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Asymmetric Hydrovinylation of Vinylindoles. A Facile Route to Cyclopenta[*g*]indole Natural Products (+)-*cis*-Trikentrin A and (+)-*cis*-Trikentrin B

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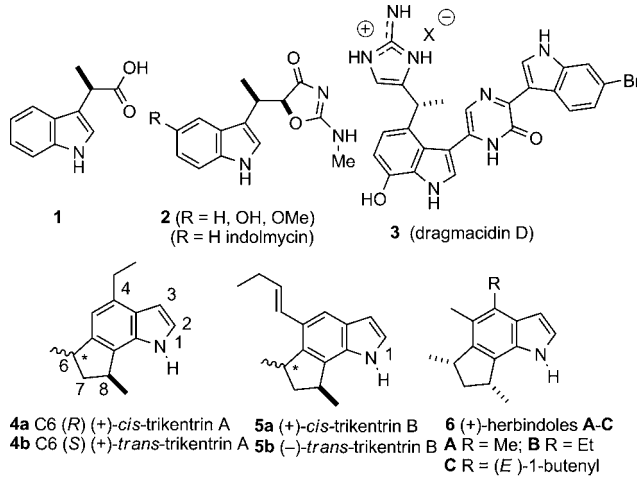
Supporting Information

ABSTRACT: Vinylindoles undergo Ni(II)-catalyzed asymmetric hydrovinylation under very mild conditions (−78 °C, 1 atm ethylene, 4 mol % catalyst) to give the corresponding 2-but-3-enyl derivatives in excellent yields and enantioselectivities. Hydroboration of the alkene and oxidation to an acid, followed by Friedel−Crafts annulation, gives an indole-annulated cyclopentanone that is a suitable precursor for the syntheses of *cis*-trikentrins and all known herbindoles. For example, the cyclopentanone from 4-ethyl-7-vinylindole is converted into (+)-*cis*-trikentin A in four steps (Wittig reaction, alkene isomerization, diastereoselective hydrogenation, and nitrogen deprotection). The previous synthesis of this molecule from (*S*)-(−)-malic acid involved more than 20 steps and a preparative HPLC separation of diastereomeric intermediates.

Many biologically important indole derivatives are adorned with methyl-bearing secondary stereogenic centers at one or more of their peripheral carbons. Examples include the potent neuroprotective agent indole-3-propioinc acid (**1**),[1] anti-bacterial (−)-indolmycin (**2**),[2] protein phosphatase inhibitors such as dragmacidin D (**3**),[3] anti-bacterial trikentrins (**4**, **5**),[4a] and cytotoxic herbindoles (**6**) (Figure 1).[4b]

While many efficient catalytic procedures have been developed for the stereoselective attachment of a chiral side chain to the reactive C_3 position, there is a paucity of such methods if this chain is appended to any of the other carbons of the indole nucleus.[5] Apart from notable addition of an indole-2-trifluoro(organo)borate to α,β-unsaturated aldehydes catalyzed by an organocatalyst,[6] no general procedures for the installation of chiral appendages at other positions of indole have been reported. While considering a broadly applicable enantioselective approach to the cyclopenta[*g*]indole natural products, trikentrins, herbindoles, and related molecules,[7] we wondered whether asymmetric hydrovinylation (Scheme 1)[8] of an appropriately substituted vinylindole might provide an expeditious entry into this important class of compounds.

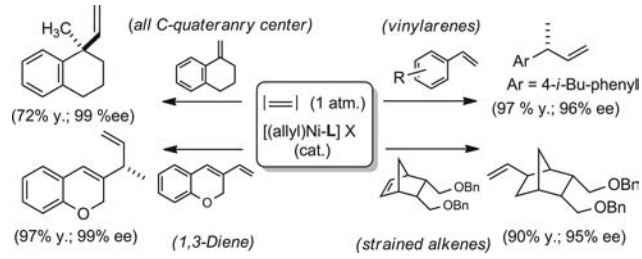
In this paper we report that Ni(II)-catalyzed asymmetric hydrovinylations of C_2, C_3, C_4, C_5, C_6, and C_7 vinylindoles proceed with surprising efficiency and excellent selectivity, even when the indole nitrogen is unprotected. Details of this study, along with applications of the resulting (2-but-3-enyl)indole derivatives for the syntheses of (+)-*cis*-trikentrins A (**4a**) and (+)-*cis*-trikentrin-B (**5a**), are documented here. Also reported is a novel application of a recently disclosed[9] [LPd(II)-H]$^+$-catalyzed isomerization of a double bond to set up a highly diastereoselective reduction of a functionalized 1,3-dimethylcyclopent-1-ene.



