

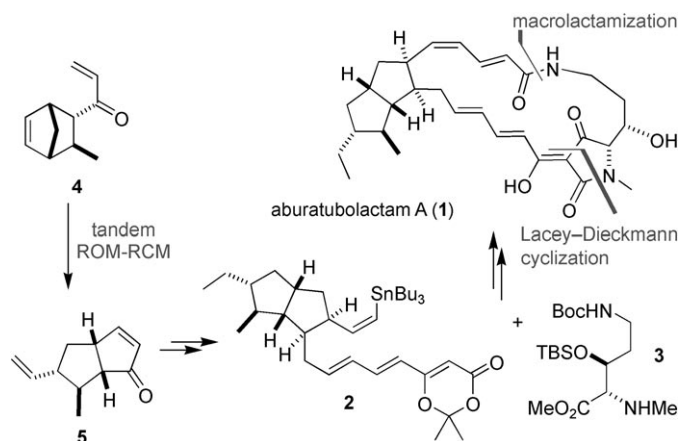
Total Synthesis of Aburatubolactam A**

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Recently, Uemura and co-workers described the structure of aburatubolactam A (**1**; Scheme 1), a macrolactam isolated from the culture broth of a *Streptomyces* sp. bacterium,

signed to arise from a tandem ring-opening/ring-closing (ROM/RCM) metathesis of functionalized bicyclo-[2.2.1]heptene **4**.^[3,4]

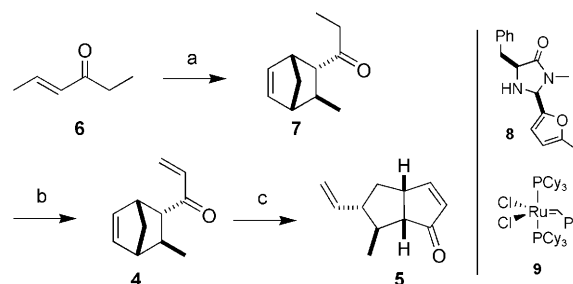
The synthesis commenced with a Diels–Alder reaction of commercially available ketone **6** with cyclopentadiene in the presence of MacMillan's catalyst **8** (20 mol %) to give ketone **7** in 65 % yield (*endo:exo* > 98:2, 93 % *ee*; Scheme 2).^[5]



Scheme 1. Structure of aburatubolactam A (**1**) and synthetic strategy. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

SCRC-A20, which was separated from a marine mollusk collected near Aburatubo, Kanagawa Prefecture, Japan.^[1a] Aburatubolactam A is a member of a growing class of tetramic acid containing macrolactams that include cylindramide A,^[1b] geodin A,^[1c] xanthobaccin A,^[1d] ikarugamycin,^[1e] discoderamide,^[1f] and the alteramides.^[1g] These mixed polyketide amino acid metabolites have been isolated from a number of sources including marine sponges and bacteria, as well as terrestrial bacteria.^[2] These compounds display a diverse range of biological activities including cytotoxicity, antimicrobial activity, and the inhibition of superoxide generation. Herein, we describe a synthesis of aburatubolactam A.

Our strategy for the synthesis of **1** is based on the coupling of two domains: a subunit containing the bicyclo[3.3.0]octane (**2**), and a 3-hydroxyornithine-derived subunit (**3**; Scheme 1). The bicyclo[3.3.0]octane ring system was ultimately envi-



Scheme 2. Synthesis of the bicyclo[3.3.0]octene. Reagents and conditions: a) 20 mol % **8**, H₂O, 65%; b) LiHMDS, TMSCl, THF; then Pd(OAc)₂, MeCN, 80%; c) 2.5 mol % **9**, CH₂=CH₂ (1 atm), CH₂Cl₂, 90%. Cy = cyclohexyl, HMDS = hexamethyldisilazide, TMS = trimethylsilyl.

