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A Suzuki-Miyaura Coupling of Ortho Hydroxy Aryl Bromide with Isopropenylboronic Pinacol Ester and its Application: Synthesis of the Potassium-Channel Opener (+)-Callitrisic Acid

Xiongyu Wu,*[a] Malin Silverå Ejneby,[b] Nina E Ottosson,[b] Fredrik Elinder,[b] Peter Konradsson[a]

Abstract: *A Suzuki-Miyaura coupling reaction of ortho hydroxy aromatic bromide **8** with isopropenylboronic acid pinacol ester has been investigated. It was found that the catalyst of $Pd_2(dba)_3/PCy_3$ in dioxan-water gave good yield by suppressing the formation of isomeric side product **14**. (+)-Callitrisic acid was synthesized from (+)-podocarpic acid using this condition with an overall yield of 54% in about five steps. (+)-Callitrisic acid was found to be almost three times more potent than dehydroabietic acid to open a voltage-gated potassium channel.*

There are more than five thousand bioactive small molecules containing ortho-hydroxy-isopropyl or ortho-hydroxy-isopropenyl phenyl moiety, including natural products ferruginol (**1**), carnosol (**2**), lambertic acid (**3**), nepetaefolin H (**4**), teydeadione (**5**) and synthetic eprotirome (**6**) (**Figure 1**).[1] Several methods have been developed for the synthesis of isopropyl/alkyl arenes.[2] However, some of the ligands are not commercially available and none of those investigated starting materials contains an ortho-hydroxyl group. To the best of our knowledge, all the ortho hydroxy group are protected. An ortho-hydroxy group could be problematic because of its participation to the cross-coupling reaction. From the literature, we find there are just a few reports on the Suzuki-Miyaura coupling conditions using ortho-hydroxybromobezene analogues as starting materials to synthesize isopropenyl phenyl moiety. One of them give low yield (31%) using $Dppf \cdot PdCl_2 \cdot CH_2Cl_2$ complex as the catalyst. Others give high yields after ortho-phenolic hydroxy group(s) is/are protective.[3] The free phenolic hydroxy group at ortho position of bromo group seems to be one of the reasons to give a low yield in Suzuki-Miyaura coupling reaction. Now we want to investigate the Suzuki-Miyaura coupling reaction of ortho hydroxy aryl bromide with isopropenylboronic acid pinacol ester for further applications, since isopropenyl group of the products is easily reduced to isopropyl group, and they can also be used as starting materials to synthesize other derivatives.[4]

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Recently we have special interest in resin acid derivatives because it is found that some of them have the potential to be developed to pharmaceutical drugs to improve the condition for patients suffering from hyperexcitability diseases such as epilepsy and pain related disorders.[5] Compound **8**, which was synthesized from bromination of podocarpic acid **7** (a resin acid), was then used as the starting material for reaction investigation (**Table 1**).

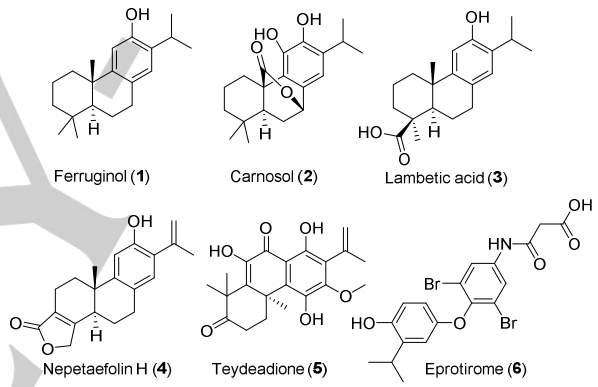


Figure 1: Structures of some natural products containing hydroxyl isopropyl/isopropenyl phenyl ring.

Bromination of podocarpic acid using NBS under microwave irradiation (MW) at 90 °C gave **8** in 97% yield. Reaction was very slow at rt. Unlike the bromination, Suzuki-Miyaura coupling of **8** with 2-isopropenylboronic acid pinacol ester was more problematic.

