Construction of Spiro[pyrrolidine-3,3′-oxindoles] − Recent Applications to the Synthesis of Oxindole Alkaloids

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The spiro[pyrrolidine-3,3′-oxindole] ring system is found at the core of a number of alkaloids, which possess significant biological activity and are interesting, challenging targets for chemical synthesis. In the present review, we report on the different strategies for the synthesis of the spiro[pyrrolidine-3,3′-oxindole] ring system in the context of recent synthesis of coerulescine, horsfiline, elacomine, salacin, pteropodine, alstonisine, spirotryprostatin A and B, and strychnofoline.

1. Introduction

The first oxindole alkaloids were found in the roots of *Gelsemium sempervirens* (wild yellow jasmine). Additional oxindoles were isolated from *Aspidosperma, Mitragyna, Ourouparia, Rauwolfia* and *Vinca*.[1] Most of these oxindole alkaloids possess a common basic framework derived from tryptamine and are characterized by a unique spiro fusion to a pyrrolidine ring at the 3-position of the oxindole core. They can be further classified into two substructural classes: the tetracyclic secoyohimbane type [e.g. rhynchophylline (**1**)] and the pentacyclic heteroyohimbane type [e.g. formosanine (**2**)]. Other spiro[pyrrolidine-3,3′-oxindole] alkaloids that have been isolated are exemplified by (−)-horsfiline (**3**)[2], spirotryprostatin A (**4**), spirotryprostatin B (**5**)[3] and (+)-elacomine (**6**)[4] (Figure 1).

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Christiane Marti studied chemistry at the Saarland University, Germany and the ECPM-Strasbourg, France and graduated in chemical engineering in June 1998. During her Diploma thesis at the ETH Zürich (Switzerland) under the guidance of Prof. Dr. François Diederich she performed studies towards the synthesis of a new ligand for asymmetric phase-transfer catalysis bearing binaphthyl and cinchona alkaloid moieties. She carried out her Ph.D. studies under the supervision of Prof. Dr. Erick M. Carreira at the ETH Zürich working on the development of a novel method for the synthesis of spiro[pyrrolidine-oxindoles] and its application to the synthesis of (±)-horsfiline and (−)-spirotryprostatin B. She received her Ph.D. in February 2003 and is currently working as a postdoctoral fellow in the group of Prof. Robert H. Grubbs.

Erick M. Carreira obtained a B.S. degree in 1984 from the University of Illinois at Urbana−Champaign under the supervision of Prof. Scott E. Denmark and a Ph.D. degree in 1990 from Harvard University under the supervision of Prof. David A. Evans. After carrying out postdoctoral work with Prof. Peter Dervan at the California Institute of Technology through late 1992, he joined the faculty at the same institution as an assistant professor of chemistry and subsequently was promoted to the rank of associate professor of chemistry in spring 1996, and full professor in spring 1997. Since September 1998, he has been full professor of Organic Chemistry at the ETH Zürich. His research program focuses on the asymmetric synthesis of biologically active, stereochemically complex, natural products. He is a member of the International Advisory Board of European Journal of Organic Chemistry.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

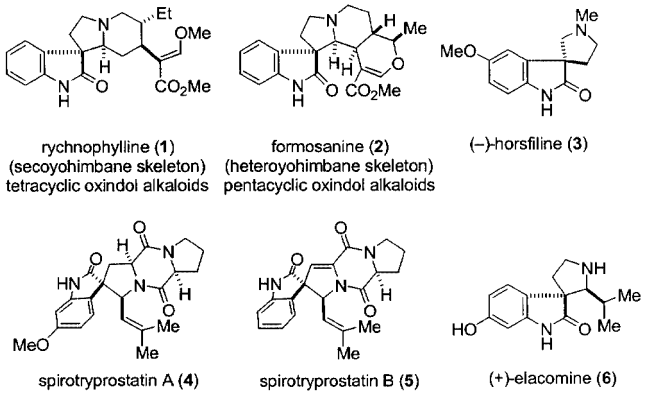


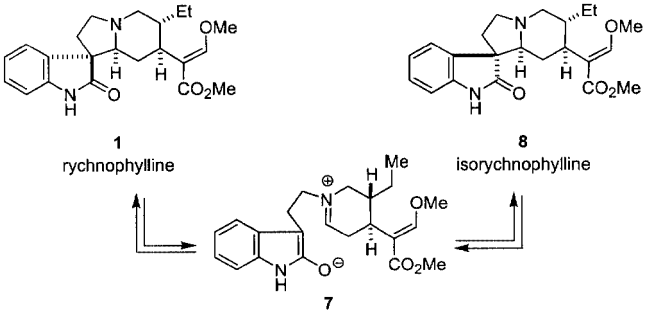
Figure 1. Spiro[pyrrolidine-3,3′-oxindole] alkaloids

The appealing spiro architecture often associated with significant biological activity render the spiro[pyrrolidine-3,3′-oxindole] alkaloids interesting synthetic targets. In the present paper, we report on the different strategies for the synthesis of the spiro[pyrrolidine-3,3′-oxindole] ring system in the context of recent natural product synthesis.

2. Methods for the Synthesis of the Spiro[pyrrolidine-3,3′-oxindole] Moiety

2.1. Intramolecular Mannich Reactions

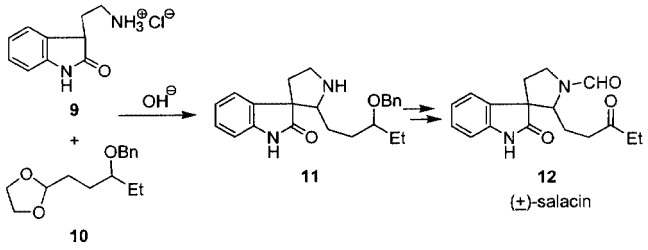
In nature, oxindole alkaloids often occur as pairs of interconvertible isomers [e.g. rhynchophylline (**1**) and isorychnophylline (**8**), the (3*S*) epimer of rhynchophylline]. This observation can be explained by an isomerization mechanism, wherein both forms can be equilibrated through the ring-opened form **7** that is accessed by retro-Mannich reaction (Scheme 1).[5]



Scheme 1. Isomerization of spiro[pyrrolidine-3,3′-oxindoles] through Mannich/retro-Mannich reaction

