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Report

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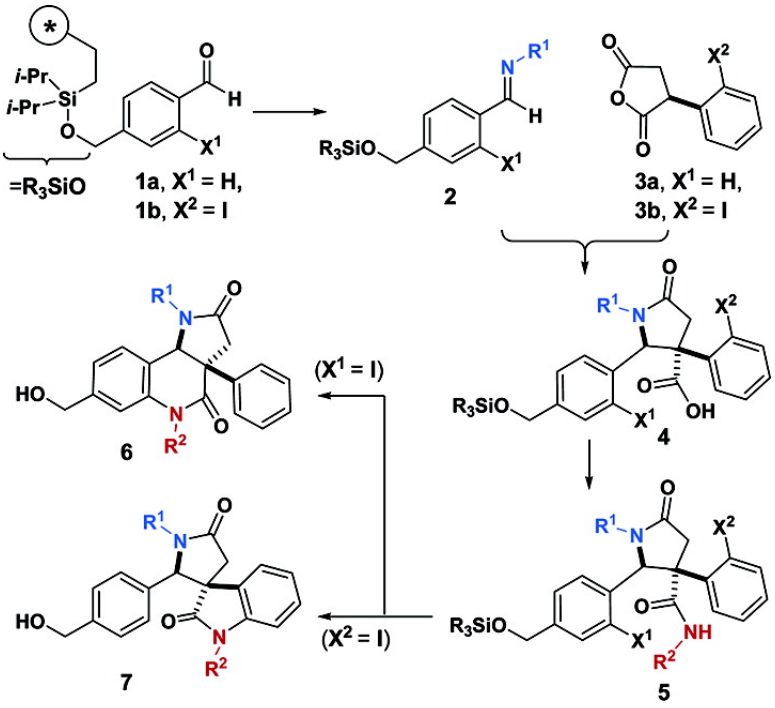

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Divergent Structural Complexity from a Linear Reaction Sequence: Synthesis of Fused and Spirobicyclic γ-Lactams from Common Synthetic Precursors

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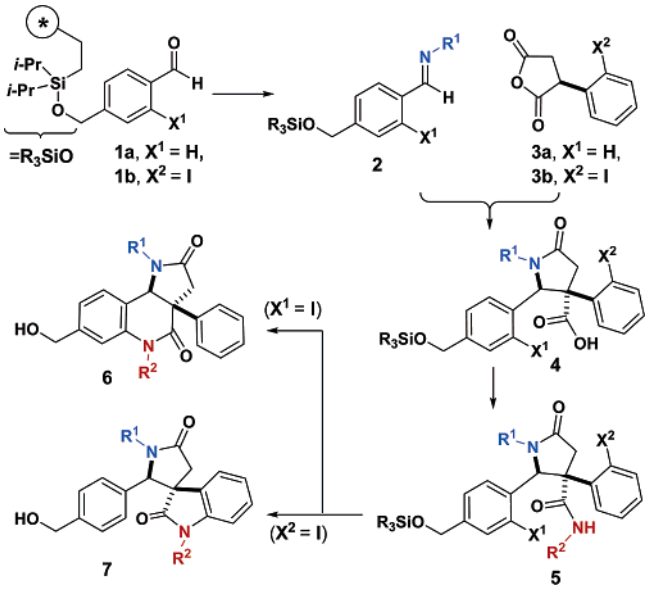
Efficient synthesis of stereochemically defined, structurally complex small molecules is important for both diversity-oriented synthesis (DOS) and the target-directed synthesis of natural products and other biologically active compounds.[1] The success of small molecule libraries for chemical genetics relies on high levels of chemical diversity to elucidate new biological pathways using high-throughput phenotypic screening.[2] The synthesis of natural product targets remains an important tool for the elucidation of complex structures[3] and for the preparation of analogues[4] for biological studies. Our investigations strive to advance both goals by developing a methodology which offers a high level of flexibility for the synthesis of small molecule libraries as well as a high level of efficiency for the synthesis of complex targets.

