# Studies Toward Gymnodimine: Development of a Single-Pot Hua Reaction for the Synthesis of Highly Hindered Cyclic Imines

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## Supporting Information

General experimental procedures for α-dialkylation and imine synthesis; complete characterization data including $^{1}H$ and $^{13}C$ NMR spectra for compounds **7**, **8**. **9**, **10b**, **10e** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org

**General**

All reactions were carried out under $N_2$ in oven-dried glassware. Benzene ($C_6H_6$), diisopropylamine (*i*-$Pr_2NH$), and trimethylsilyl chloride (TMSCl) were distilled from $CaH_2$ immediately prior to use. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled immediately prior to use from sodium/benzophenone. The molarities indicated for organolithium reagents were determined by titration with 2,6-di-tert-butyl-4-methylphenol and 1,10-phenanthroline as indicator. All other commercially obtained reagents and starting materials were used as received.

**General Procedure for α-Dialkylation as Described for Lactam 8.**[1]

δ-Valerolactam (12.45 g, 125.6 mmol, 1.0 equiv) was dried by azeotropic distillation with benzene (2 × 100 mL) in a 250 mL round bottom flask. TMSCl (34.10 mL, 276.3 mmol, 2.2 equiv) was added dropwise to a stirred solution of the lactam and $Et_3N$ (42.00 mL, 301.4 mmol, 2.4 equiv) in benzene (650 mL). The solution was heated to reflux for 2.5 h. The reaction was monitored by $^1H$ NMR analysis of reaction aliquots until all starting material was consumed. The solution was cooled, filtered through a pad of celite, and the filtered solid was washed with benzene (2 × 100 mL). Concentration of the filtered solution under reduced pressure afforded crude *N*-silyl lactam **8** as a clear yellow oil. Purification by short path distillation under reduced pressure (66-68 °C, 0.5 mm Hg) afforded 16.18 g (75%) of 3,3-dimethyl-1-(trimethylsilyl)-piperidin-2-one as a colorless oil. Spectral data matched that

1) (a) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447-1459. (b) Grieco, P. A.; Kaufman, M. D. J. Org. Chem. **1999**, *64*, 6041-6048. (c) Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651-6668.

previously reported.[2] The *N*-silyllactam was used for the next step immediately upon isolation as it undergoes slow desilylation even when stored at -10 °C.

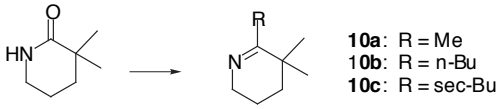
Two lithium diisopropylamide (LDA) solutions (1.2 equiv in a 1 L round-bottomed flask and 1.2 equiv in a 500 mL round bottom flask) were prepared by adding 52.0 mL of 2.20 M *n*–BuLi solution (1.2 equiv, 113.6 mmol) in hexane to a pre-cooled (–78 °C) solution of *i*-$Pr_2NH$ (16.0 mL, 1.2 equiv, 113.56 mmol) in THF (130 mL). After 15 min, the LDA solutions were warmed to 25 °C, stirred for 15 min, and re-cooled to –78 °C. To the LDA solution in the 1 L round bottom flask was added a precooled (–78 °C) solution of silyl lactam **8** (16.18 g, 94.63 mmol) in THF (130 mL) dropwise via cannula. After 15 min, MeI (6.50 mL, 104.1 mmol, 1.1 equiv) was added neat in a dropwise fashion. The solution was warmed to –20 °C, stirred for 15 min, and re-cooled to –78 °C. The second solution of LDA was added dropwise via cannula. After stirring for 15 min at –78°C, neat MeI (6.50 mL, 104.1 mmol, 1.1 equiv) was added dropwise to the lactam solution. The solution was warmed to 25 °C and allowed to stir for 30 min. The reaction was quenched with 2 N HCl (40 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 500 mL). The combined organic layers were washed with water (200 mL) and brine (400 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 24.95 g of crude dimethylated lactam **8** as a yellow solid. Flash chromatography (0.2% MeOH/EtOAc) gave 9.16 g (76%) of dimethylated lactam **8** as an off-white solid: $R_f$ = 0.2 (1:1 $Et_2O$/hexane); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.51 (NH, 1), 3.28 (dt, *J* = 2.4, 6.1 Hz, 2 H), 1.84-1.70 (m 2 H), 1.68-1.64 (m, 2 H), 1.21 (s, 6H); $^{13}$C NMR (75 MHz,

2) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990** , *55*, 3682-3684.

$CDCl_3$) δ 178.6, 42.5, 37.4, 36.0, 35.8, 27.2, 19.1 ; IR (KBr) 3185, 2945, 1658; Anal. Calcd. For $C_7H_{13}NO$: C, 66.10; H, 10.30. Found: C, 66.19; H, 10.31.

