# A Total Synthesis of (+)- and (–)-Dihydrokavain with a Sonochemical Blaise Reaction as the Key Step

**Fang-Dao Wang[a] and Jian-Min Yue*[a]**

**Keywords:** Dihydroxykavain / Mitsunobu reaction / Natural products / Sonochemistry / Total synthesis

Starting from 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**) as chiral material, the naturally occurring (*S*)-(+)-dihydrokavain (**1a**) was synthesized by a procedure that involves a sonochemical Blaise reaction as the key step. The absolute configuration of (*S*)-(+)-dihydrokavain (**1a**) is demonstrated for the first time by total synthesis from a chiral source. Its opposite enantiomer, (*R*)-(–)-dihydrokavain (**1b**), was also synthesized after inversion of the chiral center in a Mitsunobu reaction.


## Introduction

(*S*)-(+)-dihydrokavain (**1a**), isolated from the kava plant (*Piper methysticum*, a Polynesian shrub of the *Piperaceae* family), has been demonstrated to be an inhibitor of TNF-α formation and could be useful for the treatment of TNF-α related diseases.[1] The extract of the roots and stems of the plant *P. methysticum* are utilized as a folklore medicine and as the major ingredient in the formulation of a ceremonial beverage in the South Pacific.[2] Some other structurally closely related chemical constituents of the kava plant, such as kavain (**1c**), methysticin (**1d**), and dihydrokavain-5-ol (**1e**),[3] also display significant biological activities, including sedative, anticonvulsive, anaesthetic, and antifungal properties[4] (Figure 1).

Intrigued by the important biological activities of (+)-dihydrokavain (**1a**), a number of synthetic procedures have been reported. For example, Spino's method[5] is carried out at a high pressure of 100 atm in methanol in the presence of a catalytic chiral ligand. Baiker's synthetic route[6] gives only a relatively low *ee* in the presence of chirally modified metal catalysts. Smith and coworkers[7] have recently reported highly efficient and elegant pathways to synthesize (+)-dihydrokavain (**1a**) asymmetrically in the presence of stoichiometric chiral auxiliaries and Carreira's catalyst. Other[8] syntheses of dihydrokavain only gave the racemates. In this paper, we describe a practicable way to synthesize (+)- and (–)-dihydrokavain, in which D-mannitol is used to produce the vital chiral source 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**).[9] The naturally occurring (*S*)-(+)-dihydrokavain (**1a**) was synthesized by a procedure that involves a sonochemical Blaise reaction[10] as the key step. Its opposite enantiomer, (*R*)-(–)-dihydrokavain (**1b**), was also synthesized, and the inversion of the chiral center of **5a** by a Mitsunobu reaction was the key step.

