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Medicinal Chemistry

Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents

*Chris V. Galliford and Karl A. Scheidt**

antitumor agents · medicinal chemistry · natural products · spirooxindoles · total synthesis

Dedicated to Professor W. Robert Scheidt on the occasion of his 65th birthday

The 3,3′-pyrrolidinyl-spirooxindole unit is a privileged heterocyclic motif that forms the core of a large family of alkaloid natural products with strong bioactivity profiles and interesting structural properties. Significant recent advances in the synthesis of this fused heterocyclic system have led to intense interest in the development of related compounds as potential medicinal agents or biological probes.

1. The 3,3′-Pyrrolidinyl-Spirooxindole Heterocycle in Natural Products

Based on a structural core derived from tryptamine, the spirooxindole alkaloids belong to a family of natural products that were first isolated from plants of the *Apocynaceae* and *Rubiacae* families.[1] The key structural characteristic of these compounds is the spiro ring fusion at the 3-position of the oxindole core, with varying degrees of substitution around the pyrrolidine and oxindole rings. In addition to the interesting molecular architecture and densely functionalized core, several natural products possessing this heterocyclic motif exhibit significant bioactivity (Figure 1). Alstonisine (**1**) was first isolated from *Alstonia muelleriana*,[2] and its biomimetic transformations have been studied by LeQuesne and Garnick.[3] Isolated in 1991,[4] the relatively unsubstituted spirooxindole core of (−)-horsfiline (**2a**) has proven to be a popular target among chemists, with numerous syntheses reported. The related compound coerulescine (**2b**), which possesses an even simpler structure, was isolated in 1998; its synthesis is often reported together with that of horsfiline.[5] Chitosenine (**3**) is another structurally interesting natural product, which exhibits short-lived inhibitory activity of ganglionic transmission in vivo in rats and rabbits.[6]

Strychnofoline (**4**) inhibits mitosis in a number of cell lines including mouse melanoma B16, Ehrlich, and Hepatom HW165.[7] The spirotryprostatins A and B (**5** and **6**) were isolated from the fermentation broth of *Aspergillus fumigatus* and have been shown to

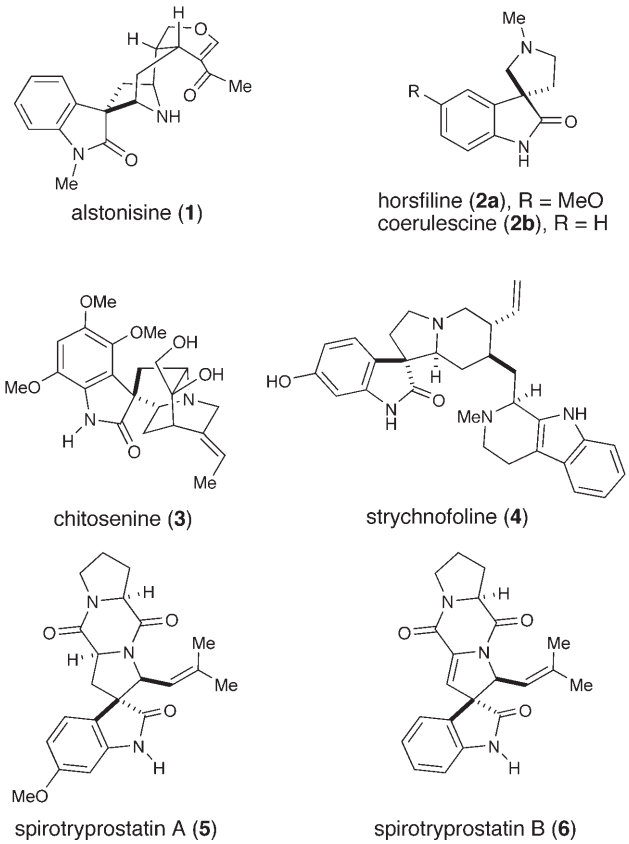


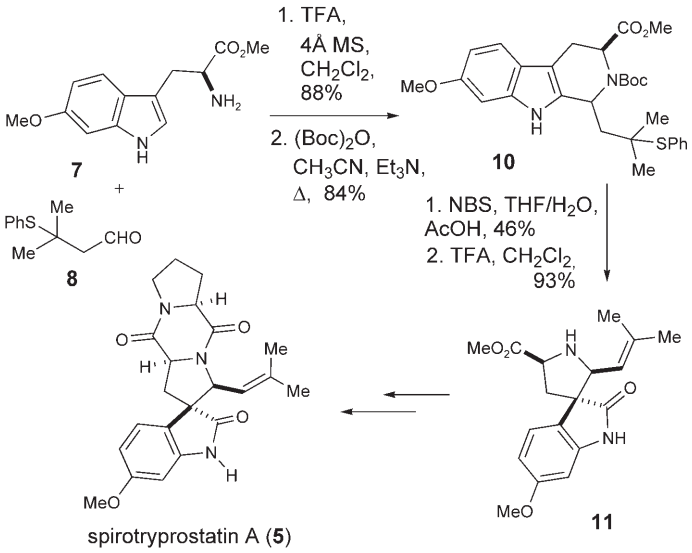
Figure 1. Representative pyrrolidinyl-spirooxindole natural products.

