Total Synthesis of (*R*)-(+)-Kavain via $(MeCN)_2PdCl_2$-Catalyzed Isomerization of a *cis* Double Bond and Sonochemical Blaise Reaction

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Abstract: From the chiral source 2,3-*O*-isopropylidene-D-glyceraldehyde **2**, the natural product (*R*)-(+)-kavain **1a** was efficiently synthesized in a total yield of 25% via $(MeCN)_2PdCl_2$-catalyzed isomerization of the *cis* double bond of an olefin as the key step and sonochemical Blaise reaction. The chiral center adjacent to the *cis* double bond was retained without protection of the free allylic hydroxy during the isomerization process.

Key words: kavain, total synthesis, $(MeCN)_2PdCl_2$-catalyzed, isomerization , *cis* double bond, sonochemical Blaise reaction

(*R*)-(+)-Kavain **1a** was isolated from the kava plant *Piper methysticum* (Piperaceae) which grows widely in the south pacific islands.[1] The extracts of its root and stem are used as a folk medicine or as a ceremonial drink in this region.[2] (*R*)-(+)-Kavain **1a** and its analogues such as methysticin **1b** (Figure **1**), which exhibited anti-convulsive,[3a] muscle-relaxing,[3b] sedative[3c] and antithrombotic[4] activities, have been attracting attention in both pharmaceutical and chemical research.

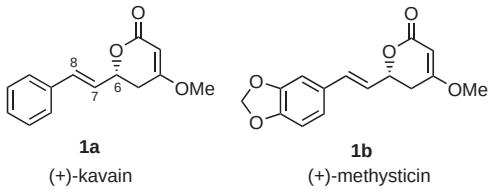

Figure 1

Several synthetic works on kavain and its analogues have been reported.[5] However, the first synthesis of (*R*)-(+)-kavain **1a** with a *trans* Δ^7 double bond adjacent to the C-6 chiral center was reported recently, by Smith and coworkers,[6] using stoichiometric chiral auxiliaries and Carreira's catalyst. In this paper, we report a more practical synthesis of (*R*)-(+)-kavain **1a** via $(MeCN)_2PdCl_2$-catalyzed isomerization of the *cis* double bond of an olefin as the key step and sonochemical Blaise reaction.[7] More interestingly, the chiral center adjacent to the *cis* double bond was retained without protection of the free allylic hydroxy during the isomerization process.

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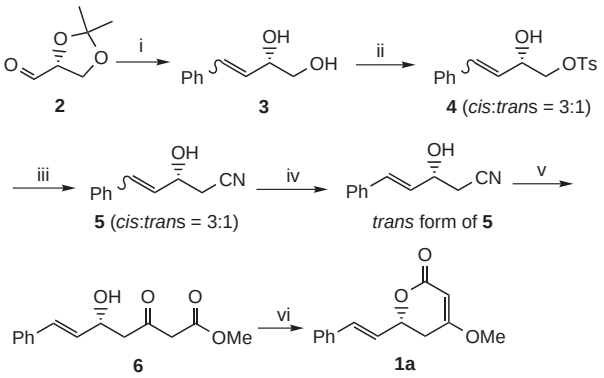
The synthesis of (*R*)-(+)-kavain **1a** is shown in Scheme 1. The chiral aldehyde **2**, obtained easily from D-mannitol on a large scale according to the literature procedure,[8] was subjected to Wittig olefination to give acetonides (80%), which underwent hydrolysis to yield diols **3** (96%). Selective tosylation of the primary hydroxyl group on the diols **3** with TsCl in anhydrous pyridine (−17 °C to r.t.) produced tosylates **4** (*cis*/*trans* = 3:1 as monitored by ^{1}H NMR spectroscopy) in 83% yield. Reaction of tosylates **4** with KCN in aqueous ethanol at room temperature gave a mixture of nitriles **5** (*cis*/*trans* = 3:1, 76%). Although the mixture of nitriles **5** could be separated easily by silica gel column chromatography to give the *cis* form {$[\alpha]_D^{21}$ –17.9 (*c* 0.98, $CHCl_3$)} and *trans* form {$[\alpha]_D^{20}$ +29 (*c* 1.44, $CHCl_3$)}, the desired *trans* form was only one-third of the total. How to transfer the *cis* form to its *trans* form is therefore crucial for this synthetic routine from the viewpoint of synthetic economy and efficiency.



