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Stereoselective synthesis of spirocyclic oxindoles based on a one-pot Ullmann coupling/Claisen rearrangement and its application to the synthesis of a hexahydropyrrolo[2,3-*b*]indole alkaloid

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ABSTRACT

An efficient and convenient approach to the synthesis of spirocyclic oxindoles from iodoindoles has been developed. The most striking feature of this approach is that the sequential intramolecular Ullmann coupling and Claisen rearrangement proceeds in a one-pot manner to afford 3-spiro-2-oxindoles in good yield with excellent diastereoselectivity. Application of this one-pot reaction to chiral non-racemic tertiary alcohol substrates resulted in complete chirality transfer to the spirocyclic quaternary carbon. Using this method, asymmetric total synthesis of (−)-debromoflustramine B was accomplished.

1. Introduction

Oxindoles that incorporate a quaternary stereogenic center at C3 are attractive targets in organic synthesis because of their significant biological activity as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals (Fig. 1).[1] As such, a number of synthetic methods have been developed in pursuit of this structure, including intermolecular alkylations,[2] transition-metal-mediated reactions,[1g,3] cycloadditions,[4] and sigmatropic rearrangements.[5] During the course of our studies of the synthesis of spirocyclic terpenes, we developed a stereoselective Claisen rearrangement using bicyclic dihydropyran **A** as the rearrangement substrate to provide multifunctionalized spiro[4.5]decane **B** (Scheme 1).[6,7] On the basis of this result, we envisioned that a Claisen rearrangement of pyranoindole **D** would produce spirocyclic oxindole (3-spiro-2-oxindole) **E** in a stereoselective manner.[8] The pyranoindole **D** starting material for this transformation can be generated from 2-haloindole **C** via an intramolecular Ullmann coupling (IUC) (Scheme 2).

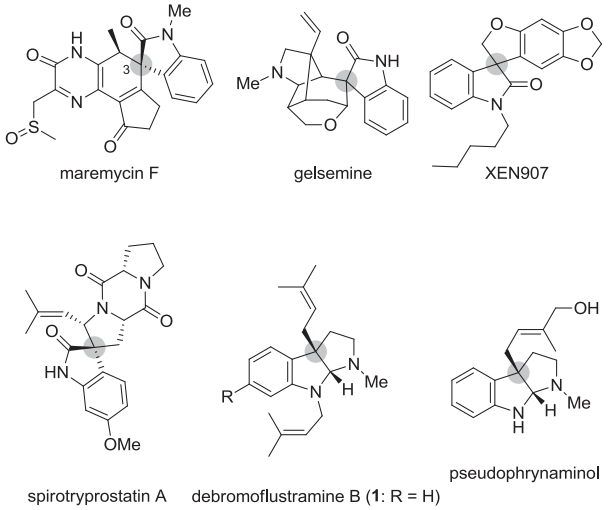

Fig. 1. Alkaloids and clinical pharmaceuticals having a quaternary stereogenic center at C3 position of oxindole or related scaffold.

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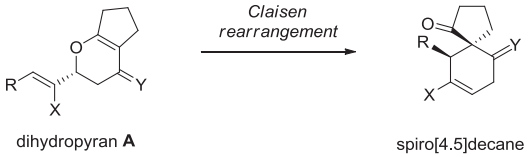
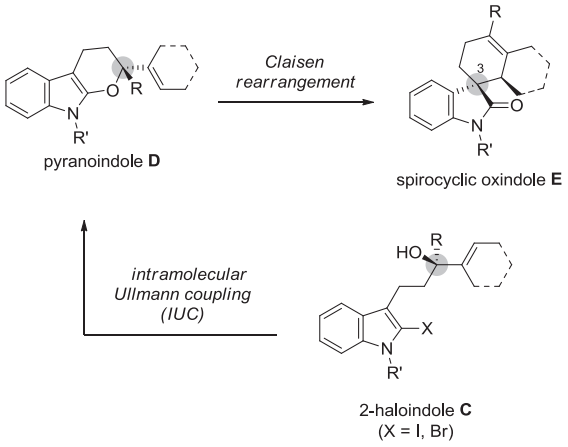
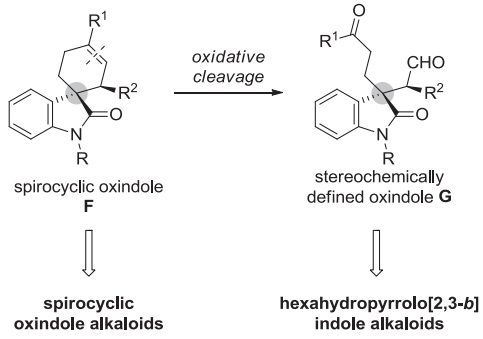


Scheme 1. Synthesis of spiro[4.5]decane **B** through Claisen rearrangement of bicyclic dihydropyran **A**.



Scheme 2. Key transformations in this report.

Stereoselectively synthesized spirocyclic oxindole **F** is expected to be potentially useful because it can be converted directly into a biologically active spirocyclic oxindole alkaloid (Scheme 3). In addition, after cleavage of the internal double bond of the cyclohexene ring in **F**, a stereochemically defined oxindole **G** having a quaternary chiral center results, and oxindole **G** is also considered to be a useful chiral building block for the synthesis of biologically active compounds including hexahydropyrrolo[2,3-*b*]indole alkaloids,[9] such as debromoflustramine B,[9b] flustramine B[9c,d] and pseudophrynaminol.[9e]



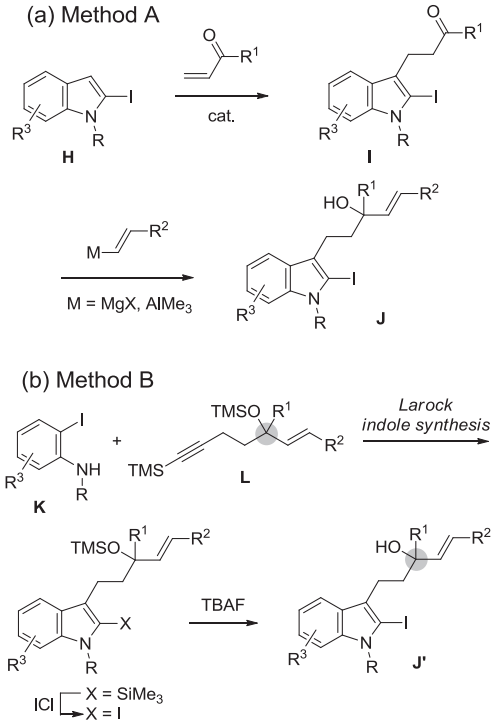
Scheme 3. Two approaches to the synthesis of indole alkaloids using a stereochemically defined spirocyclic oxindole.

We reported a one-pot synthesis involving a sequential IUC of 2-haloindole **C** followed by a Claisen rearrangement of the in situ generated 2-(alkenyl)pyranoindole **D** affording spirocyclic oxindole **E** in good yield with excellent diastereoselectivity (Scheme 2),[10,11] and we also demonstrated total synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids.[12] Reported herein are the full details of our development of a highly stereoselective method for the synthesis of spirocyclic oxindole derivatives. Utilizing our procedure, synthesis of chiral non-racemic spirocyclic oxindoles by asymmetric transmission is newly described. Moreover, this one-pot procedure is applied to the asymmetric synthesis of (−)-debromoflustramine B (**1**) based on our previously reported strategy.[12]

