# CHAPTER II

# EXPERIMENTAL

## 2.1 Materials and methods

The weight of all chemical substances was determined on a Mettler AE200 electrical balance. Evaporation of solvents was carried out on a Buchi Rotavapor R-114 equipped with a Büchi B-480 Water bath. All reactions were performed in oven-dried glasswares. The progress of the reaction was followed by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 $F_{254}$ 0.2 mm precoated aluminium plates and visualized using UV light (254 nm), $KMnO_4$, $Co(SCN)_2$ or anisaldehyde reagent. Column chromatography was proformed on 60-400 mesh silica gel.

Gas chromatographic (GC) experiments were performed by Miss Jirawit Yanchinda and Miss Ornuma Konghuirob and Assistant Professor Dr. Aroonsiri Shitangkoon on a gas chromatography (Agilent 6890) equipped with a flame ionization detector using chiral capillary column containing modified β-cyclodextrins (heptakis(2,3-di-*O*-methyl)-6-*O*-tert-butyldimethylsilyl)cyclomaltoheptaose) for the separation of enantiomers. Normal phase high performance liquid chromatography (HPLC) experiments were performed on Water 600$^{TM}$ using Daicel Chiralcel OD column and Chiralpak AD column in attempts for the separation of enantiomers.

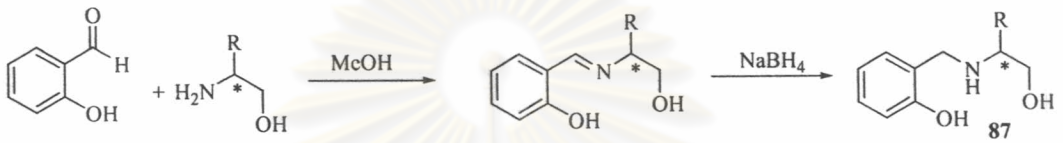
Proton ($^1$H) and carbon ($^{13}$C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-400 plus operating at 400 MHz ($^1$H) and 100 MHz ($^{13}$C) respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Coupling constant (*J*) were proton-proton coupling unless otherwise noted and reported in Hertz (Hz). Multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Melting points were measured on an Electrothermal 9100 melting point apparatus and were uncorrected. The optical rotations were measured at 26°C with Jasco P-1010 Polarimeter.

All chemicals were obtained from Fluka, Merck or Aldrich Chemical Co., Ltd. THF was distilled from sodium benzophenone ketyl radical prior to use. Other solvents for reaction were AR grade and were used without further purification. High purity nitrogen gas, hydrogen gas, and air for GC experiments were purchased from TIG.

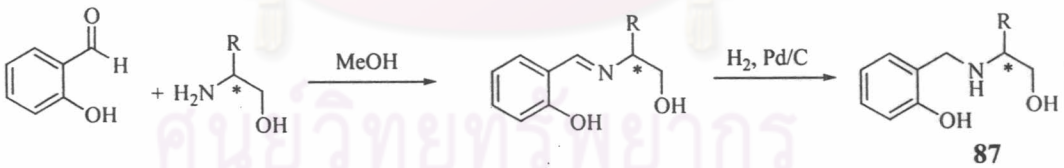
**2.2 General procedure for the synthesis of ligands 87**

**Method A : $NaBH_4$**



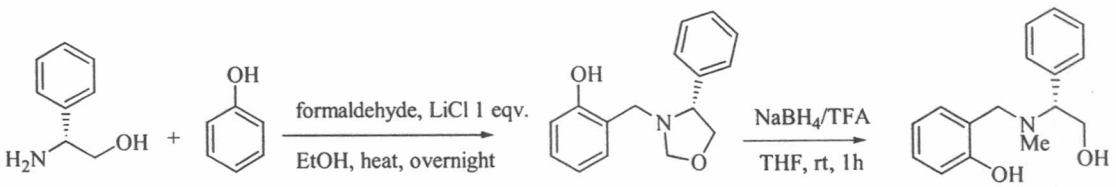

A mixture of amino alcohol (1 mmol) and aldehyde (1 mmol) in methanol (2 mL) was stirred at room temperature for 4h, then treated with $NaBH_4$ (1 mmol) after stirring for 0.5h. The reaction mixture was quenched with dil. HCl. After neutralization with $NaHCO_3$, the reaction mixture was extracted with ethyl acetate (3× 10 mL). The organic layer was washed with brine, dried with $Na_2SO_4$, and the solvent removed by rotary evaporation followed by purification by flash chromatography ($SiO_2$, hexanes/ethyl acetate).

