

An Approach to the Imine Ring System  
of Pinnatoxins

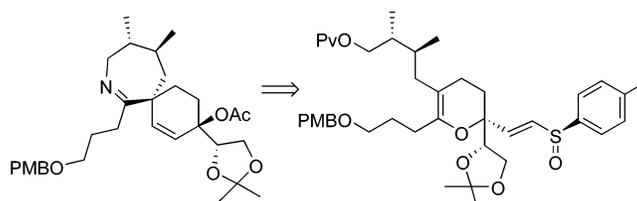
Matthew J. Pelc and Armen Zakarian\*

Department of Chemistry and Biochemistry, Florida State University,  
Tallahassee, Florida 32306-4390

zakarian@chem.fsu.edu

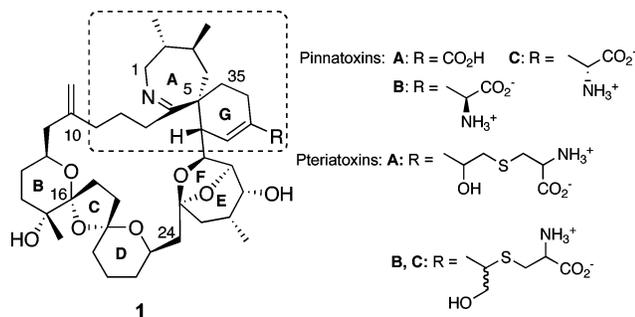
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## ABSTRACT



A concise stereoselective approach to the spirobicyclic imine fragment of pinnatoxins and pteriatoxins is described. The approach relies on a tandem reaction sequence involving consecutive sigmatropic rearrangements to build the quaternary chiral center at the core of the spirobicyclic ring system.

The imine group is typically considered to be a reactive functional group sensitive to hydrolysis. For this reason, its presence in the structure of an emerging group of natural products exemplified by pinnatoxins (**1**)<sup>1</sup> and gymnodimine<sup>2</sup> is intriguing. These natural products incorporate an imine group as a part of a spirobicyclic ring system within their molecular framework. The seven-membered cyclic imine in closely related spirolides C and D has been shown to be completely stable to hydrolysis upon treatment with aqueous acids.<sup>3</sup> This atypical chemical behavior of the cyclic imines has been linked to the biological profile of the natural products<sup>3a</sup> and has also been observed during the pioneering total synthesis of pinnatoxin A by Kishi and in a recent insightful study described by Romo.<sup>4,5</sup>



In addition to the presence of the imine group, perhaps a more significant challenge for synthesis is posed by the quaternary chiral center at the core of the spirobicyclic ring system. A number of synthetic studies toward gymnodimine and pinnatoxins that address this problem have been described.<sup>6</sup> A recent formal synthesis of pinnatoxin A relies on an intramolecular epoxide opening by a nitrile anion to form the A,G-ring portion of the target molecule.<sup>7</sup>

In this communication, we report a new approach to the A,G-spirobicyclic ring system (**2**) of pinnatoxins and pteriatoxins based on a cascade sigmatropic rearrangement of vinylic sulfoxide **3** (Scheme 1).

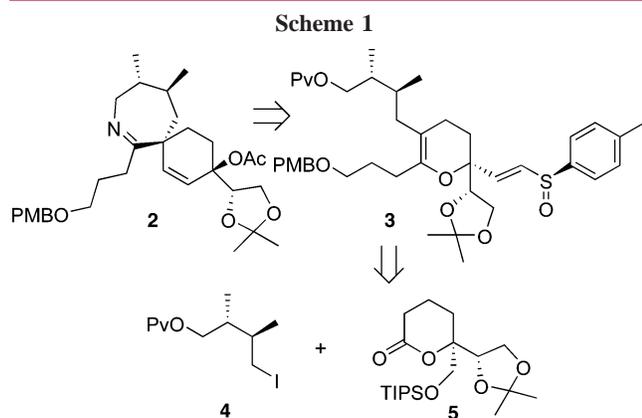
(1) (a) Uemura, D.; Chuo, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155–1156. (b) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3491–3494. Pteriatoxins: (c) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3495–3498.

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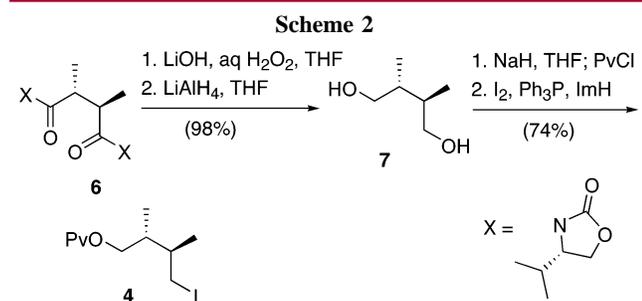
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The synthesis of iodide **4** commenced with a known diimide **6** obtained by oxidative dimerization of the lithium enolate of commercially available 4-(*S*)-isopropyl-3-propionyl-2-oxazolidinone (Scheme 2).<sup>8</sup> Conversion of **5** to diol



