A Facile Synthesis of Enantiomerically Pure 1-(Piperazin-2-yl)ethan-1-ol Derivatives from (2*S*,3*R*)-Threonine

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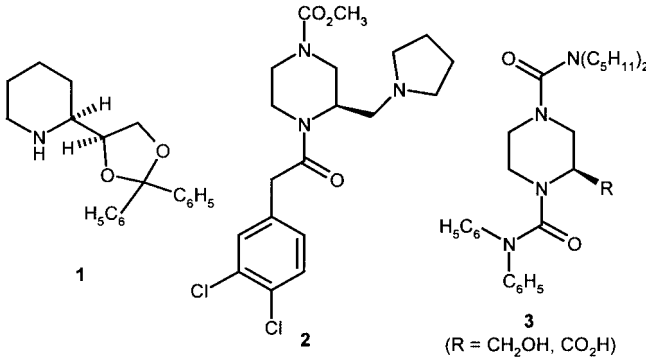
Abstract: Starting from the proteinogenic amino acid (2*S*,3*R*)-threonine (**4**) a novel method for the preparation of enantiomerically pure 1-(1-benzylpiperazin-2-yl)ethan-1-ols with various substituents in position 4 (**15 – 20**) is described. The sequence involves as key step the $LiAlH_4$ reduction of the bicyclic piperazinediones **11a**,**b–14a**,**b**, which establishes the 1-benzyl protective group and simultaneously liberates the 1-hydroxyethyl side chain for further transformations.

Key words: EPC (enantiomerically pure compounds) synthesis, 1-(piperazin-2-yl)ethan-1-ols, enantiomerically pure threonine, 1,3-oxazolidines, alcohols, heterocycles, reductions

Various piperidines and piperazines with substituents in position 2 are known to be potent ligands for different central nervous system (CNS) receptors. Thus, the piperidine **1** (dexoxadrol) bearing a 1,3-dioxolane ring system in position 2 binds with high affinity to the phencyclidine binding site of the NMDA receptor (channel blocker).[1] The pyrrolidinylmethyl substituted piperazine derivative **2** belongs to the most potent and selective κ opioid receptor agonists (IC_{50} = 0.018 nM),[2] and the 1,4-diacylpiperazines **3** represent a novel class of substance P antagonists (NK_1 antagonists).[3]



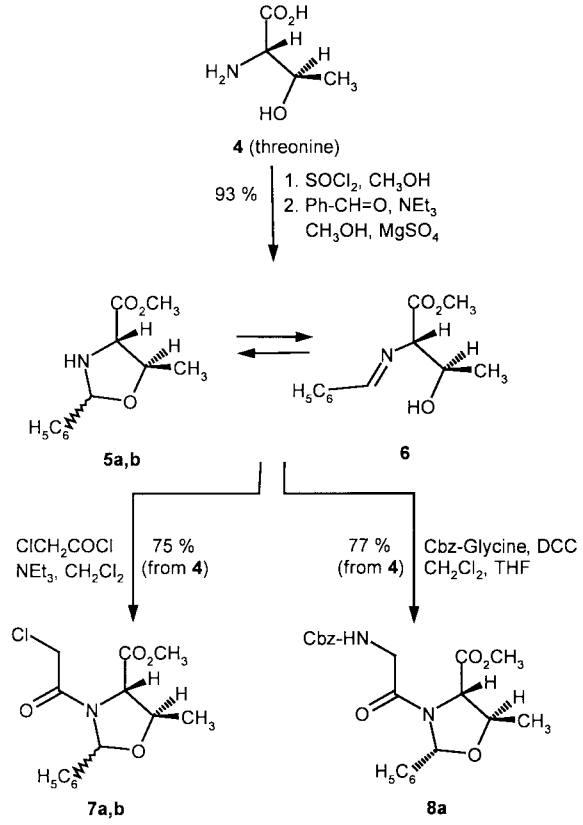
In the course of our work on novel ligands for CNS receptors we became interested in 2 substituted piperazine derivatives, which should be available by transformations of 1-(piperazin-2-yl)ethan-1-ols. In the literature the 1-(piperazin-2-yl)ethan-1-ol moiety is mentioned as a part of sleep inducing agents,[4] aminoglycosides,[5] and antidepressants.[6] However, only few methods for the synthesis of 1-(piperazin-2-yl)ethan-1-ols have been described: cyclization of a protected glycine-threonine dipeptide,[7] Ugi reaction of glycine, arabinose and cyclohexyl isocyanide,[8] and hydroxyalkylation of lithiated *N*-nitrosopiperazines with aldehydes.[9]

Therefore, we developed a novel method for the preparation of *enantiomerically pure* 1-(piperazin-2-yl)ethan-1-ol derivatives **15–20**. According to our procedure, which starts with the proteinogenic amino acid (2*S*,3*R*)-threonine **(4)**, versatile substituents (e.g. alkyl, aryl, arylalkyl, acyl, alkoxycarbonyl) may be regioselectively introduced in position 4 of the piperazine ring system. The N-1 benzyl residue of **15** – **20** should be readily cleavable by hydrogenolysis opening the possibility to obtain N-1 unsubstituted (cf. **1**), N-1 alkylated or acylated piperazines (cf. **2**, **3**). In particular, the 1-hydroxyethyl residue in position 2 of the piperazine ring should be suitable for the introduction of pharmacophoric elements, e.g. oxygen heterocycles like the 1,3-dioxolane ring (cf. **1**), amine substituents (cf. **2**) or oxygen containing functional groups (cf. **3**).

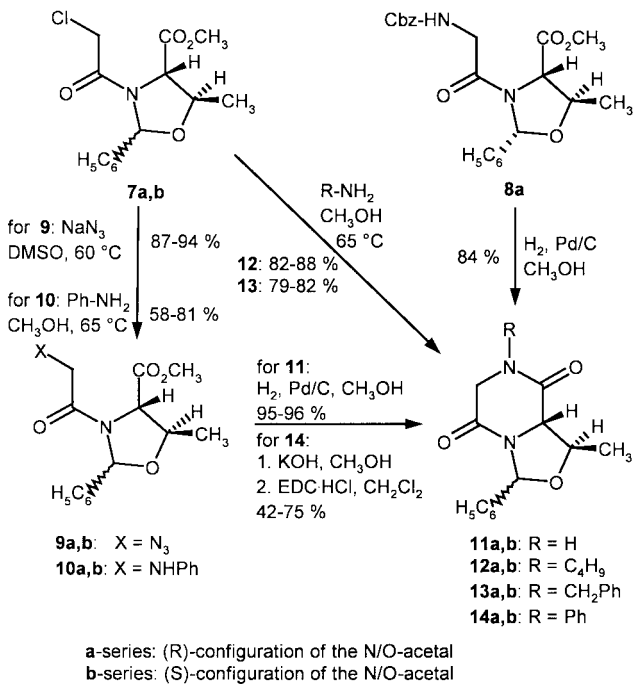
Condensation of benzaldehyde with (2*S*,3*R*)-threonine methyl ester hydrochloride, obtained by reaction of (2*S*,3*R*)-threonine (**4**) with thionyl choride and methanol,[10] provided a mixture of the diastereomeric 1,3-oxazolidines **5a**, **5b** and the hydroxyimine **6** (ratio **5a**:**5b**:**6** = 43:36:21).[11] Since **5a**, **5b** and **6** are in a dynamic equilibrium a separation of the three compounds was not possible. However, after treatment of the **5a**, **5b**, **6** mixture with chloroacetyl chloride at –5°C the diastereomeric chloroacetyl derivatives **7a** and **7b** (75:25) could be separated by flash chromatography (Scheme 1). Performing the acylation of the **5a**, **5b**, **6** mixture at room temperature changed the diastereomeric ratio in favour of the main diastereomer **7a** (**7a**:**7b** = 94:6).

S_N2 substitution of the separated diastereomers **7a** and **7b** with NaN_3 furnished the diastereomeric azides **9a** and **9b**, respectively. Reduction of the azides **9a** and **9b** succeeded with H_2/Pd/C to afford the corresponding primary amines, which directly cyclized to yield the bicyclic piperazinediones **11a** and **11b**, respectively (Scheme 2).

