Synthesis of 3-(1-Hydroxyethyl)-2-azetidinones via Ester–Imine Condensations

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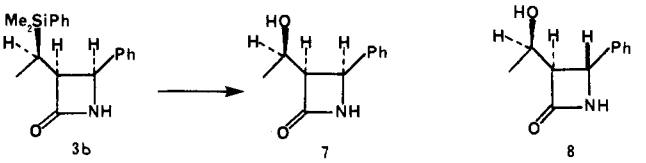
The lithium enolate of ethyl β-(dimethylphenylsilyl)butyrate (1) reacts with imines to afford β-lactams with modest to excellent stereoselectivity.

We recently showed that the dianion derived from ethyl β-hydroxybutyrate reacts with *N*-(trimethylsilyl)imines to afford 3-(1-hydroxyethyl)-2-azetidinones in modest yields.[1,2] In an effort to improve the stereoselectivity of this process, we have examined ethyl β-(dimethylphenylsilyl)butyrate (1)[3] in ester–imine condensations. Our initial results are reported here.

Treatment of a tetrahydrofuran solution of the lithium enolate derived from **1** with benzaldimine **2a** (method A)[4] gave β-lactams **3a** (35%), **4a** (11%), **5a** (5%), and **6a** (15%).[5] The relative stereochemistry at C-3 and C-4 was assigned on the basis of coupling constants,[6] and the complete structure of **3a** was established by degradation to **3b** (ceric ammonium nitrate, 80%)[7], whose structure was determined by X-ray crystallography.[8] The stereochemical relationships between **3a** and **6a** (**4a** and **5a**) were established by epimerization experiments.[9] Thus, while *N*-arylimine **2a** reacts with **1** to give reasonable yields of β-lactams, the reaction is stereochemically complex.

Some of the aforementioned stereochemical problems can be removed by minor alterations in reaction conditions. Thus, when HMPA and **2a** were added in sequence to a tetrahydrofuran solution of the lithium enolate of **1** (method B), only **5a** (19%) and **6a** (61%) were obtained.[10] Our earlier studies suggest that the kinetic distribution of β-lactams in this experiment is the same as in the absence of HMPA but that, under these conditions, subsequent epimerization of **3a** and **4a** to **6a** and **5a**, respectively, takes place.[1] Finally, when the enolate of **1** was generated in the presence of HMPA (method C), reaction with **2a** once again gave only **5a** (35%) and **6a** (45%).[11] In this case, both enolate geometry and epimerization appear to play roles in determining the product distribution[1] (Chart I).

We next turned to the reaction of **1** with *N*-(trimethylsilyl)benzaldimine (**2b**). We began by preparing all of the possible products (**3b–6b**) by ceric ammonium nitrate oxidation of **3a–6a**.[7,12] Treatment of a tetrahydrofuran solution of the lithium enolate of **1** with pure **2b** gave mainly **3b** (63%) along with trace amounts of **6b**. Thus, the anticipated cis selectivity[1] at C-3 and C-4 was observed along with unexpected diastereoselectivity at C-1′.[13] To establish that the carbon–silicon bond in β-lactams of type **3** could be converted to the carbon–oxygen bond that appears in most carbapenem antibiotics,[14] procedures recently developed by Kumada[15] and Fleming[3] were applied to **3b**. Thus, sequential treatment of **3b** with $HBF_4 \cdot Et_2O$ in dichloromethane, followed by potassium fluoride and *m*-chloroperbenzoic acid in *N*,*N*-dimethylformamide gave β-lactam **7** in 48% yield. The structure of **7** was confirmed by X-ray crystallography.[8] In contrast with the behavior of **1**, treatment of the dianion of racemic ethyl β-hydroxybutyrate with **2b** in tetrahydrofuran or tetrahydrofuran–HMPA gave 15–25% yield of mixtures of β-lactams



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(1) Hart, D. J.; Ha, D.-C.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819.

(2) For closely related publications see: Georg, G. I. *Tetrahedron Lett.* **1984**, 3779. Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927. Cainelli, G.; Contento, M.; Gracomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, 937.

(3) The equivalence between β-silyl ester enolates and β-hydroxy ester dianions has been established: Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.

(4) Method A: The enolate of **1** was generated with LDA at −70 °C in THF. The benzaldimine was added at −70 °C, the cooling bath was removed, and the mixture was allowed to warm to room temperature over a 2-h period. Method B: The enolate was generated as above, HMPA was added followed by the imine, and the solution was warmed as above. Method C: As Method A, only the enolate was generated in the presence of HMPA–THF. For similar procedures see ref 1 and references therein.

