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LETTER

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Application of 6,7-Indole Aryne Cycloaddition and Pd(0)-Catalyzed Suzuki−Miyaura and Buchwald−Hartwig Cross-Coupling Reactions for the Preparation of Annulated Indole Libraries

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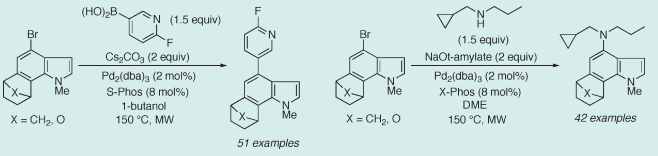
Supporting Information

ABSTRACT: The construction of an unprecedented class of an indole-based library, namely, a 6,7-annulated-4-substituted 93-member indole library, using a strategic combination of 6,7-indolyne cycloaddition and cross-coupling reactions under both Suzuki−Miyaura and Buchwald−Hartwig conditions is described. This work represents the *first* example of library development that employs the indole aryne methodology. Annulated indoles, with the exception of only a few biologically active natural products (i.e., the trikentrins, herbindoles, teleocidins, and nodulisporic acids), have no representation in the PubChem or MLSMR databases. These structural entities are therefore predicted to have unique chemical property space characteristics and a high probability of exhibiting interesting biological activity.



KEYWORDS: indole, aryne, indolyne, cycloaddition, Suzuki−Miyaura, Buchwald−Hartwig, libraries

Indole arynes or indolynes are a completely new class of reactive aryne intermediate that we discovered and reported beginning in 2007.[1−5] As their unusual and fascinating chemistry is revealed, they are becoming versatile and powerful tools for use in organic synthesis, including natural products total synthesis. Indeed, indolyne cycloaddition methodologies have already proven their value, as we recently demonstrated in the total synthesis of the trikentrins and the herbindoles. Subsequent work from the Garg[6−11] and Lautens[12] laboratories using indolyne chemistry helped to validate this point of view.

During the course of a second-generation formal total synthesis of *cis*-trikentrin A,[4] we found that the 4,6,7-tribromoindole **1** underwent highly selective metal−halogen exchange at the C7 bromo position, followed by 6,7-indole aryne formation and subsequent cycloaddition with cyclopentadiene (Scheme 1) to give the cycloadduct **3**.

The C4 bromine was completely unaffected by these conditions, but readily participated in transition metal-catalyzed cross-coupling such as the Negishi reaction to afford the common late stage intermediate **4**. This reaction orthogonality appears to be general in these systems, and has also been observed with **3** in the Suzuki−Miyaura and Buchwald−Hartwig cross-coupling manifolds.[4]

Encouraged by these results, and in connection with our ongoing efforts to identify interesting chemotypes for library development,[13,14] we decided to apply the indole aryne methodology to the synthesis of novel, polycyclic annulated indoles. Our strategy makes use of the unique advantages and properties of indole aryne chemistry. This goal is significant because annulated indoles, with the exception of only a few biologically active natural products such as the trikentrins,[15] herbindoles,[16] teleocidins,[17] and nodulisporic acids,[18] (Figure 1) have no representation in the PubChem or MLSMR databases.

These structural entities are therefore predicted to have unique chemical property space characteristics. The indole aryne methodology offers the most efficient access to these useful and potentially valuable compounds. Without this methodology, the construction of annulated indole scaffolds would be rendered much more difficult, and as a consequence, the therapeutic potential of their libraries would likely be overlooked. We now report the first 93-member annulated indole library using a combination of indole cycloaddition and cross-coupling chemistry.

The 4,6,7-tribromoindole scaffold was synthesized using the Bartoli reaction,[19] and follows our previously published route (Scheme 2).[4] Thus, *o*-nitroaniline **11** was first brominated at C2 and C4 (Br_2, MeOH/CH_2Cl_2 (1:1), 95%), followed by diazotization to afford the 2,3,5-tribromonitrobenzene **12**. Application of the Bartoli reaction conditions (vinylmagnesium bromide, 3.0 equiv, tetrahydrofuran (THF), −45 °C) consistently gave the desired indole in 45% yield on a 5−10 g scale. The indole nitrogen was then alkylated with methyl iodide (88%) to afford the desired *N*-methyl indole scaffold **13**.

