Published in final edited form as:

Tetrahedron. 2010 June 26; 66(26): 4687–4695. doi:10.1016/j.tet.2010.02.050.

Exploration of the interrupted Fischer indolization reaction†

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Abstract

A convergent method to access the fused indoline ring system present in a multitude of bioactive molecules has been developed. The strategy involves the condensation of hydrazines with latent aldehydes to ultimately deliver indoline-containing products by way of an interrupted Fischer indolization sequence. The method is convergent, mild, operationally simple, broad in scope, and can be used to access enantioenriched products. In addition, our approach is amenable to the synthesis of furoindoline and pyrrolidinoindoline natural products as demonstrated by the concise formal total syntheses of physovenine and debromoflustramine B. The strategy will likely enable the synthesis of more complex targets such as the communesin alkaloids.

Keywords

indoline; natural products; Fischer indole synthesis; total synthesis; heterocycles

1. Introduction

The discovery of efficient methods to synthesize complex bioactive molecules continues to be a vital area of research.ⁱ A subset of compounds that have received substantial interest due to their medicinal properties and impressive structures are those that possess a fused indoline motif, of the type **1** (Figure 1 and Scheme 1). The simplest of these compounds are the acetylcholinesterase inhibitors physovenine (**2**) and physostigmine (**3**),^{ii,iii} which are composed of basic furo- and pyrrolidinoindoline motifs, respectively (Figure 1). Numerous relatives of pyrrolidinoindoline **3** have been isolated, including bis(prenylated) derivatives,^{iv} dimeric structures,^v and compounds possessing a heteroatom substituent at C3 (e.g., **4–7**, respectively).^{vi,vii} Beyond these compounds, a variety of more architecturally complex indoline containing natural products are known, such as the akuammiline alkaloids (e.g., **8–11**),^{viii,ix} perophoramidine (**12**),^x the communesins (e.g., **13**),^{xi} diazonamide A (**14**),^{xii} and bipleiophylline (**15**).^{xiii} Many of these molecules possess interesting biological properties, which further enhance their appeal as targets for total synthesis.

[†]This manuscript is dedicated to Professor Brian M. Stoltz on the occasion of his receipt of the Tetrahedron Young Investigator Award.

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Supplementary Data

Supplementary data associated with this article, including experimental procedures, characterization data, and NMR spectra, can be found in the online version.

The importance of indoline-containing compounds has prompted the development of a number of methods to access such motifs, with numerous studies particularly in the area of pyrrolidinoindoline synthesis. In most cases, the fused indoline ring systems **1** are constructed by cyclization of precursors of the type **16**, which in turn are derived from substituted indole or oxindole intermediates (Scheme 1). Herein, we report the development of a powerful cascade reaction that allows direct access to **1** (via **16**) from the coupling of two simple fragments.^{xvi} The transformation is convergent, broad in scope, proceeds under mild reaction conditions, and can be used to synthesize a variety of natural product scaffolds.

Our approach to the indoline scaffold **1** of compounds **2–15** is inspired by the classic Fischer indole synthesis,^{xvii·xviii} and is presented in Scheme 2. We envisioned that an arylhydrazine **17** and an α -disubstituted aldehyde **18** would react in the presence of acid to afford enamine intermediate **19**. Subsequent [3,3]-sigmatropic rearrangement and re-aromatization would provide aniline **20**, which in turn would cyclize with loss of NH₃ to furnish transient indolenine **16**. Intramolecular attack by a proximal heteroatom substituent (X=NR or O) would deliver the desired product **1**. This interrupted Fischer indolization process would allow for the formation of three new bonds, two heterocyclic rings and two stereogenic centers, one of which is quaternary (C3).

