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Total Synthesis of (±)-Herbindole B and (±)-*cis*-Trikentrin B

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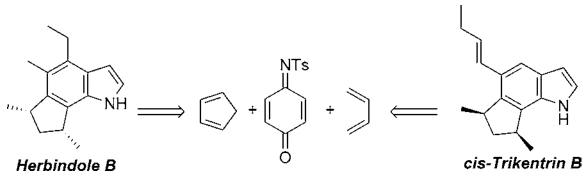
ABSTRACT



Herbindole B and *cis*-trikentrin B are naturally occurring indoles having the unusual and synthetically challenging pattern of carbon substitution at the 4–7 and 5–7 positions, respectively, with no substitution at the 1–3 positions. The total syntheses of these polyalkylated indoles have been achieved in 19 and 12 steps, respectively. The synthesis of herbindole B relies on two iterations of a quinine monoimine Diels–Alder reaction, while *cis*-trikentrin B uses a single cycloaddition of a suitable quinone monoimine. Indolization of the adducts provides suitably substituted benzopyrrole nuclei for elaboration to the natural products.

The herbindoles are a series of structurally similar polyalkylated cyclopent[*g*]indoles which were isolated from the orange Western Australian sponge *Axinella* sp. (Figure 1).[1]

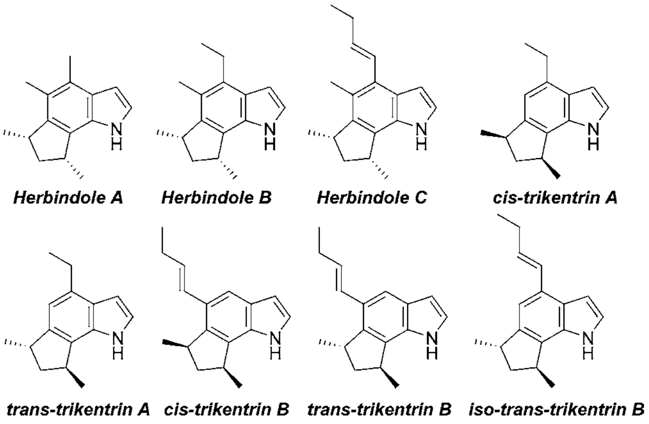


Figure 1. Herbindole and trikentrin indoles.

They are related to the better known trikentrins, isolated from the marine sponge *Trikentrion flabelliforme* by Capon and co-workers.[2] The trikentrins differ only in the nature of the substitution at the 4- and 5-positions (indole numbering). The herbindoles exhibit cytotoxicity against KB cells and are active as a general fish antifeedant whereas the trikentrins show growth inhibitory activity against the Gram-positive bacteria *Bacillus subtilis*.

The herbindoles and the trikentrins bear extensive substitution on the benzenoid portion of the indole ring system. This well-known synthetic challenge coupled with the stereochemical issues related to the relative stereochemistry of the two benzylic stereogenic centers make these compounds synthetic targets whose relatively small size belies their complexity. Indeed, the only synthesis of any of the herbindoles comes from the laboratory of Natsume, whose complex synthetic scheme[3] is evidence of the challenge posed by such a visually unassuming target.

The trikentrins, on the other hand, have received more attention from the synthetic community. Successful ap-

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(1) Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J. *Tetrahedron* **1990**, 46, 3089.

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(3) (a) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, 42, 854. (b) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, 42, 846.

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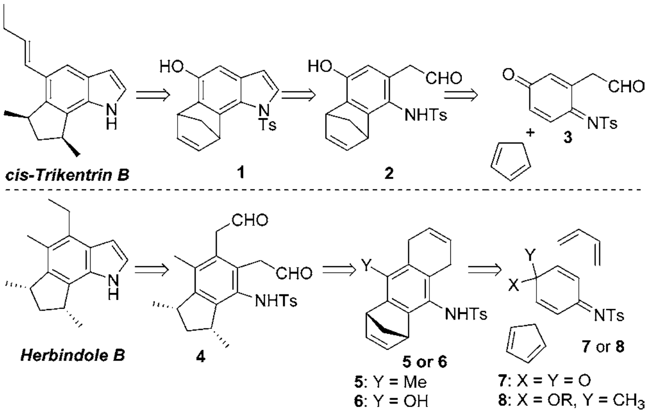
proaches have employed aryl radical cyclizations,[4] an intramolecular Heck coupling,[5] a sequential heteroaromatic azadiene Diels–Alder approach,[6] indolization of pyrrole derivatives,[7] and an intramolecular Diels–Alder reaction of allenic dienamides.[8]

In recent years, we have studied the Diels–Alder reactions of quinoid imines[9] and have developed a practical method of converting the adducts to indoles which bear a high degree of substitution.[10] The process involves the Diels–Alder reaction of a quinoid imine and a subsequent Pleininger indole formation.[11] We have been able to prepare a variety of indoles with diverse substitution patterns. Herein we report the application of a variant of these methods to the preparation of *cis*-trikentrin B and herbindole B.

