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Synthesis of HKI 0231B

Alex Scopton and T. Ross Kelly*

E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

ross.kelly@bc.edu

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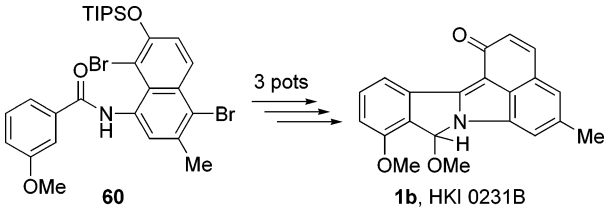

The total synthesis of HKI 0231B (**1b**) was completed in 12 linear steps and 15.6% overall yield. An unusual anionic cyclization provided access to intermediate **61** and the embedded benz[*cd*]-indol-3-(1*H*)-one ring system **3**. Directed ortho-lithiation in the presence of a ketone followed by formylation and finally acid-catalyzed methanolysis complete the synthesis. Studies directed toward the construction and reactivity of the lactam acetal functionality present in HKI 0231A (**1a**) are also reported.

Introduction

In 2001, scientists at the Hans Knoll Institute in Jena, Germany, reported the isolation, structure, and biological activity of two novel alkaloids from the fermentation broth of *Streptomyces* sp. HKI 0231.[1] The structural assignments were made primarily on the basis of mass spectrometry and 1D and 2D NMR measurements. The compounds (Figure 1), designated as 0231A (**1a**) and 0231B (**1b**), were shown to inhibit one of the key enzymes involved in the inflammatory process, 3α-hydroxysteroid dehydrogenase.[2] On the basis of their unique polycyclic framework and potential as lead structures for the development of antiinflammatory agents, their synthesis was undertaken. Our initial focus was on the simpler of the two compounds, 0231B (**1b**). Shortly after our efforts had commenced, Komoda et al.[3] proved the structure of **1b** through total synthesis. Their key step was a regioselective cyclization of the 6-methyl-3-cinnamoylindole derivative **2**, which allowed access to the embedded benz[*cd*]indol-3-(1*H*)-one ring system **3**.[4] Herein, we now report a full account of our synthesis of **1b** and efforts toward the synthesis of **1a**.

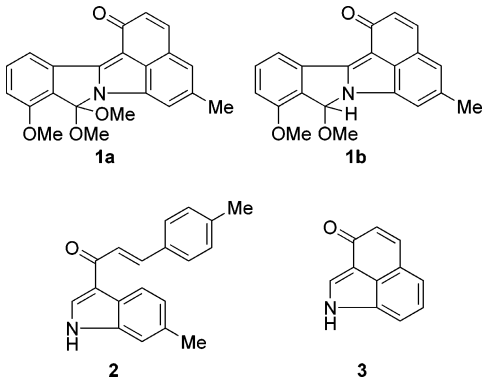

FIGURE 1.

Results and Discussion

Our initial retrosynthetic analysis (Figure 2) suggested that the tetrasubstituted double bond in **1b** might be formed at a late stage in the synthesis via an intramolecular aldol-type condensation of **4**. Compound **4** should be accessible via directed lithiation of **5** followed by quenching with a suitable electrophile. The amide **5** would in turn be prepared from the commercially available *m*-anisoyl chloride (**6**) and the appropriately functionalized aminonaphthol derivative **7**.

We initially thought that the most direct route to access the desired **7** was via an electrophilic substitution

(1) Kleinwächter, P.; Schlegel, B.; Groth, I.; Härtl, A.; Gräfe, U. *J. Antibiot.* **2001**, *54*, 510.

(2) Penning, T. M. *J. Pharm. Sci.* **1985**, *74*, 651.

(3) (a) Komoda, T.; Shinoda, Y.; Nakatsuka, S. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 659. (b) For another attempted synthesis, see: Wu, T.; Kraus, G. *Abstracts of Papers*; 226th National Meeting of the American Chemical Society, New York, Sept 7−11, 2003; American Chemical Society: Washington, DC, 2003.

(4) For another synthesis of this tricyclic ring system, see: Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141.

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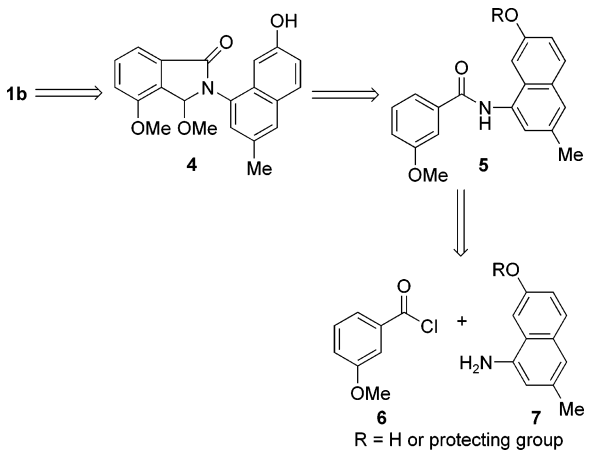
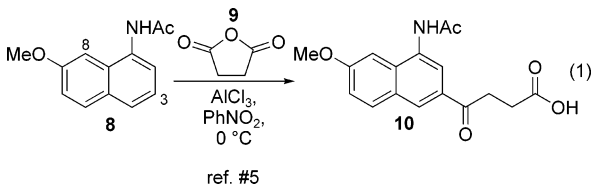
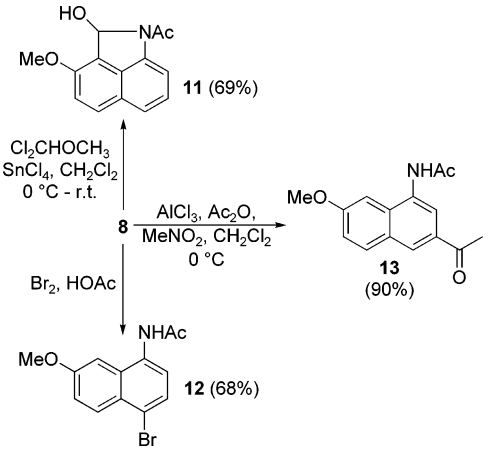


FIGURE 2.

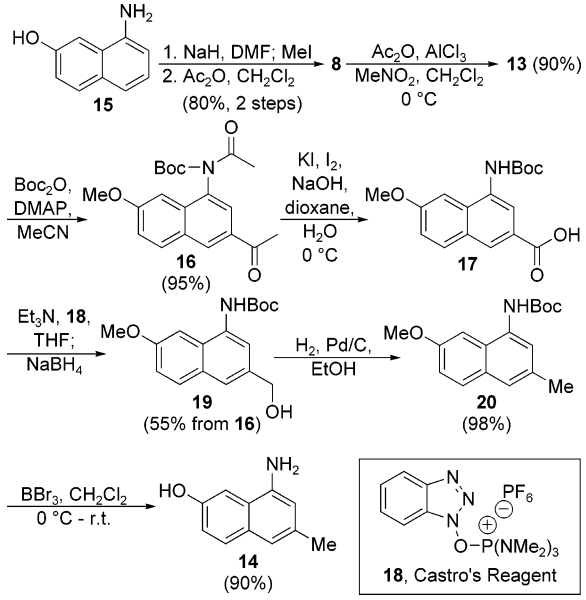
of a suitably functionalized naphthalene unit. A search of the literature revealed work by Miller and Morello[5] in 1948, which was later confirmed by Harnik and Jensen[6] in 1965. Both publications reported that substitution of aminonaphthol derivative **8** by succinic anhydride (**9**) occurred exclusively in the 3-position to give the acid **10** (eq 1). We thought that if the regiochemistry of substitution proved to be general for other electrophiles, then this would offer a very quick route to a specific embodiment of the desired naphthalene fragment **7**. Despite the fact that we were able to reproduce the specific reaction in eq 1, its scope appeared limited. Numerous attempts to directly methylate the 3-position under Lewis acid catalysis, with a variety of electrophiles (i.e., MeI, MeBr, MeCl), were all met with failure. The regioselectivity of electrophilic substitution on this system (**8**) appeared to be extremely sensitive to the conditions employed. Formylation with α,α-dichloromethyl methyl ether[7] occurred in the 8-position to give **11**, and treatment with 1 equiv of elemental bromine[8] gave substitution in the 4-position to yield **12** (Scheme 1). Ultimately, it was found that by slightly modifying the conditions in eq 1, acylation with acetic anhydride occurred with the desired regioselectivity and in good yield.[9,10] Initially ketone **13** appeared as a promising substrate for the construction of the desired naphthalene fragment. Unfortunately it required five more steps (Scheme 2) to convert **13** to **14**; an eight-step sequence to install a methyl group on an aromatic ring was unacceptable. Development of a shorter route to **14** was thus undertaken (vide infra).