A key feature of our approach to **1** is the ready availability of starting materials **17** and **18**. The arylhydrazine coupling partners **17** could be easily prepared or accessed from commercial sources.^{xix} Although the required α -branched aldehyde fragments **18** would not be obtainable commercially, isomeric lactols and hemiaminals **21** could likely serve as suitable aldehyde surrogates in the desired transformation (Scheme 3).^{xx·xxi} In turn, lactols and hemiaminals **21** could be accessed by reduction of readily available lactones or lactams **22**.^{xxii}

Only scattered examples of the interrupted Fischer indolization process have been reported over the past fifty years.^{xxiii·xxiv·xxv} Most notable are the seminal studies by Grandberg summarized in Figure 2.^{xxiii} In 1967, C2 substituted pyrrolidinoindoline **25** was prepared by reacting phenylhydrazine (**23**) and 5-chloro-3-methylpentan-2-one (**24**).^{xxiiia} However, this method is not applicable to the synthesis of furoindolines, or to the more complex ring systems encountered in numerous natural products. It was later demonstrated that furoindolines could be accessed by the acid-promoted reaction of phenylhydrazines with α -disubstituted lactones.^{xxiiib} For example, reaction of hydrazine **26** and lactone **27** in HCl/*i*PrOH afforded furoindoline **28** in 22% yield. This method bears limitations, such as the modest yields of products, the use of strongly acidic conditions, and the constraint to furoindoline ring systems. Despite these laudable efforts, and those of others,^{xxiv·xxv} a general and mild method to access **1** using the interrupted Fischer indolization strategy outlined in Scheme 2 has remained elusive. Moreover, with the exception of our studies,^{xvi} the notion that such a method could be used to prepare the indoline scaffold present in a multitude of complex biologically important compounds has not been realized.

2. Results and discussion

2.1. Synthesis of furoindolines

The feasibility of the proposed cascade reaction sequence of Scheme 2 was established in the context of furoindoline synthesis. Thus, the reaction between commercially available phenylhydrazine (**23**) and latent aldehyde **29** (1 equiv) was carried out under a variety of acidic conditions (Table 1). Lewis acids were examined and found to be ineffective (entries 1 and 2). However, use of *p*-toluenesulfonic acid, trifluoroacetic acid, or HCl each afforded the desired product **30** in modest yield (entries 3–5). Sulfuric acid-mediated reaction

conditions were also explored, and ultimately provided the desired product in 87% yield (entry 6). Recognizing that a milder acid source would be more generally useful, acetic acid was examined. Although the use of glacial acetic acid afforded modest product yields (entry 7), employment of a 1:1 mixture of acetic acid and water at 60 °C furnished indoline **30** in 89% isolated yield (entry 8).

As shown in Table 2, a number of arylhydrazines bearing *N*-substitution were examined in the interrupted Fischer indolization reaction. In addition to parent arylhydrazine **23** (entry 1), *N*-methyl-, *N*-benzyl-, and *N*-allyl substituted hydrazines were deemed competent coupling partners (entries 2–4). Interestingly, the use of *N*-acetyl and *N*-Boc phenylhydrazines (entries 5 and 6) led predominantly to the recovery of unreacted starting materials.

Substitution on the aryl ring of the hydrazine component was also investigated (Table 3). It was found that para, meta, and ortho substituents were tolerated under the reaction conditions (entries 1–6). Importantly, use of chlorohydrazines furnished haloindolines (entries 4 and 5), which could be further functionalized by transition metal-catalyzed cross-coupling chemistry. The transformation proceeded smoothly with *p*-methoxyphenylhydrazine as a substrate, thus affording C5-oxygenated products in good yields (entry 6). However, use of *p*-(trifluoromethyl)phenylhydrazine as a substrate led to low yields of product (entry 7).

The scope of the lactol component for furoindoline synthesis was examined in the interrupted Fischer indolization process (Table 4). Allyl and phenyl substituents were tolerated, thus providing fused indolines with alternate C3 substitution (entries 1 and 2). It should be noted, however, that substrates bearing either a *t*-butyl or a methyl ester substituent led only to trace amounts of product formation (entries 3 and 4). Nonetheless, a 6-membered homologue of the furoindoline framework was accessible using this methodology using our standard reaction conditions (entry 5).

2.2. Synthesis of pyrrolidinoindolines

Having established the viability of the interrupted Fischer indolization approach for the synthesis of furoindolines, we sought to develop the corresponding transformation that would enable the synthesis of pyrrolidinoindolines and related derivatives. Thus, hemiaminal **31** was prepared from the corresponding lactam following a known procedure, and then subjected to phenylhydrazine (**23**) in the presence of 1:1 H₂O/AcOH (Scheme 4). To our delight, the interrupted Fischer indolization reaction proceeded smoothly at 100 °C and delivered the desired indoline **32** in 88% yield.

