Coupling of N-heterocycle-fused enyne aldehydes with γ,δ-unsaturated Fischer carbene complexes

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SUPPLEMENTARY MATERIAL

General Experimental. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Varian 200 MHz or a 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). The following symbols have been used to indicate multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). A Nicolet Perkin-Elmer 1720X spectrometer was used to record the infrared spectra and band positions are reported in reciprocal centimeters (cm^{-1}). Only key diagnostic bands are reported, C-H stretching frequencies in the region 2800-3100 cm^{-1} are not reported. Mass spectra (MS) were obtained at the University of California at Riverside or at the University of Nebraska. Flash column chromatography was performed using thick walled glass columns and "flash grade" silica. Thin layer chromatography was done using precoated 0.25mm silica gel plates purchased from Sorbtech. The relative proportion of solvents in mixed chromatography solvents refers to the volume: volume

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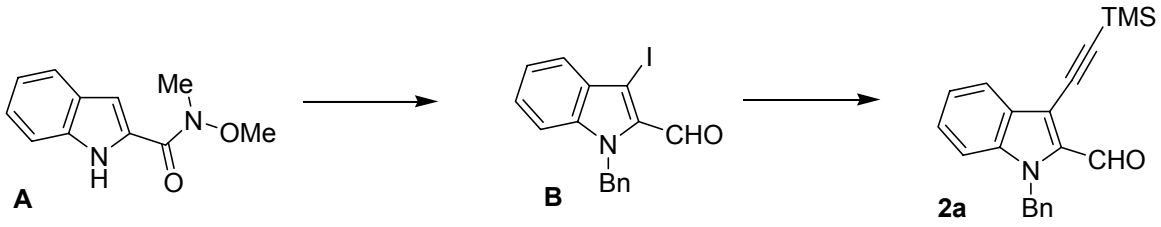
ratio. All commercially available reagents were purchased in reagent grade and used without purification. Diethyl ether, THF and dioxane were distilled from sodium benzophenone ketyl. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of nitrogen.

General Procedure I – Sonogashira coupling. A mixture of iodoaldehyde (1.0 eq), $Pd(PPh_3)_2Cl_2$ (0.05 eq), triphenylphosphine (0.03 eq), terminal alkyne (1.7 eq), and triethylamine (1.7 eq) in THF (sufficient for 0.1M concentration of iodoaldehyde) was stirred for 20 min at room temperature and cuprous iodide (0.1 eq) was then added. After being stirred for 20 h, the solvent was evaporated, and the residue was treated with ethyl acetate, followed by filtration through Celite and evaporation of the solvent on a rotary evaporator. Final purification was achieved by flash chromatography (silica gel; hexane / ethyl acetate mixtures) yielded 660 mg (95%).

General Procedure II – Conversion of diiodoimidazoles to the corresponding monoaldehydes. Ethylmagnesium bromide (1.1 eq of a 1.0M ether solution) was added to a stirred solution of diiodoimidazole derivative (1.0 eq) in anhydrous THF (sufficient for 0.3M concentration of diiodoimidazole derivative) under nitrogen at 0 °C. The mixture was then stirred for 6 h, and N-methyl-N-(2-pyridyl)formamide (1.1 eql) was added, and the mixture was further stirred for 18 h at 25 °C. Saturated aqueous ammonium chloride solution (10 mL) was added and the mixture extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, washed with saturated aqueous ammonium chloride solution (20 mL) and saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. Final purification was achieved by flash chromatography (silica gel; hexane / ethyl acetate mixtures).

SYNTHESIS OF INDOLE DERIVATIVE **2a**



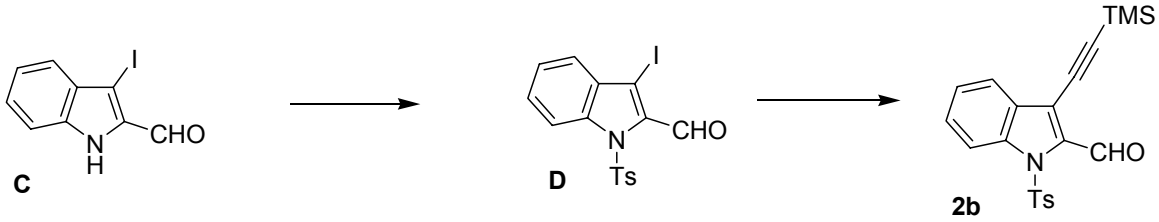
Preparation of **B**. A solution of amide **A** [3] (l.02 g, 5.1 mmol) in anhydrous THF (20 mL) at -30°C was added dropwise to a 1M solution of lithium aluminum hydride in THF (5 mL). The reaction mixture was stirred for 1 h before ice water was added to the solution to destroy the excess hydride. The reaction mixture was evaporated under vacuum, and then was extracted with dichloromethane. The organic fractions were dried over sodium sulfate and the solvent was removed on a rotary evaporator. The residue was dissolved in DMF (30 mL) at 0°C. To this solution was added KOH (0.94 g, 16.8 mmol), followed by the addition of a solution of iodine (l.20 g, 4.8 mmol) in DMF (13mL). After stirring at

[3] Dekhane, M.; Dodd, R. H. *Tetrahedron* **1994**, *50*, 6299-6306.

room temperature for 3 h, to this solution was added benzyl bromide (0.98 g, 5.76 mmol) and tetrabutylammonium iodide (37 mg, 0.1 mmol). The mixture was stirred at room temperature for another 10 h, and then concentrated in vacuo to a total volume of 10 mL. The mixture was diluted with water (50 mL) and extracted with ethyl acetate. The extratct was washed with water and saturated sodium chloride solution, and was dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography on silica gel using hexane: ethyl acetate (6:1) as eluent. After final purification a yellow solid identified as iodoindole-aldehyde **B** (1.50 g, 82%) was obtained.
Iodoaldehyde **B**: ^{1}H NMR ($CDCl_3$): δ 9.99 (s, 1H), 7.61 (d, 1H, J = 8.3 Hz), 7.50-7.10 (m, 6H), 7.08 (dd, 1H, J = 7.8, 2.8 Hz), 5.82 (s, 2H). The spectral data were completely in agreement with those reported in the literature.[4]

