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Metathesis-based synthesis of 3-methoxy α,β-unsaturated lactones: total synthesis of (*R*)-kavain and of the C1–C6 fragment of jerangolid D

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Abstract

The total synthesis of (*R*)-kavain and of the C1–C6 fragment of jerangolid D has been achieved in nine and seven steps, respectively, from commercially available dimethyl D-malate. A metathesis reaction of vinyl ethers and a sulfoxide-modified Julia olefination have been employed as the key steps.
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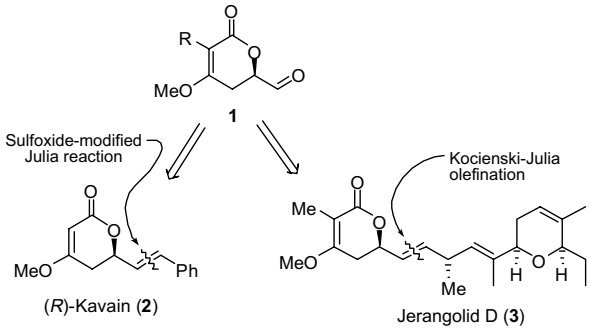
Keywords: Kavain; Jerangolid D; Metathesis; Julia olefination; Sulfoxide-modified Julia olefination

A wide variety of natural products contain a lactone core in their structures. In many cases, these compounds display antitumor activities and the presence of an *endo*- or *exo*-cyclic α,β-unsaturated lactone[1] typically confers to the molecule some antineoplastic activities (among others).[2]

As a part of our ongoing research program toward the efficient synthesis of natural products possessing anticancer and antifungal properties, we became interested in the development of novel approaches for the assembly of various lactone-bearing subunits. Our initial efforts in this field culminated recently in the establishment of two novel strategies leading to *exo*-methylenelactones. More recently, the synthesis of 3-methoxy α,β-unsaturated lactones of the general structure **1** was targeted.[3]

We became attracted by this particular class of lactones because of their presence in various natural products, such as kavain **2** and jerangolid D **3** (Scheme 1).

Kavain **2** belongs to the group of styryl lactone-derivatives and it can be found in the Kava plant (*Piper methysticum*). The Kava plant has a long and colorful history spanning several thousand years.[4] 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 mostly reported for its purported anxiolytic[5] and soporific qualities. Analgesic,[6] anesthetic, antifungal, antithrombotic,[7] anticonvulsive,[8] and muscle-relaxing[9] properties have also been reported.[4]



Scheme 1. Retrosynthesis of kavain (**2**) and jerangolid D (**3**).

Jerangolid D[10] is a secondary metabolite produced by the myxobacterium *Sorangium cellulosum* (strain So ce 307), a myxobacterium isolated in 1987 in the soil of Jerusalem. In vitro tests suggested that jerangolid D might be a

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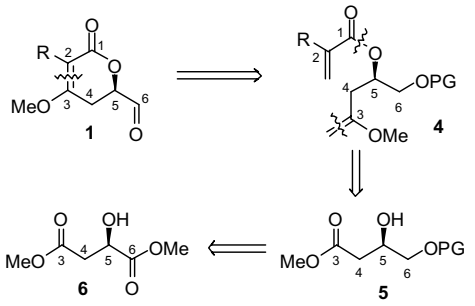
potentially useful antifungal agent, since it exhibits interesting activities against the developing cells of *Hansenula anomala* and *Mucor hiemalis* (~70 ng/mL); *Pichia membranaefaciens*, *Debaryomyces hansenii*, and *Trichosporon terrestre* (0.1–0.4 μg/mL); and *Trichoderma hamata*, *Botritis cinerea*, and *Candida albicans* (4–7 μg/mL). The mechanism of its action is believed to be similar to that of ambruticin,[11] another well-known myxobacterium isolate, for which the mode of action is still unclear.