Analogous to our studies in the area of furoindoline synthesis, the interrupted Fischer indolization reaction was found to be an effective means to access a range of pyrrolidinoindolines. As shown in Table 5, a variety of arylhydrazines were tolerated in the transformation. Reactions of *N*-substituted arylhydrazines furnished the desired indoline products in good yield (entries 1–3), whereas a range of arylhydrazines bearing benzenoid substitution were deemed competent coupling partners (entries 4–9). Similar to the results obtained in our furoindoline studies, use of *p*-(trifluoromethyl)phenylhydrazine as a substrate led to low yields of product (entry 10).

The scope of the hemiaminal component was also investigated (Table 6). C3-allylated and -phenylated pyrrolidinoindolines could be accessed without difficulty (entries 1 and 2). Of note, these pyrrolidinoindoline motifs are present in an array of medicinally important compounds, such as debromoflustramine B (**5**, Figure 1) and the hodgekinsine alkaloids. Furthermore, a 6-membered homologue was prepared in 81% yield (entry 3)

reminiscent of the communesin and perophoramidine core structures. Finally, it was determined that a carbamylated hemiaminal could be employed in place of a sulfonamide (entry 4).

As shown in Figure 3, the *N*-substituents of our pyrrolidinoindoline products can easily be manipulated. The sulfonamide group of **33** was removed upon treatment with Mg and NH₄Cl in MeOH to provide pyrrolidinoindoline **34** in 79% yield. Additionally, carbamate **35** was converted to the corresponding *N*-methylated product **36** when reacted with Red-Al. The latter of these results is particularly notable given that many pyrrolidinoindoline natural products possess this *N*-methylated substitution pattern (e.g., Figure 1, **3–7**).

2.3. Formal total syntheses of physovenine and debromoflustramine B, and assembly of the communesin indoline scaffold

Having developed a powerful means to synthesize fused indoline ring systems, we examined the scope and limitations of our methodology in more complex settings. As shown in Scheme 5, the newly discovered transformation has been utilized to achieve a concise formal total synthesis of the furoindoline natural product physovenine (**2**). Reaction of hydrazine **37** with lactol **29** in AcOH furnished furoindoline **38** in 77% yield, which has previously been converted to physovenine (**2**) in two additional steps. Although asymmetric routes to intermediate **38** have previously been reported, our single step route to (±)-**38** is substantially shorter (one step compared to 7 or 18 steps). Furthermore physovenine (**2**) can be optically resolved, on preparative scale, using column chromatography with cellulose triacetate.

The interrupted Fischer indolization reaction could also be used to complete a formal total synthesis of the pyrrolidinoindoline natural product debromoflustramine B (**5**). Pyrrolidinone **39** was elaborated to hemiaminal **40** using a standard two-step sequence. Treatment of **40** with 1-allyl-1-phenylhydrazine in H₂O/AcOH at 100 °C facilitated the key condensation/sigmatropic rearrangement to deliver bis(allylated)pyrrolidinoindoline **41**. In turn, **41** was reacted with 2-methyl-2-butene in the presence of Grubbs' second generation catalyst to afford bis(prenylated) derivative **42** which was converted to **5** by reduction with Red-Al.

Finally, we explored the scope and limitations of our methodology in the context of the communesin natural products (Scheme 7). Known sulfonamide **43** was reacted with 1-ethoxypropene in the presence of Cs₂CO₃ to afford hetero-Diels–Alder product **44**, following the general procedure described by Corey. Exposure of **44** to *N*-methyl phenylhydrazine (**26**) in 1:1 AcOH/H₂O delivered indoline **45**, which possesses the tetracyclic 6,5,6,6-ring system of the communesin alkaloids. As noted earlier, the previously described [3,3]-sigmatropic rearrangement strategies for the synthesis of fused indoline ring systems are not amenable to this complex scaffold.

2.4. Access to enantioenriched indoline products

Having demonstrated that the interrupted Fischer indolization reaction provides an effective means to access indoline scaffolds, we hoped to uncover a variant that would give access to enantioenriched indoline products. The most appealing scenario to achieve this goal would involve asymmetric catalysis. Thus, efforts were put forth to carry out the interrupted Fischer indolization reaction in the presence of chiral non-racemic phosphoric acids.

