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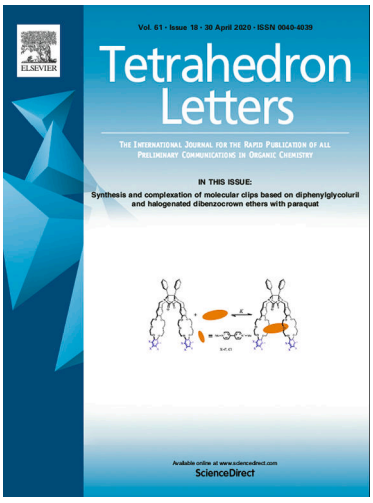

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Isaac T. Smith, Jared B. Neeley, Tanner D. Brinley, Peter R. Fullmer, Merritt B. Andrus

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Synthesis of Pyrroloindolines through Formal [3+2]-Cycloaddition of Indoles with Chiral *N*-2-Acetamidoacrylyl Oxazolidinones

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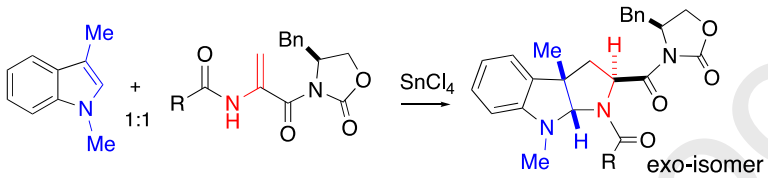

85% yield, >20:1

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Synthesis of pyrroloindolines through formal [3+2]-cycloaddition of indoles with chiral *N*-2-acetamidoacrylyl oxazolidinones

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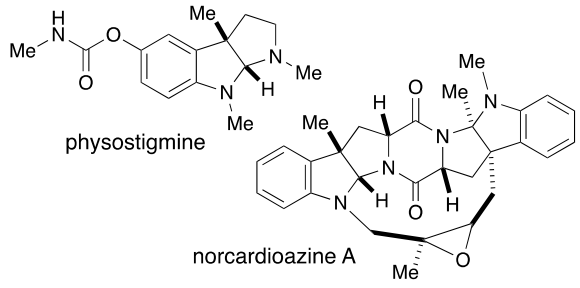
ABSTRACT

Chiral *N*-2-acetamidoacrylyl oxazolidinones were produced and reacted with indoles under Lewis acid conditions to generate hexahydropyrrolo[2,3-*b*]indole products in a formal [3+2] cycloaddition process. Optimal conditions included the use of tin(IV) chloride in methylene chloride at 0 °C. Pyrroloindoline products were obtained from various indoles with shorter reaction times (12 hr) up to 91% yield with high, >20:1 exo selectivity. A mechanism involving reversible conjugate addition followed by an enamine lone-pair-iminium capture, tautomerization, and tin-enolate protonation accounts for the selectivity. The method enables selective applications to pyrroloindoline targets and further refinement with chiral catalysts.

Introduction

Pyrroloindoline (hexahydropyrrolo[2,3-*b*]indole) containing natural products constitute an important class of alkaloids that possess challenging structural features and diverse biological activities.[1] Derived bio-synthetically through tryptophan cyclization, these agents hold medicinal value and potential as seen with physostigmine, isolated from the calabar bean, used to treat glaucoma and gastric disorders (Scheme 1).[2] Common pyrroloindoline polycyclic variations include diketopiperidines, typified by norcadioazine A, which possesses an unusual epoxide containing tether, and the more complex dimeric calycanthine/chimonanthine type compounds joined contiguous indole C3-quaternary stereocenters.[3] Variations include prenylation, hydroxylation, and *N*-indole substitutions at the C3-pyrroloindoline position and numerous disulfide diketopiperidine variations.[1] A highly selective synthesis of the pyrroloindoline core common to these agents is now reported using a formal [3+2]-cycloaddition of indoles reacted with chiral acetamidoacrylate substituted oxazolidinones.

