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Stereodivergent Total Synthesis of Hapalindoles, Fischerindoles, Hapalonamide H, and Ambiguine H Alkaloids by Developing a Biomimetic, Redox-Neutral, Cascade Prins-Type Cyclization

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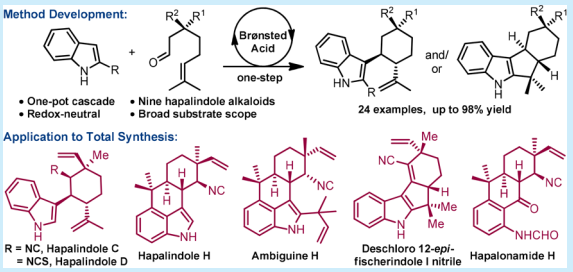
Supporting Information

ABSTRACT: A stereoselective, redox-neutral, Brønsted acid-catalyzed cascade Prins-type cyclization between indole and aldehyde is described to access several structurally diverse indole terpenoid scaffolds in a single step. Applying this concept, stereodivergent total syntheses of nine hapalindole-type alkaloids are accomplished. Key transformations include allylation using geometrically isomeric allylboronic acid followed by a *p*-toluenesulfonic acid mediated deprotection−cyclization cascade.



Natural products possess an exclusive chemical and structural diversity which has evolved over the years for their ultimate interaction with biomolecules, enabling them to be a fundamental source of drugs. Hapalindoles are arguably the largest and most comprehensive subclass of indole alkaloids isolated from secondary metabolites released by cyanobacteria.[1] Originally isolated by Moore et al.,[1a] these secondary metabolites exhibit a wide array of biological activities[2] such as antimicrobial,[3] insecticidal,[4] anticancer,[5] antialgal,[6] phytotoxic,[7] and antimycotic,[8] etc. For example, hapalindole C (**2**) and hapalindole H (**10**) were found to have potent anticancer activity against human HT-29 (colon), MCF-7 (breast), NCI-H460 (large cell lungs), and SF268 (glioblastoma) cancer cell lines with moderate IC_{50} values.[3d,5c] Parallel pharmacological research has also found these to be a potential lead for drug discovery.[3b,c] Structural investigation of over 80 indole alkaloids isolated to date has revealed certain similarities, likely to originate from shared biosynthetic pathways. It contains a *trans*-1-indolyl-2-isopropenylcyclohexane **1** framework (Figure 1) where an indole core is connected to a highly functionalized cyclohexane unit (with up to five contiguous stereocenters) through the C3-position.The aforementioned biological importance coupled with a unique amalgamation of rings, stereocenters, and functionalities has stimulated the interest of synthetic chemists, resulting in a number of racemic[9] as well as asymmetric syntheses.[10] A Cu(II)-mediated enolate coupling of indoles with carvone **11** by Baran et al. (Scheme 1a)[10c] and DDQ-promoted benzylic oxidation of 3-alkylated indoles[9j] are the two prominent methods for synthesizing **1**. However, it requires tedious prefunctionalization of indoles (up to seven steps to get the product), stoichiometric use of Sc(III) triflate, an oxidizing agent, and high temperature. In addition, the corresponding indolyl ketone is formed as a side product.[9j] Despite several reports, direct access to these structurally unique scaffolds is

