Natural Product Synthesis

DOI: 10.1002/anie.200802729

Total Synthesis of Pinnatoxin A**

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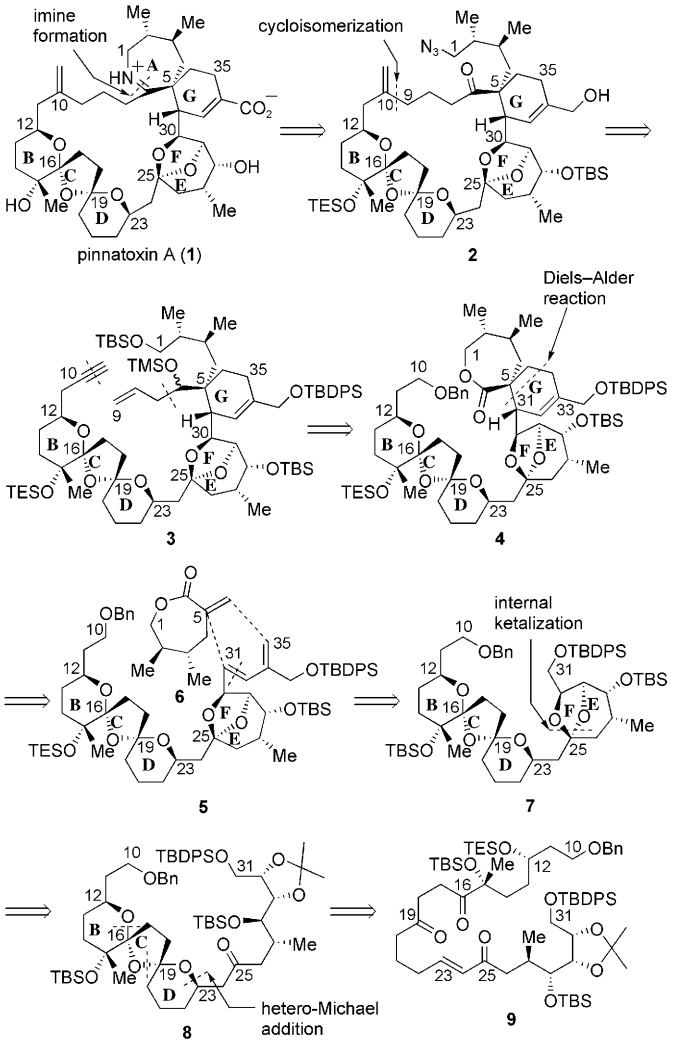
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Pinnatoxins and pteriatoxins are structurally related marine toxins which were isolated and characterized by Uemura and co-workers.[1,2] Pinnatoxin A (**1**), isolated along with pinnatoxins B–D from the shellfish *Pinna muricata* in 1995, is the first and most prominent member of the marine iminium alkaloid family; it was reported to activate Ca^{2+} channels,[3] although the scarcity of a natural supply has prevented additional biological evaluation. Pinnatoxin A (**1**) possesses a striking array of structural features, including a 27-membered carbocycle incorporating a [6,5,6]-dispiroketal (BCD rings), a [5,6]-bicycloketal (EF rings), and a cyclic imine (A ring) spirolinked to a cyclohexene ring (G ring), which suggests that it originates biosynthetically from an intramolecular [4+2] cycloaddition event.[1a,2] Owing to its structural complexity, biological properties, and limited availability, **1** has been a target of considerable synthetic interest. In 1998, Kishi and co-workers[4] accomplished the first total synthesis of (−)-**1** by utilizing a biomimetic intramolecular Diels–Alder reaction to construct the G ring and the macrocycle, establishing that the absolute stereochemistry was enantiomeric to that illustrated by Uemura and co-workers. A formal total synthesis of **1** was documented by the group of Hirama in 2004,[5] and very recently a total synthesis was completed by the group of Zakarian.[6] Other studies directed toward the synthesis of the pinnatoxin framework have also been reported by several groups, including ours.[7–9] In this communication, we disclose a route to the synthesis of pinnatoxin A (**1**), capitalizing on the *exo*-selective intermolecular Diels–Alder reaction devised by the Roush group[10,11] and the Ru-catalyzed cycloisomerization methodology developed by the Trost group.[12–14]

In our retrosynthetic strategy, we envisioned the late-stage formation of the cyclic imine and a Ru-catalyzed cycloisomerization of the appropriate enyne **3** to construct the 27-membered carbocycle in **2** (Scheme 1). Since the stereochemical arrangement of the G ring would require an *exo*-selective Diels–Alder reaction with diene **5**, we decided to take advantage of the striking *exo* preference of the conformationally restricted *s-cis* enone and enoate dienophiles.[10,11] α-Methylene lactone **6** was then chosen as the



Scheme 1. Retrosynthetic analysis of pinnatoxin A (**1**). Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; TMS = trimethylsilyl.