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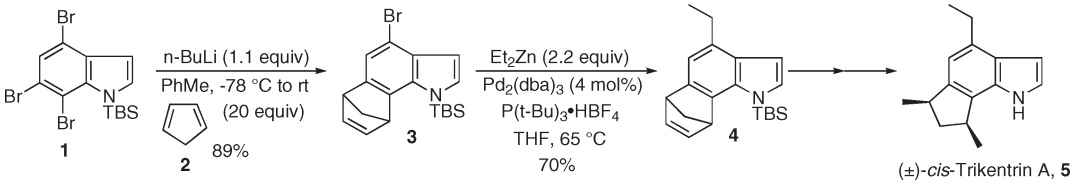
Scheme 1. Reaction Orthogonality in the 4,6,7-Tribromoindole System



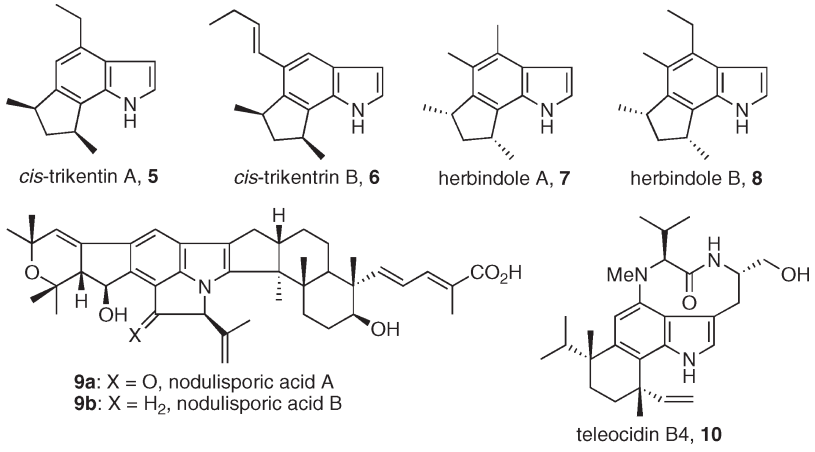
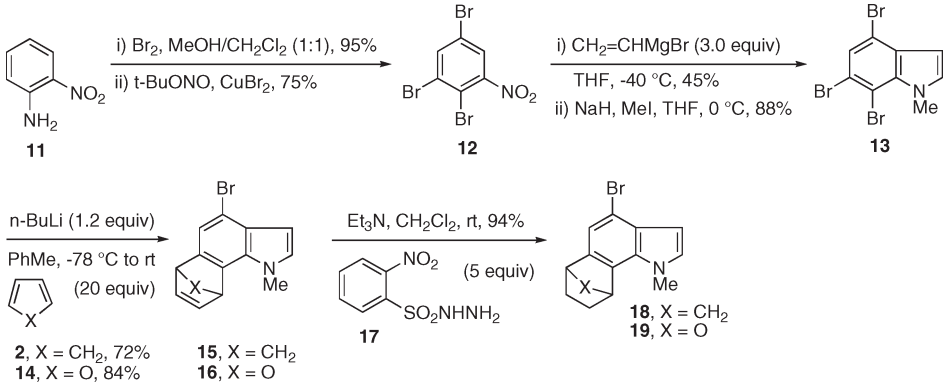
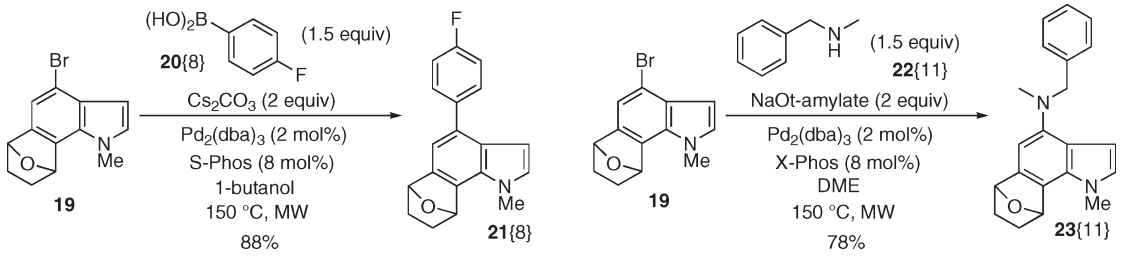


Figure 1. Annulated indole alkaloid natural products.

