A Nitrone Based Route to Polyhydroxylated Lactams and Piperidines: An Expeditious Synthesis of *rac*-Fagomine

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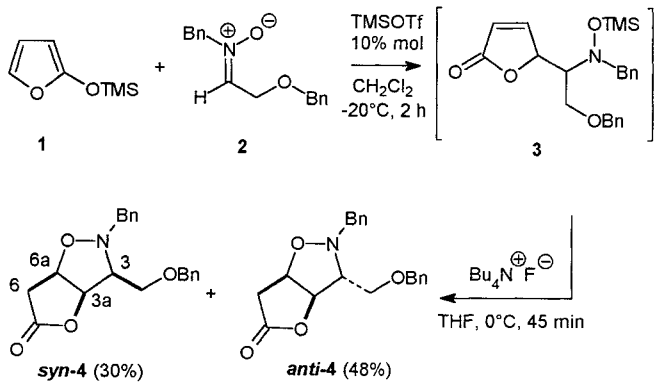
The synthetic versatility of tetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)-ones, obtained from TMSOTf-promoted addition of 2-trimethylsilyloxyfuran to nitrones, is demonstrated in a two-step reductive sequence to give the title compounds. The cycloadducts obtained from a glycolaldehyde derived nitrone are first reduced with DIBAH, then hydrogenolyzed in the presence of $Pd(OH)_2$ to give polyhydroxylated piperidines, including *rac*-fagomine. Direct hydrogenolysis of the same cycloadducts gives an easy entry to polyhydroxylated lactams.

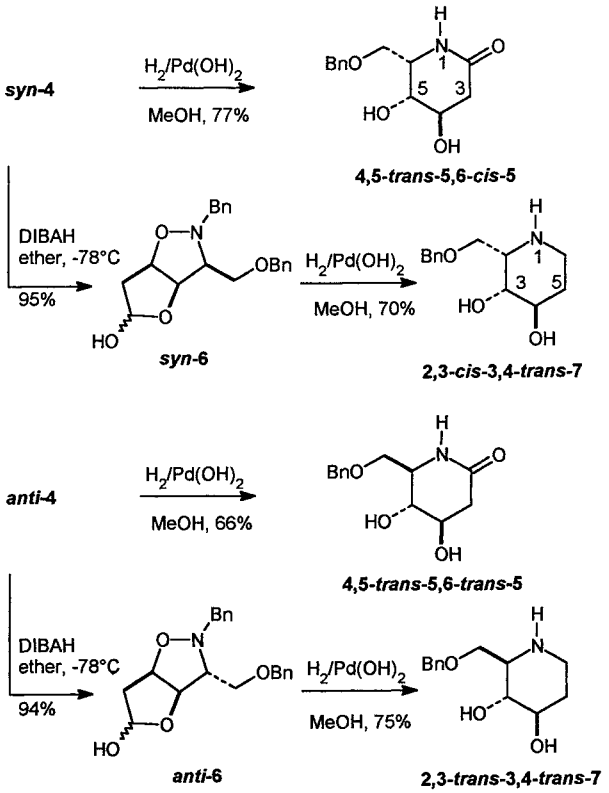
Nitrones have recently received much attention as candidates not only in 1,3-dipolar cycloaddition reactions[1] but also in nucleophilic additions with organometallic compounds.[2] For example, we recently reported the trimethylsilyl triflate (TMSOTf)-promoted addition of silylated nucleophiles, including 2-trimethylsilyloxyfuran (**1**), to nitrones.[3]

Here we wish to report the addition of **1** to *N*-benzyl nitrone **2** derived from glycolaldehyde (Scheme 1), and to emphasize the synthetic versatility of tetrahydrofuro-[2,3-*d*]isoxazol-5(2*H*)-ones **4** as precursors of polyhydroxylated lactams and piperidines. Thus, according to a previously reported protocol,[3a] nitrone **2** and 2-trimethylsilyloxyfuran (**1**) were stirred in CH_2Cl_2 for 2 hours at −20 °C in the presence of 10% mol TMSOTf. After quenching with $NaHCO_3$ and extraction with CH_2Cl_2, the crude mixture of butenolides **3** was treated with $Bu_4N^+F^-$ in THF at 0 °C for 45 min in order to promote the cyclization of **3** to tetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)-ones **4**. *syn*-**4** and *anti*-**4** were isolated after flash chromatography in 78% overall yield in a ratio of 38 : 62. A slight predominance of the *trans*-cycloadduct was previously observed as a general trend when *N*-benzyl *C*-alkyl nitrones are used.[3c]