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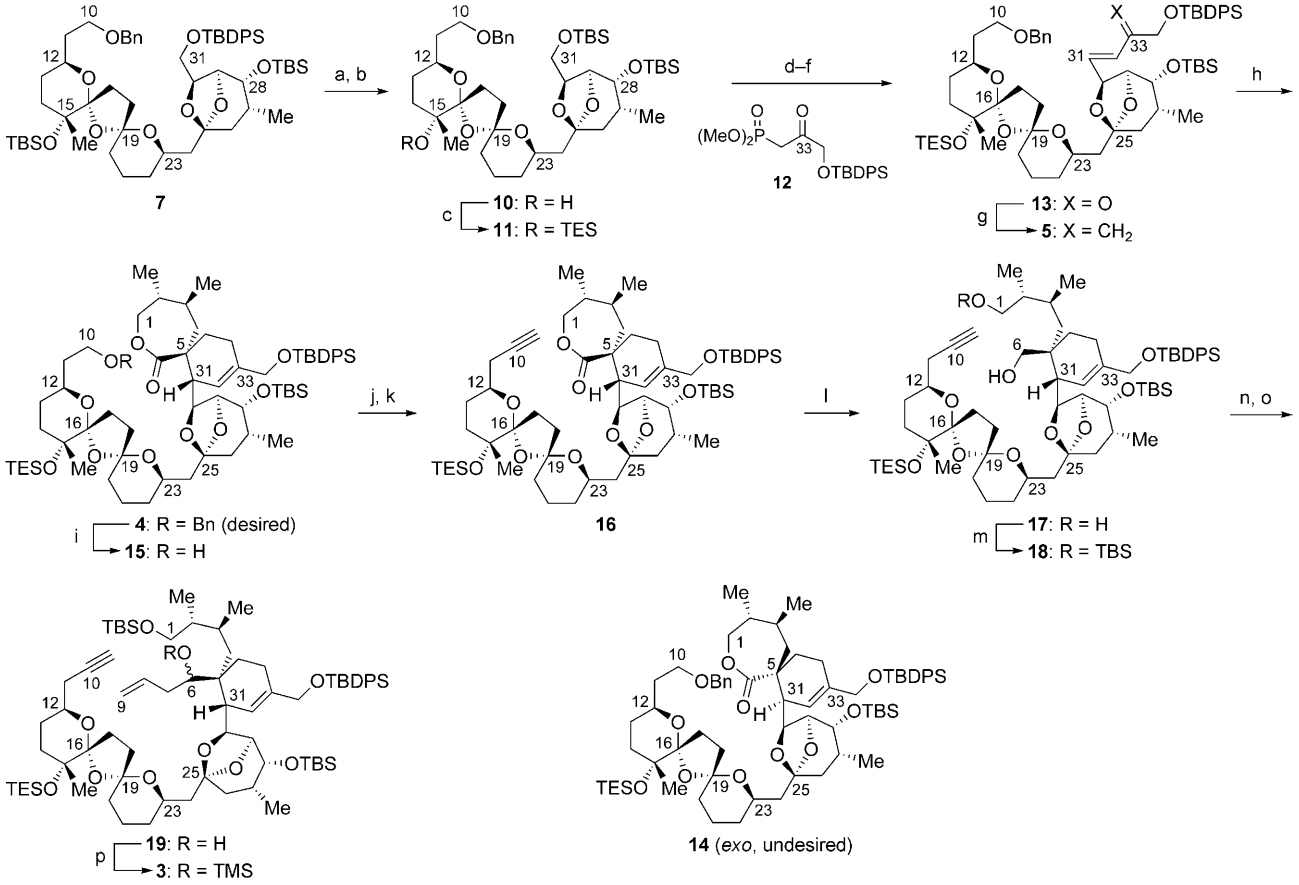
[**] This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and Priority Areas 17035002 and 18032002 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Akiyama Foundation. We are grateful to Prof. Daisuke Uemura of Keio University for helpful advice. We also thank Seiko Oka, Hiroko Matsumoto, Akiko Maeda, Miwa Kiuchi, and Tomohiro Hirose of the Center for Instrumental Analysis, Hokkaido University and Dr. Eri Fukushi of the Faculty of Agriculture, Hokkaido University for technical assistance in NMR, mass, and elemental analyses. The early stages of our pinnatoxin A synthesis were developed by Dr. Jun Inagaki, Tomohiro Sugimoto, and Masashi Kudo.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802729.