Alternatively, acylation of the 1,3-oxazolidine/hydroxyimine mixture **5a**, **5b**, **6** with *N*-Cbz protected glycine and dicyclohexyl carbodiimide (DCC) at room temperature stereoselectively led to the glycinamide **8a** (Scheme 1). In the ^1H NMR spectrum of the unpurified product signals for the diastereomeric dipeptide **8b** could not be detected. Again, the one-pot deprotection/cyclization of **8a** succeeded by hydrogenolysis to give the bicyclic piperazine



Scheme 1



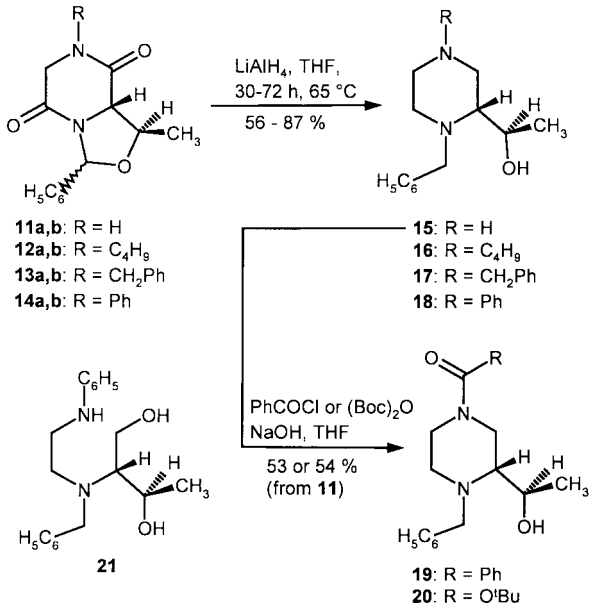
Scheme 2

11a (Scheme 2). For the preparation of great amounts of **11a** this method was chosen as standard procedure.

Reaction of the diastereomeric chloroacetyl derivatives **7a** and **7b** with butylamine and benzylamine resulted in direct formation of the *N*-substituted bicyclic piperazinediones **12a**, **12b**, **13a**, and **13b**, respectively. In contrast to the reaction of the aliphatic amines butylamine and benzylamine, the aromatic amine aniline gave only the substitution products **10a** and **10b**. After hydrolysis with KOH the corresponding anilino acids were cyclized with ethyl dimethylaminopropyl carbodiimide (EDC•HCl) to furnish the *N*-phenyl substituted bicyclic piperazinediones **14a** and **14b** (Scheme 2).

The reduction of the bicyclic piperazinediones **11a,b–14a,b** was performed with $LiAlH_4$ in refluxing THF. Thereby, the lactam carbonyl groups as well as the *N*/*O*-acetal were reduced to furnish the 1-(1-benzylpiperazin-2-yl)ethan-1-ol derivatives **15–18** (Scheme 3). Since the stereogenic centre of the *N*/*O*-acetal as destroyed during this reduction, the **a**- and **b**-diastereomers led to the same products, respectively. Therefore, the **a**- and **b**-diastereomers need not be separated and for the preparation of large amounts of the piperazines **15–18** mixtures of **a**/**b**-diastereomers were usually employed.

The 1-(piperazin-2-yl)ethan-1-ols **15–17** were isolated in good yields (>74%). A somewhat lower yield (48%) was obtained after reduction of the *N*-phenyl substituted derivatives **14a**,**b**. In this case reductive ring opening occurred as side reaction due to the diminished electron releasing activity of the aniline nitrogen atom resulting in the bu-



Scheme 3

tane-1,3-diol **21** (26% yield). The N-4 acyl piperazines **19** and **20** were obtained by acylation of the secondary amine **15** with benzoyl chloride or $(BOC)_2O$ (Scheme 3).

In summary, the method presented opens an efficient access to orthogonally protected, enantiomerically pure 1-(piperazin-2-yl)ethan-1-ol derivatives from commercially available (2*S*,3*R*)-threonine. These 1-(piperazin-2-yl)ethan-1-ols will be used as starting material for the preparation of novel CNS receptor ligands.

Unless otherwise noted, moisture sensitive reactions were conducted under dry N_2. THF was distilled from sodium/benzophenone ketyl prior to use. Petroleum ether used refers to the fraction boiling at 40-60 °C. TLC: Silica gel 60 F_{254} plates (Merck). Flash chromatography (FC):[12] Silica gel 60, 0.040–0.063 mm (Merck); parentheses include diameter of the column (cm), eluent, fraction size (mL), R_f. Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected. Optical rotation: Polarimeter 241 (Perkin Elmer); 1.0 dm tube; concentration *c* [g/100 mL]; temperature 20°C. Elemental analyses: CHN elemental analyzer Rapid (Heraeus) and Elemental Analyzer 240 (Perkin Elmer). MS: Mass spectrometer 5989A (Hewlett Packard), MAT 312, MAT 8200, MAT 4456, and TSQ 7000 (Finnigan); EI = electron impact, CI = chemical ionization, ESI = electron spray ionization. IR: IR spectrophotometer 1600 FT-IR, 2000 FT-IR, and 841-IR (Perkin-Elmer) (br = broad, m = medium, s = strong). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): GSX FT NMR spectrometer (Jeol); ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian), TMS as internal standard, δ in ppm; coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and of ^{1}H NMR signals were supported by 2D NMR techniques (COSY, DEPT); in the case of rotational isomers, the signals of the minor rotamer are marked as mr in superscripts.

The synthesis of the **5a**, **5b**, **6** mixture is described in Ref.11. However, our protocol is slightly modified and improved, a new interpretation of the ^{1}H NMR spectrum as well as additional analytical data are given.

(2*R*,4*S*,5*R*)- and (2*S*,4*S*,5*R*)-Methyl 5-Methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (5a and 5b) and (2*S*,3*R*) Methyl 2-(Benzylideneamino)-3-hydroxybutanoate (6)

1. (2*S*,3*R*)-Threonine Methyl Ester Hydrochloride

This compound was prepared by adding (2*S*,3*R*)-threonine (**4**; 10.0 g, 84 mmol) to a solution of $SOCl_2$ (22 mL, 300 mmol) in anhyd MeOH (100 mL) following the procedure in Ref. 10. According to the ^{1}H NMR data, threonine methyl ester HCl was obtained in quantitative yield as a colourless, viscous foam which required no further purification. ^{1}H NMR (400 MHz, D_2O): δ = 1.33 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$), 3.85 (s, 3 H, CO_2CH_3), 4.11 (d, *J* = 3.9 Hz, 1 H, C*H*CO_2CH_3), 4.43 (qd, *J* = 6.4, 3.9 Hz, 1 H, C*H*CH_3).

2. Preparation of a Mixture of 5a,b and 6

A mixture of threonine methyl ester HCl (18.55 g, prepared as described above from 0.10 mol of **4**), Et_3N (16.7 mL, 0.12 mol), benzaldehyde (11.2 mL, 0.11 mol), $MgSO_4$, and anhyd MeOH (100 mL) was stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue was suspended in Et_2O (300 mL). The precipitate was filtered off and the filtrate was evaporated to dryness to yield a mixture of **5a**, **5b** and **6** (ratio 43:36:21; 20.58 g, 93% from **4**) as a colourless oil, which was used without further purification. For analytical purposes the traces of benzaldehyde in a small sample were distilled off under reduced pressure.

Anal. calcd for $C_{12}H_{15}NO_3$ (221.2): C, 65.14; H, 6.83; N, 6.33. Found C, 65.13; H, 6.76; N, 6.55.

MS (CI): *m*/*z* (%) = 222 (M + H, 100), 178 (M – C_2H_3O, 28), 116 (M – PhCO, 17). IR (film): ν = 3500–3200 (br, O–H, N–H), 1740 (s, C=O), 1642 (m, C=N), 1451, 1437 (m), 1209 (m, C–O), 759, 699 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (400 MHz, $CDCl_3$; starred (*) δ values designate signals of the minor diastereomer): δ = 1.22 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$, **6**), 1.43, 1.46* (each d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$, **5a**, **5b**), 3.00 – 3.40 (br m, NH, OH, **5a**, **5b**, **6**), 3.59* (d, *J* = 6.4 Hz, 1 H, C*H*CO_2CH_3, **5b** or **5a**), 3.64 (d, *J* = 6.8 Hz, 1 H, C*H*CO_2CH_3, **5a** or **5b**), 3.74 (s, 3 H, CO_2CH_3, **6**), 3.77 (s, 3 H, CO_2CH_3, **5a,b**), 3.87 (d, *J* = 5.1 Hz, 1 H, C*H*CO_2CH_3, **6**), 4.11 (quint, *J* = 6.3 Hz, 1 H, C*H*CH_3, **5a,b**), 4.29 (quint, *J* = 6.1 Hz, 1 H, C*H*CH_3, **6**), 5.54, 5.59* (each s, 1 H, NCHO, **5a**, **5b**), 7.30–7.50 (m, 5 H, arom, **5a**, **5b**, and 4 H, arom, **6**), 7.77 (d, *J* = 1.7 Hz, 1 H, arom, **6**), 8.29 (s, 1 H, CH=N, **6**).

