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Direct approaches to annulated indoles. A formal total synthesis of 0231B

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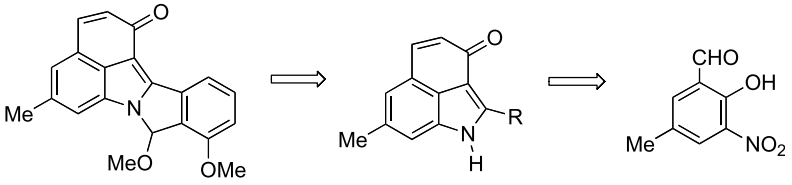
Abstract—An advanced intermediate in the Nakatsuka synthesis of 0231B was prepared using a fluoride-mediated indole formation in the key step. Both palladium-based approaches and hydride-based approaches failed to generate the indole.

1. Introduction

In 2001 the structure of 0231B (**1**), a novel inhibitor of 3a-hydroxysteroid dehydrogenase, was reported from *Streptomyces* sp. HKI0231.[1] Recently, Nakatsuka reported a clever synthesis of **1** utilizing a novel Friedel-Crafts alkylation reaction.[2] Because compounds that inhibit this enzyme may be useful leads for new anti-inflammatory agents, we developed a synthetic approach via **2** beginning with known aldehyde[3] **3**. We report herein a concise preparation of **2b**, a key intermediate in Nakatsuka's synthesis, from **3**.



In our first approach, we envisioned constructing a 2,3,4,6-tetrasubstituted indole from, which the enone moiety could be generated by way of an intramolecular aldol reaction. As a model system we decided to construct **2a**. As shown in Scheme 1, aldehyde **3**, prepared in one step from commercially available starting materials, underwent reductive acetylation (Pd/C, H_2, Ac_2O) followed by conversion of the phenol into a triflate to provide triflate **4** in 70% yield from **3**. Triflate **4** was subjected to a Sonogashira coupling using the method of Wang[4] to afford aldehyde **5** in 86% yield.

Attempts to convert acetylene **5** into an indole using palladium chloride (10 mol%) in boiling acetonitrile failed, despite close literature precedent.[5] Using different palladium catalysts was not effective. Both NMR and thin-layer chromatography indicated that a complex mixture of products had been produced. Base mediated indole formation methods (KH/NMP and *t*-BuOK/NMP) also failed.[6] Fortunately, treatment of acetylene **5** with tetrabutylammonium fluoride[7] in THF at reflux provided indole **6** in 67% yield. Surprisingly, acetylation of **6** using a variety of Lewis acids ($AlCl_3$, $SnCl_4$, Et_2AlCl) and acetylating agents (AcCl, Ac_2O, CH_3CN) afforded at best a 46% yield of keto aldehyde **7**.[8] This modest yield may be related to Lewis acid coordination to the aldehyde, which would be expected to attenuate the reactivity of the indole towards electrophiles. Steric hindrance from the phenyl group at C-2 may also have been a factor. Intramolecular aldol condensation using potassium *tert*-butoxide in THF at ambient temperature afforded enone **2a**; however, the aldol reaction was not reproducible upon scale up beyond

