Chapter IV

Experimental

General NMR spectra were obtained in $CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C) on a Varian Gemini Instrument. Chemical shift (δ) are in ppm and coupling constant (*J*) are in Hz. All reactions were followed by thin layer chromatography (TLC): glass sheet coated with silica gel F_{254} (Merck) and visualized using uv light (254 nm), iodine, molybdate, cobaltthiocyanate or $KMnO_4$. Flash chromatography was carried out on siliga gel: 230 – 400 Mesh. MeOH was refluxed with iodine and magnesium and distilled. Tetrahydrofuran and dioxane were distilled from Na/benzophenone, dichloromethane and acetonitrile were distilled from CaH_2, dimethylsulfoxide was distilled from CaH_2 under reduced pressure. Other chemicals were obtained from Fluka and Merck and used as received. Carbon monoxide was obtained from Praxair. Evaporation refers to the rotary evaporation of solvent under aspirator pressure. Infrared spectra were acquired using a Perkin Elmer 1760X. Mass spectrometry and high-resolution mass spectrometry were determined using a GCQ Mass spectrometer from Finigand a Mat 90 from Finigan. Elemental analysis results were obtained at the Instrument Center of Chulalongkorn University.

General Procedure for the Cyclofunctionalization Reaction
A mixture of palladium (II) chloride (10 mole%) and copper (II) acetate hydrate (3 eq.) in acetonitrile (*ca* 0.1 M) was cooled to 0°C under nitrogen. A solution of the hydroxylamine in methanol (*ca* 0.1 M) was added. The atmosphere was changed to carbon monoxide (1 atm) and tetramethylguanidine (3 eq.) was added. The mixture was allowed to warm to room temperature and stirred overnight. Precipitated solids were removed by filtration through a pad of silica gel, washing with ethyl acetate. The solvents were evaporated and the residue was purified by flash column chromatography on silica gel, eluting with 5-15% ethyl acetate/ hexane.

Homoallylic alcohol (7a) A mixture of benzaldehyde (10.16 ml 0.1 mole), allyl bromide (10.4 ml, 0.12 mole) and zinc powder (7.85 g 0.12 mol) in 100 ml of NH_4Cl (sat.) and 30 ml of THF was stirred at 0° C and then the mixture was allowed to warm up to room temperature. After 4 h

the organic layer was extracted with EtOAc. The organic extract was dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was purified by distillation (~ 120° C, 4 mmHg) to give the alcohol **(11)** (12.69 g 86 %).[32]

Homoallylic alcohol (7b) A mixture of isobutylaldehyde (1.3 ml 13.87 mmole), allyl bromide (1.44 ml 16.64 mmole) and zinc powder (2.2 g 16.64 mmol) in 30 ml of NH_4Cl (sat.) and 10 ml of THF was stirred at 0° C and then the mixture was allowed to warm up to room temperature. After 4 h the organic layer was extracted with diethylether. The organic extract was dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was purified by distillation (~ 45° C, 4 mmHg) to give the alcohol **(12)** (934 mg, 60 %). Colorless oil $\mathbf{R_f}$ = 0.41 (25% EtOAc: Hexane) **m/z** (EI) 130(M^++H)(19), 79(45) **IR** (Neat) 3363 (NH), 2948 (aliphatic), 1557, 1420, 1396 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 0.89 (d, *J* 7, 3H, Me), 0.91(d, *J* 7, 3H, Me), 1.9 (m, 1H, $Me_2C\underline{H}$), 2.27 (m, 2H, $C\underline{H_2}$), 3.35 (dt, *J* 5.5 and 6.6, 1H, $OC\underline{H}$), 5.08 (m, 2H, $=C\underline{H_2}$), 5.26 (brs, 2H, NH_2), 5.87 (ddt, 17.2, 10.2 and 7, 1H, $C\underline{H}=$) δ_C (50 MHz, $CDCl_3$) 18.0, 18.3, 29.1, 33.6, 88.0, 115.8, 135.4

General Procedure for the Preparation of *O*-Homoallyl Hydroxylamines.

A solution of DEAD (1.2 eq.) in THF (0.25 M) was added dropwise to a solution of the homoallylic alcohol, triphenylphosphine (1.2 eq.) and N-hydroxyphthalimide (1.2 eq.) in THF (0.25 M) under nitrogen at 0°C. The mixture was allowed to warm to room temperature and stirred for four hours. THF was then evaporated and the residue was dissolved in dichloromethane (*ca* 0.3 M). Hydrazine hydrate (3 eq.) was added and the mixture was stirred at room temperature for two hours. The mixture was filtered through celite, washing with dichloromethane, and the dichloromethane was removed under reduced pressure. The residue was preabsorbed on silica gel and purified by flash chromatography on silica gel, eluting with 5 - 15% ethyl acetate/ hexane.

***O*-Homoallyl Hydroxylamine (8a)** Colorless oil (90% yield). $\mathbf{R_f}$ = 0.27 (25% EtOAc:Hexane) **IR** (Neat) 3316, 3031, 2893, 1641, 1564, 1494, 1455, 1360, 1178 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.42 (dt, *J* 14.3 and 7.3, 1H, $C\underline{H_2}CH=$), 2.60 (dt, *J* 14.3 and 7.3, 1H, $C\underline{H_2}CH=$), 4.56 (dd, *J*

6.2 and 7.7, 1H, OC<u>H</u>), 5.08 (m, 2H, =C<u>H</u>$_2$), 5.25 (s, 2H, N<u>H</u>$_2$), 5.76 (ddt, *J*, 17.2, 10.2 and 7, 1H, C<u>H</u>=), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 40.6, 86.6, 117.1, 126.7, 127.8, 128.5, 134.4, 141.0

