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Theonellamide F Synthetic Studies. Stereoselective Synthesis of (*3S,4S,5E,7E*)-3-Amino-8-(4-bromophenyl)-4-hydroxy-6-methyl-5,7-octadienoic Acid (Aboa)[1]

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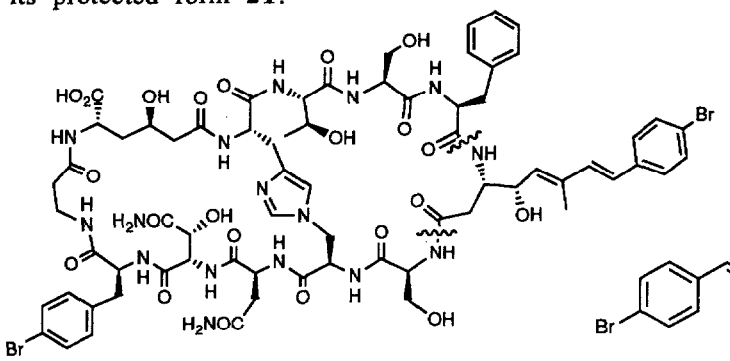
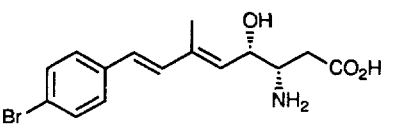
Abstract : A convergent, stereocontrolled synthesis of (*3S,4S,5E,7E*)-3-amino-8-(4-bromophenyl)-4-hydroxy-6-methyl-5,7-octadienoic acid (Aboa, **2**), a constituent of theonellamide F from a marine sponge, has been achieved. The key steps include the carboalumination of the enyne **5a**, the formation of the ate complex **16**, followed by the reaction with the aluminum complex **10** of the homoserinal derivative.

Theonellamide F has been isolated from a marine sponge, genus *Theonella*, collected at Hachijo Island by Fusetani and co-workers.[2] This bicyclic dodecapeptide has quite a unique structure containing unusual amino acids, as shown in **1**. It shows inhibition of growth of various pathogenic fungi, *Candida spp.*, *Trichophyton spp.*, and *Aspergillus spp.*, together with cytotoxicity against L1210 and P388 leukemia cells.[2] Its structural uniqueness as well as intriguing biological activity has led us to investigate its total synthesis.[1] In this paper, we report an efficient, regio and stereoselective, convergent synthesis of (*3S,4S,5E,7E*)-3-amino-8-(4-bromophenyl)-4-hydroxy-6-methyl-5,7-octadienoic acid (Aboa, **2**), a constituent of theonellamide F, as its protected form **21**.

