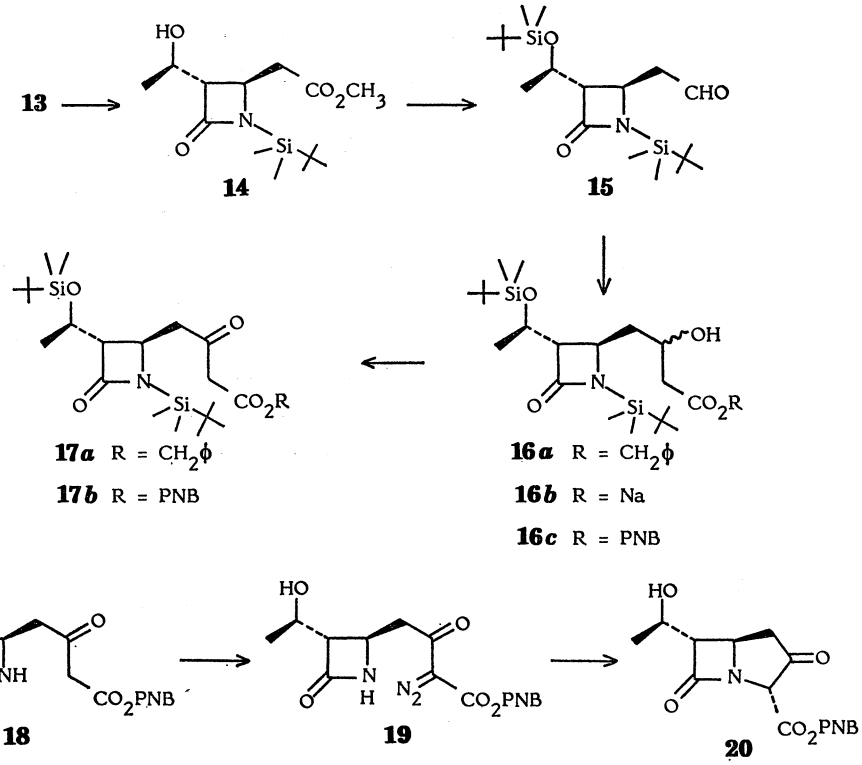
Construction of the 1-carbapenem nucleus

To add the remaining carbon framework to **13**, it seemed desirable to first convert it into its aldehyde counterpart. Compound **13** was converted to methyl ester **14** by treatment with $HgCl_2$ in methanol containing a trace of *p*-toluenesulphonic acid. Silylation of **14** with t-butyldimethylchlorosilane followed by reduction of the resulting product with DIBAL in toluene at −78 °C yielded aldehyde **15**. Condensation of **15** with lithio benzyl acetate gave **16*a*** as a mixture of isomers which was subsequently oxidized to keto ester **17*a*** with CrO_3Py_2. Since *p*-nitrobenzyl esters are much more efficiently removed than the corresponding benzyl esters, we attempted to repeat the above scheme by using lithio *p*-nitrobenzyl acetate; however, this reagent cannot be successfully generated. An alternative procedure involved hydrogenolysis of the benzyl ester **16*a*** in the presence of an equivalent of sodium bicarbonate to yield sodium salt **16*b*** which was then realkylated with *p*-nitrobenzyl bromide in DMF to yield **16*c***. Oxidation as previously described gave **17*b***. Deblocking of the silyl protecting groups was effected with methanol–HCl at room temperature to give **18**.



The final problem in the synthesis of the bicyclic ring system involves closure of **18**. From the outset we had envisaged a carbene insertion into the N—H bond as a method of effecting the C-3 to N closure. This procedure was based upon prior syntheses of 1-oxabisnorpenicillin G (Cama & Christensen 1978*c*) and homothienamycin (Salzmann *et al.* 1978). Diazo transfer to **18** readily afforded the desired diazo intermediate **19**. Generation of the carbene and ring insertion occurred upon treatment of **19** with $Rh_2(OAc)_4$ in toluene at 75 °C.

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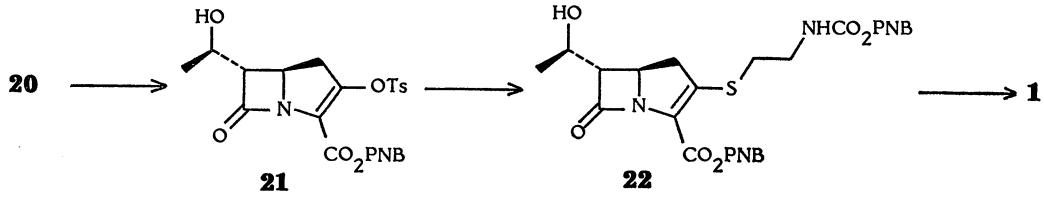
Elaboration of the cysteamine side chain and deblocking

Previous studies based on a cephalosporin (L. D. Cama, personal communication) and the homothienamycin analogue indicated that a vinyltosylate would react with cysteamine. Treatment of **20** with tosic anhydride and Pr^i_2NEt readily afforded the desired tosylate **21**. Reaction of the *p*-nitrobenzyloxycarbonyl derivative of cysteamine with **21** again in the presence of Pr^i_2NEt in DMF gave the diblocked derivative of thienamycin **22**. Catalytic deblocking of **22** afforded thienamycin identical in all respects to natural thienamycin.



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