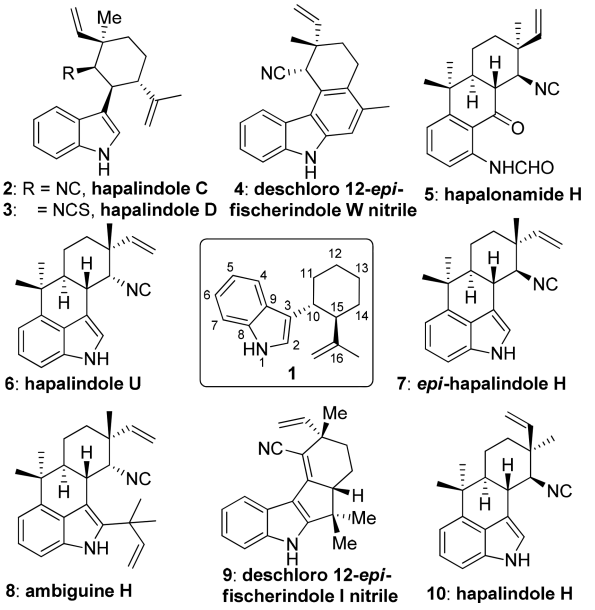


Figure 1. Hapalindole-type natural products.

elusive and still a challenging task. In view of the above literature and our interest in developing efficient synthetic methods for functionalized indoles,[11] we herein report synthesis of **1** in one step by a direct reaction of unprotected indoles and aldehydes (Scheme 1b) through Brønsted acid catalysis and its application toward the total synthesis of hapalindoles, fischerindoles, and the hapalonamide series of nine alkaloids in 9−12 steps.

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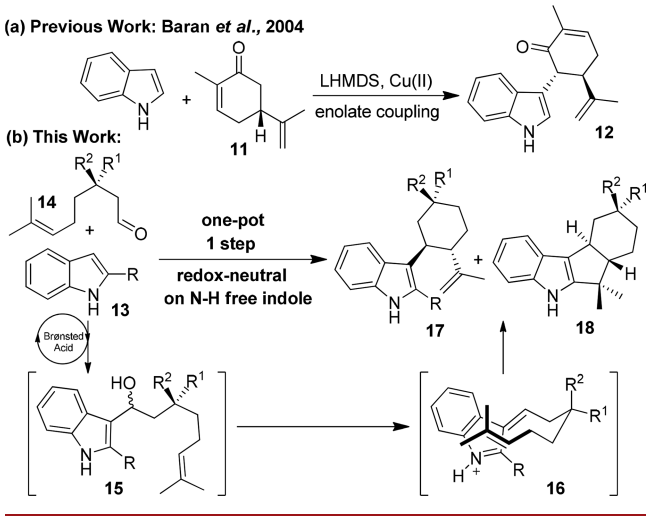
Scheme 1. Previous Report and Proposed Hypothesis

