Indole Synthesis

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Application of a Palladium-Catalyzed C–H Functionalization/ Indolization Method to Syntheses of *cis*-Trikentrin A and Herbindole B

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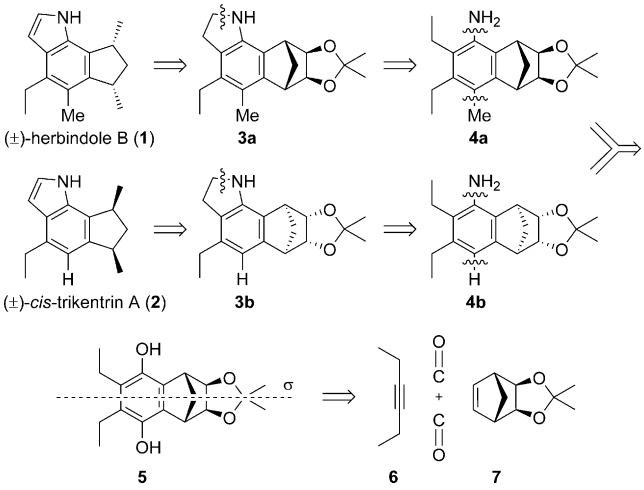
Abstract: *We describe herein formal syntheses of the indole alkaloids cis-trikentrin A and herbindole B from a common meso-hydroquinone intermediate prepared by a ruthenium-catalyzed [2+2+1+1] cycloaddition that has not been used previously in natural product synthesis. Key steps include a sterically demanding Buchwald–Hartwig amination as well as a unique C(sp³)–H amination/indole formation. Studies toward a selective desymmetrization of the meso-hydroquinone are also reported.*

The trikentrin and herbindole alkaloids (e.g., **1** and **2**, Scheme 1) comprise two families of similarly structured, but pseudoenantiomeric, polyalkylated cyclopent[*g*]indoles. The herbindole alkaloids were isolated by the Scheuer group in 1990 from the Western Australian sponge, *Axinella* sp., and were shown to exhibit cytotoxicity against KB cells (5–10 μg mL^{-1}) and to act as fish antifeedants.[1] The more well-known trikentrin alkaloids were isolated in 1986 by the Capon group from the marine sponge *Trikentron flabelliforme* off the northern coast of Australia, and were shown to possess antimicrobial activity against Gram-positive bacteria.[2] Since their isolation, both the trikentrin and herbindole alkaloids have been the target of many non-asymmetric as well as enantioselective syntheses by numerous research groups, including those of MacLeod, Kanematsu, Silva, Natsume, Blechert, Funk, Buszek, Boger, Kerr, RajanBabu, and Saito.[3–5] In the majority of these syntheses, herbindole B (**1**) and *cis*-trikentrin A (**2**) served mainly to highlight new synthetic methods given their modest complexity.

Herein, we report formal syntheses of both (±)-herbindole B (**1**) and (±)-*cis*-trikentrin A (**2**) that highlight a novel C(sp³)–H amination/dehydrogenation reaction, which promotes a net indolization of the corresponding *ortho*-ethyl anilines **4a**/**b** to provide the core of these natural products (Scheme 1). This powerful reaction brings the syntheses of **1** and **2** back to a common *meso*-hydroquinone intermediate **5**. It was envisaged that hydroquinone **5**, in turn, could be prepared by a ruthenium-catalyzed [2+2+1+1] cycloaddition, following the precedent of Mitsudo and co-workers.[6] Finally, an early-stage enantioselective diol desymmetrization of the *meso*-hydroquinone **5** was planned to facilitate enantiodivergent syntheses of herbindole B and *cis*-trikentrin A.



Scheme 1. Retrosynthesis of herbindole B and *cis*-trikentrin A.

Our studies commenced with the preparation of the *exo*-acetonide–norbornene derivative **7** by a known procedure.[7] This strained bicyclic alkene **7** was subjected to a ruthenium-catalyzed [2+2+1+1] cycloaddition with CO and commercially available 3-hexyne to yield hydroquinone **5** in 39% yield. The hydroxy groups of *meso*-hydroquinone **5** were differentially activated by sequential monotriflation and monotosylation to provide **9** (Scheme 2). With a focus on herbindole B as an initial target, Stille cross-coupling of aryl triflate **9** with $SnMe_4$ gave the methylated aryl tosylate **10a**.

