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Versatile Asymmetric Synthesis of the Kavalactones: First Synthesis of (+)-Kavain

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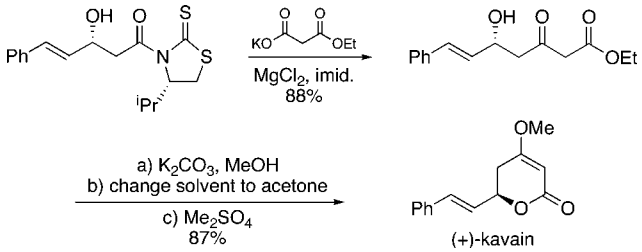
ABSTRACT



Three asymmetric pathways to the kavalactones have been developed. The first method is chiral auxiliary-based and utilizes aldol reactions of *N*-acetyl thiazolidinethiones followed by a malonate displacement/decarboxylation reaction. The second approach uses the asymmetric catalytic Mukaiyama additions of dienolate nucleophile equivalents developed by Carreira and Sato. Finally, tin-substituted intermediates, prepared by either of these routes, can serve as advanced general precursors of kavalactone derivatives via Pd(0)-catalyzed Stille couplings with aryl halides.

The Kava plant (*Piper methysticum*) has a long and colorful history spanning several thousand years.[1] Kava has been used by Pacific Island societies to prepare an intoxicating ceremonial beverage renowned for its relaxing effects and ability to promote sociability. Modern use of Kava root, commonly available in dietary supplements labeled "Kava Kava", is also for its purported anxiolytic[2] and soporific qualities. Analgesic,[3] anesthetic, antifungal, antithrombotic,[4] anticonvulsive,[5] and muscle-relaxing[6] properties also have been reported.[1] The psychoactive principals are a family of 15 α-pyrone derivatives known as the kavalactones that comprise roughly 15% of the dried rootstock. The more prevalent of these include kavain (**1**, Figure 1), dihydrokavain (**2**), and methysticin (**3**). Structurally, the kavalactones differ chiefly with respect to their arene substitution patterns and the presence or absence of double bonds along their carbon backbones. Although a few of the kavalactones, such as yangonin (**5**), are achiral, the majority have a single stereogenic center at C6 and are homochiral.

Several clinical studies indicate that the kavalactones have a demonstrable anxiety-reducing effect.[2] The pharmacological mechanism of this anxiolysis, however, is still unclear.[7] Recent warnings by the FDA and CDC of rare but severe cases of liver injury, possibly associated with the use of kava-

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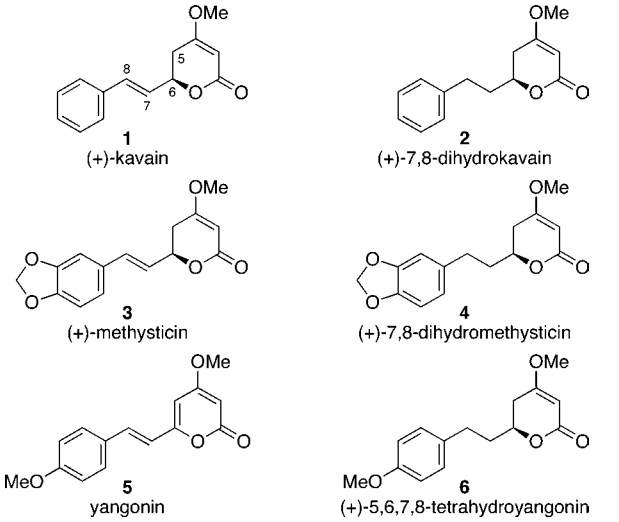


Figure 1. Representative kavalactones from *P. methysticum*.

containing dietary supplements, further accentuate the need for additional studies on the individual kavalactones and structural analogues.[8]

Although mixtures of the kavalactones are readily available from the crude extract of cultivated Kava, large quantities of isolated enantiopure kavalactones are not.[9] Similarly, although racemic syntheses of the kavalactones are numerous,[10] no generally applicable asymmetric synthesis has been developed. Enantioselective reductions of β-ketoester intermediates have led to the preparation of (+)-7,8-dihydrokaviain (**2**), but these methods currently are not amenable to the synthesis of kavalactones having C7−C8 unsaturation.[11] Somewhat surprisingly, no enantioselective synthesis of (+)-kavain has been reported to date.[12]

