First Synthesis of Totally Orthogonal Protected α-(Trifluoromethyl)- and α-(Difluoromethyl)arginines

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The first synthesis of a series of totally orthogonal protected racemic α-(trifluoromethyl)- and α-(difluoromethyl)arginines is described. The key steps of the synthesis are the mild guanidinylation procedure and the selective hydrogenation of a CC triple bond in the presence of a Cbz-group.

Introduction

The amino acid arginine exhibits several potentially beneficial properties.[1,2] However, the effect of arginine on tumor growth is a controversial issue; the vast majority of collected data from animal experiments provides favorable results with natural killer cells giving increased cytolytic activity, enhanced macrophage tumor cytotoxicity, stimulation of the protein synthesis in the host but not in the tumor, and a decrease in tumor growth.[3] In contrast, little is known on the effect of arginine on human tumors.[4]

Arginine is a constituent of biological relevant peptides, like RGD peptides, well-known as an universal binding and recognition sequence involved in cell−cell and cell−matrix interactions, inducing blood platelet aggregation, tumor cell adhesion, and osteoporosis.[5]

Replacement of the α-H by trifluoromethyl (Tfm) or difluoromethyl (Dfm) groups in natural amino acids has received considerable attention recently, because several *β*-fluoro-containing α-amino acids are biologically active, exhibiting antibacterial, antihypertensive, cancerostatic, and cytotoxic effects. α-Dfm-ornithine seems to be a superior drug for treatment of the "sleeping sickness". *β*-Fluoro-substituted amino acids in general are potent irreversible inhibitors of pyridoxal phosphate-depending enzymes, like decarboxylases, transaminases, and racemases. Regulation of enzymatic decarboxylation reactions of amino acids by using highly specific inhibitors is of fundamental therapeutic interest. Incorporation of α-Tfm- or α-Dfm-amino acids into key positions of biological active peptides increases metabolic stability, stabilizes secondary structures, improves lipophilicity,[6] and provides an useful NMR label for secondary structure elucidation.

The two known routes to α-fluoroalkylated arginines are low yielding and provide the modified arginine either already incorporated into peptides or partially unprotected.[7,8]

In this paper, we wish to disclose a convenient, preparatively simple three step synthesis of fully orthogonal protected α-Tfm- and α-Dfm-arginines starting from readily available partially fluorinated *N*-acylimines.

Results and Discussion

To obtain orthogonally protected α-Tfm- and α-Dfm-arginines **7a**−**d**, we tested two synthetic routes. First, we introduced a side chain of five-carbon atoms having a CC double bond in the terminal position via Grignard addition into Boc- and Cbz-protected imines of trifluoro- and difluoropyruvate (1 → 2), respectively[6,8,9] (Scheme 1). Then the CC double bond was oxidized with $KMnO_4/H_2SO_4$, and the carboxylic acids obtained (**3a**,**c**) were activated with pentafluorophenol (PfpOH) and transformed into amides **4a**,**c** on treatment with NH_4OH/DCC. Finally, **4a**,**c** were converted into the α-Tfm- and α-Dfm-ornithines **5a**,**c** via a Hofmann-type degradation with 1,1-bis(trifluoroacetoxy)iodobenzene (TIB). Since compounds **5a**,**c** are only stable as salts or as *δ*-N-protected derivatives, they are readily transformed under the basic conditions of the guanidinylation step into *δ*-lactams