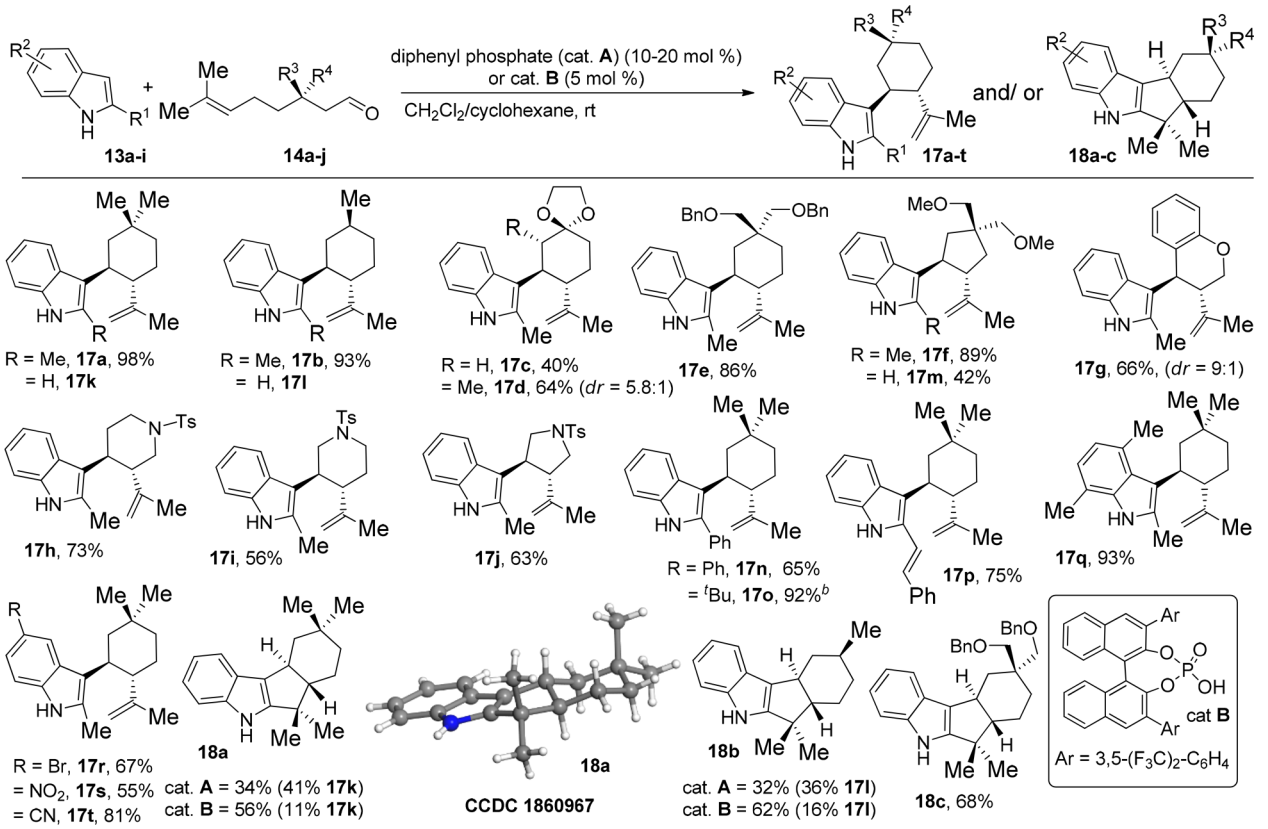


Development of a new C−C bond-forming strategy is one of the central pillars of organic synthesis, providing easy access to complex structural architectures. The proposed idea is based on a one-pot tandem reaction pathway. First, in situ generated indolyl alcohol **15**, formed by reaction of indole **13** and aldehyde **14** in the presence of Brønsted acid, should undergo a rapid water elimination to generate vinylogous iminium intermediate **16**, which would undergo intramolecular Prins-type cyclization to provide the *trans*-1-indolyl-2-isopropenylcyclohexane scaffold **17** via an all equatorial chairlike TS. The success of this strategy exclusively depends on the selectivity at which two competing reactions namely, (a) the generation of **15** and (b) the intramolecular ene reaction of **14** (a decomposition pathway), takes place.

To explore this hypothesis, 2-methylindole **13a** and 3,3,7-trimethyloct-6-enal **14a** were chosen as the model substrate and treated with various acid catalysts in CH_2Cl_2 (Scheme 2).[12] A brief optimization study shows 20 mol % of diphenyl phosphate is an excellent acid promoter giving **17a** in 98% yield in 30 min with exclusive *trans* geometry. The generality of the reaction was subsequently investigated by a reaction with various aldehydes. Citronellal was found to be a suitable reaction partner, providing **17b** in 93% yield. Remarkably the mild reaction conditions have enabled us to use the ketal functional group which remained intact, furnishing **17c,d** in 40% and 64% yields, respectively. Five-membered as well as six-membered ring formations proceeded elegantly with aldehydes bearing benzyl- and methyl-protected ethers at the backbone (**17e,f,m**, 42−89%). Chromane derivative **17g** can also be synthesized with good diastereoselectivity by taking *O*-homoprenylated salicylaldehyde **14g** as a coupling partner. Nitrogenous aldehydes **14h−j** were also subjected to the standard reaction conditions, and products **17h−j** were isolated in moderate to good yields (56−73%).