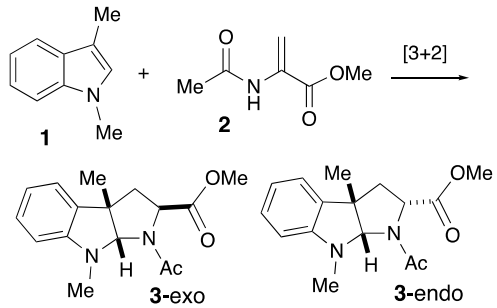
Synthetic approaches to pyrroloindolines commonly involve cyclization of tryptophan derivatives initiated by C3-protonation[1a] and other electrophilic halogen,[4] sulfur, and selenium-based reagents.[5] Cyclization has also been developed for oxygen and nitrogen based reagents giving C3-hydroxy and amino products.[6] Allyl and aryl couplings with indoles at C3 also lead to pyrroloindolines in similar fashion using transition-metal catalysis.[7] More recent routes to pyrroloindolines from indoles include the use of aziridines,[8] phenyltriazoles,[9] conjugated enones under organo-catalysis,[10] intramolecular photo-catalysis with aryloxyamides,[11] and reductive coupling of tethered malonic diamides.[12] Multistep alkylation routes using amino oxindoles also generate pyrroloindolines upon reductive cyclization.[13] Other routes include the use of anilines reacted with isocyanoacetate,[14] ketonitrones with activated alkynes,[15]



Scheme 1. Pyrroloindoline natural products.

and intramolecular reactions with aryl isocyanate amides.[16]

ride Lewis acid (2 equiv.) with indoles **1** added to methyl *N*-acetamidoacrylate **2** (Scheme 2). Exo-products **3** were obtained as the major diastereomer with up to 9:1 selectivity in modest yield.[17] Reisman and co-workers concurrently developed an enantioselective [3+2] approach using (*R*)-BINOL (20 mol%) and tin(IV) chloride (1.2 equiv.) at room temperature employing the more selective substrate, *N*-trifluoroacetamidoacrylate adding to indoles.[18] The exo-product was favored with modest 3:1 to 6:1 selectivity over the minor endo-isomer. Yields were good to excellent with enantiomeric excesses ranging from 84 to 94% for various indole substrates. Epimerization using DBU was shown to provide access to the thermodynamic endo-isomer (10:1). Follow up publications included an analysis of the step-wise mechanism and a multistep synthetic application.[19]



Scheme 2. Formal [3+2]-cycloaddition.

Results and Discussion

In an effort to access pyrroloindolines with enhanced exo-selectivity and to explore a wider range of acetamidoacrylate reactivity, new chiral auxiliary based substrates were envisioned. Enhanced reactivity was anticipated through bidentate two-point Lewis acid binding using acyl oxazolidinones,[20] in contrast to the single point binding of previous acetamidoacrylate esters **2**. Oxazolidinone auxiliaries remain the standard for many asymmetric transformations, including alkylation, aldol, and cycloadditions, and they also often serve as the starting point for catalytic asymmetric development with achiral oxazolidinone substrates.[21]

To initiate the effort, new acetamidoacrylate substituted oxazolidinones were designed and produced (Figure 1). Known (*S*)-4-benzyl-*N*-methacryloxazolidin-2-one **4**[22] was treated with ozone to access the pyruvyl derivative **5**.[23] Direct acylation efforts to form **5** using either pyruvic acid or pyruvyl chloride were unsuccessful. Oxime **6** was generated allowing for production of either the acetamidoacrylate or the trifluoro acetamidoacrylate **7** using trifluoroacetic acid (TFA) and the anhydride (TFAA) reacted with iron powder in DMF (52 °C).[24]

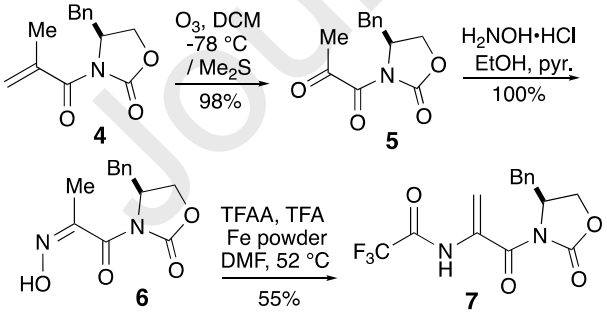
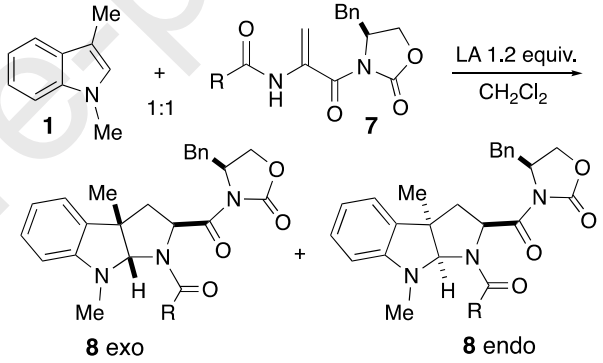


Figure 1. Acetamidoacrylate oxazolidinone synthesis.