Preparation of **2a**. General Procedure I was followed using iodoindole **B** (1.50 g, 4.14 mmol), $(PPh_3)_2PdCl_2$ (0.220 g, 0.32 mmol), trimethylsilylacetylene (0.590 g, 6.00 mmol), triethylamine (0.606 g, 6.00 mmol), and cuprous iodide (0.078 g, 0.40 mmol) in THF (20 mL). After final purification, a yellow solid identified as alkyne-aldehyde **2a** was obtained (1.26 g, 90% yield).
Compound **2a**. ^{1}H NMR ($CDCl_3$): δ 10.2 (s, 1H), 7.84 (d, 1H, J = 8.1 Hz), 7.38-7.02 (m, 8H), 5.80 (s, 2H), 0.29 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 181.9, 139.0, 137.0, 135.6, 128.5, 127.9, 127.8, 127.3, 126.4, 122.1, 121.8, 112.4, 111.0, 103.1, 95.3, 47.9, -0.1; IR (neat): 2149 (w), 1668 (s) cm^{-1}; CI-HRMS: calcd for $C_{21}H_{22}NOSi$ 332.1465, found 332.1468.

SYNTHESIS OF INDOLE DERIVATIVE **2b**.

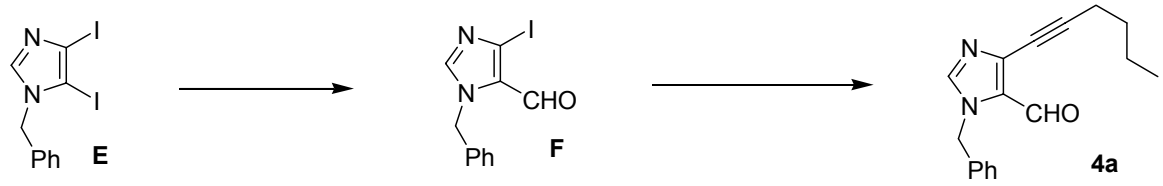


Compound **2b**. To a stirred solution of indole **C** (an intermediate in the previous synthesis) (480 mg, 1.77 mmol) in DMF (15 mL) at 0 ^{o}C was added sodium hydride (59 mg, 2.48 mmol)in three parts. After stirring at 0 ^{o}C for 30 min and room temperature for another 30 min, *p*-toluenesulfonyl chloride (527 mg, 2.76 mmol) was added at 0 ^{o}C. The resulting mixture was stirred for 1 h before it was warmed to room temperature and stirred for 4 h. The solution was concentrated under vacuum to a total volume of 5 mL and then diluted with water (30 mL). The solution was extracted with ethyl acetate. The combined organic fraction was washed with water and saturated sodium chlorde solution, and then dried over sodium sulfate. The resulting solution was dried *in vacuo*. The residue was briefly purified by flash chromatography on silica gel using (6:1) hexane/ethyl acetate as the eluent to get rid of the unreacted *p*-toluenesulfonyl chloride. A yellow solid, identified as protected indole **D** (520 mg, 69%) was obtained. This

[4] Zhang, H.; Larock, R. L. *J. Org. Chem.* **2002**, *67*, 7948.

product was used immediately in the next step. General Procedure I was followed using **D** (520 mg, 1.22 mmol), $(PPh_3)_2PdCl_2$ (60 mg, 0.090 mmol), triphenyphosphine (11 mg, 0.04 mmol), trimethylsilylacetylene (140 mg, 1.6 mmol), triethylamine (150 mg, 1.5 mmol), and cuprous iodide (20 mg, 0.1 mmol) in THF (10 mL). After final purification, a light brown solid identified as alkyne-aldehyde **2b** was obtained (440 mg, 91% yield). Indole **2b**. ^{1}H NMR. ($CDCl_3$): δ 10.44 (s, 1H), 8.25 (d, 1H, J = 8.8 Hz), 7.74 (br d, 3H, J = 8.4 Hz), 7.56 (ddd, 1H, J = 8.8, 7.3, 1.5 Hz), 7.38 (t, 1H, J = 7.3 Hz), 7.20 (br d, 2H, J = 8.1 Hz), 2.34 (s, 3 H), 0.31 (s, 9 H); ^{13}C NMR ($CDCl_3$): δ 180.9, 145.5, 137.5, 137.3, 134.6, 129.7, 129.3, 129.2, 126.8, 124.7, 122.1, 115.4, 115.2, 106.6, 94.6,21.4, -0.4; IR (neat): 2156 (w), 1683 (s) cm^{-1}; CI-HRMS: calcd for $C_{21}H_{22}NO_3SSi$ 396.1084, found 332.1082.

SYNTHESIS OF ALKYNYLIMIDAZOLE **4a**.

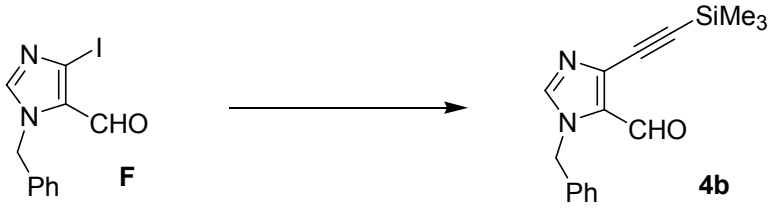


Compound **F**. General Procedure II was followed using ethylmagnesium bromide (2.67 mL of a 1.0M ether solution, 2.67 mmol), diiodoimidazole **E**[5] (1.000 g, 2.43 mmol), and N-methyl-N-(2-pyridyl)formamide (0.32 mL, 2.683mmol) in anhydrous THF (10 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 2:1) afforded aldehyde **F** (710 mg, 93%) as a yellow oil.
Compound **F**. ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1H), 7.63 (s, 1H), 7.40-7.34 (m, 3H), 7.22 (d, 2H, J = 6.4 Hz), 5.51 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 181.0, 144.6, 144.6, 135.0, 129.2, 129.1, 128.7, 127.9, 101.2, 50.5.