The cycloaddition reaction between imines and cyclic anhydrides was discovered by Castagnoli and Cushman[5] and subsequently employed in a variety of natural product syntheses.[6] Cushman's efforts focused mainly on the reactions of homophthalic anhydride and its derivatives, whereas the use of other substrates, that is, substituted succinic anhydrides, was largely unexplored. We initiated a program to fully explore the synthetic potential of the imine anhydride cycloaddition as a means to develop efficient routes to structurally diverse libraries of small molecules. During the course of these investigations, we made several observations regarding the reactivity and selectivity of this reaction which greatly increase this reaction's utility for the synthesis of small molecule libraries and target-oriented synthesis. In this Report, we disclose our preliminary results in the development of pathways that are employed in the synthesis of a complex library of polycyclic lactams.

We initially envisioned a short synthetic sequence that would produce structurally divergent core structures in a linear synthetic reaction sequence (Scheme 1). We planned to condense aldehydes **1a** and **1b** with a variety of amines, which would be subsequently used in a cycloaddition reaction with succinic anhydrides **3a** and **3b**. The reaction partners would be segregated such that each lactam product possessed only one iodine substituent, originating from either the

Scheme 1. Synthetic Plan for Structurally Divergent Library



aldehyde or the anhydride. These substrates would be pooled and split into amide formation reactions using primary amines. Finally, these iodoaryl amides would be cyclized to form either fused or spirocyclic products, depending on where the iodide was located.[7] Thus, the structural complexity that emerges from this sequence emanates from the strategic placement of key functional groups which undergo a reaction that defines the three-dimensional array of the products, in analogy to another library recently published from our laboratories.[8] This three-step sequence would provide diverse products reminiscent of a variety of bioactive small molecules of natural and unnatural origin (Figure 1).[9]

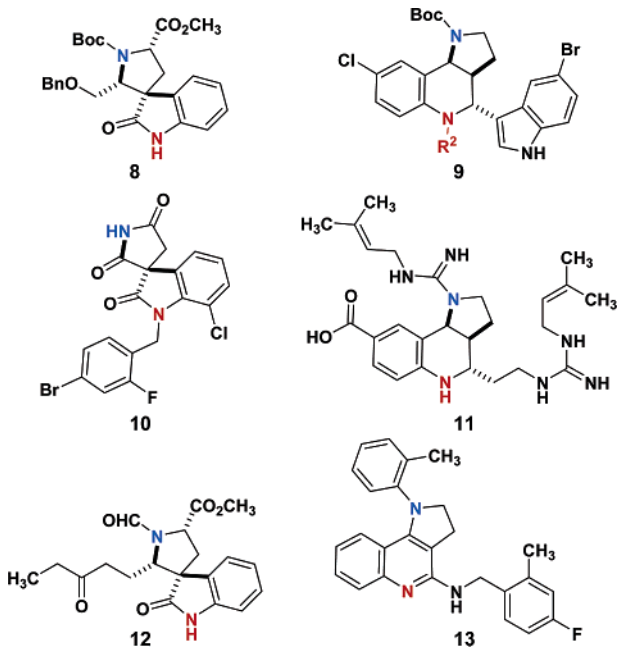


Figure 1. Natural (**11**, **12**) and unnatural (**8**−**10**, **13**) bioactive compounds featuring spirobicyclic and fused tricyclic core structures related to **6** and **7**.

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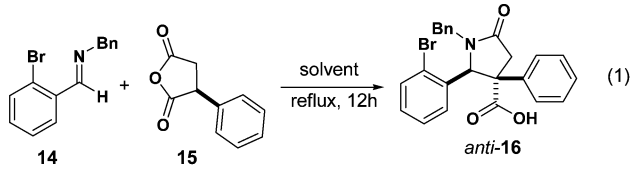
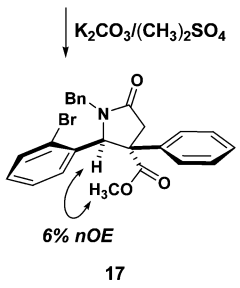
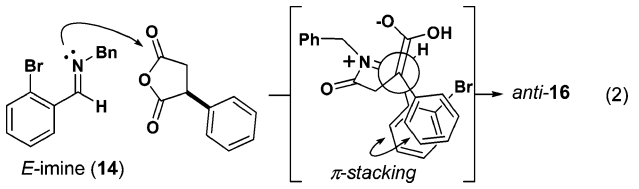
Table 1. Optimization of Phenylsuccinic Anhydride Cycloaddition



