JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

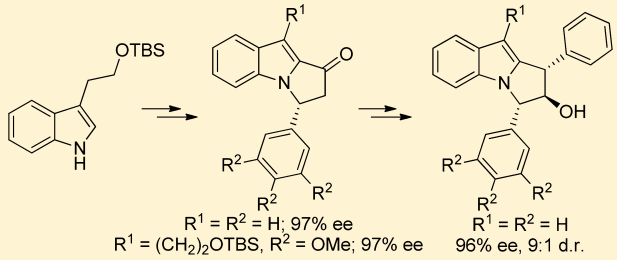
Enantioselective Model Synthesis and Progress toward the Putative Structure of Yuremamine

Avipsa Ghosh, David T. Bainbridge, and Levi M. Stanley*

Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

Supporting Information

ABSTRACT: An enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core of the putative structure of yuremamine is reported in 39% overall yield and 96% ee over five steps. The model synthesis leverages enantioselective, rhodium-catalyzed hydroacylation of an *N*-vinylindole-2-carboxaldehyde as the key step in the installation of the stereochemical triad. An enantioselective synthesis of a densely functionalized dihydropyrroloindolone that maps onto the putative structure of yuremamine is demonstrated in 26% yield and 97% ee over eight steps.



INTRODUCTION

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]-indole and oxidized derivatives are recurring motifs in natural products and drug candidates including the antimalarial flinderoles[1] and isoborreverines,[2] the antitumor antibiotic mitomycin C,[3] the PKC inhibitor JTT-010,[4] and isatisine A[5] which exhibits antiviral activity. Yuremamine, a phytoindole alkaloid with hallucinogenic and psychoactive properties, was isolated from the stem bark of *Mimosa hostilis* in 2005 by Callaway and co-workers.[6] The structure of yuremamine, originally proposed to be the densely functionalized dihydropyrroloindole **1** with three contiguous stereogenic centers, was recently revised to the flavonoidal indole **2** by Sperry and co-workers (Figure 1).[7]

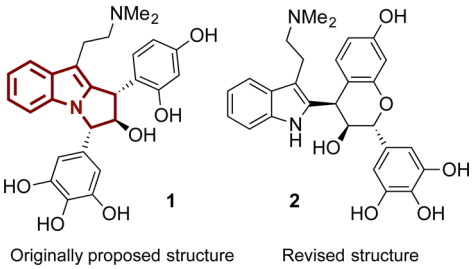
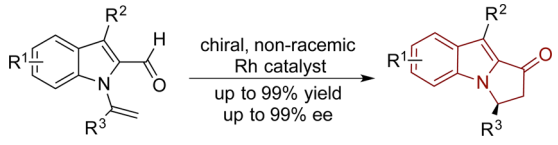


Figure 1. Originally proposed structure and revised structure of yuremamine.

The intriguing molecular architecture of **1** prompted numerous synthetic studies toward the putative structure since the isolation of yuremamine. While several synthetic strategies toward the dihydropyrroloindole core of **1** have been developed by the Kerr, Shi, Dethe, Chen, France, You, Sperry, and Zu groups,[8] the first racemic total synthesis was reported by the Iwasawa group in 2015.[9] Despite these synthetic efforts during the past decade, enantioselective total synthesis of **1** or synthetic approaches to generate the chiral dihydropyrroloindole core with control of the absolute configuration of the stereochemical triad have not been reported.

Compound **1** is a fundamentally challenging target due to the lack of well-established enantioselective methods to generate chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indoles.[10] The dihydropyrroloindole core of **1** contains three contiguous stereogenic centers that must be formed in a stereocontrolled fashion. Recently, we reported catalytic, intramolecular hydroacylations of *N*-vinylindole-2-carboxaldehydes to form *β*-substituted dihydropyrroloindolones with high enantioselectivities that offer the potential to address these challenges (Scheme 1).[11]

Scheme 1. Enantioselective Hydroacylation of *N*-Vinylindole-2-carboxadehydes To Access Chiral Dihydropyrroloindolones



The enantioselective hydroacylation would enable control of the absolute configuration of one of the requisite stereogenic centers present in the dihydropyrroloindole core. In addition, the ketone functionality present in the dihydropyrroloindolone product of hydroacylation can serve as a synthetic handle to install the additional stereogenic centers with precise control of the absolute and relative configuration of the stereochemical triad.

Herein, we report an enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core of **1** utilizing enantioselective rhodium-catalyzed hydroacylation of an *N*-vinylindole-2-carboxaldehyde as the key step for installation of the

Received: July 19, 2016
Published: August 5, 2016

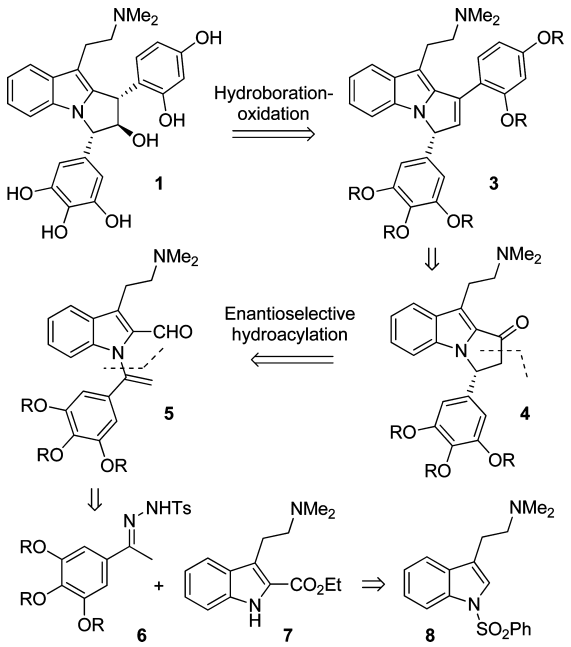
DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

three contiguous stereogenic centers. We also report an enantioselective synthesis of a functionalized chiral dihydropyrroloindolone that maps onto the structure of **1**.