Scheme 1

The usefulness of products **4** is made apparent by the synthetic equivalence with 5-amino-3,4,6-trihydroxyhexanoic acid as well as with 2,4-dideoxy-4-aminohexoses, in turn precursors of azasugars. In fact, we were able to transform **4** into lactams **5** and piperidines **7** by a proper choice of reductive steps, as depicted in Scheme 2.



Scheme 2

Direct hydrogenolysis of *syn*-**4** and *anti*-**4** in the presence of Pearlman catalyst gave a nice cascade reaction sequence involving N—O bond cleavage, chemoselective *N*-debenzylation[4] and spontaneous lactamization affording products **5** in very good yields. It is worth noticing the integrity of the *O*-benzyl group which makes an orthogonal protection of the ring hydroxy group possible. It is known[5] that lactams are reduced to piperidines upon treatment with $BH_3 \cdot THF$ or $BF_3 \cdot SMe_2$. However, in our hands reduction of both 4,5-*trans*-5,6-*cis*-**5** and 4,5-*trans*-5,6-*trans*-**5** with $BH_3 \cdot THF$ gave disappointing results (yields < 20%). We describe here an alternative route which involves, (i) reduction of cycloadducts **4** to the corresponding lactols **6** by reaction with DIBAH in almost quantitative yield,[6] (ii) subsequent hydrogenolysis in the presence of Pearlman catalyst which directly afforded *rac*-fagomine (2,3-*trans*-3,4-*trans*-**7**)[7] and its epimer 2,3-*cis*-3,4-*trans*-**7** via N—O bond cleavage, *N*-debenzylation, and intramolecular reductive amination.

In summary, we have shown the potentiality of a nitrone based route to polyhydroxylated lactams and piperidines with excellent overall yields, ranging from 65 to 80%. Further developments using a similar approach for the synthesis of enantiomerically pure azasugars are in progress.

^{1}H NMR and ^{13}C NMR spectra were recorded in various deuterated solvents at 300 and 75 MHz, respectively. Chemical shifts were reported in ppm relative to internal standard TMS. H_2O content of anhydrous solvents used was determined by Karl-Fisher titration. Reactions were performed in oven-dried glassware in an atmosphere of dry argon. Hydrogenations were performed at 45 p.s.i. on a Parr apparatus. Moist 20% $Pd(OH)_2$ on carbon (Degussa type E101) was purchased from Aldrich. Melting points are uncorrected.

***N*-Benzyl-(2-benzyloxyethylidene)amine *N*-Oxide (2):**

To a solution of *O*-benzylglycolaldehyde (1.0 g, 6.7 mmol) in CH_2Cl_2 (5 mL) was added a solution of *N*-benzylhydroxylamine (0.84 g, 6.8 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at r.t. for 12 h in the presence of Na_2SO_4. The organic layer was filtered and evaporated under reduced pressure. Recrystallization (cyclohexane/Et_2O, 9:1) of the crude residue afforded nitrone **2**; yield 1.7 g (99%); R_f 0.17 (EtOAc/cyclohexane, 3:2); mp 95–96°C.

^{1}H NMR ($CDCl_3$): δ = 4.48 (d, 2H, J = 4.1 Hz, CH_2OBn), 4.54 (s, 2H, OCH_2Ph), 4.87 (s, 2H, NCH_2Ph), 6.79 (t, 1H, J = 4.1 Hz, NCH), 7.32–7.40 (m, 10H, ArH).

^{13}C NMR ($CDCl_3$): δ = 66.1 (OCH_2Ph), 69.0 (CH_2O), 73.8 (NCH_2Ph), 127.9, 128.0, 128.5, 129.0, 129.2, 129.6, 132.0, 137.1 (C_{arom}), 137.4 (N=CH).