SCHEME 1. Various Electrophilic Substitutions of 8



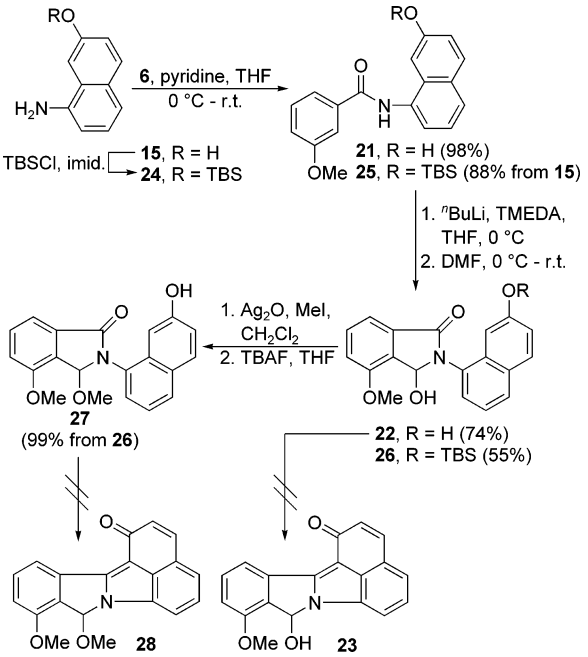
SCHEME 2. Synthesis of Aminonaphthol 14



Meanwhile, we turned our attention toward constructing the pentacyclic core found in **1b**. For the initial studies we chose to use the commercially available **15** as a model system for the naphthalene unit. We were fairly confident that the chemistry would be transferable since the real system only differed by a methyl group. As shown in Scheme 3, acylation of **15** with **6** in the presence of 1 equiv of pyridine[11] gave **21** in near-quantitative yield. Directed ortho-lithiation of **21** with 3.2 equiv of ^{n}BuLi in THF at 0 °C, followed by addition of DMF and warming to room temperature, gave hydroxylactam **22** in 74% yield.[12] Unfortunately, all at-

(5) Miller, L. E.; Morello, E. F. *J. Am. Chem. Soc.* **1948**, *70*, 1900.
(6) Harnik, M.; Jensen, E. V. *Isr. J. Chem.* **1965**, *3*, 13.
(7) Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1969; Vol. 2, p 120.
(8) In the presence of excess Br_2, further substitution occurred in the 8-position.
(9) Although reaction of Ac_2O did occur with the desired regioselectivity in $PhNO_2$, the yield was not nearly as high (~50%) and removal of the $PhNO_2$ proved difficult and time-consuming on a large scale.
(10) For discussions of the effects of $MeNO_2$ on $AlCl_3$-catalyzed aromatic substitution, see: (a) DeHaan, F. P.; Covey, W. D.; Delker, G. L.; Baker, N. J.; Feigon, J. F.; Ono, D.; Miller, K. D.; Stelter, E. D. *J. Org. Chem.* **1984**, *49*, 3959. (b) DeHaan, F. P.; Delker, G. L.; Covey, W. D.; Bellomo, A. F.; Brown, J. A.; Ferrara, D. M.; Haubrich, R. H.; Lander, E. B.; MacArthur, C. J.; Meinhold, R. W.; Neddenriep, D.; Schubert, D. M.; Stewart, R. G. *J. Org. Chem.* **1984**, *49*, 3963. (c) Covey, W. D.; DeHaan, F. P.; Delker, G. L.; Dawson, S. F.; Kilpatrick, P. K.; Rattinger, G. B.; Read, W. G. *J. Org. Chem.* **1984**, *49*, 3967.
(11) Acylation without the presence of a proton scavenger gave incomplete reaction, and stronger bases such as Et_3N or Hunig's base led to acylation at the phenol. Schotten–Baumann conditions also proved ineffective in completing this transformation.

SCHEME 3. Aldol-type Condensation Model Studies



tempts to effect the intramolecular aldol-type condensation to form **23**, under a variety of conditions, resulted in either recovery of **22** or complete decomposition of the material. We initially thought that the acidic O*H* proton in the hemiaminal functionality present in **22** might be impeding the ring closure. To eliminate this variable, a slightly modified sequence to that described for the construction of **22** was employed. The phenol in **15** was first TBS-protected[13] and the crude TBS ether **24** was acylated as before to give **25** in 88% yield over two steps. Lithiation of **25** with 2.2 equiv of ^{n}BuLi followed by quenching with DMF gave **26** in 55% yield.[12] Many attempts to methylate the hemiaminal in **26** under acidic and basic conditions led either to decomposition or to a complex mixture of products. However, it was eventually found that reacting **26** with a large excess of MeI (>20 equiv) in the presence of 5 equiv of Ag_2O led smoothly to the desired methylated product,[14] which was treated directly with TBAF to remove the TBS ether and give isoindolone **27** in 99% yield from **26**. Unfortunately, all attempts to advance **27** to the desired **28** resulted in either recovered starting material or complete decomposition (as with **22**).

At this point we decided to rework our strategy for the ring construction. Specifically, it was thought that the troublesome carbon−carbon bond should be formed at an earlier stage in the synthesis. We felt that the most direct way to accomplish this was through the generation of a lithiated species such as **29**, followed by quenching with a suitably functionalized electrophile (**30**; known compound[15]) to give **31** (Figure 3). Ultimately this strategy

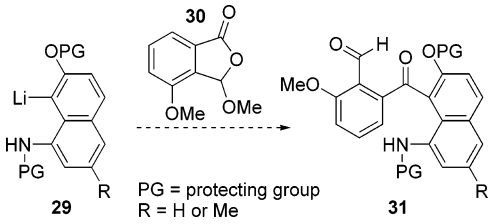


FIGURE 3.

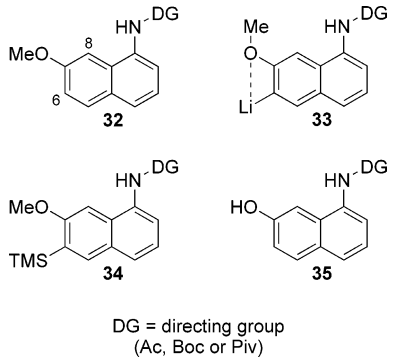


FIGURE 4.

solved our problem, but not in the way we had initially anticipated.

