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A Stereoselective Synthesis of C4-C18 Fragment of Arenicolide A

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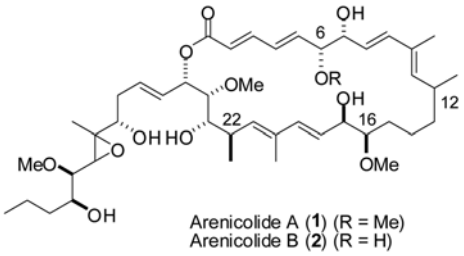
Arenicolide A (**1**) and B (**2**), isolated from the large-scale fermentation of the *S. arenicola* strain CNR-005 in 2007, displayed cytotoxicity toward the human colon adenocarcinoma cell line HCT-116 (IC_{50} = 30 μg/mL) and three cell lines in the National Cancer Institute.[1] Arenicolide A (**1**) is a 26-ring macrolide with three conjugated dienes, nine chiral centers, and one side chain, and its molecular formula is consistent with the high-resolution ESI-FTMS data of the $[M+Na]^+$ peak at *m/z* 827.4916. Regarding the synthesis of arenicolide A (**1**), our group published the synthesis of C26-C36 fragment of arenicolide A (**1**) in 2009[2a] and Miyashita group reported another synthesis of C25-C36 fragment in 2010.[2b]



Although its relative stereochemical relationships were proposed by various spectroscopic and chemical degradation methods, chiral centers at C12, C30, and C31 were not elucidated clearly by W. Fenical in 2007.[1] If we assume that C6-C12 and C16-C22 sequences should be repeated, then we can assign the chiral center at C12 to be (*S*)-configuration. We report herein the stereoselective synthesis of the plausible C4-C18 skeleton **3** of arenicolide A (**1**) based on this assumption.

Retrosynthesis is summarized in Figure 1. The target molecule **3** would be prepared by transition-metal mediated cross-coupling[3] of vinylstanne **4** and 1,1-dibromide **5**. Brown asymmetric methoxyallylation of aldehyde **6** would provide the intermediate **4**, and 1,1-dibromide **5** should be derived from Wittig reaction of aldehyde **7** and phosphonium salt **8**.[4]

The commercially available D-mannitol (**9**) was converted to the aldehyde **10** by acetal protection of two 1,2-diol moieties and subsequent oxidative cleavage of the remaining 1,2-diol in 46% two-step yield.[5] (Scheme 1) Although there are many methods available to convert the aldehyde **10** into *syn*-alcohol **11**,[6] we decided to utilize asymmetric reduction strategy. Addition of allylmagensium bromide to aldehyde **10** and PCC oxidation provided the β,γ-unsaturated ketone

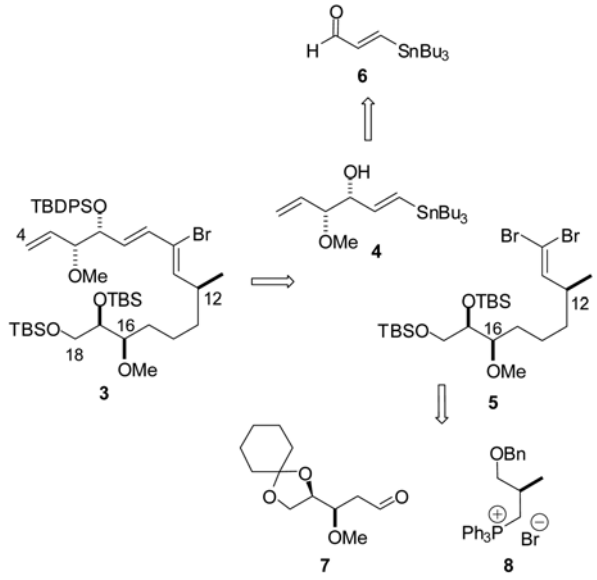
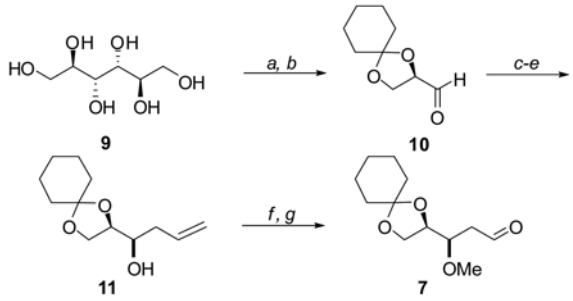


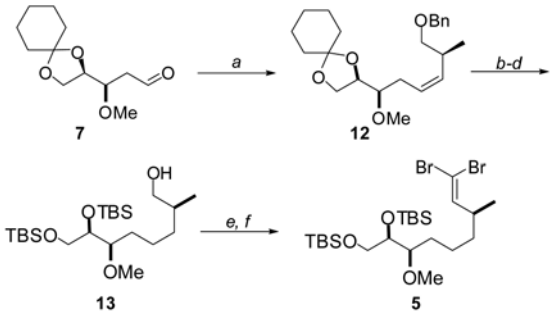
Figure 1. Retrosynthesis of C4-C18 skeleton **3**.