**Method B : Hydrogenation**



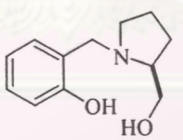

A mixture of amino alcohol (1 mmol) and aldehyde (1 mmol) in methanol (2 mL) was stirred at room temperature for 4h. Then, Pd/C (10 mol %) was added. The reaction mixture was stirred under $H_2$ at atmospheric pressure until the yellow solution turned colorless. The reaction mixture was filtered through paper filter, and the solvent was removed under vacuum. The crude product was purified by chromatography on silica gel column with hexanes/ethyl acetate (80/20).

**Method C: Three-component coupling**



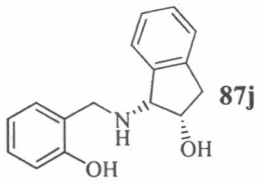

oxazolidine **89** ligand **87v**

A mixture of phenol (1 mmol), formaldehyde (200 mg), D-phenylglycinol (1 mmol) and LiCl (1 mmol) in ethanol was heated at 80 °C for 18h. After purification by flash column chromatography, the oxazolidine **89** was obtained. The next step, trifluoroacetic acid was added dropwise to a suspension of the metal hydride ($NaBH_4$, 5 mmol) and TFA (5 mmol) in anhydrous THF (5 mL) at 0°C. A solution of the oxazolidine **89** (1 mmol) in anhydrous THF (5 mL) was added dropwise to the cooled mixture. After stirring 1h at room temperature, the mixture was cooled and decomposed cautiously by 10 % sodium hydroxide aqueous solution. The mixture was then concentrated and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The oily residue was column chromatographed (hexanes/ethyl acetate 70/30, v/v).



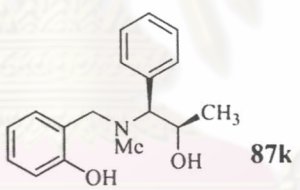

**87i**

***N*-(2'-hydroxyphenyl)methyl-(*S*)-2-hydroxymethylpyrrolidine (87i)** was prepared from the reaction of L-prolinol (202 mg, 2.0 mmol) and salicylaldehyde (268 mg, 2.2 mmol) using method A. The product was obtained as a viscous yellowish oil (235 mg, 1.2 mmol, 60 % yield). $[\alpha]^{23}_D$ = -75.0 (*c* 1.8, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.76-208 (4H, m, pyrrolidine $(CH_2)_2$), 2.37 (1H, m, pyrolidine, N-C$H_a$CH$_b$), 2.79 (1H, m, pyrrolidine, N-CH$_a$C$H_b$), 3.10 (1H, m, N-C$H$CH$_2$OH), 3.57 (1H, AB, $J$ = 14.0 Hz, ArCH$_a$$H_b$N), 3.69 (1H, A<u>B</u>X, $J_{AB}$ = 11.2, $J_{AX}$ = 3.8 Hz, CH$_a$$H_b$OH), 3.75 (1H, <u>A</u>BX, $J_{AB}$ = 11.2, $J_{AX}$ = 3.8 Hz, C$H_a$H$_b$OH), 4.33 (1H, AB, $J$ = 14.0 Hz, ArCH$_a$$H_b$N), 6.18 (br s, OH ), 6.80 (1H, apparent t, $J$ = 7.2 Hz, Ar), 6.84 (1H, d, $J$ = 8.0 Hz, Ar), 7.00 (1H, d, $J$ = 7.6 Hz, Ar), 7.18 (1H, apparent t, $J$ = 7.6 Hz, Ar); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 23.2, 27.5, 54.5, 58.3, 64.0, 65.5, 116.0, 119.1, 122.9, 128.1, 128.6, 157.6.



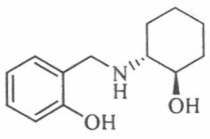
**87j**

**1-(2-Hydroxy-benzylamino)-indan-2-ol (87j)** was prepared from the reaction of (1*S*,2*R*)-1-Amino-indan-2-ol (258 mg, 2.0 mmol) and salicylaldehyde (260 mg, 2.1 mmol) using method A and B. The product was obtained as colorless oil (method A, 170 mg, 33 % yield and method B, 282 mg, 1.1 mmol, 67 % yield). $[\alpha]^{26}_{D}$ = +26.62 (*c* 1.6, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.92 (1H, ABX, $J_{AB}$ = 1.2, $J_{BX}$ = 16.8 Hz, PhC$H_a$H$_b$CHOH), 3.07 (1H, ABX, $J_{AB}$ = 4.8, $J_{BX}$ = 16.8 Hz, PhCH$_a$$H_b$CHOH), 4.06 (1H, AB, *J* = 13.6 Hz, C$H_a$H$_b$NH), 4.11 (1H, *J* = 4.8 Hz, NHC*H*CHOH), 4.23 (1H, AB, *J* = 13.6 Hz, CH$_a$$H_b$NH), 4.65 (1H, ABX, m, PhCH$_a$H$_b$C*H*OH), 5.20-5.45 (br, OH and NH), 6.83 (2H, m, Ar), 7.08 (1H, d, Ar), 7.22 (4H, m, Ar of salicyl moiety), 7.38 (1H, d, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 39.9, 50.4, 64.4, 71.6, 116.5, 119.4, 122.5, 124.8, 125.5, 127.2, 128.3, 128.9, 129.0, 139.9, 141.2, 158.0.



