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A practical, multi-gram synthesis of (±)-herbindole A, (±)-herbindole B, and (±)-herbindole C from a common intermediate via 6,7-indole aryne cycloaddition and Pd(0)-catalyzed cross-coupling reactions

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ABSTRACT

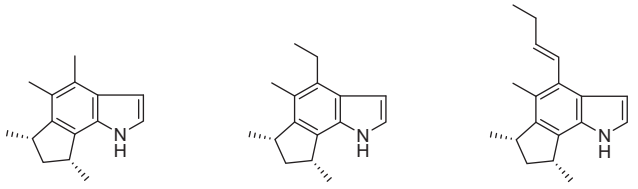
A practical, multi-gram 10-step synthesis of racemic herbindole A, B, and C from a common intermediate is described. The key step features a remarkably regioselective C-7 metal–halogen exchange and elimination from a Bartoli-generated *N*-*t*-butyldimethylsilyl-4,6,7-tribromo-5-methylindole scaffold to afford the 6,7-indole aryne. Cycloaddition with cyclopentadiene, oxidative cleavage, and Fujimoto reduction gave a common intermediate from which all three herbindoles were readily derived. A final Pd(0)-catalyzed Negishi and Stille cross-coupling reaction at the C-4 bromide afforded each of the herbindoles on a multigram scale.

The herbindoles **1**–**3** are three analogous 6,7-benzannulated indole natural products that were isolated from the Western Australian sponge *Axinella* sp. and reported by Scheuer in 1990 (Fig. 1).[1] They are close structural relatives of the trikentrins that were discovered four years earlier[2] and are members of a larger though still uncommon class of sinistrally annulated or substituted indoles.

The other benzannulated members include the teleocidins (6,7-benzannulation),[3] the nodulisporic acids (5,6-benzannulation),[4] the penetrems (4,5-benzannulation),[5] and the notoamides and related stephacidins (6,7-heterobenzannulation).[6] The biosynthetic origins of the herbindoles (and the trikentrins) remain unknown, though they are probably not derived from tryptophan due to the lack of substitution at the C-3 position.

The herbindoles were reported to exhibit cytotoxic and antifeedant properties, although the levels of these activities were not given in the original citation or to our knowledge in any subsequent report. We recently synthesized the first library of benzannulated indoles inspired by the herbindoles and the trikentrins in an effort to develop new chemotypes in support of drug discovery initiatives currently underway by us and our collaborators.[7] Several members of this library exhibited provocative levels of antiproliferative activity that mimicked the effect of vincristine, but not that of taxol, on tubulin polymerization.[7a] Other members of these annulated indole libraries remarkably increased the rate and level of actin polymerization in a manner similar to jasplakinolide, suggesting, *inter alia*, that they might also stabilize the cleavage furrow to block cytokinesis.[7b] Since these compelling biological results have already validated the significance of such libraries, the development of additional small molecule collections based on these systems clearly has much merit.

The synthesis of this library relied on a key strategy of regioselective C-7 metal–halogen exchange of a Bartoli-generated[8]



(-)-Herbindole A, **1** (-)-Herbindole B, **2** (-)-Herbindole C, **3**

Figure 1. Structures of the herbindoles.

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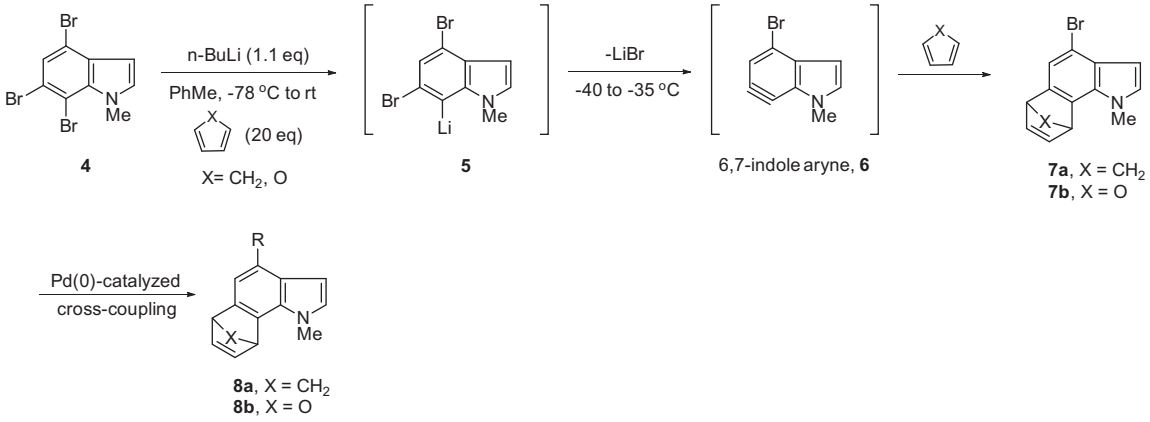