dienophile to give cycloadduct **4** with the correct stereochemistry at both C5 and C31. Bicycloketal **7** could be derived from the internal ketalization of ketone **8**, which could be constructed by removal of the C12 TES protecting group of the open-chain precursor **9**, and a subsequent double hemiketal formation/hetero-Michael addition reaction.

We previously developed a route to access the C10–C31 fragment (**7**),[9] wherein a tandem double hemiketal formation/intramolecular hetero-Michael addition sequence was employed for the stereoselective construction of the BCD ring system. Since Kishi and co-workers suggested that the C15 TBS protecting group could not be removed during the later stages of the synthesis,[4b] a protecting group exchange appeared to be the first task to advance intermediate **7** to **1**. Thus, removal of the silyl protecting groups with Bu_4NF in THF at reflux and subsequent selective reprotection of the hydroxy groups at C28 and C31 as TBS ethers afforded alcohol **10** in 95% yield in two steps; **10** was then silylated with TESOTf to give **11** in 94% yield (Scheme 2). After selective removal of the C31 TBS ether with Bu_4NF in THF at 0°C, the alcohol, which is prone to isomerization, was immediately oxidized with Dess–Martin periodinane[15] buffered with pyridine. The aldehyde was then homologated by a Horner–Wadsworth–Emmons reaction with β-ketophosphonate **12**[16] under Masamune conditions[18] to provide enone **13** in 78% overall yield in three steps. Enone **13** was subjected to a Wittig reaction to yield diene **5** in 92% yield, which set the stage for the crucial Diels–Alder reaction.