As shown in Scheme 8, this asymmetric transformation proved challenging. Despite an extensive survey of reaction conditions (e.g., variations in substrates, phosphoric acid promoter, stoichiometry, solvent, and temperature), only modest levels of enantioselectivity

could be obtained. For example, reaction of hydrazine **23** and lactol **29** in the presence of 1.2 equivalents of phosphoric acid **46** (prepared from (*R*)-BINOL)^{xlii} in benzene at 40 °C provided furoindoline **30** in 62% yield and 28% ee.^{xliii} Similar results were obtained when hemiaminal substrates were employed in place of lactols.

Given the difficulty in achieving a reagent or catalyst-controlled asymmetric interrupted Fischer indolization, we turned to an auxiliary-based approach.^{xliv} Thus, Nishida's enantioenriched arylhydrazine **50** was prepared using the sequence shown in Scheme 9.^{xxv}^{xlv}^{xlvi} Bromobenzene (**47**) was coupled with commercially available enantioenriched amine (–)-**48** under Pd catalysis to provide aniline **49**. Using a standard protocol, aniline **49** was converted to the targeted hydrazine **50** in 81% yield over two steps.

The utility of arylhydrazine **50** in our interrupted Fischer indolization process was evaluated in the context of furoindoline synthesis (Figure 4). Gratifyingly, the reaction of **50** and lactol **29** proceeded smoothly under a variety of acidic conditions. When the reaction was carried out in the presence of 3 equivalents of chloroacetic acid in benzene at 40 °C, an 80% yield of diastereomeric indoline products **51** and **52** was obtained (d.r.=2.4:1).^{xlvii} The isomers were easily separable using conventional flash column chromatography on silica gel. The major isomer **51** was treated with Pd(OH)₂ and 1,4-cyclohexadiene in EtOH to remove the auxiliary and deliver optically enriched indoline **30**.^{xlviii}^{xlix} The ee of **30** was found to be 97%,^{xxii} thus demonstrating that our methodology can be utilized to access enantioenriched products. The absolute configuration of **30** was determined based on correlation to known data,^{xxxiic} and was found to be as depicted in Figure 4.

3. Conclusions

In summary, we have developed an efficient method to access the fused indoline ring systems present in a variety of natural products. Our interrupted Fischer indolization strategy involves the condensation of readily available hydrazines with latent aldehydes to deliver indoline-containing products by way of a tandem [3,3]-sigmatropic rearrangement / cyclization cascade sequence. The method is convergent, mild, operationally simple, broad in scope, and can be used to access enantioenriched products. In addition, our approach is amenable to the synthesis of furoindoline and pyrrolidinoindoline natural products as demonstrated by the concise formal total syntheses of physovenine and debromoflustramine B. We expect that the interrupted Fischer indolization strategy will enable the synthesis of more complex targets such as the communesins and akuammiline alkaloids. Such studies in the realm of natural product synthesis are currently underway in our laboratory.

4. Experimental

4.1 Representative experimental procedure for furoindoline synthesis (Table 2, entry 1)

Lactol **29** (126 mg, 1.22 mmol) was dissolved in a 1:1 mixture of acetic acid and water (6 mL). Phenylhydrazine (**23**) (0.121 mL, 1.23 mmol) was added to the resulting mixture. The reaction was heated to 60 °C for 4.5 h, then cooled to 23 °C, and quenched with a solution of sat. aq. NaHCO₃ (15 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over MgSO₄. Evaporation of the solvent under reduced pressure afforded the crude product. Purification by flash chromatography (7:1 hexanes:EtOAc) afforded indoline **30** (196 mg, 89% yield). *R*_f 0.7 (1:1 EtOAc:hexanes); ¹H NMR (300 MHz, CDCl₃): δ 7.08 (d, *J* = 7.2, 1H), 7.05 (t, *J* = 7.5, 1H), 6.76 (t, *J* = 7.5, 1H), 6.59 (d, *J* = 7.8, 1H), 5.28 (s, 1H), 3.96 (ddd, *J* = 8.4, 7.2, 1.8, 1H), 3.56 (ddd, *J* = 10.8, 8.4, 5.1, 1H), 2.13 (ddd, *J* = 11.7, 5.4, 1.5, 1H), 2.07 (ddd, *J* = 11.7, 7.2, 4.2, 1H), 1.47 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 148.8, 133.9, 127.9, 122.9, 118.8, 108.8, 99.5, 67.3,

53.8, 41.4, 24.7; IR (film): 2967, 2845, 1611, 1486, 1265, 1055 cm^{-1} ; HRMS-ESI (m/z) [$M + H$]⁺ calcd for $\text{C}_{11}\text{H}_{14}\text{NO}$, 176.1075; found 176.1078.