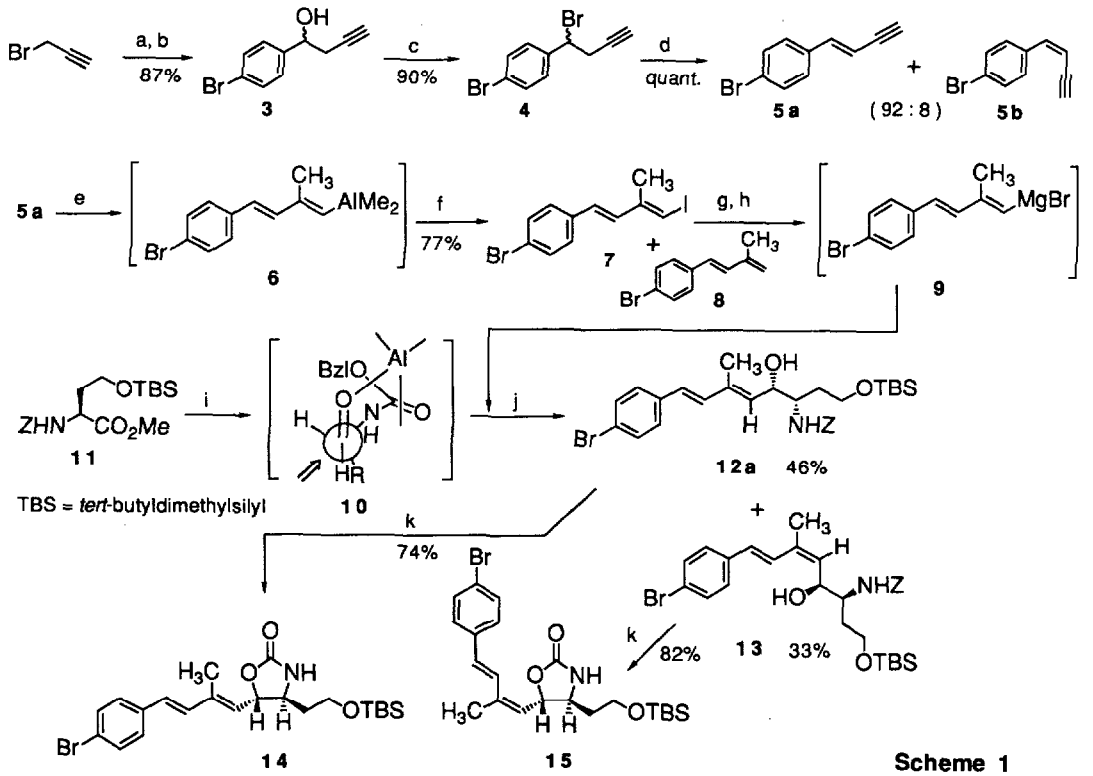


Theonellamide F (1)



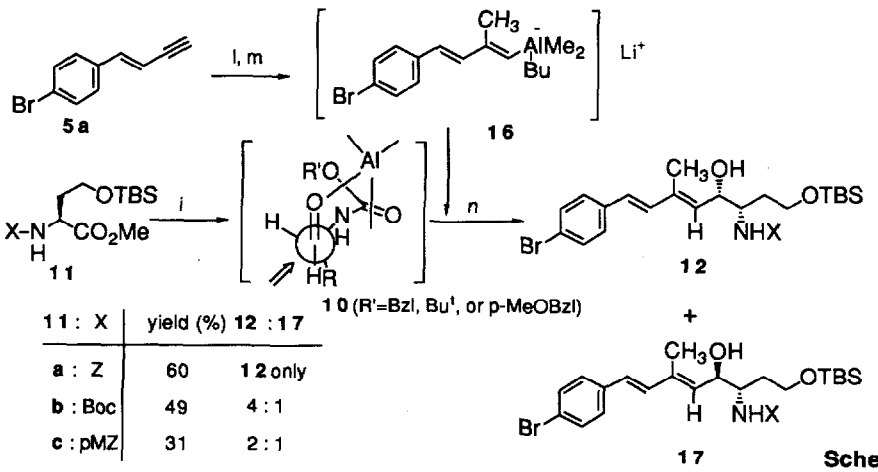
Aboa (2)

Grignard type reaction of 4-bromobenzaldehyde with propargyl aluminum bromide[3] afforded the acetylenic alcohol **3**, which was treated with a mixture of triphenylphosphine and carbon tetrabromide to give the corresponding bromide **4**. Dehydrobromination of **4** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[3] furnished a mixture of the (*E*)- and (*Z*)-enynes, **5a** (mp 68-70°C) and **5b** (mp 70-71°C), in a ratio of 92:8. Carboalumination of the (*E*)-enyne **5a** with trimethylalane was easily carried out in the presence of zirconocene dichloride (Cp_2ZrCl_2).[4] After treatment of the resulting dienylalane **6** with iodine, the dienyl iodide **7**, mp 98-104°C (hot plate) was obtained as the major product accompanied with a small amount of the diene **8**, mp 62-64°C (hot plate). Regioselective formation of the Grignard reagent **9** from the bromo-iodide **7** was achieved by treatment with butyllithium followed by magnesium bromide. Addition of the Grignard reagent **9** to the aluminum complex **10** prepared from benzyloxycarbonyl-(*S*)-homoserine derivative **11** by its reaction with diisobutylaluminum hydride (DIBAL)[5] afforded a mixture of the (*E*)- and (*Z*)-dienes, **12a** and **13**, in 46 and 33% yields, respectively, as shown in Scheme 1. Configurational assignment was made by an NOE measurement in their ^{1}H-NMR spectra: the (*E*)-diene **12a**, $[\alpha]_D^{24.5}$ = -82.15° (c=1.0, MeOH), shows an NOE between the C_6-methyl hydrogens and C_4-hydrogen whereas the (*Z*)-diene **13**, $[\alpha]_D^{24.5}$ = -9.4° (c=1.0, MeOH), shows an NOE between the C_6-methyl hydrogens and C_5-hydrogen. Treatment of **12a** and **13** with sodium hydride afforded the corresponding oxazolidinones **14** and **15**, respectively, both of which have revealed to have the trans configuration by their ^{1}H-NMR spectra, $J_{3,4}$ = ca.7.7 Hz without an NOE between the C_3- and C_4-hydrogens. Formation of **12a** and **13** will be explained by the chelation controlled anti-Cram's rule (see the attacking site shown by the arrow in **10**), and **13** will be formed by the (*E*)-(*Z*) isomerization during the formation of the Grignard reagent **9**. To improve the stereoselectivity of the coupling reaction, we adopted the use of the ate complex **16** obtained by the successive treatment of the enyne **5a** with trimethylalane and Cp_2ZrCl_2, then butyllithium. Addition of the ate complex **16** thus formed to the aluminum complex **10** proceeded without the (*E*)-(*Z*) isomerization to give the (*E*)-diene **12a** as a sole product in 60% yield. Interestingly, replacement of the benzyloxycarbonyl (Z) group with tert-butyloxycarbonyl (Boc) and 4-methoxybenzyloxycarbonyl (pMZ) functions resulted in decrease of both yields and stereoselectivity, and another isomers **17b** and **17c** were concomitantly formed, as shown in Scheme 2. Treatment of **12a** with methoxymethyl (MOM) chloride afforded the MOM derivative **18**, which yielded the primary alcohol **19**, mp 116-118°C, $[\alpha]_D^{24.5}$ = +16.7° (c=0.76, MeOH), with tetrabutylammonium fluoride (TBAF). Although the direct conversion of the alcoholic function to the carboxyl function with pyridinium dichlorochromate sluggishly proceeded, the two step conversion via the aldehyde was rather straightforward. Thus, the Swern oxidation of the alcohol **19** smoothly afforded the aldehyde **20**. Further oxidation of the aldehyde **20** was