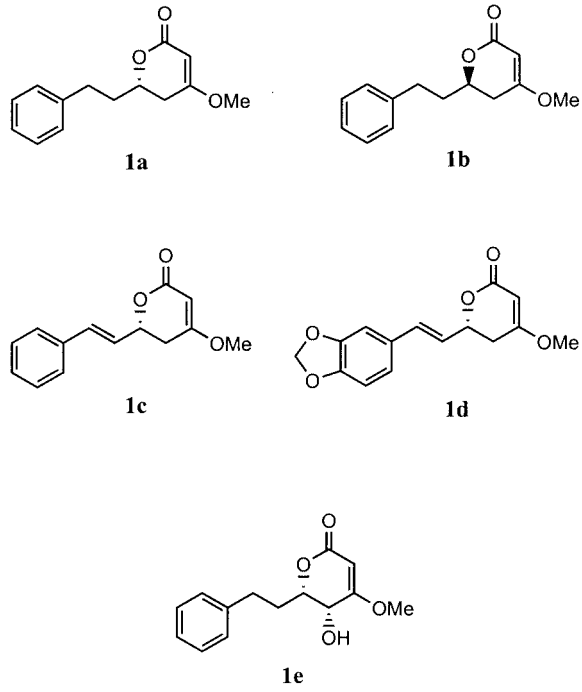
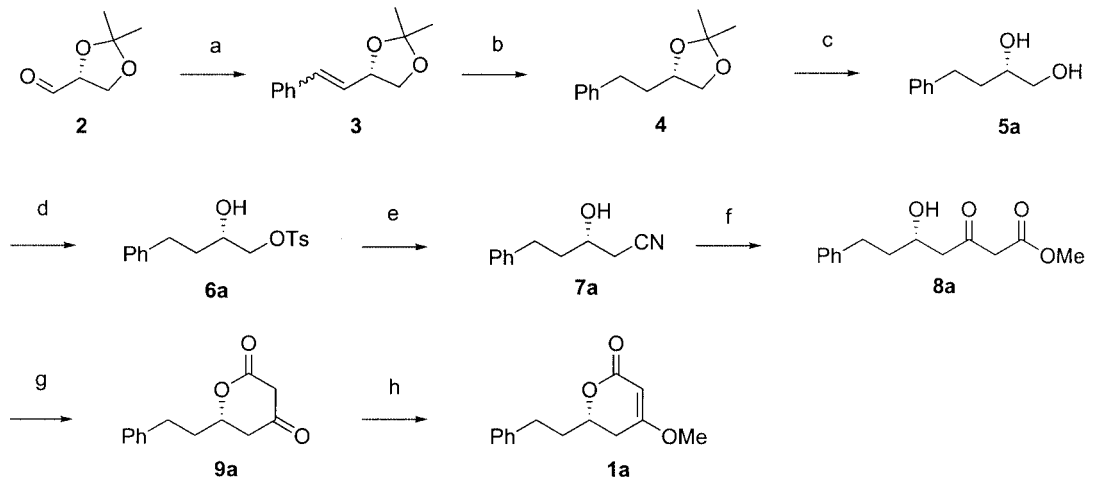



Figure 1. Important kavain derivatives.

## Results and Discussion

The synthesis of (+)-dihydrokavain (**1a**) is shown in Scheme 1. The chiral aldehyde **2**, obtained easily from D-mannitol on a large scale, was subjected to a Wittig reaction to give compound **3** in a yield of 80%. Hydrogenation of

[a] State Key Laboratory of Drug Research, Institute of Materia Medica, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences,
555 Zuchongzhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, P. R. China
Fax: +86-21-50806718
E-mail: jmyue@mail.shcnc.ac.cn




Scheme 1. Conditions, reagents and yields: (a) $[PhCH_2Ph_3P]Br$ (1.0 equiv.), *n*BuLi (1.0 equiv.), THF, 0 °C, 2 h, 80%; (b) $H_2$, 10% Pd-C, MeOH, room temp., 8 h, 98%; (c) 2 M HCl, MeOH, 1 h, room temp., 97%; (d) TsCl (1.1 equiv.), dry pyridine, ice-salt bath (–15 °C), 12 h, 75%; (e) KCN (1.5 equiv.), room temp., 12 h, 89%; (f) $BrCH_2COOMe$ (5 equiv.), activated zinc (10 equiv.), ultrasound, THF, 5 h, 50 °C, 69%; (g) Catalytic amount of *p*-toluenesulfonic acid, $CH_2Cl_2$, room temp., 2 h, 84%; (h) $Me_2SO_4$ (2 equiv.), $K_2CO_3$ (2 equiv.), acetone, room temp., 12 h, 86%.

compound **3** over 10% Pd/C gave compound **4** in a yield of 98%, and hydrolysis of the acetonide **4** then afforded diol **5a** in 97% yield. Selective tosylation of the primary hydroxyl group of **5a** with TsCl in dry pyridine (cooled in an ice-salt bath) produced tosylate **6a** in 75% yield; a minor tosylate at the secondary hydroxyl group of **5a** was also obtained. Reaction of tosylate **6a** with KCN in a mixture of EtOH and $H_2O$ (3:2) at room temperature gave the nitrile **7a** in a yield of 89%. With the nitrile **7a** at hand, the subsequent Blaise reaction is the key step in the whole synthesis. Irrespective of whether nitrile **7a** or **7a** protected with TMSCl[11] was used, stirring and refluxing the starting materials in THF in the presence of activated Zn powder[12] under a nitrogen atmosphere gave no compound **8a** after quenching the reaction, and the reaction materials **7a** or protected **7a** were also totally lost.

