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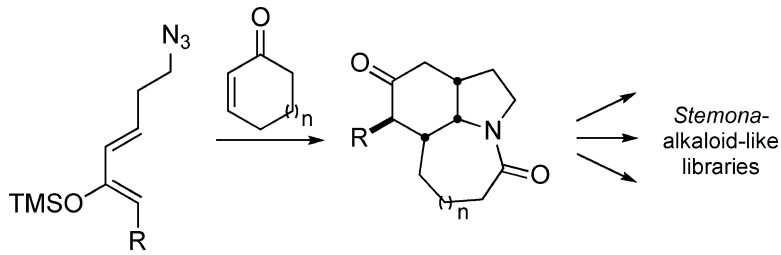

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Explorations of *Stemona* Alkaloid-Inspired Analogues: Skeletal Modification and Functional Group Diversification

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A tandem Diels−Alder/Schmidt reaction provided an efficient route for the exploration of unnatural *Stemona* alkaloid analogues. Thus, a series of tricyclic scaffolds were efficiently prepared and then elaborated into seven sets of functionalized analogues. These derivatives incorporated appended heterocycles, such as indoles and quinolines, or other diversity-incorporating moieties such as carbamates and amines. Both the scaffold-generation sequence and the diversification steps could be manipulated to provide regio- and diastereochemically pure products.

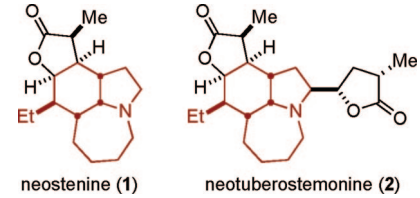
There is considerable interest in the synthesis of structurally diverse analogues of biologically active natural products.[1] *Stemona* alkaloid congeners should provide an excellent focus for such an approach because of their extensive history in Chinese traditional medicine. Diverse activities such as antitussive, antiparasitic, and the ability to treat ocular disease have been ascribed to various members of this extensive class.[2] In one recent study, the antitussive activities of several individual alkaloids were verified in an animal model.[3] However, the systematic preparation of *Stemona* alkaloid analogues is challenging because of the structural complexity of these alkaloids.

The tandem Diels−Alder/azido Schmidt reaction has proved useful for the rapid construction of multicyclic scaffolds containing appropriate functional groups for further elaboration.[4] In particular, this reaction sequence was used in the target-directed synthesis of the *Stemona* alkaloids stenine and neostenine.[5] In this work, we report an efficient approach to variations of the *Stemona* alkaloid core and demonstrate the diversification of these compounds into a series of previously unreported *Stemona* alkaloid chemotypes.

Scaffold Synthesis. We began by preparing scaffolds based on the potent antitussive agents[3a] neostenine **1** and neotuberostemonine **2** in which the lactone ring was eliminated (Figure 1). A tandem Diels−Alder/azido Schmidt reaction using siloxy diene **3** converted simple cycloalkenone precursors into the 7,6,5-nitrogenous core of the natural products as well as two 6,6,5-analogues (Scheme 1). The relative stereochemistry at the ring junction of each scaffold arises from an endo selective Diels−Alder step coupled with retention of stereochemistry in the ring expansion step. Previous studies had established that $BF_3 \cdot OEt_2$ was necessary to obtain clean endo selectivity in trisubstituted dienes (i.e., **3** where R = alkyl).[5b] In most other cases, the more reactive $SnCl_4$ could be used. For example, treating **3** (R = H) and cyclohexanone with $SnCl_4$, a mixture of endo- and exo-tricycles were obtained in 66% total yield (the major endo-isomer could be isolated by recrystallization). Alternatively, $BF_3 \cdot OEt_2$ conditions provided the endo-isomer exclusively in 27% yield. In all examples, only the endo-isomers were purified for use in subsequent steps. Where appropriate, α-substituted ketones were treated with base to epimerize the alkyl group into the thermodynamically favored *β*-orientation, corresponding to that observed in the natural series. Scheme 1 displays the full range of scaffolds produced; 0.5−2.0 g quantities of each were routinely obtained. Importantly, these scaffolds contained a ketone useful for diversification, providing opportunities for modification not readily available in the natural products themselves.