2. Results and discussion

2.1. Synthesis of 2-haloindoles as one-pot cyclization precursors

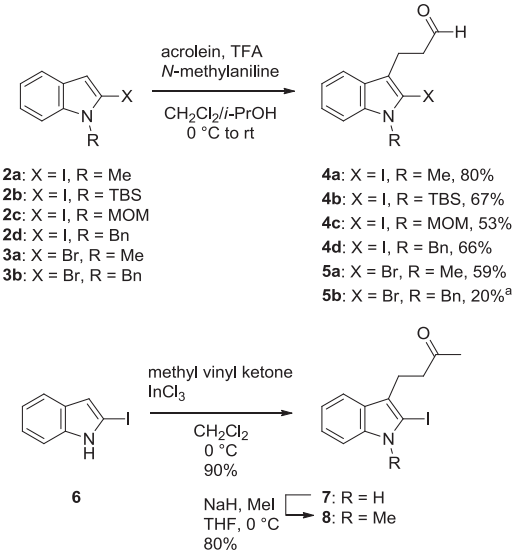
In order to define the scope of this rearrangement process, we began with the development of a general route for assembling cyclization precursors via two different approaches: method A starting from 2-iodoindole **H** (Scheme 4, a), and method B involving a Larock indole synthesis (Larock heteroannulation)[13] as the key reaction (Scheme 4, b). Method A involves a Michael addition of 2-iodoindole **H** and nucleophilic addition of an alkenyl metal species, such as alkenyl aluminate or a Grignard reagent to prevent reduction of the 2-iodo group. Although this method is the shorter of the reaction sequences, it is not suitable for the synthesis of enantioenriched products. In contrast, method B involves the Larock indole synthesis of readily available silylalkyne **L** with a stereochemically defined allylic alcohol moiety and 2-iodoaniline **K**. The Larock indole synthesis is among the most reliable processes for the synthesis of indole frameworks in terms of substitution and functionality; and it is ideally suited to the construction of the chiral non-racemic 2-haloindole **J′** because the annulation of **K** and **L** proceeds with excellent regioselectivity to give 2-silylindoles, which can be readily converted to the 2-iodoindoles **J′** by iododesilylation followed by deprotection of the hydroxy group. This method is advantageous for the introduction of substituents to the aromatic ring, as well as in the preparation of enantioenriched precursors.



Scheme 4. General schemes for preparation of 2-iodoindole.

Initial efforts focused on preparation of the racemic cyclization precursors of the one-pot reaction using Method A. In order to synthesize the aldehydes or ketones needed for nucleophilic

addition to the alkenyl metal, a Michael addition of *N*-protected indoles to α,β-unsaturated carbonyl compounds was performed (Scheme 5). *N*-Methylindole, a commercially available substance, can be conveniently converted to the desired 2-iodoindole **2a** (*n*-BuLi in Et_2O at reflux, followed by quenching with iodine).[14] Electrophilic alkylation of **2a** at the C3 position with acrolein using trifluoroacetic acid and *N*-methylaniline provides the aldehyde **4a**.[15] Other indole derivatives **4b**–**d**, **5a**, and **5b** containing *N*-protecting groups, such as TBS, MOM, and Bn, as well as a bromine functionality were synthesized in a similar manner.



Scheme 5. Preparation of 2-haloindoles. [a]Yield from indole.

The ketone **8** was prepared via $InCl_3$-catalyzed conjugate addition[16] of **6**[17] with methyl vinyl ketone followed by N-alkylation (Scheme 5). However, alkenylation of the aldehyde and ketone in the next step was somewhat troublesome. Initial attempts at alkenylation of the aldehyde **4a** using isopropenylmagnesium bromide **12** resulted in low yields of **20d** due to the competing unfavorable deiodination by an alkenylmetal species. It was found, however that use of excess alkenyl Grignard reagents and rapid quenching after the disappearance of starting material afforded **20d** in good yield (Table 1, entry 4). Similarly, addition of alkenyllithium in the presence of $AlMe_3$ was effective in avoiding the deiodination (Table 1, entries 1–3, 6, 8, and 9).[18] However, since this reaction was often accompanied by addition of a methyl group (derived from $AlMe_3$) to the aldehyde, the Grignard method is considered more advantageous.

According to the similar manner, the cyclization precursor **29** for the synthesis of five-membered ring system was prepared as shown in Scheme 6. Methyl *N*-methylindoleacetate **26**, prepared from commercially available 3-indoleacetic acid in two steps, was treated with $LiAlH_4$ to provide primary alcohol **27**. And lithiation and subsequent iodination of the C2 position, followed by oxidation of the primary hydroxy group by Dess–Martin periodinane, led to the corresponding aldehyde **28**. Addition of vinylmagnesium bromide to this aldehyde provided the precursor **29** in good overall yield.

Multisubstituted and/or chiral non-racemic 2-iodoindoles **37** and (*R*)-**42** were prepared efficiently via Method B (Scheme 4), a palladium-catalyzed Larock indole synthesis from *N*-benzyl *ortho*-iodoaniline **31** and silylalkyne **35** or **40** (Schemes 9 and 10, respectively). *N*-Benzyl *ortho*-iodoanilines **31a**–**c** were prepared by reductive amination of benzaldehyde and the corresponding iodoanilines with $NaBH_3CN$ and $ZnCl_2$ in MeOH (Scheme 7).[19] Starting materials **30a**–**c** are commercially available or were synthesized via literature methods.[20]

The synthesis of 7-(trimethylsilyl)hept-1-en-6-yn-3-ol **35** and enantioenriched (*R*)-**35** is illustrated in Scheme 8. The synthesis began with commercially available 5-(trimethylsilyl)pent-4-yn-1-ol **32**, which was oxidized using DMSO/$(COCl)_2$ to the aldehyde **33**, and this compound was converted to the allylic alcohol **34** by addition of vinyllithium. The racemic alcohol **34** was subjected to Sharpless kinetic resolution conditions using *t*-BuOOH, Ti(O*i*-Pr)$_4$, and (+)-diisopropyl L-tartrate (DIPT) in CH_2Cl_2 at −20 °C to give (*R*)-**34** (>98% ee) in 41% yield.[21] Finally, protection of the hydroxy group with chlorotriethylsilane furnished (*R*)-**35** in 97% yield through resolution, or racemic **35** in 97% yield if the resolution step is omitted.

With the required coupling partners now in hand, the next task was to synthesize the indole nucleus. The crucial, palladium-catalyzed Larock indole synthesis was accomplished using Walsh's conditions (Scheme 9).[22] Reaction of **35** or (*R*)-**35** and **31a**–**c** in DMF at 100 °C using $Pd(OAc)_2$ (5 mol %) and PPh_3 (5 mol %) in the presence of 1 equiv of LiCl and 2.5 equiv of K_2CO_3 afforded the 2-silylindoles **36a**–**c** in 39–71% yields. Iododesilylation of **36a**–**c** using ICl in CH_2Cl_2 at −78 °C followed by a standard silyl deprotection provided racemic **37a**–**c** in 30–72% yield from 2-silylindole and enantioenriched (*R*)-**37a** and (*R*)-**37b** with high optical purity (>99% ee). In the iododesilylation step, the allylic alcohol double bond of **36a**–**c** was iodinated easily in a side reaction. For **36a** and (*R*)-**36a**, this side reaction was suppressed by cooling the reaction to −78 °C. However, the side reaction was not suppressed for **36b**, (*R*)-**36b**, and **36c**, and the yields of **37b**, (*R*)-**37b**, and **37c** were diminished. These results presumably reflect the difference in reactivity toward ICl derived from the substituents on the indole ring.

It was possible to synthesize the tertiary allylic alcohol (*R*)-**42**, a more complex compound, via the same Larock protocol (Scheme 10). The two building blocks for synthesis, compounds **31a** and **40**, are both readily available. With respect to the chiral, non-racemic silylalkyne **40**, a facile and short synthesis was achieved commencing with ozonolysis of (*R*)-(−)-linalool (>98% ee). Employing a known procedure, oxidative cleavage of the more electron-rich double bond of (*R*)-(−)-linalool with ozone in CH_2Cl_2/pyridine at −78 °C afforded lactol **38** as a mixture of diastereomers in 66% yield.[23] It is important that the reaction be carried out to only about 60–70% completion to minimize overoxidation. Treatment of the resulting lactol with Ohira–Bestmann reagent gave the corresponding propargylic alcohol **39**,[24] on, which the terminal acetylene and hydroxyl groups were simultaneously silylated with chlorotrimethylsilane using *n*-BuLi as a base to furnish the desired **40** in 93% yield. Subjection of **40** to a palladium-catalyzed coupling reaction with **31a** in the same manner as described in Scheme 9 gave the 2-silylindole **41** in 82% yield. Iododesilylation with ICl, followed by removal of the TMS group with tetra-*n*-butylammonium fluoride provided (*R*)-**42** with 97% ee in 58% yield from **41**.

