First Asymmetric Synthesis of a 6-Alkoxy-5,6-Dihydro-1,3-Oxazine
A Promising Enantioselective Route to β-Amido-Aldehydes

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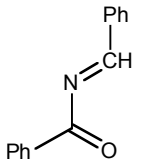
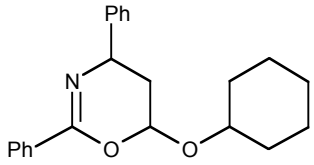
Supporting Information

N-benzoyl-benzaldimine **1**



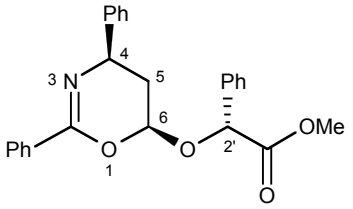
A solution of freshly chromatographied N-[(phenyl)(methoxy)methyl]benzamide **2**[10] (1g, 4.14 mmol) in 150 mL anhydrous toluene under nitrogen was stirred at 110 °C for 1d. After filtration of insoluble parts concentration of the filtrate provides amorphous N-acylimine **1** (0.82 g, 95 %) with a purity ≥ 85%[27] (rate of bis(amido)methylphenyl < 2%). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.76 (1H, s, CH), 8.16 (2H, d, J = 8.4 Hz, *o*-Ph-C=N), 7.96 (2H, d, J = 7.8 Hz, *o*-BzN), 7.59 and 7.58 (2H, 2m, *p*-Ph), 7.50 and 7.47 (4H, 2m, *m*-Ph) ; ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 180.9 (CO), 164.5 (CH), 134.5 (*n*-BzN), 133.5 (*p*-BzN), 133.3 (*n*-Ph-C=N), 133.2 (*p*-Ph-C=N), 130.1 and 130.0 (*o*-Ph), 128.9 and 128.5 (m-Ph).

Dihydrooxazine **4a**

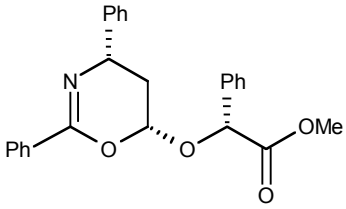


A suspension of N-benzoyl-benzaldimine **1** (113 mg[27], 0.41 mmol), cyclohexyl vinyl ether **3a** (52 mg, 0.41 mmol) and $Yb(fod)_3$ (22 mg, 0.02 mmol) in 4 mL cyclohexane under nitrogen was stirred at 80°C for 1d. After concentration the crude product (187 mg) was flash chromatographied (silica gel 3 g, toluene / AcOEt 50:50) to provide amorphous dihydrooxazine **4a** as a 3:2 *endo*/*exo* mixture (97.3 mg, 70 %). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.05 (2H, d, J = 6.9 Hz, *o*-PH-C=N), 7.50 - 7.30 (7H, m, Ph), 7.26 (1H, t, J = 7.1 Hz, p-Ph), 5.62 (dd, $J_{6\text{-}5ax}$ = 9.8 Hz, $J_{6\text{-}5eq}$ = 3.0 Hz, H-6 *endo*), 5.49 (dd, $J_{6\text{-}5ax}$ = 3.0 Hz, $J_{6\text{-}5eq}$ = 2.5 Hz, H-6 *exo*), 4.92 (dd, $J_{4\text{-}5ax}$ = 10.8 Hz, $J_{4\text{-}5eq}$ = 4.9 Hz, H-4 *exo*), 4.77 (dd, $J_{4\text{-}5ax}$ = 11.8 Hz, $J_{4\text{-}5eq}$ = 4.4 Hz, H-4 *endo*), 3.88 (1H, m, CH-*cyclohex*), 2.42 (ddd, J_{AB} = 13.3 Hz, $J_{5eq\text{-}4}$ = 4.4 Hz, $J_{5eq\text{-}6}$ = 3.0 Hz, H-5_{eq} *endo*), 2.25 (ddd, J_{AB} = 13.3 Hz, $J_{5eq\text{-}4}$ = 4.9 Hz, $J_{5eq\text{-}6}$ = 2.5 Hz, H-5_{eq} *exo*), 2.15 – 1.15 (11H, m, CH_2-*cyclohex* + H-5_{ax}).