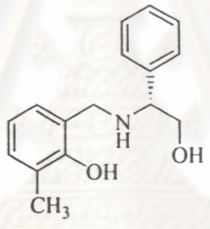
**87k**

**2-[(2-Hydroxy-1-phenyl-propylamino)-methyl]-phenol (87k)** was prepared from the reaction of (1*S*,2*R*)-1-amino-1-phenylpropan-2-ol (317 mg, 1.8 mmol) and salicylaldehyde (250 mg, 2.1 mmol) using method A. The product was obtained as white crystal (163 mg, 0.6 mmol, 60 % yield); m.p. 142.0-143.0 °C; $[\alpha]^{26}_{D}$ = +109.00 (*c* 1.8, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, d, *J* = 7 Hz), 2.35 (3H, s), 3.13 (1H, m), 3.82 (1H, $J_{AB}$ = 13.6 Hz, C$H_a$CH$_b$NMe), 3.98 (1H, $J_{AB}$ = 13.6 Hz, CH$_a$C$H_b$NMe), 4.62 (1H, d, *J* = 9.6), 6.82 (1H, m, Ar), 6.86 (1H, d, *J* = 8.4, Ar), 7.03 (1H, d, *J* = 7.2 Hz, Ar), 7.21 (1H, m, Ar), 7.39 (5H, m, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 8.65, 34.5, 57.8, 64.2, 75.9, 116.3, 118.9, 122.2, 127.1, 128.3, 128.7, 142.5, 158.3



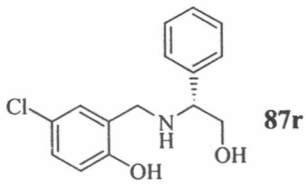
**87l**

**2-[(2-Hydroxy-cyclohexylamino)-methyl]-phenol (87l)** was prepared from the reaction of (+)-2-amino-cyclohexanol (453 mg, 4.4 mmol) and salicylaldehyde (610 mg, 5.0 mmol) using method A. The product was obtained as white crystal (217 mg, 0.9 mmol, 20 % yield); m.p. 138.0-139.0 °C; $[\alpha]^{26}_{D}$ = +86.57 (*c* 0.7, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.27 (4H, m, $CH_2CH_2$), 1.73 (2H, m, $CH_2$), 1.99-2.20 (2H, m, $CH_2$), 2.44 (1H, m, *CH*NH), 3.42 (1H, m, *CH*OH) 3.95 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 4.08 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 5.17 (br, NH and OH), 6.78 (2H, m, Ar), 7.00 (1H, d, *J* = 7.2 Hz, Ar), 7.18 (1H, m, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 24.3, 24.4, 29.9, 34.6, 50.0, 63.2, 73.8, 116.5, 119.1, 123.4, 128.1, 128.7, 158.1.



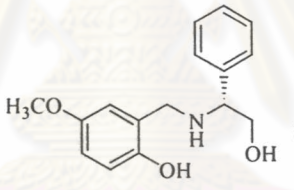
**87q**

**2-[(2-Hydroxy-1-(*R*)-phenyl-ethylamino)-methyl]-6-methylphenol (87q)** was prepared from the reaction of D-phenylglycinol (137mg, 1 mmol) and 2-hydroxy-3-methyl-benzaldehyde (290 mg, 2.1 mmol) using method A. The product was obtained as white crystal (306 mg, 1.2 mmol, 60 % yield); m.p. 101.3-102.4 °C; $[\alpha]^{26}_{D}$ = -43.38 (*c* 1.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.28 (3H, s), 3.74 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 3.80-3.91(3H, m, $CH_2OH$ and *CH*NH), 3.96 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 6.70 (1H, m, Hz, Ar of salicyl moiety), 6.79 (1H, d, *J* = 7.2 Hz, Ar of salicyl moiety), 7.07 (1H, d, *J* = 6.8 Hz, Ar of salicyl moiety), 7.36-7.46 (5H, m, Ar); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 15.8, 50.4, 64.0, 66.6, 118.9, 122.1, 125.3, 126.2, 127.5, 128.2, 129.0, 130.1, 138.7, 155.9.