Scheme 2. Synthesis of the 4-Bromo-6,7-annulated Indole Scaffolds



Scheme 3. Validation for the Suzuki−Miyaura and Buchwald−Hartwig Cross-Coupling Chemistry



Indole aryne formation (n-BuLi, 1.2 equiv, toluene, −78 °C to rt) followed by cycloaddition with either cyclopentadiene or furan gave the corresponding cycloadducts **15** and **16** in 72% and 84% yields, respectively. We elected to reduce the olefin with diimide (generated in situ from *o*-nitrobenzosulfonhydrazide **17** and triethylamine)[20] as the presence of the alkene resulted in sharply

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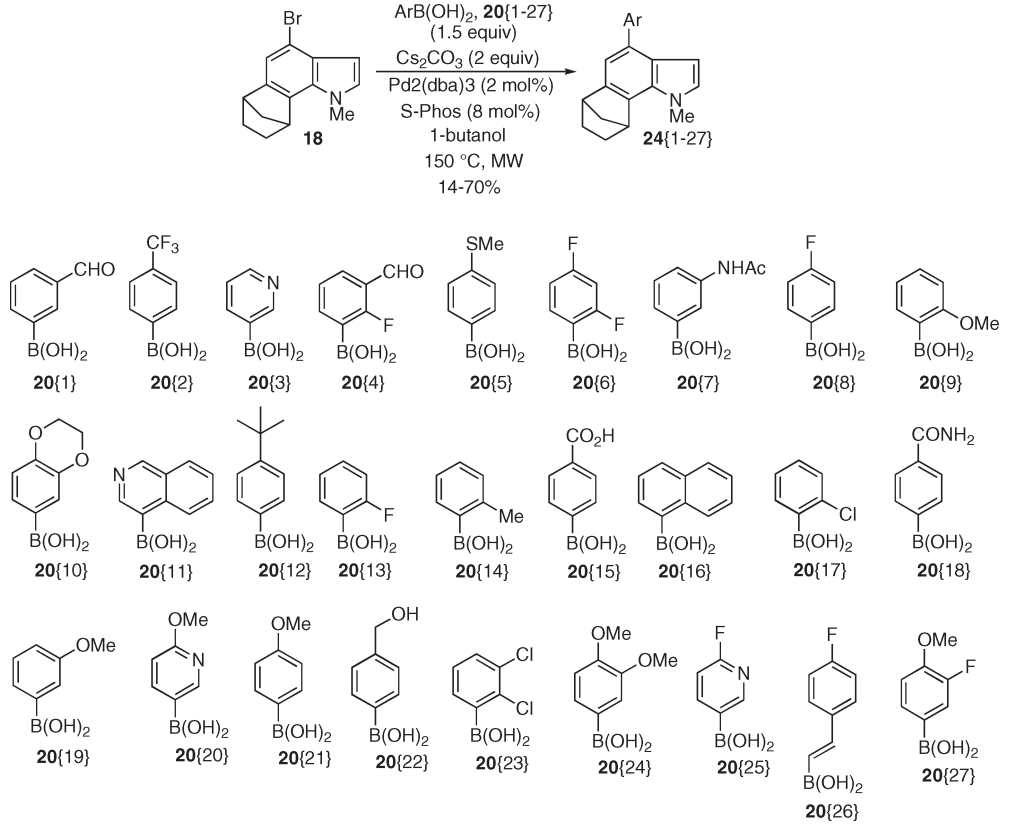
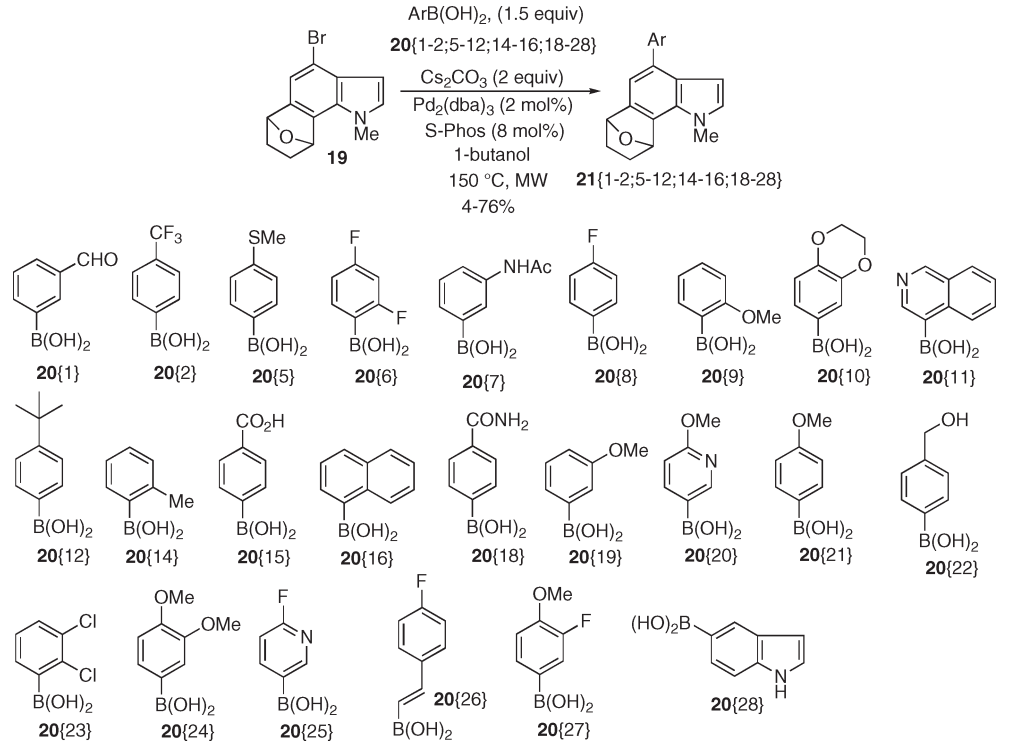
Scheme 4. Synthesis of the Cyclopentadiene-Annulated Suzuki−Miyaura Cross-Coupled Library