Our next goal was to prepare aniline **4a** from aryl tosylate **10a**. Initial attempts at a Buchwald–Hartwig amination under conditions developed by Stradiotto[8] and by Hartwig[9] led to modest yields of the desired aniline along with recovery of the corresponding phenol (by cleavage of the tosyl group) and starting material. A brief optimization study in which we used

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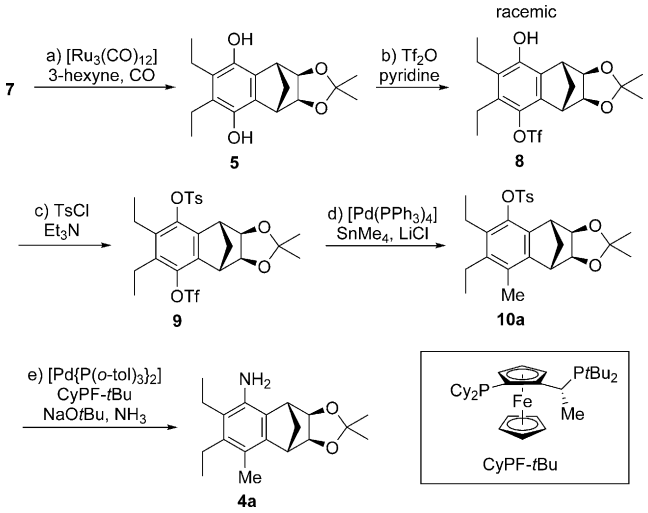
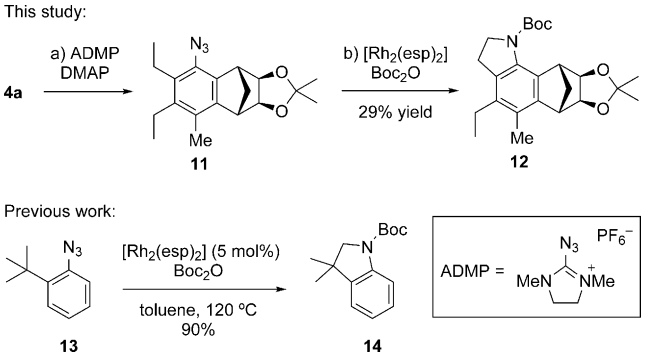


Scheme 2. Synthesis of aniline intermediate **4a** toward herbindole B (**1**). Reagents and conditions: a) $[Ru_3(CO)_{12}]$ (4 mol%), 3-hexyne (1.1 equiv), CO (1200 psi), *N*-methylpiperidine, 160°C, 2 days, 39%; b) Tf_2O (1.05 equiv), pyridine (1.2 equiv), CH_2Cl_2, 0→20°C, 2 h, 58%; c) TsCl (1.1 equiv), Et_3N (3 equiv), CH_2Cl_2, 0→20°C, 12 h, 93%; d) $SnMe_4$ (1.5 equiv), $[Pd(PPh_3)_4]$ (10 mol%), LiCl (5 equiv), DMF, 150°C (microwave), 6 h, 91%; e) $[Pd\{P(o\text{-}tol)_3\}_2]$ (3 mol%), CyPF-*t*Bu (3 mol%), NaO*t*Bu (1.0 equiv), NH_3 (4 equiv), 1,4-dioxane, 100°C, 22 h, 54%. Tf = trifluoromethanesulfonyl, Ts = tosyl, DMF = *N*,*N*-dimethylformamide, tol = tolyl.



