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Studies toward the Synthesis of Pinnatoxins: The B,C,D-Dispiroketal Fragment

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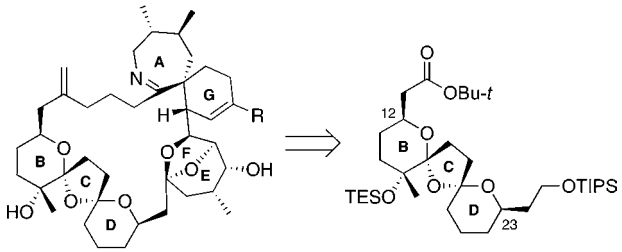
ABSTRACT



pinnatoxin macrocyclic core

A stereoselective synthesis of the tricyclic B,C,D-dispiroketal fragment of pinnatoxins is described. Both products of an efficient enzymatic resolution reaction are used to set the stereochemistry of C12 and C23, which have opposite configuration. The configuration of the ketal centers is established upon an optimized thermodynamically controlled spiroketalization.

Pinnatoxins[1] are "fast-acting" toxins that belong to an expanding group of marine natural products that now includes pteriatoxins,[2] spirolides,[3] prorocentrolides,[4] and gymnodimine.[5] In a previous communication, we reported an approach to the A,G-spiroimine fragment of pinnatoxins.[6] Our current convergent synthesis plan calls for the preparation of two large fragments incorporating the A,G-spiroimine and the B,C,D-dispiroketal followed by late-stage fragment coupling and ketalization to install the F,E-ketal. The synthesis of the tricyclic B,C,D-dispiroketal fragment is described in this communication.

The synthesis was guided by two objectives: (1) application of an efficient enzymatic resolution reaction where both products would be used to install stereocenters at C12 and C23, which have an enantiomeric relationship, and (2) convergency of the approach (Scheme 1). After some experimentation, we focused our efforts on a kinetic resolution of allylic alcohol **4** with Amano lipase PS developed by Tan and Holmes in their synthesis of (+)-allopumiliotoxin 323B′.[7]

Acylation of racemic alcohol **4** with vinyl acetate in the presence of Amano lipase PS-D in refluxing pentane was

(1) Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454.
(2) (a) Takada, N.; Umemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3491. (b) Takada, N.; Umemura, N.; Suenaga, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3495.
(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. (b) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159. (c) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671.
(4) (a) Torigoe, T.; Murata, M.; Yasumoto, T.; Iwashita, T. *J. Am. Chem. Soc.* **1988**, *110*, 7876. (b) Hu, T.; DeFreitas, A. S. W.; Curtis, J. M.; Oshima, Y.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **1996**, *59*, 1010. (c) Lu, C.-K.; Lee, G.-H.; Huang, R.; Chou, H.-N. *Tetrahedron Lett.* **2001**, *42*, 1713.
(5) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889.
(6) Pelc, M. J.; Zakarian, A. *Org. Lett.* **2005**, *7*, 1629.
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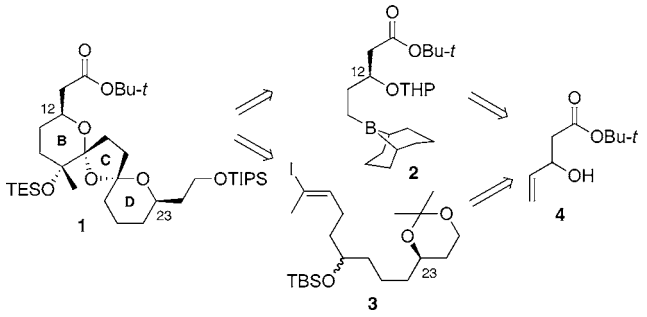
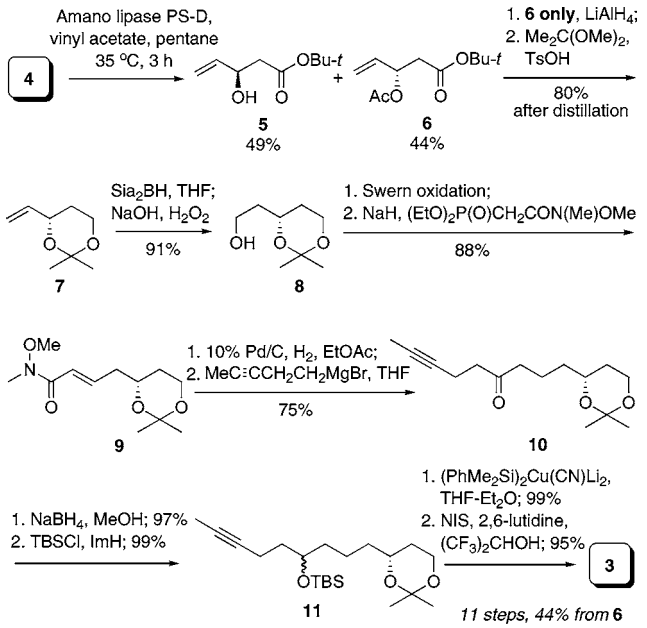
Scheme 1