Conditions for the formal [3+2] reaction of the acetamidoacrylates **7** with 1,3-dimethylindole **1** were explored using various Lewis acids to generate the desired pyrroloindoline product **8** (Table 1). Reactions with acetamidoacrylate (R=Me) **7** and **1** performed at –78 °C with various Lewis acids and equivalents gave no product formation (entry 1). Reaction of **1** and **7** (1:1 equiv.) with $SnCl_4$ (1.2 equiv.) added last at 0 °C or at room temperature in methylene chloride for 24 hours, gave product **8** in 69% isolated yield (entries 2,3). Diastereoselectivity was poor at 1:3.2 and 1:1 exo/endo ratio in these cases. Only two of the four possible diastereomeric products were obtained in these reactions. Use of $TiCl_4$ added last gave product in lower yield, 40% with improved selectivity to 5:1 exo/endo (entry 4). Adding $TiCl_4$ first to **7** followed by addition of **1** led to increased yield to 77% and selectivity, 6:1 (entry 5). Trifluoroacetamidoacrylate **7** (R=CF_3) was found to react at faster rates and higher selectivity.

Table 1. [3+2]-Cycloaddition to pyrroloindolines **8** exo and **8** endo.



entry	R=	LA	LA order	time, hr	temp °C	yield %[a]	**8** exo/ endo[b]
1	Me	$SnCl_4$	last	24	–78	-	
2	Me	$SnCl_4$	last	24	0	69	1:3.2
3	Me	$SnCl_4$	last	24	rt	69	1:1
4	Me	$TiCl_4$	last	24	0	40	5:1
5	Me	$TiCl_4$	first	24	0	77	6:1
6	CF_3	$SnCl_4$	first	3	rt	59	>20:1
7	CF_3	$SnCl_4$	first	3	0	43	4:1
8	CF_3	$SnCl_4$	first	6	0	84	6:1
9	CF_3	$SnCl_4$	first	72	0	85	>20:1

[a]Isolated yield following silica gel chromatography.
[b]Selectivity determined by ^{1}H NMR.

Use of Lewis acid added first to **7** (R=CF_3), followed by **1** at room temperature for 3 hours, gave product exo-**8** as a single isomer (>20:1, entries 6). Extended reaction times at room temperature did not improve the yield. Use of $SnCl_4$ at 0 °C for 3 hours surprisingly eroded the selectivity to 4:1 exo/endo (entry 7). The same conditions for 6 hours improved both the yield (84%) and selectivity (6:1, entry 8). Extended time (72hr) at 0 °C was found to give optimal yield (85%) with complete selectivity, >20:1. Equilibrium favoring the exo-Lewis acid complex may account for these findings. Diagnostic ^{1}H NMR signals at 6.54 ppm for exo-**8** and 6.47 ppm for endo-**8** were used to assign the selectivity, in accord with previous results with the methyl acetamido acrylate substrate **2**.[18] Both exo-**8** and endo-**8** isomers are observed as ~3:1 mixtures of *N*-amide rotamers by NMR.

The major product **8** exo was confirmed by conversion and comparison to the known exo methyl ester product as discussed below. An X-ray structure was also obtained from a product with an indole variant used to explore the scope of the process below. The two other diastereomeric products, *iso* **8** exo and *iso* **8** endo, were not seen under the conditions explored, being formed in only trace amounts (Scheme 3).