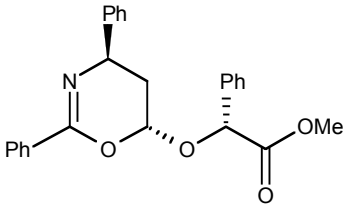
Dihydrooxazines **4b**



4b endo β



4b endo α



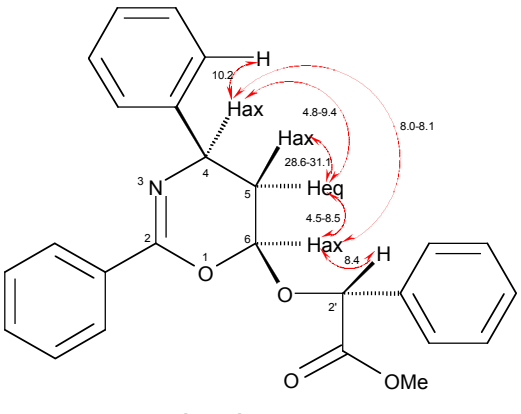
4b exo α +exo β

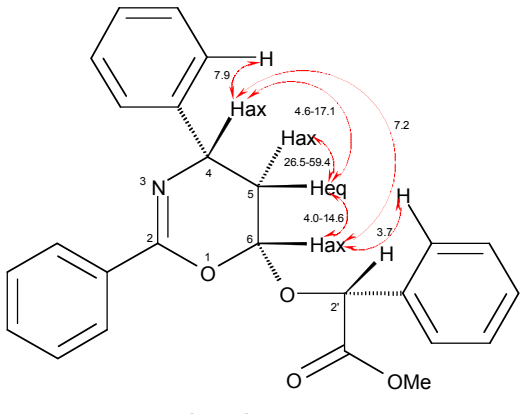
A suspension of N-benzoyl-benzaldimine **1** (500 mg[27], 1.79 mmol), *O*-vinyl methyl mandelate **3b** (350 mg, 1.79 mmol) and $Yb(fod)_3$ (95 mg, 0.09 mmol) in 14 mL cyclohexane under nitrogen was stirred at 80°C for 3d. After concentration the crude product (945 mg) was chromatographied (silica gel 47 g, cyclohexane / AcOEt 97:3 to 80:20) to provide dihydrooxazines **4b-endo-β** (215 mg, 30 %) as a colorless oil, **4b-endo-α** (93 mg, 13 %) as a colorless oil and **4b-exo α + β** (129 mg, 18 %) as an amorphous solid.

dihydrooxazine **4b-endo-β** : ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 7.88 (2H, d, J = 7.4 Hz, *o*-PH-C=N), 7.50 (2H, d, J = 7.7 Hz, *o*-Ph), 7.45 - 7.30 (10H, m, Ph), 7.28 (1H, t, J = 7.2 Hz, *p*-Ph), 5.67 (1H, dd, $J_{6\text{-}5ax}$ = 9.2 Hz, $J_{6\text{-}5eq}$ = 3.3 Hz, H-6), 5.60 (1H, s, H-2'), 4.78 (1H, dd, $J_{4\text{-}5ax}$ = 11.4 Hz, $J_{4\text{-}5eq}$ = 4.5 Hz, H-4), 3.78 (3H, s, OCH_3), 2.67 (1H, ddd, J_{AB} = 13.5 Hz, $J_{5eq\text{-}4}$ = 4.5 Hz, $J_{5eq\text{-}6}$ = 3.3 Hz, H-5_{eq}), 1.93 (1H, ddd, J_{AB} = 13.5 Hz, $J_{5ax\text{-}4}$ = 11.4 Hz, $J_{5ax\text{-}6}$ = 9.2 Hz, H-5_{ax}); ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 170.6 (C-1'), 154.4 (C-2), 143.3, 135.8, 132.9, 130.5, 128.6, 128.5, 128.3, 127.8, 127.2, 127.1, 126.7, 126.3, 98.0 (C-6), 77.9 (C-2'), 55.5 (C-4), 52.3 (OCH_3), 35.9 (C-5); HMRS calc'd for $C_{25}H_{24}NO_4$ [M + H] : 402.1705, found 402.1714.