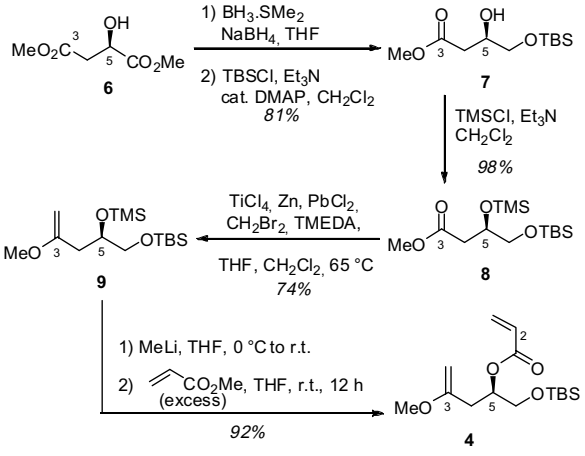
Our retrosynthesis of lactone **1** was designed to use the metathesis reaction as a key step (Scheme 2). As a consequence, lactone **1** was disconnected at the C2–C3 positions, leading to acrylate **4**. The required vinyl ether function present in **4** could then be prepared from ester **5** via titanium alkylidenation of the C3 carbonyl group.

The synthesis began with the selective reduction of the C6 ester of (*R*)-dimethyl malate **6** to the corresponding primary alcohol,[12] followed by the transformation of the resulting C6 alcohol[13] into a TBS ether (Scheme 3). The remaining C5 alcohol was masked as a TMS ether and the resulting compound **8** was reacted with titanium alkylidene reagents. In our hands, Rainer's modification of the Takai–Utimoto reaction[14] gave the best results,[15] affording the desired enol ether **9** in 74% yield.

Finally, a selective one pot TMS group removal/base mediated esterification of the resulting C5 alkoxide accomplished the synthesis of the metathesis precursor **4**.



Scheme 2. Retrosynthesis of lactone **1**.



Scheme 3. Synthesis of metathesis precursor **4**.

Having established an easy access to the desired intermediate **4**, our first key step, the Grubbs' metathesis, could be challenged. From the literature precedents, it is known that the metathesis reaction of electron-rich olefins,[16] in particular enol ethers, is rather difficult and requires harsh conditions, for example, prolonged reaction times, high temperatures and high catalyst loading. For this reason, the use of Schrock's more reactive, though more sensitive, catalyst[17] is generally preferred.

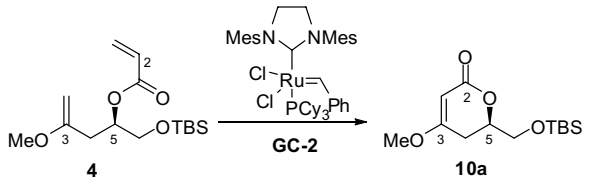
The sensitivity of the Schrock carbene prompted us to perform our reactions using the 2nd generation Grubbs' catalyst (**GC-2**) in a non-polar solvent.[16a] Thus, ester **4** was treated with **GC-2** in deuterated toluene and the influence of the reaction conditions on the conversion was monitored (Table 1).

It was observed that the metathesis reaction proceeded somewhat better at 50 °C (Table 1, entry 1) than at higher temperatures. In all cases, the catalyst was fully decomposed under the reaction conditions within 4–7 h. Therefore, constant addition of the catalyst over a period of 66 h (5 mol % of **GC-2** every 6 h) was performed. The starting material **4** gradually disappeared, yielding the desired lactone **10** in 88% yield (Table 1, entry 5). Unfortunately, up to 55 mol % of **GC-2** was consumed in this single experiment.

