ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

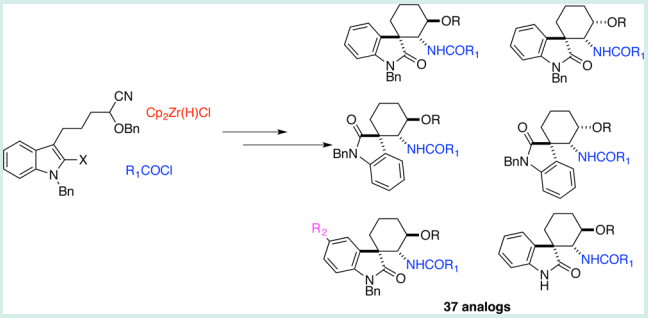
# Construction of a Spirooxindole Amide Library through Nitrile Hydrozirconation-Acylation-Cyclization Cascade

Matthew G. LaPorte,*[,†] Sammi Tsegay,[†] Ki Bum Hong,[†] Chunliang Lu,[†] Cheng Fang,[‡] Lirong Wang,[‡] Xiang-Qun Xie,[‡] and Paul E. Floreancig*[,†]

[†]Department of Chemistry, Chemical Methodologies and Library Development, and [‡]Department of Pharmaceutical Sciences, School of Pharmacy, Computational Chemical Genomics Screening Center, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

**ABSTRACT:** A library of spirooxindoles containing varied elements of structural and stereochemical diversity has been constructed via a three step, one pot nitrile hydrozirconation-acylation-cyclization reaction sequence from common acyclic indole intermediates. The resulting library was evaluated for novelty through comparison with MLSMR and Maybridge compound collections.




**KEYWORDS:** *nitrile hydrozirconation-acylation-cyclization cascade, spirooxindoles*

## INTRODUCTION

The 2-oxindole motif has proven to be a valuable functionality as witnessed by the marketed pharmaceutical agents Sutent (anticancer), Requip (Parkinson's disease), and Zeldox (schizophrenia and bipolar disorder).[1] This interesting heterocyclic core is contained in numerous biologically active spirocyclic-containing natural products such as rychnophylline, gelsemine, and spirotryprostatin B (Figure 1). These and many other spirooxindoles have received significant attention from synthetic and medicinal chemists resulting in many elegant synthetic approaches originating primarily from isatins and derivatives.[2−4]

Recognition of these factors has led several groups to assemble diversely substituted chemical libraries upon these heterocyclic scaffolds (Figure 2),[5] and interest persists in developing new synthetic strategies to construct these important heterocyclic structures. We recently reported a stereoselective approach to amide containing spirooxindoles through a nitrile zirconation, acylation, and cyclization cascade process.[6] This manuscript will detail the assembly of a uniquely substituted library of spirooxindoles using this convenient methodology. A chemical diversity analysis will be provided through structural comparison with the MLSMR compound collection.

## RESULTS AND DISCUSSION

Our approach began with the preparation of the pivotal 2-chloro- and 2-triisopropylsiloxyindoles (**3{1}** and **3{2}**, respectively) that contain the pendant cyanohydrin-benzylether functionality (Scheme 1).[6]

Hydrozirconation of nitriles **3{1}** and **3{2}** using freshly prepared Schwartz' reagent ($Cp_2Zr(H)Cl$) provides metallo-imine intermediates that undergo acylation upon treatment with hydrocinnamoyl chloride (Scheme 2).[7] The resulting spirooxindoles are produced via Friedel−Crafts cyclizations with the indole-2-substituent providing the conformational control. In these cases, the less sterically hindered 2-chloro indole substrate adopts a pseudoaxial conformation (**I**), whereas larger moieties such as the triisopropylsiloxy group prefer pseudoequatorial orientation (**II**).