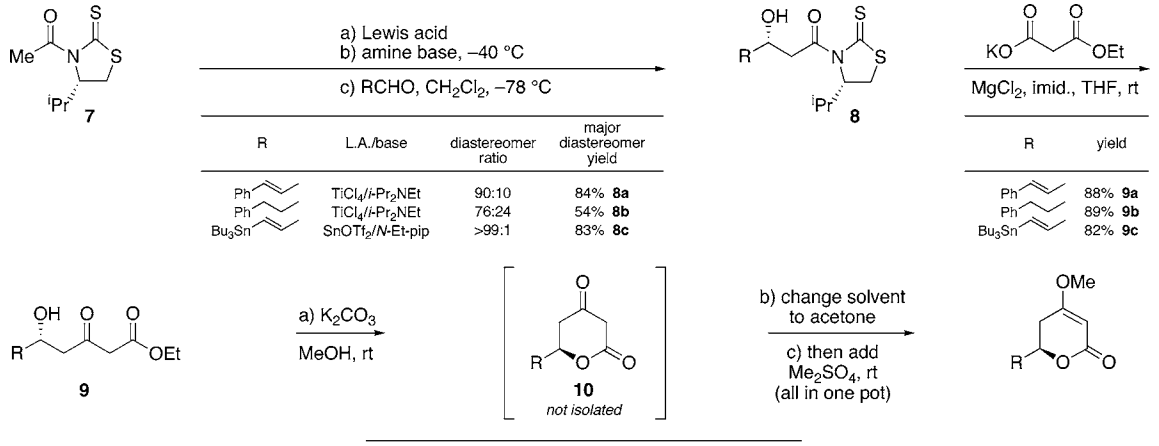
Our first approach to a general asymmetric synthesis of the kavalactones utilizes acetate aldol reactions based upon thiazolidinethione chiral auxiliaries (Scheme 1).[13] The titanium enolate of valine-derived *N*-acetyl thiazolidinethione **7** was reacted with cinnamaldehyde or dihydrocinnamaldehyde to give aldol adducts **8a**[13c] and **8b**, respectively. Similar reactions with an analogous tributyltin-substituted aldehyde led to protodestannylated products. Use of the original Nagao tin triflate enolization conditions[13a,b] alleviated this problem. Although tin-based aldol reactions of this type generally give higher levels of diastereocontrol, the titanium counterparts provide useful yields of purified major diastereomers with less expense and operational complexity. The boron-based system very recently reported by Sammakia would also be an attractive option here.[13e]

Critical to the efficiency of our plan was the discovery that the thiazolidinethione auxiliaries can be displaced by a carbon nucleophile without the need for protection of the free hydroxyl group. Thus, treatment of aldol adducts **8a**−**c** with the potassium salt of monoethyl malonate and $MgCl_2$ in the presence of imidazole led to β-ketoesters **9a**−**c**. The intermediacy of acyl imidazolides is presumed.[14] This *direct* homologation of thiazolidinethione aldol adducts represents a powerful method for the preparation of polyacetate fragments.

Lactonization of the δ-hydroxy-β-ketoesters (**9**) is smoothly accomplished with potassium carbonate in methanol. Although it is possible to isolate and purify the polar β-ketolactone intermediates (**10**), we have found it more efficient to simply remove the methanol solvent in vacuo and then carry out the standard enol ether formations in the same pot to afford the kavalactone products. In this fashion, the first asymmetric synthesis of (+)-kavain (**1**) was completed in 64% overall yield in three steps from cinnamaldehyde.