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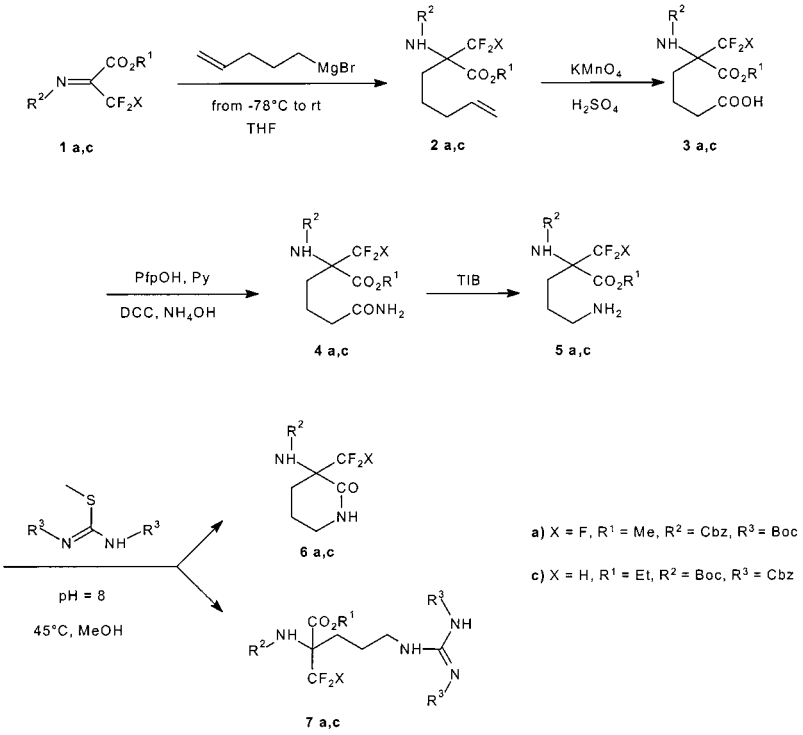
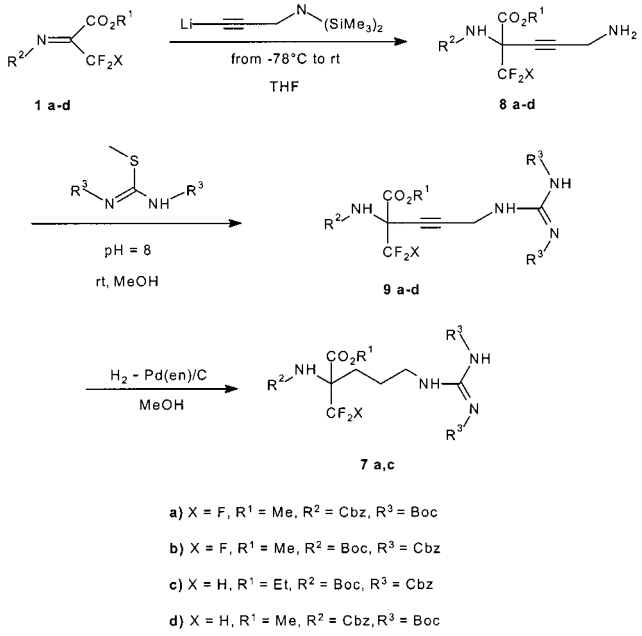
Scheme 1



Scheme 2



(**6a**,**c**, 60%). The arginine derivatives **7a**,**c** could only be isolated as byproducts (35%).

In a second approach, again we started from Boc- and Cbz-protected imines of trifluoro- and difluoropyruvates **1a**−**d**. The side chain of arginine consisting of three carbon atoms was introduced together with the δ-amino group via addition of readily available lithium *N*,*N*-bis(trimethylsilyl)aminomethyl acetylide,[10] which gave the corresponding adducts **8a**−**d** in quantitative yield (Scheme 2). The presence of the triple bond prevents ring closure. The δ-amino group is deblocked on workup and guanidinylated at room temperature at pH 8 without the risk of the unwanted lactamization.

A particularly critical step is the catalytic hydrogenation. If hydrogenation of the CC triple bond of compounds **8** is performed in the presence of Pd/C before guanidinylation, a spontaneous lactamization accompanied by a simultaneous loss of the Cbz-group yielding 2-piperidone derivatives in high yield is observed. Ring opening of the 2-piperidone system and simultaneous cleavage of the Boc-group can be achieved under acid conditions and affords the unprotected ornithines.[11] They are less stable, and guanidinylation experiments gave low yields.