Conversion of the trimethylsilyl enol ether derived from **7** into the enone **4** was readily achieved in 80 % yield by using the oxidation procedure developed by Ito and Saegusa.^[6] When enone **4** was treated with first-generation Grubbs catalyst **9** (2.5 mol %) under an atmosphere of ethylene, rapid and smooth reorganization to the desired bicyclo[3.3.0]octene **5** occurred in 90 % yield.^[7]

Further elaboration of **5** was accomplished by reduction of both alkene groups (Pd/C, H₂) to give fused bicyclic ketone **10** in 94 % yield (Scheme 3). Introduction of the C6 and C13 side chains was achieved by a sequence beginning with enolate acylation using Mander's reagent^[8] and subsequent reduction of the ketone with NaBH₄. Elimination of the resultant alcohol by mesylation and treatment with sodium hydride in MeOH/THF (5:1) provided **11** in 64 % overall yield from **10**. The side chain at C13 was introduced by employing Majetich's fluoride-mediated Sakurai allylation,^[9] carried out in DMF/DMPU to give **12** in 78 % yield as a 4:1 mixture of inseparable C6 diastereomers in favor of the undesired configuration (**12a**). This ratio could be improved to 2:1 in favor of the desired configuration (**12b**) by protonation (1N HCl) of the silylketene acetal derived from **12a**. Subsequent iodolactonization facilitated separation of the diastereoisomers, and gave **13** in 58 % yield (over 2 steps), along with recovered **12a**. This sequence also provided a means for recycling of material. Treatment of iodolactone **13** with Zn dust in AcOH, THF/H₂O and subsequent reduction of the

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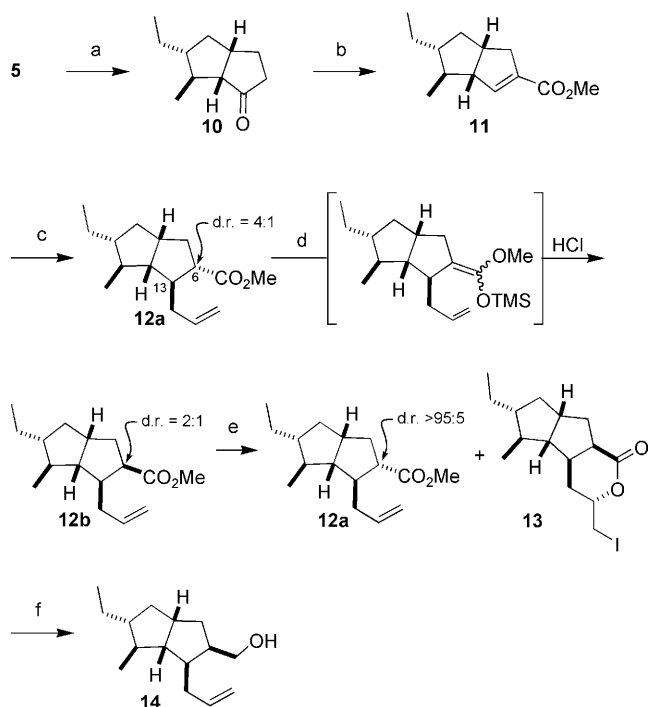
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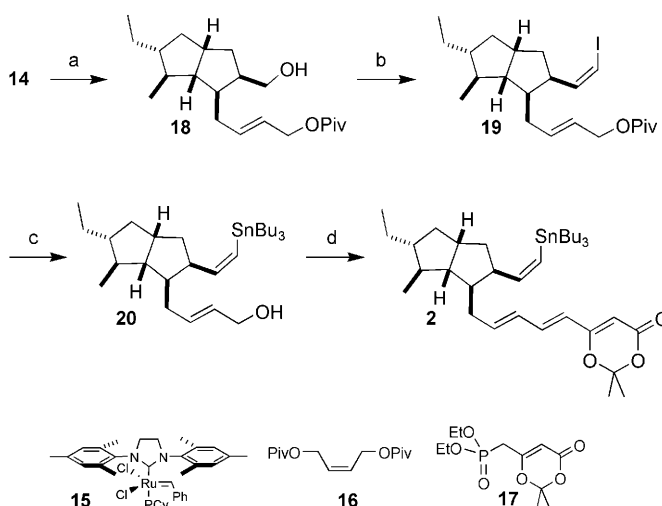
acid with LAH provided alcohol **14** in 86% yield (over 2 steps).