RESULTS AND DISCUSSION

Scheme 2 illustrates the strategy we originally envisioned to complete an enantioselective synthesis of **1**. Installation of the

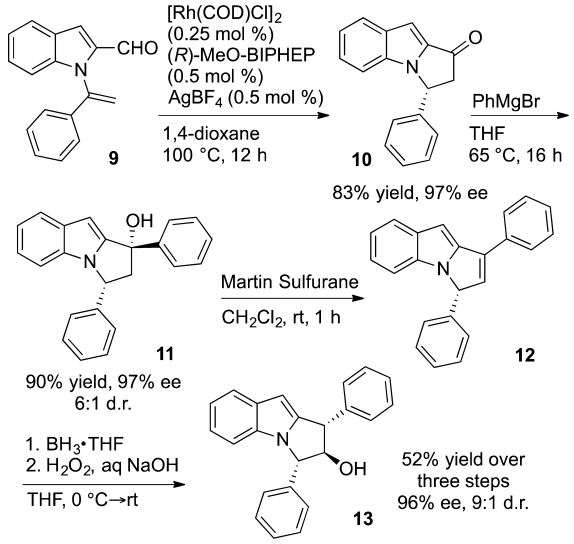
Scheme 2. Retrosynthetic Analysis for the Enantioselective Synthesis of Compound 1



stereochemical triad in **1** would be achieved by a sequence of hydroboration and oxidation occurring on the face of the olefin opposite to the aryl group attached to the stereogenic center in **3**.[12] Compound **3** would be synthesized by a sequence of Grignard addition to the chiral dihydropyrroloindolone **4** followed by dehydration of the resulting tertiary alcohol to form the required alkene. Based on our previous studies, we planned the synthesis of **4** from *N*-vinylindole-2-carboxaldehyde **5** by an enantioselective, intramolecular rhodium-catalyzed hydroacylation reaction.[11] Compound **5** would be generated by a palladium-catalyzed cross-coupling reaction of indole **7** and hydrazone **6**.[13] Indole **7** could be derived from **8** by direct installation of the ester functionality at the 2-position of the indole followed by removal of the protecting group from the indole nitrogen.

We were aware that intermediate **3** may be susceptible to olefin isomerization that could racemize the stereogenic center set by enantioselective hydroacylation. To test our strategy to install the three contiguous stereogenic centers in an enantioselective and diastereoselective fashion, we conducted a model study starting from *N*-vinylindole-2-carboxaldehyde **9** (Scheme 3). Enantioselective hydroacylation of **9** in the presence of 0.5 mol % of a Rh catalyst prepared in situ from $[Rh(COD)Cl]_2$, (*R*)-MeO-BIPHEP, and $AgBF_4$ formed dihyropyrroloindolone **10** in 83% yield with 97% ee. Addition of phenylmagnesium bromide to **10** generated the tertiary alcohol **11** in 90% yield as a 6:1 mixture of diastereomers with complete retention of enantiomeric excess (97% ee). Subsequent dehydration of the resulting tertiary alcohol with

Scheme 3. Enantioselective Model Synthesis of the 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole Core of 1

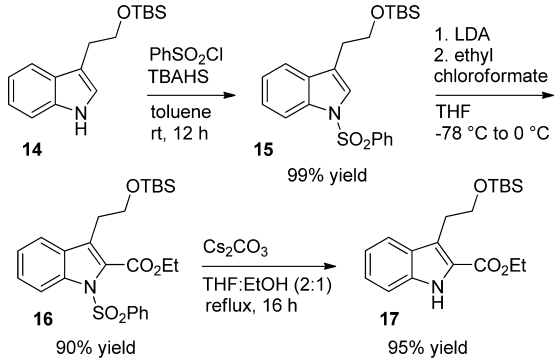


Martin sulfurane generated (*R*)-1,3-diphenyl-3*H*-pyrrolo[1,2-*a*]indole **12**.[14] The carbon skeleton present in the dihydropyrroloindole core of **1** was established by immediate hydroboration of **12** followed by oxidation of the resulting alkylborane with basic hydrogen peroxide. Dihydropyrroloindole **13** was isolated as a 9:1 mixture of diastereomers in 52% yield over three steps without significant loss of enantioselectivity (96% ee). Consistent with hydroboration and oxidations of 1,3-diarylcyclopent-1-enes, the hydroboration and oxidation of **12** preferentially occurs on the face of the olefin opposite to the phenyl group attached to the stereogenic center.[12] This sequence occurs to set a stereochemical triad with both aryl groups *trans* to the hydroxyl group. The relative stereochemistry of the dihydropyrroloindole core **13** was established by geminal carbon−proton spin-coupling constant ($^2J_{C,H}$) values (*J*-based configuration analysis) and the dependence of these values on dihedral angles (see Supporting Information for details).[15]

Encouraged by the results of our model synthesis, we initiated studies toward an enantioselective synthesis of **1**. Preliminary studies of the key hydroacylation step with *N*,*N*-dimethyltryptamine derivatives were not encouraging, presumably due to coordination of the basic nitrogen in the *N*,*N*-dimethyltryptamine derivative to the rhodium center. Thus, we conducted our studies starting from the TBS ether of tryptophol **14**. Scheme 4 illustrates the synthesis of indole **17** from the TBS ether of tryptophol **14**.[16] The indole nitrogen in **14** was protected using benzenesulfonyl chloride in the presence of tetrabutylammonium hydrogensulfate (TBAHS) to furnish **15** in 99% yield.[17] We envisioned direct installation of an ester at the 2-position of indole via lithiation followed by quenching with an appropriate electrophile. Interestingly, common lithiating agents such as *n*-BuLi, *sec*-BuLi, and *tert*-BuLi led to the formation of complex mixtures of multiple products even with less than 1 equiv of base.[18] However, lithiation in the presence of freshly prepared lithium diisopropylamide (LDA) at −78 °C followed by reaction with diethyl carbonate or ethyl chloroformate formed the desired ethylindole-2-carboxylate **16** as the only product in 30−75% yield (Table 1, entries 1 and 2). The use of ethyl chloroformate as the electrophile and increasing the reaction

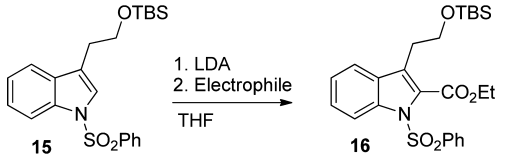
DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

Scheme 4. Synthesis of Indole 17



temperature improved the yield of the desired product to 90% (Table 1, entry 3).

