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A Diverging DOS Strategy Using an Allene-Containing Tryptophan Scaffold and a Library Design that Maximizes Biologically Relevant Chemical Space While Minimizing the Number of Compounds

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Abstract

A diverging diversity-oriented synthesis (DOS) strategy using an allene-containing tryptophan as a key starting material was investigated. An allene-yne substituted derivative of tryptophan **12** gave indolylmethylazabicyclooctadiene **17** when subjected to a microwave-assisted allenic [2 + 2] cycloaddition reaction. This same tryptophan-derived precursor afforded an indolylmethyldihydrocyclopentapyridinone **14** when subjected to a rhodium(I)-catalyzed cyclocarbonylation reaction and an indolylmethylpyrrolidinocyclopentenones **16** when reacted with molybdenum hexacarbonyl. Construction of allenic tetrahydro-β-carboline scaffolds via a Pictet-Spengler reaction and subsequent silver(I)-catalyzed cycloisomerization afforded tetrahydroindolizinoindoles (**21)**. Attachment of allene and alkyne groups to the tetrahydro-β-carboline followed by a microwave-assisted allenic [2 + 2] cycloaddition reaction provided tetrahydrocyclobutaindoloquinolizinones **24** and the tetrahydrocyclopentenone indolizinoindolone **26** when reacted with molybdenum hexacarbonyl. These six scaffolds were used as a template for the construction of a virtual library of 11,748 compounds employing 44 indoles, 12 aldehydes, and 51 alkynes. Diversity analyses using a combination of cell-based chemistry space computations using BCUT (Burden (B) CAS (C) Pearlman at the University of Texas (UT)) metrics and Tanimoto coefficient (Tc) similarity calculations using two-dimensional (2D) fingerprints showed that the compounds in the virtual library occupied new chemical space when compared to the 327,000 compounds in the molecular libraries small molecule repository (MLSMR). A subset of fifty-three compounds was identified from the virtual library using the DVS package of Sybyl 8.0; this subset represents the most diverse compounds within the chemical space defined by these compounds and will be synthesized and screened for biological activity.

Keywords

Thermal [2 + 2] cycloaddition; allene; allene-yne; cyclocarbonylation; cycloisomerization; microwave-assisted; Pictet-Spengler; rhodium(I)-catalyzed; tetrahydro-β-carboline; tryptophan; virtual library; Pauson-Khand; BCUT; Tanimoto; MLSMR; chemical space

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Supporting Information Available. Experimentals procedures and characterization data are provided for all new compounds. Computational studies supporting the stereochemical assignment of compound **21b** are discussed. Compound selection charts for the virtual library of fifty-three compounds are also included in the supporting information.

Introduction

Chemical synthesis of complex organic molecules has recently undergone some revolutionary transformations, including the emerging area of diversity-oriented synthesis (DOS); the synthesis of a diverse set of small molecules for the identification of new ligands for a variety of biological targets.[1] The DOS synthetic strategy is used to access structurally unique compounds and employs a combination of building block-, appendage-, stereochemical-, and skeletal-diversity.[2] Of these, skeletal diversity is the most challenging to achieve,[3] and at the same time is considered the most powerful because it provides molecularly distinct scaffolds that occupy separate regions of chemical space.[4]

Skeletal diversity is commonly achieved by a substrate-based approach that employs a common set of reagents to elaborate functionally and structurally unique precursors.[5] A substrate-based approach can be time intensive for a variety of reasons, such as understanding the wide range of chemistries employed during substrate preparation. Alternatively, a reagent-based approach utilizes a common intermediate that when subjected to a variety of reaction conditions or reagents, affords different scaffolds.[6] The challenge associated with the reagent-based approach, especially when operating under transition metal catalysis conditions, are that small structural changes in a precursor can render an otherwise high yielding reaction, unsuccessful.

