Modified Yamaguchi Reagent : Convenient and Efficient Esterification

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I. General Experimental

NMR spectra were recorded on a 500 NMR spectrometer operating at JAOL ECA500, respectively in CDCl₃ unless otherwise noted. Coupling constant (*J*) values are reported in Hertz.

Mass Spectra (MS) were performed at JAOL JMS-700 MStation at the University of Kitasato using chemical ionization or electron impact techniques.

HPLC experiments were performed on a LC solution ($\lambda = 254$ nm) system using a wakosil-II 3C18 HG (3.0 mm ϕ x 75 mm) column.

Assay yields calculated by HPLC using an internal standard method under 40 °C, 0.8 mL/min. The calibration curve was prepared from various concentrations of each esters.

Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Compounds were visualized located by UV (254 nm) and spraying the TLC plate with a solution of phosphomolybdic acid followed by heating until color developed.

Optimized geometry and molecular orbital were calculated by Density Function Theory (DFT) method using the Materials Studio DMol3 package of Accelrys Inc.^{1,2} First, optimized geometry was obtained using the Perdew-Wong GGA functional (PWC)³ and double numerical plus d-functional (DND) basis set. Second, the optimized geometry obtained were further calculated for molecular orbital using the Becke exchange plus Lee-Young-Parr correlation (B3LYP)⁴ and the double numerical plus polarization (DNP) basis set.

II. Synthetic Chemistry

Synthesis of the TCB-DMAP

2,4,6-trichlorobenzoyl-4-dimethylaminopyridinium chloride (TCB-DMAP) (1)

To a solution of DMAP (5.5 mmol) in 20 mL of dry THF was added 2,4,6-trichlorobenzoylchloride (5 mmol), and the mixture was stirred for 24 h. The precipitate was collected by suction filtration, washed with THF, and recrystallized from THF-CH₂Cl₂ mixed solvent to give TCB-DMAP (90% yield).

¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 6H), 7.54 (s, 2H), 7.79 (br, 2H), 8.41 (br, 2H); ¹³C NMR (500 MHz, CDCl₃) δ 162.2, 158.92, 139.7, 135.9, 133.5, 129.3, 127.4, 110.3, 42.8; IR (Acetonitrile / film, cm⁻¹) 1751; HRMS [M-Cl]⁺ calcd for C₁₄H₁₂N₂OCl₃ 329.0015, found 329.0012; Anal. calcd for C₁₄H₁₂Cl₄N₂O·H₂O : C, 43.78; H, 3.67; N, 7.29 Found : C, 43.77; H, 3.62; N, 7.29; mp: 126-128.5 °C

Effect of Solvents and Bases

Table 1S

solvent	yield(%)*	base	yield(%)*
Toluene	99	Et ₃ N	80
Dichloroethane	22	DIPEA	99
Acetonitrile	31		
Chloroform	<1		

*Assay yields calculated by HPLC using an internal standard method.

We screened a variety of solvents and bases to determine their efficiency in esterification of phenylpropionic acid with *l*-menthol at room temperature in the presence of TCB-DMAP. The best yields were obtained with a non-polar solvent such as toluene. The reaction also proceeded with the base *N,N'*-diisopropylethylamine (DIPEA) in excellent yield (Table 1S).

Effect of Molar Ratios of Substrates and Reagents

Table 2S

entry	W	X	Y	Z	yield (%) [*]
1	1.0	1.0	1.0	1.0	68
2	1.0	1.0	1.1	1.1	83
3	1.0	1.0	1.2	1.2	94
4	1.0	1.0	1.3	1.3	99
5	1.0	1.0	1.2	2.0	88
6	1.1	1.0	1.0	1.0	74
7	1.1	1.0	1.1	1.1	79
8	1.1	1.0	1.2	1.2	88
9	1.1	1.0	1.3	1.3	97
10	1.1	1.0	1.2	2.0	88

^{*}Assay yields of **2** calculated by HPLC using an internal standard method.

