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TETRAHEDRON

Potential Silicon-Containing Antifolates

Edward C. Taylor*, Rajendra P. Chaudhuri

Department of Chemistry, Princeton University, Princeton, NJ 08544-1009

and

Samuel E. Watson

Department of Chemistry, Long Island University, One University Plaza, Brooklyn, New York 11201

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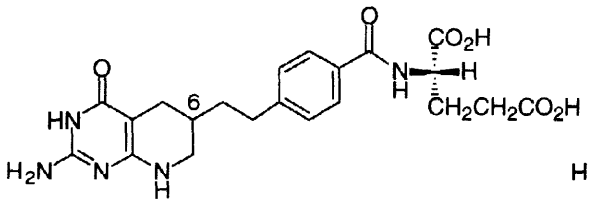
Abstract: Novel silicon-containing folate derivatives were synthesized as potential inhibitors of folate-dependent enzymes in an attempt to develop more effective antitumor agents. A dimethylsilyl moiety was inserted into the sidechain of two known antifolates with the aim of improving passive transport properties and sidechain conformational flexibility. An efficient, convergent palladium-catalyzed coupling methodology was used to link known heterocycles to novel, highly functionalized vinyl and ethynyl silanes.

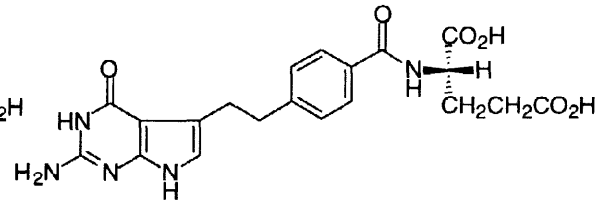
Keywords: Antitumor compounds, coupling reactions, enzyme inhibitors, silicon compounds

INTRODUCTION

As a part of our program on the synthesis of potential inhibitors of folate-dependent enzymes as antitumor agents, we were intrigued by the potential consequences of replacement of the $-CH_2CH_2-$ bridge in DDATHF (**1**)[1] and in LY231514 (MTA, **2**)[2,3] by a 1,1-dimethyl-1-silapropyl bridge. The present paper describes some novel applications of vinyl and ethynyl silanes in the synthesis of the target silicon-containing analogues **3** and **4**.



1 (6R,S) DDATHF



2 (LY231514, MTA)

RESULTS AND DISCUSSION

It was believed that compounds **3** and **4** could be synthesized in a convergent manner using palladium-catalyzed coupling methodology previously developed for the synthesis of DDTHF.[4] The key vinyldimethylsilane **6** was readily accessible from commercially available chlorovinyldimethylsilane and the Grignard reagent generated from the protected 4-bromobenzoic acid **5**[5] (Scheme 1). Meyers' dimethyloxazoline carboxylic acid equivalent proved to be the ideal protecting group in these cases.[5] The normal deprotection protocol as developed by Meyers involving quaternization followed by basic hydrolysis was compatible with the phenyl-silicon and vinyl-silicon linkages, and the free acid **7** could be generated in good overall yields in multigram quantities. Coupling with dimethyl L-glutamate using 2-chloro-4,6-dimethoxy-1,3,5-triazine as the coupling agent[6] completed the synthesis of **8**.

