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# Suzuki coupling reactions of 2,4,6-trialkoxyphenylboronic acids with enol triflates: asymmetric synthesis of a lactone template for calyxin assemblage

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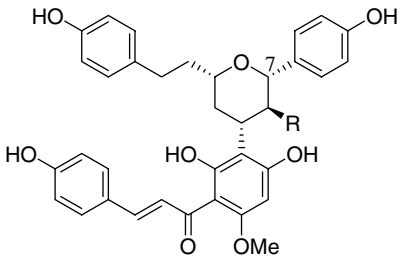
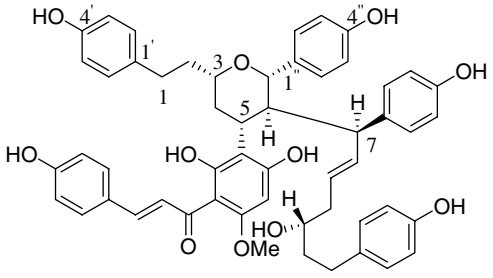
**Abstract**—Suzuki coupling reactions between 2,4,6-trialkoxyphenylboronic acids and enol triflates have been found to occur in excellent yield, while the use of an enol tosylate failed to give any of the desired product. This coupling reaction has led to the synthesis of a lactone which could serve as a precursor to several calyxin analogues.


Efforts in our lab are currently focused on developing a general strategy for synthesizing several members of the calyxin family of natural products, such as 6-hydroxycalyxin F (**1**),[1] epicalyxin F (**2**),[2] and blepharocalyxin E (**3**).[3] Isolated by Kadota and co-workers, all three have been shown to possess significant antiproliferative activity against HT-1080 fibrosarcoma and colon 26-L5 carcinoma cell lines, making them potential drug candidates for the treatment of human tumors. Most of our work to date has centered on the most complex of these, blepharocalyxin E, using the tetrahydro-4*H*-furo[2,3-*b*]pyran-2-one ring system to control the stereochemistry at C7.[4,5] Herein, we address the stereocontrolled synthesis of the core tetrahydropyran unit.

Lactones **4** (Scheme 1) were viewed as useful targets for their potential as common intermediates for the synthesis of several calyxin analogs, including compounds **1**–**3**. We envisioned deriving these lactones from a Suzuki coupling between enol triflate **5**, prepared from the known lactone **6**,[6] and the arylboronic acids **7**. Yao and Deng have reported the synthesis of 4-aryl coumarins using a related coupling strategy,[7] while others have found success using enol tosylates.[8] However, to the best of our knowledge an example of a successful coupling of either substrate with a 2,4,6-trialkoxyphenylboronic acid derivative has not been reported.[9] In light of this, a study was initiated to determine the feasibility of the proposed coupling reaction.




**1** R = OH (6-Hydroxycalyxin F)
**2** R = H (Epicalyxin F)




**3** (Blepharocalyxin E)

*Keywords*: Calyxins; Epicalyxins; Suzuki coupling; Trialkoxyphenylboronic acids.
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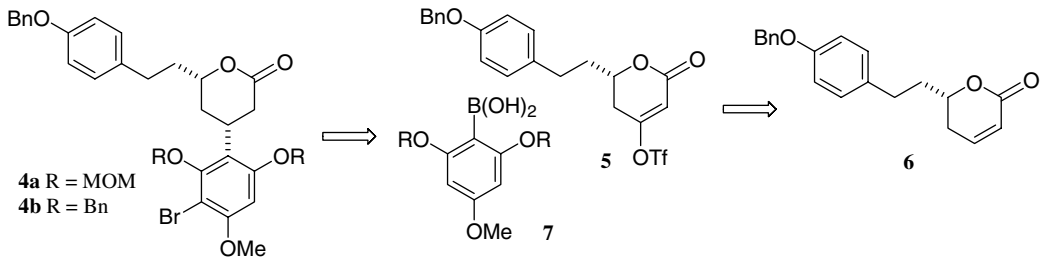



