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

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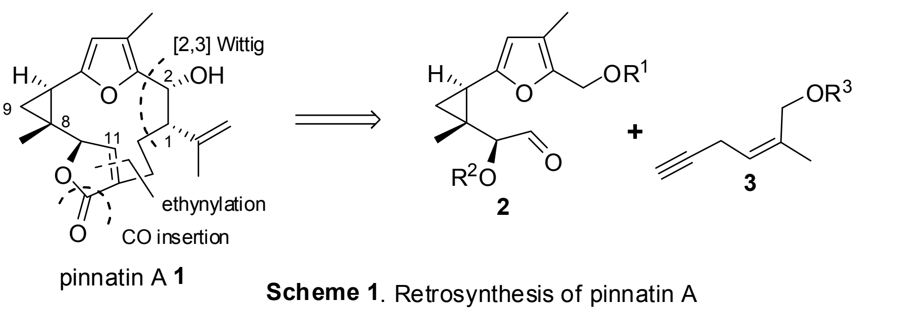
Abstract – Synthesis of the C(2)-C(11) segment, cyclopropylfuran derivative, of pinnatin A was accomplished by Suzuki cross-coupling between chiral cyclopropylboronic acid and bromofuran as a key step. Addition of silver (I) oxide was found to promote the Suzuki cross-coupling reactions.

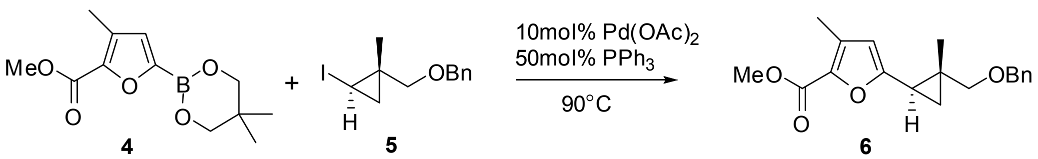
Pinnatin A **1** is a unique gersolane-type furanoditerpene isolated from a Caribbean gorgonian, *Pseudopterogorgia bipinnata*.[1] The compound shows significant differential antitumor activity in the National Cancer Institute's 60-cell-line tumor panel. Pinnatin A has a highly functionalized polycyclic 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

Dedicated with respect to Dr. Albert Eschenmoser on the occasion of his 85th birthday.

We first investigated Suzuki cross-coupling between furanboronic ester **4**[3] and cyclopropyl iodide **5**[4] under Charette's conditions[5a] (eq. 1). $Pd(OAc)_2$-catalyzed cross-coupling reaction with K_2CO_3 and Bu_4NBr gave the adduct **6** in only 6% yield. The addition of CsF instead of K_2CO_3 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]

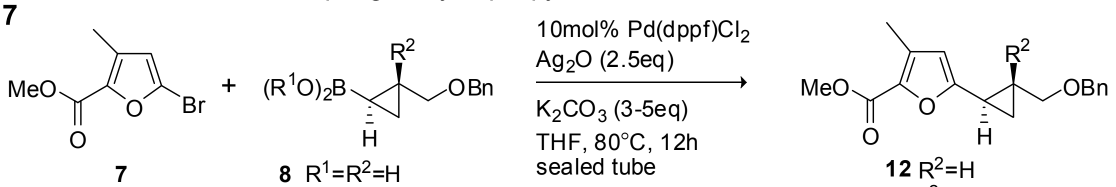


4 **5** **6** (eq. 1)

additive	solvent	time (h)	yield (%)
K_2CO_3 (3.0 eq) Bu_4NBr (2.0 eq)	DMF-H_2O (3:1)	13	6
CsF (4.5 eq)	DMF	16	25

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 conditions[8] (Table 1). Moderate to good yields of the cross-coupling products **6** and **12** were obtained using a combination of Ag_2O-K_2CO_3. Increasing amounts of K_2CO_3 (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

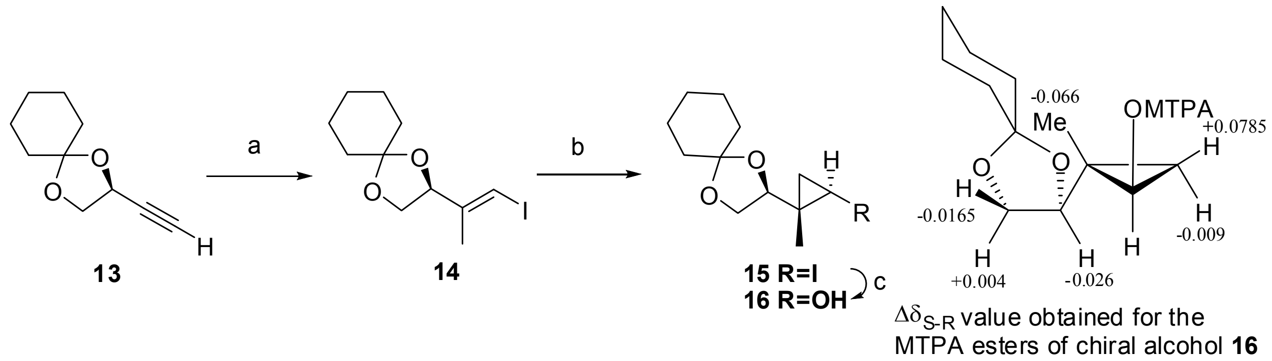
8 R^1=R^2=H
9 R^1=H; R^2=Me
10 R^1O=pinacolato; R^2=H
11 R^1O=pinacolato; R^2=Me

