ALKYLIDENECARBENE INSERTION INTO A NITROGEN LONE PAIR: AN UNEXPECTED SYNTHESIS OF DIHYDROPYRROLES FROM ALKYNYLIODONIUM SALTS

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Abstract- A novel intramolecular reaction between an alkylidenecarbene and the lone pair of electrons on a carbamate's nitrogen is described. The reaction occurs preferentially over an available 1,5 C-H insertion and gives substituted dihydropyrroles upon workup.

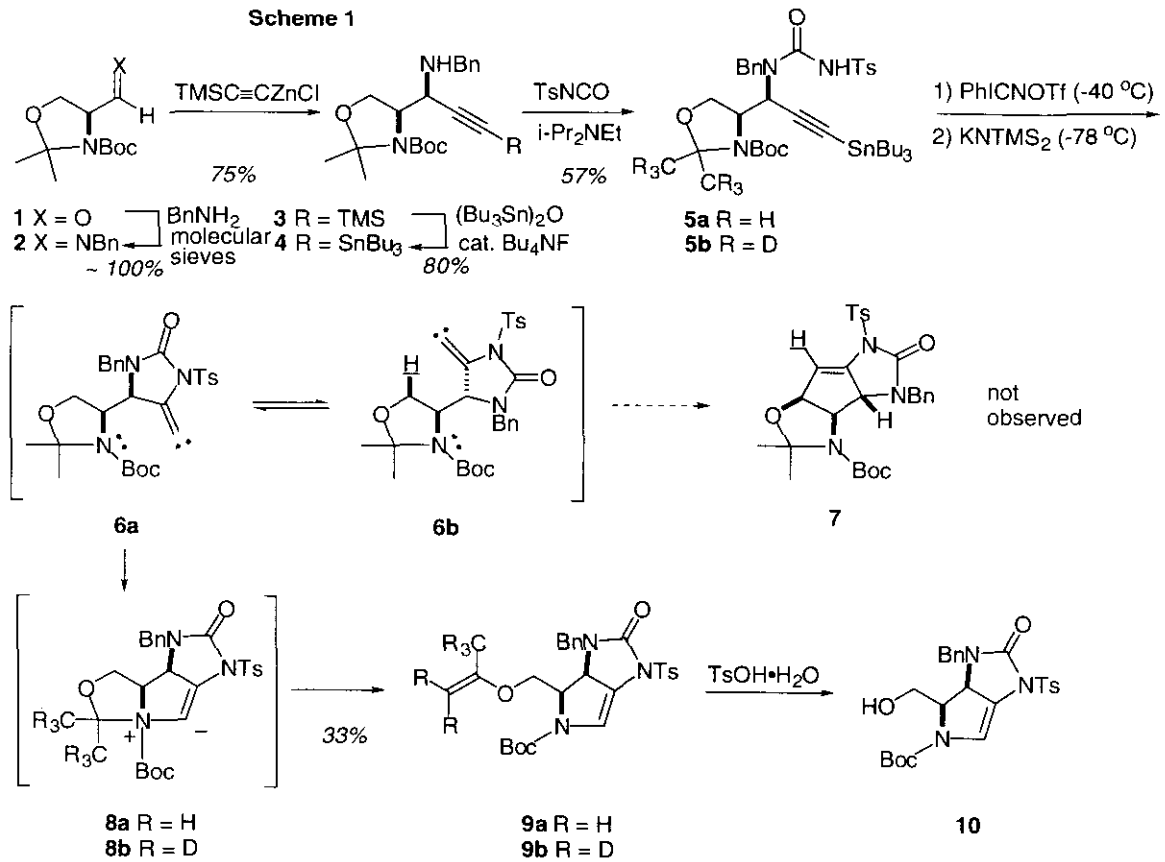
Alkylidenecarbenes undergo three distinct intramolecular bond forming reactions: 1) 1,2 substituent shift to generate an alkyne, 2) 1,5 (or rarely, 1,3) C-H insertion to furnish substituted cyclopentenes (or cyclopropenes), and 3) cycloaddition with an alkene to afford methylenecyclopropanes.[1] Scattered examples of alkylidenecarbene insertion into O-H,[2] O-Si,[3] and Si-H[4] bonds have been documented as well, although the analogous reaction with an N-X moiety has not been reported. Herein the unprecedented intramolecular combination of an alkylidenecarbene with the lone pair of electrons on a carbamate nitrogen, which leads through subsequent rearrangement of the first-formed ylide to dihydropyrrole products, is described.

