Angewandte Chemie

DOI: 10.1002/anie.200803593

Natural Product Synthesis

# Total Synthesis of Aburatubolactam A**

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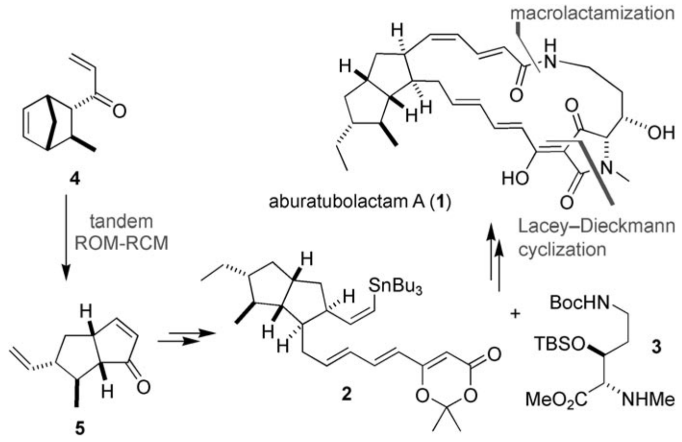
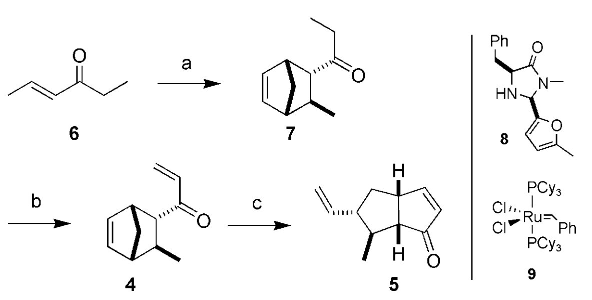
Recently, Uemura and co-workers described the structure of aburatubolactam A (**1**; Scheme 1), a macrolactam isolated from the culture broth of a *Streptomyces* sp. bacterium, SCRC-A20, which was separated from a marine mollusk collected near Aburatubo, Kanagawa Prefecture, Japan.[1a] Aburatubolactam 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] discodermide,[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.



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

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 envisioned 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 2.*** Synthesis of the bicyclo[3.3.0]octene. Reagents and conditions: a) 20 mol % **8**, $H_2O$, 65 %; b) LiHMDS, TMSCl, THF; then $Pd(OAc)_2$, MeCN, 80 %; c) 2.5 mol % **9**; $CH_2{=}CH_2$ (1 atm), $CH_2Cl_2$, 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, $H_2$) 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 $NaBH_4$. 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 (1 N 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/$H_2O$ and subsequent reduction of the

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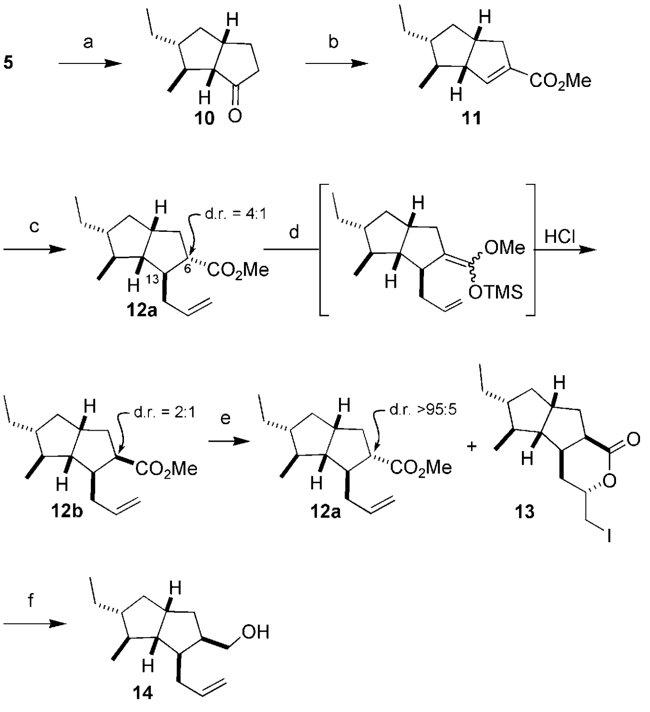
[**] This research was supported by the National Cancer Institute (NCI CA110246). We thank Prof. Daisuke Uemura (Nagoya University) for providing an authentic sample of aburatubolactam A.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803593.

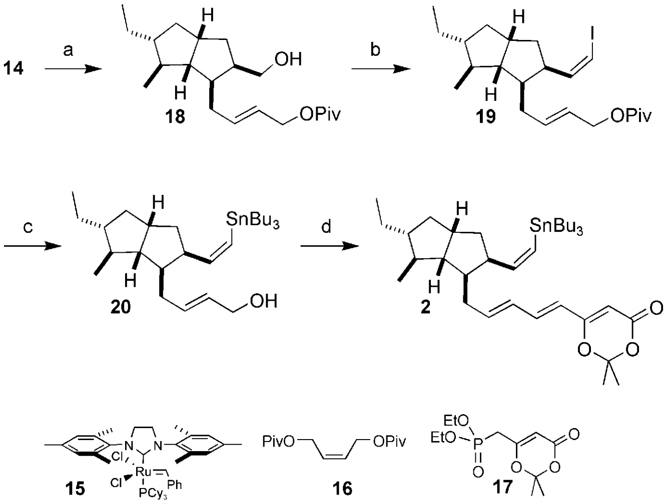
acid with LAH provided alcohol **14** in 86% yield (over 2 steps).