Compound **4a**: General Procedure I was followed using aldehyde **F** (814 mg, 2.61 mmol), $Pd(PPh_3)_2Cl_2$ (146 mg, 0.21 mmol), triphenylphosphine (27 mg, 0.10 mmol), 1-hexyne (0.60 mL, 5.19 mmol), triethylamine (0.72 mL, 5.18 mmol), and cuprous iodide (50 mg, 0.26 mmol) in THF (10 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 3:1) yielded 660 mg (95%) of alkyne-aldehyde **4a** as an brown oil.
Alkyne-aldehyde **4a**: ^{1}H NMR ($CDCl_3$): δ 9.82 (s, 1H), 7.63 (s, 1H), 7.28-7.13 (m, 5H), 5.41 (s, 2H), 2.40 (t, 2H, J = 6.8 Hz), 1.47 (m, 4H), 0.88 (t, 3H, J = 7/2 Hz); ^{13}C NMR ($CDCl_3$): δ 179.5, 135.2, 128.8, 128.7, 128.2, 128.2, 127.4, 127.2, 96.6, 71.8, 50.3, 30.0, 21.8, 19.0, 13.3; IR (neat): 2234 (m), 1664 (s) cm^{-1}; MS (EI): 266 (4), 224 (50), 91 (100); HRMS: calcd for $C_{17}H_{18}N_2O$ 266.1419, found 266.1414.

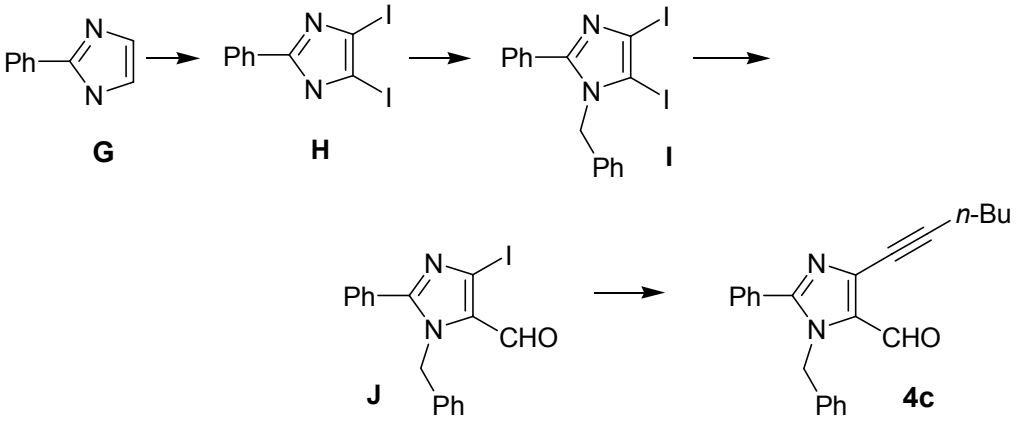
[5] Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1-7.

SYNTHESIS OF ALKYNYLIMIDAZOLE **4b**.



General Procedure I was followed using iodo-aldehyde **F** (100 mg, 0.32 mmol), $Pd(PPh_3)_2Cl_2$ (31 mg, 0.044 mmol), triphenylphosphine (7 mg, 0.028 mmol), (trimethylsilyl)acetylene (0.076 mL, 1.05 mmol), triethylamine (0.149 mL, 1.07 mmol), and cuprous iodide (10 mg, 0.055 mmol) in THF (4 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 3:1) yielded 70 mg (78%) of alkyne-aldehyde **xx** as a brown oil.
Alkynylimidazole **4b**: ^{1}H NMR ($CDCl_3$): δ 9.90 (s, 1H), 7.59 (s, 1H), 7.35-7.27 (m, 3H), 7.19-7.15 (m, 2H), 5.460 (s, 2H), 0.239 (s, 9H); ^{13}C NMR: δ 179.7, 142.8, 142.7, 137.6, 135.3, 132.2, 129.2, 128.7, 127.9, 101.7, 95.2, 50.7, -0.21; IR (neat): 2165 (m), 1674 (s) cm^{-1}; Mass Spec (EI): 288 (11), 287 (16), 197 (7), 91 (100); HRMS: calcd for $C_{16}H_{18}N_2OSi$ 288.1188, found 288.1186.

SYNTHESIS OF THE 2-PHENYLIMIDAZOLE DERIVATIVE **4c**



Compound **H**. To an aqueous solution of 2-phenylimidazole (**G**) (3.6 g, 24.97 mmol) in water (17 mL) at 50 °C was added at room temperature $KICl_2$ (31.25 mL of a 2.0M aqueous solution, 62.5 mmol). After stirring at room temperature for 6 h, 2M aqueous sodium hydroxide solution was added to give a clear solution which in turn was neutralized to pH 7 with concentrated hydrochloric acid, resulting in the precipitation of 4,5-diiodo-2-phenylimidazole (**H**) (5.5 g, 56% yield).

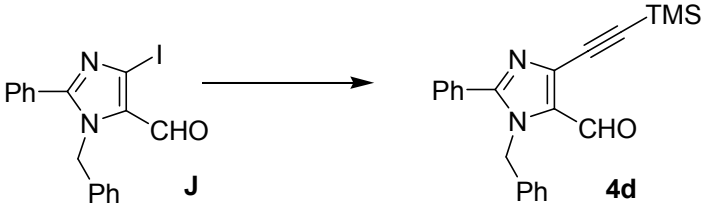
Compound **I**. Crude compound **H** (600 mg, 1.51 mmol) was added to a stirred suspension of sodium hydride (100 mg of a 40% oil dispersion, 1.66 mmol) in DMF (3 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature and recooled to 0 °C, benzyl bromide (0.198 mL, 1.66 mmol) was added dropwise. The reaction was then allowed to stir for 5 h at room temperature. The resultant suspension was diluted with saturated aqueous ammonium chloride solution (10 mL) at 0 °C and extracted with

dichloromethane (3 x 40 mL). The combined extracts were washed with saturated aqueous ammonium chloride solution (30 mL) and saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. Flash chromatography (silica gel; hexane / ethyl acetate, 4:1) afforded diiodoimidazole **I** (702 mg, 95%).
Diiodoimidazole **I**. ^{1}H NMR ($CDCl_3$): δ 7.46-7.32 (m, 8H), 6.99 (d, 2H, J = 6.8 Hz), 5.31 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 153.3, 135.9, 129.8, 129.6, 129.1, 128.8, 128.7, 128.0, 126.1, 96.8, 84.9, 52.6.