The hydrozirconation-acylation-cyclization cascade of **3{1}** and **3{2}** affords spirooxindoles **4** and **5** bearing versatile functionalities

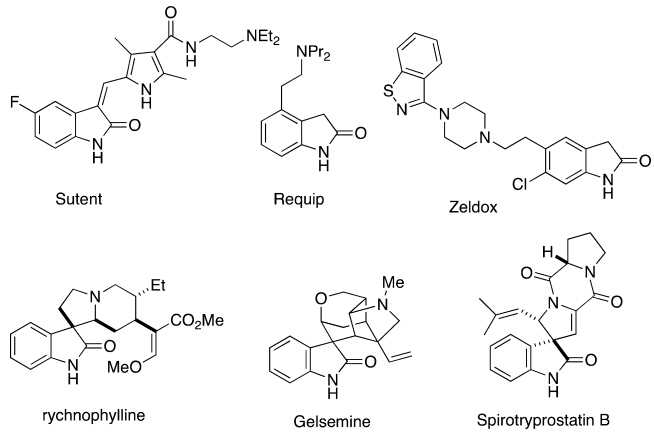



**Figure 1.** Oxindole marketed drugs and spirooxindole natural products.

**Received:** April 23, 2013
**Revised:** May 30, 2013
**Published:** June 3, 2013

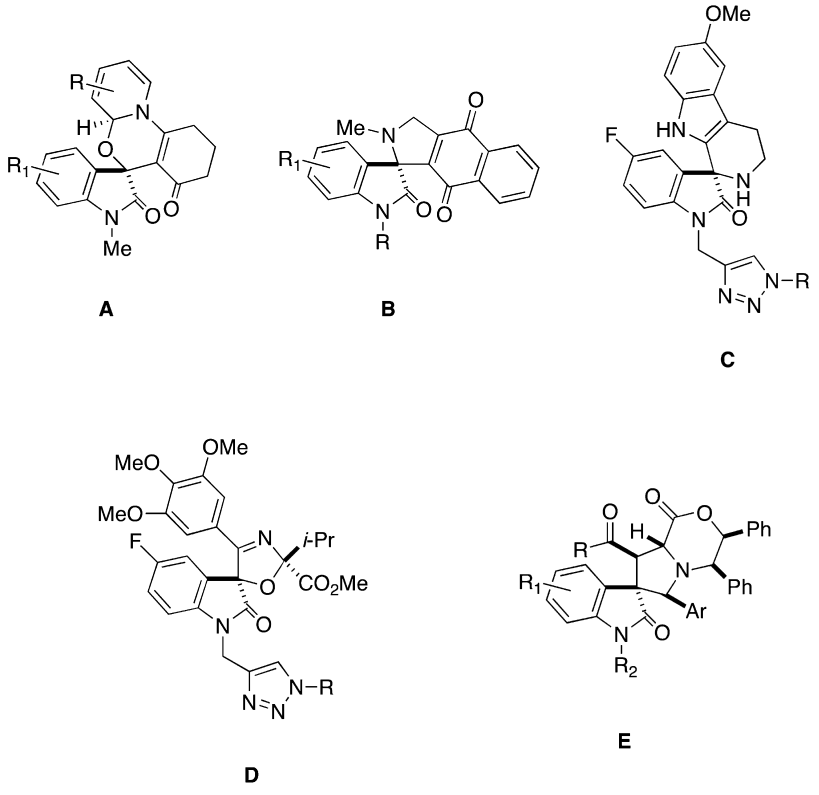
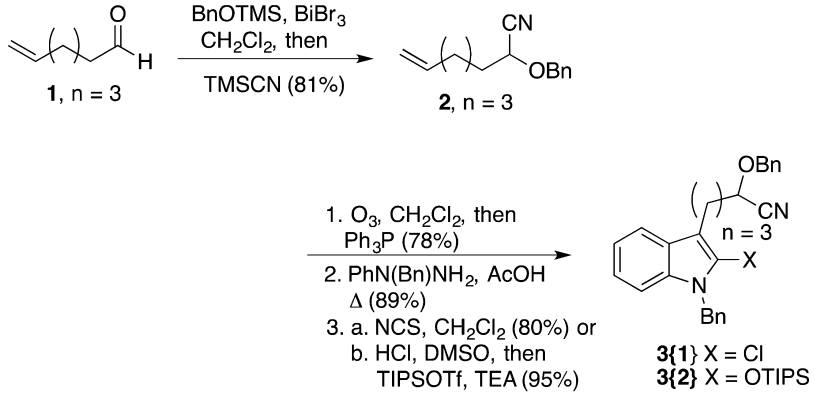
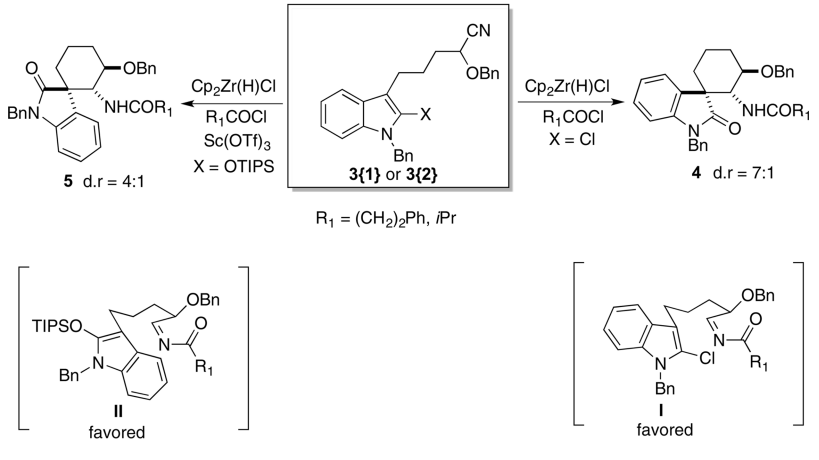