2.2. Optimization of reaction conditions

At the outset of this project, the plan was to examine the synthesis of 2-(alkenyl)pyranoindole **O** as a precursor for Claisen rearrangement from indole **M** having no halogen substituent at the C2 position (Scheme 11). To our knowledge, few general procedures are available for the preparation of the pyranoindole scaffold and/or related structures. In 1978, Nakagawa and co-workers reported that oxidative cyclization of 3-indolepropanol and 3-indolepropanethiol with *N*-bromosuccinimide in CH_2Cl_2 gave the corresponding pyranoindole and thiopyranoindole, respectively, in good yields.[25] Likewise, Rainier and co-workers also reported the formation of

Table 1
Synthesis of 2-haloindoles

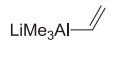
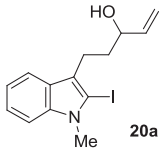
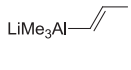
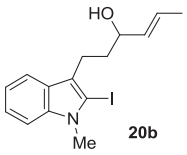
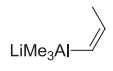
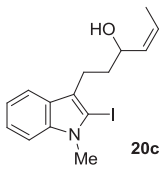
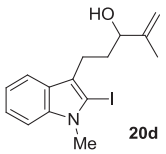
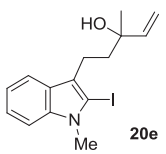
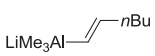
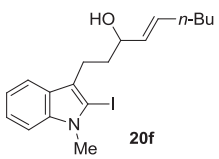
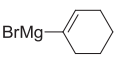
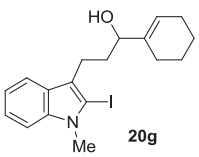
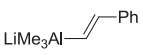
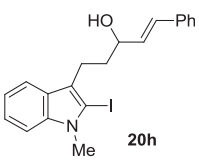
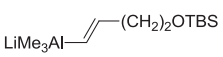
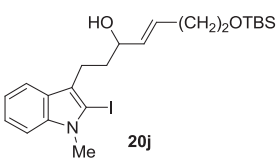
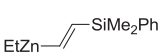
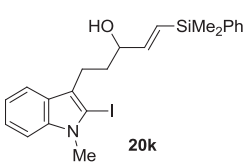
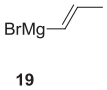
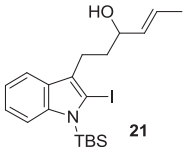
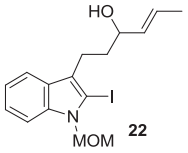
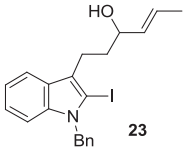
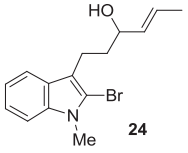
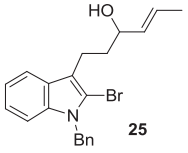
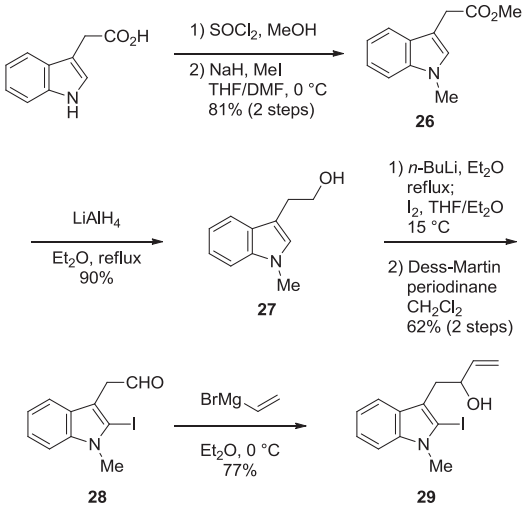
Entry	Formyl or ketoindole	Alkenyl metal	Product	Yield [%][a] (*EIZ*)[b]
1	**4a**	 **9**	 **20a**	61
2	**4a**	 **10**	 **20b**	82 (>95% *E*)
3	**4a**	 **11**	 **20c**	42 (>95% *Z*)
4	**4a**	 **12**	 **20d**	71
5	**8**	 **13**	 **20e**	72
6	**4a**	 **14**	 **20f**	82 (>95% *E*)
7	**4a**	 **15**	 **20g**	85
8	**4a**	 **16**	 **20h**	44 (>95% *E*)
9	**4a**	 **17**	 **20j**	73 (>95% *E*)
10	**4a**	 **18**	 **20k**	14 (>95% *E*)

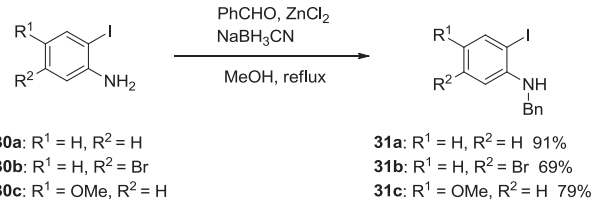
Table 1 (*continued*)

Entry	Formyl or ketoindole	Alkenyl metal	Product	Yield [%][a] (*EIZ*)[b]
11	**4b**	 **19**	 **21**	65 (>95% *E*)
12	**4c**	**19**	 **22**	75 (>95% *E*)
13	**4d**	**19**	 **23**	73 (>95% *E*)
14	**5a**	**10**	 **24**	70 (>95% *E*)
15	**5b**	**19**	 **25**	79 (>95% *E*)

[a] Yield of isolated product.
[b] Determined by ^{1}H NMR spectroscopic analysis.



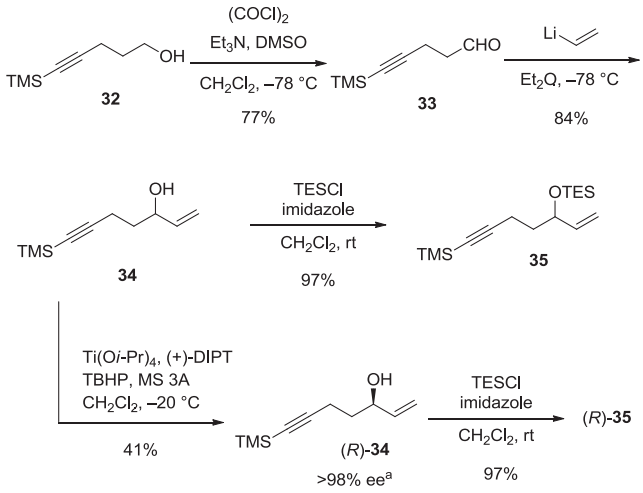
Scheme 6. Preparation of 2-iodoindole **29**.



30a: R^1 = H, R^2 = H
30b: R^1 = H, R^2 = Br
30c: R^1 = OMe, R^2 = H

31a: R^1 = H, R^2 = H 91%
31b: R^1 = H, R^2 = Br 69%
31c: R^1 = OMe, R^2 = H 79%

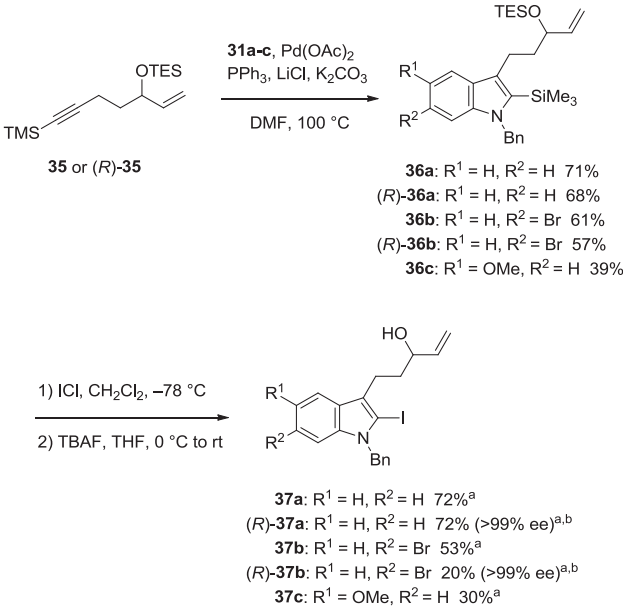
Scheme 7. Preparation of *N*-benzyl-2-iodoanilines **31a**–**c**.