To work out the conditions to generate a lithiated species such as **29**, we again called upon the desmethyl **15** for use as a model system. Initial studies did not show much promise. All attempts at directed peri-lithiation[16] on compounds such as **32** (Figure 4) resulted in only recovered starting material; 2−3 equiv of the standard alkyllithiums (i.e., ^{n}BuLi, ^{s}BuLi, and ^{t}BuLi) at a range of temperatures failed to show lithiation at any position on the ring system. In the presence of excess ^{t}BuLi (>5 equiv) at room temperature for extended periods of time (≥4 h) lithiation did occur, albeit at the undesired 6-position (**33**).[17] In an attempt to force peri-lithiation, the 6-position was blocked with a TMS group[18] (treatment of **33** with TMSCl) to give **34**. However, further functionalization of this ring system via directed lithiation failed. The demethylated **35** also proved to be of no use.

Since we were unable to directly lithiate the necessary ring system, our attention was turned toward generating the desired anion by metal−halogen exchange (Scheme 4). Thus, aminonaphthol **15** was *N*-acylated, brominated at the 8-position (contrast **8** → **12**) and TIPS-protected[19,20] in a very efficient three-step sequence to give, after one

(12) For related reactions, see: (a) Broadhurst, M. J.; Hassall, C. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2227. (b) Mali, R. S.; Yeola, S. N. *Synthesis* **1986**, 755. (c) Epsztajn, J.; Jóźwiak, A.; Kołuda, P.; Sadokierska, I.; Wilkowska, I. D. *Tetrahedron* **2000**, *56*, 4837.

(13) Swenton, J. S.; Bonke, B. R.; Chen, C. P.; Chou, C. T. *J. Org. Chem.* **1989**, *54*, 51.

(14) Mizutani, T.; Honzawa, S.; Tosaki, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4680.

(15) (a) Weeks, D. P.; Crane, J. P. *J. Org. Chem.* **1973**, *38*, 3375. (b) Jung, M. E.; Blum, R. B. *J. Chem. Soc., Chem. Commun.* **1981**, 962.

(16) (a) Clayden, J. Regioselective Synthesis of Organolithiums by Deprotonation. In *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series; Elsevier Science: London, 2002; Vol. 23, Chapt. 2, pp 30−31. (b) Betz, J.; Bauer, W. *J. Am. Chem. Soc.* **2002**, *124*, 8699. (c) Kraus, G. A.; Kim, J. *J. Org. Chem.* **2002**, *67*, 2358.

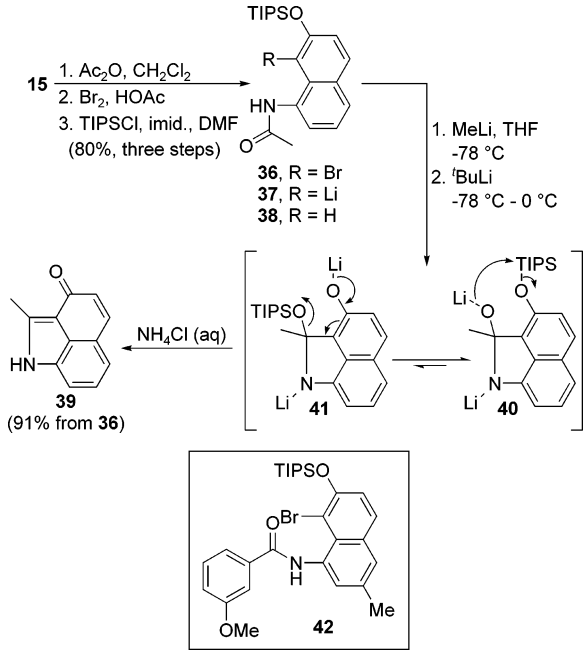
(17) Determined on the basis of D_2O quench, which gave two new singlets in the ^{1}H NMR spectrum.

(18) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.

(19) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999.

(20) Only silyl-based protecting groups could be successfully introduced on the phenol after the bromination reaction. Various benzyl groups were attempted, but all led to either recovered starting material or low yields.

SCHEME 4. Carbon−Carbon Bond Formation via Metal−Halogen Exchange



recrystallization, **36** in 80% overall yield. In this particular case, it was found that metal−halogen exchange occurred at a faster rate than deprotonation of the acidic amide proton, so that once the initial carbanion was formed it was rapidly quenched via either an intra- or intermolecular protonation.[21] To prevent this complication, **36** was treated first with 1 equiv of MeLi (for N*H* deprotonation)[22] and then with 2 equiv of ^{t}BuLi at low temperature. Warming to 0 °C readily generated what was thought to be anion **37**.[23] But when the reaction mixture was quenched with a proton source, the expected **38** was not formed; instead the cyclized product **39** was obtained, which contained the three rings of the right-hand side of the desired ring system (vide supra). We felt that this reaction, thought to be driven by migration of the TIPS[24] and then elimination of TIPSO$^-$ (**40** → **41**), could be utilized if the key intermediate **42** could be synthesized.

To work out conditions to not only synthesize but also cyclize **42**, amide **21** was employed as a model system. To our dismay, reaction of **21** under the bromination conditions (1 equiv of Br_2 in HOAc) shown in Scheme 4

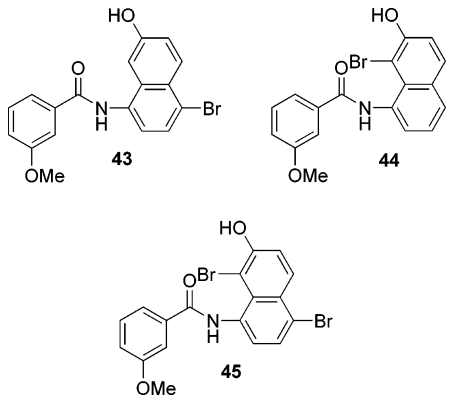
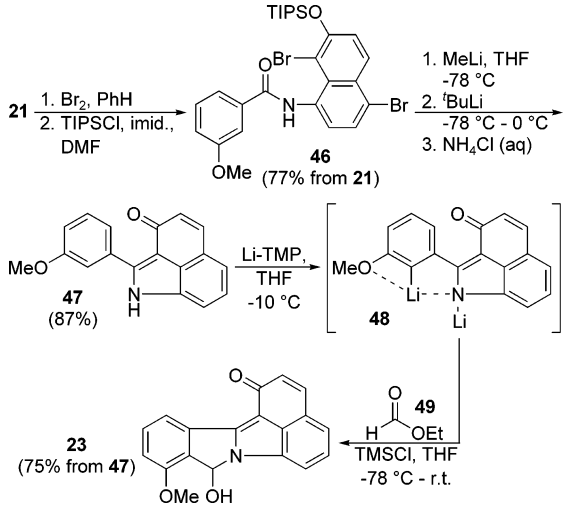


FIGURE 5.

SCHEME 5. Ring Construction Model Study



yielded only undesired regioisomer **43** (Figure 5). Changing to a less polar solvent (benzene, CH_2Cl_2 or CCl_4) gave mixtures of **44** and **45** along with recovered **21**. Despite many attempts, the desired **44** could not be separated from crude reaction mixtures. All other brominating agents tried (NBS, pyridinium tribromide, and cyanogen bromide) gave exclusively **43**, under a wide range of conditions.