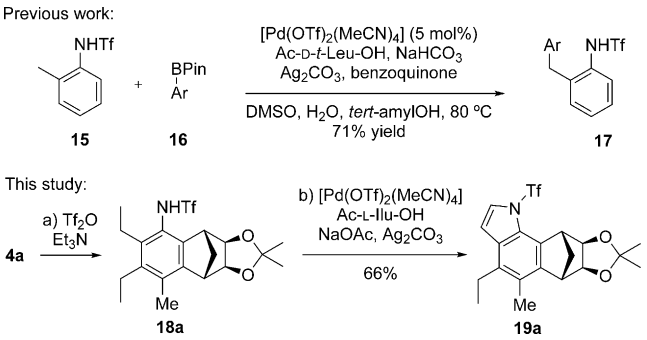
Scheme 3. Rhodium-catalyzed azide decomposition to form the indoline system. Reagents and conditions: a) ADMP (2 equiv), DMAP (3 equiv), MeCN, 50°C, 3 h, 56%; b) $[Rh_2(esp)_2]$ (5 mol%), Boc_2O (1 equiv), toluene, 120°C, 16 h, 29%. ADMP = 2-azido-1,3-dimethylimidazolinium hexafluorophosphate, DMAP = 4-dimethylaminopyridine, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid, Boc = *tert*-butoxycarbonyl.

the Hartwig conditions as a starting point revealed that higher temperatures as well as fewer equivalents of ammonia (which likely attenuates tosyl cleavage) led to higher yields of **4a** (54%).

We considered two main strategies for the construction of the C–N bond between the aniline amino group and the adjacent ethyl group that would ultimately provide the indole moiety resident in the trikentrin and herbindole alkaloids. The first entailed conversion of the aniline amino group into the corresponding aryl azide, which could be utilized in a nitrenoid insertion.[10] The second strategy was to use a directing group on the aniline nitrogen atom to effect C–H activation of the proximal ethyl group, thus culminating in C–N bond formation.[11]

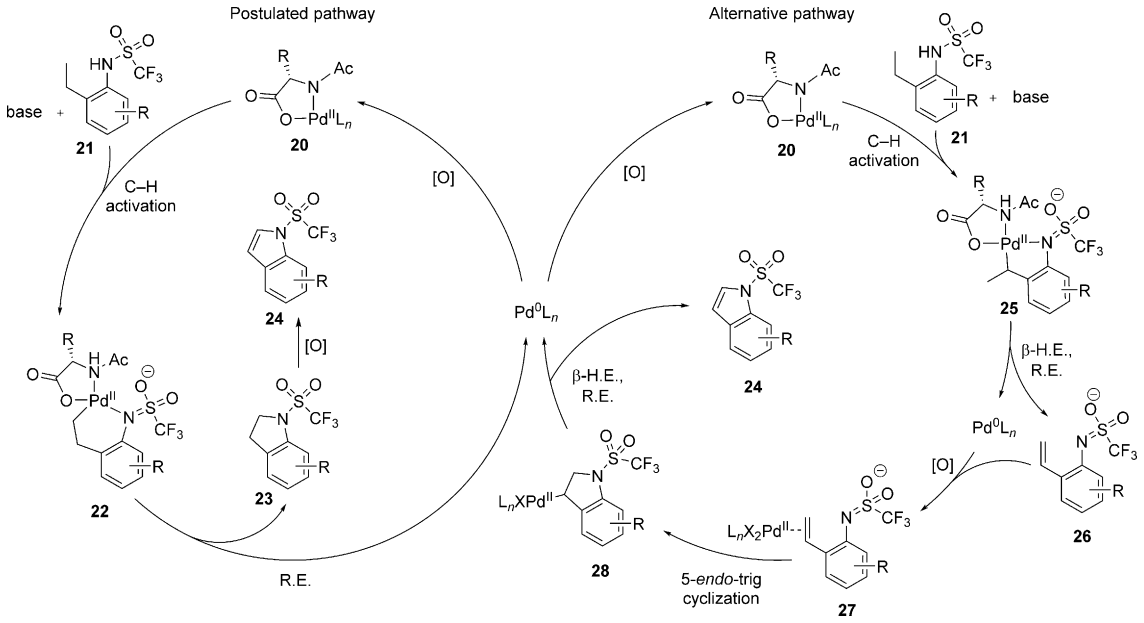
Aryl azide **11** was readily formed from aniline **4a** by the use of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[12] as the diazo-transfer reagent (Scheme 3). By following the precedent of Driver and co-workers[13] and using $[Rh_2(esp)_2]$ as a catalyst, we obtained indoline **12** in 29% yield (after in situ Boc protection). This transformation probably occurs in low yield (as compared to the Driver example, i.e., **13**→**14**) because **11** does not enjoy a favorable Thorpe–Ingold effect or the statistical advantage of the *tert*-butyl group.