(5) The yields are based on integration of appropriate signals in the NMR spectrum of a pure mixture of **3a–6a**. Pure samples of **3a**, **5a**, and **6a** were obtained by column chromatography. Compound **4a** was only obtained as a mixture with **6a**.

(6) For **3a**, **3b**, **4a**, and **4b**, $J_{3,4}$ = 5.1–5.5 Hz. For **5a**, **5b**, **6a**, and **6b**, $J_{3,4}$ = 2.2–2.4 Hz.

(7) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(8) The structures of **3** and **7** were determined by X-ray crystallography by Dr. Judith Gallucci at The Ohio State University Chemistry Department Crystallographic Facility. Clear, colorless crystals of compound **3** belong to the triclinic space group $P\bar{1}$ with $Z = 2$ in a cell of dimensions a = 6.722 (1) Å, b = 13.956 (2) Å, c = 10.148 (2) Å, α = 77.01 (1)°, β = 103.66 (1)°, and γ = 92.65 (1)°. The final full-matrix least-squares refinement yielded agreement indices of R and R^w (on F) of 0.043 and 0.047, respectively, for the 2938 intensities with $F_o^2 > 3\sigma(F_o^2)$ and 247 variable parameters. The non-hydrogen atoms were refined with anisotropic thermal parameters, selected hydrogen atoms (all methyl group hydrogens and hydrogen atoms bonded to N, C2, and C3) were refined with isotropic thermal parameters, and the remainder of the hydrogen atoms were fixed at calculated positions. Clear, colorless crystals of compound **7** belong to the orthorhombic space group *Pbca* with $Z = 8$ and unit cell constants of a = 7.866 (1) Å, b = 27.615 (9) Å, and c = 9.150 (2) Å at 20 °C. The final full-matrix least-squares refinement yielded agreement indices of R and R_w (on F) of 0.053 and 0.053 of the 1331 unique intensities with $F_o^2 > 2\sigma(F_o^2)$ and 139 variable parameters. The non-hydrogen atoms were refined with anisotropic thermal parameters, and selected hydrogen atoms (i.e., those bonded to N, C2, and C3) were refined with isotropic thermal parameters. The remainder of the hydrogen atoms were included in the model as fixed contributions in their calculated positions. The position of the hydroxy hydrogen atom could not be determined unambiguously, and this hydrogen was not included in the model.

(9) Catalytic amounts of LDA in THF–HMPA or NaO-*t*-Bu–*t*-BuOD were used to interconvert **3a** and **6a** (**4a** and **5a**). The latter conditions established that the isomerization occurred at C-3. It was shown that isomerization did not take place during ester–imine reactions in the absence of HMPA but did occur in the presence of HMPA.

(10) These represent isolated yields.

(11) Yields determined by NMR analysis of a purified mixture of **5a** and **6a**.

(12) The yields of **3b**, **5b**, and **6b** from **3a**, **5a**, and **6a** were 80%, 79%, and 77%, respectively. Oxidation of a mixture of **4a** and **6a** gave a separable mixture of **4b** and **6b**.

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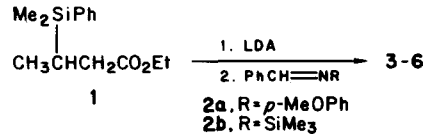
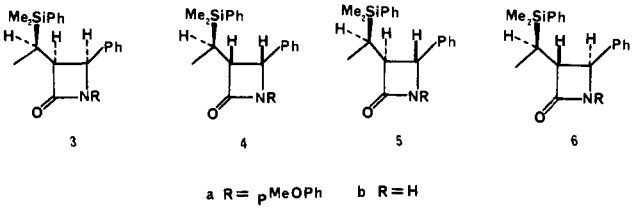
Chart I. Reaction of Ethyl β-(Dimethylphenylsilyl)butyrate with Imines



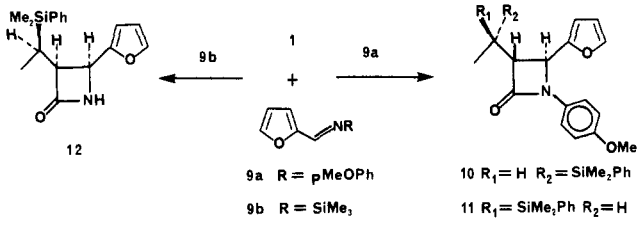
imine	conditions[4]	% 3	% 4	% 5	% 6
2a	A	35	11	5	15
2a	B			19	61
2a	C			35	45
2b	A	63			trace



a R = pMeOPh b R = H

in which **8** and **7** were the major and minor components, respectively.[16] Thus, the use of **1** as a β-hydroxybutyrate equivalent and ethyl β-hydroxybutyrate itself afford different stereochemical results.