E-mail: sunup@chemvax.princeton.edu

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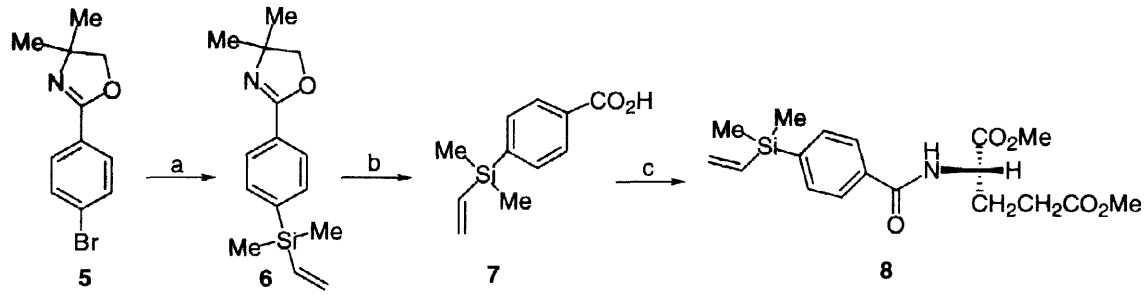
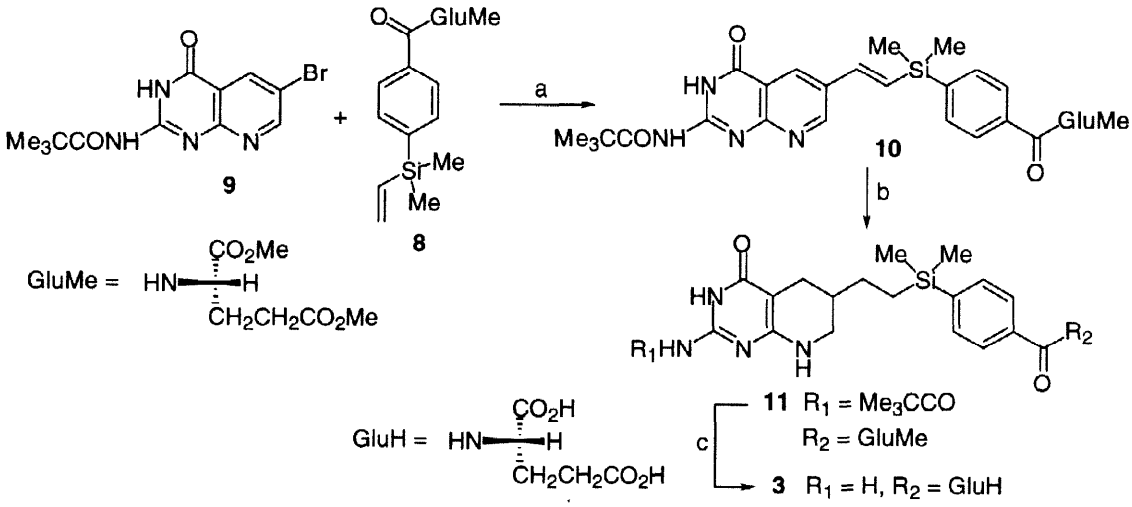
Scheme 1



(a) i. Mg, I_2, THF, reflux; ii. chlorodimethylvinylsilane, 68%. (b) i. MeI, MeCN; ii.1N NaOH, 93% (combined yield (c) i. 2-chloro-4,6-dimethoxy-1,3,5-triazine, N-methylmorpholine; ii. dimethyl L-glutamate hydrochloride, 84%

Heck coupling of **8** with 2-pivaloyl-6-bromo-5-deazapterin (**9**), readily available in multigram amounts by previously developed methodology,[7] proceeded smoothly and in excellent yields (Scheme 2). Although

Scheme 2



(a) cat. $Pd(OAc)_2$, $P(o\text{-}tol)_3$, CuI, TEA, MeCN, 85%. (b) PtO_2, H_2 (50 psi), MeOH, rt, 12 h, 95% (c) 1 N NaOH, 3 days, 80%

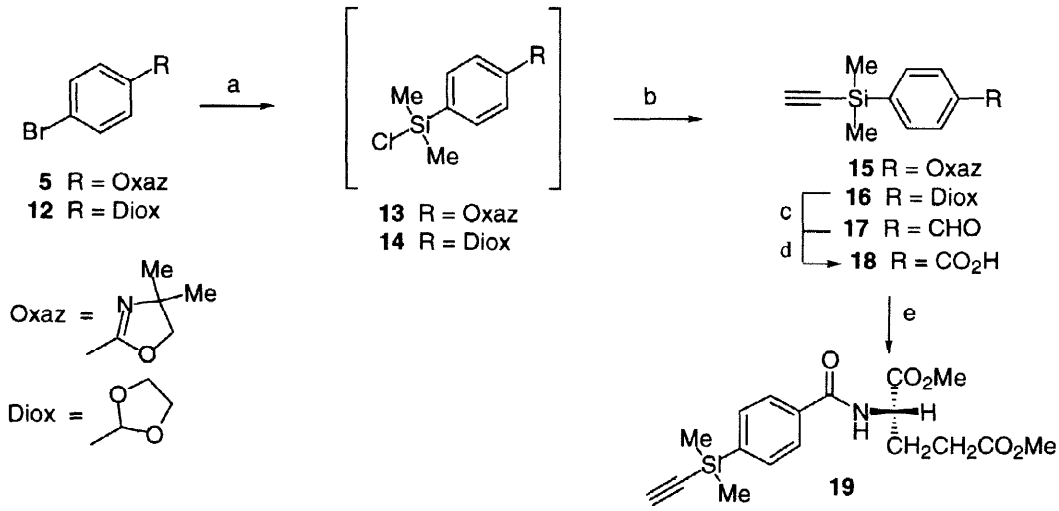
coupling at the α-position is sometimes observed with silylated alkenes, presumably due to the well-known electronic effects of the silicon atom, in our case the only products detected were those resulting from coupling at the sterically more accessible β-position. Hydrogenation of **10** in the presence of a catalytic amount of platinum oxide reduced the sidechain olefin and the pyridine ring in one step. Final saponification provided **3** in high yield.