Scheme 5. Synthesis of the Furan-Annulated Suzuki−Miyaura Cross-Coupled Library



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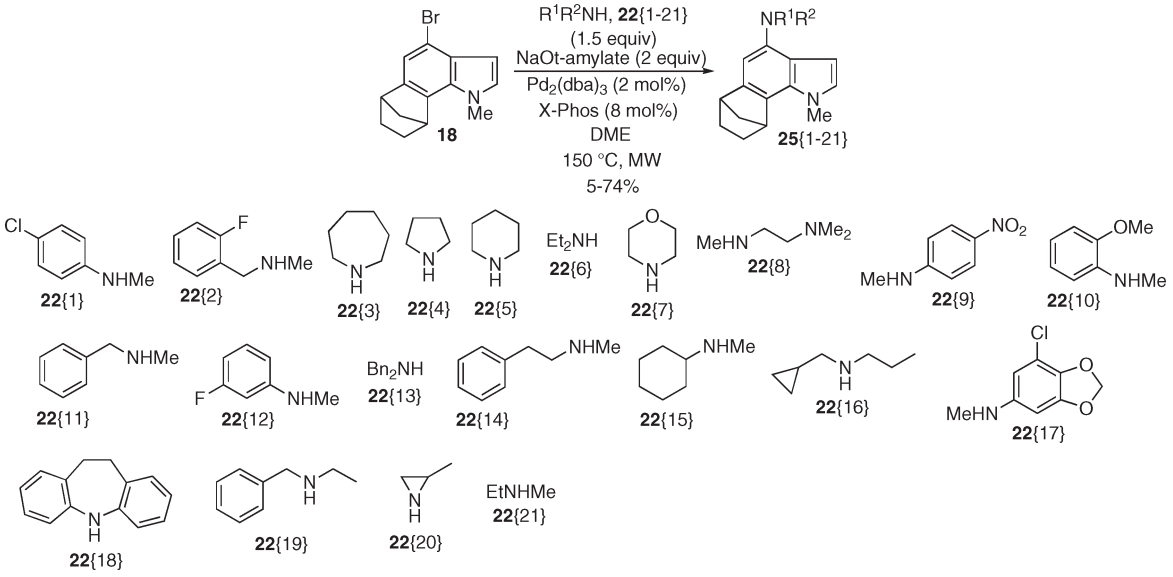
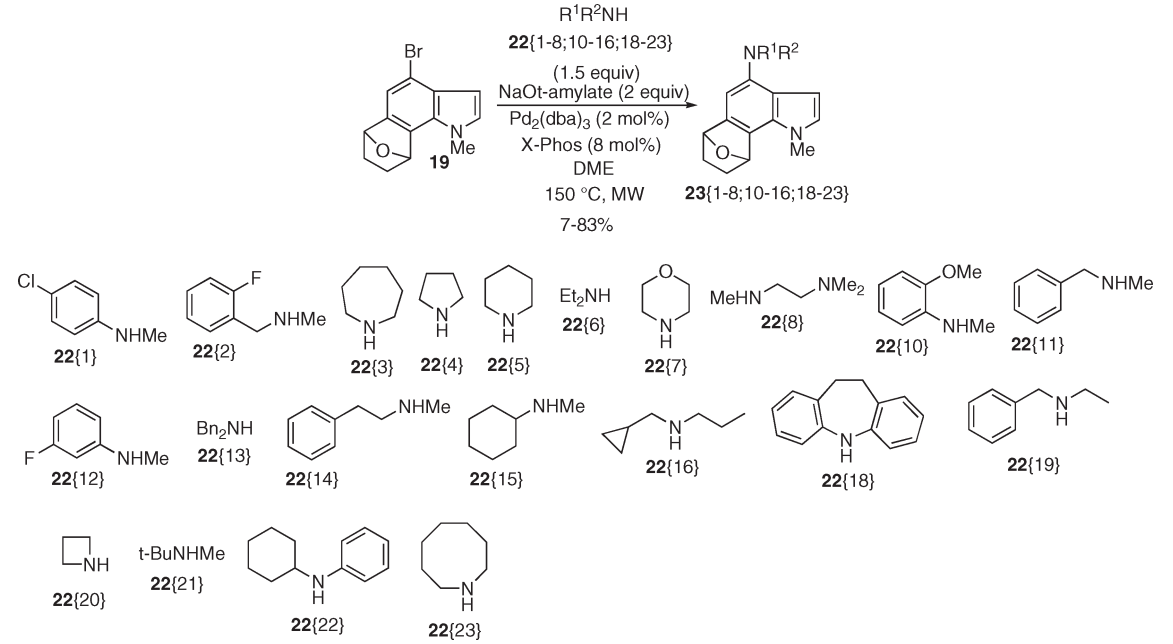
Scheme 6. Synthesis of the Cyclopentadiene-Annulated Buchwald−Hartwig Cross-Coupled Library



Scheme 7. Synthesis of the Furan-Annulated Buchwald−Hartwig Cross-Coupled Library



diminished yields in the subsequent cross-coupling reactions. In this manner the final scaffolds **18** and **19** were each produced in 94% yield. The bridged bicyclic system is an uncommon structural motif in library design. A recent report[21] suggests that the presence of additional sp^3-hybridized content in complex library structures correlates with an increased number of hits for activity in certain cell-based assays, particularly in the area of CNS (e.g., histone deacetylase, or HDAC, inhibition).

With the key scaffolds in hand, our attention turned to the cross-coupling reactions. We elected to use the Suzuki−Miyaura and Buchwald−Hartwig reactions based on our successful previous experience and the fact that a diverse collection of boronic acid and amine cross-coupling partners for these reactions are readily available. During the development and validation studies, we found that microwave heating gave superior results in terms of yield and the minimization of side-products. Optimization for the Suzuki−Miyaura and Buchwald−Hartwig reactions was carried out with the furan-based scaffold (Scheme 3). The production library targeted 128 compounds (2 scaffolds × 32 boronic acids; 2 scaffolds × 32 amines) on a reaction scale of 105 mg per scaffold.