[*] C. V. Galliford, Prof. K. A. Scheidt
Chemistry Department
Northwestern University
2145 Sheridan Road, Evanston IL 60201 (USA)
Fax: (+1) 847-467-2184
E-mail: scheidt@northwestern.edu
Homepage: http://www.chem.northwestern.edu/~scheidt/

completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mg mL^{-1}.[8]

In 2003, Carreira and Marti published a review on the synthesis of natural products containing this fused heterocyclic system.[9] The authors discussed approaches based on intramolecular Mannich reactions,[10,19c] various methods involving the classical oxidative rearrangement of tetrahydro-β-carbolines,[11,19a,b] radical cyclizations,[12] intramolecular Heck reactions,[13] a nitroolefination strategy,[14] a novel rearrangement of 3-[(aziridinyl)(methylthio)methylene]-2-oxindoles,[15] and dipolar cycloadditions,[16] as well as their own MgI_2-catalyzed ring-expansion methodology.[17,20–22] Since this review, several alternative methods have been reported.[18]

These synthetic advances have been fueled by the continued isolation of attractive bioactive molecules possessing this core structure. In particular, the efforts of Carreira, Danishefsky, and Williams towards the synthesis of pyrrolidinyl-spirooxindole natural products such as the spirotryprostatins have generated new strategies to construct these compact alkaloids. In turn, the resulting synthetic methodologies employed and developed by these laboratories have facilitated the synthesis of sufficient quantities of material for biological evaluation, as well as the preparation of analogues for studies on the structure–activity relationship (SAR). These studies represent the first significant efforts to synthesize these natural product analogues and test this attractive heterocyclic system. The promising biological data from these analogues prompts the provocative question: "Can a therapeutic agent or important biological tool be derived from spirooxindole natural products?"



Scheme 1. Danishefsky's synthetic approach to the core of **5**. Boc = *tert*-butyloxycarbonyl, MS = molecular sieves, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid.

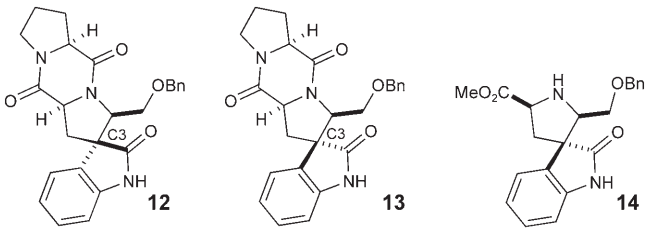
1.1. Danishefsky's Synthetic Approach

In 1998, Danishefsky and Edmonton reported the first total synthesis of spirotryprostatin A using a NBS-promoted oxidative rearrangement of the corresponding β-carboline (Scheme 1).[19a] In 1999, an improved synthesis was reported, utilizing the same NBS-promoted oxidative rearrangement chemistry in the key step. With the synthesis completed, the natural product and several analogues were evaluated using MCF7 and MDA MB-468 human breast cancer cells. Compounds **12**–**14** were clearly superior to the natural product spirotryprostatin A against both cell lines (Figure 2).[19b] Notably, the highly active spirooxindole **14** is prepared in only three steps from commercially available starting materials. Interestingly, the configuration of the spirooxindole's stereogenic center (C3) appears unimportant, given the high activities of epimers **12** and **13**. Compound **12**, lacking both the prenyl group and diketopiperazine portions of the natural product also retains a high level of activity.

The total synthesis of the more active spirotryprostatin B from the Danishefsky group followed in 2000 (Scheme 2).[19c] In this approach, the synthesis featured an intramolecular Mannich reaction between L-tryptophan-derived methyl ester and aldehyde **15**, rather than the oxidative rearrangement strategy they had previously published. This reaction generated a mixture of diastereoisomers, which were separated later in the synthesis. Using this route, spirotryprostatin B could be accessed in batch quantities of 500 mg by means of a five-step sequence. Although these approaches were not

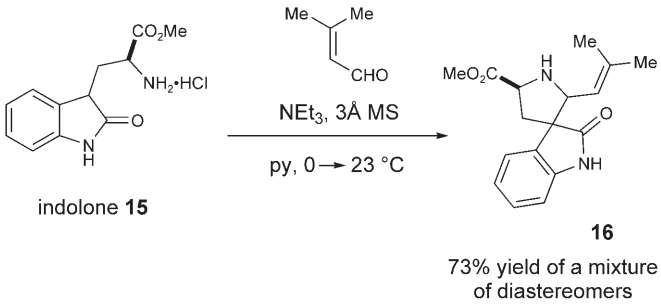
Karl Scheidt was exposed to chemistry at a young age thanks to the influence of his father. He obtained his PhD with William Roush from Indiana University in 1999. After an NIH postdoctoral fellowship under the direction of David A. Evans (Harvard University), he joined the faculty of Northwestern University (Evanston, IL, USA) in 2002. His research focuses on the development of new organic methodology and the synthesis of bioactive molecules. He is a recent Sloan Foundation Fellow and Novartis Lecturer as well as the recipient of awards from Abbott Laboratories, Amgen, AstraZeneca, Boehringer-Ingelheim, and 3M.

Chris Galliford, born in Bridgend, Wales (UK) in 1975, received his bachelor's degree at the University of Manchester. He then pursued a master's degree there under the direction of Jonathan Clayden. After working as a medicinal chemist at RiboTargets Ltd from 2000 to 2002, he joined the laboratory of Karl Scheidt in 2002. He is currently engaged in graduate research focusing on the multicomponent reactions for the synthesis of heterocycles and exploring new methodology using acylsilanes. His doctoral studies have been supported in part by the Elizabeth Tuckerman Foundation.



Anchorage-dependent human breast cancer cell line	5	12	13	14
IC_{50} MDA MB-468	110 μM	25 nM	20 nM	20 nM
IC_{50} MCF7	>>300 μM	10 μM	80 μM	40 μM

Figure 2. Improved performance of synthetic analogues of **5**. Bn = benzyl.