Cyclopentene (**7**) was desired as an intermediate in a natural product synthesis project (Scheme 1). Access to this tricycle through bicyclization of an alkynyliodonium salt[5] derived from tosylimide (**5a**), using chemistry previously developed in-house,[6] was anticipated. The synthesis of the tosylimide cyclization precursor (**5a**) commenced with Garner aldehyde (**1**)[7] and proceeded through the derived imine (**2**). Chelation-controlled addition of trimethylsilylethynylzinc chloride to this imine gave exclusively the *syn* adduct (**3**) in analogy to a related case reported by Fujisawa.[8] Using conditions developed by Buchwald,[9] the alkynylsilane moiety in **3** was converted to the stannane analog in **4**. The secondary amino group in **4** was then acylated with tosylisocyanate to afford the sensitive tosylimide cyclization precursor (**5a**).

Bicyclization of the tosylimide (**5a**) was pursued using conditions previously developed for similar transformations.[6] Reaction of **5a** with one equivalent of Stang's reagent [cyano(phenyl)iodonium triflate][10] at –40 °C, followed by addition of 1.1 equivalent of potassium hexamethyldisilazide, led to isolation of a single cyclization product in modest yield. This material exhibited the correct MS and a characteristic vinyl signal (^{1}H NMR) for the desired tricycle (**7**), but further examination of the spectral

data soon eliminated this structure from consideration. The ^{1}H NMR spectrum clearly indicated loss of the acetonide methyls, whereas the DEPT ^{13}C NMR spectrum revealed two CH_3's and three $-CH_2$-'s instead of the three CH_3's and one $-CH_2$- expected for **7**. These data are consistent only with the structure shown as **9a**. Further evidence in support of this assignment was obtained by subjecting **9a** to mild hydrolysis, which furnished the well-characterized alcohol (**10**).

Scheme 1

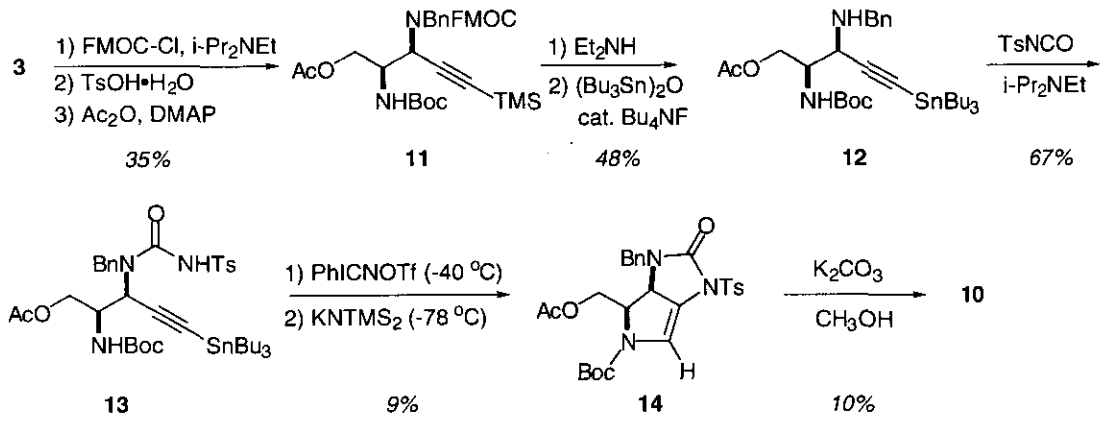


A mechanism for the formation of this unexpected product is proposed in Scheme 1. Presumably, the electrophilic alkylidenecarbene (**6a/6b**) generated by intramolecular addition of the tosylimide-derived anion to the alkynyliodonium salt formed from the alkynylstannane of **5a** inserts into the carbamate nitrogen's lone pair of electrons to furnish an intermediate ylide (**8a**). Loss of a proton from an acetonide methyl and protonation of the vinyl anion gives the observed product (**9a**). Interestingly, this formal hydrogen shift does not proceed in an intramolecular manner. Similar reaction of the d_6-deuterated version of **5a**, **5b** (prepared as per **5a** using Garner's aldehyde-d_6 (from acetone-d_6 and serine methyl ester)), afforded the pentadeuteriodihydropyrrole (**9b**). No deuterium incorporation at the vinylic position was detected. This result unequivocally demonstrates that the proton lost from the acetonide

methyl is not responsible for protonating the vinyl anion in **8**. Studies to determine the source of this hydrogen are underway.