Diastereoselective Synthesis of *cis* or *trans*-Trikentrins and Herbindoles
(see ref. 7a for highly readable graphical summaries of various syntheses)
(−)-*cis*-A: stereorandom from (−) pulegone 10 steps, Natsume, ref. 14a.
(+)-*cis*-A: from (−)-malic acid 21 steps, Natsume, ref. 14b.
(−)-*trans*-A: stereorandom from (−) pulegone 10 steps, Natsume, ref. 14a.
(+)-*cis*-B: from (−)-malic acid 21 steps, Natsume, ref. 14b.
(+)-*cis*-B: from (+)-menthol 30 steps, Kanematsu, ref. 14c.
(+)-*trans*-B: from (−)-malic acid 21 steps, Natsume, ref. 14b.
Herbindoles A, B or C: from (−)-malic acid >20 steps Natsume, ref. 14b.

Figure 1. Some biologically active indole derivatives.

Scheme 1. Selected Examples of Asymmetric Hydrovinylation of Alkenes[8]



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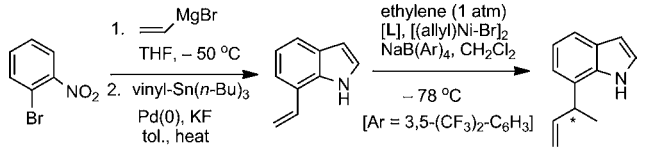
Our initial studies directed toward optimization of the reaction conditions for the asymmetric hydrovinylation of prototypical vinylindoles revealed that these compounds were among the most reactive substrates, with the reactions proceeding at −78 °C under 1 atm of ethylene, even when the nitrogen was left unprotected. Of the numerous ways of synthesizing indole derivatives, we resorted to the operationally simple, yet broadly applicable Bartoli method,[10] which is illustrated for 7-vinylindole in Scheme 2. The asymmetric

Scheme 2. Synthesis and Asymmetric Hydrovinylation of a Prototypical Vinylindole



hydrovinylation of this substrate shows the subtle effects of the highly tunable phosphoramidite ligands (Figure 2)[11] on the

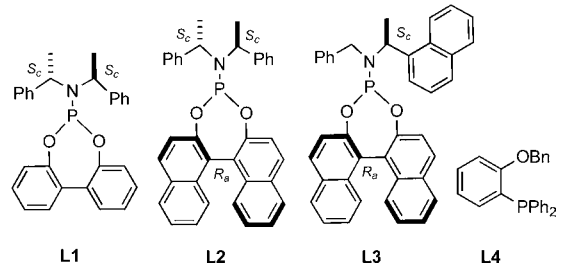


Figure 2. Ligands for asymmetric hydrovinylation of vinylindoles.

selectivity of this reaction.[12] While each of the ligands **L1**−**L3** gave excellent yield (>97%) of the product, the C_1-symmetric ligand **L3** gave the best enantioselectivity (99% ee), as determined by chiral stationary phase GC. A racemic sample of the product was prepared using the ligand **L4** or using racemic **L2**.

Results of asymmetric hydrovinylation of other vinylindoles are shown in Table 1, and the major products are shown in Figure 3.[12] In general, excellent yields and very good to excellent ee's were obtained for the hydrovinylations of a variety of substrates with as little as 4 mol % of the catalyst. For 2- and 7-VIs (entries 1, 7, and 8), the ligand **L3** appears to be significantly better than **L1** and **L2**, whereas for the others, there is little perceptible difference. The enantioselectivity in the reaction of 5-VI (entry 4) was determined after conversion of the terminal alkene into an alcohol and analysis of the Mosher ester derived from this compound by NMR.[12] The uncertainty in the ee measurements reflects the limits of this method rather than a less selective reaction. An *N*-Ts derivative (entry 6), which required a higher catalyst loading for comparable conversions, gave slightly lower ee's than the corresponding unprotected derivative (entry 5). Finally, the 7-vinyl derivatives shown in entries 7 and 8 gave excellent yields and selectivities of products that are potentially useful for enantioselective syntheses of trikentrins and herbindoles.