We examined the effect of molar ratios of substrates and reagents on the reaction (Table 2S). The corresponding carboxylic ester, (–)-menthyl 3-phenylpropionate (**2**), was afforded in more than 80% yield in almost of all reactions (Table 2S, entries 2-5, 8-10). Under the same reaction conditions, the use of 2.0 molar equivalents of DIPEA (entries 5, 10) gave similar results as those of reactions with a 1.2 equivalents of DIPEA (entries 3, 8). Nearly quantitative yields (99%) were obtained under conditions where the molar ratio was carboxylic acid / alcohol / TCB-DMAP / DIPEA (1.0 : 1.0 : 1.3 : 1.3) (entry 4). This outcome indicates that this esterification proceeds with high yields by treating equimolar amounts of the carboxylic acid and alcohol with a 30% molar excess of both TCB-DMAP and DIPEA. Increasing the reaction time from 2 to 24 h improved the yield from 93% to 99% (only 24 h data shown).

General Procedure for the Synthesis of Esters

(-)-menthyl 3-phenylpropionate (2) (Table 1, entry 1) (general method A)

To a solution of phenylpropionic acid (0.20 mmol) and DIPEA (0.26 mmol) in 2 mL of anhydrous toluene was added TCB-DMAP (**1**) (0.26 mmol) and stirred for 1 min. The mixture was added *l*-menthol (0.20 mmol) over 1 min and stirred for 24 h at room temperature. The portion (50 μ L) of the mixture was added coumarin as internal standard substance, and diluted with 2 mL of acetonitrile / H₂O (5 : 1). The solution was analyzed by HPLC using an internal method of coumarin (99% yield).

¹H NMR (500 MHz, CDCl₃) δ 0.70 (d, 3H, *J*=6.9 Hz), 0.88 (m, 8H), 1.03 (m, 1H), 1.33 (m, 1H), 1.47 (m, 1H), 1.69 (m, 3H), 1.93 (m, 1H), 2.61 (dd, 2H, *J*=8.6, 7.5 Hz), 2.95 (dd, 2H, *J*=7.7, 7.2 Hz), 4.67 (m, 1H), 7.19 (m, 3H), 7.27 (m, 2H); ¹³C NMR (500 MHz, CDCl₃) δ 172.5, 140.5, 128.4, 128.3, 126.1, 74.1, 46.9, 40.9, 36.2, 34.2, 31.3, 31.0, 26.1, 23.3, 22.0, 20.1, 16.2; IR (neat, KBr, cm⁻¹) 1731; HRMS [M]⁺ calcd for C₁₉H₂₈O₂ 288.2089, found 289.2177

benzyl 3-phenylpropionate (3) (Table 1, entry 2) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (94% yield).

¹H NMR (500 MHz, CDCl₃) δ 2.68 (t, 2H, *J*=7.7 Hz), 2.97 (t, 2H, *J*=7.7 Hz), 5.10 (s, 2H), 7.28 (m, 10H); ¹³C NMR (500 MHz, CDCl₃) δ 153.5, 127.7, 124.1, 118.2, 118.1, 118.0, 117.9, 116.4, 68.4, 44.1, 40.1; IR (neat, KBr, cm⁻¹) 1736; HRMS [M]⁺ calcd for C₁₆H₁₆O₂ 240.1150, found 240.1146

DL-1-phenylethyl 3-phenylpropionate (4) (Table 1, entry 3) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (88% yield).

¹H NMR (500 MHz, CDCl₃) δ 1.50 (d, 3H, *J*=6.6 Hz), 2.65 (m, 2H), 2.95 (t, 2H, *J*=7.8 Hz), 5.88 (q, 1H, *J*=6.6 Hz), 7.18 (m, 3H), 7.23-7.35 (m, 7H); ¹³C NMR (500 MHz, CDCl₃) δ 153.1, 128.7, 127.7, 118.1, 118.0, 117.6, 116.3, 116.2, 73.3, 44.3, 40.1, 33.1; IR (neat, KBr, cm⁻¹) 1735; HRMS [M]⁺ calcd for C₁₇H₁₈O₂ 254.1307, found 254.1333

(*E*)-3-phenyl-2-propenyl 3-phenylpropionate (5) (Table 1, entry 4) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (93% yield).

