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Enantioselective Total Synthesis of (+)-Hinckdentine A via a Catalytic Dearomatization Approach

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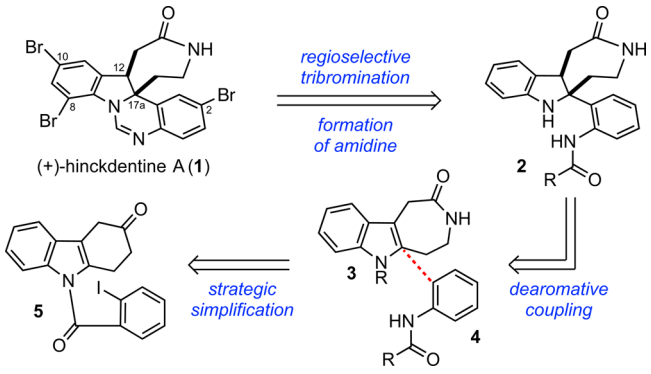
Supporting Information

ABSTRACT: Optically pure hinckdentine A was synthesized on a 300 mg scale via an asymmetric catalysis-based strategy. The key steps to the first asymmetric synthesis involved (i) enantioselective dearomative cyclization of an achiral *N*-acyl indole that allowed for the efficient construction of the key polycyclic indoline intermediate with a crucial tetrasubstituted stereogenic carbon center, (ii) Beckmann fragmentation-mediated ring expansion, (iii) rearrangement-based introduction of an anilinic nitrogen atom, (iv) regioselective tribromination, and (v) final closure of the cyclic amidine moiety.

Rapid construction of architecturally complex polycyclic systems is one of the most important frontiers in the field of natural products/pharmaceuticals synthesis.[1] A potent solution to this challenging mission is a dearomatization strategy wherein a functionalized planar aromatic framework acquires a three-dimensional character. Catalytic asymmetric dearomative cyclization is particularly attractive for the efficient construction of chiral polycyclic systems. Substantial efforts have been devoted to this field[2] after the pioneering works of Buchwald,[3] Bedford,[4] and You.[5] These dearomatization strategies have been applied to the synthesis of a variety of natural products and demonstrated their potential for constructing complex structures with rich sp^3 architectures.[6] It occurred to us that the application of this strategy could be advantageous in the synthesis of the screw-shaped hinckdentine A (**1**), which was isolated from the marine bryozoan *Hincksinoflustra denticulata* in 1987.[7] The structure, unambiguously determined by single X-ray crystallographic analysis, is characterized by a highly brominated indolo[1,2-*c*]quinazoline core fused to a seven-membered lactam unit through the consecutive stereogenic centers at C12 and C17a, and a cyclic amidine moiety. The biological activities of this compound have not been reported due to a shortage of **1** isolated from natural sources. A synthetic supply of this material,[8] therefore, is clearly important for uncovering the biological activity of **1** and its derivatives.[9]

Scheme 1 shows our retrosynthetic analysis of **1**. McWhorter's synthetic study[8b] indicated that the C8-selective bromination of 8-desbromohinckdentine A would be problematic, giving an inseparable mixture of various tribromides and tetrabromides. Accordingly, Kawasaki employed a protected cyclic aminal intermediate for selective tribromination, leading to the sole example of a racemic total synthesis.[10] We thus selected the indoline/anilide **2** as our key intermediate. Compound **2** was expected to favor *ortho*−*para* -dibromination at C8 and C10 on the left-hand indoline as well as single *para*-bromination at C2 on the right-hand anilide. The dearomatized indole **2**, in which an aromatic moiety was wedged into the indole 2-position at C17a, could be disconnected to form two planar synthons **3** and **4** on the basis of an asymmetric dearomative coupling. The nitrogen functionalities in the azepanone moiety in **3** and the acylamino group in **4** were retrosynthetically excised. The simple *N*-acyl tetrahydrocarbazole **5** was thus chosen for the execution of a pivotal asymmetric dearomative cyclization.

Scheme 1. Retrosynthetic Analysis



First, the palladium-catalyzed asymmetric dearomative Heck-type cyclization of **5** to **6** was investigated. Table 1 summarizes the results. The substrate **5** was prepared in 89% yield in two steps from the known 5-oxo-tetrahydrocarbazole ethylene ketal.[11,12] A nonasymmetric variant using the related *N*-acyl indoles have been reported originally by Grigg[13] in 2001 and later developed by Wu,[14] Jia,[15] and Lautens.[16] We attempted to render the reaction asymmetric by using an appropriate chiral ligand. Extensive investigations revealed that Feringa's phosphoramidite ligands **7**[17] gave the most promising results.