**Scheme 1.** Retrosynthesis of lactone targets.

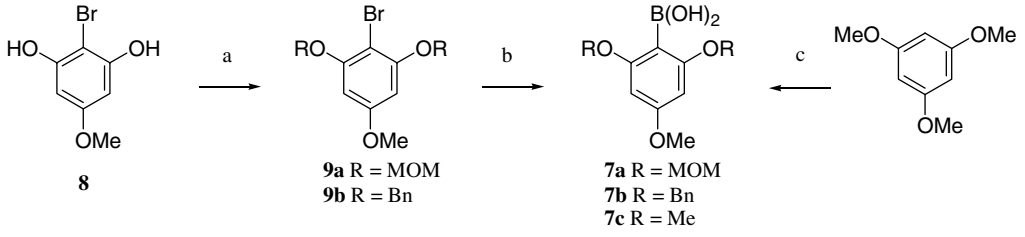
Initial work focused on the synthesis of the hindered trialkoxyphenylboronic acids **7**. Attempts to synthesize all three derivatives **7a**–**c** met with limited success. The known trimethoxy derivative **7c** (Scheme 2) was prepared according to the published procedure by direct lithiation of 1,3,5-trimethoxybenzene in the presence of TMEDA.[10] For derivatives **7a** and **7b**, lithiation was attempted by metal–halogen exchange from their bromo precursors **9a** and **9b**, respectively. In the event, the yield of formation of **7a** was disappointing, whereas none of compound **7b** formed under these conditions.

Two different enol triflates were prepared for studying Suzuki coupling reactions. The synthesis of benzyl derivative **5** is representated in Scheme 3. Lactone **6** was synthesized asymmetrically according to the published procedures[6] and converted to alcohol **10** by an epoxidation-reductive cleavage strategy.[11] Oxidation of compound **10** gave dione **11**, which was converted to enol triflate **5** using standard conditions.

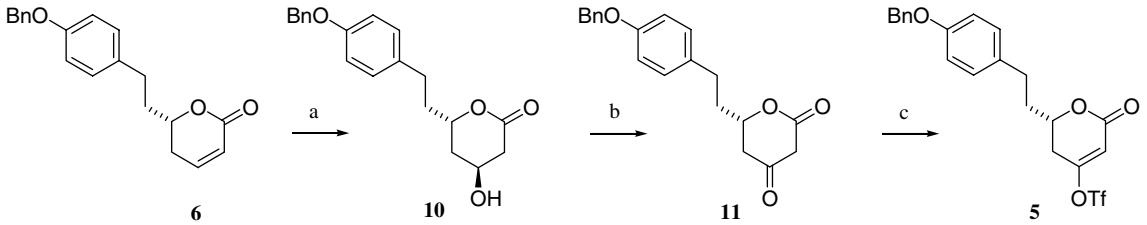
Table 1 summarizes the results of Suzuki couplings. The first attempt between enol triflate **12** and trimethoxy derivative **7c** (entry 1) was disappointing. However, the addition of water (entry 2) gave the desired product in excellent yield. Variations in protective groups also gave reproducible high yields using the same conditions (entries 3 and 5). Interestingly, when the corresponding enol tosylate **13** was used in place of the triflate, none of the desired product was isolated (entry 4).

Compound **16** (Scheme 4) was treated with catalytic hydrogenation conditions with the intention of selectively reducing the lactone double bond. However, phenol **17** was the only product. Continued catalytic hydrogenation eventually gave compound **18** as a single diastereomer, which was benzylated to provide intermediate **19**. Finally, aromatic bromination of compound **19** with NBS proceeded without incident to give the target lactone **4a**.

In summary, a general strategy for preparing lactones **4** has been demonstrated, although limitations clearly exist concerning the choice of protective groups at positions 2 and 6 on the trialkoxyphenyl substituent. Total syntheses of calyxin analogues **1**–**3** are planned using the lactone template **4a**.

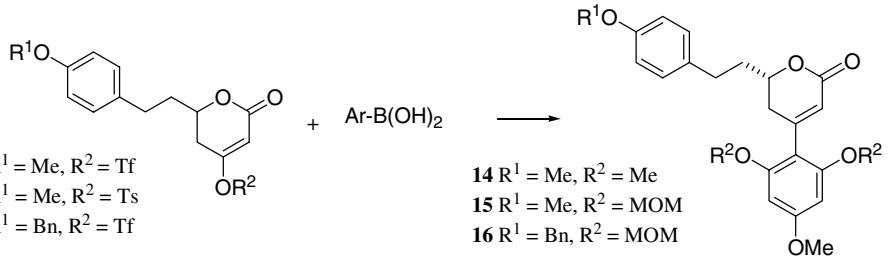



**Scheme 2.** Synthesis of trialkoxyphenylboronic acids. Reagents and conditions: (a) **9a**: NaH, MOMCl, DMF, 0 °C–rt, 12 h (76%); **9b**: BnBr, NaH, DMF, rt, 12 h (87%); (b) **7a**: *n*-BuLi, $B(OMe)_3$, −78 °C then rt, 5 h (32%); **7b**: *n*-BuLi, $B(OMe)_3$, −78 °C then rt, 12 h (0%); (c) **7c**: *n*-BuLi, TMEDA, $B(OMe)_3$, THF, −78 °C to rt, 12 h, then $NH_4Cl$(aq) (62%).



