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Total synthesis of (±)-*cis*-trikentrin B via intermolecular 6,7-indole aryne cycloaddition and Stille cross-coupling

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This Letter is warmly dedicated to Professor Michael E. Jung on the occasion of his 65th birthday.

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ABSTRACT

An efficient total synthesis of the annulated indole natural product (±)-*cis*-trikentrin B was accomplished by means of a regioselectively generated 6,7-indole aryne cycloaddition via selective metal–halogen exchange from a 5,6,7-tribromoindole. The unaffected C-5 bromine was subsequently used for a Stille cross-coupling to install the butenyl side chain and complete the synthesis. This strategy provides rapid access into the trikentrins and the related herbindoles, and represents another application of this methodology to natural products total synthesis. The required 5,6,7-indole aryne precursor was prepared using the Leimgruber–Batcho indole synthesis.

The family of trikentrins[1,2] and herbindoles[3] are the most prominent representatives of an uncommon class of indole alkaloid natural products in which annulation is present around the benzene nucleus (Fig. 1). Other architecturally complex members of this type include the teleocidins,[4] the penitrims,[5] and the nodulisporic acids.[6]

These biologically active compounds are fascinating structures and they present remarkable synthetic challenges. The trikentrins and the structurally related herbindoles in particular have been the subject of numerous synthetic efforts over the years. The difficulty in their construction is evident by many different creative approaches that have emerged from several laboratories.[1,3]

We recently were the first to generate the indole and benzofuran arynes associated with the benzene side of their respective systems[7] and reported a general method for their generation via metal–halogen exchange (Scheme 1), and later from *o*-silyl triflates.[7b] Garg subsequently reported a different route to the same *o*-silyl triflates[8a] which were used for other indole aryne studies.[8b–e]

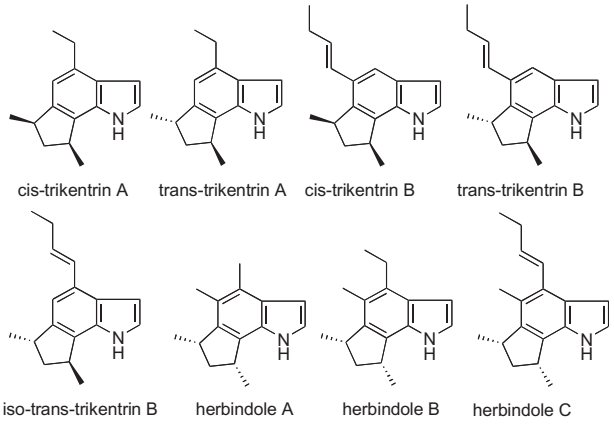

Figure 1. The trikentrin and herbindole natural products.

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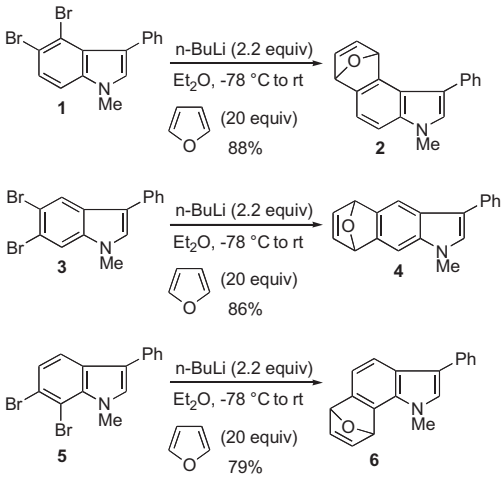
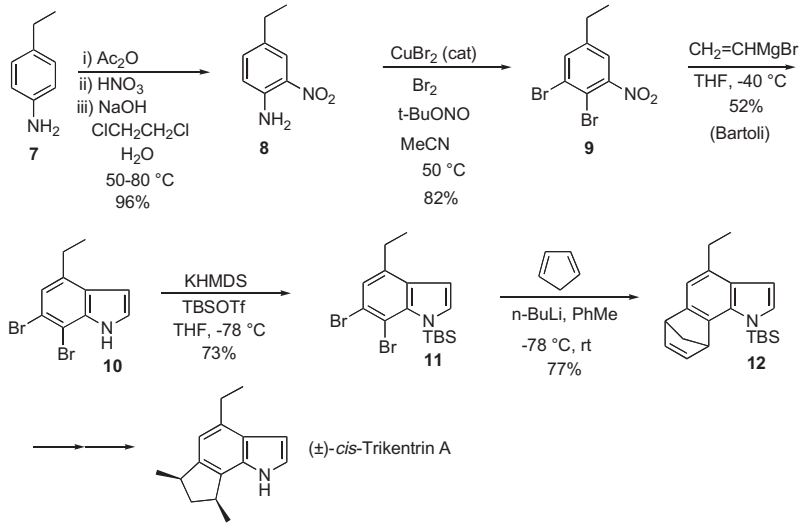


Scheme 1. Indole arynes via metal–halogen exchange and their cycloadditions with furan.