In 2004, one of the authors reported a reagent-based approach to skeletal diversity whereby an allene-yne was subjected to three different transition metal catalysts to afford three unique scaffolds.[7] This overall strategy was likened to nature's construction of the carbon skeletons of secondary metabolites from unsaturated substrates such as farnesyl pyrophosphate. The power of this reagent-based approach as a DOS strategy has subsequently been demonstrated by the preparation of multiple libraries of compounds possessing scaffolds and compounds with interesting biological activity.[8]

The work described herein is an extension of this diversification strategy with a focus on the cyclocarbonylation and carbocyclization reactions of allene and/or alkyne groups attached to an indole nucleus.[9] The indole nucleus was selected as an ideal starting point due to its presence in many naturally occurring, bioactive molecules.[10] Furthermore, the cyclocarbonylation and carbocyclization reactions described within offer a novel approach to the preparation of terpene indole alkaloids.[11] Underscoring the importance of this class of compounds is the recent discovery of a β-carboline-containing compound from a library of 12,000 natural products and synthetic compounds, possessing nanomolar activity against *plasmodium falciparum*.[12]

The diversification protocol delineated within (Scheme 1), involves functionalization of the conformationally mobile indolylaminopentadienoate **1** with an alkyne followed by: 1) a Rh(I)-catalyzed cyclocarbonylation reaction,[13] 2) a thermal [2 + 2] cycloaddition reaction,[14] or 3) a molybdenum mediated Pauson-Khand-type reaction[15] 4) to give **2**, **4** and **6**, respectively. The Ag(I)-catalyzed cycloisomerization reaction of **1** to give **8** was not performed since a library of structurally similar compounds has already been prepared in our laboratories.[16] Alternatively, a conformationally locked tetrahydro-β-carboline can be generated by subjecting a deprotected **1** to a Pictet-Spengler reaction. This allene-containing tetrahydro-β-carboline can then be subjected to a Ag(I)-catalyzed cycloisomerization reaction to give **9**.[17,18] Alternatively, functionalization of the allene-containing tetrahydro-β-carboline with an alkyne and reaction with molybdenum hexacarbonyl gives the Pauson-Khand product **5**; reaction of the same allene-yne to the thermal [2 + 2] cycloaddition reaction gives **7**. Attempts to effect the Rh(I)-catalyzed cyclocarbonylation reaction to give **3**

under the standard conditions were not successful. The details for accessing these skeletally unique compounds are delineated within.

Results and Discussion

Methodology Development

To obtain the requisite allene-yne for the indolylmethyl-containing scaffolds **2**, **3** and **4**, tryptophan was benzoyl protected and then converted to corresponding propargyl ester using dicyclohexylcarbodiimide and N,N-dimethylaminopyridine in 84% yield over two steps. The Boc group was then appended to the indolyl nitrogen to afford **10** in 88% yield.[19] Propargyl ester **10** was subjected to triphenylphosphine, carbon tetrachloride, and triethylamine to effect a dehydrative Claisen rearrangement followed by treatment with methanol and triethylamine provided allenic amino-ester **11** in 67% yield.[20] Allene-ynes **12a–c** were then obtained via reaction of **11** with propargyl bromides **13a–c** in the presence of sodium hydride in DMF in 45–78% yield (Scheme 2).

Next, the allene-ynes were subjected to the cyclocarbonylation reaction conditions. Reaction of allene-ynes **12a–c** with 5 mol% rhodium biscarbonylchloride dimer $[Rh(CO)_2Cl]_2$ under one atmosphere of carbon monoxide at 50 °C in DCE for 1–2 h afforded 84%, 88% and 70% yields of **14a, 14b** and **14c**, respectively (Scheme 2). Attempts to effect the cyclocarbonylation in the absence of the Boc protecting group afforded only products resulting from decomposition and no recovered starting material. However, it was subsequently shown that the Boc group could be removed from **14b** by heating in DMSO at 180 °C for 10 min to give **15** in 78% yield.

The molybdenum-mediated cyclocarbonylation of **12c** was previously demonstrated in our group;[21] the yield and diastereoselectivity for the formation of **16c** are shown in Scheme 2. To determine whether the groups on the terminus of the alkyne affected the yield and/or the diastereoselectivity of the cyclocarbonylation reaction, substrates **12a–b** were reacted molybdenum hexacarbonyl and DMSO in toluene to afford α-alkylidene cyclopentenones **16a–b** (Scheme 2). Unfortunately, the cyclocarbonylation of the aryl and alkyl substituted alkynes (**12a–b**) afforded the major diastereomers of **16a** and **16b** in about the same yield as terminal alkyne 43–50% yield. There was only a marginal increase in the diastereoslectivity observed for the reaction of **12b**. The diastereomeric ratios were determined by the ^{1}H NMR of the crude sample, and the major diastereomer was separated via column chromatography. The stereochemical assignments were made by analogy to compounds reported previously.