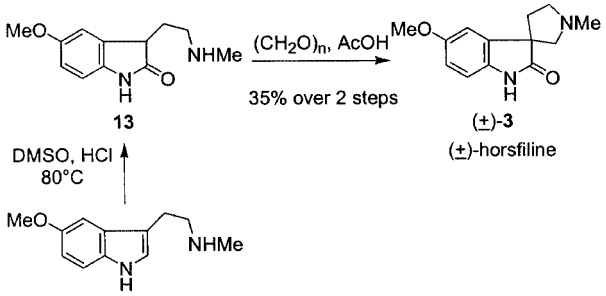
This mechanism was noted as early as 1959 and independently elucidated by two research groups. Wenkert and Marion both proposed a retro-Mannich reaction involving the open-ring intermediate **7**.[6,7] Synthetically, the spiro[pyrrolidine-3,3′-oxindoles] core can be assembled by an intramolecular Mannich reaction. The precursors are available from tryptamine or a tryptophane-derived oxindole and an aldehyde. By this method, the total synthesis of a mixture of (±)-rhynchophyllol and (±)-isorhynchophyllol was achieved by van Tamelen in 1969.[8] Ban and Oishi employed the Mannich reaction to elucidate the stereochemistry of (±)-rhynchophylline [(±)-**1**] and (±)-isorhynchophylline by comparison of the IR spectra of oxindoles synthesized by intramolecular Mannich reaction with a degradation product obtained from rhynchophylline.[9] The Mannich reaction found application in the synthesis of a number of spiro[pyrrolidine-3,3′-oxindoles] alkaloids for example (±)-formosanine [(±)-**2**],[10] (±)-rhynchophylline [(±)-**1**] and (±)-isorhynchophylline,[11] (±)-19-hydroxyaspidofractinine,[12] as well as a range of unnatural spirooxindoles.[13]

In 1990, salacin was isolated from *Uncaria salaccensis*, a Thai medicinal plant. The research team confirmed the structural assignment for salacin by the synthesis of (±)-salacin (**12**) from oxytryptamine hydrochloride (**9**). Condensation of this amine with acetal **10**, followed by intramolecular Mannich reaction afforded spiro[pyrrolidine-3,3′-oxindole] **11**. From **11**, (±)-salacin (**12**) was obtained in 3 steps (Scheme 2).[14]



Scheme 2. Synthesis of (±)-salacin through intramolecular Mannich reaction

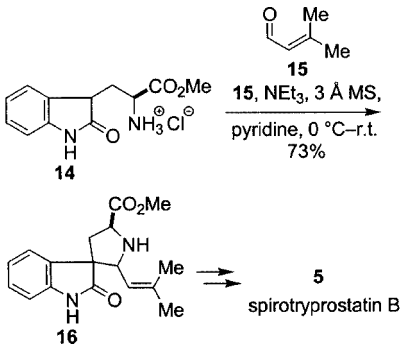
Laronze achieved the synthesis of horsfiline through an intramolecular Mannich reaction by a spiro cyclization of tryptamine-oxindole (**13**) with formaldehyde (Scheme 3).[15]



Scheme 3. Laronze's synthesis of (±)-horsfiline

One of the most notable recent applications of the Mannich reaction in complex natural product synthesis was documented by Danishefsky in his approach to spirotryprostatin B (**5**).[16] Reaction of oxindole **14** with aldehyde **15** afforded a mixture of diastereoisomeric spiro[pyrrolidine-3,3′-oxindoles] **16**. These compounds were separable at a

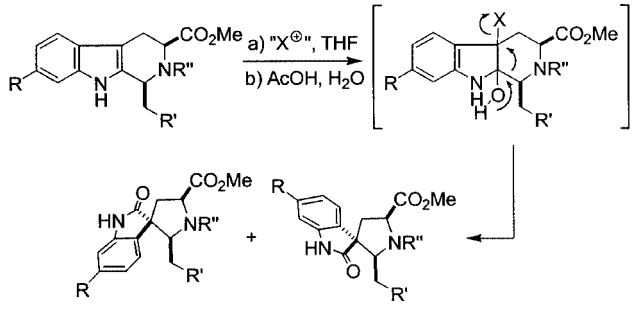
later stage in the synthesis and afforded spirotryprostatin B (**5**) in a very efficient sequence of reactions (Scheme 4).



Scheme 4. The Mannich reaction in Danishefsky's synthesis of spirotryprostatin B

2.2. Oxidative Rearrangement Sequences

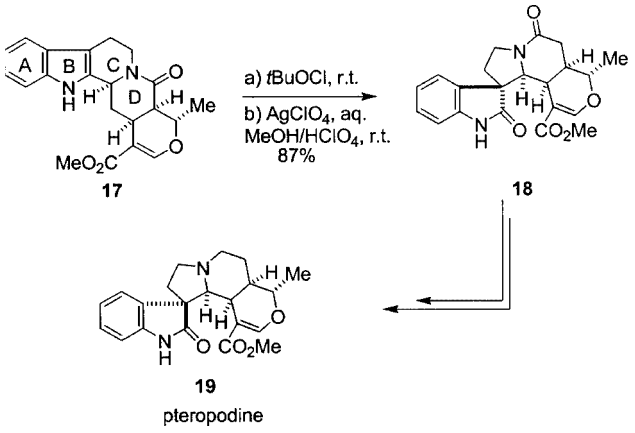
A widely employed method for the construction of the spiro[pyrrolidine-3,3′-oxindole] ring system is the oxidative rearrangement of a tetrahydro-β-carboline. Tetrahydro-β-carbolines are conveniently accessible from derivatives of tryptophane or tryptamine by Pictet−Spengler reaction.[17] Alternatively, the tetrahydro-β-carboline can also be prepared from tryptophane by a Bischler−Napieralski reaction followed by reduction. Treatment of tetrahydro-β-carbolines with a suitable oxidant in combination with a hydroxide source results in oxidative rearrangement to the spiro[pyrrolidine-3,3′-oxindole] ring system (Scheme 5).[18]



Scheme 5. Mechanism for an oxidative spiro rearrangement

2.2.1. Halogenating Agents as Oxidants

An early study by Taylor revealed that rhynchophylline (**1**) can be obtained from dihydrocorynantheine in a three-step procedure by oxidative rearrangement using *tert*-butyl hypochloride, via a chloroindolenine intermediate.[19,20] As a consequence, a general relationship between indole alkaloids and their oxindole analogues has been postulated by Shavel and Zinnes.[21] Martin used this method for the oxidation of indoles, where N_b is incorporated in a D-ring lactam. The critical rearrangement of **17** to **18** was achieved by addition of silver perchlorate to initiate rearrangement of the chloroindolenine and led ultimately to pteropodine (**19**) (Scheme 6).[22]