***O*-Homoallyl Hydroxylamine (8b)** Colorless oil (55% yield) $\mathbf{R_f}$ = 0.41 (25% EtOAc: Hexane) **m/z** (EI) 130(M^++H)(19), 79(45) **IR** (Neat) 3363 (NH), 2948 (aliphatic), 1557, 1420, 1396 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 0.89 (d, *J* 7, 3H, Me), 0.91 (d, *J* 7, 3H, Me), 1.9 (m, 1H, Me_2C<u>H</u>), 2.27 (m, 2H, C<u>H</u>$_2$), 3.35 (dt, *J* 5.5 and 6.6, 1H, OC<u>H</u>), 5.08 (m, 2H, =C<u>H</u>$_2$), 5.26 (brs, 2H, NH_2), 5.87 (ddt, 17.2, 10.2 and 7, 1H, C<u>H</u>=) δ_C (50 MHz, $CDCl_3$) 18.0, 18.3, 29.1, 33.6, 88.0, 115.8, 135

***O*-Homoallyl Hydroxylamine (8c)** Colorless oil (51% yield) $\mathbf{R_f}$ = 0.47 (25% EtOAc: Hexane) **IR** (Neat) 3315, 2929, 1476, 1372, 1256, 1112, 838, 777 **NMR** δ_H (200 MHz, $CDCl_3$) 0.07 (s, 6H, Me_2Si), 0.91 (S, 9H, *t*-Boc), 2.31 (m, 2H, C<u>H</u>$_2$CH=), 3.68 (m, 3H, OC<u>H</u> and TBSOC<u>H</u>$_2$), 4.82 (bs, 2H, N<u>H</u>$_2$), 5.10 (m, 2H, =C<u>H</u>$_2$), 5.84 (ddt, *J* 17.2, 10.3 and 7, 1H, C<u>H</u>=) δ_C (50 MHz, $CDCl_3$) –5.2, 13.7, 17.8, 25.4, 34.0, 63.2, 82.5, 116.3, 134.4

N-alkyl Hydroxylamine (9) Sodium sulfate (285 mg, 2.0 mmol) was added to a solution of the hydroxylamine **(14a)** (195 mg, 1.0 mmol) and *p*-methoxybenzaldehyde (146 µl, 1.2 mmol) in CH_2Cl_2. The mixture was stirred for 6 h and then filtered. The volatiles were evaporated and the residue was taken up in MeOH (5 ml). $NaCNBH_3$ (150 mg, 2.4 mmol) and bromocresol green were added. HCl/MeOH (2 M) was used to maintain the color of the solution as yellow. The mixture was stirred for 2 h, and the NH_4Cl (sat.)(10 ml) was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography eluting with 5% and then 10% EtOAc to give the N-alkyl derivative **(15)** (150 mg, 44%) $\mathbf{R_f}$ 0.34 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 2.42 (dt, *J* 14.3 and 7, 1H, C<u>H</u>$_2$CH=), 2.61 (dt, 14.3 and 14.3, 1H, C<u>H</u>$_2$CH=), 3.82 (s, 3H, OMe), 3.96 (dd, *J* 18.0 and 12.6, 2H, NHC<u>H</u>$_2$), 4.62 (t, *J* 6.6, 1H, OC<u>H</u>), 5.05 (m, 2H, =C<u>H</u>$_2$), 5.48 (bs, 1H, N<u>H</u>), 5.75 (ddt, *J* 16.8, 10 and 7, 1H, C<u>H</u>=), 6.87 (d, *J* 8.79, 2H, C$_6$<u>H</u>$_4$OMe), 7.24 (d, *J* 8.79, 2H, C$_6$<u>H</u>$_4$OMe), 7.34 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 40.4, 55.1, 55.8, 84.7, 113.6, 117.0, 126.7, 128.2, 129.6, 130.2, 134.7, 142.1, 158.8

Methoxy carbonyl derivative (9a) Methyl chloroformate (360 μl, 4.65 mmol)was added to a mixture of the hydroxylamine **(14)** (690 mg, 4.23 mmol) and potassium carbonate (878 mg 6.35 mmol) in dichloromethane. The mixture was refluxed overnight, cooled, filtered and evaporated. The residue was purified by flash column chromatography, eluting with 10, 15 and then 20% EtOAc:Hexane to give the product as a yellow oil (852 mg, 91%) $\mathbf{R_f}$ = 0.27 (25% EtOAc : Hexane) **m/z (EI)** 222(14)(M^+ +H), 131(100)(M^+ -$C_7H_7^+$), 91(22)($C_7H_7^+$) **IR (Neat)** 3279 (NH), 2956 (aliphatic), 1736 (C=O), 1643 (C=O) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.4 (m, 1H, OCHC<u>H</u>$_2$), 2.8 (m, 1H, OCHC<u>H</u>$_2$), 3.70 (s, 3H, OMe), 4.81 (t, *J* 7.0, 1H, PhC<u>H</u>), 5.08 (m, 2H, =C<u>H</u>$_2$), 5.78 (m, 1H, C<u>H</u>=), 7.10 (s, 1H, N<u>H</u>), 7.30 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 39.5, 52.6, 87.4, 117.5, 127.2, 128.1, 128.4, 128.5, 139.5, 133.6, 157.6