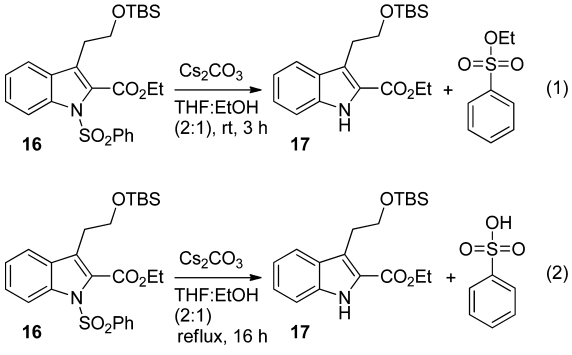
Table 1. Identification of Reaction Conditions for Synthesis of Ester 16[a]



entry	temp (°C)	electrophile	yield (%)[b]
1	−78	diethyl carbonate	30
2	−78	ethyl chloroformate	75
3	−78→0	ethyl chloroformate	90

[a]Reaction conditions: **15** (1.20 mmol, 1.00 equiv), LDA (1.20 mmol, 1.00 equiv), electrophile (1.44 mmol, 1.20 equiv), and THF (7.0 mL). [b]Isolated yield of **16** after column chromatography.

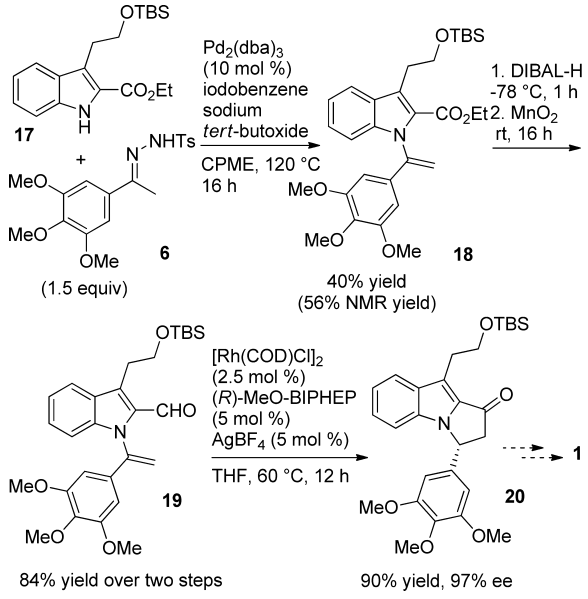
With a suitable method to install the ester functionality, we attempted to remove the benzenesulfonyl protecting group in **16**. Although many methods are established to accomplish similar transformations, the deprotection of **16** proved challenging.[19] Deprotection in the presence of Na−Hg/Na_2HPO_4 led to incomplete conversion (60%) of **16** to indole **17**.[19a] The reaction of **16** in the presence of sodium *tert*-butoxide in 1,4-dioxane was plagued by undesired transesterification and hydrolysis of the ester.[19b] Deprotection of **16** in the presence of Cs_2CO_3 in a 2:1 mixture of THF/ethanol at room temperature led to 99% conversion of **16** to **17** along with the formation of ethylbenzenesulfonate (eq 1).[20]



However, the similar polarities of **17** and ethylbenzenesulfonate rendered isolation of pure **17** challenging by standard chromatographic techniques. Conducting the reaction at reflux for 16 h led to the formation of **17** in 95% yield along with benzenesulfonic acid, which were easily separable by flash column chromatography (eq 2). All of the synthetic transformations shown in Scheme 4 are robust and were conducted in multi-millimolar scale (up to 20 mmol).

Scheme 5 illustrates the enantioselective synthesis of the functionalized chiral dihydropyrroloindolone **20**. Palladium-

Scheme 5. Synthesis of Dihydropyrroloindolone 20



catalyzed cross-coupling of **17** with hydrazone **6** generated ethyl *N*-vinylindole-2-carboxylate **18** in 40% isolated yield. A sequence of DIBAL-H-mediated reduction of **18** followed by oxidation of the resulting crude alcohol with MnO_2 furnished *N*-vinylindole-2-carboxaldehyde **19** in 84% yield over two steps. Enantioselective, intramolecular hydroacylation of **19** in the presence of a catalyst generated in situ from $[Rh(COD)Cl]_2$, (*R*)-MeO-BIPHEP, and $AgBF_4$ formed dihyropyrroloindolone **20** in 90% yield with 97% ee.

Chiral dihydropyrroloindolone **20** is suitably functionalized to complete an enantioselective synthesis of **1** based on the model synthesis illustrated in Scheme 2. However, we elected to terminate our efforts toward **1** following the structural reassignment of yuremamine from a dihydropyrroloindole to a flavonoidal indole.[7]

CONCLUSION

In conclusion, we have developed an enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core present in the putative structure of yuremamine. The 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core containing three contiguous stereogenic centers was synthesized in 39% overall yield and 96% ee in five steps. The catalytic protocol for enantioselective rhodium-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehyde reported by our group was utilized in multi-milllimolar scale as the key step for installation of the stereochemical triad. The ketone functionality present in the hydroacylation product served as a synthetic handle for the installation of additional stereocenters with precise control of absolute and relative stereochemistry. Progress toward enantioselective synthesis of the putative structure of yuremamine is reported, and the enantioselective synthesis of a

DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

densely functionalized dihydropyrroloindolone core that maps onto this structure has been demonstrated in 26% yield and 97% ee over eight steps. The synthetic strategy is likely to be amenable to the synthesis of other natural products containing a 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indole core and highlights the utility of our hydroacylation protocol in the construction of complex molecular scaffolds.

