Complete Stereoselective Synthesis of Chiral Intermediates for Thienamycin and Related Antibiotics

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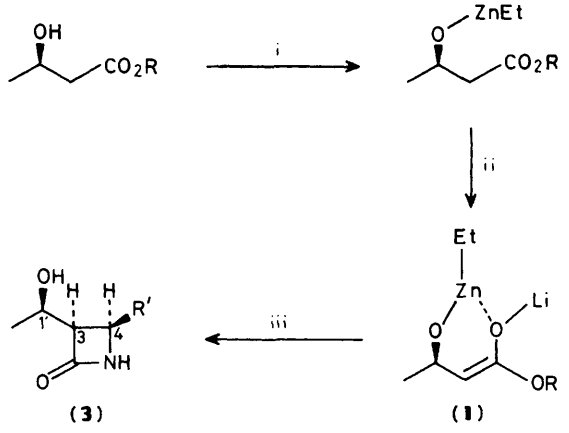
The complete stereoselective synthesis of (3*R*,4*R*)-3-[(*S*)-1′-hydroxyethyl]-4-phenylethynyl-2-azetidinone and its 4-phenyethenyl derivative were accomplished by the reaction of the organozinc derivative of (*R*)-methyl-3-hydroxybutyrate with *N*-trimethylsilylimines.

The carbapenem-β-lactam antibiotics represented by thienamycin have attracted interest as a synthetic target. Georg and Hart first demonstrated that 3-hydroxybutyrates can be used as chiral building blocks for the synthesis of 3-(1′-hydroxyethyl)-2-azetidinones.[1] Since then, many reports have been published on the synthesis of carbapenem precursors by similar methods.[2] Nevertheless, the stereoselectivity in these reported methods was low and afforded a mixture of *cis*- and *trans*-3-(1-hydroxyethyl)-2-azetidinones by the reaction of the dilithium anion of 3-hydroxybutyrate with various imines even at low temperatures (−78 °C). Here we report the complete stereoselective synthesis of optically pure *cis*-3-(1′-hydroxyethyl)-4-substituted-2-azetidinones starting from (*R*)-methyl-3-hydroxybutyrate.

We were interested in the strong co-ordination of organozinc compounds to electron donor molecules. The ethylzinc-oxylithium enolate (**1**) was prepared by the reaction of (*R*)-methyl-3-hydroxybutyrate (optical purity, 98%)[3] with diethylzinc followed by the reaction with lithium hexamethyldisilazane (HMDS) in tetrahydrofuran (THF) at room temperature. The resulting compound (**1**) was treated with *N*-trimethylsilylphenylpropargylidenimine (**2a**) or



(**1**) **a**: R = Me, **b**: R = Pr^{i}

(**2**,**3**) **a**: R′ = C≡CPh, **b**: R′ = CH=CHPh (*E*)

Scheme 1. *Reagents and conditions*: i, Et_2Zn in THF; ii, lithium hexamethyldisilazane in THF, room temp.; iii, $Me_3SiN{=}CHR'$, (**2**), THF, room temp.

N-trimethylsilyl-*trans*-cinnamylidenimine (**2b**) in THF at room temperature, which afforded only single (3,4-*cis* and 1′,3-*syn*)-isomers: (1′*R*,3*R*,4*S*)-3-hydroxyethyl-4-phenylethynyl-2-azetinone (**3a**)† or (1′*R*, 3*R*, 4*R*)-3-hydroxyethyl-4-(*E*)-styryl-2-azetidinone (**3b**)† in yields of 85 and 78%, respectively, of the possible four isomers. The compounds (**3a**) and (**3b**) can be easily transformed to the (3,4-*trans*)-isomers which have the same configuration as those of natural thienamycin.[4]

† The new compound (**3a**) gave i.r. and ^{1}H n.m.r. spectra and elemental analysis consistent with the assigned structure. $[\alpha]_D^{22}$ −7.29° (*c* 1.10, ethanol). 400 MHz N.m.r. spectrum data in $CDCl_3$: δ 7.43, 7.30 (m, 5H, arom.), 6.16 (br. s, 1H, NH), 4.61 (d, 1H, *J* 5.37 Hz, C^4H), 4.40, 4.36 (m, 1H, CH), 3.42 (dd, 1H, *J* 6.1 Hz, C^3H), 2.76 (d, 1H, *J* 2.44 Hz, OH), 1.41 (d, 3H, *J* 6.34 Hz, Me). The structure of compound (**3b**) was confirmed by comparison with the *O*-t-butyldimethylsilyl ether of (**3b**) reported by Georg and Gill in ref. 2.

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