**Figure 2.** Representative spirooxindole libraries.

**Scheme 1. Preparation of Indoles 3{1-2}**



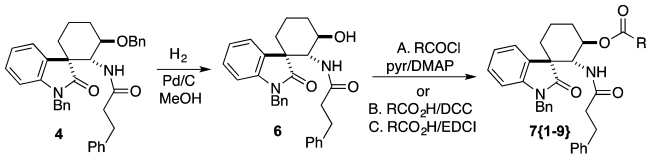

**Scheme 2. Nitrile Hydrozirconation-Acylation-Cyclization Cascade**





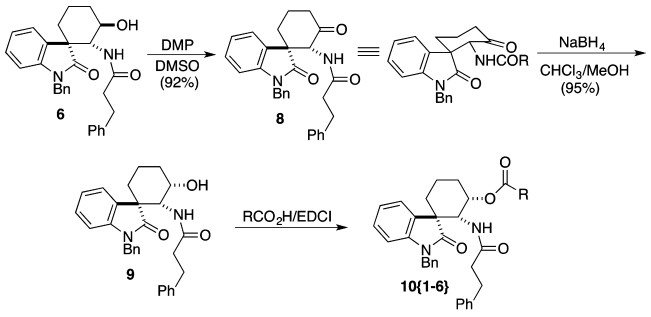

dx.doi.org/10.1021/co4000387 | ACS Comb. Sci. 2013, 15, 344−349

**Scheme 3. Preparation of an Ester Containing Library**




| entry | (R) | yield[a] | purity[b] | cLogP[c] | PSA[c] |
|---|---|---|---|---|---|
| 1 | - | **4**, 61% | 97 | 7.42 | 57.3 |
| 2 | - | **6**, 95% | nd | 5.02 | 79.5 |
| 3 |  | **7{1}**, 93%[A] | 99 | 6.54 | 81.4 |
| 4 |  | **7{2}**, 74%[A] | 99 | 5.78 | 97.4 |
| 5 |  | **7{3}**, 63%[A] | 97 | 6.97 | 96.1 |
| 6 |  | **7{4}**, 70%[B] | 99 | 6.64 | 95.4 |
| 7 |  | **7{5}**, 83%[B] | 99 | 6.43 | 101.2 |
| 8 |  | **7{6}**, 84%[C] | 99 | 4.52 | 108.6 |
| 9 |  | **7{7}**, 85%[B] | 99 | 5.23 | 97.7 |
| 10 |  | **7{8}**, 84%[C] | 99 | 5.44 | 115.9 |
| 11 |  | **7{9}**, 94%[C] | 99 | 5.30 | 102.5 |

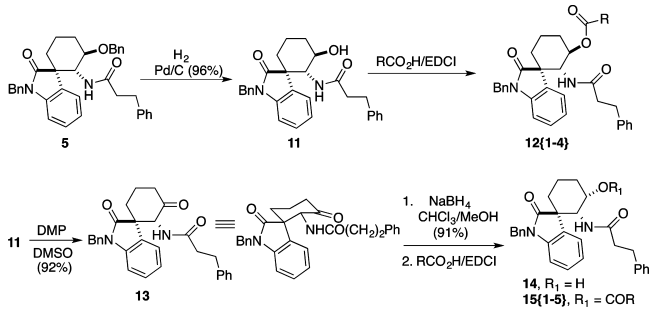
**Scheme 4. Preparation of *syn*-Amido Ester Analogues**