**3,3-dimethylpyrrolidin-2-one (7):** *N*-Trimethylsilylpyrrolidin-2-one was prepared according to the general procedure using pyrrolidin-2-one (**5**) (21.66 g, 254.5 mmol, 1.0 equiv), $Et_3N$ (85.20 mL, 610.8 mmol, 2.4 equiv) and TMS-Cl (69.20 mL, 559.9 mmol, 2.2 equiv). Filtration followed by fractional distillation (85-87 °C, 10 mm Hg) gave 24.31 g (61%) of *N*-trimethylsilylpyrrolidin-2-one as a clear oil. Spectral data matched that previously reported.[2] The dimethyl lactam was prepared according to the general procedure using the silyl lactam (24.31 g, 154.4 mmol) in THF (200 mL), LDA (2 × 1.2 equiv, 2 × 185.5 mmol) in THF (200 mL), MeI (2 ×10.58 mL, 2 × 170.0 mmol). Workup followed by flash chromatography (gradient elution: 0 → 2% MeOH/$Et_2O$) gave 8.52 g (69%) of lactam **7** as a white solid. Spectral data matched that previously reported. m.p. = 69-71 °C (20:1; hexane/$CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.51 (NH, 1), 3.28 (dt, *J* = 2.4, 6.1 Hz, 2 H), 1.84-1.70 (m, 2 H), 1.68-1.64 (m, 2 H), 1.21 (s, 6H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 178.6, 42.5, 37.4, 36.0, 35.8, 27.2, 19.1 ; IR (KBr) 3185, 2945, 1658; Anal. Calcd. For $C_6H_{11}NO$: C, 63.68; H, 9.80. Found: C, 63.66; H, 9.89.

**General Procedure for In Situ Silylation/Alkylation as Described for Cyclic Imine 10a.**




**8**

Dimethyl lactam **8** (1.00 g, 7.87 mmol) was dried by azeotropic distillation with xylenes (2 × 5 mL) in a 100 mL round-bottomed flask. To a pre-cooled (–78 °C) solution of **8** in dimethoxyethane (DME) (80 mL) was added 5.37 mL *n*-BuLi (2.20 M in hexane, 11.81 mmol, 1.5 equiv) dropwise. After stirring for 20 min, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2.14 mL, 11.81 mmol, 1.5 equiv) was added neat dropwise and the solution was warmed to -20 °C. Methylithium (6.61 mL,1.43 M in $Et_2O$, 9.45 mmol, 1.2 equiv) was added dropwise and the solution was allowed to warm to 0 °C. Reaction progress was monitored by thin layer chromatography (TLC) (10% MeOH/$CH_2Cl_2$). After stirring for 8 h, the reaction was quenched with 1N HCl (75 mL). The aqueous layer was washed with $Et_2O$ (2 × 100 mL), made basic with 2N NaOH (150 mL), and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 920 mg (93%) of crude imine **10a** as an amber-colored oil. Purification by Kugelrohr distillation gave 570 mg (58 %) of imine **10a**. Spectral data matched that previously reported.[3]

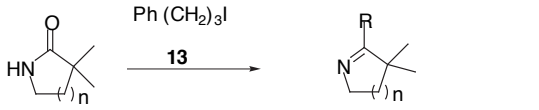
**3,3-Dimethyl-2-*n*-butyl-3,4,5,6-tetrahydropyridine (10b):** This imine was prepared according to the general procedure using lactam **8** (500 mg, 3.94 mmol, 1.0 equiv), 2.96 mL of *n*-BuLi (2.37 M in hexanes, 7.2 mmol, 1.8 equiv) in hexanes, TMSOTf (1.30 mL, 7.09 mmol, 1.8 equiv)

3) Larcheveque, M.; Debal, A.; Cuvigny, T. *Bull. Soc. Chim. Fr.* **1974**, 1710-1714.

and 2.46 mL of *n*-BuLi (2.37 M in hexanes, 5.83 mmol, 1.5 equiv) in $Et_2O$. Workup provided 524 mg (80%) of crude imine **10b** as a yellow oil. Purification by flash chromatography (0 $\rightarrow$ 5% $\rightarrow$ 10% MeOH/$CH_2Cl_2$) gave 321 mg (49%) of imine **10b** as a clear oil. Spectral data matched that previously reported.[3]

**3,3-Dimethyl-2-*sec*-butyl-3,4,5,6-tetrahydropyridine (10c):** This imine was prepared according to the general procedure using **8** (255 mg, 2.00 mmol, 1.0 equiv), 1.70 mL of *n*-BuLi (2.12 M in hexanes, 3.6 mmol, 1.8 equiv), TMSOTf (0.652 mL, 3.6 mmol, 1.8 equiv) in DME (30 mL) and *sec*-BuLi (2.54 mL of 1.18 M solution, 1.5 equiv, 3.0 mmol). Workup gave crude imine **10c** along with unreacted lactam **8** as an oil. $^1$H NMR analysis of the crude product indicated that ~10% of the desired imine **10c** had been formed. Due to the low conversions, this imine was not characterized further.