In an effort to devise a synthesis that would provide rapid access to the entire family of kavalactones and structural

Scheme 1. Chiral-Auxiliary-Based Synthesis of Kavalactones

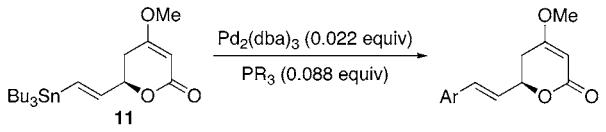


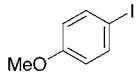
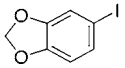
R	L.A./base	diastereomer ratio	major diastereomer yield
Ph	$TiCl_4$/*i*-Pr_2NEt	90:10	84% **8a**
Ph	$TiCl_4$/*i*-Pr_2NEt	76:24	54% **8b**
Bu_3Sn	$SnOTf_2$/*N*-Et-pip	>99:1	83% **8c**

R	yield
Ph	88% **9a**
Ph	89% **9b**
Bu_3Sn	82% **9c**

R	lactonization/ methylation yield	3-step overall yield	final product
Ph	87%	64%	**(+)-kavain (1)**
Ph	83%	40%	**(+)-dihydrokavain (2)**
Bu_3Sn	79%	54%	**11**

Table 1. Stille Couplings of Tin-Substituted Kavalactones

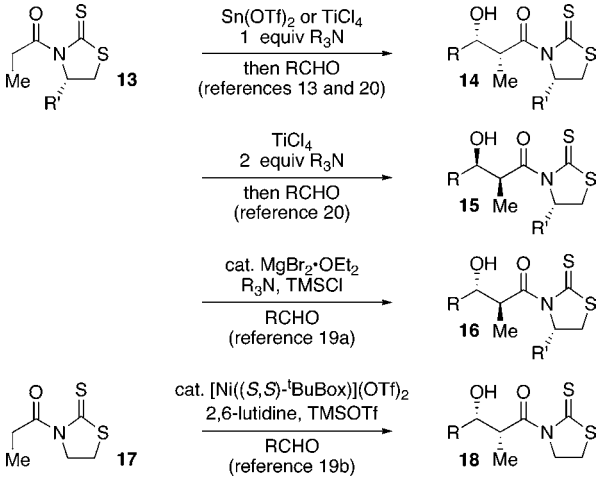


ArI	R	solvent	temp. (°C)	prod.	yield (%)
	2-furyl	THF	50	**1**	75
	*o*-MeO-Ph	tol.	115	**1 2**	52
	*o*-MeO-Ph	tol.	115	**3**	44

analogues, we have prepared vinylstannane **11** as a common advanced precursor. In several unoptimized initial experiments (Table 1), Stille couplings[15] with three appropriate aryl iodides provided (+)-kavain (**1**), (+)-5,6-dihydroyangonin (**12**), and (+)-methysticin (**3**).[16] This coupling strategy circumvents the difficulties associated with the preparation of electron-rich cinnamaldehyde derivatives and their diminished reactivity in aldol reactions and allows for the rapid generation of aryl-substituted kavain analogues.[17,18] A complementary Suzuki coupling approach is currently under investigation.

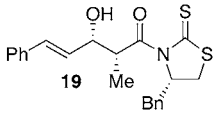
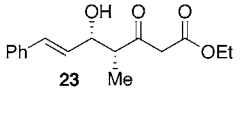
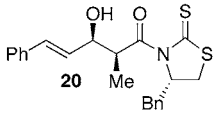
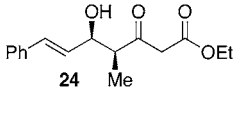
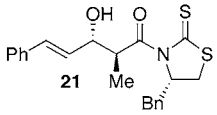
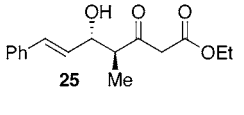
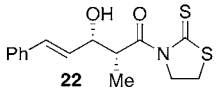
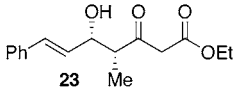
Having demonstrated the utility of the aldol/trans-acylation sequence, we chose to explore the scope of this interesting reaction. Recent studies by Evans[19] and Crimmins[20] have elevated the utility of thiazolidinethione auxiliaries as applied to propionate aldol reactions (Scheme 2). Three of the four

Scheme 2. Representative Aldol Reactions of *N*-Propionyl Thiazolidinethiones



possible diastereomeric products can now be accessed with appropriate selection of enolization conditions.[21] The catalytic asymmetric variant of this process is particularly elegant.[19b] We prepared the known cinnamaldehyde adducts of the phenylalanine-derived thiazolidinethiones (**19**−**22**) and subjected them to our reaction conditions (Table 2). Gratifyingly,

Table 2. Malonate Displacements of Thiazolidinethiones[a]

propionate aldol adduct	malonate addition product	yield (%)
 **19**	 **23**	60
 **20**	 **24**	60
 **21**	 **25**	52
 **22**	 **23**	61

[a] Conditions: potassium ethyl malonate (2 equiv), $MgCl_2$ (1 equiv), imid. (1 equiv), THF, rt, overnight.

the expected β-ketoester products (**23**−**25**) were produced, albeit in moderate yields.