12 R^2=H
6 R^2=Me

entry	boronic acid derivative	product	yield (%)
1	**8**	**12**	75[a]
2	**9**	**6**	70[a]
3	**8**	**12**	81[b]
4	**9**	**6**	74[b]
5	**10**	**12**	71[b]
6	**11**	**6**	55[b]

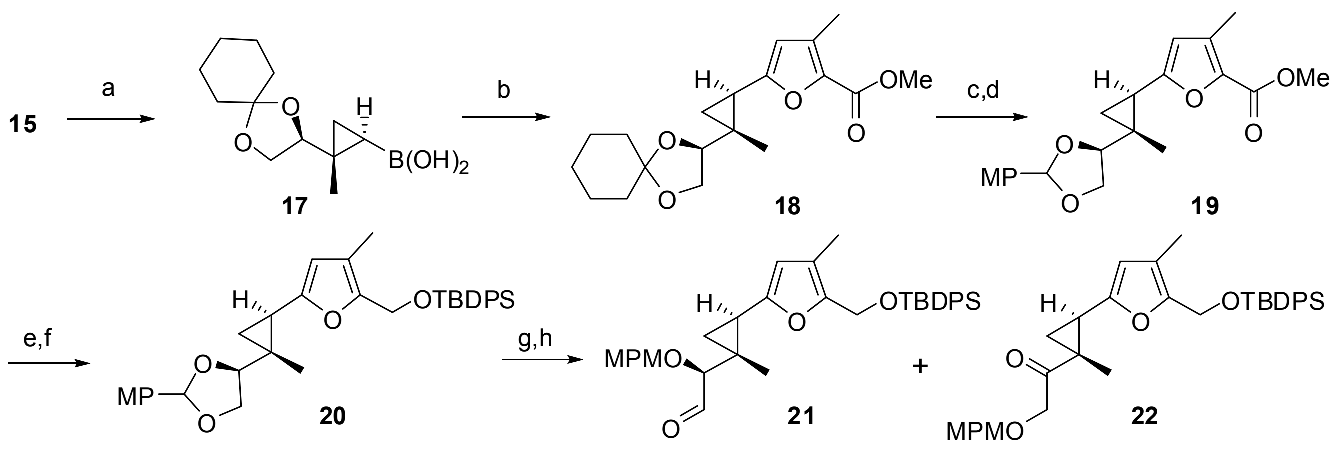
[a] K_2CO_3 (3 eq) was used. [b] K_2CO_3 (5 eq) was used.

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 conditions[10] to provide vinyl iodide **14** in one-pot sequence. Cyclopropanation of vinyl iodide **14** under Shi's conditions[11] 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) $Bu_3SnCu(Bu)(CN)Li_2$, THF, -78 °C, then MeI, HMPA, then I_2, 74%; (b) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, rt, 85%; (c) *t*-BuLi, THF, -78 °C, then B(O*i*-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 B(*i*-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*-methoxy-benzylidene by acid hydrolysis followed by acetalization of the corresponding diol with *p*-methoxy-benzaldehyde 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*-BuLi, THF, -78 °C, then B(O*i*-Pr)$_3$, -78 °C to rt ,then 1N HCl; (b) Pd(dppf)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, $CHCl_3$); IR (thin film) cm^{-1}: 1110, 1740; ^{1}H-NMR ($CDCl_3$ 270 MHz) δ: 0.91 (1H, dd, *J* = 5.1 and 5.9 Hz, 3'-C*H*H), 0.96 (3H, s, 2'-CCH_3), 1.02 (9H, s, $SiC(CH_3)_3$), 1.08 (1H, dd, *J* = 5.1 and 9.2 Hz, 3'-CH*H*), 1.75 (3H, s, $ArCH_3$), 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, OCH_3), 4.54 (2H, s, $ArCH_2O$), 4.59 (2H, s, CH_2OSi), 5.82 (1H, s, ArH), 6.89 and 7.29 (each 2H, each d, *J* = 8.6 Hz, $CH_3OC_6H_4$)

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 $C_{36}H_{42}O_5Si$: 582.2801. Found; 582.2800.