Diversification Studies: Introduction of Basic Nitrogen. We now turned our attention to examining different ways of diversifying the scaffolds, beginning with the reactions designed to introduce a basic nitrogen atom into the structures. Thus, tricyclic amides **5**{*1b*}, **5**{*5a*}, and **5**{*6a*} were converted to the corresponding tertiary amines via a previously reported[5] two-step sequence (Scheme 2 and Table 1).

We had envisioned that direct reductive amination of the ketone carbonyl using $NaBH(OAc)_3$[6] would provide another tack for introducing basic nitrogen. However, scaffolds with substitution adjacent to the ketone carbonyl proved difficult substrates for direct reductive amination conditions, proceeding with low to no conversion. Acceptable yields[7] of amines could be obtained across the full range of ketone substrates by pre-forming the imine using a mixture of $TiCl_4$ and Ti(O-



neostenine (**1**) neotuberostemonine (**2**)

Figure 1. Selected antitussive *Stemona* alkaloids.

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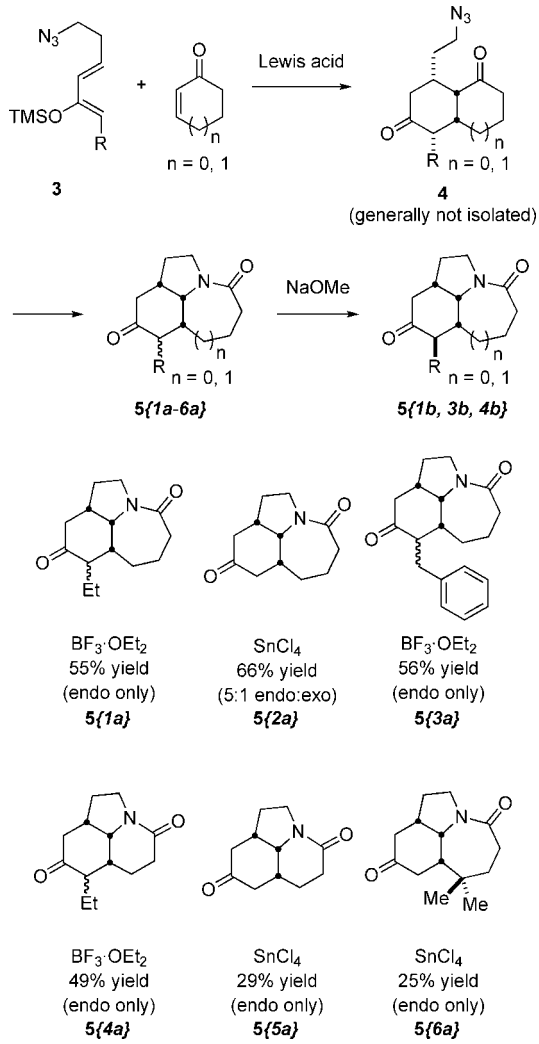
Scheme 1



Scheme 2

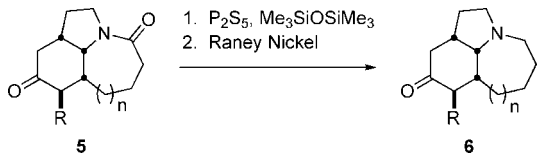
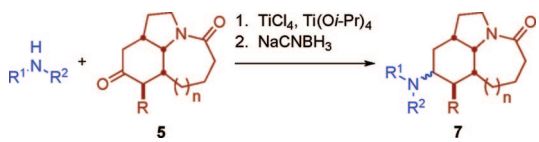


Table 1. Reduction of the Tricyclic Amides **5** to the Tertiary Amines **6**

entry	amide	product	yield (%)
1	**5{1b}**	**6{1}**	74
2	**5{5a}**	**6{2}**	22
3	**5{6a}**	**6{3}**	32