Scheme 1. Formation of 6,7-indole aryne and cycloaddition via regioselective metal–halogen exchange and elimination.

4,6,7-tribromoindole scaffold **4** that permitted the facile generation of the 6,7-indole aryne, **6**[9,10] followed by cycloaddition with cyclopentadiene and furan (Scheme 1).

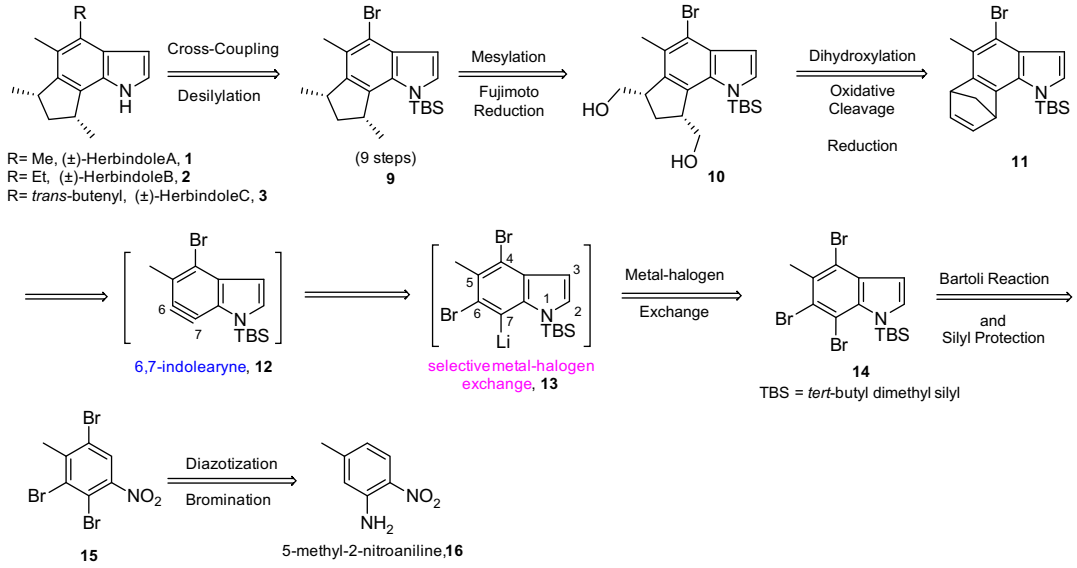
The remaining C-4 aryl bromide was subjected to various Pd(0)-catalyzed cross-coupling reactions to create a diverse library of compounds **8a** and **8b** that were predicted to show a priori favorable pharmacokinetic properties.[7a] During the course of these investigations, it occurred to us that a practical, multi-gram synthesis of each of the herbindoles should be possible by a simple modification of the library tactic. Practical and efficient routes to important natural products have been recognized as major contemporary objectives of synthetic organic chemists.[11] We now report in this Letter an efficient, practical and economical route to the herbindoles from a common intermediate via our indole aryne cycloaddition and cross-coupling methodology,[7a] and on a scale that is sufficient to meet the demand for these fascinating compounds.