The optimal $SnCl_4$ conditions developed using dimethylindole **1** were applied to various indole substrates to explore the scope of the process (Table 2). High selectivity was seen with **1** reacted for 72 hours, 85% yield. Electron deficient 5-Fluoro **9** required 27 hours reacting with **7** giving the pyrroloindoline product **10** with complete exo-selectivity in 83% isolated yield. More hindered *N*-Methyl tetrahydrocarbazole **11** reacted to access product **12** in reduced yield. Single crystal X-ray analysis of product **12** confirmed the absolute exo-stereochemistry as indicated (supplementary material). 5-Methoxy-1,3-dimethylindole **13** reacted (12 hr) with acetamidoacrylate **7** with high exo-selectivity and yield, 89% to access product **14**. 3-Allyl-1-methylindole **15** reacted to give **16** in 91% yield with excellent exo-selectivity (12 hr). 1-Allyl-3-methylindole **17** required 24 hr to generate product **18** with the selectivity lowered to 6:1 exo/endo ratio obtained.

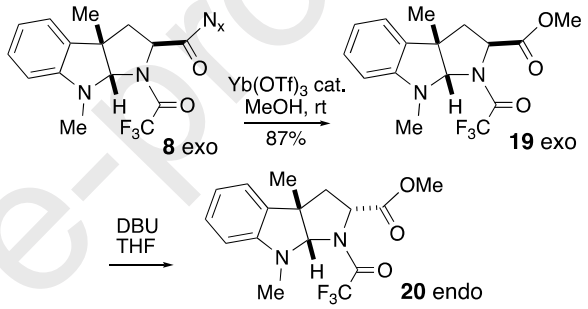
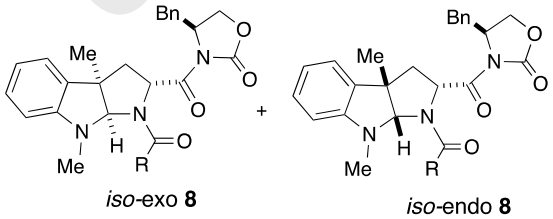


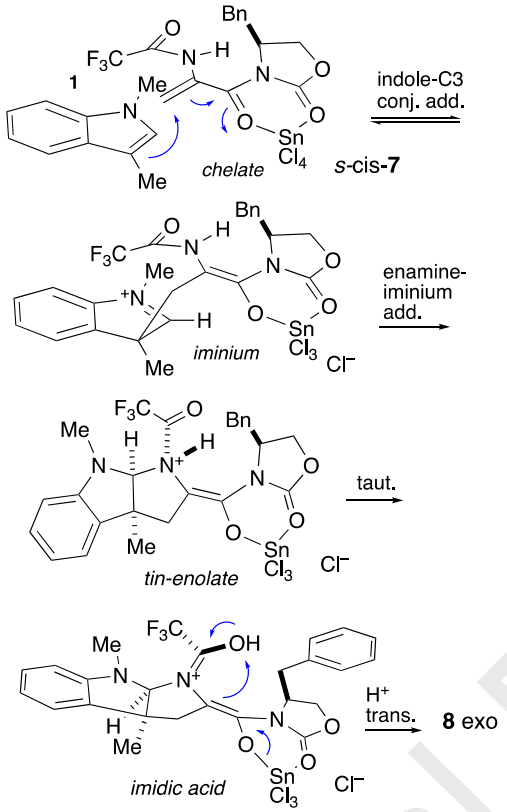
Figure 2. Conversion to exo-**19** and epimerization to endo-**20**.

Acylated oxazolidinones are readily converted to the corresponding carboxylic acids using base mediated hydrolysis.[21c] The versatile Weinreb *N*-methoxy-*N*- methylamide can also be formed in one step. Alternatively, reductive conditions can be used to access alcohols. In the case of exo-product **8**, the known methyl ester exo- **19** was directly obtained from exo-**8** using ytterbium(III) triflate-methanol conditions reported recently by Stevens and Frantz (Figure 2).[25] The deacylated oxazolidinone was also recovered in this step. Spectral data for ester exo-**19** matched that reported previously.[18,19] Treatment with DBU was reported previously with exo-**19** to access the more stable thermodynamic endo-**20** isomer with 10:1 selectivity (85%).[1,18,19]



Scheme 3. Other diastereomeric pyrroloindolines.