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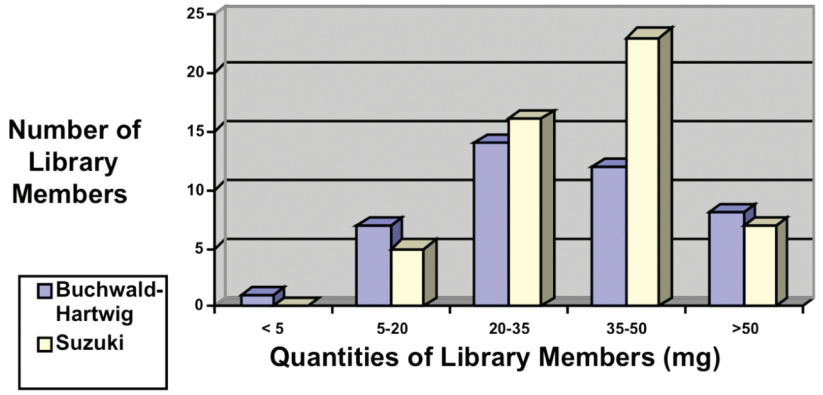

Figure 2. Suzuki−Miyaura and Buchwald−Hartwig product distribution.

Of the 128 compounds targeted, 93 were produced and purified to a threshold of approximately 90% or better via mass-directed fractionation (MDF), which represents a 73% pass rate. There were 51 Suzuki−Miyaura reaction products (Schemes 4 and 5) and 42 Buchwald−Hartwig coupled products (Schemes 6 and 7). Both the Suzuki−Miyaura and Buchwald−Hartwig library sets showed a broad range of aromatic and heteroaromatic moieties that support a diverse array of substitution and functional groups (aldehydes, alcohols, alkenes, amides, ethers, thioethers, halides). The majority of library members in the Suzuki−Miyaura series were obtained with a yield of 4−76%, while those in the Buchwald−Hartwig manifold were realized in 5−83%. All library members were produced in quantities between 20 and 50 mg, with 12 in excess of 50 mg, and six in the range of 5−20 mg (Figure 2).

In silico profiling[22−26] of physicochemical and ADME properties, which is reported in detail in Supporting Information, Table 1, suggests that the 6,7-indole aryne products generated from both the Suzuki−Miyaura and Buchwald−Hartwig libraries should be reasonably amenable to both biochemical and cell-based assays. In general, the libraries are fully compliant with the Lipinski Rule of Five[23] in that none of the constituent compounds have more than one violation, and nearly two-thirds of the species have no violations. The observed violations entail marginally high cLogP values, which range up to 7.75 among violators. Predicted solubility in aqueous and 2% DMSO solutions is correspondingly marginal for these violators, but the vast majority had solubilities adequate for our analytical and preparative processing and thus should be viable for screening. The library products are generally predicted to yield good cell permeability profiles, volume distribution, and albumin binding. Our models suggest that the compounds are not generally very likely to display hERG blocking tendencies. Many of them are predicted to exhibit blood-brain-barrier permeability, which might prove useful for probing central nervous system targets. As a whole, compounds in this study are exceptionally unique relative to the current MLPCN screening set that forms our reference for comparison. The full product manifold spans 46 distinct cells in chemical space, which bespeaks a significant amount of chemical diversity in these library elaborations. Only six compounds (**24**{7}, **24**{15}, **24**{18}, **21**{6}, **21**{15} and **21**{18}) were found to occupy regions of chemical space whose compound density was above the mean, while 75 products occupied areas with less than half the mean density, 23 were in areas with less than 10% of the mean density, and three compounds (**25**{13}, **25**{18}, and **23**{13}) occupied cells with zero existing MLPCN compounds.