These results, though rather encouraging, could not be reconciled with our idea of a useful synthetic transformation. It was suggested that the low reactivity of **4** could be due, among other potential problems, to its difficulty in adopting an (*S*)-*cis* conformation and hence, enabling the two alkene termini to reach a proper distance for the reaction to occur.[18] To overcome this problem and to reduce the catalyst loading, it was decided to use the modified metathesis precursor **11** (Fig. 1).[19]

The synthesis of **11** began with the monoprotected diol **7**, which was transformed into acetals **12a** and **12b** via

Table 1
Metathesis reaction of the precursor **4**



Entry	Conditions	Conversion[a] (%)	Yield[a] (%)
1	5 mol %, toluene-d_8, 12 h, 50 °C	20	20
2[b]	5 mol %, toluene-d_8, 12 h, 60 °C	18	18
3[b]	5 mol %, toluene-d_8, 12 h, 70 °C	10	10
4[c]	5 mol %, toluene-d_8, 12 h, 80 °C	5	5
5[d]	55 mol %, toluene-d_8, 66 h, 50 °C	91	88[e]
6	10 mol %, toluene-d_8, 72 h, rt	8	<5

[a] Based on ^{1}H NMR spectra.
[b] Conversion stopped after 5–7 h.
[c] Conversion stopped after 4 h.
[d] 5 mol % of **GC-2** was added every 6 h.
[e] Isolated yield.

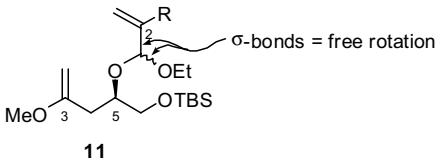
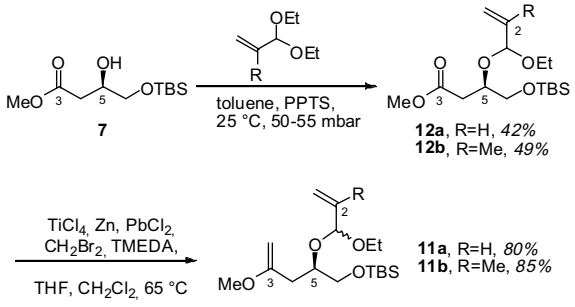


Fig. 1. Alternative metathesis precursor **11**.

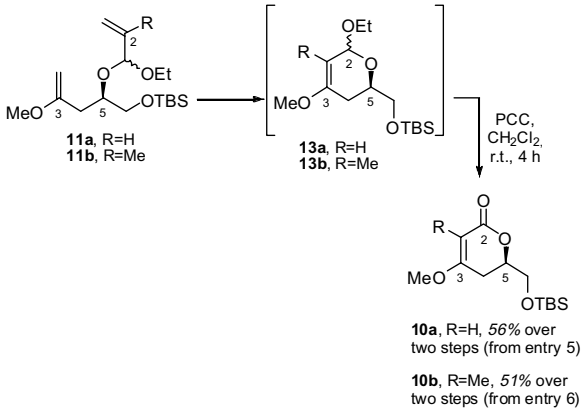
PPTS-catalyzed *trans*-acylation of acrolein diethyl acetal and methacrolein diethyl acetal,[20] respectively (Scheme 4). Acetals **12a** and **12b** were then submitted to the Takai–Utimoto olefination yielding the desired precursors **11a** and **11b** in 80% and 85% yields.

With the desired substrates in hand, the crucial ring closing metathesis could be tested again (Table 2). To our surprise, no important changes in the reactivity of **11a**, as compared to substrate **4**, were observed (Table 2, entries 1–3).



Scheme 4. Synthesis of precursor **11**.

Table 2
RCM reaction of **11**



Entry	R	**GC-2** loading (mol %)	Conditions	Yield[a] (%)
1	H	20[b]	Benzene, 50 °C, 4 h	21
2	H	30[b]	Benzene, 70 °C, 6 h	26
3	H	30[b]	Toluene, 50 °C, 6 h	21
4	H	50	Benzene, rt, 24 h	39
5	H	10	Benzene, rt, 72 h	93
6	Me	10	Benzene rt, 84 h	95

[a] Based on the ^{1}H NMR spectra.
[b] 10 mol % of **GC-2** was added every 2 h.

The reaction proceeded with a slightly higher conversion, but the decomposition of the catalyst under the reaction conditions was still significant.

To avoid this decomposition, the reaction was attempted at rt. in the presence of 50 mol % of **GC-2** (Table 2, entry 4). After 24 h, a 39% conversion of **11a** to cyclic acetal **13a** was reached. Allowing the cyclization to proceed longer led to improved conversions.