However, an attempt to effect a similar Heck coupling of 2-pivaloylamino-4(3H)-oxo-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**20**, Scheme 4)[2] with the vinyldimethylsilane **8** led to very low yields of the desired coupling product; the major product was the reductively dehalogenated heterocycle. Attempts to suppress this

side reaction through the use of inorganic bases under phase-transfer conditions[9] resulted only in decreased reactivity and incomplete conversion to product. As a consequence, since the original synthesis of LY231514[2] had utilized a copper iodide-mediated palladium-catalyzed coupling between the pyrrolo[2,3-d]pyrimidine **20** and dimethyl 4-ethynylbenzoyl glutamate, we decided to proceed via an ethynylsilyl intermediate.

After considerable experimentation, the sensitive 4-ethynylsilylbenzoyl glutamate **19** (Scheme 3) was prepared from dichlorodimethylsilane following methodology developed by Barcza.[10] Our first attempts utilized the Grignard reagent formed from the oxazoline-protected *p*-bromobenzoic acid equivalent **5**. The key to ensuring monoaddition to the doubly electrophilic dichlorosilane proved to be formation of the Grignard reagent in the presence of a large excess of the dichlorosilane under carefully controlled conditions. The hydrolytically sensitive chlorodimethylsilane **13** was not isolated but, after removal of excess dichlorodimethylsilane by low pressure distillation, was treated directly with ethynylmagnesium bromide in

Scheme 3



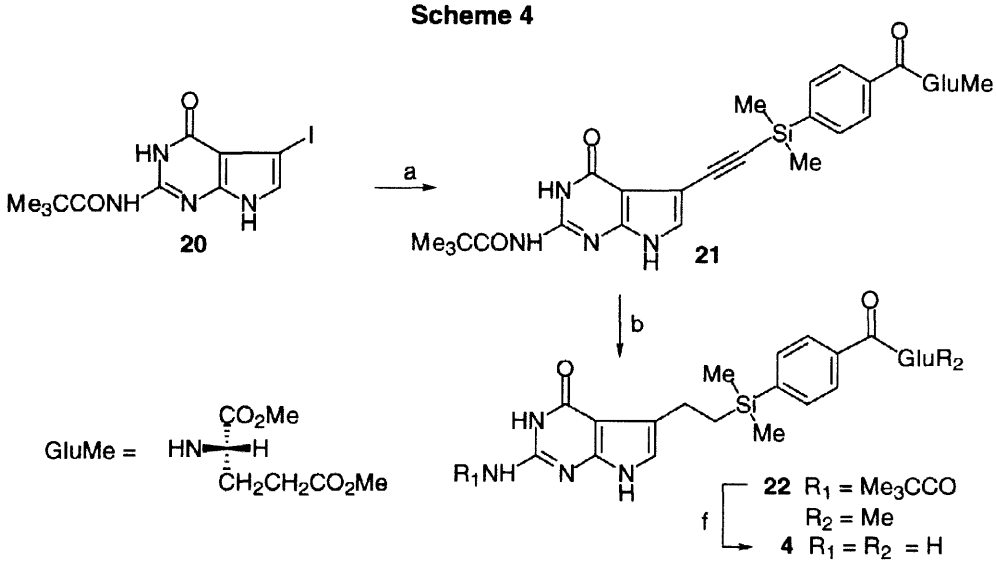
(a) Mg, I_2, Cl_2SiMe_2, THF,40-50° C. (b) ethynyl magnesium bromide, THF, 4° to rt, 50-60%. (c) For **17:** SiO_2, oxalic acid, H_2O, CH_2Cl_2. (d) $NaOCl_2$, $NaH_2PO_4.H_2O$, 30% H_2O_2, pH 2-3, 88% for two steps. (e) i. 2-chloro-4,6-dimethoxy-1,3,5-triazine, N-methylmorpholine ii. dimethyl L-glutamate hydrochloride, 77%

fresh tetrahydrofuran. The oxazoline-protected ethynylsilane **15** was produced in moderate but consistently reproducible yields of 50 - 55% over the two steps on a multigram scale. All attempts, however, to remove the oxazoline protecting group without concomitant hydrolysis of the sensitive ethynyl-silicon bond failed. Several strategies were examined before it was discovered that the simple 1,3-dioxolane **16** could be converted to the carboxylic acid **18** in excellent overall yields. Starting from the 1,3-dioxolane **12**, the ethynyldimethylsilyl compound **16** was prepared in the same way as **15**, and in comparable yields. Treatment of **16** with silica gel impregnated with aqueous oxalic acid[11] provided the aldehyde **17** in virtually quantitative

yields. Mild sodium chlorite oxidation of the crude aldehyde in buffered conditions[12] provided the acid **18** in excellent yields. Glutamate coupling proceeded without incident to give **19**.