dihydrooxazine **4b-endo-α** : ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.02 (2H, d, J = 7.0 Hz, *o*-PH-C=N), 7.47 (3H, m, *o*-Ph + *p*-Ph), 7.41 (2H, m, *m*-Ph-C=N), 7.40 - 7.35 (7H, m, Ph), 7.27 (1H, t, J = 7.2 Hz, *p*-Ph), 5.51 (1H, s, H-2'), 5.46 (1H, dd, $J_{6\text{-}5ax}$ = 9.1 Hz, $J_{6\text{-}5eq}$ = 3.2 Hz, H-6), 4.69 (1H, dd, $J_{4\text{-}5ax}$ = 11.2 Hz, $J_{4\text{-}5eq}$ = 4.6 Hz, H-4), 3.70 (3H, s, OCH_3), 2.49 (1H, ddd, J_{AB} = 13.5 Hz, $J_{5eq\text{-}4}$ = 4.5 Hz, $J_{5eq\text{-}6}$ = 3.2 Hz, H-5_{eq}), 2.01 (1H, ddd, J_{AB} = 13.5 Hz, $J_{5ax\text{-}4}$ = 11.2 Hz, $J_{5ax\text{-}6}$ = 9.1 Hz, H-5_{ax}); ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 170.4 (C-1'), 154.3 (C-2), 143.3, 135.0, 133.1, 130.7, 129.1, 128.8, 128.3, 128.0, 127.4, 127.3, 126.8, 126.4, 97.1 (C-6), 78.6 (C-2'), 55.5 (C-4), 52.3 (OCH_3), 35.7 (C-5).

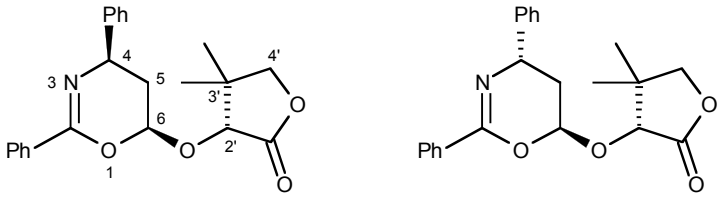
dihydrooxazines **4b-endo-β** and **4b-endo-α** : ^{1}H-NMR NOE mult (400 MHz, $CDCl_3$) :





dihydrooxazine **4b-exo** α + **exo-**β (5/6) ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.05 (J = 6.7 Hz) and 7.88 (J = 7.2 Hz) (2H, 2d, *o*-PH-C=N), 7.60 - 7.20 (13H, m, Ph), 5.61 (m, H-6, α), 5.45 (m, H-6 β), 5.54 (s, H-2', α), 5.38 (1H, 2s, H-2', β), 5.06 (dd, $J_{4\text{-}5ax}$ = 11.9 Hz, $J_{4\text{-}5eq}$ = 4.8 Hz, H-4, β), 4.95 (dd, $J_{4\text{-}5ax}$ = 11.7 Hz, $J_{4\text{-}5eq}$ = 4.9 Hz, H-4, α), 3.79 (s, OCH_3, α), 3.44 (s, OCH_3, β), 2.53 (ddd, J_{AB} = 13.8 Hz, $J_{5eq\text{-}4}$ = 4.9 Hz, $J_{5eq\text{-}6}$ = 2.1 Hz, H-5_{eq}, α), 2.41 (ddd, J_{AB} = 13.8 Hz, $J_{5eq\text{-}4}$ = 4.8 Hz, $J_{5eq\text{-}6}$ = 1.9 Hz, H-5_{eq}, β), 1.91 (ddd, J_{AB} = 13.8 Hz, $J_{5ax\text{-}4}$ = 11.7 Hz, $J_{5ax\text{-}6}$ = 2.9 Hz, H-5_{ax}, α), 1.83 (ddd, J_{AB} = 13.8 Hz, $J_{5ax\text{-}4}$ = 11.9 Hz, $J_{5ax\text{-}6}$ = 3.0 Hz, H-5_{ax}, β).