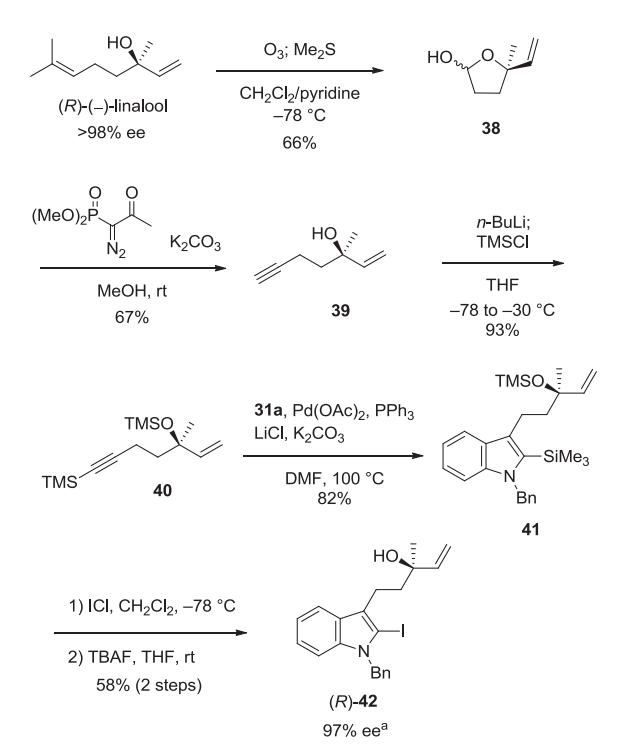
Scheme 8. Synthesis of silylalkynes **35** and (*R*)-**35**. [a]Enantiomeric excess was determined by chiral HPLC analysis.

substituted thiopyranoindoles from the corresponding thiols by oxidative cyclization using iodine.[26]

Following these precedents, we initially attempted oxidative cyclization of the corresponding indole **43** containing a 3-hydroxynon-4-enyl side chain at the C3 position with *N*-bromosuccinimide, iodine or other oxidants. However, the reactions led to no desired product **45**; undesired spirocyclic products were observed together with a mixture of polymerization products of **43** (Scheme 12). For example, when **43** was treated with iodine in

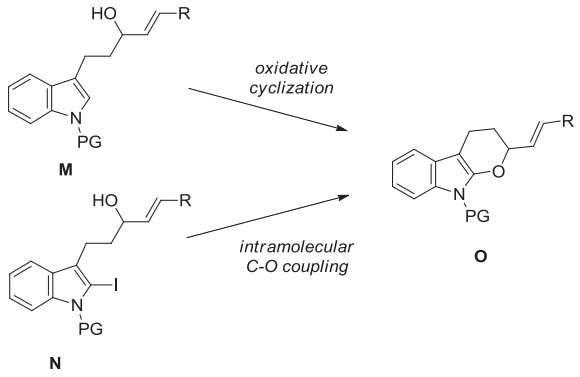


Scheme 9. Synthesis of *N*-benzyl-2-iodoindoles. [a]Yield for the two steps; [b]Enantiomeric excess was determined by chiral HPLC analysis.



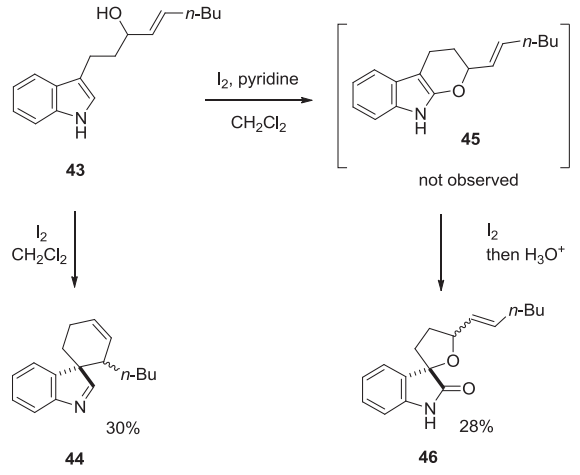
Scheme 10. Synthesis of (*R*)-**42**. [a]Enantiomeric excess was determined by chiral HPLC analysis.

CH_2Cl_2, a diastereomeric mixture of the spirocyclic indolenine **44** was obtained in 30% yield. The formation of **44** probably proceeds via initial activation of the hydroxyl group of **43** by a proton, followed by cyclization of the resulting allylic cation intermediate, giving rise to a more thermodynamically favorable six-membered ring. While making use of pyridine as an acid scavenger under the same reaction conditions, the undesired spirocyclic oxindole **46** resulted in 28% yield with low diastereoselectivity. This oxindole product presumably is formed via an iodination at the C3 position of the desired pyranoindole **45**, followed by the addition of H_2O at the C2 position, with concomitant skeletal rearrangement.[27] These



Scheme 11. Synthetic plans of 2-(alkenyl)pyranoindole **O**.

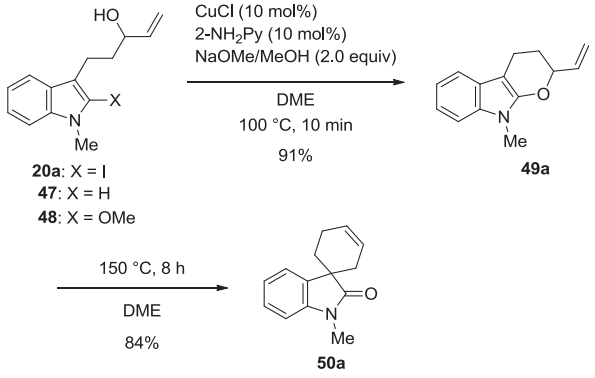
failures suggest that both **43** and **45** are more sensitive to electrophiles, including a proton, than the compounds used in the literature. Since careful control to prevent side reactions is required in the oxidative cyclization method, much milder conditions were required.



Scheme 12. Attempted oxidative cyclization of **43**.

It was decided that the next step would be to examine the transition-metal-catalyzed intramolecular C–O coupling of 2-haloindole, which is usually carried out under basic conditions (from 2-iodoindole **N** to pyranoindole **O** in Scheme 11). For C–O bond formation, a copper-mediated Ullmann-type reaction was chosen for its ease and low cost.[28] Although several recent syntheses have involved IUC, these examples are much rarer than intermolecular versions. As a preliminary survey, several known procedures using two 2-iodoindoles **20a** and **20b** as model substrates were compared. The methods of Buchwald (CuI/1,10-phenanthroline, Cs_2CO_3),[29] Song (CuCl/2,2,6,6-tetramethylheptane-3,5-dione, Cs_2CO_3),[30] and Zhu (CuCl, NaH)[31] all gave poor results in our system; either a large amount of starting material remained unchanged or reductive dehalogenation of starting material was observed. In contrast, the Hauptman protocol (CuCl/2-aminopyridine, NaOMe)[32] was found to be effective, proceeding in moderate yield (up to 60%). However, direct application of the Hauptman method to our indole substrates suffered from poor reproducibility. After many trials, this problem was overcomed by employing two minor modifications: (1) addition of a small amount of MeOH (approx. 2% *v*/*v*); and (2) an increase in the amount of base

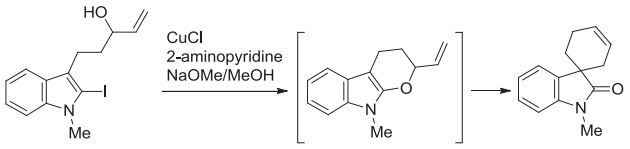
(NaOMe). (Using 2.0 equiv of commercial NaOMe in MeOH solution (25 wt %) gave the best results, with good reproducibility.) Under the optimized conditions, the IUC of **20a** proceeded rapidly (completed within 10 min) to give pyranoindole **49a** in 91% yield (Scheme 13). Interestingly, neither the dehalogenated product **47** nor the methoxylated product **48** was obtained. Finally, **49a** underwent Claisen rearrangement to afford the desired oxindole **50a** by heating in 1,2-dimethoxyethane (DME) at 150 °C.



Scheme 13. Synthesis of spirocyclic oxindole **50a** through IUC and Claisen rearrangement.

