Enantioselective Synthesis of a Chiral Intermediate for Aztreonam and Related Monobactam Antibiotics

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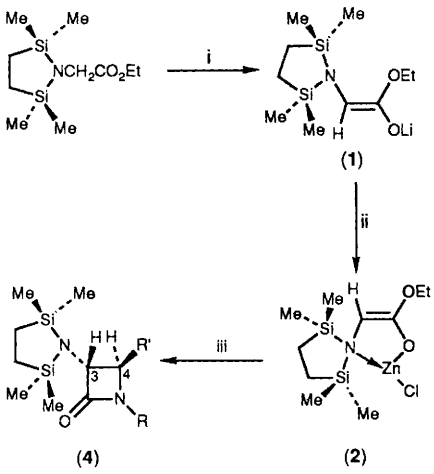
The enantioselective synthesis of *trans*-(3*R*,4*S*)-1-(*R*)-α-methylbenzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-*N*-(*R*)-α-methylbenzyliminoazetidin-2-one has been accomplished by reaction of the chlorozinc enolate of an *N,N*-diprotected glycine ethyl ester with a chiral α-diimine.

Recently, we have demonstrated that zinc enolates of disubstituted glycine esters are effective reagents for the diastereoselective synthesis of 3-amino-2-azetidinones, the principal building blocks for the synthesis of aztreonam and related monobactam antibiotics.[1] Whereas most studies in the field of β-lactam synthesis have dealt with the development of enantioselective routes to chiral intermediates for thienamycin and related antibiotics,[2,3] little attention has been paid to the enantioselective synthesis of 3-aminoazetidin-2-ones.[4]



a; R = Bu^t, R' = C(H)=N–R

b; R = (*R*)-C(H)(Me)Ph, R' = C(H)=N–R

c; R = (*R*)-C(H)(Me)Ph, R' = 2-pyridyl

Scheme 1. *Reagents and conditions*: i, lithium diamide (LDA) in THF, −78 °C; ii, $ZnCl_2$ in Et_2O, −78 °C; iii, R–N=C(H)–R' (**3**), THF, −78 °C → room temperature.

Here we report the first enantioselective zinc-mediated synthesis of *trans*-(3*R*,4*S*)-1-(*R*)-α-methylbenzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-*N*-(*R*)-α-methylbenzyliminoazetidin-2-one starting from *N,N'*-bis(*R,R'*)-α-methylbenzyl-1,4-diazabuta-1,3-diene [(*R*)-α-methylbenzyl-DAB].[5]

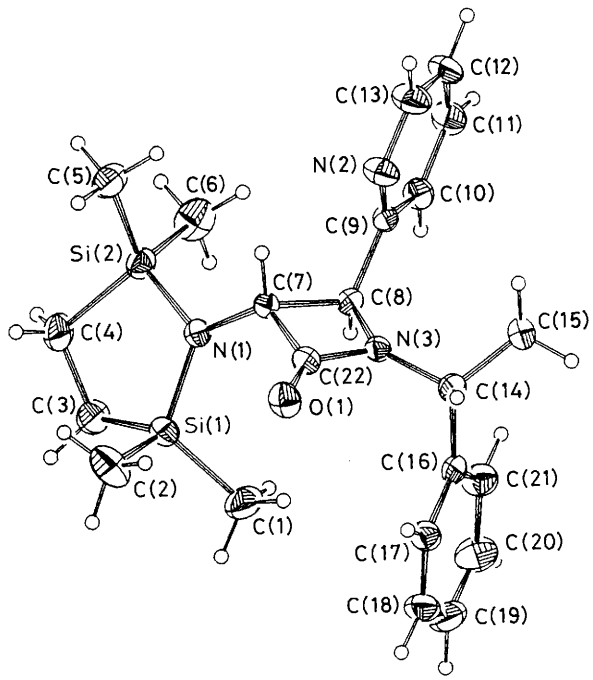


Figure 1. An ORTEP drawing (30% probability level) of *trans*-(3*R*,4*S*)-1-(*R*)-α-methylbenzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)azetidin-2-one (**4c**) together with the adopted numbering scheme.

We were interested in the reactions of zinc enolates with 1,4-disubstituted 1,4-diazabuta-1,3-dienes [(*R*)-DAB] to form 3-amino-4-imino-β-lactams because the 4-imino group represents a protected aldehyde function, which is suitable for further derivatisation.[6] These reactions, which display a very high diastereoselectivity (Scheme 1), surprisingly proceeded also with a high enantioselectivity using the easily available (*R*)-α-methylbenzyl-DAB. Thus the zinc enolate (**2**) was prepared *in situ*,[1] and reacted with t-butyl-DAB (**3a**) or (*R*)-α-methylbenzyl-DAB (**3b**) in tetrahydrofuran (THF) at −70 °C to afford *trans*-1-t-butyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-*N*-t-butyliminoazetidin-2-one (**4a**)† in 98% yield and *trans*-(3*R*,4*S*)-1-(*R*)-α-methylbenzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-*N*-(*R*)-α-methylbenzyliminoazetidin-2-one (**4b**)† in 90% chemical and 86% optical‡ yields respectively. The latter compound is a threefold protected intermediate for the synthesis of aztreonam and related monobactam antibiotics.