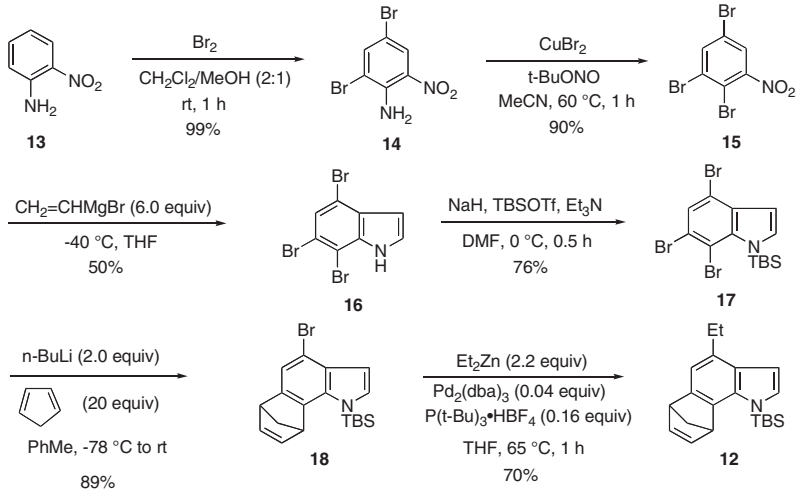
We applied our methodology to the total synthesis of (±)-*cis*-trikentrin A using a novel indole aryne cycloaddition as the key step for installing the annulation at the 6,7-position of the benzene ring (Scheme 2).[9] In this first-generation synthesis,[9a] the 6,7-indole aryne was generated from the corresponding *N*-*tert*-butyldimethylsilyl-6,7-dibromo-4-ethylindole **11** (prepared from **9** using the Bartoli indole synthesis[10]) via metal–halogen exchange and elimination, followed by cycloaddition with cyclopentadiene. Oxidative cleavage of the olefin bridge in **12**, bisdithioacetylization, and Raney nickel reduction gave the desired final target.

In a subsequent second-generation effort involving the 4,6,7-tribromoindole **16**,[9b] we found that selective metal–halogen exchange occurred at the C-7 bromine in **17** (Scheme 3).

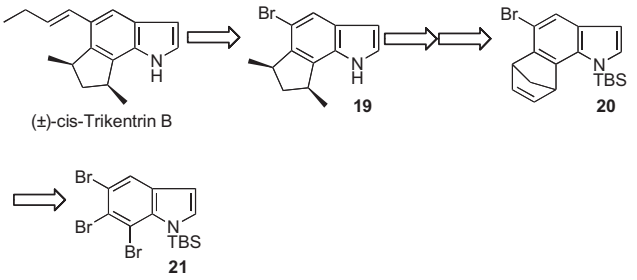
This observation made it possible to effect the generation of the 6,7-indole aryne while retaining the C-4 bromine thus making it available for later transition-metal cross-coupling chemistry (reaction orthogonality). Indeed, the Negishi reaction with **18** was used in this case to introduce the required ethyl group that afforded the same late-stage intermediate **12** as was obtained in the first approach. We recently used this same tactic for the preparation of novel annulated polycyclic indole libraries using Pd(0)-catalyzed



Scheme 2. First-generation (±)-*cis*-trikentrin A synthesis.



Scheme 3. Second-generation (±)-*cis*-trikentrin A synthesis.



Scheme 4. Retrosynthetic analysis of *cis*-trikentrin B.

Suzuki–Miyaura and Buchwald–Hartwig cross-coupling reactions.[11]

With the success of the second-generation synthesis of (±)-*cis*-trikentrin A, it occurred to us that an analogous approach might be possible for the total synthesis of (±)-*cis*-trikentrin B, which features a butenyl side-chain at the C-5 position and which could be installed via Stille cross-coupling with the ArBr **19** at C-5 (Scheme 4).