Palladium-catalyzed coupling of 2-pivaloylamino-4(3H)-oxo-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**20**)[2] with the ethynylsilane **19** in the presence of copper iodide (Scheme 4) was accomplished in moderate yields (50 - 60%). Reduction to **22** and deprotection under standard conditions completed the synthesis of **4**.

Scheme 4



(a) **19**, $Pd(Ph_3)_4$, CuI, Et_3N, DMF, 53%. (b) H_2, $Pd(OH)_2$, MeOH, 68%. (c) 1 N NaOH, rt, 3 days, 53%.

The silicon-containing analogues **3** and **4** were screened for *in vitro* activity against mouse L1210 and human CCRF-CEM lymphoblastic leukemia cells, but neither exhibited significant cell growth inhibitory activity. It seems possible that the increased steric bulk of the two additional sidechain methyl groups precludes recognition by the enzyme.

EXPERIMENTAL SECTION

2-[4-(Vinyldimethylsilyl)phenyl]-4,4-dimethyloxazoline (6). The 2-(4-bromophenyl)-4,4-dimethyloxazoline **5** (2.98 g, 11.73 mmol), prepared as described by Meyers,[5] in dry THF (75 ml) was added slowly with mild heating and stirring under nitrogen (10-15 ml at first to initiate the reaction) to Mg turnings (0.32 g, 12.99 mmol) and an I_2 crystal at such a rate as to maintain a gentle reflux. When the addition was complete (1.5 h), the reaction mixture was maintained at reflux a further 4 h until most of the Mg had been consumed. The reaction mixture was then cooled to 4 °C and commercially available chlorovinyldimethylsilane (1.43 ml, 11.81 mmol) in dry THF (10 ml) was slowly added dropwise. The reaction mixture was allowed to warm slowly to rt overnight, heated to reflux 1 h to ensure completion of the reaction, cooled, quenched with H_2O (75 ml) and saturated NH_4Cl (30 ml) and extracted with Et_2O (2 x 100 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated under vacuum to a pale oil which was chromatographed over silica gel (10% EtOAc-hexanes) to give **6** (2.1 g, 8.11 mmol, 69%) as a colorless oil. ^1H NMR (300 MHz,

$CDCl_3$) δ 0.35 (s, 6H), 1.37 (s, 6H), 4.09 (s, 2H), 5.78 (dd, 1H), 6.07 (m, 2H), 7.55 (dd, 2H), 7.91 (dd, 2H). FABMS *m/z* calcd for $C_{15}H_{22}NOSi$ (MH^+) 260.1471, found 260.1463

4-(Vinyldimethylsilyl)benzoic Acid (7). 2-[4-(Vinyldimethylsilyl)phenyl]-4,4-dimethyloxazoline (**6**) (2.0 g, 7.72 mmol) and MeI (2.40 ml, 38.6 mmol) in MeCN (50 ml) were heated at 120 °C in a sealed tube for 2 d. After cooling, the solution was concentrated to 20 ml and diluted with Et_2O (50 ml). The pale yellow crystals which formed were collected by filtration, washed with cold Et_2O and immediately dissolved in 1N NaOH (50 ml). The reaction mixture was stirred at rt for 24 h and neutralized with 6N HCl. The precipitate that formed was collected by filtration, washed with H_2O and dried under reduced pressure at 50 °C for 6 hours to give **7** (1.48 g, 7.18 mmol, 93%) as a white solid suitable for further use: mp 62 - 64 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.31 (s, 6H), 5.73 (m, 1H), 6.10 - 6.26 (m, 2H), 7.59 (dd, 2H), 7.88 (dd, 2H). HRMS *m/z* calcd for $C_{11}H_{14}O_2Si$: 206.0763, found 206.0751.