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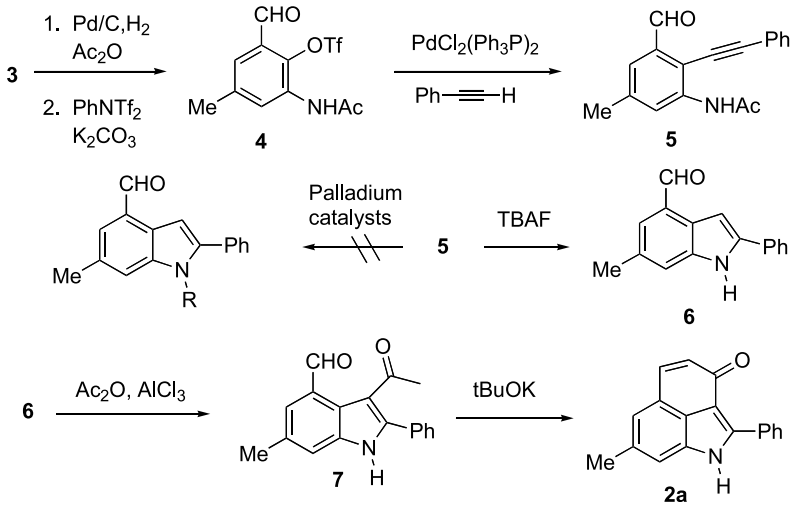
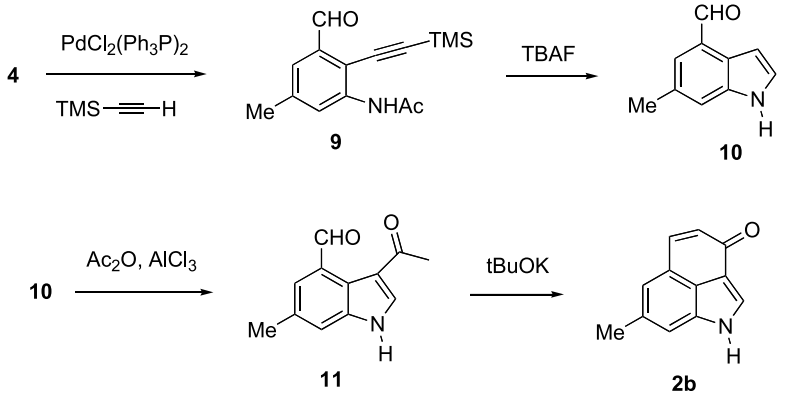


Scheme 1.



Scheme 2.

milligram amounts. The problems with reproducibility may be related to substitution at C-2, since indole keto aldehydes without a substituent at C-2 readily and reproducibly cyclize as shown in Scheme 2.

The modest yields in the acylation step and the problematic aldol step prompted us to evaluate the approach depicted in Scheme 2. The objective now became **2b**, an advanced intermediate in the Nakatsuka synthesis of 0231B. The synthesis of indole **2b** began with triflate **4**. This compound underwent a Sonogashira coupling with trimethylsilylacetylene (**8**) to provide acetylene **9** in 80% yield. Fluoride-mediated cyclization, desilylation and deacetylation occurred in a one-pot reaction and led to the conversion of **9** into indole **10** in 34% yield. In contrast to the reaction with indole **6**, acetylation of indole **10** at C-3 proceeded smoothly using acetic anhydride and aluminum chloride at sub ambient temperature. The resulting keto aldehyde **11** was produced in 72% yield. Aldol condensation using potassium *tert*-butoxide in THF afforded enone **2b** in 98% yield. In this case the aldol step was reproducible. The proton NMR and ^{13}C NMR of **2b** were identical to the literature spectra. Unfortunately, no melting point data was reported in the literature.

An advanced intermediate for the synthesis of **1** was synthesized in only six steps from **3**. This strategy should also be applicable to 3,4-annulated indoles such as the isonitrile-containing hapalindole alkaloids,[9] agroclavine[10] and abeo-ergoline.[11]

2. Experimental

2.1. General

2.1.1. 2-Acetylamino-6-formyl-4-methylphenyl trifluoromethanesulfonate (4). To a solution of phenol **3** (906 mg, 5.0 mmol) in 50 ml of ethyl acetate was added 10% Pd on charcoal (106 mg, 0.10 mmol) and acetic anhydride (2.4 ml, 25 mmol). The reaction mixture was stirred under a H_2 atmosphere at room temperature overnight. The solid was filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (715 mg, 74% yield), mp 124–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.17 (s, 1H), 9.34 (s, 1H), 8.35 (s, 1H), 7.81 (br, 1H), 6.99 (s, 1H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 168.7, 148.1, 129.6, 127.7, 127.2, 127.0, 119.5, 24.7, 20.8; MS (*m/z*): 193, 165, 152, 151, 150, 123, 105; HRMS: calcd for $C_{10}H_{11}NO_3$:

193.0739, found: 193.0741. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17%; H, 5.74%; N, 7.25. Found: C, 62.30%; H, 5.77%; N, 7.39%.

The product from reduction and acetylation (966 mg, 5.0 mmol), K_2CO_3 (898 mg, 6.5 mmol) and *N*-phenyltriflimide (1.96 g, 5.5 mmol) in 25 ml of THF were stirred at room temperature overnight. The solid was filtered and solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (1.54 g, 95% yield), mp 118–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.09 (s, 1H), 7.80 (br, 1H), 7.51 (s, 1H), 2.39 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.9, 169.1, 140.1, 138.1, 131.7, 131.2, 139.0, 127.7, 118.7 (q, J = 319 Hz), 24.0, 21.2; MS (*m*/*z*): 325, 193, 192, 176, 150, 122; HRMS: calcd for $C_{11}H_{10}F_3NO_5S$: 325.0232, found: 325.0237.