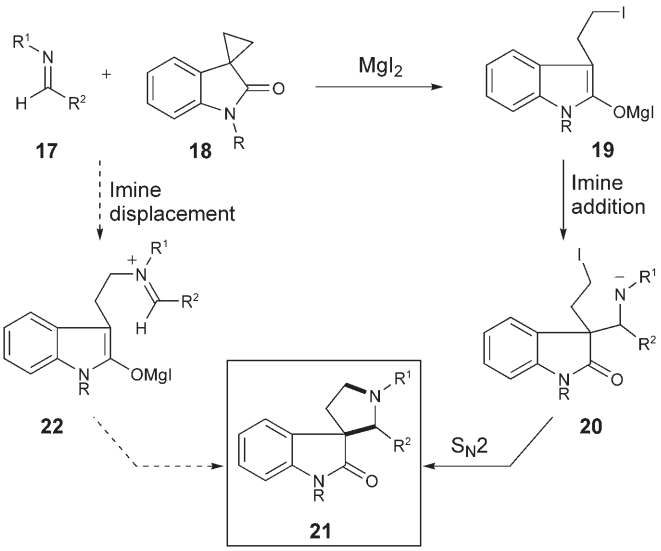
Scheme 2. Danishefsky's synthetic approach to spirotryprostatin B (**6**). py = pyridine.

enantioselective, each route allowed for sufficient quantities to be prepared to allow for both analogue synthesis and biological studies.

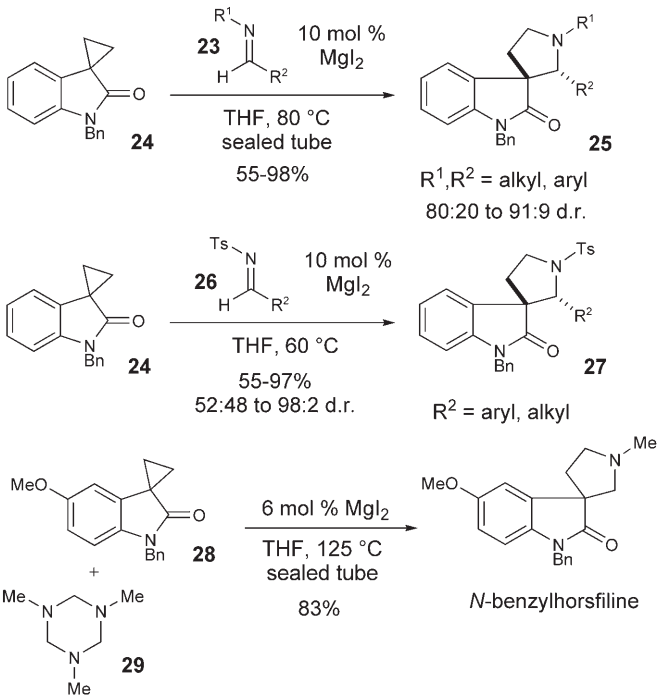
1.2. MgI_2-Promoted Ring Expansion of Cyclopropyloxindolones

Carreira and co-workers have developed a reliable methodology to access the pyrrolidinyl-spirooxindole structure starting from imines and spirocyclopropyl oxindoles.[17,20–22] The dual role of the MgI_2 is proposed to provide Lewis acid activation as well as a nucleophilic counterion to promote the ring expansion. The authors proposed mechanistic pathway is shown in Scheme 3. They suggest that intermediate **19** is the initial product of ring opening, followed by either enolate attack of the oxindole to the imine and subsequent nucleophilic displacement of the iodide to form the pyrrolidine ring (**20** then **21**), or these last two steps in the reverse order. There is some likelihood that the electronic nature of the starting imine may determine the order of these last two steps of the mechanism. The alternative possibility, involving the direct ring opening of the cyclopropane by the imine leading directly to **22**, was judged less plausible by the authors.

The reaction can accommodate several imine precursors and can be employed to produce the pyrrolidinyl-oxindole structure in good to excellent yield with useful levels of diastereoselectivity (Scheme 4). A range of alkyl and aryl



Scheme 3. Carreira's proposed pathway for the MgI_2-catalyzed ring expansion.



Scheme 4. Synthetic utility of the catalytic ring-expansion reaction. Ts = toluenesulfonyl.

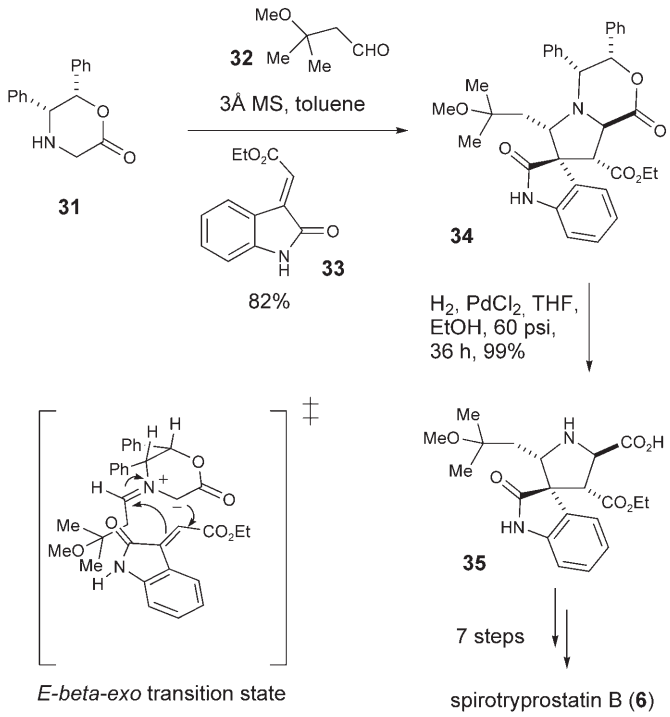
imines, *N*-tosyl imines **26**, and even *N*-tosylisocyanate are compatible substrates;[17] the cyclopropyl unit can also be monosubstituted allowing for significant elaboration in the resulting products.