Scheme 1 *Reagents and conditions:* (i) (a) $Br^-PPh_3CH_2Ph^+$, BuLi, THF, 0 °C to r.t., 2 h, 80%; (b) 2 M HCl, THF, 10 h, r.t., 96%; (ii) TsCl (1.1 equiv), anhyd pyridine (−17 °C to r.t.), 12 h, 83%; (iii) KCN (5 equiv), EtOH–H_2O (3:2), 0 °C to r.t., 24 h, 76%; (iv) $(CH_3CN)_2PdCl_2$ (10 mol%), benzene, reflux, 5 h, 91%; (v) $BrCH_2COOMe$ (5 equiv), activated zinc (10 equiv), ultrasound, THF, 5 h, 50 °C, then H_3O^+, 70%; (vi) (a) MeOH, K_2CO_3, r.t., 5 h; (b) Me_2SO_4, acetone, r.t., 12 h, 81% (two steps in one pot).

Known methods of thiophenol-mediated olefin inversion[9] and iodine-initiated olefin inversion[10] were attempted, but our substrate, the *cis* form of **5** did not react under either set of reaction conditions. Recently, Spencer and coworkers[11] reported an efficient way to convert *cis* arylalkenes to their *trans* isomers via $(MeCN)_2PdCl_2$-catalyzed isomerization in dichloromethane at room temperature.

To our delight, although substrate **5** has a free hydroxy at the chiral center and a cyano group, Spencers' conditions completely converted the *cis* form of **5** to its *trans* form {$[\alpha]_D^{20}$ +28.7 (*c* 1.29, $CHCl_3$)} without racemizing the chiral center at C-6, but it took a whole week to complete the isomerization reaction at room temperature. An effort was thus made to modify the isomerization conditions (Table 1) aiming to speed up the reaction. The optimum reaction conditions were employed benzene as the solvent at reflux; after a reaction time of nine hours the *cis* form of **5** was completely transformed to its *trans* form in a yield of 80%, and the chirality at C-6 was retained as judged by its optical rotation {$[\alpha]_D^{20}$ +28.8 (*c* 1.37, $CHCl_3$)}. Under these optimized isomerization conditions (Table 1, entry 8), a mixture of nitriles **5** (*cis*/ *trans* = 3:1) was conveniently converted to the pure *trans* form of **5** in a high yield of 91%, without having to separate the isomers.[12]

Table 1 Optimization of the Solvents and Temperatures

Entry	Solvents	Temperature	Time (h)	*cis*/*trans*	Yield[a]
1	CH_2Cl_2	r.t.	24	42:58[b]	–
2	CH_2Cl_2	reflux	24	20:80[b]	–
3	$CHCl_3$	r.t.	24	49:51[b]	–
4	$CHCl_3$	reflux	8	0:100[c]	41%
5	THF	r.t.	24	47:53[b]	–
6	THF	reflux	24	25:75[b]	–
7	Benzene	r.t.	24	62:38[b]	–
8	Benzene	reflux	9	0:100[c]	80%

[a] The isolated yield.
[b] Checked by HPLC.
[c] Monitored by TLC

With the pure *trans* form of **5** in hand, the next key step was an ultrasound-assisted Blaise reaction to prepare the important intermediate **6**. The Blaise reaction has been neglected for a long time in organic synthesis due to its shortcomings such as low yield, narrow scope, and the competing side reactions. Fortunately, several research groups[13] recently reported that ultrasound could improve the yield of the Blaise reaction dramatically. By simply using Lee's conditions[13a] [commercial zinc powder containing ZnO (10%) and $BrCH_2COOEt$ (1.0 equiv)], the majority of the *trans* form of **5** did not react, and only a small amount of desired product was obtained after work-up. Optimized reaction conditions[14] based on Uang's conditions[13b] were thus adopted to afford, the desired compound **6** in 70% yield, as pale yellow oil {$[\alpha]_D^{20}$ +19.4 (*c* 1.15, $CHCl_3$), lit.[15] $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$)}. In practice, $BrCH_2COOMe$ was used in place of $BrCH_2COOEt$ since the latter had a R_f value very close to that of the *trans* form of **5** and the desired product **6**, which made monitoring the reaction and the reaction work-up more difficult. Finally, according to the literature procedure,[6] compound **6** was then converted to the target molecule **1a**[16] in 81% yield by a two-step one-pot reaction. The ^{1}H NMR data,[17] melting point, as well as optical rotation[18] of (*R*)-(+)-kavain **1a** were very close to those of the natural product.

