Diastereoselective Aldol Reactions of β-Silylenolates: A Formal Synthesis of Thienamycin†

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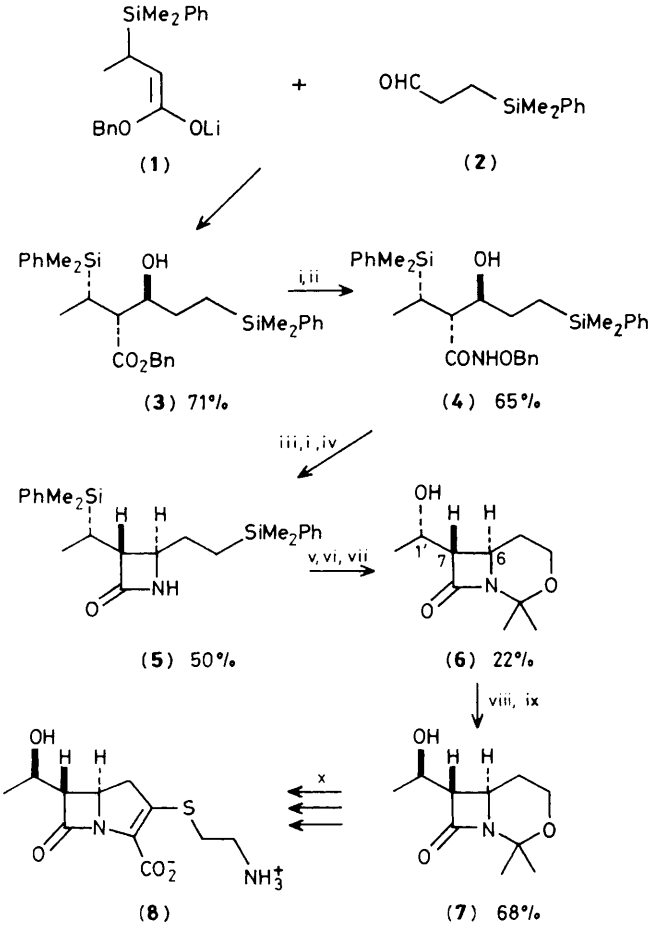
The lithium enolate (**1**) of benzyl β-phenyldimethylsilylbutanoate reacts with β-phenyldimethylsilylpropionaldehyde (**2**) to give, with high diastereoselectivity, the aldol product (**3**), which is converted into the β-lactam (**7**), a known precursor of thienamycin.

Earlier this year we reported that β-silylenolates react with aldehydes in an aldol reaction showing remarkably high diastereoselectivity with respect to both new chiral centres.[1] In this and the following communication we report two applications of this finding. In this communication we describe a formal synthesis of racemic thienamycin (**8**), in which the phenyldimethylsilyl group is twice used as a masked hydroxy group, into which it can be converted in two simple steps, with retention of configuration.[2]

For the synthesis of thienamycin, we needed a three-carbon aldehyde in which C-3 must be functionalised in such a way that it either is, or can be converted into, a hydroxymethyl, aldehyde, or carboxylic acid group. This poses obvious problems unless the functional group is heavily masked or protected. A β-phenyldimethylsilyl group[2] is ideal for this situation, since it is not a nucleofugal group, and it also discourages enolisation.[3] We prepared the aldehyde (**2**) by hydrosilylation of allyloxytrimethylsilane[4] ($PhMe_2SiH$, Wilkinson's catalyst), hydrolysis of the silyl ether (HCl, MeOH), and oxidation of the alcohol (pyridinium dichromate or Swern), in 62% overall yield. We also prepared the (*Z*) lithium enolate (**1**) by conjugate addition of our silyl-cuprate reagent to benzyl crotonate, quenching the mixture with ammonium chloride solution, and regenerating the enolate by treating the β-silyl ester with lithium di-isopropylamide. The enolate (**1**) reacted with the aldehyde (**2**) to give the aldol product, with high diastereoselectivity: we isolated the pure ester (**3**) in 71% yield based on the ester from which the enolate (**1**) was derived. The formation of the *O*-benzyl hydroxamate (**4**), the cyclisation, and the removal of the benzyloxy group followed conventional chemistry,[5] and gave us the β-lactam (**5**). The phenyldimethylsilyl groups had now served their purpose. One had controlled the relative stereochemistry (and, incidentally, had served to differentiate the hydroxy group present in thienamycin from the hydroxy group which is displaced in the β-lactam-forming step), and the other

† No reprints available.



Scheme 1. Bn = $PhCH_2$. *Reagents:* i, H_2, Pd, C; ii, $H_2NOBn \cdot HCl$, 1-ethyl-3-[3-(dimethylamino)propyl]carbodi-imide hydrochloride; iii, $EtO_2CN{=}NCO_2Et$, Ph_3P; iv, $TiCl_3$; v, $BF_3 \cdot 2AcOH$; vi, $MeCO_3H$, Et_3N, tetrahydrofuran, MeOH; vii, $Me_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$; viii, $EtO_2CN{=}NCO_2Et$, Ph_3P, HCO_2H; ix, NaOH, H_2O, dioxane; x, ref. 7.

has stood in for a hydroxy group which might have been troublesome had it not been masked in so electronically stable a form. We converted both silyl groups into hydroxy groups in the usual way,[2] except that we have not optimised the yields other than by using peracetic acid in place of *m*-chloroperbenzoic acid, so that we could remove excess of reagent and acetic acid by-product simply by evaporation. We could detect the diol by t.l.c., but we did not isolate it as such. Instead we treated the crude reaction mixture with 2,2-dimethoxypropane and toluene-*p*-sulphonic acid, and isolated the tetrahydro-oxazine (**6**). This compound has the correct relative configuration between C-1′ and C-7 for the olivanic acids,[6] and inversion of configuration at C-1′ (Mitsunobu conditions) gave us the tetrahydro-oxazine (**7**), which has already been converted into thienamycin.[7]

Our synthesis is versatile in that the geometrical isomer of the enolate (**1**) is also available (by conjugate addition of the silyl-cuprate reagent to benzyl crotonate), and it reacts with the aldehyde (**2**) to give, as the major product (70:30 with respect to the aldol geometry), the isomer of (**3**), diastereoisomeric at the hydroxy carbon. This compound is suitable for an otherwise exactly analogous synthesis of β-lactams with *cis*-geometry as found in some of the olivanic acids.[6]

We thank Beecham Pharmaceuticals for a CASE award to J. D. K. and Drs. R. Southgate and D. F. Corbett for their help in this work.

Received, 9th May 1986; Com. 623

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