Supporting Information

Boric Acid-Catalyzed, Chemoselective Esterification of α-Hydroxycarboxylic Acids

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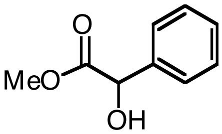
General Experimental Methods:

Commercial reagents and solvents were used for all reactions without additional purification. The boric acid (Merck, 99.8%) used in these reactions was purchased from BDH (Victoria, Australia). Ethanol was dried by storage over activated molecular sieves. ^{1}H- and ^{13}C-NMR spectra were all recorded on a 200 MHz Varian Gemini 2000 spectrophotometer. Chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (7.26 ppm for ^{1}H-NMR and 77.23 ppm for ^{13}C-NMR) or acetone (2.05 ppm for ^{1}H-NMR). The procedure described for the mandelic acid was used for all other acids except malic acid. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography.

Preparation of Methyl Mandelate

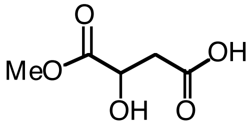


To a stirring solution of (+/-)-mandelic acid (2.06 g, 13.5 mmol) in methanol (30 mL) was added boric acid (90 mg, 0.14 mmol) in one portion and the mixture soon became homogeneous. The reaction was stirred at room temperature for 18 hours and the bulk solvent was removed *in vacuo* with mild heating (40-45˚C) to afford methyl mandelate as a clear oil. The residue was dissolved in Et_2O, filtered through a short plug of Celite, and concentrated to afford 2.23 g (99%) of methyl (+/-)-mandelate. The ^{1}H-NMR chemical shifts matched values for authentic samples of the methyl ester.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3 H, OCH_3), 5.20 (s, 1H, C*H*OH), 5.25 (br s, 1H, O*H*), 7.35 – 7.55 (m, 5H, aromatic C*H*).

Note: This procedure (2 grams hydroxyacid in 30 mL methanol) was used for glycolate, lactate, and citrate methyl ester formation and tartarate dimethyl ester formation.

Preparation of Methyl Malate

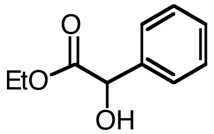


To a stirring solution of (+/-)-malic acid (1.0 g, 7.5 mmol) in methanol (30 mL) was added boric acid (47 mg, 0.76 mmol) in one portion. The mixture was stirred at room temperature for 16 hours. All volatiles were removed *in vacuo* with mild heating (40-45˚C) to afford the product as an amorphous solid that was purified by column chromatography (50→100% EtOAc/Hex) to yield 0.78 g (71%) of the monoester product. The ^{1}H-NMR chemical shifts matched known values for the monomethyl ester.[7]

^{1}H NMR (200 MHz, acetone-d_6) δ 2.6–2.9 (m, 2H, CH_2CO), 3.71 (s, 3H, OCH_3), 4.52 (dd, 1H, J = 6.0, 4.4 Hz, C*H*OH).

Note: Prolonged exposure to boric acid (>36 h) resulted in significant amounts (>30%) of diester being formed. As mentioned in the article, diester and dimeric byproducts became a more significant problem when the reaction was run at higher concentrations.

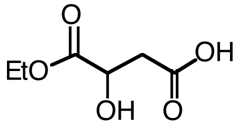
Preparation of Ethyl Mandelate



To a stirring solution of (+/-)-mandelic acid (2.0 g, 13 mmol) in dry ethanol (30 mL) was added boric acid (170 mg, 2.6 mmol) in one portion. The mixture was stirred at room temperature for 18 hours. The bulk solvent was removed *in vacuo* with mild heating (40-45˚C) to afford a crude residue that was extracted into CH_2Cl_2 (75 mL) and then washed with 1N $NaHCO_3$ (100 ml) and H_2O (50 ml). The organic fraction was dried with Na_2SO_4, decanted, and the solvent removed under reduced pressure to afford ethyl (+/-)-mandelate as clear oil (1.6 g, 68%). The ^{1}H-NMR chemical shifts matched values for authentic samples of the ethyl ester.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz, $\mathrm{OCH_2C}H_3$), 3.58 (br d, 1H, J = 5 Hz, $\mathrm{O}H$), 4.10–4.40 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.18 (d, 1H, J = 4.6 Hz, $\mathrm{C}H\mathrm{OH}$), 7.25–7.60 (m, 5H, aromatic $\mathrm{C}H$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.34 ($\mathrm{OCH_2}C\mathrm{H_3}$), 62.50 ($\mathrm{O}C\mathrm{H_2CH_3}$), 73.17 ($C$HOH), 126.74 (aromatic CH), 128.60 (aromatic CH), 128.76 (aromatic CH), 138.65 (aromatic C), 173.84 (CO).

Preparation of Ethyl Malate

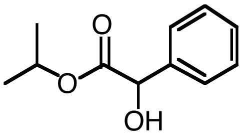


To a stirring solution of (+/-)-malic acid (1.0 g, 7.5 mmol) in dry ethanol (30 mL) was added boric acid (90 mg, 1.5 mmol) in one portion. The mixture was stirred at room temperature for 18 hours. All volatiles were removed *in vacuo* with mild heating (40-45˚C) to afford the product as a clear oil (1.4 g) that was purified by column chromatography (50→100% EtOAc/Hex) to yield 0.79 g (65%) ethyl (+/-)-malate. The ^{1}H-NMR chemical shifts matched known values for the monoethyl ester.[7]

^{1}H NMR (200 MHz, CDCl$_3$) δ 1.31 (t, 3H, *J* = 7.2 Hz, CH$_2$C*H*$_3$), 2.70-2.95 (m, 2H, C*H*$_2$CO), 4.26 (q, 2H, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 4.50 (dd, 1H, *J* = 6.0, 4.4 Hz, C*H*OH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 14.36 (OCH$_2$*C*H$_3$), 38.72 (*C*H$_2$CO), 62.54 (O*C*H$_2$CH$_3$), 67.29 (*C*HOH), 173.39 (*C*O$_2$CH$_2$CH$_3$), 175.81 (*C*O$_2$H).

Note: Prolonged exposure to boric acid (>36 h) or excessive heating (EtOH reflux) resulted in significant amounts (>30%) of diester being formed.