Therefore, it is advantageous to perform the guanidinylation step before hydrogenation of the CC triple bond and to use a modified catalyst. When the commercial catalyst (5% Pd/C) was treated with a 10-fold excess (vs Pd metal of Pd/C) of ethylenediamine as described by Hirota et al.,[12] a catalyst was obtained (Pd(en)/C), perfectly suitable for a selective hydrogenation of the CC triple bond in the presence of the Cbz-group. Hydrogenation of compounds **9a**−**d** gave the fully orthogonal protected α-Tfm- and α-Dfm-arginines **7a**−**d** in about 95% yield.

Conclusion

We developed a new preparatively simple high-yielding three-step synthesis of racemic orthogonally protected α-Tfm- and α-Dfm-arginines **7a**−**d**. They are stable compounds and can be stored for a long time. Scale-up of the synthesis can be easily achieved, thus making these compounds available in sufficient quantities to study their chemical and biological properties; in fact, any biological data are available so far on protected arginines of this type. They can be selectively deprotected

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to provide useful building blocks for peptide modification and combinatorial chemistry.

Experimental Section

General Remarks. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at 360, 90, and 339 MHz, respectively. TMS was used as internal standard for ^{1}H NMR and ^{13}C NMR spectra. ^{19}F NMR spectra were recorded with trifluoroacetic acid as external standard, downfield shifts being designated as positive. Mass spectra were obtained using EI ionization at 70 eV. Elemental microanalyses were carried out by the Microanalytical Laboratory of the Chemistry Department, University of Leipzig. All compounds have been fully characterized and gave correct microanalytical data (±0.4%). All reactions were routinely monitored by ^{19}F NMR spectroscopy or TLC. Analytical TLC was performed using Merck silica gel 60F-254 plates (0.25 mm). For flash chromatography, silica gel 60 (30−60 μm) was used with hexane/ethyl acetate or $CHCl_3$/MeOH as eluent system. Organic solvents were dried and distilled prior to use.

All reagents used were purchased from commercial suppliers and used without further purification. Boc- and Cbz-imines **1a**−**d**, lithium *N*,*N*-bis(trimethylsilyl)aminomethyl acetylide, and Pd(en)/C were synthesized by published methods.[9−12] Spectroscopical data of the lactams **6a**,**c** and of other products from Scheme 1 are available as Supporting Information.

General Procedure for Preparation of 8a−d. To a cooled solution (−78 °C) of 8 mmol of lithium *N*,*N*-bis-(trimethylsilyl)aminomethyl acetylide (1.643 g) in situ prepared[10] in 20 mL of dry THF, under argon atmosphere were added 6.7 mmol of imine **1** (**a**, 1.937 g; **b**, 1.709 g; **c**, 1.683 g; **d**, 1.817 g) dissolved in 5 mL of dry THF. The temperature of reaction mixture was allowed to increase slowly to room temperature; afterward the solution was stirred overnight. The reaction was quenched at 0 °C with 80 mL of 1 M HCl and then adjusted to pH = 8 by addition of a 5% aqueous solution of $NaHCO_3$; finally, diethyl ether was added. The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 20 mL). The collected organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The purity of products **8** was sufficient for further reactions.

8a: 2.191 g, 6.4 mmol, yield 95%; ^{1}H NMR (acetone-d_6) δ 2.91 (br s, 2H), 3.81 (s, 3H), 4.11 (s, 2H), 5.16 (d_{AB}, ^2J = 12.0 Hz, 2H), 7.41 (m, 5H), 8.09 (br s, 1H). ^{19}F NMR (acetone-d_6) δ 3.32 (s, 3F); MS (EI, 70 eV) *m*/*z* 344 (M^+, 10), 329 (100), 367 (12), 238 (30), 169 (23). Anal. Calcd for $C_{15}H_{15}F_3N_2O_4$: C, 52.33; H, 4.39; N, 8.14. Found: C, 52.47; H, 4.38; N, 8.11.