Scheme 3

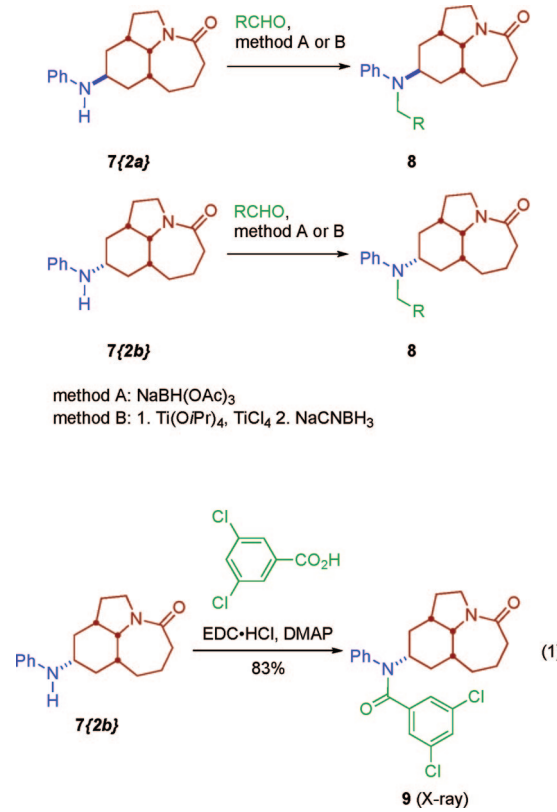


i-Pr)$_4$,[8] followed by reduction with $NaCNBH_3$, to afford amine products (Scheme 3 and Table 2). Unfortunately, inseparable mixtures of diastereomers were obtained using either the two-step reductive amination approach or by direct reductive amination with $NaBH(OAc)_3$. All ring systems examined gave nonselective aminations, presumably, because of insufficient diastereofacial direction in the iminium ion intermediates.

Table 2. Reductive Amination of the Tricycles **5**

entry	scaffold	amine	product	yield (%)
1	**5{1b}**	aniline	**7{1}**	55
2	**5{2a}**	aniline	**7{2}**	79
3	**5{3b}**	aniline	**7{3}**	55
4	**5{4b}**	aniline	**7{4}**	60
5	**5{5a}**	aniline	**7{5}**	31
6	**5{6a}**	aniline	**7{6}**	35
7	**5{1b}**	4-phenylpiperizine	**7{7}**	22
8	**5{2a}**	4-phenylpiperizine	**7{8}**	54
9	**5{3b}**	4-phenylpiperizine	**7{9}**	38
10	**5{4b}**	4-phenylpiperizine	**7{10}**	30
11	**5{5a}**	4-phenylpiperizine	**7{11}**	41
12	**5{6a}**	4-phenylpiperizine	**7{12}**	33

Scheme 4



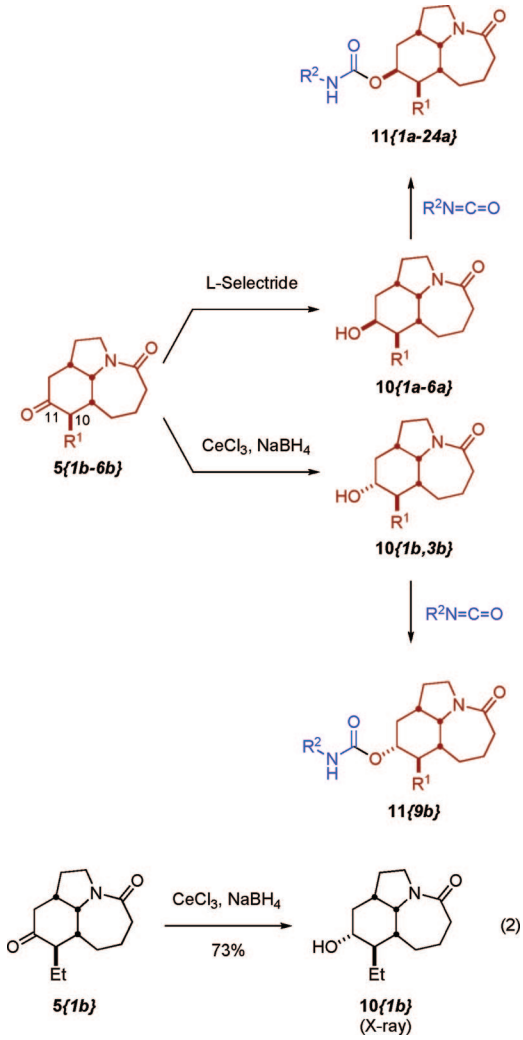
One route to diastereomerically pure amine derivatives is outlined in Scheme 4. Preparative TLC purification of the reductive amination product **7**{*2*} afforded diastereomerically pure secondary amines **7**{*2a*} and **7**{*2b*}. The relative stereochemistry of the phenylamine group was assigned from the X-ray crystal structure of the amide **9**, afforded by coupling of 3,5-dichlorobenzoic acid with amine **7**{*2a*} (eq 1). Amines **7**{*2a*} and **7**{*2b*} were then reacted with a selection of aldehydes in a second reductive amination to obtain diastereomerically pure tertiary amines **8**{*1*−*4*} (Table 3).