¹H NMR (500 MHz, CDCl₃) δ 2.68 (dd, 2H, *J*=8.0, 7.5 Hz), 2.98 (dd, 2H, *J*=8.0, 7.5 Hz), 4.73 (d, 2H, *J*=6.3 Hz), 6.25 (m, 1H), 6.62 (d, 1H, *J*=15.5 Hz), 7.19-7.39 (m, 10H); ¹³C NMR (500 MHz, CDCl₃) δ 172.8, 140.6, 136.3, 134.3, 128.7, 128.6, 128.5, 128.2, 126.8, 126.4, 123.3, 65.2, 36.0, 31.1; IR (neat, KBr, cm⁻¹) 1735; HRMS [M]⁺ calcd for C₁₈H₁₈O₂ 266.1307, found 266.1315

(-)-menthyl benzoate (6) (Table 1, entry 5) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (95% yield).

^1H NMR (500 MHz, CDCl_3) δ 0.79 (d, 3H, $J=6.9$ Hz), 0.92 (m, 7H), 1.11 (m, 2H), 1.55 (m, 2H), 1.73 (m, 2H), 1.96 (m, 1H), 2.12 (m, 1H), 4.93 (m, 1H), 7.43 (t, 1H, $J=7.7$, 7.7 Hz), 7.54 (t, 1H, $J=7.5$, 7.5 Hz), 8.04 (d, 2H, $J=6.8$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 166.2, 132.8, 131.0, 129.6, 128.4, 74.9, 47.4, 41.1, 34.4, 31.6, 26.6, 23.7, 22.2, 20.9, 16.6; IR (neat, KBr, cm^{-1}) 1716; HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ 261.1855, found 261.1855

benzyl benzoate (7) (Table 1, entry 6) (general method B)

To a solution of benzoic acid (0.20 mmol) and DIPEA (0.26 mmol) in 2 mL of anhydrous toluene was added TCB-DMAP (**1**) (0.26 mmol) and stirred for 1 min. The mixture was added Benzyl alcohol (0.20 mmol) over 1 min and stirred for 24 h at room temperature. The residue was dissolved in EtOAc (20 mL), and the solution was washed with H_2O (15 mL x 2), sat. NaHCO_3 (15 mL x 2), H_2O (15 mL x 2), 1 M HCl (15 mL x 2) and brine (15 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (Hex : EtOAc, 100 : 1) to give benzyl benzoate (88% yield).

^1H NMR (500 MHz, CDCl_3) δ 5.37 (s, 2H), 7.40 (m, 7H), 7.55 (m, 1H), 8.07 (m, 2H); ^{13}C NMR (500 MHz, CDCl_3) δ 166.6, 136.2, 133.2, 130.2, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8; IR (neat, KBr, cm^{-1}) 1720; HRMS $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2$ 212.0837, found 212.0838

DL-1-phenylethyl benzoate (8) (Table 1, entry 7) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (88% yield).

^1H NMR (500 MHz, CDCl_3) δ 1.67 (dd, 3H, $J=6.5, 6.5$ Hz), 6.14 (q, 1H, $J=6.5$, 6.5 Hz), 7.31 (m, 1H), 7.37 (t, 2H, $J=7.5$, 7.2 Hz), 7.44 (m, 4H), 7.55 (t, 1H, $J=7.4$, 7.4 Hz), 8.08 (d, 2H, $J=7.2$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 148.0, 128.8, 121.7, 119.8, 119.1, 118.2, 118.0, 117.7, 116.2, 73.7, 33.3; IR (neat, KBr, cm^{-1}) 1717; HRMS $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{O}_2$ 226.0994, found 226.0999

(E)-3-phenyl 2-propenyl benzoate (9) (Table 1, entry 8) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (77% yield).