EXPERIMENTAL SECTION

General Experimental Details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled drybox or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture-sensitive reactions was dried at 140 °C in an oven. THF, DMF, CH_2Cl_2, and diethyl ether were degassed by being purged with argon for 45 min and dried with a solvent purification system by passing through a 1 m column of activated alumina. Flash column chromatography was performed on SiliFlash P60 silica gel (40−63 μm, 60 Å) using hexanes/EtOAc or hexanes/ether mixtures. Reaction products were visualized on thin layer chromatography by UV light or by staining with $KMnO_4$ or 2,4-dinitrophenylhydrazine.

HRMS (ESI) analysis was performed on a QTOF spectrometer. Optical rotations were measured on an automatic polarimeter. HPLC analyses were carried out on a HPLC system with a separations module and a UV/vis dual wavelength detector. NMR spectra were acquired on 400 and 600 MHz NMR spectrometers. Chemical shifts are reported in parts per million relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.16 ppm for ^{13}C; C_6D_6 = 7.16 for ^1H and 128.06 for ^{13}C). Coupling constants are reported in hertz.

Materials. *N*-Vinylindole-2-carboxaldehyde **9** was synthesized according to a literature procedure from ethylindole-2-carboxylate.[11] 3′,4′,5′-Trimethoxyacetophenone was synthesized from 3′,4′,5′-trimethoxybenzoic acid according to a literature procedure.[21] $[Rh(COD)Cl]_2$, $Pd_2(dba)_3$, *rac*-BINAP, (*R*)-MeO-BIPHEP, and silver tetrafluoroborate were purchased from Strem Chemicals and used without further purification.

Synthesis of (*R*)-3-Phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indol-1-one (10).[11] In a nitrogen-filled glovebox, *N*-vinylindole-2-carboxaldehyde **9** (500 mg, 2.02 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.5 mg, 0.0050 mmol, 0.0025 equiv), (*R*)-MeO-BIPHEP (5.8 mg, 0.010 mmol, 0.0050 equiv), $AgBF_4$ (1.9 mg, 0.010 mmol, 0.0050 equiv), and 1,4-dioxane (14.0 mL) were added to a 20 mL scintillation vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 100 °C in an oil bath for 12 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 100 mL of 3:2 hexanes/EtOAc). The crude reaction mixture was concentrated under reduced pressure. The mixture was purified by flash column chromatography (90:10 hexanes/EtOAc) to give (*R*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **10** as a light yellow solid in 83% yield (415 mg, 1.68 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C): t_R 17.7 min (major); t_R 21.1 min (minor) [Chiracel AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) hexanes/*i*-PrOH, 95:5, 1.0 mL/min] to be 97%; $[\alpha]_D^{24}$ = +232.2 (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.07 (dd, *J* = 18.4, 4.0 Hz, 1H), 3.68 (dd, *J* = 18.4, 8.0 Hz, 1H), 5.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.93−6.95 (m, 1H), 7.11−7.21 (m, 5H), 7.32−7.39 (m, 3H), 7.77−7.79 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 50.4, 57.3, 99.3, 111.8, 121.7, 124.3, 125.4, 126.1, 128.6, 129.4, 132.6, 135.0, 136.3, 140.1, 192.2; HRMS (ESI) calcd for $C_{17}H_{14}NO$ ($[M + H]^+$) 248.1070, found 248.1069.

Synthesis of (1*S*,3*R*)-1,3-Diphenyl-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]indol-1-ol (11). A 3.0 M solution of phenylmagnesium bromide (0.67 mL, 2.0 mmol, 2.5 equiv) in diethyl ether was added to a solution of (*R*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **10** (200 mg, 0.808 mmol, 1.00 equiv) in THF (5.0 mL) under a nitrogen atmosphere. The reaction mixture was heated at 65 °C and stirred for 16 h. The mixture was cooled in an ice/water bath and then quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous phase was extracted with ether (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (85:15 hexanes/EtOAc) to give (1*S*,3*R*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indol-1-ol **11** as a yellow oil in 90% yield (237 mg, 0.728 mmol) as a 6.1:1 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C): t_R 13.6 min [(1*R*,3*R*)]; t_R 16.2 min [(1*S*,3*S*)], t_R 20.5 min [(1*S*,3*R*)]; t_R 36.3 min [(1*R*,3*S*)] [Chiracel AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) hexanes/*i*-PrOH, 93:7, 1.0 mL/min] to be 96% for the (1*R*,3*R*)-diastereomer and 97% for the (1*S*,3*R*)-diastereomer; $[\alpha]_D^{24}$ = +78.7 (*c* 0.25, $CHCl_3$); ^1H NMR (600 MHz, C_6D_6) δ 1.87 (s, 1H), 2.72 (dd, *J* = 13.3, 4.2 Hz, 1H), 2.95 (dd, *J* = 13.3, 8.1 Hz, 1H), 5.02 (dd, *J* = 8.1, 4.2 Hz, 1H), 6.27 (s, 1H), 6.88−6.96 (m, 3H), 7.02−7.03 (m, 3H), 7.06 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.17−7.21 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (151 MHz, C_6D_6) δ 57.6, 59.7, 78.7, 93.85, 111.3, 120.45, 122.0, 122.1, 126.1, 126.75, 127.7, 128.35, 128.5, 129.0, 132.85, 133.7, 141.3, 145.7, 148.8; HRMS (ESI) calcd for $C_{23}H_{20}NO$ ($[M + H]^+$) 326.1539, found 326.1546.

