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Towards synthesis of kavalactone derivatives

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ABSTRACT

Kavalactone derivatives were synthesized using a Heck reaction of the 4-methoxy-6-vinyl-5,6-dihydropyran-2-one with aryl iodides. The Suzuki–Miyaura reaction of an aryl boronic acid and (*Z*)-4-methoxy-6-(2-iodovinyl)-5,6-dihydropyran-2-one has also been successfully used to produce both *Z* and *E* isomers of lactones.

Piper methysticum (kava-kava) is a plant native to the oceanic Islands of the South Pacific, which has been used as a folklore medicine and in the preparation of a traditional ceremonial beverage for thousands of years.[1] Modern use of kava root as a natural anxiolytic in several studies showed favourable results compared to a number prescription medications including benzodiazepines. In fact, kavalactones comprise 15% of the dried rootstock and display various and important biological properties such as sedative, anxiolytic, anti-inflammatory and analgesic effects.[2] The psychoactive ingredients consist of a group of structurally related lipophilic lactones derivatives with an arylethylene-α-pyrone core known as kavalactones (Fig. 1). Among these compounds, yangonin **1** is one of the major components of kava extract and it has been reported to be responsible for the pharmacological activity.[3] It has shown a promising TNF-α release inhibitory activity.[4]

The pharmacological actions found for the kavalactones justify their synthesis and the preparation of original analogues. The lack of systematic studies of the pharmacological activities for the isolated kavalactones[5] motivates their production in sufficient quantities for further structure–activity relationship investigations. In addition, it is still unknown which compound is responsible for the pharmacological effects observed for the vegetal extracts or even whether these actions are due to one or more of these compounds.

The synthesis of six-membered unsaturated δ-lactones has generated a widespread interest, due to their occurrence in a large number of natural products possessing potent biological activities.[6] Various synthetic pathways, aiming to racemic[7] or enantiopure compounds,[8] have been studied to access kavalactones via standard aldol-based strategies involving the corresponding electron-rich cinnamaldehydes but none of them are generally applicable to the synthesis of oxygen-substituted kavalactone derivatives such as yangonin and methysticin.

In connection with a programme devoted to the synthesis of 4-oxo valerolactones derivatives and the evaluation of their in vivo analgesic effect,[9] we present in this work two approaches to the

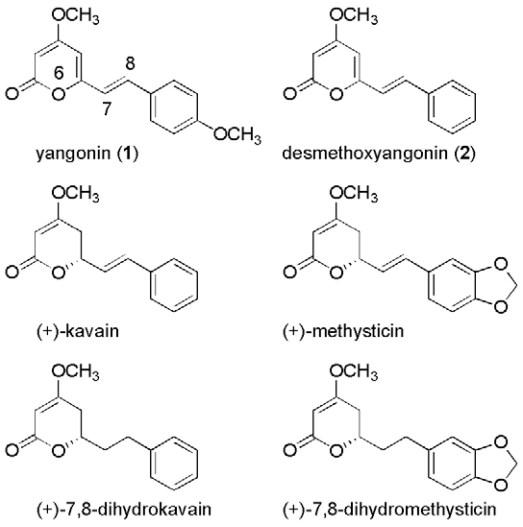

Figure 1. Kavalactones isolated from *Piper methysticum*.

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synthesis of yangonin **1**, desmethoxyyangonin **2** and structural analogues.

In order to devise a synthesis that would provide rapid access to novel compound libraries for biological evaluation, we first planned a strategy based on the Heck[10] cross-coupling reaction between the pyrone **3** and various aryl iodides (Fig. 2).

The precursor for the Heck reaction was successfully prepared by aldol condensation of ethyl acetoacetate with acrolein and subsequent lactonization according to a reported method.[9] Although it was possible to isolate and purify the β-ketone-intermediate, we decided to carry out the methylation with dimethyl sulfate in acetone at room temperature[8e] to afford **3** in a 52% yield overall (Scheme 1).

We then focused on the palladium-catalyzed cross coupling of **3** with some aryl iodides. To the best of our knowledge, no example related to the transformation of **3** to **4** has been reported in the literature.

First, reactions were carried out using various substituted iodobenzenes as the coupling partners, 5 or 10 mol % of tetrakis(triphenylphosphine) palladium(0) in the presence of Hünig's base in DMF for 16 h at 80 °C (Table 1).

Under these conventional thermal heating conditions, we observed that reactions did not proceed satisfactorily due to the heat-induced decomposition of the pyrone **3**. In addition, we noticed that increasing the reaction temperature to 180 °C or longer reaction time led to total pyrone moiety decomposition. This prompted us to run the reaction under controlled microwave irradiation.