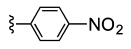



| entry | (R) | yield[a] | purity[b] | cLogP[c] | PSA |
|---|---|---|---|---|---|
| 1 |  | **10{1}**, 86% | 99 | 5.30 | 95.4 |
| 2 |  | **10{2}**, 79% | 98 | 6.28 | 78.4 |
| 3 |  | **10{3}**, 78% | 99 | 5.85 | 82.3 |
| 4 |  | **10{4}**, 84% | 100 | 4.66 | 107.9 |
| 5 |  | **10{5}**, 76% | 100 | 5.75 | 93.9 |
| 6 |  | **10{6}**, 84% | 100 | 5.42 | 112.4 |

that can be modified to incorporate additional elements of diversity. Our initial library construction was directed toward

**Scheme 5. Preparation of Additional Spirooxindole Library**




| entry | (R) | yield[a] | purity[b] | cLogP[c] | PSA |
|---|---|---|---|---|---|
| 1 | - | **11**, 96% | 98 | 5.15 | 74.4 |
| 2 |  | **12{1}**, 72%<br>**15{1}**, 79% | 98<br>98 | 5.54<br>5.54 | 97.8<br>97.8 |
| 3 |  | **12{2}**, 68%<br>**15{2}**, 79% | 98<br>94 | 4.88<br>4.88 | 105.2<br>108.4 |
| 4 |  | **12{3}**, 78%<br>**15{3}**, 80% | 99<br>98 | 5.90<br>5.83 | 93.9<br>95.0 |
| 5 |  | **12{4}**, 68%<br>**15{4}**, 80% | 98<br>98 | 5.28<br>5.34 | 110.2<br>113.5 |
| 6 |  | **15{5}**, 77% | 99 | 6.01 | 127.4 |

the functionalization of the hydroxyl group. The *O*-benzyl group can readily be removed under mild hydrogenolysis conditions (Scheme 3). Subsequent acylations were accomplished in high yields either through treatment with the corresponding acyl chlorides or through carbodiimide mediated acid couplings (**7{1−9}**, Scheme 3). To modulate the clogP's of the final ester containing analogues, various heterocyclic groups were appended (entries 8−11).

The hydroxyl group of **6** was also used to introduce additional elements of stereochemical diversity through oxidation followed by selective ketone reduction (*d.r.* > 20/1, Scheme 4). In this case, the axial-alcohol functionality was converted to a complementary subset of *syn*-amido ester analogues containing small alkyl and heteroaromatic groups (**10{1−6}**).

To complete the diastereomeric set of oxindoles from the common acyclic indole intermediate (not shown), the 2-siloxy indole cyanohydrin **3{2}** was subjected to the hydrozirconation-acylation conditions in the presence of $Sc(OTf)_3$ to provide the spirocyclic oxindoles **5** with high selectivity.[6] The alcohol group was unmasked and converted to a diverse group of esters in a manner described earlier (Scheme 5). The relative stereochemistry was unequivocally established by single X-ray crystallography of the *p*-nitrobenzoate derivative **15{5}** (Figure 3).

Additional structural variations of nonester containing analogues were accomplished through derivatizations of the spirooxindole heterocyclic core (Scheme 6). Various heterocycles or amino-propyl substitutions could be efficiently incorporated through Suzuki couplings utilizing either the iodo- or the pinacol ester-containing spirooxindole scaffolds (**16{1}** and **16{2}**, respectively).[8−10] Despite the incorporation of numerous heteroatom containing functionalities, the lipophilicities of this sublibrary were significantly increased although calculated PSA values remained below 130 (Scheme 6).


