Total Synthesis of Pinnatoxin A

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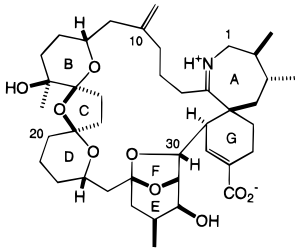
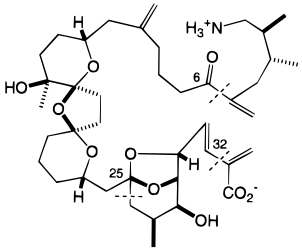
In 1995, Uemura and co-workers isolated pinnatoxin A (**1**) from the shellfish *Pinna muricata*, determined its gross structure and relative stereochemistry, and proposed a biosynthetic pathway, i.e., **2** → **1**.[1] Pinnatoxin A is one of the major toxic principles responsible for outbreaks of *Pinna* shellfish intoxication in China and Japan.[2] Its unique molecular architecture, accompanied by



Pinnatoxin A (**1**)



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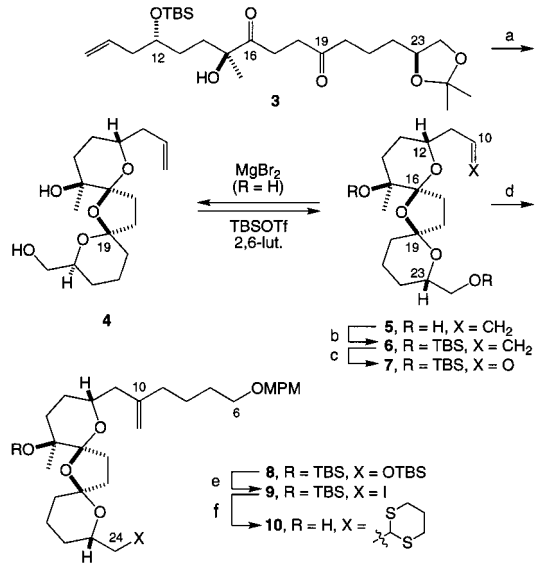
its pronounced biological activity as a Ca^{2+}-channel activator, makes pinnatoxin A an intriguing synthetic target.[3] In this paper, we report the first total synthesis of pinnatoxin A, which allowed the assignment of its absolute configuration as the antipode of **1**.

Our retrosynthetic analysis of pinnatoxin A is based on Uemura's biosynthetic proposal, entailing an intramolecular Diels−Alder reaction to construct the G-ring as well as the macrocycle, followed by imine formation to establish the 6,7-spiro-ring system. Functional group arrangements similar to the AG-ring system of pinnatoxin A are found in other natural products, including the spirolides[4] and gymnodimine,[5] and perhaps arise via a similar biogenetic pathway, i.e., an intramolecular Diels−Alder reaction followed by imine formation or vice versa.[6] To investigate these key cyclizations, we envisioned the requisite diene **2** as available via a dithiane-based coupling to form the C.25−C.26 bond and sequential Ni(II)/Cr(II)-mediated couplings between vinyl iodides with suitable advanced C.6 and C.32 aldehydes, cf. structure **2**. At the outset of this work, the absolute stereochemistry of pinnatoxin A had not been determined.

As the entry point into the bis-spiroketal system, we chose the acid-catalyzed cyclization of diketone **3**, prepared from 1-pentynol in 12 steps.[7] Treatment with camphorsulfonic acid (CSA)

Scheme 1[a]



[a] Reagents and yields: (a) CSA, MeOH, **5** (51%) + **4** (30%); (b) TBSOTf, 2,6-lutidine, 95%; (c) OsO_4, NMO; $NaIO_4$, 85%; (d) (i) 4-iodobutyl-*p*-methoxybenzyl ether, *t*-BuLi, Et_2O, −78 °C, 88%; (ii) Swern oxidation, 92%; (iii) PPh_3CH_3Br, *n*-BuLi, 0 °C, 89%; (e) (i) TBAF, rt, quantitative; (ii) I_2, PPh_3, imidazole, 92%; (f) (i) 1,3-dithiane, *t*-BuLi, 10% HMPA/THF, 92%; (ii) TBAF, 70 °C, 95%.

afforded primarily a 2:3 mixture of C.19 epimeric bis-spiroketals **4** and **5** whose structures were determined by X-ray analysis of their corresponding mono-*p*-nitrobenzoate derivatives (Scheme 1).[8] The ratio of **4** and **5** was affected by choice of acids, solvents, and addition of metal ions. In fact, the desired bis-spiroketal **5** completely epimerized to the undesired bis-spiroketal **4** in the presence of magnesium bromide, whereas the undesired bis-spiroketal **4** epimerized back exclusively to the natural series under standard silylation conditions, i.e., **4** → **6**. Once silylated at the tertiary hydroxyl, the bis-spiroketal system became configurationally stable[9] and could be transformed into dithiane **10** via standard synthetic methods without loss of its stereochemical integrity.

