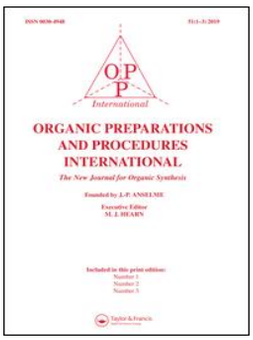

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OPPI BRIEF



# Metamifop on Kilogram Scale

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Metamifop (**1**, Figure 1), developed by the Korea Research Institute of Chemical Technology, is a post-emergent aryloxyphenoxypropionic herbicide, and only the *R*-isomer has bioactivity. It is mainly used in the cultivation of rice and works against annual perennial grass weeds.[1] Metamifop is unusual among herbicides in being safe for rice. It can effectively control major weeds in paddy fields, including valerian, ginseng, crabgrass and goose grass.[2] It had been introduced to China by FMC Corporation with great success in 2010.[3–5]

The reported synthetic route of racemic metamifop ((+/–)-**1**) was developed[6] as shown in Scheme 1. 2-Amino-5-chlorophenol (**2**) and potassium ethyl xanthogenate were chosen as the starting materials, cyclized and chlorinated to give 2,6-dichlo-benzo[*d*]oxazole (**4**) in 46% over-all yield. 2-Bromo-*N*-(2-fluorophenyl)-*N*-methylpropanamide (**6**) was prepared through the dehydrative coupling of 2-fluoro-*N*-methylaniline (**5**) and 2-bromopropionic acid in 87% yield. Intermediate **7** was obtained by etherification of 1,4-hydroquinone with **6** using $K_2CO_3$ and TBAB, in 79% yield. Compound (+/–)-**1** was obtained in 78% yield by coupling compound **4** and **7** under similar etherification conditions. Notwithstanding the value of this preparation, the starting materials are relatively expensive, and the over-all yield is not as high as desirable, making this route less harmonious with industrial goals.

In order to develop a practical preparation of metamifop (**1**, *R*-isomer), we designed a new convergent synthetic route, as shown in Scheme 2. The method is simple to complete and has a high yield. It is suitable for large-scale industrial production. Two key intermediates were prepared respectively, including compounds **4** and **14**.

We prepared compound **4** on an 800 g scale in high purity, based on the reported synthesis route after optimization.[7,8] Commercially available materials 2-aminophenol (**8**) and urea were heated in *o*-dichlorobenzene at 180 °C for 2 h to give benzo[*d*]xazol-2-(3*H*)-one (**9**) in 98% yield. Compound **9** was then treated with $SO_2Cl_2$ in chlorobenzene at 45 – 50 °C for 3 h to give 6-chlorobenzo[*d*]oxazol-2(3*H*)-one (**10**) in 86% isolated yield. After chlorination of **10** by $PCl_5$, **4** was obtained in 84% yield.

The (*R*)-propanoic acid compound **14** was prepared by a new method after optimization.[9] (*S*)-2-Chloropropanoic acid (**11**) and 1,4-hydroquinone (**12**) were used as the starting materials through an $SN_2$ type substitution reaction to give compound **13** in

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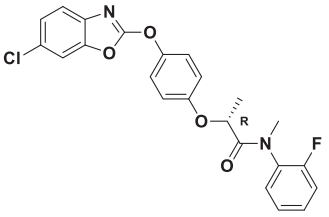
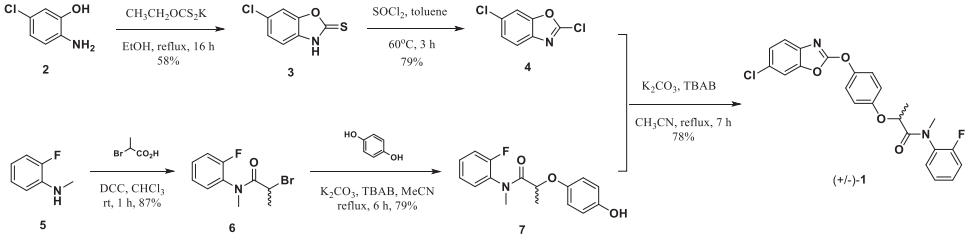
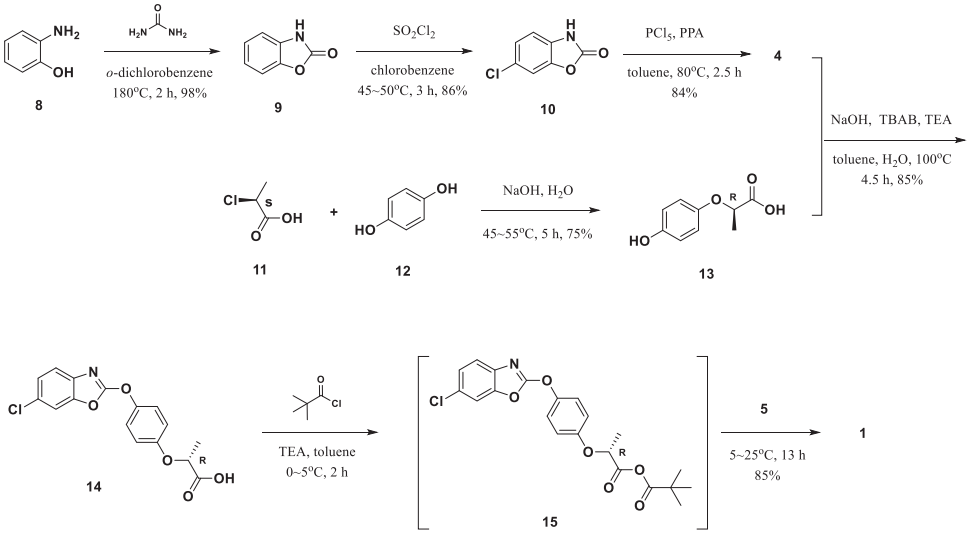