The herbindoles and the trikentrins have been characterized as 'deceptively simple'[12] natural products 'whose relatively small size belies their complexity'.[13a] Indeed, several novel approaches to address these challenging systems have been reported by other laboratories. The first successful total synthesis efforts by Natsume in 1992 were ostensibly designed to confirm the structure of the herbindoles and to establish their absolute configuration.[14] Subsequent total syntheses by Kerr relied on a novel quinone imine cycloaddition as the key step,[13] while a more recent report by Sato used a Rh(I)-catalyzed [2+2+2] cyclization process to access an optically pure late-stage 2,3-dihydro indole intermediate.[15] None of these approaches, notwithstanding their importance and synthetic elegance, appeared to be amenable to a scalable synthesis of the herbindoles.

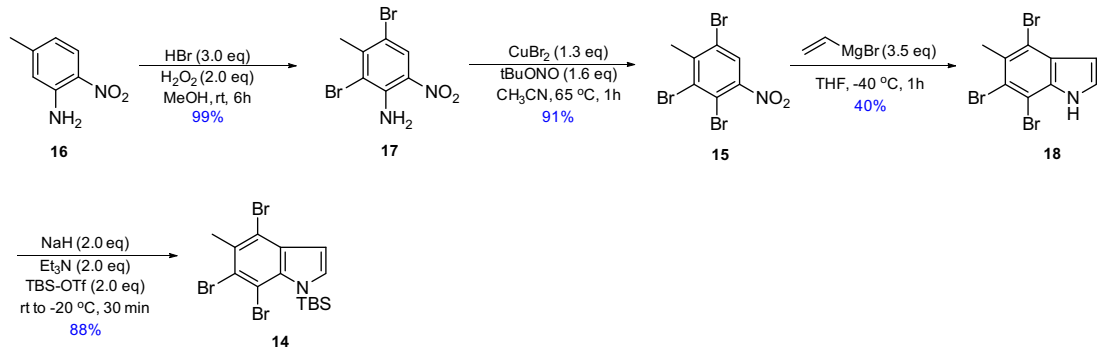
Our retrosynthetic analysis is shown in Scheme 2, and was influenced in part by our own previous experience with the total synthesis of herbindole A and B.[16] The aim was to effect a regioselective metal–halogen exchange from the 4,6,7-tribromo-5-methylindole system **14** at C-7, thereby generating the requisite indole aryne **12**.

Although we previously demonstrated that similar regioselective exchanges occurred at C-7 in the 4,6,7-tribromo- and 5,6,7-tribromoindole cases,[17,18] it was not at all obvious that the presence of an electron-donating alkyl group at C-5 would favorably impact the proposed regioselectivity. Presumably the alternative exchange at C-6 would still afford the indole aryne; however, preferential or exclusive exchange at C-4 would render the plan moot.

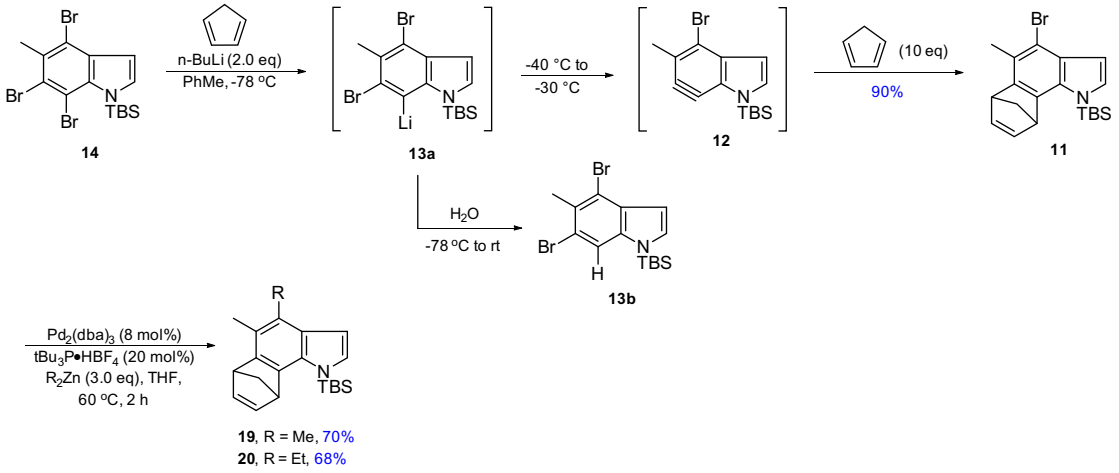
The synthesis of the 4,6,7-tribromo-5-methylindole began with commercially available and economically feasible 5-methyl-2-nitroaniline **16** (Scheme 3). Bromination (HBr, 3 equiv; H_2O_2,



Scheme 2. Retrosynthetic analysis of the herbindoles.