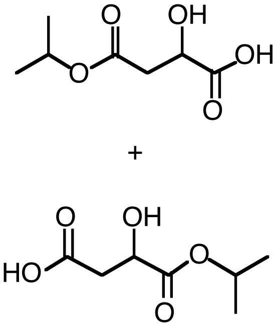
Preparation of Isopropyl Mandelate



To a stirring solution of (+/-)-mandelic acid (2.0 g, 13 mmol) in isopropanol (30 mL) was added boric acid (170 mg, 2.6 mmol) in one portion. The mixture was stirred at room temperature for 18 hours. The bulk solvent was removed *in vacuo* with mild heating (45-50˚C) to afford a crude residue that was extracted into CH_2Cl_2 (75 mL) and then washed with 1N $NaHCO_3$ (100 ml) and H_2O (50 ml). The organic fraction was dried with Na_2SO_4, decanted, and the solvent removed under reduced pressure to afford isopropyl (+/-)-mandelate as clear oil (2.35 g, 93%). The ^{1}H-NMR chemical shifts matched literature values for the isopropyl ester: Basavaiah, D.; Ramma Krishna, P. *Tetrahedron* **1995**, *51*, 2403.

^{1}H NMR (200 MHz, $CDCl_3$) □ 1.08 (d, 3H, *J* = 6.2 Hz, OCHC*H*$_3$), 1.25 (d, 3H, *J* = 6.2 Hz, OCHC*H*$_3$), 3.46 (br d, 1H, *J* = 6.2 Hz, O*H*), 5.04 (hept, 1 H, *J* = 6.2 Hz, OC*H*(CH_3)$_2$), 5.09 (d, 1H, *J* = 6 Hz, C*H*OH), 7.25–7.40 (m, 5H, aromatic C*H*).

Preparation of Isopropyl Malate



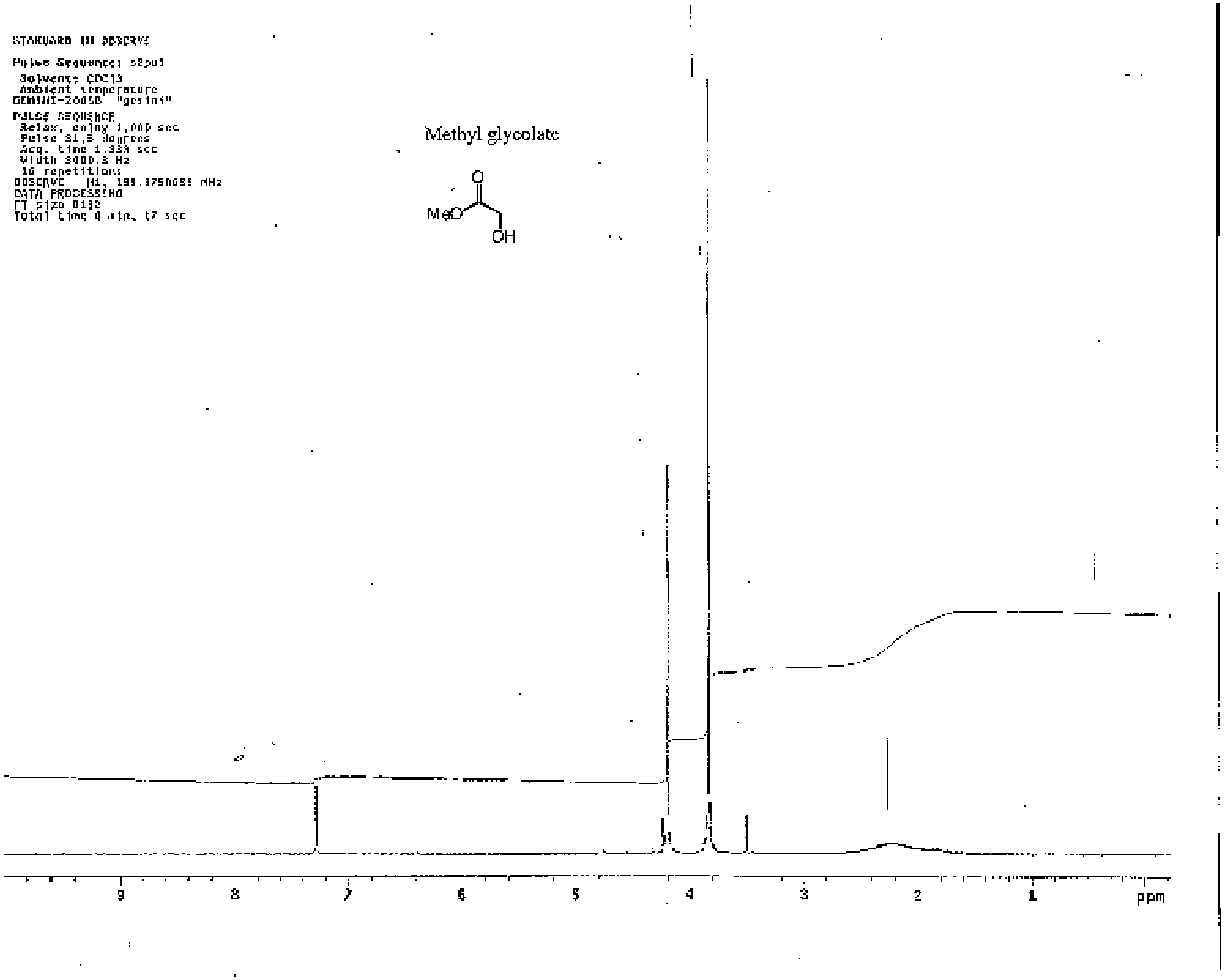
To a stirring solution of (+/-)-malic acid (1.0 g, 7.5 mmol) in isopropanol (30 mL) was added boric acid (90 mg, 1.5 mmol) in one portion. The mixture was stirred at room temperature for 18 hours. All volatiles were removed *in vacuo* with mild heating (45-50˚C) to afford the product as an oily solid (1.3 g) that was purified by column chromatography (50→100% EtOAc/Hex) to yield 0.78 g (59%) of a mixture of isopropyl (+/-)-malate isomers [/ 3:1]. The ^{1}H-NMR chemical shifts matched known values for the monoisopropyl -ester.[7]

^{1}H NMR (200 MHz, $CDCl_3$) 1.26 (m, 6H, OCH(CH_3)$_2$), 2.75-3.0 (m, 2H, CH_2CO), 4.56 (dd, 1H, *J* = 6.0, 4.4 Hz, C*H*OH) + 4.48 (dd, 1H, *J* = 6.0, 4.4 Hz, C*H*OH), 5.11 (hept, 1 H, *J* = 6.2 Hz, OC*H*(CH_3)$_2$).