Finally, the use of ester **1** in ester–imine condensations was extended to 2-furaldimines **9a** and **9b**. For example, ester **1** and imine **9a** gave **10** (22%) and **11** (44%) by method B while **1** and **9b** gave **12** (72%) by method A.[17] Applications and extensions of these developments are in progress.



9a R = pMeOPh 10 R_1 = H R_2 = $SiMe_2Ph$

9b R = $SiMe_3$ 11 R_1 = $SiMe_2Ph$ R_2 = H

Experimental Section

All melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H magnetic resonance spectra were recorded on a Varian Associates EM-390 or Brüker WP-200 MHz spectrometer and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, br s = broad singlet), coupling constants (in Hertz), integration, interpretation]. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on an Kratos MS-30 instrument. Samples on which exact masses were obtained exhibited no significant peaks at m/e values greater than that of the parent. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use: tetrahydrofuran, ether (distilled from sodium metal); *N,N*-dimethylformamide (distilled from barium oxide); dichloromethane (passed through activity I alumina); potassium fluoride (azeotropic removal of residual water with toluene). Reactions requiring inert atmosphere were run under a blanket of argon. Analytical thin-layer chromatography was performed by using EM Laboratories 0.25-mm precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel (70–230 mesh). Medium-pressure liquid chromatography was performed over EM Laboratories Lobar prepacked silica gel columns. All reaction temperatures refer to those of the reaction mixture.

The preparation of **3b**, **7**, **10**, and **11** are outlined in detail. These experiments are representative of the techniques used during this study. Spectral data on all other new compounds are also reported below.

***rel*-(1′*R*,3*S*,4*S*)-3-[1′-(Dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (3b). From 1 and 2b**: To a solution of lithium diisopropylamide [prepared from 0.85 g (8.5 mmol) of diisopropylamine and 5.3 mL (8.4 mmol) of 1.58 N *n*-butyllithium in hexane] in 10 mL of dry tetrahydrofuran cooled to −70 °C under argon was added a solution of 1.85 g (7.4 mmol) of ester **1** in 2 mL of tetrahydrofuran keeping the temperature below −65 °C. The mixture was stirred for 1 h at −70 °C, and a solution of 1.31 g (7.4 mmol) of distilled *N*-(trimethylsilyl)benzaldimine (**2b**)[18] in 4 mL of tetrahydrofuran was added as above. The mixture was stirred for 1 h at −70 °C, the cold bath was removed, and the solution was stirred for an additional 2 h. The mixture was diluted to 150 mL with ether and washed with two 100-mL portions of 1.3 N aqueous hydrochloric acid. The washes were extracted with three 200-mL portions of ether. The combined ether layers were dried ($MgSO_4$) and concentrated in vacuo to give 2.20 g of a yellow oil that was chromatographed over 100 g of silica gel (eluted with hexane–ethyl acetate, 3:1) to give 1.43 g (63%) of lactam **3b** as a crystalline solid: mp 120.0–121.0 °C; IR ($CHCl_3$) 3410, 1750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.35 (s, 3 H, CH_3Si), 0.39 (d, J = 7.1 Hz, 3 H, $CHCH_3$), 0.45 (s, 3 H, CH_3Si), 0.98 (dq, J = 12.5, 7.1 Hz, 1 H, $CHCH_3$), 3.31 (dd, J = 12.5, 5.1 Hz, 1 H, CHCO), 4.77 (d, J = 5.1 Hz, 1 H, CHN), 5.93 (br s, 1 H, NH), 7.29–7.56 (m, 8 H, ArH), 7.71–7.75 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ −4.08 (q), −3.08 (q), 13.54 (q), 16.34 (d), 55.73 (d), 61.66 (d), 127.52 (d), 127.85 (d), 128.20 (d), 128.29 (d), 128.78 (s), 134.40 (d), 137.98 (s), 170.60 (s); mass spectrum, m/e (relative intensity) 309 (2), 294 (40), 216 (31), 189 (12), 135 (100), 105 (14), 91 (13); exact mass for $C_{19}H_{23}NOSi$ calcd m/e 309.1549, found m/e 309.1552. Anal. Calcd for $C_{19}H_{23}NOSi$: C, 73.74; H, 7.49. Found: C, 73.58; H, 7.61.