The direct conversion of aniline **4a** (or its acylated or sulfonated derivatives) into the desired indoline (or corresponding indole) proved to be more effective. On the basis of literature precedent for $C(sp^2)$–H amination, a variety of directing groups on the aniline amino group, including the acetyl, tosyl,[14] and *N*,*N*-diisopropyloxalyl amide[15] groups, were tested in the more challenging $C(sp^3)$–H amination but to no avail. Inspired by a C–H activation/cross-coupling method developed by one of us (**15**+**16**→**17**, Scheme 4),[11c] we envisioned an alternative pathway, through which, in the absence of a boronic acid coupling partner, perhaps C–N bond formation could be achieved.



Scheme 4. Direct indole formation by C–H activation. Reagents and conditions: a) Tf_2O (1.05 equiv), 2,6-dtbpy (1.2 equiv), CH_2Cl_2, −78→20°C, 95%; b) $[Pd(OTf)_2(MeCN)_4]$ (20 mol%), Ac-L-Ile-OH (40 mol%), NaOAc (6 equiv), Ag_2CO_3 (2.5 equiv), *tert*-amyl alcohol, 100°C, 12 h, 66%. 2,6-dtbpy = 2,6-di-*tert*-butyl pyridine, Ac-L-Ile-OH = *N*-acetyl-L-isoleucine, Ar = 4-(methoxycarbonyl)phenyl, DMSO = dimethyl sulfoxide.

An untested variable was whether less-activated alkyl sites, such as the ethyl group in **18a** unlike the benzylic *ortho*-tolyl group in **15**, could be activated under these conditions. Surprisingly, aniline triflamide **18a** reacted to give indole **19a** in 66% yield (one C–N bond and one C–C double bond formed; average 81% yield per event).[16] Not only was the desired C–N bond forged, but attendant oxidation yielded the indole moiety resident in natural product targets **1** and **2**. Although the mechanism of this transformation has not been rigorously established, it may proceed by sequential $C(sp^3)$–H activation and C–N bond formation to give an indoline (intermediate **23** in Scheme 5), which is subsequently oxidized to the indole **24** at a faster rate than indoline formation. Although an alternative mechanism in which benzylic palla-

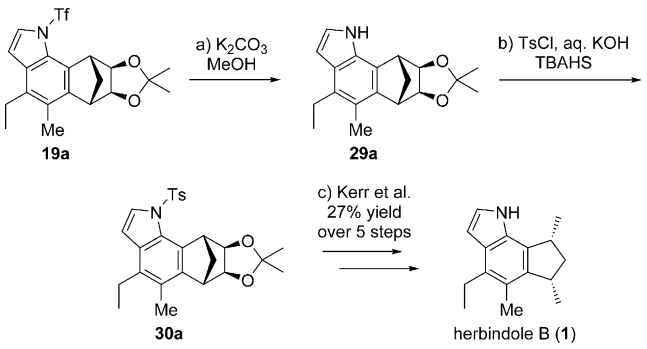


Scheme 5. Two possible catalytic cycles for the indolization reaction. β-H.E. = β-hydride elimination, R.E. = reductive elimination.