Synthesis of (1*S*,2*R*,3*S*)-1,3-Diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-2-ol (13).[12,14] Martin sulfurane[22] (465 mg, 0.691 mmol, 1.50 equiv) was added to the solution of (1*S*,3*R*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ol **11** (150 mg, 0.461 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL) under a nitrogen atmosphere. The reaction was stirred for 30 min at 23 °C. The reaction was quenched with saturated aq $NaHCO_3$ solution, extracted with EtOAc, and washed with 1 M NaOH (4×). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was immediately purified by flash column chromatography using silica gel, pretreated with 0.1% triethylamine, (95:5 hexanes/EtOAc) to give (*R*)-1,3-diphenyl-3*H*-pyrrolo[1,2-*a*]indole, **12** as a bluish white solid (132 mg, 0.429 mmol).

After isolation, compound **12** (60.0 mg, 0.195 mmol) was immediately dissolved in anhydrous THF (2.0 mL) and cooled to 0 °C under a nitrogen atmosphere, and a 1.0 M solution of BH_3·THF (3.50 mL, 3.51 mmol, 18.0 equiv) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then cooled to 0 °C and treated with 15% aqueous sodium hydroxide (0.25 mL) and 30% hydrogen peroxide (0.50 mL). This mixture was stirred at room temperature for 2 h and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (80:20 hexanes/EtOAc) to give (1*S*,2*R*,3*S*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-2-ol **13** as a yellow solid in 52% yield (35.6 mg, 0.109 mmol) over three steps as a 9:1 mixture of diastereomers. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C): t_R 17.8 min [(1*R*,2*S*,3*S*)]; t_R 23.0 min [(1*S*,2*R*,3*R*)]; t_R 28.3 min [(1*S*,2*R*,3*S*)]; t_R 38.0 min [(1*R*,2*S*,3*R*)] [Chiracel AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) hexanes/*i*-PrOH, 95:5, 1.0 mL/min] to be 97% for the (1*R*,2*S*,3*S*)-diastereomer and 96% for the (1*S*,2*R*,3*S*)-diastereomer; $[\alpha]_D^{24}$ = +107.6 (*c* 0.23, $CHCl_3$); ^1H NMR (600 MHz, C_6D_6) δ 1.37 (d, *J* = 6.1 Hz, 1H), 3.96 (m, 1H), 4.18 (d, *J* = 8.1 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 6.26 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 7.05−7.09 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 3H), 7.40 (d, *J* = 7.6 Hz, 3H), 7.68 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (151 MHz, C_6D_6) δ 52.7, 68.1, 91.5, 95.7, 111.2, 120.1, 121.2, 121.3, 127.5, 127.7, 128.35, 128.6, 129.96, 129.00, 129.2, 133.2, 138.5, 140.5, 143.2; HRMS (ESI) calcd for $C_{23}H_{20}NO$ ($[M + H]^+$) 326.1539, found 326.1535.

Synthesis of 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1*H*-indole (14).[16,23] To a stirred solution of indole (11.0 g, 93.9 mmol, 1.00 equiv) in anhydrous diethyl ether (200 mL) at 0 °C was added dropwise oxalyl chloride (9.50 mL, 113 mmol, 1.20 equiv) over 30 min. The reaction mixture was stirred at the same temperature for 2 h. The resulting yellow crystals of 3-indolylglyoxylyl chloride were filtered and washed with anhydrous diethyl ether.

DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

3-Indolylglyoxylyl chloride (19.0 g, 91.5 mmol, 1.00 equiv) was refluxed for 30 min in a mixture of ethanol (60 mL) and triethylamine (13.4 mL, 96.1 mmol, 1.05 equiv). The reaction mixture was cooled to 0 °C, and the solid ethyl indolylglyoxylate was isolated by filtration. The solid was washed with cold diethyl ether, dried under reduced pressure, and used directly for the next step.

A solution of ethyl indolylglyoxylate (18.0 g, 82.9 mmol, 1.00 equiv) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (11.6 g, 290 mmol, 3.50 equiv) in THF (300 mL) at 0 °C. The reaction mixture was refluxed for 4 h, cooled to 0 °C, and quenched with a saturated aqueous solution of potassium sodium tartrate (400 mL). The resulting solution was then filtered and washed with EtOAc (500 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was dried and used directly for the next step without further purification.

To a cooled solution (0 °C) of tryptophol (12.4 g, 76.7 mmol, 1.00 equiv) and imidazole (11.6 g, 169 mmol, 2.20 equiv) in anhydrous DMF (120 mL) was added TBS-Cl (13.1 g, 84.3 mmol, 1.10 equiv), and the reaction mixture was stirred for 16 h at room temperature. Ethyl acetate (250 mL) was then added, and the organic phase was washed with brine (200 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column silica gel (98:2 hexanes/EtOAc) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole **14** as a yellow solid in 81% yield over four steps (21.0 g, 76.2 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.93 (s, 9H), 3.02 (t, J = 7.4 Hz, 2H), 3.91 (t, J = 7.4 Hz, 2H), 7.04 (s, 1H), 7.13 (ddd, J = 7.8, 7.4, 1.2 Hz, 1H), 7.20 (ddd, J = 8.1, 7.4, 1.2 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ −5.1, 18.5, 26.1, 29.1, 64.05, 111.2, 113.0, 118.95, 119.3, 121.9, 122.2, 127.7, 136.2.