From 3a: To a solution of 145 mg (0.35 mmol) of lactam **3a** in 5.6 mL of acetonitrile cooled to 0 °C was added a solution of 0.58 g (1.1 mmol) of ceric ammonium nitrate over a 3-min period. The mixture was stirred over 25 min, diluted with 24 mL of water, and extracted with three 15-mL portions of ethyl acetate. The combined extracts were washed with 12 mL of saturated aqueous sodium bicarbonate, three 10-mL portions of 10% aqueous sodium sulfite, 5 mL of saturated aqueous sodium bicarbonate, and 10 mL of brine. The organic phase was stirred over Norit, and some solid sodium sulfate was added. The mixture was filtered through Celite, dried ($MgSO_4$), and concentrated in vacuo to give 116 mg of a dark yellow oil. This material was chromatographed over

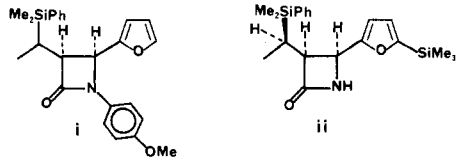
(13) The relationship between this result (**1** + **2b**) and a recent interpretation of the stereochemical course of ester enolate alkylations requires further experimentation: McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. We have now observed several instances where *N*-(trimethylsilyl)- and *N*-arylimines give different stereochemical results under conditions where β-lactam isomerization does not occur. The mechanistic differences between the reactions are under investigation.

(14) Ratcliffe, R. W.; Albers-Schönberg, G. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 227–313.

(15) Tamao, K.; Kakin, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983.

(16) Oxidative degradation of **6b** gave the 1′-isomer of **8** along with ring-opened material, thus confirming the assignment of structure **8**.

(17) Stereochemical assignments at C-1′ are by analogy with the results obtained with benzaldimines **2a** and **2b**. In the reaction of **9a**, a 3% yield of a single *cis*-β-lactam, presumably **i**, was also obtained. In the reaction of **9b**, an 11% yield of β-lactam **ii** was also obtained. The origin of **ii** is under investigation.



(18) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.

6 g of silica gel (eluted with hexane–ethyl acetate, 3:1) to give 86 mg (80%) of **3b** (mp 120–121 °C), identical with that prepared from **1** and **2b**.

***rel*-(1′*R*,3*R*,4*S*)-3-(1′-Hydroxyethyl)-4-phenyl-2-azetidinone (7).** To a solution of 0.80 g (2.6 mmol) of lactam **3b** in 6 mL of dry dichloromethane was added 0.42 g (2.6 mmol) of tetrafluoroboric acid–diethyl ether complex. The mixture was stirred at room temperature for 3.5 h, and the volatiles were removed in vacuo to give 0.83 g of *rel*-(1′*R*,3*S*,4*S*)-3-[1′-(fluorodimethylsilyl)ethyl]-4-phenyl-2-azetidinone as a white solid: mp 145–149 °C; NMR (90 MHz, $CDCl_3$) δ 0.23 (d, *J* = 3 Hz, 3 H, CH_3Si), 0.33 (d, *J* = 3 Hz, 3 H, CH_3Si), 0.57 (d, *J* = 7 Hz, 3 H, CH_3CH), 0.87–1.34 (m, 1 H, $CHCH_3$), 3.68 (dd, *J* = 12, 5 Hz, 1 H, CHCO), 5.26 (d, *J* = 5 Hz, 1 H, CHN), 7.20–7.55 (m, 5 H, ArH), 7.89 (br s, 1 H, NH); mass spectrum, *m/e* (relative intensity) 251 (2), 236 (100), 146 (10), 131 (29), 106 (47), 105 (10), 77 (96); exact mass for $C_{13}H_{18}FNOSi$ calcd *m/e* 251.1142, found *m/e* 251.1142. This material was used without further purification.

To a solution of 0.81 g of the crude fluorosilane in 2 mL of dry *N*,*N*-dimethylformamide under argon was added 2.24 g (10.4 mmol) of *m*-chloroperbenzoic acid and 0.51 g (8.8 mmol) of anhydrous potassium fluoride. The mixture was stirred at room temperature for 5 h, diluted with 200 mL of water, and extracted with six 200-mL portions of ether. The combined ether layers were washed with 120 mL of 10% aqueous sodium bisulfite, three 120-mL portions of saturated aqueous sodium bicarbonate, and 110 mL of water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.35 g of a white oily solid. The combined aqueous layers were extracted with three 200-mL portions of ether. The ether layers were dried ($MgSO_4$) and concentrated in vacuo to give 110 mg (23%) of lactam **7** as a white solid, mp 136.5–137.5 °C. The 0.35 g of oily solid isolated previously was recrystallized from 1 mL of hexane–ethyl acetate (2:1) to give 64 mg (13.4%) of lactam **7**, mp 137.5–138.0 °C. The mother liquor was chromatographed over 12 g of silica gel (eluted with ethyl acetate–hexane, 2:1, gradually increased to ethyl acetate) to give 58 mg (12.1%, 48.5% total) of lactam **7**: mp 131.0–134.0 °C; IR ($CDCl_3$) 3560, 3400, 1755 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.98 (br s, 1 H, OH), 3.42 (ddd, *J* = 8.2, 5.5, 1.8 Hz, 1 H, CHC=O), 3.77 (dq, *J* = 8.2, 6.1 Hz, 1 H, CHOH), 4.90 (d, *J* = 5.5 Hz, 1 H, CHN), 6.17 (br s, 1 H, NH), 7.30–7.49 (m, 5 H, ArH); mass spectrum, *m/e* (relative intensity) 191 (3), 176 (16), 148 (67), 146 (18), 133 (21), 115 (13), 106 (100), 91 (27), 77 (28); exact mass for $C_{11}H_{13}NO_2$ calcd *m/e* 191.0946, found *m/e* 191.0944. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.67; H, 6.71.