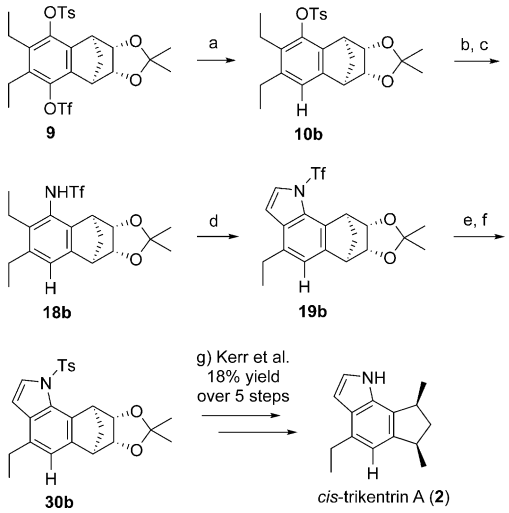
dation/β-hydride elimination to form *ortho*-vinyl compound **26** is followed by 5-*endo*-trig aminopalladation/β-hydride elimination cannot be discounted, we have not observed vinyl aniline **26** as an intermediate and therefore favor the former mechanism.

Removal of the triflyl group from **19a** and tosylation provided **30a** (Scheme 6), which is an intermediate in the synthesis of herbindole B by the Kerr group,[4c] thus completing a formal synthesis.

The flexible aryl triflate functional handle allowed us to use **9** as a common intermediate and also develop a formal synthesis of *cis*-trikentrin A (**2**, Scheme 7).[17] For the preparation of **2**, aryl triflate **9** was subjected to hydrogenolysis with H_2 under high pressure to give **10b** in 89% yield. Aryl tosylate **10b** was advanced to aniline triflamide **18b** by Buchwald–Hartwig amination followed by triflation of the resulting aniline. When triflamide **18b** was subjected to our newly developed indolization reaction, the corresponding indole



Scheme 6. Formal synthesis of herbindole B (**1**). Reagents and conditions: a) K_2CO_3 (3.5 equiv), MeOH, 50°C, 19 h, 96%; b) TsCl (1.5 equiv), concentrated aqueous KOH (1.1 equiv), TBAHS (0.5 equiv), PhMe, 20°C, 1 day, 80%; c) synthesis of herbindole B (**1**) by the Kerr group.[4c] TBAHS = tetrabutylammonium hydrogen sulfate.

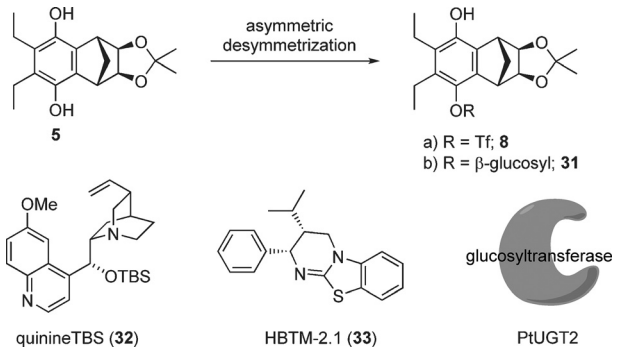


Scheme 7. Formal synthesis of *cis*-trikentrin A. Reagents and conditions: a) 10% Pd/C (50 mol%), 4 Å MS (100 wt%), H_2 (700 psi), acetone, 50°C, 5 days, 89%; b) [Pd{P(*o*-tol)$_3$}$_2$] (4 mol%), CyPF-*t*Bu (4 mol%), NaO*t*Bu (1.1 equiv), NH_3 (5 equiv), 1,4-dioxane, 100°C, 23 h, 82%; c) Tf_2O (1.05 equiv), 2,6-dtbpy (1.2 equiv), CH_2Cl_2, −78 to 5°C, 1.5 h, 87%; d) $Pd(OAc)_2$ (20 mol%), Ac-L-Ilu-OH (40 mol%), NaOAc (6 equiv), Ag_2CO_3 (2.5 equiv), *tert*-amyl alcohol, 100°C, 12 h, 61%; e) K_2CO_3 (3.5 equiv), MeOH, 50°C, 6 h, 88%; f) TsCl (1.5 equiv), concentrated aqueous KOH (1.1 equiv), TBAHS (0.5 equiv), toluene, 20°C, 12 h, 84%; g) synthesis of *cis*-trikentrin A (**2**) by the Kerr group.[4d]

19b was isolated in 61% yield (one C–N bond and one C–C double bond formed; average 78% yield per event). *N*-Triflyl indole **19b** was transformed into *N*-tosyl indole **30b**, which is an intermediate in the synthesis of *cis*-trikentrin A (**2**) by Jackson and Kerr,[4d] thus completing its formal synthesis.