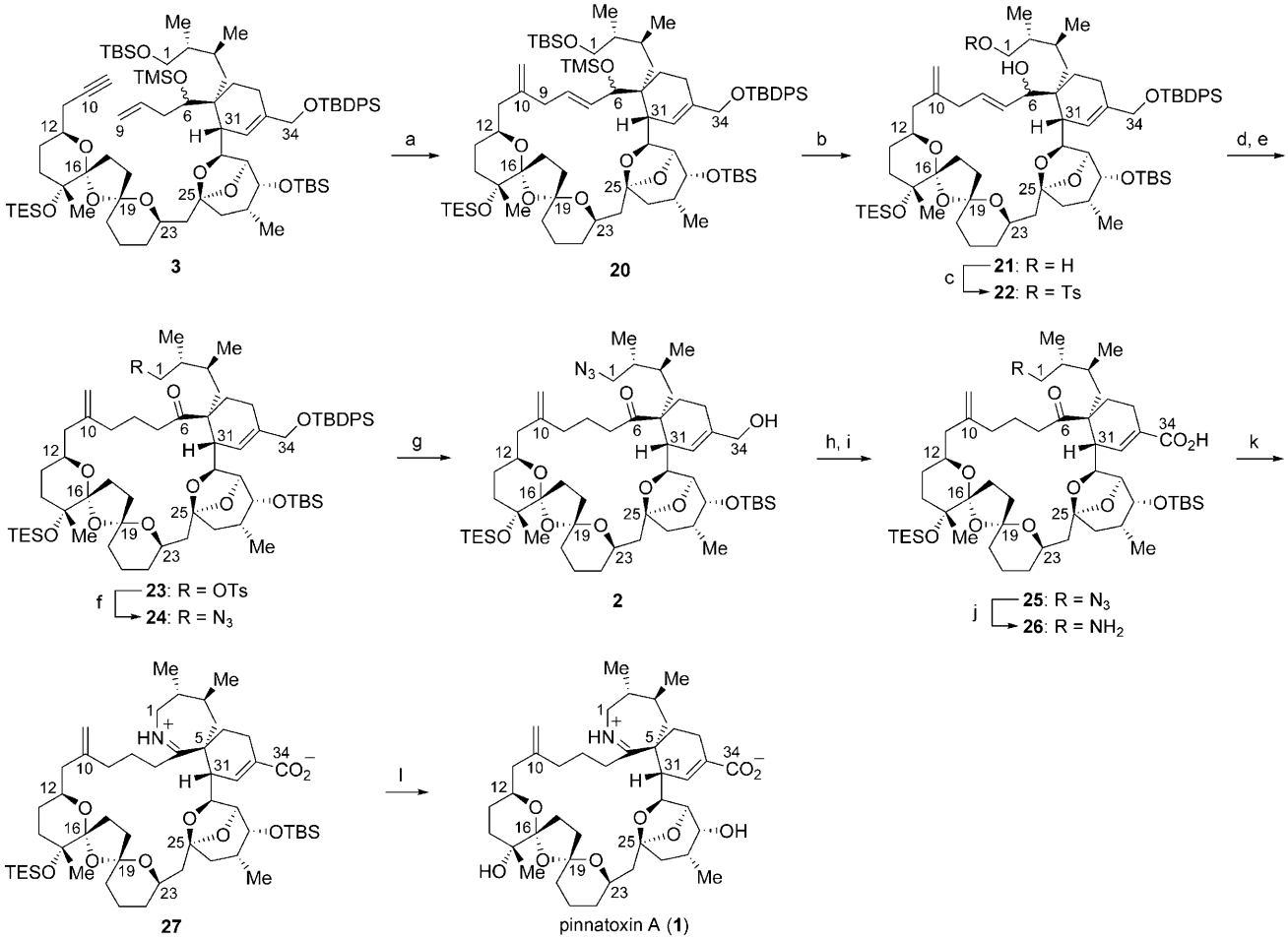
The cycloaddition of **5** with α-methylene lactone **6**[19] in *p*-xylene at 160°C in a sealed tube proceeded with complete regioselectivity to provide a mixture of four of the eight possible stereoisomers in a 45:27:18:10 ratio and a total yield of 83%. Modest *exo* selectivity (72:28) was obtained as expected from known precedent,[11b] albeit with a poor diastereofacial selection (63:37). After separation of the isomers, desired adduct **4** was isolated in 35% yield along with 23% of adduct **14**. At this stage, we were faced with the task of removing the benzyl group at C10 without affecting the olefin functionality. After considerable experimentation, it was found that the desired transformation could be achieved by addition of **4** to a premixed suspension of Pd/C and HCO_2H[20] in EtOH. The resultant alcohol **15** was uneventfully converted into alkyne **16** in 77% yield by Dess–Martin oxidation, and subsequent treatment with the Ohira–Best-



Scheme 2. Synthesis of cyclization precursor **3**. a) Bu_4NF, THF, reflux, 72 h; b) TBSCl, imidazole, DMF, 3.5 h, 95% (2 steps); c) TESOTf, 2,6-lutidine, CH_2Cl_2, 15 min, 94%; d) Bu_4NF (1.05 equiv), THF, 0°C, 4 h, 91%; e) Dess–Martin periodinane, pyridine, CH_2Cl_2, 3 h; f) phosphonate **12**, LiCl, iPr_2NEt, MeCN, 18 h, 86% (2 steps); g) $MePPh_3Br$, BuLi, THF, 0°C, 30 min, 92%; h) lactone **6** (10 equiv), 4 Å molecular sieves, *p*-xylene, 160°C, 12 h, 35% of **4**, 23% of **14**, and 23% of *endo* isomers; i) 10% Pd/C, HCO_2H, EtOH, 12 h, 81%; j) Dess–Martin periodinane, pyridine, CH_2Cl_2, 1 h, 95%; k) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 72 h, 82%; l) $LiAlH_4$, THF, −78 to 0°C, 6 h, 90%; m) TBSCl, imidazole, CH_2Cl_2, 1 h, 98%; n) Dess–Martin periodinane, pyridine, CH_2Cl_2, 1 h, 96%; o) $CH_2=CHCH_2MgBr$, THF, −78 to 0°C, 2 h, 97%; p) 1-(trimethylsilyl)imidazole, THF, reflux, 48 h, 98%.

mann reagent in the presence of K_2CO_3 in MeOH.[21] To set up the three-carbon homologation, the lactone moiety was reduced with $LiAlH_4$ to diol **17**, which was monosilylated at the C1 hydroxy group with TBSCl to provide alcohol **18** in 88% yield in two steps. Dess–Martin oxidation of **18** and then addition of allylmagnesium bromide furnished alcohol **19** in 93% yield in two steps, which, upon silylation with 1-(trimethylsilyl)imidazole in THF at reflux, gave enyne **3** in 98% yield.

