An Efficient Stereoselective Method for the Synthesis of Thienamycin Intermediates

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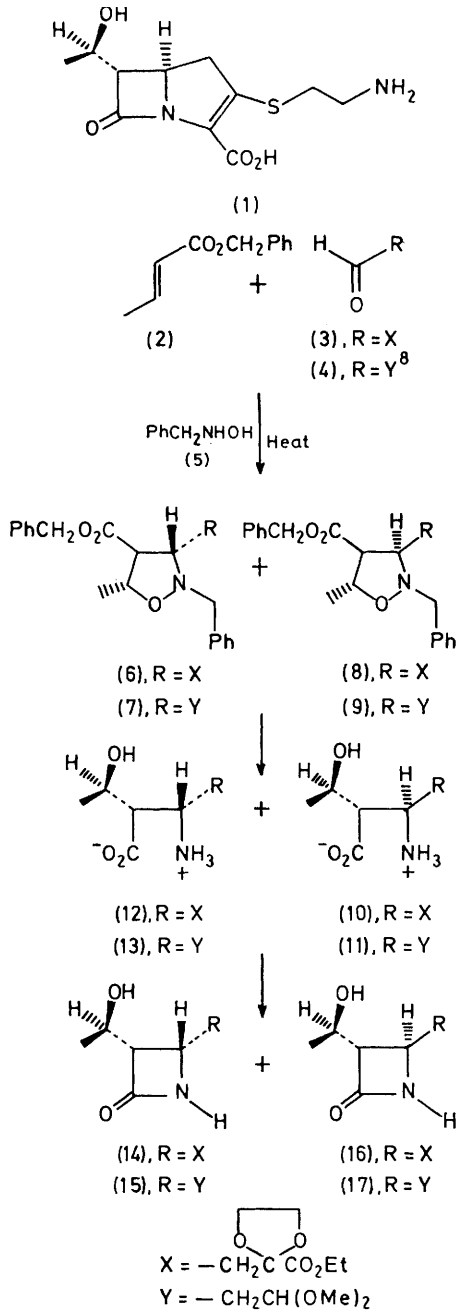
A three-step procedure for the synthesis of *trans*-3,4-disubstituted azetidin-2-ones which utilizes 1,3-dipolar cycloaddition reactions as the key step has led to the synthesis of the azetidinones (**16**) and (**17**).

Thienamycin (**1**) is an exceptionally potent β-lactam antibiotic possessing marked resistance to bacterial β-lactamase.[1] This unusual property and its novel structure has generated intense interest in the synthesis of (**1**)[2] and analogues thereof.[3–5] Herein, we report efficient and stereoselective routes to useful intermediates for the synthesis of thienamycin and its analogues.



A mixture of the aldehyde (**3**),[6] *N*-benzylhydroxylamine (**5**),[7] and benzyl crotonate (**2**) in a ratio of 1 : 1 : 4 was heated in toluene at 100 °C for 5 h providing an 85% yield of the isoxazolidines (**6**) and (**8**)[8] in a ratio of 1 : 5, respectively. The mixture was purified by flash chromatography on silica gel and hydrogenolysed in methanol at atmospheric pressure over PtO_2 for 20 h at ambient temperature to afford a mixture of the amino-acids (**10**) and (**12**). The latter mixture was cyclized with dicyclohexylcarbodi-imide in MeCN at 60 °C for 4 h[2c] to give the azetidinones (**16**) and (**14**) in 30 and 5% overall yield, respectively, from (**10**) and (**12**), after chromatography on silica gel. Structures were assigned by proton decoupling of the 200 MHz ^{1}H n.m.r. spectra as well as from i.r. and mass spectral data.† Thus, the desired *trans*-azetidinone (**16**) is available in 3 steps from the readily available aldehyde (**3**) in 21% overall yield. Utilizing the same set of reactions and conditions, the azetidinones (**17**) and (**15**) were prepared in 31 and 1% overall yields respectively. Similar intermediates have been synthesized previously in comparable yields although *via* somewhat more lengthy routes.[2a] While the present investigation was in progress (**17**) was prepared by an alternative, less stereoselective, route[2b] and converted into racemic thienamycin by previously published methodology thus establishing the validity of the approach reported herein.

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† All new compounds gave satisfactory i.r., ^{1}H n.m.r., and mass spectral data. The i.r. and ^{1}H n.m.r. spectra of (**17**) were identical to those reported previously.[2b]