^1H NMR (500 MHz, CDCl_3) δ 4.99 (d, 2H, $J=6.4$ Hz), 6.41 (m, 1H), 6.75 (d, 1H, $J=16.0$ Hz), 7.26 (m, 1H), 7.33 (m, 1H), 7.44 (m, 4H), 7.57 (m, 1H), 8.01 (d, 1H, $J=7.4$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 166.4, 136.1, 134.2, 133.0, 130.2, 129.6, 128.6, 128.4, 128.1, 126.6, 123.2, 65.5; IR (neat, KBr, cm^{-1}) 1735; HRMS $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2$ 266.1307, found 266.1315

(-)-menthyl (E)-phenylacrylate (10) (Table 1, entry 9) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (>99% yield).

¹H NMR (500 MHz, CDCl₃) δ 0.79 (d, 3H, *J*=6.9 Hz), 0.92 (m, 7H), 1.07 (m, 2H), 1.50 (m, 2H), 1.70 (m, 2H), 1.93 (m, 1H), 2.07 (m, 1H), 4.83 (m, 1H), 6.44 (d, 1H, *J*=16.1 Hz), 7.37 (m, 3H), 7.53 (m, 2H), 7.67 (d, 1H, *J*=16.1 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 166.7, 144.5, 134.6, 130.3, 129.0, 128.1, 118.8, 74.4, 47.3, 43.6, 41.1, 34.4, 31.5, 26.4, 23.6, 22.1, 20.9, 16.5; IR (neat, KBr, cm⁻¹) 1709; HRMS [M]⁺ calcd for C₁₉H₂₆O₂ 286.1933, found 286.1934

benzyl (*E*)-phenylacrylate (11) (Table 1, entry 10) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (91% yield).

¹H NMR (500 MHz, CDCl₃) δ 5.25 (s, 2H), 6.49 (d, 1H, *J*=15.9 Hz), 7.37 (m, 8H), 7.51 (m, 2H), 7.73 (d, 1H, *J*=15.9 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 166.8, 145.2, 136.0, 134.3, 130.4, 128.9, 128.6, 128.3, 128.3, 128.1, 117.8, 66.4; IR (neat, KBr, cm⁻¹) 1714; HRMS [M]⁺ calcd for C₁₆H₁₄O₂ 238.0994, found 238.0987

DL-1-phenylethyl (*E*)-phenylacrylate (12) (Table 1, entry 11) (general method A)

Assay yields calculated by HPLC using an internal standard method of coumarin (90% yield).

¹H NMR (500 MHz, CDCl₃) δ 1.62 (d, 2H, *J*=6.5 Hz), 6.03 (q, 1H, *J*=6.6, 6.5 Hz), 6.48 (d, 1H, *J*=16.1 Hz), 7.27-7.53 (m, 10H), 7.70 (d, 1H, *J*=16.1 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 166.4, 145.0, 141.9, 134.5, 130.5, 130.4, 129.0, 128.7, 128.2, 128.0, 126.3, 118.5, 72.5, 22.4; IR (neat, KBr, cm⁻¹) 1711; HRMS [M]⁺ calcd for C₁₇H₁₆O₂ 252.1150, found 252.1156

(*E*)-3-phenyl-2-propenyl (*E*)-phenylacrylate (13) (Table 1, entry 12) (general method A)

Assay yields calculated by HPLC (acetomitrile / H₂O (4 : 1)) using an internal standard method of coumarin 84% yield).