8b: 1.891 g, 6.1 mmol, yield 91%; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.62 (br s, 2H), 3.48 (s, 2H), 3.90 (s, 3H) 5.49 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 2.48 (s, 3F); MS (EI, 70 eV) *m*/*z* 310 (M^+, 7), 253 (100), 238 (27), 169 (11). Anal. Calcd for $C_{12}H_{17}F_3N_2O_4$: C, 46.45; H, 5.52; N, 9.03. Found: C, 46.53; H, 5.50; N, 8.99.

8c: 1.908 g, 6.2 mmol, yield 93%; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 1.62 (br s, 2H), 3.48 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 5.51 (br s, 1H), 6.21 (t, $^2J_{HF}$ = 56.0 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ −50.48 (dd_{ABX}, $^2J_{FF}$ = 276.2 Hz, $^2J_{FH}$ = 56.0 Hz, 1F), −47.90 (dd_{ABX}, $^2J_{FF}$ = 276.2 Hz, $^2J_{FH}$ = 56.0 Hz, 1F); MS (EI, 70 eV) *m*/*z* 306 (M^+, 8), 249 (100), 220 (44), 169 (30). Anal. Calcd for $C_{13}H_{20}F_2N_2O_4$: C, 50.98; H, 6.58; N, 9.14. Found: C, 51.17; H, 6.56; N, 9.10.

8d: 2.033 g, 6.2 mmol, yield 93%; ^{1}H NMR ($CDCl_3$) δ 2.00 (br s, 2H), 3.70 (s, 2H), 3.90 (s, 3H), 5.11 (d_{AB}, ^2J = 12.4 Hz, 2H) 5.51 (br s, 1H), 6.20 (t, $^2J_{HF}$ = 55.1 Hz, 1H), 7.36 (s, 5H); ^{19}F NMR ($CDCl_3$) δ −48.00 (dd_{ABX}, $^2J_{FF}$ = 276.3 Hz, $^2J_{FH}$ = 55.1 Hz, 1F), −50.50 (dd_{ABX}, $^2J_{FF}$ = 276.3 Hz, $^2J_{FH}$ = 55.1 Hz, 1F); MS (EI, 70 eV) *m*/*z* 326 (M^+, 11), 311 (100), 268 (17), 133 (42). Anal. Calcd for $C_{15}H_{16}F_2N_2O_4$: C, 55.21; H, 4.94; N, 8.58. Found: C, 55.28; H, 4.92; N, 8.54.

General Procedure for Preparation of 9a−d. To a solution of 6 mmol of **8** (**a**, 2.065 g; **b**, 1.861 g; **c**, 1.531 g; **d**, 1.957 g) in 30 mL of THF was added 6 mmol of *N*,*N*′-di(Boc or Cbz)-*S*-methylisothiourea (1.742 g and 2.150 g, respectively) were added. The reaction was allowed to stay at room temperature overnight, and then the solvent was evaporated in vacuo and the crude product purified by flash chromatography (eluent: *n*-hexane/ethyl acetate 80:20) to obtain pure **9**.

9a: 3.272 g, 5.6 mmol, yield 93%; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 3.85 (s, 3H), 4.31 (d, ^2J = 26 Hz, 2H), 5.12 (s 2H), 5.84 (s, 1H), 7.34 (s, 5H), 8.47 (t, ^2J = 26 Hz, 1H), 11.42 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 2.64 (s, 3F); MS (EI, 70 eV) *m*/*z* 586 (M^+, 3), 384 (100), 369 (11), 234 (37). Anal. Calcd for $C_{26}H_{33}F_3N_4O_8$: C, 53.23; H, 5.67; N, 9.55. Found: C, 53.31; H, 5.65; N, 9.51.

9b: 3.425 g, 5.5 mmol, yield 92%; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.84 (s, 3H), 4.32 (d, ^2J = 26.2 Hz, 2H), 5.20 (d, ^2J = 12.4 Hz, 4H), 5.83 (s, 1H), 7.38 (s, 10H), 8.50 (t, ^2J = 26.2 Hz, 1H), 11.85 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 2.60 (s, 3F); MS (EI, 70 eV) *m*/*z* 620 (M^+, 6), 519 (100), 504 (18), 234 (12). Anal. Calcd for $C_{29}H_{31}F_3N_4O_8$: C, 56.13; H, 5.04; N, 9.03. Found: C, 56.25; H, 5.02; N, 8.99.