In conclusion, a chiral approach for the synthesis of (*R*)-(+)-kavain **1a**, giving an overall yield of 25%, was complete in eight steps from 2,3-*O*-isopropylidene-D-glyceraldehyde **2**. The $(MeCN)_2PdCl_2$-catalyzed isomerization of the *cis* form of nitriles **5** to a single *trans* form of **5**, and sonochemical Blaise reaction were the key merits of this synthetic approach. This approach offers an efficient way to synthesize optically active kava derivatives with a Δ^7 double bond. This is also the first research work to demonstrate the absolute configuration of (*R*)-(+)-kavain **1a** by total synthesis from a chiral source.

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(12) Isomerization of the *cis* double bond: A solution of nitriles **5** (145 mg, 0.84 mmol) and bis(acetonitrile)palladium(II) chlorine (17.5 mg, 0.07 mmol) in benzene (5 mL) was stirred at reflux for ca. 5 h until the *cis* form of **5** was fully consumed (monitored by TLC). After removal of the solvent in vacuo, the residue was dissolved in EtOAc (50 mL) and

filtered to remove the insoluble solid. The EtOAc soluble fraction was then purified by flash column chromatography on silica gel (EtOAc–petroleum ether, 1:4) to afford the desired pure *trans* form of **5** (132 mg, 91%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.25 (br, 1 H), 2.63–2.69 (dd, *J* = 6.2, 16.7 Hz, 1 H), 2.69–2.75 (dd, *J* = 5.5, 16.7 Hz, 1 H), 4.652 (m, 1 H), 6.25 (dd, *J* = 6.7, 15.9 Hz, 1 H), 6.74 (d, *J* = 15.9 Hz, 1 H), 7.27–7.40 (m, 5 H); EI-MS: *m*/*z* =173 (M^+).

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(14) Sonochemical reactions: A mixture of the *trans* form of **5** (205 mg, 1.18 mmol) and activated Zn (0.80 g, 12.3 mmol) in anhyd THF (10 mL) was subjected to ultrasonic irradiation at 50 °C for 10 min and then methyl bromoacetate (0.70 ml, 5.86 mmol) was added dropwise under a nitrogen atmosphere. The resultant mixture was irradiated under the same conditions for another 5 h, then acidified with 2 M HCl (to pH 3), stirred at r.t. for 10 min, and diluted with EtOAc (60 mL). The organic phase was washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), and then dried over anhyd Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc, 10:3) to afford the desired product **6** (206 mg, 70%), as a pale yellow oil. $[\alpha]_D^{20}$ +19.4 (*c* 1.15, $CHCl_3$), {lit.[15] $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$)}. ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.88 (d, *J* = 6.1 Hz, 2 H), 3.53 (s, 2 H), 3.75 (s, 3 H), 4.79 (m, 1 H), 6.22 (dd, *J* = 6.2, 15.9 Hz, 1 H), 6.67 (dd, *J* = 1.1, 15.9 Hz, 1 H), 7.25–7.39 (m, 5 H). EIMS: *m*/*z* = 248 (M^+).

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(16) (*R*)-(+)-Kavain **1a**: white crystals; mp 115–116 °C (lit.[18] 105–106 °C); $[\alpha]_D^{20}$ +110.2 (*c* 1.1, EtOH), {lit.[18] $[\alpha]_D^{20}$ +105 (*c* 1, EtOH)}. IR (KBr): 1704.8, 1623.8, 1392.4, 1247.7, 1230.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58–2.53 (dd, *J* = 4.4, 16.9 Hz), 2.71–2.64 (dd, *J* = 10.7, 16.9 Hz), 3.77 (s, 3 H), 5.07 (m, 1 H), 5.20 (s, 1 H), 6.29–6.24 (dd, *J* = 6.2, 16.1 Hz), 6.76 (d, *J* = 16.1 Hz), 7.41–7.26 (m, 5 H). EI-MS: *m*/*z* = 230 (M^+). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.33; H, 6.12..

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