¹H NMR (500 MHz, CDCl₃) δ 4.88 (d, 2H, *J*=6.4 Hz), 6.37 (dt, 1H, *J*=6.4, 15.9 Hz), 6.49 (d, 1H, *J*=16.0 Hz), 6.71 (d, 1H, *J*=16.0 Hz), 7.25-7.54 (m, 11H), 7.74 (d, 1H, *J*=16.0 Hz); ¹³C NMR (500 MHz, CDCl₃) δ 145.3, 136.3, 134.5, 134.4, 130.5, 129.0, 128.7, 128.24, 128.21, 126.8, 123.4, 118.0; IR (neat, KBr, cm⁻¹) 1713; HRMS [M]⁺ calcd for C₁₈H₁₆O₂ 265.150, found 264.1154

Synthesis of the Pheromone of *Linyphia triangularis*

methyl (*R*)-(-)-3-(*tert*-butyldimethylsilyloxy)butyrate (15**)**

To a solution of methyl (*R*)-(-)-3-hydroxybutyrate (**14**) (10.2 mmol) and imidazole (25.5 mmol) in 9 mL of dry-DMF was added dropwise to a TBDMS-Cl (13.0 mmol) in 1 mL of dry-DMF over 2 min, and the mixture was stirred for 24 h. The residue was dissolved in EtOAc, and the solution was washed with sat. NaHCO₃, H₂O and brine. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (10 : 1)) to give (**15**) (>99% yield).

¹H NMR (500 MHz, CDCl₃) δ : 0.05 (d, 6H, *J*=11.5 Hz), 0.86 (s, 9H), 1.19 (d, 3H, *J*=5.5 Hz), 2.38 (dd, 1H, *J*=5.2, 14.3 Hz), 2.48 (m, 1H), 3.66 (s, 3H), 4.28 (m, 1H)

(*R*)-(-)-3-(*tert*-butyldimethylsilyloxy)butyric acid (16**)**

To a solution of LiOH·H₂O (0.75 mmol) in 2 mL of THF / H₂O (5 : 3) was added compound (**15**) (0.50 mmol) in 0.25 mL THF. The mixture was stirred for 17 h and concentrated in vacuo. The residue was dissolved in CHCl₃, and the solution was washed with 1 M HCl. The organic layer was dried over MgSO₄ and concentrated in vacuo to give colorless oil (**16**)(>99% yield).

¹H NMR (500 MHz, CDCl₃) δ : 0.09 (d, 6H, *J*=6.9 Hz), 0.88 (s, 9H), 1.24 (d, 3H, *J*=6.3 Hz), 2.49 (d, 2H, *J*=5.7 Hz), 4.28 (m, 1H)

(*R*)-(-)-3-(*tert*-butyldimethylsilyloxy)butyrate (17**)**

To a solution of (**16**) (0.46 mmol) and DIPEA (0.60 mmol) in 2 mL of anhydrous toluene was added TCB-DMAP (0.60 mmol) and stirred for 1 min. The mixture was added benzyl alcohol (0.46 mmol) over 1 min and stirred for 24 h. The residue was dissolved in EtOAc (20 mL), and the solution was washed with H₂O, sat. NaHCO₃, H₂O, 1 M HCl and brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (10 : 1)) to give (**17**) (>99% yield).

¹H NMR (500 MHz, CDCl₃) δ : 0.04 (d, 6H, *J*=14.3 Hz), 0.85 (s, 9H), 1.19 (d, 3H, *J*=6.3 Hz), 2.43 (dd, 1H, *J*=5.2, 14.3 Hz), 2.53 (m, 1H), 4.30 (m, 1H), 5.10 (m, 2H), 7.30-7.36 (m, 5H)

(*R*)-(-)-3-hydroxybutyrate (18**)**

(**17**) (1.33 mmol) was dissolved in 2 mL of CH₂Cl₂. The solution was added 2 mL of TFA and stirred for 1 min. The residue was diluted by adding CH₂Cl₂, and the solution was quenched by sat. NaHCO₃. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (1 : 1)) to give (**18**) (74% yield).