Advancement of alcohol **14** to **2** involved the cross-metathesis of butene-1,4-diol derivative **16** catalyzed by the second-generation Grubbs catalyst **15** to give **18** in 95% yield (Scheme 4). Oxidation with Dess–Martin periodinane followed by olefination with (iodomethylene)triphenylphosphorane under the conditions developed by Stork and Zhao^[10] provided vinyl iodide **19** in 82% yield. Conversion of **19** into the stannane by treatment with *t*BuLi in the presence of tributyltin chloride also resulted in removal of the pivalate group to give alcohol **20** in 85% yield. Treatment of this alcohol with Dess–Martin periodinane and a subsequent Horner–Wadsworth–Emmons reaction yielded stannyl dioxenone **2** in 60% yield (over 2 steps).

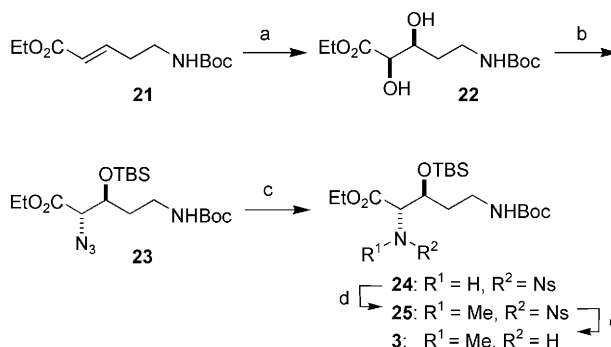
The synthesis of the β -hydroxyornithine subunit **3** began with the Sharpless asymmetric dihydroxylation of α,β -unsaturated ester **21** to give diol **22** in 90% yield and >98% *ee* (Scheme 5). Introduction of the nitrogen functionality was achieved by formation of the cyclic sulfite and ring-opening with sodium azide. Subsequent silylation provided ether **23** in 80% yield (over 3 steps). Reduction of the azide and nosylation^[11] led to **24** in 94% yield, and subsequent introduction of the methyl group by the Mitsunobu reaction



Scheme 3. Elaboration of the bicyclo[3.3.0]octene. Reagents and conditions: a) 10% Pd/C (10 wt %), EtOAc, H₂, 94%; b) 1. LDA, NCCO₂Me, THF/DMPU; then NaBH₄, MeOH, 74% (over 2 steps); 2. MsCl, DMAP, Et₃N, CH₂Cl₂; then NaH, MeOH/THF (5:1), 87% (over 2 steps); c) allyltrimethylsilane, TBAF, DMF/DMPU, 78%, d.r. 4:1; d) LDA, TMSCl, THF; then HCl (1 N), d.r. 2:1; e) I₂, MeCN, RT, 58% (over 2 steps); f) 1. Zn, AcOH, THF/H₂O; 2. LAH, THF, 86% (over 2 steps). DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, LAH = lithium aluminum hydride, LDA = lithium diisopropylamide, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.