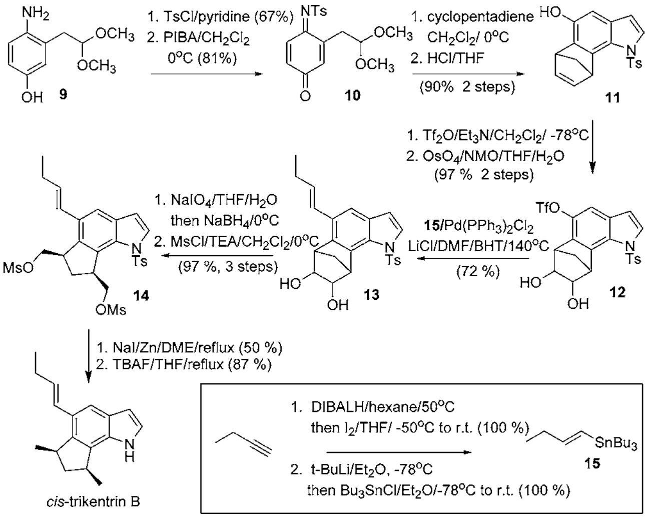
The retrosyntheses we had envisaged from the beginning are shown in Scheme 1. For both targets, the required *cis*-dimethylcyclopentane unit would be revealed via oxidative cleavage of the benzonorbornene system in **1**, **5**, or **6**. For *cis*-trikentrin B, the key intermediate **1** results from indolization of aldehyde **2**, which in turn is the product of a Diels–Alder reaction of **3** with cyclopentadiene. In contrast to the strategy for *cis*-trikentrin B, where the aldehyde necessary for indolization is built into the dienophile, for herbindole B the aldehyde necessary for indolization (see compound **4**) would arise by oxidative cleavage of a cyclohexenyl moiety in **5** or **6**. Both **5** and **6** are products of two iterations of a Diels–Alder reaction (with appropriate reoxidation) of a suitable dienophile **7** or **8** with butadiene and cyclopentadiene.

Scheme 1. Retrosynthesis of *cis*-Trikentrin B and Herbindole B



Our synthesis of *cis*-trikentrin B commenced with the preparation of a suitable dienophile for the key Diels–Alder reaction. Synthesis of the desired quinone imine **10** (Scheme 2) was straightforward from the *p*-aminophenol[12] **9** via tosylation and phenyliodo bis-acetate (PIBA)[13] oxidation of the resultant sulfonamide. Reaction of quinone imine **10** with cyclopentadiene at 0 °C resulted in clean formation of the desired cycloadduct. We were gratified to see that treatment of the cycloadduct with acid not only catalyzed the aromatization to the desired dihydronaphthalene but also facilitated the *in situ* indolization to afford the desired 5-hydroxyindole **11** in excellent yield (90% over two steps). Protection of the hydroxyl group as a triflate and dihydroxylation gave the diol **12**. It was found at this stage that the triflate functionality was incompatible with elaboration of the dimethylcyclopentane ring. This suggested that installation of the 1-butenyl group should precede formation of the dimethylcyclopentane ring.

Scheme 2. Synthesis of *cis*-Trikentrin B



It was felt that Stille coupling with the organotin reagent **15** would be the most efficient method for installation of the 1-butenyl group since it required no subsequent functional group manipulation. 1-Butenyltributylstannane **15** was formed from 1-butyne via hydroalumination and iodonolysis,[14] followed by metal–halogen exchange and *trans*-metalation, which afforded the desired *trans*-organotin reagent **15** (*trans*/*cis* = 12: 1).[15] Stille coupling proceeded smoothly with nearly complete control of the olefin geometry, generating

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(12) For an excellent preparative procedure of **9** from 3-methyl-4-nitrophenol, see: Todd, M. H.; Oliver, S. F.; Abell, C. *Org. Lett.* **1999**, *1*, 1149.

(13) For the preparation of PIBA, see: Smith, J. G. *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley: Toronto, 1990; Vol. 1, p 508.