metamifop, 1

**Figure 1.** The chemical structure of metamifop.




**Scheme 1.** Reported synthetic route.




**Scheme 2.** New convergent route.

75% isolated yield.[10] Compound **13** was reacted with **4** to give the intermediate **14** in 85% yield. At the last step, compound **14** was reacted with pivaloyl chloride to give the propanoic pivalic anhydride intermediate **15**, which was not isolated. Intermediate **15** reacted with 2-fluoro-*N*-methylaniline (**5**) directly to give the final product **1** in 85% yield after purification, with 98% purity.

In summary, a new, practical, kilogram scale preparation of metamifop (**1**) has been developed. Firstly, 2,6-dichlorobenzoxazole **4** was prepared on 800 g scale in 71% yield over 3 steps, with 98.5% purity (HPLC). Secondly, (*R*)-2-(4-hydroxyphenoxy)-propanoic acid **13** was prepared from **11** and **12** in 75% yield and 99% purity. Thirdly, compound **14** was obtained by reaction of compounds **4** and **13** in 85% yield and 99.2% purity.

Finally, **1** was prepared from compound **14** under mild conditions in 85% yield over two steps. The prepared compound **1**, and compound (+/-)-**1** were compared with the commercial metamifop through chiral HPLC and optical rotation tests (see Experimental section and supplementary material).

## Experimental section

All commercially available materials and solvents were used as received without any further purification. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained on a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and are uncorrected. The optical rotation data were measured on a Jingruo SGWZZ-3 automatic polarimeter and are uncorrected. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds was based on the areas of HPLC peaks (UV).

### *Benzo[d]oxazol-2(3H)-one (9)*

A mixture of 2-aminophenol (**8**) (660 g, 6.04 mol), urea (400 g, 6.64 mol) in *o*-dichlorobenzene (3 L) was heated and stirred at 180 °C for 2 h to give a light-brown solution. After cooling to room temperature, the resulting solid was collected by suction filtration, washed with *o*-dichlorobenzene (300 mL × 2), and dried at 80 °C for 4 h to obtain **9** (799 g, 98%), as an off-white solid, mp 136.7 – 138.8 °C (lit mp[7] 137 – 139 °C). $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.01 (brs, 1H), 7.72 (d, $J$ = 1.8 Hz, 1H), 7.33 (dd, $J$ = 8.4, 1.9 Hz, 1H), 7.31–7.19 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 154.85, 143.82, 130.82, 124.18, 122.25, 110.20, 109.91.

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 $\mu$L; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 80/20, $t_R$: 4.33 min, purity: 99.55%.

*Anal.* Calcd for $C_7H_5NO_2$: C, 66.22; H, 3.73; N, 10.37. Found: C, 66.03; H, 3.77; N, 10.46.