As noted above, pyranoindole **49a** is relatively unstable, especially under acidic conditions; and thus, significant decomposition of **49a** was observed during purification by silica gel column chromatography. Therefore, in the next phase of the reaction optimization, a one-pot synthesis of **50a** was attempted (Table 2). A mixture of **20a**, CuCl, 2-aminopyridine, and NaOMe/MeOH in DME was heated to 100 °C for 24 h, and **50a** was obtained in 53% yield with 22% of **49a** also recovered (Table 2, entry 1). Upon raising the reaction temperature to 150 °C after complete formation of **49a** (at 100 °C for 10 min; judged by HPLC), the rearrangement of **49a** proceeded more efficiently to afford **50a** in 84% yield (Table 2, entry 2). Using CH_3CN or toluene as the solvent led to a considerable decrease in yield (Table 2, entries 3 and 4). Catalyst and ligand loadings of 10 mol % and 5 mol % gave similar results, but a longer reaction time was required for the latter case (Table 2, entries 2 and 5). Increasing the concentration of **20a** to 0.10 mol/L resulted in a slight decrease in yield due to side reactions during the IUC step (Table 2, entry 6). In the absence of CuCl and 2-aminopyridine the IUC was sluggish, and the yield of **50a** dropped to 6% with 74% of **20a** recovered (Table 2, entry 7), suggesting that CuCl and 2-aminopyridine efficiently catalyze the IUC.

Table 2
One-pot synthesis of spirocyclic oxindole **50a**[a]



Entry	CuCl [mol %]	2-NH_2Py [mol %]	Solvent	[**20a**] [mol L^{-1}]	Conditions	Yield [%][b]	
						49a	**50a**
1	10	10	DME	0.05	100 °C, 24 h	22	53
2	10	10	DME	0.05	100 °C, 10 min 150 °C, 12 h	0	84
3	10	10	CH_3CN	0.05	100 °C, 24 h	26	36
4	10	10	Toluene	0.05	100 °C, 1 h 150 °C, 12 h	0	41
5	5	5	DME	0.05	100 °C, 3 h 150 °C, 12 h	0	80
6	10	10	DME	0.10	100 °C, 10 min 150 °C, 12 h	0	72
7	0	0	DME	0.05	100 °C, 24 h	10	6[c]

[a] Reaction conditions: indole **20a** (0.50 mmol), NaOMe/MeOH (25 wt %; 2.0 equiv), Ar, sealed tube.
[b] Yield of isolated product.
[c] **20a** was recovered in 74% yield.

2.3. Scope and limitation

To study the effect of substituents on the Claisen rearrangement, compound **20a** with a variety of substituents on the allylic alcohol unit were investigated next. The results are summarized in Table 3. It is noteworthy that all of the indoles with *trans*-oriented substituents on the allylic double bond afforded the corresponding oxindoles as a single diastereomer, irrespective of the substituent (Table 3, entries 1, 2, 6–11). The relative stereochemistry was assigned based on an X-ray crystal structure of oxindole **50h**,[33] and NOE experiments (Fig. 2).

The stereochemistry of these products indicates that the Claisen rearrangement proceeds through a boat-like transition state analogous to previous results (Scheme 14).[34] In contrast, the reaction of the *cis*-isomer **20c** did not give the desired product; instead, decomposition of the corresponding pyranoindole **49c** initially formed was observed (Table 3, entry 3). This result can be rationalized by considering the unfavorable transition state, which would result from steric repulsion between the *cis*-oriented methyl group and the hydrogen atoms of the dihydropyran ring (Scheme 14). The rate of Claisen rearrangement is strongly dependent on the presence of substituents on the allylic double bond. The reaction of substrates with an alkyl or aryl substituent on the allylic double bond is fast (Table 3, entries 1, 6, 8–10).[35] In contrast, substrates with no substituent on the allylic double bond react slowly (Table 2, entry 2).[7a] For bromoindole **24**, although the reactivity in the IUC is apparently lower than that of iodide **20b**, the reaction did proceed to afford oxindole **50b** in 55% yield (Table 3, entry 2). Notably, sterically hindered substrates, such as **20e** (tertiary alcohol) and **20g** (trisubstituted olefin) gave the desired **50e** and **50g**, respectively, in good yield (Table 3, entries 5 and 7). It was possible to accelerate the slow reaction of **20g** by raising the reaction temperature, without any side reactions. The fact that diol **20i** gave **50i** exclusively, in 93% yield, indicates that the allylic hydroxyl group reacts selectively and that the IUC is tolerant of unprotected hydroxy groups (Table 3, entry 9). The low yield observed for silyl-bearing **20k** is due to the formation of the desilylated product **50a** and its double bonded isomer (Table 3, entry 11).

In contrast, five-membered ring closure using precursor **29** was found to provide neither desired furanoindole **51** nor the corresponding spirocyclic oxindole **52**; 2-methoxyindole **53a** and the dehalogenated product **53b** were obtained (Scheme 15). This result indicates that intramolecular C–O bond formation would be retard by some unfavorable conformation in the transition state to form five-membered cyclic ether.

The synthetic utility of *N*-methylated oxindoles is rather limited due to difficulty in deprotecting the *N*-methyl group. However, the direct conversion of unprotected *N*-free iodoindoles to the corresponding *N*-free oxindoles is difficult because of the unstable nature of unprotected iodoindoles. Thus, in order to eliminate these limitations, a suitable *N*-protecting group for the iodoindole, which does not alter the reactivity of the indole nucleus and can be removed under facile conditions was examined next (Table 4). *N*-*tert*-Butyldimethylsilyl (TBS) indole **21** afforded deprotected oxindole **54b** in 57% yield (Table 4, entry 1). In this reaction, all of **21** was initially converted to an *N*-free iodoindole **21** upon heating to 100 °C, as monitored by HPLC analysis. However, the subsequent IUC of **21** was rather slow, and the reaction temperature had to be

Table 3
Synthesis of *N*-methyl spirocyclic oxindoles[a]

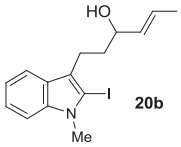
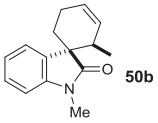
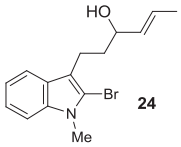
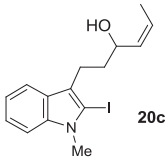
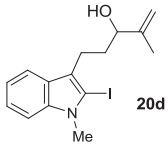
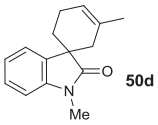
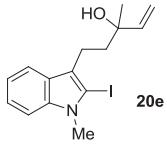
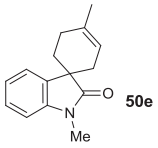
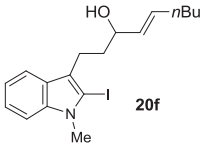
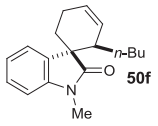
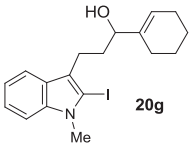
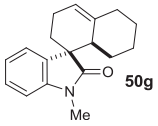
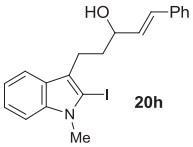
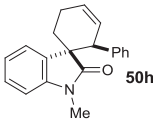
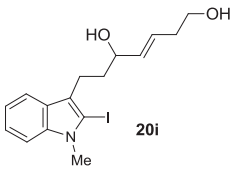
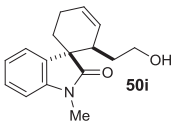
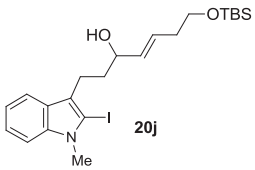
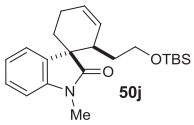
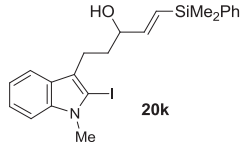
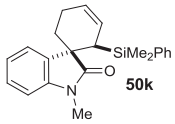
Entry	Substrate	Product	Conditions	Yield[b] (% de[c])
1	 **20b**	 **50b**	100 °C, 0.5 h 150 °C, 1 h	89 (>95)
2	 **24**	**50b**	100 °C, 24 h	55[d] (>95)
3	 **20c**	ND[e]	100 °C, 1.5 h 150 °C, 6h	—
4	 **20d**	 **50d**	100 °C, 4 h 150 °C, 1 h	80
5	 **20e**	 **50e**	130 °C, 21 h 150 °C, 1 h	84
6	 **20f**	 **50f**	100 °C, 1 h 150 °C, 1 h	92 (>95)
7	 **20g**	 **50g**	100 °C, 22 h 120 °C, 11 h	89 (>95) 90 (>95)
8	 **20h**	 **50h**	100 °C, 1 h	84 (>95)
9	 **20i**	 **50i**	100 °C, 0.5 h 150 °C, 1 h	93 (>95)
10	 **20j**	 **50j**	100 °C, 1 h 150 °C, 0.7 h	66[f] (>95)

Table 3 (*continued*)

Entry	Substrate	Product	Conditions	Yield[b] (% de[c])
11	 **20k**	 **50k**	100 °C, 5 h 150 °C, 2 h	20[g] (>95)

[a] Reaction conditions: substrate (0.50 mmol), CuCl (10 mol %), 2-aminopyridine (10 mol %), DME (0.05 M), NaOMe/MeOH (25 wt %; 2.0 equiv), Ar, sealed tube, Reaction time and temperature were not optimized for each substrate.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] **24** was recovered (31%).
[e] Complex mixture was obtained.
[f] **50i** was isolated in 25% yield (>95% de).
[g] **50a** and its regioisomer were isolated in 47% yield (**50a**/isomer=2:1).