Tolerance of a variety of aldehydes next prompted us to extend the scope of this reaction to other substituted indoles. In the case of 2-phenylindole, the optimized conditions gave 65% of the desired product **17n**. Sterically hindered 2-*tert*-

Scheme 2. Scope of Aldehydes and Indoles[a]



[a]All of the reactions were carried with **13** (0.25 mmol), **14** (0.25 mmol), and catalyst **A** (0.025−0.05 mmol) or catalyst **B** (0.0125 mmol) in CH_2Cl_2 (2.5 mL) or cyclohexane (2.5 mL) at rt. [b]Batchwise addition of aldehyde at 60 °C. dr = diastereomeric ratio.

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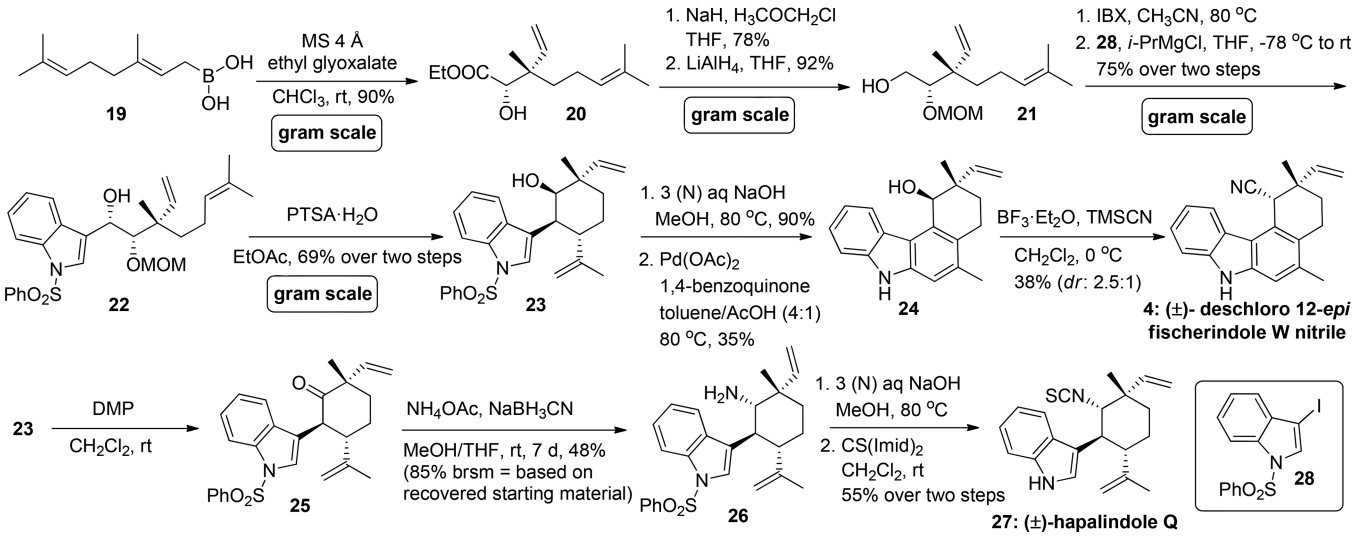
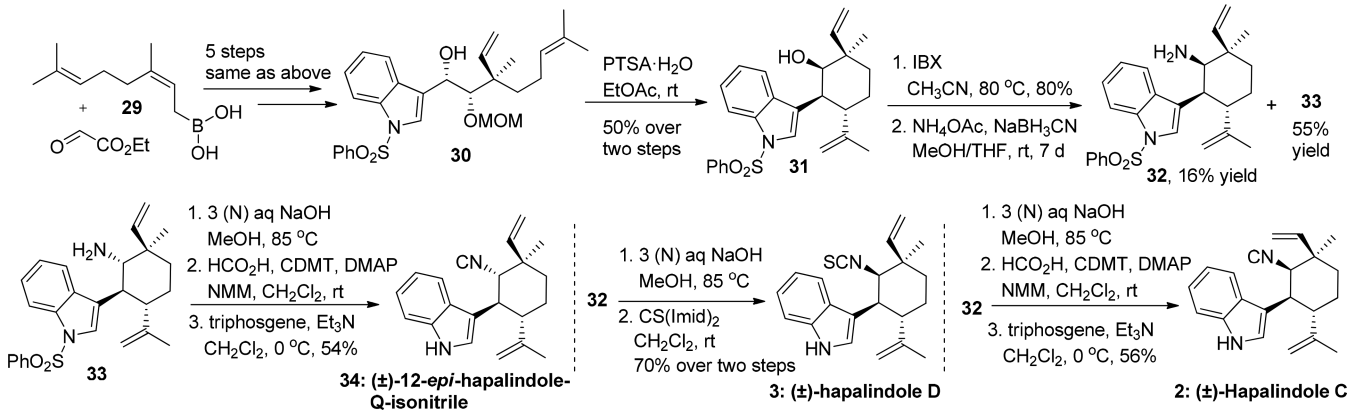
Scheme 3. Total Synthesis of (±)-Deschloro-12-*epi*-fischerindole W Nitrile and (±)-Hapalindole Q