It has been reported that the use of ultrasound can improve the yield of the Blaise reaction,[13] but the reaction conditions in the literature were not perfectly suitable for our substrate and gave a relatively low yield of 38% (entry 1 in Table 1). We therefore optimized the reaction conditions, including the molar ratio of reagents, reaction time, temperature and type of zinc (activated or commercial; Table 1). The reaction conditions of entry 3 gave good yield of compound **8a**. In our experiment, $BrCH_2COOMe$ replaced $BrCH_2COOEt$[13] since the latter has a very similar $R_f$ value to that of nitrile **7a** in TLC, and this made monitoring the reaction more difficult.

δ-Hydroxy-β-oxo ester **8a** was then converted into lactone **9a** in high yield by treatment with a catalytic amount of *p*-toluenesulfonic acid in $CH_2Cl_2$ at room temperature. Finally, the target molecule **1a** was obtained by treating lactone **9a** with dimethyl sulfate in acetone in the presence of potassium carbonate.[5] The $^1H$ and $^{13}C$ NMR, IR, and EI mass spectroscopic data are identical to those of the natural product.

Table 1. Optimizing the reaction conditions (from **7a** to **8a**).

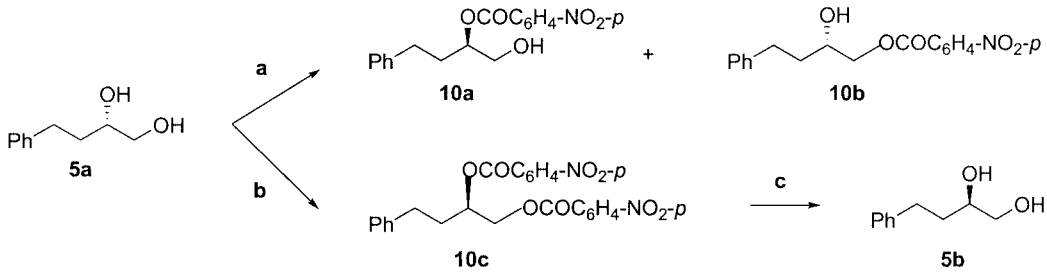
| Entry | Molar ratio[a] | Temp. [°C] | Time [h] | Zinc | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | 1:10:15 | 30 | 2 | activated | 38 |
| 2 | 1:10:15 | 50 | 5.5 | activated | 58 |
| 3 | 1:5:10 | 50 | 5.5 | activated | 69 |
| 4 | 1:5:10 | 50 | 5.5 | commercial[c] | 40 |

[a] Molar ratio of nitrile **7a**:methyl bromoacetate:zinc. [b] Isolated yield. [c] Commercial zinc powder consists of 90% Zn and 10% ZnO.

To synthesize the opposite enantiomer of **1a**, (*R*)-(–)-dihydrokavain (**1b**), the crucial step is to invert the configuration of the asymmetric center by the Mitsunobu reaction[14] (Scheme 2). The synthetic route **a** reported by Voelter et al.[15] gave a predominant monosubstituted product **10a** with a free primary hydroxy group, but it also contained a minor by-product **10b**. It was found to be very tedious to separate the by-product **10b** from the major compound. So we developed a synthetic route **b** using two equivalents of the reagent to produce a crystalline diester **10c** in 88% yield, which was then transformed into the desired diol **5b** in 91% yield with 98.4% *ee*[16] by treatment with a catalytic amount of sodium in methanol.

In conclusion, we have successfully completed a practicable route for the synthesis of natural product (*S*)-(+)-dihydrokavain in eight steps with an overall yield of 25% and its enantiomer (*R*)-(–)-dihydrokavain in 10 steps with an overall yield of 20% from 2,3-*O*-isopropylidene-D-glyceraldehyde (**2**). The absolute stereochemistry of (*S*)-(+)-dihydrokavain was elucidated previously by CD spectroscopy[17] and the Mosher method.[5] This work demonstrates and confirms the absolute configuration of (*S*)-(+)-dihydrokavain and (*R*)-(–)-dihydrokavain by total synthesis from a chiral source, and this efficient synthetic procedure can be extended easily to synthesize other optically active kava derivatives.