Synthesis of 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole (15).[17] To a stirred mixture of **14** (6.00 g, 21.8 mmol, 1.00 equiv) and tetrabutylammonium hydrogensulfate (1.10 g, 3.30 mmol, 0.150 equiv) in toluene (90 mL) at 0 °C was added aq NaOH (50 wt %, 90 mL) followed by benzenesulfonyl chloride (4.20 mL, 32.7 mmol, 1.50 equiv). The resulting suspension was allowed to warm to room temperature and vigorously stirred at this temperature for 15 h. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (250 mL). The organic layer was washed with water (250 mL) and brine (250 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column silica gel (99:1 hexanes/EtOAc) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole **15** as a white solid in 99% yield (9.00 g, 21.6 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 6H), 0.87 (s, 9H), 2.88 (t, J = 6.7 Hz, 2H), 3.87 (t, J = 6.7 Hz, 2H), 7.22−7.25 (m, 1H), 7.29−7.33 (m, 1H), 7.40−7.44 (m, 3H), 7.49−7.53 (m, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.99 (d, J = 8.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ −5.2, 18.4, 26.1, 28.7, 62.7, 113.8, 119.7, 120.45, 123.2, 123.6, 124.75, 126.85, 129.3, 131.4, 133.8, 135.2, 138.5; HRMS (ESI) calcd for $C_{22}H_{29}NO_3SSiNa$ ([M + Na]$^+$) 438.1530, found 438.1538.

Synthesis of Ethyl 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (16).[18] To a solution of lithium diisopropylamide (19.3 mmol, 1.00 equiv) prepared from diisopropylamine (2.80 mL, 20.2 mmol, 1.05 equiv) and *n*-butyllithium (13.5 mL, 1.43 M in hexane; 19.3 mmol, 1.00 equiv) in dry THF (50 mL) under argon at −78 °C was added dropwise via syringe over 5 min a solution of **15** (8.00 g, 19.3 mmol, 1.00 equiv) in dry THF (50 mL). The mixture was stirred for 1 h at −78 °C and then allowed to warm slowly to 0 °C over 3 h. The resulting solution was cooled to −78 °C and treated with a solution of ethyl chloroformate (2.20 mL, 23.1 mmol, 1.20 equiv) in THF (10 mL). The reaction mixture was stirred for 3 h at the same temperature and then warmed to room temperature overnight. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) at 0 °C and extracted with diethyl ether (2 × 250 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (95:5 hexanes/ether) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate **16** as a yellow oil in 90% yield (8.50 g, 17.4 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.10 (s, 6H), 0.79 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H), 3.00 (t, J = 6.9 Hz, 2H), 3.78 (t, J = 6.9 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 7.22−7.28 (m, 1H), 7.35−7.43 (m, 3H), 7.46−7.58 (m, 2H), 7.89 (d, J = 7.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ −5.4, 14.2, 18.4, 26.0, 28.4, 62.2, 63.1, 115.5, 121.3, 124.1, 126.9, 127.0, 127.3, 128.9, 129.1, 130.5, 133.8, 137.1, 137.7, 162.4; HRMS (ESI) calcd for $C_{25}H_{34}NO_5SSi$ ([M + H]$^+$) 488.1921, found 488.1925.

NaO*t*Bu-Mediated Synthesis of Ethyl 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate (17).[19b] To a solution of **16** (0.500 g, 1.03 mmol, 1.00 equiv) in 1,4-dioxane (7.5 mL) was added NaO*t*Bu (0.148 g, 1.54 mmol, 1.50 equiv) under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 3 h, cooled to room temperature, and filtered through a short plug of Celite (eluting with 150 mL of EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction product obtained was a mixture of compounds **17**, the corresponding *tert*-butyl ester, and the corresponding carboxylic acid. The crude mixture was purified by flash column chromatography on silica gel (90:10 hexanes/ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **17** as a white solid in 20% yield (0.0710 g, 0.204 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 6H), 0.85 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H), 3.36 (t, J = 7.3 Hz, 2H), 3.86 (t, J = 7.3 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 7.09−7.19 (m, 1H), 7.28−7.34 (m, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ −5.2, 14.6, 18.5, 26.1, 28.8, 60.9, 63.8, 111.7, 120.2, 121.3, 121.4, 123.8, 125.7, 128.7, 135.9, 162.4; HRMS (ESI) calcd for $C_{21}H_{34}NO_3Si$ ([M + C_2H_5]$^+$) 376.2302, found 376.2308.

Cs_2CO_3-Mediated Synthesis of Ethyl 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate (17). Ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **16** (10.0 g, 20.5 mmol, 1.00 equiv) was dissolved in a mixture of THF (150 mL) and EtOH (75 mL) at room temperature. Cesium carbonate (20.4 g, 61.5 mmol, 3.00 equiv) was added to the clear solution. The resulting mixture was stirred at reflux for 16 h, cooled, and concentrated under reduced pressure. The mixture was treated with water (200 mL) and extracted with diethyl ether (3 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (90:10 hexanes/ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **17** as a white solid in 95% yield (6.80 g, 19.6 mmol). ^{1}H NMR and ^{13}C NMR spectra of the isolated product comply with the characterization data of **17** as reported above: HRMS (ESI) calcd for $C_{21}H_{34}NO_3Si$ ([M + C_2H_5]$^+$) 376.2302, found 376.2311.

Synthesis of (*E*)-4-Methyl-*N*′-(1-(3,4,5-trimethoxyphenyl)-ethylidene)benzenesulfonohydrazide (6).[13] 1-(3,4,5-Trimethoxyphenyl)ethanone (10.0 g, 47.6 mmol, 1.00 equiv), *p*-toluenesulfonyl hydrazide (9.10 g, 47.6 mmol, 1.00 equiv), and dry methanol (120 mL) were charged in a round-bottom flask equipped with a reflux condenser. The reaction mixture was heated to 60 °C and stirred for 1 h. The mixture was cooled to 0 °C, and the product was collected by filtration on a Buchner funnel, washed with diethyl ether, and then dried under reduced pressure to afford the pure product (*E*)-4-methyl-*N*-(1-(3,4,5-trimethoxyphenyl)ethylidene)-benzenesulfonohydrazide **6** as a light yellow solid in 61% yield (11.0 g, 29.1 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.41 (s, 3H), 3.85 (s, 3H), 3.86 (s, 6H), 6.86 (s, 2H), 7.31 (d, J = 8.2 Hz, 2H) 7.92 (d, J = 8.2 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.8, 21.6, 56.1, 60.9, 103.8, 128.3, 129.5, 132.9, 135.4, 139.5, 144.3, 152.7, 152.9.