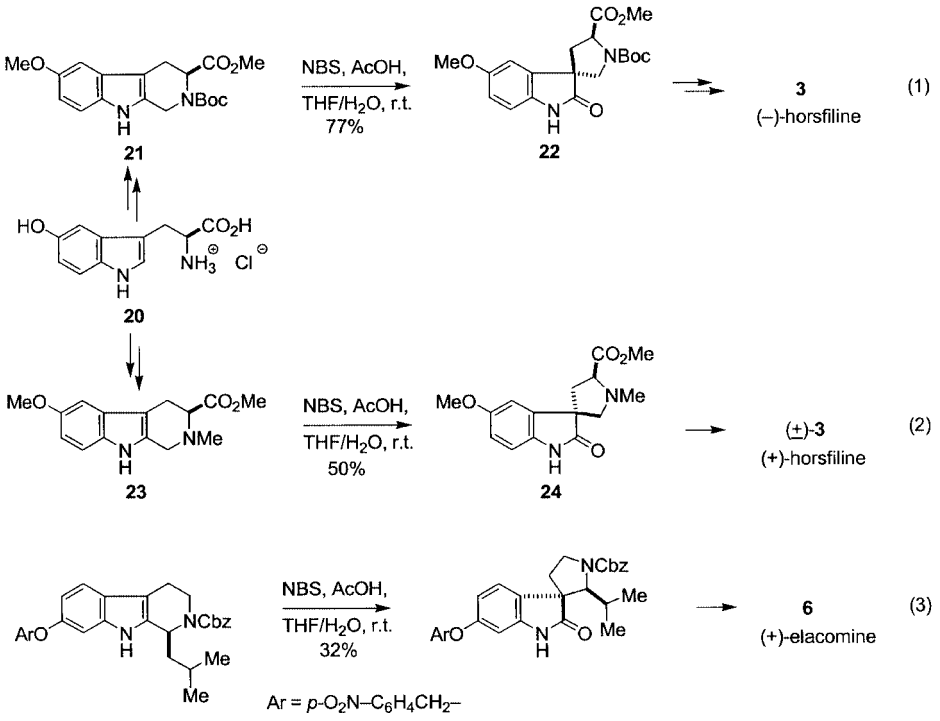
Scheme 6. Hypochloride-induced oxidative rearrangement in Martin's synthesis of pteropodine

The oxidative-rearrangement reaction can also be applied to N_a-hydroxy-tetrahydro-β-carbolines.[23] Cook and coworkers have documented that isomeric spiro[pyrrolidine-3,3′-oxindole] products can be obtained stereospecifically upon reaction of tetrahydro-β-carbolines with *t*BuOCl/NEt_3, followed by treatment with acetic acid. It is interesting to note that the absence or presence of the *N*-benzyl protecting group allows access of alsonisine- or voachalotine-related oxindoles, respectively. It is believed that the diastereoselection is of steric origin.[24]

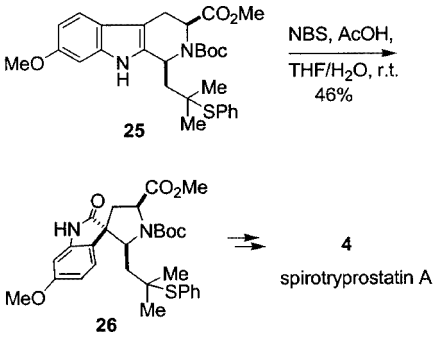
N-Bromosuccinimide (NBS) as oxidant is frequently used instead of *t*BuOCl and was employed in first investigations towards the elucidation of the absolute configuration of horsfiline through the synthesis of both enantiomers of horsfiline by Borschberg. In this context, it was observed that different substituents at the piperidine nitrogen atom led to significant preferences for formation of one diastereomer over the other in the rearrangement reaction. It was therefore preferable to access spiro[pyrrolidine-3,3′-oxindole] **22** from Boc derivative **21**, and **24** from the *N*-methyl derivative **23**. NOE experiments allowed for the structural assignments of the relative stereochemistry of **22** and **24** and thus of the absolute configuration of their reduced counterparts **3** and (+)-**3** [Equations (1) and (2), Scheme 7].[25] Borschberg synthesized (+)-elacomine (**6**) according to the same strategy [Equation (3), Scheme 7].[4]

In Danishefsky's synthesis of spirotryprostatin A (**4**), *N*-Boc-protected tetrahydro-β-carboline **25** was used in the oxidative spiro rearrangement to **26**. Spirotryprostatin A (**4**) was obtained by deprotection of the carbamate, installation of the dioxopiperazine by coupling with *N*-Troc-L-proline and conversion of the tertiary sulfide to the unsaturated prenyl substituent (Scheme 8).[26,27]

In Ganesan's route to spirotryprostatin B (**5**), rearrangement precursor **27** was obtained by Pictet−Spengler reaction. The use of **27**, a tetrahydro-β-carboline already bearing the *N*-Fmoc-L-proline moiety, allowed for the crucial oxidative rearrangement without using unnecessary protec-



Scheme 7. Borschberg's syntheses of (+)-horsfiline, (−)-horsfiline and (+)-elacomine employing an oxidative rearrangement reaction using *N*-bromosuccinimide (NBS)

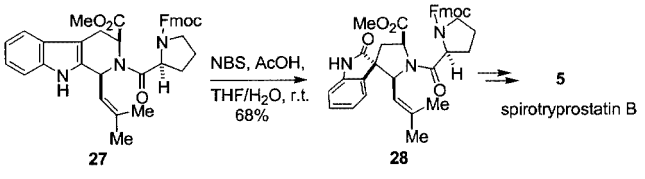


Scheme 8. Oxidative spiro rearrangement in Danishefsky's synthesis of spirotryprostatin A (NBS = *N*-bromosuccinimide)

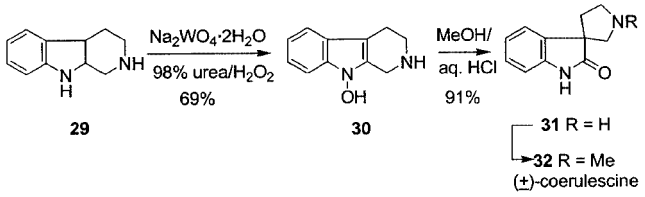
tions and deprotection sequences. Chemoselectivity issues related to the presence of the prenyl olefin were controlled by careful monitoring of the reaction and by avoiding large excesses of NBS. This route allows for the very efficient assembly of **28**, made possible by the direct implementation of prenal in the Pictet−Spengler reaction and the introduction of the L-proline moiety prior to oxidative rearrangement. Unfortunately, selective introduction of the C-8−C-9 double bond after closure of the dioxopiperazine could not be achieved (Scheme 9).[28]