***rel*-(1′*S*,3*R*,4*S*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-(2-furyl)-2-azetidinone (10) and *rel*-(1′*R*,3*R*,4*S*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-(2-furyl)-2-azetidinone (11).** To a solution of lithium diisopropylamide [prepared from 0.68 g (6.7 mmol) of diisopropylamine and 4.17 mL (6.6 mmol) of 1.58 N *n*-butyllithium in hexane] in 9 mL of tetrahydrofuran cooled to −70 °C under argon was added a solution of 1.45 g (5.8 mmol) of ester **1** in 1.8 mL of dry tetrahydrofuran, keeping the temperature below −65 °C. The mixture was stirred for 1 h at −70 °C, and 3.1 mL of dry hexamethylphosphoramide was added. The mixture was stirred for 5 min, and a solution of 1.17 g (5.8 mmol) of aldimine **9a**[18] in 3.6 mL of dry tetrahydrofuran was added at −65 to −70 °C. The mixture was stirred for 1 h at −70 °C, the cold bath was removed, and the mixture was stirred an additional 2.75 h. The mixture was diluted with 200 mL of dichloromethane and washed with two 100-mL portions of 1.3 N aqueous hydrochloric acid. The aqueous layers were extracted with two 100-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 4.74 g of a black oil that was chromatographed over 150 g of silica gel (eluted with hexane–ethyl acetate, 8:1) to give in sequence 0.22 g of a mixture of lactams **11** and **i**,[17] 0.55 g (24%) of lactam **11** as a colorless oil, 0.88 g of a mixture of lactams **11** and **10** as a light yellow solid, and 0.07 g (3%) of lactam **10** as a yellow oil. The fractions containing mixtures were independently chromatographed over Lobar silica gel columns (eluted with hexane–ethyl acetate, 8:1) to give 0.47 g (20%, 44% total) of lactam **11** as a colorless oil, 0.40 g (17%, 20% total) of lactam **10** as a white solid, and 0.06 g (3%) of lactam **i** as a colorless oil.

β-Lactam 11: IR ($CHCl_3$) 1735, 1510, 1250 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.32 (s, 3 H, $SiCH_3$), 0.34 (s, 3 H, $SiCH_3$), 1.22 (d, *J* = 7.2, 3 H, $CHCH_3$), 1.36–1.59 (m, 1 H, $CHCH_3$), 3.41 (dd, *J* = 2.5, 8.5, 1 H, CHC=O), 3.73 (s, 3 H, OCH_3), 4.56 (d, *J* = 2.5, 1 H, CHN), 6.21 (d, *J* = 3.1, 1 H, CH=CRO), 6.32 (dd, *J* = 3.1, 1.9, 1 H, CH=CHOR), 6.77 (d, *J* = 9.0, 2 H, ArH), 7.23 (d, *J* = 9.0, 2 H, ArH), 7.31–7.44 (m, 6 H, ArH, OC*H*=CH); mass spectrum *m/e* (relative intensity) 405 (5), 390 (8), 256 (24), 201 (10), 186 (6), 135 (100); exact mass for $C_{24}H_{27}NO_3Si$ calcd *m/e* 405.1760, found *m/e* 405.1764.

