ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

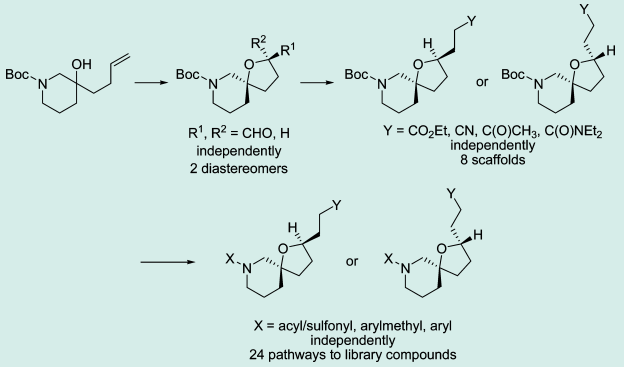
Diversity by Divergence: Solution-Phase Parallel Synthesis of a Library of *N*-Diversified 1-Oxa-7-Azaspiro[4.5]decan-2-yl-Propanes and -Butanes

Sarvesh Kumar, Paul D. Thornton, and Conrad Santini*

Center for Chemical Methodologies and Library Development, The University of Kansas, 2034 Becker Drive, Lawrence, Kansas 66047, United States

Supporting Information

ABSTRACT: The synthesis of a 162-member compound library derived from a single precursor via a multistage divergence strategy is described. Divergence is sequentially introduced in three ways: (1) by early preparation of two separable spirocyclic diastereomers, (2) by elaboration of each spirocyclic diastereomer to a different scaffold using four Horner−Emmons−Wadsworth reagents, and (3) by employing three different modes of nitrogen diversification with each scaffold to afford the final compounds. This 2 diastereomers × 4 reagents × 3 modes of diversification strategy leads to 24 unique synthetic pathways that ultimately afforded, in parallel format, the 162-compound set.



KEYWORDS: *stereogenic spirocycles, divergent synthesis, branching pathways, multistage diversification, saturated scaffolds, saturated library compound synthesis*

INTRODUCTION

In recent years, there has been growing recognition that incorporating higher numbers of saturated carbons into compounds that comprise screening collections is necessary to more effectively explore chemical space in three dimensions.[1] The discovery, development, and application of parallel synthetic methodology to prepare compound libraries featuring both increased sp^3 carbon content along with multiple stereocenters has assumed an increasingly and deservedly prominent place in the chemical biology discovery landscape. In particular, methodology that can provide multiple diastereomeric scaffolds suitable for wide diversification offer the promise of filling in areas of structural diversity that have previously been relatively unexplored.[2]

Completely saturated spirocycles are a class of scaffolds that have not been employed for compound library synthesis as frequently as others that incorporate aromatic moieties, such as benzeneoid or heterocycles. In a high-throughput setting, where analytical and preparative detection most often relies on UV absorption, library compounds with few or no unsaturated atoms can be challenging to work with given the lack of strong chromophores. This liability can, in many cases, be addressed by using non-UV dependent techniques like evaporative light scattering detection (ELSD) for automated HRMS preparative purification and analysis.[3] Even with such processing options available, the compound libraries most often reported in the literature are produced from scaffolds containing aromatic rings.

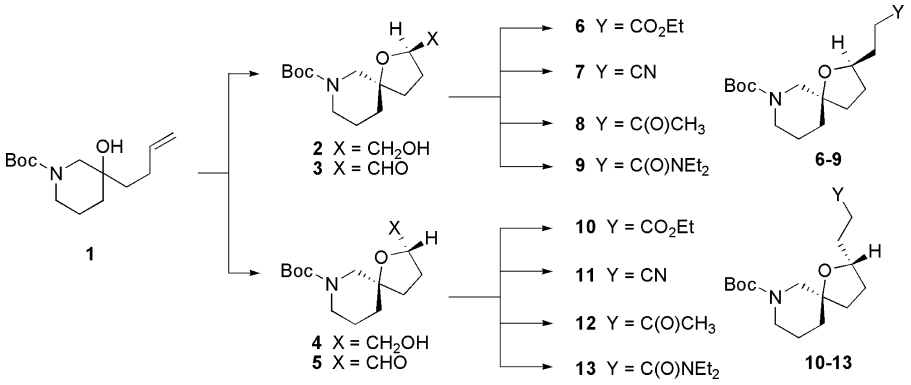
As part of our mission to discover and deploy new chemical methodology in the pursuit of novel structural diversity we embarked on studies designed to create versatile, saturated scaffolds with multiple stereocenters that could be used for parallel synthesis. This report describes our early studies leading to the production of a 162-member library of compounds derived from a pair of saturated, diastereomerically pure spirocyclic amino aldehydes.