entry	solvent	*yield*	*anti:syn*
1	CH_2Cl_2	80	83:17
2	$CHCl_3$	90	83:17
3	EtOAc	88	75:25
4	THF	85	70:30
5	EtOH	79	70:30
6	DMF	[a]	-
7	CH_3CN	92	65:35
8	Benzene	94	75:25
9	***Toluene***	***93***	90:10



Scheme 2. Mechanism of the Reaction of Imine **14** with Phenylsuccinic Anhydride



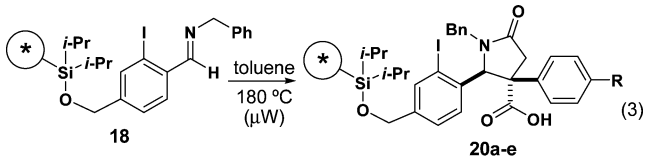
Given the importance of structural diversity on broad biological activity,[10] we anticipate that a library of compounds including these structures will display a wide variety of biological activities.

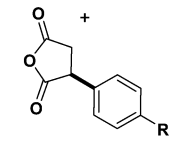
Our initial studies examined the selectivities of the reaction with the imine derived from benzylamine and *o*-bromobenzaldehyde (Table 1). A survey of solvents demonstrated that the highest yield and selectivity were observed when toluene was employed, showing a slight improvement over chloroform, which was Cushman's solvent of choice. In all cases, the anti product was formed as the major product, and we were able to confirm Cushman's stereochemical assignment with nOE experiments.

An acylative mechanism has been proposed for the reaction of imines with homophthalic anhydrides, and it is likely that a related mechanism is operative for the reaction with phenylsuccinic anhydride (Scheme 2). Cushman proposes that the kinetically favored syn diastereomer resulting from the homophthalic anhydride reaction results from a reaction with the *E* isomer of imine. We believe that the major isomer of the phenylsuccinic anhydride reaction also results from a reaction with the *E* imine, and in this case, a π-stacking interaction would favor the proposed transition state.[11]

We next investigated the feasibility of conducting this reaction using our solid-phase platform, anticipating that higher temperatures might be necessary for high conversion (Table 2). We found that use of a microwave reactor was necessary, and the diastereoselectivity was reduced. A survey of various para-substituted anhydrides[12] revealed that a methoxy group impeded the reaction slightly, whereas inductively electron-withdrawing substituents had little effect on conversion or diastereoselection. The reaction of *p*-nitrophenylsuccinic anhydride resulted in a highly diastereoselective reaction, and more importantly, the reaction could be conducted at room temperature in equally high conversion.

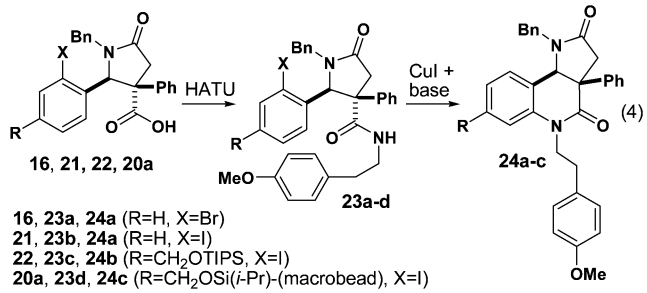
Table 2. Diastereoselectivity in the Addition of *Para*-Substituted Phenylsuccinic Anhydride to Solid-Phase Bound Imine **18**





entry	substrate	product	R	*conversion*	*anti:syn*
1	**15**	**20a**	**H**	>95	83:17
2	**19a**	**20b**	**OCH_3**	80	83:17
3	**19b**	**20c**	**Cl**	>95	75:25
4	**19c**	**20d**	**CF_3**	>95	70:30
5	**19d**	**20e**	**NO_2**	***>95***	***>95:5***
6	**19d**	**20e**	**NO_2**	***>95*** *(23 °C)*	***>95:5***