Aldehyde **J**. General Procedure II was followed using ethylmagnesium bromide (2.22 mL of a 1.0M ether solution, 2.22 mmol), diiodoimidazole **I** (1.035 g, 2.12 mmol), and N-methyl-N-(2-pyridyl)formamide (0.255 mL, 2.12 mmol) in anhydrous THF (9 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 4:1) afforded aldehyde **J** (620 mg, 75%) as a yellow oil.
Aldehyde **J**. ^{1}H NMR ($CDCl_3$): δ 9.63 (s, 1H), 7.37 (m, 8H), 6.96 (m, 2H), 5.62 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 180.8, 156.2, 136.6, 130.8, 129.4, 129.0, 128.1, 126.9, 126.2, 102.5, 82.3, 49.5; IR (neat): 1668 (s) cm^{-1}.

Alkynylimidazole **4c**. General Procedure I was followed using iodoaldehyde **J** (216 mg, 0.56 mmol), $Pd(PPh_3)_2Cl_2$ (31 mg, 0.044 mmol), triphenylphosphine (6 mg, 0.028 mmol), 1-hezyne (0.128 mL, 1.11 mmol), triethylamine (0.154 mL, 1.71 mmol) and cuprous iodide (18 mg, 0.094 mmol) in THF (4 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 5:1) yielded 156 mg (82%) of alkynylimidazole **4c** as an brown oil.
Alkynylimidazole **4c**. ^{1}H NMR ($CDCl_3$): δ 9.90 (s, 1H), 7.55 (dd, 2H, J = 9.8, 1.6 Hz), 7.48-7.38 (m, 3H), 7.30-7.22 (m, 3H), 6.96 (d, 2H, J = 6.8Hz), 5.60 (s, 2H), 2.49 (t, 2H, J = 7.2 Hz), 1.62 (m, 2H), 1.50 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 179.3, 153.9, 138.8, 136.8, 132.4, 130.5, 129.4, 129.0, 128.9, 128.5, 127.8, 126.2, 97.3, 72.0, 49.6, 30.4, 22.2, 19.4, 13.7; IR (neat): 2237 (m), 1669 (s) cm^{-1}; MS (EI): 342 (7), 300 (46), 91 (100); HRMS: calcd for $C_{23}H_{22}N_2O$ 342.1732, found 342.1721.

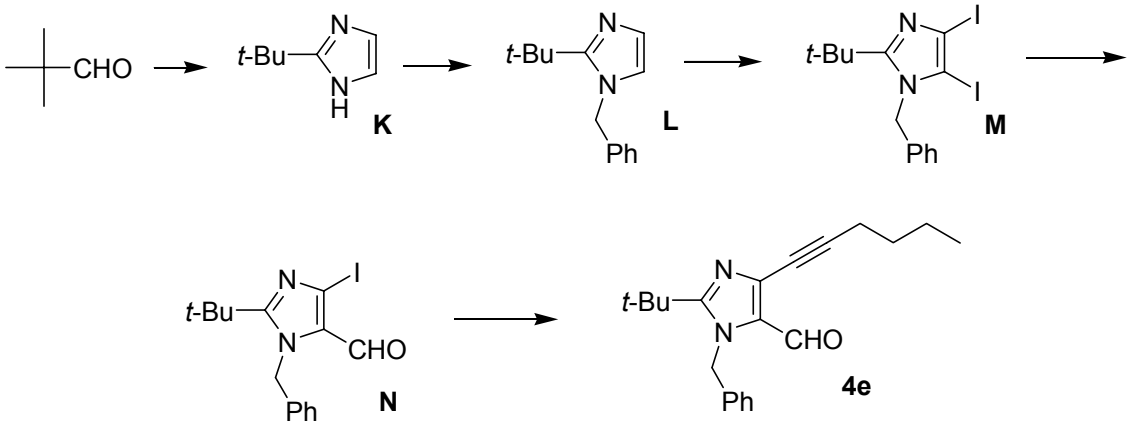
SYNTHESIS OF THE 2-PHENYLIMIDAZOLE DERIVATIVE **4d.**



Alkynylimidazole **4d**. General Procedure I was followed using iodoaldehyde **J** (455 mg, 1.17 mmol), $Pd(PPh_3)_2Cl_2$ (66 mg, 0.094 mmol), triphenylphosphine (12 mg, 0.047 mmol), trimethylsilylacetylene (0.169 mL, 2.29 mmol), triethylamine (0.33 mL, 2.27 mmol), and cuprous iodide (12 mg, 0.12 mmol) in THF (10 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 8:1) yielded 150 mg (72%) of alkynylimidazole **4d** as an brown oil.

Alkynylimidazole **4d**. ^{1}H: 9.93 (s, 1H), 7.56-7.54 (m, 2H), 7.50-7.40 (m, 3H), 7.30-7.25 (m, 3H), 6.96-6.94 (m, 2H), 5.61 (s, 2H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 179.3, 154.1, 137.7, 136.7, 133.3, 130.7, 129.5, 129.03, 128.99, 128.5, 128.0, 126.2, 101.9, 95.4, 49.7, -0.2; IR (neat): 2163 (m), 1670 (s) cm^{-1}; MS (EI): 358 (16), 267 (8), 91 (100), 73 (10); HRMS: calcd for $C_{22}H_{22}N_2OSi$ 358.1501, found 358.1509.

SYNTHESIS OF THE 2-t-BUTYLIMIDAZOLE **4e**.



t-butulimidazole (**K**).[6] To a solution of pivaladehyde (2.0 g, 23 mmol) in methanol (20 mL) was added a solution of glyoxal (3.39 g of the commercial 40% aqueous solution, 23 mmol) in water (50 mL). The solution was cooled to 0 °C and 28% aqueous ammonia solution (11.44 g, 188 mmol) was added. After the mixture was stirred for 15 h, the white solid precipitate was collected by filtration. The solid was dried in air to yield 2.0 g (69%) of *t*-butylimidazole (**K**).