**7**, its monoprotection with pivaloyl chloride, and iodo-dehydroxylation afforded **4** in only five steps.

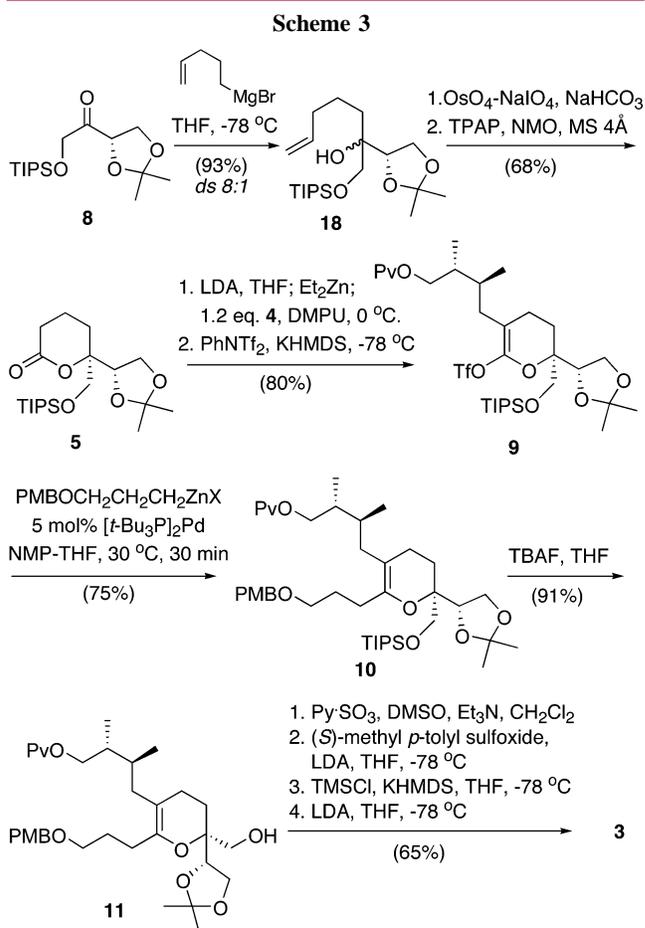
Ketone **8**, readily available from ascorbic acid, served as the starting material for the preparation of lactone **5** (Scheme 3).<sup>9</sup> Addition of 4-pentenylmagnesium bromide proceeded with 8:1 diastereoselectivity, giving the desired stereoisomer as the major product.<sup>9</sup> Cleavage of the double bond followed by oxidation of the lactol afforded **5**. Alkylation of the zincate enolate generated from the lactone with iodide **4** gave a 5:1 epimeric mixture of the desired products in an excellent yield. Triflate **9** formed from the alkylation products served as the substrate for Negishi coupling. Under the standard

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conditions, the reaction proved to be sluggish (5 mol % Pd(dppf)Cl<sub>2</sub>, 14% conversion after 12 h at 60 °C). However, when the reaction conditions developed by Fu were employed, the desired product **10** was formed in a 75% yield after 30 min at 30 °C.<sup>10</sup>

Further elaboration required deprotection of the primary hydroxyl group to **11**, oxidation of **11** to the aldehyde, and a three-step transformation of the aldehyde into vinyl sulfoxide **3**.

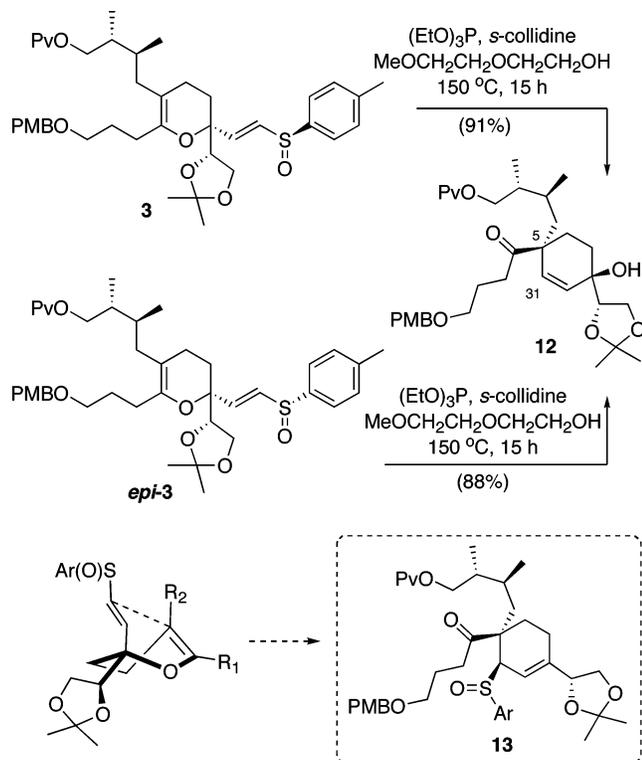
At this stage, we set out to examine the key tandem sigmatropic reorganization of **3** and of its epimer at the sulfur center (*epi-3*, Scheme 4).<sup>11</sup> Heating of each diastereomer in the presence of triethyl phosphite and *s*-collidine as a buffer in a high-boiling alcohol resulted in a clean rearrangement to the predicted product, allylic alcohol **12**.<sup>12</sup> Thus, the designed reaction cascade holds a promise for efficient formation of the quaternary chiral center at C-5, addressing one of the major challenges posed by the target spirobicyclic structure. In addition, the reaction accomplishes a stereoselective introduction of the tertiary allylic alcohol within the six-membered ring that will serve as a template for the