(2*R*,4*S*,5*R*)-(+)-Methyl 3-(2-Chloroacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (7a) and (2*S*,4*S*,5*R*)-(-)-Methyl 3-(2-Chloroacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (7b)

A solution of chloroacetyl chloride (3.1 mL, 39 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred and cooled (–5°C) mixture of **5a**, **5b** and **6** (6.95 g, obtained as described above from 3.57 g, 30 mmol of **4**) and Et_3N (6.3 mL, 45 mmol) in CH_2Cl_2 (30 mL). After 1 h, the mixture was allowed to reach r.t. and stirring was continued for 16 h. Then Et_3N•HCl was filtered off, the solvent was evaporated and the residue was dissolved in Et_2O (150 mL). The solution was washed with 0.5 N HCl (100 mL) and brine (75 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by FC (8 cm, petroleum ether/EtOAc, 3:1, 25 mL) to afford **7a** (R_f 0.37, 4.89 g, 55% from **4**) as a clear, viscous oil, $[\alpha]_{589}$ +27.7 (*c* = 1.97, CH_2Cl_2), and **7b** (R_f 0.45, 1.80 g, 20%) as colourless needles (*i*-Pr_2O); mp 145°C; $[\alpha]_{589}$ –133.0 (*c* = 0.57, CH_2Cl_2).

Compound 7a

Anal. calcd for $C_{14}H_{16}ClNO_4$ (297.7): C, 56.48; H, 5.41; N, 4.70. Found C, 55.90; H, 5.38; N, 4.61.

MS (CI): *m*/*z* (%) = 300/298 (M + H, 33/94), 262 (M – Cl, 29), 220 (M – $ClCH_2CO$, 21), 194/192 (M – PhCO, 43/100).

IR (film): ν = 1749 (s, ester C=O), 1676 (s, amide C=O), 1413 (s), 1214 (s, C–O), 760, 735, 702 cm^{-1} (m, C–Cl, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (br s, 3 H, CHC*H*$_3$), 3.71 (br s, 2 H, CH_2Cl), 3.80 (s, 3 H, CO_2CH_3), 3.87^{mr} (br s), 3.98–4.12^{mr} (br m), 4.30 (br s, 2 H, C*H*CH_3 and C*H*CO_2CH_3), 4.36–4.56^{mr} (br m), 6.34 (br s, 1 H, NCHO), 6.47^{mr} (br s), 7.26–7.51^{mr} (br m), 7.41 (br s, 3 H, arom.), 7.73 (br s, 2 H, arom).

Compound 7b

Anal. calcd for $C_{14}H_{16}ClNO_4$ (297.7): C, 56.48; H, 5.41; N, 4.70. Found C, 55.90; H, 5.38; N, 4.61.

MS (CI): *m*/*z* (%) = 300/298 (M + H, 27/81), 262 (M – Cl, 24), 220 (M – $ClCH_2CO$, 16), 194/192 (M – PhCO, 60/100).

IR (KBr): ν = 1747 (s, ester C=O), 1657 (s, amide C=O), 1434 (s), 1201 (s, C–O), 764 (m, C–Cl , γ_{aryl}), 702 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 5.6 Hz, 3 H, CHC*H*$_3$), 3.30 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Cl), 3.37 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Cl), 3.80 (s, 3 H, CO_2CH_3), 4.23 (dq, *J* = 8.4, 5.9 Hz, 1 H, C*H*CH_3), 4.31 (d, *J* = 8.1 Hz, 1 H, C*H*CO_2CH_3), 6.15 (s, 1 H, NCHO), 7.44 (br s, 5 H, arom).

^{1}H NOE: After irradiation at δ = 6.15 (NCHO) a NOE was found at δ = 4.26 (C*H*CH_3).

(2*R*,4*S*,5*R*)-(+)-Methyl 3-[2-(Benzyloxycarbonylamino)acetyl]-

5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (8a)
To a stirred and cooled (0°C) mixture of **5a**, **5b** and **6** (12.0 g, obtained as described above from 7.14 g, 60 mmol of **4**) in anhyd CH_2Cl_2 (75 mL) was added slowly in succession a solution of Cbz-glycine (13.74 g, 66 mmol) in anhyd THF (30 mL) and then a solution of dicyclohexyl carbodiimide (DCC, 18.54 g, 89 mmol) in anhyd CH_2Cl_2 (30 mL). The mixture was allowed to stir for 16 h at r.t. The precipitate was filtered off, the solvent was removed in vacuo and the residue was dissolved in EtOAc (300 mL). The solution was washed with 1 N HCl (2 × 75 mL) and brine (50 mL), the combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Purification of the residue by FC (8 cm, petroleum ether/EtOAc, 2:1, 80 mL, R_f 0.20) yielded **8a** (19.1 g, 77% from **4**) as a clear oil, which solidified upon standing in the refrigerator, colourless prisms (EtOAc); mp 111°C; $[\alpha]_{589}$ +28.4 (*c* = 1.49, CH_2Cl_2).

Anal. calcd for $C_{22}H_{24}N_2O_6$ (412.4): C, 64.07; H, 5.86; N, 6.79. Found C, 64.05; H, 5.88; N, 6.76.

MS (CI): *m*/*z* (%) = 413 (M + H, 4), 305 (M – $PhCH_2O$, 100).

IR (film): ν = 3331 (br, N–H), 1725 (s, ester, carbamate C=O), 1670 (s, amide C=O), 1433 (m), 1214 (s, C–O), 741, 700 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$, ratio of rotamers, 76:24): δ = 1.42 (d, *J* = 3.9 Hz, 3 H, CHC*H*$_3$), 1.48^{mr} (d, *J* = 5.9 Hz, 3 H, CHC*H*$_3$), 3.44 (dd, *J* = 17.5, 3.8 Hz, 1 H, NHC*H*$_2$), 3.78^{mr}, 3.80 (each s, 3 H, CO_2CH_3), 3.74–3.80^{mr} (m, 1 H, NHC*H*$_2$), 3.94 (dd, *J* = 17.1, 5.4 Hz, 1 H, NHC*H*$_2$), 4.03–4.09^{mr} (m, 1 H, NHC*H*$_2$), 4.20–4.27 (m, 2 H and 1 H^{mr}, $CH_3CHCHCO_2CH_3$ and C*H*CO_2CH_3^{mr}), 4.32–4.44^{mr} (m, 1 H, C*H*CH_3), 5.04, 5.09^{mr} (each s, 2 H, C*H*$_2$Ph), 5.47, 5.59^{mr} (each br s, 1 H, NH), 6.24, 6.51^{mr} (each s, 1 H, NCHO), 7.30, 7.39^{mr} (each br s, 8 H, arom), 7.48^{mr} (br s, 2 H, arom), 7.68 (d, *J* = 5.8 Hz, 2 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.4^{mr} (each 1 C, CH*C*H$_3$), 43.0^{mr}, 43.3 (each 1 C, NHCH_2), 52.4, 52.8^{mr} (each 1 C, CO_2CH_3), 63.5^{mr}, 64.5 (each 1 C, *C*HCO_2CH_3), 66.6 (1 C, *C*H$_2$Ph), 74.6, 76.6^{mr} (each 1 C, *C*HCH_3), 89.3, 89.9^{mr} (each 1 C, NCHO), 126.7 – 129.5 (10 C, arom CH), 136.2–137.0 (2 C, arom C), 156.0 (1 C, NH*C*O$_2$Bn), 166.8, 167.6^{mr} (each 1 C, N*C*OCH$_2$), 169.2 (1 C, *C*O$_2$CH$_3$).

(2*R*,4*S*,5*R*)-(–)-Methyl 3-(2-Azidoacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (9a); Typical Procedure
A solution of **7a** (1.00 g, 3.36 mmol) and NaN_3 (0.54 g, 8.31 mmol) in DMSO (25 mL) was stirred at 60°C for 24 h. H_2O (100 mL) was added and the mixture was extracted with Et_2O (4 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. FC of the residue (3 cm, petroleum ether/EtOAc, 2:1, 20 mL, R_f 0.47) afforded **9a** (0.96 g, 94%) as a colourless oil; $[\alpha]_{589}$ –2.7 (*c* = 1.45, CH_2Cl_2).

Anal. calcd for $C_{14}H_{16}N_4O_4$ (304.3): C, 55.26; H, 5.30; N, 18.41. Found C, 55.42; H, 5.36; N, 17.88.

MS (ESI): *m*/*z* (%) = 343 (M + K, 12), 327 (M + Na, 100).

