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A concise synthesis of 5-demethyl-HKI 0231A and 5-demethyl-HKI 0231B

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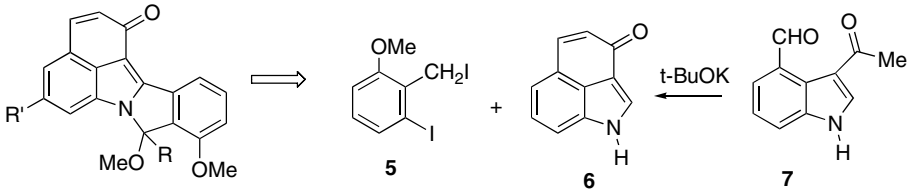
Abstract—The pentacyclic skeleton of HKI 0231A and HKI 0231B was synthesized by a novel radical cyclization/oxidation followed by DDQ oxidation to introduce the methoxyl groups. This is the first synthetic pathway to both the HKI 0231A and the HKI 0231B series.

The structures of HKI 0231A (**1**) and HKI 0231B (**2**), novel inhibitors of 3a-hydroxysteroid dehydrogenase, were reported from *Streptomyces* sp. HKI0231.[1] Compounds that inhibit this enzyme may be useful leads for new anti-inflammatory agents. In 2003, Nakatsuka and co-workers reported a synthesis of **1** utilizing a novel Friedel–Crafts alkylation reaction.[2] In 2005, Scopton and Kelly reported an innovative synthesis of **1** featuring an intramolecular aryl lithium cyclization.[3] In 2005, we reported a formal synthesis of **1** wherein the key tricyclic indole was synthesized by way of an ethynyl aniline.[4] We report herein, a very convenient and flexible preparation of 5-demethyl HKI 0231A (**3**) and HKI 0231 B (**4**) using an intramolecular radical cyclization.

Both **3** and **4** were envisioned to come from indole **6**, readily available by an intramolecular aldol reaction (*t*-BuOK, DMF, 23 °C, 96%) of **7** that in turn was prepared from commercially available 4-formyl indole by a Friedel–Crafts reaction (Ac_2O, 0 °C, 61%). Indole **6** would be coupled with benzylic iodide **5**, available from iodoanisic acid[5] by reduction (BH_3, THF, reflux, 74%) followed by iodide formation (Ph_3P, I_2; 65%). The reaction of **6** with iodide **5** in the presence of potassium hydroxide afforded indole **8** in 92% yield. Unfortunately, despite several experiments, the conversion of **8** to **9** using organopalladium methodologies[6] failed. At temperatures below 50 °C, starting material was recovered. At higher temperatures (80–120 °C), complex mixtures were obtained. This intramolecular Heck reaction



1: R = OMe, R' = Me
2: R = H, R' = Me
3: R = OMe, R' = H
4: R = R' = H

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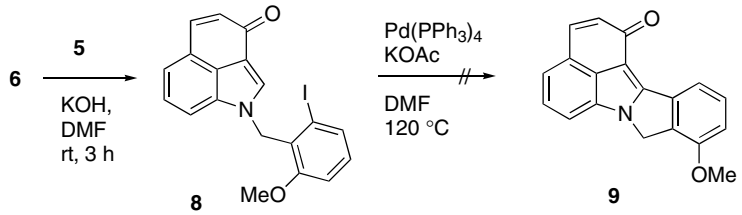
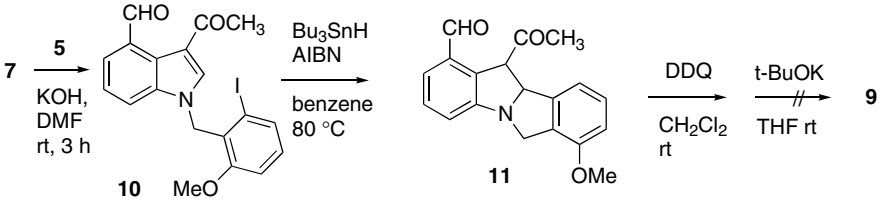
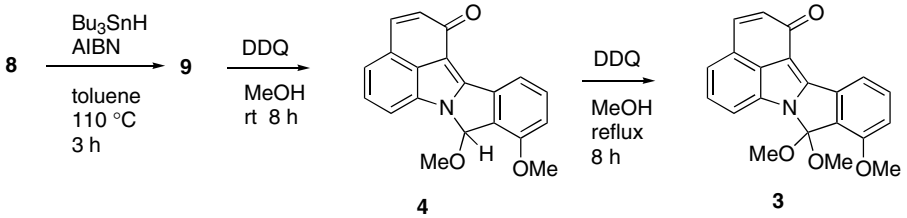


requires *syn*-addition and *syn*-elimination. The latter process would be hard to achieve in this system.

We then synthesized indole **10** in 93% yield by alkylation of keto aldehyde **7** with **5** and potassium hydroxide. Although the use of organopalladium chemistry to convert **10** into **11** failed, these conditions were successful in the system lacking an acetyl group at C-3 of the indole. Radical cyclization with tributyltin hydride and AIBN[7] in boiling benzene afforded **11** in 58% yield. DDQ oxidation of **11** generated the corresponding indole that failed to cyclize to **9** using potassium *tert*-butoxide.



