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 anxiolytic2 and soporific qualities. Analgesic,3 anesthetic, antifungal, antithrombotic,4 anticonvulsive,5 and muscle-relaxing6 properties also have been reported.1 The psychoactive principals are a family of 15 α-pyrene 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-
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 $\beta$-ketoester intermediates have led to the preparation of (±)-7,8-dihydrokavain (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 valve-derived N-acetyl thiazolidinethione 7 was reacted with cinnamaldehyde or dihydrocinnamaldehyde to give aldol adducts 8a–c and 8b, respectively. Similar reactions with an analogous tributyltin-substituted aldehyde led to protodeastannylated products. Use of the original Nagao tin triflate enolization conditions13a,b alleviated this problem. Although tin-based aldol reactions of this type generally give higher levels of diastereosecontrol, 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 $\beta$-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 $\delta$-hydroxy-$\beta$-ketoesters (9) is smoothly accomplished with potassium carbonate in methanol. Although it is possible to isolate and purify the polar $\beta$-keto-lactone 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

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

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**Scheme 1.** Chiral-Auxiliary-Based Synthesis of Kavalactones

<table>
<thead>
<tr>
<th>R</th>
<th>L.A.base</th>
<th>diastereomer ratio</th>
<th>major diastereomer yield</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>TiCl$_4$-Pr$_2$NEt</td>
<td>90:10</td>
<td>84%</td>
<td>8a</td>
</tr>
<tr>
<td>Ph</td>
<td>TiCl$_4$-Pr$_2$NEt</td>
<td>76:24</td>
<td>54%</td>
<td>8b</td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>SnOT$_3$-Et/MeOH-pip</td>
<td>&gt;99:1</td>
<td>85%</td>
<td>8c</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>lactonization/methylation yield</th>
<th>3-step overall yield</th>
<th>final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>87%</td>
<td>64%</td>
<td>(±)-kavain (1)</td>
</tr>
<tr>
<td>Ph</td>
<td>83%</td>
<td>40%</td>
<td>(+)-dihydrokavain (2)</td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>79%</td>
<td>54%</td>
<td>(-)-kavain (2)</td>
</tr>
</tbody>
</table>
analalogues, we have prepared vinylstannane 11 as a common advanced precursor. In several unoptimized initial experiments (Table 1), Stille couplings have with three appropriate aryl iodides provided (+)-kavain (1), (+)-5,6-dihydroxyangonin (12), and (+)-methysticin (3). 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. 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 approach. New variants of this process are 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, possible diastereomeric products can now be accessed with appropriate selection of enolization conditions. The catalytic asymmetric variant of this process is particularly elegant. 19b We have demonstrated that 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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### Table 1. Stille Couplings of Tin-Substituted Kavalactones

<table>
<thead>
<tr>
<th>Arl</th>
<th>R</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>prod.</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>BuSn(1)</td>
<td>THF</td>
<td>50</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>MeO-Ph</td>
<td>(o-MeO-Ph)</td>
<td>tol.</td>
<td>115</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>MeO-Ph</td>
<td>(o-MeO-Ph)</td>
<td>tol.</td>
<td>115</td>
<td>3</td>
<td>44</td>
</tr>
</tbody>
</table>

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

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\begin{align*}
 & \text{Scheme 2. Representative Aldol Reactions of N-Propionyl Thiazolidinethiones} \\
 & \text{13} \quad \text{then RCHO} \\
 & \text{14} \quad \text{then RCHO} \\
 & \text{15} \quad \text{then RCHO} \\
 & \text{16} \quad \text{then RCHO} \\
 & \text{17} \quad \text{RCHO} \\
 & \text{18} \quad \text{RCHO} \\
\end{align*}
\]

### Table 2. Malonate Displacements of Thiazolidinethiones

<table>
<thead>
<tr>
<th>propionate aldol adduct</th>
<th>malonate addition product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Me</td>
<td>20 Me</td>
<td>60</td>
</tr>
<tr>
<td>19 Me</td>
<td>21 Me</td>
<td>60</td>
</tr>
<tr>
<td>19 Me</td>
<td>22 Me</td>
<td>52</td>
</tr>
<tr>
<td>19 Me</td>
<td>23 Me</td>
<td>61</td>
</tr>
</tbody>
</table>

* Conditions: potassium ethyl malonate (2 equiv), MgCl₂ (1 equiv), imidazol (1 equiv), THF, rt, overnight.

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the products of the asymmetric Mukaiyama aldol reactions developed by Carreira\textsuperscript{22} (Scheme 3) and Sato\textsuperscript{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,\textsuperscript{24} use of the Carreira catalyst would render this an extremely efficient enantioselective route to 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.

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

(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. \textit{J. Am. Chem. Soc.} \textbf{1991}, \textit{113}, 6313). This problem was alleviated by the use of tris(\textit{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.


(24) Racemic 28 was prepared from 26 using TiCl\textsubscript{4} as the Lewis acid.