Scheme 3. Synthesis of the 4,6,7-tribromo-5-methylindole scaffold.



Scheme 4. Regioselective C-7 metal–halogen exchange/elimination and cycloaddition.

2 equiv; MeOH, rt, 6 h) afforded the 2,4-dibromo-3-methyl-6-nitroaniline, **17** in quantitative yield on a 20 g scale. Diazotization ($CuBr_2$, 1.3 equiv; *t*-BuONO, 1.6 equiv; MeCN, 65 °C, 1 h) consistently gave the 1,3,4-tribromo-2-methyl-5-nitrobenzene **15** in 91% yield, again on a 20 g scale.

Application of the Bartoli reaction (CH_2=CHMgBr, 3.5 equiv; THF, −40 °C, 1 h) to this intermediate on a 15 g scale gave the desired indole **18** (40%) in only three steps. While we have successfully employed the Bartoli reaction previously in natural products' total synthesis and library efforts, our experience has been that the yields with polyhalogenated systems are significantly diminished at scales above about 5 g.[7a] The current example is therefore a fortuitous exception. Finally, the indole nitrogen was protected in 88% yield with a TBS group (NaH, 2.0 equiv; Et_3N, 2.0 equiv; TBSOTf, 2.0 equiv; rt, 0.5 h) which we found to be quite robust.[19]

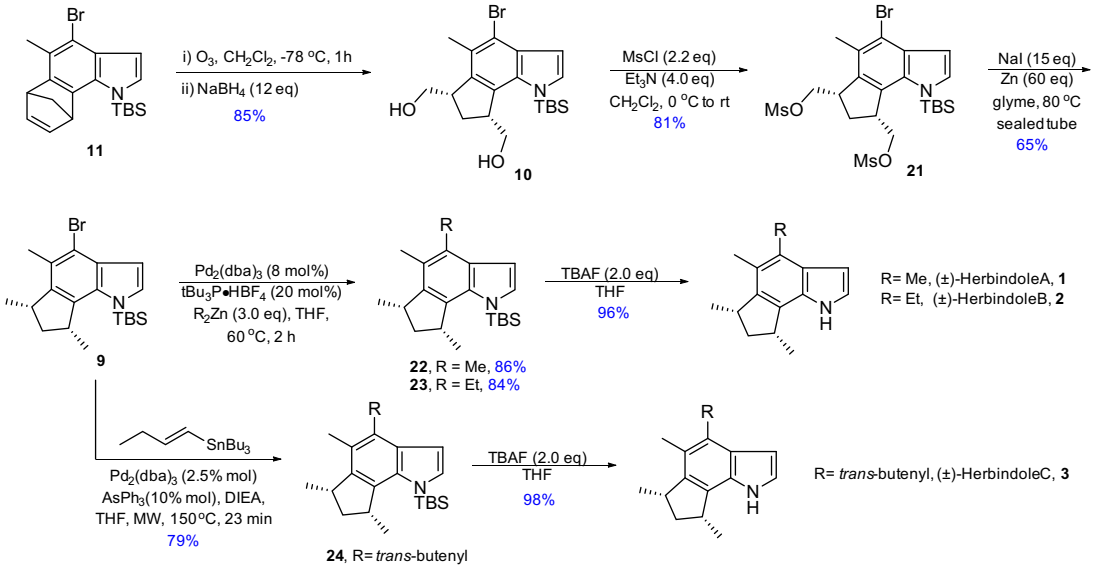
With the desired scaffold in hand, we tested the concept of regioselective C-7 metal–halogen exchange by treating the indole with *n*-BuLi (2.0 equiv; PhMe, −78 °C) and quenching with water (Scheme 4). Gratifyingly, only the C-7 protonated product **13b** was isolated, although the reasons for this selectivity remain a mystery.[20] Repeating this process in the presence of cyclopentadiene (10 equiv) and slowing warming to room temperature gave the desired Diels–Alder cycloadduct **11** in 90% yield on a 10+ g scale.