MS: m/z (%) = 108 (82), 107 (60), 91 (14), 89 (8), 80 (10), 79 (100), 77 (6), 65 (7), 51 (28).

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.72; N, 5.49. Found: C, 75.13; H, 6.82; N, 5.33.

2-Benzyl-3-benzyloxymethyltetrahydrofuro[2,3-*d*]isoxazol-5(2*H*)-ones (4):

To a solution of nitrone **2** (1.7 g, 6.7 mmol) in dry CH_2Cl_2 (10 mL) cooled at −20°C were added 2-trimethylsilyoxyfuran (**1**; 1.3 mL, 7.4 mmol) and TMSOTf (0.120 mL, 0.67 mmol). After stirring for 2 h at 0°C the reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuum to give crude butenolide **3** as a yellow oil. To a solution of crude **3** in anhyd THF (5 mL) was added Bu_4NF (7.4 mL, 1.0 M solution in THF, 7.4 mmol) at 0°C. The mixture was stirred for 45 min while temperature was allowed to raise to 25°C. Silica gel was directly added to the solution, the solvent was evaporated in vacuum and products were separated by flash chromatography eluting with EtOAc/cyclohexane (1:9) to give *syn*-**4** (0.682 g, 30%) as a white solid that was recrystallized from cyclohexane/Et_2O, and *anti*-**4** (1.09 g, 48%) as an oil.

syn-**4**: R_f 0.28 (EtOAc/cyclohexane, 3:7); mp 83–85°C.

^{1}H NMR ($CDCl_3$): δ = 2.66 (dd, 1H, J = 3.5, 19.5 Hz, H-6), 2.74 (dd, 1H, J = 6.6, 19.5 Hz, H-6), 3.02 (dt, 1H, J = 7.1, 4.4 Hz, H-3), 3.65 (dd, 1H, J = 7.1, 10.4 Hz, CH_2OBn), 3.80 (d, 1H, J = 14.6 Hz, NCH_2Ph), 3.95 (dd, 1H, J = 4.4, 10.4 Hz, CH_2OBn), 4.45 (d, 1H, J = 14.6 Hz, NCH_2Ph), 4.56 (s, 2H, OCH_2Ph), 4.86 (dt, 1H, J = 3.5, 6.6 Hz, H-6a), 5.27 (dd, 1H, J = 4.4, 6.6 Hz, H-3a), 7.30–7.35 (m, 10H, ArH).

^{13}C NMR ($CDCl_3$): δ = 34.9 (C-6), 60.2 (NCH_2Ph), 66.9 (CH_2OBn), 68.7 (C-3), 73.9 (OCH_2Ph), 74.7 (C-6a), 85.9 (C-3a), 127.2, 127.8, 128.2, 128.4, 128.5, 137.0, 137.5 (C_{arom}), 175.2 (OC=O).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.77; H, 6.24; N, 4.13. Found: C, 70.56; H, 6.31; N, 4.22.

anti-**4**: R_f 0.23 (EtOAc/cyclohexane, 3:7).

^{1}H NMR ($CDCl_3$): δ = 2.67 (dd, 1H, J = 2.3, 18.8 Hz, H-6), 2.74 (dd, 1H, J = 4.9, 18.8 Hz, H-6), 3.33 (dt, 1H, J = 2.6, 5.4 Hz, H-3), 3.59 (dd, 1H, J = 5.4, 10.1 Hz, CH_2OBn), 3.66 (dd, 1H, J = 5.4, 10.1 Hz, CH_2OBn), 4.01 (d, 1H, J = 14.7 Hz, NCH_2Ph), 4.21 (d, 1H, J = 14.7 Hz, NCH_2Ph), 4.57 (s, 2H, OCH_2Ph), 4.66 (dt, 1H, J = 2.6, 4.9 Hz, H-6a), 5.08 (dd, 1H, J = 2.6, 4.9 Hz, H-3a), 7.28–7.40 (m, 10H, ArH).