TBS = *tert*-butyldimethylsilyl

Scheme 1

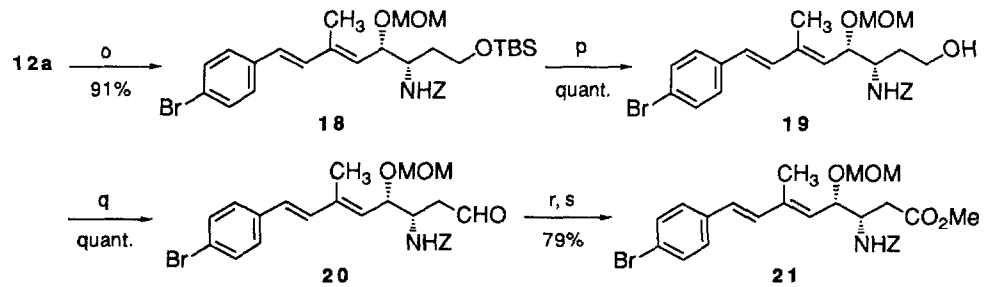


11 : X	yield (%)	12 : 17
a : Z	60	**12** only
b : Boc	49	4 : 1
c : pMZ	31	2 : 1

Scheme 2

a) Al powder, I_2, $HgCl_2$, THF, <45°C, 1h. b) 4-bromobenzaldehyde, THF, -78°C to 0°C, 1.5h. c) CBr_4 (3eq.), Ph_3P (3eq.), Et_2O, r t, 1h. d) DBN (3eq.), DMF, r t. e) Me_3Al (3eq.), Cp_2ZrCl_2 (1eq.), $ClCH_2CH_2Cl$, r t, 1day. f) I_2 (3eq.), THF, 0°C, 1h. g) BuLi (1eq.), Et_2O, -78°C, 30min. h) $MgBr_2$, Et_2O, -78°C, 20min. i) DIBAL (1.3eq.), Et_2O, -78°C, 2h. j) **9** (4eq.), -78°C to r t, 1h. k) NaH, THF, r t, 3h. l) Me_3Al(1eq.), Cp_2ZrCl_2 (1eq.), $ClCH_2CH_2Cl$, rt, 1day then evaporation under Ar. m) BuLi (1eq.), hexane, 0°C, 5min then THF. n) **16** (4eq.), -78°C to r t, 1h.

accomplished with sodium chlorite,[6] and the resulting carboxylic acid underwent the methyl esterification with trimethylsilyldiazomethane ($TMSCHN_2$) in the presence of methanol,[7] giving the desired Aboa as its protected form **21**, mp 72-75°C, $[\alpha]_D^{24.5}$ = +13.2° (c=0.77, MeOH).



Scheme 3

o) MOMCl (3eq.), i-Pr_2NEt (3eq.), CH_2Cl_2, r t, 20h. p) Bu_4NF (2eq.), THF, r t, 0.5h. q) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 2h then Et_3N. r) $NaClO_2$ (10eq.), 2-methyl-2-butene, $NaHPO_4$, t-BuOH-H_2O, r t, 5min. s) $TMSCHN_2$, MeOH-PhH (1:1), r t, 10min.

Further progress toward the total synthesis of theonellamide F (**1**) was actively under investigation in our laboratories.

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References and Notes

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