An open-chain analog (**13**) of the alkynylstannane (**5a**) was prepared to test the premise that an alkylidenecarbene generated in a less constrained system would reliably follow the expected reaction pathway and form the 1,5 C-H insertion product (Scheme 2). Amine (**3**) was protected as its FMOC derivative, the acetonide was removed by hydrolysis, and the resulting alcohol was acylated to furnish the acetate (**11**). Carbamate deprotection proceeded uneventfully, and after a tin-for-silicon exchange, the derived secondary amine was converted to the imide (**13**) with tosylisocyanate. Cyclization of the alkynylstannane imide (**13**) was effected using the conditions described for reaction of **5a**. As with the previous substrate, only a single cyclization product was isolated in poor yield. This dihydropyrrole product (**14**) apparently resulted again from preferential alkylidenecarbene insertion into the carbamate nitrogen lone pair to the exclusion of C-H insertion. Confirmation of this structure was achieved by hydrolysis of the acetate to furnish the alcohol (**10**), identical in every way with the alcohol formed earlier by enol ether hydrolysis within **9a**.

Scheme 2



In conclusion, a novel reaction of alkylidenecarbenes, which occurs in preference to well-known 1,5 C-H insertion, has been observed. This N-lone pair insertion pathway has potential in dihydropyrrole synthesis if yields could be improved. Efforts to study less complicated substrates with this goal in mind are underway.

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EXPERIMENTAL

THF and Et_2O were dried by distillation from sodium/benzophenone under Ar immediately before use. Methylene chloride and methanol were dried by distillation from CaH_2 and Mg, respectively, under an argon atomosphere immediately before use. Liquid (flash)[11] chromatography was carried out using 32-63 μm silica gel and the indicated solvent system. Hexane and Et_2O used in flash chromatography were distilled from CaH_2 prior to use. Ethyl acetate used in flash chromatography was distilled prior to use. All moisture and air sensitive reactions were carried out in predried glassware under an Ar atmosphere. EIMS, CIMS, and FABMS were obtained from the Mass Spectroscopy Laboratory at The Pennylvania State University, while HRMS spectra were obtained from the University of Texas at Austin. All melting points are uncorrected. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

4*R*-Benzyliminomethyl-2,2-dimethyloxazolidine-3-carboxylic acid 1,1-dimethylethyl ester (**2**).

A solution of aldehyde (**1**)[7] (410 mg, 1.8 mmol) in 1 mL of CH_2Cl_2 was added to a 0 °C suspension of 4Å molecular sieves (7 g) in 10 mL of CH_2Cl_2. $BnNH_2$ (0.2 mL, 1.9 mmol) was added and the flask was sealed and stored in a 4 °C refrigerator for 18 h. Filtration followed by concentration *in vacuo* gave 571 mg (1.8 mmol, quantitative yield) of imine (**2**) (mixture of rotamers) as a cloudy yellow oil. The compound was used without further purification. IR: 1690 (C=O, C=N) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 7.74 (br s, 1H); 7.51 (br s, 1H); 7.25-7.06 (m, 5H); 4.39-3.54 (m, 5H); 1.80-1.19 (m, 15H).

4*R*-(1*S*-Benzylamino-3-trimethylsilylprop-2-ynyl)-2,2-dimethyloxazolidine-3-carboxylic acid 1,1-dimethylethyl ester (**3**).

n-BuLi (2.5 M in hexanes, 16.0 mL, 37 mmol) was added dropwise *via* syringe pump over 35 min to a 0 °C flask charged with trimethylsilylacetylene (13.4 mL, 98 mmol) and 220 mL of Et_2O. After stirring the resulting solution at 0 °C for an additional 30 min, $ZnCl_2$ (4.8 g, 36 mmol) was added in one portion. The heterogeneous mixture was stirred for 30 min at 0 °C and then cooled to -78 °C. A solution of imine (**2**) (7.8 g, 24 mmol) in 40 mL of Et_2O was added dropwise *via* cannula. The reaction mixture was stirred at -78 °C for 30 min, warmed to rt, and stirred for an additional 18 h. After cooling to 0 °C, the mixture was poured into a 0 °C solution of saturated $NaHCO_3$. The aqueous phase was extracted