Scheme 4. Total Synthesis of (±)-12-*epi*-Hapalindole Q Isonitrile, (±)-Hapalindole C, and (±)-Hapalindole D[a]



[a]PTSA = *p*-toluenesulfonic acid, IBX = 2-iodoxybenzoic acid, CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazene, DMAP = 4-(dimethylamino)-pyrridine; NMM = *N*-methylmorpholine; $CS(Imid)_2$ = 1,1′-thiocarbonyldimidazole.

butylindole was reactive enough and provided **17o** in excellent yield (92%), although the reaction required higher temperature and the batchwise addition of **14a** to minimize the intramolecular ene reaction. Compatibility of 2-styrylindole under the standard reaction conditions opens up the further possibility of functional group transformation for product **17p**. Indoles bearing −Br, $-NO_2$, and −CN functionalities in the benzene ring were also found to be suitable reaction partners, providing **17r−t** in 55−81% yields.

For indole having no C2-substitution, cyclohexane was found to be the solvent of choice. In the presence of BINOL-derived phosphoric acid catalyst **B** (5 mol %), we pleasingly found that fully cyclized product **18a** was the major product (56% yield) along with **17k** as the minor (11%). Single-crystal X-ray analysis of **18a** confirmed the stereochemical outcome of Prins-type cyclization. This cascade reaction provided an unprecedented direct access to the fischerindole scaffold which previously required two separate steps,[10c,f,h] whereas, catalyst **A** was not selective, providing **17k** and **18a** in 41 and 34% yields, respectively. Similar results were recorded for aldehyde **14b** when reacted with indole in the presence of either catalyst **A** or **B** (**17l**, **18b**). Gratifyingly product **18c** was isolated as the sole product in 68% yield. Even prolonging the reaction time does not convert the monocyclized products **17k,l** to their fully cyclized counterpart **18a,b**.

With the developed method in hand, we were curious to learn whether this method could be applied to the synthesis of hapalindole-type natural products. The reaction of geranyl boronic acid[13] with ethyl glyoxalate furnished homoallylic alcohol **20** in >20:1 dr and 90% yield (Scheme 3). In contrast, Zn-mediated allylation of geranyl bromide under similar conditions yielded **20** with almost no diastereoselectivity. Then **20** was protected as TBDPS as well as *p*-methoxybenzyl ethers, and finally, the esters were converted to their corresponding aldehydes. However, under the standard conditions both aldehydes did not give any desired products, probably due to steric bulk adjacent to the aldehydes retarding the initial attack of indole. We then moved toward methoxymethyl ether as a protecting group, which possesses moderate steric bulk and can also be deprotected under acidic conditions. However, it also did not provide fruitful results. To overcome this, MOM-protected aldehyde **14k** was coupled first with Grignard generated from **28** to obtain secondary alcohol **22** as a single diastereomer in 75% yield over two steps as we envisioned using Cram's chelate model.[12] To our joy, the treatment of **22** with 2.0 equiv of PTSA in ethyl acetate