Dimethyl N-[(4-Vinyldimethylsilyl)benzoyl]-L-glutamate (8). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (1.61 g, 9.17 mmol) was added as a solid, with stirring under nitrogen at 4 °C, to a mixture of the crude acid **7** (1.78 g, 8.64 mmol) and N-methylmorpholine (1.00 ml, 9.10 mmol) in dry CH_2Cl_2 (75 ml). After 2 h a second aliquot of N-methylmorpholine (1.00 ml, 9.15 mmol) followed by dimethyl L-glutamate (1.60 g, 9.17 mmol) were added, and the reaction mixture was allowed to warm slowly to rt overnight. The reaction mixture was diluted with additional CH_2Cl_2 (50 ml), washed with 5% Na_2CO_3 (50 ml), 0.5 N HCl (50 ml), H_2O (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to a pale oil which was chromatographed over silica gel (2% MeOH-CH_2Cl_2) to give **8** (2.63 g, 7.24 mmol, 84%) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.35 (s, 6H), 2.12 - 2.60 (m, 4H), 3.64 (s, 3H), 3.76 (s, 3H), 4.79 - 4.81 (m, 1H), 5.73 (dd, 1H, *J* = 18.2 Hz), 6.05 (dd, 1H, *J* = 3.71 Hz), 6.25 (dd, 1H, *J* = 14.6 Hz), 7.12 (d, 1H, *J* = 7.3 Hz), 7.57 (dd, 2H), 7.8 (dd, 2H). HRMS *m/z* calcd for $C_{18}H_{26}NO_5Si$ (MH^+): 364.1580, found 364.1591.

Dimethyl N-{4-[3-(2-Pivaloylamino-4(3H)-oxopyrido[2,3-d]pyrimidin-6-yl)-1,1-dimethyl-1-sila-2-propenyl]benzoyl}-L-glutamate (10). A mixture of 2-pivaloyl-6-bromo-5-deazapterin **9**[7] (0.65 g, 2.0 mmol), triethylamine (1.32 ml), palladium acetate (4.5 mg), cuprous iodide (2.0 mg) and tri-o-tolylphosphine (12.2 mg) in dry, degassed MeCN (35 ml) was heated to reflux under nitrogen. Dimethyl N-[4-(vinyldimethylsilyl)benzoyl]-L-glutamate **8** (0.87 g, 2.4 mmol) in MeCN (5 ml) was added, and the reaction mixture was heated under reflux for 12 h. The solvent was removed under reduced pressure and the resultant solid was taken up in EtOAc, washed with H_2O, and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography over silica gel (3% MeOH-CH_2Cl_2) provided **10** as a white solid (1.03 g, 1.70 mmol, 85%): mp 101 - 104 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.48 (s, 6H), 1.33 (s, 9H), 2.15 - 2.54 (m, 4H), 3.66 (s, 3H), 3.78 (s, 3H), 4.82 - 4.84 (m, 1H), 6.78 (d, 1H, *J* = 19.2 Hz), 6.95 (d, 1H, *J* = 19.2 Hz), 7.15 (d, 1H, *J* = 7.4 Hz), 7.63 (dd, 2H), 7.80 (dd, 2H), 8.35 (br, 1H), 8.55 (d, 1H, *J* = 1.73 Hz), 8.90 (br, 1H), 12.06 (br, 1H). FABHRMS *m/z* calcd for $C_{30}H_{38}N_5O_7Si(MH^+)$: 608.2541, found: 608.2528. Anal. Calcd for $C_{30}H_{37}N_5O_7Si$: C, 59.29; H, 6.10; N, 11.41. Found: C, 59.01; H, 6.10; N, 11.41.

Dimethyl N-{4-[3-(2-Pivaloylamino-4(3H)-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)-1,1-dimethyl-1-sila-2-propyl]benzoyl}-L-glutamate (11). A mixture of **10** (0.607 g, 1 mmol) and PtO_2 (40 mg) in MeOH (25 ml) was shaken under an H_2 atmosphere (Parr apparatus, 50 psi) for 12 h. The reaction mixture was filtered through Celite, the solvent was removed under reduced pressure, and the resulting solid was chromatographed on silica gel (3% MeOH-CH_2Cl_2) to give **11** (0.582 g, 0.95 mmol, 95%) as a white solid: mp 205 - 207 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.23 (s, 6H), 1.15 (s, 9H), 1.34 - 3.30 (m, 13H), 3.54 (s, 3H), 3.60 (s, 3H), 4.40 - 4.46 (m, 1H), 6.40 (br, 1H), 7.57 (dd, 2H), 7.80 (dd, 2H), 8.73 (d, 1H, *J* = 7.37 Hz), 10.56 (br, 1H), 11.16 (br, 1H). FABHRMS *m/z* calcd for $C_{30}H_{44}N_5O_7Si(MH^+)$: 614.3010, found 614.3004. Anal. Calcd for $C_{30}H_{43}N_5O_7Si$: C, 58.71; H, 7.06; N, 11.41. Found: C, 58.41; H, 7.34; N, 10.98.

