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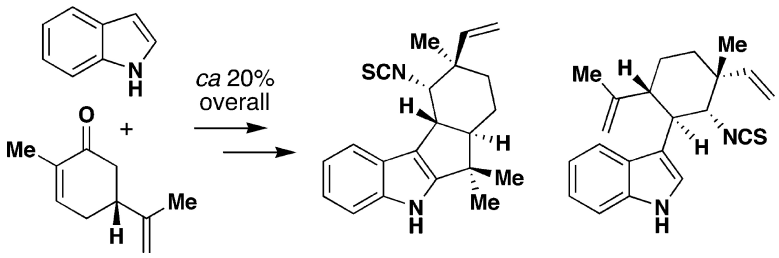

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Direct Coupling of Indoles with Carbonyl Compounds: Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families

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Embedded in countless natural products and medicinally relevant compounds, the indole heterocycle has served to inspire synthetic chemists for well over a century.[1] The hapalindole and fischerindole classes of natural products piqued our interest by virtue of their structural beauty and bioactivity.[2] Our retrosynthetic analysis of hapalindole Q (**1**, Figure 1)[2] led to hypothetical indole- and carvone-derived synthons **2**+ and **3**− (Figure 1). By analogy to Barton's classic synthesis of usnic acid, which utilized a phenolate radical coupling,[3] we reasoned that bond formation between **2** and **3** could conceivably be accomplished through a coupling of radicals **2**• and **3**• which should be accessible via oxidation of the corresponding anions $\mathbf{2}^-$ and $\mathbf{3}^-$. While oxidative dimerization of enolates is known,[4] the analogous process with indoles (or metallo-enamines) is not. In fact, the heterocoupling of enolates has seen little use in synthesis since the process is plagued by low yields, the use of equimolar quantities of metal salts relative to those of all enolate species present, and the requirement of a large excess (3−10 equiv) of one of the partners to avoid homocoupling. Described herein are short, enantioselective, protecting group-free total syntheses of (+)-**1** and 12-*epi*-fischerindole U isothiocyanate (−)-**10**[8] based on the analysis outlined above. Further, these syntheses overcome the limitations of enolate coupling and set a precedent that is extended to the coupling of indoles with a diverse set of ketones, esters, and amides.

Empirical validation of our design (Figure 1) was obtained by employing "standard" conditions for ketone enolate couplings.[4] Thus, as shown in Table 1 (entry 1), addition of LDA (4.0 equiv) to a 3-fold excess of **3** relative to **2** followed by $FeCl_3$ (4.0 equiv) resulted in ca. 15% yield of adduct **4** as a single diastereomer (colorless cubes, mp 129−130 °C, see Scheme 1 for X-ray crystallographic analysis). After evaluating numerous oxidants we found that copper(II)2-ethylhexanoate[5] consistently provided higher yields and eliminated the need to use DMF as cosolvent (entry 2). Similar results were obtained by using equimolar amounts of both **2** and **3** (entry 3). Another increase in yield occurred using a 3-fold excess of **2** (entry 4). The optimum protocol emerged upon addition of LHMDS (3.0 equiv) to a solution of **2** (2.0 equiv) and **3** (1.0 equiv) in THF at −78 °C followed by addition of 1.5 equiv of copper(II)2-ethylhexanoate to furnish **4** in 53% isolated yield (70% based on recovered starting material (sm), entry 5). The remainder of the material consists of recovered **2** and **3** and a small amount of carvone dimer (indole dimer was not observed). The yield is not diminished even on >100 mmol scale. The use of substoichiometric quantities of oxidant (relative to moles of all anionic species) in an enolate coupling is without precedent,[4] and the mechanistic implications of this finding will be discussed elsewhere.[6]

With a simple route to obtain multigram quantities of **4** from (*R*)-carvone, completion of the total synthesis of (+)-**1**[7] was accomplished by executing the following operations (Scheme 1): (1) deprotonation of the indole N−H of **4** (LHMDS, THF, −78 °C),[9] conjugate reduction[10] and stereoselective quenching of the resulting enolate with acetaldehyde (L-Selectride, THF, −78 °C, 1 h; then CH_3CHO, −78 → 23 °C, 2 h); (2) dehydration of the crude alcohol **5** (Martin sulfurane, $CHCl_3$, 23 °C, 10 min) to give indole **6**[7a] in 75% overall yield, intersecting with the Albizati synthesis;[7a] (3) microwave-enhanced[11,12] reductive amination ($NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), MeOH, THF, 150 °C, 2 min) to furnish the amine **7** as a 6:1 mixture of diastereomers; and (4) conversion to (+)-**1** by isothiocyanate formation[7a] ($(CS(imid)_2$ (1.1 equiv, CH_2Cl_2, 23 °C).[13]