2.2.2. Sodium Tungstate as Oxidant

In 2000, Somei introduced a new oxidant for the synthesis of chloroindolenines that can be rearranged to spiro[pyrrolidine-3,3′-oxindoles]. This method has been applied to the synthesis of (±)-coerulescine (**32**). N_a-Hydroxy-tetrahydro-β-carboline (**30**) was obtained from the corresponding hexahydro-β-carboline (**29**) by oxidation with sodium tungstate (catalytic amount, using urea/hydrogen peroxide as reoxidant). Treatment with concentrated, aqueous HCl in methanol yielded the chloroindolenine, which undergoes rearrangment to **31**. *N*-Methylation completed the synthesis of (±)-coerulescine (**32**) (Scheme 10).[29]



Scheme 9. Ganesan's route to spirotryprostatin B (NBS = *N*-bromosuccinimide)

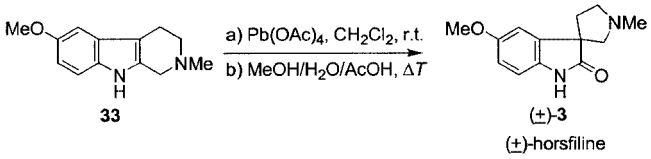


Scheme 10. Two-step oxidative rearrangement of hexahydro-β-carboline (**29**) with sodium tungstate

2.2.3. Lead Tetraacetate as Oxidant

For oxidative rearrangement tetrahydro-β-carbolines to spiro[pyrrolidine-3,3′-oxindoles] lead tetraacetate has first been investigated by Taylor in 1963.[30] Bodo employed this procedure to confirm the structure of (±)-horsfiline [(±)-

3] by oxidation of the N_b-methyl-tetrahydro-β-carboline **33** (Scheme 11).[2] Lead tetraacetate was also used by Borschberg in a model study for the synthesis of (+)-elacomine (**6**).[4]

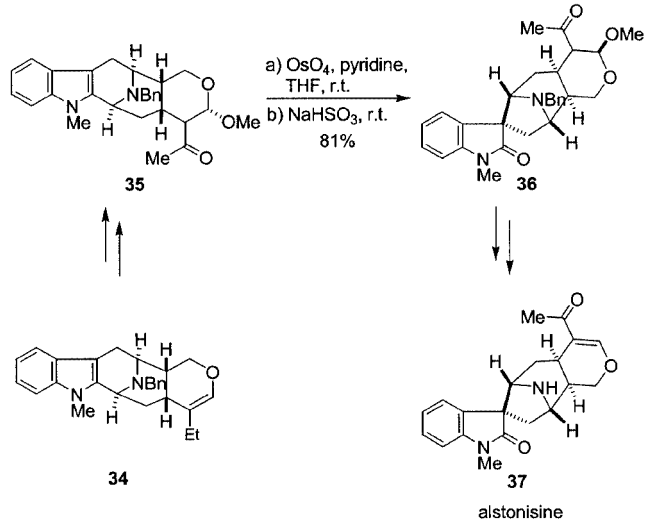


Scheme 11. Confirmation of the structure of (±)-horsfiline

2.2.4. Osmium Tetroxide as Oxidant

Another way to access spiro[pyrrolidine-3,3′-oxindoles] from tetrahydro-β-carbolines employs osmium tetroxide. In 1989, Sakai introduced osmium tetroxide as reagent for the spiro rearrangement according to mechanistic considerations for the selective formation the humantenirine skeleton.[31]

Cook also showed that osmium tetroxide reacts with tetrahydro-β-carbolines selectively to afford a single diastereomer. The osmium atom is probably first complexed to the piperidine nitrogen atom and then dihydroxylation occurs intramolecularly from one face of the substrate. The opposite face of the tetrahydro-β-carbolines undergoes dihydroxylation by the use of bulky ligands such as cinchona alkaloid derivatives DHQ-CLB and $(DHQ)_2PHAL$ ultimately leading to the spiro epimers.[32,33] The key step in the total synthesis of alstonisine by Cook uses an oxidative rearrangement of keto acetal **35** obtained from olefin **34**.[34] The spiro[pyrrolidine-3,3′-oxindole] **36** is obtained as sole diastereomer in 81% yield. The rationale for this selective transformation is the complexation of osmium tetroxide to the piperidine nitrogen atom. The synthesis of alstonisine (**37**) was completed from **36** by deprotection of the N_b atom followed by base-induced elimination of methanol (Scheme 12).[35]

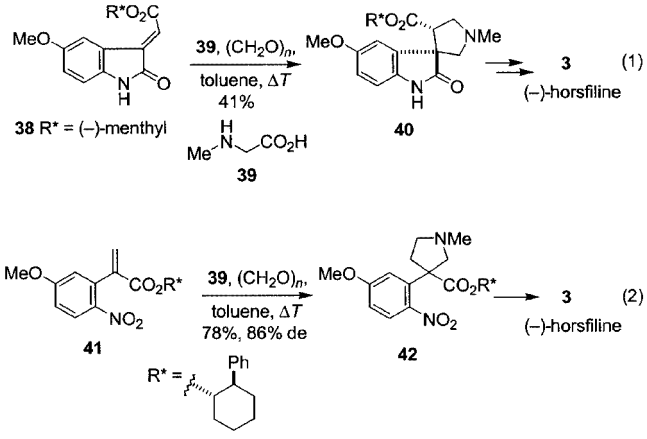


Scheme 12. Osmium tetroxide induced oxidative rearrangement in Cook's synthesis of alstonisine

2.3. Dipolar Cycloaddition Reactions

Grigg was the first to successfully use 1,3-dipolar cycloadditions for a completely different approach to the synthesis of the spiro[pyrrolidine-3,3′-oxindole] skeleton. He reported that *N*-substituted and α,α-disubstituted amino acids react with carbonyl compounds to yield azomethine ylides by decorboxylative transamination. Spiro[pyrrolidine-3,3′-oxindoles] are obtained from the reaction of azomethine ylides with oxindolylidene 3-ylidene acetate.[36] Azomethine ylides obtained from different precursors can also react with oxindolin-3-ylidene dipolarophiles leading to the spiro[pyrrolidine-3,3′-oxindole] ring system.[37]

Palmisano used a 1,3-dipolar cycloaddition as method for the construction of the spiro[pyrrolidine-3,3′-oxindole] system in the context of natural product synthesis. He was able to access (−)-horsfiline (**3**) in five steps from dipolarophile **38**, bearing a chiral auxiliary [R = (−)-menthyl]. Dipolarophile **38** was obtained by Wittig olefination of 5-methoxyisatin. Dipolar cycloaddition with *N*-methylazomethine yilde, prepared in situ from formaldehyde and sarcosine (**39**), yielded **40**. Hydrolysis of the ester and formal decarboxylation afforded (−)-horsfiline (**3**) [Equation (1), Scheme 13].[38]