In a last-ditch effort to utilize the novel cyclization methodology of Scheme 4, we decided to drive the bromination to dibromide **45**. At least in theory, having two bromines on the molecule should not matter. Since the reaction would ultimately be quenched with a proton source, the second bromine present could simply be exchanged off by use of excess ^{t}BuLi. This idea was ultimately borne out as shown in Scheme 5. Amide **21** was forcibly dibrominated (3 days) with excess bromine (5 equiv) and then TIPS-protected to yield **46** in 77% yield over two steps. By slightly modifying the conditions used on **36** (4 equiv of ^{t}BuLi instead of 2), **46** was smoothly transformed into **47** in very good overall yield.

At this stage, all that was needed to complete the desired ring system was an aldehyde unit. After a considerable amount of experimentation, it was found that ortho-lithiation of **47** could be effected in the presence of excess lithium tetramethylpiperidide (5 equiv)

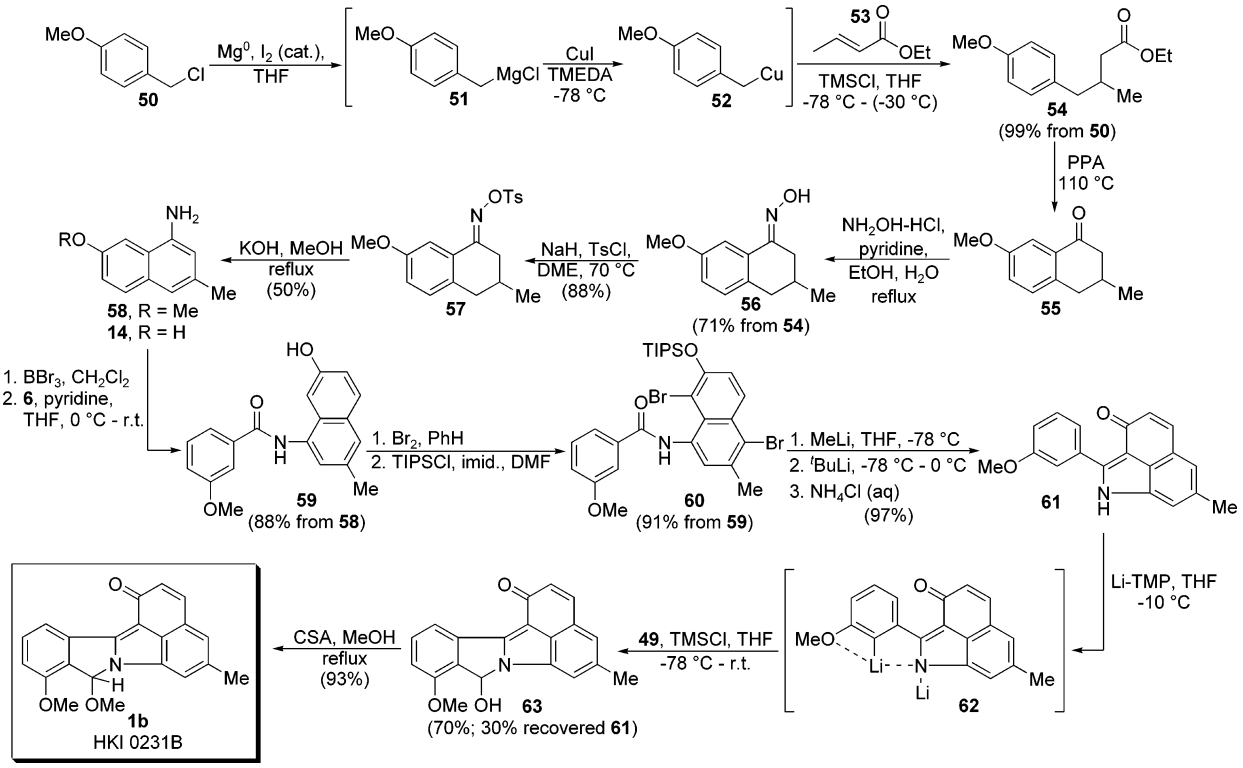
(21) This was ultimately determined when the reaction was quenched with D_2O and deuterium failed to incorporate into the ring system.

(22) For other examples of where this has been necessary, see: (a) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072. (b) Kelly, T. R.; Silva, R. A.; De Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935.

(23) For a discussion on the kinetics of halogen−lithium exchange, see: Clayden, J. Regioselective Synthesis of Organolithiums by X-Li Exchange. In *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series; Elsevier Science: London, 2002; Chapt. 3, pp 116−117.

(24) For discussions of silicon group migrations, see: (a) Colvin, E. Rearrangement reactions with migration of silicon. In *Silicon in Organic Synthesis*; Butterworth Monographs in Chemistry and Chemical Engineering; Butterworth: London, 1981; pp 30−39. (b) Brook, M. A. Rearrangements. In *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley & Sons: New York, 2000; pp 511−551. (c) Clayden, J. Organolithium Rearrangements. In *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series; Elsevier Science: London, 2002; Chapt. 8, pp 340−346.

SCHEME 6. Synthesis of HKI 0231B (1b)



at −10 °C.[25,26] Despite the fact that dianion **48** could be formed, attempts to react this species with electrophiles other than D_2O initially led to either rapid decomposition of the starting material or unproductive consumption of the carbanion.[27] By screening various conditions it was eventually realized that when the temperature was lowered to −78 °C, **48** would react in the appropriate manner with TMSCl-activated ethyl formate (**49**) to give the desired cyclic hemiaminal **23** in a hard-fought 75% yield.

Now that we possessed the necessary tools to construct the ring system in **1b**, we decided to revisit our synthesis of the essential aminonaphthol **14**. As already noted, despite the fact that our synthesis of **14** was workable, its length seemed less than ideal when compared with the rapid manner in which we were able to construct the pentacyclic core. For the final solution to this problem we opted to construct the appropriately functionalized naphthalene unit from the readily available *p*-methoxybenzyl chloride (**50**; Scheme 6). Thus, reaction of the derived Grignard reagent **51** with CuI at −78 °C generated benzylic copper(I) species **52**.[28] Simultaneous addition of ethyl crotonate (**53**) and TMSCl,[29] followed by warming to −30 °C provided ester **54** in near-quantitative yield.[28] Dehydrative cyclization of **54** in hot PPA[30] gave tetralone **55**, which due to its volatility was not purified but treated directly with hydroxylamine hydrochloride and pyridine in refluxing aqueous ethanol to yield oxime **56** in 71% yield over two steps. Oxime **56** could be tosylated in good yield in dimethoxyethane to furnish **57**.[31] With tosyl oxime **57** in hand we were only an aromatization and a deprotection away from the desired aminonaphthol **14**. After unsuccessfully exhausting virtually all common literature methods for the Semmler−Wolff reaction,[32−34] the aromatization was finally achieved in reasonable yield by the action of KOH in refluxing methanol.[35] The methyl ether in **58** was cleaved with BBr_3, to give **14**. Despite the fact that this route to **14**

(25) Flippin, L. A.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 2631.

(26) This temperature is extremely important for the success of the transformation. Running the reaction at slightly higher (0 °C) or lower (−20 °C) temperatures resulted in incomplete lithiation.

(27) Presumably due to the base-induced decomposition of ethyl formate, DMF (when used as the aldehyde source), or THF.

(28) van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1996**, *52*, 12313.

(29) For discussions and examples where TMSCl has been used to accelerate the conjugate addition of organocopper and organocuprate reagents, see: (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Horiguchi, Y.; Matsuzawa, S.; Nadamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (d) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (e) van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383.

(30) (a) Gilmore, R. C. *J. Am. Chem. Soc.* **1951**, *73*, 5879. (b) He, W.; Huang, F. C.; Gavai, A.; Chan, W. K.; Amato, G.; Yu, K. T.; Zilberstein, A. *Bioog. Med. Chem. Lett.* **1998**, *8*, 3659.