9c: 2.743 g, 4.45 mmol, yield 89%; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 3.48 (d, ^2J = 26.2 Hz, 2H), 4.31 (q, J = 7.2 Hz, 3H), 5.19 (d_{AB}, ^2J = 12.0 Hz, 4H), 5.51 (br s, 1H), 6.21 (t, $^2J_{HF}$ = 56.0 Hz, 1H), 7.39 (s, 10H), 8.50 (t, ^2J = 26.2 Hz, 1H), 11.80 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ −50.48 (dd_{ABX}, $^2J_{FF}$ = 276.1 Hz, $^2J_{FH}$ = 56.0 Hz, 1F), −47.90 (dd_{ABX}, $^2J_{FF}$ = 276.1 Hz, $^2J_{FH}$ = 56.0 Hz, 1F); MS (EI, 70 eV) *m*/*z* 616 (M^+, 12), 587 (56), 486 (100), 351 (18). Anal. Calcd for $C_{30}H_{34}F_2N_4O_8$: C, 58.43; H, 5.56; N, 9.09. Found: C, 58.66; H, 5.53; N, 9.05.

9d: 3.138 g, 5.5 mmol, yield 92%; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.52 (s, 9H), 3.71 (d, ^2J = 25.9 Hz, 2H), 3.92 (s, 3H), 5.11 (d_{AB}, ^2J = 12.4 Hz, 2H), 5.53 (br s, 1H), 6.19 (t, $^2J_{HF}$=58.4 Hz, 1H), 7.36 (s, 5H), 8.49 (t, ^2J = 25.9 Hz, 1H), 10.98 (br s, 1H). ^{19}F NMR ($CDCl_3$) δ −48.91 (dd_{ABX}, $^2J_{FF}$ = 296.1 Hz, $^2J_{FH}$ = 58.4 Hz, 1F), −50.50 (dd_{ABX}, $^2J_{FF}$ = 296.1 Hz, $^2J_{FH}$ = 58.4 Hz, 1F); MS (EI, 70 eV) *m*/*z* 568 (M^+, 7), 336 (61), 316 (100), 134 (21). Anal. Calcd for $C_{26}H_{34}F_2N_4O_8$: C, 54.92; H, 6.03; N, 9.85. Found: C, 55.04; H, 6.01; N, 9.81.

General Procedure for Synthesis of Protected α-Tfm- and α-Dfm-arginines (7a−d). To a solution of 4 mmol of **9** (**a**, 2.346 g; **b**, 2.482 g; **c**, 2.466 g; **d**, 2.274 g) in 8 mL of MeOH was added a catalytic amount of freshly prepared Pd(en)/C (10% of the weight of the substrate) under an atmosphere of argon with stirring. Then the solution was stirred overnight under an atmosphere of hydrogen. The solid material was filtered off, and the organic layer was evaporated to dryness in vacuo. The crude product was purified by flash chromatography (eluent: $CHCl_3$/MeOH) to provide the pure fluorinated arginine derivatives **7**.

7a: 2.267 g, 3.8 mmol, yield 96%; ^{1}H NMR ($CDCl_3$) δ 1.35−1.53 (m, 1H), 1.44 (s, 9H), 1.45 (s, 9H), 1.54−172 (m, 1H), 2.12−2.27 (m, 1H), 2.35−2.40 (m, 2H), 2.75−2.91 (m, 1H), 3.87 (s, 3H), 5.11 (s, 2H), 5.91 (s, 1H), 7.36 (s, 5H), 8.47 (t, ^2J = 26.1 Hz, 1H), 11.42 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 3.07 (s, 3F); MS (EI, 70 eV) *m*/*z* 590 (M^+, 6), 476 (100), 461 (77), 370 (8). Anal. Calcd for $C_{26}H_{37}F_3N_4O_8$: C, 52.88; H, 6.32; N, 9.48. Found: C, 53.07; H, 6.30; N, 9.44.