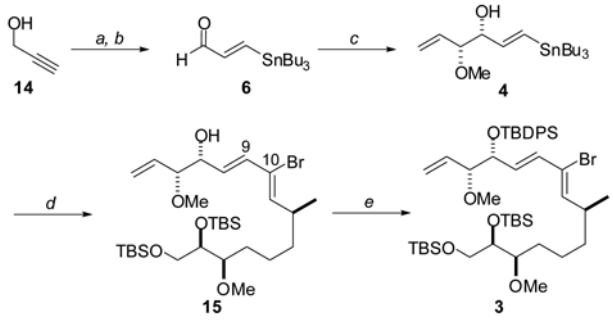
Scheme 1. Synthesis of aldehyde **7**. (a) Cyclohexanone, BF_3-OEt_2, $CH(OMe)_3$, DMSO, 24 hr. (b) $NaIO_4$, Bu_4NBr (cat.), Et_2O, H_2O, 2 hr, 46% (over 2 steps). (c) AllylMgBr, THF, 0 °C to rt, 15 hr, 88%. (d) PCC, NaOAc, CH_2Cl_2, 0 °C to rt, 12 hr, 80% (e) K-selectride, THF, −78 °C, 4 hr, 82%. (f) NaH, MeI, THF, 0 °C, 8 hr, 95%. (g) O_3, CH_2Cl_2:MeOH = 5:1, −78 °C, then DMS, pH 7 buffer, 61%.

in 70% two-step yield, and Felkin-type reduction of β,γ-unsaturated ketone using K-selectride was carried out to afford the *syn*-alcohol **11** in 82% yield.[6d] Allylic alcohol **11** was further converted to the aldehyde **7** *via* methylation of the C16 hydroxy group in 95% yield and ozonolysis of terminal double bond in 61% yield.

Benzyl protected intermediate **12** was prepared by Wittig reaction of aldehyde **7** and phosphonium salt **8**[4] in 55% yield (Scheme 2). The acetal protecting group of **12** was removed



Scheme 2. Synthesis of 1,1-dibromo alkene **5**. (a) Phosphonium salt **8**, *n*-BuLi, THF, −78 °C to 0 °C, 3 hr, 55%. (b) TFA, MeOH/H_2O, rt, 54%. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 82%. (d) Pd/C, H_2 (g), MeOH, 3 days, rt, 99%. (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 86%. (f) CBr_4, PPh_3, Et_3N, THF, 0 °C to rt, 87%.



Scheme 3. Synthesis of target molecule **3**. (a) *n*-Bu_3SnH, AIBN, Toluene, reflux, 5 hr, 51%. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl, −78 °C, 1 hr, 99%. (c) Allyl methyl ether, *sec*-BuLi, BF_3-OEt, (−)-Ipc_2BOMe, THF, −78 °C, 3 hr, 71%. (d) 1,1-Dibromo alkene **5**, $Pd_2(dba)_3$, (2-furyl)$_3$P, toluene, 100 °C, 24 hr, 52%. (e) TBDPSCl, imidazole, CH_2Cl_2, rt, 92%.

by TFA in aqueous methanol in 54% yield, and the resulting 1,2-diol was treated with TBSOTf and 2,6-lutidine to afford the *bis*-TBS product in 82% yield. The primary alcohol **13** was synthesized by hydrogenation of the internal double bond and hydrogenolysis of the benzyl protecting group using Pd/C in MeOH under H_2 atmosphere for 3 days in 99% yield. Sequentially, Swern oxidation and conversion of aldehyde functionality to 1,1-dibromo alkene moiety by Corey-Fuchs protocol[7] provided the intermediate **5** in 75% two steps yield.

The synthesis of target molecule **3** was shown in Scheme 3. The commercially available propargyl alcohol (**14**) was converted to α,β-unsaturated aldehyde **6** by hydrostannylation reaction of terminal alkyne using Bu_3SnH and AIBN in 51% yield and subsequent Swern oxidation in 99% yield. Brown asymmetric methoxyallylation[8] to aldehyde **6** using (−)-Ipc_2BOMe, *sec*-BuLi and allyl methyl ether furnished vinylstanne **4** in 71% yield, and the construction of C9-C10 bond was completed by $Pd_2(dba)_3$-mediated regioselective Stille coupling[3] of the stanne **4** and 1,1-dibromo alkene **5**. Finally, the synthesis of target **3**[9] was completed by protection of TBDPS group at C7 in 92% yield.

In summary, the plausible C4-C18 building block **3** was prepared in total 18 steps (15 linear-steps, 1.3% overall yield from **9**). The key steps are Brown asymmetric methoxyallylation, Wittig reaction, and regioselective Stille coupling.

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9. $[\alpha]_D$ = −7.36 (c = 0.0125 $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70-7.62 (m, 4H), 7.42-7.31 (m, 6H), 5.95-5.92 (m, 2H), 5.70-5.64 (m, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 5.21 (d, *J* = 17.6 Hz, 1H), 4.38 (t, 1H), 3.72-3.67 (m, 2H), 3.51-3.47 (m, 1H), 3.45-3.40 (m, 1H), 3.38 (s, 3H), 3.15-3.14 (m, 1H), 3.09 (s, 3H), 2.71-2.67 (m, 1H), 1.42-1.23 (m, 6H) 1.08 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08-0.04 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.29, 141.36, 139.83, 139.45, 139.04, 137.30, 136.33, 135.05, 134.97, 132.90, 132.84, 128.72, 124.17, 90.94, 87.40, 82.63, 79.78, 79.49, 69.61, 63.95, 62.08, 42.03, 41.61, 35.02, 32.44, 32.39, 31.41, 31.33, 29.40, 25.05, 24.81, 23.77, 23.55, 1.19, 0.558, 0.09, 0.00 ppm; IR (neat) 2949.5, 2924.3, 2853.5, 1740.7, 1470.2, 1460.9, 1360.2, 1252.1, 1107.4, 833.85, 776.16, 701.53 cm^{-1}; HRMS: *m/z* calcd. for $C_{46}H_{77}BrO_5Si_3$ $[M+Na]^+$ 897.4139, found: 897.4142.