Preparation of Ns-derivative (10a) *p*-Nosyl chloride (204 mg, 0.92 mmole) was added to a solution of the hydroxylamine **3a** (100 mg, 0.61 mmole) in 1:1 dichloromethane/ water (4 ml). Sodium carbonate (97 mg, 0.92 mmole) was added and the mixture was stirred overnight. The layers were separated and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (1.5 g) eluting with 5 and 10% ethyl acetate/hexane to give the sulfonamide (150 mg, 70%). Yellow solid m.p. = 132 –133 $\mathbf{R_f}$ = 0.29 (25% EtOAc:Hexane) **EA** found: C(55.56), H (4.45), N(8.15) require: C(55.16), H(4.63), N(8.04) $C_{16}H_{16}N_2SO_5$ **m/z** (EI) 131(60), 91(100)($C_7H_7^+$) **IR** (KBr) 3236 (NH), 3112 (Ar), 2931 (aliphatic), 1606 (NO_2), 1348, 1170 (SO_2) **NMR** δ_H (200 MHz, $CDCl_3$) 2.55 (m, 2H, C<u>H</u>$_2$), 4.99 (m, 2H, =C<u>H</u>$_2$), 5.78 (m, 1H, C<u>H</u>=), 6.98 (s, 1H, ON<u>H</u>SO_2), 7.30 (m, 5H, C_6<u>H</u>$_5$CH), 8.08 (d, *J* 8.4, 4H, SO_2C_6<u>H</u>$_4NO_2$), 8.35 (d, *J* 8.4, 4H, SO_2C_6<u>H</u>$_4NO_2$) δ_C (50 MHz, $CDCl_3$) 39.1, 88.2, 117.5, 123.6, 126.6, 128.1, 129.6, 138, 133.1

General Procedure for the Preparation of *t*-Boc derivatives
Di-*t*-butyldicarbonate (1.1 eq.) was added to a solution (0.05 M) of the alcohol in dichloromethane/water (1:1). Solid sodium hydroxide (2 eq.) was added and the mixture was stirred overnight. The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel eluting with hexane and 5% ethyl acetate/ hexane.

The *t*-Boc derivative (11a) The general procedure gave 90% yield. Colorless oil $\mathbf{R_f}$ = 0.38 (25% EtOAc:Hexane) **m/z** (EI) 263(13)(M^+), 131 (93), 115(43), 91(100)($C_7H_7^+$) **IR** (Neat) 3289 (NH), 3066 (aromatic), 2979 (aliphatic), 1718 (C=O), 1643 (Ar) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 1.44 (s, 9H, $C(CH_3)_3$), 2.46 (dt, *J* 14.6 and 6.6, 1H, $C\underline{H}_2$), 2.73 (dt, *J* 14.6 and 6.6, 1H, $C\underline{H}_2$), 4.79 (t, *J* 7.0, 1H, PhC<u>H</u>), 5.05 (m, 1H, =$C\underline{H}_2$), 5.13 (m, 1H, =$C\underline{H}_2$), 5.80 (ddt, *J* 17.2, 10.3 and 7.0, 1H, C<u>H</u>=), 6.90 (s, 1H, N<u>H</u>), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 28.0, 39.5, 81.3, 86.9, 117.3, 127.1, 128.0, 128.3, 139.7, 133.7, 139.7

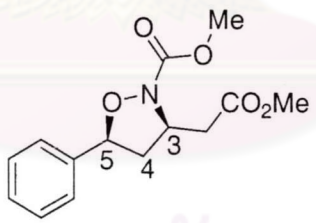
Compound (11b) The general procedure gave 56% yield. Colorless oil $\mathbf{R_f}$ = 0.38 (25% EtOAc:Hexane) **m/z** (EI) 263(13)(M^+), 131(93), 115(43), 91(100)($C_7H_7^+$) **IR** (Neat) 3289 (NH), 3066(aromatic), 2979 (aliphatic), 1718 (C=O), 1643 (Ar) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 1.44 (s, 9H, C $(CH_3)_3$), 2.46 (dt, *J* 14.6 and 6.6, 1H, $C\underline{H}_2$), 2.73 (dt, *J* 14.6 and 6.6, 1H, $C\underline{H}_2$), 4.79 (t, *J* 7.0, 1H, PhC<u>H</u>), 5.05 (m, 1H, =$C\underline{H}_2$), 5.13 (m, 1H, =$C\underline{H}_2$), 5.80 (ddt, *J* 17.2, 10.3 and 7.0, 1H, C<u>H</u>=), 6.90 (s, 1H, N<u>H</u>), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 28.0, 39.5, 81.3, 86.9, 117.3, 127.1, 128.0, 128.3, 139.7, 133.7, 139.7

General Procedure for the Preparation of Cbz derivatives
N-Benzyloxycarbonyloxysuccinimide (1.2 eq.) was added to a solution (ca 0.05 M) of the hydroxylamine in dichloromethane/water (1:1). Sodium hydrogen carbonate (2 eq.) was added and the mixture was stirred overnight. The layers were separated and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel eluting with 5 and 10% ethyl acetate/hexane.

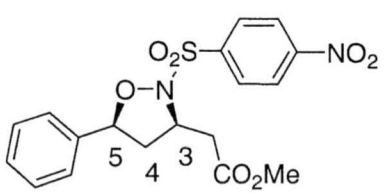
The Cbz derivative (12a) The general procedure gave 90% yield. Yellow Oil $\mathbf{R_f}$ = 0.31 (25% EtOAc : Hexane) **m/z** ($HFAB^+$) found: 298.1466 [M^++ H] $C_{18}H_{20}NO_3$ requires: 298.1365[M] (FAB^+) 298.1 (7), (M^++ H), 131.1(70) and 91.0(100)($C_7H_7^+$) **IR** (Neat) 3280 (NH), 3033 (Ar), 2945 (aliphatic), 1724 (C=O) cm^{-1}**NMR** δ_H (200 MHz, $CDCl_3$) 2.48 (dt, *J* 14.7 and 7, 1H, OCHC$\underline{H}_2$), 2.76 (dt, *J* 14.7 and 7, 1H, OCHC$\underline{H}_2$), 4.81 (t, *J* 7, 1H, PhC<u>H</u>), 5.02 (m, 2H, =$C\underline{H}_2$), 5.10 (d, *J* 12, 1H, $C\underline{H}_2$Ph), 5.18 (d, *J* 12, 1H, $C\underline{H}_2$Ph), 5.78 (ddt, *J* 17.2, 10.3 and 7, 1H, C<u>H</u>=), 7.15 (s, 1H, N<u>H</u>), 7.33 (m, 10H, Ph) δ_C (50 MHz, $CDCl_3$) 39.6, 67.4, 87.4, 117.5, 127.2, 128.2 128.4, 128.5, 135.5, 139.4, 133.6, 156.9