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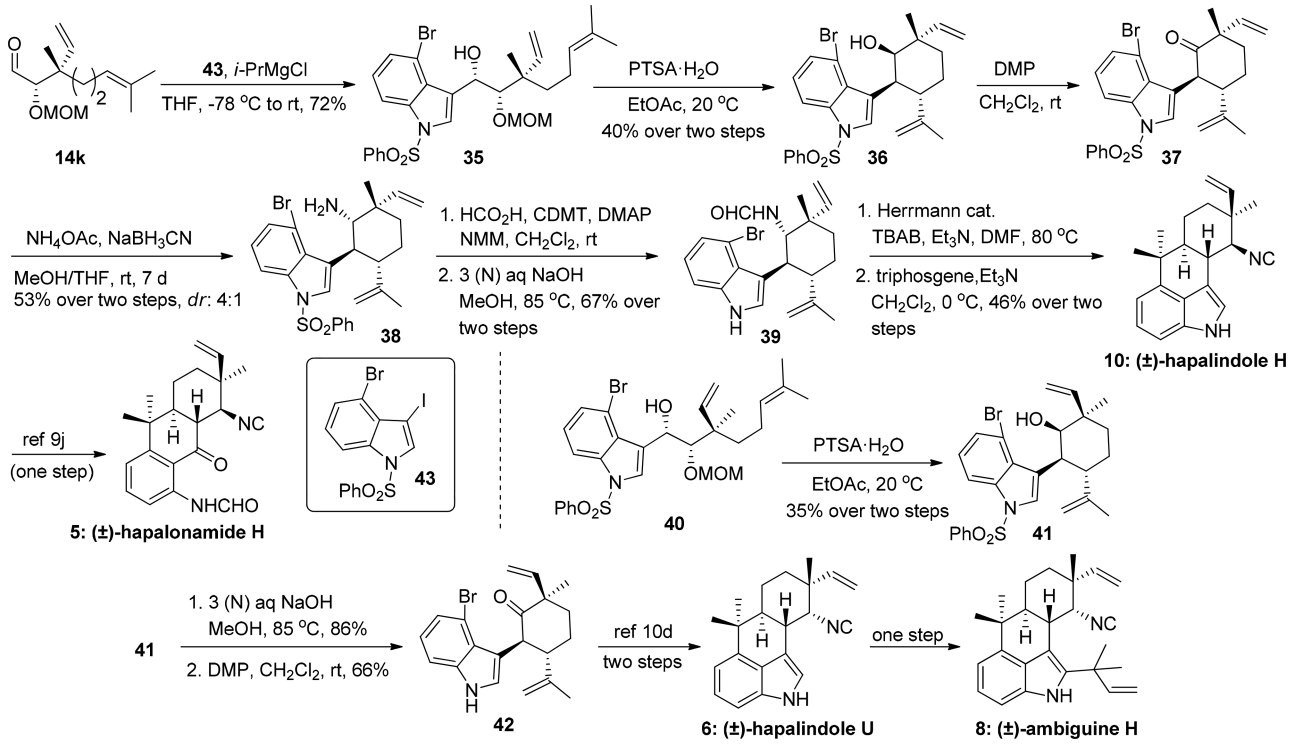
Scheme 5. Total Synthesis of (±)-Hapalindole H, (±)-Hapalonamide H, (±)-Hapalindole U, and (±)-Ambiguine H