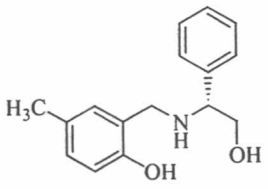

**87r**

**4-Chloro-2-[(2-hydroxy-1-(*R*)-phenyl-ethylamino)-methyl]-phenol (87r)** was prepared from the reaction of D-phenylglycinol (274 mg, 2.0 mmol) and 5-chloro-2-hydroxy-benzaldehyde (344 mg, 2.2 mmol) using method A. The product was obtained as white crystal (457 mg, 1.7 mmol, 82 % yield); m.p. 139.0-140.0 °C; $[\alpha]^{26}_{D}$ = -86.23 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.70 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 3.77-3.89 (3H, m, $CH_2OH$ and CHNH), 3.93 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 5.05 (br, s, NH and OH), 6.77 (1H, d, *J* = 8.4 Hz, Ar of salicyl moiety), 6.88 (1H, d, *J* = 2.4 Hz, Ar of salicyl moiety), 7.13 (1H, dd, *J* = 2.4 and *J* = 8.4 Hz, Ar of salicyl moiety), 7.30-7.45 (5H, m, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$), δ 49.2, 63.9, 66.2, 117.8, 123.9, 123.9, 127.8, 128.2, 128.4, 128.8, 129.8, 138.4, 156.4.



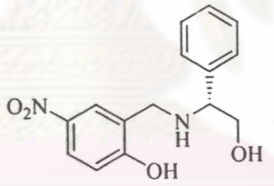

**87s**

**2-[(2-Hydroxy-1-(*R*)-phenyl-ethylamino)-methyl]-4-methoxyphenol (87s)** was prepared from the reaction of D-phenylglycinol (274 mg, 2.0 mmol) and 2-hydroxy-5-methoxy-benzaldehyde (320 mg, 2.1 mmol) using method A. The product was obtained as white crystal (272, 1.0 mmol, 50 % yield); m.p. 88.8-90.1 °C; $[\alpha]^{23}_{D}$ = -70.82 (*c* 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.68 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 3.73 (3H, s), 3.76-3.86 (3H, m, $CH_2OH$ and CHNH), 3.93 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 5.05 (br, s, NH and OH), 6.50 (1H, d, *J* = 2.8 Hz, Ar of salicyl moiety), 6.74 (1H, dd, *J* = 3.2 and *J* = 8.8 Hz, Ar of salicyl moiety), 7.79 (1H, d, *J* = 8.8 Hz, Ar of salicyl moiety), 7.29-7.43 (5H, m, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 50.3, 55.8, 63.9, 66.5, 113.7, 114.4, 116.7, 123.5, 127.5, 128.2, 128.9, 138.8, 151.5, 152.6.



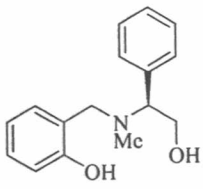

87t

**2-[(2-Hydroxy-1-(*R*)-phenyl-ethylamino)-methyl]-4-methylphenol (87t)** was prepared from the reaction of D-phenylglycinol (274 mg, 2.0 mmol) and 2-hydroxy-5-methyl-benzaldehyde (280 mg, 2.1 mmol) using method A. The product was obtained as white crystal (232 mg, 0.9 mmol, 45 % yield); m.p. 131.7-133.5 °C; $[\alpha]^{23}_{D}$ = -74.75 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.52 (3H, s), 3.70 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 3.75-3.87 (3H, m, $CH_2OH$ and CHNH), 3.93 (1H, AB, *J* = 13.6 Hz, $CH_aH_bNH$), 5.05 (br, s, NH and OH), 6.74 (1H, apparent t, *J* = 7.2 Hz , Ar of salicyl moiety), 6.78 (1H, d, *J* = 8.0 Hz, Ar of salicyl moiety), 7.00 (1H, dd, *J* = 8.0 and *J* = 1.6 Hz, Ar of salicyl moiety), 7.29-7.45 (5H, m, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.5, 50.2, 63.9, 66.5, 116.1, 122.5, 127.5, 128.2, 128.4, 129.0, 129.1, 129.2, 138.8, 155.3.




87u

**4-Nitro-2-[(2-hydroxy-1-(*R*)-phenyl-ethylamino)-methyl]-phenol (87u)** was prepared from the reaction of D-phenylglycinol (137mg, 1 mmol) and 2-hydroxy-5-nitro-benzaldehyde (350 mg, 2.1 mmol) using method A. The product was obtained as yellow crystal (247 mg, 0.9, 41 % yield); m.p. 127.5-128.3 °C; $[\alpha]^{26}_{D}$ = -58.94 (*c* 1.2, ethanol); $^1$H NMR (DMSO, 400 MHz) δ 3.92 (2H, m), (1H, AB, *J* = 13.2 Hz, $CH_aH_bNH$), 4.05 (1H, AB, *J* = 13.2 Hz, $CH_aH_bNH$), 4.36 (1H, broad), 7.03 (1H, d, *J* = 9.2 Hz, Ar of salicyl moiety), 7.43 (5H, m, Ar), 8.12 (1H, dd, *J* = 2.8, *J* = 9.2 Hz, Ar of salicyl moiety), 8.15 (1H, d, *J* = 2.8 Hz, Ar of salicyl moiety); $^{13}$C NMR (100 MHz, DMSO) δ 47.0, 64.0, 65.7, 116.5, 125.4, 125.4, 128.1, 128.2, 128.9, 137.6, 139.8, 166.9.