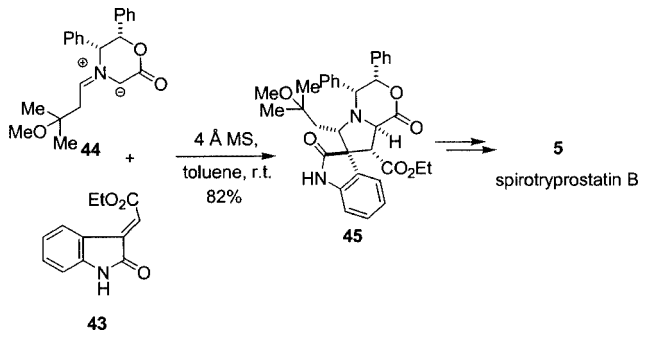


Scheme 13. Synthesis of (−)-horsfiline by dipolar cycloaddition

In his subsequent work, Palmisano employed the [2+3]-cycloaddition with chiral auxiliaries in a more straightforward process on aromatic acrylate **41**, the ester functionality of resulting **42** being ultimately incorporated into the indole core of (−)-horsfiline (**3**) [Equation (2), Scheme 13].[39] Selvakumar prepared (±)-coerulescine (**32**) and (±)-horsfiline [(±)-**3**] using the same key step as in the second-generation synthesis by Palmisano.[40]

A notable recent application of the 1,3-dipolar cycloaddition to the synthesis of spiro[pyrrolidine-3,3′-oxindole] alkaloids is found in the synthesis of spirotryprostatin B (**5**) by Williams. He employed chiral azomethine ylide **44**, which is prepared in situ by addition of 3-methoxy-3-methyl-1-butanal to 5,6-diphenylmorpholin-2-one. Reac-

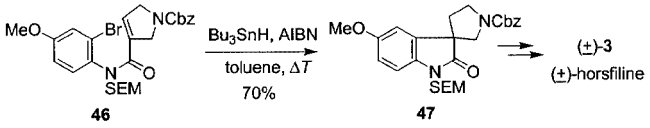
tion with oxindole **43** led to cycloadduct **45** in 82% yield (Scheme 14).[41,42]



Scheme 14. Key transformation in Williams' synthesis of spirotryprostatin B

2.4. Radical Cyclization Reactions

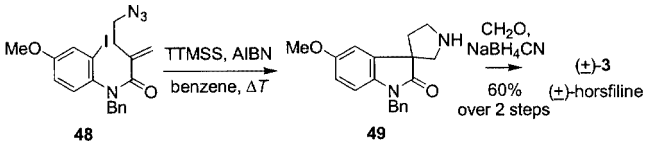
Radical cyclization has also proved successful for the construction of the spiro[pyrrolidine-3,3′-oxindole] nucleus. The synthetic route to (±)-horsfiline [(±)-**3**] by Jones and Wilkinson used a radical reaction as a key step. The precursor **46** for the cyclization reaction was prepared from 2-bromo-4-methoxyaniline and Cbz-protected glycine ethyl ester in a multistep sequence. Protection of the indole nitrogen atom proved important, as radical cyclization of unprotected derivative of **46** led only to reduction and transient TMS protection led to considerable amounts of the undesired product from 6-*endo* cyclization. (±)-Horsfiline [(±)-**3**] is obtained after deprotection of **47** followed by methylation under Eschweiler−Clarke conditions (Scheme 15).[43] Another interesting radical approach by Jones ultimately led to oxindoles with a higher degree of substitution at the pyrrolidine part.[44] Cossy used a very similar approach to access spiro[pyrrolidine-3,3′-oxindoles].[45]



Scheme 15. Synthesis of (±)-horsfiline by radical cyclization (AIBN = 2,2′-azoisobutyronitrile)

Jones also showed that cyclization of pyrrole-derived radical precursors led to the spiro[dihydropyrrole-3,3′-oxinloles] the ring system present in spirotryprostatin B (**5**).[46]

An aryl iodoazide tandem radical cyclization sequence was used for the synthesis of (±)-horsfiline [(±)-**3**] by Murphy. Cyclization of azide **48** with tris(trimethylsilyl)silane (TTMSS) afforded spiro[pyrrolidine-3,3′-oxindole] **49**, which was methylated in situ. (±)-Horsfiline [(±)-**3**] was obtained after deprotection of the indole nitrogen atom. No 6-*endo* product was observed in this reaction (Scheme 16).[47]

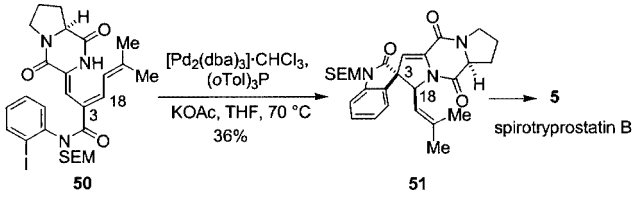


Scheme 16. Synthesis of (±)-horsfiline using an aryl iodoazide tandem radical cyclization [TTMSS = tris(trimethylsilyl)silane, AIBN = 2,2′-azoisobutyronitrile]

2.5. Intramolecular Heck Reactions

The use of the Heck reaction has been pioneered by Overman,[48] and has found application to the synthesis of highly complex spiro-oxindole alkaloids.[49]

Among the synthesis of spiro[pyrrolidine-3,3′-oxindole] alkaloids, Overman's synthesis of spirotryprostatin B (**5**) relies on an asymmetric Heck reaction followed by trapping of an η^3-allylpalladium species by a tethered nitrogen nucleophile.[50] Key intermediate **50** was accessed from a known allylic alcohol in eight steps. Several conditions for the one-pot Heck reaction/η^3-allylpalladium trapping were tested and finally best results were obtained with 10% $[Pd_2(dba)_3]\cdot CHCl_3$, 40% tri-*o*-tolylphosphane and excess potassium acetate in THF at 70 °C, giving a 1:1 mixture of **51** and its isomer (inverse configuration at C-3 and C-18) in combined 72% yield. Cleavage of the SEM protecting group from **51** cleanly provided spirotryprostatin B (**5**). In a first route, where the Heck reaction was carried out with the isomer of **50** bearing the C-3−C-18 (*Z*)-olefin, the stereochemical outcome of the key step could be tuned by using Pd/BINAP and excess PMP in DMA at 100 °C by employing either (*R*)- or (*S*)-BINAP to a 6:1 ratio in either way. This was not possible in the reaction with **50** as temperatures over 80 °C in the presence of excess PMP in DMA led to rapid isomerization of **50** to the isomer of **50** bearing the C-3−C-18 (*Z*)-olefin, leading to formation of the undesired isomers (Scheme 17).