In addition, the reaction has been used to synthesize a range of natural products by employing modified imine equivalents or more complex imine and appropriately substituted spirocyclopropylindolones in the reaction. The first, and simplest of these total syntheses is illustrated by the bottom reaction in Scheme 4. The synthesis of racemic

horsfiline was executed using trimethyltriazinane (**29**) in just five steps and 41% overall yield using commercially available reagents.[20] Other targets completed using this methodology include strychnofoline (**4**),[21] and spirotryprostatin B (**6**).[22]

1.3. Strategy Based on Asymmetric 1,3-Dipolar Cycloaddition

In their synthesis of spirotryprostatin B, Williams and Sebehar accessed both enantiomers of the target molecule and prepared analogues of the natural products.[23] In their elegant approach, a three-component reaction (3-CR) of morpholinone **31**, aldehyde **32**, and oxindolylideneacetate **33**, is used to construct the spirooxindole core (Scheme 5). The



Scheme 5. Williams's asymmetric 3-CR for the synthesis of spirotryprostatin B.

combination of **31** and **32** generates a chiral azomethine ylide with an *E* geometry which efficiently undergoes [3+2] cycloaddition with dipolarophile **33** affording cycloadduct **34**.[24] The product is formed as a single diastereoisomer in 82% yield with the desired stereochemistry of the natural product. The stereochemical outcome of this reaction was confirmed by single-crystal X-ray analysis, with the authors describing the required geometry of cycloaddition as "*E-beta-exo*" (*E* referring to the ylide geometry, *beta* to the top face of the approach of the dipolarophile, *exo* to the transition state). The removal of the dibenzyl portion of the oxazinone occurred readily to yield amino acid **35**.

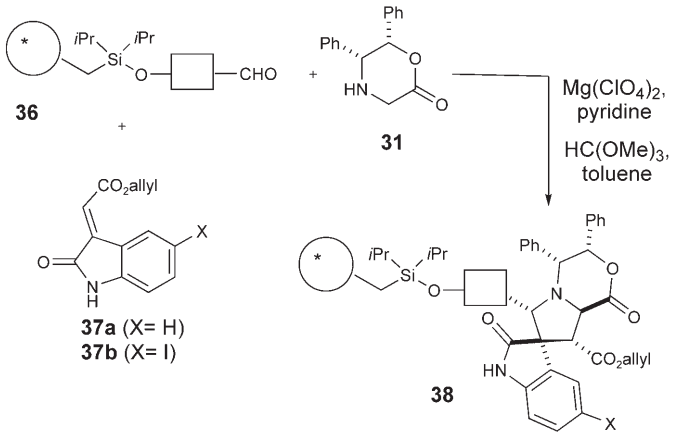
The synthesis was completed in a further seven steps: the diketopiperazine unit was installed by a coupling reaction with D-proline benzyl ester, and the isoprenyl olefin was installed by treatment with TsOH in refluxing toluene (without the formation of other olefin isomers). Finally, the ester group was removed using a three-step sequence involving hydrolysis followed by a modified Hunsdieker reaction to afford (−)-spirotryprostatin B (**6**). In 2003 Williams and co-workers reported the synthesis of spirotryprostatin A (**5**) by a similar route.[25]

2. Schreiber's Approach Based on Diversity-Oriented Synthesis

Schreiber and his group have pioneered "diversity-oriented synthesis" (DOS) as a method of generating small molecules with useful biological properties.[26] The rigid three-dimensional structure of the pyrrolidinyl-spirooxindole core allows for the exploration of neighboring space along a variety of trajectories. Additionally, this architecture is featured in numerous bioactive alkaloids and patented medicinal compounds making it an ideal scaffold for DOS. Schreiber et al. have reported a combinatorial-based approach to the development of active natural product-like compounds for biological evaluation.[27] The stereoselective 3-CR of Williams and co-workers was utilized as the key synthetic operation for generating the pyrrolidinyl-spirooxindole core (Schemes 5 and 6). The Williams 3-CR was particularly attractive for library synthesis, providing a highly convergent approach and allowing for simple diversification of stereochemistry and structure.

The spirooxindole skeleton was assembled in the first step, through a highly diastereoselective cycloaddition using macrobead-supported aldehydes, with either enantiomer of the Williams's chiral auxiliary **31**, and an isatin-derived dipolarophile bearing the allyl ester **37**. The spirooxindoles were then elaborated using building blocks having diverse structural features and compatible functionalities. Initially, Schreiber and co-workers were unable to effect the 3-CR on solid support using the original solution-phase conditions (3-Å molecular sieves, toluene). However, after investigating a range of Lewis acids to promote the reaction, they found $Mg(ClO_4)_2$ to be successful in furnishing the 3-CR products in high purity and excellent diastereoselectivity. The reaction medium was buffered with pyridine to minimize acidic cleavage of the loaded aldehyde from the silicon linker, and molecular sieves were replaced with methyl orthoformate as the dehydrating agent. With these new reaction conditions, the authors chose aromatic aldehydes of various substitution patterns, which afforded good yields and high levels of diastereoselectivity in the range of 72:28 to > 95:5 depending on the starting aldehyde structure.

The desired library was generated by a split–pool solid-phase synthesis.[28] The elaboration reactions were carefully chosen according to their solid-phase efficiency and ability to modify the initial chemical properties of the starting material, such as the number of rotatable bonds or lipophilicity ($c\log P$ value—The $c\log P$ value is the industry standard measure of the lipophilicity of a compound, a key parameter that is used as a guideline for drug development). To elaborate the macrobead-supported heterocyclic core, the feasibility of the following three synthetic operations was evaluated:



Entry	Aldehyde	Dipolarophile	Conv. [%]	d.r.
1	36a	37a	89	88:12
2		37b	89	>95:5
3	36b	37a	>95	>95:5
4		37b	>95	>95:5
5	36c	37a	>95	>95:5
6		37b	>95	>95:5
7	36d	37a	>95	91:9
8		37b	94	92:8
9	36e	37a	>95	77:23
10		37b	>95	72:28
11	36f	37a	>95	82:18
12		37b	>95	85:15

Scheme 6. Schreiber's preliminary rendering of the macrobead 3-CR.

a) palladium-catalyzed carbon–carbon bond formation with concomitant allyl ester cleavage;
b) amide formation between the resultant carboxylic acid with amines; and
c) N acylation of δ-lactams with electrophiles.