Compound (12b) The general procedure gave 52% yield. Yellow oil $\mathbf{R_f}$ = 0.39 (25% EtOAc:Hexane) **m/z** (HFAB$^+$) found: 264.1600[M$^+$+ H] $C_{15}H_{21}NO_3$ requires: 263.1521[M] (FAB$^+$) 264.1(M$^+$+ H) and 91.0(100)($C_7H_7^+$)**IR** (Neat) 3288 (NH), 3068 (Ar), 2962 (aliphatic), 1718 (C=O) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 0.92 (d, *J* 7, 3H, Me), 0.95 (d, *J* 7, 3H, Me), 1.94 (m, 1H, $Me_2C\underline{H}$), 2.32 (m, 2H, $OCHC\underline{H_2}$), 3.62 (q, *J* 5.6, 1H, $OC\underline{H}$), 5.09 (m, 1H, $=C\underline{H_2}$), 5.16 (s, 2H, CO_2CH_2Ph), 5.89 (ddt, *J* 17.2, 10.2 and 7, 1H, $C\underline{H}=$), 7.25 (s, 1H, $N\underline{H}$), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 18.0, 18.3, 29.6, 33.9, 67.6, 90.4, 117.0, 128.5, 128.7, 135.8, 133.8, 157.1

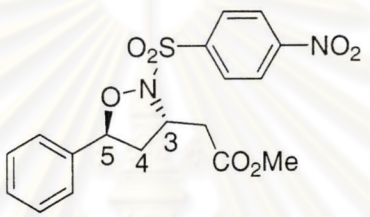
Compound (12c) The general procedure gave 55% yield. Colorless Oil $\mathbf{R_f}$ = 0.67 **m/z** (EI) 91(100), 117(43), 165(18), 178(15) **IR** (Neat) 3269, 3016, 2947, 1735, 1506, 1431, 1406, 1272, 1117, 1043 **NMR** δ_H (200 MHz, $CDCl_3$) 0.08 (s, 6H, $SiMe_2$), 0.90 (s, 9H, *t*-Boc), 2.37 (t, *J* 6.6, 2H, $OCHC\underline{H_2}$), 3.75 (d, *J* 5, 2H, $TBSOC\underline{H_2}$), 3.88 (p, *J* 6.23, 1H, $OC\underline{H}$), 5.13 (m, 2H, $=C\underline{H_2}$), 5.18 (s, 2H, $C\underline{H_2}Ph$), 5.87 (ddt, *J* 17.2, 10.3 and 7, 1H, $C\underline{H}=$), 7.36 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) –3.4, 8.1, 25.3, 33.4, 46.2, 61.2, 67.6, 86.2, 117.2, 122.9, 128.1, 133.3, 158.6



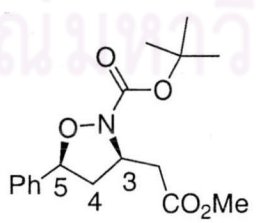
Isoxazolidine (13) Yellow oil $\mathbf{R_f}$ = 0.14 (25% EtOAc:Hexane) **m/z** (EI) 280(100)(M$^+$+H), 129(22)($C_5H_7NO_3^+$) **IR** (Neat) 2955(Aliphatic), 1737 (C=O) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.05 (ddd, *J* 6.2, 10.3 and 12.6, 1H, H4), 2.63 (dd, *J* 8.6 and 16.2, 1H, $C\underline{H_2}CO_2$), 2.97 (m, 2H, $C\underline{H_2}CO_2$), 3.68 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.73 (tt, *J* 8.6 and 6.2, 1H, H3), 4.91 (dd, *J* 6.2 and 9.9, 1H, H5), 7.30 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 40.6, 43.2, 51.8, 53.5, 57.4, , 83.4, 126.4, 126.6, 128.5, 136.5, 158.5, 170.8



Isoxazolidine (*cis*-14) Yellow solid **Mp** 101 - 104 °C **R_f** = 0.22 (25% EtOAc:Hexane) **EA** found: C(53.23), H(4.26), N(6.89) require: C(53.20), H(4.46), N(6.89) $C_{18}H_{18}N_2SO_7$ **IR** (Neat) 3105 (Ar), 2955 (aliphatic), 1739 (C=O), 1608 (NO_2), 1349, 1014 (SO_2) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.08 (ddd, *J* 7.3, 10 and 12.5, 1H, H4), 2.68 (dd, *J* 8.2 and 15.8, 1H, H4), 3.08 (m, 2H, $C\underline{H}_2CO_2$), 3.66 (s, 3H, OMe), 4.76 (ddd, *J* 5.9, 7.3 and 15.8, 1H, H3), 5.24 (dd, *J* 5.9 and 10.2, 1H, H5), 7.24 (m, 5H, Ph), 8.10 (d, *J* 8.9, 2H, $SO_2C_6\underline{H}_4NO_2$), 8.3 (d, *J* 8.9, 2H, $SO_2C_6\underline{H}_4NO_2$)

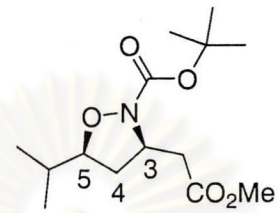


Isoxazolidine (*trans*-14) Yellow solid **Mp** 108 - 110 °C **R_f** = 0.15 (25% EtOAc:Hexane) **m/z** (FAB^+) 185(90)($SO_2C_6H_4NO_2$), 93(100) **IR** (Neat) 3107(Ar), 2955(aliphatic), 1733 (C=O), 1608 (NO_2), 1362, 1015 (SO_2) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.38 (m, 2H, H4), 2.68 (dd, *J* 8.8 and 16.3, 1H, $C\underline{H}_2CO_2$), 2.93 (dd, *J* 5.9 and 16.3, 1H, $C\underline{H}_2CO_2$), 3.69 (s, 3H, OMe), 4.72 (m, 1H, H3), 5.18 (t, *J* 9.8, 1H, H5), 7.24 (m, 5H, Ph), 8.01 (d, *J* 8.9, 2H, $SO_2C_6\underline{H}_4NO_2$), 8.22 (d, *J* 8.9, 2H, $SO_2C_6\underline{H}_4NO_2$) δ_C (50 MHz, $CDCl_3$) 39.2, 41.0, 52.1, 58.3, 83.0, 123.9, 127.1, 128.7, 129.1, 136.3, 140.8, 170.3