dx.doi.org/10.1021/co4000387 | *ACS Comb. Sci.* 2013, 15, 344−349

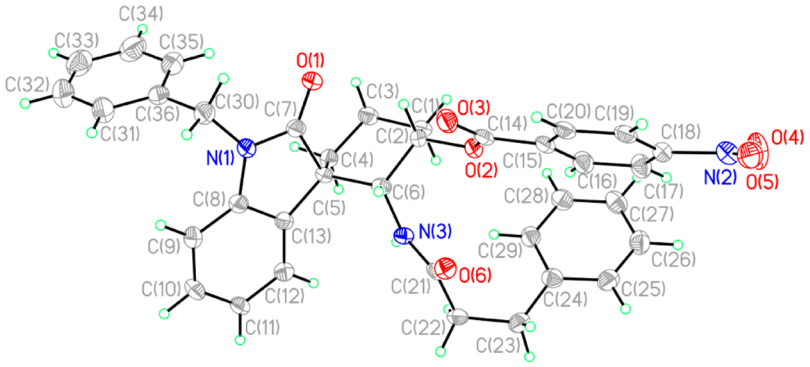
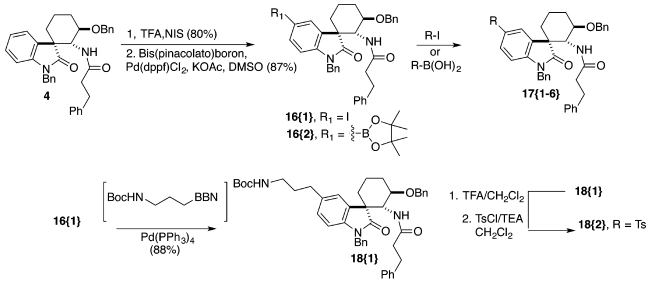
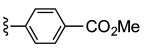



**Figure 3.** X-ray structure of **15{5}**.

## Scheme 6. Spirooxindole Derivatizations




| entry | (R) | yield[a] | purity[b] | cLogP[c] | PSA |
|---|---|---|---|---|---|
| 1 |  | **17{1}**, 65% | 100 | 8.53 | 68.0 |
| 2 |  | **17{2}**, 71% | 100 | 7.47 | 81.4 |
| 3 |  | **17{3}**, 82% | 100 | 9.01 | 57.3 |
| 4 |  | **17{4}**, 62% | nd | 7.43 | 89.3 |
| 5 |  | **17{5}**, 74% | 98 | 8.75 | 93.4 |
| 6 |  | **17{6}**, 86% | 98 | 10.08 | 60.0 |
| 7 |  | **18{1}**, 88% | 100 | 9.38 | 102.4 |
| 8 |  | **18{2}**, 51% | 99 | 8.95 | 109.2 |

We have generated more polar analogues via removal of the *N*-benzyl group using dissolving metal conditions (Scheme 7).[11] In these cases, the isopropylamide spirooxindoles proved compatible for the *N*-debenzylation reaction conditions and produced much lower molecular weight compounds and increased product polarities.[6a] The acetate **20{2}** was obtained directly using ethyl acetate as solvent during reaction workup and extraction.

With the completion of this spirooxindole amide library, the compiled physical chemical properties have been evaluated with the majority of analogues having MWs between 500 and 600 (Figure 4). Many of these compounds were lipophilic (cLogP's >6), but incorporation of numerous heterocycles upon the scaffold helped modulate the overall polarities (*vide supra*).

