Stereo- and Enantio-controlled Synthesis of Chiral Intermediates for the Total Synthesis of Thienamycin and Related β-Lactam Antibiotics from 3-Hydroxybutyrates

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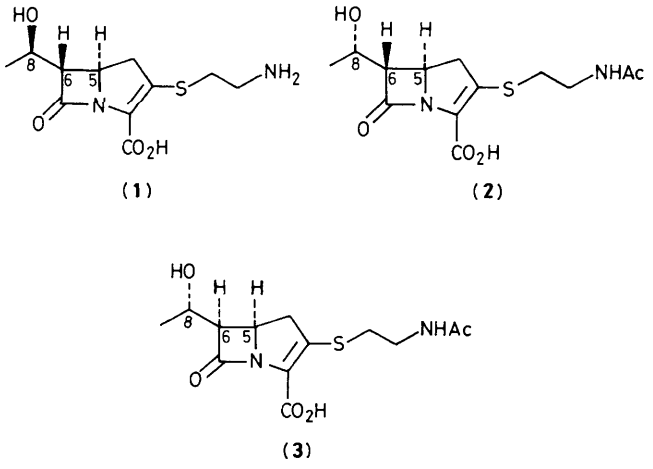
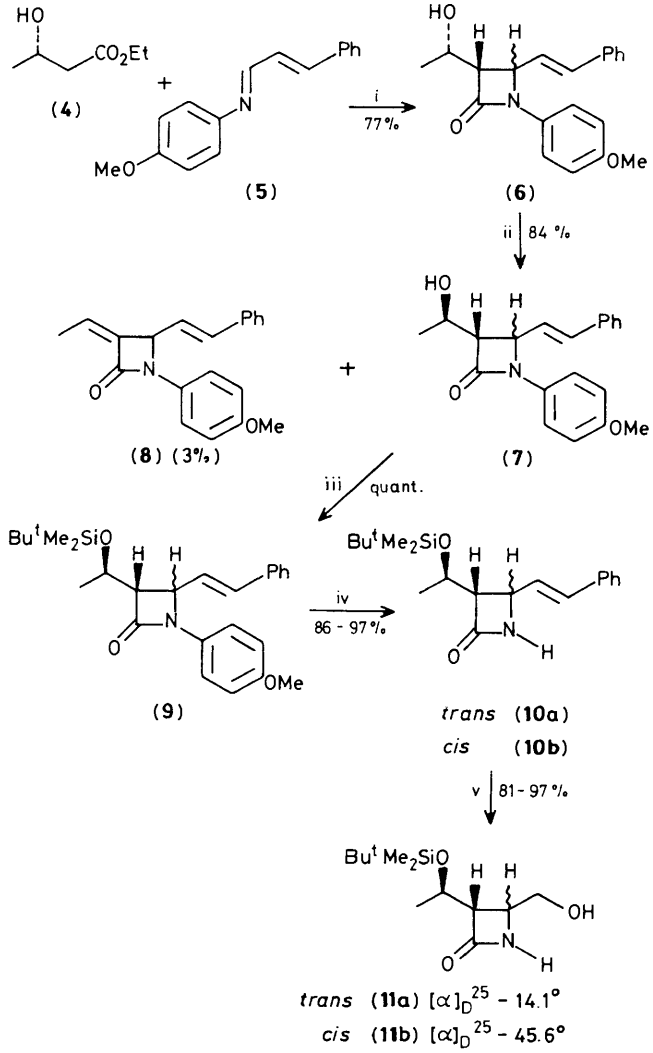
The synthesis of (1′*R*,3*S*,4*S*)- and (1′*R*,3*S*,4*R*)-3-(1′-t-butyldimethylsilyloxyethyl)-4-hydroxymethyl-2-azetidinone from ethyl (*S*)-3-hydroxybutyrate is reported.

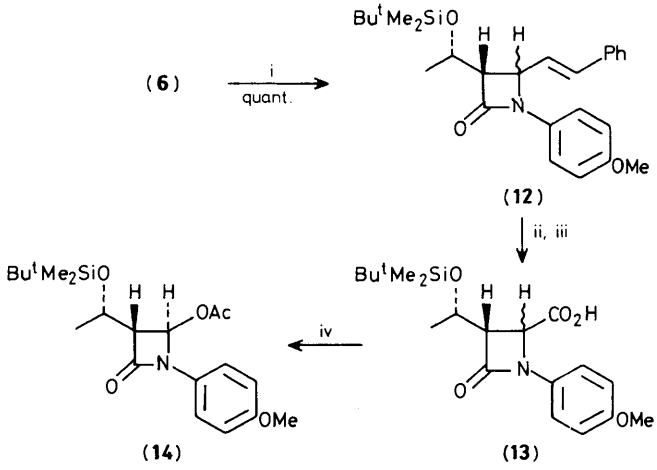
One major difficulty in the synthesis of thienamycin (**1**) and related β-lactam antibiotics (**2**) and (**3**) is the control of the relative and absolute stereochemistry of the three contiguous chiral centres.[1]