Dihydrooxazines **4c** (**endo-**β and **exo-**α)

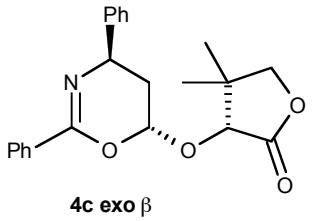


a) chromatographic protocol :
A suspension of N-benzoyl-benzaldimine **1** (1.5 g[27], 4.78 mmol), *O*-vinyl pantolactone **3c** (747 mg, 4.78 mmol) and $Yb(fod)_3$ (252 mg, 0.24 mmol) in 50 mL cyclohexane under nitrogen was stirred at 80°C for 3d. After concentration the crude product (2.5 g) was chromatographied (silica gel 80 g, toluene / AcOEt 95:5) to provide dihydrooxazines **4c-endo-**β (1.29 g, 74 %) as colorless crystals and **4c-exo-**α (246 mg, 14 %) as colorless crystals.
b) crystallisation protocol :
Alternatively the crude product (2,5 g) was recrystallized in Et_2O to provide dihydrooxazine **4c-endo-**β (1.22 g, 70 %) as colorless crystals.

dihydrooxazine **4c-endo-**β mp = 134 °C (ether); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.04 (2H, d, J = 6.9 Hz, *o*-PH-C=N), 7.50 - 7.20 (8H, m, Ph), 5.99 (1H, dd, $J_{6\text{-}5ax}$ = 8.9 Hz, $J_{6\text{-}5eq}$ = 3.5 Hz, H-6), 4.81 (1H, dd, $J_{4\text{-}5ax}$ = 10.8 Hz, $J_{4\text{-}5eq}$ = 4.9 Hz, H-4), 4.44 (1H, s, H-2'), 4.02 and 3.99 (2H, 2d, J_{AB} = 8.9 Hz, CH_2-4'); 2.63 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5eq\text{-}4}$ = 4.9 Hz, $J_{5eq\text{-}6}$ = 3.5 Hz, H-5_{eq}), 1.89 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5ax\text{-}4}$ = 10.8 Hz, $J_{5ax\text{-}6}$ = 8.9 Hz, H-5_{ax}), 1.26 (3H, s, CH_3), 1.01 (3H, s, CH_3); ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 173.8 (C-1'), 153.2 (C-2), 142.5, 132.2, 129.8, 127.4, 127.1, 126.3, 125.8, 125.4, 96.4 (C-6), 77.8 (C-2'), 75.3 (C-4'), 54.1 (C-4), 39.1 (C-3'), 34.7 (C-5), 21.9 (CH_3), 18.3 (CH_3); Analysis calc'd for $C_{22}H_{23}NO_4$: C, 72.31 ; H, 6.34 ; N, 3.83 ; found C, 72.16 ; H, 6.41 ; N, 3.68.

dihydrooxazine **4c-exo-**α : mp = 175°C (ether) ; ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.05 (2H, d, J = 8.4 Hz, *o*-PH-C=N), 7.55 - 7.20 (8H, m, Ph), 5.89 (1H, ~ t, J = 2.5 Hz, H-6), 4.90 (1H, dd, $J_{4\text{-}5ax}$ = 12.3 Hz, $J_{4\text{-}5eq}$ = 4.9 Hz, H-4), 4.42 (1H, s, H-2'), 4.04 and 3.98 (2H, 2d, J_{AB} = 8.9 Hz, CH_2-4'); 2.50 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5eq\text{-}4}$ = 4.9 Hz, $J_{5eq\text{-}6}$ = 2.0 Hz, H-5_{eq}), 1.90 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5ax\text{-}4}$ = 12.3 Hz, $J_{5ax\text{-}6}$ = 3.0 Hz, H-5_{ax}), 1.11 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 174.8 (C-1'), 152.3 (C-2), 143.7, 133.3, 130.8, 128.5, 128.1, 127.1, 126.9, 126.6, 94.9 (C-6), 78.4 (C-2'), 76.4 (C-4'), 50.6 (C-4), 40.2 (C-3'), 34.2 (C-5), 23.0 (CH_3), 19.6 (CH_3).