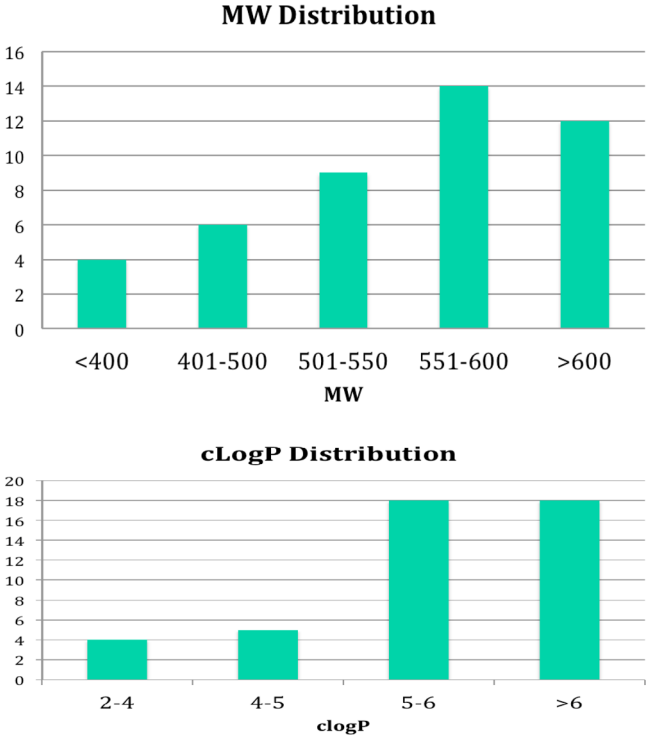



**Figure 4.** MW and cLogP distribution of spirooxindole library.

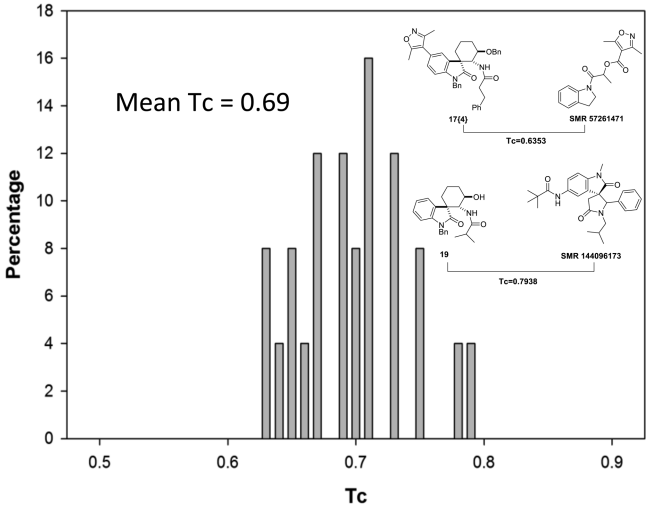



**Figure 5.** Tanimoto coefficient (Tc) comparisons of spirooxindoles vs MLSMR collection.


dx.doi.org/10.1021/co4000387 | *ACS Comb. Sci.* 2013, 15, 344−349

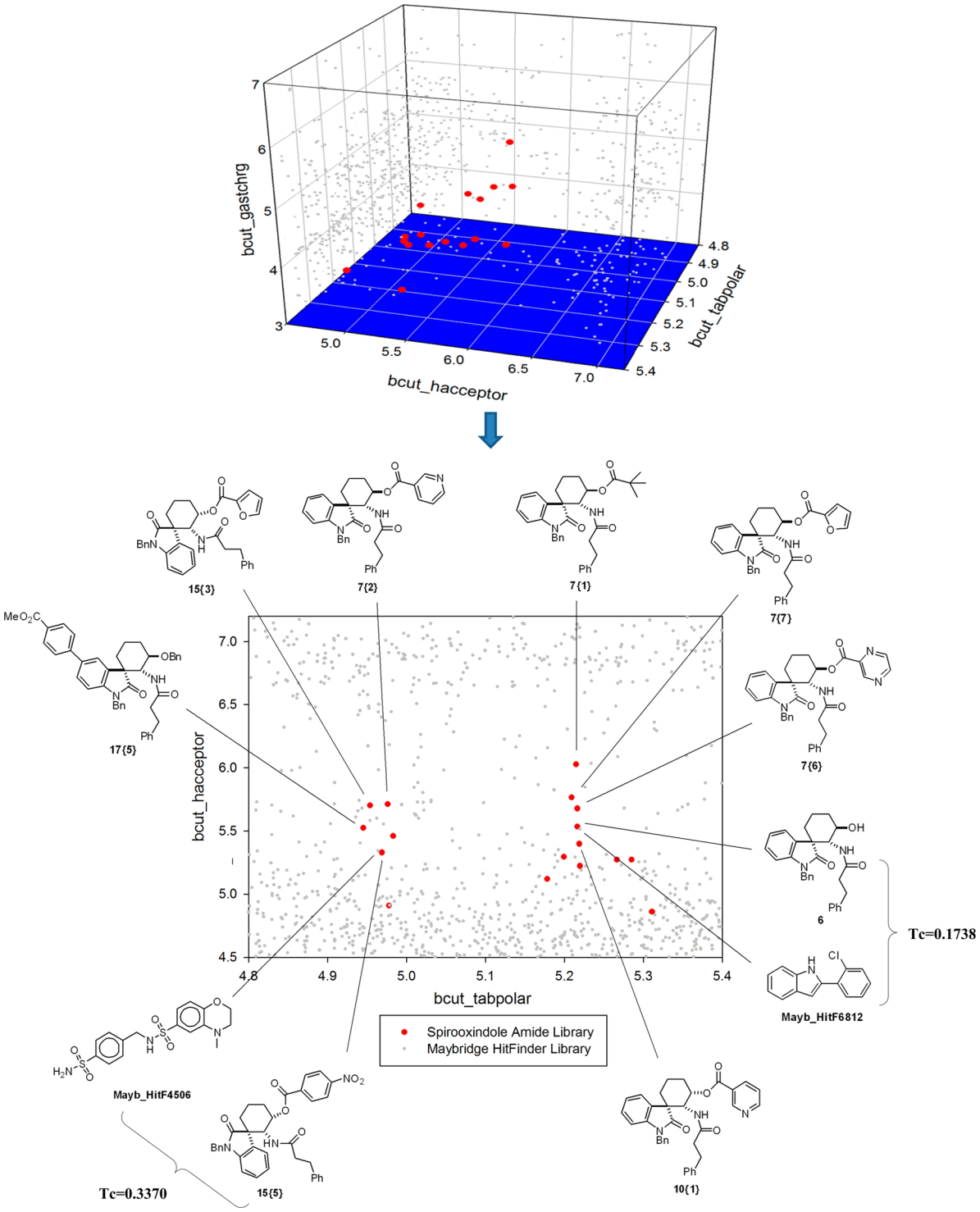


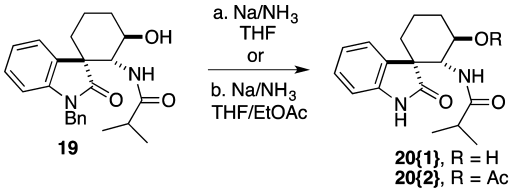

**Figure 6.** 3D Chemistry space matrix analyses of spirooxindoles vs Maybridge HitFinder library.

The structural novelty of this library was compared to the NIH Molecular Libraries Small Molecule Repository (MLSMR) using chemistry space BCUT metrics as well as 2-dimensional fingerprint calculations.[12] Using these parameters, the new spirooxindole-based library displayed favorable chemical diversity with an average Tanimoto coefficient (Tc) of <0.7 when evaluated against the 430,000 compounds in the NIH MLSMR collection (Figure 5).[13,14] Representative library structures that exhibit the highest and lowest similarities are also represented in Figure 5. These spirooxindoles have been deposited into the MLSMR to serve as novel biological screening candidates.[15,16]

To further illustrate the structural uniqueness of the described spirooxindole library, perspective 3D chemistry space views were constructed against the Maybridge HitFinder library (Figure 6). Space coordinates for each compound were generated using 3-dimensional BCUT metric calculations based upon four principal molecular property descriptions consisting of charge, polarity, and hydrogen bond donor/acceptor abilities. The 3-dimensional chemical space representation of the spirooxindoles