with Et_2O (2 x 50 mL), and then the combined organic layers were washed with water (1 x 50 mL), brine (1 x 50 mL), and dried over Na_2SO_4. Filtration and concentration *in vacuo* gave a yellow oil which was purified by flash column chromatography using 33% Et_2O in hexanes as eluent to give 7.7 g (75%) of amine (**3**) (mixture of rotamers) as a yellow oil. IR (CH_2Cl_2) 3342 (NH), 2167 (C≡C), 1690 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 7.43-7.22 (m, 2H); 7.16-7.03 (m, 3H); 4.26-3.75 (m, 6H); 1.92-1.02 (m, 15H); 0.19 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 153.3, 152.2, 141.1, 140.6, 129.3, 129.0, 127.7, 127.5, 106.8, 106.2, 95.3, 94.5, 90.1, 80.0, 79.8, 65.8, 61.2, 60.9, 53.6, 53.0, 52.4, 28.7, 27.8, 26.9, 25.6, 24.3, 0.5. FABMS m/z (relative intensity) 417 (m^+, 55), 361 (36), 216 (48), 91 (100). Anal. Calcd for $C_{23}H_{36}N_2O_3Si$: C, 66.31; H, 8.71; N, 6.72. Found: C, 66.63; H 8.72; N, 6.69.

4*R*-(1*S*-Benzylamino-3-tri-*n*-butylstannyl-prop-2-ynyl)-2,2-dimethyloxazolidine-3-carboxylic acid 1,1-dimethylethyl ester (**4**).

Bis(tributyltin) oxide (2.6 mL, 5.0 mmol) was added to a solution of alkyne (**3**) (4.2 g, 10 mmol) in 112 mL of THF. Tetrabutylammonium fluoride (1 M in THF, 152 µL, 0.15 mmol) was added, and the mixture was heated to 65 °C for 2.5 h. After cooling to rt, the solvent was removed *in vacuo* to give a yellow oil. Purification of the residue by flash column chromatography on deactivated SiO_2 (20 wt% H_2O) using 35% Et_2O in hexanes as eluent gave 5.1 g (80%) of stannane (**4**) (mixture of rotamers) as a pale yellow oil. IR (CH_2Cl_2) 3460 (NH), 2132 (C≡C), 1690 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 7.35-7.03 (m, 5H); 4.51-3.72 (m, 7H); 1.91-0.90 (m, 42H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 153.2, 152.1, 140.6, 140.0, 128.4, 128.3, 127.0, 126.9, 109.7, 109.2, 94.7, 94.0, 88.0, 87.4, 80.1, 80.0, 65.8, 60.6, 53.7, 53.0, 51.8, 29.2, 29.0, 28.9, 28.5, 27.4, 27.0, 26.7, 25.1, 23.9, 13.7, 13.6, 11.2, 8.7, 8.6. FABMS m/z (relative intensity) 633 (M^+, 20), 91 (100). HRMS calcd for $C_{32}H_{54}N_2O_3Sn$ 631.3230, found 631.3238.

1-Benzyl-1-[1*S*-(2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidin-4*R*-yl)-3-tributylstannylprop-2-ynyl]-3-*p*-toluenesulfonylurea (**5a**).

Tosyl isocyanate (1.7 mL, 8.8 mmol) was added to a 0 °C solution of stannane (**4**) (5.3 g, 8.4 mmol) and diisopropylethylamine (1.6 mL, 9.2 mmol) in 93 mL of CH_2Cl_2. The reaction was stirred at 0 °C for 30

min and then poured into ice cold water containing a few drops of 0.5M H_3PO_4. The separated organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash column chromatography on deactivated SiO_2 (20 wt % H_2O) using 25% EtOAc in hexanes as eluent gave 4.0 g (57%) of tosylimide (**5a**) (mixture of rotamers) as a viscous yellow. IR (CH_2Cl_2) 3365 (NH), 1731 (C=O), 1689 (C=O), 1654 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 8.13 (br s, 1H); 7.51-7.01 (m, 7H); 6.74-6.70 (m, 2H); 5.50 (br s, 1H); 5.23-5.14 (m, 1H); 4.67-4.60 (m, 1H); 3.95-3.87 (m, 2H); 3.49-3.31 (m, 1H); 1.87-0.83 (m, 36H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 158.8, 153.7, 152.0, 143.8, 137.7, 137.1, 136.1, 129.2, 128.8, 128.7, 128.3, 127.7, 127.3, 95.6, 94.1, 79.7, 74.7, 52.6, 51.7, 47.6, 45.2, 34.5, 31.6, 29.0, 28.9, 28.7, 28.4, 27.4, 27.0, 26.9, 26.6, 25.3, 24.3, 23.6, 22.7, 21.6, 14.2, 13.7, 11.0, 8.9. FABMS m/z (relative intensity) 832 (MH^+, 18), 477 (100). HRMS calcd for $C_{40}H_{62}N_3O_6SSn$ 828.3377, found 828.3368.