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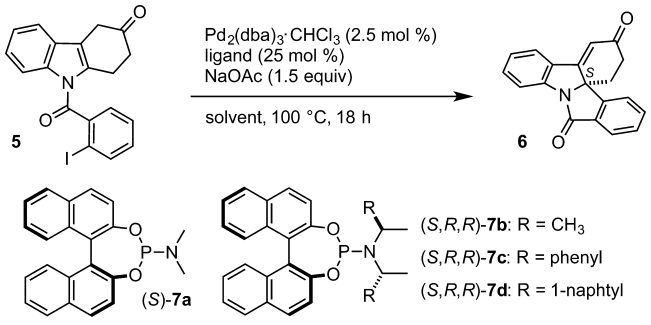
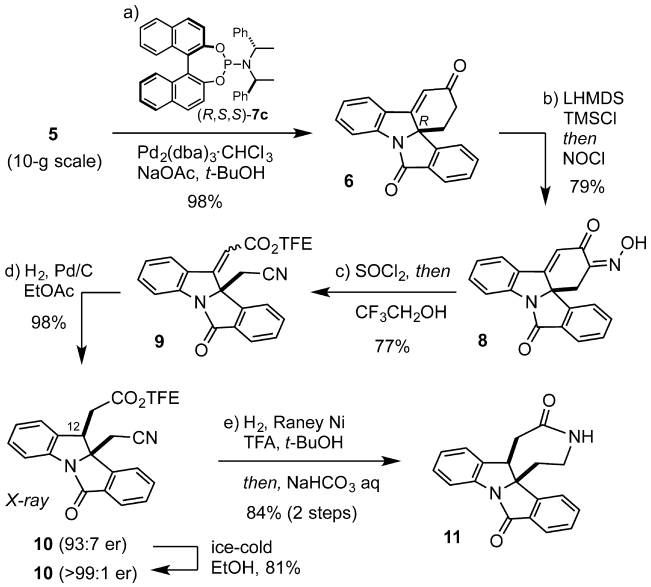
Table 1. Palladium-Catalyzed Dearomative Cyclization and Optimization of the Reaction Conditions[a]



entry	ligand	solvent	NMR yield[b]	er[c]
1	**7a**	*t*-BuOH	94	70/30
2	**7b**	*t*-BuOH	95	88/12
3	**7c**	*t*-BuOH	99	93/7
4	**7d**	*t*-BuOH	99	66/34
5	**7c**	DMA	99	67/33
6	**7c**	DMSO	93	68/32
7	**7c**	1,4-dioxane	47	91/9
8	**7c**	CH_3CN	43	85/15
9	**7c**	1,2-dichloroethane	38	86/14
10	**7c**	toluene	16	93/7

[a]All reactions were carried out under standard reaction conditions: **5** (100 μmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), **7** (25 mol %), NaOAc (1.5 equiv), solvent (1.5 mL), 100 °C, 18 h. [b]Determined by ^1H NMR analysis using dimethyl sulfone as an internal standard. [c]The enantiomeric ratio (er) was determined by HPLC analysis on DAICEL CHIRALCEL OJ-H (*n*-hexane/*i*-PrOH = 60:40; 1.0 mL/min).

Scheme 2. Construction of Seven-Membered Lactam[a]



[a]Reagents and conditions: (a) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), (*R*,*S*,*S*)-**7c** (25 mol %), NaOAc (1.5 equiv), *t*-BuOH, 100 °C, 18 h, 98%, 93:7 er; (b) LHMDS, TMSCl, THF, −78 °C, 1 h, then NOCl, 3 h, 79%; (c) $SOCl_2$, 1,2-dichloroethane, 0 °C to rt, 1 h, then CF_3CH_2OH, 40 °C, 22 h, 77%; (d) H_2 (1 atm), Pd/C (10 mol %), EtOAc, 40 °C, 17 h, 98%, washing with ice-cold EtOH, 81%, >99:1 er; (e) H_2 (50 atm), Raney Ni, TFA, *t*-BuOH, 80 °C, 22 h, then $NaHCO_3$ aq, CH_2Cl_2, 40 °C, 18 h, 84% (2 steps). dba = dibenzylidene acetone, TFE = 2,2,2-trifluoroethyl.