The authors found Sonogashira coupling with aryl iodospirooxindoles to be the most reliable, and the alkynes shown in Figure 3 were found to be proficient coupling partners and were employed in the elaboration studies. High catalyst loadings of palladium and copper were used to ensure reliable coupling on the solid support. The authors took great care to remove excess metal reagents by using glyoxal bis(thiosemicarbazone) as a metal scavenger.

On solid support, the amide-coupling conditions using PyBOP/$(i\text{Pr})_2$NEt were consistently effective (Scheme 7). Finally, three electrophiles from a panel of isocyanates and chloroformates were identified for the N acylation, with optimal conditions showing a strong dependency on the electrophile used.

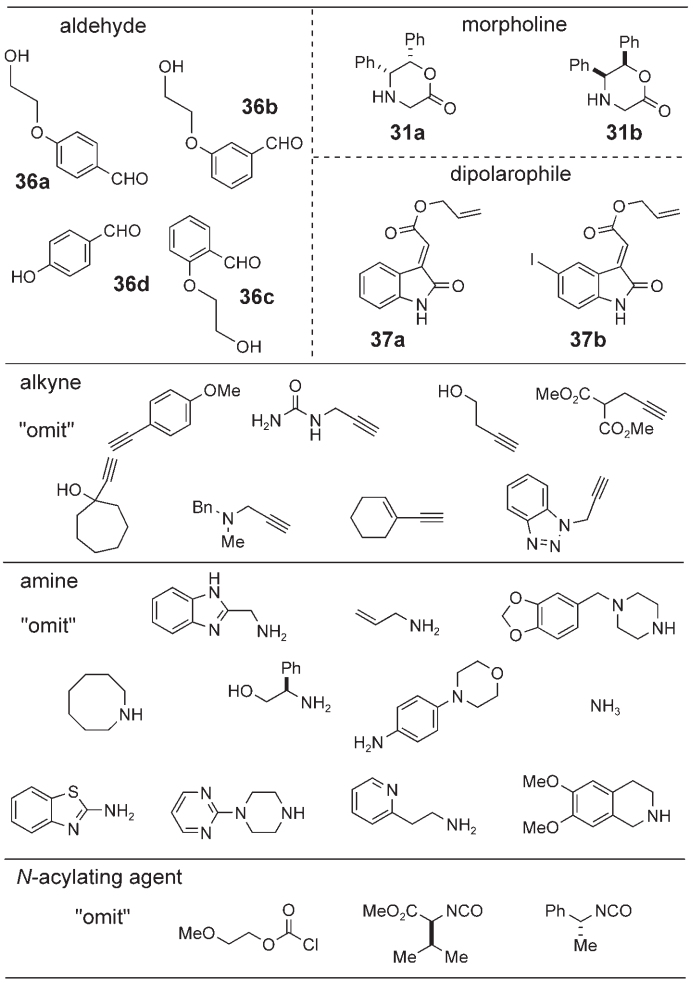
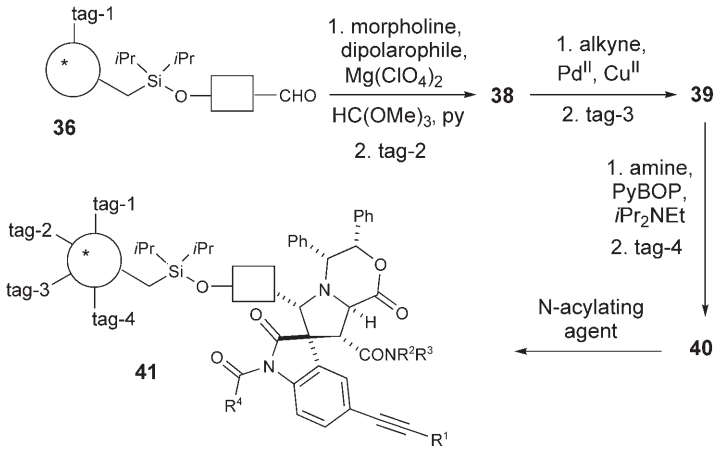


Figure 3. Diversity elements used in Schreiber's elaboration of the 3-CR template.

With the three candidate diversification reactions chosen and validated, the library synthesis was executed. Starting from solid-supported aldehydes, a Lewis acid mediated 3-CR was performed with 4 aldehydes, 2 morpholinones, and 2 dipolarophiles to yield 16 spirooxindole cores. Each diversification operation was accompanied by a tagging step for later decoding of the beads.[29] The sequence of reactions for the eight cores containing the aryl iodide is given in Scheme 7.

Over 3000 compounds were generated from this sequence of reactions. The sequence of reactions for the eight cores lacking the aryl iodide were as follows: a) ester cleavage ("omit" + deprotection); b) amidation ("omit" + 11 amines); and c) N acylation ("omit" + 3 N-acylating reagents). An additional 416 members were generated using this sequence, leading to a total of 3520 theoretical compounds. The selection of different building blocks was based on factors aimed at maximizing diversity (e.g. functional groups, heterocycles, degree of substitution) and on calculations to diversify the *c* log *P* values of the library members. To verify the success of the approach, thirteen library compounds—with each building block represented at least once—were randomly selected for synthesis on the macrobead support, and full characterization data was obtained.



Scheme 7. Schreiber's library scaffold-diversification strategy. PyBOP = 1-benzotriazolyloxy-tris(pyrollidino)phosphonium.

With robust and proven conditions in hand, split–pool synthesis was used to construct the library. The four aromatic aldehydes **36** (Figure 3) were loaded onto the solid support.[30] Encoding difficulties associated with two of the building blocks were encountered during the library's development. The beads from these two reactions were separated and the remaining synthetic operations performed in parallel. As a result of this change, the number of library members was reduced to 3232.[31]

The authors then employed a chemical genetic modifier screen to search for bioactive compounds. An assay was developed to identify enhancers of the growth arrest induced by latrunculin B, a natural product that sequesters monomeric actin and prevents the formation of actin microfilaments.[32] The initial screen was performed in 384-well plates using wild-type yeast growing in a nutrient-rich medium. Latrunculin B was added to a final concentration of 7 μM, followed by pin transfer of library stock solutions to a final concentration of approximately 33 μM. A total of 36 compounds were then scored as enhancers, based on a comparison of the observed growth in the assay wells to that in control wells lacking library members. Two building blocks, aldehyde **36d**, and the (5*R*,6*S*)-morpholinone **31**, were strongly represented in the positive results. Compound **42** was chosen for resynthesis and tested further (Figure 4).

