

A Novel Use of the Ionic Hydrosilation in the Synthesis of Carbapenem Key Intermediate

Yuko KOBAYASHI, Yoshio ITO, and Shiro TERASHIMA*

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

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Synopsis. The ionic hydrosilation of the 3-acetyl-2-azetidinone derivative in the presence of boron trifluoride etherate was found to effect highly stereoselective reduction of the acetyl group (at most, 17:1), giving rise to the desired 3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative as a major product. Simultaneous reductive removal of the bis(*p*-methoxyphenyl)methyl group was also observed depending upon the reaction conditions.

We have recently succeeded in exploring an efficient synthetic route to the important carbapenem key intermediate (**1**) starting from commercially available and inexpensive ethyl (*S*)-lactate (**2**).¹⁾ Thus, the 3-acetyl-2-azetidinone derivative (**4**) bearing the desired absolute stereochemistry could be produced stereoselectively by the [2+2]-cycloaddition of the chiral imine (**3**) derived from **2** with diketene. Subsequent reduction of **4** with K-selectride® or potassium triethylhydroborate according to the reported procedures,²⁾ afforded the 3-[(*R*)-1-hydroxyethyl]-2-azetidinone (**5a**) in a highly stereoselective manner, from which **1** could be readily elaborated by way of the *N*-unprotected 2-azetidinone and the 3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone derivatives (**5b** and **5c**).

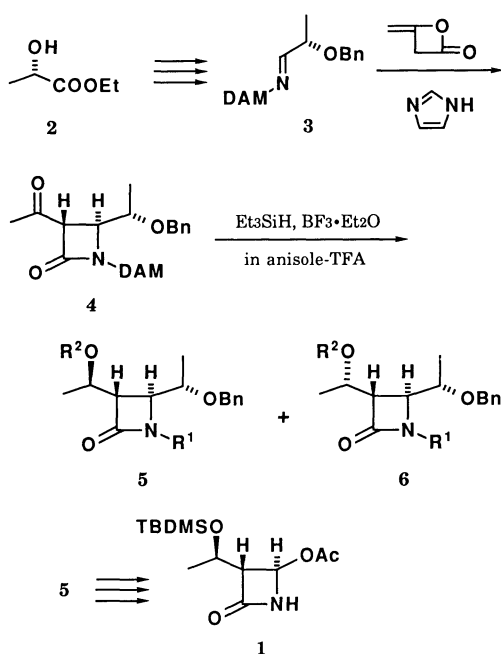
Since a number of the methods which may effect stereoselective reduction of **4** to **5a** are limited^{3,4)} and

the reducing agents so far examined by us seem to be fairly expensive, another efficient reduction method was sought which can produce **5a** from **4** highly stereoselectively. After numerous experimentations surveying various reducing agents, we found that the ionic hydrosilation⁵⁾ of **4** underwent in a highly stereoselective manner, affording a good yield of **5a** or **5b** depending upon the reaction conditions.

Thus, when **4** was treated with triethylsilane in a mixture of trifluoroacetic acid (TFA) and anisole in the presence of a catalytic amount of boron trifluoride etherate (BF₃·Et₂O) (0.08 equivalent to the amount of triethylsilane used) at −10 °C, a mixture of **5a** and the 3-[(*S*)-1-hydroxyethyl]-2-azetidinone (**6a**) could be obtained in 71% combined yield along with a small amount of the mixture of **5b** and **6b** (10% combined yield). The formation ratio of **5a** to **6a** was determined as 8:1 by comparing the ¹H NMR spectrum of the mixture with those of authentic samples of **5a** and **6a**.¹⁾ On the other hand, treatment of **4** with a mixture of TFA and anisole in the presence of BF₃·Et₂O (0.35 equivalent to the amount of triethylsilane used) at 0 °C was found to effect simultaneous stereoselective reduction of the acetyl group and reductive removal of the bis(*p*-methoxyphenyl)methyl (DAM) group, giving rise to a mixture of **5b** and **6b** in 64% combined yield. The latter hydrosilation conditions is anticipated to be more severe than the former. The ratio of **5b** and **6b** could be determined as 17:1 by the ¹H NMR spectrum after conversion to a mixture of the *t*-butyldimethylsilyl (TBDMS) ethers (**5c** and **6c**). Independent syntheses of **6b,c** from **6a** which had already been converted to **5a** by the Mitsunobu reaction,¹⁾ could rigorously establish the stereochemistries of **6b,c**.