Dithiane **10** and iodide **11**[7] were coupled under *t*-BuLi in 10% HMPA/THF conditions[10] and converted to diol **12** in two steps (Scheme 2). Following oxidation, Ni(II)/Cr(II)-mediated coupling[11] of the aldehyde with vinyl iodide **13**[7] proceeded smoothly to generate a mixture of C.6-diastereomeric allylic alcohols. Removal of the primary TBS group and oxidation then furnished a single diketo-aldehyde **14**. Completion of the pinnatoxin carbon skeleton, cf. **16**, entailed a second Ni(II)/Cr(II)-mediated coupling between aldehyde **14** and iodide **15**,[7] in the presence of a bispyridinyl ligand.[12] It is noteworthy that the vinylchromium species adds selectively to the C.32 aldehyde in the presence of a carbamate carbonyl, an enone, and a ketone.

Our first attempt directed at the biomimetic Diels−Alder reaction began with removal of the acetonide and formation of

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(5) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; 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) Prorocentrolides possess a fused cyclohexene/cyclic imine ring system which may also arise through an intramolecular Diels−Alder reaction: (a) Torigoe, K.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 7876. (b) Hu, T.; deFreitas, S. W.; Curtis, J. M.; Oshima, Y.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **1996**, *59*, 1010.

(7) Experimental details for the synthesis of **3**, **11**, **13** and **15**, and the structures of **18b**−**c** are included in Supporting Information.

(8) Bis-spiroketals **4** and **5** can be distinguished readily from the chemical shifts of the C.12 and C.23 resonances in ^{1}H NMR.

(9) For similar examples, see: Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187, and references therein.

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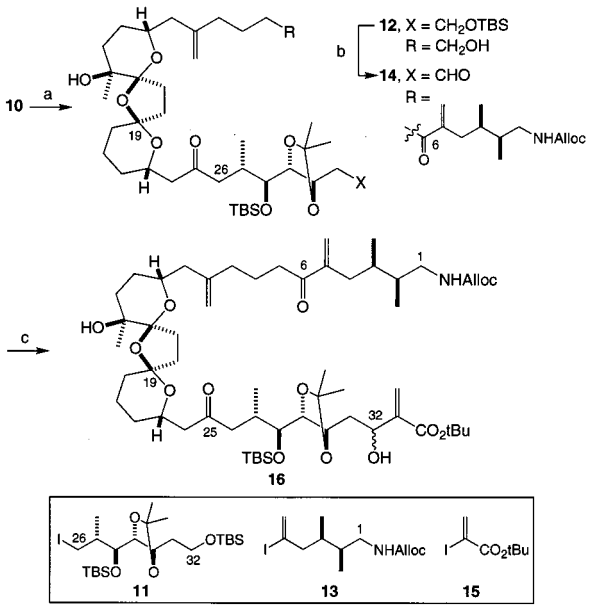
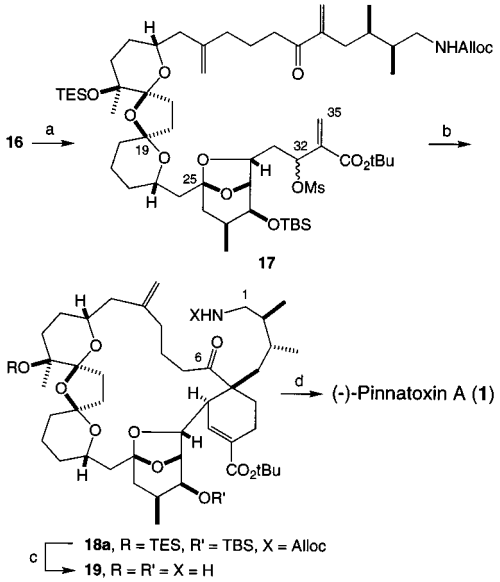
Scheme 2[a]



[a] Reagents and yields: (a) (i) **10**, *t*-BuLi, 10% HMPA/THF, then addition of **11**, 71%; (ii) $(CF_3CO_2)_2IPh$, $CaCO_3$, 82%; (iii) DDQ, 85%; (b) (i) Dess−Martin oxidation, 90%; (ii) **13**, 1% $NiCl_2/CrCl_2$, DMSO, 55%; (iii) HF·pyridine, pyridine, THF, 91%; (iv) Dess−Martin oxidation, 91%; (c) **15**, 33% $NiCl_2/CrCl_2$, bispyridinyl ligand, THF, 88%.