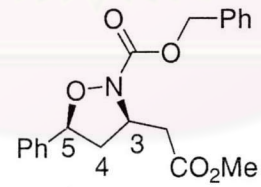


Isoxazolidine (15a) White solid **Mp** 74 – 76 °C **R_f** = 0.28 (25% EtOAc:Hexane) **m/z** (EI) 321(1)(M^+) 221(62)(M^+-$C_5H_8O_2$), 189(51), 129 (100) **IR**(KBr) 3325 (NH), 2982 (CH), 1733 (C=O), 1693 (C=O) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 1.52(s, 9H, -Boc), 2.05 (m, 1H, $C\underline{H}_2CO_2$),

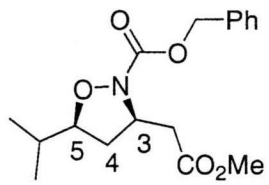
2.63 (dd, 1H, *J* 5.9 and 15.8, C<u>H</u>$_2$CO$_2$), 2.96 (m, 2H, H4), 3.69 (s, 3H, OMe), 4.71 (m, 1H, H3), 4.90 (dd, 1H, *J* 6.3 and 9.8, H5), 7.38 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 28.4, 40.9, 43.4, 51.9, 57.6, 82.4, 83.0, 126.8, 128.6, 128.7, 137.3, 157.5, 171.4



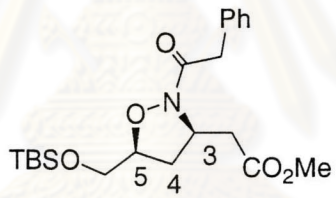
Isoxazolidine (15b) Colorless oil $\mathbf{R_f}$ = 0.24 (50% EtOAc:Hexane) **m/z** (EI) 288(M^++H)(100), 232(M^+-C_7H_7)(30), 188(M^+-*t*-Boc+2H^+(16) **IR** (Neat) 2975 (aliphatic), 1741, 1717 (C=O), 1438, 1369, 1333, 1256, 1167 (cm^{-1}) **NMR** δ_H (200 MHz, $CDCl_3$) 0.90 (d, *J* 6.6, 3H, Me), 0.96 (d, *J* 6.6, 3H, Me), 1.47 (s, 9H, *t*-Boc), 1.59 (ddd, *J* 12.5, 9.9 and 6, 1H, H4), 1.90 (m, 1H, C<u>H</u>Me$_2$), 2.47 (dd, *J* 9 and 16, 1H, C<u>H</u>$_2$CO2), 2.52 (m, 1H, H4), 2.81 (dd, *J* 5.5 and 16, 1H, C<u>H</u>$_2$CO2), 3.58 (ddd, *J* 13.9, 6.6 and 9.9, 1H, H5), 3.68 (s, 3H, OMe), 4.55 (tt, *J* 8.6 and 6, 1H, H3) δ_C (50 MHz, $CDCl_3$) 18.2, 19.2, 28.1, 30.8, 38.3, 40.6, 51.6, 56.9, 81.6, 86.6, 157.4, 171.3



Isoxazolidine (16a) Yellow oil $\mathbf{R_f}$ = 0.28 (25% EtOAc:Hexane) **m/z** (HFAB$^+$) found: 356.1497[M^++ H] $C_{20}H_{22}NO_5$ requires: 356.1420[M] (FAB$^+$) 356.1(78)(M^+ +H), 312.1(30)(M^+-CO_2) and 91.0(100)($C_7H_7^+$) **IR** (Neat) 3031 (Ar), 2958 (aliphatic), 1738 (C=O)cm^{-1}, 1700 **NMR** δ_H (200 MHz, $CDCl_3$) 2.06 (ddd, *J* 6.2, 10.3 and 12.4, 1H, H4), 2.64 (dd, *J* 8.6 and 16.1, 1H, C<u>H</u>$_2$CO$_2$), 2.98 (m, 2H, H4 and C<u>H</u>$_2$CO$_2$), 3.66 (s, 3H, OMe), 4.76 (tt, *J* 6.2 and 8.6, 1H, H3), 4.90 (dd, *J* 6.2 and 10.3, 1H, H5), 5.21 (d, *J* 12, 1H, OC<u>H</u>$_2$Ph), 5.27 (d, *J* 12, 1H, OC<u>H</u>$_2$Ph), 7.40 (m, 10H, Ph) δ_C (50 MHz, $CDCl_3$) 40.4, 43.1, 51.7, 57.5, 68.0, 83.4, 126.6, 128.1, 128.3, 128.5, 128.6, 128.7, 135.8, 136.6, 161.0, 170.9