In these ionic hydrosilation reactions, TFA and BF₃·Et₂O were found to be essential. Thus, complex mixtures of the decomposition products were always produced in the absence of BF₃·Et₂O probably due to slowdown of the reaction rate. Uses of other Lewis acids such as boron tribromide or titanium tetrachloride in place of BF₃·Et₂O were shown to be unrewarding, giving rise to complex decomposition products. Additionally, the ionic hydrosilation reactions attempted using trichloroacetic acid or acetic acid as a protic acid in place of TFA resulted in simple recovery of **4**.

Thus, it appeared that the ionic hydrosilation holds promise as an effective method for reducing the acetyl group of **4** to the (*R*)-1-hydroxyethyl group in a highly stereoselective manner and affords a good yield of **5a** or **5b** depending upon the reaction conditions.⁶⁾ Furthermore, direct synthesis of **5b** from **4** may have high practical value since the DAM group of **5a** is removable only by oxidation with fairly expensive



a: R¹=DAM, R²=H, b: R¹=R²=H, c: R¹=H, R²=TBDMS

cerium(IV) ammonium nitrate (CAN).

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. ^1H NMR spectra were recorded with a Hitachi R-90H (90 MHz) and a Bruker AM spectrometer (400 MHz). All signals were expressed as ppm downfield from tetramethylsilane used as an internal standard (δ -value). Wakogel C-200 and C-300 kieselgel 60 were used as an adsorbent for column chromatography.

(3*S*,4*S*)-4-[(*S*)-1-Benzoyloxyethyl]-3-[bis(*p*-methoxyphenyl)-methyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone and Its 3-[(*S*)-1-Hydroxyethyl] Isomer (5a** and **6a**).** Trifluoroacetic acid (0.640 ml, 8.31 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6.0 μl , 0.049 mmol) were added to a mixture of **4** (98.1 mg, 0.207 mmol), anisole (68.0 μl , 0.626 mmol), and triethylsilane (0.100 ml, 0.626 mmol) at -10°C . After stirring at -25°C for 1.5 h, the mixture was concentrated in vacuo and the concentration residue was diluted with aqueous NaOH and ether. The organic layer was separated and washed successively with 1 mol dm^{-3} HCl and saturated aqueous NaCl, then dried over anhydrous MgSO_4 . Filtration and concentration in vacuo gave an oily residue, which was purified with column chromatography (SiO_2 , CH_2Cl_2 -AcOEt 1:0–2:1) to give a mixture of **5a** and **6a** (69.6 mg, 71%) from the less polar fraction. The ratio of **5a** to **6a** could be calculated as 8:1 by comparing the ^1H NMR spectrum of the mixture with those of authentic samples of **5a** and **6a**.¹⁾ A mixture of **5b** and **6b** (4.9 mg, 10%) was also isolated as the minor products from the more polar fraction. Comparison of the ^1H NMR spectrum of the mixture with those of pure samples of **5b** and **6b** (vide infra) obviously established the structures of the products (**5b** and **6b**).

(3*S*,4*S*)-4-[(*S*)-1-Benzoyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone and Its 3-[(*S*)-1-Hydroxyethyl] Isomer (5b** and **6b**).** Trifluoroacetic acid (0.690 ml) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (25.0 μl , 0.203 mmol) were added to a mixture of **4** (0.106 g, 0.223 mmol), anisole (73.0 μl , 0.672 mmol), and triethylsilane (0.107 ml, 0.670 mmol) at 0°C . After stirring at the same temperature overnight, the mixture was concentrated in vacuo and the residue was diluted with saturated aqueous NaHCO_3 and AcOEt. The organic layer was separated, washed successively with 1 mol dm^{-3} HCl and saturated aqueous NaCl, then dried over anhydrous MgSO_4 . Filtration and concentration in vacuo gave an oily residue, which was purified with column chromatography (SiO_2 , CH_2Cl_2 -AcOEt 2:1) to give a mixture of **5b** and **6b** (35.5 mg, 64%). The stereochemistries of the reduction products were determined by converting the mixture of **5b** and **6b** to that of **5c** and **6c** in 84% yield under the same conditions as described for silylation of a pure sample of **6b** with *t*-butylchlorodimethylsilane. As **5c** had been obtained from **5a** by way of **5b**,¹⁾ an authentic sample of **6c** was prepared by silylation of a pure sample of **6b** (vide infra). The ratio of **5b** to **6b** could be calculated as 17:1 by the integration ratio of $\text{C}_3\text{-H}$ in the ^1H NMR spectrum of the mixture (vide infra). A single recrystallization of the mixture of **5b** and **6b** from hexane-AcOEt readily afforded a pure sample of **5b**, mp 130.5°C and $[\alpha]_{\text{D}}^{25} + 66.2^\circ$ (*c* 1.24, CHCl_3) [lit.^{1b)} mp $129\text{--}130^\circ\text{C}$ and $[\alpha]_{\text{D}}^{25} + 61.5^\circ$ (*c* 1.45, CHCl_3)]. IR and ^1H NMR