IR (film): ν = 2954 (m, C–H), 2108 (s, N_3), 1747 (s, ester C=O), 1672 (s, amide C=O), 1429, 1276, 1213 (s), 762, 702 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (br s, 3 H, CHC*H*$_3$), 1.60^{mr} (br s), 3.46 (d, *J* = 15.9 Hz, 1 H, CH_2N_3), 3.61 (d, *J* = 15.6 Hz, 1 H, CH_2N_3), 3.80 (br s, 3 H, CO_2CH_3), 4.09 – 4.48^{mr} (br m), 4.29 (br s, 2 H, C*H*CH_3 and C*H*CO_2CH_3), 6.16 (s, 1 H, NCHO), 6.63^{mr} (br s, 19 H, NCHO), 7.26 – 7.53^{mr} (br m), 7.40 (br s, 3 H, arom), 7.67 (br s, 2 H, arom).

(2*S*,4*S*,5*R*)-(–)-Methyl 3-(2-Azidoacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (9b)
A mixture of **7b** (750 mg, 2.52 mmol), NaN_3 (405 mg, 6.23 mmol), and DMSO (15 mL) was reacted as described for **9a**. Extractive workup and FC (3 cm, petroleum ether/EtOAc, 2:1, 20 mL, R_f 0.43) gave **9b** (67 mg, 87%) as a colourless solid; mp 88°C; $[\alpha]_{589}$ –179.6 (*c* = 0.82, CH_2Cl_2).

Anal. calcd for $C_{14}H_{16}N_4O_4$ (304.3): C 55.26; H, 5.30; N, 18.41. Found C, 55.43; H, 5.31; N, 18.16.

MS (CI): *m*/*z* (%) = 305 (M + H, 22), 277 (M + H – N_2, 9), 199 (M – PhCO, 86), 91 ($PhCH_2$, 100).

IR (KBr): ν = 2113 (s, N_3), 1747 (s, ester C=O), 1660 (s, amide C=O), 1435 (s), 1283 (m), 1206 (s), 743, 704 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 5.8 Hz, 3 H, CHC*H*$_3$), 3.15 (d, *J* = 15.8 Hz, 1 H, CH_2N_3), 3.22 (d, *J* = 15.9 Hz, 1 H, CH_2N_3), 3.84 (s, 3 H, CO_2CH_3), 4.25 (dq, *J* = 8.2, 5.9 Hz, 1 H, C*H*CH_3), 4.34 (d, *J* = 8.3 Hz, 1 H, C*H*CO_2CH_3), 6.08 (s, 1 H, NCHO), 7.40–7.48 (m, 5 H, arom).

(2*R*,4*S*,5*R*)-Methyl 3-(2-Anilinoacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (10a); Typical Procedure
A solution of **7a** (1.30 g, 4.37 mmol) and aniline (3.6 mL, 39 mmol) in MeOH (30 mL) was refluxed for 72 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc (130 mL). After washing with 1 N HCl (60 mL) and brine (25 mL), the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by FC (4 cm, petroleum ether/EtOAc, 2:1, 30 mL, R_f 0.48) yielded **10a** (1.26 g, 81%) as a pale yellow oil.

MS (EI): *m*/*z* (%) = 354 (M, 2), 260 (M – $PhNH_3$, 9), 220 (M – $PhNHCH_2CO$, 5), 106 ($PhNHCH_2$, 100).

IR (film): ν = 3384 (w, N–H), 1748 (s, ester C=O), 1669 (s, amide C=O), 1412 (s), 1211 (s, C–O), 752, 698 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 5.2 Hz, 3 H, CHC*H*$_3$), 1.41^{mr} (br d), 3.24^{mr} (br d), 3.32 (d, *J* = 16.6 Hz, 1 H, C*H*$_2$NH), 3.61 (d, *J* = 16.6 Hz, 1 H, C*H*$_2$NH), 3.67^{mr} (br s, 3 H, CO_2CH_3), 3.69 (s), 3.76 (br s), 4.08–4.15^{mr} (br m), 4.16–4.29 (m, 2 H, C*H*CH_3 and C*H*CO_2CH_3), 4.30–4.57^{mr} (br m), 6.11 (br s), 6.17 (s, 1 H, NCHO), 6.30 (d, *J* = 7.8 Hz, 2 H, arom), 6.43–6.52^{mr} (br m), 6.57 (t, *J* = 7.5 Hz, 1 H, arom), 6.53–6.68^{mr} (br m), 7.00 (t, *J* = 7.6 Hz, 2 H, arom), 7.00–7.11^{mr} (br m), 7.18 – 7.30^{mr} (br m), 7.29–7.38 (m, 3 H, arom), 7.40–7.49^{mr} (br m), 7.65 (d, *J* = 6.6 Hz, 2 H, arom). A signal for the proton of the NH group could not be detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 18.4^{mr} (1 C, CH*C*H$_3$), 46.3 (1 C, *C*H$_2$NH), 52.5 (1 C, CO_2CH_3), 63.8^{mr}, 64.6 (1 C, *C*HCO_2CH_3), 74.7 (1 C, *C*HCH_3), 89.3, 90.2^{mr} (1 C, NCHO), 112.8 (2 C, arom CH), 117.7 (1 C, arom CH), 126.8^{mr}, 127.2 (2 C, arom CH), 128.1^{mr}, 128.8 (2 C, arom CH), 129.0 (2 C, arom CH), 129.6 (1 C, arom CH), 136.9 (1 C, arom C), 146.8 (1 C, arom C), 167.7, 169.0^{mr}, 169.4, 170.9^{mr} (each 1 C, C=O).

(2*S*,4*S*,5*R*)-Methyl 3-(2-Anilinoacetyl)-5-methyl-2-phenyl-1,3-oxazolidine-4-carboxylate (10b)
A solution of **7b** (500 mg, 1.68 mmol) and aniline (1.5 mL, 16.5 mmol) in MeOH (10 mL) was refluxed for 72 h. The workup procedure as described for **10a** followed by FC (3 cm, petroleum ether/EtOAc, 1:1, 15 mL, R_f 0.43) yielded **10b** (346 mg, 58%) as a pale yellow oil.

MS (EI): *m*/*z* (%) = 354 (M, 7), 260 (M – $PhNH_3$, 23), 220 (M – $PhNHCH_2CO$, 18), 106 ($PhNHCH_2$, 100).

IR (film): n = 3390 (w, N–H), 1747 (s, ester C=O), 1666 (s, amide C=O), 1436 (m), 1210 (s, C–O), 739, 689 cm^{-1} (γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 5.9 Hz, 3 H, CHC*H*$_3$), 2.90 (d, *J* = 16.6 Hz, 1 H, C*H*$_2$NH), 3.38 (d, *J* = 16.9 Hz, 1 H, C*H*$_2$NH), 3.81 (s, 3 H, CO_2CH_3), 4.27 (dq, *J* = 8.0, 6.0 Hz, 1 H, CHC*H*$_3$), 4.36 (d, *J* = 8.0 Hz, 1 H, C*H*CO_2CH_3), 6.13 (s, 1 H, NCHO), 6.24 (d, *J* = 7.6 Hz, 2 H, arom), 6.66 (t, *J* = 7.3 Hz, 1 H, arom), 7.08 (t, *J* = 7.9 Hz, 2 H, arom), 7.46 (s, 1 H, arom), 7.49 (s,

4 H, arom). A signal for the proton of the NH group could not be detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 (1 C, $CHCH_3$), 47.0 (1 C, CH_2NH), 52.5 (1 C, CO_2CH_3), 66.1 (1 C, $CHCO_2CH_3$), 76.9 (1 C, $CHCH_3$), 90.6 (1 C, NCHO), 112.6 (2 C, arom CH), 117.5 (1 C, arom CH), 127.7 (2 C, arom CH), 128.9 (2 C, arom CH), 129.1 (2 C, arom CH), 130.5 (1 C, arom CH), 136.6 (1 C, arom C), 146.8 (1 C, arom C), 167.6, 169.4 (each 1 C, C=O).

(1*R*,3*R*,8a*S*)-(–)-1-Methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (11a)

From **9a**: To a solution of **9a** (450 mg, 1.48 mmol) in MeOH (10 mL) was added Pd/C (10%, 60 mg) and the suspension was stirred under a H_2 atmosphere (balloon) at r.t. for 16 h. The catalyst was filtered through a pad of Celite and the filtrate was concentrated to yield **11a** (350 mg, 96%) as a colourless solid; mp 200°C; $[\alpha]_{589}$ –41.5 (*c* = 0.75, CH_2Cl_2).

Anal. calcd for $C_{13}H_{14}N_2O_3$ (246.3): C, 63.40; H, 5.73; N, 11.37. Found C, 63,63; H, 5.70; N, 11.75.

MS (EI): *m*/*z* (%) = 246 (M, 64), 169 (M – Ph, 64), 105 (PhCO, 100).