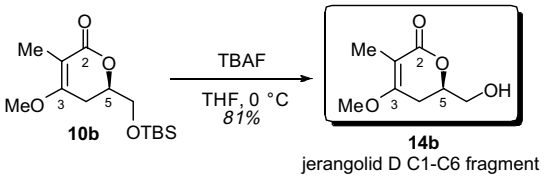
Under the optimized conditions, only 10 mol % of **GC-2** was required to fully transform **11** to **13** (Table 2, entries 5 and 6).[21] The oxidation of acetals **13** with PCC then afforded the desired lactones **10a** and **10b** in 56% and 51% yields, respectively, over two steps.

Removal of the TBS group of **10b** furnished alcohol **14b**, the left-hand fragment of jerangolid D (**3**), in 81% yield (Scheme 5).[22]

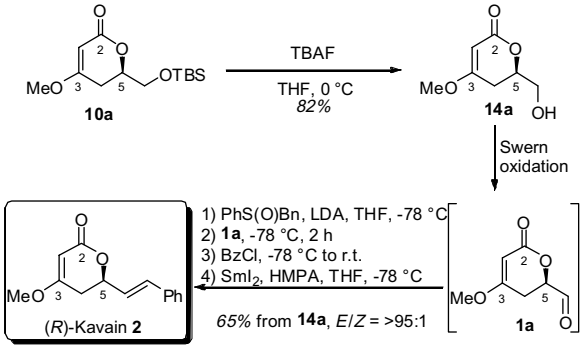
The C2 desmethyl lactone **10a** was also deprotected (82% yield) and the resulting alcohol **14a** was then used in the synthesis of (*R*)-kavain[23] **2** (Scheme 6). Thus, alcohol **14a** was transformed into aldehyde **1a** via Swern oxidation. Lactone **1a** was immediately reacted with benzyl phenyl sulfoxide under our sulfoxide-Julia olefination conditions[24] (Scheme 6), affording (*R*)-kavain **2** in 65% yield and with an excellent *E*/*Z* selectivity.

The necessity to employ the sulfoxide version of the Julia olefination reaction in this ultimate transformation had been discussed previously.[24c]

In summary, the penultimate precursor of the left-hand fragment of jerangolid D, alcohol **14b**, was prepared in seven steps and 16% overall yield from commercially available dimethyl D-malate **6**. Similarly, (*R*)-kavain[25] **2** was



Scheme 5. Synthesis of the C1–C6 fragment of jerangolid D.



Scheme 6. Total synthesis of (*R*)-kavain **2**.

synthesized in nine steps and in 7.7% overall yield. To achieve these goals, a simple approach toward 3-methoxy α,β-unsaturated lactones of the general structure **1**, based upon the metathesis reaction of electron-rich alkenes, coupled with our sulfoxide Julia olefination procedure was employed.

Acknowledgments

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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.2007.12.113.

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25. *Experimental data for* (*R*)-(+)-*kavain* **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.55 (dd, 1H, $J = 17.1$ Hz, $J = 4.6$ Hz), 2.68 (dd, 1H, $J = 17.1$ Hz, $J = 10.7$ Hz), 3.77 (s, 3H), 5.06–5.09 (m, 1H), 5.20 (s, 1H), 6.27 (dd, 1H, $J = 16.1$ Hz, $J = 6.3$ Hz), 6.73 (d, 1H, $J = 16.0$ Hz), 7.29–7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 33.8, 56.5, 76.5, 91.1, 125.8, 133.2, 167.2, 127.0, 128.8, 129.2, 136.3, 172.6. Mp = 113–114 °C; lit. 112–113 °C.[23a] IR (KBr) ν (cm^{-1}): 3063, 2967, 1703, 1626, 1394, 1248, 1233, 1063, 1024, 971, 747, 693. $[\alpha]_D^{20}$ +120.3 (*c* 1.02, EtOH); lit. $[\alpha]_D^{25}$ +124.3 (*c* 1.00, EtOH).[23a]