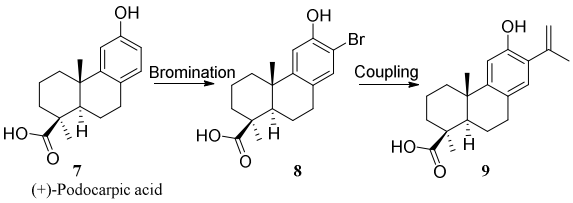


Table 1. Optimization of coupling of bromide **8** to give compound **9**

	Catalyst	Solvent	T. and time	**9**[a]	Side product	Ratio of **9:14**[b]
1	$Pd(PPh_3)_4$	DME/ H_2O	140ºC, 30 min	trace	**7**, **10**-13[c]	
2	$Pd(PPh_3)_4$	Tol/EtOH /H_2O	140ºC, 30 min	trace	**7**, **12**[d]	
3	$Pd(PPh_3)_4$	Dioxane/ H_2O	135ºC, 30 min	50%	**7**, **10**, **13**-14[e]	3.3:1
4	Pd-Peppsi-iPr	Dioxane/ H_2O	135ºC, 30 min	70%	**14**	1.7:1

5	$Pd_2(dba)_3/PCy_3$	Dioxane/ H_2O	135ºC, 30 min	81%	**10**, **14**	10:1
6[f]	$Pd_2(dba)_3/PCy_3$	Dioxane/ H_2O	135ºC, 7 min	91%	**10**, **14**	11:1
7	Pd-Peppsi-iPent	Dioxane/ H_2O	135ºC, 7 min	94%	**14**	1:1.3

[a] isolated yield; [b] ^{1}H-NMR ratio; [c] LC ratio of **7**/**11**/**12**/**13**: 2:1:1.8:5; [d] LC ratio of **7**/**12**: 1:1.3; [e] LC ratio of **7**/**9**(**14**)/**10**/**13**: 6:39:1:24; [f] Reaction condition: The mixture of bromide **8** (0.284 mmol), 3 equiv of isopropenylboronic acid pinacol ester, 3 mol% $Pd_2(dba)_3$, 6 mol% PCy_3, 4 equiv of Na_2CO_3, 3.5 mL dioxane/water (4:1), was irradiated under MW at 135 ºC for 7 min.

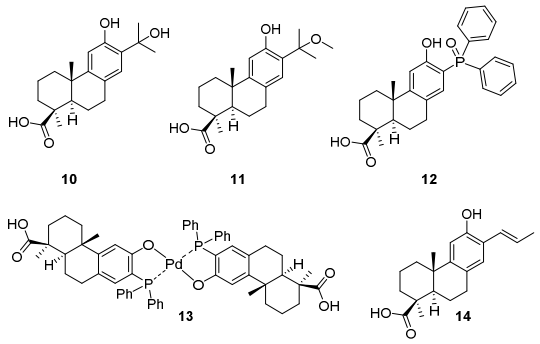
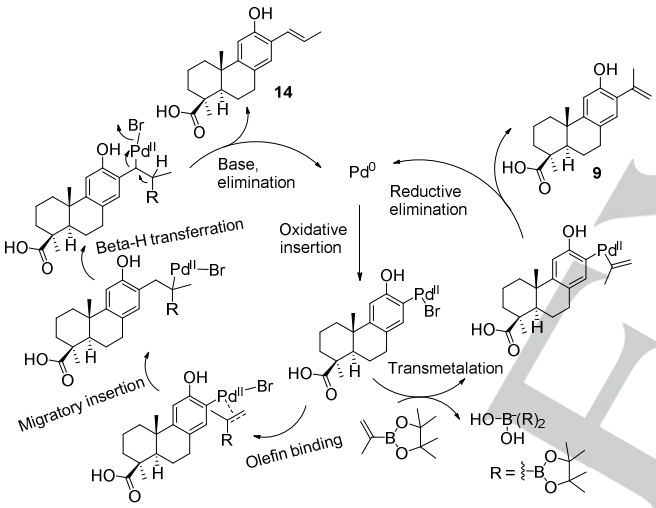


Figure 2: Different side products from Suzuki-Miyaura coupling reaction step under different conditions.