3-Benzyl-4*R*-isopropenyloxymethyl-2-oxo-1-*p*-toluenesulfonyl-2,3,3a*R*,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]imidazole-5-carboxylic acid 1,1-dimethylethyl ester (**9a**).

A solution of stannane (**5a**) (1.53 g, 1.8 mmol) in 16 mL of CH_2Cl_2 was added to a -45 °C suspension of PhICNOTf (746 mg, 1.9 mmol) in 13 mL of CH_2Cl_2. After stirring for 30 min at -45 °C, 100 mL of chilled (-78 °C) hexane was added *via* cannula. The reaction mixture became cloudy with an oily precipitate. The supernatent was decanted and the yellow oil was washed twice with 50 mL of chilled (-78 °C) hexane. The oil was then dried *in vacuo* at -45 °C for 2 h and dissolved in 65 mL of prechilled (-45 °C) THF. KHMDS (0.5 M in toluene, 3.8 mL, 1.9 mmol) was added, and the solution was allowed to warm to -20 °C. The reaction solution was poured into ice cold water containing several drops of 1 M H_3PO_4. The mixture was then extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash column chromatography on deactivated SiO_2 (20 wt% H_2O) using 10% EtOAc and 0.1% EtOH in petroleum ether as eluent gave 328 mg (33%) of dihydropyrrole (**9a**) as a white foam. IR (CH_2Cl_2) 1752 (C=O), 1693 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, 48 °C, C_6D_6) δ: 7.99 (d, *J*=8.2 Hz, 1H); 6.97 (br s, 6H); 6.72 (d, *J*=8.2 Hz, 2H); 4.71 (d, *J*=14.6, 1H); 4.46 (br s, 1H); 4.03 (dd, *J*=7.5, 2.8 Hz, 1H); 3.92 (d, *J*=14.6 Hz, 1H); 3.77 (s, 2H); 3.63 (s, 2H); 1.84 (s, 3H); 1.54 (s, 3H); 1.37

(s, 9H). ^{13}C-NMR (300 MHz, 48 °C, C_6D_6) δ: 159.0, 156.9, 151.6, 145.3, 135.4, 129.9, 129.3, 129.2, 128.8, 128.4, 128.4, 110.0, 83.0, 81.1, 62.6, 61.9, 59.9, 48.3, 28.4, 21.3, 20.7. FABMS m/z (relative intensity) 539 (M^+, 88), 440 (100). HRMS calcd for $C_{28}H_{33}N_3O_6S$ 540.2168, found 540.2148.

3-Benzyl-4*R*-hydroxymethyl-2-oxo-1-*p*-toluenesulfonyl-2,3,3a*R*,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]imidazole-5-carboxylic acid 1,1-dimethylethyl ester (**10**).

p-TsOH•H_2O (24 mg, 0.12 mmol) was added to a solution of pyrrole (**9a**) (186 mg, 0.34 mmol) in 8 mL of CH_3OH and 2 mL of H_2O at rt. The reaction solution was stirred at rt for 2.5 h and then poured into 20 mL of saturated $NaHCO_3$ solution. The mixture was extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a pale yellow oil. Purification of this residue by flash column chromatography using 25% EtOAc in hexanes as eluent gave 147 mg (85%) of alcohol (**10**) as a white foam. IR (CH_2Cl_2) 3611 (OH), 3440 (OH), 1752 (C=O), 1690 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 8.04 (d, *J*=8.2 Hz, 2H); 6.92 (br s, 5H); 6.77 (br s, 1H); 6.64 (d, *J*=8.1 Hz, 2H); 4.65 (d, *J*=14.6 Hz, 1H); 4.17-4.14 (m, 1H); 3.94-3.72 (m, 2H); 3.51-3.31 (m, 2H); 2.06 (br s, 1H); 1.74 (s, 3H); 1.35 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 156.8, 152.7, 145.4, 135.1, 129.8, 129.1, 128.9, 128.7, 128.3, 128.3, 120.6, 109.0, 81.4, 64.6, 59.1, 59.0, 48.1, 28.2, 21.2. FABMS m/z (relative intensity) 499 (M^+, 15), 416 (55), 400 (96), 244 (100). HRMS calcd for $C_{25}H_{29}N_3O_6S$ 500.1855, found 500.1860.