In conclusion, we have prepared the first annulated and polycyclic 93-member indole library using 6,7-indole aryne cycloaddition chemistry combined with versatile cross-coupling reactions to afford a diverse suite of novel structures. All of the compounds thus produced have been submitted to the NIH Molecular Libraries Screening Centers Network (MLSCN) for biological evaluation with a broad range of biochemical and cell-based assays. Other drug-like designs based on the annulated indole platform are in progress and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, ^{1}H and ^{13}C NMR data for a representative number of compounds reported, computed in silico parameters, and methods for the in silico analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; Vander Velde, D. Indole-Derived Arynes and Their Diels-Alder Reactivity with Furans. *Org. Lett.* **2007**, *9*, 4135–4137.

(2) Buszek, K. R.; Brown, N.; Luo, D. Concise Total Synthesis of (±)-*cis*-Trikentrin A and (±)-Herbindole A via Intermolecular Indole Aryne Cycloaddition. *Org. Lett.* **2009**, *11*, 201–204.

(3) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. Regioselective Diels-Alder Cycloadditions and Other Reactions of 4,5-, 5,6-, and 6,7-Indole Arynes. *Tetrahedron Lett.* **2009**, *50*, 63–65.

(4) Brown, N.; Luo, D.; Decapo, J. A.; Buszek, K. R. New Synthesis of (±)-cis-Trikentrin A via Tandem Indole Aryne Cycloaddition/Negishi Reaction. Applications to Library Development. *Tetrahedron Lett.* **2009**, *50*, 7113–7115.

(5) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. Experimental and Theoretical Investigations into the Unusual Regioselectivity of 4,5-, 5,6-, and 6,7-Indole Aryne Cycloadditions. *Org. Lett.* **2010**, *12*, 96–99.

(6) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. Indolynes as Electrophilic Surrogates: Fundamental Reactivity and Synthetic Applications. *Org. Lett.* **2009**, *11*, 1007–1010.

(7) Tian, X.; Huters, A. D.; Douglas, C. J.; Garg, N. K. Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via an Indolyne Cyclization. *Org. Lett.* **2009**, *11*, 2349–2351.

(8) Bronner, S. M.; Garg, N. K. Efficient Synthesis of 2-(Trimethylsilyl)-phenyl Trifluoromethanesulfonate: A Versatile Precursor to *o*-Benzyne. *J. Org. Chem.* **2009**, *74*, 8842–8843.

(9) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-T. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivities. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

(10) Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. Indolyne Experimental and Computational Studies: Synthetic Applications and Origins of Selectivities of Nucleophilic Additions. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.

(11) Bronner, S. M.; Goetz, A. E.; Garg, N. K. Overturning Indolyne Regioselectivities and Synthesis of Indolactam V. *J. Am. Chem. Soc.* **2011**, *133*, 3832–3835.

(12) Nguyen, T. D.; Webster, R.; Lautens, M. Rh(I)-Catalyzed Ring-Opening of Hetaryne-Furan Diels-Alder Adducts: Rapid Access to Stereochemically Defined Heterocyclic Scaffolds. *Org. Lett.* **2011**, *13*, 1370–1373.

(13) Brown, N.; Xie, B.; Markina, N.; VanderVelde, D.; Perchellet, J.-P. H.; Perchellet, E. M.; Crow, K. R.; Buszek, K. R. Synthesis of a Natural Product-Inspired Eight-Membered Ring Lactam Library via Ring-Closing Metathesis. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4876–4879.

(14) Brown, N.; Gao, G.; Minatoya, M.; Xie, B.; VanderVelde, D.; Lushington, G. H.; Perchellet, J-P. H.; Perchellet, E. M.; Crow, K. R.; Buszek, K. R. Design and Synthesis of Medium-Ring Libraries Inspired by Octalactin A. A Convergent-Divergent Approach. *J. Comb. Chem.* **2008**, *10*, 628–631.

(15) (a) Jackson, S, K.; Kerr, M. A. Total Synthesis of (±)-Herbindole A, (±)-Herbindole B, and (±)-*cis*-Trikentrin A. *J. Org. Chem.* **2007**, *72*, 1405–1411. (b) Huntley, R. J.; Funk, R. L. Total Synthesis of (±)-*cis*-Trikentrin A and (±)-*cis*-Trikentrin B via Electrocyclic Ring Closures of 2,3-Divinylpyrrolines. *Org. Lett.* **2006**, *8*, 3403–3406. (c) MacLeod, J. K.; Monahan, L. C. The Synthesis of (±)-*cis*-Trikentrin A. *Tetrahedron Lett.* **1988**, *29*, 391–392.