IR (KBr): ν = 3320 (br, N–H), 1695 (s, C=O), 1450 (s), 760, 706 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.54 (d, *J* = 5.9 Hz, 3 H, $CHCH_3$), 3.85 (dd, *J* = 17.0, 4.6 Hz, 1 H, $NHCH_2$), 3.91 (d, *J* = 9.3 Hz, 1 H, COCH), 4.06 (dd, *J* = 17.1, 1.5 Hz, 1 H, $NHCH_2$), 4.40 (dq, *J* = 9.2, 5.9 Hz, 1 H, $CHCH_3$), 6.29 (s, 1 H, NCHO), 7.11 (dd, *J* = 4.1, 1.5 Hz, 1 H, NH), 7.31–7.41 (m, 5 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (1 C, CH_3), 46.9 (1 C, CH_2), 61.8 (1 C, *C*HCO), 73.7 (1 C, *C*HCH_3), 89.0 (1 C, NCHO), 126.3 (2 C, arom CH), 128.7 (2 C, arom CH), 129.3 (1 C, arom CH), 137.1 (1 C, arom C), 162.7 (1 C, NC=O), 168.2 (1 C, NC=O).

From **8a**: A suspension of **8a** (18.9 g, 46 mmol) and Pd/C (10%, 3.0 g) in MeOH (250 mL) was stirred under a H_2 atmosphere (balloon) for 8 h at r.t. After filtration through a pad of Celite and removal of the solvent under reduced pressure, the residue was subjected to FC (8 cm, EtOAc/MeOH, 85:15, 80 mL, R_f 0.60) to yield **11a** as colourless solid (9.52 g, 84%).

(1*R*,3*S*,8a*S*)-(–)-1-Methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (11b)

A mixture of **9b** (687 mg, 2.26 mmol), Pd/C (10%, 80 mg), and MeOH (15 mL) was stirred under H_2 (balloon) at r.t. for 16 h. After filtration through a pad of Celite and removal of the solvent in vacuo **11b** (530 mg, 95.3%) was isolated as a colourless solid; mp 211°C; $[\alpha]_{589}$ –118.4 (*c* = 0.88, CH_2Cl_2).

Anal. calcd for $C_{13}H_{14}N_2O_3$ (246.3): C, 63.40; H, 5.73; N, 11.37. Found C, 63.42; H, 5.77; N, 11.29.

MS (EI): *m*/*z* (%) = 246 (M, 42), 105 (PhCO, 100).

IR (KBr): ν = 3600–3200 (br, N–H), 1668 (s, C=O), 1455 (m), 754, 697 cm^{-1} (w, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (d, *J* = 5.9 Hz, 3 H, $CHCH_3$), 3.84 (dd, *J* = 16.6, 4.0 Hz, 1 H, $NHCH_2$), 3.91 (dd, *J* = 9.0, 1.9 Hz, 1 H, COC*H*), 4.09 (dd, *J* = 16.6, 1.8 Hz, 1 H, $NHCH_2$), 4.18 (dq, *J* = 9.1/5.9 Hz, 1 H, $CHCH_3$), 6.29 (s, 1 H, NC*H*O), 6.75 (br s, 1 H, NH), 7.33–7.41 (m, 3 H, arom), 7.47–7.51 (m, 2 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (1 C, CH_3), 46.4 (1 C, CH_2), 60.9 (1 C, *C*HCO), 76.6 (1 C, *C*HCH_3), 88.7 (1 C, NCHO), 126.7 (2 C, arom CH), 128.4 (2 C, arom. CH), 129.3 (1 C, arom CH), 137.8 (1 C, arom C), 161.3 (1 C, NC=O), 166.4 (1 C, NC=O).

(1*R*,3*R*,8a*S*)-(–)-7-Butyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (12a); Typical Procedure

A solution of **7a** (2.0 g, 6.7 mmol) and butan-1-amine (2.7 mL, 27 mmol) in DMSO (70 mL) was stirred at 60°C for 48 h. After addition of H_2O (150 mL) the mixture was extracted with Et_2O (3 × 100 mL), the combined organic layers were washed with 2 N HCl (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo followed by FC (4 cm, petroleum ether/EtOAc, 1:1, 40 mL, R_f 0.28) gave **12a** (1.66 g, 82%) as a colourless solid; mp 83–84°C; $[\alpha]_{589}$ –13.0 (*c* = 0.80, CH_2Cl_2).

Anal. calcd for $C_{17}H_{22}N_2O_3$ (302.4): C, 67.53; H, 7.33; N, 9.26. Found C, 67.11; H, 7.30; N, 9.06.

MS (EI): *m*/*z* (%) = 302 (M, 45), 197 (M – PhCO, 29), 105 (PhCO, 55), 42 (C_3H_6, 100).

IR (film): ν = 2962, 2929 (m, C–H), 2869 (w, C–H), 1683, 1653 (s, C=O), 1445 (m), 764, 700 cm^{-1} (w, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.35 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.54 (d, *J* = 5.8 Hz, 3 H, $CHCH_3$), 1.50–1.62 (m, 2 H, $CH_2CH_2CH_2CH_3$), 3.40 (dt, *J* = 13.9, 7.3 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.51 (dt, *J* = 13.9, 7.3 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.79 (d, *J* = 17.1 Hz, 1 H, $COCH_2$), 3.89 (dd, *J* = 9.0, 1.2 Hz, 1 H, COCH), 4.17 (dd, *J* = 17.1, 1.5 Hz, 1 H, $COCH_2$), 4.41 (dq, *J* = 9.0, 5.9 Hz, 1 H, $CHCH_3$), 6.25 (s, 1 H, NCHO), 7.26–7.37 (m, 5 H, arom).

(1*R*,3*S*,8a*S*)-(–)-7-Butyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (12b)

Compound **7b** (1.19 g, 4.0 mmol) was reacted with butan-1-amine (1.6 mL, 16 mmol) in DMSO (40 mL) as described for **12a**. The residue obtained after workup was subjected to FC (4 cm, petroleum ether/EtOAc, 1:1, 30 mL, R_f 0.49) to afford **12b** (1.07 g, 89%) as a colourless oil; $[\alpha]_{589}$ –82.3 (*c* = 1.87, CH_2Cl_2).

Anal. calcd for $C_{17}H_{22}N_2O_3$ (302.4): C, 67.53; H, 7.33; N, 9.26: Found C, 67.03; H, 7.15; N, 8.97.

MS (EI): *m*/*z* (%) = 302 (M, 88), 197 (M – PhCO, 15), 105 (PhCO, 100), 45 (C_2H_5O, 78).

IR (film): ν = 2959, 2872 (s, C–H), 1668 (s, C=O), 1450 (s), 750, 698 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.31 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.52 (quint, *J* = 7.6 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.67 (d, *J* = 5.9 Hz, 3 H, $CHCH_3$), 3.30 (dt, *J* = 13.6, 7.2 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.49 (dt, *J* = 13.7, 7.4 Hz, 1 H, $CH_2CH_2CH_2CH_3$), 3.75 (d, *J* = 16.6 Hz, 1 H, $COCH_2$), 3.92 (dd, *J* = 9.1, 1.7 Hz, 1 H, COCH), 4.13 (dd, *J* = 16.5, 1.7 Hz, 1 H, $COCH_2$), 4.16 (dq, *J* = 9.0, 6.0 Hz, 1 H, $CHCH_3$), 6.27 (s, 1 H, NCHO), 7.32–7.40 (m, 3 H, arom), 7.46 – 7.52 (m, 2 H, arom).

(1*R*,3*R*,8a*S*)-(+)-7-Benzyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (13a)

Compound **7a** (1.0 g, 3.35 mmol) was reacted with benzylamine (1.1 mL, 10 mmol) in DMSO (25 mL) as described for **12a**. After purification by FC (3 cm, petroleum ether/EtOAc, 1:2, 20 mL, R_f 0.49) **13a** (0.92 g, 82%) was obtained as colourless solid; mp 87°C; $[\alpha]_{589}$ +36.5 (*c* = 0.74, CH_2Cl_2).

Anal. calcd for $C_{20}H_{20}N_2O_3$ (336.4): C, 71.41; H, 5.99; N, 8.33. Found C, 71.22; H, 6.23; N, 8.27.

MS (CI): *m*/*z* (%) = 337 (M + H, 100), 231 (M – PhCO, 6).

IR (film): ν = 1668 (s, C=O), 1454 (s), 736 (m, γ_{aryl}), 699 cm^{-1} (s, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 5.9 Hz, 3 H, $CHCH_3$), 3.80 (d, *J* = 16.8 Hz, 1 H, $COCH_2$), 3.98 (dd, *J* = 9.0, 1.2 Hz, 1 H,

COCH), 4.07 (dd, *J* = 17.1, 1.5 Hz, 1 H, $COCH_2$), 4.49 (dq, *J* = 9.0, 5.8 Hz, 1 H, C*H*CH_3), 4.61 (d, *J* = 14.6 Hz, 1 H, C*H*$_2$Ph), 4.71 (d, *J* = 14.4 Hz, 1 H, C*H*$_2$Ph), 6.28 (s, 1 H, NCHO), 7.26–7.33 (m, 4 H, arom), 7.33–7.42 (m, 6 H, arom).