Given that the monotriflation of **5** to give **8** (Scheme 2) is the enantiodetermining step for the syntheses described

herein, we investigated several strategies to render this step enantioselective. Historically, enzymes,[18] metal catalysts,[19] and organocatalysts[20] have been employed in diol desymmetrization. Of these catalysts, organocatalysts have proven to be the most general. Therefore, we elected to investigate this avenue first. However, despite recorded successes in the organocatalytic enantioselective acylation, phosphorylation, and silylation of aliphatic diols, only limited success has been reported for phenol (and hydroquinone) substrates. Furthermore, only two examples of organocatalytic sulfonation are known.[21] Our preliminary studies to overcome these existing challenges have focused on the use of quinine derivatives,[22] peptides,[21a,23] and chiral isothioureas[24] as catalysts. Additional challenges inherent to the use of hydroquinone **5** as a substrate include its ready oxidation to the corresponding quinone as well as oversulfonation. The use of quinine derivative **32** (Scheme 8) as a sulfonation catalyst led to low



Scheme 8. Reagents and catalysts tested in the enantioselective triflation and diastereoselective glucosylation of *meso*-hydroquinone **5**. Reagents and conditions: a) Tf_2O (1.1 equiv), HBTM-2.1 (2.1 equiv), CH_2Cl_2, −78→−40 °C, 1.5 days, 42% (63% *ee*); b) PtUGT2 glucosyltransferase (0.034 mol%), DMSO, aqueous buffer, 20 °C, 5 days, 58% (d.r. 20:1).

conversion and no detectable enantiomeric excess. The use of chiral isothioureas proved more effective for the desired enantioselective sulfonation. Whereas the use of isothiourea catalyst HBTM-2.1 (**33**; 20 mol%) and Tf_2O gave monotriflated hydroquinone **8** with 19% *ee* (21% yield), a higher *ee* value (63% *ee*; 42% yield)[25] was observed with 2 equivalents of **33**. In the latter case, **33** may serve as a chiral base for deprotonation of the hydroquinone substrate, instead of effecting asymmetric group transfer of the triflyl group. Notably, **33** could be recovered (in 69% yield) following the triflation and reused without any loss of enantioselectivity.

We also investigated the enzymatic desymmetrization of hydroquinone **5**. We observed that with the glucosyltransferase PtUGT2,[26] glucosylation of hydroquinone **5** occurred in 58% yield to provide glucoside **31** with d.r. 20:1. This unprecedented desymmetrization with cheap and readily available glucose now provides an effective platform for the synthesis of the herbindoles and trikentrins in enantiomerically enriched form.

In summary, we have completed formal syntheses of herbindole B and *cis*-trikentrin A by using an unprecedented palladium-catalyzed C(sp^3)–H functionalization/indolization reaction of an unbiased ethyl group. The syntheses diverge from a *meso*-hydroquinone intermediate **5**, which provided an opportunity to investigate an unusual desymmetrizing sulfonation of a hydroquinone. Use of the chiral isothiourea HBTM-2.1 (**33**) enabled the enantioselective monotriflation of **5** to give **8** with 63–67% *ee*. An enzymatic glucosylation of hydroquinone **5** effected desymmetrization with 20:1 selectivity. The use of this unprecedented enzymatic desymmetrization to complete enantioselective syntheses of the herbindoles and trikentrins is the subject of ongoing studies in our laboratory.

Acknowledgments

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Keywords: C–H activation · desymmetrization · indole alkaloids · indolization · natural products

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[25] On a 0.03 mmol scale, the reaction gave **8** in 30% yield (67% *ee*). On a 0.16 mmol scale, the reaction gave **8** in 42% yield (63% *ee*), along with 22% recovered starting material **5**, the bistriflated product (8% yield), and the quinone resulting from oxidation of the starting material (17% yield).
[26] PtUGT2 is UDP-glucose glucosyltransferase isolated from Polygonum tinctorium, obtained from the Dueber laboratory (unpublished data).

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