RESULTS AND DISCUSSION

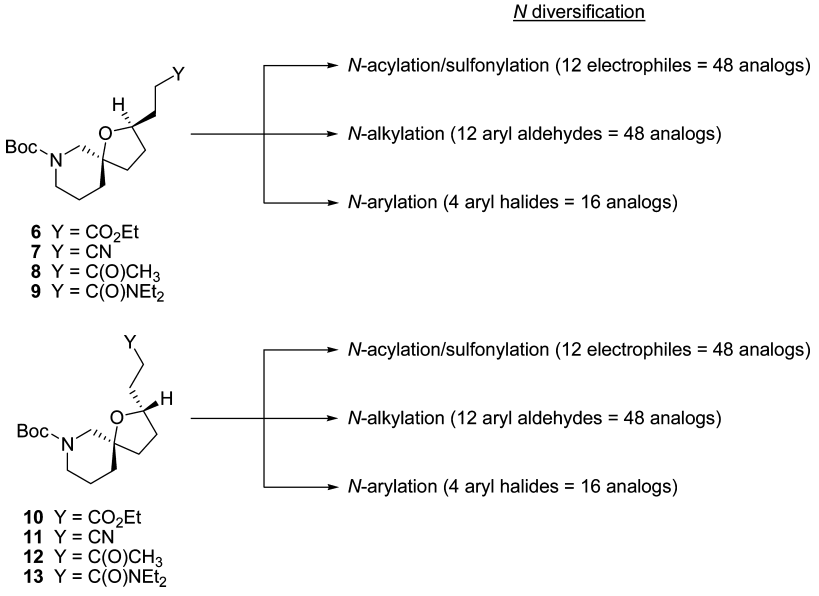
General Library Design and Synthesis. We began our library studies based on our previously reported preparation of both diastereomers of racemic *tert*-butyl 2-(hydroxymethyl)-1-oxa-7-azaspiro[4.5]decane-7-carboxylates **2** and **4**.[4] We pursued two goals in this first foray into parallel synthesis using these new spirocyclic N-Boc protected amino alcohols. The first goal was to design the synthetic sequence in a way that quickly and divergently afforded multiple scaffolds. Scheme 1 illustrates the concept. Starting from alcohol **1**, epoxidation followed by spontaneous spirocycliztion via 5-exo-trig[5] attack of the hydroxyl group on the terminal epoxide affords a mixture of the readily separable diastereomers **2** and **4**. The generation of two stereocenters in **2** and **4** provides the first point of divergence. Oxidation of alcohols **2** and **4** to their

Received: August 12, 2013
Revised: September 16, 2013
Published: September 30, 2013

Scheme 1. Plan for Scaffold Diversification by Divergence



Scheme 2. Proposed N-Diversification of Scaffolds 6−13



corresponding aldehydes **3** and **5** is followed by the division of each diastereomer into four parallel synthetic pathways that constitute a second point of divergence. Each path involves a two-step Horner−Emmons−Wadsworth (HEW)/hydrogenation sequence. These transformations afforded eight scaffolds **6−13**, each with one of four different functional groups at the end of the appended 2-carbon chain. Thus, in only four steps from the nonstereogenic precursor **1**, we obtained eight diastereomerically pure scaffolds via two points of divergence.

Our second goal was to determine if the functional groups that were appended onto the carbon side chains of scaffolds **6−13** were compatible with the N-diversification chemistry that we envisioned using (Scheme 2). The three major modes of N-diversification were acylation/sulfonylation, reductive alkylation and transition metal catalyzed arylation. Employing these three types of N-diversification would create a third point of synthetic divergence. In this way a single readily available starting material would serve as the source for a wide variety of library compounds.

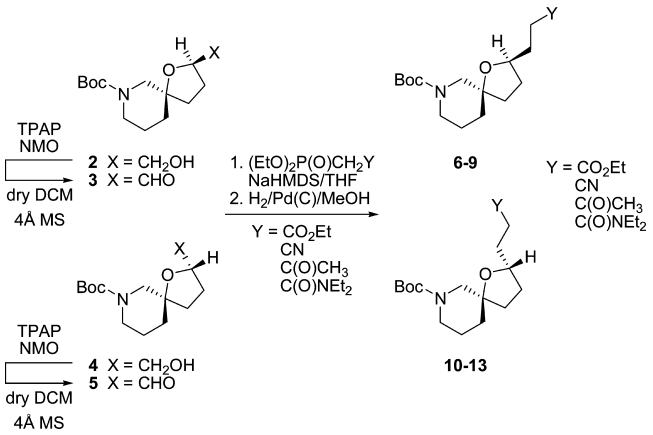
Preparation of Scaffolds 6−13. The protected spirocyclic amino alcohols **2** and **4** were obtained as previously reported.[4] We wanted to minimize the number of isolation steps in the synthetic sequence before reaching the desired final library compounds, which would then be purified at the end by high resolution mass directed fractionation (HR-MDF). Thus, alcohols **2** and **4** were oxidized to their respective aldehydes **3** and **5** using the Swern method.[6] We previously reported the isolation of **3**. Although there was clear evidence, based on ^{1}H NMR spectroscopy of the crude reaction mixture, that aldehyde **5** was being generated we never obtained it in analytically pure form.[7]

In the event we found that aldehydes **3** and **5** could be generated using the Swern oxidation and carried forward without rigorous purification. To ensure that stereochemical integrity was preserved during the oxidation, samples of the two aldehydes **3** and **5** were reduced ($NaBH_4$, EtOH, rt) back to the widely separated (TLC) alcohols **2** and **4**. Examination of the reduction products (TLC, ^{1}H NMR) revealed no cross contamination, indicating no epimerization of the oxygen substituted methine proton as a result of the Swern procedure. The two aldehydes were converted to the corresponding acrylates derived from HEW reaction with ethyl 2-(diethoxyphosphoryl)acetate (acrylates not shown). The acrylates were obtained as the trans isomer based on the coupling constants observed by ^{1}H NMR spectroscopy of the crude products. However, the acrylates derived in this manner were unacceptably sluggish substrates for catalytic hydrogenation. We suspected catalyst poisoning by residual sulfur containing contaminants derived from the Swern reaction. For process simplification purposes we chose to avoid the Swern

dx.doi.org/10.1021/co4001056 | ACS Comb. Sci. 2013, 15, 564−571

protocol altogether and to instead generate aldehydes **3** and **5** using the combination of TPAP/NMO (Scheme 3).[8] Rigorous

Scheme 3. Preparation of Scaffolds 6−9 and 10−13



exclusion of solvent borne water (<50 μg/mL by KF titration), use of fresh NMO·0.21 H_2O and close monitoring were important for obtaining the highest crude yields of **3** and **5** from these oxidations. The crude aldehydes were recovered by filtration and promptly used for the next steps without further purification after again verifying stereochemical integrity. Aldehydes **3** and **5** were each divided into four portions, combined with the four depicted phosphonate reagents and exposed to NaHMDS as base.

