



## Enantioselective Synthesis of (+)- and (-)-Dihydrokawain.

Claude Spino\*, Nigel Mayes, and Hélène Desfossés

Université de Sherbrooke, Département de Chimie, Sherbrooke, Qc, Canada, J1K 2R1

Subramaniam Sotheeswaran

University of the South Pacific, School of Pure and Applied Sciences, Suva, Fiji

**Abstract:** The first asymmetric synthesis of (+)- and (-)-Dihydrokawain, an  $\alpha$ -dihydropyrone isolated from the roots of *Piper myhisticum*, is reported. (+)-Dihydrokawain is the natural product and is of *S*-configuration.

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(+)-Dihydrokawain **1** is a member of a small class of  $\alpha$ -pyrones and 5,6-dihydro- $\alpha$ -pyrones found in the roots, stem, and rhizomes of the tropical plant *Piper myhisticum* growing in the South Pacific and, in particular, on the islands of Fiji, Vanuatu, and Hawaii.<sup>1</sup> The beverage prepared from the powdered roots or stem has been an integral part of traditional ceremonies in some Pacific islands but has been cause of concern in Northern Australia due, in part, to the narcotic effect of (+)-dihydrokawain.<sup>1</sup> This, and other kava constituents such as methysticin **2** and yangonin **3**, have attracted considerable interest from the pharmaceutical industry because of their sedative, anti-convulsive, anaesthetic, and antifungal properties (Figure 1).<sup>1,2</sup>

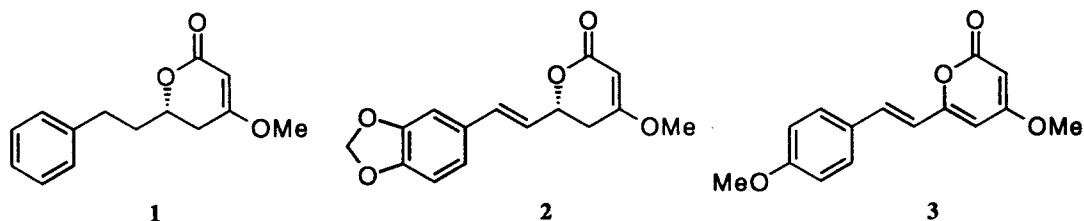
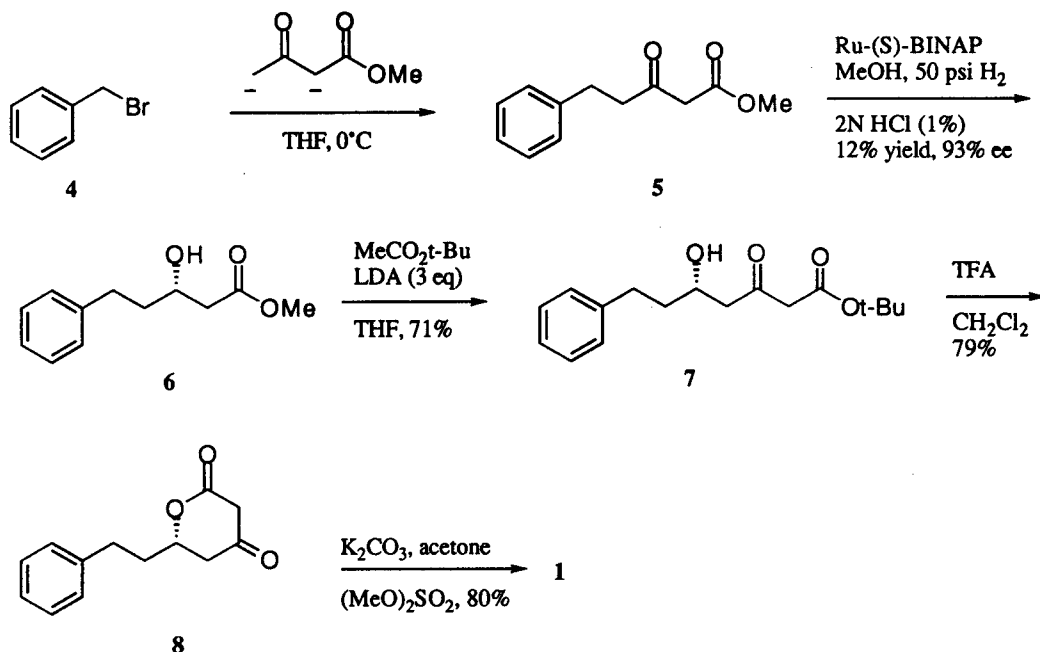


Figure 1

Though several syntheses of dihydrokawain<sup>3</sup> and other Kava lactones<sup>4</sup> have been reported, none were easily amenable to an asymmetric version except perhaps for the synthesis by Gallagher who could have used a chiral phenethyloxiran as starting material.<sup>3c</sup> We describe here the first asymmetric synthesis of (+)-dihydrokawain and a formal synthesis of its unnatural enantiomer (-)-dihydrokawain in five steps from easily available starting materials via the catalytic hydrogenation of  $\beta$ -keto ester **5** with a chiral ruthenium catalyst.