For these assays, the amount of latrunculin B was reduced to 1.0 μM, which is 12.5% of the experimentally determined EC_{50} value. At this concentration, latrunculin B has no observable effect on yeast growth. When **42** was added to this same medium, the inhibitory effect of latrunculin B was enhanced. The EC_{50} value for **42** was determined to be 550 nM. As a control experiment, yeast cells were treated with **42** alone, up to the solubility limit of 30 μM, and yeast growth was unaffected. This experiment shows that **42** does not show the same phenotype as latrunculin B and that it is only lethal in tandem with latrunculin B.

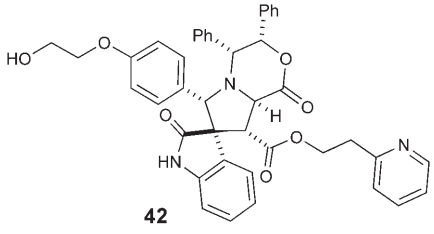


Figure 4. Schreiber's lead compound.

From the biological screening, spirooxindole **42** is interesting in terms of its synergistic activation of latrunculin B's actin polymerase inhibition. However, Schreiber notes that the future for this compound as a potential molecular therapeutic is unpromising. The four-step library synthesis is significant since the exercise clearly establishes that natural product inspired compounds made in parallel can drive a medicinal or chemical biology program when efficient synthetic methods are in place.

3. Structure-Based Design of Potent MDM2 Inhibitors

Wang and co-workers have employed a structure-based-design approach toward the development of a non-peptide-based small-molecule inhibitor of the interaction between the tumor suppressor p53 and its regulatory protein MDM2.[33] As a starting point, the authors used the known structure of the p53–MDM2 complex, which has been established by X-ray crystallographic studies. Furthermore, the crystal structure reveals that the interaction between p53 and MDM2 is primarily mediated by three hydrophobic residues (Phe19, Trp23, and Leu26) of p53 and a small and deep hydrophobic cleft in MDM2.[34] The authors envisaged this hydrophobic cleft to be an ideal site for designing small-molecule MDM2 inhibitors that can block the p53–MDM2 interaction. In p53, the indole ring of the Trp23 residue of p53 is buried deeply inside a hydrophobic cavity in MDM2 (Figure 5). As a hydrogen bond is formed between the amino group and a backbone carbonyl in MDM2, Trp23 appears to be the most critical residue for binding of p53 to MDM2. The authors targeted this key interaction for their structure-based design of a small molecule that can mimic the interaction of Trp23 with MDM2.

Initially, a substructure search led to the key observation that the oxindole core structure is a potential replacement for the tryptophan residue. The authors then went on to identify the bioactive natural products spirotryprostatin A (**5**) and alstonisine (**1**), which both contain a spirooxindole core structure (Figure 6). With these structures as a starting point, the authors undertook computational modelling studies and determined that these compounds fit poorly into the MDM2 pocket because of steric hindrance. Despite this initial setback, the heterocyclic core structure was used as the scaffold from which to develop other potential MDM2 binders.

The next key insight was that the oxindole can closely mimic the Trp23 side chain in p53 in both hydrogen-bonding formation and hydrophobic interactions with MDM2. Addi-

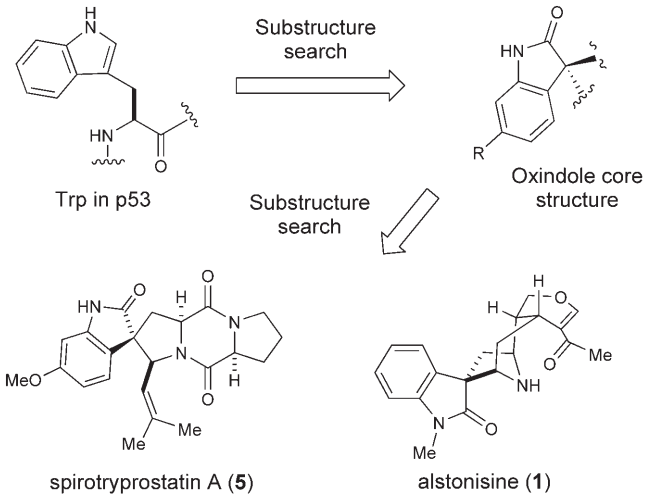


Figure 5. Rational structure-based approach by Wang and co-workers.

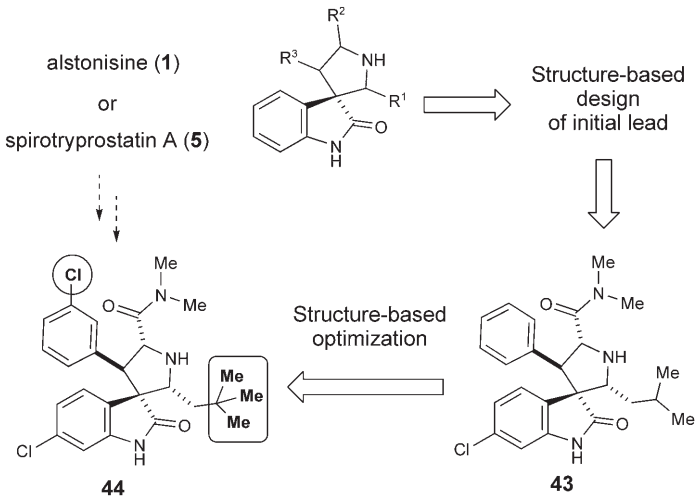


Figure 6. Development and optimization of a potent MDM2-binding compound.