(1*R*,3*S*,8a*S*)-(–)-7-Benzyl-1-methyl-3-phenyl-1,6,7,8a-tetrahydro[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (13b)

As described for the preparation of **12a** the chloroacetyl derivative **7b** (1.0 g, 3.35 mmol) was reacted with benzylamine (1.1 mL, 10 mmol) in DMSO (25 mL). Purification by FC (3 cm, petroleum ether/EtOAc, 1:1, 20 mL, R_f = 0.64) yielded **13b** (0.89 g, 79%) as a colourless oil; $[\alpha]_{589}$ –110.6 (*c* = 1.72, CH_2Cl_2).

Anal. calcd for $C_{20}H_{20}N_2O_3$ (336.4): C 71.41; H, 5.99; N, 8.33. Found C, 71.29; H, 5.98; N, 8.23.

MS (CI): *m*/*z* (%) = 337 (M + H, 15), 336 (M, 100), 245 (M – $PhCH_2$, 78).

IR (film): ν = 1667 (s, C=O), 1448 (s), 735, 700 cm^{-1} (each m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, *J* = 5.9 Hz, 3 H, CHC*H*$_3$), 3.77 (d, *J* = 16.1 Hz, 1 H, $COCH_2$), 4.02 (d, *J* = 16.4 Hz, 1 H, $COCH_2$), 4.04 (d, *J* = 9.6 Hz, 1 H, COCH), 4.24 (dq, *J* = 9.0, 5.8 Hz, 1 H, C*H*CH_3), 4.45 (d, *J* = 14.4 Hz, 1 H, C*H*$_2$Ph), 4.77 (d, *J* = 14.4 Hz, 1 H, C*H*$_2$Ph), 6.32 (s, 1 H, NCHO), 7.24–7.30 (m, 2 H, arom), 7.31–7.42 (m, 6 H, arom), 7.46–7.54 (m, 2 H, arom).

(1*R*,3*R*,8a*S*)-(–)-1-Methyl-3,7-diphenyl-1,6,7,8a-tetrahydro-[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (14a); Typical Procedure

A solution of **10a** (1.12 g, 3.16 mmol) and 3 N KOH (15 mL) in MeOH (25 mL) was allowed to stir at r.t. for 16 h. After complete saponification (TLC control, petroleum ether/EtOAc, 1:1) the mixture was concentrated in vacuo. The residue was neutralized with 2 N HCl, extracted with EtOAc (3 × 50 mL), the aqueous layer was acidified to pH 4–5 with 2 N HCl and extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. Without purification, the residue (1.50 g) was dissolved in anhyd CH_2Cl_2 (50 mL) and *N*-(3-dimethylaminopropyl)-*N*'-ethyl carbodiimide hydrochloride (EDC, 1.00 g, 5.22 mmol) was added at 0°C. The mixture was allowed to stir at r.t. for 24 h. Then CH_2Cl_2 (100 mL) was added and the solution was washed with aq satd $NaHCO_3$ solution (25 mL), H_2O (20 mL), 1 N HCl (2 × 25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness. FC (3 cm, petroleum ether/EtOAc, 1:1, 15 mL, R_f 0.30) of the residue furnished **14a** (760 mg, 75%) as a colourless solid; mp 128°C; $[\alpha]_{589}$ –17.1 (*c* = 1.74, CH_2Cl_2).

Anal. calcd for $C_{19}H_{18}N_2O_3$ (322.4): C, 70.79; H, 5.63; N, 8.69. Found C, 70.74; h, 5.65; N, 8.64.

MS (EI): *m*/*z* (%) = 322 (M, 81), 245 (M – Ph, 23), 105 (PhCO, 100).

IR (film): ν = 1684 (s, C=O), 1434 (m), 734 (w, γ_{aryl}), 698 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 5.8 Hz, 3 H, CHC*H*$_3$), 4.11 (dd, *J* = 8.9, 1.1 Hz, 1 H, COCH), 4.21 (d, *J* = 16.6 Hz, 1 H, $COCH_2$), 4.54 (dq, *J* = 9.0, 5.9 Hz, 1 H, C*H*CH_3), 4.65 (dd, *J* = 16.6, 1.2 Hz, 1 H, $COCH_2$), 6.36 (s, 1 H, NCHO), 7.30–7.48 (m, 10 H, arom).

(1*R*,3*S*,8a*S*)-(–)-1-Methyl-3,7-diphenyl-1,6,7,8a-tetrahydro-[1,3]oxazolo[3.4-*a*]pyrazine-5,8-dione (14b)

As described for the preparation of **14a**, hydrolysis of **10b** (346 mg, 0.92 mmol) was carried out with 3 N KOH (5 mL) in MeOH (10 mL) to provide the crude amino acid (400 mg). After reaction with EDC (269 mg, 1.40 mmol) in anhyd CH_2Cl_2 (7 mL), workup, and FC purification (2 cm, petroleum ether/EtOAc, 1:1, 5 mL, R_f 0.47) **14b** (126 mg, 43%) was obtained as pale yellow solid; mp 170°C; $[\alpha]_{589}$ –104.6 (*c* = 1.53, CH_2Cl_2).

Anal. calcd for $C_{19}H_{18}N_2O_3$ (322.4): C, 70.79; H, 5.63; N, 8.69. Found C, 70.70; H, 5.68; N, 8.62.

MS (EI): *m*/*z* (%) = 322 (M, 58), 105 (PhCO, 100).

IR (film): ν = 1657 (s, C=O), 1454 (m), 764 (w, γ_{aryl}), 703 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 5.9 Hz, 3 H, CHC*H*$_3$), 4.12 (dd, *J* = 9.0, 1.5 Hz, 1 H, COCH), 4.13 (d, *J* = 16.0 Hz, 1 H, $COCH_2$), 4.34 (dq, *J* = 8.9, 5.9 Hz, 1 H, C*H*CH_3), 4.58 (dd, *J* = 16.2, 1.2 Hz Hz, 1 H, $COCH_2$), 6.44 (s, 1 H, NCHO), 7.23–7.46 (m, 8 H, arom), 7.52–7.58 (m, 2 H, arom).

(1*R*)-(–)-1-[(2*R*)-1-Benzylpiperazin-2-yl]ethan-1-ol (15)

To a stirred solution of 1 M $LiAlH_4$ in Et_2O (27.5 mL, 28 mmol) and anhyd THF (80 mL) was added dropwise a solution of **11a** (845 mg, 3.45 mmol) in anhyd THF (100 ml). The mixture was refluxed for 72 h, then H_2O was added cautiously. The precipitate was filtered off, the solvent removed in vacuo, the residue dissolved in 2 N HCl (50 mL) and the solution was washed with Et_2O (2 × 80 mL). After addition of KOH (pH 10) the aqueous layer was extracted with CH_2Cl_2 (5 x 80 mL), the CH_2Cl_2 layer was washed with 2 N NaOH (25 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. Recrystallization (*i*-Pr_2O) of the residue gave **15** (576 mg, 76%) as pale yellow crystals; mp 128°C; $[\alpha]_{589}$ –2.1 (*c* = 0.80, CH_2Cl_2).

Anal. calcd for $C_{13}H_{20}N_2O$ (220.3): C, 70.87; H, 9.15; N, 12.71. Found C, 70.90; H, 9.14; N, 12.68.

MS (CI): *m*/*z* (%) = 221 (M + H, 100), 203 (M – OH, 17), 175 (M – C_2H_5O, 38).

IR (film): ν = 3292 (m, O–H, N–H), 3113 (br, O–H, N–H), 2968, 2806 (s, C–H), 1452 (m), 1081 (s, C–O, C–N), 743, 696 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.4 Hz, 3 H, CHC*H*$_3$), 2.10–2.21 (m, 1 H, 2-H), 2.39–2.44 (m, 1 H, 6-H), 2.45 – 2.55 (m, 1 H, 5-H), 2.68 (dd, *J* = 13.0, 2.3 Hz, 1 H, 3-H), 2.92–3.00 (m, 2 H, 5-H and 6-H), 3.12 (dd, *J* = 13.2, 3.8 Hz, 1 H, 3-H), 3.83 (d, *J* = 13.2 Hz, 1 H, C*H*$_2$Ph), 3.87 (d, *J* = 13.7 Hz, 1 H, C*H*$_2$Ph), 4.16 (dq, *J* = 8.6, 6.1 Hz, 1 H, C*H*CH_3), 7.16–7.22 (m, 1 H, arom), 7.24–7.28 (m, 4 H, arom). Signals for the protons of the OH and NH groups could not be detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (1 C, CH_3), 40.7 (1 C, C-5), 41.2 (1 C, C-3), 46.6 (1 C, C-6), 57.0 (1 C, *C*H_2Ph), 63.5 (1 C, C-2), 63.7 (1 C, *C*HCH_3), 127.2 (1 C, arom CH), 128.3 (2 C, arom CH), 128.7 (2 C, arom CH), 138.6 (1 C, arom C).

