Communication

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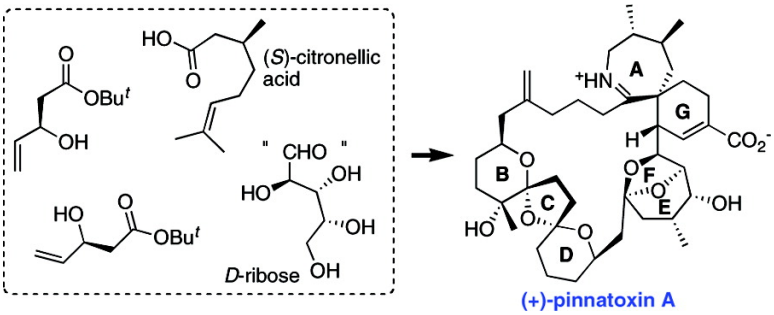

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Total Synthesis of (+)-Pinnatoxin A

Craig E. Stivala and Armen Zakarian*

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

Received January 25, 2008; E-mail: zakarian@chem.ucsb.edu

The remarkable and intricate structure of pinnatoxin A secured its place as a compelling target for chemical synthesis.[1] In a report published in 1990, Zheng and co-workers linked massive human intoxication following the consumption of shellfish of the *Pinna* species to the presence of a neurotoxin.[2] A few years later, the group of Uemura isolated two toxins from 45 kg of the viscera of *Pinna muricata* and elucidated the structure of pinnatoxin A, which is comprised of a 27-membered carbocycle incorporating a unique A,G-spiroimine and B,C,D-spirotricyclic bis-ketal fragments.[3,5] The mechanism of bioactivity of the marine toxins remains unknown, although it has been suggested that pinnatoxin A is a calcium channel activator.[2a] The biosynthetic pathway to the natural product proposed by Uemura invokes a notable intramolecular Diels−Alder cycloaddition that forms ring G and installs the macrocycle. The proposed biosynthesis served as the basis for the pioneering total synthesis of (−)-pinnatoxin A by the group of Kishi,[4] an extension of which has recently provided a complete stereochemical assignment for pinnatoxins B, C, and related pteriatoxins A−C.[5,6]

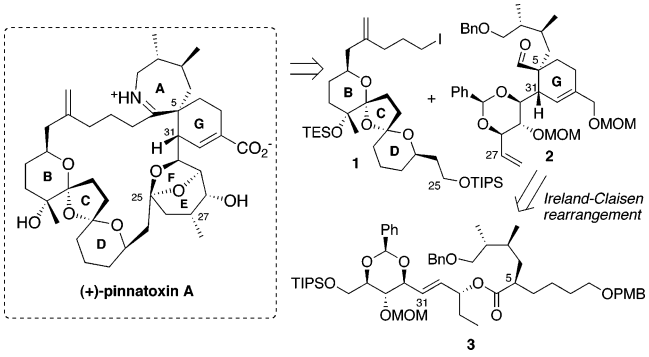
Here, we describe our studies that culminated in the total synthesis of the natural enantiomer of pinnatoxin A. In terms of strategy, a major focus of our effort was the assembly of the cyclohexene ring (ring G) including the quaternary stereocenter C5 at the core of the A,G-spirocyclic imine (Scheme 1). In an attempt to achieve improved stereocontrol, we chose to depart from the apparent Diels−Alder approach in favor of the Ireland−Claisen rearrangement-based strategy, which prompted the development of a method for stereoselective enolization of acyclic alpha-branched esters.[7] This analysis identified two subtargets, **1** and **2**, with allylic ester **3** as the key precursor to the advanced building block **2**.

Ester **3** was prepared in a convergent manner from the corresponding allylic alcohol and carboxylic acid, underscoring the power of the Ireland−Claisen strategy. The synthesis of the allylic alcohol commenced with D-ribose thioacetal **4** (Scheme 2).[8] After installation of the protecting groups,[9] the dithiane ring was cleaved and the exposed aldehyde was used in the Horner−Emmons olefination to afford **6** (80%). The ester was advanced to unsaturated aldehyde **7** in two steps in 85% yield. The diastereoselective addition of diethylzinc catalyzed by 1,2-aminoalcohol **9**[10] delivered **8** in 79% yield along with its diastereomer (10%).