Table 3. Development of the Intramolecular Amidation Reaction in Solution and on Solid Phase



16, **23a**, **24a** (R=H, X=Br)
21, **23b**, **24a** (R=H, X=I)
22, **23c**, **24b** (R=CH_2OTIPS, X=I)
20a, **23d**, **24c** (R=CH_2OSi(*i*-Pr)-(macrobead), X=I)

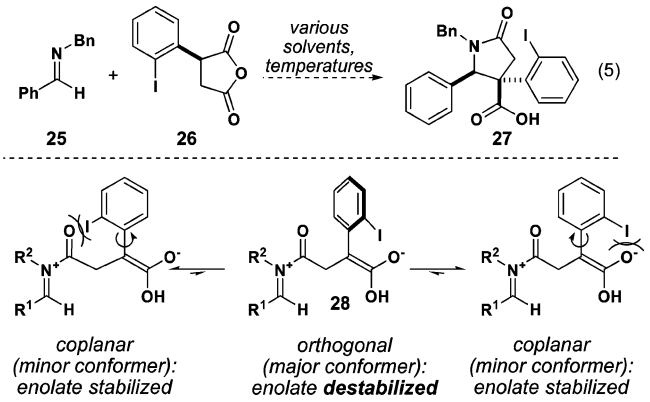
entry	substrate	solvent	*CuI (mol%)*	*base*	*T (°C)*	*yield*
1	**23a**	dioxane	5[a]	K_3PO_4	80	-
2	**23a**	dioxane	5[b]	K_3PO_4	90	-
3	**23b**	dioxane	5[a]	K_3PO_4	88	-
4	**23b**	dioxane	5[b]	K_3PO_4	85	-
5	**23a**	DMSO	200	CsOAc	90	-
6	**23b**	***DMSO***	***200***	***CsOAc***	***90***	***85***
7	**23c**	***DMSO***	***200***	***CsOAc***	***90***	***95***
8	**23d**	***DMSO***	***200***	***CsOAc***	***120***	***>95***[c,d]

[a] *N*-*N*′-dimethylethylenediamine used as ligand (10 mol %). [b] (±)-*N*-*N*′-dimethyldiaminocyclohexane used as ligand (10 mol %). [c] Conversion based on LC/MS after cleavage from resin. [d] Conducted in a microwave reactor (see Supporting Information).

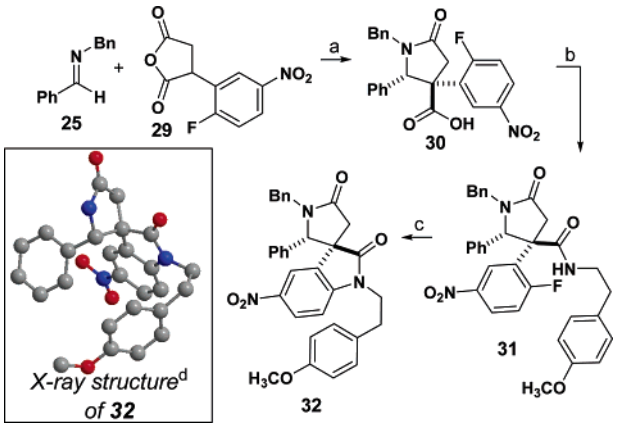
The desired tricyclic products were formed in high yield in a two-step process (Table 3). The carboxylic acid products were converted to amides under standard conditions. A highly activating coupling reagent was necessary due to the high steric demand of the carboxylic acid. Cyclization was initially attempted using catalytic amounts of diamine-complexed CuI under conditions described by Buchwald,[13] but none of the cyclized product was observed using either aryl bromide **23a** or iodide **23b** (Table 3, entries 1−4). The complimentary conditions reported by Fukuyama,[14] which use stoichiometric quantities of ligandless CuI, were unsuccessful with aryl bromide **23a**, but afforded the product in high yield when aryl iodides **23b**−**d** (Table 3, entries 5−8) were employed. This short, selective, and high-yielding sequence demonstrated the feasibility of producing the fused tricyclic core structure.