Table 1. Asymmetric Hydrovinylation of Vinylindoles[a]

		yield (%)/ee (%)[b]			
entry	substrate	L1	L2	L3	L4[c]
1	2-VI	96/80	98/82	99/94	98
2	3-VI	93/91	98/90	96/92	98
3	7-Et-4-VI	96/89	97/93	98/94	91
4	5-VI	96/>90[d]	98/>96[d]	96/>92[d]	98[e]
5	6-VI	95/94	96/95	97/93	97[e]
6	1-Ts-6-VI[f]	92/91	93/90	93/89	–
7	7-VI	97/91	98/93	98/99	90
8	4-Et-7-VI	96/86	95/87	99/96	90

[a]See Scheme 2 and Supporting Information for details. [b]Determined by chiral stationary phase GC on cyclodex-B column except for entry 4. [c]Yield of racemic product. [d]Determined by Mosher method. [e]Using [**L2** + *ent*-**L2**]. [f]8 mol % catalyst. %ee of the product determined by GC after detosylation.

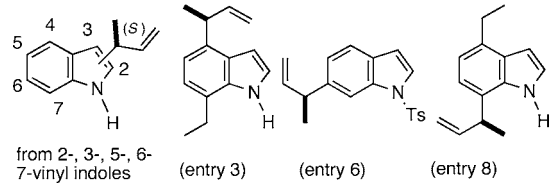
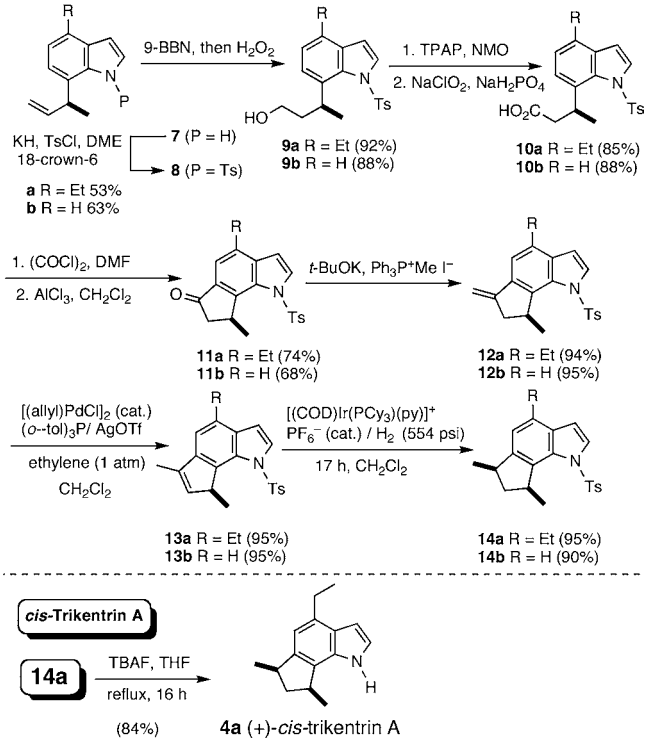


Figure 3. Major products from hydrovinylation of vinylindoles using ligands **L1**−**L3**.