Scheme **1**: Plausible mechanism of formations of compounds 9 and 14.[6]

Different conditions have been carried out to afford a good yield of the coupling step. When $Pd(PPh_3)_4$ was used as the catalyst, different side products were obtained in different solvents under microwave irradiation (**Table 1** and **Figure 2**). Compound **11** was found to be one of the major side products when DME and water were used as solvents. It seemed that the methoxy group was transferred from DME to the desired product to form a methyl ether. The solvent mixture of toluene/EtOH/H_2O was then used to suppress the formation of side product **11**. Although the presence of EtOH didn't give any problem of formation of ethyl ether side product like **11**, unfortunately another side product of **12** together with podocarpic acid **7** (from debromination) were dominated. The desired product was trace in both conditions (entries 1 and 2). Dioxane/H_2O were then used, and the reaction mixture was irradiated under MW at 135 °C for 30 min. The reaction gave moderate yield at about 50%. The yield was increased from trace to moderate with compound **14** as one of the major side products. The mechanism of the formation of **14** was shown in Scheme **1**.[6]

Another major side product was compound **13**, a palladium complex with diphenylphosphinylated podocarpic acid, which was probably formed after the Oxidative insertion step of palladium catalytic cycle due to the ortho-group participation of free phenol. Since triphenylphosphine ligand was problematic here, another type of catalysts, Peppsi-iPr, was then tested. It was found that no palladium complex like **13** was formed and the yield of Suzuki-Miyaura coupling product was improved to about 70%. But the product was a mixture with a ratio of compounds **9**/**14** at about 1.7:1, which was worse than that acheived from catalyst of $Pd(PPh_3)_4$. Bulky ligands in coupling reactions are found to reduce the isomerization problem of isopropyl group in the Suzuki-Miyaura and Negishi coupling reactions.[2b,2g] Peppsi-iPent, which is more bulky, was also tested for this reason, although the mechanisms were probably different. Unfortunately, the reaction was worse and gave a ratio of **9**/**14** at about 1:1.3 according to ^{1}H NMR, with the n-propenyl side product as major under our condition. For other coupling conditions (entries 1-3) that gave low yields, it was found that some side products contained phenylphosphine moiety. Other non-phenylphosphine ligands could be helpful for the coupling reaction. Another catalytic system of $Pd_2(dba)_3/PCy_3$ was then tried and finally good yield (91%) was achieved for this step with a ratio of **9**/**14** at about 11:1 according to ^{1}H NMR. Compound **10** was formed as a minor side product in most of the coupling conditions (trace, entries 4 and 7). It was probably formed from compound **9**. The isopropenyl group of **9** was possibly protonated by the ortho phenolic group to form a benzylic cation, followed by the attack from water and deprotonation to give **10**. It was found that the amount of **10** was increased obviously if the reaction mixture was placed at rt for a few hours after work up. It was probably difficult to avoid it completely, but the optimized condition with $Pd_2(dba)_3/PCy_3$ as catalysts was ready for further application.

Dehydroabietic acid (**15**) (**Figure 3**) and its derivatives have been widely explored in material and pharmaceutical studies.[7a] They could be used as anti-hyperexcitability, anti-tumor, anti-inflammatory, and anti-allergic agents,[7] or even as starting material for synthesis of other natural products, such as 3-oxosapriparaquinone, (+)-pisiferic acid and pygmaeocine E.[8]

Compared to dehydroabietic acid, callitrisic acid (**16**) and derivatives are less investigated due to the commercial non-availability, although callitrisic acid is also a bioactive substance.[9] Synthesis of callitrisic acid and other epimers of dehydroabietic acid have been investigated before, but the synthetic routes are either lengthy and/or giving racemates.[10] With the compound **9** synthesized from the Suzuki-Miyaura coupling reaction above, further steps were exploited to synthesize (+)-callitrisic acid (**16**) (**Scheme 2**).