^1H NMR (500 MHz, CDCl_3) δ : 1.23 (d, 3H, $J=6.3$ Hz), 2.45-2.57 (m, 2H), 4.22 (m, 1H), 5.15 (m, 2H), 7.31-7.39 (m, 5H)

(*R*)-(-)-2-benzyloxycarbonyl-1-methylethyl (*R*)-(-)-3-(*tert*-butyldimethylsilyloxy)butyrate (19)

To a solution of (**16**) (0.69 mmol) and DIPEA (0.88 mmol) in 1 mL of anhydrous toluene was added TCB-DMAP (0.90 mmol) and stirred for 1 min. The mixture was added (**18**) (0.69 mmol) in 2 mL of anhydrous toluene 1 min and stirred for 24 h. The residue was dissolved in EtOAc (20 mL), and the solution was washed with H_2O , sat. NaHCO_3 , H_2O , 1 M HCl and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (10 : 1)) to give (**19**) (>99% yield).

^1H NMR (500 MHz, CDCl_3) δ : 0.05 (d, 6H, $J=6.8$ Hz), 0.87 (s, 9H), 1.17 (d, 3H, $J=6.3$ Hz), 1.29 (d, 3H, $J=6.3$ Hz), 2.27-2.73 (m, 4H), 4.30 (m, 1H), 5.12 (s, 2H), 5.27 (m, 1H), 7.32-7.36 (m, 5H)

(*R*)-(-)-2-benzyloxycarbonyl-1-methylethyl (*R*)-(-)-3-hydroxybutyrate (20)

(**19**) (0.50 mmol) was dissolved in 1 mL of CH_2Cl_2 . The solution was added dropwise to 2 mL of TFA over 1 min, and stirred for 1 min. The residue was diluted by adding CH_2Cl_2 , and the solution was quenched by sat. NaHCO_3 . The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (3 : 2)) to give (**20**) (94% yield).

^1H NMR (500 MHz, CDCl_3) δ : 1.20 (d, 3H, $J=6.3$ Hz), 1.31 (d, 3H, $J=6.3$ Hz), 2.30-2.70 (m, 4H), 4.15 (m, 1H), 5.12 (s, 2H), 5.34 (m, 1H), 7.32-7.37 (m, 5H)

(*R*)-(-)-2-[(*R*)-(-)-2-benzyloxy carbonyl-1-methylethoxycarbonyl]-1-methylethyl (*R*)-(-)-3-(*tert*-butyldimethylsilyloxy)butyrate (21)

To a solution of (**16**) (0.44 mmol) and DIPEA (0.57 mmol) in 2 mL of anhydrous toluene was added TCB-DMAP (0.58 mmol) and stirred for 1 min. The mixture was added (**20**) (0.44 mmol) in 1 mL of anhydrous toluene over 1 min, and stirred for 24 h. The residue was dissolved in EtOAc, and the solution was washed with sat. NaHCO_3 , 1 M HCl and brine. The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (10 : 1)) to give (**21**) (91% yield).

^1H NMR (500 MHz, CDCl_3) δ : 0.05 (d, 6H, $J=6.9$ Hz), 0.86 (s, 9H), 1.18 (d, 3H, $J=6.3$ Hz), 1.26 (d, 3H, $J=6.3$ Hz), 1.28 (d, 3H, $J=6.9$ Hz), 2.35-2.70 (m, 6H), 4.23 (m, 1H), 5.12 (s, 2H), 5.20 (m, 1H), 5.30 (m, 1H), 7.32-7.37 (m, 5H); $[\alpha]_{\text{D}}^{24} = -9.7$ (c 1.0, CHCl_3)

(*R*)-(-)-2-[(*R*)-(-)-2-benzyloxycarbonyl-1-methyl ethoxycarbonyl]-1-methyl ethyl (*R*)-(-)-3-hydroxybutyrate (22)