proceeded smoothly to furnish deprotected monocyclized secondary alcohol **23** as a single diastereomer in 69% yield over two steps in one pot. It is important to mention that lower equivalency as well as changing to other acids or solvents were found to be less effective for this transformation. The relative stereochemistry of **23** was assigned by comparing its spectral data with the literature report after desulfonylation.[9j] After desulfonylation, $Pd(OAc)_2$/1,4-benzoquinone-mediated oxidative Heck annulation gave carbazole alcohol **24** in 35% yield.[9j] Total synthesis of deschloro-12-*epi*-fischerindole W nitrile **4** was accomplished in 38% overall yield as the major diastereomer (dr 2.5:1) by treatment of **24** with TMSCN in the presence of $BF_3{\cdot}Et_2O$.[9j] To synthesize hapalindole Q, **23** was oxidized to the corresponding ketone **25** using Dess−Martin periodinane oxidant. The resulting ketone was then converted to amine **26** in 48% yield (85% brsm) through reductive amination using NH_4OAc and $NaBH_3CN$.[10h] Removal of the protecting group followed by isothiocyanate formation using $CS(Imid)_2$ gave hapalindole Q **27** in 55% yield over two steps.

In a similar fashion as described above, *cis*-boronic acid **29** was converted to its secondary alcohol **30** (Scheme 4). Treatment of **30** with PTSA proceeded as anticipated, providing **31** in 50% yield over two steps. Alcohol functionality was converted to ketone using IBX oxidation, and the resulting ketone was then subjected to reductive amination giving two isomeric amines **32** and **33** in 16% and 55% yields, respectively.[10h] Desulfonylation of **33** followed by isocyanide formation gave 12-*epi*-hapalindole-Q-isonitrile (**34**) in 54% yield over three steps. Similarly, desulfonylation of another isomeric amine **32** followed by isothiocyanate as well as isocyanate formation gave hapalindole D (**3**) and hapalindole C (**2**), respectively.

Having achieved tricyclic hapalindoles, we next concentrated our attention toward tetracyclic subclass having *trans*-fused decalin ring system with a quaternary vinyl group at the C12-position and isonitrile group at the C11-position. To achieve this, we took 4-bromo-*N*-(benzenesulfonyl)-3-iodoindole **43** as an indole coupling partner.[10d] The reaction of aldehyde **14k** with Grignard generated from **43** provided alcohol **35** as a single diastereomer in 72% yield (Scheme 5). Treatment of **35** with 2.0 equiv of PTSA at a lower temperature (~20 °C) proceeded as hypothesized to give **36** in 40% overall yield over two steps. It is important to maintain the temperature at around 20 °C for optimal yield. DMP oxidation of **36** gave the ketone **37**. Similar reductive amination as mentioned previously proceeded smoothly to give amine **38** as a mixture of inseparable diastereomers (dr 4:1) in 53% combined yield. In the next step, amine was converted to the formamide functionality, and the benzenesulfonyl group was deprotected. During this time, major diastereomer **39** was separated and obtained in 67% yield. Formamide **39** was subjected to reductive Heck annulation and successive dehydration using triphosgene to give hapalindole H (**10**) in 46% yield over two steps.[9j] Hapalindole H has been used as an advanced intermediate for the synthesis of hapalonamide H (**5**) by Li et al.[9j] Thus, the formal synthesis of hapalonamide H (**5**) was also achieved.

The other isomeric alcohol **40**, prepared by using **43** and aldehyde **14l** obtained from **29**, was similarly treated with PTSA to obtain **41** in 35% yield. Desulfonylation followed by DMP oxidation gave ketone **42**, which has been used as a synthetic intermediate for the synthesis of hapalindole U (**6**) and ambiguine H (**8**), thus completing their formal synthesis.[10d]

In conclusion, we have successfully synthesized diverse functionalized *trans*-1-indolyl-2-isopropenylcyclohexane scaffolds via Brønsted acid catalyzed one-pot cascade protocol. Simplicity and mild conditions significantly enhance the appeal of this method toward other systems. To show the

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applicability, nine hapalindole-type alkaloids were synthesized in a stereodivergent manner. Out of four stereocenters, diastereoselective allylation using allylboronic acids fixed two adjacent stereocenters, whereas a PTSA-mediated deprotection−cyclization cascade sealed the other two. An enantioselective version of this Prins-type cyclization is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02804.

Experimental procedures and spectroscopic data of compounds; NMR spectra of compounds (PDF)

Accession Codes

CCDC 1860967 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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