Our synthesis starts with the alkylation of the dianion of methyl acetoacetate with benzyl bromide in THF at 0°C to afford a distillable  $\beta$ -keto ester **5** in 82% yield (Scheme 1).<sup>5</sup> Initial attempts at the asymmetric hydrogenation of **5** failed to give any alcohol under variations of the Noyori's Ru-(S)-BINAP system

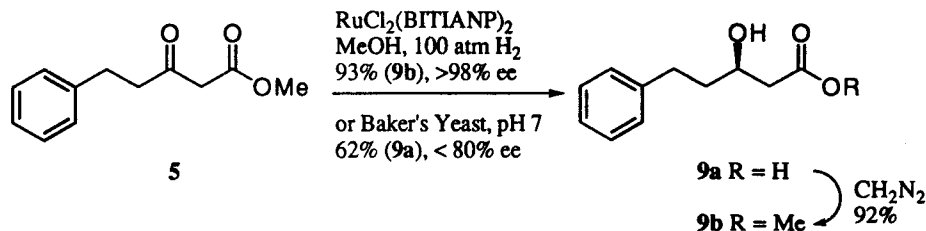
generated from polymeric  $[\text{RuCl}_2(\text{cyclooctadiene})]_n$ .<sup>6,7</sup> Eventually, hydrogenations were carried out in methanol under 4 atm of hydrogen but trace amount of con. HCl was necessary to obtain any hydrogenation product at all. Low temperatures gave no product while more forcing conditions (24h, 70°C, 50 psi  $\text{H}_2$ ) resulted in a 12%-25% of the (-)-(S)- $\beta$ -hydroxy ester **6** ( $[\alpha]_D = -2.6$ ,  $c = 2.71$ ,  $\text{CH}_2\text{Cl}_2$ ) along with approximately 70% yield of 4-phenylbutan-2-one resulting from ester cleavage and decarboxylation. The  $\beta$ -hydroxyester **6** was thus obtained in 93% ee (vide infra). We became aware that the triethylamine used in the preparation of the Ru-(S)-BINAP catalyst could adversely affect the yield and rate of the hydrogenation but not the enantioselectivity.<sup>8</sup> We thus prepared the complex Ru-(+)-BITIANP<sup>9</sup> under Noyori's alternate conditions,<sup>8</sup> and mixed it with  $\beta$ -keto ester **5** under a hydrogen pressure of 100 atm in methanol at room temperature. A 93% yield of (+)-(R)- $\beta$ -hydroxy ester **9b** ( $[\alpha]_D = +2.7$ ,  $c = 2.89$ ,  $\text{CH}_2\text{Cl}_2$ ) in greater than 98% ee (vide infra) was obtained using this methodology. This compound was identical in all respect to **6** with the exception of the sign of rotation of the plane polarized light. Since BITIANP is available in either enantiomerically pure form,<sup>9</sup> the same results can be extrapolated to the natural enantiomeric compound **6**, and the latter was used to complete the synthesis.



Scheme 1

Alternatively,  $\beta$ -keto ester **5** could be enzymatically reduced and hydrolysed with Baker's yeast to the enantiomeric (+)-(R)- $\beta$ -hydroxy acid **9a** in 62% yield (Scheme 2) and approximately 80% ee (vide infra).<sup>10</sup> The acid could be converted with diazomethane to the ester **9b** ( $[\alpha]_D = +1.22$ ,  $c = 0.98$ ,  $\text{CH}_2\text{Cl}_2$ ) which proved

identical in all respect to compound **6** except for the sign and magnitude of rotation of the plane polarised light.