β-Lactam 10: mp 123.0–124.0 °C; IR ($CHCl_3$) 1735, 1505, 1240 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.26 (s, 3 H, $SiCH_3$), 0.32 (s, 3 H, $SiCH_3$), 1.08 (d, *J* = 7.4, 3 H, $CHCH_3$), 1.55–1.65 (m, 1 H, CHSi), 3.53 (dd, *J* = 4.4, 2.7, 1 H, CHC=O), 3.73 (s, 3 H, OCH_3), 4.66 (d, *J* = 2.7, 1 H, CHN), 6.31 (d, *J* = 3.2, 1 H, CH=CRO), 6.35 (dd, *J* = 3.2, 1.9, 1H, C*H*=CHOR), 6.78 (d, *J* = 9.0, 2 H, ArH), 7.25 (d, *J* = 9.0, 2 H, ArH), 7.28–7.49 (m, 6 H, ArH, OC*H*=CH); mass spectrum, *m/e* (relative intensity) 405 (4), 390 (3), 256 (16), 201 (5), 186 (5), 135 (100); exact mass for $C_{24}H_{27}NO_3Si$ calcd *m/e* 405.1760, found *m/e* 405.1754.

β-Lactam i:[17] IR ($CDCl_3$) 1740, 1510, 1250 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.41 (s, 3 H, $SiCH_3$), 0.52 (s, 3 H, $SiCH_3$) 0.57 (d, *J* = 7, 3 H, $CHCH_3$) 1.17–1.77 (m, 1 H, CHSi), 3.46 (dd, *J* = 12, 6, 1 H, CHC=O), 3.77 (s, 3 H, OCH_3), 5.14 (d, *J* = 6, 1 H, CHN), 6.40 (m, 2 H, C*H*C*H*CHOR), 6.83 (d, *J* = 8, 2 H, ArH), 7.27–7.87 (m, 8 H, ArH, CHOR); mass spectrum, *m/e* (relative intensity) 405 (5), 390 (10), 205 (17), 201 (11), 186 (5), 135 (100), 86 (43); exact mass for $C_{24}H_{27}NO_3Si$ calcd *m/e* 405.1760, found *m/e* 405.1769.

β-Lactam ii:[17] IR ($CHCl_3$) 3400, 1760, 1250, 840 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.22 (s, 9 H, $SiMe_3$), 0.35 (s, 3 H, $SiCH_3$), 0.42 (s, 3 H, $SiCH_3$), 0.50 (d, *J* = 7.2, 3 H, $CHCH_3$), 1.07–1.18 (m, 1 H, $CHCH_3$), 3.30 (ddd, *J* = 1.3, 5.0, 12.2, 1 H, CHC=O), 4.79 (d, *J* = 5.0, 1 H, CHN), 5.85 (br s, 1 H, NH), 6.29 (d, *J* = 3.2, 1 H, C*H*CH=COR), 6.57 (d, *J* = 3.2, 1 H, CHC*H*=COR), 7.27–7.35 (m, 3 H, ArH), 7.51–7.56 (m, 2 H, ArH), mass spectrum, *m/e* (relative intensity) 371 (13), 356 (30), 278 (23), 135 (100), 73 (25); exact mass for $C_{20}H_{29}NO_2Si_2$ calcd *m/e* 371.1736, found *m/e* 371.1740.

***rel*-(1′*R*,3*S*,4*S*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (3a)**: mp 153.0–154.0 °C; IR ($CHCl_3$) 1735, 1520 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.34 (s, 3 H, CH_3Si), 0.44 (d, *J* = 7.1, 3 H, $CHCH_3$), 0.51 (s, 3 H, CH_3Si), 0.99–1.10 (m, 1 H, $CHCH_3$), 3.38 (dd, *J* = 12.3, 5.4, 1 H, CHCO), 3.72 (s, 3 H, OCH_3), 5.06 (d, *J* = 5.4, 1 H, CHN), 6.73 (d, *J* = 9.1, 2 H, ArH), 7.19 (d, *J* = 9.1, 2 H, ArH), 7.24–7.60 (m, 10 H, ArH); mass spectrum, *m/e* (relative intensity) 415 (5), 400 (14), 211 (21), 196 (11), 181 (19), 135 (100); exact mass for $C_{26}H_{29}NO_2Si$ calcd *m/e* 415.1967, found *m/e* 415.1965. Anal. Calcd for $C_{26}H_{29}NO_2Si$: C, 75.14; H, 7.03. Found: C, 75.23; H, 7.21.

***rel*-(1′*R*,3*R*,4*R*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (4a).** This compound was isolated as an inseparable mixture with lactam **6a**. The following peaks due to lactam **4a** in the ^1H NMR may be distinguished (90 MHz, $CDCl_3$): δ 0.20 (s, 3 H, $SiCH_3$), 0.32 (s, 3 H, $SiCH_3$), 3.70 (s, 3 H, OCH_3), 4.92 (d, *J* = 5.9, 1 H, CHN), 6.78 (d, *J* = 9, 2 H, ArH), 7.00–7.50 (m, 12 H, ArH).