Next, we were interested in examining the thermal [2 + 2] cycloaddition of the tryptophan-substituted allene-ynes. Heating allene-yne **12a** and **12b** at 225 °C under microwave irradiation for 7–10 min afforded bicyclo[4.2.0]octa-1,6-dienes **17a** {*1, 0, 29*} and **17b**{*1, 0, 37*} in 45% and 50% yields respectively; with the Boc-group removed during these high reaction temperatures (Scheme 2). Structurally similar terminal alkynes have previously been shown to decompose under these reaction conditions, thus substrate **12c** was not subjected to the thermal cycloaddiiton.

Conformationally constrained compounds have a number of advantages over flexible ones, including the orientation of functional groups in very specific ways that can allow for more rapid determination of the pharmacophore conformation. Thus strategies to inhibit the conformational mobility of allene-ynes **12** were considered. Emerging as an interesting option was an allene containing tetrahydro-β-carboline via a Pictet-Spenger reaction. Interestingly, no examples of a Pictet-Spengler reaction performed in the presence of an allene could be identified in the literature, probably due to the strong acids and elevated reaction temperatures typically required for the cyclization.[22] We reasoned that hydrolysis

of the allene of **19** during the Pictet-Spengler reaction could be avoided if the reaction was performed at ambient temperature and in the presence of an organic acid and molecular sieves.

Preparation of the Pictet-Spengler precursor **19** was accomplished from benzamide protected tryptophan via the same strategy as that described for the synthesis of allene **11** (see supporting information). Removal of the benzoyl-protecting group of the α-allenic amino-ester **18** with Meerwein's reagent to provide amine **19** in 59% yield (Table 1).[20,23] With amine **19** in hand, we investigated the cyclization reaction via Pictet-Spengler reaction conditions. Amine **19** was subjected to aqueous formaldehyde and trifluoroacetic acid in the presence of 4 Å molecular sieves in methanol at room temperature to afford allene-containing tetrahydro-β-carboline **20a**{*1, 2, 0*} in 71% yield (Table 1, entry 1). Reaction of **19** with *p*-fluorobenzaldehyde under similar conditions in CH_2Cl_2 gave **20b**{*1, 5, 0*} in 70% yield as a 2 : 1 *trans : cis* isomeric mixture (Table 1, entry 2). Reacting **19** with *n*-butanal under the same conditions gave tetrahydro-β-carboline **20c**{*1, 9, 0*} in 68% yield, also as a 2 : 1 *trans : cis* isomeric mixture (Table 1, entry 3). The *trans*-isomer was determined to be the major product based upon calculations of the products of the subsequent allenic cycloisomerization reaction (see supporting information). [24,25]

Allene-containing tetrahydro-β-carbolines **20a–b** were next subjected to a Ag(I)-catalyzed cycloisomerization reaction (Scheme 3).[22] Reaction of tetrahydro-β-carboline derivative **20a**{*1, 2, 0*} with 20 mol% silver nitrate in acetone in a vial wrapped in aluminum foil for 18 h afforded **21a**{*1, 2, 0*} in 56% yield. Treatment of a 2 : 1 *trans : cis* mixture of tetrahydro-β-carboline **20b**{*1, 5, 0*} to the same conditions gave **21b**{*1, 5, 0*} in 72% yield as a 2 : 1 *trans : cis* isomeric mixture (Scheme 3). Equilibration of the 2 : 1 *trans : cis* isomeric mixture of **21b**{*1, 5, 0*} to a 1 : 4 *trans : cis* isomeric mixture was accomplished by via reaction of a solution of **21b**{*1, 5, 0*} in $CDCl_3$ to 2.5 equiv. of TFA for 2.5 h in quantitative yield (see supporting information). The isomers were separated via column chromatography on silica gel and characterized. Due to the lack of diastereocontrol observed in the silver catalyzed cyclization of **21b**, the cyclization of **21c** was not examined