Alternatively, the generation of the 6,7-indole aryne could be generated at 0 °C in toluene with only a slight diminution of yield (83–85%). Pd(0)-catalyzed Negishi cross-coupling [$Pd_2(dba)_3$, 8 mol %; *t*-$Bu_3P{\cdot}HBF_4$, 20 mol %; R_2Zn, 3.0 equiv; THF, 60 °C, 2 h] at the remaining C-4 aryl bromide with Me_2Zn and Et_2Zn gave the corresponding and previously reported late-stage intermediates **19** and **20** in 70% and 68% yields, respectively, thus comprising a formal total synthesis of herbindole A and B.[16]

Ozonolysis of **11** followed by reduction of the ozonide with sodium borohydride (12 equiv) gave the diol **10** in 85% yield (Scheme 5). Adapting the Fujimoto reduction[21] used by Kerr[13a] to our intermediate (MsCl, 2.2 equiv; Et_3N, 4.0 equiv; CH_2Cl_2, 0 °C to rt; then NaI (15 equiv); Zn (60 equiv); glyme, 80 °C, 12 h) afforded the late-stage common intermediate **9** that was used for all three racemic herbindoles.

The intermediate **9** was routinely prepared on a 10-gram scale and was subjected to the same Negishi cross-coupling conditions as described earlier. The yields with the respective dialkylzinc reactants improved to 86% (R = methyl) and 84% (R = ethyl) with this scaffold compared to the cycloadduct **11**. This improved cross-coupling reaction has been ascribed to the lack of a potentially interfering strained olefin, an observation also made during our benzannulated indole library synthesis.[7a] Desilylation with tetrabutylammonium fluoride in THF was unexceptional and delivered in each case herbindole A **1** and herbindole B **2** in 96% yield. To complete the series with herbindole C, we elected, after much trial and error, to adapt the same Stille cross-coupling tactic that was used in the final step of our recent total synthesis of (±)-*cis*-trikentrin B.[18] As before, the use of the triphenylarsine ligand and microwave heating (150 °C, 23 min) was necessary to achieve acceptable yields of protected herbindole C **24**. Deprotection afforded the desired product in 98% yield.

The present work provides yet another important and instructive example of a regioselective metal–halogen exchange reaction and indole aryne cycloaddition in a tribromoindole scaffold. This



Scheme 5. Fujimoto reduction and Pd(0)-catalyzed Negishi and Stille cross-coupling reactions for herbindole A, B, and C.

finding, combined with the scalability of the reactions, affords for the first time the synthesis of each of the herbindoles in the multi-gram quantities that are needed for further study and research. To put this achievement into some perspective, the Scheuer report of the isolation of the herbindoles in 1990 resulted in just 230 mg of all three herbindoles combined, from about 0.75 kg dry weight of the sponge.

Given that benzannulated indole libraries inspired by the herbindoles and the structurally similar trikentrins show promising preliminary results (e.g., vincristine surrogates),[7a–c] the need for a practical synthesis of the herbindoles is clear and compelling. With sufficient quantities in hand, modification of the herbindoles, primarily around the pyrrole ring, is presently underway. A report of this activity, along with the biological annotation of the resulting libraries, will be disclosed as developments warrant.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR data for all new compounds reported and experimental details.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.064.

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20. Ab initio calculations with DFT methods (reference **9c**) performed on the indole aryne, benzofuran, and benzothiophene systems revealed the 6,7-aryne bond to be highly polarized, with a nucleophilic C-7 carbon. See also: Brown, N.; Buszek, K. R. *Tetrahedron Lett.* **2012**, *53*, 4022–4025.
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