Finally, as a complementary alternative to this chiral auxiliary-based approach, we also have demonstrated that

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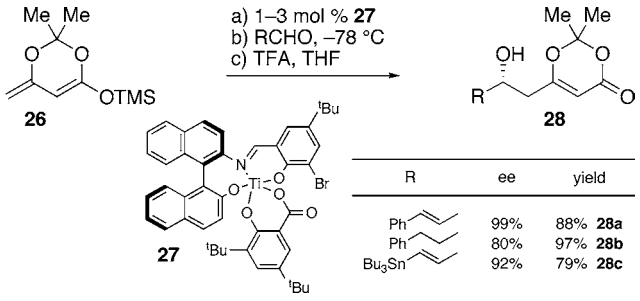
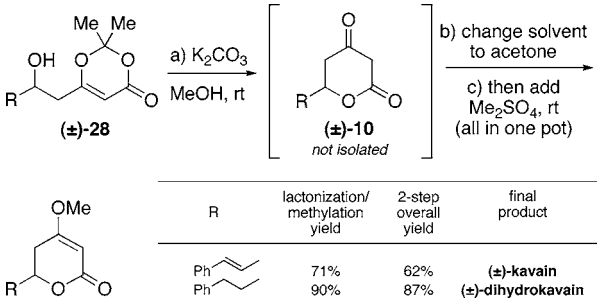
Scheme 3. Carreira's Catalytic Asymmetric Dienolate Additions to Aldehydes[a]



[a] As reported in ref 22a.

the products of the asymmetric Mukaiyama aldol reactions developed by Carreira[22] (Scheme 3) and Sato[23] can be transformed directly into the kavalactone ring system in a single pot (Scheme 4). Although we have only tested our lactonization/methylation process on racemic substrates,[24] use of the Carreira catalyst would render this an extremely efficient enantioselective route to the kavalactones.

Scheme 4. Asymmetric Catalysis-Based Synthesis of the Kavalactones



In conclusion, we have developed three simple and efficient approaches to the asymmetric synthesis of the kavalactones and have completed the first enantioselective synthesis of (+)-kavain.

Acknowledgment. This research was supported by the Petroleum Research Fund, administered by the American Chemical Society (36453-GB1), the National Science Foundation (CHE-0237658), and Williams College. We are grateful to Dr. François Béland of SiliCycle, Inc. for providing samples of functionalized silica gels, functionalized TLC plates, and analysis of tin scavenging experiments. We thank Mr. James P. Sieradzki for preliminary studies.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Although the coupling reactions proceeded more rapidly with tri-2-furylphosphine, small amounts of furyl-substituted kavalactones were observed as a result of phosphorous-to-palladium aryl migration (Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313). This problem was alleviated by the use of tris(*o*-methoxyphenyl)phosphine.

(17) The 7,8-dihydrokavalactone derivatives are available from these coupled products via selective catalytic hydrogenation (ref 10e).

(18) The tributyltin iodide byproducts of these coupling reactions could not be completely removed by chromatography using normal silica gel. However, simply stirring for 1 h with a slurry of triamine-functionalized silica gel (SiliCycle, *Si*-Triamine) succeeded in scavenging 95% of the residual tin contaminants. Chromatography with diol-functionalized silica gel (SiliCycle, *Si*-Diol) was also required to achieve clean chromatographic separation of tin-substituted aldol adduct **8c**.

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(21) The final diastereomeric possibility is accessible via the corresponding oxazolidinone: Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

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(24) Racemic **28** was prepared from **26** using $TiCl_4$ as the Lewis acid.