Note: We are denoting the top isomer shown above as the -isomer.

^{1}H-NMR Spectra of Esters:

The ^{1}H-NMR spectra for products from all reactions, including one biproduct (dimethyl malate), are included. The spectra for the methyl esters of glycolate, lactate and tartrate are crude reaction mixtures to highlight the efficiency of this method.



STANDARD 1H OBSERVE

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Solvent: CDCl3
Ambient temperature
GEMINI-2000BB "gemini"

PULSE SEQUENCE
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Pulse 31.5 degrees
Acq. time 1.999 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 199.9750655 MHz
DATA PROCESSING
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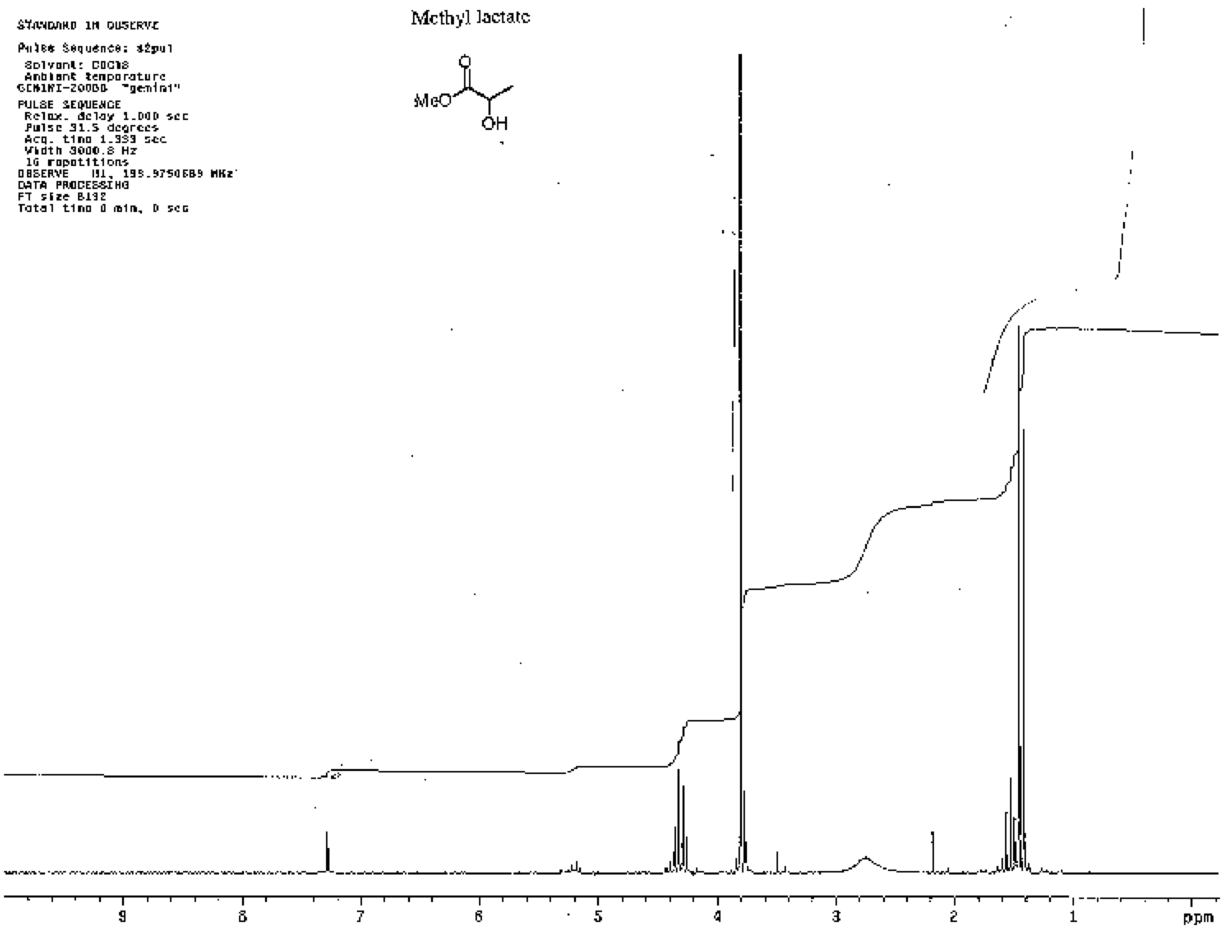
Total time 0 min, 57 sec

Methyl glycolate



Methyl lactate

STANDARD 1H OBSERVE

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Acq. time 1.999 sec
Width 3000.8 Hz
16 repetitions
OBSERVE H1, 199.9750689 MHz
DATA PROCESSING
FT size 8192
Total time 0 min, 0 sec

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 Ambient temperature
GEMINI-2000BB  "gemini"
PULSE SEQUENCE
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 Pulse 31.5 degrees
 Acq. time 1.333 sec
 Width 3000.3 Hz
 8 repetitions
OBSERVE   H1, 199.9750689 MHz
DATA PROCESSING
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Total time 0 min, 8 sec
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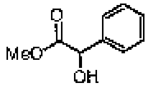
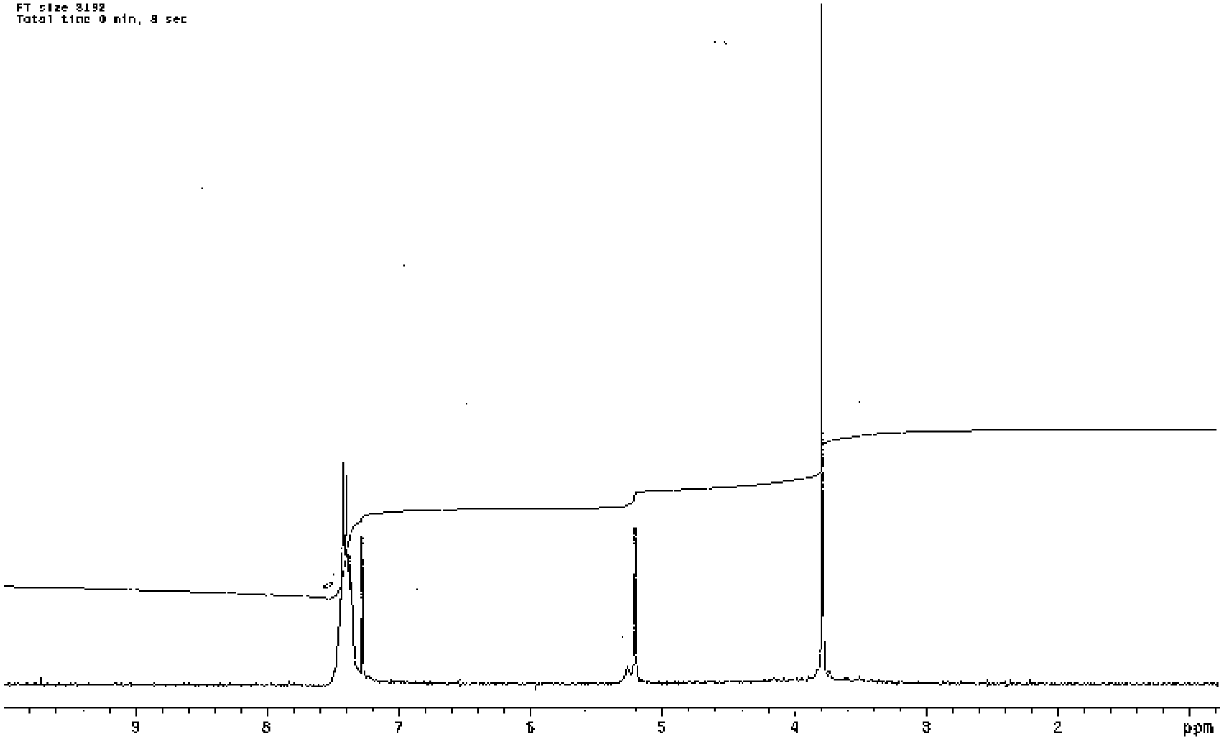
Methyl mandelate