Synthesis of Alcohol Derivatives. In contrast to the problematic amine reductions, the ketone moiety of the tricycles **5** could be selectively reduced to either diastereomeric alcohol by varying reaction conditions (Scheme 5). Thus, reduction of ketone **5**{*1b*} with $NaBH_4/CeCl_3$ occurred with axial addition of hydride[9] stereoselectively afforded

Table 3. Reductive Amination of the Diastereomerically-Pure Amines **7** with Aldehydes

entry	substrate	R	method	product	yield
1	**7**{*2a*}	*n*-hexyl	A	**8**{*1*}	85%
2	**7**{*2b*}	2-benzo[*b*]thiophene	A	**8**{*2*}	51%
3	**7**{*2b*}	2-naphthyl	B	**8**{*3*}	91%
4	**7**{*2b*}	*n*-hexyl	A	**8**{*4*}	75%

Scheme 5



10{*1b*} as verified by X-ray crystallography (eq 2). Alternatively, Selectide reduction afforded scaffolds **10**{*1a*−*6a*}, which were then converted into a library of carbamates **11**{*1*−*24*} (Table 4).

Additional stereoisomeric carbamates were prepared by pairing the alkyl epimerization step with the subsequent reduction step (Scheme 6). Both unepimerized **5**{*3a*} and epimerized **5** {*3b*}were reduced by the two complementary reduction methods and subsequently coupled with butyl isocyanate to provide four isomeric carbamate derivatives.

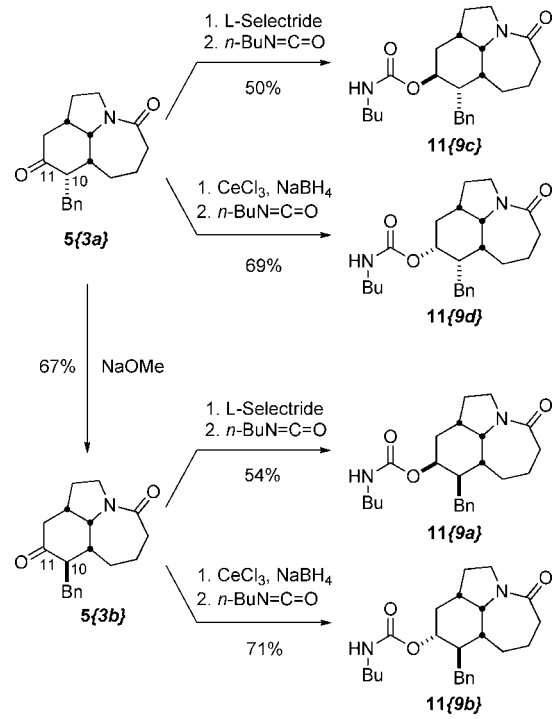
The tricyclic scaffolds **5**{*1b*} and {*3b*} could be regio- and stereoselectively alkylated with primary bromides or iodides (Scheme 7 and Table 5). This method provides a straightforward route to regioisomeric ketones, such as **12**{*1*} and **12**{*2*}, as well as introduces functionalized side chains (e.g., R_2 = *p*-bromophenyl) suitable for follow up chemistry (e.g., by palladium-catalyzed cross coupling). Terminating the side chain with an ester functionality would allow for

Table 4. Construction of a 24-Member Carbamate Library[a]