(31) Running this reaction in DMF, DMSO, or THF resulted in only recovered starting material.

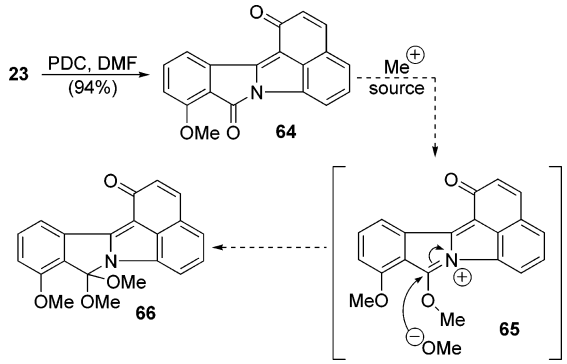
(32) Acidic conditions: (a) Bauer, L.; Hewitson, R. E. *J. Org. Chem.* **1962**, *27*, 3982. (b) Newman, M. S.; Hung, W. M. *J. Org. Chem.* **1973**, *38*, 4073. (c) El-Sheikh, M. I.; Cook, J. M. *J. Org. Chem.* **1980**, *45*, 2585. (d) Tamura, Y.; Yoshimoto, Y.; Sakai, K.; Kita, Y. *Synthesis* **1980**, 483. (e) Mallory, F. B.; Luzik, E. D.; Mallory, C. W.; Carroll, P. J. *J. Org. Chem.* **1992**, *57*, 366.

(33) Basic conditions: (a) Garst, M. E.; Cox, D. D.; Harper, R. W.; Kemp, D. S. *J. Org. Chem.* **1975**, *40*, 1169. (b) Kelly, T. R.; Chandrakumar, N. S.; Saha, J. K. *J. Org. Chem.* **1989**, *54*, 980.

(34) Neutral conditions: (a) Weidner, J. J.; Weintraub, P. M.; Schnettler, R. A.; Peet, N. P. *Tetrahedron* **1997**, *53*, 6303. (b) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228.

(35) Inferior yields were obtained with LiOH, NaOH, or CsOH. The use of other alcohols (i.e., EtOH, ^{i}PrOH, ^{n}BuOH) as solvent also resulted in a reduction in yield.

SCHEME 7. Attempted Synthesis of Amide Acetal



utilizes more bond-forming reactions as opposed to functional group transformations, it is in actuality not much shorter than the synthesis of **14** described in Scheme 2. The crude amine (**14**) was then acylated with **6** as before to give amide **59**[36] in 88% yield for the two steps. This time dibromination was effected much more rapidly than with **21**, presumably due to the increased electron density caused by the methyl group. Bromination was then followed by TIPS protection to furnish key intermediate **60** in very good yield. Treatment of **60** under conditions identical to those used to convert **46** to **47** provided **61** in almost quantitative yield. Generation of dianion **62** and then formylation produced a 70% yield of **63**, with all unreacted **61** being recoverable. Acid-catalyzed methylation then completed the 12-step sequence and finally allowed us access to HKI 0231B (**1b**). Spectra for synthetic **1b** are in excellent agreement with those reported for naturally occurring HKI 0231B.[1]

With the ability to construct and isolate hemiaminal **63**, it was thought that if the correct oxidation state could be achieved, we might be able to advance that intermediate to HKI 0231A (**1a**). Due to lack of material, the desmethyl **23** was used as a model system. As shown in Scheme 7, obtaining the correct oxidation state proved easy enough. Thus, treatment of hemiaminal **23** with PDC in DMF gave lactam **64** in excellent yield.[37] Based on the known literature methods,[38,39] our strategy was to generate immonium intermediate **65** in situ by treating **64** with a strong methylating agent (Meerwein's salt or methyl triflate), followed by adding a solution of methoxide in MeOH.[40] Ultimately, formation of lactam acetal **66** was never realized, despite screening of a range of solvents (CH_2Cl_2, $CHCl_3$, and MeCN) and methoxide sources [NaOMe, $Mg(OMe)_2$, and LiOMe]. Depending upon the conditions employed, the only product that ever appeared to be present (as judged by ^1H NMR spectra of crude reaction mixtures) was **67**, which presumably arose from initial formation of the delocalized cationic adduct **68** from **64** (Figure 6).

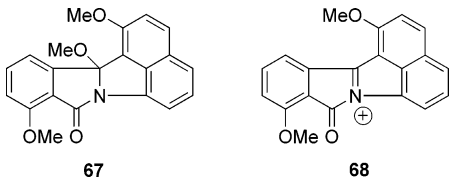
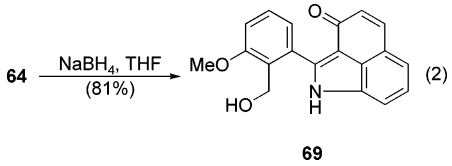


FIGURE 6.

At least qualitatively, failure to form the acetal appears to be due to the lack of donation from the lone pairs of the nitrogen into the carbonyl of lactam **64**. Instead, the nitrogen appears to be participating in the extended π-system of the ketone, as is evidenced by formation of **67**. Further evidence for this participation is shown in eq 2. Thus, treatment of **64** with $NaBH_4$ yields compound **69**, where only the lactam has been reduced and the "ketone" remains untouched.



It is not surprising that the majority of amide/lactam acetals known in the literature are inherently unstable in the presence of water.[41] The simplest of amide acetals rapidly decompose in water, with a half-life of <1 s at all values of pH.[41a] It is interesting to note that, during isolation, the lactam acetal functionality in **1a** survives not only column chromatography on SiO_2 but also further purification by reverse-phase HPLC in the presence of an aqueous mobile phase.[1] The inherent stability of this classically sensitive functionality would appear to be due to the electron sink created by the embedded α,β-unsaturated ketone, which draws electron density from the nitrogen lone pair and thereby prevents decomposition of the acetal via expulsion of methanol. Therefore, the very α,β-unsaturated ketone functionality that stabilizes the lactam acetal may also be preventing its formation from **64**.

In conclusion, we report the synthesis of HKI 0231B (**1b**) in 12 steps and 15.6% overall yield, as summarized in Scheme 6. Our experiments regarding construction and reactivity of the lactam acetal functionality present in **1a** have also been summarized.

Experimental Section[42]

Preparation of Grignard Reagent 51.[28] To a three-necked, 100 mL round-bottomed flask equipped with an addition funnel, reflux condenser and argon inlet adapter, were added magnesium turnings (9.55 g, 393 mmol), THF (36 mL), and a catalytic amount of iodine (one crystal; ca. 10−20 mg). To the rapidly stirred mixture was added *p*-methoxybenzyl chloride (PMBCl, **50**, 13 mL, 95 mmol) as a solution in THF (24 mL) via the addition funnel. After the reaction had initiated (as evidenced by the reaction becoming cloudy), the solution was added at such a rate as to maintain a gentle reflux. Once the addition was complete (ca. 1 h), the now

(36) All attempts at applying the chemistry that afforded **11** to desmethyl derivatives of **59** were met with failure.

(37) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.

(38) For reviews of amide/lactam acetal formation, see: (a) Meerwein, v. H.; Florian, W.; Schön, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1. (b) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675. (c) Anand, N.; Singh, J. *Tetrahedron* **1988**, *44*, 5975.

(39) For related transformations that result in amide cleavage, see: (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163. (b) Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875.