Synthesis of Ethyl 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxylate (18).[13] A 50 mL pressure reaction tube was charged with indole **17** (0.200 g, 0.575 mmol, 1.00 equiv), *N*-tosylhydrazone **6** (0.327 g, 0.863 mmol, 1.50 equiv), iodobenzene (0.10 mL, 0.860 mmol, 1.50 equiv),

DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

$Pd_2(dba)_3$ (0.0527 g, 0.0575 mmol, 0.100 equiv), NaO*t*Bu (0.155 g, 1.61 mmol, 2.80 equiv), and CPME (25 mL). The flask was immersed in a preheated oil bath and stirred at 120 °C for 24 h. The crude reaction mixture was allowed to cool to room temperature, and EtOAc was added and stirred for 10 min. The reaction mixture was filtered through Celite (eluting with 50 mL EtOAc), and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (80:20 hexanes/ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxylate **18** as a colorless oil in 40% yield (0.125 g, 0.232 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 6H), 0.86 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 3.35 (t, J = 7.3 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 6H), 3.88 (t, J = 7.3 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 5.32 (s, 1H), 5.90 (s, 1H), 6.33 (s, 2H), 7.19 (ddd, J = 8.0, 6.6, 1.3 Hz, 1H), 7.32−7.27 (m, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.2, 14.3, 18.5, 26.1, 29.1, 56.2, 60.7, 61.0, 64.0, 103.1, 111.1, 111.6, 120.9, 121.2, 122.8, 125.8, 126.8, 127.7, 133.6, 138.8, 139.3, 144.3, 153.3, 161.8; HRMS (ESI) calcd for $C_{30}H_{42}NO_6Si$ ([M + H]$^+$) 540.2776, found 540.2772.

Synthesis of 3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde (19). A 1.0 M solution of DIBAL-H in toluene (0.83 mL, 0.83 mmol, 3.50 equiv) was added to a solution of **18** (125 mg, 0.239 mmol, 1.00 equiv) in anhydrous dichloromethane (1.0 mL) at −78 °C under a nitrogen atmosphere. The resulting solution was stirred for 1 h at the same temperature. The mixture was then quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude alcohol was directly taken to the next step without further purification.

Activated manganese dioxide (311 mg, 3.60 mmol, 15.0 equiv) was added to an acetonitrile (1.0 mL) solution of the crude alcohol (115 mg) in a round-bottom flask. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. The reaction mixture was filtered through Celite, washed with a 1:1 mixture of hexanes/EtOAc, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (80:20 hexanes/ether) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde **19** as colorless oil in 84% yield (96.0 mg, 0.200 mmol) over two steps: ^{1}H NMR (400 MHz, C_6D_6) δ −0.03 (s, 6H), 0.91 (s, 9H), 3.20 (s, 6H), 3.34 (t, J = 6.5 Hz, 2H), 3.76 (s, 3H), 3.89 (t, J = 6.5 Hz, 2H), 5.07 (s, 1H), 5.63 (s, 1H), 6.41 (s, 2H), 7.09 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H), 7.20 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.70 (dt, J = 8.1, 0.9 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ −5.3, 18.5, 26.1, 28.25, 30.5, 55.75, 60.5, 63.9, 104.0, 111.9, 112.7, 121.5, 122.0, 125.9, 126.0, 127.4, 133.3, 133.4, 140.0, 140.7, 143.4, 154.4, 181.3; HRMS (ESI) calcd for $C_{28}H_{38}NO_5Si$ ([M + H]$^+$) 496.2514, found 496.2516.

Synthesis of (*R*)-9-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (20).[11] In a nitrogen-filled glovebox, **19** (20.0 mg, 0.0400 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (0.5 mg, 0.001 mmol, 0.025 equiv), (*R*)-MeO-BIPHEP (1.2 mg, 0.0020 mmol, 0.050 equiv), $AgBF_4$ (0.4 mg, 0.002 mmol, 0.05 equiv), and THF (0.50 mL) were added to a 1 dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 60 °C in an oil bath for 12 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 20 mL of 3:2 hexanes/EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (80:20 hexanes/ether) to give (*R*)-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **20** as a white solid in 90% yield (18.0 mg, 0.0360 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C): t_R 14.3 min (minor); t_R 17.3 min (major) [Chiracel AD-H (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd.) hexanes/*i*-PrOH, 95:5, 1.0 mL/min] to be 97%; $[\alpha]_D^{25}$ = −76.9 (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 0.070 (s, 3H), 0.077 (s, 3H), 0.97 (s, 9H), 2.79 (dd, J = 18.2, 4.4 Hz, 1H), 3.09 (dd, J = 18.2, 8.0 Hz, 1H), 3.20 (s, 6H), 3.55 (t, J = 7.0 Hz, 2H), 3.78 (s, 3H), 4.18 (t, J = 7.0 Hz, 2H), 4.76 (dd, J = 8.0, 4.4 Hz, 1H), 6.14 (s, 2H), 6.95 (dd, J = 6.4, 2.6 Hz, 1H), 7.08−7.03 (m, 2H), 7.78 (dd, J = 6.1, 2.6 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ −5.1, 18.5, 26.2, 28.5, 30.5, 50.8, 55.8, 57.2, 60.5, 64.15, 103.5, 110.4, 112.0, 113.95, 121.2, 123.2, 125.5, 125.9, 128.1, 133.3, 134.0, 135.2, 136.0, 139.3, 154.8, 191.2; HRMS (ESI) calcd for $C_{28}H_{38}NO_5Si$ ([M + H]$^+$) 496.2514, found 496.2517.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01730.