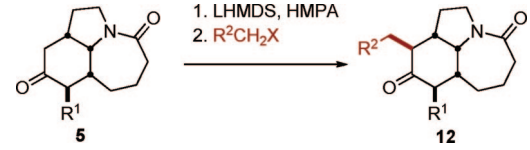
entry	alcohol	R^1	R^2	carbamate	yield (%)	purity (%)
1	**10**{*1a*}	Et	*n*-butyl	**11**{*1a*}	25	95
2	**10**{*1a*}	Et	phenyl	**11**{*2a*}	67	90
3	**10**{*1a*}	Et	4-bromophenyl	**11**{*3a*}	25	100
4	**10**{*1a*}	Et	5-benzo[*d*][1,3]dioxole	**11**{*4a*}	43	93
5	**10**{*2a*}	H	*n*-butyl	**11**{*5a*}	90	100
6	**10**{*2a*}	H	phenyl	**11**{*6a*}	0	
7	**10**{*2a*}	H	4-bromophenyl	**11**{*7a*}	5	100
8	**10**{*2a*}	H	5-benzo[*d*][1,3]dioxole	**11**{*8a*}	30	100
9	**10**{*3a*}	Bn	*n*-butyl	**11**{*9a*}	35	100
10	**10**{*3a*}	Bn	phenyl	**11**{*10a*}	28	96
11	**10**{*3a*}	Bn	4-bromophenyl	**11**{*11a*}	2	100
12	**10**{*3a*}	Bn	5-benzo[*d*][1,3]dioxole	**11**{*12a*}	33	100
13	**10**{*4a*}	Et	*n*-butyl	**11**{*13a*}	0	
14	**10**{*4a*}	Et	phenyl	**11**{*14a*}	19	100
15	**10**{*4a*}	Et	4-bromophenyl	**11**{*15a*}	37	100
16	**10**{*4a*}	Et	5-benzo[*d*][1,3]dioxole	**11**{*16a*}	26	85
17	**10**{*5a*}	H	*n*-butyl	**11**{*17a*}	49	100
18	**10**{*5a*}	H	phenyl	**11**{*18a*}	45	100
19	**10**{*5a*}	H	4-bromophenyl	**11**{*19a*}	15	100
20	**10**{*5a*}	H	5-benzo[*d*][1,3]dioxole	**11**{*20a*}	34	100
21	**10**{*6a*}	H	*n*-butyl	**11**{*21a*}	52	100
22	**10**{*6a*}	H	phenyl	**11**{*22a*}	82	99
23	**10**{*6a*}	H	4-bromophenyl	**11**{*23a*}	20	100
24	**10**{*6a*}	H	5-benzo[*d*][1,3]dioxole	**11**{*24a*}	98	81

[a] See Scheme 5 for the structures of **10** and **11**.

Scheme 6



Scheme 7



the synthesis of lactone-containing derivatives that more closely mimic the natural *Stemona* alkaloids by a ketone reduction/lactonization sequence analogous to that used for the syntheses of stenine[5b] and neostenine.[5c] The stereochemical assignments of the cis-alkylation product are based on

Table 5. Regioselective Alkylation of Tricyclic Ketones **5**

entry	substrate	R^1	R^2	product	yield (%)
1	**5**{*1b*}	Et	Ph	**12**{*1*}	74
2	**5**{*3b*}	Bn	Me	**12**{*2*}	30
3	**5**{*1b*}	Et	CO_2Et	**12**{*3*}	95
4	**5**{*1b*}	Et	2-Br-C_6H_5)	**12**{*4*}	74

Scheme 8

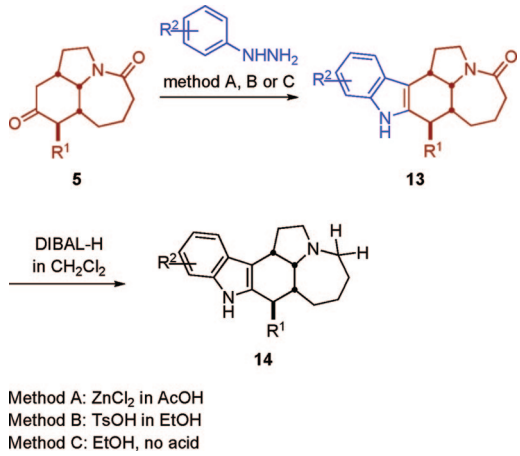


Table 6. The Fischer Indole Synthesis on Tricyclic Ketones **5**

entry	R^1	R^2	method	product	yield (%)
1	Et	4-*i*-Pr	C	**13**{*1*}	26
2	Et	4-OMe	C	**13**{*2*}	77
3	H	H	A	**13**{*3*}	76
4	H	4-*i*-Pr	B	**13**{*4*}	24
5	H	4-OMe	B	**13**{*5*}	18
6	H	2-Cl	B	**13**{*6*}	37
7	H	2,5-Cl,Cl	B	**13**{*7*}	37