(**21**) (0.34 mmol) was dissolved in 0.35 mL of CH_2Cl_2 . The solution was added dropwise to 0.35 mL

of TFA over 1 min, and stirred for 1 min. The residue was diluted by adding CH₂Cl₂, and the solution was quenched by sat. NaHCO₃. The organic layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Hex / EtOAc (1 : 1)) to give **(22)** (>99% yield). ¹H NMR (500 MHz, CDCl₃) δ : 1.22 (d, 3H, *J*=6.3 Hz), 1.28 (m, 6H), 2.35-2.70 (m, 6H), 4.17 (m, 1H), 4.29 (m, 1H), 5.12 (s, 2H), 5.29 (m, 2H), 7.31-7.37 (m, 5H); [α]_D²⁴ = -1.6 (c 1.0, CHCl₃)

(R)-(-)-2-[(R)-(-)-2-carboxy-1-methylethoxy carbonyl]-1-methylethyl

(R)-(-)-3-hydroxybutyrate (23)

(22) (0.418 mmol) was dissolved in 10 mL of EtOH. To the solution was added Pd/C (5%) (10 mg), and stirred under H₂ for 24 h. The residue was filtrated and concentrated in vacuo to give colorless oil **(23)** (>99% yield).

¹H NMR (500 MHz, CDCl₃) δ : 1.25 (d, 3H, *J*=6.9 Hz), 1.30 (m, 6H), 2.41-2.64 (m, 6H), 4.29 (m, 1H), 5.37 (m, 2H); ¹³C NMR (500 MHz, CDCl₃) δ 173.5, 171.9, 170.0, 68.1, 67.8, 64.9, 43.1, 41.2, 40.8, 22.4, 20.2, 20.1; HRMS [M+H]⁺ calcd for C₁₂H₂₁O₇ 277.1287, found 277.1291; [α]_D²⁴ = -23.8 (c 1.0, CHCl₃)

Synthesis of Reaction Intermediate

2,4,6-trichlorobenzoic phenylpropionic anhydride (24) (II)

Phenylpropionic acid (0.5 mmol) and triethylamine (0.5 mmol) were dissolved in 2 mL of toluene. The solution was added to 2,4,6-trichlorobenzoyl chloride (0.5 mmol) and stirred for 4 h. The mixture solution was dissolved in Hexane and filtered. The residue was concentrated in vacuo. The mixed anhydride (II) in the reaction mixture was observed in IR spectrum at room temperature but decompose quickly in isolation operation.

^1H NMR (500 MHz, CDCl_3) δ :2.74 (t, 2H, $J=7.7$ Hz), 2.96 (t, 2H, $J=7.7$ Hz), 7.20 (m, 3H), 7.29 (m, 2H), 7.39 (s, 2H); ^{13}C NMR (500 MHz, CDCl_3) δ 168.6, 157.7, 139.7, 137.7, 133.2, 129.9, 128.8, 128.5, 128.4, 126.7, 36.9, 30.3; IR (Acetonitrile / film, cm^{-1}) 1819, 1784, 1761

4-dimethylamino-1-(3-phenylpropionyl)-pyridinium chloride (25) (III)

DMAP (0.5 mmol) was dissolved in 5 mL of THF. The solution was added to phenylpropionyl chloride (0.5 mmol) and stirred for 2 h. The precipitate was collected by suction filtration, washed with THF to give (III).