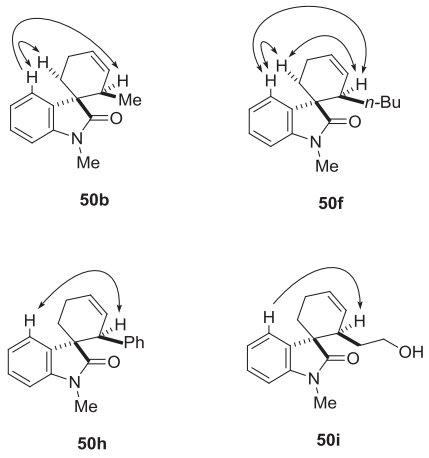
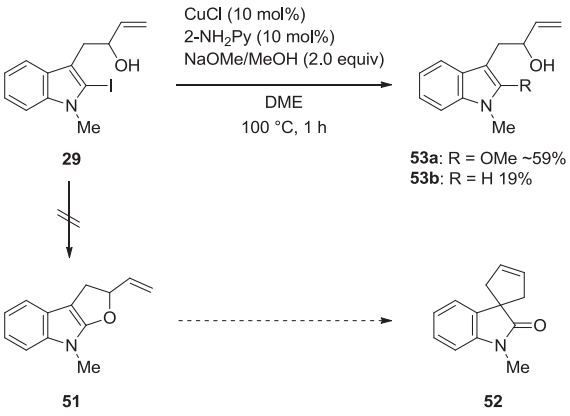
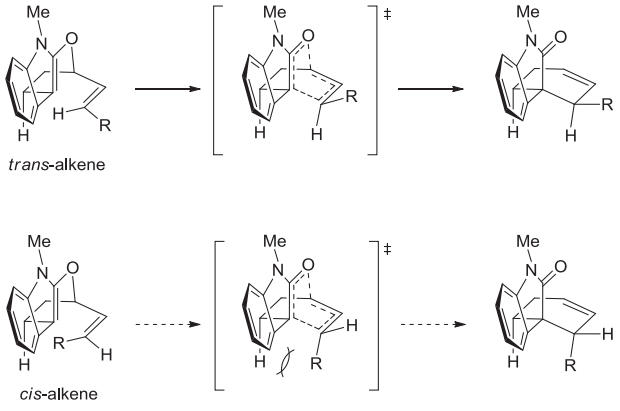


Fig. 2. NOE experiments to determine the stereochemistry of spirocyclic oxindoles.



Scheme 15. Attempted one-pot sequence to provide furanoindole **51**.



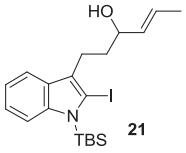
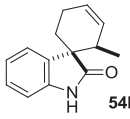
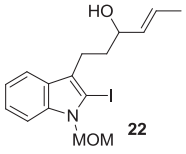
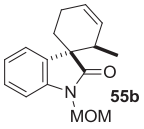
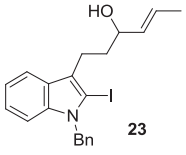
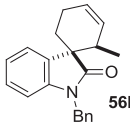
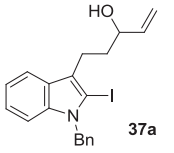
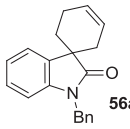
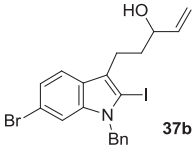
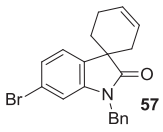
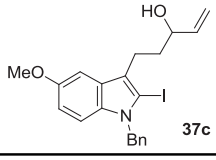
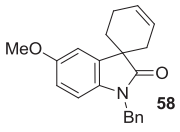
Scheme 14. Possible transition states of Claisen rearrangement.

elevated to 150 °C to achieve complete consumption of **21**. In contrast, the methoxymethyl (MOM) and benzyl groups were found to be suitable *N*-protecting groups for the present transformation. The IUC of **22** and Claisen rearrangement of the resulting pyranoindole occurred smoothly to give **55b** in 92% yield as a single isomer (Table 4, entry 2). Similarly, the reaction of *N*-benzylindole **23** proceeded in high yield with high diastereoselectivity to give **56b** (Table 4, entry 3). Deprotection of the MOM group was readily achieved in 81% yield utilizing the Fukuyama procedure (Scheme 16).[36]

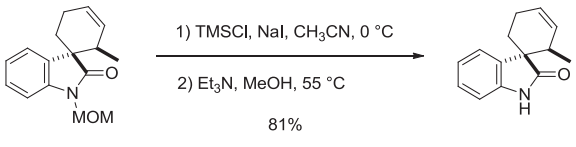
An attempt using the benzenesulfonyl group failed cleavage of the protecting group followed by methylation of the resulting *N*-free indole occurred.[37] In an effort to enhance the practicality of these transformations, the reaction of **23** at atmospheric pressure was carried out using diglyme as a solvent. Interestingly, acceleration of the IUC step was observed, and oxindole **56b** was obtained in almost same yield as in DME (Table 4, entry 3). This result suggests that Claisen rearrangement of pyranoindole can be readily accomplished without carrying out the reaction in a sealed tube. Exposure of **37b** to the standard reaction conditions using DME provided an oxindole product **57** in 87% yield (Table 4, entry 5). In this case, the complete conversion of **37b** to the pyranoindole intermediate was observed following heating at 100 °C for 1 h, and the subsequent rearrangement to **57** was achieved by heating at 150 °C for 6 h. At this point, no trace of the methoxy-substituted product was detected. This result suggests that the present catalytic system could be applied to bromo-functionalized substrates, which are generally reactive to copper-mediated alkoxydehalogenations or reductive dehalogenations. In contrast to the bromo derivative **37b**, the methoxy-substituted iodoindole **37c** was apparently less reactive in the IUC (Table 4, entry 6). Although 76% yield of oxindole **58** was obtained, starting material **37c** was recovered in 10% yield, even after a prolonged reaction time (120 °C, 13 h).

Encouraged by the results with diglyme, the accelerating effect of other ethereal solvents was next investigated (Table 5). Reactions were carried out at 150 °C using bromoindole **25**, which was found to be sluggish in the IUC. Under the standard reaction conditions using DME, the IUC of **25** did not complete even after 45 h, and debrominated **59** was isolated in 4% yield as a side product (Table 5,

Table 4
Synthesis of spirocyclic oxindoles[a]

Entry	Substrate	Product	Conditions	Yield[b] (% de[c])
1	 **21**	 **54b**	100 °C, 1 h 150 °C, 24 h	57 (>95)
2	 **22**	 **55b**	100 °C, 1 h 150 °C, 0.5 h	92 (>95)
3	 **23**	 **56b**	100 °C, 1 h 150 °C, 0.5 h 100 °C, 0.5 h 150 °C, 0.5 h	89 (>95) 83[d] (>95)
4	 **37a**	 **56a**	100 °C, 0.5 h 150 °C, 4 h 120 °C, 6 h	71 72[d]
5	 **37b**	 **57**	100 °C, 1 h 150 °C, 6 h	87
6	 **37c**	 **58**	100 °C, 4 h 120 °C, 13 h 150 °C, 3 h	76[e]

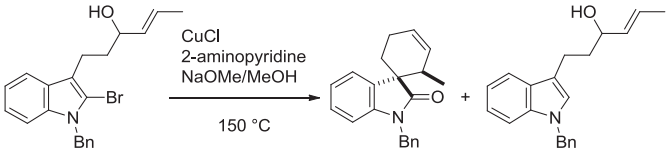
[a] Reaction conditions: substrate (0.50 mmol in entries 1–5, 0.27 mmol in entry 6), CuCl (10 mol %), 2-aminopyridine (10 mol %), DME (0.05 M), NaOMe/MeOH (25 wt %; 2.0 equiv), Ar, sealed tube, Reaction time and temperature were not optimized for each substrate.
[b] Yield of isolated product.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Reaction was performed in diglyme as a solvent in an open vessel.
[e] **37c** was recovered in 10% yield.