With a more conformationally constrained allene-containing β-carboline in hand, functionalization with an alkyne group was examined. Reacting tetrahydro-β-carboline **20a**{*1, 2, 0*} with 2-butynoic acid (**22**) and isobutyl chloroformate at room temperature for 18 h afforded allene-yne **23a**{*1, 2, 37*} in 72% yield after flash chromatography (Scheme 4). Reacting **20b**{*1, 5, 0*} or **20c**{*1, 9, 0*} under similar conditions afforded no product even after refluxing in THF; suggesting that the steric bulk surrounding the N-2 position of tetrahydro-β-carbolines impedes this condensation reaction.

With allene-yne **23a**{*1, 2, 37*} in hand, we proceeded with the allenic [2 + 2] cycloaddition reaction. Heating a DMF solution of **23a**{*1, 2, 37*} in the microwave at 225 °C for 7 min afforded tetrahydrocyclobutaindoloquinolizinone **24**{*1, 2, 37*} in a 39% yield (Scheme 4). Attempts to effect a Rh(I)-catalyzed cyclocarbonylation reaction of **23a**{*1, 2, 37*} afforded an unidentifiable brown precipitate. However, protecting the nitrogen on the indole **23a** with a Boc group to give **25** enabled the reaction of propiolamide **25** in presence of molybdenum hexacarbonyl and DMSO in toluene afforded the desired α-alkylidene cyclopentenone **26** in 73% yield as a 1:1 mixture of diastereomers (Scheme 4). Interestingly, the Rh(I)-catalyzed cyclocarbonylation reaction of **25** afforded a 45% yield of a ~ 1 : 3 mixture of regioisomeric products with the major product being the α-alkylidene cyclopentenone **26,** the same product that was obtained for the molybdenum mediated process. The minor product was the desired 4-alkylidene cyclopentenone, resulting from the reaction with the distal double bond of the allene. We have observed regioselective discrepancies on occasion in our lab, and it nearly

always involves precursors with coordinating heteroatoms near the reacting alkyne or allene. The low yield of this reaction is attributed to the long reaction times (15 h).

The scope and limitation studies described above support the premise that the allene and allene-yne containing tryptophans provide entry into a multiple skeletally unique scaffolds. Below we have delineated a virtual library development exemplifying the uniqueness of this scaffold and its occupation of new chemical space when compared to the compounds in the NIH molecular repository.

Virtual Library Development and Diversity Analysis

With the synthetic methodology for the synthesis of six molecularly distinct scaffolds in place, a large virtual library composed of these scaffolds was created and data–mining methods were used to identify which and how many compounds should be synthesized to provide a representative subset of the chemical space. The ultimate goal of the data-mining task was to maximize biologically relevant chemical space with the minimum number of compounds in an effort to optimize resources. The compounds in the virtual library were assembled from commercially available building blocks from Aldrich and because very few tryptophan, propiolic acid, and propargyl bromide derivatives were commercially available, indoles and alkynes were used for the virtual library design. This substitution is plausible based upon the known syntheses of tryptophan derivatives from indoles and serine,[26] propiolic acids from alkynes and carbon dioxide, and propargyl bromides from alcohols derived from alkynes and formaldehyde. The library consists of Scaffolds 1–6 provided by the synthetic methodology (Scheme 5).

The Aldrich chemical database was mined for commercially available indoles, aldehydes and alkynes using a generic substructure search. The structures were downloaded as SD files and converted into a Microsoft Excel format and the undesired reactants were filtered out manually. For example, compounds possessing isotopes or incompatible reactive functionalities were removed from the database; although compounds containing reactive functional groups that we deemed could be easily protected were left in the list to give the best representation of potentially accessible chemical space. The aldehyde database was further refined by imposing a molecular weight constraint of < 250. The complete database consisted of 44 indoles (Chart 1A), 12 aldehydes (Chart 1B), and 51 alkynes (Chart 1C). Next, the virtual library was constructed using the Legion package of Sybyl 8.0 to generate *528* compounds of the Scaffold 4 and 2,244 compounds of each of the scaffolds 1, 2, 3, 5 and 6 for a total of 11,748 compounds.

