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Multicomponent Solution Phase Synthesis of Dehydroamino Acid Derivatives Based on the Passerini Reaction

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Abstract: We have synthesized a library of dehydroamino acid derivatives using a Passerini three component condensation reaction. A number of structurally diverse inputs were used, thus demonstrating a large tolerance of functionality for the key transformation.

Combinatorial organic synthesis involving solution or solid phase reactions has developed into an important technology for the generation of large libraries of small molecules for biological screening.[3] While it is often necessary to perform chemical transformations on solid support to generate large libraries of compounds,[4] it is often difficult and time consuming to adapt solution phase methods to solid support. Thus, it is frequently advantageous to carry out solution phase parallel synthesis to generate these libraries.

A multiple component condensation (MCC) reaction requires only a single synthetic transformation to create a molecule which would otherwise require multiple synthetic steps to generate the same amount of functionality and is a useful alternative for the generation of chemical libraries.[5] Unlike libraries constructed by a sequence of reactions, whose potential sizes are determined by *both* the number of reaction steps and input availability; the size of MCC-based libraries are limited only by the availability of the components in the MCC reaction. Thus, when applicable, it offers a quick and efficient means of constructing a synthetic target.

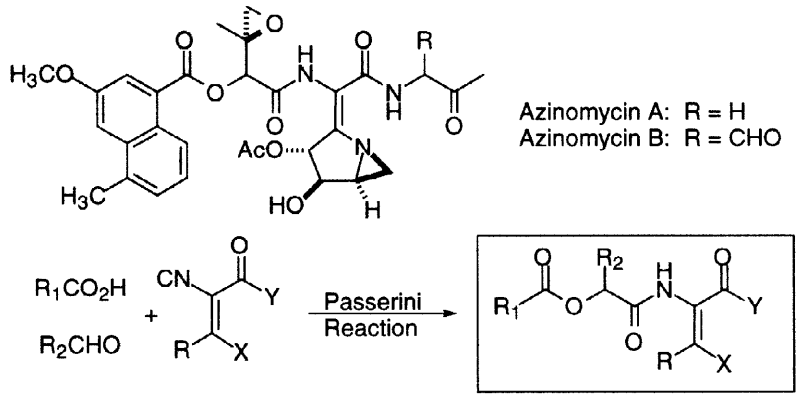

Figure 1

The antitumor antibiotics azinomycin A and B (Figure 1) were isolated from the fermentation broth of *Streptomyces griseofuscus* and are known to cross-link duplex DNA in the major groove[6] with the aziridine, epoxide, and napthyl ester functionality thought to play a role. To probe the importance of these functional

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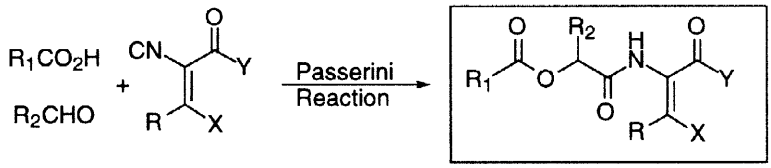
groups we decided to undertake a structure-activity relationship (SAR) binding study using a combinatorial chemical approach that employed a Passerini three-component condensation (3CC) (figure 1). We therefore investigated this strategy as a means for the rapid construction of a library of dehydroamino acid derivatives and wish to report our efforts toward a library of azinomycin analogues based on solution phase 3CC methodology.

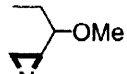
For this study we choose to vary the functionality contained on two of the components of the 3CC in an attempt to explore the range of functionality that would be tolerated by the reaction and generate a library of compounds which would probe steric requirements for binding. The carboxylic acid and aldehyde inputs were used as available from commercial vendors, while the isocyanide was prepared using known methodology.[7] The reaction procedure was as follows:[8] (without aziridine) To a solution of isocyanide (0.1-0.2 mmol) in CH_2Cl_2 (2-3 mL) was added sequentially aldehyde (3.0 equiv) then acid (1.0 equiv) at room temperature under nitrogen. The reaction mixture was stirred overnight after which time the solvent was removed *in vacuo* and the crude products were purified by flash chromatography (silica gel, pretreated with 5% TEA / hexanes). For those cases containing an aziridine the procedure was the same as above order of reagents was: pyridine (1.1 equiv), aldehyde (3.0 equiv), then acid (1.0 equiv).

Table 1



R	X	Y	R_2	Yield	R	X	Y	R_2	Yield
—n-Pr	—H	—OEt	—n-Pr	55	—Ph	—N(n-Bu)	—OMe	1-napthyl	52
	—Br	—OEt	—n-Pr	61		—N(n-Bu)	—OMe	—(S)-Me-glycidyl	36
	—H	—OMe	—n-Pr	54		—N(n-Bu)	—OMe	—n-Pr	57
	—N(n-Bu)	—OEt	—(S)-Me-glycidyl	0		—N(n-Bu)	—OMe	—(S)-Me-glycidyl	56
	—N(n-Bu)	—OEt	—n-Pr	0		—N(n-Bu)	—OMe	—(S)-Me-glycidyl	37
	—Br	—OMe	—(S)-Me-glycidyl	39		—N(n-Bu)	—OMe	—n-Pr	68
	—Br	—OMe	—n-Pr	69					
	—Br	—NHBu	—i-Pr	30					

Table 1 (continued)

R	X	Y	R_2	Yield	R	X	Y	R_2	Yield
—Ph	—N 	—OMe	—n-Pr	60	—PhBr	—H	—OMe	—i-Pr	84
	—N 	—OMe	—(S)-Me-glycidyl	53		—Br	—OMe	—i-Pr	81
	—N	—OMe	—(S)-Me-glycidyl	42		—H	—OEt	—i-Pr	90
mMTr = monomethoxy trityl						—Br	—OEt	—i-Pr	0

The results of the study are reported in Table 1. First, it should be pointed out that the addition of pyridine was necessary in those cases containing the aziridine moiety. Without the addition of base, only decomposition was observed. However, we were surprised to discover that this was completely reversed by the addition of pyridine, and that the addition of base had no detrimental effect on the reaction. This is important as the aziridine is believed to be important for the biological activity of the molecule.

Overall, the procedure afforded good yields of almost all products with the alkene geometry conserved in virtually all the cases with the exception of those where R = Ph. Here, when the aziridine was *trans* to the isocyanide the reaction gave large amounts of the opposite isomer in all cases. As this was only observed in cases containing R = Ph and X = aziridine, it may demonstate a steric limit to the reaction as these are the most demanding examples.

Interestingly, the two cases where R = PhBr no isomerization was observed and yields were quite respectable even though they share the same geometry as those which underwent isomerization and are also quite hindered. As these reactions were not performed with added pyridine, this suggests that the added base may be the mechanism by which the isomerization is occurring. This may be overcome by using a less nucleophilic or more hindered base, reducing the possibility of Michael addition.

In summary, we have synthesized a solution phase library based on the Passerini 3CC. The work demonstrated the scope and limitations of the reaction and resulted in a library of dehydroamino acid derivatives. We found that the reaction gives retention of alkene geometry in nearly all cases (*vide supra)* and that the *cis* geometry seems to react more favorably.

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References and Notes:

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8. Conditions: a) 1-naphthoic acid, isobutyraldehyde, CH_2Cl_2, RT, 8-12h, b) 1-naphthoic acid, butyraldehyde, CH_2Cl_2, RT, 8-12h, c) 1-naphthoic acid, (s)-2-(methyl)-glycidal, CH_2Cl_2, RT, 8-12h, d) 1-naphthoic acid, 1- naphthaldehyde, CH_2Cl_2, RT, 8-12h.