Compound **L-M**. To a solution of 2-t-butylimidazole (**K**) (3.125 g, 24.98 mmol) in water (83 mL) at 50 °C was added a room temperature 2.0M aqueous solution of $KICl_2$ (31 mL, 6.25 mmol, 2.5 eq). After stirring at room temperature for 6 h, 2.0M aqueous sodium hydroxide solution (200 mL) was added to give a clear solution. This solution was neutralized to pH 7 with concentrated aqueous hydrochloric (28 mL), resulting in the precipitation of 4,5-diiodo-2-phenylimidazole (**L**) (9.0 g, 95%) which was subsequently isolated as a red solid by filtration and used immediately in the next step of the reaction. Compound **L** (1.00 g, 2.65 mmol) was added to a stirred suspension of sodium hydride (0.175 g of a 40% oil dispersion, 2.92 mmol) in DMF (5.3 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature and recooled to 0 °C, benzyl bromide (0.345 mL, 2.90 mmol) was added dropwise. The reaction was then allowed to stir for 5 h at room temperature. The resultant suspension was diluted with saturated aqueous ammonium chloride solution (14 mL) at 0 °C and extracted with dichloromethane (3 x 40 mL). The combined extracts were washed with saturated aqueous ammonium chloride solution (30 mL) and saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated on a roatary evaporator. Flash chromatography

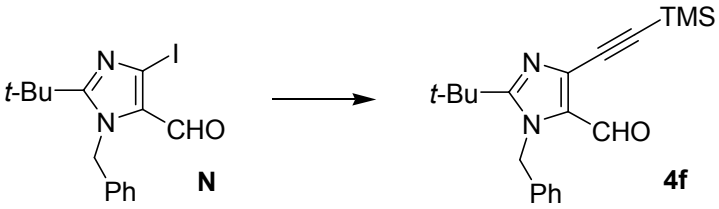
[6] This is a literature procedure. Ikezaki, A.; Nakamura, M. *Inorg. Chem.* **2002**, *41*, 6225-6236.

(silica gel; hexane / ethyl acetate, 6:1) afforded diiodoimidazole **M** (1.1 g, 88%) as a brown syrup.
Diiodoimidazole **M**. ^{1}H NMR ($CDCl_3$): δ 7.32 (m, 3H), 6.87 (d, 2H, J = 6.8 Hz), 5.45 (s, 2H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 160.1, 136.2, 129.0, 127.7, 125.7, 94.8, 84.9, 52.9, 34.6, 30.0.

Aldehyde **N**. General Procedure II was followed using ethylmagnesium bromide (0.939 mL of a 3.0M ether solution, 2.817 mmol), diiodoimidazole **N** (1.2 g, 2.56 mmol), and N-methyl-N-(2-pyridyl)formamide (0.31 mL, 2.60 mmol) in anhydrous THF (11 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 7:1) afforded aldehyde **N** (836 mg, 88%) as a yellow oil.
Aldehyde **N**. ^{1}H NMR ($CDCl_3$): δ 9.48 (s, 1H), 7.36-7.20 (m, 3H), 6.85 (d, 2H, J = 8 Hz), 5.75 (s, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 180.4, 163.4, 136.8, 130.3, 129.1, 128.8, 127.5, 126.8, 125.2, 101.5, 49.7, 34.6, 30.0. IR (neat): 1670 (s) cm^{-1}.

Alkynylimidazole **4e**. General Procedure I was followed using aldehyde **N** (344 mg, 0.96 mmol), $Pd(PPh_3)_2Cl_2$ (54 mg, 0.077 mmol), triphenylphosphine (10 mg, 0.028 mmol), 1-hexyne (0.022 mL, 1.93 mmol), triethylamine (0.27 mL, 1.712 mmol), and cuprous iodide (18 mg, 0.096 mmol) in THF (6 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 8:1) yielded 201 mg (76%) of alkynylimidazole **4e** as an brown oil.
Alkynylimidazole **4e**. ^{1}H NMR ($CDCl_3$): δ 9.75 (s, 1H), 7.27 (m, 2H), 7.20 (m, 1H), 6.84 (d, 2H, J = 8.0 Hz), 5.73 (s, 2H), 2.46 (t, 2H, J = 7.2 Hz), 1.60 (m, 2H), 1.462 (m, 2H), 1.371 (s, 9H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 178.9, 161.2, 137.4, 137.1, 133.0, 128.8, 127.4, 125.3, 96.9, 72.2, 49.9, 34.3, 30.5, 29.8, 22.2, 19.5, 13.7; IR (neat): 2239 (m), 1670 (m) cm^{-1}; MS (EI): 322 (3), 280 (36), 91 (100); HRMS: calcd for $C_{21}H_{36}N_2O$ 322.2045, found 322.2040.

SYNTHESIS OF THE *t*-BUTYLIMIDAZOLE **4f**.

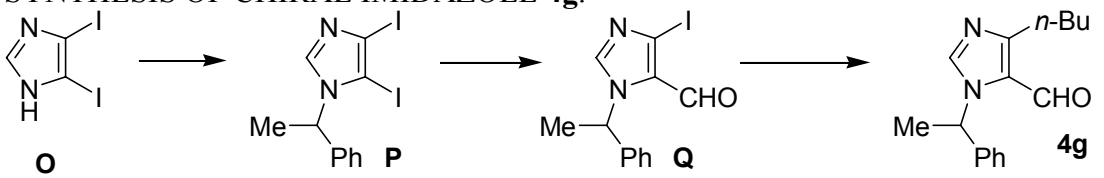


N **4f**

Alkynylimidazole **4f**. General Procedure I was followed using aldehyde **N** (257 mg, 0.70 mmol), $Pd(PPh_3)_2Cl_2$ (39 mg, 0.056 mmol 6), triphenylphosphine (7 mg, 0.028 mmol), trimethylsilylacetylene (0.098 mL, 1.40 mmol), triethylamine (0.193 mL, 1.39 mmol), and cuprous iodide (13 mg, 0.070 mmol) in THF (6 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 7:1) yielded 203 mg (86%) of alkynylimidazole **4f** as an brown oil.
Alkynylimidazole **4f**. ^{1}H NMR ($CDCl_3$): δ 9.79 (s, 1H), 7.26-7.24 (m, 3H), 6.83 (d, 2H, J = 8.0 Hz), 5.74 (s, 2H), 1.37 (s, 9H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 179.0, 161.3, 136.9, 136.2, 134.0, 128.8, 127.5, 125.2, 101.5, 95.6, 50.0, 34.4, 29.8, -0.2; IR (neat):

2163 (m), 1669 (s) cm^{-1}; MS (EI): 338 (39), 91 (100); HRMS: calcd for $C_{20}H_{26}N_2OSi$ 338.1814, found 338.1810.