Scheme 16. Removal of MOM group of spirocyclic oxindole **55b**.

entry 1). In contrast, the use of diglyme as a solvent dramatically improved the reaction rate, and the desired **56b** was obtained as a single isomer in 79% yield, without **59** (Table 5, entry 2). Furthermore, surprisingly, the use of triglyme was found to be extremely effective and led to a substantially higher reaction rate than diglyme (Table 5, entry 3). Since the use of triglyme as a solvent for the Ullmann reaction is not common, its accelerating effect is noteworthy. The factors responsible for the increase in rate of the

Table 5
Accelerating effect of ethereal solvents[a]



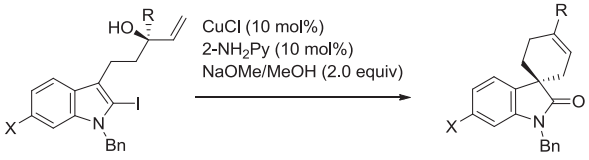
Entry	Solvent	Time	Yield [%][b]		
			25	**56b**	**59**
1	DME	45 h	4	75	4
2	Diglyme	2 h	0	79	Trace
3	Triglyme	1 h	Trace	82	0

[a] Reaction conditions: substrate (0.5 mmol), CuCl (10 mol %), 2-aminopyridine (10 mol %), solvent (0.05 M), NaOMe/MeOH (25 wt %; 2.0 equiv), Ar, sealed tube. Diastereomeric excess was determined by ^{1}H NMR spectroscopic analysis.
[b] Isolated yield.

IUC are not clear at present, however, we speculate that higher polarity and an increase in oxygen lone pairs from the diglyme or triglyme prompt the IUC reaction.[32,38]

A one-pot IUC/Claisen rearrangement of chiral non-racemic precursors was also examined (Table 6). A sequential reaction of the secondary alcohol (*R*)-**37a** (>99% ee) was carried out under the same conditions as for the racemic alcohol. Contrary to expectations, the desired spirocyclic oxindole (*S*)-**56a** was isolated in 74% yield with a decrease in the enantiomeric excess, regardless of the

Table 6
Synthesis of chiral non-racemic spirocyclic oxindoles[a]



(*R*)-**37a**: R = H, X = H
(*R*)-**37b**: R = H, X = Br
(*R*)-**42**: R = Me, X = H

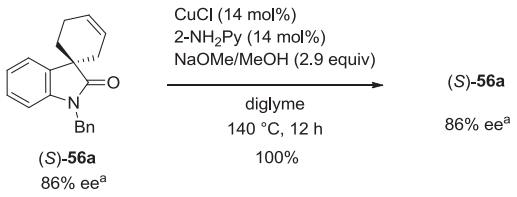
(*S*)-**56a**: R = H, X = H
(*S*)-**57**: R = H, X = Br
(*S*)-**60**: R = Me, X = H

Entry	Substrate	Method[b]	Conditions	Yield [%][c]	% ee[d]	Product
1	(*R*)-**37a** (>99% ee)	A	100 °C, 1 h 150 °C, 4 h	74	86	(*S*)-**56a**
2		B	120 °C, 10 h	73	88	(*S*)-**56a**
3	(*R*)-**37b** (>99% ee)	A	100 °C, 1 h 150 °C, 5 h	83	90	(*S*)-**57**
4		B	120 °C, 7 h	84	91	(*S*)-**57**
5	(*R*)-**42** (97% ee)	B	120 °C, 5 h	85	97	(*S*)-**60**

[a] Reaction scale: substrate (0.50 mmol in entries 1,2. 0.3 mmol in entries 3–5).
[b] Method A: solvent=DME (0.05 M), sealed tube. Method B: solvent=diglyme (0.05 M), open vessel.
[c] Yield of isolated product.
[d] Enantiomeric excess was determined by chiral HPLC analysis.

reaction conditions (Table 6, entries 1 and 2). In addition, reactions using 6-bromoindole (*R*)-**37b** (>99% ee) resulted in the formation of (*S*)-**57** at the same level of enantiomeric excess (Table 6, entries 3 and 4). In sharp contrast, the sequential reaction gave the corresponding oxindole (*S*)-**60** with perfect asymmetric transmission (97% ee) when the tertiary alcohol (*R*)-**42** (97% ee) was used (Table 6, entry 5). The details of the racemization of spirocyclic oxindoles in the secondary alcohol system are obscure at this time. However, the racemization would be expected to take place during the IUC process or after the formation of the pyranoindole intermediate[39]

based on the control experiment shown in Scheme 17; no racemization was observed when (*S*)-**56a** was subjected to the IUC conditions. Racemization mechanism in the IUC process could be rationalized by the thermal decomposition of copper(I) alkoxide intermediate leading to enone and copper(I) hydride and subsequent reduction of the resulting enone by copper(I) hydride.[40]

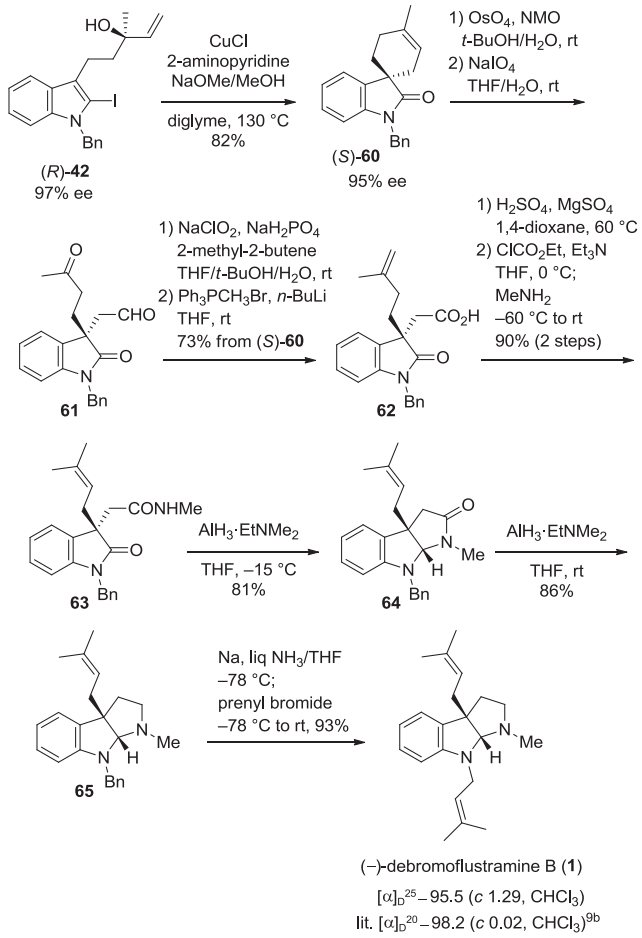


Scheme 17. Control experiment for racemization of the spirocyclic oxindole. [a]Enantiomeric excess was determined by chiral HPLC analysis.