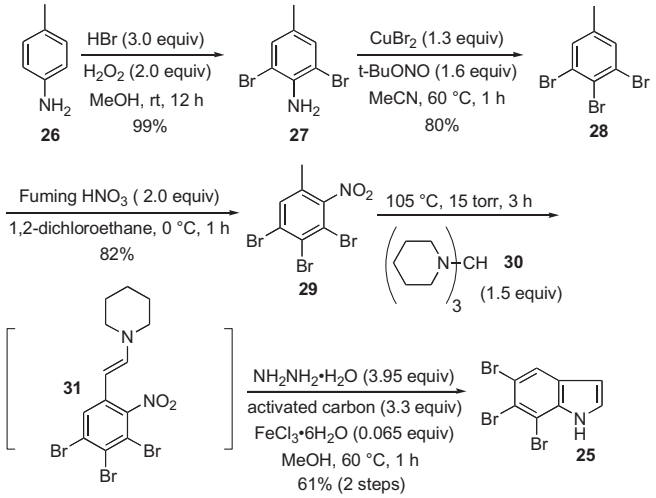
The key question centered on the intriguing issue of again achieving selective metal–halogen exchange at C-7 but in the 5,6,7-tribromo indole system **21**. We are delighted to report that this is the case, and we now present the total synthesis of (±)-*cis*-trikentrin B.

The first objective involved the synthesis of the 5,6,7-tribromoindole system **25**. We envisioned a strategy that paralleled the successful synthesis of 4,6,7-tribromoindole using the Bartoli indole synthesis[10] (Scheme 5). Thus, commercially available 2,6-dibromoaniline **22** was diazotized and brominated with $CuBr_2$ to give 1,2,3-tribromobenzene **23**[12] in 80% yield.

Nitration was achieved with fuming nitric acid to afford exclusively 2,3,4-tribromonitrobenzene **24**[13] in 82% yield. Unfortunately, application of the Bartoli indole synthesis (CH_2=CHMgBr, 3.0 equiv, −40 °C) afforded the desired 5,6,7-tribromoindole in only 32% yield. Silylation (NaH, 4.0 equiv; Et_3N, 2.0 equiv; TBSOTf, 3.0 equiv) then produced the desired indole aryne precursor **21**.

In an effort to increase the yield of **25**, we examined other potentially attractive approaches to the indole. The Leimgruber–Batcho indole synthesis[14] seemed especially suited to our needs due to its combination of generally high yields and scalable reactions.

Thus, inexpensive *p*-toluidine **26** was subjected to in situ bromination (HBr, 3.0 equiv; H_2O_2, 2.0 equiv) in methanol to afford quantitatively 2,6-dibromotoluidine, followed by diazotization as described above to yield in 80% 3,4,5-tribromotoluene **28** (Scheme 6). Nitration was again achieved in 82% yield with fuming nitric acid on a 14 g scale. Reaction of **29** with tripiperidinylmethane at 105 °C under vacuum for 3 h gave the enamine intermediate **31**, which was used immediately and without isolation for the next step. $FeCl_3$-catalyzed reaction with hydrazine hydrate in methanol



Scheme 6. Synthesis of 5,6,7-tribromoindole via Leimgruber–Batcho route.

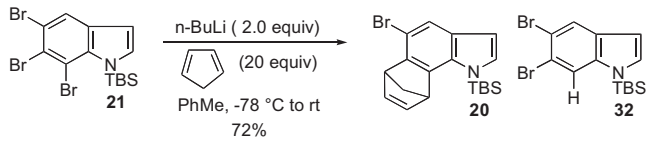
at 60 °C consistently afforded the desired 5,6,7-tribromoindole **25** in 61% yield in two steps from **29**. Protection as its *N*-TBS ether was accomplished as described above (78%).

Gratifyingly, the reaction of **21** with *n*-BuLi (2.0 equiv) at −78 °C in toluene with an excess of cyclopentadiene and then warming the mixture to room temperature over a period of 1 h gave the desired cycloadduct **20** in 72% yield (Scheme 7).

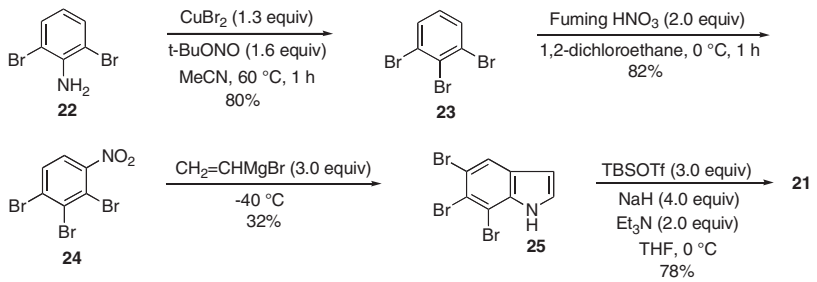
We have also established that quenching the mixture at −78 °C with water affords exclusively the *N*-TBS-5,6-dibromoindole **32**, thus confirming that the metal–halogen exchange is occurring only at the C-7 bromo position. No other protonated compounds were detected by this method. The basis for this selectivity is subject of continuing investigations.