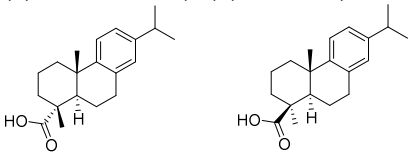
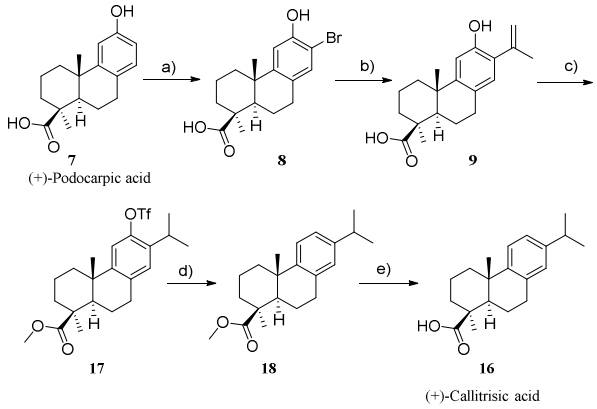


Figure 3: Structures of Dehydroabietic acid and Callitrisic acid.



Scheme 2: a) NBS, 90 °C, MW, 30 min, 97%; b) $Pd_2(dba)_3$, PCy_3, Na_2CO_3, Dioxan/H_2O, 135 °C, MW, 7 min. 90%, ratio of **9**:**14** at about 11:1; c) i) Pd/C, H_2, rt; ii) $TMSCH_2N_2$, rt; iii) triflic anhydride, Py, DCM, rt, 80%; d) $Pd(OAc)_2$, dppf, HCOOH, DiPEA, DMF, 110 °C, MW, 30 min, 81%; e) *t*-BuOK, DMSO, 150 °C, MW, 20 min, 95%.

Hydrogenation and methyl esterification using $TMSCH_2N_2$ followed by the formation of triflate of compound **17** were carried out smoothly under the described conditions above (**Scheme 2**). A good yield was also achieved. But it was problematic for the reduction of triflate **17**. Reduction with Peppsi-iPr/HCOOH/DiPEA, $Pd_2(dba)_3$/HCOOH/DiPEA and Pd/C/Mg didn't give any desired product. When $Pd(PPh_3)_4$ was used as a catalyst, the reaction gave a moderate yield of 53%. But side products of **19** and **20** were also obtained, which caused the lower yield (**Figure 4**). After optimization with other catalysts, the yield was successfully increased to 81% when dppf/$Pd(OAc)_2$ was used. After hydrolysis of **18** with *t*-BuOK in DMSO under MW at 150 °C for 20 min, the (+)-callitrisic acid **16** was got in 95% yield. The (+)-callitrisic acid was then synthesized in an overall yield of 54% from podocarpic acid.

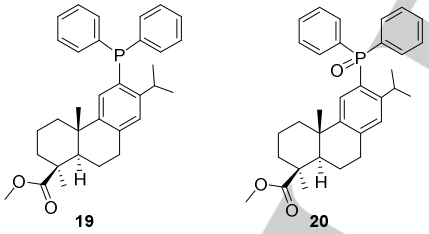


Figure 4: Different side products from reduction of trifluoromethan sulfonate using $Pd(PPh_3)_4$/HCOOH/DiPEA.

Table 2. Optmization of reduction of triflate **17** to give compound **18**.

Entry	Catalyst	T. and time	Compd. **18**[a]	S.P.
1	Peppsi-iPr	125 ºC, 45 min, MW	-	-
2	$Pd(PPh_3)_4$	120 C, 30 min, then 125 ºC, 1h	53%,	**19**, **20**[b]
3	$Pd(PPh_3)_4$	100 ºC, 7.5 h in total	21%	**19**, **20**
4	Pd/C/Mg	rt	trace	-
5[c]	Dppf/$Pd(OAc)_2$	110 ºC, 30 min, MW	81%	

[a] isolated yield; [b] LC ratio of **18**/**19**/**20**: 4.2:1:1.9; [c] The mixture of triflate **17** (0.204 mmol), 10 mol% $Pd(OAc)_2$, 20 mol% dppf, HCOOH (5 equiv.) and DiPEA (4 equiv.) in DMF was irradiated under MW at 110 °C for 30 min.