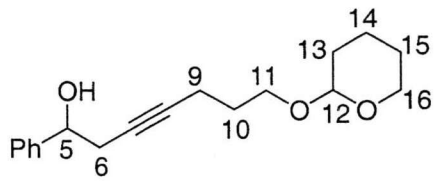


Isoxazolidine (16b) Colorless oil $\mathbf{R_f}$ = 0.34 (25% EtOAc : Hexane) **m/z** (HFAB$^+$) found: 322.1649[M$^+$+ H] $C_{17}H_{24}NO_5$ requires: 322.1576[M] (FAB$^+$) 322.2, 278.2, 204.1, 172.1, 91.0 91(100)($C_7H_7^+$) **NMR** δ_H (200 MHz, $CDCl_3$) 0.91 (d, *J* 7, 3H, Me), 1.1 (d, *J* 7, 3H, Me), 1.65 (ddd, *J* 12.4, 9.9 and 5.9, 1H, H4), 1.85 (m, 1H, $Me_2C\underline{H}$), 2.51 (dd, *J* 8.8 and 15.8, 1H, $C\underline{H}_2CO_2$), 2.54 (m, 1H, H4), 2.85 (dd, *J* 5.9 and 15.8, 1H, $C\underline{H}_2CO_2$), 3.63 (m, 1H, H5), 3.66 (s, 3H, OMe), 4.63 (tt, *J* 5.9 and 8.8, 1H, H3), 5.25 (d, *J* 12.5, 1H $C\underline{H}_2Ph$), 5.15 (d, *J* 12.5, 1H, $C\underline{H}_2Ph$), 7.19 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 19.0, 19.3, 29.6, 33.9, 42.1, 50.1, 57.8, 67.6, 80.3, 128.3, 128.7, 135.8, 156.2, 168.8

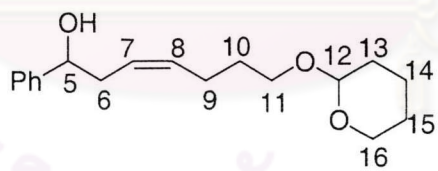


Isoxazolidine (16c) Colorless oil $\mathbf{R_f}$ = 0.27 (25% EtOAc:Hexane) **m/z** (EI) 145(9)(M$^+$-ONHBoc), 91(100)($C_7H_7^+$) **IR** (KBr) 3251 (NH), 2985 (aliphatic), 1713 (C=O), 1644 (Ar) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 1.46 (s, 9H, *t*-Bu), 2.00 (m, 4H, $O(C\underline{H}_2)_2$), 4.74 (t, *J* 6.8, 2H, PhC$\underline{H}$), 5.00 (m, 2H, $=C\underline{H}_2$), 5.82 (ddt, *J* 16.8, 10 and 6, 1H, C$\underline{H}$=), 6.87 (s, 1H, N$\underline{H}$), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 28.3, 29.8, 34.5, 81.5, 87.2, 117.6, 127.3, 128.4, 128.6, 140.0 133.9, 156.5

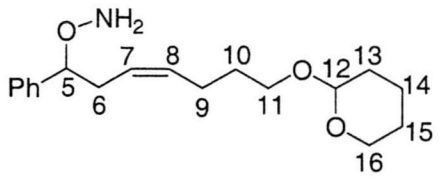
Compound 21 The general procedure to make hydroxylamine gave a colorless oil (80% yield) $\mathbf{R_f}$ = 0.45 (25% EtOAc:Hexane) **m/z** (FAB$^+$) 178.0(5)(M$^+$+H), 145.1(30)(M$^+$-ONH_2), 91(100)($C_7H_7^+$) **IR** (Neat) 3319 (NH), 3050 (Ar), 2937 (aliphatic), 1641 (Ar), 1186 (C-O) cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.00 (m, 4H, $(CH_2)_2CH$=), 4.50 (t, *J* 7, 1H, PhC$\underline{H}$), 5.00 (m, 2H, $=C\underline{H}_2$), 5.20 (s, 2H, $N\underline{H}_2$), 5.83 (ddt, *J* 17.2, 10.3 and 7, C$\underline{H}$=), 7.30 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 29.6, 35.0, 86.5, 114.6, 126.5, 127.5, 128.3, 141.5, 138.8



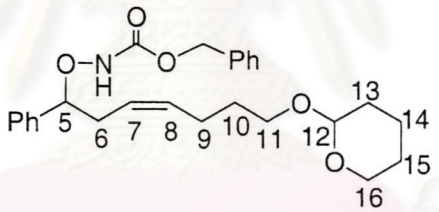
Compound 24 *n*-BuLi was added dropwise to a solution of the alkyne **(26)** (785 mg, 6.54 mmol) in THF (10 ml) at –20 °C under nitrogen. The mixture was stirred for 30 min, then was cooled to –78 °C. DMPU (15 ml) was added and the mixture was stirred for 15 min. Styrene epoxide was added and the mixture was allowed to warm up to room temperature and stirred overnight. NH_4Cl (sat.) was added and the mixture was extracted with EtOAc. The organic layer was washed with brine dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography eluting with 10 – 15% EtOAc in Hexane to give alkyne (145 mg, 50%) as a yellow oil. $\mathbf{R_f}$ = 0.30 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 1.6 (m, 8H, H10, H13, H14, H15), 2.30 (m, 2H, H9), 2.60 (m, 2H, H6), 3.50 (m, 2H, H16), 3.80 (m, 2H, H11), 4.58 (t, *J* 3.3, 1H, H5), 4.83 (t, J 5.9, 1H, H12), 7.34 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 15.8, 19.7, 25.6, 29.1, 30.2, 30.8, 62.1, 66.1, 72.8, 82.8, 99.0, 125.9, 127.9, 128.5,143.0



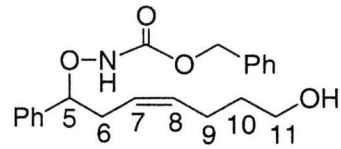
Compound 25 The alkyne **(24)** (628 mg, 2.18 mmol) was dissolved in dry THF and Lindlar's catalyst (80 mg) and a small amount of pyridine (17.5 µl, 0.2mmol) was added. The reaction mixture was stirred for 3 hours under hydrogen. The mixture was filtered through celite and the volatiles were evaporated. The residue was purified by flash column chromatography eluting with 10 – 15% EtOAc:Hexane to give alkene **(25)** (368 mg, 58%) as an oil. $\mathbf{R_f}$ = 0.35 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 1.61 (m, 8H, H10, H13, H14, H15), 2.12 (m, 2H, H9), 2.55 (m, 2H, H6), 3.45 (m, 2H, H11 and H16), 3.77 (m, 2H, H11 and H16), 4.57 (t, *J* 4, 1H, H5), 4.70 (m, 1H, H12), 5.5 (m, 2H, H_7, H8), 7.25 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 19.8, 24.1, 25.6, 29.6, 30.9, 37.4, 62.7, 66.9, 74.0, 99.0, 125.5, 125.8, 126.0, 127.6, 128.4, 132.8