The four crude acrylates, obtained by liquid/liquid extraction, were subjected to catalytic hydrogenation under balloon pressure to give the eight saturated scaffolds **6−13**. The rate of hydrogenation, as judged qualitatively from LCMS analysis performed every hour, varied depending on the identity of the substituent Y. Reaction times varied from 4 to 18 h. The substituents are depicted in the order of increasing reaction time, from ethyl ester to nitrile to methyl ketone to diethyl amide. The order was the same for both diastereomeric spirocycles.

Diversification by N-Acylation/Sulfonylation. We chose this avenue of diversification first because it was the most straightforward and offered us the opportunity to use scaffolds **6−13** as crude materials. We selected nine carboxylic acid chlorides and three sulfonyl chlorides as our component set, comprising a target library of 96 compounds. The acid and sulfonyl chlorides are shown in Figure 1.

Nitrogen deprotection of scaffolds **6−13** generated the crude TFA salts which were rendered free of excess TFA by serial dilution with toluene and evaporation (Scheme 4). The TFA salts were combined with the electrophiles shown in Figure 1. Liberation of the amine in situ led to acylation/sulfonylation. Liquid/liquid extraction in parallel followed by solid phase extraction (SPE) afforded the crude amides/sulfonamides. Parallel evaporation followed by processing with HR-MDF as described in the General Methods gave the purified products. As anticipated based on the results of small validation libraries prepared in advance (results not shown), the conversion of the eight crude scaffolds **6−13** to the 96-membered acylation/sulfonylation library was gratifyingly successful.

Twelve of these library compounds had very weak or no absorbance at 214 nm. Compounds derived from scaffolds not having the diethylamide moiety, that is, scaffolds **6−8** and **10−12**, when diversified with electrophiles AC10 and AC12 (Figure

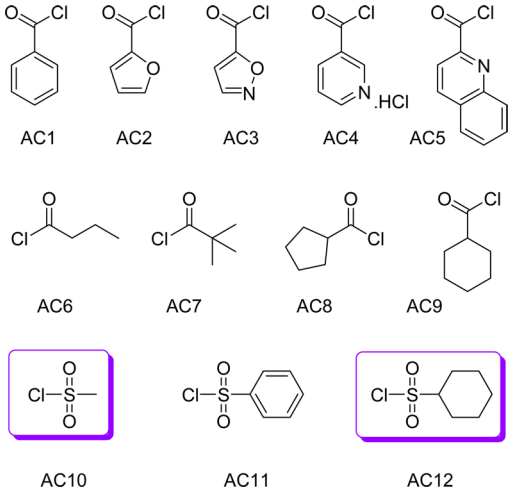
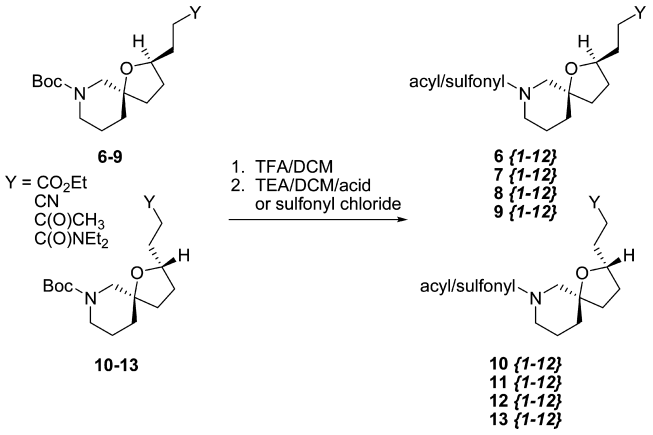


Figure 1. Carboxylic acid chlorides and sulfonyl chlorides used for 96-member library.

Scheme 4. Diversification of Scaffolds 6−13 by N-Acylation/Sulfonylation



1, boxed structures), could not be detected by UV absorbance. In these twelve cases, the compounds were purified by HR-MDF with mass trigger only. The ELSD technique was employed for final analysis.

Of the 96 compounds originally targeted 90 were obtained in our target purity of ≥90% (area% by HPLC) and ≥5 mg quantity. The library compound amounts and overall yield, from alcohols **2** and **4** are shown in Table 1. Thus the acylation/sulfonylation library was produced in seven steps from commercially available starting materials with the only intermediate purification being the required separation of diastereomers **2** and **4**.

Diversification by N-Reductive Alkylation. We chose the aldehyde components for N-reductive alkylation shown in Figure 2. On the basis of results from validation libraries (not shown) the ketone bearing scaffolds **8** and **12** were removed because of consistently poor performance. This left 72 target compounds.

Reductive alkylation was performed by N-deprotection to generate the TFA salts as above. The salts were redissolved in DCM and the amine liberated with DBU. The aldehyde was added followed by sodium triacetoxyborohydride (STAB). After the reactions were complete water was added, the phases

dx.doi.org/10.1021/co4001056 | ACS Comb. Sci. 2013, 15, 564−571

Table 1. Final Results from N-Acylation/Sulfonylation Library Synthesis

	MDF amounts mg (overall yield from 2 or 4 (%))							
	scaffold							
acid Cl	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
AC1	26(27)	23(27)	11[a]	25(24)	44(45)	29(34)	23(26)	17(16)
AC2	39(41)	22(27)	19(22)	27(26)	39(41)	31(38)	19(22)	33(32)
AC3	10(11)	12(15)	5(6)	13(13)	15(16)	20(25)	9(10)	36(35)
AC4	23(24)	18(21)	5(6)	14(13)	21(21)	0[a]	1[a]	8(8)
AC5	32(29)	26(26)	16(15)	29(24)[b]	40(36)	21(21)	25(24)	43(36)
AC6	10(11)	21(28)	15(19)	16(17)	38(43)	27(36)	22(28)	36(38)
AC7	26(28)	0[a]	15(18)	26(26)	41(45)	28(36)	19(23)	16(16)
AC8	8(8)	20(24)	19(22)	21(20)[b]	41(43)	30(37)	9(10)	15(15)
AC9	35(35)	28(33)	12(13)	26(24)	4[a]	11(13)	17(19)	19[a]
AC10	22(24)	12(16)	6(7)	16(16)	33(37)	28(36)	15(18)	27(28)
AC11	29(27)	28(30)	13(13)	17(15)	39(36)	37(39)	32(32)	8(7)
AC12	18(16)	12(12)	13(13)	16(14)	25(23)	23(24)	17(17)	21(18)[b]