Dihydrooxazine **4c-exo-**β



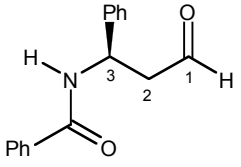
4c exo β

To a solution at -78°C of N-benzoyl-benzaldimine **1** (372 mg[27], 1.48 mmol) and *O*-vinyl pantolactone **3c** (232 mg, 1.48 mmol) in 19 mL dichloromethane was rapidly added $SnCl_4$ (1.48 mL, 1.48 mmol). After stirring 30 min. under nitrogen at -78°C the mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and diluted with AcOEt (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to provide crude dihydrooxazine **4c** as a 1:6 *endo*/*exo* mixture (488 mg, 90 %). After crystallization in ether, purified dihydrooxazine **4c-exo-**β was obtained as white microcrystalline powder (336 mg, 62 %); mp =129 °C (ether), ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 8.06 (2H, d, J = 6.9 Hz, *o*-PH-C=N), 7.40 (7H, m, Ph), 7.27 (1H, t, J = 7.4 Hz, *p*-Ph); 5.53 (1H, ~ t, J = 3.0 Hz, H-6), 4.95 (1H, dd, $J_{4\text{-}5ax}$ = 10.8 Hz, $J_{4\text{-}5eq}$ = 4.9 Hz, H-4), 4.26 (1H, s, H-2'), 4.04 and 3.94 (2H, 2d, J_{AB} = 8.9 Hz, CH_2-4'); 2.36 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5eq\text{-}4}$ = 4.9 Hz, $J_{5eq\text{-}6}$ = 2.9 Hz, H-5_{eq}), 1.93 (1H, ddd, J_{AB} = 13.8 Hz, $J_{5ax\text{-}4}$ = 10.8 Hz, $J_{5ax\text{-}6}$ = 3.0 Hz, H-5_{ax}), 1.27 (3H, s, CH_3), 1.17 (3H, s, CH_3).

Preparation of benzamidoaldehyde (±)-**5**

A solution of N-benzoyl-benzaldimine **1** (1.17 g[27], 4.68 mmol) and $Eu(fod)_3$ (248 mg, 0.23 mmol) in 8 mL ethyl vinyl ether (6 g, 83 mmol) under nitrogen was stirred at 33°C for 3h. After concentration the crude 6-ethoxy-dihydrooxazine **4**, thus obtained as a *endo*/*exo* mixture, was stirred in acetone (19 mL) and water (300 μL) with Amberlyst-15 H^+ (180 mg) for 15 min at room temperature under nitrogen. After filtration and concentration the residue was chromatographied (silica gel 38 g, cyclohexane / AcOEt 60:40 to 50 :50) to provide benzamidoaldehyde (±)-**5** (793 mg, 67 %) as amorphous solid. ^{1}H-NMR study using 25 %mol of $Eu(tfc)_3$: ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 9.99 (0.5H, s, CHO-(*R*)-**5**), 9.94 (0.5H, s, CHO-(*S*)-**5**).

Benzamidoaldehyde (R)-**5**

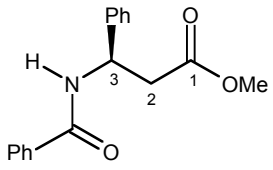


(R)-**5**

A solution of dihydrooxazine **4c endo** β (720 mg, 1.97 mmol) in a mixture of acetone (8 mL) and water (1.2 mL) was stirred with Amberlyst-15 H^+ (195 mg) for one night at room temperature under nitrogen. After filtration and concentration the residue was dissolved in AcOEt (50 mL). The organic layer was carefully washed with water (5 × 20 mL) to remove (R)-(-)-pantolactone, dried ($MgSO_4$) and concentrated. The residual pantolactone was removed by sublimation with bulb-to-bulb distillation apparatus (100°C, 10^{-1} torr) to provide benzamidoaldehyde (R)-**5** (474 mg, 96 %) as white microcrystalline powder