A Diversity analysis was performed using a combination of cell partition based chemistry space matrix computations using BCUT (Burden (B) CAS (C) Pearlman at the University of Texas (UT)) metrics and Tanimoto coefficient (Tc) similarity calculations using two-dimensional (2D) fingerprints.[27] NIH Molecular Libraries Small Molecule Repository (MLSMR) collects samples for high throughput biological screening and distributes them to the NIH Molecular Libraries Probe Production Center Network. As our group is in this network, we applied 3D chemistry space BCUT metrics calculations to analyze the structural diversity of the virtual library and to determine whether the virtual library contributes chemical diversity value to the existing MLSMR library. The calculations showed that compounds found within this virtual library fill new chemical space or void regions when compared to the 327,000+ compounds from NIH small molecule repository (MLSMR).[28] The BCUT matrix considers physical properties including atomic Gasteiger-Huckel charges, polarizabilities, H-bond donor (HBD), and H-bond acceptor (HBA) descriptors. These four descriptors correspond to electrostatic, dispersion, and H-bonding modes of the important bimolecular interactions. For the three-dimensional plot shown in Figure 1, we selected the three molecular property descriptors that gave the most diverse

representation of our library of compounds when compared to comparison to the MLSMR. Each scaffold is color-coded and each dot represents a compound in the chemistry space matrix. All compounds from the scaffolds occupy the void regions except for scaffold 4 that is imbedded among the grey regions of MLSMR chemical space (Fig. 1).

A pairwise similarity comparison was also performed for each core in order to evaluate the similarity properties of the new virtual library versus the entire MLSMR database by using a 2D fingerprint Tanimoto coefficient (Tc) calculation. In this step, the most similar compound in the MLSMR database was identified for each individual molecule in the virtual library and the corresponding Tanimoto coefficient (Tc) value of these two compounds was recorded. The compound similarity results shown in Table 2 indicated that all the compounds derived from Scaffolds 1, 3, 5 and 6 have Tc values less than 0.75 and, none of the compounds in the virtual library have Tc value larger than 0.8, when compared to the compounds in the MLSMR database; all six scaffolds have a mean Tc value well below 0.75 (0.63, 0.74, 0.64, 0.73, 0.67 and 0.67 for Scaffolds 1–6, respectively). Moreover, the largest Tc value is 0.71 for compounds derived from Scaffold 3, which means none of these compounds has Tc score more than 0.71 when compared with any of the MLSMR compounds.

Because synthesis of a compound subset from this virtual library of 11,748 compounds is the final goal of these calculations, fifty-three representative compounds were extracted from the library by cell-based diverse subset selection using the DVS package of Sybyl 8.0. This subset consisted of nine compounds from Scaffold 1, seven compounds from Scaffold 2, thirteen compounds from Scaffold 3, seven compounds from Scaffold 4, five compounds from Scaffold 5 and twelve compounds from Scaffold 6. For comparison purposes, this fifty-three compound subset has been highlighted within the overall virtual library (Fig. 2).

Methodology for the synthesis of six tryptophan-derived scaffolds has been developed using the Pictet-Spengler, metal-catalyzed allenic cyclocarbonylation, microwave-assisted allenic [2 + 2] cycloaddition, and Ag(I)-catalyzed allenic cycloisomerization reactions. The scaffolds were used as the basis for a virtual library possessing 11,748 compounds virtual library that occupies new regions of chemical space when compared to the MLSMR using the BCUT metrics and 2-D fingerprint analysis methods. A subset of fifty-three compounds was selected to represent chemical space within the entire virtual library with the aid of the DVS package of Sybyl 8.0, molecular weight filtering, and manual selection of synthetically feasible building blocks. This approach to library synthesis should aid in future endeavors to fill chemical space and expedite the generation of compound diversity. The synthesis of and biological evaluation of these fifty-three compounds will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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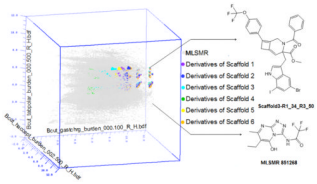


Figure 1.