Acetic acid 3*S*-[benzyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2*R*-*tert*-butoxycarbonylamino-5-trimethylsilylpent-4-ynyl ester (**11**).

9-Fluorenylmethyl chloroformate (15.9 g, 60.3 mmol) was added to a 0 °C solution of amine (**3**) (22.9 g, 55.0 mmol) and diisopropylethylamine (20 mL, 110 mmol) in 450 mL of CH_2Cl_2. The reaction was stirred at 0 °C for 1 h and then washed with water (1 x 200 mL) and brine (1 x 200 mL). Concentration *in vacuo* followed by flash column chromatography using 25% EtOAc in hexanes as eluent gave 33.0 g (94%) of 4*R*-[1*S*-benzyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)]-2,2-dimethyloxazolidine-3-carboxylic acid 1,1-dimethylethyl ester as a viscous yellow oil. IR (CH_2Cl_2) 2167 (alkyne), 1696 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, C_6D_6) δ: 7.49 (d, *J*=7.4 Hz, 4H); 7.36-7.34 (m, 2H); 7.26-6.97 (m, 7H); 5.84-

5.81 (m, 1H); 5.17 (d, *J*=17.3 Hz, 1H); 4.76 (d, *J*=17.6 Hz, 1H); 4.54 (br s, 1H); 4.37-4.15 (m, 3H); 3.93-3.91 (m, 1H); 3.73-3.68 (m, 1H); 1.92 (s, 3H); 1.33 (s, 3H); 1.32 (s, 9H); -0.08 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 159.1, 153.4, 145.2, 144.8, 143.3, 142.1, 140.6, 129.2, 128.0, 127.9, 127.8, 127.3, 127.1, 126.1, 125.8, 120.8, 120.5, 102.9, 95.4, 92.2, 80.3, 73.8, 69.0, 66.2, 59.9, 53.3, 49.8, 48.2, 46.7, 28.7, 27.9, 25.2, -0.02. EIMS m/z (relative intensity) 582 (M-*t*-Bu, 0.3), 178 (60), 57 (96), 28 (100). Anal. Calcd for $C_{38}H_{46}N_2O_5Si$: C, 71.44; H, 7.26; N, 4.38. Found: C, 71.55; H, 7.39; N, 4.25.

p-TsOH•H_2O (710 mg, 3.8 mmol) was added in one portion to a rt solution of the above carbamate (15.3 g, 24.0 mmol) in 220 mL of MeOH. The reaction was stirred at rt for 16h and then poured into 150 mL of saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography using 33% EtOAc in hexanes as eluent to give 7.6 g (53%) of 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-1-hydroxymethyl-4-trimethylsilylbut-3-ynyl)carbamic acid 1,1-dimethylethyl ester as a white solid. mp 152-154 °C. IR (CH_2Cl_2) 3613 (OH), 3413 (NH), 2179 (C≡C), 1712 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, C_6D_6) δ: 7.60-7.05 (m, 13H); 5.74-5.66 (m, 2H); 4.84 (d, *J*=16.8 Hz, 1H); 4.68 (d, *J*=17.2 Hz, 1H); 4.49-4.44 (m, 1H); 4.26-4.19 (m, 2H); 3.99-3.92 (m, 2H); 3.70 (br s, 1H); 2.60 (br s, 1H); 1.39 (s, 9H); -0.07 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 158.2, 156.5, 144.8, 144.7, 144.3, 142.0, 139.8, 128.9, 128.2, 127.8, 127.7, 127.3, 127.2, 125.8, 125.7, 120.6, 120.5, 102.3, 92.5, 79.4, 70.2, 69.2, 62.9, 56.1, 51.4, 49.5, 48.0, 47.5, 28.9, -0.14. EIMS m/z (relative intensity) 598 (M^+, 0.36), 178 (74), 91 (83), 41 (100). Anal. Calcd for $C_{35}H_{42}N_2O_5Si$: C, 70.20; H, 7.07; N, 4.68. Found: C, 70.56; H, 7.28; N, 4.02.