mp = 130 - 131 °C (AcOEt); α_{20}^{D} ~ 0 (1, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 9.81 (1H, dd, J = 1 Hz, CHO), 7.77 (2H, d, J = 7.9 Hz, *o*-BzN), 7.50 (1H, t, J = 7.4 Hz, *p*-BzN), 7.42 (2H, t, J = 7.4 Hz, *m*-BzN), 7.4 - 7.0 (5H, m, Ph), 6.95 (1H, d, J_{NH-3} = 7.9 Hz, NH), 5.71 (1H, m, H-3), 3.21 (1H, ddd, J_{AB} = 17.2 Hz, J_{2A-3} = 6.4 Hz, J_{2A-1} = 1.5 Hz, H-2_A), 3.06 (1H, dd, J_{AB} = 17.2 Hz, J_{2B-3} = 5.9 Hz, H-2_B); ^{13}C-NMR (100 Mz, $CDCl_3$, δ ppm) : 200.6 (C-1), 166.8 (CONH), 140.4 (*n*-Ph), 133.9 (*n*-BzN), 131.7 (*p*-BzN) , 128.8 (*o*-BzN), 128.5 (*m*-Ph), 127.8 (*p*-Ph), 127.0 (*m*-BzN), 126.5 (*o*-Ph), 49.1 (C-3), 48.8 (C-2). HMRS calc'd for $C_{16}H_{15}NO_2$ [$M^{+\bullet}$] : 253.1103, found 253.1133.

Benzamidoester (R)-**6**



(R)-**6**

To a solution at -10°C of benzamidoaldehyde (R)-**5** (100 mg, 0.395 mmol) in anhydrous acetone (1 mL) was added Jones reagent (120 μL, 0.969 mmol) and the mixture was stirred at room temperature for 1h. After addition of isopropanol (1 mL) and aqueous H_2SO_4 2 % (1 mL), the mixture was extracted with AcOEt (3 × 5 mL). The combined organic layers were concentrated to provide the crude N-benzoyl-phenyl propanoic acid (96 mg, 90.5 %). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 7.79 (2H, d, J = 7.9 Hz, *o*-BzN), 7.50 (1H, t, J = 7.4 Hz, *p*-BzN), 7.41 (2H, t, J = 7.6 Hz, *m*-BzN), 7.40 – 7.25 (6H, m, Ph + NH), 5.64 (1H, m, H-3), 3.10 and 2.98 (2H, 2dd, J_{AB} = 16.2 Hz, J_{2-3} = 5.4 Hz, CH-2).
A solution of N-benzoyl-phenyl propanoic acid (78 mg, 0.289 mmol) in 4 mL of HCl-MeOH (0.1 g/mL) was refluxed for 5 min. After concentration the crude product was chromatographied (silica gel 5 g, cyclohexane / AcOEt 8:2) to provide benzamidoester (R)-**6** (78 mg, 95 %) as white needles ; mp = 120 - 121 °C (CH_2Cl_2-Et_2O), Litt. : mp = 120 – 121 °C,[22] α_{20}^{D} = -20.6 (0.85, $CHCl_3$), Litt : α_{20}^{D} = -20.2 (1.2, $CHCl_3$),[16] ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) : 7.83 (2H, d, J = 6.9 Hz, *o*-BzN), 7.56 (1H, d, J_{NH-3} = 8.4 Hz, NH), 7.50 (1H, t, J = 7.4 Hz, *p*-BzN), 7.43 (2H, t, J = 7.4 Hz, *m*-BzN), 7.34 (4H, *o,m*-Ph), 7.26 (1H, m, *p*-Ph), 5.63 (1H, ddd, J_{3-NH} = 8.4 Hz, J_{3-2B} = 5.9 Hz, J_{3-2A} = 5.4 Hz, H-3), 3.63 (3H, s, OCH_3), 3.04 (1H, dd, J_{AB} = 15.8 Hz, J_{2A-3} = 5.4 Hz, H-2_A), 2.95 (1H, dd, J_{AB} = 15.8 Hz, J_{2B-3} = 5.9 Hz, H-2_B).

Note :

(27) For all reactions the mass of acylimine **1** took apart of the purity (85 % mass).