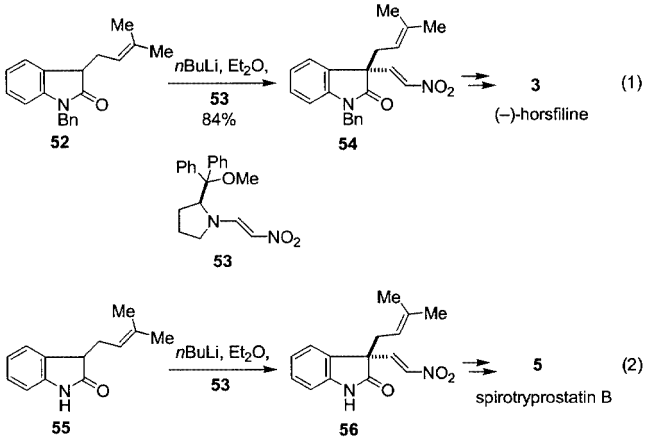
Scheme 17. One-pot Heck reaction/η^3-allylpalladium trapping employed for the synthesis of spirotryprostatin B

2.6. Nitroolefination Reactions

Asymmetric nitroolefination proved a powerful tool for the efficient introduction of the spiro center in spiro-oxindoles. Fuji showed that the enolates can react with chiral nitro enamines to form quaternary carbon centers with high *ee* values through an addition elimination process.[51] This method found application to the synthesis of indole and oxindole alkaloids.[52] It has also been successfully em-

ployed by Fuji for the synthesis of spiro[pyrrolidine-3,3′-oxindole] alkaloids.

Fuji's synthesis of (−)-horsfiline (**3**) is characterized by early introduction of the chiral quaternary center by asymmetric nitroolefination of oxindole **52** with **53**. (−)-Horsfiline (**3**) was obtained after oxidation-state adjustments and functional-group interconversions [Equation (1), Scheme 18].[53]

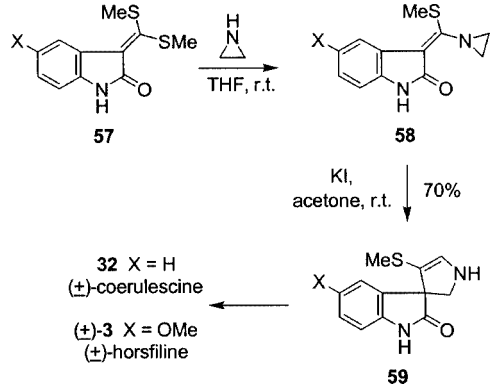


Scheme 18. Syntheses of (−)-horsfiline and spirotryprostatin B by asymmetric nitroolefination

Fuji's synthesis of spirotryprostatin B commenced with chiral precursor **56**, obtained by asymmetric nitroolefination of **55**. Several steps had to be devoted to functional-group and oxidation-state adjustments in order to obtain spirotryprostatin B (**5**) [Equation (2), Scheme 18].[54]

2.7. Rearrangement of 3-[(Aziridin-1-yl)(methylthio)-methylene]-2-oxindoles

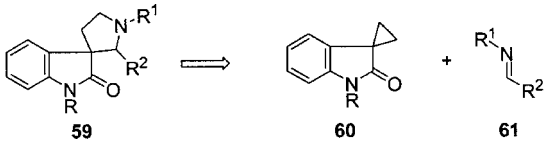
A novel approach to access the spiro[pyrrolidine-3,3′-oxindole] ring system was introduced by Ila and Junjappa in 2001 and applied to the synthesis of (±)-coerulescine (**32**) and (±)-horsfiline [(±)-**3**]. *N*-Vinylaziridine **58**, obtained from **57** upon treatment with an equimolar amount of aziridine, was shown to undergo facile, iodide-induced rearrangement to **59**. From **59**, the natural products can be obtained in a single step by treatment with Raney nickel (W2) in refluxing methanol (Scheme 19).[55]



Scheme 19. Iodide ion induced rearrangement of 3-[(aziridin-1-yl)-(methylthio)methylene]-2-oxindoles

2.8. Magnesium Iodide Catalysed Ring-Expansion Reactions

We envisioned a very direct, alternate bond construction strategy to spiro[pyrrolidine-3,3′-oxindole] ring systems **59**, relying on a cyclopropane-opening/ring-expansion reaction of a spiro[cyclopropane-1,3′-oxindole] (**60**) with an aldimine **61** (Scheme 20).

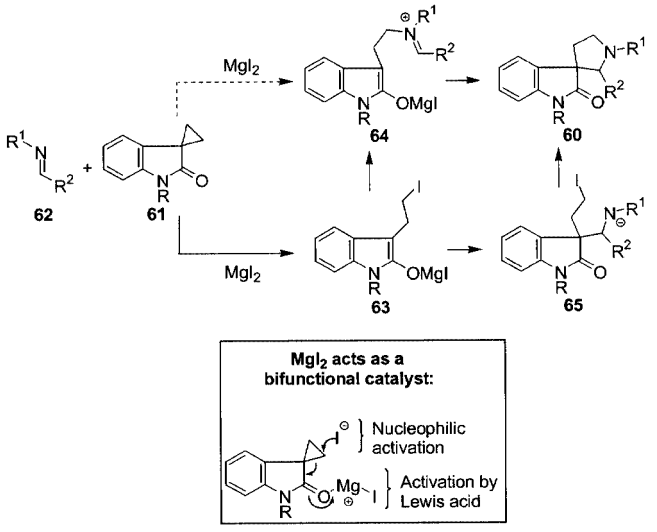


Scheme 20. Ring-expansion reaction of a spiro[cyclopropane-1,3′-oxindole] (**61**) with an aldimine **62**

This strategy would not only present an alternative to existing methods, but also allow for efficient late-stage coupling of two functionalized fragments in a convergent fashion. The charge-affinity pattern of cyclopropanes, when substituted with electron-withdrawing groups, is manifest in their well-known reactivity as homo-Michael acceptors,[56] and complements that of aldimines.[57] Pioneering work by Danishefsky had established the participation of doubly activated cyclopropanes in tandem reactions resulting in ring formation.[58] Generally, only doubly activated cyclopropanes show reactivity, monoactivated cyclopropanes are normally only opened upon nucleophilic attack when these cyclopropanes are found in ring systems which render them particularly strained or occur with strong nucleophiles such as metal selenides.[59] Nickel-catalyzed additions of organoaluminum compounds are also known with monoactivated cyclopropanes.[60] Singly activated cyclopropyl ketones undergo ring opening in reactions with trimethylsilyl halides, reagents combining a potent, oxophilic electrophile with a nucleophile.[61] Our strategy necessitates nucleophilic ring opening of a singly activated ring system by a weakly nucleophilic aldimine. We envisioned that the use of a catalyst exhibiting dual electrophilic and nucleophilic activation would enable the desired reaction, provided competitive intramolecular cyclization (by *O*-alkylation) is precluded.