**87v**

**2-{[(2-Hydroxy-1-(*S*)-phenyl-ethyl)-*N*-methyl-amino]-methyl}-phenol (87v)** was prepared from the reaction of L-phenylglycinol (135 mg, 1.0 mmol), p-formaldehyde (202 mg), phenol (130 mg, 1.4 mmol) and LiCl (56 mg, 1.3 mmol) using method C. The product was obtained as white crystal (56 mg, 0.2 mmol, 22 % yield); m.p. 96.0-97.0 °C; $[\alpha]^{26}_{D}$ = +27.58 (*c* 1.6, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.27 (3H, s, NC*H*$_3$), 3.68 (1H, AB, *J* = 13.8 Hz, C*H*$_2$NH), 3.82 (1H, AB, *J* = 13.8 Hz, C*H*$_2$NH), 3.88 (1H, A<u>B</u>X, $J_{AB}$ = 5.8, $J_{BX}$ = 8.0 Hz, $CH_aH_bOH$), 3.98 (1H, <u>A</u>BX, $J_{AB}$ = 5.8, $J_{AX}$ = 11.6 Hz, $CH_aH_bOH$), 4.19 (1H, AB<u>X</u>, $J_{AX}$ = 8.0, $J_{BX}$ = 11.4 Hz, MeN$CH_X$Ph), 4.85 (br s, N*H* and O*H* ), 6.81 (1H, m, Ar), 6.87 (1H, d, *J* = 8.0 Hz, Ar of salicyl moiety), 6.95 (1H, d, *J* = 7.2 Hz, Ar of salicyl moiety), 7.21 (1H, m, Ar), 7.28-7.46 (5H, m, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 37.4, 58.0, 62.3, 69.1, 116.2, 119.3, 121.9, 128.4, 128.7, 128.8, 129.1, 135.2, 157.8.

## 2.3 General procedure for Michael addition reaction of dialkyl malonate to cyclic enones

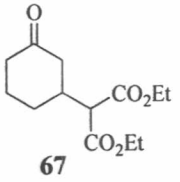
### 2.3.1 General procedure for Michael adduct catalyzed by $LiAlH_4$

A solution of $LiAlH_4$ (50 μL, 0.1 M in THF) was added to dry round bottom flask (dried THF, 2 mL) under $N_2$ gas and then added dialkyl malonate (0.5 mmol) stirred at room temperature for 1h. The mixture was added cyclohex-2-enone (0.5 mmol). The reaction was stirred for 15 h, and then the mixture was dissolved by evaporator *in vacuo*. The residue was purified by silica gel chromatography ($SiO_2$, 10 % EtOAc : Hexane).

### 2.3.2 General procedure for Michael addition of dialkyl malonate to enone catalyzed by the Li-Al-*N*-salicyl-β-amino alcohol complex

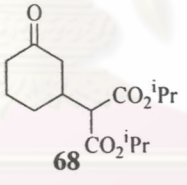
The chiral amino alcohol (0.05 mmol) in dry THF was added to a solution of $LiAlH_4$ (50 μL, 0.1 M in THF) under $N_2$ gas stirred at room temperature for 1h. Then, to the mixture was added diethyl malonate (75 μL, 0.5 mmol) and cyclohex-2-enone (48 μL, 0.5 mmol). The reaction was stirred for 15 h, and then the mixture was

concentrated by evaporator *in vacuo*. The residue was purified by silica gel chromatography ($SiO_2$, 10% EtOAc : Hexane).



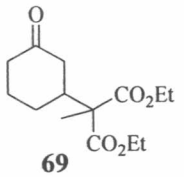

**67**

**3-[Bis(ethoxycarbonyl)methyl]cyclohexanone (67)** was prepared from diethyl malonate (76 μL, 0.50 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as colorless oil (103 mg, 0.40 mmol, 80 %) $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.28 (2×3H, apparent t, $J$ = 7.2 Hz, 2×$CH_2CH_3$), 1.51 (1H, m, $CH_2CH_aH_bCO$), 1.68 (1H, m, $CH_cH_dCH_2CO$), 1.95 (1H, m, $CH_2CH_aH_bCO$), 2.07 (1H, m, $CH_cH_dCH_2CO$), 2.28 (2H, m, $CH_cH_dCH_2CH$), 2.43 (2H, m, $CHCH_2CO$), 2.55 (1H, m, $CHCH(CO_2Et)_2$), 2.39 (1H, d, $J$=8, $CH(CO_2Et)_2$), 4.21 (2x2H, m, 2x $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$), δ 14.1, 24.5, 28.9, 38.4, 41.2, 44.5, 56.9, 61.8, 168.5, 209.8.