The starting material for a short synthesis of (+)-*cis*-trikentrin A (Scheme 3) is the hydrovinylation product **7a**, which is formed in 99% yield and 96% ee from 4-ethyl-7-vinylindole (entry 8, Table 1, using **L3**). The *N*-tosylated alkene **8a** was subjected to hydroboration followed by oxidation to prepare the carboxylic acid **10a**. An intramolecular Friedel−Crafts reaction followed by a Wittig reaction gave the *exo*-methylene

Scheme 3. Enantioselective Synthesis of (+)-*cis*-Trikentrin A



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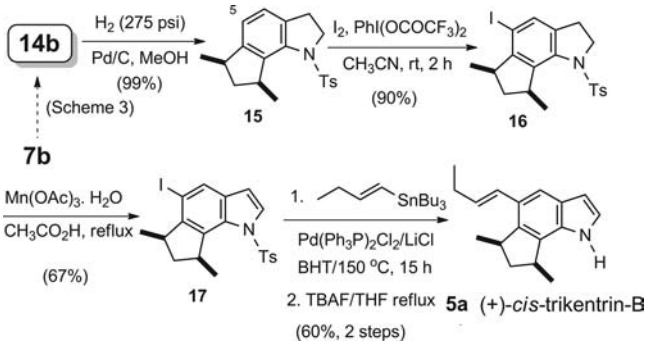
compound **12a** in ~70% yield from the acid **10a**. Apart from the asymmetric hydrovinylation, the major challenge in this synthesis turned out to be the *direct* stereoselective hydrogenation of **12a** to a trikentrin derivative. Repeated attempts under a variety of homogeneous and heterogeneous hydrogenation conditions[15] led to a mixture of *cis*- and *trans*-trikentrin derivatives (both useful for syntheses of the corresponding natural products, albeit in a less selective fashion). A satisfactory solution to the problem involved the use of our recently published[9] Pd(II)-catalyzed isomerization of the terminal **12a** into an internal alkene **13a**, followed by Crabtree hydrogenation,[16] which gave exclusively the *N*-Ts derivative **14a** as a single diastereomer. Removal of the *N*-Ts derivative using TBAF in refluxing THF[17] gave the natural product (+)-*cis*-trikentrin (**4a**), identical in all respects with the reported natural product.[4a,14b]

Synthesis of a more complex natural product, (+)-*cis*-trikentrin B, shown in Scheme 4, illustrates the use of the

Scheme 4. Enantioselective Synthesis of *cis*-Trikentrin B



hydrovinylation product, **7b** (entry 7, Table 1), from 7-VI and a late-stage functionalization of a 6,8-dimethylcyclopent[*g*]indole nucleus (**15**). Using the chemistry described earlier, **7b** was converted into **14b** in nearly the same yields and selectivities. Not unexpectedly, the direct electrophilic reactions at the C_5-peri position of **14b** were not feasible in the presence of the more reactive indole C_3 position, even with the deactivating *N*-Ts moiety. We resorted to hydrogenation of the C_2-C_3 bond before iodination of the substrate using I_2 and $PhI(OCOCF_3)_2$. A highly regioselective reaction ensued, giving **16** as the exclusive product. Subsequent dehydrogenation using $Mn(OAc)_3$, followed by Stille reaction to install the (*E*)-1-butenyl side chain, gave a good yield of *N*-Ts (+)-*cis*-trikentrin-B. Deprotection of the *N*-Ts group using TBAF gave the natural product.[4a,14b]

Finally it should be noted that the chemistry outlined here is compatible with the substitution patterns in other known trikentrins and herbindoles,[7] and it should be possible to prepare any of the *cis*-congeners with complete stereoselectivity using a similar route with only slight modifications. Preparation of the compounds in the *trans*-series can be envisioned using alternate chemistry of the key ketone **11a** or **11b**.[18] Such studies and application of this chemistry to prepare other complex indole alkaloids are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details for the preparation of the intermediates and hydrovinylation reactions; spectroscopic and chromatographic data for characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The reported syntheses of these deceptively simple-looking compounds are lengthy, low-yielding, and stereorandom and involve difficult separations of diastereomeric intermediates. For example, (−)-*cis*-trikentrin A (*ent*-**4a**) and (−)- *trans*-trikentrin A (*ent*-**4b**) have been synthesized in very low yields in a stereorandom fashion starting from (−)-pulegone. (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771. *cis*-Trikentrin-A (**4a**) and *cis*-trikentrin-B (**5a**) were synthesized in more than 20 steps starting with (−)-malic acid through diastereomeric intermediates that were separated by HPLC. (b) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 854 and references cited therein. For another synthesis of *cis*-trikentrin-B starting with (+)-menthol (30 steps), see: (c) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 3406.

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