SYNTHESIS OF CHIRAL IMIDAZOLE **4g**.



Diiodoimidazole **P**. 4,5-diiodoimidazole (**O**)[7] (200 mg, 0.631 mmol) was added to a stirred suspension of sodium hydride (55 mg, 40% oil dispersion, 0.694 mmol) in DMF (1 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature and recooled to 0 °C, (1-bromoethyl)benzene (0.094 mL, 0.6943 mmol) was added dropwise. The reaction was then allowed to stir for 15 h at room temperature. The resulting suspension was diluted with saturated aqueous ammonium chloride solution (10 mL) at 0 °C and then extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with saturated aqueous ammonium chloride solution (20 mL) and saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, filtered, and concentrated on a totary evaporator. Flash chromatography (silica gel; hexane / ethyl acetate, 3:1) afforded diiodoimidazole **P** (178 g, 67%).
Diiodoimidazole **P**. ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1H), 7.36-7.26 (m, 3H), 7.12 (d, 2H, J = 6.8 Hz), 5.40 (q, 1H, J = 7.2 Hz), 1.84 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 140.1, 139.5, 139.4, 129.2, 128.5, 126.5, 96.6, 59.9, 22.2.

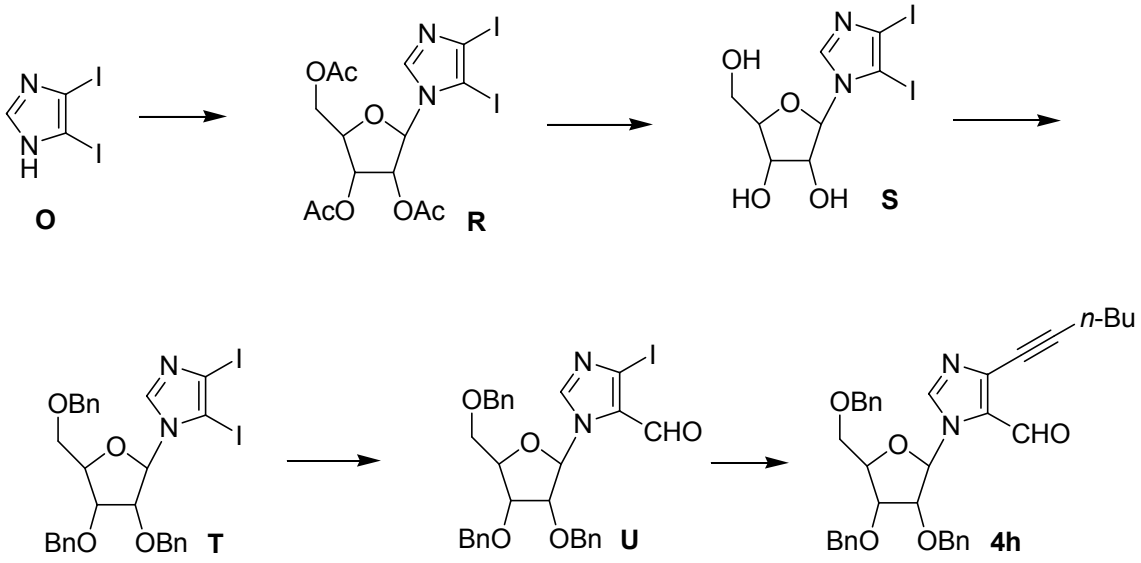
Aldehyde **Q**. General Procedure II was followed using ethylmagnesium bromide (1.46 mL of a 0.82M ether solution, 1.10 mmol), diidoimidazole **P** (360 mg, 1.09 mmol), and N-methyl-N-(2-pyridyl)formamide (0.13 mL, 1.09 mmol) in anhydrous THF (4.5 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 2:1) afforded aldehyde **Q** (140 mg, 39%) as a yellow oil.
Aldehyde **Q**. ^{1}H NMR ($CDCl_3$): δ 9.62 (s, 1H), 7.70 (s, 3H), 7.38-7.30 (m, 3H), 7.22 (d, 2H, J = 6.4 Hz), 6.35 (q, 1H, J = 6.8 Hz), 1.84 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 181.1, 142.4, 142.4, 129.0, 128.9, 128.5, 126.6, 102.1, 56.0, 21.6.

Alkynylimidazole **4g**. General Procedure I was followed using aldehyde **Q** (169 mg, 0.52 mmol), $Pd(PPh_3)_2Cl_2$ (29 mg, 0.042 mmol), triphenylphosphine (5 mg, 0.021 mmol), 1-hexyne (0.12 mL, 1.04 mmol), triethylamine (0.144 mL, 1.04 mmol) and cuprous iodide (10 mg, 0.052 mmol) in THF (4 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 3:1) yielded 130 mg (89%) of alkynylimidazole **4g**.
Alkynylimidazole **4g**. ^{1}H NMR ($CDCl_3$): δ 9.84 (s, 1H), 7.74 (s, 1H), 7.38-7.10 (m, 5H), 6.30 (q, 1H, J = 6.8 Hz), 2.44 (t, 2H, J = 6.8 Hz), 1.83 (d, 3H, J = 6.8 Hz), 1.52 (m, 4H),

[7] Garden, S. J.; Torres, J. C.; de Souza Melo, S. C.; Lima, A. S.; Pinto, A. C.; Lima, E. L. S. *Tetrahedron Lett.* **2001**, *42*, 2089-2092.

0.92 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 179.9, 140.1, 129.0, 128.4, 126.6, 96.9, 71.1, 60.0 56.2, 30.4, 22.1, 21.7, 19.3, 13.7; IR (neat): 2234 (m), 1670 (s) cm^{-1}; MS (EI): 280 (2), 134 (11), 105 (100), 77 (38); HRMS: calcd for $C_{18}H_{20}N_2O$ 280.1576, found 280.1581.

SYNTHESIS OF THE RIBOSYLATED ALKYNE-ALDEHYDE **4h**.