Scheme 2. Conditions and reagents: (a) $PPh_3$ (1 equiv.), DIAD (1 equiv.), *p*-$NO_2C_6H_4COOH$ (1 equiv.), THF, room temp., 2 h; (b) $PPh_3$ (2 equiv.), DIAD (2 equiv.), *p*-$NO_2C_6H_4COOH$ (2 equiv.), THF, room temp., 2 h; (c) catalytic Na, MeOH, room temp., 1 h.

## Experimental Section

**General:** All moisture-sensitive reactions were carried out under nitrogen. The reagents were purchased from Shanghai Chemical Reagent Company and Acros, and were used without further purification unless otherwise stated. Melting points are uncorrected. IR spectra were recorded on a Nicolet Magna 750 spectrometer and only characteristic absorptions are reported. The $^1H$ NMR spectra were measured with a Bruker AM-400 (400 MHz) spectrometer, and the coupling constants (*J*) are reported in hertz. EI mass spectra were recorded on a MAT-95 spectrometer. All solvents were purified and dried prior to use according to standard procedures.[18] PE refers to petroleum ether (boiling range 60–90 °C); DIAD refers to diisopropyl azodicarboxylate.

**(*S*)-4-Phenyl-1,2-butanediol (5a):** *n*BuLi (2.5 M in hexane; 12.0 mL, 30 mmol) was added at 0 °C to a suspension of $[PPh_3CH_2Ph]Br$ (13.0 g, 30 mmol) in THF (50 mL) and stirred for 20 min. A solution of ketal **2** (3.9 g, 30 mmol) in THF (10 mL) was then added dropwise and the mixture was allowed to stir for an additional 2 h at room temperature. The reaction was quenched with saturated $NH_4Cl$ solution (40 mL), and was extracted with diethyl ether (3 × 40 mL). The ether solution was washed with brine and dried with anhydrous $Na_2SO_4$. After removal of solvent, the crude product was purified on a flash column of silica gel (eluent PE/EtOAc, 50:1) to afford compound **3** (4.9 g, 80%) as a mixture of geometric isomers.

Hydrogen was passed through a MeOH (10 mL) solution of compound **3** (2.3 g, 11.3 mmol) containing 10% Pd/C (160 mg) as catalyst at room temperature and stirred overnight. After removal of the catalyst and solvent, 2.28 g of compound **4** was obtained in a yield of 98%.

HCl (2 M, 10 mL) was added to a MeOH (10 mL) solution of compound **4** (1.67 g, 8.11 mmol), and the mixture stirred for 1 h at room temperature. The solution was then neutralized with solid $K_2CO_3$. After removal of the methanol, the mixture was further diluted with water (20 mL) and extracted with ethyl acetate three times. The ethyl acetate solution was dried with anhydrous $Na_2SO_4$ and the solvent was removed to obtain the crude product **5a**, which was purified on a flash column of silica gel (eluent PE/EtOAc, 1:1) to afford a colorless oil (1.30 g, 97%). $[\alpha]_D^{20} = -34$ (*c* = 1.33, EtOH), [ref.[19] $[\alpha]_D^{20} = -32.3$ (*c* = 1.02, EtOH)]. IR (KBr): $\tilde{\nu}$ = 3384.5, 3025.8, 2929.4, 1646.9, 1602.6, 1496.5, 1454.1 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.73–1.81 (m, 2 H, C*H*$_2$), 2.30 (s, 1 H, O*H*), 2.49 (s, 1 H, O*H*), 2.66–2.71 (m, 1 H, one of PhC*H*$_2$), 2.78–2.85 (m, 1 H, one of PhC*H*$_2$), 3.44–3.49 (m, 1 H, C*H*), 3.64–3.74 (m, 2 H, C*H*$_2$O), 7.18–7.21 (m, 3 H, *H*, arom.), 7.26–7.31 (m, 2 H, *H*, arom.) ppm. EIMS: *m*/*z* (%) = 166 (10) [$M^+$], 148 (38), 117 (38), 91 (100).