[a]Compounds that were not obtained in sufficient quantity or purity (mg). [b]Compounds reprocessed by pTLC after HR-MDF to reach target purity of ≥90%

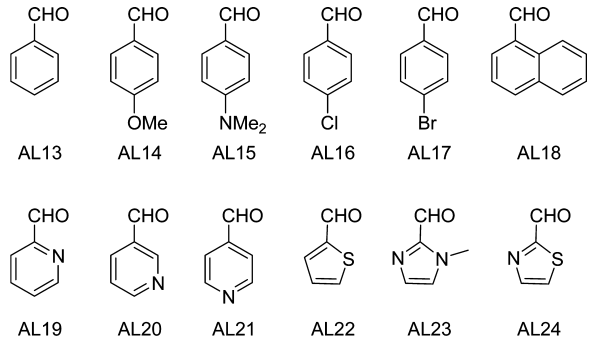
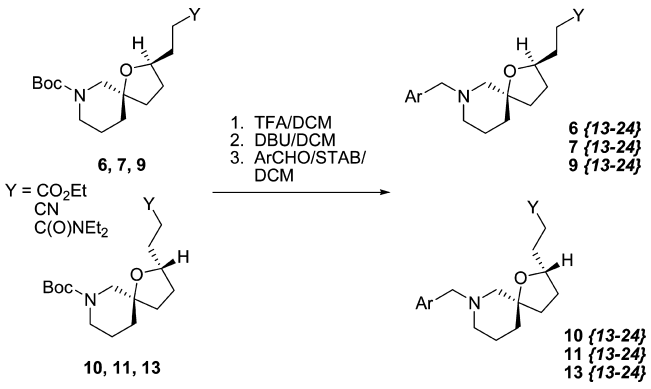


Figure 2. Aromatic aldehydes used for 72-member reductive alkylation library.

separated and the reactions evaporated in parallel and processed by HR-MDF (Scheme 5).

Scheme 5. Diversification of Scaffolds 6, 7, 9, 10, 11, and 13 by N-Reductive Alkylation



This diversification sequence had a lower success rate than acylation/sulfonylation. Overall yields were diminished and more of the compounds required additional processing to reach the 90% (area% by HPLC) target purity requirement. Having removed the methyl ketone bearing scaffolds **8** and **12**, there remained the unexpectedly poor performance of scaffold **10** (Table 2). Examination of the final results reveals that aldehydes **14** and **15** were also poor performers. By contrast

Table 2. Final Results from N-Reductive Alkylation Library Synthesis

	MDF amounts mg (overall yield from 2 or 4 (%))					
	scaffold					
aldehyde	**6**	**7**	**9**	**10**	**11**	**13**
AL13	12(4)[b]	10[a]	7(2)[b]	11[a]	33(12)	41(12)
AL14	13[a]	5[a]	12[a]	14[a]	7(3)	55(18)
AL15	5[a]	4[a]	11[a]	10[a]	6[a]	41(11)
AL16	12(4)[b]	15(6)	32(9)	3[a]	19(6)	65(19)
AL17	10[a]	19(7)	37(10)	5[a]	22(7)	61(16)
AL18	30(9)	7(6)	32(9)	53(16)	20(7)	86(24)
AL19	17(6)	13(6)	29(9)	0[a]	42(15)	146(46)
AL20	16(6)	18(8)	29(9)	0[a]	6[a]	182(57)
AL21	17(6)	12(5)	26(8)	3[a]	17[a]	68(22)
AL22	12(4)[b]	22(10)	6(2)	5[a]	7(3)	63(20)
AL23	17(6)	6(3)	lost	7(2)	49(17)	lost
AL24	6(2)	5(2)	26(8)	4[a]	23[a]	26(8)

[a]Compounds that were not obtained in sufficient quantity or purity (mg). [b]Compounds reprocessed by pTLC after HR-MDF to reach target purity of ≥90%

diethyl amide scaffold **13** was an excellent performer, significantly better than even its corresponding diastereomer **9**. The reasons for these behaviors were not rigorously investigated. Of the 72 compounds originally targeted 48 were obtained in our target purity of ≥90% (area% by HPLC) and ≥5 mg quantity with two compounds being lost due to handling errors.

Diversification by N-Arylation. Transition metal catalyzed N-arylation in a parallel synthesis format was anticipated to be the most challenging avenue of diversification. For this reason we designed our library with a more limited number of possible combinations. Using the aryl halides shown in Figure 3, we targeted a 24-compound library.