**General Procedure for Imine Synthesis Using Freshly Prepared Organolithiums as Described for Imine 10e.**




**8**: n = 2 **10e**: n = 2 R = -$(CH_2)_3$Ph

**7**: n = 1 **9a**: n = 1 R = -$(CH_2)_3$Ph

A solution of *N*-silyl lactam was prepared by addition of 6.17 mL of *n*-BuLi (2.08 M in hexanes, 12.96 mmol, 2.0 equiv) was added to a pre-cooled (-78 °C) solution of lactam **8** (1.23 g, 9.72 mmol, 1.5 equiv) in anhydrous DME (30 mL) and the solution was stirred for 15 min. To this solution, neat TMSOTf (2.38 mL, 12.96 mmol, 2 equiv) was added dropwise. After 15 min, the solution was warmed to -20 °C and used directly in the next step. A solution of 3-

phenylpropyl lithium (**14**)[4] was freshly prepared by dropwise addition of 9.47 mL of *t*-BuLi (1.51 M in hexanes, 14.3 mmol, 2.2 equiv) to a pre-cooled (–78 °C) solution of 1-iodo-3-phenyl propane[5] (**13**) (1.59 g, 6.48 mmol, 1.0 equiv) in $Et_2O$ (30 mL). The solution was stirred at -78 °C for 20 min, and then added dropwise via cannula to the solution of *N*-silyl lactam at -20 °C. The mixture was allowed to warm to 25 °C. After 2 h, the reaction was quenched with 1N HCl (150 mL). The solution was washed with $Et_2O$ (100 mL), made basic with 2 N NaOH (300 mL), and extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to obtain 1.24 g of crude product as a yellow oil. Flash chromatography on silica gel (1:1 $Et_2O$/hexane) gave 942 mg (63 %) of imine **10e** as a colorless oil with the following spectral characteristics: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 3.59-3.54 (m, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.27-2.21 (m, 2H), 1.95-1.85 (m, 2H), 1.65-1.57 (m, 2H), 1.54-1.49 (m, 2H), 1.07 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 175.6, 142.3, 128.3, 128.0, 125.5, 49.8, 36.1, 35.7, 35.5, 33.3, 28.8, 27.1, 19.6 ; IR (KBr) 2930, 2848, 1650, 1455; FAB HRMS Calcd. For $C_{16}H_{23}N$: 230.19087 [M+H]. Found: 230.19166.

**3,3-Dimethyl-2-(3-phenyl-propyl)-2,3-dihydropyrrole (9a):** This imine was prepared according to the general procedure using 3,3-dimethylpyrrolidin-2-one (**7**) (150 mg, 1.33 mmol, 1.0 equiv), 1.14 mL of *n*-BuLi (2.08 M in hexanes, 2.39 mmol, 1.8 equiv), TMSOTf (0.433 mL, 2.39 mmol, 1.8 equiv) in DME (5 mL) and 1-iodo-3-phenylpropane (**13**) (490 mg, 1.99 mmol, 1.5 equiv), and 2.92 mL of *t*-BuLi (1.51 M in pentanes, 4.38 mmol, 3.3 equiv) in $Et_2O$ (5 mL).

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4) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404-5406.

5) Prepared by Finkelstein reaction of commercially available 1-bromo-3-phenyl –propane (Aldrich). For procedures, see: (a) Vidari, G.; Lanfranchi, G.; Masciaga, F.; Moriggi, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3009-3020. (b) Ceruti, M.; Rocco, F.; Viola, F.; Balliano, G.; Milla, P. *J. Med. Chem.* **1998**, *41*, 540-554.

This gave 171 mg (60 %) of imine **9a** as a colorless oil with the following spectral characteristics: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 3.73-3.67 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.23-2.18 (m, 2H), 2.05-1.95 (m, 2H), 1.74 (t, *J* = 7.1, 2H), 1.08 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 183.4, 142.0, 128.4, 128.1, 125.6, 56.6, 49.4, 39.3, 35.5, 27.8, 27.7, 25.0; IR (KBr) 2954, 2865, 1639, 1455; FAB HRMS Calcd. For $C_{15}H_{21}N$: 216.17522 [M+H]. Found: 216.17476.