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Total Synthesis of Aburatubolactam A**

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Recently Uemura and co-workers described the structure of aburatubolactam A (**1**, Figure 1), a macrolactam isolated from the culture broth of a *Streptomyces* sp. bacterium, SCRC-A20, that 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 including 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 sponges, marine bacteria and terrestrial bacteria,[2] and display a diverse range of biological activities including cytotoxicity, anti-microbial activity, and inhibition of superoxide generation. In this Communication we describe a synthesis of aburatubolactam A.

Our strategy for the synthesis of aburatubolactam A 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**, Figure 1). The bicyclo[3.3.0]octane ring system was ultimately envisioned to arise from a ring-opening—ring-closing 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 20 mol % of MacMillan's catalyst **8** to give ketone **7** in 65% yield (*endo:exo* >98:2, 93% ee, Scheme 1).[5] Conversion to the enone **4** was readily achieved in 80% yield by Saegusa oxidation of the trimethylsilyl enol ether derived from **7**. [6] When enone **4** was subjected to 2.5 mol% of Grubbs' catalyst **9** under an ethylene atmosphere, 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 alkenes (Pd/C, H₂) to give fused bicyclic ketone **10** in 94% yield (Scheme 2). Introduction of the C6 and C13 side chains was achieved by a sequence beginning with enolate acylation with Mander's reagent,[8] followed by 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 C13 side chain was introduced by employing Majetich's fluoride-mediated Sakurai allylation⁹ in DMF-DMPU to give **12** in 78% yield as a 4:1 mixture of inseparable C6 diastereomers favoring the undesired stereochemistry (viz **12a**). This ratio could be improved to 2:1 in favor of the desired stereochemistry (viz **12b**) by protonation of the silylketene acetal

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derived from **12a** with HCl. Subsequent iodolactonization facilitated separation of the diastereoisomers, and gave **13** in 58% yield for the two steps, along with recovered **12a**. This sequence also provided a mechanism for recycling material. Treatment of iodolactone **13** with Zn dust in AcOH/EtOH, followed by reduction of the acid with LAH provided alcohol **14** in 86% yield (2 steps).

Advancement of alcohol **14** to **2** involved cross metathesis of butene-1,4-diol derivative **16** catalyzed by **15** to give **13** in 95% yield (Scheme 3). Oxidation with Dess-Martin periodinane, followed by olefination with (iodomethylene)triphenylphosphorane under Stork-Zhao[10] conditions provided vinyl iodide **19** in 82% yield. Conversion of the iodide to the stannane by treatment with *tert*-BuLi in the presence of tributyltin chloride also resulted in removal of the pivalate to give alcohol **20** in 85% yield. Treatment of this alcohol with Dess-Martin periodinane and subsequent Horner-Wadsworth-Emmons reaction yielded stannyl dioxenone **2** in 60% overall yield (2 steps).

The synthesis of the β -hydroxyornithine subunit **3** began with Sharpless asymmetric dihydroxylation of α,β -unsaturated ester **21** to give diol **22** in 90% yield and >98% ee (Scheme 4). Introduction of the nitrogen was achieved by cyclic sulfite formation and opening with sodium azide. Subsequent silylation provided ether **23** in 80% yield over the three steps. Reduction of the azide and nosylation[11] led to **24** in 94% yield, and was followed by introduction of the methyl group by Mitsunobu reaction to give **25**, and 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 cylindramide, the synthesis was completed as shown in Scheme 5.[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 (Scheme 5). Subjection of the sensitive β -ketoamide product to Stille coupling with *tert*-butyl- β -iodoacrylate, followed by Lacey-Dieckmann cyclization, led to tetramic acid **26** in 50% yield (over three steps from **2**). Macrocyclization was achieved by simultaneous removal of the Boc carbamate and *tert*-butyl ester with TFA and treatment of the resulting compound with DEPC[and Et₃N in DMF for 12 hours. Removal of the TBS group with HF provided aburatubolactam A in 46% yield for the 3 steps. Data for an analytical sample of synthetic aburatubolactam A obtained by semi-preparative HPLC matched that obtained for an authentic sample provided by Professor Daisuke Uemura.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structure of Aburatubolactam A (1) and synthesis strategy.

Scheme 1.

Synthesis of the bicyclo[3.3.0]octene. a) 20 mol% **8**, H₂O, 65%; b) LiHMDS, TMSCl, THF then Pd(OAc)₂, MeCN, 80%; c) 2.5% **9**, CH₂=CH₂ (1 atm), CH₂Cl₂, 90%. LiHMDS=lithiumhexamethyl disilazide, TMS=trimethylsilyl.

Scheme 2.

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

Scheme 3.

Completion of the carbocyclic domain **2**. a) **16**, 10% **15**, CH₂Cl₂, 95%; b) 1. Dess-Martin periodinane, CH₂Cl₂; 2. [Ph₃P⁺ CH₂I]⁻, NaHMDS, THF, 82% (2 steps); c) *t*-BuLi, Bu₃SnCl (internal quench), THF, 85%; d) 1. Dess-Martin periodinane, CH₂Cl₂; 2. **17**, KHMDS, THF, 60% (2 steps). KHMDS=potassium hexamethyldisilazide, NaHMDS=sodium hexamethyldisilazide.

Scheme 4.

Synthesis of the β -hydroxyornithine subunit. 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% (3 steps); c) 1. Pd/C, H_2 , EtOAc; 2. NsCl, *i*-Pr₂NEt, CH_2Cl_2 , 94% (2 steps); d) MeOH, Ph_3P , DEAD, THF; e) PhSH, K_2CO_3 , DMF, 82% (2 steps). Boc=*tert*-butoxycarbonyl, DEAD=diethyl azodicarboxylate, DMF=*N,N*-dimethylformamide, Ns=*o*-nitrophenyl sulfonyl, TBS=*tert*-butyldimethylsilyl.

Scheme 5.

Completion of the synthesis. a) 1. PhMe, 110 °C; 2. *tert*-butyl-β-iodoacrylate, Pd₂(dba)₃, Ph₃As, NMP; 3. NaOMe, MeOH, 50% (3 steps); b) 1. TFA, CH₂Cl₂; 2. DEPC, Et₃N, DMF, rt; 3) HF, MeCN, 46% (3 steps). NMP=*N*-methylpyrrolidinone, TFA=trifluoroacetic acid, DEPC=diethylphosphoryl cyanide, DMF=*N,N*-dimethylformamide.