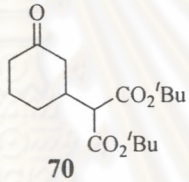

**68**

**3-[Bis(*iso*-propoxycarbonyl)methyl]cyclohexanone (68)** was prepared from diisopropyl malonate (92 μL, 0.50 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as colorless oil (118 mg, 0.41 mmol, 83 %); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.21 (2×6H, d, 2×$CH(CH_3)_2$), 1.46 (1H, m, $CH_2CH_aH_bCO$), 1.49 (1H, m, $CH_cH_dCH_2CO$), 1.63 (1H, m, $CH_2CH_aH_bCO$), 1.95 (1H, m, $CH_cH_dCH_2CO$), 2.24 (2H, m, $CH_cH_dCH_2CH$), 2.47 (2H, m, $CHCH_2CO$), 2.49 (1H, m, $CHCH(CO_2Et)_2$, 3.18 (1H, d, $J$ = 8, $CH(CO_2Et)_2$), 5.02 (4H, m, 2×$CH(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.7, 24.6, 28.7, 37.9, 41.0, 45.1, 57.1, 69.1, 167.3, 167.4, 209.8.



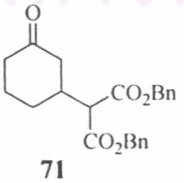

**69**

**3-[Bis(ethoxycarbonyl)ethyl]cyclohexanone (69)** was prepared from diiethyl methylmalonate (85 μL, 0.50 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as colorless oil (112 mg, 0.41 mmol, 83 %); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.24 (2×6H, apparent *t*, 2×$CH_2CH_3$), 1.39 (3H, s, $CCH_3$) 1.47 (1H, m, $CH_2CH_aH_bCO$), 1.61 (1H, m, $CH_cH_dCH_2CO$), 1.87 (1H, m, $CH_2CH_aH_bCO$), 2.07 (1H, m, $CH_cH_dCH_2CO$), 2.22 (2H, m, $CH_cH_dCH_2CH$), 2.36 (2H, m, $CHCH_2CO$), 2.49 (1H, m, $CH(CO_2Et)_2$), 4.17 (2×2H, m, 2×$CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.0, 16.7, 24.7, 26.6, 41.1, 42.5, 43.4, 56.7, 61.4, 170.8, 171.0, 210.3.




**70**

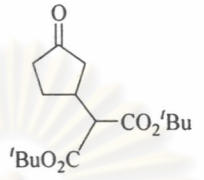
**3-[Bis(*tert*-butoxycarbonyl)methyl]cyclohexanone (70)** was prepared from di-*tert*-butyl malonate (112 μL, 0.50 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as colorless oil (139 mg, 0.45 mmol, 89 %); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.49 (2x9H, s, 2×$C(CH_3)_3$), 1.53 (1H, m, $CH_cH_dCH_aH_bCO$), 1.68 (1H, m, $CH_cH_dCH_2CO$), 2.01 (1H, m, $CH_2CH_aH_bCO$), 2.10 (2H, m, $CH_cH_dCH_2CH$), 2.28 (2H, m, $CHCH_2CO$), 2.43 (1H, m, $CH(CO_2{}^tBu)_2$), 3.10 (1H, d, *J* = 7.6, $CH(CO_2{}^tBu)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$), δ 24.6, 27.9, 27.9, 28.8, 37.9, 41.1, 45.2, 58.7, 81.9, 167.2, 167.3, 210.1.




**71**

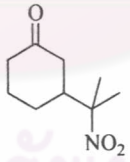
**3-[Bis(benzyloxycarbonyl)methy]cyclohexanone (71)** was prepared from dibenzyl malonate (125 μL, 0.50 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as white solid (108 mg, 0.44 mmol, 87 %); mp: 44.2-45.4 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.45 (1H, m, $CH_2CH_aH_bCO$), 1.65 (1H, m,

C$H_c$H$_d$CH$_2$CO), 1.92 (1H, m, CH$_2$CH$_a$$H_b$CO), 2.03 (1H, m, CH$_c$$H_d$CH$_2$CO), 2.23 (2H, m, CH$_c$H$_d$C$H_2$CH), 2.49 (2H, m, CHC$H_2$CO), 2.59 (1H, m, C$H$CH(CO$_2$Et), 3.44 (1H, d, $J$ = 8, C$H$(CO$_2$Et)$_2$), 5.19 (2×2H, s, 2×C$H_2$Bn), 7.36 (10H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.5, 28.7, 38.2, 41.0, 45.1, 56.8, 67.2, 67.3, 128.3, 128.5, 128.7, 135.2, 135.2, 167.5, 167.6, 209.4.