dx.doi.org/10.1021/co4000387 | ACS Comb. Sci. 2013, 15, 344−349

**Scheme 7. Unsubstituted Spirooxindoles**




| entry | yield[a] | purity[b] | cLogP[c] | PSA |
|---|---|---|---|---|
| 1 | **20{1}**, 31% | 100 | 1.39 | 92.3 |
| 2 | **20{2}**, 54% | 100 | 2.07 | 107.2 |

(red dots) versus the 14,400 Maybridge compounds (gray dots) generally indicates that our new library occupies less populated or void regions. The corresponding 2D evaluations further establish novelties with nine compounds (**6**, **7**{**1**−**2**, **5**−**7**}, **10**{**1**}, **15**{**5**}, **17**{**5**}) in vacant chemical space cells with the nearest Maybridge compounds to **6** and **15**{**5**} possessing very low Tanimoto coefficients of 0.17 and 0.34, respectively (Figure 6).

## CONCLUSIONS

We have described the synthesis of a stereochemically and structurally diverse library of spirooxindoles (37 total analogues) using a three step nitrile hydrozirconation-acylation-cyclization reaction cascade. These poly functional spirooxindoles were assembled with high stereoselectivities with pivotal cyclizations controlled by the 2-indole substitutions that were generated from a common intermediate. Structural elaborations were provided by a series of acylations or palladium mediated couplings. The resulting compound library demonstrated good chemical novelty when evaluated against the MLSMR and Maybridge compound collections.