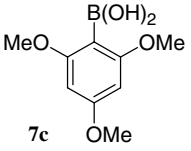
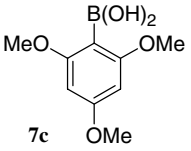
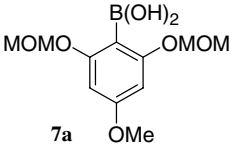
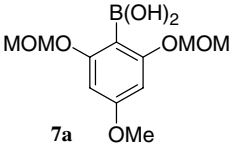
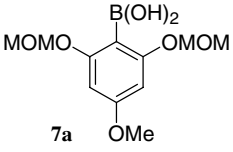

**Scheme 3.** Synthesis of enol triflate **5**. Reagents and conditions: (a) (i) $H_2O_2$, 6 N NaOH(aq), EtOH, 0 °C, 2 h; (ii) PPTS, PhH, reflux, 2 h (79%, two steps); (iii) $Ph_2Se_2$, $NaBH_4$, EtOH, 0 °C, 2 h (88%); (b) PCC, $CH_2Cl_2$, 0 °C–rt, 12 h (62%); (c) $Tf_2O$, $NEt_3$, $CH_2Cl_2$, −78 °C, 30 min (74%).

**Table 1.** Results of Suzuki coupling reactions

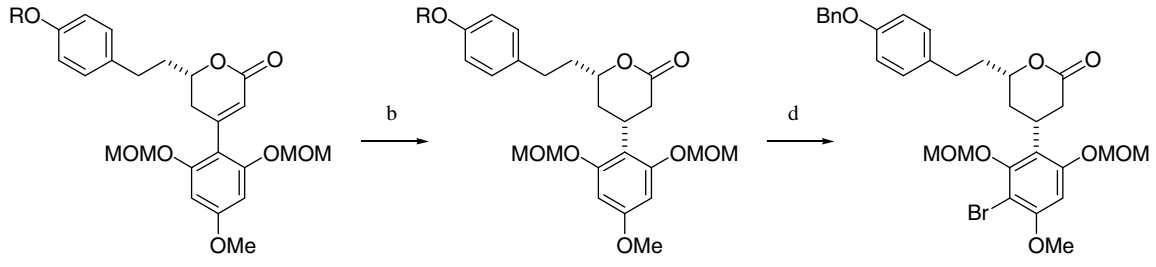



**12** $R^1$ = Me, $R^2$ = Tf
**13** $R^1$ = Me, $R^2$ = Ts
**5** $R^1$ = Bn, $R^2$ = Tf

**14** $R^1$ = Me, $R^2$ = Me
**15** $R^1$ = Me, $R^2$ = MOM
**16** $R^1$ = Bn, $R^2$ = MOM

| Entry | Substrate | Ar–B(OH)$_2$ | Reaction conditions | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **12** |  **7c** | 5% $PdCl_2(PPh_3)_2$, THF, $K_2CO_3$, reflux, overnight | **14** | 24 |
| 2 | **12** |  **7c** | 5% $PdCl_2(PPh_3)_2$, THF, 2 N $K_2CO_3$, reflux, 2 h | **14** | 92 |
| 3 | **12** |  **7a** | 5% $PdCl_2(PPh_3)_2$, THF, 2 N $K_2CO_3$, reflux, 2 h | **15** | 94 |
| 4 | **13** |  **7a** | 5% $PdCl_2(PPh_3)_2$, THF, 2 N $K_2CO_3$, reflux, 6 h | **15** | 0 |
| 5 | **5** |  **7a** | 5% $PdCl_2(PPh_3)_2$, THF, 2 N $K_2CO_3$, reflux, 3 h | **16** | 98 |

[a] All products were fully characterized by $^1$H NMR, $^{13}$C NMR, and HRMS.
[b] Yield refers to the isolated product of Suzuki coupling.




**16** R = Bn
**17** R = H
a

**18** R = H
**19** R = Bn
c

**4a**

**Scheme 4.** Synthesis of compound **4a**. Reagents and conditions: (a) $H_2$, Pd/C (10 mol %), EtOAc–EtOH (1:1), rt, 45 h (92%); (b) $H_2$, Pd/C (10 mol %), EtOAc–EtOH (1:1), rt, 72 h (76%); (c) BnBr, NaH, DMF, 0 °C, 1 h (87%); (d) NBS (2 equiv), $CH_2Cl_2$, rt, 3 h (94%).

## Acknowledgements

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## Supplementary data

The following supplementary data are available with the paper: a $^{1}H$ NMR peak listing for compound **17**, $^{1}H$ and $^{13}C$ NMR peak listings for compounds **4a**, **5**, **7a**, **9a**, **9b**, **10**, **12**–**16**, **18**, and **19**, HRMS data for compounds **4a**, **14**–**16**, **18**, and **19**, and a general procedure for the Suzuki coupling. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.159.

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