### *6-Chlorobenzo[d]oxazol-2(3H)-one (10)*

To a stirred suspension of **9** (740 g, 5.5 mol) in chlorobenzene (8 L) was slowly added sulfonyl chloride (814 g, 6.03 mol) over 2 h at room temperature. The reaction solution was stirred at 45–50 °C for another 2 h. {***Safety Notes:*** The reaction was accompanied by gas generation (HCl), which should be safely vented and quenched by aqueous NaOH solution. Workers must be thoroughly trained in the safe use of $SO_2Cl_2$ before doing this operation.} Then the reaction solution was cooled to room temperature, the solid was collected by suction filtration, washed with chlorobenzene (300 mL × 2), and dried at 60 °C for 5 h to obtain the product **10** (798.6 g, 86%), as a light yellow solid, mp 194.2 – 196.0 °C (lit mp[11] 196 °C). $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.87 (s, 1H),

7.55 (d, $J = 1.8$ Hz, 1H), 7.26 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 154.61, 144.27, 129.94, 126.24, 124.11, 111.17, 110.67.

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 $\mu$L; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 70/30, $t_R$: 5.03 min, purity: 97.46%.

*Anal.* Calcd for $C_7H_4ClNO_2$: C, 49.58; H, 2.38; N, 8.26. Found: C, 49.70; H, 2.42; N, 8.17.

### 2,6-Dichlorobenzo[d]oxazole (4)

Phosphorus pentachloride (***Caution! Good ventilation and personal protective gear are required.)*** (2.4 kg, 11.5 mol) and polyphosphoric acid (240 g, 0.71 mol) were added to toluene (8 kg), the resulting solution was stirred and heated at 80 °C. Then **10** (800 g, 4.72 mol) was added and the suspension was stirred at 80 °C for 2.5 h to give a homogeneous reaction solution. The reaction mixture was cooled to 45–50 °C and then added to 10 kg warm water (30–40 °C) over 1 h and stirred for another 1 h. Then the organic layer was separated, washed by water (5 L × 1), and concentrated in vacuo to afford a brown solid. The crude product was further purified through vacuum distillation (120–130 °C/18 mmHg), the fraction solidified at room temperature to give **4** (887 g, 84%) as a white solid, mp 55.8 – 57.0 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J = 8.5$ Hz, 1H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.35 (dd, $J = 8.5$, 1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.54, 151.41, 139.91, 131.36, 125.81, 120.23, 111.05.

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 $\mu$L; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 95/5, $t_R$: 10.18 min, purity: 98.54%.

*Anal.* Calcd for $C_7H_3Cl_2NO$: C, 44.72; H, 1.61; N, 7.45. Found: C, 44.89; H, 1.62; N, 7.39.

### (R)-2-(4-Hydroxyphenoxy)propanoic acid (13)

*Flask A*: 40% NaOH aqueous solution (840 g, 8.4 mol) was added over 2 h to the solution of (*S*)-2-chloropropanoic acid (**11**) (870 g, 8.0 mol) in 1 kg water at 5–20 °C.

*Flask B*: 40% NaOH aqueous solution (2.1 kg, 21.0 mol) was added over 1 h to the suspension of 1,4-hydroquinone (**12**) (1.0 kg, 10.0 mol) in 2 kg water at room temperature. Then the reaction solution was heated to 45–50 °C.

The solution in *Flask A* was added to *Flask B* over 2 h at 45–50 °C and stirred at 55–60 °C for another 1 h. After cooling to 0–5 °C, concentrated hydrochloric acid (~2 L, 24 mol) was added slowly to achieve pH 4 and the mixture was stirred at 0 °C for 1 h. The resulting solid was removed by filtration. Then concentrated hydrochloric acid (200 mL, 2.4 mol) was added into the filtrate to achieve pH 1 and the mixture was stirred at 0 °C for 1 h, the resulting solid was collected by filtration, washed with water (300 mL), and dried at 45 °C for 6 h to give **13** (1.09 kg, 75%) as a white solid, mp 143.7 – 144.8 °C (lit mp[12] 144 °C). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.88 (brs, 1H),

8.97 (brs, 1H), 6.69 (q, $J = 9.2$ Hz, 4H), 4.64 (q, $J = 6.7$ Hz, 1H), 1.46 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.93, 152.07, 150.73, 116.56, 116.15, 72.86, 18.83. Optical rotation $[\alpha]^{20}_{D} = +0.396$ (c = 0.1, MeOH).

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 2 $\mu$L; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 90/10, $t_R$: 2.04 min, purity: 99.06%.

*Anal.* Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.13; H, 5.55.

### *(R)-2-[4-((6-Chlorobenzo[d]oxazol-2-yl)oxy)phenoxy]propionic acid (14)*

*Flask A*: Compound **4** (681 g, 3.62 mol), tetrabutylammonium bromide (TBAB) (35 g, 0.11 mol) and triethylamine (TEA) (11 g, 0.11 mol) were added to 1.8 L toluene respectively, the resulting solution was stirred at 50 °C.