Discussion on stereochemical analysis of compound **13**, NMR traces, and HPLC chromatograms for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lstanley@iastate.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Iowa State University and National Science Foundation (CHE-CAREER 1353819) for financial support of this work. We thank Dr. Sarah Cady and the Chemical Instrumentation Facility at Iowa State University for helpful discussions and assistance with 2D NMR experiments. We thank Professor Jason Chen (Iowa State University) for helpful discussions and suggestions.

■ REFERENCES

(1) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329−332.

(2) (a) Pousset, J. L.; Cavé, A.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Chem. Commun.* **1977**, 261−262. (b) Fernandez, L. S.; Sykes, M. L.; Andrews, K. T.; Avery, V. M. *Int. J. Antimicrob. Agents* **2010**, *36*, 275−279.

(3) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477−2496.

(4) Sasase, T.; Yamada, H.; Sakoda, K.; Imagawa, N.; Abe, T.; Ito, M.; Sagawa, S.; Tanaka, M.; Matsushita, M. *Diabetes, Obes. Metab.* **2005**, *7*, 586−594.

(5) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127−4129.

(6) Vepsäläinen, J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. *Planta Med.* **2005**, *71*, 1053−1057.

(7) Calvert, M. B.; Sperry, J. *Chem. Commun.* **2015**, *51*, 6202−6205.

(8) (a) Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 3497−3500. (b) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820−5823. (c) Chen, K.; Zhang, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 7696−7699. (d) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737−5740. (e) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183−5187. (f) Dethe, D. H.; Boda, R.; Das, S. *Chem. Commun.* **2013**, *49*, 3260−3263. (g) Li, H.; Wang, Z.; Zu, L. *RSC Adv.* **2015**, *5*, 60962−60965. (h) Calvert, M. B.; Sperry, J. *Org. Biomol. Chem.* **2016**, *14*, 5728−5743.

(9) Ohyama, T.; Uchida, M.; Kusama, H.; Iwasawa, N. *Chem. - Asian J.* **2015**, *10*, 1850−1853.

DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951

(10) (a) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3250−3254. (b) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2006**, *8*, 1745−1747. (c) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192−7193. (d) Schrader, T. O.; Johnson, B. R.; Lopez, L.; Kasem, M.; Gharbaoui, T.; Sengupta, D.; Buzard, D.; Basmadjian, C.; Jones, R. M. *Org. Lett.* **2012**, *14*, 6306−6309. (e) Janssen-Müller, D.; Schedler, M.; Fleige, M.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 12492−12496. (f) Ni, Q.; Zhang, H.; Grossmann, A.; Loh, C. C. J.; Merkens, C.; Enders, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 13562−13566. (g) Lu, H.; Lin, J.-B.; Liu, J.-Y.; Xu, P.-F. *Chem. - Eur. J.* **2014**, *20*, 11659−11663. (h) Bera, K.; Schneider, C. *Chem. - Eur. J.* **2016**, *22*, 7074−7078. (i) Enders, D.; Greb, A.; Deckers, K.; Selig, P.; Merkens, C. *Chem. - Eur. J.* **2012**, *18*, 10226−10229.

(11) Ghosh, A.; Stanley, L. M. *Chem. Commun.* **2014**, *50*, 2765−2768.

(12) Prashad, M.; Tomesch, J. C.; Wareing, J. R.; Larsen, D.; de Fex, H. *Eur. J. Med. Chem.* **1992**, *27*, 413−418.

(13) Roche, M.; Frison, G.; Brion, J.-D.; Provot, O.; Hamze, A.; Alami, M. *J. Org. Chem.* **2013**, *78*, 8485−8495.

(14) Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291−1294.

(15) (a) Marquez, B. L.; Gerwick, W. H.; Thomas Williamson, R. *Magn. Reson. Chem.* **2001**, *39*, 499−530. (b) Oikawa, M.; Adachi, S.; Kusumoto, S. *Org. Lett.* **2005**, *7*, 661−664. (c) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876. (d) Schulte, J. r.; Lauterwein, J. r.; Klessinger, M.; Thiem, J. *Magn. Reson. Chem.* **2003**, *41*, 123−130. (e) Bifulco, G.; Bassarello, C.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2004**, *6*, 1025−1028. (f) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(16) Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; de Lima, E. C.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596−1606.

(17) Che, Z.; Zhang, S.; Shao, Y.; Fan, L.; Xu, H.; Yu, X.; Zhi, X.; Yao, X.; Zhang, R. *J. Agric. Food Chem.* **2013**, *61*, 5696−5705.

(18) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757−761.

(19) (a) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864−2867. (b) Viaud-Massuard, M.-C.; Chaulet, C.; Croix, C.; Basset, J.; Pujol, M.-D. *Synlett* **2010**, *2010*, 1481−1484. (c) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455−9461.

(20) Bajwa, J. S.; Chen, G.-P.; Prasad, K.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425−6427.

(21) (a) Pierce, L. T.; Cahill, M. M.; McCarthy, F. O. *Tetrahedron* **2011**, *67*, 4601−4611. (b) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805−4808.

(22) Pooppanal, S. *Synlett* **2009**, *2009*, 850−851.

(23) (a) Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G.; Armstrong, M. D. *J. Org. Chem.* **1958**, *23*, 1171−1178. (b) Nogrady, T.; Doyle, T. W. *Can. J. Chem.* **1964**, *42*, 485−486.

DOI: 10.1021/acs.joc.6b01730
J. Org. Chem. 2016, 81, 7945−7951