***rel*-(1′*R*,3*S*,4*R*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (5a)**: mp 141.5–142 °C; IR ($CHCl_3$) 1735, 1520 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.26 (s, 3 H, CH_3Si), 0.34 (s, 3 H, CH_3Si), 1.13 (d, *J* = 7.4, 3 H, $CHCH_3$), 1.52–1.75 (m, 1 H, CHSi), 3.19 (dd, *J* = 5.3, 2.3, 1 H, CHC=O), 3.71 (s, 3 H, OCH_3), 4.60 (d, *J* = 2.3, 1 H, CHN), 6.73 (d, *J* = 9.1, 2 H, ArH), 7.17 (d, *J* = 9.1, 2 H, ArH), 7.21–7.36 (m, 10 H, ArH); mass spectrum, *m/e* (relative intensity) 415 (3), 400 (3), 211 (6), 196 (9), 135 (100); exact mass for $C_{26}H_{29}NO_2Si$ calcd *m/e* 415.1967, found *m/e* 415.1967.

***rel*-(1′*R*,3*R*,4*S*)-1-(*p*-Methoxyphenyl)-3-[1′-(dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (6a)**: mp 110.5–111.0 °C; IR ($CHCl_3$) 1733, 1520 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.30 (s, 3 H, CH_3Si) 0.36 (s, 3 H, CH_3Si), 1.22 (d, *J* = 7.3, 3 H, $CHCH_3$), 1.52–1.67 (m, 1 H, CHSi), 3.15 (dd, *J* = 6.6, 2.4, 1 H, CHC=O), 3.71 (s, 3 H, OCH_3), 4.56 (d, *J* = 2.4, 1 H, CHN), 6.74 (d, *J* = 9.1, 2 H, ArH), 7.17 (d, *J* = 9.1, 2 H, ArH), 7.25–7.49 (m, 10 H, ArH); mass spectrum, *m/e* (relative intensity)

415 (8), 400 (13), 211 (17), 196 (11), 135 (100); exact mass for $C_{26}H_{29}NO_2Si$ calcd m/e 415.1967, found m/e 415.1962. Anal. Calcd for $C_{26}H_{29}NO_2Si$: C, 75.14; H, 7.03. Found: C, 75.12; H, 7.18.

***rel*-(1′*R*,3*R*,4*R*)-3-[1′-(Dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (4b)**: IR ($CHCl_3$) 3400, 1750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.20 (s, 3 H, CH_3Si), 0.30 (s, 3 H, CH_3Si), 0.80 (d, J = 7.4, 3 H, CH_3CH), 1.01 (dq, J = 4.5, 7.4, 1 H, CH_3CH), 3.62 (ddd, J = 5.6, 4.5, 2.1, 1 H, CHC=O), 4.65 (d, J = 5.6, 1 H, CHN), 6.11 (s, 1 H, NH), 7.13–7.45 (m, 10 H, ArH); ^{13}C NMR ($CDCl_3$) δ −4.80 (q), −4.58 (q), 11.44 (q), 16.20 (d), 55.56 (d), 57.64 (d), 126.96 (d), 127.73 (d), 127.89 (d), 128.44 (d), 129.10 (d), 134.02 (d), 137.79 (s), 137.95 (s), 170.48 (s); mass spectrum m/e (relative intensity) 309 (2), 294 (43), 216 (22), 189 (9), 135 (100), 91 (12), 85 (23); exact mass for $C_{19}H_{23}NOSi$ calcd m/e 309.1549, found m/e 309.1529.

***rel*-(1′*R*,3*S*,4*R*)-3-[1′-(Dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (5b)**: mp 116.5–118.0 °C; IR ($CHCl_3$) 3400, 1750 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.22 (s, 3 H, CH_3Si), 0.30 (s, 3 H, CH_3Si), 1.13 (d, J = 7.4, 3 H, $CHCH_3$), 1.55 (dq, J = 5.1, 7.4, 1 H, CH_3CH), 3.18 (ddd, J = 5.1, 2.4, 0.9, 1 H, CHC=O), 4.35 (d, J = 2.4, 1 H, CHN), 6.03 (s, 1 H, NH), 7.16–7.44 (m, 10 H, ArH); mass spectrum m/e (relative intensity) 309 (2), 294 (30), 216 (17), 189 (9), 135 (100); exact mass for $C_{19}H_{23}NOSi$ calcd m/e 309.1549, found m/e 309.1545.