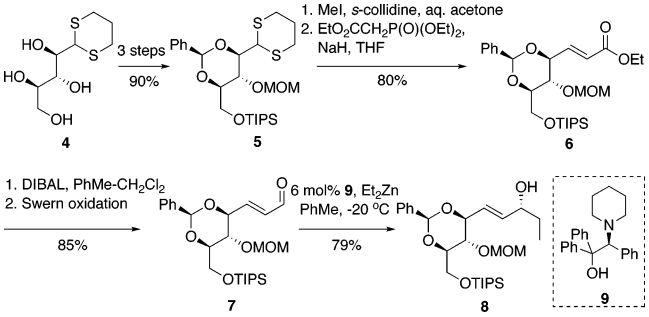
Previously, we described a 10-step synthesis of carboxylic acid **10** from (*S*)-citronellic acid.[7b] Acid **10** was combined with allylic alcohol **8** using EDC in the presence of DMAP to form ester **3** in high yield (Scheme 3). In the key event, ester **3** was subjected to stereoselective enolization using chiral Koga-type chiral lithium amide **11**. The resulting lithium enolate was intercepted as silyl ketene acetal **12**, which underwent a highly diastereoselective [3,3]-sigmatropic shift delivering carboxylic acid **13** in high yield. Thus, two challenging stereogenic centers, C5 and C31, were established efficiently by this transformation.

The synthesis of aldehyde **2** was accomplished as illustrated in Scheme 4. Reduction of the acid, acylation of the resulting alcohol, and removal of the PMB group was followed by ozonolysis, which

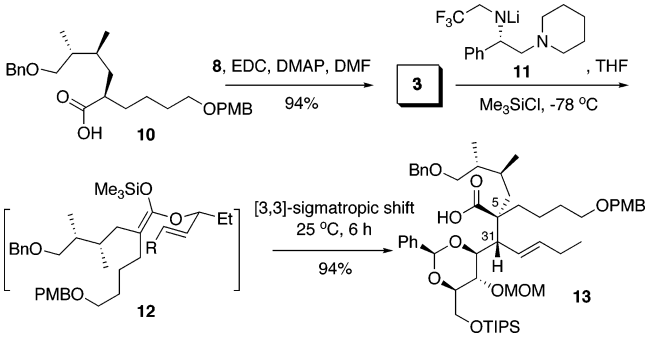
Scheme 1. Synthesis Plan



Scheme 2



Scheme 3



was performed under the conditions developed by Dussault and co-workers.[11] Direct oxidation of the resulting hydroxy aldehyde using a variety of protocols was unproductive; therefore, reduction to diol **15** was carried out. Double oxidation of **15** under Swern conditions provided the dialdehyde, which underwent a smooth regioselective aldol cyclization to **16** in the presense of dibenzylammonium trifluoroacetate in 80% yield over two steps,[12] installing the requisite cyclohexene ring. The aldehyde was masked as the allylic MOM ether (**16** → **17**). Removal of the silyl protecting group, oxidation, and Wittig olefination gave the C27 olefin **18** (82%). Deprotection of the primary alcohol and oxidation with the Dess−Martin periodinane[13] delivered aldehyde **2**.