(1*R*)-(–)-1-[(2*R*)-1-Benzyl-4-butylpiperazin-2-yl]ethan-1-ol (16)

A solution of **12a** (1.80 g, 5.95 mmol) in anhyd THF (150 mL) was added to a stirred suspension of $LiAlH_4$ pellets (2.19 g, 58 mmol) in anhyd THF(150 mL) and the mixture was refluxed for 48 h. Under N_2 and with cooling (ice bath) H_2O (3 mL), 3 N NaOH (3.0 ml), and again H_2O (3 mL) were successively added. The suspension was refluxed for 30 min and stirring at r.t. was continued for 16 h. The precipitate was filtered off and after removal of THF under reduced pressure aq 2 N NaOH (25 mL) was added. The solution was extracted with EtOAc (2 × 100 mL), the organic layer was washed with brine (25 mL) and dried ($MgSO_4$). Evaporation to dryness and purification by FC (4 cm, EtOAc, 35 mL, R_f 0.39) provided **16** (1.43 g, 87%) as colourless viscous oil; $[\alpha]_{589}$ –6.3 (*c* = 1.45, CH_2Cl_2).

Anal. calcd for $C_{17}H_{28}N_2O$ (276.4): C, 73.87; H, 10.21; N, 10.13. Found C, 73.60; H, 10.15; N, 9.88.

MS (CI): *m*/*z* (%) = 277 (M + H, 37), 231 (M – C_2H_5O, 17), 91 ($PhCH_2$, 100).

IR (film): ν = 3386 (br, O–H), 2931 (s, C–H), 2808 (m, C–H), 1667 (m), 1453 (s), 1081 (m), C–O), 739, 698 cm^{-1} (s, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_2CH_3$), 1.18 (d, *J* = 6.1 Hz, 3 H, $CHCH_3$), 1.34 (sext, *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 1.41–1.51 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.27 (t, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_2CH_3$), 2.31–2.44 (m, 3 H, 2-H and 5-H), 2.49 (dd, *J* = 11.8, 3.5 Hz, 1 H, 3-H), 2.52–2.62 (m, 2 H, 6-H and 3-H), 3.15 (ddd, *J* = 14.0, 8.4, 5.7 Hz, 1 H, 6-H), 3.85 (s, 2 H, CH_2Ph), 4.08 (br s, 1 H, OH), 4.19 (dq, *J* = 7.8, 6.2 Hz, 1 H, $CHCH_3$), 7.22–7.29 (m, 1 H, arom), 7.31–7.32 (m, 4 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (1 C, $CH_2CH_2CH_2CH_3$), 19.6 (1 C, $CHCH_3$), 20.5 (1 C, $CH_2CH_2CH_2CH_3$), 28.7 (1 C, $CH_2CH_2CH_2CH_3$), 46.1 (1 C, C-6), 48.2 (1 C, C-5), 48.9 (1 C, C-3), 57.2 (1 C, CH_2Ph), 58.9 (1 C, $CH_2CH_2CH_2CH_3$), 63.9 (1 C, C-2), 65.4 (1 C, $CHCH_3$), 127.2 (1 C, arom CH), 128.4 (2 C, arom CH), 128.8 (2 C, arom CH), 139.0 (1 C, arom C).

(1*R*)-(+)-1-[(2*R*)-1,4-Dibenzylpiperazin-2-yl]ethan-1-ol (17)

A solution of **13a** (690 mg, 2.05 mmol) in anhyd THF (50 ml) was cautiously added to a solution of 1 M $LiAlH_4$ in Et_2O (13 mL, 13 mmol) and anhyd THF (50 ml) and the mixture was refluxed for 30 h. The mixture was worked up as described for **15** and after purification of the residue by FC (3 cm, petroleum ether/EtOAc, 1:2, 20 mL, R_f 0.26) **17** (470 mg, 74%) was obtained as pale yellow oil; $[\alpha]_{589}$ +18.3 (*c* = 1.44, CH_2Cl_2).

Anal. calcd for $C_{20}H_{26}N_2O$ (310.4): C, 77.38; H, 8.44; N, 9.02. Found C, 77.29; H, 8.45; N, 9.00.

MS (CI): *m*/*z* (%) = 311 (M + H, 100), 265 (M – C_2H_5O, 29).

IR (film): ν = 3396 (br, O–H), 2930 (s, C–H), 2806 (s, C–H), 1451 (m), 1108 (s, C–O, C–N), 741, 700 cm^{-1} (s, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.1 Hz, 3 H, $CHCH_3$), 2.46–2.59 (m, 3 H, 2-H and 6-H), 2.60–2.68 (m, 2 H, 3-H), 2.73 (dd, *J* = 14.7, 2.7 Hz, 1 H, 5-H), 3.35 (ddd, *J* = 14.3, 9.0, 5.5 Hz, 1 H, 5-H), 3.53 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.70 (d, *J* = 13.1 Hz, 1 H, CH_2Ph), 3.98 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.06 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.36 (br s, 1 H, OH), 4.43 (qd, *J* = 6.0, 2.4 Hz, 1 H, $CHCH_3$), 7.37–7.44 (m, 2 H, arom), 7.46–7.48 (m, 8 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 (1 C, CH_3), 45.7 (1 C, C-5), 47.8 (1 C, C-6), 48.1 (1 C, C-3), 57.1 (1 C, CH_2Ph), 63.4 (1 C, CH_2Ph), 64.2 (1 C, C-2), 64.5 (1 C, $CHCH_3$), 127.0–128.7 (10 C, arom CH), 138.0 (1 C, arom C), 138.8 (1 C, arom C).

(1*R*)-(–)-1-[(2*R*)-1-Benzyl-4-phenylpiperazin-2-yl]ethan-1-ol (18) and (2*R*,3*R*)-2-[*N*-(2-Anilinoethyl)-*N*-benzylamino]butane-1,3-diol (21)

A solution of **14a** (3.14 g, 9.75 mmol) in anhyd THF (150 mL) was slowly added to a suspension of $LiAlH_4$ pellets (2.98 g, 62 mmol) in anhyd THF (200 mL). After refluxing for 48 h the mixture was worked up as described for **15** to afford a residue, which was separated and purified by FC (5 cm, petroleum ether/EtOAc, 7:3, 40 mL, **18**: R_f 0.46; **21**: R_f 0.07) to yield **18** (1.40 g, 48%) as a pale yellow solid; mp 95–96°C; $[\alpha]_{589}$ –5.0 (*c* = 1.50, CH_2Cl_2) and **21** (0.811 mg, 26%) as a pale yellow oil.

Compound 18

Anal. calcd for $C_{19}H_{24}N_2O$ (296.4): C, 76.99; H, 8.16; N, 9.45. Found C, 76.89; H, 7.99; N, 9.26.

MS (EI): *m*/*z* (%) = 296 (M, 7), 251 (M – C_2H_5O, 100), 91 ($PhCH_2$, 82).

IR (film): ν = 3415 (br, O–H), 1600, 1500 (m, C=C), 1454 (w), 753, 695 cm^{-1} (s, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.1 Hz, 3 H, $CHCH_3$), 2.54 (dtd, *J* = 8.2, 3.4, 0.7 Hz, 1 H, 2-H), 2.74 (dtd, *J* = 13.5, 3.1, 0.8 Hz, 1 H, 6-H), 3.08–3.14 (m, 2 H, 5-H), 3.18–3.24 (m, 1 H, 6-H), 3.27 (t, *J* = 3.0 Hz, 2 H, 3-H), 3.89 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.95 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 4.22 (dq, *J* = 9.0, 6.1 Hz, 1 H, $CHCH_3$), 6.86 (dt, *J* = 7.3, 1.0 Hz, 1 H, arom), 6.89–6.91 (m, 1 H, arom), 6.91–6.94 (m, 1 H, arom), 7.25–7.32 (m, 3 H, arom), 7.34–7.37 (m, 4 H, arom). A signal for the proton of the OH group could not be detected.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (1 C, CH_3), 43.5 (1 C, C-5), 44.3 (1 C, C-3), 45.4 (1 C, C-6), 56.8 (1 C, CH_2Ph), 63.5 (1 C, $CHCH_3$), 64.5 (1 C, C-2), 115.9 (2 C, arom CH), 119.8 (1 C, arom CH), 127.4 (1 C, arom CH), 128.5 (2 C, arom CH), 128.8 (2 C, arom CH), 129.1 (2 C, arom CH), 138.3 (1 C, arom C), 151.7 (1 C, arom C).