Acetic anhydride (37 μL, 0.37 mmol) was added to a rt solution of the above alcohol (200 mg, 0.34 mmol) and DMAP (10 mg, 0.074 mmol) in 5 mL of $CHCl_3$. The solution was stirred for 2 h at rt and then washed with H_2O (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 200 mg (93%) of acetate (**11**) as a yellow oil, which was used without further purification. IR (CH_2Cl_2) 3425 (NH), 2179 (alkyne), 1743 (C=O), 1713 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 7.52-7.48 (m, 2H); 7.15 (br s, 9H); 5.69-5.64 (m, 1H); 5.29-5.25 (m, 1H); 4.93-4.79 (m, 1H); 4.66-4.25 (m, 6H); 3.97 (br s, 1H); 1.52 (s, 3H); 1.37 (s, 9H); -0.01 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 170.3, 158.1, 156.0, 144.8, 144.6, 141.9, 139.7, 128.9, 128.4, 128.2, 127.8, 127.3, 125.8, 125.7, 120.5, 101.2, 93.4, 79.7,

69.2, 64.7, 53.8, 51.4, 49.0, 48.0, 28.8, 20.9, -0.2. EIMS m/z (relative intensity) 583 (M-*t*-Bu, 0.16), 178 (*100*), 91 (58). Anal. Calcd for $C_{37}H_{44}N_2O_6Si$: C, 69.35; H, 6.92; N, 4.37. Found: C, 69.62; H, 7.23; N, 4.27.

Acetic acid 3*S*-benzylamino-2*R*-*tert*-butoxycarbonylamino-5-tri-*n*-butylsilylpent-4-ynyl ester (**12**).

Diethylamine (2.0 mL, 19 mmol) was added to a 0 °C solution of acetate (**11**) in 20 mL of THF. The solution was warmed to rt and stirred for 18 h. Concentration *in vacuo* followed by flash column chromatography of the residue using 25% EtOAc in hexanes as eluent gave acetic acid-3-benzylamino-2-*tert*-butoxycarbonylamino-5-trimethylsilylpent-4-ynyl ester (632 mg, 80%) as a yellow oil. IR (CH_2Cl_2) 3425 (NH), 3331 (NH), 2167 (C≡C), 1743 (C=O), 1713 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ: 7.28-7.07 (m, 5H); 4.91-4.86 (m, 1H); 4.30-4.27 (m, 2H); 3.87 (d, *J*=13.1 Hz, 1H); 3.68 (d, *J*=13.1 Hz, 1H); 3.52 (d, *J*=5.9 Hz, 1H); 1.56 (s, 3H); 1.44 (s, 9H); 1.28 (br s, 1H); 0.17 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: 170.4, 156.2, 140.6, 129.0, 128.9, 127.6, 105.6, 90.3, 79.5, 68.1, 64.2, 53.6, 52.1, 52.0, 28.8, 20.7, 0.4. EIMS m/z (relative intensity) 216 (95), 91 (100). Anal. Calcd for $C_{22}H_{34}N_2O_4Si$: C, 63.12; H, 8.19; N, 6.69. Found: C, 63.04; H, 8.42; N, 6.60.

Tetrabutylammonium fluoride (1 M in THF, 99 μL, 0.1 mmol) was added to a rt solution of the above amine (2.6 g, 6.4 mmol) and $(Bu_3Sn)_2O$ (1.7 mL, 3.2 mmol) in 78 mL of THF. The reaction was heated to 65 °C for 2.5 h and then concentrated *in vacuo*. The residue was purified by flash column chromatography on deactivated SiO_2 (20 wt% H_2O) using 25% EtOAc in hexanes as eluent to give 2.4 g (60%) of stannane (**12**) as a yellow oil. IR (CH_2Cl_2) 3425 (NH), 2131 (C≡C), 1737 (C=O), 1708 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.34-7.30 (m, 2H); 7.20-7.02 (m, 3H); 4.90-4.86 (m, 1H); 4.48-4.47 (m, 2H); 4.45 (br s, 1H); 3.99-3.92 (m, 1H); 3.81-3.74 (m, 1H); 3.65-3.58 (m, 1H); 1.73-1.53 (m, 5H); 1.56 (s, 3H); 1.47-1.24 (m, 7H); 1.44 (s, 9H); 1.08-0.91 (m, 15H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 170.7, 155.5, 139.8, 128.3, 127.0, 107.9, 88.5, 79.5, 64.0, 52.4, 51.9, 51.2, 28.9, 28.3, 26.9, 20.8, 13.6, 11.0. FABMS m/z (relative intensity) 635 (M^+, 2), 147 (100), 91 (47). HRMS calcd for $C_{31}H_{52}N_2O_4Sn$ 637.3027, found 637.3035.

Acetic acid 3*S*-(1-benzyl-3-*p*-toluenesulfonylureido)-2*R*-*tert*-butoxycarbonylamino-5-tri-*n*-butylstannyl-pent-4-ynyl ester (**13**).