3D chemistry-space matrix plots of a virtual library of 11,748 compounds constructed from Scaffolds 1–6 (Scaffold 1 = purple dots, Scaffold 2 = blue dots, Scaffold 3 = cyan dots, Scaffold 4 = green dots, Scaffold 5= yellow dots, Scaffold 6 = light orange dots) and the 327,000+ compound MLSMR (gray dots) by Sybyl diversity analysis based on the BCUT metrics calculation. The new compounds clearly fill voids in chemical space when compared to the MLSMR database.

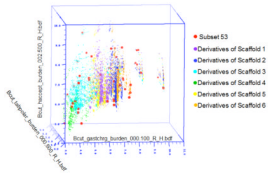
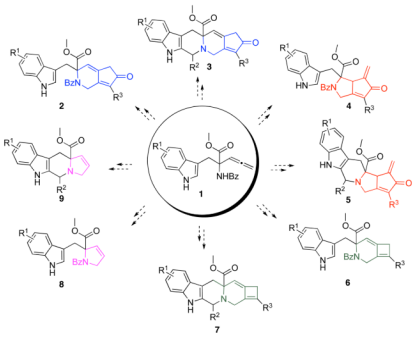
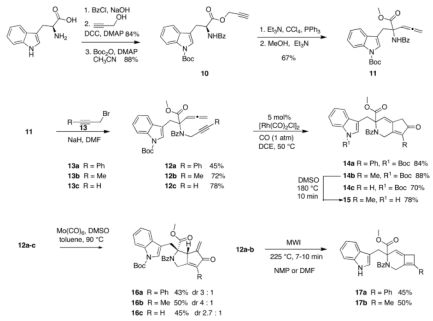


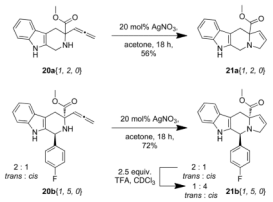
Figure 2.
3D chemical space comparison plot of the 53 representative compounds (red dots) vs. the 11,748 compound virtual combinatorial library built from six scaffolds (color coded).



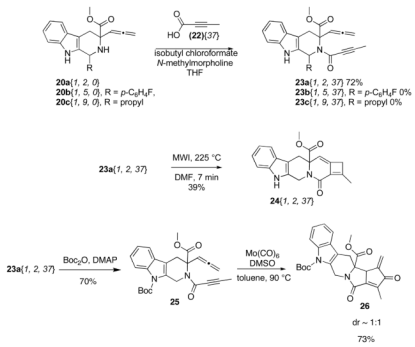
Scheme 1.
Diverging DOS Strategy for an Allene-containing Tryptophan



Scheme 2.
Synthesis, Cyclocarbonylation and Carbocyclization Reactions of Allene-ynes **12a–c**

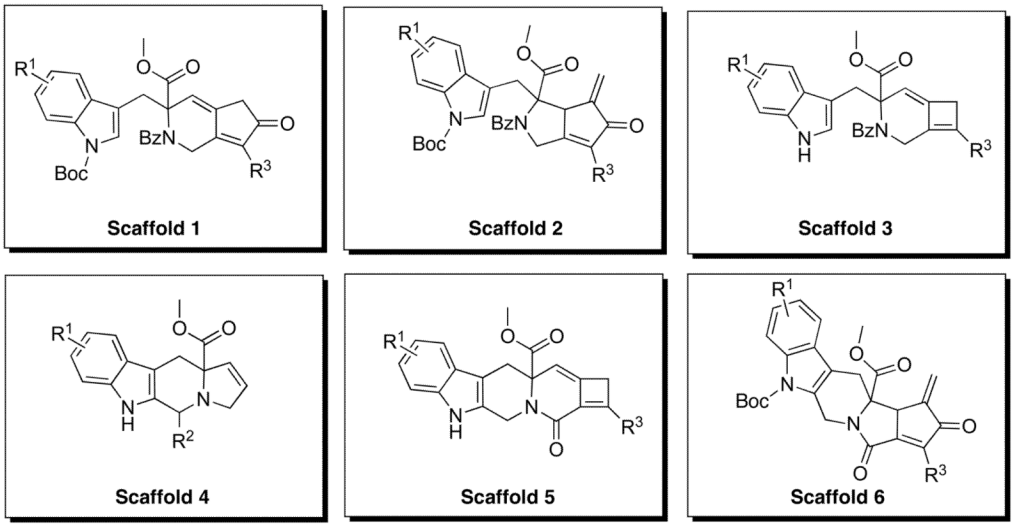


Scheme 3.
Synthesis of Tetrahydroindolizinoindoles



Scheme 4.