Diiodoimidazole **R**. To a stirred solution of tetraacetyl-ribofuranose (264 mg, 0.83 mmol) and diiodoimidazole[7] (400 mg, 1.24 mmol) in anhydrous acetonitrile (7 mL) was added N,O-bis(trimethylsilyl)acetamide (1.43 mL, 5.82 mmol). The reaction mixture was stirred at reflux for 1 h, then cooled to 0 °C. Trimethylsilyl triflate (0.34 mL, 1.83 mmol) was added dropwise under stirring and the solution was stirred at 65 °C for 2 h. The reaction was quenched with a cold saturated aqueous solution of sodium bicarbonate (10 mL). The combined organic phases were washed with saturated aqueous of sodium bicarbonate solution (2x 10 mL) and saturated aqueous sodium chloride solution (2 x 10 mL), and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography using hexane / ethyl acetate as the eluent (1:1) to give nucleoside derivative **R** (354 mg, 74%).
Nucleoside **R.** ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 5.76 (d, 1H, J = 5.6 Hz), 5.44 (t, 1H, J = 4.8 Hz), 5.31 (t, 1H, J = 4.8 Hz), 4.35 (m, 1H), 4.28 (d, 2H, J = 2.4 Hz), 2.05 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 170.1, 169.4, 169.0, 139.3, 97.5, 90.4, 80.8, 80.2, 74.1, 69.8, 62.6, 20.8, 20.5, 20.4; IR (neat): 1747 (s) cm^{-1}.

Nucleoside **S**. Nucleoside peracetate **R** (2.43g, 4.19 mmol) was dissolved in 2.0M ammonia/methanol solution (30 mL) at 0 °C. The solution was stirred for 30 min at 0 °C and warmed to room temperature and stirred for 3 days. The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography on silica gel using chloroform: methanol (9:1) as the eluent. A white solid identified as nucleoside **S** was obtained (1.72 g, 90% yield).

Nucleoside **S**. ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 1H), 5.68 (d, 1H, J = 4.8 Hz), 4.44 (t, 1H, J = 4.8 Hz), 4.35 (t, 1H, J = 4.8Hz), 4.08 (m, 1H), 3.85 (dd, 1H, J = 12.0, 2.8 Hz), 3.77 (dd, 1H, J = 12.0, 2.8 Hz), 3.20 (br s, 3H); ^{13}C NMR ($CDCl_3$): δ 141.3, 93.9, 86.2, 76.7, 70.8, 64.1, 61.8; IR (neat): 3600-3000 (br) cm^{-1}.

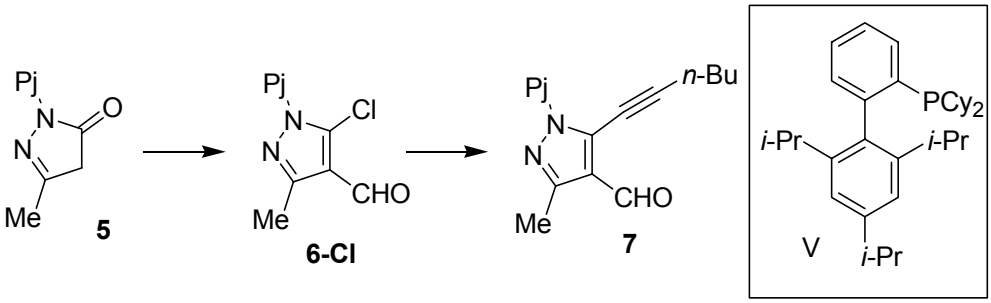
Perbenzylated nucleoside **T**. A solution of nucleoside **S** (1.72 g, 3.79 mmol) in THF (28 mL) was added to a stirred suspension of sodium hydride (0.637 g of a 60% oil dispersion, 15.92 mmol) in THF (18 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature and recooled to 0 °C, benzyl bromide (1.85 mL, 15.55 mmol) was added dropwise followed by tetrabutylammonium iodide (0.14 g, 0.38 mmol). The reaction was then allowed to stir for 1 day at room temperature. The resulting suspension was diluted with saturated aqueous ammonium chloride solution (14 mL) at 0 °C and extracted with dichloromethane (3 x 40 mL). The combined extracts were washed with saturated aqueous ammonium chloride solution (30 mL) and saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated on a rotary evaporator. Flash chromatography (silica gel; hexane / ethyl acetate, 2:1) afforded perbenzylated nucleoside **T CC** (2.7 g, 93%) as a colorless syrup.
Perbenzylated nucleoside **T**. ^{1}H NMR ($CDCl_3$): δ 8.04 (s, 1H), 7.38-7.25 (m, 15H), 5.86 (d, 1H, J = 3.6 Hz), 4.70 (d, 1H, J = 12.0 Hz), 4.66 (d, 1H, J = 12.0 Hz), 4.60 (d, 1H, J = 12.0 Hz); 4.57 (d, 1H, J = 12.0 Hz), 4.52 (d, 1H, J = 12.0 Hz), 4.48 (d, 1H, J = 12.0 Hz), 4.364 (ddd, 1H J = 5.0, 2.4, 2.4 Hz), 4.19 (dd, 1H, J = 9.6, 5.0 Hz), 4.15 (dd, 1H, J = 9.6, 3.6 Hz), 3.78 (dd, 1H, J = 11.2, 2.4 Hz), 3.56 (dd, 1H, J = 11.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$): δ 140.3, 137.3, 137.3, 137.0, 128.7, 128.6, 128.2, 128.1, 128.1, 128.03, 127.98, 127.89, 96.9, 92.1, 82.0, 81.1, 80.1, 75.8, 73.6, 72.9, 72.7, 68.5.

Nucleoside aldehyde **U**. General Procedure II was followed using ethylmagnesium bromide (0.468 mL of 3.0M ether solution, 1.40 mmol), perbenzylated nucleoside **T** (970 mg, 1.27 mmol), and N-methyl-N-(2-pyridyl)formamide (0.152 mL, 1.276 mmol) in anhydrous THF. Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 2:1) afforded nucleoside aldehyde **U** (390 mg, 46%) as a yellow syrup and afforded 50 mg of recovered starting material.
Nucleoside aldehyde **U**. ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1H), 8.61 (s, 1H), 7.41-7.18 (m, 15H), 6.50 (s, 1H), 4.98 (d, 1H, J = 12.0 Hz), 4.88 (d, 1H, J = 12.0 Hz), 4.60 (d, 1H, J = 12.0 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.40 (d, 1H, J = 11.6 Hz), 4.39 (ddd, 1H, J = 4.8, 2.4, 2.4 Hz), 4.27 (d, 1H, J = 11.6 Hz), 4.18 (dd, 1H, J = 8.4, 4.8 Hz), 3.97 (d, 1H, J = 4.8 Hz), 3.92 (dd, 1H, J = 11.6, 2.4 Hz), 3.62 (dd, 1H, J = 11.6, 2.4 Hz); ^{13}C NMR ($CDCl_3$): δ 181.1, 143.6, 137.9, 137.5, 137.4, 128.83, 128.79, 128.76, 128.62, 128.60, 128.41, 128.26, 128.19, 128.09, 127.9, 102.5, 89.9, 81.1, 80.2, 74.4, 73.6, 72.8, 72.3, 67.1; IR (neat): 1669 (s) cm^{-1}.

