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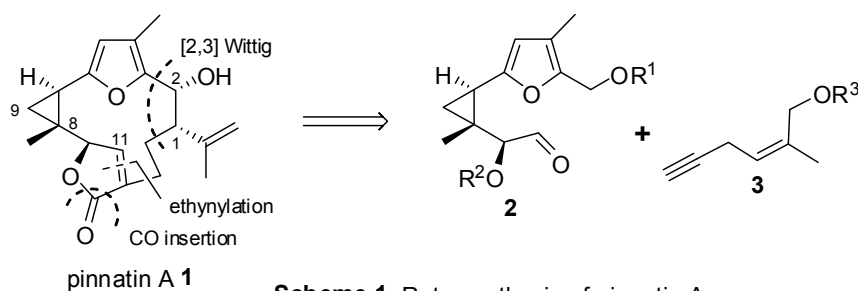
ENANTIOSELECTIVE SYNTHESIS OF THE C(2)-C(11) CYCLOPROPYLFURAN SEGMENT OF PINNATIN A

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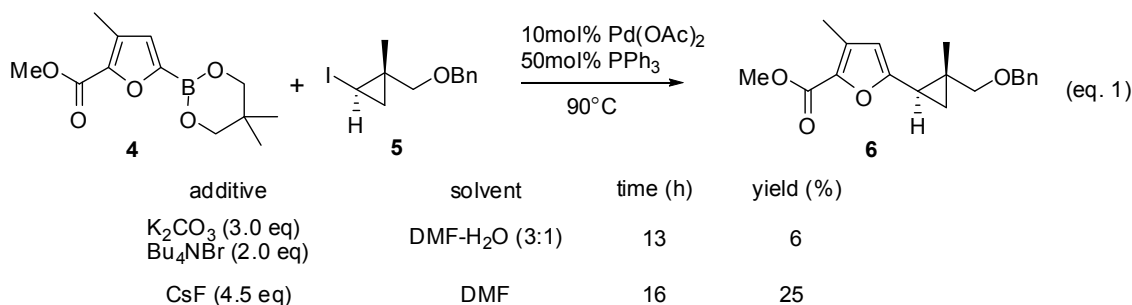
Abstract – Synthesis of the C(2)-C(11) segment, cyclopropylfuran derivative, of pinnatin A was accomplished by Suzuki cross-coupling between chiral cyclopropylboronic acid and bromofuran as a key step. Addition of silver (I) oxide was found to promote the Suzuki cross-coupling reactions.

Pinnatin A **1** is a unique gersolane-type furanoditerpene isolated from a Caribbean gorgonian, *Pseudopterogorgia bipinnata*.¹ The compound shows significant differential antitumor activity in the National Cancer Institute's 60-cell-line tumor panel. Pinnatin A has a highly functionalized polycyclic α,γ -disubstituted α,β -unsaturated γ -lactone and consists of bicyclo[11.1.0]carbon skeleton joined in a *trans* fashion. With its unusual structural features and specific cytotoxic properties, pinnatin A is a challenging target. No total synthesis of pinnatin A has been reported to date. Recently, we have achieved a diastereoselective construction of *syn*- and *anti*-isopropenyl alcohol moieties at the C(1) and C(2) positions of 2,5-bridged furanocycles based on the [2,3] Wittig rearrangement of cyclic furfuryl ethers as a key step.² Thus we intended to study the synthesis of pinnatin A using this strategy. We report here the stereoselective synthesis of the C(2)-C(11) segment **2**, cyclopropylfuran part, of pinnatin A **1**.



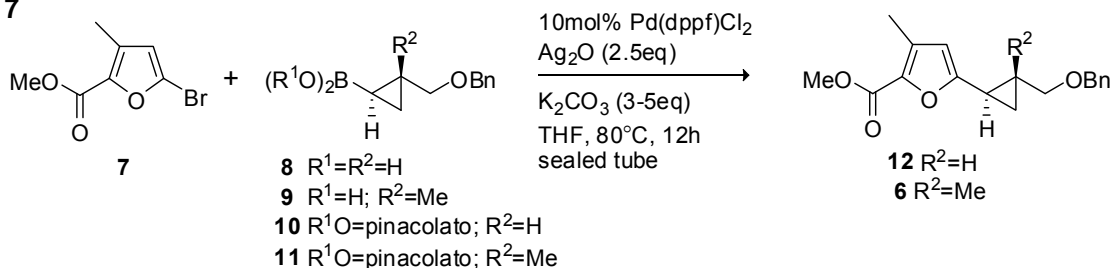
Scheme 1. Retrosynthesis of pinnatin A

We first investigated Suzuki cross-coupling between furanboronic ester **4**³ and cyclopropyl iodide **5**⁴ under Charetté's conditions^{5a} (eq. 1). Pd(OAc)₂-catalyzed cross-coupling reaction with K₂CO₃ and Bu₄NBr gave the adduct **6** in only 6% yield. The addition of CsF instead of K₂CO₃ afforded trisubstituted cyclopropane **6** in 25% yield. Poor yields and lower reactivities in this Suzuki cross-coupling could be due to the steric effect of geminal substitution in **5**, since the coupling reaction of 2-alkyl-1-iodocyclopropanes with arylboronic acids gave good yields.⁵