^{13}C NMR ($CDCl_3$): δ = 34.2 (C-6), 61.3 (NCH_2Ph), 68.1 (CH_2OBn), 71.1 (C-3), 73.5 (OCH_2Ph), 75.9 (C-6a), 89.1 (C-3a), 127.6, 127.9, 128.4, 128.5, 128.8, 136.7, 137.5 (C_{arom}), 174.7 (OC=O).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.77; H, 6.24; N, 4.13. Found: C, 70.63; H, 6.15; N, 4.16.

4,5-*trans*-5,6-*cis*-6-Benzyloxymethyl-4,5-dihydroxypiperidin-2-one (5a); Typical Procedure:

A mixture of *syn*-**4** (0.430 g, 1.3 mmol) and 20% $Pd(OH)_2$ on carbon (0.10 g) in anhydrous MeOH (10 mL) was hydrogenated for 12 h. Silica gel was added, the solvent was removed under vacuum and 4,5-*trans*-5,6-*cis*-**5** was isolated as an oil after flash chromatography, eluting first with EtOAc and then with EtOAc/MeOH (9:1); yield: 0.250 g (77%); R_f 0.41 (EtOAc/MeOH, 9:1).

IR (neat): ν = 3388, 2990, 2931, 2985, 1664, 1447, 1250, 1103, 744, 696 cm^{-1}.

^{1}H NMR (D_2O): δ = 2.47 (dd, 1H, J = 2.9, 18.5 Hz, H-3), 2.90 (dd, 1H, J = 4.7, 18.5 Hz, H-3), 3.81 (dd, 1H, J = 7.7, 10.0 Hz, CH_2OBn), 3.92 (dd, 1H, J = 4.8, 10.0 Hz, CH_2OBn), 4.02 (dt, 1H, J = 4.8, 7.7 Hz, H-6), 4.11 (dd, 1H, J = 3.3, 4.8 Hz, H-5), 4.29 (dt, 1H, J = 2.9, 4.7 Hz, H-4), 4.76 (s, 2H, OCH_2Ph), 7.52–7.60 (m, 5H, ArH).

^{13}C NMR (CD_3OD): δ = 35.0 (C-3), 52.0 (C-6), 66.6 (C-4+C-5), 69.6 (CH_2OBn), 73.8 (OCH_2Ph), 129.0, 129.1, 129.4, 138.0, 173.8 (NC=O).

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 62.33; H, 6.74; N, 5.46.

4,5-trans-5,6-trans-6-Benzyloxymethyl-4,5-dihydroxypiperidin-2-one **(5b)**:

According to the previously reported procedure, *anti*-**4** (0.520 g, 1.5 mmol) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (0.12 g). Purification by flash chromatography eluting first with EtOAc then with EtOAc/MeOH, 9:1 afforded 4,5-*trans*-5,6-*trans*-**5** as an oil; yield: 0.250 g (66%); R_f 0.44 (EtOAc/MeOH, 9:1).

^{1}H NMR (D_2O): δ = 2.21 (dd, 1H, J = 10.0, 17.6 Hz, H-3), 2.90 (dd, 1H, J = 6.0, 17.6 Hz, H-3), 3.30 (ddd, 1H, J = 3.3, 5.2, 8.4 Hz, H-6), 3.50 (t, 1H, J = 9.3 Hz, H-5), 3.57 (dd, 1H, J = 5.2/10.7 Hz, CH_2OBn), 3.66 (dd, 1H, J = 3.3, 10.7 Hz, CH_2OBn), 3.97 (ddd, 1H, J = 6.0, 9.3, 10.0 Hz, H-4), 4.48 (s, 2H, OCH_2Ph), 7.52–7.60 (m, 5H, ArH).

^{13}C NMR (CD_3OD): δ = 36.9 (C-3), 55.7 (C-6), 67.8 (C-5), 69.3 (CH_2OBn), 69.4 (C-4), 73.4 (OCH_2Ph), 128.5, 128.7, 128.8, 137.4 (C_{arom}), 173.1 (NC=O).

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 61.92; H, 6.73; N, 5.64.