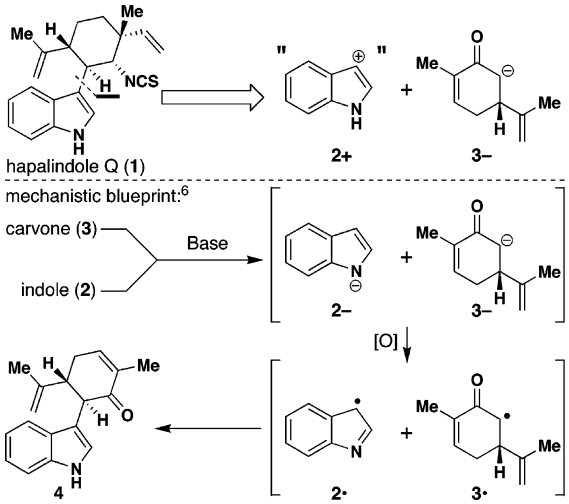


Figure 1. Retrosynthetic analysis of (+)-**1** leads to the invention of a direct coupling of indoles with carbonyl compounds.

Table 1. Selected Optimization Results of **2** + **3** → **4**

indole (**2**) + carvone (**3**) —THF, Base, then [O]; [O] = $FeCl_3$/DMF (Fe) or Copper(II)2-ethylhexanoate (Cu)→ **4**

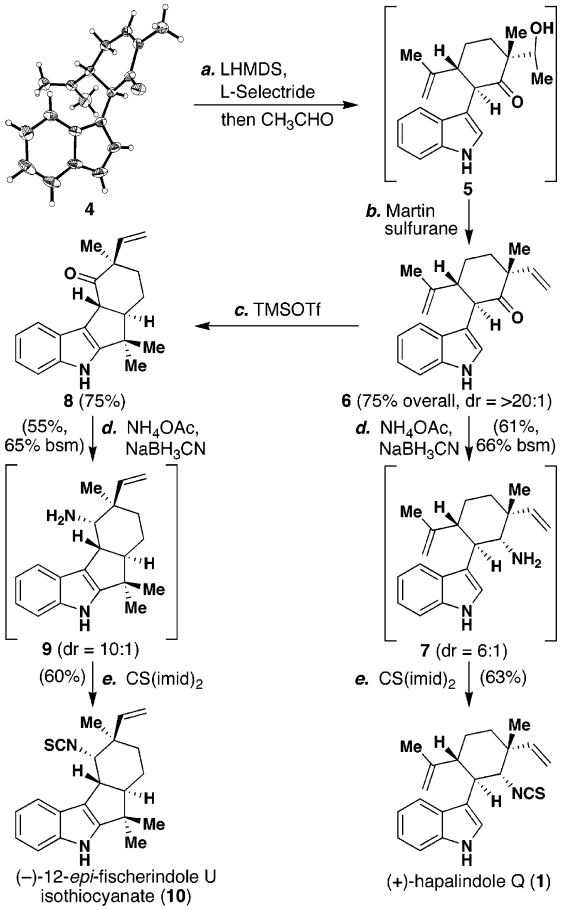
Entry	Conditions	Yield (%)[a]
1	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Fe (4.0 eq), –78 to 23 °C	*ca* 15
2	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 23 °C	24
3	**2** (1.0 eq), **3** (1.0 eq), LDA (2.0 eq), Cu (2.0 eq), –78 to 0 °C	24
4	**2** (3.0 eq), **3** (1.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 0 °C	32
5	**2** (2.0 eq), **3** (1.0 eq), LHMDS (3.0 eq), Cu (1.5 eq), –78 °C	53 (70)[b]

[a] Isolated yield after chromatography. [b] Yield based on recovered sm.

The total synthesis of (−)-**10**[8] was completed from indole **6** by the following short sequence: (1) biomimetic[8,14] acid-catalyzed ring closure (TMSOTf, 25 °C, 1 h) of **6** to afford ketone **8** in 75% yield based on recovered sm; (2) standard reductive amination of **8** to furnish the amine **9** as a 10:1 mixture of diastereomers in 60% yield; and (3) conversion of **9** to (−)-**10** by isothiocyanate formation. Based on the optical rotation of synthetic (−)-**10** {$[\alpha]_D$ −200 (CH_2Cl_2, *c* 0.020), lit. $[\alpha]_D$ +231 (CH_2Cl_2, *c* 0.035)}, the absolute configuration of natural (+)-**10** is opposite that depicted in Scheme 1 (9*S*,10*R*,11*R*,12*R*). The synthetic pathway to (+)-hapalindole Q

10.1021/ja047874w CCC: $27.50

Scheme 1. Enantioselective Total Syntheses of (+)-**1** and (−)-**10**[a]



[a] Reagents and conditions: (a) LHMDS (1.5 equiv), THF, −78 °C, 20 min then L-Selectride (1.05 equiv), 1 h, then CH_3CHO (6.0 equiv), −78→23 °C, 2 h; (b) Martin sulfurane (1.1 equiv), $CHCl_3$, 10 min, 75% overall; (c) TMSOTf (3.0 equiv), MeOH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 75% bsm; (d) $NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), MeOH, THF, 150 °C, 2 min, 61% (**7**); for **9**: same reagents, 23 °C, 48 h, 55%; (e) $CS(imid)_2$ (1.1 equiv), CH_2Cl_2, 0→23 °C, 3 h, 63% (**1**), 60% (**10**).