terminated at 50% conversion (3 h), and the products were separated by column chromatography, furnishing acetate **5** in 44% yield (>95% ee) and alcohol **6** in 49% yield (>95% ee) (Scheme 2). Alcohol **6** was reduced with lithium

Scheme 2



aluminum hydride, and the resultant diol was converted to acetonide **7**. Hydroboration−oxidation delivered alcohol **8**, which was advanced to Weinreb amide[8] **9** in two steps: (1) oxidation to aldehyde[9] and (2) Horner−Wadsworth−Emmons olefination.

After hydrogenation of the double bond, coupling with 3-pentynylmagnesium bromide[10] in THF afforded ketone **10**. Reduction of **10** with sodium borohydride, silylation, and two-step conversion of **11** to the *E*-iodoalkene[11] completed the synthesis of **3** in 44% yield and 11 steps from **6**.

(8) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(9) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
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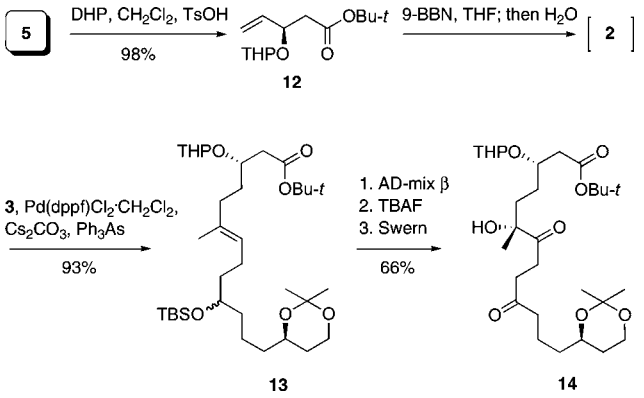
(11) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.

At this stage, the two products of the enzymatic resolution reaction were reunited by the Suzuki−Miyaura cross-coupling as depicted in Scheme 3.[12] The hydroxyl group in

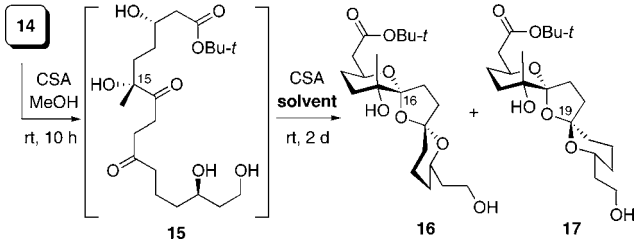
Scheme 3



5 was protected as a tetrahydropyranyl ether, and the resultant product (**12**, 2 equiv) was subjected to hydroboration with 9-BBN. The intermediate borane was treated with 1 equiv of iodide **3** in the presence of $Pd(dppf)Cl_2$ (0.10 equiv), Ph_3As (0.10 equiv), and cesium carbonate (1.5 equiv) at room temperature for 2 h to give coupling product **13** in high yield (93%). Subsequent Sharpless asymmetric dihydroxylation,[13] desilylation with tetra-*n*-butylammonium fluoride, and oxidation delivered diketone **14** in 66% overall yield from **13**.