**(*S*)-3-Hydroxy-5-phenylpentanenitrile (7a) and its Enantiomer 7b:** A solution of TsCl (378 mg, 1.98 mmol) in dry pyridine (1.0 mL) was added dropwise to a solution of diol **5a** (300 mg, 1.81 mmol) in dry pyridine (1.0 mL) at –17 °C (ice-salt bath), and the mixture was stirred at the same temperature for about 12 h. The reaction mixture was then poured into cold water (10 mL) and partitioned with EtOAc. The EtOAc solution was washed successively with 2 N HCl (15 mL) and brine, and dried with anhydrous $Na_2SO_4$. After removal of the solvent the crude product was purified on a column of silica gel eluting with PE/EtOAc (10:3) to give tosylate **6a** (433.8 mg, 75% yield) as a waxy solid.

Tosylate **6a** (0.52 g, 1.625 mmol) was dissolved in 5 mL of 60% ethanol in water, cooled to 0 °C, and then KCN (0.13g, 2 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, the ethanol was then evaporated under vacuum and diluted with water (10 mL). The aqueous mixture was partitioned with EtOAc, and the organic phase was washed with brine and dried with anhydrous $Na_2SO_4$. After removal of solvent, the crude residue was purified on a flash column of silica gel, eluting with PE/EtOAC (10:3), to afford **7a** (0.25 g, 89%) as a colorless solid. M.p. 42–43 °C. $[\alpha]_D^{20} = -20$ (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3453.9, 2952.5, 1600.7, 1492.7 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.89–1.96 (m, 2 H, C*H*$_2$), 2.15(br., 1 H, O*H*), 2.47–2.59 (m, 2 H, C*H*$_2$CN), 2.71–2.76 (m, 1 H, one of PhC*H*$_2$), 2.79–2.85 (m, 1 H, one of PhC*H*$_2$), 3.95 (m, 1 H, C*H*), 7.18–7.21 (m, 3 H, *H*, arom.), 7.26–7.31 (m, 2 H, *H*, arom.) ppm. Its enantiomer **7b** was prepared from the diol **5b** by using the same procedure as for compound **7a**. The spectroscopic data of compound **7b** were identical to those of **7a**, except that the optical rotation value is opposite: $[\alpha]_D^{20} = +20$ (*c* = 1.6, $CHCl_3$).

**(*S*)-Methyl-5-hydroxy-3-oxo-7-phenylheptanoate (8a) and its Isomer 8b:** A mixture of **7a** (220 mg, 1.26 mmol) and activated Zn (0.85 g, 13.1 mmol) in anhydrous THF (15 mL) was subjected to ultrasonic irradiation at 50 °C for 10 min and then methyl bromoacetate (0.75 mL, 6.59 mmol) was added dropwise under nitrogen. The resultant mixture was irradiated under the same conditions for another 5.5 h, then acidified with 2 M HCl to pH 3 and stirred at room temperature for 10 min.. The mixture was then diluted with EtOAc (60 mL). The organic phase was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), in that order, and then dried with anhydrous $Na_2SO_4$. After evaporation of the solvent in vacuo, the residue was purified on a column of silica gel, eluting with PE/EtOAc (10:3), to afford the desired product **8a** (178 mg, 69%) and the starting material **7a** (41 mg, 18% recovery). Compound **8a** was obtained as a colorless oil. $[\alpha]_D^{20} = -5$ (*c* = 0.83, acetone). IR (KBr): $\tilde{\nu}$ = 3377.6, 3029.9, 2952.5, 1743.4, 1712.5, 1436.7 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3COCD_3$): $\delta$ = 1.71–1.76 (m, 2 H, C*H*$_2$), 2.64–2.77 (m, 4 H, C*H*$_2$CO and PhC*H*$_2$), 3.34 (s, 2 H, COC*H*$_2$CO), 3.69 (s, 3 H, OC*H*$_3$), 4.04 (m, 1 H, C*H*), 7.14–7.27 (m, 5 H, *H*, arom.) ppm. EIMS: *m*/*z* (%) = 250 (5) [$M^+$], 232 (45), 14 (50), 91 (100). HREIMS calcd. for $C_{14}H_{18}O_4$: 250.1205; found 250.1208. Enantiomer **8b** was synthesized in a similar manner from compound **7b**.

The spectroscopic data of **8b** were identical to those of **8a**, except for the opposite optical rotation value: $[\alpha]_D^{20}$ = +5 (*c* = 1.73, acetone).