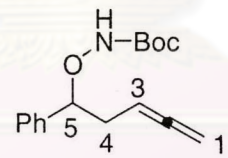
Compound 26 The general procedure for hydroxylamine gave a yellow oil (86%). $\mathbf{R_f}$ = 0.29 (25% EtOAc:Hexane) **m/z** (EI) 306(40), 171(43), 129(100), 128(81), 91(58) and 77(57) **IR** (Neat) 3320 (NH), 3028 (Ar), 2943 (aliphatic), 1560, 1494, 1455, 1354, 1201 (cm^{-1}) **NMR** δ_H (200 MHz, $CDCl_3$) 1.60 (m, 8H, H_{10}, H_{13}, H_{14}, H_{15}), 2.20 (m, 2H, H_9), 2.39 (dt, *J* 14.5 and 7, 1H, H_9), 2.58 (dt, *J* 14.5 and 7, 1H, H_9), 3.31 (dt, *J* 9.8 and 6.6, 1H, H_{16}), 3.48 (m, 1H, H_{11}), 3.64 (dt, *J* 9.8 and 6.6, 1H, H_{16}), 3.84 (m, 1H, H_{11}), 4.52 (t, *J* 6.6, 1H, H_5), 4.55 (m, 1H, H_{12}), 5.2 (bs, 2H, $N\underline{H}_2$), 5.40 (m, 2H, H_7, H_8), 7.25 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 19.8, 24.1, 25.6, 29.6, 30.9, 34.2, 62.4, 67.0, 87.1, 99.0, 125.4, 126.0, 127.6, 128.6, 131.7, 141.6



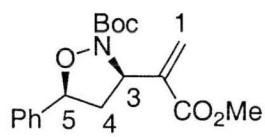
Compound 27 The general procedure for the preparation of CBZ derivatives gave yellow oil (95%) $\mathbf{R_f}$ = 0.32 (25% EtOAc:Hexane) **IR** (Neat) 3256 (NH), 3022 (Ar), 2942 (aliphatic), 1748 (C=O), 1502, 1455, 1405, 1342, 1239, 1120, 1030 (cm^{-1}) **NMR** δ_H (200 MHz, $CDCl_3$) 1.26 (t, *J* 7, 2H, H10), 1.57 (m, 6H, H_{13}, H_{14}, H_{15}), 2.05 (m, 2H, H_9), 2.51 (m, 1H, H_6), 2.70 (m, 1H, H_6), 3.32 (m, 1H, H_{16}), 3.48 (m, 1H, H_{16}), 3.67 (m, 1H, H_{11}), 3.84 (m, 1H, H_{11}), 4.53 (m, 1H, H_5), 4.76 (m, 1H, H_{12}), 5.12 (d, *J* 12.5, $OC\underline{H}_2Ph$), 5.17 (d, *J* 12.5, $OC\underline{H}_2Ph$), 5.42 (m, 2H, H_7, H_8), 7.33 (m, 11H, 2Ph and N$\underline{H}$) δ_C (50 MHz, $CDCl_3$) 19.2, 23.6, 25.1, 29.0, 30.4, 32.8, 61.9, 66.5, 67.0, 87.3, 98.4, 124.1,126.8, 127.9, 128.0, 128.1, 131.5, 139.3



Compound 22 The compound **(28)** (200 mg, 0.46 mmol) was dissolved in dry MeOH (10 ml) and then a small amount of $TsOH.H_2O$ (cat.) was added. The reaction mixture was stirred for 1 h at Rt . K_2CO_3 was added as acid scavenger. The mixture was filtrated, extracted with EtOAc and then washed with brine and Na_2SO_4. Volatiles were evaporaed. The residue was purified by flash column chromatography eluting with 25% - 30% EtOAc:Hexane to give yellow oil compound(136 mg 85% yield). $\mathbf{R_f}$ = 0.10 (25% EtOAc:Hexane) **IR** (Neat) 3256, 2941, 1724, 1455, 1333, 1257, 1112 and 700 **NMR** δ_H (200 MHz, $CDCl_3$) 1.53 (h, *J* 6.8, 2H, $C\underline{H}_2CH_2OH$), 1.67 (broad-s, 1H, $O\underline{H}$), 2.05 (m, 2H, H_6), 3.56 (t, *J* 6.2, 2H, H_{11}), 4.76 (t, *J* 7, 1H, H_5), 5.12 (d, *J* 12, 1H, $OC\underline{H}_2Ph$), 5.17 (d, *J* 12, 1H, $OC\underline{H}_2Ph$), 5.42 (m, 2H, $C\underline{H}_2{=}C\underline{H}_2$), 7.32 (m, 10H, 2Ph) δ_C (50 MHz, $CDCl_3$) 23.8, 32.1, 33.4, 62.2, 67.6, 87.8, 124.9, 127.3, 128.4, 128.6, 128.7, 131.9, 135.7, 139.8 and 157.2

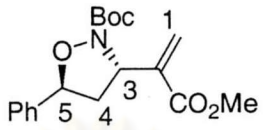


Compound 31 The general procedure gave 84% yield. White solid **mp** 66 – 68 °C $\mathbf{R_f}$ = 0.38 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 1.45 (s, 9H, Boc), 2.45 (m, 1H, H4), 2.68 (m, 1H, H4), 4.62 (dt, *J* 7 and 2.6, 2H, H1), 4.81 (t, *J* 7, 1H, H5), 5.2 (p, *J* 7, 1H, H3), 7.0 (bs, 2H, $N\underline{H}$), 7.35 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 28.3, 34.5, 81.9, 81.8, 85.8, 87.3, 127.4, 128.4, 128.6, 139.7, 156.6, 209.5