We began our studies by using the ester bearing scaffold **10** as a model substrate. Crude scaffold **10**, obtained as described above, was deprotected. The TFA salt derived from crude **10** was subjected to the conditions shown on line 1 of Table 3 with bromobenzene as the aryl source. Only trace amounts of the N-phenylated product **10**{25} were detected. Reasoning that the crude scaffold substrate was unsuitable for N-arylation we

dx.doi.org/10.1021/co4001056 | ACS Comb. Sci. 2013, 15, 564−571

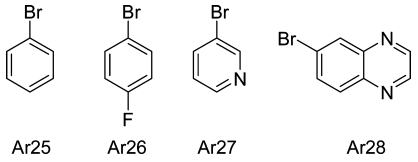


Figure 3. Aryl halides used for 24-member N-arylation library.

introduced an isolation step into the synthetic sequence. The scaffold **10** was therefore purified by column chromatography and then subjected to the same N-arylation conditions as above. This second attempt afforded a 27% yield of the desired product after column chromatography, thus indicating that the intermediate scaffold purification was crucial to the success of the sequence. The purified **10** was used for catalyst, ligand, and reaction screening as shown in the partial list depicted in Table 3. A complete list of the screened conditions is contained in the Supporting Information (SI).

The best results were obtained using the conditions shown in entry 9 (Table 3).[9] Once again, based on the results of small validation libraries, ketone bearing scaffolds **8** and **12** were removed as substrates. To complete the library production we therefore prepared the scaffolds **6**, **7**, **9**, **10**, **11**, and **13** as before and purified them by chromatography (see Experimental Procedures for details and SI for yields).

With the slight modification of a 48 h reaction time these six substrates were adopted for production of the 24-member N-arylation library using the conditions from entry 9. The N-arylated compounds were poorly absorbing at 214 nm but were highly visible at 254 nm. Because of ease of isolation we purified the library compounds at the benchtop instead of processing them using HR-MDF. The results are shown in Table 4. All 24 of the targeted library compounds were successfully produced.

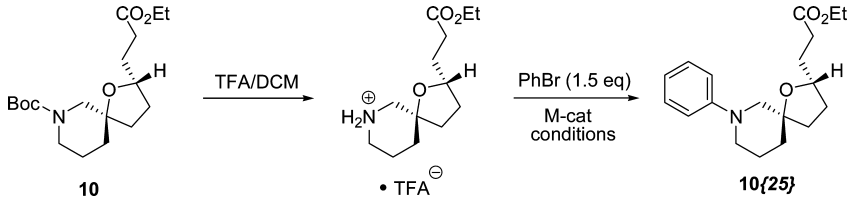
CONCLUSIONS

A strategy to synthesize libraries of compounds by rapid spirocycle scaffold divergence has been demonstrated. The early generation of two stereocenters in the fully saturated scaffolds provided a two-prong point of divergence. After oxidation, the scaffolds were divided into a Horner−Emmons−Wadsworth/hydrogenation sequence to provide a four-prong point of divergence. Each of the eight resultant scaffolds were then subjected to nitrogen functionalization (i.e., acylation/sulfonylation, reductive alkylation and arylation) to provide a three-prong point of diversification. In this way, 24 unique synthetic pathways were formulated for execution in parallel format. The methyl ketone bearing scaffolds **8** and **12** were less versatile than the others studied in this work and were not diversifiable using either N-reductive alkylation or N-arylation. The resultant library of 162 compounds was not only novel, but featured many analogs which were pairs of complementary diastereomers. This characteristic provides the opportunity to determine the effect of localized stereochemical changes on the biological activity of the compounds. All the compounds reported in this work were provided to the NIH Molecular Libraries and Small Molecule Repository (MLSMR).

EXPERIMENTAL PROCEDURES

General Methods. All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gastight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. CH_2Cl_2 was purified by passage through a purification system employing activated Al_2O_3. CH_2Cl_2 described as "dry" was assayed using an automated Karl Fischer titration apparatus and determined to contain <50 μg/mL of water. Flash column chromatography was performed with SiO_2 from Sorbent Technology (30930M-25, Silica Gel 60A, 40−63 μm) or by using an automated chromatography instrument with an

Table 3. Catalyst/Ligand and Reaction Screening for N-Phenylation of Scaffold 10

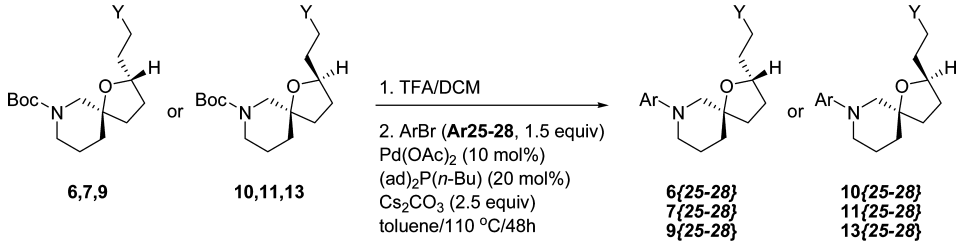


10 **10{25}**

exp. no.	Pd cat (mol %)	ligand (mol %)	base (equiv)	solvent	temp (°C)	time (h)	product (%)
1	$Pd(OAc)_2$ (10)	BINAP (20)	Cs_2CO_3 (2.5)	tol	90−110	25	27
2	$Pd(OAc)_2$ (10)	dppf (20)	Cs_2CO_3 (2.5)	tol	95	35	<5
3	$Pd(OAc)_2$ (10)	X-Phos (20)	Cs_2CO_3 (2.5)	tol	120	43	47
4	$Pd(OAc)_2$ (10)	DavePhos (20)	Cs_2CO_3 (2.5)	tol	110	45	45
5	$Pd(OAc)_2$ (10)	RuPhos (20)	Cs_2CO_3 (2.5)	tol	110	45	45
6	$Pd(OAc)_2$ (10)	XANTPHOS (20)	Cs_2CO_3 (2.5)	tol	110	45	0
7	$Pd(OAc)_2$ (10)	*t*-Bu_3P (20)	Cs_2CO_3 (2.5)	tol	110	43	0
8	$Pd(OAc)_2$ (10)	PCy_3 (20)	Cs_2CO_3 (2.5)	tol	110	19	0
9	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	Cs_2CO_3 (2.5)	tol	110	43	88
10	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	Cs_2CO_3 (2.5)	THF	110	48	71
11	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	Cs_2CO_3 (2.5)	dioxane	110	17	0
12	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	Cs_2CO_3 (2.5)	DMSO	110	17	0
13	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	K_2CO_3 (2.5)	tol	110	15	0
14	$Pd(OAc)_2$ (10)	$(1\text{-ad})_2P(n\text{-Bu})$ (20)	K_3PO_4 (2.5)	tol	110	15	<5
15	$Pd(OAc)_2$ (5)	$(1\text{-ad})_2P(n\text{-Bu})$ (10)	Cs_2CO_3 (2.5)	tol	110	40	52
16	CuI (10)	L-proline (20)	K_2CO_3 (3.0)	DMF	90−120	15	0