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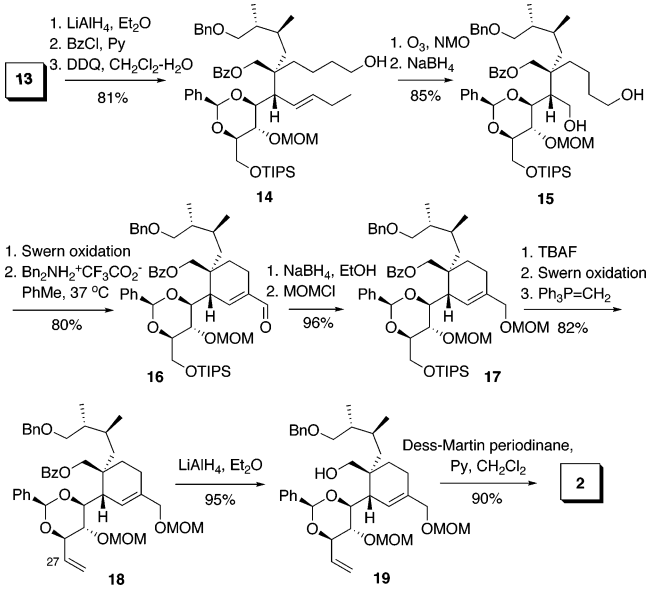
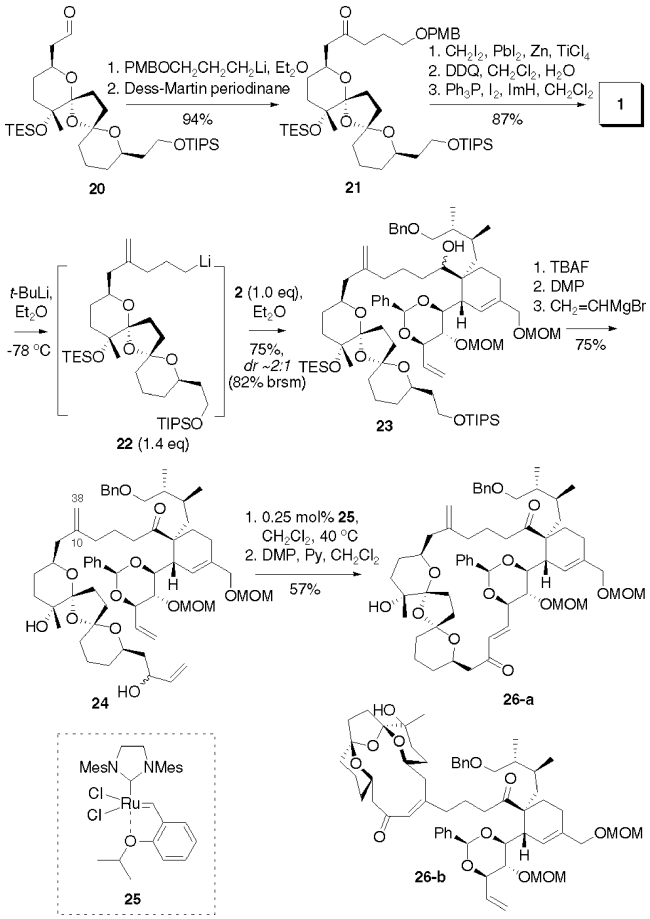
Scheme 4



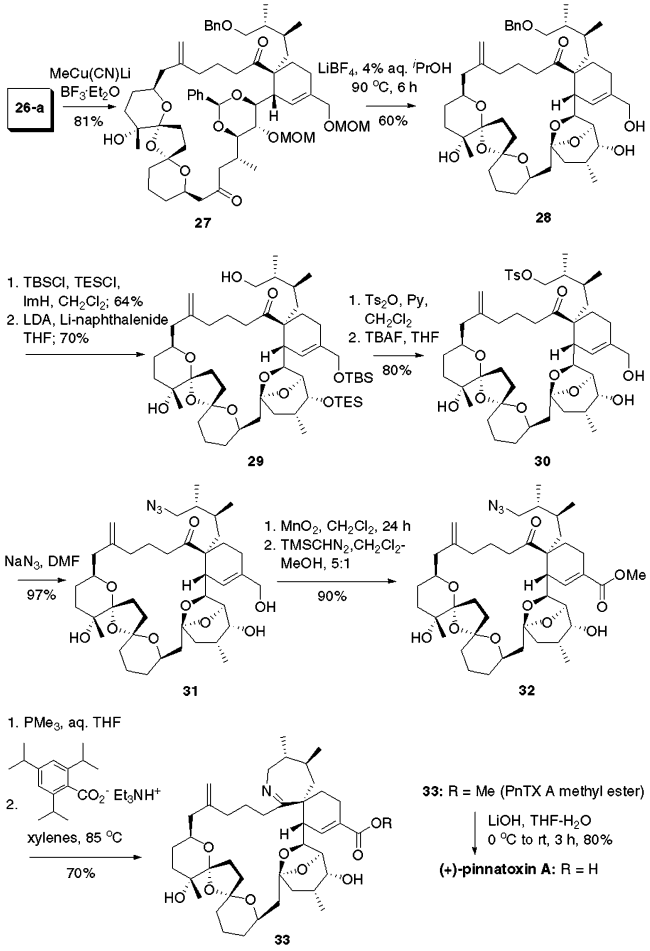
Aldehyde **20**, prepared previously,[14] was employed in the preparation of iodide **1** for the fragment coupling (Scheme 5). Addition of 3-(*p*-methoxybenzyloxy)-1-propyllithium followed by oxidation with the Dess−Martin periodinane furnished ketone **21** in high yield. Takai methylenation,[15] removal of the PMB group, and iodo-dehydroxylation afforded iodide **1**.