Compound 21

MS (CI): *m*/*z* (%) = 315 (M + H, 100), 297 (M – OH, 2).

IR (film): ν = 3391 (br, O–H, N–H), 1602, 1503 (m, C=C), 734 (s, γ_{aryl}), 696 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.1 Hz, 3 H, $CHCH_3$), 2.63 (ddd, *J* = 8.9, 7.6, 4.7 Hz, 1 H, $NCHCH_2OH$), 2.88–3.13 (m, 4 H, NCH_2CH_2N), 3.64–3.80 (m, 4 H, CH_2OH, CHPh and $CHCH_3$), 3.95 (d, *J* = 13.3 Hz, 1 H, CHPh), 6.44 (br d, 2 H, *o*-NHC_6H_5), 6.66 (tt, *J* = 7.3, 1.1 Hz, 1 H, *p*-NHC_6H_5), 7.10 (br t, 2 H, *m*-NHC_6H_5), 7.23–7.37 (m, 5 H, $NCH_2C_6H_5$). Signals for the protons of the NH and OH groups were not detected.

(+)-{(3*R*)-4-Benzyl-3-[(1*R*)-1-hydroxyethyl]piperazin-1-yl} Phenyl Ketone (19)

As described for the preparation of **15**, a solution of the bicyclic piperazinedione **11a** (300 mg, 1.22 mmol) in anhyd THF (50 mL) was reduced with a solution of 1 M $LiAlH_4$ in Et_2O (11 mL, 11 mmol) and anhyd THF (20 mL). After hydrolysis of excess $LiAlH_4$ with H_2O, benzoyl chloride (0.14 mL, 1.22 mmol) was added to the suspension. The mixture was stirred for 24 h ar r.t., filtered and the filtrate concentrated in vacuo. The residue was dissolved in EtOAc, the solution was washed with 3 N NaOH (25 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated to dryness. Purification of the residue by FC (3 cm, petroleum ether/EtOAc, 1:1, 20 mL, R_f 0.21) provided **19** (210 mg, 53%) as a pale yellow oil; $[\alpha]_{589}$ +1.3 (*c* = 1.74, CH_2Cl_2).

Anal. Calcd for $C_{20}H_{24}N_2O_2$ (324.4): C, 74.04; H, 7.45; N, 8.63. Found C, 74.07; H, 7.43; N, 8.46.

MS (CI): *m*/*z* (%) = 325 (M + H, 2), 279 (M – C_2H_5O, 100), 188 (279 – $PhCH_2$, 43), 105 (PhCO, 72).

IR (film): ν = 3407 (br, O–H), 1624 (s, C=O), 1445 (m), 1285 (m), 736, 702 cm^{-1} (m, γ_{aryl}).

^{1}H NMR (300 MHz, DMSO-d_6, 90°C): δ = 1.07 (d, *J* = 6.1 Hz, 3 H, $CHCH_3$), 2.23 (ddd, *J* = 12.3, 8.9, 3.4 Hz, 1 H, 5-H), 2.44 (ddd, *J* = 8.2, 5.7, 3.5 Hz, 1 H, 3-H), 2.78 (ddd, *J* = 12.5, 5.4, 3.4 Hz, 1 H, 5-H), 3.13 (ddd, *J* = 12.8, 9.1, 3.5 Hz, 1 H, 6-H), 3.20 (dd, *J* = 13.1, 7.8 Hz, 1 H, 2-H), 3.43 (d, *J* = 13.7 Hz, 1 H, CH_2Ph), 3.62–3.74 (m, 1 H, 6-H), 3.91 – 3.94 (m, 1 H, 2-H), 4.00 (d, *J* = 13.9 Hz, 1 H, CH_2Ph), 4.12 (quint, *J* = 6.1 Hz, 1 H, $CHCH_3$), 4.28 (br s, 1 H, OH), 7.19–7.25 (m, 1 H, arom), 7.30–7.34 (m, 4 H, arom), 7.35–7.38 (m, 2 H, arom), 7.39–7.44 (m, 3 H, arom).

^{13}C NMR (75 MHz, DMSO-d_6, 70°C): δ = 17.4 (1 C, CH_3), 42.8 (1 C, C-2), 43.5 (1 C, C-6), 49.1 (1 C, C-5), 56.7 (1 C, CH_2Ph), 63.1 (1 C, $CHCH_3$), 64.1 (1 C, C-3), 126.4 (1 C, arom CH), 126.5 (2 C, arom CH), 127.8 (2 C, arom CH), 127.9 (2 C, arom CH), 128.2 (2 C, arom CH), 128.9 (1 C, arom CH), 135.8 (1 C, arom C), 138.6 (1 C, arom C), 168.7 (1 C, C=O).

(3*R*)-(–)-*tert*-Butyl 4-Benzyl-3-[(1*R*)-1-hydroxyethyl]piperazine-1-carboxylate (20)

As described for the preparation of **15**, a solution of the bicyclic piperazinedione **11a** (1.50 g, 6.8 mmol) in anhyd THF (100 mL) was

reduced with $LiAlH_4$ pellets (2.30 g, 61 mmol) suspended in anhyd THF (200 mL). The mixture was refluxed for 72 h. After hydrolysis of excess $LiAlH_4$ with H_2O, di-*tert*-butyl dicarbonate (1.7 mL, 8 mmol) was added to the cooled (0 °C) resulting suspension. The mixture was allowed to warm to r.t. and stirring was continued for 24 h. The suspension was filtered, the filtrate was concentrated in vacuo and the residue was dissolved in EtOAc (100 mL). The solution was washed with 3 N NaOH (25 mL) and brine (50 mL), the organic layer dried ($MgSO_4$) and evaporated to dryness. FC purification (4 cm, petroleum ether/EtOAc, 2:1, 40 mL, R_f 0.43) of the residue gave **20** (1.18 g, 54%) as a clear, colourless oil; $[\alpha]_{589}$ –5.0 (*c* = 0.70, CH_2Cl_2).

Anal. Calcd for $C_{18}H_{28}N_2O_3$ (320.4): C, 67.47; H, 8.80; N, 8.74. Found C, 67.80; H, 8.84; N, 8.36.

MS (CI): *m*/*z* (%) = 321 (M + H, 100), 275 (M – C_2H_5O, 10), 265 (MH – C_4H_8, 30), 91 ($PhCH_2$, 62).

IR (film): ν = 3448 (br, O–H), 1694 (s, C=O), 1173 (m, C–O), 741, 699 cm^{-1} (w, γ_{aryl}).

^{1}H NMR (300 MHz, DMSO-d_6, 60°C): δ = 1.09 (d, *J* = 6.4 Hz, 3 H, $CHCH_3$), 1.38 [s, 9 H, $C(CH_3)_3$], 2.13 (ddd, *J* = 12.3, 8.7, 3.5 Hz, 1 H, 5-H), 2.31 (ddd, *J* = 7.4, 6.1, 3.6 Hz, 1 H, 3-H), 2.67 (ddd, *J* = 12.2, 5.6, 3.4 Hz, 1 H, 5-H), 2.97–3.10 (m, 2 H, 6-H and 2-H), 3.39 (d, *J* = 13.7 Hz, 1 H, CH_2Ph), 3.46 (dddd, *J* = 12.9, 5.4, 3.7, 1.1 Hz, 1 H, 6-H), 3.73 (ddd, *J* = 13.3, 3.5, 1.2 Hz, 1 H, 2-H), 3.96 (d, *J* = 13.7 Hz, 1 H, CH_2Ph), 4.08 (quint, *J* = 6.3 Hz, 1 H, $CHCH_3$), 4.50 (br s, 1 H, OH), 7.20–7.40 (m, 5 H, arom).

^{13}C NMR (75 MHz, DMSO-d_6, 60°C): δ = 17.8 (1 C, CH_3), 27.8 [3 C, $C(CH_3)_3$], 40.3 (1 C, C-2), 41.3 (1 C, C-6), 48.4 (1 C, C-5), 56.8 (1 C, CH_2Ph), 63.4 (1 C, $CHCH_3$), 63.8 (1 C, C-3), 78.3 [1 C, $C(CH_3)_3$], 126.5 (1 C, arom CH), 127.8 (2 C, arom CH), 128.3 (2 C, arom CH), 138.7 (1 C, arom C), 153.7 (1 C, C=O).

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