We next turned our attention to the formation of the spirocyclic ring system (Scheme 3). Cushman's study

Scheme 3. Attempted Reaction between Imine **25** and *o*-Iodophenylsuccinic Anhydride **26**



Scheme 4. Synthesis of Spirobicyclic Lactam **32**



[a] Toluene, 23 °C, 12 h, 69:31 (anti/syn). [b]PyBroP, 4-methoxyphenethylamine, 80% (2 steps). [c]K_2CO_3, DMF 95 °C, 3 h (86%). [d]N−Bn group of **32** removed for clarity.

examined only the reactions of the unsubstituted phenylsuccinic anhydride. Unfortunately, *ortho*-iodophenylsuccinic anhydride **26** did not undergo cycloaddition under a variety of conditions (eq 6). Although we did not anticipate this lack of reactivity, it is not surprising in light of the proposed mechanism. Stabilization of enolate intermediate **28** requires a coplanar arrangement of the phenyl ring with the enolate π-system. This conformation is likely disfavored by ortho substitution of the aromatic ring.

On the basis of our observations concerning the conformational and electronic effects on the reactivity of substituted phenyl succinic anhydrides, we prepared an alternate substrate to produce the spirocyclic products (Scheme 4). We envisioned that the use of an ortho fluoride would evade the detrimental conformational influence of the ortho iodide. Effective amide N-arylation would require activation by at least one nitro group, and both of these electron withdrawing groups would enhance the rate of cycloaddition. 2-Fluoro-5-nitrophenylsuccinic anhydride **29** reacted smoothly with imine **25** to provide lactam **30** in high yield (Scheme 4), albeit in modest diastereoselection. The reaction proceeds at room temperature, indicating that the combined inductive effects of the fluoro and nitro groups do contribute greatly to the reactivity of this substrate. Acid **30** could be converted to amide **31** under standard conditions. This amide was cyclized to spirocyclic oxindole **32** using K_2CO_3 in DMF, and X-ray crystallographic analysis of a single crystal confirmed the anti stereochemical assignment of **32**.

We have demonstrated that a short, linear synthetic sequence can lead to structurally diverse final products that are reminiscent of natural products and other bioactive small molecules. In this sequence, only one reaction component is varied, which leads to the placement of a key functional group that determines the three-dimensional structure of the final product. We have employed this reaction sequence in conjunction with the diastereoselective reactions of other anhydride substrates in the solid-phase synthesis of a complex library of small molecules.[15] In addition, we are currently pursuing several natural product targets using the described chemistry and developing an asymmetric variant, the results of which will be disclosed shortly.

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Supporting Information Available. Experimental Procedures, ^{1}H NMR Spectra, LC/MS Data, and X-ray Crystal Data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Recent calculations reported by Kaneti suggest a concerted, though seemingly asynchronous, addition between the imine and the monoenol isomer of the anhydride. See: Kaneti, J.; Bakalova, S. M.; Pojarlieff, I. G. *J. Org. Chem.* **2003**, *68*, 6824−6827. Given the enormous temperature differences for the reactions of various anhydrides with imines (−60 °C for homophthalic anhydride, 160 °C for succinic anhydride) it may be difficult to propose an accurate and still unified mechanism for these reactions. The acylative mechanism is consistent with our findings with regard to electronic influences and is not wholly inconsistent with the hypotheses of Kaneti.

(12) Prepared by alkylation of the corresponding arylacetic esters with an α-chloroacetic ester. See Supporting Information.

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(15) The chemistry described in this report was used in conjunction with a related sequence, which produces fused and spirocyclic δ-lactams, and these experiments will be reported shortly. A complete description of the library of 570 structurally diverse products along with preliminary screening results will be described in a full account of this work.

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