N-{4-[3-(2-Amino-4(3H)-oxo-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-6-yl)-1,1-dimethyl-1-silapropyl]benzoyl}-L-glutamic Acid (3). A suspension of **11** (0.220 g, 0.36 mmol) in 1N NaOH (4 ml) was stirred at rt for 3 d. The mixture was carefully acidified with concentrated HCl with cooling in an ice bath. The white precipitate which formed was collected by filtration, washed with H_2O, Et_2O and dried to give **3** (0.144 g,

0.288 mmol, 80%) as a white solid, mp 234 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.22 (s, 6H), 0.77 - 3.40 (m, 13H), 4.40 - 4.35 (m, 1H), 7.00 (br, 1H), 7.19 (br, 2H), 7.50 (dd, 2H), 7.81 (dd, 2H), 8.61 (d, 1H, J = 7.41 Hz), 11.88 - 11.97 (br, 3H). FABHRMS *m/z* calcd for $C_{23}H_{32}N_5O_6Si(MH^+)$: 502.2122, found: 502.2096. Anal. Calcd for $C_{23}H_{31}N_5O_6Si$: C, 55.07; H, 6.23; N, 13.96. Found: C, 54.21; H, 6.31; N, 14.21.

2-[4-(Ethynyldimethylsilyl)phenyl]-4,4'-dimethyloxazoline (15). To a flask containing Mg turnings (0.97 g, 39.92 mmol), an I_2 crystal, mercuric chloride (5 mg), and commercially available dichlorodimethylsilane (12.06 ml, 99.45 mmol) in dry THF (10 ml), 2-(*p*-bromophenyl)-4,4'-dimethyloxazoline[5] (**5**) (5.0 g, 19.86 mmol) in THF (50 ml) was added with stirring under nitrogen and mild initial heating to 40 °C. The first 10 ml were added quickly to initiate the reaction and then at such a rate as to maintain the temperature below 50 °C. When the addition was complete (45 min), the reaction mixture was stirred at 45°C for 2 h. The solvent and excess dichlorodimethylsilane were removed under reduced pressure, and the residue was washed with dry THF (30 ml) which was subsequently removed under reduced pressure. The washed residue was taken up in fresh, dry THF (75 ml) and transferred via cannula away from the excess Mg into a new dry flask under nitrogen. Commercially available ethynylmagnesium bromide (79.56 ml, 0.5 M solution in THF) was added dropwise at 4 °C over 30 min. The reaction mixture was allowed to warm slowly to rt overnight and refluxed for 1 h. The reaction mixture was cooled to rt, quenched by addition of H_2O (25 ml) and the THF was removed under reduced pressure. The residue was partitioned between Et_2O (100 ml) and saturated NH_4Cl (50 ml), the ethereal layer was separated, washed with H_2O and brine, dried ($MgSO_4$) and concentrated to give an amber oil which was chromatographed on silica gel (5% EtOAc-hexanes) to give **15** (2.94 g, 11.45 mmol, 58%) as a clear, colorless oil that slowly crystallized to a white solid upon standing; mp 54 - 55 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.43 (s, 6H), 1.36 (s, 6H) 2.53 (s, 1H), 4.08 (s, 2H), 7.65 (dd, 2H), 7.92 (dd, 2H); MS *m/z* (relative intensity) 257 (4%), 242 (100%), 232 (8%), 186 (20%), 83 (25%). IR (neat) 2953, 2925, 2886, 1430, 1390 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NOSi$: C, 69.99; H, 7.44; N, 5.44. Found: C, 70.32; H, 7.63; N, 5.22.

4-(Ethynyldimethylsilyl)benzaldehyde 1,3-dioxolane (16). *p*-Bromobenzaldehyde 1,3-dioxolane (**12**) (6.0 g, 26.2 mmol) in dry THF (60 ml) was added with stirring under nitrogen and gentle heating (bath temperature initially at 40 °C) to a suspension of Mg turnings (1.278 g, 52.59 mmol), an I_2 crystal and dichlorodimethylsilane (14.92 ml, 131 mmol) in dry THF (10 ml) as described above for the preparation of **15**. The reaction mixture was stirred 2 h at 50 °C and treated as described above. Ethynylmagnesium bromide (105 ml, 0.5 M solution in THF) was added and the reaction mixture was allowed to warm slowly to rt overnight and worked up as before to give a pale oil that on chromatography over silica gel (10% EtOAc in hexanes) gave **16** (3.45 g, 14.87 mmol, 57%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (s, 6H), 2.55 (s, 1H), 4.05 - 4.18 (m, 4H), 5.86 (s, 1H), 7.51 (dd, 2H), 7.68 (dd, 2H). HRMS *m/z* calcd for $C_{13}H_{16}O_2Si$ (MH^+) 232.0920, found: 232.0928.