With the cyclization precursor in hand, we then investigated the key cycloisomerization reaction. Gratifyingly, the reaction of enyne **3** occurred with complete regioselectivity by application of the Trost procedure[12,14] (10 mol% of $[CpRu(MeCN)_3]PF_6$, acetone, 50°C) to provide desired cyclization product **20** in 79% yield with no signs of dimerization (Scheme 3). Exposure of 27-membered ring compound **20** to pyridinium *p*-toluenesulfonate (PPTS) in EtOH resulted in selective removal of the silyl protecting groups at C1 and C6 to afford diol **21**, which, upon tosylation of the liberated primary alcohol gave **22** in 82% yield over two steps. The C7–C8 double bond was saturated by oxidation of the allylic alcohol at C6 with Dess–Martin periodinane and subsequent conjugate reduction with the Stryker reagent in wet benzene,[22] providing ketone **23** in 93% yield in two steps. After displacement of tosylate **23** with NaN_3 in DMF at 70°C, the C34 TBDPS ether was selectively removed with Bu_4NF in THF at 0°C to give alcohol **2** in 88% yield over two steps; **2** was then transformed into carboxylic acid **25** by two successive oxidations (Dess–Martin periodinane; $NaClO_2$). The azide group at C1 in **25** was chemoselectively reduced to amine **26** under a hydrogen atmosphere in the presence of Lindlar's catalyst in preparation for formation of the cyclic imine. In the total syntheses of the pinnatoxins and pteriatoxins, Kishi and co-workers reported that ε-aminoketones could be converted into the corresponding seven-membered cyclic imines either by heating at 200°C without a solvent under high vacuum,[4a] or by treatment with the Et_3N salt of 2,4,6-triisopropylbenzoic acid in xylene at 80°C.[4c,e] We found that the carboxy group in the molecule facilitated the formation of the cyclic imine from ε-aminoketone **26** under thermolysis conditions: iminoacid **27** was obtained in 74% yield upon heating in chlorobenzene at 120°C for 18 hours.



Scheme 3. Completion of the total synthesis of pinnatoxin A (**1**). a) $[CpRu(MeCN)_3]PF_6$ (10 mol%), acetone, 50°C, 15 min, 79%; b) PPTS, EtOH, 72 h, 89%; c) TsCl, pyridine, CH_2Cl_2, 2 h, 92%; d) Dess–Martin periodinane, pyridine, CH_2Cl_2, 6 h; e) $[\{(Ph_3P)CuH\}_6]$, wet benzene, 12 h, 93% (2 steps); f) NaN_3, DMF, 70°C, 18 h, 93%; g) Bu_4NF, THF, 0°C, 10 h, 95%; h) Dess–Martin periodinane, pyridine, CH_2Cl_2, 1 h; i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (4:1), 6 h, 80% (2 steps); j) H_2, Lindlar's catalyst, EtOH, 36 h, 83%; k) chlorobenzene, 120°C, 18 h, 74% (84% based on recovered ketoamino acid **26**); l) 46% aqueous HF/MeCN (1:9), 12 h, 91%. Cp = cyclopentadienyl; Ts = *p*-toluenesulfonyl.

Finally, removal of the silyl groups with HF in aqueous MeCN completed the total synthesis of pinnatoxin A (**1**), which was identical in all respects with the literature data.[1a]

In conclusion, the total synthesis of pinnatoxin A was completed in 53 steps for the longest linear sequence from a known compound and in 0.21 % overall yield. Late stages of the synthesis feature the *exo*-selective Diels–Alder reaction by using α-methylene lactone **6** as a dienophile for construction of the G ring, the Ru-catalyzed cycloisomerization to fashion the 27-membered carbocyclic ring, and the formation of the seven-membered cyclic imine by self-catalyzed dehydration of ketoamino acid **26**. Notably, the successful application of the Trost protocol attests to the power and vitality of the transition-metal-catalyzed process in natural product synthesis.

Received: June 10, 2008
Published online: July 30, 2008

Keywords: cyclization · cycloaddition · macrocycles · natural products · ruthenium

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