(**1**) and (−)-12-*epi*-fischerindole U isothiocyanate (**10**) proceeds in 22% and 15% overall yield from (*R*)-carvone, respectively.

The scope of the direct indole coupling was briefly evaluated by the study of the examples summarized in Table 2 using conditions established for the synthesis of **4**. Free alcohols are tolerated (**12**, additional LHMDS added), hindered indoles such as **13** are accessible, and amides also participate in this reaction (**14**−**18**) as illustrated with Evans and Oppolzer auxiliaries. The latter substrates (**15**−**18**) proceed with high diastereoselectivity. The method also works with functionalized indole substrates (**16**−**18**) and *tert*-butyl esters (**19**).

In conclusion, we have developed a new and practical method for the direct coupling of indoles with carbonyl compounds that has been applied to the most concise and efficient synthesis of (+)-**1** yet reported and to the first total synthesis and absolute configuration assignment of a fischerindole [(−)-**10**]. This protocol can be used to construct quaternary carbon centers, is amenable to asymmetric synthesis, and can be performed on a multigram scale. Indoles that would be otherwise unobtainable in a single step from readily available materials are now easily accessed, thus filling a gap in indole synthesis methodology.[1]

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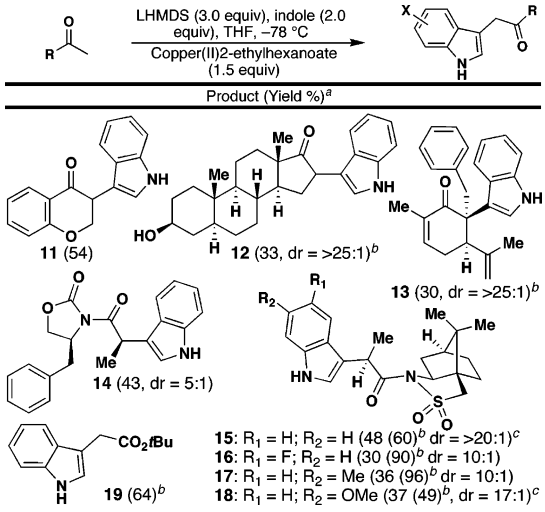
Table 2. Preparation of α-Indole Carbonyl Compounds



[a] Isolated yield after chromatography. [b] Yield based on recovered sm. [c] LDA used.

Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. X-ray crystallographic file in CIF format. This material is available via the Internet at http://pubs.acs.org.

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(1) One-third of the following book is dedicated to indole-containing natural products: Nicolaou, K. C.; Snyder S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; Chapters 5, 8, 12, 18, 19, 20, and 22, p 639. For an excellent overview of indole synthesis and reactivity, see: Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996; p 175.
(2) Hapalindole isolation: Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036−1043; Fischerindole isolation: Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257−3260.
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(4) (a) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605−4606. (b) Dessau, R. M.; Heiba, E. I. *J. Org. Chem.* **1974**, *39*, 3457−3459. (c) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912−2914. (d) Ito, Y.; Konoike, T.; Harada, T.; Saegusa T. *J. Am. Chem. Soc.* **1977**, *99*, 1487−1493. (e) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408−5411. (f) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277−7283.
(5) Commercially available from several sources, including Aldrich.
(6) We initially imagined the mechanism shown in Figure 1, but other mechanistic pathways may be operative such as addition of **3**• to **2**$^-$ to give **4**$^{\bullet-}$ followed by oxidation to **4**.
(7) Total syntheses of (+)-**1**: (a) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499−3502 (ca. 4% yield). (b) Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120−14125 (ca. 1.0% yield). Total synthesis of racemic **1**: Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189−3191 (ca. 9% yield). Yields are from commercially available material.
(8) Isolation (+)-**10**: Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935−9942.
(9) Addition of L-Selectride (1−3 equiv) to **4** followed by addition of acetaldehyde led only to the corresponding saturated ketone due to internal quenching of the resulting enolate onto the indole N−H.
(10) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194−2200.
(11) The conditions used by Albizati (ref 7a) for reductive amination were $NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), 7 days, dr = 3:1.
(12) For recent uses of microwave irradiation in complex natural product synthesis, see: Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706−707; Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674−2677.
(13) The minor amine diastereomer was identical to 12-*epi*-hapalindole D isothiocyanate (ref 8), see Supporting Information for details.
(14) Fukuyama observed this ring closure as an undesired byproduct during the course of a beautiful total synthesis of (−)-hapalindole G: Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125−3126.

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