(40) Attempts to isolate the immonium intermediate in dry form and then treat it with methoxide in MeOH also failed.

(41) (a) McClelland, R. A. *J. Am. Chem. Soc.* **1978**, *100*, 1844. (b) McClelland, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7579.

(42) See Supporting Information for general experimental procedures.

darkgreen reaction mixture was allowed to stir for an additional hour and then standardized.[43] The solution of **52** was used immediately in the next step without further manipulation.

Ethyl 4-(Methoxyphenyl)-3-methylbutanoate (54).[28] A 1 L round-bottomed flask was charged with freshly pulverized CuI (9.55 g, 50.1 mmol), THF (250 mL), and TMEDA (8.3 mL, 55 mmol). Once all the CuI had dissolved (ca. 5−10 min), the colorless solution was cooled to −78 °C and **51** (41.5 mL of a 1.21 M solution in THF, 50.2 mmol) was added dropwise via syringe over 20 min. The resulting dark brown reaction mixture was stirred for 30 min and then a solution of ethyl crotonate (**53**, 3.1 mL, 25 mmol), TMSCl (16.0 mL, 125 mmol), and THF (125 mL; made by adding **53** to THF followed by the TMSCl) was added via cannula over 20 min. The reaction mixture was then allowed to warm to −30 °C and stir at that temperature for 18 h. The still cold reaction was poured into a mixture of saturated NH_4Cl (600 mL) and concentrated NH_4OH (400 mL). The resulting blue mixture was extracted with Et_2O (2 × 500 mL). The organic extracts were pooled, washed with H_2O (2 × 500 mL) and saturated NaCl solution (1 × 500 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave a mixture of solid and oil. The crude product was triturated with hexanes (200 mL) and filtered under vacuum. The white solid (Wurtz-like coupling product from excess organocopper reagent **52**) was washed with hexanes (2 × 25 mL) and discarded. Concentration of the filtrate and washes in vacuo gave 9.45 g of a slightly cloudy oil. Purification by flash column chromatography (4.5 × 15 cm silica), initially with 19:1 hexanes/Et_2O and then 9:1 hexanes/Et_2O, yielded 5.84 g (99%) of the title compound as a clear, colorless oil. This material was homogeneous by ^1H and ^{13}C NMR; an analytically pure sample was obtained by vacuum distillation: bp 134−135 °C/9 Torr; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.10 (q, J = 7.3 Hz, 2H), 3.77 (s, 3H), 2.56 (dd, J = 13.6 and 6.6 Hz, 1H), 2.43 (dd, J = 13.6 and 7.3 Hz, 1H), 2.30 (dd, J = 14.5 and 5.9 Hz, 1H), 2.26−2.18 (m, 1H), 2.10 (dd, J = 14.5 and 7.7 Hz, 1H), 1.24 (t, J = 7.3 Hz, 3H), 0.93 (d, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 157.6, 132.1, 129.9, 113.5, 60.1, 55.2, 42.1, 41.1, 32.5, 19.6, 14.3; IR (neat) ν 2963, 2930, 2910, 2871, 2832, 1735, 1614 cm^{-1}; *m/z* (ESI-MS) 259.13 (MNa^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.13; H, 8.61.

3,4-Dihydro-7-methoxy-3-methyl-1(*2H*)-naphthalenone, Oxime (56). A 100 mL round-bottomed flask (undried) was charged with PPA (63 g) and **54** (4.95 g, 21.0 mmol). The mixture was heated at 110 °C with magnetic stirring for 1 h. The resulting brown mixture was poured (while hot) into H_2O (300 mL) and extracted with Et_2O (3 × 150 mL). The organics were pooled, washed with saturated $NaHCO_3$ solution (3 × 200 mL), H_2O (1 × 200 mL), and saturated NaCl solution (1 × 200 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 3.40 g of orange oil. The crude tetralone [**55**; ^1H NMR (400 MHz, $CDCl_3$) 7.50 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0 and 2.8 Hz, 1H), 3.83 (s, 3H), 2.93−2.89 (m, 1H), 2.76−2.58 (m, 2H), 2.32−2.24 (m, 2H), 1.13 (d, J = 6.4 Hz, 3H); *m/z* (ESI-MS) 191.13 (MH^+), 213.11 (MNa^+)] was dissolved in a mixture of EtOH (140 mL) and H_2O (35 mL). Hydroxylamine hydrochloride (2.92 g, 42.0 mmol) and pyridine (5.1 mL, 63 mmol) were then added, and the resulting orange solution was heated at reflux overnight. After 12 h the reaction was poured into H_2O (150 mL), and the cloudy mixture was extracted with Et_2O (3 × 150 mL). The organic extracts were pooled, washed with 1 N HCl (1 × 150 mL), H_2O (1 × 150 mL), and saturated NaCl solution (1 × 150 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 3.30 g of an orange solid. Recrystallization from hexanes (ca. 250 mL) yielded 3.05 g (71% over two steps) of the title compound as pale orange prisms, mp 122−123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.4 and 2.8 Hz, 1H), 3.80 (s, 3H), 3.19 (ddd, J = 17.6, 4.4, and 1.8 Hz, 1H), 2.73 (ddd, J = 15.4, 3.7, and 1.8 Hz, 1H), 2.38 (dd, J = 17.6 and 11.0 Hz, 1H), 2.13 (dd, J = 15.4 and 11.7 Hz, 1H), 1.96 (m, 1H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 155.5, 131.7, 130.8, 129.6, 116.8, 107.1, 55.4, 37.4, 31.7, 28.4, 21.5; IR (KBr) ν 3397, 3050, 2999, 2957, 2838, 1630 cm^{-1}; *m/z* (ESI-MS) 206.16 (MH^+). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.44; H, 7.45; N, 6.89.

3,4-Dihydro-7-methoxy-3-methyl-1(*2H*)-naphthalenone, *O*-[(4-Methylphenyl)sulfonyl]oxime (57). To a two-necked 250 mL round-bottomed flask equipped with a septum and an argon inlet adapter was added NaH (1.21 g, 60% dispersion in mineral oil, 50 mmol), which was then washed with hexanes (3 × 30 mL). After the NaH was dried to a fine powder under a stream of argon, TsCl (5.73 g, 30.1 mmol) and 1,2-dimethoxyethane (DME; 20 mL) were added. The oxime (**56**, 2.05 g, 10.0 mmol), as a solution in DME (50 mL), was transferred into the vigorously stirred slurry via cannula over 5 min **[CAUTION: H_2 gas released]**. The flask and cannula were then washed thoroughly with DME (10 mL) and the resulting heterogeneous reaction mixture was stirred at 70 °C for 24 h. After being cooled to room temperature, the mixture was poured into H_2O (150 mL) **[CAUTION: possible remaining NaH]** and extracted with EtOAc (3 × 100 mL). The organic extracts were pooled, washed with H_2O (1 × 150 mL) and saturated NaCl solution (1 × 150 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 4.10 g of a pale orange solid. Recrystallization from Et_2O (ca. 600 mL) yielded 3.17 g (88%) of the title compound as colorless prisms, mp 150−151 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.34 (app dd, J = 8.2 and 2.8 Hz, 3H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 8.4 and 2.8 Hz, 1H), 3.79 (s, 3H), 3.14 (ddd, J = 17.9, 4.4, and 1.8 Hz, 1H), 2.71 (ddd, J = 15.5, 4.1, and 1.8 Hz, 1H), 2.44 (s, 3H), 2.34 (dd, J = 15.5 and 11.0 Hz, 1H), 2.14 (dd, J = 17.9 and 11.6 Hz, 1H), 1.92 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 157.6, 144.8, 132.9, 132.5, 129.7, 129.3, 128.8, 128.2, 118.3, 108.3, 55.3, 36.8, 33.0, 28.4, 21.7, 21.1; IR (KBr) ν 2965, 2922, 2860, 1595 cm^{-1}; *m/z* (ESI-MS) 360.17 (MH^+), 382.16 (MNa^+). Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.44; H, 5.88; N, 3.86.