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STANDARD 1H OBSERVE

Pulse Sequence: s2pul

 Solvent: CDCl3
 Ambient temperature
GEMINI-2000BB "gemini"

PULSE SEQUENCE
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 Pulse 31.5 degrees
 Acq. time 1.333 sec
 Width 3000.3 Hz
 8 repetitions
OBSERVE   H1, 199.9750686 MHz
DATA PROCESSING
FT size 8192
Total time 0 min, 8 sec
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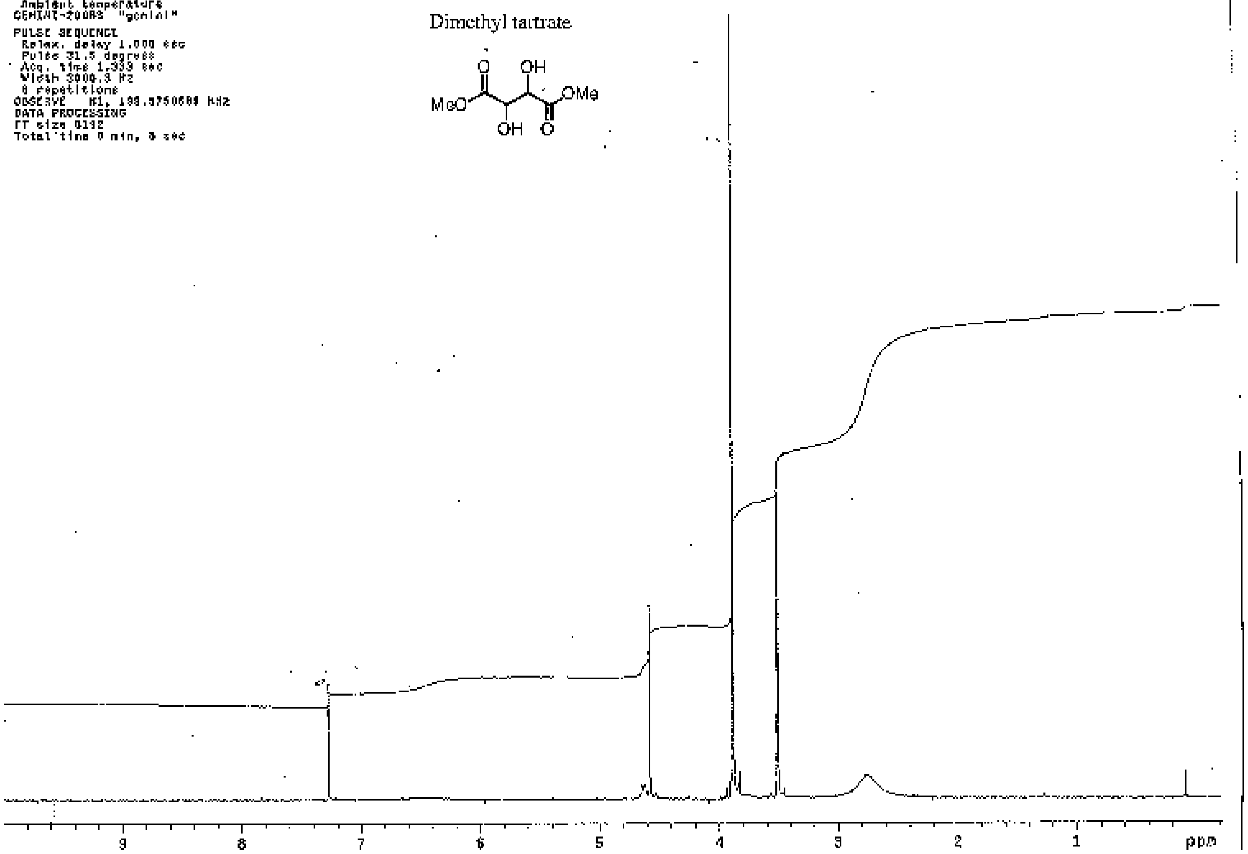
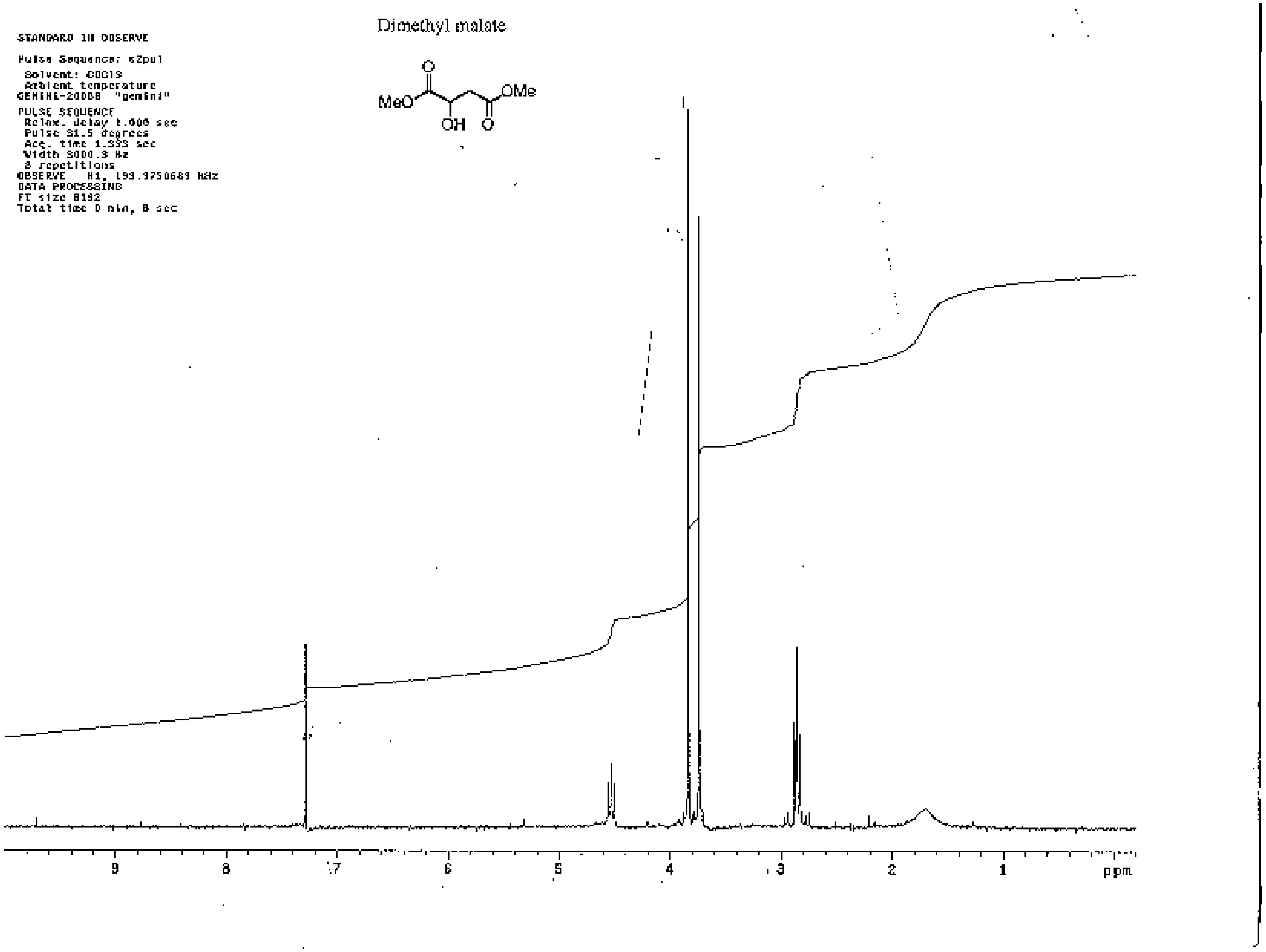
Dimethyl tartrate