2.4. Total synthesis of (−)-debromoflustramine B

Flustramines are the simplest members of hexahydropyrrolo[2,3-*b*]indole alkaloids, which display significant biological activity.[41] (−)-Debromoflustramine B (**1**) and the related (−)-flustramine B were first isolated from the marine byrozoan *Flustra foliacea*.[9c,d] (−)-Flustramine B has been found to exhibit muscle relaxant activity, affecting both skeletal and smooth muscles.[42] The hexahydropyrrolo[2,3-*b*]indole having a quaternary carbon prenylated at C-3a is the defining structural feature of these alkaloids and therefore many efficient methods have been developed for their synthesis.[5h,43]

To demonstrate the potential usefulness of our methodology for natural product synthesis, the total synthesis of (−)-debromoflustramine B (**1**) was performed based on the previously reported our strategy using racemic 2-iodoindole **42** with a slight modification.[12a] For preparing (*S*)-**60**, the IUC and Claisen rearrangement procedure of chiral non-racemic iodoindole (*R*)-**42** (97% ee), prepared from (*R*)-(−)-linalool shown in Scheme 10, was readily carried out on a multigram scale (Scheme 18). Oxidative cleavage of the carbon–carbon double bond of (*S*)-**60** with OsO_4–$NaIO_4$ gave aldehyde **61**, which was subsequently converted to *exo*-methylene **62** via $NaClO_2$ oxidation followed by a Wittig olefination of the resulting keto-carboxylic acid with the ylide generated from methyltriphenylphosphonium bromide and *n*-BuLi in 73% yield from (*S*)-**60**. Exposure of **62** to concentrated H_2SO_4-dioxane in the presence of $MgSO_4$ resulted in isomerization to an internal olefin, providing the requisite carboxylic acid as a 20:1 mixture with **62**. The carboxylic acid was then transformed to the amide **63** via the mixed anhydride method using ethyl chloroformate and $MeNH_2$ in 90% yield from **62**.[43c] The overall yield of **63** was improved when the reaction temperature of the amidation of mixed anhydride was elevated to rt (cf. 65% overall yield from **62** at −60 °C). Minor *exo*-isomer derived from **62** was separated at this stage by silica gel chromatography. Amide **63** containing a prenyl side chain was transformed to the hexahydropyrrolo[2,3-*b*]indole derivative **65** using Kawasaki's protocol[43a] involving reductive cyclization of **63** with an excess of $AlH_3{\cdot}NEtMe_2$ at −15 °C to produce 2-oxopyrroloindoline **64** in 81% yield, followed by an additional alane reduction at room temperature to afford **65** in 86% yield.[44] Finally, reductive debenzylation of **65** with sodium in liquid ammonia and quenching of the resulting amide anion with prenyl bromide completed the total synthesis of (−)-debromoflustramine B (**1**), $[\alpha]_D^{25}$ −95.5 (*c* 1.29, $CHCl_3$) (lit.[9b] $[\alpha]_D^{20}$ −98.2 (*c* 0.02, $CHCl_3$)), in 93% yield.[43b] The ^1H and ^{13}C NMR spectra of the synthetic (−)-debromoflustramine B are identical to those of reported data.[43i]



Scheme 18. Total synthesis of (−)-debromoflustramine B (**1**).

3. Conclusions

We have developed a convenient and efficient method for the preparation of spirocyclic oxindoles, with vicinal stereogenic centers, from the corresponding 2-haloindoles via a one-pot IUC and Claisen rearrangement. IUC is a simple and low cost method for the preparation of the rearrangement precursors, alkenyl pyranoindoles. The Claisen rearrangement of the pyranoindoles proceeds smoothly to give the desired 3-spiro-2-oxindoles in good yield and with high diastereoselectivity. In addition, a remarkable acceleration of the IUC/Claisen sequence using diglyme or triglyme was observed. Since the Claisen rearrangement is stereospecific in the tertiary alcohol system, this methodology would also be applicable to the enantioselective synthesis of spirocyclic oxindoles. The application of this reaction to the asymmetric total synthesis of a hexahydropyrrolo[2,3-*b*]indole alkaloid has been demonstrated.

4. Experimental section

4.1. Synthesis of alkenyl pyranoindole 49a by intramolecular Ullmann coupling (Scheme 13)

A screw cap test tube (Pyrex®, 61 mL) was charged with CuCl (5 mg, 0.05 mmol), 2-aminopyridine (5 mg, 0.05 mmol) and a small amount of DME. The tube was evacuated and backfilled with argon. The substrate **20a** (0.50 mmol) in DME (10 mL) was added. After bubbling with argon for 3 min, NaOMe solution in MeOH (25 wt %, 0.23 mL, 1.00 mmol) was added. The test tube was sealed with screw cap and stirred vigorously at 100 °C for 10 min until all **20a**

was consumed as judged by TLC and HPLC analysis. After cooling to rt, the reaction mixture was quenched with satd aq NH_4Cl (3 mL) and H_2O (10 mL), and extracted with AcOEt (3×20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (alumina, benzene) to afford **49a** (97 mg, 91% yield) as a white solid. Mp 63–64 °C; R_f 0.36 (hexane/AcOEt=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.32 (m, 1H), 7.18–7.13 (m, 1H), 7.09–7.04 (m, 2H), 6.05 (dddd, J=17.3, 10.5, 5.6, 1.4 Hz, 1H), 5.41 (dd, J=17.3, 1.4 Hz, 1H), 5.27 (dd, J=10.5, 1.4 Hz, 1H), 4.76–4.72 (m, 1H), 3.56 (s, 3H), 2.75–2.69 (m, 2H), 2.18–2.10 (m, 1H), 1.98–1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 136.7, 132.1, 126.4, 119.2, 118.7, 116.5, 116.2, 108.0, 85.9, 79.3, 28.4, 27.3, 17.3; IR (KBr, cm^{-1}) 2924, 1627, 1580, 1473, 1323, 739; HRMS (EI) calcd for $C_{14}H_{15}NO$: 213.1153, found: 213.1153; HPLC Analytical Condition: L-column ODS (4.6×250 mm), CH_3CN/0.02 M $AcONH_4$ water=80/20, flow rate=1.0 mL/min, Detection=UV at 220 nm, Temperature=40 °C.

4.2. Synthesis of spirocyclic oxindole 50a by Claisen rearrangement (Scheme 13)

To a screw cap test tube (Pyrex®, 61 mL) substrate **49a** (94 mg, 0.44 mmol) in DME (10 mL) was added. The test tube was sealed with screw cap and stirred vigorously at 150 °C for 8 h until all **49a** was consumed as judged by TLC and HPLC analysis. After cooling to rt, the reaction was quenched with H_2O (10 mL) and extracted with AcOEt (3×20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexane/AcOEt=9:1) to afford **50a** (79 mg, 84% yield) as a white solid. Mp 69–70 °C; R_f 0.37 (hexane/AcOEt=2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J=7.6, 1.0 Hz, 1H), 7.28 (td, J=7.6, 1.0 Hz, 1H), 7.02 (td, J=7.6, 1.0 Hz, 1H), 6.87 (br d, J=7.6 Hz, 1H), 5.97–5.84 (m, 2H), 3.23 (s, 3H), 2.70–2.61 (m, 1H), 2.37–2.29 (m, 2H), 2.07 (ddd, J=13.2, 9.5, 7.8 Hz, 1H), 1.95 (ddt, J=17.8, 4.9, 1.7 Hz, 1H), 1.56–1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 142.7, 134.4, 127.5, 126.6, 124.8, 123.8, 122.2, 107.8, 45.8, 31.6, 28.9, 26.2, 21.7; IR (KBr, cm^{-1}) 2912, 1703, 1610, 1470, 767; HRMS (EI) calcd for $C_{14}H_{15}NO$: 213.1153, found: 213.1153; HPLC Analytical Condition: L-column ODS (4.6×250 mm), CH_3CN/0.02 M $AcONH_4$ water=80/20, flow rate=1.0 mL/min, Detection=UV at 220 nm, Temperature=40 °C.

4.3. One-pot synthesis of oxindoles in DME (Tables 2–4)

The preparation of oxindole **50a** is representative. A screw cap test tube (Pyrex®, 61 mL) was charged with CuCl (5 mg, 0.05 mmol), 2-aminopyridine (5 mg, 0.05 mmol) and a small amount of DME. The tube was evacuated and backfilled with argon. The substrate **20a** (0.50 mmol) in DME (10 mL) was added. After bubbling with argon for 3 min, NaOMe solution in MeOH (25 wt %, 0.23 mL, 1.00 mmol) was added. The test tube was sealed with screw cap and stirred vigorously at 100 °C for 10 min until all **20a** was consumed as judged by TLC and HPLC analysis, and then at 150 °C for 12 h until the resultant **49a** was consumed. After cooling to rt, the reaction was quenched with satd aq NH_4Cl (3 mL) and H_2O (10 mL), extracted with AcOEt (3×20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexane/AcOEt=10:1) to afford **50a** (89 mg, 84% yield) as a white solid. HPLC Analytical Condition: L-column ODS (4.6×250 mm), CH_3CN/0.02 M $AcONH_4$ water=80/20, flow rate=1.0 mL/min, Detection=UV at 220 nm, Temperature=40 °C.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.057.

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