Concomitant removal of the tetrahydropyranyl and isopropylidene protecting groups by exposure to acidic methanol delivered the substrate for the bis-spiro-ketalization (Scheme 4). Our goal was to selectively generate the doubly ano-

Scheme 4



merically stabilized bis-ketal **16** upon equilibration under acidic conditions. Similar thermodynamcally controlled spiroketalizations were used by Kishi in the total synthesis of pinnatoxin A[14] and by Inoue/Hirama in the formal synthesis of pinnatoxin A[15] with contrasting results. In Kishi's studies, the spiroketalization afforded a 3:2 mixture of dispiroketals where the undesired C19 epimer similar to **17** predominated. Silylation of the tertiary alcohol at C15

(12) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

effected epimerization to the desired configuration at the spiroketal center. In the Inoue/Hirama work, the desired spiroketal was formed selectively with an *unprotected* tertiary hydroxyl group at C15. The authors hypothesize that the observed selectivity is due to a long-range hydogen-bond stabilization (Figure 1),[15] which is likely to be highly specific

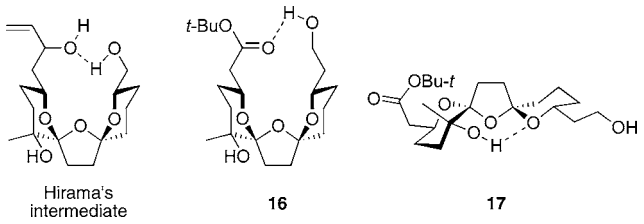


Figure 1. Analysis of hydrogen bond stabilization in **16**, **17**, and Inoue/Hirama's intermediate.

to the structure of the product and therefore not general.[16] On the other hand, we noted that one of the significant differences between the Kishi and Inoue/Hirama spiroketalizations was the solvent. Because the effect of the solvent on the extent and sometimes even the position of anomeric equilibria is well-established,[17] we undertook a brief study to determine the inluence of the solvent on the selectivity of bis-spiroketalization of diketone **15** (Table 1).

Table 1. Solvent Effect on the Spiroketalization

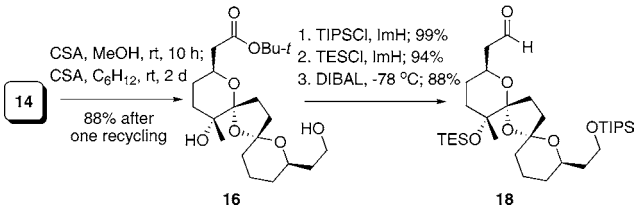
		isolated yield (%)	
entry	solvent	16	17
1	methanol	49	22
2	dichloromethane	62	23
3	toluene	63	13
4	cyclohexane	78	8

When the spiroketalization was performed in methanol, a 2.2:1 ratio of diastereomeric spiroketals was obtained favoring the desired diastereomer (**16**), along with other isomers and partially ketalized byproducts. This result is almost identical to that observed recently by Kishi and co-workers in the course of the total synthesis of pteriatoxins (2.1:1 ratio of the isomers in methanol).[18]

In subsequent experiments, after the protecting group removal (CSA, MeOH, rt, 10 h), methanol was replaced by solvents of decreasing polarity listed in Table 1. As the solvent polarity decreased, we observed an increased ratio of the desired diastereomer to its C19 epimer. Equilibration in dichloromethane delivered a 2.7:1 ratio of **16** and **17**, the ratio in toluene was 4.8:1, and the optimal selectivity (9.8:1) was achieved when cyclohexene was used as the solvent. We attribute this increased selectivity to a more pronounced anomeric effect in nonpolar solvent[17] rather than to a hydrogen-bond stabilization related to that proposed by Hirama and co-workers,[15] especially because an alternative hydrogen bonding is possible in the C19 epimer **17** (Figure 1).[14]

In an optimized protocol, we achieved an 88% yield of desired spiroketal **16** after only one recycling of **17** and other byproducts (Scheme 5). Protecting group installation was

Scheme 5



accomplished using successive treatment with TIPSCl and TESCl, and the *tert*-butyl ester was efficiently reduced to aldehyde **18** directly with DIBAL at −78 °C.

In summary, we developed a convergent enantioselective synthesis of the B,C,D-dispiroketal fragment of pinnatoxins using an efficient enzymatic resolution to establish the stereocenters at C12 and C23. The tricyclic ring system was assembled by an optimized acid-catalyzed spiroketalization in a nonpolar solvent to enhance the anomeric stabilization of the desired diastereomer.

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

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