4.2. Representative experimental procedure for pyrrolidinoindoline synthesis (Table 6, entry 1)

3-Allyl-1-tosylpyrrolidin-2-olxxii (105 mg, 0.37 mmol) was dissolved in a 1:1 mixture of acetic acid and water (1.8 mL). Phenylhydrazine **23** (0.036 mL, 0.36 mmol) was added to the resulting mixture. The reaction was heated to 100 °C for 1 h 40 min, cooled to 23 °C, and then diluted with Et_2O (20 mL). The reaction mixture was then quenched with sat. aq. NaHCO_3 (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , and concentrated *in vacuo* to afford the crude indoline product. Purification by flash chromatography (18:1:1 benzene: Et_2O : CH_2Cl_2) afforded the 3-allyl-indoline (Table 6, entry 1) as a yellow oil (88.0 mg, 68% yield). R_f 0.6 (8:1:1 benzene: Et_2O : CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ 7.75 (d, $J = 8.0$, 2H), 7.32 (d, $J = 8.0$, 2H), 7.08 (t, $J = 7.5$, 1H), 7.00 (d, $J = 7.0$, 1H), 6.75 (t, $J = 7.5$, 1H), 6.62 (d, $J = 7.5$, 1H), 5.55 (ddt, $J = 16.8$, 10.0, 7.5, 1H), 5.13 (s, 1H), 4.96–5.00 (m, 2H), 4.84 (s, 1H), 3.43 (ddd, $J = 10.0$, 8.0, 2.0, 1H), 3.13 (ddd, $J = 10.5$, 10.5, 6.0, 1H), 2.44 (s, 3H), 2.31 (ddd, $J = 19.5$, 13.5, 7.5, 2H), 2.07 (ddd, $J = 6.5$, 6.0, 2.0, 1H), 1.84 (ddd, $J = 10.5$, 8.0, 6.5, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 149.1, 143.7, 136.4, 133.5, 131.4, 130.0, 128.8, 127.3, 123.2, 119.3, 118.8, 109.7, 82.7, 58.0, 47.6, 42.3, 36.2, 21.7; IR (neat): 3391, 3076, 1611, 1485, 1337, 1160 cm^{-1} ; HRMS-ESI (m/z) [$M + \text{Na}$]⁺ calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{SNa}$, 377.1300; found, 377.1298.