^1H NMR (500 MHz, CDCl_3) δ :2.75 (t, 2H, $J=8.0$ Hz), 2.96 (t, 2H, $J=8.0$ Hz), 3.26 (s, 6H), 6.79 (d, 2H, $J=6.9$ Hz), 7.20 (m, 3H), 7.30 (m, 2H), 8.14 (d, 2H, $J=6.9$ Hz); ^{13}C NMR (500 MHz, CDCl_3) δ 150.1, 141.1, 126.9, 126.5, 118.2, 117.9, 116.5, 100.7, 47.5, 44.7, 39.4; IR (Acetonitrile / film, cm^{-1}) 1769, 1646

III. NMR spectra

2,4,6-trichlorobenzoyl-*N,N'*-dimethyl-4-aminopyridinium chloride (TCB-DMAP) (1)

(-)-menthyl 3-phenylpropionate (2)

benzyl 3-phenylpropionate (3)

DL-1-phenylethyl 3-phenylpropionate (4)

(E)-3-phenyl-2-propenyl 3-phenylpropionate (5)

(-)-menthyl benzoate (6)

benzyl benzoate (7)

DL-1-phenylethyl benzoate (8)

(E)-3-phenyl 2-propenyl benzoate (9)

(-)-menthyl (*E*)-phenylacrylate (10)

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P3            0.0 ms
Loop1
Point         1310172(ZeroFilt $\times$ 8)
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DummyScan
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RGain         52
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IRAttn0
Spinning
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Printed 2012/Apr/11 14:37:02

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P2           0.0 ms
P3           0.0 ms
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Dummy/Scan   4
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Spinning     0.0 Hz
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Printed      2012/APR/26 15:54:00

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benzyl (*E*)-phenylacrylate (11)

DL-1-phenylethyl (*E*)-phenylacrylate (12)

(E)-3-phenyl-2-propenyl (E)-phenylacrylate (13)

(R)-(-)-3-hydroxybutyrate (23)

2,4,6-trichlorobenzoic phenylpropionic anhydride (24) (II-1)

4-dimethylamino-1-(3-phenylpropionyl)-pyridinium chloride (25) (III-1)

IV. HPLC DATA

(-)-menthyl 3-phenylpropionate (2)

(-)-menthyl 3-phenylpropionate

benzyl 3-phenylpropionate (3)

benzyl 3-phenylpropionate

DL-1-phenylethyl 3-phenylpropionate (4)

(E)-3-phenyl-2-propenyl 3-phenylpropionate (5)

(-)-menthyl benzoate (6)

(-)-menthyl benzoate

DL-1-phenylethyl benzoate (8)

(*E*)-3-phenyl 2-propenyl benzoate (9)

(*E*)-3-phenyl-2-propenyl benzoate

(-)-menthyl (*E*)-phenylacrylate (10)

(-)-menthyl (*E*)-phenylacrylate

benzyl (*E*)-phenylacrylate (11)

DL-1-phenylethyl (*E*)-phenylacrylate (12)

(*E*)-3-phenyl-2-propenyl (*E*)-phenylacrylate (13)

V. FT-IR spectra

2,4,6-trichlorobenzoyl-*N,N'*-dimethyl-4-aminopyridinium chloride (TCB-DMAP) (1)

2,4,6-trichlorobenzoic phenylpropionic anhydride (24) (II-1)

4-dimethylamino-1-(3-phenylpropionyl)pyridinium chloride (25) (III-1)

(-)-menthyl 3-phenylpropionate (2)

Intermediate Spectrum

VI. Crystallographic Information

Triclinic, space group $P\bar{1}$ (#2), $a = 7.9346(14)$ Å, $b = 8.3841(15)$ Å, $c = 13.346(2)$ Å, $\alpha = 80.733(2)^\circ$, $\beta = 86.1421(2)^\circ$, $\gamma = 70.885(2)^\circ$, $V = 827.9(3)$ Å³, $Z = 2$, $D_c = 1.541$ g cm⁻³, $R_I = 0.042$ ($I > 2.00\sigma(I)$), 0.051 (all data) $R_w = 0.12$ ($I > 2.00\sigma(I)$), 0.13 (all data), GOF = 1.075. Among a total of 2838 reflections measured, 1915 were unique and the observed ($I > 2.00\sigma(I)$) 1629 reflections were used for the refinement (201 parameters). The crystal structure was solved by SIR2004 program and refined by the full matrix least-squares method on Yadokari-XG software

VII. References

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