Tosyl isocyanate (889 μL, 4.6 mmol) was added to a 0 °C solution of amine (**12**) (3.2 g, 5.1 mmol) and diisopropylethylamine (973 μL) in 60 mL of CH_2Cl_2. The reaction solution was stirred at 0 °C for 30 min and then poured into ice cold water containing a few drops of 0.5 M H_3PO_4. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash column chromatography on deactivated SiO_2 (20 wt % H_2O) using 25% EtOAc in hexanes as eluent gave 2.8 g (67%) of tosylimide (**13**) as a viscous pale yellow oil. IR (CH_2Cl_2) 3424 (NH), 3342 (NH), 1742 (C=O), 1707 (C=O), 1678 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.48-7.19 (m, 9H); 5.36 (m, 1H); 5.07 (d, *J*=10.5 Hz, 1H); 4.82 (d, *J*=17.3 Hz, 1H); 4.49-3.95 (m, 4H); 2.40 (s, 3H); 2.07 (s, 3H); 1.51 (s, 9H); 1.42-1.15 (m, 14H); 0.87-0.78 (m, 13H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 170.5, 155.7, 152.1, 144.3, 136.1, 135.9, 129.3, 129.2, 128.3, 127.9, 126.9, 103.6, 92.6, 80.4, 64.3, 52.6, 49.8, 47.8, 28.7, 28.2, 26.8, 21.6, 20.7, 13.5, 10.9. FABMS m/z (relative intensity) 637 (42), 177 (97), 91 (100). HMRS calcd for $C_{39}H_{60}N_3O_7SSn$ 834.3174, found 834.3149.

3-Benzyl-4*R*-acetoxymethyl-2-oxo-1-*p*-toluenesulfonyl-2,3,3a*R*,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]imidazole-5-carboxylic acid 1,1-dimethylethyl ester (**14**).

A solution of stannane (**13**) (2.80 g, 3.4 mmol) in 40 mL of CH_2Cl_2 was added to a -45 °C suspension of PhICNOTf (1.31 g, 3.4 mmol) in 30 mL of CH_2Cl_2. After stirring for 30 min at -45 °C, 210 mL of chilled (-78 °C) hexane was added *via* cannula. The reaction mixture became cloudy with an oily precipitate. The supernatent was decanted off and the yellow oil was washed twice with 100 mL of chilled (-78 °C) hexane. The oil was dried *in vacuo* at -45 °C for 2 h and then dissolved in 111 mL of prechilled (-78 °C) THF. KHMDS (0.5 M in toluene, 3.8 mL, 1.9 mmol) was added, and the solution was allowed to warm to -20 °C. The reaction solution was poured into ice cold water containing several drops of 1 M H_3PO_4. The mixture was then extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash column chromatography using 35% EtOAc in hexanes as eluent gave 160 mg (9%) of dihydropyrrole (**14**) as a white foam. IR (CH_2Cl_2) 1749 (C=O), 1696 (C=O) cm^{-1}.

^{1}H-NMR (200 MHz, C_6D_6) δ: 8.06 (d, *J*=8.4 Hz, 2H); 6.96-6.75 (m, 6H); 6.65 (d, *J*=8.2 Hz, 2H); 4.45-4.37 (m, 2H); 3.98-3.56 (m, 4H); 1.73 (s, 3H); 1.60 (s, 3H); 1.37 (s, 9H). ^{13}C-NMR (300 MHz, C_6D_6) δ: FABMS m/z (relative intensity) 541 (M^+, 12), 286 (54), 91 (100). HRMS calcd for $C_{27}H_{31}N_3O_7S$ 542.1961, found 542.1952.

3-Benzyl-4*R*-hydroxymethyl-2-oxo-1-*p*-toluenesulfonyl-2,3,3a*R*,4-tetrahydro-1*H*-pyrrolo[3,4-*d*]imidazole-5-carboxylic acid 1,1-dimethylethyl ester (**10**).

A solution of acetate (**14**) (56 mg, 0.1 mmol) and K_2CO_3 (190 mg, 1.4 mmol) in 5 mL of a 2:1 mixture of water and MeOH was stirred at rt for 1 h. The mixture was extracted with EtOAc (2 x 5mL) and the organic phase was dried over $MgSO_4$. Filtration, followed by concentration *in vacuo* gave a yellow oil. Purification of this residue by flash column chromatography using 33% EtOAc in hexanes gave 5.0 mg (10%) of alcohol (**10**) as a pale yellow oil. The spectral data matched those reported above.

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