***rel*-(1′*R*,3*R*,4*S*)-3-[1′-(Dimethylphenylsilyl)ethyl]-4-phenyl-2-azetidinone (6b)**: mp 97.5–98.5 °C; IR ($CHCl_3$) 3400, 1750 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.27 (s, 3 H, CH_3Si), 0.33 (s, 3 H, CH_3Si), 1.21 (d, J = 7.3, 3 H, $CHCH_3$), 1.48 (q, J = 7.3, 1 H, CH_3CH), 3.11 (ddd, J = 6.8, 2.2, 0.7, 1 H, CHC=O), 4.32 (d, J = 2.2, 1 H, CHN), 6.02 (s, 1 H, NH), 7.15–7.48 (m, 10 H, ArH); mass spectrum, m/e (relative intensity) 309 (2), 294 (34), 216 (17), 189 (10), 135 (100); exact mass for $C_{19}H_{23}NOSi$ calcd m/e 309.1549, found m/e 309.1548.

***rel*-(1′*R*,3*R*,4*R*)-3-(1′-Hydroxyethyl)-4-phenyl-2-azetidinone (8)**: mp 94.5–96.0 °C; IR ($CHCl_3$) 3500, 3400, 1755 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.39 (d, J = 6.4, 3 H, CH_3), 2.14 (br s, 1 H, OH), 3.09 (dd, J = 5.9, 2.3, 1 H, CHC=O), 4.19–4.26 (m, 1 H, $CHCH_3$), 4.60 (d, J = 2.3, 1 H, CHN), 6.13 (br s, 1 H, NH), 7.31–7.55 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 191 (2), 173 (10), 148 (62), 130 (12), 106 (100), 105 (85), 91 (34), 77 (35), 68 (49); exact mass for $C_{11}H_{13}NO_2$ calcd m/e 191.0946, found m/e 191.0904.

***rel*-(1′*R*,3*S*,4*S*)-3-[1′-(Dimethylphenylsilyl)ethyl]-4-(2-furyl)-2-azetidinone (12)**: mp 80.5–81.5 °C; IR ($CHCl_3$) 3400, 1760 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.37 (s, 3 H, CH_3Si), 0.45 (s, 3 H, CH_3Si), 0.53 (d, J = 7.2, 3 H, $CHCH_3$), 1.10–1.20 (m, 1 H, $CHCH_3$), 3.31 (ddd, J = 12.1, 5.0, 1.1, 1 H, CHC=O), 4.76 (d, J = 5.0, 1 H, CHN), 5.84 (br s, 1 H, NH), 6.34 (d, J = 3.0, 1 H, CH=CROR), 6.39 (dd, J = 3.0, 1.8, 1 H, CH=CHOR), 7.31–7.35 (m, 3 H, ArH), 7.41 (d, J = 1.8, 1 H, CHOR), 7.52–7.59 (m, 2 H, ArH); mass spectrum, m/e (relative intensity) 299 (7), 284 (37), 206 (32), 135 (100); exact mass for $C_{17}H_{21}NO_2Si$ calcd m/e 299.1342, found m/e 299.1350.

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Supplementary Material Available: Crystallographic information, final positional and thermal parameters, structure factor tables, bond lengths and angles, and an ORTEP for compounds **3** and **7** (10 pages). Ordering information is given on any current masthead page.

Synthesis and Chemistry of Some Furazano- and Furoxano[3,4-*b*]piperazines[1]

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A series of N,N′-disubstituted furazano- and furoxano[3,4-*b*]piperazines **1a–d** and **2b–d** have been synthesized from N,N′-disubstituted 2,3-piperazinedione dioximes **5a–d** by base-promoted dehydration and by basic potassium ferricyanide oxidation, respectively. The N,N′-disubstituted 2,3-piperazinedione dioximes were synthesized by reacting the appropriate N,N′-disubstituted ethylenediamine with dichloroglyoxime. Also studied was the reaction of 3,4-diaminofurazan with glyoxal and formaldehyde. The compounds have been studied by ^1H and ^{13}C NMR spectroscopy.

There have been numerous studies[2] of compounds with furazan ([1,2,5]oxadiazolo-) and furoxan ([1,2,5]oxadiazolo 1-oxide) rings fused to aromatic rings and saturated carbocyclic rings, but few studies of compounds with furazan or furoxan rings fused to saturated heterocyclic rings have been reported in the open literature.[2] We became interested in compounds with furazan and furoxan rings fused to saturated nitrogen heterocycles because calculations[3,4] predict that nitrated derivatives of some of these compounds would be quite dense and energetic. In this paper, we report on the synthesis, chemistry, and spectroscopy of some furazano[3,4-*b*]piperazines **1a–d**, furoxano[3,4-*b*]piperazines **2b–d**, and some related compounds. These

(1) The accepted IUPAC nomenclature for these compounds is 4,5,6,7-tetrahydro-1,2,5-oxadiazolo[3,4-*b*]pyrazines and 1-oxides.

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