dx.doi.org/10.1021/co4001056 | *ACS Comb. Sci.* 2013, 15, 564−571

Table 4. Final Results from N-Arylation Library Synthesis



compound amounts mg (overall yield from N-Boc scaffolds (%))						
	scaffold					
ArBr	**6**	**7**	**9**	**10**	**11**	**13**
Ar25	49(77)	35(65)	36(53)	56(88)	42(78)	41(60)
Ar26	47(70)	35(61)	41(57)	56(83)	41(71)	47(65)
Ar27	51(80)	34(62)	34(50)	45(70)	33(61)	44(64)
Ar28	67(91)	52(81)	63(79)	68(92)	58(90)	72(90)

appropriately sized column. Thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). ^{1}H and ^{13}C NMR spectra were recorded on instruments operating at 400 or 500 MHz and 100 or 125 MHz respectively. High-resolution mass spectrometry (HRMS) spectra were obtained on a spectrometer operating on ESI-TOF. Library synthesis was carried out on a mini-block platform in 17 × 100 mm tubes with parallel evaporation. Automated preparative reverse-phase HPLC purification was performed using a mass-directed fractionation system with UV-DAD detection and a quadrapole spectrometer using a C18 column (19 × 150 mm, 5 μm, w/19 × 10 mm guard column). Samples were diluted in DMSO and purified utilizing an elution of water (modified to pH 9.8 through addition of NH_4OH) and CH_3CN, with a gradient increasing by 20% in CH_3CN over 4 min at a flow rate of 20 mL/min. The starting and ending points of the corresponding preparative CH_3CN/water gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Alternatively, for compounds having little or no absorbance at 214 nm, purification was carried out by mass trigger only. Analytical analysis of each sample after purification employed an HPLC system with UV and mass detection using an ESI-TOF mass spectrometer. The analytical method utilized a Waters Aquity BEH C18 column (2.1 × 50 mm, 1.7 μm) eluting with a linear gradient of 95% water (modified to pH 9.8 through addition of NH_4OH) to 100% CH_3CN at 0.6 mL/min flow rate where purity was determined using UV peak area at 214 nm. For compounds having little or no absorbance at 214 nm a Sedere Sedex 85 ELSD apparatus was used for purity determination.

Representative Procedure for Preparation of Crude *tert*-Butyl 2-Formyl-1-oxa-7-azaspiro[4.5]decane-7-carboxylate 3 or 5 for Library Synthesis. Crushed 4 Å mol sieves (1.250 g) were activated by flame drying (2x) under vacuum. Anhydrous NMO (1.01 g, 8.62 mmol) was added to the cooled reaction vessel and alcohol **2** (1.17 g, 4.30 mmol) was added as a solution in dry CH_2Cl_2 (32 mL). To this suspension was added tetrapropylammonium perruthenate (76 mg, 0.216 mmol, 5 mol %) at rt. The mixture turned green and then yellow and was stirred for 30 min. The mixture was filtered through a short plug of silica gel (EtOAc eluent) and the solvent was evaporated to give the aldehyde **3** (0.92 g, 79% crude yield) which was used without further purification.

Using the above procedure with alcohol **4** as starting material crude aldehyde **5** was obtained in similar crude yield and was used without further purification. See the Supporting Information for representative ^{1}H NMR spectra of aldehyde **5**.

Representative Procedure for Horner–Emmons–Wadsworth Divergence of Aldehydes 3 and 5. To a solution of ethyl diethylphosphonoacetate in THF (3.68 mL, 0.2 M, 0.736 mmol) was added NaHMDS (0.736 mL, 1.0 M in THF, 0.736 mmol) and the resulting solution was stirred for 30 min at rt. A solution of crude aldehyde **3** or **5** (2.77 mL, 0.25 M in THF, 0.669 mmol) was added to each reaction vessel and the solutions were stirred for 16 h. Saturated aqueous NH_4Cl (3 mL) was added and the mixture was extracted into CH_2Cl_2 (2 × 7 mL). The combined organic layers were evaporated and the crude acrylate used directly for hydrogenation without further purification.

Using the above procedure with crude aldehydes **3** or **5** as starting material, diethylphosphonoacetonitrile, diethylphosphonoacetone and diethyl dibutylphosphonoacetamide gave their crude respective acrylates. All eight of these intermediates were used without any further purification.