We next carried out Suzuki cross-coupling reaction between bromofuran **7**⁶ and cyclopropylboronic acid derivatives **8-11**⁷ under Falck's and Deng's conditions⁸ (Table 1). Moderate to good yields of the cross-coupling products **6** and **12** were obtained using a combination of Ag₂O-K₂CO₃. Increasing amounts of K₂CO₃ (5.0 eq) gave better coupling yields with both **6** and **12** (entries 1, 3 vs 2, 4). Boronic acids **8** and **9** were preferable to boronates **10** and **11** (entries 3, 4 vs 5, 6).

Table 1. Suzuki cross-coupling of cyclopropylboronic acid derivatives **8-11** with bromofuran **7**



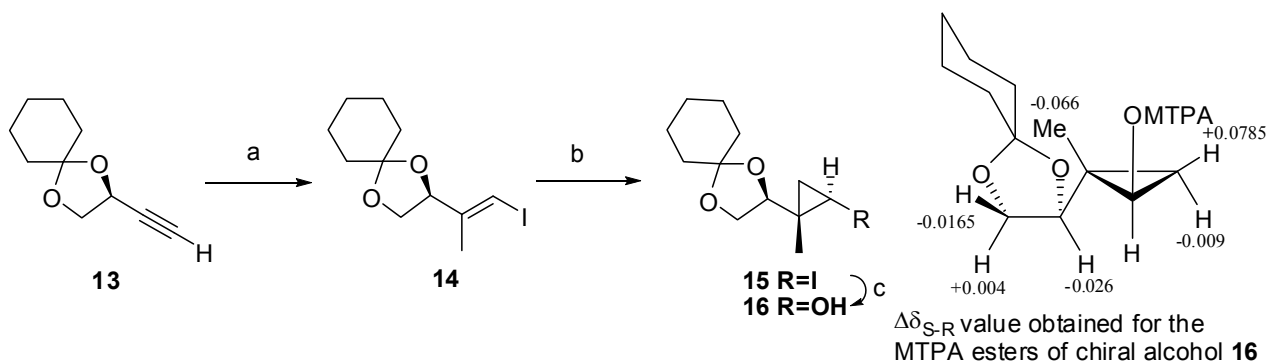
7 + $(R^1O)_2B$ $\xrightarrow[10\text{mol\% Pd(dppf)Cl}_2, \text{Ag}_2\text{O (2.5eq)}]{\text{K}_2\text{CO}_3 (3-5\text{eq}), \text{THF, } 80^\circ\text{C, 12h, sealed tube}}$

8 R¹=R²=H
9 R¹=H; R²=Me
10 R¹O=pinacolato; R²=H
11 R¹O=pinacolato; R²=Me

^a K₂CO₃ (3 eq) was used. ^b K₂CO₃ (5 eq) was used.

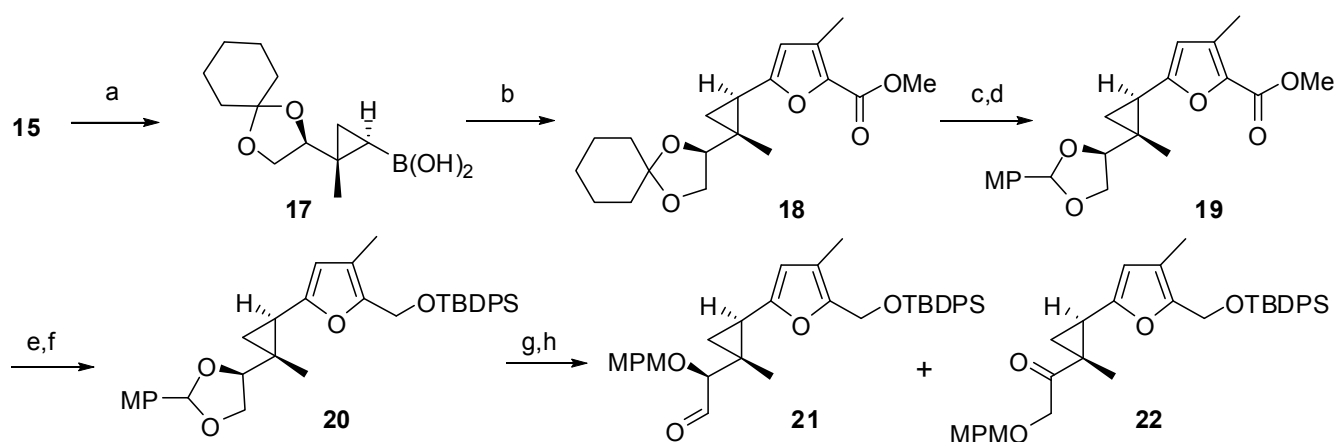
With the optimized condition in hand, we embarked on the synthesis of chiral cyclopropylfuran **2** as follows. Scheme 2 shows a preparation of cyclopropyl iodide **15** from the known alkyne **13**.⁹ Alkyne **13**

was subjected to Organ's carbometalation conditions¹⁰ to provide vinyl iodide **14** in one-pot sequence. Cyclopropanation of vinyl iodide **14** under Shi's conditions¹¹ resulted in the formation of cyclopropane **15** in a single diastereomer. The absolute configuration of cyclopropyl iodide **15** was determined by the MTPA esters of the corresponding cyclopropanol **16**.