Microwave-promoted palladium-catalyzed coupling reaction is known to reduce reaction times. In addition, the microwave irradiation procedures have received great attention due to their efficient and environmentally benign conditions.[11,12] The reaction conditions were optimized using 4-iodoanisole as substrate over a wide temperature range: 25–150 °C. After some experimentation, we found it essential to employ a moderate microwave power (300 W) to avoid decomposition of lactone **3** as observed by HPLC monitoring. The best result, 47% isolated yield of **4a**, was obtained in 5.5 min (Table 2, entry 1). If prolonged irradiation or higher temperatures were used, more side products resulting from total decomposition of the pyrone moiety were observed by ^{1}H NMR. It has been noticed that the decomposition pathway might involve a 'ring-opening-decarboxylation' sequence. No improvement was observed by increasing the amounts of Pd catalyst or change the source of Pd. Employing this protocol to other aryl iodides afforded the compounds **4b**, **4c** and **4d** within 5.5 min (entries 2–5), but the yields were only slightly improved. Less-activated aryl iodide (*p*-nitro-iodobenzene), which failed to afford the corresponding cross-coupling product regardless of heating procedure, is used (Table 1, entry 5 and Table 2, entry 5).

According to the disappointing results, we decided to investigate the Suzuki–Miyaura cross-coupling reaction of various aryl boronic acids with (*Z*)-6-(2-iodovinyl)-4-methoxy-5,6-dihydro-2*H*-pyran-2-one **5**. Therefore, the pyrone **5** was prepared following our optimized reaction conditions for the synthesis of the pyrone **3** (Scheme 1). Aldol condensation of ethyl acetoacetate with (*Z*)-iodoacrolein,[13] subsequent lactonization and then methylation afforded *Z* isomer in 46% yield overall.

In order to optimize the yield of cross-coupled products **4**, we focused on the employment of efficient catalyst system with $Pd(OAc)_2$ and 2-(2,6-dimethoxybiphenyl)dicyclo-hexyl-phosphine (*S*-Phos)[14,15] as ligand. Thus, treatment of pyrone **5** with boronic acids in toluene at 80 °C for 20 h in the presence of K_3PO_4 as base afforded the required kavalactone derivatives **4a**, **4b** and **4e** in satisfactory yields (Scheme 2). However, we were surprised to obtain

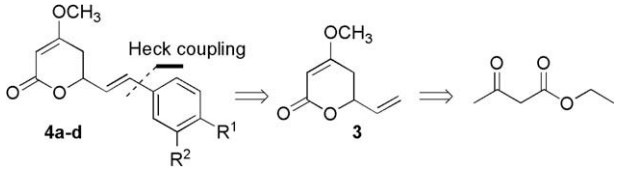
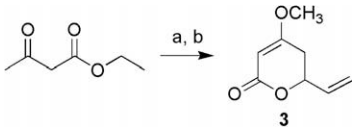
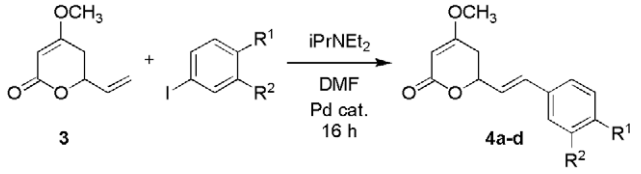


Figure 2. Retrosynthetic analysis.



Scheme 1. Reagents and conditions: (a) LDA, THF 0 °C, acrolein; (b) dimethyl sulfate, K_2CO_3, dry acetone, rt.

Table 1
Heck cross-coupling reactions under thermal heating conditions



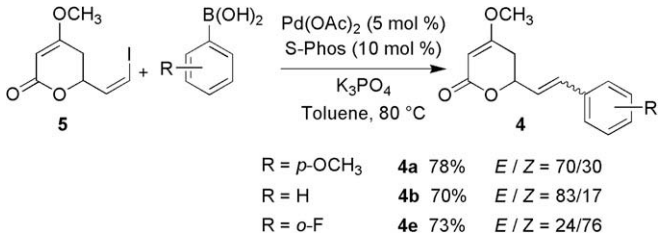
Entry	Aryl iodide		Mol %/catalyst	Product/yield (%)	
	R^1	R^2			
1	OCH_3	H	5% $Pd(PPh_3)_4$	**4a**	35
2	H	H	10% $Pd(PPh_3)_4$	**4b**	40
3	O–CH_2–O		10% $Pd(PPh_3)_4$	**4c**	40
4	F	H	10% $Pd(PPh_3)_4$	**4d**	40
5	NO_2	H	10% $Pd(PPh_3)_4$	nr[a]	

[a] No reaction.

