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+4+1+1] cyclodaddition 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) 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 Trikentrion 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+1] cyclodaddition, 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 enantiomeric syntheses 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+1] cyclodaddition 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 SnMe₃ 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...
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. The second strategy was to use the corresponding aryl azide, which could be utilized in the Thorpe–Ingold effect or the statistical advantage of the tert-butyl group.

Surprisingly, aniline triflamide 4a, could be activated under these conditions.

Scheme 3. Rhodium-catalyzed azide decomposition to form the indole system. Reagents and conditions: a) ADMP (2 equiv), DMAP (3 equiv), MeCN, 50 °C, 3 h, 56%; b) [Rh2(esp)] (5 mol%), Boc2O (1 equiv), toluene, 120 °C, 16 h, 29%. ADMP = 2-azido-1,3-dimethylimidazolinium hexafluorophosphate, DMAP = 4-dimethylaminopyridine, esp = α,α′,α″-tetramethyl-1,3-benzenediisopropanoic acid, Boc = tert-butoxycarbonyl.

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.

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 triflimide 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).[14] 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(sp3)–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-
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 H2 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 19b was isolated in 61% yield (one C–C bond and one C=C double bond formed; average 78% yield per event).

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

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

**Scheme 6.** Formal synthesis of herbindole B (1). Reagents and conditions: a) K2CO3 (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 %), H2 (700 psig), acetone, 50 °C, 5 days, 89%; b) [Pd(P(o-tol)3)2] (4 mol %), CyPF-tBu (4 mol %), NaOAcBu (1.1 equiv), N,N,N',N'-tetramethylethylenediamine, 100 °C, 23 h, 82%; c) Tf2O (1.05 equiv), 2,6-dtbpy (1.2 equiv), CH2Cl2, 0 °C, 1.5 h, 87%; d) Pd(OAc)2 (20 mol %), AcI-Pf-A (2 mol %), NaOAcBu (6 equiv), tert-amyl alcohol, 100 °C, 12 h, 61%; e) K2CO3 (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 monofunctionalization 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. 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 conversion and no detectable enantiomeric excess. The use of chiral isothioureas proved more effective for the desired enantioselective sulfonation. Whereas the use of isothiourea chiral isothioureas proved more effective for the desired

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We also investigated the enzymatic desymmetrization of hydroquinone 5. We observed that with the glucosyltransferase PUGT2,[24] 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(sp³)–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 mon triflation 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.

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[15] Control experiments have revealed that Pd(OAc)2 or [Pd(OTf)2-(MeCN)4] is necessary for the reaction to occur, and that with Pd(OAc)2 in the absence of a ligand, the product is still formed in lower yield (7%).

[16] Compound 9 is rendered in enantiomeric form in Scheme 7 as compared to the illustration in Scheme 2.

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