*Flask B*: Compound **13** (550 g, 3.0 mol) was slowly added to a solution of NaOH (435 g, 10.8 mol) in water (1.8 kg) at 5–20 °C.

The solution in *Flask B* was added to *Flask A* over 1 h at 45–50 °C and stirred at 55–60 °C for 4 h to give a brown solution. The mixture was cooled to room temperature and the toluene solution was separated. Then concentrated hydrochloric acid was added to the aqueous solution to achieve pH 3 and stirred for 1 h until a voluminous solid was formed. The brown solid was collected by suction filtration, washed with 95% EtOH (100 mL × 2), dried at 45 °C for 6 h to give **14** (851 g, 85%) as a light yellow solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 13.12 (brs, 1H), 7.86 (d, $J = 1.8$ Hz, 1H), 7.52 (d, $J = 12.0$ Hz, 1H), 7.43 (d, $J = 12.0$ Hz, 2H), 7.35 (dd, $J = 8.4$, 2.0 Hz, 1H), 6.99 (d, $J = 12.0$ Hz, 2H), 4.88 (q, $J = 6.8$ Hz, 1H), 1.53 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.42, 163.03, 156.16, 148.65, 146.62, 139.92, 127.94, 125.33, 121.95, 119.63, 116.23, 111.26, 72.51, 18.71.

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 $\mu$L; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 90/10, $t_R$: 8.38 min, purity: 99.29%.

*Anal.* Calcd for $C_{16}H_{12}ClNO_5$: C, 57.59; H, 3.62; N, 4.20. Found: C, 57.74; H, 3.60; N, 4.22.

### *Metamifop (1)*

TEA (327.5 g, 3.24 mol) was added into a mixture of compound **14** (900 g, 2.70 mol) in toluene (3.0 L) at room temperature. The mixture was stirred for 1 h at 25 °C, and then cooled to 0–5 °C. Pivaloyl chloride (341.4 g, 2.83 mol) was added dropwise to the reaction solution over 1 h and stirred at 0–5 °C for another 1 h to give a white suspension.

2-Fluoro-*N*-methylaniline (**5**) (354.4 g, 2.83 mol) was added slowly into the reaction mixture over 1 h at 0–5 °C, and the resulting suspension was stirred at room temperature 1 h until the solid was dissolved. Then it was stirred at 20–30 °C for 12 h. The reaction mixture was filtered to remove the salt (triethylamine hydrochloride), then washed with toluene (200 mL × 2). The combined filtrate was washed with water (2 L × 1) and

saturated $NaHCO_3$ aqueous solution (2 L × 1) respectively. The organic layer was concentrated in vacuo to obtain a yellow solid (1.2 kg). *n*-Heptane (5 L) was added into the solid and the resulted mixture was stirred at room temperature for 5 h. The resulting solid was collected by suction filtration, dried at 45 °C for 6 h to give **1** (1010 g, 85%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46–7.38 (m, 3H), 7.28–7.19 (m, 5H), 6.84–6.79 (m, 2H), 4.70–4.65 (m, 1H), 3.30 (d, $J$ = 2.8 Hz, 3H, 3H), 1.48 (dd, $J$ = 18.4, 12.4 Hz, 3H). $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 170.20, 162.90, 155.52, 148.63, 146.69, 139.92, 130.60, 127.99, 125.32, 121.84 (d, $J$ = 19.5 Hz), 119.61, 117.39 (d, $J$ = 19.5 Hz), 116.65, 116.07, 111.21, 71.44, 37.20, 18.03, 17.73. MS (ESI): $m/z$ = 441.1 $[M+H]^+$, 881.1 $[2M+H]^+$. Optical rotation $[\alpha]^{20}_D$ = –2.496 (c = 0.1, MeOH). > 99% ee.

HPLC Conditions — Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 μL; Solvent: methanol; Run time: 30 min; Mobile phase: methanol/water = 80/20, $t_R$: 14.95 min, purity: 99.95%.

Chiral HPLC Conditions — Column: (Daicel CHIRALPAK IC); Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 45 °C; Injection load: 2 μL; Solvent: methanol; Run time: 45 min; Mobile phase: *n*-hexane/*i*-PrOH = 90/10, $t_R$: 20.49 min (compound **1**), 26.39 min (compound –**1**), purity: 95.42%, > 99% ee.

*Anal.* Calcd for $C_{23}H_{18}ClFN_2O_4$: C, 62.66; H, 4.12; N, 6.35. Found: C, 62.79; H, 4.10; N, 6.38.

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