The reaction of **8** with tributyltin hydride and AIBN in boiling toluene afforded indole **9** *directly* in 58% yield.[8] We speculate that oxidation occurs via small amounts of oxygen present in the system. The higher reaction temperature could also be a factor. This reaction has been reproduced three times with essentially the same yields each time. Introduction of the methoxyl group, a low yield transformation in the Nakatsuka synthesis, was selectively achieved in high yield using DDQ[9] in methanol. At ambient temperature the reaction provided only **4**[10] in 63% yield. However, **4** could be converted into **3**[11] in 58% yield with DDQ in boiling methanol. This was unexpected, since **4** might be expected to be more reactive to hydride abstraction than **9**. We attribute the differential reactivity to allylic strain[12] between the two methoxyl groups in **4**, forcing the benzylic methoxyl group to an axial position. Compound **9** could be converted to **3** in 62% yield in a one-pot reaction using 2 equiv of DDQ in boiling methanol.



The synthetic approach to **3** and **4** is sufficiently direct and flexible to permit the synthesis of a variety of analogs. The novel radical cyclization/oxidation protocol should prove useful in other systems where the organopalladium approach failed. This represents the first synthetic pathway to both the HKI 0231A and the HKI 0231B series.

References and notes

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8. To a boiling solution of iodide **8** in toluene was added a solution of *n*-Bu_3SnH (0.48 mL, 1.8 mmol) and AIBN (99 mg, 0.36 mmol) in 3 mL of toluene in 3 h via syringe pump. The reaction mixture was kept in reflux for three more hours. After removal of toluene, the residue was stirred for 1 h with 10 mL of ether and 10 mL of saturated KF solution. The mixture was extracted with ether. The organic layer was dried and concentrated. The crude product was purified by flash chromatography (ethyl

acetate/hexane = 3:1) to give **9** as a yellow solid (100 mg, 58% yield), mp: 188–190 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, $J = 5.7$ Hz, 1H), 7.66 (d, $J = 7.2$ Hz), 7.44–7.50 (m, 3H), 7.33 (t, $J = 5.7$ Hz, 1H), 6.95 (d, $J = 6.2$ Hz, 1H), 6.73 (d, $J = 7.1$ Hz, 1H), 5.12 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 154.7, 152.6, 137.0, 133.0, 132.3, 131.2, 130.8, 130.6, 124.8, 123.6, 122.6, 118.1, 112.2, 112.2, 108.5, 55.7, 48.4; MS (*m*/*z*): 288, 287, 286, 273, 272, 271, 244, 243; HRMS: calcd for $C_{19}H_{13}NO_2$: 287.0946. Found: 287.0949.

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10. To a solution of compound **9** (29 mg, 0.05 mmol) in 5 mL of methanol was added DDQ (34 mg, 0.15 mmol) at −78 °C. The reaction mixture was stirred at −78 °C to rt overnight. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane = 2:1) to give **4** as a yellow oil (10 mg, 63% yield).
Spectra for **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.268 (d, $J = 7.4$ Hz, 1H), 7.716 (d, $J = 9.7$ Hz, 1H), 7.664 (d, $J = 8.0$ Hz, 1H), 7.599 (t, $J = 7.9$ Hz, 1H), 7.513 (d, $J = 7.5$ Hz, 1H), 7.398 (t, $J = 7.7$ Hz, 1H), 7.067 (d, $J = 8.3$ Hz, 1H), 6.842 (s, 1H), 6.743 (d, $J = 9.6$ Hz), 4.004 (s, 3H), 2.984 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.46, 156.31, 149.58, 137.93, 133.18, 132.89, 132.57, 131.15, 130.89, 128.03, 124.95, 124.65, 122.93, 118.31, 113.54, 113.21, 109.33, 87.08, 56.05, 51.31; MS (*m*/*z*): 318, 317, 316, 286, 285, 243, 242, 214; HRMS: calcd for $C_{20}H_{15}NO_3$: 317.1052. Found: 317.1059.
11. To a solution of demethyl HKI 0231B **4** (13 mg, 0.04 mmol) in 5 mL of methanol was added DDQ (27 mg, 0.12 mmol) at rt. The reaction mixture was stirred at reflux overnight. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane = 2:1) to give **3** as a yellow oil (8 mg, 58% yield).
Spectra for **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.255 (d, $J = 7.5$ Hz, 1H), 7.720 (d, $J = 9.3$ Hz, 2H), 7.622 (t, $J = 7.9$ Hz, 1H), 7.516 (d, $J = 7.3$ Hz, 1H), 7.407 (t, $J = 7.6$ Hz, 1H), 7.084 (d, $J = 8.3$ Hz, 1H), 6.742 (d, $J = 9.7$ Hz), 4.001 (s, 3H), 3.020 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.78, 155.95, 146.97, 138.19, 134.10, 132.84, 132.55, 130.91, 130.20, 125.52, 125.14, 125.04, 123.08, 118.57, 114.53, 114.09, 109.75, 56.17, 52.88; MS (*m*/*z*): 348, 347, 346, 318, 317, 316, 315, 301, 300, 272; HRMS: calcd for $C_{21}H_{17}NO_4$: 347.1158. Found: 347.1163.
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