The reactivity and enantioselectivity were optimized by fixing the standard conditions as follows: **5** (100 μmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), ligand **7** (25 mol %), NaOAc (1.5 equiv), *t*-BuOH (1.5 mL), temp 100 °C, and time 18 h. Among the ligands tested (**7a**−**d**), the phenyl-substituted ligand **7c** gave the best enantioselectivity (entries 1−4). In DMA and DMSO, the selectivity decreased (entries 5 and 6). The reactivity decreased when 1,4-dioxane, CH_3CN, or 1,2-dichloroethane was used as the solvent (entries 7−9), and the reaction was sluggish in toluene (entry 10). Our preliminary experiments on the application to other substrates also afforded the dearomatized products with good enantiomeric ratio.[18] The absolute stereochemistry of the major enantiomer of **6** obtained through the use of (*S*,*R*,*R*)-**7c** was determined to be *S* by comparing the calculated and observed CD/VCD spectra.[19,20]

With the optimized reaction conditions (entry 3) in hand, we turned to synthetic studies of **1** from the chiral intermediate **6** bearing the crucial tetrasubstituted stereogenic carbon center (Scheme 2). The synthesis of the natural enantiomer of hinckdentine A (**1**) required the (*R*)-**6** intermediate. Thus, the enantiomeric ligand (*R*,*S*,*S*)-**7c** was employed. The reproducibility of the optimized conditions was confirmed on a 10 g scale (98% isolated yield, *R*/*S* = 93:7). Subsequent transformations from **6** to **11** represented the ring expansion of the cyclohexenone moiety via the introduction of a nitrogen atom. Our initial attempts at the Beckmann rearrangement via the corresponding oxime tosylate afforded the complex mixture, which may indicate the increased donation from the amide nitrogen electron pair compared to the case of McWhorter's.[8b,16a] Therefore, the Beckmann fragmentation strategy was employed. An oxime functionality was introduced at the α-position of the ketone by treatment of the intermediary silyl enolate with NOCl that was generated in situ from TMSCl and *i*-AmONO.[21] The Beckmann fragmentation of **8** was efficiently mediated by $SOCl_2$ and subsequent treatment with CF_3CH_2OH gave a 1:11 *E*/*Z* mixture of the α,β-unsaturated 2,2,2-trifluoroethyl esters **9** bearing a cyanomethyl group at C17a. Catalytic hydrogenation of **9** occurred from the face opposite to the cyanomethyl group with perfect diastereoselectivity, giving **10**[22] in 98% with 93:7 er. The enantiomerically pure **10** was then obtained in 81% yield simply by rinsing the crystals with ice-cold ethanol. The heterochiral racemic crystals of **10** appear to be more soluble than the homochiral crystals. The nitrile functionality in **10** was hydrogenated on Raney nickel to provide the corresponding amine, which spontaneously reacted with the 2,2,2-trifluoroethyl ester group to give the seven-membered lactam intermediate **11**.

The remaining obstacles to be cleared toward **1** involved the conversion of **11** to the indoline/anilide intermediate corresponding to **2**, prior to the selective tribromination and formation of the amidine moiety. The solutions are illustrated in Scheme 3. Reduction of the tertiary amide functionality in **11** was attained by a modified Soai's method[23] ($NaBH_4$−CH_3OH−THF), leaving the secondary amide of the seven-membered lactam intact to give the amino alcohol **12** in 78% yield. After protection of the amino alcohol moiety as a TFA amide and TES ether, the resulting **13** was oxidized with Jones reagent to provide an aldehyde, which was immediately transformed to the aldoxime **14**, setting the stage for the modified Kim's protocol.[24] Conversion of **14** to the nitrile oxide in situ, followed by the reaction with tetrahydro-2-pyrimidinethione (**15**) afforded the cycloaddition/rearrangement product, isothiocyanate **16**, as a sole product in 72% yield from **13**. The TFA group in **16** thus obtained was too labile under basic conditions, readily forming the cyclic thiourea **17**. Extensive

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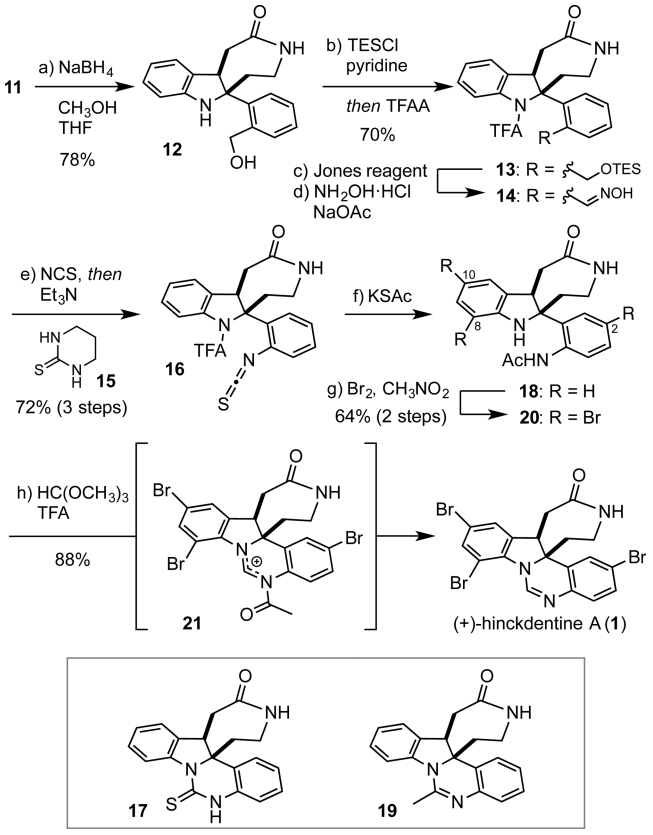
Scheme 3. Total Synthesis of Hinckdentine A[a]