(16) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. Total Synthesis of (±)-Herbindole B and (±)-*cis*-Trikentrin B. *Org. Lett.* **2005**, *7*, 1215–1218, and references cited therein.

(17) (a) Hitotsuyanagi, Y.; Fujiki, H.; Suganuma, M.; Aimi, N.; Sakai, S.-I.; Endo, Y.; Shudo, K.; Sugimura, T. Isolation and Structure Elucidation of Teleocidin B-1, B-2, and B-4. *Chem. Pharm. Bull.* **1984**, *32*, 4233–4236. (b) Nakatsuka, S.; Matsuda, T.; Asano, O.; Terame, T.; Goto, T. Synthetic Studies on Teleocidin. I. Regioselective Introduction of 4-Amino and 7-Acyl Groups on Indole Derivative. *Tetrahedron Lett.* **1986**, *27*, 4327–4330. (c) Nakatsuka, S.; Masuda, T.; Goto, T. Synthetic Studies on Teleocidin. II. Synthesis of Indole Derivatives Containing the Same Substituent to Teleocidin B at 6- and 7-Positions of Indole Nucleus. *Tetrahedron Lett.* **1986**, *27*, 6245–6248. (d) Nakatsuka, S.; Masuda, T.; Goto, T. Total Synthesis of (±)-Teleocidin B-3 and B-4. *Tetrahedron Lett.* **1987**, *28*, 3671–3674.

(18) (a) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. Nodulisporic Acids D-F: Structure, Biological Activities, and Biogenetic Relationships. *J. Nat. Prod.* **2004**, *67*, 1496–1506. For recent synthetic studies, see:(b) Smith, A. B., III; Kuerti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. Indole Diterpene Synthetic Studies: Development of a Second-Generation Synthetic Strategy for (+)-Nodulisporic Acids A and B. *J. Org. Chem.* **2007**, *72*, 4611–4620.

(19) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. The Reaction of Vinyl Grignard Reagents with 2-Substituted Nitroarenes: A New Approach to the Synthesis of 7-Substituted Indoles. *Tetrahedron Lett.* **1989**, *30*, 2129–2132. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. Reactivity of Nitro- and Nitroso-Arenes with Vinyl Grignard Reagents: Synthesis of 2-(Trimethylsilyl)indoles. *J. Chem. Soc. PT1* **1991**, 2757–2761. (c) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. Mechanistic Studies on the Reaction of Nitro- and Nitrosoarenes with Vinyl Grignard Reagents. *J. Chem. Soc. PT2* **1991**, 657–663. (d) Dalpozzo, R.; Bartoli, G. Bartoli Indole Synthesis. *Curr. Org. Chem.* **2005**, *9*, 163–178.

(20) Buszek, K. R.; Brown, N. Improved Method for the Diimide Reduction of Multiple Bonds on Solid-Supported Substrates. *J. Org. Chem.* **2007**, *72*, 3125–3128.

(21) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. An Aldol-Based Build/Couple/Pair Strategy for the Synthesis of Medium- and Large-Sized Rings: Discovery of Macrocyclic Histone Deacetylase Inhibitors. *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976.

(22) *SYBYL 8.0*; The Tripos Associates: St. Louis, MO, 2008.

(23) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.

(24) *Concord 8.0*; The Tripos Associates: St. Louis, MO, 2008.

(25) Cruciani, G., Meniconi, M., Carosati, E., Zamora, I., Mannhold, R. VOLSURF: A Tool for Drug ADME-Properties Prediction. In *Methods and Principles in Medicinal Chemistry*; van de Waterbeemd, H., Lennernäs, H., Artursson, P., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2003.

(26) Pearlman, R. S.; Smith, K. M. Metric Validation and the Receptor-Relevant Subspace Concept. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28–35.