4-(Ethynyldimethylsilyl)benzaldehyde (17). Silica gel (4.0 g, Merck Kieselgel 60) was suspended in CH_2Cl_2 (20 ml) with vigorous stirring and a 10% aqueous oxalic acid solution (400 mg) was added. Stirring was continued for a few minutes until the oxalic acid solution had been adsorbed onto the silica gel, and 4-(ethynyldimethylsilyl)benzaldehyde 1,3-dioxolane (**16**) (1.0 g, 4.31 mmol) was then added neat. After 2 h the reaction mixture was diluted with CH_2Cl_2 (30 ml), filtered through Celite and concentrated to give **17** (0.81 g, 4.31 mmol, quant.) as a pale oil suitable for further use. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (s, 6H), 2.59 (s, 1H), 7.81 (dd, 2H), 7.88 (dd, 2H), 10.04 (s, 1H).

4-(Ethynyldimethylsilyl)benzoic acid (18). To crude 4-(ethynyldimethylsilyl)benzaldehyde (**17**) (0.81 g, 4.31 mmol) in MeCN (20 ml) and H_2O (10 ml) was added $NaH_2PO_4{\cdot}H_2O$ (140 mg) in H_2O (10 ml) and 30% H_2O_2 (2.5 ml). The pH was adjusted to 2-3 with 6N HCl, and sodium chlorite (546 mg) in H_2O (10 ml) was added slowly dropwise with cooling so as to maintain the reaction temperature at 25 - 30 °C. Stirring was continued for 2 h, and the excess H_2O_2 was quenched by cautious addition of Na_2SO_3 (500 mg). The reaction mixture was diluted with H_2O (25 ml), extracted with CH_2Cl_2 (2 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give **18** (0.77 g, 3.77 mmol, 88%) as a white solid suitable for further use: mp 93 - 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6H), 2.48 (s, 1H), 7.65 (dd, 2H), 7.88 (dd, 2H), 12.5 (br, 1H). IR (neat) 3620 - 3200 (br, s), 2960, 2687, 2543, 1889, 1555, 1419, 1291, 1283, 1100, 835 cm^{-1}. MS *m/z* (relative intensity) 204 (25%), 203 (14%), 190 (30%), 189 (100%), 143 (14%).

Dimethyl 4-(Ethynyldimethylsilyl)benzoyl-L-glutamate (19). To crude 4-(ethynyldimethylsilyl)benzoic acid (**18**) (1.45 g, 7.1 mmol) and N-methylmorpholine (0.95 ml, 8.69 mmol) in dry CH_2Cl_2 (75 ml) with stirring under nitrogen at 4 °C was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.53 g, 8.70 mmol). After 2 h at 4 °C, additional aliquots of N-methylmorpholine (0.95 ml, 8.69 mmol) and dimethyl L-glutamate hydrochloride (1.84 g, 8.69 mmol) were added. The reaction mixture was allowed to warm slowly to rt overnight, washed with H_2O (2 x 50 ml), 5% Na_2SO_4 (50 ml), 0.5 N HCl (25 ml), brine (25 ml), and then dried (Na_2SO_4) and concentrated to a pale syrup which on chromatography over silica gel (40% EtOAc-hexanes) gave **19** (1.98 g, 5.47 mmol, 77%) as a colorless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (s, 6H), 2.1 - 2.52 (m, 4H), 2.55 (s, 1H), 2.65 (s, 3H), 2.78 (s, 3H), 4.79 - 4.85 (m, 1H), 7.1 (br, 1H), 7.71 (dd, 2H), 7.85 (dd, 2H). MS *m/z* (relative intensity) 361 (4%), 302 (42%), 203 (20%), 188 (48%), 187 (100%), 174 (45%). Anal. Calcd for $C_{18}H_{23}NO_5Si$: C, 59.81; H, 6.41; N, 3.87. Found: C, 59.93; H, 6.35; N, 3.95.