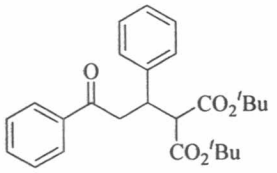

**72**

**3-[Bis(*tert*-butoxycarbonyl)methyl]cyclopentanone (72)** was prepared from di-*tert*-butyl malonate (112 μL, 0.50 mmol) and cyclopent-2-enone (40 μL, 0.50 mmol). The product was obtained as white solid (120 mg, 0.42 mmol, 85 %); mp: 78.4-79.5 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.42 (2×9H, s, 2×C(CH$_3$)$_3$), 1.60 (1H, m, CH$_2$C$H_a$H$_b$CO), 1.94 (1H, m, C$H_c$H$_d$CH$_2$CO), 2.21 (3H, m), 2.42 (1H, dd, $J$ = 8 Hz, $J$ = 18.4 Hz, C$H_e$H$_f$CO), 2.72 (1H, m, C$H$CH(CO$_2$$^t$Bu)$_2$), 3.07(1H, d, $J$ = 8 Hz, C$H$(CO$_2$$^t$Bu)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 27.4, 27.8, 27.9, 36.2, 38.2, 42.9, 58.5, 81.8, 81.8, 167.4, 167.5, 217.6.



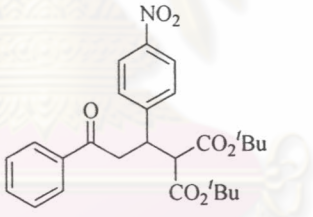

**73**

**3-(1-Methyl-1-nitro-ethyl)cyclohexanone (73)** was prepared from 2-nitropropane (120 μL, 1.20 mmol) and cyclohex-2-enone (48 μL, 0.50 mmol). The product was obtained as yellow solid (31 mg, 0.17 mmol, 34 %); $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.29 (1H, m, CH$_2$C$H_a$H$_b$CO), 1.60 (2xCH$_3$, s, 2×C(CH$_3$)$_2$), 1.64 (1H, m, C$H_c$H$_d$CH$_2$CO), 1.81 (2H, m, CH$_c$$H_d$CH$_a$$H_b$CO), 2.11 (2H, m, C$H_2$CHCH$_2$CO), 2.29 (1H, m, CH$_2$C$H$CH$_2$CO), 2.42 (2H, m, CHC$H_2$CO); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.5, 22.9, 24.6, 26.1, 40.9, 42.8, 46.7, 90.6, 209.8.




74

**3-[Bis(*tert*-butoxycarbonyl)methyl]1,3-diphenyl-propanone) (74)** was prepared from di-*tert*-butyl malonate (112 μL, 0.50 mmol) and 1,3-diphenyl-propenone (105 mg, 0.50 mmol). The product was obtained as white solid (159 mg, 0.38 mmol, 75 %); mp: 122.4-124.7 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.22 (9H, s, $CH_3$), 1.50 (9H, s, $CH_3$), 1.61 (1H, s, $H_2O$), 3.42 (1H, dd, ABX, $J_{AX}$ = 16.2, $J_{AB}$ = 9.8, $CH_aH_bCH_xPh$), 3.53 (1H, dd, ABX, $J_{BX}$ = 4.0, $J_{AB}$ = 9.8, $CH_aH_bCH_xPh$), 3.67 (1H, d, $J$ = 10.4, $CH(CO_2{}^tBu)_2$, 4.11 (1H, td, $J$ = 10.0, $J$ = 4.0, $CH$Ph), 7.16 (1H, m, Ar), 7.28 (4H, m, Ar), 7.45 (2H, m, Ar), 7.55 (1H, m, Ar), 7.91 (2H, d, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 27.54, 27.95, 40.89, 43.38, 59.35, 76.76, 77.08, 77.40, 81.52, 82.04, 126.95, 128.17, 128.24, 128.53, 128.58, 132.95, 136.93, 140.74, 167.04, 167.83, 197.89.