Alkynylimidazole **4h**. General Procedure I was followed using bucleoside aldehyde **U** (313 mg, 0.48 mmol), $Pd(PPh_3)_2Cl_2$ (27 mg, 0.038 mmol), triphenylphosphine (5 mg, 0.019 mmol), 1-hexyne (0.11mL, 0.95 mmol), triethylamine (0.134 mL, 0.96 mmol), and cuprous iodide (9 mg, 0.048 mmol) in THF (4 mL). Final purification using flash chromatography (silica gel; hexane / ethyl acetate, 3:1) yielded 250 mg (86%) of alkynylimidazole **4h** as an brown oil.

Alkynylimidazole **4h**. ^{1}H NMR ($CDCl_3$): δ 9.89 (s, 1H), 8.51 (s, 1H), 7.40-7.20 (m, 15H), 6.48 (s, 1H), 4.98 (d, 1H, J = 12.4 Hz), 4.87 (d, 1H, J = 12.4 Hz), 4.60 (d, 1H, J = 11.6 Hz), 4.51 (d, 1H, J = 11.6 Hz), 4.40 (d, 1H, J = 11.6 Hz), 4.39 (ddd, 1H, J = 8.8, 2.4, 2.4 Hz), 4.27 (d, 1H, J = 11.6 Hz), 4.19 (dd, 1H, J = 8.8, 4.4 Hz), 3.96 (d, 1H, J = 4.4 Hz), 3.93 (dd, 1H, J = 10.8, 2.4 Hz); 3.64 (dd, 1H, J = 10.8, 2.4 Hz); 2.48 (t, 2H, J = 7.2 Hz), 1.63 (quintet, 2H, J = 7.2 Hz), 1.49 (sextet, 2H, J = 7.2 Hz), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 179.5, 141.5, 137.9, 137.50, 137.48, 128.80, 128.60, 128.58, 128.43, 128.20, 128.15, 128.08, 127.9, 97.3, 89.9, 81.1, 80.2, 74.5, 73.6, 72.7, 72.2, 72.1, 67.3, 30.5, 22.2, 19.4, 13.8; IR (neat): 2234 (m), 1667 (s) cm^{-1}; MS (FAB): 580 (M+2H, 37), 579 (M+H, 62), 324 (68), 181 (66), 154 (100), 136 (90); HRMS: calcd for $C_{36}H_{39}N_2O_5$ 579.2859, found 579.2862.

SYNTHESIS OF THE PYRAZOLE DERIVATIVES



Aldehyde **6**. A solution of 3-methyl-1-phenyl-2-pyrazolin-5-one (**5**) (2.0 g, 11.48 mmol) in DMF (5.7 mL) was cooled to 0 °C in an ice bath, then phosphorus oxychloride (2.3 mL, 34.44mmol) was added dropwise at such a rate as to maintain the temperature between 10-20 °C. The reaction mixture was heated at 100 °C for 90 min after completion of the addition. The mixture was then poured into ice-water (100 mL) and the resulting mixture allowed to stand overnight at 25 °C. The solid product thus obtained was filtered, washed with water, dried over sodium sulfate. Final purification was achieved by flash chromatography (silica gel, hexane / ethyl acetate 6:1) to give 1.35 g of aldehyde **6** in 53 % yield.
Aldehyde **6**. ^{1}H NMR ($CDCl_3$): δ 9.92 (s, 1H), 7.51-7.43 (m, 5H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 183.8, 151.7, 137.0, 133.4, 129.3, 129.2, 125.2, 117.4, 13.8. The spectral data were in agreement with those previously reported for this compound.[8]

Alkynylpyrazole **7**. A mixture of aldehyde **6** (300 mg, 1.347 mmol), $PdCl_2(CH_3CN)_2$ (28 mg, 0.108 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-I-propyl-1,1'-biphenyl (ligand **II**) (19 mg, 0.040 mmol), 1-hexyne (0.20mL, 1.76 mmol), and cesium carbonate (1.141 g, 1.76 mmol) in acetonitrile (5 mL) was stirred for 3 h at 85 °C . The solvent was evaporated, and the residue was treated with ethyl acetate. Filtration through Celite and evaporation of the solvent afforded a liquid residue which was purified by flash

[8] Barreiro, E. J.; Camara, C. A.; Verli, H.; Brazil-Mas, L.; Castro, Newton G.; Cintra, W. M.; Aracava, Y.; Rodrigues, C. R.; Fraga, Carlos A. M. *J. Med. Chem.* **2003**, *46*, 1144-1152.

chromatography (silica gel; hexane / ethyl acetate, 6:1) yielded 320 mg (88%) of alkynylpyrazole **7**.

Alkynylpyrazole **7**. ^{1}H NMR ($CDCl_3$): δ 10.03 (s, 1H), 7.73 (d, 2H, J = 8.0 Hz), 7.46 (t, 2H, J = 8.0 Hz), 7.38 (t, 1H, J = 8.0 Hz), 2.53 (s, 3H), 2.46 (t, 2H, J = 7.2 Hz), 1.56 (quintet, 2H, J = 7.2 Hz), 1.40 (sextet, 2H, J = 7.2 Hz), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 185.4, 150.7, 139.0, 131.7, 129.1, 128.4, 123.7, 123.5, 104.0, 67.9, 30.1, 22.1, 19.5, 13.6; IR (neat): 2235 (m), 1682 (s) cm^{-1}; MS (EI): 266 (6), 265 (10), 251 (8), 237 (20), 224 (100), 195 (11), 154 (5), 135 (20), 77 (11); HRMS: calcd for $C_{17}H_{18}N_2O$ 266.1419, found 266.1406.