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An Approach to the Imine Ring System of Pinnatoxins

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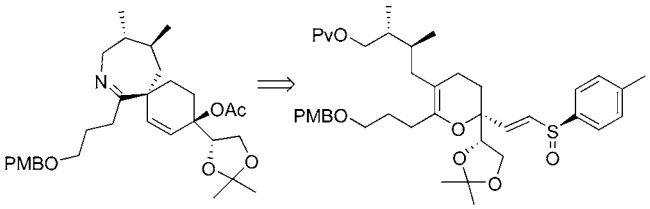
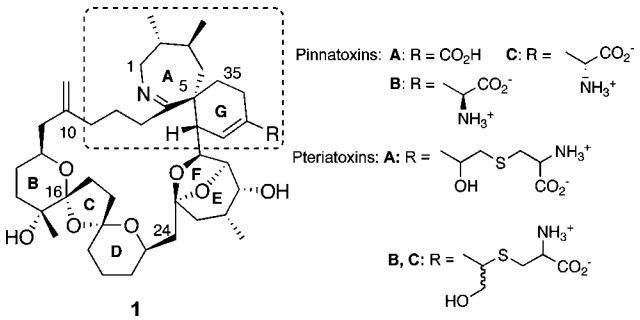
ABSTRACT



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**)[1] and gymnodimine[2] 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.[3] This atypical chemical behavior of the cyclic imines has been linked to the biological profile of the natural products[3a] and has also been observed during the pioneering total synthesis of pinnatoxin A by Kishi and in a recent insightful study described by Romo.[4,5]



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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.[6] 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.[7]

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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(3) (a) Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 308−312. (b) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671−7674.

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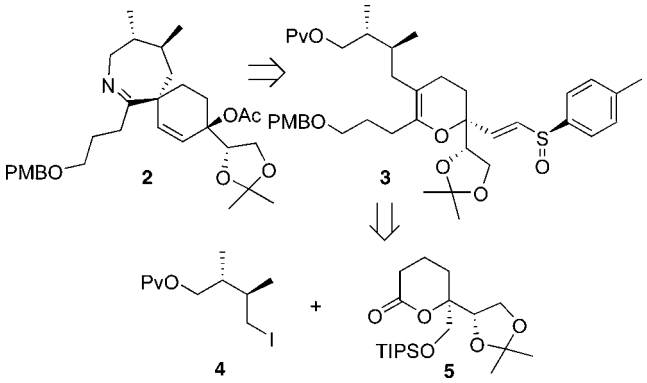
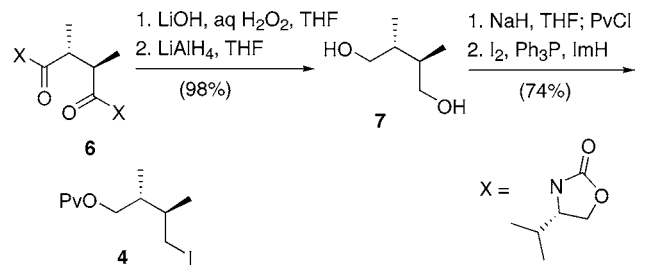
Scheme 1



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).[8] Conversion of **5** to diol

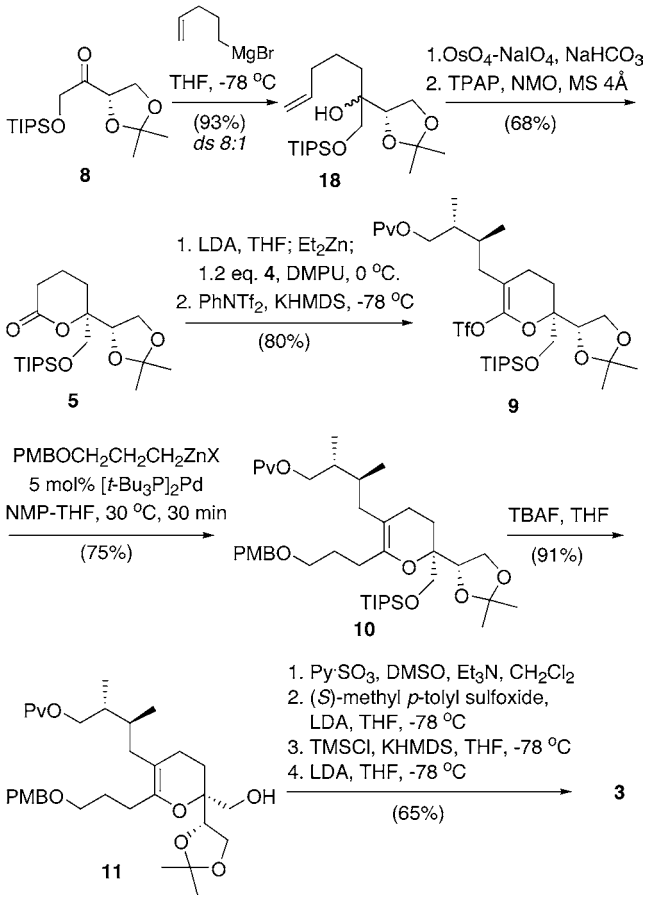
Scheme 2



7, its monoprotection with pivaloyl chloride, and iododehydroxylation 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).[9] Addition of 4-pentenylmagnesium bromide proceeded with 8:1 diastereoselectivity, giving the desired stereoisomer as the major product.[9] 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