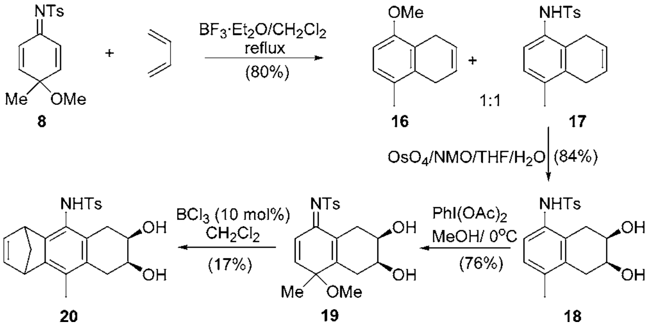
(14) Alexakis, A.; Duffault, J. M. *Tetrahedron* **1988**, *29*, 6243.

(15) Analyses of the integration values for the well-separated vinyl signals of the ^{1}H NMR were used to determine the trans/cis ratio.

13 predominantly as the *trans*-isomer in 72% yield (*trans*/*cis* > 20:1).[15] In an attempt to minimize epimerization of the dialdehyde, the oxidative cleavage of **13** with NaIO$_4$ was immediately followed by the *in situ* reduction with NaBH$_4$ in a one-pot procedure. *Caution: this is an extremely vigorous reaction and must be conducted with slow portionwise addition of NaBH$_4$.* Treatment with MsCl produced the bis-mesylate **14** in excellent yield (97% over three steps). Reductive deoxygenation via the Fujimoto[16] procedure followed by detosylation with TBAF[17] completed the diastereoselective synthesis of (±)-*cis*-trikentrin B.

Our approach to herbindole B began with the cycloaddition of dienophile **8** with 1,3-butadiene (Scheme 3). In the event, a 1:1 separable mixture of adducts **16** and the desired **17** were obtained in an overall yield of 80%. The production of **16** presumably arises via a Lewis acid-catalyzed migration of the methoxy group in the initial adduct. Dihydroxylation of **17** proceeded without incident to produce **18**, which was reoxidized with PIBA to the dienimine **19**. Despite our best efforts and under a variety of reaction conditions, cycloaddition of **19** with cyclopentadiene proceeded to give **20** in a best yield of 17% when BCl$_3$ was used as a catalyst. Other dienophiles similar to **19** were prepared and failed to undergo cycloaddition to give the desired product.

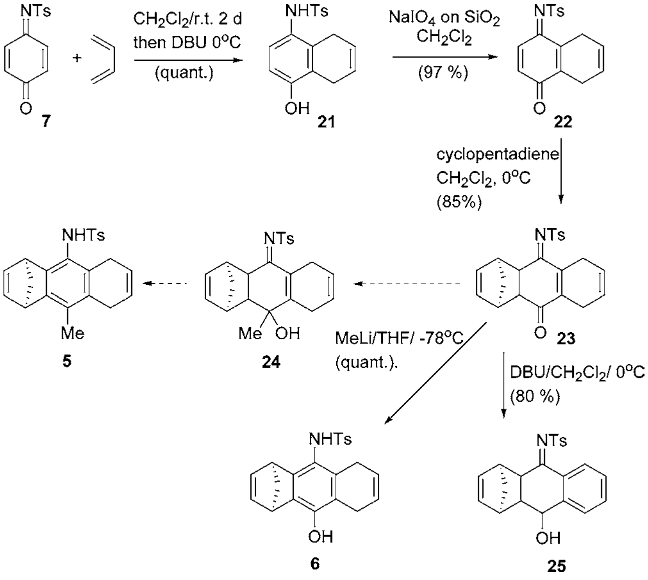
Scheme 3. Initial Approach to Herbindole B



The desire to use a dienophile such as **8** in our synthetic sequence was born in the fact that the methyl group in **8** would end up being the required 5-methyl group in the natural product. The failure of this sequence to produce satisfactory results prompted us to reevaluate our choice of dienophile. The quinone monoimine **7** when carried through a similar sequence of reactions would result in a 5-hydroxy indole (or derivative thereof) which would allow for installation of the required methyl substituent via cross-coupling. Moreover, **7** was expected to exhibit greater dienophilicity due to the presence of the carbonyl moiety.

We were delighted when our expectations met with reality and the cycloaddition of **7** with butadiene proceeded (after aromatization with DBU) to produce dihydronaphthalene **21** in quantitative yield (Scheme 4). Reoxidation with NaIO$_4$ supported on silica[18] gave **22**, which underwent a second cycloaddition with cyclopentadiene to give adduct **23**. At this stage, the usual conditions for aromatization via enolization of the ketone and sulfonylimino groups (DBU) failed to produce the desired product, giving instead **25** in excellent yield.