4.3 Synthesis of indoline diastereomers **51** and **52**

To a mixture of aryl hydrazine **50** (52.4 mg, 0.20 mmol), lactol **29** (20.6 mg, 0.20 mmol), and benzene (1 mL) was added chloroacetic acid (56.7 mg, 0.60 mmol). The resulting mixture was heated at 40 °C for 24 h. The reaction mixture was cooled to 23 °C, diluted with CH_2Cl_2 (20 mL), washed with sat. aq. NaHCO_3 (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over MgSO_4 and evaporated to dryness. Purification by flash chromatography (15:1 → 10:1 hexanes:EtOAc) afforded a mixture of diastereomers as an orange solid (53.0 mg, 80% yield, 2.4:1 dr). To separate the diastereomers the mixture was repurified by flash chromatography, under the same conditions. The stereochemical configurations of **51** and **52** were inferred after the conversion of **51** to (+)-**30**. Indoline **51**: R_f 0.5 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 8.23 (d, $J = 8.0$, 1H), 7.96 (d, $J = 7.5$, 1H), 7.82 (t, $J = 8.0$, 2H), 7.60 (t, $J = 7.0$, 1H), 7.56 (t, $J = 7.5$, 1H), 7.49 (t, $J = 8.0$, 1H), 7.11 (d, $J = 7.5$, 1H), 6.91 (t, $J = 7.5$, 1H), 6.03 (d, $J = 7.5$, 1H), 5.65 (s, 1H), 5.56 (q, $J = 7.0$, 1H), 4.03 (t, $J = 8.0$, 1H), 3.70–3.75 (m, 1H), 2.28 (dd, $J = 11.5$, 4.5, 1H), 1.86 (d, $J = 6.5$, 3H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.1, 139.4, 134.5, 133.9, 130.8, 129.1, 127.8, 127.5, 125.9, 125.8, 125.2, 123.6, 122.5, 122.4, 117.3, 106.0, 101.4, 66.7, 52.3, 51.7, 41.9, 25.8, 19.0; IR (neat): 3046, 2963, 2852, 1606, 1594, 1487, 1459, 1395, 1298, 1236, 1013 cm^{-1} ; HRMS-ESI (m/z) [$M + \text{Na}$]⁺ calcd for $\text{C}_{23}\text{H}_{23}\text{NONa}$, 352.1677; found 352.1686; $[\alpha]_D^{24.4} + 125.4$ (c 0.01, CHCl_3). Indoline **52**: R_f 0.5 (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 7.95 (d, $J = 8.5$, 1H), 7.90 (d, $J = 8.0$, 1H), 7.84 (d, $J = 8.5$, 1H), 7.74 (d, $J = 7.5$, 1H), 7.45–7.54 (m, 3H), 7.14 (t, $J = 8.0$, 1H), 7.10 (d, $J = 7.0$, 1H), 6.75 (d, $J = 7.0$, 1H), 6.51 (d, $J = 7.5$, 1H), 5.52 (q, $J = 7.0$, 1H), 4.69 (s, 1H), 3.93 (t, $J = 7.5$, 1H), 3.53 (ddd, $J = 13.0$, 8.5, 4.5, 1H), 2.18 (dd, $J = 12.0$, 4.5, 1H), 1.98 (ddd, $J = 11.5$, 11.5, 7.0, 1H), 1.90 (d, $J = 6.5$, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 148.8, 136.3, 134.7, 133.8, 131.7, 128.7, 128.1, 128.0, 126.2, 125.5, 125.4, 124.2, 123.2, 122.7, 117.3, 105.0, 101.0, 67.0, 52.2, 49.3, 41.2, 24.7, 18.1; IR (film): 3681, 2973, 2845, 1605, 1487, 1215, 1059 cm^{-1} ; HRMS-ESI (m/z) [$M + \text{Na}$]⁺ calcd for $\text{C}_{23}\text{H}_{23}\text{NONa}$, 352.1677; found 352.1680; $[\alpha]_D^{24.2} - 54.6$ (c 0.01, CHCl_3).

4.4 Synthesis of indoline (+)-30

A mixture of indoline **51** (32.9 mg, 0.1 mmol), 1,4-cyclohexadiene (80.0 mg, 1.0 mmol), and palladium hydroxide (20% wt on carbon, 10.0 mg) in ethanol (1 mL) was heated at 80 °C for 6 h. The reaction mixture was cooled to 23 °C, filtered through celite, washed with CH₂Cl₂ (10 mL), and the solvent was removed under reduced pressure. Purification by flash chromatography (5:1 hexanes:EtOAc) furnished furoindoline (+)-**30** (14.0 mg, 80% yield, 97% ee). $[\alpha]_D^{24.3} +124.5$ (*c* 0.01, CHCl₃), SFC (CHIRALPAK AS-H, CO₂/MeOH = 9/10, flow 1.5 mL/min, at 23 °C, detection at 254 nm) *t_R* 3.06 min (major) and *t_R* 4.43 min (minor). The absolute configuration of **30** was determined based on correlation to known data.xxxiiic

Supplementary Material

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Acknowledgments

The authors are grateful to the NIH-NIGMS (R00 GM079922), the University of California, Los Angeles and Boehringer Ingelheim for financial support. We also thank Materia Inc. for the donation of chemicals, the Garcia-Garibay laboratory (UCLA) for the generous access to instrumentation, Dr. John Greaves (UC Irvine) for mass spectra, and Professors Ken Houk (UCLA), Patrick Harran (UCLA), and Jon Antilla (University of South Florida) for fruitful discussions.