Dimethyl malate



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STANDARD 1H OBSERVE

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
GEMINI-2000B  "gemini"
PULSE SEQUENCE
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 Pulse 31.5 degrees
 Acq. time 1.333 sec
 Width 3000.3 Hz
 8 repetitions
OBSERVE   H1, 199.9750683 MHz
DATA PROCESSING
FT size 8192
Total time 0 min, 8 sec
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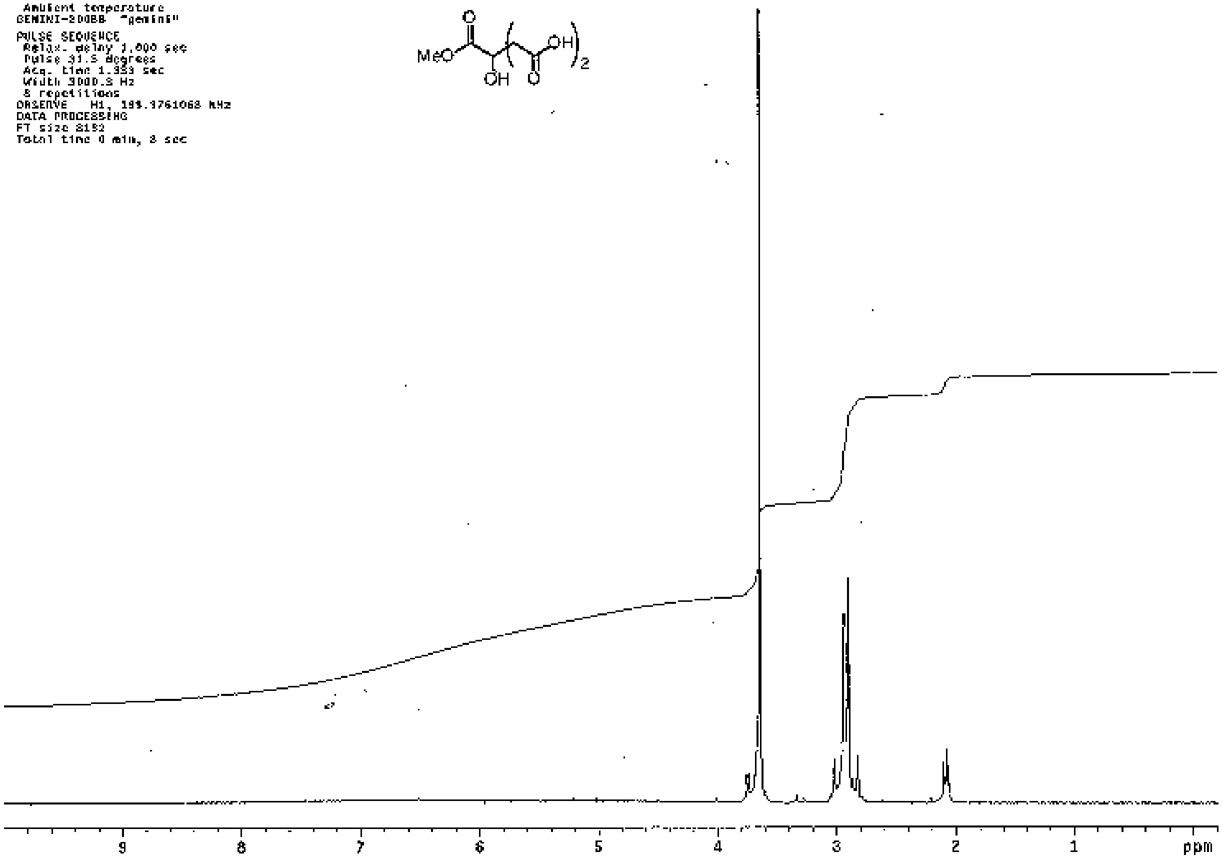
Methyl citrate



STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: Acetone
Ambient temperature
GEMINI-2000BB "gemini"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
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Width 3000.3 Hz
8 repetitions
OBSERVE H1, 199.9761062 MHz
DATA PROCESSING
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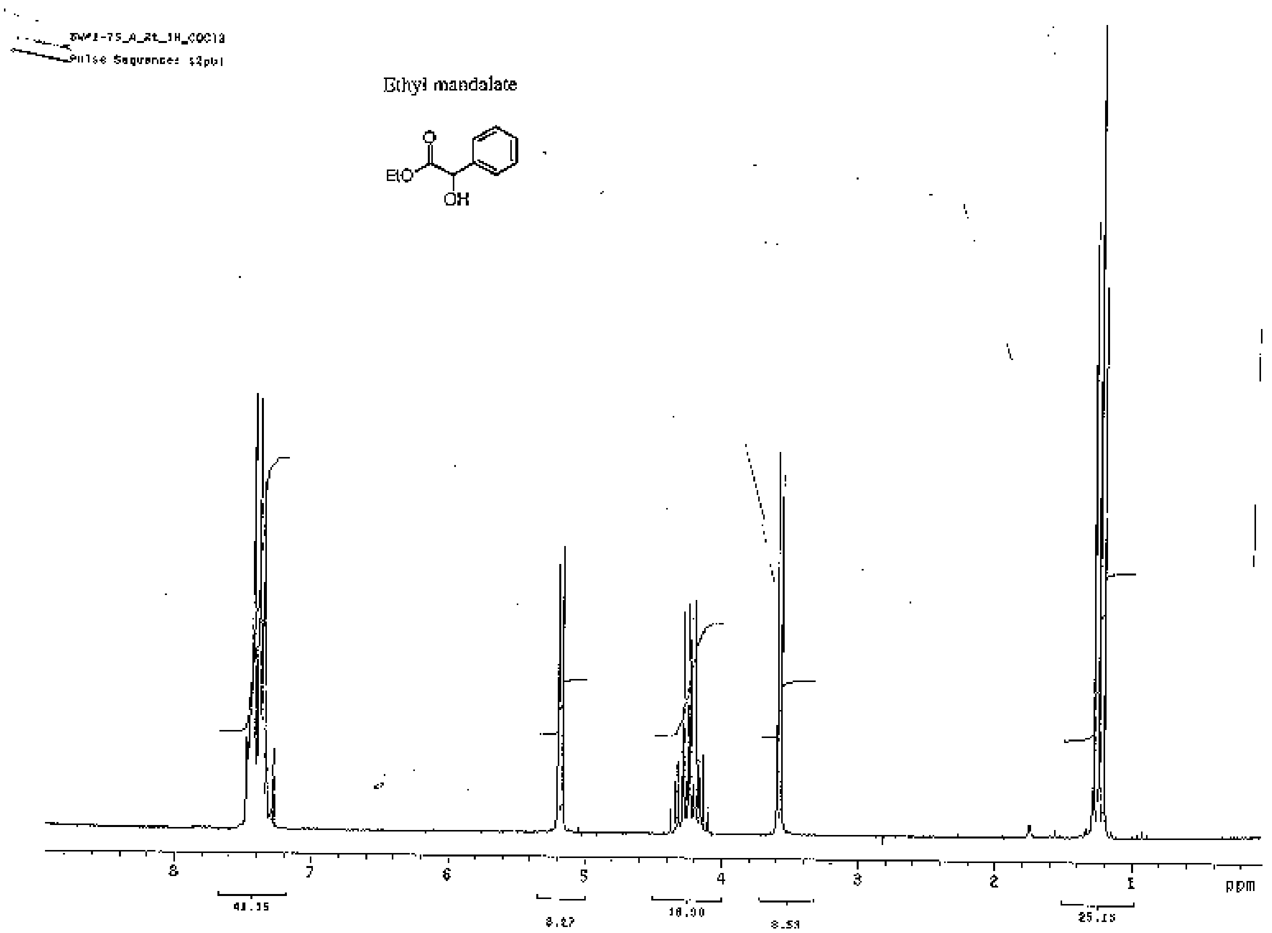
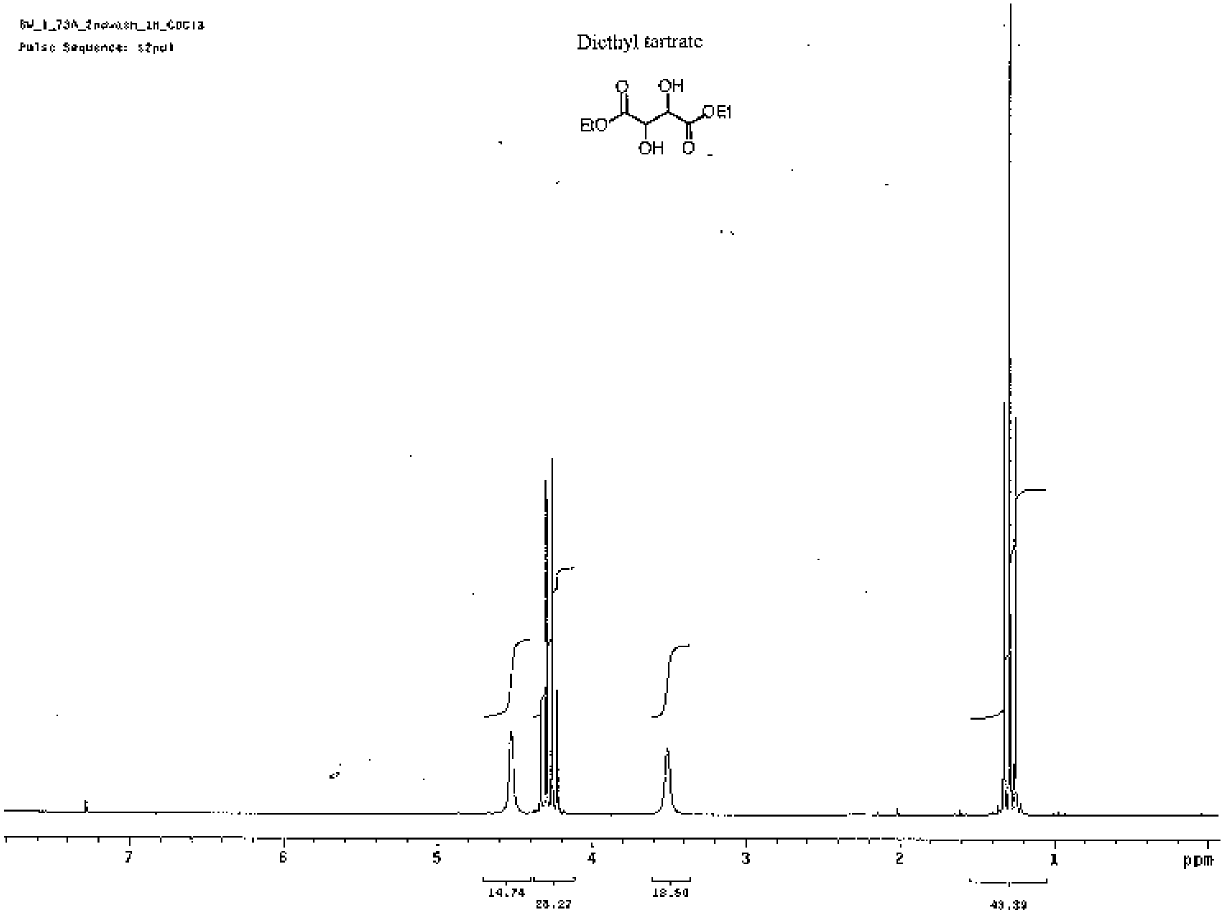
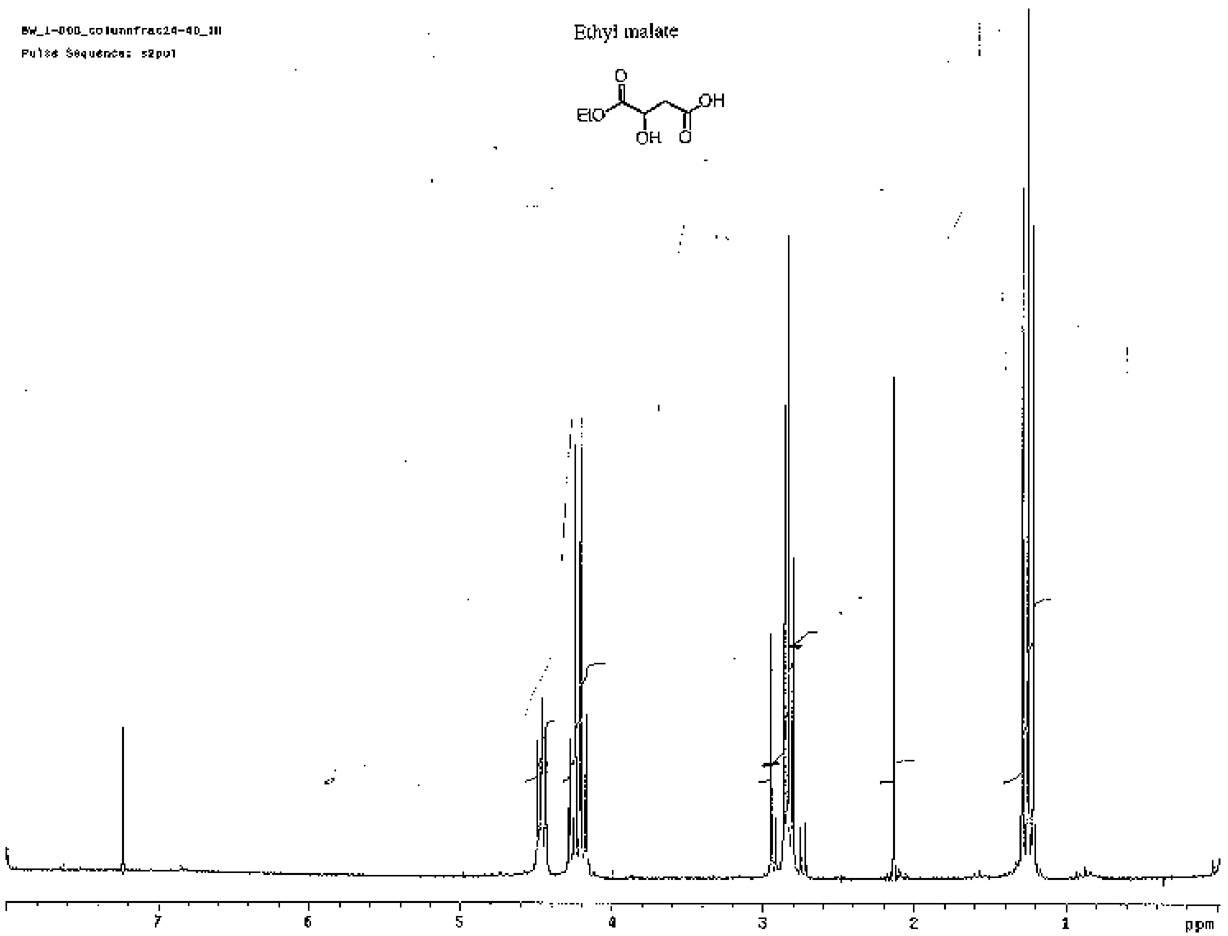
Total time 0 min, 8 sec