7b: 2.398 g, 3.8 mmol, yield 96%; ^{1}H NMR ($CDCl_3$) δ 1.36−1.54 (m, 1H), 1.45 (s, 9H), 1.55−174 (m, 1H), 2.12−2.27 (m, 1H), 2.33−2.40 (m, 2H), 2.75−2.91 (m, 1H), 3.86 (s, 3H), 5.19 (d_{AB}, ^2J = 13 Hz, 4H), 5.90 (s, 1H), 7.38 (s, 10H), 8.47 (t, ^2J = 25.2 Hz, 1H), 11.50 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 3.02 (s, 3F); MS (EI, 70 eV) *m*/*z* 624 (M^+, 5), 567 (70), 475 (100), 384 (25), 370 (10). Anal. Calcd for $C_{29}H_{35}F_3N_4O_8$: C, 55.77; H, 5.65; N, 8.97. Found: C, 55.89; H, 5.64; N, 8.93.

7c: 2.358 g, 3.8 mmol, yield 95%; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, ^2J = 7.0 Hz, 3H), 1.44−1.53 (m, 1H), 1.50 (s, 9H), 1.60−1.67 (m, 1H), 2.05−2.12 (m, 1H), 2.43−2.51 (m, 1H), 3.44−3.52 (m, 1H), 3.55−3.63 (m, 1H), 4.01 (q, ^2J = 7.0 Hz, 2H), 5.20 (s, 4H), 6.03 (br s, 1H), 6.21 (t, $^2J_{HF}$ = 57.7 Hz, 1H), 7.40 (s, 10H), 8.69 (br s, 1H), 11.49 (br s, 1H). ^{19}F NMR ($CDCl_3$) δ −51.37 (dd_{ABX}, $^2J_{FF}$ = 279.4 Hz, $^2J_{FH}$ = 57.7 Hz, 1F), −52.67 (dd_{ABX}, $^2J_{FF}$ = 279.4 Hz, $^2J_{FH}$ = 57.7 Hz, 1F); MS (EI, 70 eV) *m*/*z* 620 (M^+, 8), 563 (100), 534 (68), 352 (28). Anal. Calcd for

$C_{30}H_{38}F_2N_4O_8$: C, 58.06; H, 6.17; N, 9.03. Found: C, 58.18; H, 6.15; N, 8.99.

7d: 2.130 g, 3.7 mmol, yield 93%; ^{1}H NMR ($CDCl_3$) δ 1.45−1.55 (m, 1H), 1.50 (s, 9H), 1.51 (s, 9H), 1.60−1.67 (m, 1H), 2.00−2.10 (m, 1H), 2.41−2.51 (m, 1H), 3.44−3.52 (m, 1H), 3.55−3.63 (m, 1H), 3.91 (s, 3H), 5.1 (br s, 2H), 6.03 (br s, 1H), 6.21 (t, $^2J_{HF}$ = 55.7 Hz, 1H), 7.34 (s, 5H), 8.69 (br s, 1H), 11.49 (br s, 1H). ^{19}F NMR ($CDCl_3$) δ −50.27 (dd_{ABX}, $^2J_{FF}$ = 279.4 Hz, $^2J_{FH}$ = 55.7 Hz, 1F), −51.57 (dd_{ABX}, $^2J_{FF}$ = 279.4 Hz, $^2J_{FH}$ = 55.7 Hz, 1F); MS (EI, 70 eV) *m*/*z* 572 (M^+, 5), 458 (100), 367 (22), 352 (30). Anal. Calcd for $C_{26}H_{38}F_2N_4O_8$: C, 54.54; H, 6.69; N, 9.78. Found: C, 54.68; H, 6.67; N, 9.74.

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Supporting Information Available: Spectral data of the lactams **6a**,**c** and of the products **4**−**5 (a**,**c)** from Scheme 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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