Since we and Hart first demonstrated[2] that 3-hydroxybutyrates[3] can be used as chiral building blocks for the synthesis of 3-(1′-hydroxyethyl)-2-azetidinones in a one-flask procedure a number of other groups have reported similar findings.[4] In this paper we now convey the synthesis, from ethyl (*S*)-3-hydroxybutyrate (Scheme 1), of optically active *trans*- and *cis*-3-(1′-t-butyldimethylsilyloxymethyl)-4-hydroxymethyl-2-azetidinones, intermediates which can be converted into thienamycin and olivanic acids by a known procedure.[5] We used ethyl (*S*)-3-hydroxybutyrate with 86% optical purity,





Scheme 1. *Reagents:* i, tetrahydrofuran (THF), 2 LICA (lithium isopropylcyclohexylamine), −20—10 °C; ii, THF, PPh_3, diethyl azodicarboxylate (DEAD), HCO_2H, 0 °C—room temp., 1.5 h; MeOH, HCl, room temp., 15 h; iii, dimethylformamide (DMF), t-butyldimethylsilyl chloride, imidazole, room temp., 15 h; iv, MeCN, ammonium cerium(IV) nitrate, −20 °C, 20 min; v, CH_2Cl_2, O_3, $NaBH_4$, −78—0 °C.



Scheme 2. *Reagents:* i, DMF, t-butyldimethylsilyl chloride, imidazole, room temp., 15 h; ii, CH_2Cl_2, O_3, $NaBH_4$, −78 to −20 °C; iii, acetone, Jones reagent, −5 °C, 2 h; iv, MeCN, $Pb(OAc)_4$, $Cu(OAc)_2$, 70 °C, 0.5 h.

obtained from reduction of ethyl acetoacetate using baker's yeast.[3] The dianion imine condensation–cyclisation reaction of ethyl (*S*)-3-hydroxybutyrate (**4**) and *N*-anisylcinnamylidenimine (**5**) gave a 1 : 1 mixture of *trans*- and *cis*-β-lactam (**6**) in 77—100% yield.[6] Mitsunobu inversion[2a,7] of (**6**) followed by acid hydrolysis of the intermediate formyl esters cleanly produced the inverted (*R*)-hydroxyethyl-2-azetidinones (**7**) in 84% yield. We also isolated a small amount (3%) of the elimination product (**8**). After protection of (**7**) as its t-butyldimethylsilyl ether we were able to separate the *trans* and *cis* isomers (**9**) by flash chromatography. We then subjected them separately to oxidative dearylation[8] with ammonium cerium(IV) nitrate, to obtain the *N*-unprotected β-lactam *trans* (**10a**) {97% yield, m.p. 85—86 °C (light petroleum–CH_2Cl_2), $[\alpha]_D^{25}$ +40.7° (*c* 0.8555 $CHCl_3$)} and *cis* (**10b**) {86% yield, m.p. 80 °C (light petroleum–CH_2Cl_2), $[\alpha]_D^{25}$ −45.9° (*c* 1.06 $CHCl_3$)}. Ozonolysis of (**10a**) and (**10b**), followed by reductive work-up[9] produced the 4-hydroxymethyl-2-azetidinones *trans* (**11a**){(yield 97%, m.p. 89—90 °C (light petroleum), $[\alpha]_D^{25}$ −14.1° (*c* 0.595 $CHCl_3$)} and *cis* (**11b**)[10] (yield 81%, m.p. 94 °C (light petroleum), $[\alpha]_D^{25}$ −45.6° (*c* 0.8 $CHCl_3$)}.†

The overall yield from ethyl (*S*)-3-hydroxybutyrate for *trans* (**11a**) was 30% and 23% for *cis* (**11b**).[11] These yields are comparable to other reported methods for the synthesis of chiral thienamycin precursors.[8b,11] The optical rotation of (**11a**) was found to be identical to the literature value for (1′*R*,3*S*,4*S*)-3-(1′-t-butyldimethylsilyloxyethyl)-4-hydroxymethyl-2-azetidinone.[11b,c] After we had unequivocally established the absolute stereochemistry of the *trans* products, we decided to determine the configuration of the *cis*-azetidinones through *cis–trans* isomerization at position 4 (Scheme 2). Reider and Grabowski had previously shown,[11a] that oxidative decarboxylation of 3-(1′-hydroxyethyl)-4-(carboxylic acid)-2-azetidinone results in exclusive introduction of the acetoxy group at C-4 opposite the hydroxyethyl group at C-3.

The *cis–trans* mixture (**6**) (racemic) was quantitatively converted into the t-butyldimethylsilyl ether (**12**). Ozonolysis of (**12**) followed by reductive work-up with $NaBH_4$ and then oxidation with Jones reagent gave the carboxylic acid (**13**).

† All intermediates showed spectroscopic data in agreement with their structures.

After oxidative decarboxylation with lead tetra-acetate[12] we obtained *trans*-β-lactam (**14**) as single isomer in an overall yield of 40% (Scheme 2).

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