DWP1-75_A_Rt_1H_CDCl3
Pulse Sequence: s2pul
Ethyl mandalate
EtO
O
OH
8
7
6
5
4
3
2
1
ppm
41.35
8.27
16.30
8.53
25.15


BW_I_73A_2ndwash_1H_CDCl3
Pulse Sequence: s2pul
Diethyl tartrate
O
OH
EtO
OEt
OH
O
7
6
5
4
3
2
1
ppm
14.74
23.27
18.50
43.39

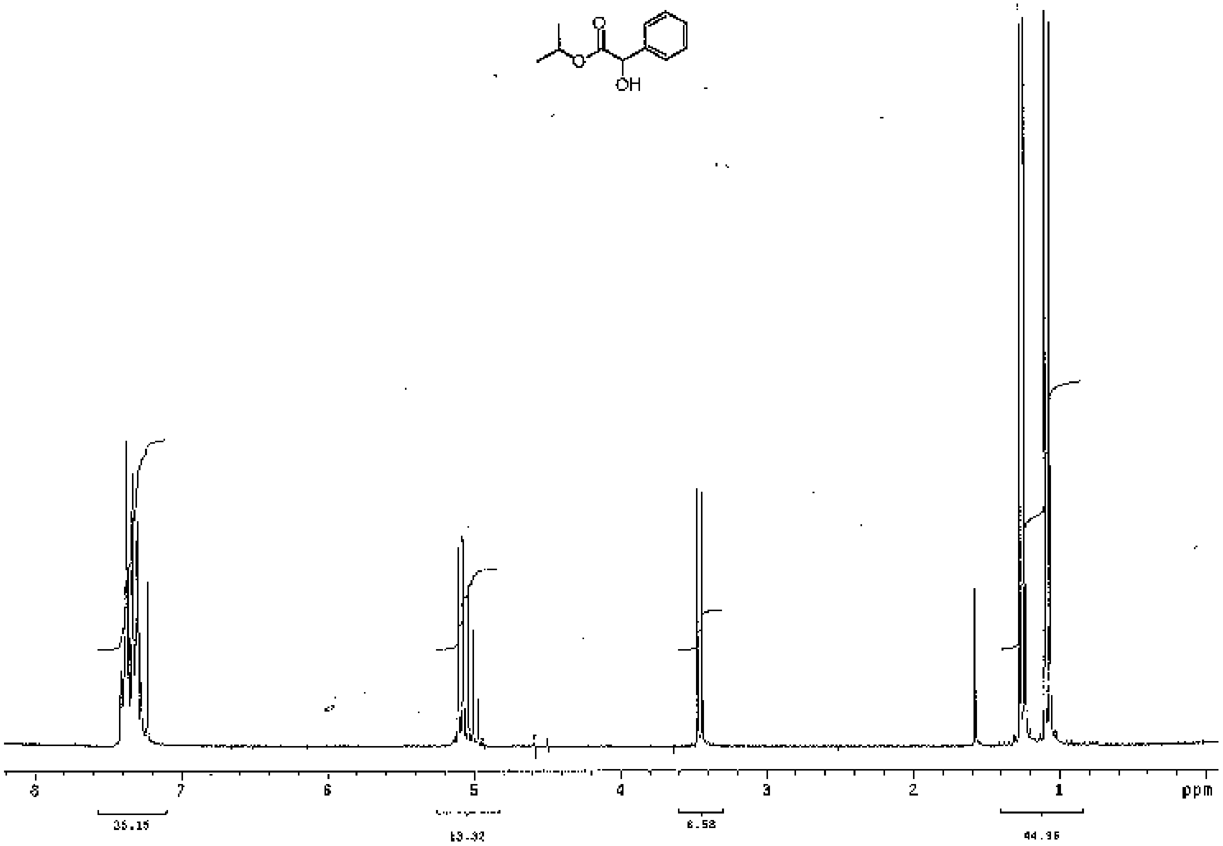
BW_1-000_columnfrac24-40_1H
Pulse Sequence: s2pul

Ethyl malate



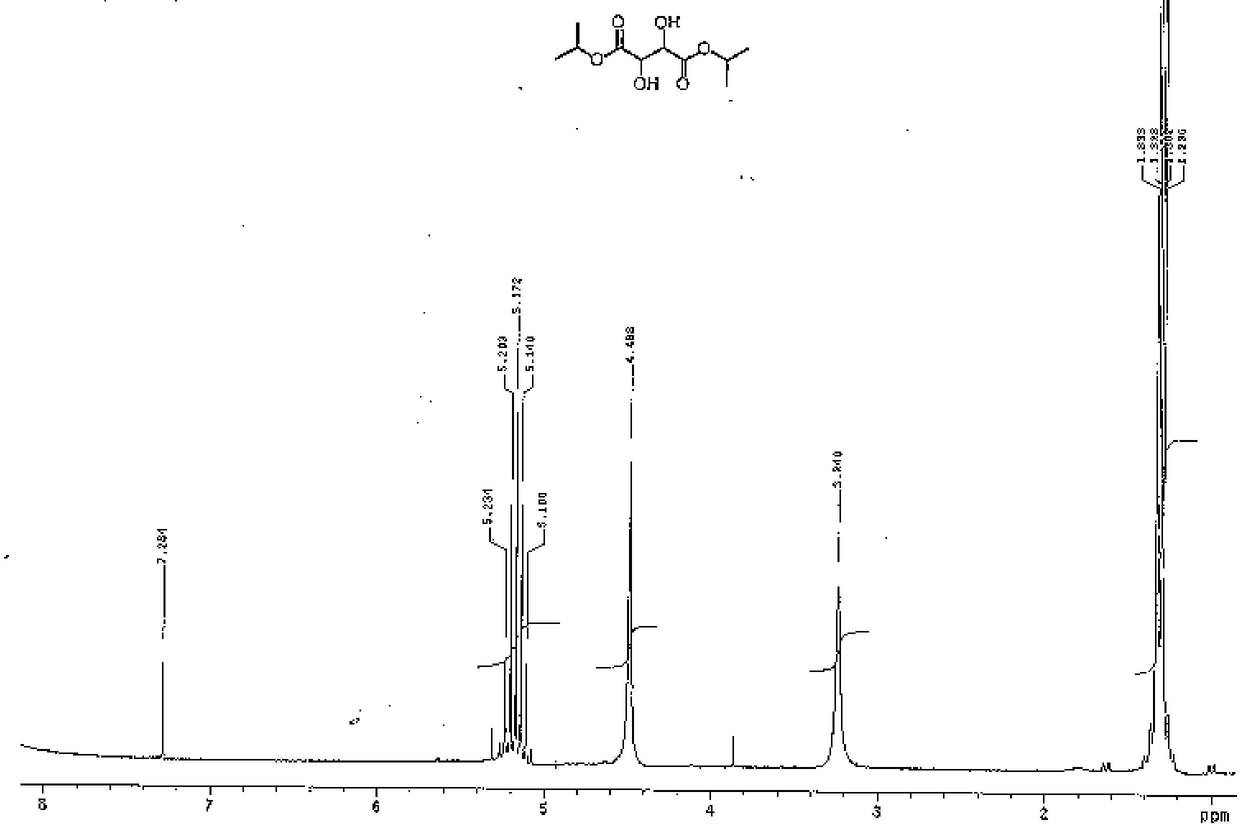
SW_I-75B_column_1H_cdcl3
Pulse Sequence: s2pul

Isopropyl mandalate



dr_s-10_crude_1H_CDCl3
Pulse Sequence: s2pul

Diisopropyl tartrate



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Pulse Sequence: s2pul

Isopropyl malate isomers