2.1.2. *N*-[3-Formyl-5-methyl-2-(phenylethynyl)phenyl acetamide (5). To a degassed solution of triflate **4** (650 mg, 2.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (12 mg, 0.06 mmol) and diisopropylethylamine (1.05 ml, 6.0 mmol) in 20 ml THF was added phenylacetylene (0.27 ml, 0.24 mmol) dropwise. The reaction mixture was stirred at 55 °C for 6 h. The solid was filtered and the filtrate was washed consecutively with saturated NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (477 mg, 86% yield), mp 145–146 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.52 (s, 1H), 8.54 (s, 1H), 8.07 (br, 1H), 7.56–7.59 (m, 2H), 7.50 (s, 1H), 7.42–7.44 (m, 3H), 2.44 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 168.5, 140.2, 139.6, 135.6, 131.5, 129.5, 128.8, 125.4, 123.3, 121.7, 112.5, 102.5, 80.6, 24.9, 21.8; MS (*m*/*z*): 277, 276, 249, 248, 247, 207, 206; HRMS: calcd for $C_{18}H_{15}NO_2$: 277.1103, found: 277.1107.

2.1.3. 2-Phenyl-6-methylindole-4-carboxaldehyde (6). A mixture of aldehyde **5** (139 mg, 0.50 mmol), 1 M TBAF (1.5 ml, 1.5 mmol) in 10 ml of THF was stirred at reflux for 1 h. Solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (78 mg, 67% yield), mp 187–189 °C.

^{1}H NMR (300 MHz, DMSO-*d*): δ 10.15 (s, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.53 (s, 1H), 7.45–7.50 (m, 4H), 7.32–7.37 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d*): δ 193.9, 141.3, 139.1, 132.4, 131.2, 129.7, 129.2, 128.7, 127.9, 126.0, 125.1, 118.4, 99.1, 21.7; MS (*m*/*z*): 235, 234, 207, 206, 204, 178, 103, 102; HRMS: calcd for $C_{16}H_{13}NO$: 235.0997, found: 235.1001. Anal. Calcd for $C_{16}H_{13}NO$: C, 71.68%; H, 5.57%; N, 5.95. Found: C, 81.39%; H, 5.68%; N, 5.99%.

2.1.4. 3-Acetyl-2-phenyl-6-methylindole-4-carboxaldehyde (7). To a suspension of $AlCl_3$ (415 mg, 1.5 mmol) in 12 ml dry CH_2Cl_2 was added acetyl anhydride (0.14 ml, 3.0 mmol) dropwise with ice water bath cooling. The reaction mixture was stirred at room temperature for 15 min before cooling to −20 °C. A solution of indole **7** (118 mg, 0.5 mmol) in 3 ml dry CH_2Cl_2 was added dropwise. The mixture was stirred at the same temperature for 1 h and quenched by slow addition of crushed ice. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, $NaHCO_3$, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow oil (64 mg, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 9.12 (br, 1H), 7.57 (s, 1H), 7.49–7.51 (m, 2H), 7.40–7.43 (m, 3H), 7.36 (s, 1H), 2.27 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 193.4, 142.1, 137.0, 133.3, 132.0, 132.0, 129.8, 129.2, 129.1, 127.5, 122.1, 117.7, 117.2, 32.5, 21.5; MS (*m*/*z*): 277, 276, 249, 248, 235, 234, 205, 204, 191, 189, 179; HRMS: calcd for $C_{18}H_{15}NO_2$: 277.1103, found: 277.1107.

2.1.5. 7-Methyl-2-phenyl-1-benz[*c*,*d*]indol-3-(1*H*)-one (2a). A mixture of indole **7** (7 mg, 0.025 mmol), *t*-BuOK (14 mg, 0.125 mmol) in 5 ml of THF was stirred for 1 h. The solvent was removed and the residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (6 mg, 92%). The yield of this reaction when scaled up was highly variable.