7-Methoxy-3-methyl-1-naphthalenamine (58). A 250 mL round-bottomed flask (undried) was charged with **57** (2.44 g, 6.79 mmol), KOH (27 mL, 1.0 M solution in MeOH, 27 mmol), and MeOH (65 mL). The deep red reaction mixture was heated at reflux with stirring for 6 h. The resulting brown solution was allowed to cool to room temperature, poured into H_2O (200 mL), and extracted with EtOAc (3 × 200 mL). The organic extracts were pooled, washed with saturated $NaHCO_3$ solution (1 × 200 mL), H_2O (1 × 200 mL), and saturated NaCl solution (1 × 200 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 1.32 g of a brown wax. Purification by flash column chromatography (4.5 × 15 cm silica), initially with 4:1 EtOAc/hexanes and then with 7:3 EtOAc/hexanes, yielded 633 mg (50%) of the title compound as a beige solid. This material was homogeneous by ^1H and ^{13}C NMR; an analytically pure sample was obtained by recrystallization from hexanes as white needles, mp 113−113.5 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.02 (dd, J = 8.8 and 2.2 Hz, 1H), 6.81 (s, 1H), 6.50 (s, 1H), 5.50 (s, 2H), 3.85 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 143.1, 132.6, 129.4, 128.4, 121.7, 117.4, 114.7, 109.7, 101.3, 55.1, 21.3; IR (KBr) ν 3369, 3307, 3210, 3004, 2926, 1634, 1603 cm^{-1}; *m/z* (ESI-MS) 188.11 (MH^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.77; H, 6.98; N, 7.48.

***N*-(7-Hydroxy-3-methyl-1-naphthalenyl)-3-methoxybenzamide (59).** To a 50 mL round-bottomed flask were added **58** (348 mg, 1.86 mmol) and CH_2Cl_2 (15 mL). The clear solution was cooled to 0 °C and BBr_3 (5.6 mL, 1.0 M solution

(43) Lin, H. S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

in hexanes, 5.6 mmol) was added dropwise via syringe over 1 min. The now cloudy white reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature and stir for an additional 14 h. The reaction was then quenched by the dropwise (over 2 min) addition of 1 N NaOH (ca. 5 mL), and the resulting mixture was partitioned between EtOAc (75 mL) and 1 N NaOH (50 mL). The layers were separated and the organics were extracted with 1 N NaOH (2 × 25 mL). The aqueous extracts were pooled, the pH was adjusted to ca. 7 (pH paper) with concentrated HCl, and then the mixture was extracted with EtOAc (3 × 75 mL). The organic extracts were pooled, washed with saturated NaCl solution (1 × 100 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 341 mg of a brown solid. The crude product (**14**) was dissolved in THF (15 mL) and transferred to a two-necked 50 mL round-bottomed flask equipped with a pressure-equalized addition funnel and argon inlet adapter. Pyridine (0.140 mL, 1.72 mmol) was then added and the solution was cooled to 0 °C. A solution of **6** (0.240 mL, 1.72 mmol) in THF (10 mL) was added dropwise via the addition funnel over 1 h. The reaction was stirred overnight and allowed to warm to room temperature as the cooling bath melted. After 12 h the reaction mixture was poured into 1 N HCl (50 mL) and extracted with EtOAc (3 × 50 mL). The organic extracts were pooled, washed with 1 N HCl (3 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL), H_2O (1 × 50 mL), and saturated NaCl solution (1 × 50 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 531 mg of a purple solid. Purification by flash column chromatography (4.5 × 5 cm silica) with 7:3 hexanes/EtOAc yielded 504 mg (88%) of the title compound as a gray solid. This material was homogeneous by ^1H and ^{13}C NMR; an analytically pure sample was obtained by recrystallization from 3:1 hexanes/EtOAc as purple needles, mp 205−206 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 9.65 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.52 (s, 1H), 7.48 (app t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.19 (dd, J = 8.0 and 2.4 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.8 and 2.2 Hz, 1H), 3.86 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 158.9, 154.4, 135.6, 131.7, 130.7, 129.3, 129.1, 128.7, 128.3, 126.3, 125.0, 119.7, 118.4, 117.2, 112.6, 104.4, 55.2, 20.9; IR (KBr) ν 3237, 1645, 1629 cm^{-1}; *m/z* (ESI-MS) 308.13 (MH^+), 330.12 (MNa^+). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.98; H, 5.55; N, 4.59.

***N*-{4,8-Dibromo-3-methyl-7-[[tris(1-methylethyl)silyl]-oxy]-1-naphthalenyl}-3-methoxybenzamide (60).** A 50 mL round-bottomed flask (undried) was charged with **59** (322 mg, 1.05 mmol) and benzene (15 mL). A pressure-equalized addition funnel was attached, sealed with a septum, and filled with a solution of Br_2 (0.215 mL, 4.18 mmol) and benzene (5 mL). The Br_2/benzene solution was added dropwise over 30 min, and the resulting heterogeneous reaction mixture was stirred for 23 h. The reaction was diluted with EtOAc (100 mL), washed with saturated $NaHSO_3$ solution (3 × 50 mL), saturated $NaHCO_3$ solution (3 × 50 mL), H_2O (1 × 50 mL) and saturated NaCl solution (1 × 50 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 472 mg of a gray solid. This material was dissolved in DMF (10 mL) and transferred into a 25 mL round-bottomed flask via syringe. To the solution was added imidazole (184 mg, 2.70 mmol) and triisopropylsilyl chloride (TIPSCl, 0.300 mL, 1.40 mmol). The resulting homogeneous red/brown reaction mixture was stirred at room temperature for 2 h, then poured into H_2O (100 mL), and extracted with EtOAc (3 × 50 mL). The organic extracts were pooled, washed with 1 N HCl (1 × 50 mL), H_2O (3 × 50 mL) and saturated NaCl solution (1 × 50 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 1.13 g of red oil, which was passed through a plug of silica (2.5 × 5 cm) with 19:1 hexanes/EtOAc and then recrystallized from hexanes (606 mg in ca. 15 mL) to yield 590 mg (91%) of the title compound as white hairs: mp 120−121 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.33 (d, J = 9.6 Hz, 1H), 7.65 (d,J = 8.1 Hz, 1H), 7.61 (app s, 1H), 7.51 (s, 1H), 7.46 (app t, J = 8.1 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H), 7.16 (dd, J = 8.1 and 2.6 Hz, 1H), 3.84 (s, 3H), 2.56 (s, 3H), 1.38 (septet, J = 7.4 Hz, 3H), 1.09 (d, J = 7.4 Hz, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 158.8, 151.2, 135.6, 134.1, 131.9, 131.7, 129.2, 128.9, 128.4, 128.3, 122.0, 120.9, 119.8, 116.9, 112.8, 106.8, 55.2, 23.1, 17.8, 12.5; IR (KBr) ν 3315, 2941, 2868, 1649 cm^{-1}; *m/z* (ESI-MS) 622.08 (MH^+), 644.06 (MNa^+). Anal. Calcd for $C_{28}H_{35}Br_2NO_3Si$: C, 54.11; H, 5.68; N, 2.25. Found: C, 54.20; H, 5.67; N, 2.32.