With the key cycloadduct in hand, we turned our attention to the installation of the 6,7-annulated 1,3-*cis*-dimethyl cyclopentane ring. The initial effort paralleled that of the (±)-*cis*-trikentrin A effort (Scheme 8). However, numerous attempts to hydrogenolyze selectively the C–S bonds in **35** in the presence of the Ar–Br under various conditions gave the desired indole **19** in only 16–31% yield, with the remainder consisting mainly of the fully reduced indole **36**.

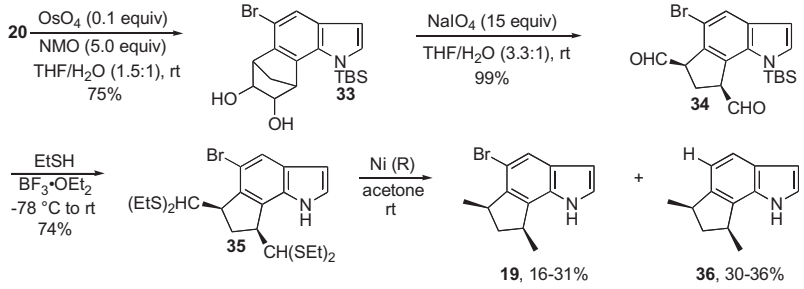
A recent (±)-*cis*-trikentrin B total synthesis by Kerr and coworkers[3] used the Fujimoto reduction[15] which we adapted for



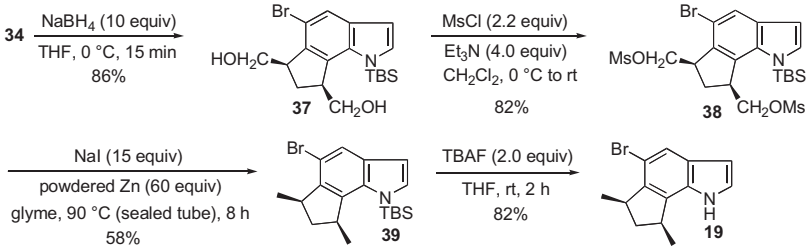
Scheme 7. Regioselective C-7 metal–halogen exchange.



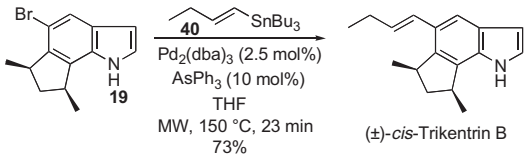
Scheme 5. Synthesis of 5,6,7-tribromoindole via Bartoli route.



Scheme 8. Raney nickel reduction of **35**.



Scheme 9. Fujimoto reduction of **34**.



Scheme 10. Final step: Stille cross-coupling.

our work (Scheme 9). The dialdehyde **34** was reduced with sodium borohydride, the resulting diol **37** mesylated, and then reduced under the Fujimoto protocol (NaI, 15 equiv; powdered Zn (60 equiv); glyme, 90 °C, sealed tube, 8 h) to afford the intermediate **39** (TBS protected **19**) in an improved and reliable 58% yield. Desilylation was accomplished with TBAF (2.0 equiv; THF, rt, 2 h) to give the 5-bromoindole **19** in 82% yield.

The last step to complete the synthesis initially involved a plan to generate the Grignard reagent from **39**, followed by reaction with butyraldehyde and then acid-catalyzed elimination. Surprisingly, all attempts with the Grignard reaction or the alternative metal–halogen exchange at this position were unsuccessful. Finally, we turned to the Stille cross-coupling for introducing the butenyl side chain (Scheme 10).

Although our initial attempts using conventional Stille cross-coupling procedures with the vinyl tin reagent **40**[16] were not effective, changing the ligand from triphenylphosphine to triphenylarsine and employing microwave heating readily afforded racemic *cis*-trikentrin B in 73% yield which was identical in all respects for the physical and spectroscopic data reported for this compound.

In conclusion we have achieved the total synthesis of (±)-*cis*-trikentrin B using a new strategy that involves the selective metal–halogen exchange in the 5,6,7-tribromoindole system and which results in regioselective 6,7-indole aryne formation. This efficient and complementary reaction orthogonality combined with robust cross-coupling chemistry is being used for the total synthesis of other members of the annulated indole alkaloid class of natural products. The results 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 for their preparation can be found under supplementary material as a PDF document) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.125.

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