Zinc enolate (**2**) also reacted smoothly with *N*-(*R*)-α-methylbenzyl(2-pyridyl)carbaldimine (**3c**), a chiral imine containing a 1,4-diazabuta-1,3-diene skeleton, to afford *trans*-(3*R*,4*S*)-1-(*R*)-α-methylbenzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)azetidin-2-one (**4c**)† in 98% chemical and ≥95% optical yield. The absolute configuration of (**4c**) and therefore also of (**4b**) was determined to be 3*R*,4*S* from an *X*-ray structure determination,§ the result of which is shown in Figure 1.

The reactions of zinc enolate (**2**) with (*R*)-DAB substrates proved to be superior to those of the corresponding lithium enolate (**1**) under the same reaction conditions. Starting from the latter enolate (**1**) compound (**4a**) was produced in only 15% yield, (**4b**) in 45% chemical and 40% optical yield, and (**4c**) in 70% chemical and 50% optical yield. A discussion on the difference in reactivity of lithium and zinc enolates will be presented in a forthcoming paper.

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† The new compounds (**4**) gave IR and ^{1}H and ^{13}C NMR spectra and elemental analyses consistent with the assigned structures. 200 MHz ^{1}H NMR($CDCl_3$) (**4a**): δ 7.46 (d, 1H, *J* 7.8 Hz, HC=N), 4.00 (d, 1H, *J* 1.8 Hz, C^{3}H), 3.82 (dd, 1H, *J* 7.8 and 1.8 Hz, C^{4}H), 1.31 [s, 9H, $C(CH_3)_3$], 1.21 [s, 9H, $C(CH_3)_3$], 0.78—0.61 (m, 4H, $SiCH_2CH_2Si$), 0.12 [s, 6H, $Si(CH_3)_2$], 0.09 [s, 6H, $Si(CH_3)_2$]. (**4b**): δ 7.53 (d, 1H, *J* 7.6 Hz, HC=N), 7.41—7.13 (m, 10H, arom.), 4.85 [q, 1H, *J* 7.2 Hz, $HC(CH_3)Ph$], 4.34 [q, 1H, *J* 6.6. Hz, $HC(CH_3)Ph$], 4.18 (d, 1H, *J* 1.9 Hz, C^{3}H), 3.67 (dd, 1H, *J* 7.6 and 1.9 Hz, C^{4}H), 1.50 [d, 3H, *J* 6.6 Hz, $CH_3C(H)Ph$], 1.39 [d, 3H, *J* 7.2 Hz, $CH_3C(H)Ph$], 0.76—0.52 (m, 4H, $SiCH_2CH_2Si$), 0.05 [s, 6H, $Si(CH_3)_2$], −0.05 [s, 6H, $Si(CH_3)_2$]. (**4c**): δ 8.62—8.59 (m, 1H, pyr.), 7.67—7.58 (m, 1H, pyr.), 7.32—7.09 (m, 7H, arom. and pyr.), 5.01 [q, 1H, *J* 7.2 Hz, $CH(CH_3)Ph$], 4.36 (d, 1H, *J* 2.0 Hz, C^{3}H), 4.04 (d, 1H, *J* 2.0 Hz, C^{4}H), 1.26 [d, 3H, *J* 7.2 Hz, $CCH_3(H)Ph$], 0.70—0.56 (m, 4H, $SiCH_2CH_2Si$), −0.09 [s, 6H, $Si(CH_3)_2$], −0.13 [s, 6H, $Si(CH_3)_2$].

‡ This is an uncorrected enantiomeric excess (e.e.); the optical purity of the starting (*R*)-α-methylbenzylamine was 93%. Therefore the optical yield of (**4b**) is better than 90%.

§ *Crystal data* for (**4c**): $C_{22}H_{31}N_3OSi_2$, *M* = 409.68, monoclinic, space group *I*2, *a* = 18.410(1), *b* = 6.813(1), *c* = 19.471(1) Å, β = 105.77(1)°, *U* = 2350.3(4) Å^3, *Z* = 4, *F*(000) = 880, D_c = 1.158 g cm^{-3}, *T* = 295 K, Mo-K_α (Zr-filtered) radiation (λ = 0.71073 Å), μ(Mo-K_α) = 1.40 cm^{-1}. A redundant set of 6910 reflections was collected on an Enraf-Nonius CAD4F diffractometer in the range 2.7 ≤ 2θ ≤ 55°. 2195 Unique reflections (R_{av} = 0.04) with $I \geq 2.5\sigma(I)$ were used in the structure solution (direct methods; SHELXS-86) and weighted full-matrix least-squares refinement (SHELX-76), which converged at *R* and R_w values of 0.046 and 0.044 respectively. The enantiomorph was chosen on the basis of the configuration of the starting (*R*)-α-methylbenzylamine. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.