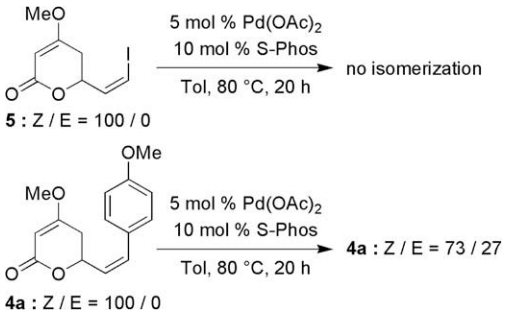
Table 2
Fast palladium-catalyzed coupling reactions under microwave irradiation (300 W, 5.5 min)

Entry[a]	Aryl iodide		Catalyst	Product/yield (%)	
	R^1	R^2			
1	OCH_3	H	10% $Pd(PPh_3)_4$	**4a**	46
2	H	H	10% $Pd(PPh_3)_4$	**4b**	42
3	F	H	10% $Pd(PPh_3)_4$	**4d**	40
4	O–CH_2–O		10% $Pd(PPh_3)_4$	**4c**	42
5	NO_2	H	10% $Pd(PPh_3)_4$	nr[b]	

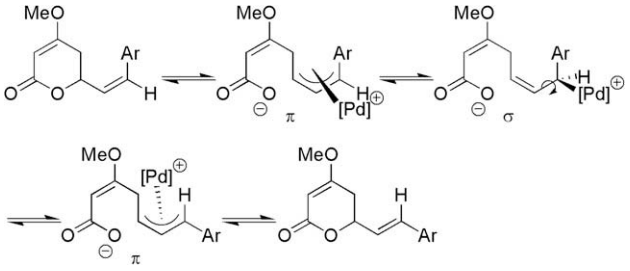
[a] Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 150 °C.
[b] No reaction.



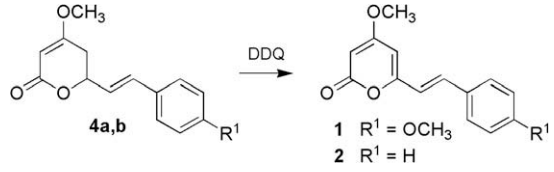
Scheme 2. Suzuki cross-coupling reaction.



Scheme 3.



Scheme 4.



Scheme 5. Synthesis of yangonin **1** and desmethoxyyangonin **2**.

a *E/Z* mixture since the Suzuki–Miyaura reaction was known to be a stereoselective cross-coupling reaction.[16,17] ^{1}H NMR analysis of each crude compound indicated the *E/Z* ratio: 70/30, 83/17 and 24/76 for **4a**, **4b** and **4e**, respectively.

Initially, we thought that the formation of *E*-isomers was the result of thermal isomerization of the pyrone **5** or the cross-coupling products **4**. Nevertheless no notable isomerization has been observed when these pyrones were heated in toluene at 80 °C for 24 h. Yet we observed that treatment of pyrone **4a** (*Z* isomer) in the cross-coupling conditions without boronic acid led to partial isomerization (*Z/E* = 100/0–73/27) after 20 h at 80 °C in toluene (Scheme 3). This could be explained by possible formation of a π-allyl-Pd(II) intermediate in the reaction mixture and well-known *syn–anti isomerization* via a π–σ–π process[18] (Scheme 4). On the other hand, no isomerization occurred with the vinylic iodide **5**. Probably, the oxidative addition of Pd(0) in the carbon–iodine bond is faster than the formation of the π-allylpalladium intermediate. More experiments are needed, and the results of these studies will be reported in due course.

In the final step of the reaction sequence products (*E*)-**4a** and (*E*)-**4b** were easily converted into the desired target yangonin **1** and desmethoxyyangonin **2**, refluxing benzene with DDQ for 2 h[4] (80% and 75% yields, respectively) (Scheme 5).

In summary, we have devised two approaches for the preparation of kavalactone derivatives, a class of compounds with interesting biological activities. The potential of yangonin to inhibit the LPS-stimulated TNF-α production in human whole blood is currently in progress. Further work to extend the Suzuki–Miyaura cross coupling to a diverse range of easily available boronic acids with *Z* and *E* iodoacrolein is underway in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.102.

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