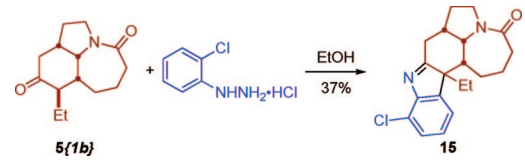
Table 7. Combined Fischer Indole Synthesis and Subsequent Amide Reduction of Ketones **5**

entry	R^1	R^2	method	product	yield (%)
1	H	4-*i*-Pr	B	**14**{*1*}	13
2	H	4-OMe	B	**14**{*2*}	8
3	H	2-Cl	B	**14**{*3*}	23

precedent for similar alkylations in the syntheses of stenine[5b] and neostenine.[5c]

Incorporation of Additional Heterocycles. Finally, we were interested in ways of appending additional heterocyclic rings to our carbocyclic skeleton. Our initial investigations were focused on applying the Fischer indole synthesis to ketones **5** (Scheme 8). Three sets of conditions for the Fischer indole synthesis were surveyed: zinc chloride in acetic acid (method A), *p*-toluenesulfonic acid in anhydrous ethanol (method B), and simple dissolution in anhydrous ethanol (method C). No one method was superior to the others for every ketone/hydrazine combination. Table 6 summarizes the indole products produced using these methods. The regiochemistry of the reaction was established by obtained an X-ray crystal structure of a representative indole product (**13**{*3*}). The amide carbonyl on the indole products could be reduced with DIBAL-H to give the indole tertiary amines **14** (Scheme 8 and Table 7) without affecting the indole ring. In all cases, the yields are the results from unoptimized, single attempt trials, which were sufficient in providing material for submission to biological screening collaborations. In one case using method C, no indole product was isolated but instead an isomeric side product **15** was formed in 37% yield (Scheme 9).

Scheme 9



Scheme 10

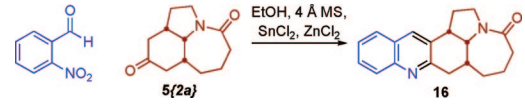


Table 8. Friedländer Quinoline Synthesis on Tricyclic Ketone **5**

entry	ketone	R	product	yield (%)
1	**5**{*2a*}	H	**16**{*1*}	68
2	**5**{*2a*}	5-OH	**16**{*2*}	83
3	**5**{*2a*}	5-Cl	**16**{*3*}	86
4	**5**{*2a*}	4-CF_3	**16**{*4*}	73
5	**5**{*2a*}	[4,5]-dioxole	**16**{*5*}	48
6	**5**{*2a*}	5-CO_2Me	**16**{*6*}	76
7	**5**{*6a*}	H	**16**{*7*}	53

Scheme 10 and Table 8 highlight one additional demonstration of the utility of *Stemona* alkaloid scaffolds for the construction of novel polycyclic compounds. The scaffolds with two methylene carbons adjacent to the ketone such as **5**{*2a*} or **5**{*6a*} were found to be excellent substrates for the Friedländer quinoline synthesis under the conditions of Miller and co-workers.[10]

In summary, we have applied an endo-selective tandem Diels−Alder/Schmidt reaction to the construction of a series of unnatural neostenine-like scaffolds. The utility of these scaffolds was demonstrated by their elaboration to six sets of functionalized derivatives. The biological evaluation of these compounds, as well as the synthesis of additional compound libraries, is currently underway and will be reported in due course.

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Supporting Information Available. Experimental details and full characterization data (including ^{1}H and ^{13}C NMR spectra) for all new individual compounds synthesized and representative members of carbamate library compounds, HPLC purity data for all library compounds, and X-ray crystallographic data (CIF) for **9**, **10**{*1b*}, and **13**{*3*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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