***syn*-2-Benzyl-3-benzyloxymethyltetrahydrofuro[2,3-*d*]isoxazol-5-(2*H*,5*H*)-ol (*syn*-6); Typical Procedure:**

A solution of *syn*-**4** (0.083 g, 0.24 mmol) in anhyd Et_2O (5 mL) was cooled at −78°C and DIBAH (0.25 mL, 1 M solution in hexane, 0.25 mmol) was added dropwise. The reaction mixture was stirred at −78°C for 1 h then poured on ice. Seignette salt was added in order to dissolve aluminum salts and, after stirring for 1 h, the solution was extracted with Et_2O. Combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give crude *syn*-**6** as a dense oil 95% pure on the basis of ^{1}H NMR; yield: 0.081 g (94%); R_f 0.43 (cyclohexane/Et_2O, 4:6).

^{1}H NMR ($CDCl_3$): δ = 2.02–2.05 (m, 2H, H-6), 2.88 (dt, 1H, J = 3.7, 7.4 Hz, H-3), 3.79 (dd, 1H, J = 7.5, 10.8 Hz, CH_2OBn), 3.83 (d, 1H, J = 14.6 Hz, NCH_2Ph), 4.06 (dd, 1H, J = 3.9, 10.8 Hz, CH_2OBn), 4.57 (d, 1H, J = 14.6 Hz, NCH_2Ph), 4.57 (s, 2H, OCH_2Ph), 4.76–4.81 (m, 1H, H-6a), 4.97 (dd, 1H, J = 4.1, 5.7 Hz, H-3a), 5.31–5.37 (m, 1H, H-5), 6.61 (d, 1H, J = 13.1 Hz, OH), 7.26–7.38 (m, 10H, ArH).

^{13}C NMR ($CDCl_3$): δ = 42.3 (C-6), 60.4 (NCH_2Ph), 67.5

(CH_2OBn), 69.1 (C-3), 73.6 (CH_2OPh), 80.0 (C-3a or C-6a), 86.6 (C-3a or C-6a), 98.4 (C-5), 127.4, 127.8, 127.9, 128.4, 128.5, 128.6, 136.5, 137.7 (C_{arom}).

anti-2-Benzyl-3-benzyloxymethyltetrahydrofuro[2,3-d]isoxazol-5(2H,5H)-ol (anti-6):

According to the previously reported procedure given above *anti*-**4** (0.176 g, 0.56 mmol) was reduced with DIBAH (0.57 mL, 1 M solution in hexane, 0.57 mmol) to give crude *anti*-**6** as a dense oil 95% pure on the basis of ^{1}H NMR; yield: 0.167 g (94%); R_f 0.39 (cyclohexane/Et_2O, 4:6).

IR (neat): ν = 3408, 3092, 3065, 3032, 2934, 2868, 1497, 1451, 1365, 1095, 1045, 1036, 749, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.01 (ddd, 1 H, J = 3.1, 6.4, 14.5 Hz, H-6), 2.32 (ddd, 1 H, J = 2.1, 5.1, 14.5 Hz, H-6), 3.19 (dt, 1 H, J = 2.9, 6.1 Hz, H-3), 3.58 (d, 2 H, J = 6.1 Hz, CH_2OBn), 4.02 (d, 1 H, J = 14.0 Hz, NCH_2Ph), 4.24 (d, 1 H, J = 14.0 Hz, NCH_2Ph), 4.56 (s, 2 H, OCH_2Ph), 4.68 (ddd, 1 H, J = 2.1, 4.7, 6.4 Hz, H-6a), 4.85 (dd, 1 H, J = 2.9, 4.7 Hz, H-3a), 5.36 (br s, 1 H, OH), 5.76 (dd, 1 H, J = 3.1, 5.1 Hz, H-5), 7.27–7.40 (m, 10 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 39.4 (C-6), 65.8 (NCH_2Ph), 71.5 (C-3), 73.5 (CH_2OPh + CH_2OBn), 80.9 (C-3a or C-6a), 89.2 (C-3a or C-6a), 100.6 (C-5), 127.6, 127.7, 127.9, 128.2, 128.5, 128.6, 136.2, 137.6 (C_{arom}).