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- xxi. Lactols and hemiaminals have previously been employed in modifications of the Fischer indole synthesis, see: a) Campos KR, Woo JCS, Lee S, Tillyer RD. *Org. Lett.* 2004; 6:79–82. [PubMed: 14703355] b) Brodfuehrer PR, Chen B-C, Sattelberg TR, Smith PR, Reddy JP, Stark DR, Quinlan SL, Reid JG, Thottathil JK, Wang S. *J. Org. Chem.* 1997; 62:9192–9202. c) Adachi H, Palaniappan KK, Ivanov AA, Bergman N, Gao Z-G, Jacobson KA. *J. Med. Chem.* 2007; 50:1810–1827. [PubMed: 17378544]
- xxii. See Supplementary Data for details.
- xxiii. a) Grandberg II, Zuyanov TI, Afonina NI, Ivanova TA. *Dokl. Akad. Nauk SSSR.* 1967; 176:583–585. [PubMed: 5623852] For a synthesis of furoindolines, albeit in modest yield, see: b) Grandberg II, Tokmakov GP. *Khim. Geterotsikl. Soedin.* 1975:207–210.
- xxiv. Takano et al. has synthesized a pyrrolidinoindoline product using an interrupted Fischer indolization reaction; see: a) Takano S, Moriya M, Iwabuchi Y, Ogasawara K. *Chem. Lett.* 1990:109–112. b) Takano S, Ogasawara K, Iwabuchi R, Moriya M. 1991 JP 03112989 A 19910514.
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- xxvii. Interestingly, the reaction between *N*-methylphenylhydrazine (**26**) and lactol **29** in 1:1 H₂O/AcOH leads to the desired product, albeit with significant (ca. 20–30%) formation of *NH* furoindoline **30**.
- xxviii. Attempts to generate furoindoline **30** from **i** and **29** using Buchwald's methodology were unsuccessful despite an extensive survey of acidic conditions. For Buchwald's modification of the Fischer indole synthesis, see: Wagaw S, Yang BH, Buchwald SL. *J. Am. Chem. Soc.* 1998; 120:6621–6622.

- xxix. Efforts to synthesize furoindoline products from the reaction of aryl hydroxylamine derivatives and **29** were not successful.

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- xxxii. The *N*-sulfonyl group of pyrrolidinoinidoline products could also be removed using Na₂K–SG(1), a solid-supported alkali metal reagent developed by SiGNa Chemistry, Inc.; see: Nandi P, Redko MY, Petersen K, Dye JL, Lefenfeld M, Vogt PF, Jackson JE. *Org. Lett.* 2008; 10:5441–5444. [PubMed: 18973332]
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- xxxvii. **42** has previously been converted to debromoflustramine B (**5**) by reduction with LiAlH₄; see ref xxxve.
- xxxviii. For the total synthesis of communesin F, see: Yang J, Wu H, Shen L, Qin Y. *J. Am. Chem. Soc.* 2007; 129:13794–13795. [PubMed: 17956099]
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- xl. Indoline **45** has previously been prepared by an intermolecular aza-Diels–Alder strategy; see ref xxxi.
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- xliii. The enantiomer formed in excess is believed to have the (*R,R*) configuration, as depicted in Scheme 8, based on correlation to known data (see ref xxxiiic).
- xliv. Takano has shown that a proximal stereogenic center can be used to induce diastereoselectivity in a Fischer indolization reaction; see ref xxiva.
- xlv. Although experimental procedures for the synthesis of **50** were not reported previously, the synthetic route shown in Scheme 9 parallels that described by Nishida (see ref xxve). Experimental details for the synthesis of **50** are included in the Supplementary Data that accompanies this manuscript.
- xlvi. Nishida has utilized **50** to synthesize an optically enriched pyrrolidinone, albeit in modest yield;
- xlvii. The stereochemical configurations of **51** and **52** were inferred after the conversion of **51** to (+)-**30**.
- xlvi. **30** can be converted to physovenine (**2**) in four steps; see ref xxxiiic.
- xlix. Numerous attempts to cleave the auxiliary using H₂ with various metal catalysts led to reduction of the *N,O*-acetal linkage, a problem that was not encountered when cleaving the auxiliary from a pyrrolidinoindoline derivative (see ref xxve).

Figure 1.
Parent indoline **1** and representative natural products **2–15**

Figure 2.
Grandberg's syntheses of pyrrolidinoindoline **25** and furoindoline **28**

Figure 3.
Manipulation of the *N*-substituent.