Scheme 2. Reagents and conditions: (a) $\text{Bu}_3\text{SnCu}(\text{Bu})(\text{CN})\text{Li}_2$, THF, -78°C , then MeI, HMPA, then I_2 , 74%; (b) Et_2Zn , CH_2I_2 , TFA, CH_2Cl_2 , rt, 85%; (c) $t\text{-BuLi}$, THF, -78°C , then $\text{B}(\text{O}i\text{-Pr})_3$, -78°C to rt, then 3N NaOH, 30% H_2O_2 , 70%

Suzuki cross-coupling of cyclopropylboronic acid **17**, prepared from **15** by lithium/halogen exchange followed by treatment with $\text{B}(i\text{-PrO})_3$, with bromofuran **7** under the optimized condition gave the desired product **18** in 77% (2 steps). Acetal group of **18** was switched from cyclohexylidene to *p*-methoxybenzylidene by acid hydrolysis followed by acetalization of the corresponding diol with *p*-methoxybenzaldehyde to give **19**. Reduction of furoate **19** with LiAlH_4 followed by etherification of the furfuryl alcohol with TBDPSCl afforded silyl ether **20**. Regioselective cleavage of *p*-methoxybenzylidene acetal **20** with DIBAL gave an inseparable mixture (ratio: 2.5 : 1) of alcohols, which were oxidized with Dess-Martin periodinane to afford the desired aldehyde **21**¹² together with ketone **22**.



Scheme 3. Reagents and conditions: (a) $t\text{-BuLi}$, THF, -78°C , then $\text{B}(\text{O}i\text{-Pr})_3$, -78°C to rt, then 1N HCl; (b) $\text{Pd}(\text{dppf})\text{Cl}_2$, Ag_2O , K_2CO_3 , **7**, THF, 80°C , sealed tube, 77% (2 steps); (c) Dowex 50WX-8, MeOH, rt, 98%; (d) *p*-MeOPhCHO, PPTS, PhH, reflux, 85%; (e) LiAlH_4 , THF, rt, 92%; (f) TBDPSCl, imidazole, CH_2Cl_2 , rt, 100%; (g) DIBAL, PhMe, -78°C , 68%; (h) Dess-Martin periodinane, CH_2Cl_2 , rt, 50%

In conclusion, we have succeeded in the enantioselective synthesis of cyclopropylfuran derivative **21**, the C(2)-C(11) segment of pinnatin A employing the silver (I) oxide promoted Suzuki cross-coupling as a key step. Further studies on the synthesis of pinnatin A are in due course.

ACKNOWLEDGEMENTS

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12. **21**: a colorless oil. $[\alpha]_D^{22}$ -24.1 (*c* 0.64, CHCl₃); IR (thin film) cm⁻¹: 1110, 1740; ¹H-NMR (CDCl₃, 270 MHz) δ : 0.91 (1H, dd, *J* = 5.1 and 5.9 Hz, 3'-CHH), 0.96 (3H, s, 2'-CCH₃), 1.02 (9H, s, SiC(CH₃)₃), 1.08 (1H, dd, *J* = 5.1 and 9.2 Hz, 3'-CHH), 1.75 (3H, s, ArCH₃), 2.11 (1H, dd, *J* = 5.9 and 9.2 Hz, 1'-CH), 3.29 (1H, d, *J* = 2.1 Hz, 1''-CH), 3.80 (3H, s, OCH₃), 4.54 (2H, s, ArCH₂O), 4.59 (2H, s, CH₂OSi), 5.82 (1H, s, ArH), 6.89 and 7.29 (each 2H, each d, *J* = 8.6 Hz, CH₃OC₆H₄)

7.28-7.64 (6H, m, ArH), 7.62-7.72 (4H, m, ArH), 9.69 (1H, d, $J = 2.1$ Hz, CHO); ^{13}C -NMR (CDCl_3 , 67.8 MHz) δ : 9.7, 14.1, 16.1, 17.3, 19.3, 23.1, 26.7, 55.2, 56.6, 71.5, 87.3, 110.5, 113.9, 117.9, 127.6, 129.3, 129.5, 129.5, 133.7, 135.6, 147.8, 151.5, 159.5, 202.0; MS (EI): 582 (M^+); HRMS (EI): calcd for $\text{C}_{36}\text{H}_{42}\text{O}_5\text{Si}$: 582.2801. Found; 582.2800.