Compound **2a** ^{1}H NMR (300 MHz, $CDCl_3$): 8.36 (s, 1H), 8.33 (s, 1H), 7.57–7.60 (d, J = 9.5 Hz 1H), 7.43–7.49 (m, 3H), 7.29–7.30 (m, 2H), 6.65–6.69 (d, J = 9.5 Hz, 1H), 2.51 (s, 3H); HRMS (ES) *m*/*z* calcd for $C_{18}H_{13}NO$: 259.0997, found: 259.0999.

2.1.6. *N*-[3-Formyl-5-methyl-2-(trimethylsilylethynyl) phenyl acetamide (9). To a degassed solution of triflate **4** (273 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol) and diisopropylethylamine (0.63 ml, 3.0 mmol) in 20 ml of THF was added trimethylsilylacetylene **8** (0.31 ml, 2.2 mmol) dropwise. The reaction mixture was stirred at 55 °C for 5 h. The solid was filtered and the filtrate was washed consecutively with saturated NH_4Cl and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:1) to give a yellow solid (191 mg, 80% yield), mp 119–120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 8.48 (s, 1H), 8.05 (br, 1H), 7.42 (s, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 0.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 168.4, 140.7, 140.3, 135.9, 124.9, 122.7, 112.4, 109.5, 96.2, 25.0, 22.0, 0.0; MS (*m*/*z*): 273, 272, 259, 258, 230, 217, 216, 202, 200, 172, 171; HRMS: calcd for $C_{15}H_{19}NO_2Si$: 273.1185, found: 273.1188.

2.1.7. 6-Methylindole-4-carboxaldehyde (10). A mixture of aldehyde **9** (190 mg, 0.80 mmol), 1 M TBAF (2.4 ml, 2.4 mmol) in 10 ml THF was stirred at reflux for 1 h. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The

ethyl acetate extract was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 1:2) to give a yellow solid (43 mg, 34% yield), mp 116–118 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.55 (br, 1H), 7.47 (s, 2H), 7.34–7.36 (m, 1H), 7.27–7.29 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.5, 137.2, 131.5, 129.2, 128.2, 127.2, 124.0, 117.8, 102.8, 21.5; MS (*m*/*z*): 160, 159, 158, 131, 130, 128, 103, 77; HRMS: calcd for $C_{10}H_9NO$: 159.0684, found: 159.0686.

2.1.8. 3-Acetyl-6-methylindole-4-carboxaldehyde (11). To a suspension of $AlCl_3$ (415 mg, 1.5 mmol) in 12 ml of dry CH_2Cl_2 was added acetyl anhydride (0.14 ml, 3.0 mmol) dropwise with ice water bath cooling. The reaction mixture was stirred at room temperature for 15 min before cooling to −20 °C. A solution of indole **10** (118 mg, 0.5 mmol) in 3 ml dry CH_2Cl_2 was added dropwise. The mixture was stirred at the same temperature for 1 h and quenched by slow addition of crushed ice. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, $NaHCO_3$, and concentrated. The crude product was purified by flash chromatography (ethyl acetate/hexane = 3:1) to give a yellow solid (64 mg, 72% yield), mp 200–201 °C.

^{1}H NMR (300 MHz, acetone-*d*): δ 11.33 (s, 1H), 8.48 (br, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 2.48 (s, 3H), 2.54 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, acetone-*d*): δ 195.5, 192.1, 139.5, 137.1, 133.1, 130.4, 122.8, 122.1, 118.8, 117.5, 27.3, 20.5; MS (*m*/*z*): 201, 200, 173, 172, 158, 157, 155, 129; HRMS: calcd for $C_{12}H_{11}NO_2$: 201.0790, found: 201.0793.

2.1.9. 7-Methyl-1-benz[*c*,*d*]indol-3-(1*H*)-one (2b). A mixture of indole **11** (15 mg, 0.075 mmol), potassium *tert*-butoxide (25 mg, 0.225 mmol) in 5 ml of THF was stirred for 30 min. The solvent was removed and the residue was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (100% ethyl acetate) to give a yellow solid (13 mg, 98% yield), mp 178–180 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.45 (br, 1H), 8.12 (s, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.49 (s, 1H), 7.40 (s, 1H), 6.73 (d, J = 9.4 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.9, 138.9, 134.8, 133.8, 132.4, 131.8, 124.9, 124.1, 123.6, 116.1, 116.1, 22.2; MS (*m*/*z*): 183, 182, 154, 153, 126; HRMS: calcd for $C_{112}H_9NO$: 183.0684, found: 183.0687.

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