After much experimentation, we could establish that spiro[cyclopropane-1,3′-oxindole] **61** can undergo ring expansion with imines and afforded the desired spiro[pyrrolidine-3,3′-oxindoles] in THF at elevated temperatures in the presence of a catalytic amount (10 mol %) of magnesium iodide.[62]

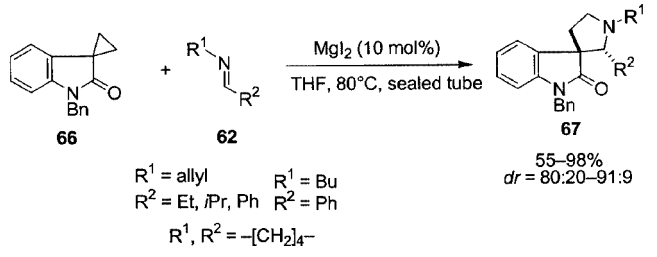
The hypothesized mechanistic pathway is depicted in Scheme 21. Cyclopropane **61** could be opened by one of the two potential nucleophiles present in the reaction mixture: (i) I^- giving rise to enolate **63** or (ii) the imine nitrogen atom leading directly to enolate **64**. We have evidence that the first intermediate of the ring-expansion reaction is enolate **63**.[63] From intermediate **63**, two possible pathways are conceivable: A nucleophilic imine could attack intermediate **63** giving rise to **64**, from which the final product **60** is obtained by cyclization of the iminium species.[64,65] This might be the pathway for *N*-alkylimines. On the other hand, with more electrophilic imines like *N*-arylsulfonyl-protected



Scheme 21. Possible mechanistic pathway for the ring-expansion reaction

imines, the reaction is likely to proceed through adduct **65**, that could close to **60** by *N*-alkylation. Considering these results, it can be concluded that MgI_2 acts as a bifunctional catalyst where both the Lewis acidic metal center (Mg^{II}) and the nucleophilic counter ion (I^-) have to operate in synergy to enable successful ring expansion.

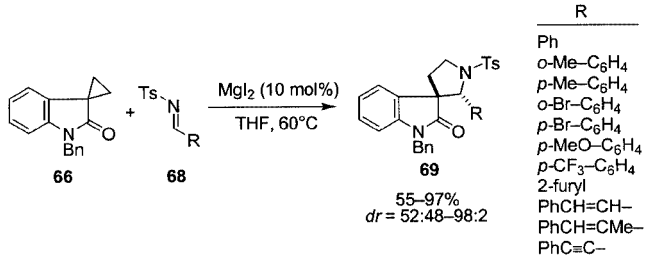
Imines **61** with *N*-aliphatic substituents reacted smoothly with cyclopropane **66** at 80 °C in a sealed tube, yielding the desired products **67** in high yields (55−98%) and with useful diastereoselectivities (80:20−91:9) (Scheme 22).



Scheme 22. Ring expansion of spiro[cyclopropane-1,3′-oxindole] **66** with *N*-aliphatic imines

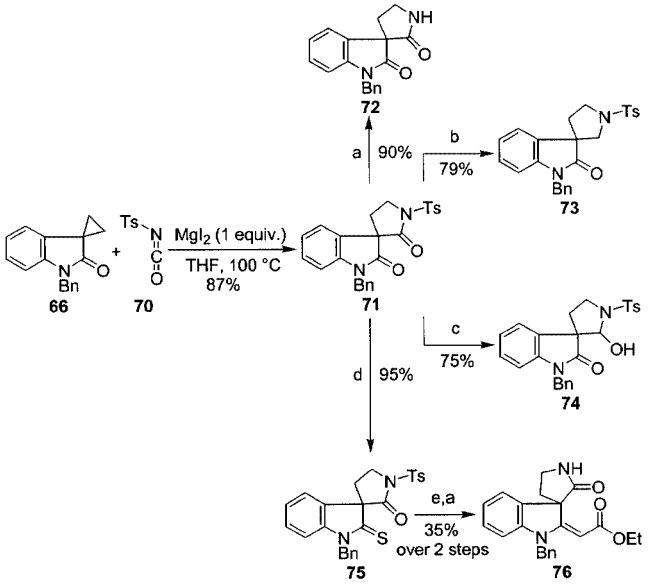
The ring-expansion reaction could also be conducted with imines **68** possessing an *N*-arylsulfonyl protecting group (Scheme 23). The temperature required for the efficient formation of **69** was 60 °C. The observation that the reaction with this substrate, a much weaker nucleophile but stronger electrophile, was found to be even faster hinted at an interesting mechanistic duality (cf. Scheme 20).[66−68]

Tosyl isocyanate (**70**) is also able to react with cyclopropyloxindole **66**, giving pyrrolidinone **71** in good yields. Pyrrolidinone **71** is a valuable synthetic precursor. In the context of these investigations, it was shown that deprotection of the tosyl group to **72** can be accomplished with Na/naphthalene in good yield. Pyrrolidinone **71** can be transformed to spiro[pyrrolidine-3,3′-oxindole] **73** by treatment with sodium borohydride. Reduction of **71** with DIBAL-H



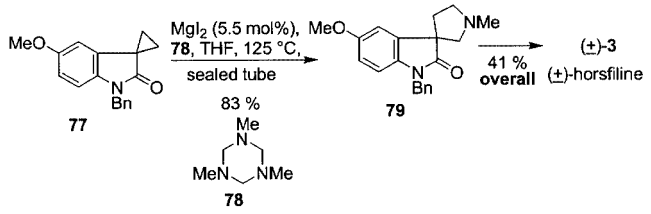
Scheme 23. Ring expansion of spiro[cyclopropane-1,3′-oxindole] **66** with *N*-tosylimines

afforded hemiacetal **74**. Thionoindole **75** was accessed from **71** upon treatment with Lawesson's reagent and could be transformed to ester **76** (Scheme 24).[69]



