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

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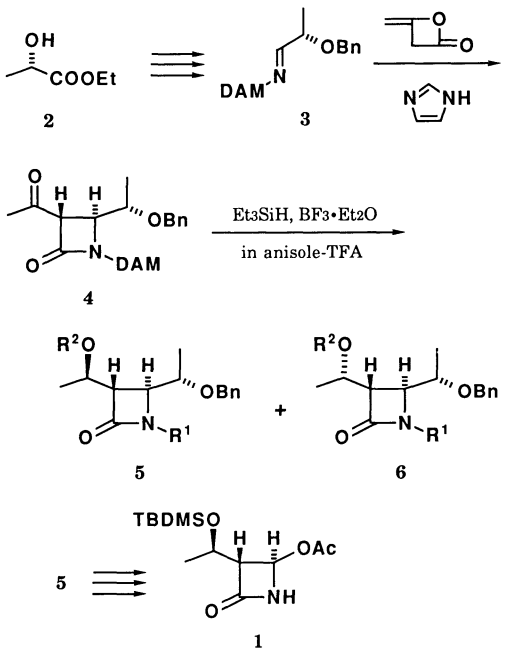
Synopsis. The ionic hydrosilation of the 3-acetyl-2-azetidinone derivative in the presence of boron trifluoride etherate was found to effect highly stereoselective reduction of the acetyl group (at most, 17:1), giving rise to the desired 3-[(*R*)-1-hydroxyethyl]-2-azetidinone derivative as a major product. 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 hydrosilation[5] of **4** underwent in a highly stereoselective manner, affording a good yield of **5a** or **5b** depending upon the reaction conditions.



DAM=(*p*-MeOC$_6$H$_4$)$_2$CH

a: R^1=DAM, R^2=H, **b:** R^1=R^2=H, **c:** R^1=H, R^2=TBDMS

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 ($BF_3 \cdot Et_2O$) (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 ^{1}H 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 $BF_3 \cdot Et_2O$ (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 ^{1}H 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 $BF_3 \cdot Et_2O$ were found to be essential. Thus, complex mixtures of the decomposition products were always produced in the absence of $BF_3 \cdot Et_2O$ probably due to slowdown of the reaction rate. Uses of other Lewis acids such as boron tribromide or titanium tetrachloride in place of $BF_3 \cdot Et_2O$ 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

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 rotaions 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. ^{1}H 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-Benzyloxyethyl]-1-[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 $BF_3 \cdot Et_2O$ (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 ^{1}H 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 ^{1}H 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-Benzyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone and Its 3-[(*S*)-1-Hydroxyethyl] Isomer (5b and 6b). Trifluoroacetic acid (0.690 ml) and $BF_3 \cdot Et_2O$ (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 C_3–H in the ^{1}H 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 $[\alpha]_D^{25}$+66.2° (*c* 1.24, $CHCl_3$) [lit,[1b)] mp 129—130 °C and $[\alpha]_D^{25}$+61.5° (*c* 1.45, $CHCl_3$)]. IR and ^{1}H 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-Benzyloxyethyl]-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%). ^{1}H 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, C_3–H), 3.4—3.5 (2H, m, CHOBn and C_4–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-Benzyloxyethyl]-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%). ^{1}H 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, C_3–H), 3.50 (2H, m, CHOBn and C_4–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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6) To our knowledge, this reaction represents the first example where the ionic hydrosilation reaction has effected reductive removal of the protecting group present at the nitrogen atom of 2-azetidinone.