(Scheme 4). Nucleophilic conjugate attack by the indole **1** below the plane of alkene, as indicated away from the *S*-oxazolidinone benzyl moiety, sets the indole 3-position stereocenter. Planar chelation activation has been established for acrylate oxazolidinones for asymmetric Diels-Alder and other related electrophilic transformations.[21] This initial addition step is assumed to be reversible in accord with the mechanistic findings of Reisman under similar tin(IV) chloride conditions at room temperature.[19a] Reversibility of this iminium Lewis acid complex may account for the improved selectivity observed with extended reactions times (Table 1). The pyrrole intermediate is then formed upon enamine lone pair addition to the indole iminium ion. The trifluoroacetamide rotates away from the oxazolidinone benzyl group placing the attached proton trans-disposed relative to the adjacent ring fusion proton. This and subsequent steps are presumed to be faster for the diastereomeric intermediate shown. Tautomerization to an imidic acid then provides a suitable proton source to set the final stereocenter. This differs from the BINOL-tin(IV) chloride conditions where the phenol complex functions



Scheme 4. Mechanism of [3+2] addition.

as the proton source. The imidic proton transfers to the tin enolate from the same face to generate the kinetic pyrroloindoline exo-product **8**. This step places the oxazolidinone benzyl group anti-disposed to the trifluoromethyl amide moiety. High 20:1 exo-selectivity in this case may be attributed to the enhanced size of the oxazolidinone substrate and the reactivity of the chelated enolate. Previous selectivities with methyl acetamidoacrylates were more modest with 6:1 exo/endo diastereoselectivity.[17–19]

Conclusions

A new approach to asymmetric pyrroloindoline formation has been developed using chiral acetamidoacrylyl oxazolidinones reacted under Lewis acid conditions. The kinetic exo-products were obtained with high selectivity with a broad range of indole substrates. A model for the origin of the stereoselectivity involves reversible conjugate addition, equilibration of the Lewis acid complex, lone-pair attack, and tin-enolate protonation steps. C3 and C5-indole variations along with *N*-1 substituents react with high yield and near complete exo-selectivity. The exo products can be readily epimerized to the endo-isomers allowing for flexibility with target directed, multi-step applications. The product is converted to the known methyl ester in one step; however, the auxiliary synthesis and removal detract from the overall efficiency compared to the catalytic BINOL method.[18,19] Success with this new bi-dentate acetamidoacrylyl oxazolidinone provides a means to achieve high diastereoselectivity and a basis for further development with chiral catalysts. Other asymmetric transformations can also be envisioned using this versatile acetamidoacrylate substrate based on these promising findings.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary material to this article can be found online at https://doi.org.

Experimental procedures, characterization, ^{1}H, ^{13}C NMR spectra, X-ray crystallography (PDF)

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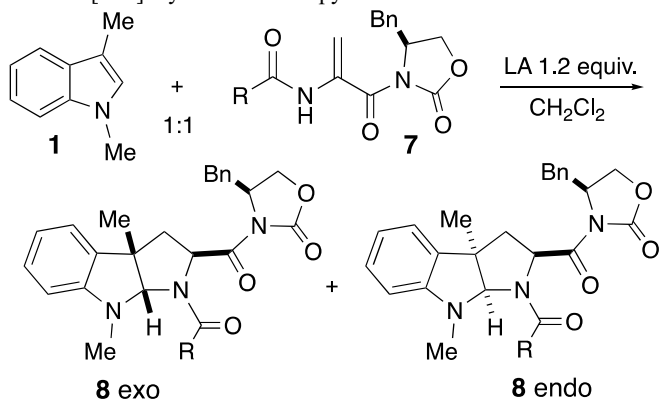
Highlights

- Chiral acetamide oxazolidinones produced
- Reactions with indoles gave pyrroloindoline products
- This structure is found in many natural products
- Numerous indoles gave up to 91% yield with high selectivity

Table 1. [3+2]-Cycloaddition to pyrroloindolines **8** exo and **8** endo.



entry	R=	LA	LA order	time, hr	temp °C	yield %[a]	**8** exo/ endo[b]
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3	Me	$SnCl_4$	last	24	rt	69	1:1
4	Me	$TiCl_4$	last	24	0	40	5:1
5	Me	$TiCl_4$	first	24	0	77	6:1
6	CF_3	$SnCl_4$	first	3	rt	59	>20:1
7	CF_3	$SnCl_4$	first	3	0	43	4:1
8	CF_3	$SnCl_4$	first	6	0	84	6:1
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[a]Isolated yield following silica gel chromatography.
[b]Selectivity determined by ^{1}H NMR.