Scheme 3[a]



[a] Reagents and yields: (a) (i) TFA, CH_2Cl_2, H_2O, 71%; (ii) MsCl, TEA, −78 °C, 85%; (iii) TESOTf, 2,6-lutidine, 79%; (b) DABCO, TEA, benzene; 70 °C, 0.2 mM diene in dodecane, 78%; (c) (i) HF·pyridine, pyridine, THF, 94%; (ii) $Pd(PPh_3)_4$, AcOH, toluene, 82%; (d) (i) 200 °C, 1−2 Torr, 70%; (ii) 1:1 TFA/CH_2Cl_2, 95%.

the bicyclic ketal (Scheme 3). Under the acidic conditions employed, the C.19 bis-spiroketal stereocenter almost completely epimerized to the undesired configuration. However, as demonstrated previously, we could epimerize the C.19 stereocenter of the mesylate derived from **16** back to the desired configuration, cf. **17**, under silylation conditions. The diene was then formed via S_N2' displacement of the C.32 allylic mesylate with DABCO[13] followed by removal of a C.31 proton by treatment with triethylamine. However, upon concentration, this diene readily underwent complete dimerization via an intermolecular cycloaddition of the diene with the C.33−C.35 olefin.[13]

In contrast, heating a 0.2 mM solution of the diene in a variety of solvents led to the desired intramolecular Diels−Alder reaction.[14] For example, heating the diene in toluene at 100 °C for 24 h gave a 1:1:1 mixture of three out of the eight possible intramolecular Diels−Alder products, which were separated by HPLC to yield pure adducts **18a**−**c**.[7] 2D NMR experiments established the structures of **18a**−**c**: desired exo product (**18a**), undesired exo product (**18b**), and one endo product (**18c**), all possessing the desired regiochemistry.[15] Interestingly, the exo/endo ratio was enhanced by changing the solvent to dodecane and reducing the temperature to 70 °C. Under these conditions, the ratio of **18a**:**18b**:**18c** was 1.0:0.9:0.4, with a ca. 5:1 exo:endo ratio in a 78% combined yield. It is worthwhile to note that the facial selectivity leading to the exo products depended on the arrangement of functional groups around the C.25−C.32 moiety.[16]

The desired Diels−Alder product **18a** was converted to amino ketone **19** in two steps. However, attempts to form the imine between the C.1 amine and C.6 ketone under a variety of acidic conditions were unsuccessful. This observation, along with the fact that pinnatoxin A exists as a stable imine in dilute aqueous acid,[1] led us to hypothesize a large energy barrier present for the imine formation/hydrolysis due to the steric strain in generating a tetrahedral intermediate adjacent to a quaternary center. To overcome this obstacle, we heated the neat amino ketone **19** to 200 °C under high vacuum for 1 h and obtained a 70% yield of the desired imine. Finally, the *tert*-butyl ester was cleaved with 1:1 TFA/CH_2Cl_2 treatment[17] to furnish synthetic pinnatoxin A [α_D −9° (*c* 0.5, MeOH)], identical in all respects to natural pinnatoxin A[18] [α_D +2.5° (*c* 0.3, MeOH)] except for the sign of optical rotation. From this information, we conclude that the absolute stereochemistry of natural pinnatoxin A is the antipode of structure **1**. This conclusion was further supported by the biological tests of synthetic (−)-pinnatoxin A in reference to natural (+)-pinnatoxin A.[18]

In conclusion, we have completed the first total synthesis of pinnatoxin A utilizing a biomimetic intramolecular Diels−Alder reaction. This synthesis has also established the absolute stereochemistry of pinnatoxin A as the antipode of the structure **1**.

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Supporting Information Available: The experimental details for the synthesis reported, including the synthesis of diketone **3**, and iodides **11**, **13**, and **15** (26 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(14) The C.19-epi-ketal derived from TFA treatment of acetonide **16** was transformed into a Diels−Alder precursor without exposure to TESOTf, furnishing a cyclization precursor with the diene and dieneophile on opposite faces of the molecule. Considering that this compound cannot meet the geometrical arrangement required for the intramolecular Diels−Alder reaction, one expects this compound would not undergo the desired intramolecular cycloaddition. Indeed, this substrate was found only to dimerize under all conditions tested.

(15) We thank Dr. Yuan Wang, Eisai Research Institute, Andover, MA, for the 2D NMR experiments.

(16) For example, treatment of **16** with MsCl, followed by DABCO, gave a Diels−Alder precursor with the C.29−C.30 acetonide intact. The intramolecular Diels−Alder reaction [toluene (0.2 mM), 100 °C] then furnished a single product in 60% yield. 2D COSY and NOESY NMR experiments indicated that this product possessed the desired stereochemistry. However, all attempts to remove the acetonide have been fruitless thus far.

(17) The configuration of the C.19 spiroketal center is stable once the macrocycle is formed. For a similar example, see ref 9.

(18) We thank Professor Uemura for a generous gift of natural pinnatoxin A. We also thank him for performing biological tests which indicated that synthetic pinnatoxin A was inactive in a mouse assay at 100 μg dosage, whereas the LD_{99} for natural pinnatoxin A is 2.7 μg per mouse.