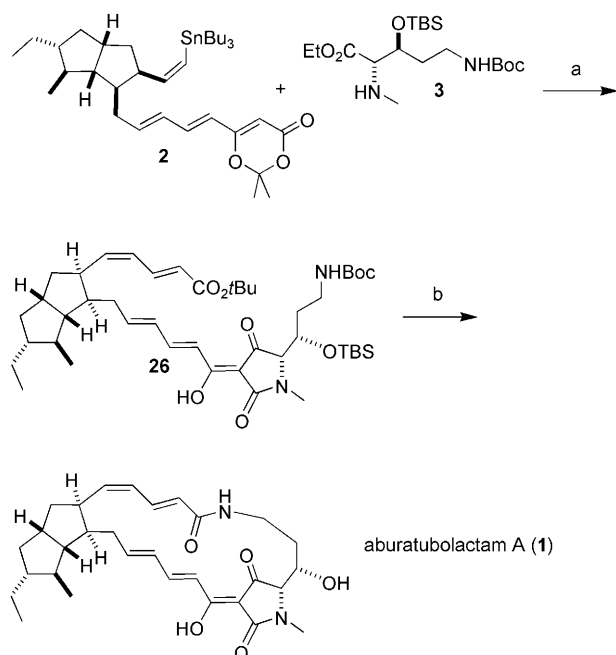
Scheme 4. Completion of the carbocyclic domain **2**. Reagents and conditions: a) **16**, 10 mol % **15**, CH₂Cl₂, 95%; b) 1. Dess–Martin periodinane, CH₂Cl₂; 2. [Ph₃P⁺CH₂I][−], NaHMDS, THF, 82% (over 2 steps); c) *t*BuLi, Bu₃SnCl (internal quench), THF, 85%; d) 1. Dess–Martin periodinane, CH₂Cl₂; 2. **17**, KHMDS, THF, 60% (over 2 steps). Piv = pivalate.



Scheme 5. Synthesis of the β -hydroxyornithine subunit **3**. Reagents and conditions: a) AD-mix- α , 90%; b) 1. SOCl₂, Et₃N; 2. NaN₃, DMF, 55 °C; 3. TBSOTf, 2,6-lutidine, CH₂Cl₂, 80% (over 3 steps); c) 1. Pd/C, H₂, EtOAc; 2. NaCl, *i*Pr₂NEt, CH₂Cl₂, 94% (over 2 steps); d) MeOH, Ph₃P, DEAD, THF; e) PhSH, K₂CO₃, DMF, 82% (over 2 steps). DEAD = diethyl azodicarboxylate, DMF = *N,N*-dimethylformamide, Ns = *o*-nitrophenylsulfonyl.

gave **25**; then removal of the nosyl group with thiophenoxide provided amine **3** (82% from **24**).

After exploring a number of unsuccessful end-game strategies that paralleled those employed for the preparation of the natural product cylindramide, we completed the synthesis as shown in Scheme 6.^[12] Coupling of the two halves of the molecule was achieved by heating dioxenone **2** with amine **3** in toluene under reflux for 6 hours. The sensitive β -ketoamide product was subjected to Stille coupling with *tert*-butyl- β -iodoacrylate, and subsequent Lacey–Dieckmann cyclization led to tetramic acid **26** in 50% yield (over 3 steps from **2**). Macrolactamization was achieved by simultaneous removal of the Boc and *tert*-butyl ester groups with TFA, and treatment of the resulting compound with DEPC and Et₃N in DMF for 12 hours.^[13] Removal of the TBS group with HF



Scheme 6. Completion of the synthesis. Reagents and conditions: a) 1. toluene, 110 °C; 2. *tert*-butyl- β -iodoacrylate, $[\text{Pd}_2(\text{dba})_3]$, Ph_3As , NMP; 3. NaOMe, MeOH, 50% (over 3 steps); b) 1. TFA, CH_2Cl_2 ; 2. DEPC, Et_3N , DMF, 0 °C; 3 HF, MeCN, 46% (over 3 steps). NMP = *N*-methylpyrrolidinone, TFA = trifluoroacetic acid, DEPC = diethylphosphoryl cyanide.

provided aburatubolactam A in 46% yield (over 3 steps). Data for an analytical sample of the synthetic aburatubolactam A obtained by semi-preparative HPLC methods matched those obtained for an authentic sample, which was provided by Prof. Daisuke Uemura.

In conclusion, we have described a 23-step route that leads to aburatubolactam A. This sequence further highlights the utility of tandem metathesis reactions in a target-oriented setting.

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