Scheme 2

The chiral  $\beta$ -hydroxy esters were transformed into their corresponding Mosher's acid derivative to verify their enantiomeric purity (Figure 2). Chiral HPLC techniques<sup>11</sup> could not resolve adequately the enantiomers **6** and **9b** to obtain reliable ratios and the esters (*S,R*)-**10a** and (*R,R*)-**10b** (not shown) could not be separated neither by GC nor HPLC. In the case of the derivative produced from **6** obtained by the Ru-(*S*)-BINAP catalysed hydrogenation, the <sup>1</sup>H NMR and the <sup>19</sup>F NMR indicated a 30:1 ratio of the two diastereomers **10a** and **10b** giving approximately 93% *ee*. The expected "*S*" stereochemistry of the reduction product **6** was confirmed using the steric model of Mosher and Dale on esters **10**.<sup>12</sup> According to this model, the fluorine signal of derivatives of "*R,S*" or "*S,R*" absolute configuration generally appear at higher field than the corresponding "*R,R*" or "*S,S*" derivatives. In our case, the largest integration of the two observed resonances in the fluorine NMR was upfield (-71.56 ppm) from the lowest intensity peak (-71.43). Since the Mosher's acid used was of *R* configuration,<sup>13</sup> hydroxy ester **6** was identified as having the "*S*" absolute configuration. This configuration was shown to be the natural one after completion of the synthesis.

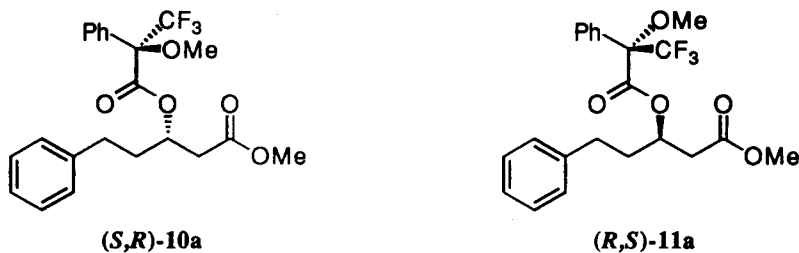


Figure 2

Compound **9b**, produced using the Ru-(+)-BITIANP catalyst, was converted to Mosher's ester (*R,S*)-**11a** via the *S*-Mosher's acid<sup>13</sup> in dichloromethane with dimethylaminopyridine and dicyclohexylcarbodiimide (Figure 2). We could not detect the other diastereomer (*S,R*)-**11b** in the proton NMR spectra meaning that we obtained greater than 98% *ee* for the hydrogenation product **9b**. Finally, compound **9b** produced via the enzymatic reduction was judged to be only approximately 80% *ee* as determined from chiral HPLC. This ratio is only approximate since the resolution of the enantiomers by chiral HPLC was only partial as mentioned

earlier, but in any case, the asymmetric induction by the yeast was evidently not as good as that provided by the asymmetric hydrogenation.

The chiral hydroxy ester **6** was then converted to the  $\beta$ -diketone **7** via a Claisen condensation with the lithium enolate of *t*-butyl acetate (3 eq) in 71% yield, followed by acid hydrolysis and lactonisation to **8** with trifluoroacetic acid in 79% yield.<sup>14</sup> The lactone was recrystallized from a mixture of ether/hexanes (m.p. 124°C;  $[\alpha]_D^{25} = +28.9$ ,  $c = 3.99$ ,  $\text{CH}_2\text{Cl}_2$ ). The synthesis was completed by treating lactone **8** with dimethyl sulfate in acetone in the presence of potassium carbonate. An isolated yield of 80% of the crystalline (+)-dihydrokawain was obtained (recrystallized from ether/hexanes, m.p. 56°C;  $[\alpha]_D^{25} = +25.7$  (MeOH,  $c = 0.6$ ); lit. m.p. 60°C,  $[\alpha]_D^{25} = +31$  (MeOH,  $c = \text{not reported}$ )).

In conclusion, we have successfully carried out the first asymmetric synthesis of (+)-dihydrokawain and a formal synthesis of its enantiomer. This is also the first confirmation of the absolute stereochemistry of a kava lactone by total synthesis.<sup>15</sup> This procedure is being applied to the synthesis of additional kava lactones such as kawain, methysticin, and others, and will be reported in due course.

**Acknowledgement:** We are grateful to Prof. F. Sannicolò and his co-workers for supplying a preparative sample of (+)-BITIANP. We thank the Natural Sciences and Engineering Research Council of Canada, the University of Victoria, the University of Sherbrooke, and BioMéga/Boehringer Ingelheim for financial support.

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(Received in USA 21 June 1996; revised 12 July 1996; accepted 15 July 1996)