Figure 4.
Synthesis of enantioenriched **30**.

Scheme 1.
Approach to indoline **1**.

Scheme 2.

Proposed fragment coupling / cyclization cascade to access indoline **1**.

Scheme 3.
Lactols and hemiaminals as latent aldehydes.

Scheme 4.
Synthesis of pyrrolidinoindoline **32**.

Scheme 5.
Formal total synthesis of physovenine (2).

Scheme 6.
Formal total synthesis of debromoflustramine B (**5**).

Scheme 7.
Synthesis of communesin indoline scaffold **45**.

Scheme 8.
Furoindoline synthesis using phosphoric acid promoter **46**.

Scheme 9.
Synthesis of arylhydrazine **50**.

Table 1

Survey of acids to promote furoindoline formation.

The reaction scheme shows the synthesis of compound 30 from 23 and 29. Compound 23 is phenylhydrazine (a benzene ring with an -NH-NH₂ group). Compound 29 is 2-methyl-2,3-dihydrofuran-3-ol (a five-membered ring with an oxygen atom, a methyl group at position 2, and a hydroxyl group at position 3). The reaction arrow points to compound 30, which is a furoindoline derivative. It consists of a benzene ring fused to a five-membered ring containing an oxygen atom and a nitrogen atom. The nitrogen atom is bonded to a hydrogen atom and a methyl group. The oxygen atom is bonded to a hydrogen atom. The methyl group is also bonded to a hydrogen atom.

entry	acid source	conditions	yield ^a
1	PCl ₃	benzene, 60 °C	< 5%
2	ZnCl ₂	EtOH, 100 °C	< 5%
3	TsOH	EtOH, H ₂ O, 60 °C	51%
4	TFA	CH ₃ CN, 60 °C	64%
5	5% HCl	CH ₃ CN, 60 °C	70%
6	4% H ₂ SO ₄	CH ₃ CN, 60 °C	87%
7	AcOH	AcOH, 60 °C	52%
8	AcOH	1:1 AcOH/H ₂ O, 60 °C	89% ^b

^a Unless otherwise noted, yields determined by ¹H NMR analysis.^b Isolated yield.

Table 2

Variation of the hydrazine *N*-substituent.

entry ^a	hydrazine	product	yield ^c
1			89%
2 ^b			70%
3			59%
4			60%
5			<5%

entry ^a	hydrazine	product	yield ^c
6			<5%

^a Conditions unless otherwise noted: lactol **29** (1 equiv), 1:1 AcOH/H₂O, 60 °C.

^b AcOH as solvent.

^c Isolated yield.

Table 3

Variation of the hydrazine aryl substituents.

entry ^a	hydrazine	product	yield ^b
1			60%
	75% (4 : 3)
2
3			62%

entry ^a	hydrazine	product	yield ^b
4			67%
5			60%
6			X = OMe; 75%
7			X = CF ₃ ; < 5%

^a Conditions unless otherwise noted: lactol **29** (1 equiv), 1:1 AcOH/H₂O, 60 °C.

^b Isolated yield.

Table 4

Variation of the lactol component.

entry ^a	lactol	product	yield ^b
1			89%
2			75%
3			<5%
4			<5%

entry ^a	lactol	product	yield ^b
5			65%

^a Conditions: hydrazine **23** (1 equiv), 1:1 AcOH/H₂O, 60 °C.

^b Isolated yield.

Table 5

Variation of the hydrazine component.

entry ^a	hydrazine	product	yield ^d
1 ^b			81%
2			83%
3			70%
4			71%

Tetrahedron. Author manuscript; available in PMC 2011 June 26.

entry ^a	hydrazine	product	yield ^d
8			84%
9 ^c			X = OMe; 70%
10			X = CF ₃ ; < 5%

^a Conditions unless otherwise noted: hemiaminal **31** (1 equiv), 1:1 AcOH/H₂O, 100 °C.

^b 23 °C, AcOH as solvent.

^c 75 °C.

^d Isolated yield.

Table 6

Variation of the hemiaminal component.

entry ^a	hemiaminal	product	yield ^b
1			68%
2			70%
3			81%
4			88%

^a Conditions: hydrazine **23** (1 equiv), 1:1 AcOH/H₂O, 100 °C.

^b Isolated yield.