The fragment coupling was accomplished directly by the addition of complex organollithium reagent **22**, generated by an iodine−

Scheme 5



Scheme 6



lithium exchange from **1**, to aldehyde **2** in good yield. When the corresponding Grignard reagent was used, a significant reduction of **2** to alcohol **19** was observed (up to 30%).

Once the silyl protecting groups (TIPS, TES) were removed from the diastereomeric mixture of the alcohols **23** with TBAF, the primary and secondary hydroxyl groups were oxidized to provide the keto aldehyde. This keto aldehyde was converted to tetraene **24** upon chemoselective addition of vinylmagnesium bromide.

Compound **24** served as the substrate for the formation of the 27-membered all-carbon macrocycle of the target molecule by ring-closing metathesis. Under a variety of reaction conditions with either Grubbs II[16] or Hoveyda−Grubbs II[17] (**25**) catalysts, a ∼3:1 ratio of two products, desired macrocycle **26-a** and undesired isomer **26-b**, was produced. The formation of **26-b** is a result of a competitive cyclization involving the 1,1-disubstituted alkene at C10−C38. Catalyst **25** generally gave cleaner reactions. No reaction was detected when the first-generation catalysts were employed. When the order of ring-closing metathesis and oxidation with Dess−Martin periodinane was reversed, the regioselectivity remained the same. Installation of the triethylsilyl protecting group on the allylic hydroxyl group in substrate **24** made it unreactive in the RCM reaction.

After oxidation, enone **26-a** was isolated in 57% overall yield.

The completion of the total synthesis was achieved following a series of transformations depicted in Scheme 6. Lewis acid mediated *anti*-addition of MeCu(CN)Li installed the stereogenic center at C27.[18] After extensive experimentation, we found that the two methoxymethyl (MOM) groups and the benzylidene acetal could be cleaved using the modified Lipshutz conditions with the

concomitant formation of the EF-ketal in a reasonable yield.[19] Silylation and reductive debenzylation gave **29**, which was converted to azide **31** in three steps. Physical data for **31** (^{1}H, ^{13}C NMR, $[\alpha]_D$, HRMS) matched those reported by Inoue/Hirama and co-workers, who previously used this intermediate in a formal synthesis of pinnatoxin A.[1a] Direct oxidation of the allylic hydroxyl group to the carboxylic acid was observed upon prolonged exposure of **31** to a suspension of manganese(IV) oxide in CH_2Cl_2,[20] which was followed by treatment with trimethylsilyl diazomethane to obtain methyl ester **32**.[21] The Staudinger reduction of the azide at C1 with trimethylphosphine in aqueous THF afforded the corresponding primary amine. In the absence of water, attempted direct cyclization of the intermediate iminophosphorane resulted in no imine formation, and only decomposition was observed under forcing conditions (~130 °C). The challenging imine formation was carried out by heating the amino ketone in the presence of triethylammonium 2,4,6-triisopropylbenoate in xylenes at 85 °C employing the reaction conditions developed previously by Kishi and co-workers.[6] Thus, pinnatoxin A methyl ester was formed in 70% overall yield.[22]

Hydrolysis of the methyl ester occurred cleanly upon exposure of **33** to lithium hydroxide in aqueous tetrahydrofuran at ambient temperature, affording (+)-pinnatoxin A in 80% yield. The cyclic imine proved to be stable under these basic reaction conditions.

In conclusion, an enantioselective total synthesis of (+)-pinnatoxin A has been accomplished. The essential features of the synthesis are the highly convergent strategy enabled by the success of the Ireland−Claisen rearrangement of alpha-branched ester **3**. The key Ireland−Claisen rearrangement allowed for the assembly of the challenging quaternary stereogenic center at C5 and the adjacent tertiary stereocenter at C31 in high yield and with a high level of stereocontrol.

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

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(21) For a recent review, see: Kühnel, E.; Laffan, D. D.; Lloyd-Jones, G. C.; del Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075−7078.

(22) Pinnatoxin A methyl ester was prepared previously from the natural (+)-pinnatoxin A by Uemura and co-workers (ref 3a). The physical data of the synthetic material match those reported for the methyl ester derived from the natural product. See Supporting Information for details.

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