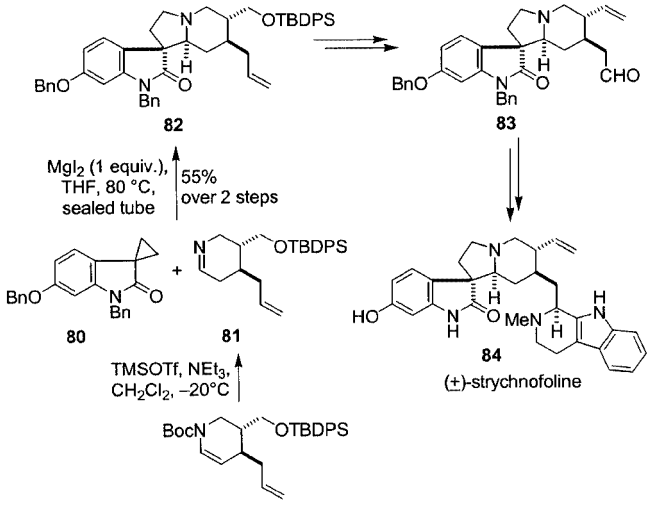
Scheme 24. Ring-expansion reaction of **66** with tosyl isocyanate (**70**) and useful transformations of the resulting pyrrolidinone **71**: a) Na/naphthalene, THF, −100 °C, 2 h; b) $NaBH_4$, MeOH/H_2O/dioxane, Δ*T*, 1 h; c) DIBAL-H, toluene, −78 to +20 °C, 2 h; d) Lawesson's reagent, toluene, 100−110 °C, 3 h; e) $Rh_2(OAc)_4$, ethyl diazoacetate, benzene, 55−65 °C, 36 h

The magnesium iodide catalyzed ring-expansion reaction was first used in our group for the short and efficient synthesis of (±)-horsfiline (41% overall yield, 5 steps). Compound **77**, the starting material for the cyclopropane-fragmentation/ring-expansion reaction was available from 5-methoxyisatin by *N*-benzylation followed by Wolff−Kishner reduction and cyclization with 1,2-dibromoethane. Treatment of **77** with 1,3,5-trimethyl-1,3,5-triazinane (**78**) and 5.5 mol % magnesium iodide in THF at 125 °C in a sealed tube furnished desired spiro[pyrrolidine-3,3′-oxindoles] **79** in 83% yield. Removal of the *N*-benzyl protecting group was achieved by dissolving-metal reduction (Na/NH_3) and afforded (±)-horsfiline [(±)-**3**] in 41% overall yield (Scheme 25).[70]



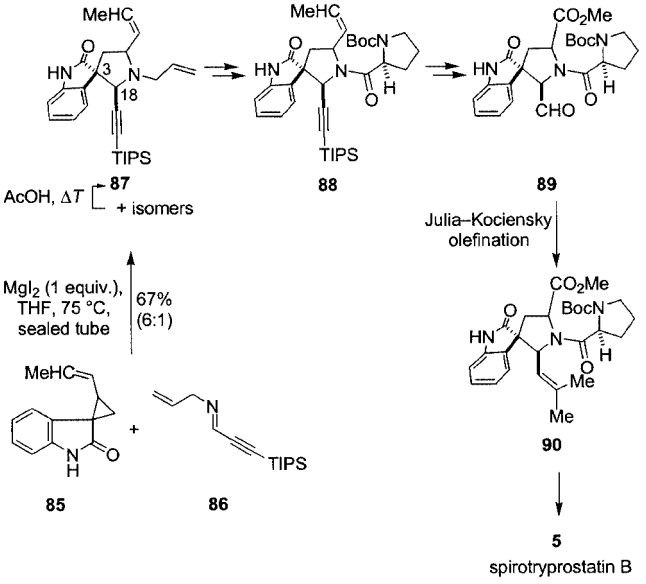
Scheme 25. The magnesium iodide catalyzed ring-expansion reaction of **77** with triazine **78** is the key step in the synthesis of (±)-horsfiline

In the first total synthesis of (±)-strychnofoline (**84**),[71] the magnesium iodide catalyzed coupling of spiro[cyclopropane-1,3′-oxindole] **80** with cyclic imine **81** yielded **82** as a single diastereoisomer. The ring expansion enables the efficient assembly of the key intermediate **82**, which was converted into aldehyde **83** by functional-group interconversions. From **83**, (±)-strychnofoline (**84**) was obtained in two steps through Pictet−Spengler reaction with *N*-methyltryptamine, followed by deprotection of the benzyl protecting groups (Scheme 26).[72]



Scheme 26. First total synthesis of (±)-strychnofoline employing the ring expansion reaction of oxindole **80** with cyclic imine **81**

Our approach to spirotryprostatin B was driven by our interest in the feasibility of using the magnesium iodide catalyzed ring-expansion reaction for the construction of spiro[pyrrolidine-3,3′-oxindoles] with a higher degree of substitution on the pyrrolidine ring. Indeed, when spiro[cyclopropane-1,3′-oxindole] **85**, available from diazooxindole and piperylene by rhodium-catalyzed cyclopropanation, was used in the cyclopropane-fragmentation/ring-expansion reaction with *N*-allylimine **86**, pyrrolidine **87** with the required C-3−C-18 *anti* relationship (*dr* = 6:1) was obtained. The corresponding *syn* isomers were found to be converted into **87** by refluxing in acetic acid. No products arising from *O*-alkylation or from 1,7-addition to the cyclopropane could be observed. In the ensuing synthetic sequence, amide coupling of *N*-deprotected **87** and *N*-Boc-L-proline with concomitant resolution of the racemic material to enantiopure **88** was carried out. The transformation to **89** was accomplished in a short synthetic sequence.[73] Application of the Julia−Kociensky reaction enabled the introduction of the prenyl side chain yielding **90**, from which spirotryprostatin B (**5**) was obtained in a one-pot procedure (Scheme 27).[74]



Scheme 27. Use of the ring-expansion reaction of **85** with imine **86** in the synthesis of spirotryprostatin B (**5**)

3. Conclusion

The development of efficient strategies and synthesis routes to alkaloids incorporating the spiro[pyrrolidine-3,3′-oxindole] ring system has seen increased attention as a result of the important biological activity that these natural products have been shown to display. A number of successful strategies have emerged for the construction the spiro[pyrrolidine-3,3′-oxindole] core which are complementary in providing a diverse set of substitution and stereochemical patterns. The recent syntheses of complex spiro[pyrrolidine-3,3′-oxindole] alkaloids, exemplified by the spirotryprostatins, strychnofoline, and alstonisine certainly attest to the synthetic value of the recent developments in synthetic methodology. The structural and stereochemical complexity of these natural products have challenged synthetic chemists to develop ever more clever strategies for their synthesis. Given the continued breathtaking pace of advances in the area of synthetic methodology which draws from synergistic developments in catalysis (homogeneous and heterogeneous, chemical and biological) and organometallic chemistry, it will certainly be exciting to witness the continuing evolution in the approaches to this class of natural products.

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