Representative Procedure for the Preparation of Crude Scaffolds 6–13 for Library Synthesis. A solution of each crude acrylate, prepared as described above, in MeOH (6 mL, ~0.11M) was added to a suspension of 10% Pd/C (70 mg) in MeOH (4 mL). The reaction vessel was fitted with a balloon filled with hydrogen and the mixture was stirred at rt. UPLC-MS and ^{1}H NMR spectroscopy were used to assess the progress of the hydrogenation. In the UPLC-MS, the strongly UV absorbing (214 nm) acrylate peak disappeared. At the same time the total ion count (TIC) of the much less absorbing hydrogenated product grew until no further changes in the analytical trace were observed. Reaction times varied according to substrate (from 4 h with the esters to 18 h with the amides). Upon complete hydrogenation, determined using ^{1}H NMR spectroscopy to confirm disappearance of the olefin signals (δ6.81 ± 0.10 (dd, J = 15.4 ± 0.7, 4.6 ± 0.6 Hz, 1H), 6.02 ± 0.39 (dd, J = 15.5 ± 0.5, 1.4 ± 0.6 Hz, 1H)) Celite was added to the mixture and the resulting suspension was eluted through a plug of Celite (EtOAc eluent). Evaporation of the solvent gave the crude scaffolds **6–13** that were used directly in the following steps.

Representative Procedure for N-Acylation/Sulfonylation of Crude Scaffolds 6–13 for Library Synthesis. Each

dx.doi.org/10.1021/co4001056 | ACS Comb. Sci. 2013, 15, 564–571

of the crude scaffolds **6**−**13** were dissolved in CH_2Cl_2 and divided into twelve portions of ∼0.23 mmol each, assuming complete conversion through the HEW/hydrogenation sequence. Using the Bohdan Miniblock platform and reaction vessels, a 20% solution of TFA/CH_2Cl_2 (2.0 mL) was added to each and the reactions were shaken at rt for 1 h. The solvent was removed under a stream of N_2. Toluene (1.0 mL) was added to each tube and evaporated under vacuum, with the operation being repeated twice more. The crude TFA salts were used without characterization.

A triethylamine solution (1.0 M in CH_2Cl_2, 1.0 mmol, 1.0 mL) was added to each vessel containing the crude TFA salts. This was followed by addition of a solution of the acid chloride/sulfonyl chloride (0.35 M in CH_2Cl_2, 1.0 mL, 0.35 mmol), and the reactions were shaken for 16 h at rt. Saturated aqueous $NaHCO_3$ (2.0 mL) was added and the mixtures extracted with CH_2Cl_2 (2 × 2.0 mL). The organic fractions were passed through a phase separator followed by an SPE using EtOAc as eluant (2 × 2.0 mL EtOAc) and collected in bar-coded CCT tubes. All volatiles were evaporated in vacuo in parallel, and the samples were submitted for HR-MDF analysis and purification.

Procedure for N-Reductive Alkylation Library Synthesis. Each of the alcohols **2** and **4** (8.65 g, 31.9 mmol) was divided in three parts in equimolar amounts to produce the corresponding TFA salts of crude saturated scaffolds **6**, **7**, **9**, **10**, **11**, and **13** following the procedure described above. Each TFA salt was dissolved in CH_2Cl_2 (12.0 mL) and equally divided in twelve parts and transferred to reactor vials (16 × 100 mm glass tubes) using the Bohdan Miniblock platform. To each reactor vial, a solution of DBU (1.77 mmol, 1 M solution in DCM, 1.77 mL, 2 equiv) was added and the reaction mixture was stirred at rt for 30 min. The aldehydes AL13−AL24 (1.77 mmol, 1 M solution in DCM, 1.77 mL, 2.0 equiv) were individually added to each reactor followed by solid sodium triacetoxyborohydride (282 mg, 1.33 mmol, 1.5 equiv). The reaction mixtures were further stirred at rt for 17 h. The reaction mixtures were diluted with H_2O (1.5 mL). The organic layer was eluted into a CCT tube through a phase separator and the aq layer was extracted with CH_2Cl_2 (2 × 2.0 mL) with the organic again eluted into the CCT tube through the phase separator. The solvent was evaporated in vacuo in a parallel evaporator and the crude amines were purified by HR-MDF.

Procedure for N-Arylation Library Synthesis. Each of the saturated scaffolds **6**, **7**, **9**, **10**, **11**, and **13**, purified by normal phase column chromatography (0% to 100% EtOAc/hexanes) were divided into portions (0.8 mmol) and dissolved in CH_2Cl_2 (3 mL) followed by the addition of 20% solution of TFA in CH_2Cl_2 (1.54 mL, 20 mmol). The solution was stirred at rt for 1h. The solvent was evaporated in a rotavapor. Toluene (2.0 mL) was added and the solution evaporated in a rotavapor, with this operation being repeated. The resulting TFA salts were dissolved in toluene (4.0 mL; 0.2 mL THF was added as a cosolvent to dissolve TFA salts from saturated scaffolds **7**, **9**, **11**, and **13**) and divided into four equal parts with each part used directly for an *N*-arylation reaction. The solution of each spirocycle TFA salt (0.2 mmol, based on Boc precursor) in toluene (1.0 mL) was added to a mixture of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), $(1\text{-ad})_2P(n\text{-Bu})$ (14 mg, 0.04 mmol, 20 mol %), and Cs_2CO_3 (163 mg, 0.5 mmol, 2.5 equiv) under argon. Halides Ar25 - Ar28 (0.3 mmol, 1.5 equiv) were individually added to each reaction vessel and the reaction mixture was heated with stirring in a closed tube at 110 °C. After 48 h, the reaction mixtures were cooled to rt and diluted with EtOAc (3 mL). Water (0.2 mL) was added and the mixture was filtered through a plug of anhy Na_2SO_4. The Na_2SO_4 was washed with EtOAc (2 × 3 mL). The combined organic extracts were evaporated in the rotavapor and the crude product was purified by silica gel column chromatography using 10−70% EtOAc-hexanes as eluent.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR spectra of aldehydes **3** and **5**, characterization data (^1H, ^{13}C, IR and HRMS) for purified scaffolds **6**, **7**, **9**, **10**, **11**, and **13**, as well as 21 library compounds, reaction/catalyst/ligand/base screening results for N-phenylation of **10**. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nyprphd@yahoo.com.