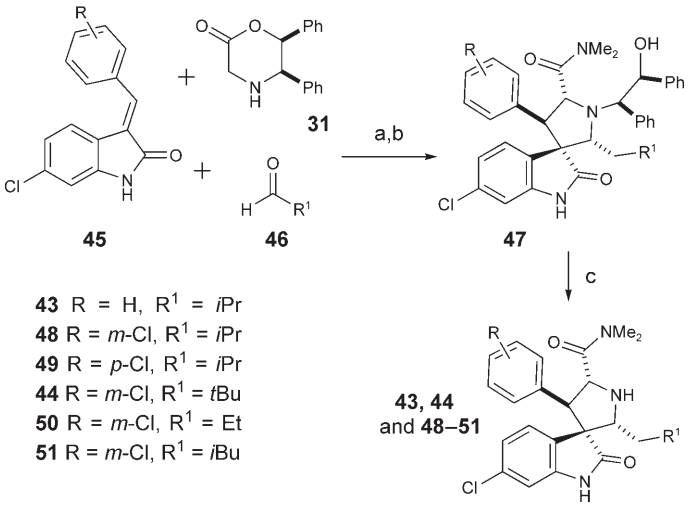
tionally, the spiropyrrolidine ring could provide a rigid scaffold from which two hydrophobic groups can be projected to mimic the side chain of Phe19 and Leu26. Candidate compounds using different substituents with different structural configurations were computationally docked into the MDM2 binding cleft. The oxindole ring of **43** bears a chloro substituent designed to occupy a second, smaller hydrophobic cavity in MDM2. The docking studies clearly showed that spirooxindole **44** could closely mimic p53 in its interaction with MDM2 (Figure 6).

An enantioselective approach based on the methodology of Sebehar and Williams afforded optically active compound **43** for biological studies. Using a fluorescence polarization (FP) based binding assay, Wang and co-workers established the in vitro efficacy of **43** as an MDM2-p53 inhibitor. The assay uses a p53-based peptide labeled with a fluorescent tag and a recombinant human MDM2 protein. The peptide has a high affinity for MDM2, (K_d value of 1 nM). As compound **43** has a K_i value of 8.46 μM in the FP-based assay, it compares well to a natural p53 peptide (16–27 residues), which was determined to have a K_i value of 1.52 μM in the binding assay. Thus spirooxindole **43** showed considerable promise as a lead compound.

Additional detailed analysis of the predicted binding model of **43** to MDM2 suggested the possibility of further refinement of the lead structure. Specifically, the authors observed that the phenyl ring occupies a hydrophobic binding pocket normally for the side chain of Phe19 and the isobutyl group almost fills the hydrophobic binding pocket for Leu26. However, for both of these hydrophobic interactions, additional space was available in the respective cavities. Thus, more analogues of lead compound **43** were specifically designed to further probe the interactions at these two hydrophobic binding sites (Scheme 8).

Guiding the synthesis were the results of the modeling studies that predicted two minor modifications of the core structure **43** would lead to occupation of the additional space in the binding site. A chlorine atom at the *meta* position to the phenyl ring of **43** was introduced to improve the established hydrophobic interaction. Additionally, compound **47** (with an *meta*-Cl substituent) was synthesized and found to have a K_i value of 300 nM—28 times more potent than earlier compound **43**. To further confirm the modeling study's predictions, **49** with a *para*-Cl substituent was synthesized and found to be 26 times less potent than **48** with a K_i value of 7.68 μM.

Addressing the isobutyl group in **43** next, Schreiber et al. further optimized the hydrophobic interaction at this site using **48** as the template. Again modeling studies served as the basis for predictions, and the isobutyl group was replaced with a neopentyl group ($R^1 = t$Bu) in an effort to enhance the hydrophobic interaction (Figure 7). The resulting compound **44** had a K_i value of 86 nM in the FP-based assay, 98 times more potent than the initial lead



Scheme 8. Modified Williams 3-CR for synthesis of p53–MDM2 inhibitors. Reagents and conditions: a) 4-Å MS, toluene, 70°C; b) dimethylamine; c) $Pd(OAc)_2$, CH_2Cl_2/MeOH (1:1), 0°C.

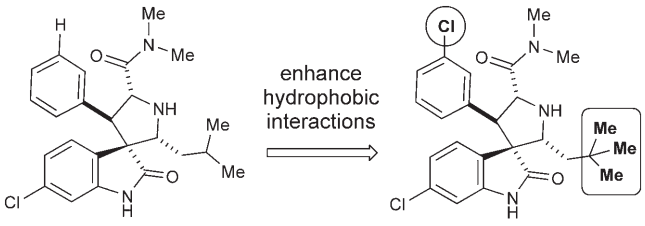


Figure 7. Lead compound **43** and optimized MDM2 inhibitor **44**.

compound **43**. To further affirm the relevance of the hydrophobic interaction at this site, the authors synthesized **50** and **51** with a hydrophobic group smaller and larger, respectively, than that in **44**. The prediction both **50** and **51** should be less potent than **44** was proven to be correct by FP-based binding experiments, which showed that **50** and **51** with K_i values of 0.65 and 0.39 μM, respectively.

A disadvantage of peptide-based MDM2 inhibitors over non-peptide inhibitors is their inferior cell permeability. Thus non-peptide-based alternatives are popular and attractive targets.[35] Wang's MDM2 inhibitors were evaluated in p53-containing wild-type LNCaP human prostate cancer cells for their ability to inhibit cell growth.[36] Spirooxindole **44** is a highly effective inhibitor of cell growth in this tumor cell line with an IC_{50} value of 830 nM. In contrast, structurally related compounds **43** and **48**, **49**, **50**, and **51** inhibit cell growth of LNCaP cells with IC_{50} values of 9.7, 2.1, 6.7, 2.7, and 1.9 μM, respectively.