Synthesis, Cyclocarbonylation and Carbocyclization of Allene-yne **23a**{*1*, *2*, *37*}



Scheme 5.
Library Scaffold Assignment

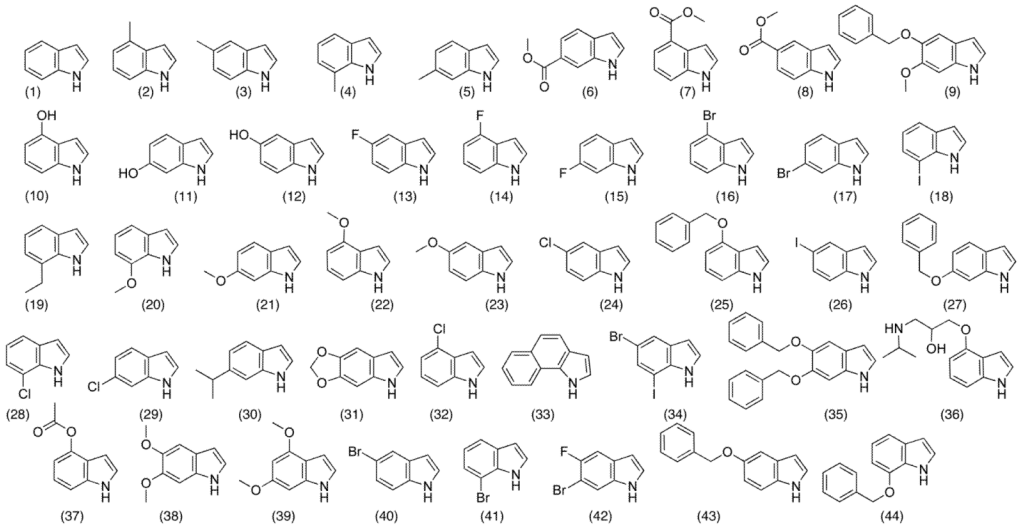


Chart 1A.
Indole Building Blocks

Chart 1B.
Aldehyde Building Blocks

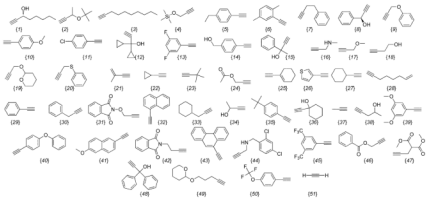
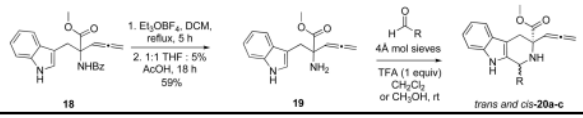


Chart 1C.
Alkyne Building Blocks

Table 1

Pictet-Spengler Reaction Affording Allenic Tetrahydro-β-Carbolines **20a–c**



18 19 *trans and cis*-**20a-c**

Entry	R	Product	Solvent	Reaction Time	Yield (%)	dr
1	H	**20a**{*1, 2, 0*}	CH_3OH	5 h	71	N/A
2	*p*-C_6H_4F	**20b**{*1, 5, 0*}	CH_2Cl_2	2.5 h	70	2 : 1
3	*n*-Pr	**20c**{*1, 9, 0*}	CH_2Cl_2	50 min	68	2 : 1

Table 2

2D Fingerprint similarity results for comparison of the derivatives of six scaffolds with the MLSMR compounds

Scaffold	Mean Tc (stdev)	% Compounds < Tc 0.75	Tc Max.
1	0.66 (0.02)	100	0.73
2	0.74 (0.03)	61.5	0.85
3	0.64 (0.02)	100	0.71
4	0.73 (0.03)	79.7	0.80
5	0.67 (0.02)	100	0.74
6	0.67(0.02)	100	0.73