2,3-*cis*-3,4-*trans*-2-benzyloxymethyl-3,4-dihydroxypiperidine (2,3-*cis*-3,4-*trans*-7):

A solution of *syn*-**6** (0.04 g, 0.12 mmol) in MeOH/THF (8:2, 10 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (0.012 g) for 20 h. After filtration through Celite, silica gel was added, the solvent was removed under reduced pressure and the residue was placed on the top of a chromatographic column. Eluting first with EtOAc and then with EtOAc/MeOH (8:2) gave 2,3-*cis*-3,4-*trans*-**7** as an oil; yield: 0.020 g (70%); R_f 0.05 (EtOAc/MeOH, 7:3).

^{1}H NMR ($CDCl_3$): δ = 1.53 (d, J = 3.1 Hz, q, J = 14.2 Hz, 1 H, H-5_{ax}), 2.00 (dddd, 1 H, J = 3.1/5.2/12.2/14.2 Hz, H-5_{eq}), 2.82 (ddd, 1 H, J = 3.1/5.2/12.2 Hz, H-6_{eq}), 2.96 (d, J = 3.1 Hz, t, J = 12.2 Hz, 1 H, H-6_{ax}), 3.24 (ddd, 1 H, J = 1.9/5.1/6.5 Hz, H-2), 3.55–3.59 (m, 1 H, H-3), 3.63–3.66 (m, 2 H, CH_2OBn), 3.93 (br q, $J \approx$ 3.3 Hz, 1 H, H-4), 4.53 (s, 2 H, OCH_2Ph), 7.27–7.38 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 28.7 (C-5), 40.4 (C-6), 54.1 (C-2), 68.3, 70.3, 72.3 (CH_2OBn), 73.7 (OCH_2Ph), 127.8, 128.5, 137.7 (C_{arom}).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.78; H, 8.07; N, 5.91. Found: C, 65.61; H, 8.17; N, 5.96.

2,3-*trans*-3,4-*trans*-2-benzyloxymethyl-3,4-dihydroxypiperidine (2,3-*trans*-3,4-*trans*-7):

A solution of *anti*-**6** (0.083 g, 0.24 mmol) in MeOH/THF 8:2 (10 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (0.027 g) for 14 h. After filtration through Celite, silica gel was added, the solvent was removed under reduced pressure and the residue was placed on the top of a chromatographic column. Eluting first with EtOAc and then with EtOAc/MeOH (8:2) gave 2,3-*trans*-3,4-*trans*-**7** as an oil; yield: 0.04 g (75%); R_f 0.16 (EtOAc/MeOH, 7:3).

IR (neat): ν = 3357, 2938, 2875, 1650, 1455, 1363, 1109, 1073, 1030, 740, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.51 (d, J = 4.2 Hz, q, J = 12.6 Hz, 1 H, H-5_{ax}), 1.97 (t, J = 2.5 Hz, dd, J = 2.5/4.9 Hz, 1 H, H-5_{eq}), 2.66 (d, J = 2.5 Hz, t, J = 12.6 Hz, 1 H, H-6_{ax}), 2.68 (ddd, 1 H, J = 4.3/6.2/9.0 Hz, H-2), 3.05 (ddd, 1 H, J = 2.5/4.2/12.6 Hz, H-6_{eq}), 3.27 (t, 1 H, J = 9.0 Hz, H-3), 3.50 (ddd, 1 H, J = 4.9/9.0/12.6 Hz, H-4), 3.62 (dd, 1 H, J = 6.2/9.1 Hz, CH_2OBn), 3.74 (dd, 1 H, J = 4.3/9.1 Hz, CH_2OBn), 4.55 (s, 2 H, OCH_2Ph), 7.29–7.35 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 33.2 (C-5), 43.5 (C-6), 59.6 (C-2), 71.4 (CH_2OBn), 73.5 (OCH_2Ph), 74.0, 74.7, 127.8, 128.4, 137.9 (C_{arom}).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.78; H, 8.07; N, 5.91. Found: C, 65.83; H, 8.22; N, 5.67.

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