2-(3-Methoxyphenyl)-7-methylbenz[*cd*]indol-3(1*H*)-one (61). A 25 mL round-bottomed-flask was charged with **60** (250 mg, 0.402 mmol) and THF (4 mL). The clear, colorless solution was cooled to −78 °C, and MeLi (0.250 mL, 1.67 M solution in Et_2O, 0.418 mmol) was added dropwise over 1 min. The resulting homogeneous yellow/green reaction was stirred for 30 min and then ^{t}BuLi (1.00 mL, 1.64 M solution in pentane, 1.64 mmol) was added dropwise over 3 min. The now orange/yellow colored reaction was stirred for 1 h and then allowed to warm to 0 °C and stirred for an additional 1 h. The reaction was quenched with saturated NH_4Cl solution (15 mL), diluted with H_2O (25 mL), and extracted with EtOAc (3 × 50 mL). The organic extracts were pooled, washed with H_2O (1 × 50 mL) and saturated NaCl solution (1 × 50 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 181 mg of an orange/yellow solid. Purification by flash column chromatography (3.5 × 15 cm silica) with 7:3 petroleum ether/EtOAc yielded 112 mg (97%) of the title compound as a bright yellow solid, mp 248−249 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.55 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 9.4 Hz, 1H), 7.51 (app t, J = 8.1 Hz, 1H; overlaps with singlet at 7.49), 7.49 (s, 1H), 7.42 (s, 1H), 7.12 (dd, J = 8.1 and 2.6 Hz, 1H), 6.59 (d, J = 9.4 Hz, 1H), 3.90 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.9, 168.6, 155.1, 145.7, 142.8, 142.6, 142.5, 140.5, 139.0, 134.4, 132.6, 132.3, 129.4, 126.0, 123.7, 122.9, 120.8, 64.8, 31.1; IR (KBr) ν 3444, 3918, 1622 cm^{-1}; *m/z* (ESI-MS) 290.12 (MH^+), 312.11 (MNa^+); HRMS (ESI) calcd for $C_{19}H_{16}NO_2$ (MH^+) 290.1181, found 290.1180.

8-Hydroxy-9-methoxy-5-methylbenz[*cd*]isoindolo[2,1-*a*]indol-1(8*H*)-one (63). A 10 mL Schlenk flask was charged with **61** (60.6 mg, 0.210 mmol) and THF (3 mL). The heterogeneous yellow reaction mixture was cooled to −10 °C (acetone/ice bath), and lithium tetramethylpiperidide (Li-TMP; 1.31 mL, 0.800 M solution in THF/hexanes, 1.05 mmol) was added via cannula over 1 min. The resulting red/brown homogeneous reaction was stirred for 1 h and then cooled to −78 °C. A solution of ethyl formate (**49**; 0.170 mL, 0.210 mmol), TMSCl (0.270 mL, 2.11 mmol), and THF (1 mL; prepared by adding **49** to THF followed by the TMSCl) was then added via cannula over 2 min. The now orange reaction mixture was allowed to warm to room temperature overnight as the cooling bath evaporated. After 12 h, the reaction was quenched with 1 N HCl (3 mL), diluted with H_2O (50 mL), and extracted with 4:1 $CHCl_3$/EtOH (3 × 50 mL). The organics were pooled, dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 73.7 mg of an orange/yellow solid. Purification by flash column chromatography (2.5 × 15 cm Brockmann I basic alumina) with 199:1 $CHCl_3$/MeOH (200 mL), 99:1 $CHCl_3$/ MeOH (200 mL), and then 98:2 $CHCl_3$/MeOH (500 mL) yielded 18.4 mg (30%) of recovered **61** and 46.3 mg (70%) of the title compound as a bright orange solid: mp 223−224 °C (decomp); ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.60 (app t, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.45 (d, J = 9.6 Hz, 1H), 7.40 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 9.6 Hz, 1H), 6.55 (d, J = 9.6 Hz, 1H), 3.93 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 188.8, 165.0, 156.6, 146.7, 143.0, 141.8, 141.4, 141.3, 140.4, 139.8, 137.4, 132.9, 132.7, 125.5, 123.5, 123.1, 117.1, 90.8, 65.2, 31.2; IR (KBr) ν 2922, 2844, 1735 cm^{-1}; *m/ z* (ESI-MS) 318.11 (MH^+); HRMS (ESI) calcd for $C_{20}H_{16}NO_3$ (MH^+) 318.1130, found 318.1124.

8,9-Dimethoxy-5-methylbenz[*cd*]isoindolo[2,1-*a*]indol-1(8*H*)-one [HKI 0231B (1b)]. A 10 mL round-bottomed flask equipped with a reflux condenser was charged with **63** (15.7 mg, 0.0495 mmol, dried by azeotropic removal of water with anhydrous toluene), camphorsulfonic acid (CSA; 11.5 mg, 0.0495 mmol), and MeOH (2 mL). The heterogeneous orange reaction mixture was heated at a gentle reflux (oil bath temperature 70 °C) for 36 h. The resulting homogeneous yellow solution was allowed to cool to room temperature, poured into saturated $NaHCO_3$ solution (25 mL), and extracted with CH_2Cl_2 (3×25 mL). The organics were pooled, washed with saturated $NaHCO_3$ solution (2×25 mL) and saturated NaCl solution (1×25 mL), dried with $MgSO_4$, and filtered. Removal of solvents in vacuo gave 20.0 mg of a yellow solid. Purification by preparative TLC with 98:2 CH_2Cl_2/MeOH (plate eluted three times) yielded 15.2 mg (93%) of **1b** as a yellow solid: mp 135−136 °C (lit.[1] mp 135 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, $J = 7.3$ Hz, 1H), 7.64 (d, $J = 9.6$ Hz, 1H), 7.58 (app t, $J = 7.8$ Hz, 1H), 7.46 (s, 1H), 7.33 (s, 1H), 7.04 (d, $J = 8.5$ Hz, 1H), 6.78 (s, 1H), 6.71 (d, $J = 9.6$ Hz, 1H), 4.00 (s, 3H), 2.98 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 156.1, 148.7, 137.5, 134.7, 133.0, 132.9, 132.6, 131.3, 128.9, 127.7, 124.5, 123.8, 118.0, 113.3, 113.1, 109.1, 86.7, 55.8, 51.0, 22.1; IR (KBr) ν 3420, 2926, 1723, 1629, 1618, 1587, 1557, 1488, 1435, 1398, 1339, 1328, 1270, 1199, 1139, 1087, 1030, 951, 895, 868, 851, 789, 736 cm^{-1}; *m/z* (ESI-MS) 332.06 (MH^+); HRMS (ESI) calcd for $C_{21}H_{18}NO_3$ (MH^+) 332.1287, found 332.1273; UV−vis (MeOH) λ_{max} (log ϵ) 463 (4.91), 437 (5.02), 419 (4.92), 383 (4.97), 366 (4.97), 288 (5.11), 238 (5.38) nm. These data are in excellent agreement with the spectra of the natural product.

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Supporting Information Available: Experimental procedures and characterization data for compounds **8**, **11**, **12**−**14**, **16**, **19**, **20**−**22**, **23**, **25**−**27**, **36**, **39**, **46**, **47**, **64**, and **69**; ^{1}H NMR spectra for compounds **13**, **23**, **39**, **47**, **61**, **63**, **64**, and **69**; and ^{1}H and ^{13}C NMR spectra for compounds **22**, **26**, **27**, and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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