Dimethyl 4-[3-(2-Pivaloylamino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,1-dimethyl-1-sila-2-propynyl]benzoyl-L-glutamate (21). Tetrakis(triphenylphosphine)palladium (642 mg, 10 mol %), Et_3N (0.78 ml, 5.56 mmol), CuI (212 mg, 20 mol %), 2-pivaloylamino-4(3H)-oxo-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**20**)[2] (1.0 g, 2.78 mmol), and dimethyl 4-(ethynyldimethylsilyl)benzoyl-L-glutamate (**19**) (1.32 g, 3.66 mmol) were dissolved in dry DMF (40 ml) and the mixture was heated at 60 °C with stirring under nitrogen for 2 h. The DMF was removed under reduced pressure, and the resulting dark solid was taken up in CH_2Cl_2 (50 ml) and filtered through a pad of Celite to remove the palladium salts. The filtrate was washed with H_2O (2 x 50 ml), dried ($MgSO_4$) and concentrated to give a dark solid. This was washed with Et_2O (25 ml) to give a light brown powder which was chromatographed over silica gel (1% MeOH-CH_2Cl_2) to give **21** (0.874 g, 1.473 mmol, 53%) as a pale powder: mp > 167 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.44 (s, 6H), 1.26 (s, 9H), 1.94 - 2.16 (m, 2H), 2.41 - 2.52 (m, 2H), 3.56 (s, 3H), 3.64 (s, 3H), 4.41 - 4.50 (m, 1H), 5.74 (s, 1H), 7.84 (AA'BB', 4H), 8.79 (d, 1H, J = 6.2 Hz), 10.92 (s, 1H), 11.90 (s, 1H), 12.05 (s, 1H). MS *m/z* (relative intensity) 482 (27%), 387 (12%), 373 (13%), 372 (32%), 371 (100%), 258 (26%), 193 (33%). Anal. Calcd for $C_{29}H_{35}N_5O_7Si$: C, 58.67; H, 5.94; N, 11.80. Found: C, 58.57; H, 5.81; N, 11.91.

Dimethyl 4-[3-(2-Pivaloylamino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidn-5-yl)-1,1-dimethyl-1-silapropyl]benzoyl-L-glutamate (22). A mixture of **21** (0.345 g, 0.582 mmol), 20% $Pd(OH)_2$ on carbon (50 mg) in dry MeOH (20 ml), and dry CH_2Cl_2 (20 ml) was hydrogenated (50 psi of H_2, Parr apparatus) for 5 h. The reaction mixture was filtered through Celite, concentrated and the residual material was chromatographed over silica gel (2% MeOH-CH_2Cl_2) to give **22** (0.236 g, 0.396 mmol, 68%) as a pale powder, mp 184 - 185 °C, dec. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.23 - 1.29 (m, 2H), 1.34 (s, 9H), 2.21 - 2.54 (m, 4H), 2.82 - 2.86 (m, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 4.86 (m, 1H), 6.37 (s, 1H), 7.16 (d, 1H, J = 7.06 Hz), 7.49 (dd, 2H), 7.63 (dd, 2H), 8.60 (s, 1H), 8.71 (s, 1H), 11.76 (s, 1H). MS *m/z* (relative intensity) 598 (38%), 597 (100%), 582 (27%), 371 (24%), 319 (34%), 318 (29%), 262 (23%), 261 (70%), 234 (24%). HRMS *m/z* calcd. for $C_{29}H_{39}N_5O_7Si$ 597.2591, found 597.2584.

Dimethyl N-{4-[3-(2-Amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidn-5-yl)-1,1-dimethyl-1-silapropyl]benzoyl}-L-glutamic Acid (4). A suspension of **22** (0.215 g, 0.360 mmol) in 1 N NaOH (2.5 ml) was stirred at rt for 3 d. Neutralization with 6 N HCl and drying of the filtered solid at 50 °C under reduced pressure provided **4** (0.093 g, 0.192 mmol, 53%) as a pale tan solid, mp > 243 °C, dec. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.43 (s, 6H), 1.22 - 1.31 (m, 2H), 2.26 - 2.61 (m, 4H), 2.83 - 2.88 (m, 2H), 4.92 (m, 1H), 6.36 (s, 1H), 7.42 (d, 1H, J = 7.128 Hz), 7.83 (dd, 2H), 7.89 (dd, 2H), 8.79 (d, 2H), 11.94 (s, 1H). FABMS *m/z* (relative intensity) 485 (13%), 470 (100%), 440 (6%), 245 (12%), 240 (8%), 219 (11%). Anal. Calcd for $C_{22}H_{27}N_5OSi$: C, 54.42; H, 5.60; N, 14.42. Found: C, 54.31; H, 5.41; N, 14.23.

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