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(11) *R*-Sulfoxide, *epi-3*, was prepared from **11** by the same method using (*R*)-methyl *p*-tolyl sulfoxide.

(12) Stereochemical configuration is supported by HMBC and NOE correlations in a model study (see Supporting Information).

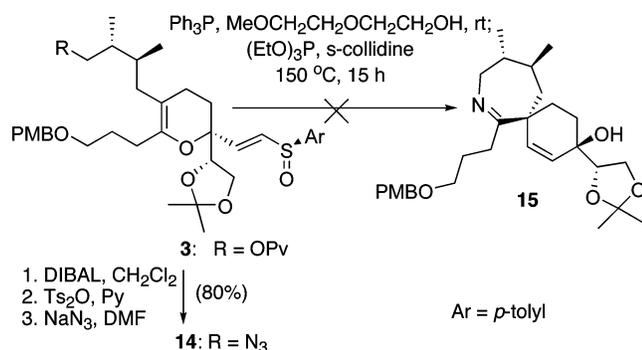
Scheme 4



required chain extension at C-31. We speculate that this tandem reaction sequence is initiated by a [3,3]-sigmatropic shift to form intermediate **13**, which then undergoes a fast Mislow–Evans rearrangement under the reaction conditions.

At this point, we wished to incorporate the aza-Wittig azepine ring closure into the reaction cascade.<sup>13</sup> Consequently, azide **14** was prepared from **3** by reductive deprotection of the primary alcohol, tosylation, and substitution with sodium azide in DMF (Scheme 5). The azido group in

Scheme 5



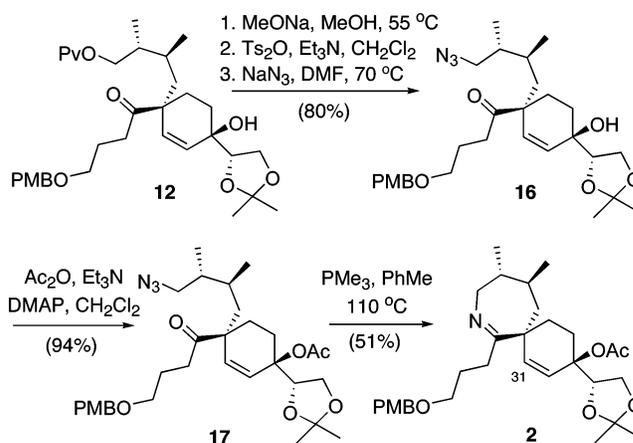
thus obtained **14** was reduced with triphenylphosphine to the corresponding iminophosphorane, which was subjected in situ to the rearrangement reaction conditions. However,

(13) Similar azepine ring closure was reported by Hiram; see ref 6f.

this reaction resulted in decomposition, and no desired imine could be identified.

On the other hand, the initial rearrangement product **12** was readily transformed into **2** (Scheme 6). Removal of the

Scheme 6



protecting group from the primary alcohol followed by tosylation and substitution with azide afforded **16**. Acetylation of the tertiary allylic alcohol gave **17**. Staudinger reduction of the azide with  $\text{Me}_3\text{P}$  resulted in smooth cyclization to imine **2** upon reflux in toluene.

In conclusion, we developed a reaction tandem for the assembly of the spirobicyclic imine ring system of pinna-toxins and pteriatoxins. The reaction sequence is initiated by a [3,3]-sigmatropic shift that is followed by a Mislow–Evans rearrangement and introduces the chiral quaternary center at the core of the spirobicyclic ring system with a high level of stereocontrol. The allylic acetate functionality in **2**, that also resulted from the tandem reaction, is favorably set up for further elaboration to introduce the side chain at C-31. We plan to exploit the  $\pi$ -allyl palladium methodology<sup>14</sup> or allylic substitutions with cuprate reagents<sup>15</sup> to achieve this goal. Studies to evaluate the viability of cyclic imine **2** as an intermediate for the synthesis of pinna-toxins are underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization data for new compounds and copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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