Scheme 3



conditions, the reaction proved to be sluggish (5 mol % $Pd(dppf)Cl_2$, 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.[10]

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).[11] 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**.[12] 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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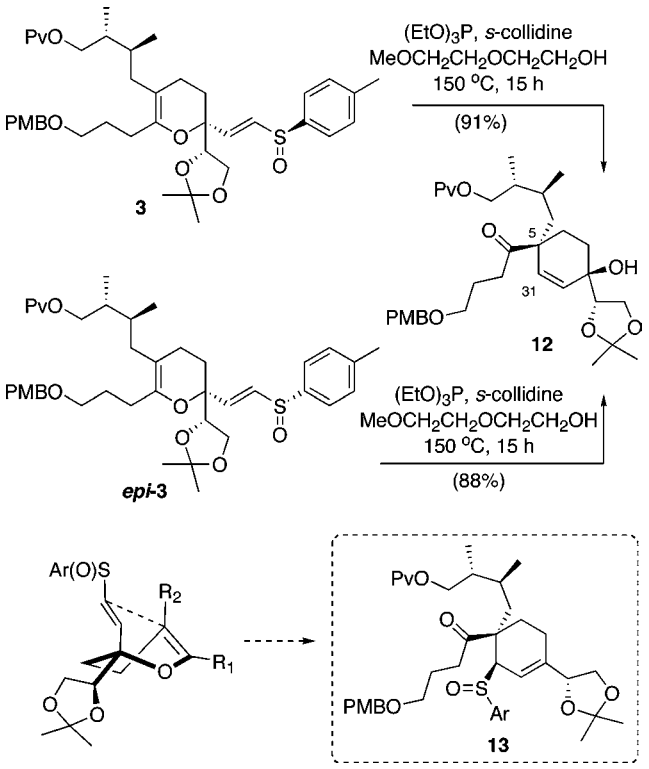
(10) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(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).

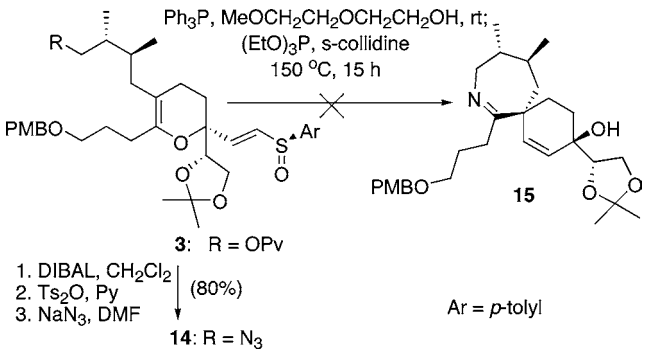
Scheme 4



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.[13] 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

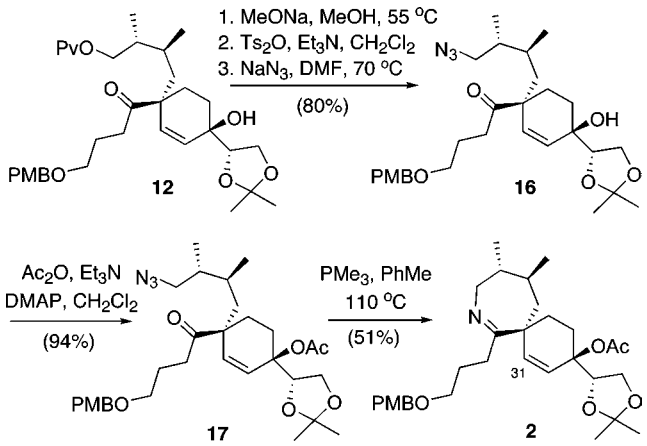
Scheme 5



thus obtained **14** was reduced with triphenylphosphine to the corresponding iminophosphorane, which was subjected in situ to the rearrangement reaction conditions. However, 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 Me_3P 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 pinnatoxins 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 π-allyl palladium methodology[14] or allylic substitutions with cuprate reagents[15] to achieve this goal. Studies to evaluate the viability of cyclic imine **2** as an intermediate for the synthesis of pinnatoxins are underway in our laboratory.

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

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

(14) Tsuji, J. *Palladium Reagents and Catalysts; New Perspectives for the 21st Century*; John Wiley & Sons: Chichester, England, 2004; Chapter 4.3, p 469.

(15) Lipshutz, B. H.; Sengupta, S. *Organic Reactions*; John Wiley & Sons: New York, 1992; Vol. 42, Chapter 1, p 135.