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).

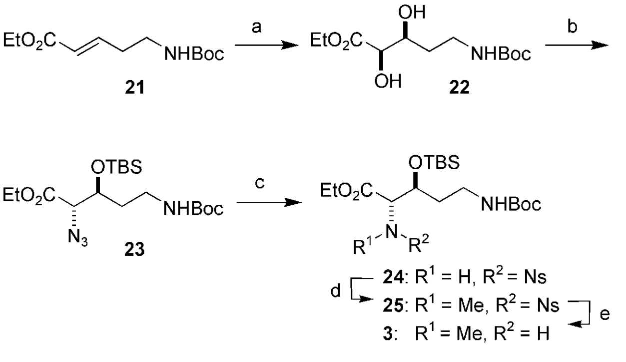
The synthesis of the β-hydroxyornithine subunit **3** began with the Sharpless asymmetric dihydroxylation of α,β-unsaturated ester **21** to give diol **22** in 90% yield and > 98% *ee* (Scheme 5). Introduction of the nitrogen functionality was achieved by formation of the cyclic sulfite and ring-opening 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 gave **25**; then removal of the nosyl group with thiophenoxide provided amine **3** (82% from **24**).



*Scheme 3.* Elaboration of the bicyclo[3.3.0]octene. Reagents and conditions: a) 10% Pd/C (10 wt%), EtOAc, $H_2$, 94%; b) 1. LDA, $NCCO_2Me$, THF/DMPU; then $NaBH_4$, MeOH, 74% (over 2 steps); 2. MsCl, DMAP, $Et_3N$, $CH_2Cl_2$; 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) $I_2$, MeCN, RT, 58% (over 2 steps); f) 1. Zn, AcOH, THF/$H_2O$; 2. LAH, THF, 86% (over 2 steps). DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, LAH = lithium aluminum hydride, LDA = lithium diisopropylamide, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.

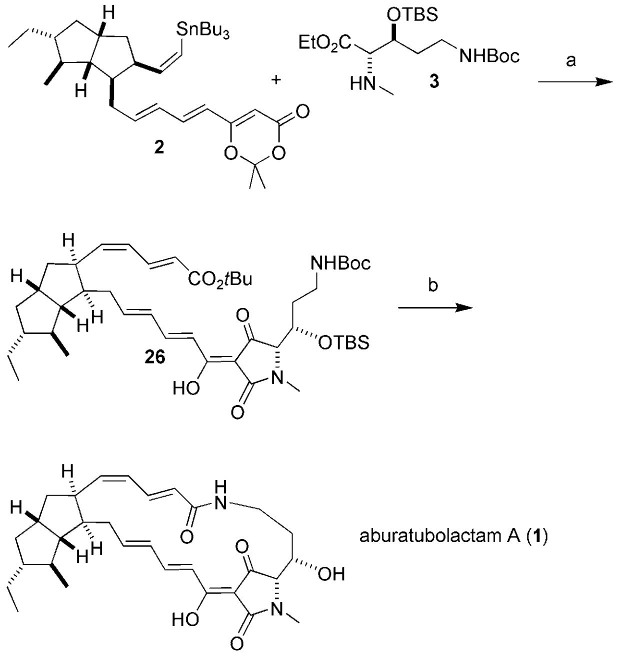


*Scheme 4.* Completion of the carbocyclic domain **2**. Reagents and conditions: a) **16**, 10 mol% **15**, $CH_2Cl_2$, 95%; b) 1. Dess–Martin periodinane, $CH_2Cl_2$; 2. $[Ph_3P^+CH_2I]I^-$, NaHMDS, THF, 82% (over 2 steps); c) *t*BuLi, $Bu_3SnCl$ (internal quench), THF, 85%; d) 1. Dess–Martin periodinane, $CH_2Cl_2$; 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. $SOCl_2$, $Et_3N$; 2. $NaN_3$, DMF, 55°C; 3. TBSOTf, 2-6-lutidine, $CH_2Cl_2$, 80% (over 3 steps); c) 1. Pd/C, $H_2$, EtOAc; 2. NsCl, *i*$Pr_2NEt$, $CH_2Cl_2$, 94% (over 2 steps); d) MeOH, $Ph_3P$, DEAD, THF; e) PhSH, $K_2CO_3$, DMF, 82% (over 2 steps). DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, Ns = *o*-nitrophenylsulfonyl.

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 $Et_3N$ 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, $[Pd_2(dba)_3]$, $Ph_3As$, 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.

Received: July 23, 2008

**Keywords:** cross-coupling · metathesis · natural products · total synthesis

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