## ASSOCIATED CONTENT

### Supporting Information

Further details are given about the experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: pflorean@pitt.edu (P.E.F.), mgl12@pitt.edu (M.G.L.).

### Author Contributions

P.E.F. conceived the methodology; P.E.F., M.G.L. designed the library strategy; S.T., K.B.H., C.L. performed the experiments; C.F., L.W.; X.-Q.X. conducted computational analyses; M.G.L., P.E.F., X.-Q.X. cowrote the manuscript.

### Funding

This investigation was supported by the NIH/NIGMS CMLD program (P50GM067082) and R21HL109654.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank Professor Peter Wipf for instructive discussions and Mr. Pete Chambers and Dr. Steven Geib for LCMS/ELSD and X-ray analyses, respectively.

## REFERENCES

(1) (a) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527−4547. (b) Zesiewicz, T. A.; Hauser, R. A. *Expert Opin. Invest. Drugs* **1999**, *8*, 697−710. (c) Serretti, A.; De Ronchi, D.; Lorenzi, C.; Berardi, D. *Curr. Med. Chem.* **2004**, *11*, 343−358.

(2) For a review of syntheses of spirocyclic-oxindole natural products, see: Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003−3025.

(3) For a recent perspective on enantioselective spirooxindole syntheses, see: Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165−5181.

(4) For an example of spirooxindoles via intramolecular Heck-reactions of non-isatin intermediates, see: Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587−2599.

(5) (a) Lo, M.M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077−16086. (b) Dai, C.; Liang, B.; Stephenson, C. R. J. *Beilstein J. Org. Chem.* **2012**, *8*, 986−993. (c) Brummond, K. M.; Osbourn, J. M. *Beilstein J. Org. Chem.* **2011**, *7*, 601−605. (d) Bhaskar, G.; Arun, Y.; Balachandran, C.; Saikumar, C.; Perumal, P. T. *Eur. J. Med. Chem.* **2012**, *51*, 79−91. (e) MacDonald, J. P.; Badillo, J. J.; Arevalo, G. E.; Silva-García, A.; Franz, A. K. *ACS Comb. Sci.* **2012**, *14*, 285−293.

(6) (a) Lu, C.; Xiao, Q.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 5112−5115. (b) Zhang, L.; Xiao, Q.; Ma, C.; Xie, X.-Q.; Floreancig, P. E. *J. Comb. Chem.* **2009**, *11*, 640−644. (c) Xiao, Q.; Floreancig, P. E. *Org. Lett.* **2008**, *10*, 1139−1142.

(7) For review of organochlorozirconocene complexes, see: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *40*, 12853−12910.

(8) For iodination conditions, see: Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047−5048.

(9) For recent review and perspectives on Suzuki cross coupling reactions, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6723−6737. (c) Heravi, M. M.; Hashemi, E. *Tetrahedron* **2012**, *68*, 9145−9178.

(10) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744.

(11) Mertens, A.; Müller-Beckmann, B.; Kampe, W.; Hölck, J.-P.; von der Saal, W. *J. Med. Chem.* **1987**, *30*, 1279−1287.

(12) (a) Pearlman, R. S.; Smith, K. M. *Perspect. Drug Discovery Des.* **1998**, *9*, 339−353. (b) Ma, C.; Lazo, J. S.; Xie, X.-Q. *ACS Comb. Sci.* **2011**, *13*, 223−231. (c) Xie, X.-Q.; Chen, J.-Z. *J. Chem. Inf. Model.* **2008**, *48*, 465−475.

(13) For additional information on this similarity method, see: Wild, D. J.; Blankley, C. J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 155−162.

(14) Matter, H. *J. Med. Chem.* **1997**, *40*, 1219−1229.

(15) These compounds have been submitted to the Molecular Libraries Small Molecule Repository (MLSMR), see: http://mli.nih.gov/mli/secondary-menu/mlscn/ml-small-molecule-repository/.

(16) For recent perspective on small molecules originating from CMLD centers and their biological discovery/evaluations, see: Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6699−6702.