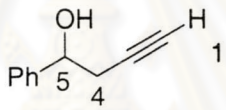


Compound 32a Colorless oil **m/z** both of **32a** and **32b** 334(46), 333(22), 201(52), 169(80) and 141(100) $\mathbf{R_f}$ = 0.53 **IR** both of **32a** and **32b** 3011, 2996, 1730, 1646, 1456. 1381, 1317, 1267, 1157, 1072, 709 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 1.51 (s, 9H, Boc), 2.05 (ddd, *J* 12.5, 10.5 and 6.6,

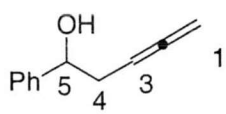
1H, H4), 3.15 (ddd, *J* 12.5, 8.5 and 6.6, 1H, H4), 3.75 (s, 3H, OMe), 4.93 (dd, *J* 10.5 and 6.6, 1H, H3), 5.20 (m, 1H, H5), 6.14 (s, 1H, H1), 6.33 (s, 1H, H1), 7.30 (m, 5H, Ph)



Compound 32b NMR δ_H (200 MHz, $CDCl_3$) 1.39 (s, 9H, Boc), 2.48 (ddd, *J* 12.5, 6.6 and 4.3, 1H, H4), 2.79 (ddd, *J* 12.5, 8.1 and 7, 1H, H4), 3.80 (s, 3H, OMe), 4.93 (dd, *J* 10.5 and 6.6, 1H, H3), 5.20 (m, 1H, H5), 6.06 (s, 1H, H1), 6.36 (s, 1H, H1), 7.30 (m, 5H, Ph)

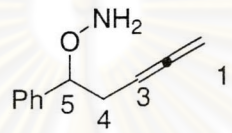


Compound 33 Dry acetylene gas in a balloon was added to a solution of TMEDA (1.2 ml, 7.9 mmol) and *n*-BuLi in hexane (1M, 3.95 ml) in THF (5 ml) at –78 °C. The mixture was stirred for 1 hour. Then a solution of styrene epoxide (528 mg, 4.4 mmol) in DMSO (5 ml) wad added. The mixture was allowed to come to room temperature and stirred for 2 hours. NH_4Cl (sat.) was added (10 ml) and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography eluting with 10 – 15% EtOAc in Hexane to give alkyne (527 mg, 82%) as a yellow oil.[43] **R_f** = 0.53 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 2.01 (t, *J* 2.6, 1H, H1), 2.41 (bs, 1H, OH), 2.57 (dd, *J* 6.2 and 2.1, 2H, H4), 4.80 (td, *J* 6.2 and 3.3, 1H, H5), 7.24 (m, 5H, Ph) δ_C (50 MHz, $CDCl_3$) 27.1, 68.9, 70.2, 78.7, 123.7, 125.8, 126.3, 140.4

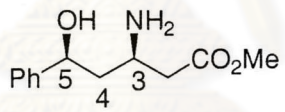


Compound 34 A solution of alkyne **(33)** (150 mg, 1 mmol) in dioxane (2 ml) was transferred to a reaction flask containing CuI (95 mg, 0.5 mmol) and paraformaldehyde (75 mg, 2.5 mmol) under nitrogen. The reaction mixture was stirred and refluxed for 15 hours. The mixture was filtered

and acidified with 2 M HCl. The mixture was extracted with EtOAc, washed with brine and dried (Na_2SO_4). The solvents were removed in *vacuo* and the residue was purified by flash column chromatography eluting with 5 – 10% EtOAc:Hexane to give the allene (114 mg, 72%) as a yellow oil. $\mathbf{R_f}$ = 0.52 (25% EtOAc:Hexane) **IR** 3375, 3030, 2909, 1956, 1494, 1455, 1318, 1055 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) 2.38 (m, 3H, H4 and O<u>H</u>), 4.65 (dt, *J* 7 and 2.6, 2H, =C<u>H</u>$_2$), 4.69 (m, 1H, OC<u>H</u>), 5.03 (p, *J* 7, 1H, C<u>H</u>=),7.30(m, 5H, Ph) δ_C 38.6, 73.8, 74.2, 86.3, 126.0, 127.7, 128.5, 143.8, 209.4



Compound 35 The general procedure for hydroxylamine gave a yellow oil (84%). $\mathbf{R_f}$ = 0.41 (25% EtOAc:Hexane) **NMR** δ_H (200 MHz, $CDCl_3$) 2.52 (m, 2H, H4), 4.65 (m, 3H, H1 and H5), 5.06 (m, 1H, H3), 5.25 (bs, 2H, N<u>H</u>$_2$), 7.35 (m, 5H, Ph)



Compound 36 The isoxazolidine **(9b)** (540 mg, 1.52 mmol) was dissolved by MeOH (10 ml), and then Palladium on carbon (40 mg) was added. The reaction was stirred for 4 hrs under H_2 atmosphere from bubble. The residue was filtrated and volatiles were remove to give a white solid crude compound (200 mg, 66%). $\mathbf{R_f}$ = 0.10 (50% EtOAc: Hexane) **IR** crude (KBr) 3375, 3026, 2957, 2179, 1745, 1651, 1571, 1536, 1461, 1411, 774 cm^{-1} **NMR** δ_H (200 MHz, $CDCl_3$) crude 1.70 (m, 2H, C<u>H</u>$_2$CO$_2$), 2.40 (m, 2H, H4), 3.50 (m, 1H, H3), 3.70 (s, 3H, OMe), 4.95 (m, 1H, H5) δ_C (50 MHz, $CDCl_3$) crude 44.4, 44.7, 49.8, 75.2, 125.8, 127.3, 144.9, 175.0