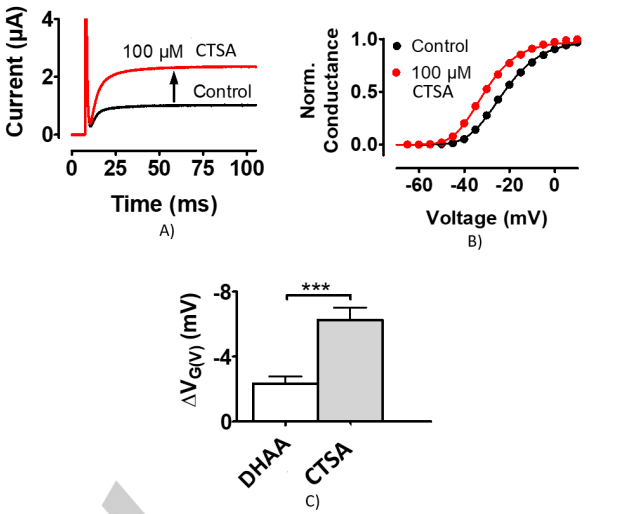


Figure 5: Different potency of the two diasteroisomers dehydroabietic acid (DHAA) and (+)-callitrisic acid (CTSA) to the wild type Shaker K_V channel. A) K currents at -30 mV and B) normalized G(V) curves (shift = -7,0) before (black) and after (red) application of 100 µM CTSA. C) *G*(*V*) shifts for 100 µM DHAA (n = 10) and CTSA (n = 6). Mean ± SEM.

A lipid protein drug-binding pocket of a potassium channel is recently discovered by us.[11a] It is found that (+)-callitrisic acid is much more potent than its epimer dehydroabietic acid in opening the genetically modified Shaker 3R K_V channel, designed to be more sensitive to compounds acting by the desired lipoelectric mechanism.[5a],[11] Here, we showed that (+)-callitrisic acid act as an opener of the wild type Shaker K_V channel (that is similar to other human K_V channels) by shifting the voltage-dependence of activation (the conductance-versus-voltage, *G*(*V*), curve) by -6.3 ± 0.8 mV (**Figure 5**). The shift was almost three times as large compared to dehydroabietic acid (-2.4 ± 0.4 mV).[5a] Therefore, (+)-callitrisic acid and its derivatives have the potential to be developed to potent K_V channel openers with the potential to reduce epileptic seizures, pain, and cardiac arrhythmia.

A Suzuki-Miyaura coupling reaction of ortho hydroxyl aryl bromide with isopropenylboronic acid pinacol ester has been investigated. Optimized condition has been discovered, which was applied in the concise synthesis of (+)-callitrisic acid from (+)-podocarpic acid. It was found that (+)-callitrisic acid was much more potent than dehydroabietic acid as a potassium channel opener. The synthetic route can also be applied in the syntheses of other analogues of dehydroabietic acid with a different chiral center at carbon 4. Interesting side products were also found during the optimizations, which help us to understand Suzuki-Miyaura coupling reaction better. Substance like **13** could probably be used as a chiral catalyst in organometallic chemistry.

Acknowledgements

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Keywords: Suzuki-Miyaura • (+)-callitrisic acid • potassium ion channel • channel opener • podocarpic acid

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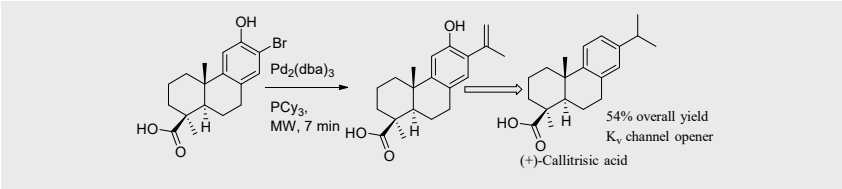

Isomeric side product was supressed successfuly by the catalyst of $Pd_2(dba)_3/PCy_3$ in dioxan-water in the Suzuki-Miyaura coupling reaction of ortho hydroxy aromatic bromide with isopropenylboronic acid pinacolester. (+)-Callitrisic acid synthesized from (+)-podocarpic acid using this condition was found to be a potent wild type voltage-gated potassium channel opener.

Drug discovery

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A Suzuki-Miyaura Coupling of Ortho Hydroxy Aryl Bromide with Isopropenylboronic Pinacol Ester and its Application: Synthesis of the Potassium-Channel Opener (+)-Callitrisic Acid