**(*S*)-6-Phenethyldihydropyran-2,4-dione (9a) and its Isomer 9b:** *p*-Toluenesulfonic acid (12 mg, 0.063 mmol) was added at room temperature to a stirred solution of **8a** (168 mg, 0.67 mmol) in $CH_2Cl_2$ (10 mL), and the reaction was stirred for 2 h. The resultant mixture was then diluted with $CH_2Cl_2$ (10 mL). After filtration, the organic phase was washed with saturated $NaHCO_3$ and brine, in that order, and then dried with anhydrous $Na_2SO_4$. The crude product obtained after removal of the solvent was crystallized from a mixture of PE and diethyl ether to give compound **9a** (123.7 mg, 84%) as colorless crystals. M.p. 126–127 °C (ref.[5] 124 °C). $[\alpha]_D^{20}$ = +47 (*c* = 1.25, $CH_2Cl_2$), [ref.[5] $[\alpha]_D^{20}$ = +28.9 (*c* = 3.99, $CH_2Cl_2$)]. IR (KBr): $\tilde{\nu}$ = 2956.4, 1685.5, 1581.4, 1388.5, 1284.4 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.96–2.12 (m, 1 H, one of C$H_2$), 2.13–2.21 (m, 1 H, one of C$H_2$), 2.50 (dd, *J* = 11.4, 18.2 Hz, 1 H, one of C$H_2$CO), 2.69 (dd, *J* = 2.7, 18.2 Hz, 1 H, one of C$H_2$CO), 2.83–2.96 (m, 2 H, PhC$H_2$), 3.43 (d, *J* = 18.7 Hz, 1 H, one of COC$H_2$CO), 3.55 (d, *J* = 18.7 Hz, 1 H, one of COC$H_2$CO), 4.55–4.62 (m, 1 H, C*H*), 7.20–2.26 (m, 3 H, *H*, arom.), 7.30–7.34 (m, 2 H, *H*, arom.) ppm. Enantiomer **9b** was synthesized in a similar manner from **8b**. The spectroscopic data of **9b** were identical to those of **9a,** except for the optical rotation value: $[\alpha]_D^{20}$ = –38 (*c* = 1.04, $CH_2Cl_2$).

**(*S*)-Dihydrokavain (1a) and its Isomer (*R*)-Dihydrokavain (1b):** Dimethyl sulfate (40 μL, 0.48 mmol) was added to a dry acetone (5 mL) solution containing **9a** (55 mg, 0.25 mmol) and potassium carbonate (60 mg, 0.48 mmol), according to a previous report,[5] and stirred for 20 h. Water (5 mL) was then added to the resultant mixture and the acetone was removed in vacuo. The aqueous solution was extracted with ethyl acetate, and the extract was dried with anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography on a column of silica gel, eluting with PE/EtOAc (10:3), to afford the target molecule **1a** (50.5 mg, 86%) as colorless crystals (from a mixture of diethyl ether and PE). M.p. 54–55 °C, [ref.[20] 56–58 °C]. $[\alpha]_D^{20}$ = +29 (*c* = 1.21, EtOH), [ref.[20] $[\alpha]_D^{0}$ = +30 (*c* = 1, EtOH)]. IR (KBr): $\tilde{\nu}$ = 2923.6, 1708.6, 1623.8, 1396.2 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.94 (m, 1 H, one of C$H_2$), 2.13–2.17 (m, 1 H, one of C$H_2$), 2.30 (dd, *J* = 17.2, 3.9 Hz, 1 H, one of C$H_2$C=C), 2.53 (dd, *J* = 17.2, 1.7 Hz, 1 H, one of C$H_2$C=C), 2.78–2.89 (m, 2 H, PhC$H_2$), 4.36 (m, 1 H, C*H*), 5.14 (d, *J* = 1.6 Hz, 1 H, C=C*H*–), 7.20–2.26 (m, 3 H, *H*, arom.), 7.30–7.34 (m, 2 H, *H*, arom.) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 30.9 (Ph*C*$H_2$), 33.0 (*C*$H_2$C=C), 36.2 (PhC$H_2$*C*$H_2$), 56.0 (O*C*$H_3$), 74.8 ($CH_2$*C*HOC$H_2$), 90.3 (= *C*HCOO), 126.1 (*C*, arom.), 128.4 (2*C*, arom.), 128.5 (2*C*, arom.), 140.8 (*C*, arom.), 167.3 (*C*=O), 172.7 (= *C*OMe) ppm. EIMS: *m*/*z* (%) = 232 (18) [$M^+$]. HREIMS calcd. for $C_{14}H_{16}O_3$: 232.1099; found 232.1098. Enantiomer **1b** was synthesized in a similar manner from **9b** as colorless crystals (m.p. 55.5–56.5 °C). The spectroscopic data of **1b** were identical to those of natural *S*-(+)-dihydrokavain except for the opposite optical rotation value: $[\alpha]_D^{20}$ = –28 (*c* = 1.92, EtOH).