In a second series of experiments, the selectivity of these compounds was then evaluated in human prostate cancer cells lacking p53 (PC-3). In these cells, spirooxindole **44** is less potent with an IC_{50} value of 22.5 μM. This observed selectivity is consistent with the inhibitor design targeting p53 since the PC-3 inhibition for heterocycle **44** is 27 times less than against LNCaP cells which express wild-type p53. Another key result is the relative toxicity of these MDM2 inhibitors towards normal cells with wild-type p53. The authors evaluated compound **44** in normal human prostate epithelial cells with wild-type p53 and determined that it has an IC_{50} value of 10.5 μM for inhibition of cell growth, 13 times less toxic than for LNCaP cancer cells.

In a subsequent publication, Wang et al. further optimized the binding affinity of spirooxindole **44** to MDM2 from K_i = 86 nM to 3 nM by further investigation of the binding mode of their compounds when "docked" to MDM2 using computation methods (Figure 8).[37] The authors also conducted a head-to-head comparison of the binding efficacy of the most potent non-peptide-based inhibitor of the p53–MDM2 interaction (termed nutlin-3) with their own first- and second-generation compounds (Figure 8).[38] From this analysis, it is clear that the second-generation optimized structure **52** is significantly more potent than nutlin-3. Spirooxindole **52** was found to have a K_i for binding to MDM2 of 3 nM (compared to 36 nM for that of nutlin-3). However, nutlin has been optimized to address pharmacokinetic criteria beyond specific binding to a target, and these practical challenges to new potential therapeutics such as **52** still remain.

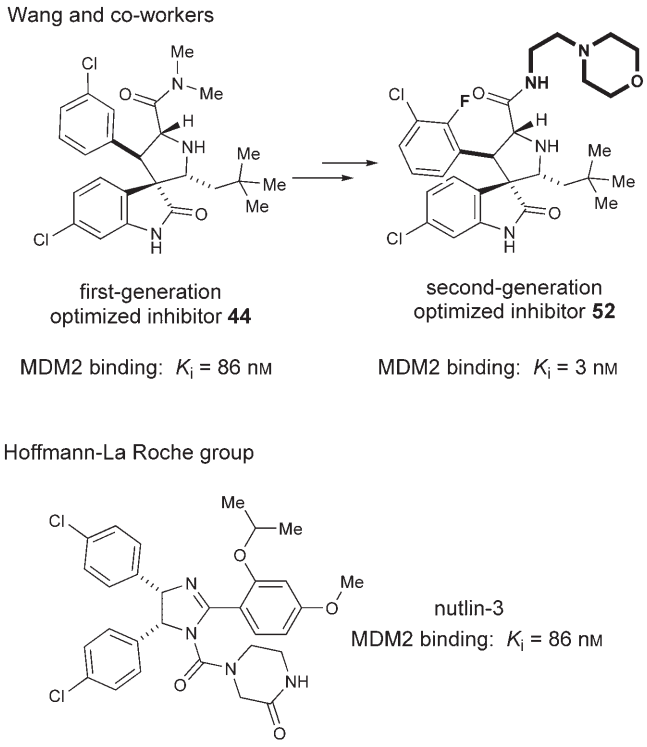


Figure 8. Non-peptide-based p53–MDM2 inhibitors.

The two optimized compounds were also evaluated for their potency of cell-growth inhibition. Prostate cancer LNCaP cells with wild-type p53 were again used for comparison, and spirooxindole **52** once again outperformed nutlin-3 with IC_{50} values of 280 nM and 1500 nM, respectively. Significantly, compound **52** retains selectivity in terms of cellular specificity, with an IC_{50} value of 18 μM in human prostate cancer PC-3 cells with deleted p53. This result also suggests that spirooxindoles **44** and **52** have the same mode of action.

4. Conclusion

Bioactive pyrrolidinyl-spirooxindole natural products such as spirotryprostatin B (**6**) and strychnofoline (**4**) have provided impetus for significant progress in the synthesis of this class of heterocycle. These new methods have led to the development of analogues that are often more efficacious and selective than the natural products themselves.

In two distinct approaches the research groups of Schreiber and Wang have attempted to capitalize on the fusion of facile and expedient analogue synthesis with the promising biological potential of this privileged heterocyclic structure. Schreiber's collection of over 3000 natural-product-inspired compounds represents a significant synthetic achievement and led to the identification of a compound that enhances the inhibitory efficacy of latrunculin B towards actin polymerase.[39] Additionally, this work resulted in several significant synthetic advances, namely the development of a sufficiently robust synthesis of a large family of

analogues using a solid-phase variant of the Williams 3-CR. Attaining sufficiently high levels of diastereoselectivity to retain the structural integrity of the library members is particularly noteworthy, although the potential of **42** as a therapeutic agent is somewhat limited. An analogous library of related bioactive compounds, furanyl spirooxindoles featuring silyl group substituents, has recently been reported by Schreiber and co-workers.[40]

Wang's rational design paid high dividends owing to the insightful computational studies combined with the authors' intuition for analogue synthesis and testing. They have successfully completed the first and second generation of a structure-based design of a novel class of potent, non-peptide small-molecule MDM2 inhibitors to target the p53–MDM2 interaction. This pathway has proven to be a popular research area and several classes of compounds have been reported, however, the spirooxindole-derived compounds are as promising as any of the other non-peptide-derived compounds.[41,38b] Additionally, the known mode of action and selectivity profile alludes to significant potential for further development as an anticancer agent.

Both Schreiber's and Wang's synthetic programs relied on a modified, stereoselective Williams 3-CR as the key synthetic tool for the production of candidate lead compounds. The many noteworthy advances in synthetic methods for the construction of the privileged pyrrolidinyl-spirooxindole core have driven the rapid access to of highly promising lead compounds worthy of further study and development. Continued research towards the synthesis of additional privileged natural products will undoubtedly make these approaches more common. By drawing inspiration from bioactive natural products in the manner summarized herein, scientists may indeed be able to obviate the traditional hit-to-lead stage of medicinal and chemical biology programs.[42]

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