75

**3-[Bis(*tert*-butoxycarbonyl)methyl]1-phenyl-3-(4-nitro-phenyl)-propanone (75)** was prepared from di-*tert*-butyl malonate (112 μL, 0.50 mmol) and 3-(4-Nitro-phenyl)-1-phenyl-propenone (126 mg, 0.50 mmol). The product was obtained as white solid (82 mg, 0.17 mmol, 35 %); $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.24 (9H, s, $CH_3$), 1.43 (9H, s, $CH_3$), 1.59 (1H, s, $H_2O$), 3.41 (1H, dd, ABX, $J_{AX}$ = 16.2, $J_{AB}$ = 9.8, $CH_aH_bCH_xPh$), 3.61 (1H, dd, ABX, $J_{BX}$ = 4.0, $J_{AB}$ = 9.8, $CH_aH_bCH_xPh$), 3.54 (1H, d, $J$ = 10.4, $CH(CO_2tBu)_2$, 4.19 (1H, td, $J$ = 10.0, $J$ = 4.0, $CH$Ph), 7.42 (4H, m, Ar), 7.58 (1H, m, Ar), 7.92 (2H, d, Ar), 8.19 (2H, d, Ar); $^{13}$C NMR (100 MHz, $CDCl_3$), δ 27.5, 27.9, 40.9, 43.4, 59.3, 81.5, 82.0, 126.9, 128.2, 128.2, 128.5, 128.6, 132.9, 136.9, 140.7, 167.0, 167.8, 197.9.

### 2.3.3 Specific rotation of Michael adducts

| compound | $[\alpha]^{26}_{D}$ [a,b] | $[\alpha]^{25}_{D}$ from reference |
|---|---|---|
| **67** | +2.76 ($CHCl_3$, *c* 5.1, 65 % *ee*) | +2.89[e] ($CHCl_3$, *c* 2.6, 81 % *ee*) |
| **68** | +3.47 ($CHCl_3$, *c* 5.9, 84 % *ee*) | -2.0[f] ($CHCl_3$, *c* 5.0, 43 % *ee* ) |
| **69** | -5.12[c]($CHCl_3$, *c* 4.1, 80 % *ee*) | - |
| **70** | +4.67 ($CHCl_3$, *c* 7.0, 80 % *ee*) | +4.2[f] ($CHCl_3$, *c* 1.0, 65 % *ee*) |
| | -4.59[d] ($CHCl_3$, *c* 4.9, 87 % *ee*) | - |
| **72** | +51.89 ($CHCl_3$, *c* 6.0, 50 % *ee*) | -37.2[g] ($CHCl_3$, *c* 1.6,.40 % *ee*) |

[a]Using ligand (*R*)-**87d** as catalyst. [b]Enantiomeric excess was determined by chiral GC. [c]Using ligand (*S*)-**87e** as catalyst. [d]Using ligand (*S*)-**87d** as catalyst. [e]reference 27. [f]reference 24. [g]reference 36.

### 2.3.4 General procedure for Michael addition of dialkyl malonate to enone catalyzed by the Na-Al-*N*-salicyl-β-amino alcohol and K-Al-*N*-salicyl-β-amino acohol complexes

Na-Al-*N*-salicyl-β-amino alcohol and K-Al-*N*-salicyl-β-amino alcohol complexes were prepared *in situ* from NaOH (0.05 mmol) or KOH (0.05 mmol), $Al(O^iPr)_4$ (0.05 mmol) and *N*-salicyl-β-amino alcohol (0.05 mmol) in methanol at room temperature for 1h. The solvent was evaporated under reduced pressure. Then, THF was added to the residue under $N_2$ gas followed with di-*tert*-butyl malonate and cyclohex-2-enone.

### 2.3.5 General procedure for Michael addition of dialkyl malonate to enone catalyzed by the Li-Ti-*N*-salicyl-β-amino alcohol complex

To a suspension of LiH (7 mg, 1mmol) in THF (2 mL) was slowly added a solution of *N*-salicyl-β-amino alcohol (1 mmol) in THF. After being stirred for 0.5h at room temperature, $Ti(O^iPr)_4$ was added to the above reaction mixture and stirred 1h at room temperature. Then, solvent was removed by reduced pressure in vacuum. The crude product (0.05 mmol) was directly used as a catalyst for asymmetric Michael reaction on a 0.5 mmol scale.

**2.4. Determination of the enantiomeric excess**

The enantiomeric excess was determined by GC using chiral column containing modified β-cyclodextrins (heptakis(2,3-di-*O*-methyl)-6-*O*-tert-butyldimethylsilyl)cyclomaltoheptaose). The enantiomeric excess was calculated by equation (1). For example, Michael adduct **70**, $t_r$ (*R*) = 16.895 min, peak area = 60, $t_r$ (*S*) = 17.405 min, peak area = 849, gave 87 % *ee*. Michael adduct **69**, $t_r$ (*R*) = 18.003 min, peak area = 168, $t_r$ (*S*) = 18.490 min, peak area = 1408, gave 79 % *ee*.

$$\% \, ee = \frac{|R\text{-}S| \times 100}{R+S} \qquad (1)$$

% *ee* = percent enantiomeric excess

*R* = peak area of *R* enantiomer  *S* = peak area of *S* enantiomer


**Figure 45**. Chromatogram of Michael adduct; (**a**) **70** (87 % *ee*) and (**b**) **69** (79 % *ee*)