Present Address

P.D.T.: GreenCentre Canada, 945 Princess Street Kingston, Ontario, K7L 3N6 Canada

Author Contributions

P.D.T. demonstrated the synthesis and stereointegrity of scaffolds **6**−**13** from **1**, performed the process development and produced the N-acylation/sulfonylation library. S.K. performed the process development and produced the N-reductive alkylation library. S.K. performed the process development, parallel catalyst, ligand, base, temperature, and solvent screening for the N-arylation library, as well as its production and benchtop purification. S.K. provided the written characterization data for all compounds shown in the Supporting Information. C.S. wrote the manuscript with editing from P.D.T., as well as editing and referencing from S.K.

Notes

The authors declare no competing financial interest.

C.S.: 24780 Chieftain Road, Lawrence, KS 66044, USA

■ ACKNOWLEDGMENTS

We gratefully acknowledge the contributions of Mr. Patrick Porubsky, KU-CMLD Compound Curator and Purification Chemist. Financial support for the KU-CMLD was provided under NIGMS Grant 5P50GM069663 (Prof. Jeff Aubé, PI). Support for the KU-NMR Center was provided under Grant No. NIH 1S10RR024664-01.

■ REFERENCES

(1) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752−6756. (b) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(2) (a) Gerard, B.; Lee, M. D., IV; Dandapani, S.; Duvall, J. R.; Fitzgerald, M. E.; Kesavan, S.; Lowe, J. T.; Marié, J.-C.; Pandya, B. A.; Suh, B.-C.; O'Shea, M. W.; Dombrowski, M.; Hamann, D.; Lemercier, B.; Murillo, T.; Akella, L. B.; Foley, M. A.; Marcaurelle, L. A. Synthesis of Stereochemically and Skeletally Diverse Fused Ring Systems from Functionalized *C*-Glycosides. *J. Org. Chem.* **2013**, *78*, 5160−5171. (b) LaPorte, M. G.; Tsegay, S.; Hong, K. B.; Lu, C.; Fang, C.; Wang, L.; Xie, X.-Q.; Floreancig, P. E. Construction of a Spirooxindole Amide Library through Nitrile Hydrozirconation−Acylation−Cyclization Cascade. *ACS Comb. Sci.* **2013**, *15*, 344−349. (c) Beierle, J. M.;

Horne, W. S.; van Maarseveen, J. H.; Waser, B.; Reubi, J. C.; Ghadiri, M. R. Conformationally Homogeneous Heterocyclic Pseudotetrapeptides as Three-Dimensional Scaffolds for Rational Drug Design: Receptor-Selective Somatostatin Analogues. *Angew. Chem., Int. Ed.* **2009**, *48*, 4725−4729. (d) Lloyd, R. C.; Smith, M. E. B.; Brick, D.; Taylor, S. J. C.; Chaplin, D. A.; McCague, R. Chemoenzymatic Synthesis of the Four Diastereoisomers of 4-Hydroxypipecolic Acid from N-Acetyl-(*R*,*S*)-allylglycine: Chiral Scaffolds for Drug Discovery. *Org. Process Res. Dev.* **2002**, *6*, 762−766. (e) Cheng, M.-N.; Wang, H.; Gong, L.-J. Asymmetic Organocatalytic 1,3-Dipolar Cycloaddition of Azomethine Ylide to Methyl 2-(2-Nitrophenyl)acrylate for the Synthesis of Diastereoisomers of Spirotryprostatin A. *Org. Lett.* **2011**, *13*, 2418−2421.

(3) Kyranos, J. N.; Lee, H.; Goetzinger, W. K.; Li, L. Y. T. One-Minute Full-Gradient HPLC/UV/ELSD/MS Analysis to Support High-Throughput Parallel Synthesis. *J. Comb. Chem.* **2004**, *6*, 796−804.

(4) Kumar, S.; Thornton, P. D.; Painter, T.; Jain, P.; Downard, J.; Douglas, J. T.; Santini, C. Synthesis of a Family of Spirocyclic Scaffolds: Building Blocks for the Exploration of Chemical Space. *J. Org. Chem.* **2013**, *78*, 6529−6539.

(5) Baldwin, J. E. Rules for Ring Closure. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

(6) Mancuso, A. J.; Brownfain, D. S.; Swern, D. Structure of the Dimethyl Sulfoxide-Oxalyl Chloride Reaction Product. Oxidations of Heteroaromatic and Diverse Alcohols to Carbonyl Compounds. *J. Org. Chem.* **1979**, *44*, 4148−4150.

(7) See ref 4. Also see the SI for the previously unreported NMR of partially purified 5.

(8) Langer, P. Tetra-*n*-propyl Ammonium Perruthenate (TPAP)—An Efficient and Selective Reagent for Oxidation Reactions in Solution and on the Solid Phase. *J. Prakt. Chem.* **2000**, *342*, 728−730.

(9) (a) Yao, W.; He, C.; Zhuo, J.; Xu, M.; Zhang, C.; Qian, D.-Q.; Burns, D.; Metcalf, B. W. Preparation of Lactams, Particularly 2,7-Diazaspiro[4.5]decan-1-one Derivatives, as 11-β Hydroxysteroid Dehydrogenase Type 1 Inhibitors and Mineralocorticoid Receptor Antagonists and Their Use As Pharmaceuticals. PCT Int. Appl. 2006053024, 18 May 2006. (b) Yao, W.; He, C.; Burns, D. M.; Zhuo, J.; Xu, M.; Zhang, C.; Qian, D.-Q.; Metcalf, B. Lactam Compounds As 11β-HDS1 Inhibitors and MR Antagonists and Their Preparation and Use in the Treatment of Diseases. U.S. Pat. Appl. Publ. 20090291946, 26 Nov 2009.