spectrum of this sample were also identical with those reported.^{1b)} An authentic sample of **6b** was prepared by oxidation of **6a** with cerium(IV) ammonium nitrate (vide infra).

(3*S*,4*S*)-4-[(*S*)-1-Benzoyloxyethyl]-3-[(*S*)-1-hydroxyethyl]-2-azetidinone (6b**).** Cerium(IV) ammonium nitrate (0.122 g, 0.222 mmol) was added to a solution of an authentic sample of **6a**¹⁾ (32.1 mg, 0.0675 mmol) in H_2O -MeCN (1:9) (0.2 ml) at -10°C . The mixture was stirred vigorously at the same temperature for 2 h, then diluted with 1 mol dm^{-3} NaOH (0.45 ml). After stirring at rt for 1 h, the mixture was extracted with AcOEt. The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. The concentration residue was purified with column chromatography (SiO_2 , hexane-AcOEt 2:3) to give **6b** (9.9 mg, 60%). ^1H NMR (CDCl_3): 1.22 (3H, d, $J=5.7$ Hz, MeCHOBN), 1.31 (3H, d, $J=6.4$ Hz, MeCHOH), 2.2–2.4 (1H, br, OH), 2.84 (1H, m, $\text{C}_3\text{-H}$), 3.4–3.5 (2H, m, CHOBN and $\text{C}_4\text{-H}$), 4.07 (1H, m, CHOH), 4.41, 4.68 (2H, two d, $J=11.9$ Hz, PhCH_2), 6.20 (1H, bs, NH), 7.32 (5H, s, C_6H_5). This sample was used as an authentic sample of **6b** (vide supra).

(3*S*,4*S*)-4-[(*S*)-1-Benzoyloxyethyl]-3-[(*S*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (6c**).** Imidazole (10.0 mg, 0.147 mmol) and *t*-butylchlorodimethylsilane (15.0 mg, 0.0995 mmol) were added to a solution of an authentic sample of **6b** (5.5 mg, 0.022 mmol) in DMF (0.1 ml). After stirring for 1 h, the mixture was diluted with H_2O and extracted with ether. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous MgSO_4 . Filtration and concentration in vacuo gave a residue, which was purified with column chromatography (SiO_2 , CH_2Cl_2) to give **6c** (7.8 mg, 98%). ^1H NMR (CDCl_3): 0.07 (6H, s, Me_2Si), 0.88 (9H, s, Me_3CSi), 1.22 (3H, d, $J=6.2$ Hz, MeCHOBN), 1.29 (3H, d, $J=6.4$ Hz, MeCHOSi), 2.88 (1H, m, $\text{C}_3\text{-H}$), 3.50 (2H, m, CHOBN and $\text{C}_4\text{-H}$), 4.17 (1H, m, CHOSi), 4.40, 4.67 (2H, two d, $J=11.7$ Hz, PhCH_2), 6.00 (1H, bs, NH), 7.32 (5H, s, C_6H_5). This was used as an authentic sample of **6c** (vide supra).

References

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- 4) It has been reported that reduction of a 3-acetyl-2-azetidinone derivative with a combination of diisopropylamine-borane complex and magnesium trifluoroacetate can proceed highly stereoselectively. S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock, *J. Am. Chem. Soc.*, **103**, 6765 (1981).
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- 6) To our knowledge, this reaction represents the first example where the ionic hydrosilylation reaction has effected reductive removal of the protecting group present at the nitrogen atom of 2-azetidinone.