**(*R*)-Diester 10c:** DIAD (94%; 0.23 mL, 1.08 mmol) was added dropwise, under nitrogen, to a solution of dry THF (5 mL) containing $PPh_3$ (284.1 mg, 1.08 mmol), diol **5a (**90.0 mg, 0.54 mmol) and *p*-nitrobenzoic acid (181.1 mg, 1.08 mmol), at 0 °C. The reaction mixture was stirred for 2 h at room temperature. After work-up, the residue was dissolved in EtOAc (25 mL), washed with saturated $NaHCO_3$ solution and brine, and dried with anhydrous $Na_2SO_4$. Evaporation of the solvent gave a crude product, which was purified by flash chromatography on a column of silica gel, eluting with dichloromethane/PE (1:1), to afford (*R*)-diester **10c** (221.5 mg, 88%) as colorless crystals (from EtOAc and PE). M.p. 114–115 °C. $[\alpha]_D^{20}$ = –6 (*c* = 1.15, acetone). IR (KBr): $\tilde{\nu}$ = 1731.8, 1716.4, 1525.4, 1348.0, 1288.2 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.05–2.30 (m, 2 H, C$H_2$), 2.77–2.86 (m, 2 H, PhC$H_2$), 4.54 (dd, *J* = 12.1, 6.9 Hz, 1 H, one of C$H_2$O), 4.68 (dd, *J* = 12.1, 3.2 Hz, 1 H, one of C$H_2$O), 5.58 (m, 1 H, C*H*), 7.19–7.20 (m, 3 H, *H*, arom.), 7.26–7.31 (m. 2 H, *H*, arom.), 8.14–8.17 (m, 4 H, *H*-$C_6H_4$-$NO_2$-*p*), 8.26–8.30 (m, 4 H, *H*-$C_6H_4$-$NO_2$-*p*) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 31.6 (*C*$H_2$), 32.3 (*C*$H_2$), 66.2 (*C*$H_2$O), 72.7 (*C*H), 123.6 (4*C*, arom.), 126.4 (*C*, arom.), 128.3 (2*C*, arom.), 128.6 (2*C*, arom.), 130.7 (4*C*, arom.), 134.8(*C*, arom.), 135.0(*C*, arom.), 140.3 (*C*, arom.), 150.6 (2*C*, arom.), 164.2 (*C*=O), 164.3 (*C*=O) ppm. $C_{24}H_{20}N_2O_8$ (464.44): calcd. C 62.07, H 4.31, N 6.03; found C 62.29, H 4.33, N 5.93.

**(*R*)-4-Phenyl-1,2-butanediol (5b):** Sodium (2.0 mg, 0.087 mmol) was added at room temperature to a solution of MeOH (10 mL) containing diester **10c** (221.5 mg, 0.48 mmol) and the mixture stirred for 1 h. Solid $NH_4Cl$ (50 mg) was then added to the mixture. After removal of MeOH in vacuo, the residue was dissolved in EtOAc (25 mL), washed with brine, and dried with anhydrous $Na_2SO_4$. After evaporation of EtOAc on a rotary evaporator, the crude product was purified by flash chromatography on a column of silica gel, eluting with PE/EtOAc (1:1), to afford the desired diol **5b** (72.1 mg, 91%) as a colorless oil. Its spectroscopic data were identical to those of **5a**, except that the optical rotation value is opposite: $[\alpha]_D^{20}$ = +33 (*c* = 1.88, EtOH).

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