[a]Reagents and conditions: (a) $NaBH_4$ (50 equiv), CH_3OH, THF, 65 °C, 10 h, 78%; (b) TESCl, pyridine, CH_2Cl_2, 0 °C, 30 min, then TFAA, 0 °C, 30 min, 70%; (c) Jones reagent, acetone, 0 °C, 1 h; (d) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, 0 °C, 1 h; (e) NCS, DMF−THF, 65 °C, 15 min, then tetrahydro-2-pyrimidinethione (**15**), Et_3N, 0 °C, 1 h, 72% (3 steps); (f) KSAc (5.0 equiv), CH_3OH, 40 °C, 4 h, then $NaHCO_3$ aq, rt; (g) Br_2 (3.0 equiv), CH_3NO_2, −20 °C to rt, 30 min, then Br_2 (8.0 equiv) rt, 1.5 h, then 2-methyl-2-butene, 0 °C, 64% (2 steps); (h) $HC(OCH_3)_3$ (50 equiv), TFA (50 equiv), rt, 30 min, then CH_3OH−H_2O, rt, 88%. TES = triethylsilyl, TFAA = trifluoroacetic anhydride, NCS = *N*-chlorosuccinimide.

screening of the reaction conditions revealed that the premature removal of the TFA group could be suppressed by the initial treatment of **16** with KSAc[25] in CH_3OH at 40 °C for 4 h, followed by a hydrolytic workup with $NaHCO_3$ aq. While the indoline/acetanilide intermediate **18** thus obtained was equipped with the electronic properties required for the crucial tribromination, the bromination was difficult at best probably due to the low solubility of **18** as well as the brominated intermediates in the solvents typically used for bromination (CH_2Cl_2, $CHCl_3$), resulting in a facile cyclization to a methylquinazoline **19**, even at room temperature. Fortunately, the undesired pathway was suppressed by employing CH_3NO_2 as the solvent. Treatment of a clear solution of **18** in CH_3NO_2 at −20 °C with 3.0 equiv of Br_2 resulted in selective bromination at C2 and C10. Further bromination with 8.0 equiv of Br_2 at room temperature proceeded at C8 without forming the byproduct **19**. The reaction was quenched with 2-methyl-2-butene to circumvent oxidative N−N bond formation, furnishing the penultimate tribromide **20** in 64% yield from the isothiocyanate **16** in a reproducible manner.[26] Finally, the amidine moiety of **1** was constructed in 88% yield by treating **20** with an excess amount of $HC(OCH_3)_3$ (50 equiv) and TFA (50 equiv), presumably via in situ removal of the acetyl group from the amidinium intermediate **21**. This final process provided hinckdentine A (**1**) on a 300 mg scale: $[\alpha]^{20}_D$ + 274 (c = 1.00, $CHCl_3$).

In conclusion, we have achieved the first enantioselective total synthesis of hinckdentine A (**1**) in 14 steps and in 8.8% total yield from the readily available **5**, establishing the basis for future biological studies. Our unique synthetic strategy consisted of five effective key processes: (i) palladium-catalyzed asymmetric dearomative cyclization of **5** to **6**, (ii) Beckmann fragmentation/lactamization sequence leading to the seven-membered lactam **11**, (iii) rearrangement-based introduction of a nitrogen atom into the anilide **18**, (iv) regioselective tribromination, and (v) the formation of the amidine moiety to afford the indolo[1,2-*c*]quinazoline core. These processes eventually realized a 300 mg scale total synthesis of **1**. Further optimization of the present catalytic dearomatization, a mechanistic study, and applications of the key reaction to other synthetic targets are currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10237.

Experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra (PDF)
Crystallographic data of **10** (CIF)

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Notes

The authors declare no competing financial interest.

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(22) CCDC 1499681 (**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
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(26) While CH_3CN as a solvent provided similar solubility and reactivity, it was not employed because of the formation of the Ritter-type reaction product (2,4,4,5-tetramethyl-4,5-dihydrooxazole), which disturbed the purification process.

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