Scheme 4. Revised Approach to Herbindole B



As an alternative to base-promoted aromatization of the adduct, attention was turned to nucleophilic addition of methyllithium to the carbonyl group in the hopes of preparing **24**. Acid treatment of **24** would produce **5**, an ideal intermediate for conversion to the natural product. To our surprise, rather that behaving nucleophilically, the methyllithium behaved as a base and promoted the aromatization which had failed with DBU. In this way, the phenolic compound **6** was prepared in superb yield.

The conversion of **6** to the target compound, herbindole B, is shown in Scheme 5. Triflation of the phenolic hydroxyl group and chemoselective dihydroxylation (presumably due to the strain energy release in the benzonorbornenyl system) produced the diol **26**. Acetonide formation generated **27** in excellent yield, and dihydroxylation of the remaining olefin afforded the intermediate diol. Oxidative cleavage of the diol with NaIO$_4$ gave a dialdehyde which upon acid treatment underwent indolization to **28**. Reduction and mesylation gave **29** which was a suitable substrate for reduction under the conditions of Fujimoto. The reduction product **30** underwent smooth Stille coupling with tetramethyltin to install the required 5-methyl substituent. Conversion of **31** to the bis-mesylate **33** was accomplished by acetonide hydrolysis, periodate cleavage of the diol, reduction to the diol **32** and treatment with mesyl chloride. Fujimoto reduction as before and detosylation with TBAF yielded herbindole B which was identical in all respects, except for optical rotation, with the natural product.

In conclusion, new diastereoselective total syntheses of (±)-*cis*-trikentrin B and (±)-herbindole B have been achieved.

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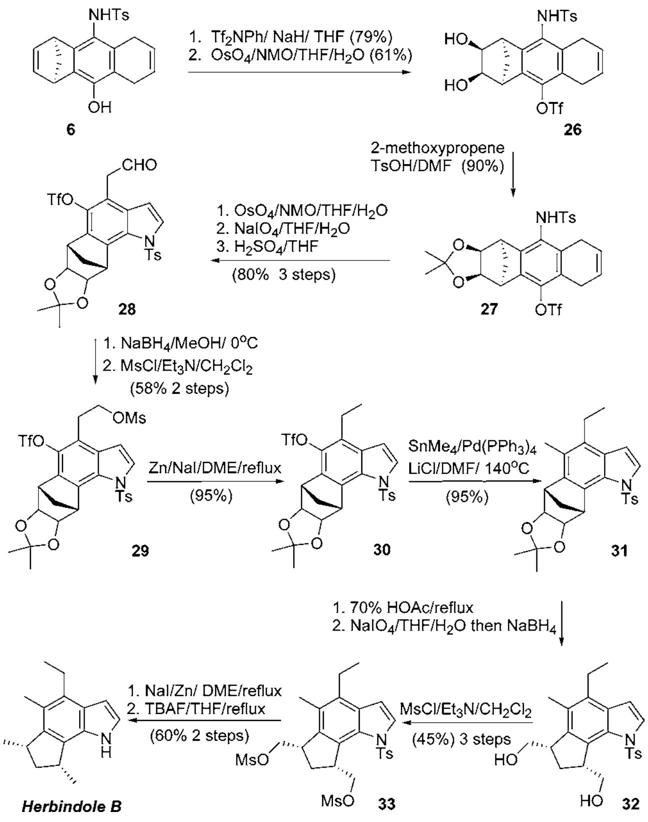
Scheme 5. Synthesis of Herbindole B



The two complementary strategies successfully address the challenge of substitution on the benzenoid porition of the indole ring system. For (±)-*cis*-trikentrin B, a Diels−Alder reaction of a suitable quinone monoimine with cyclopentadiene was the key step allowing for preparation of the natural product in 12 steps and 14% overall yield. For herbindole B, the key sequential Diels−Alder/oxidation/Diels−Alder/aromatization provided an adduct which contained all the necessary components for the tricyclic herbindole B skeleton. In this manner, the natural product was obtained in 19 steps and in 4% overall yield. In both cases a consequence of the strategy was the presence of a hydroxyl group at the indole 5-position, allowing for installation by cross-coupling of the required *trans*-butenyl (trikentrin) and methyl (herbindole) substituents. The above strategies effectively accomplished the synthesis of indoles bearing complex substitution on the benzenoid positions of the benzopyrrole ring system while leaving the more reactive 1−3 positions unsubstituted. A more detailed account of the syntheses and cross-coupling reactions of 5-triflyloxyindoles will be presented in due course.

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Supporting Information Available: Full experimental procedures and spectroscopic data for compounds **10**−**14**, (±)-*cis*-trikentrin B, **6**, **7**, **21**, **22**, **26**−**31**, **33**, and (±)-herbindole B. This material is available free of charge via the Internet at http://pubs.acs.org.

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