Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2175

www.rsc.org/obc

PAPER

Highly stereoselective double (*R*)-phenylglycinol-induced cyclocondensation reactions of symmetric aryl bis(oxoacids)†‡

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Received 2nd November 2010, Accepted 22nd December 2010
DOI: 10.1039/c0ob00970a

The double cyclocondensation of symmetric pyridyl bis(oxoacids) **2b** and **3b** with (*R*)-phenylglycinol stereoselectively gave access to bis-phenylglycinol-derived oxazolopyrrolidine **9** and oxazolopiperidone **10**, respectively. Application of the stereocontrolled cyclocondensation reaction to phenyl bis-γ-oxoacid **4b** provided **11**, which was converted to the corresponding enantiopure di(pyrrolidinyl)benzene **22**. The absolute configuration of the new stereogenic centers generated in the key cyclocondenstion step was unambiguously established by X-ray crystallographic analysis.

Introduction

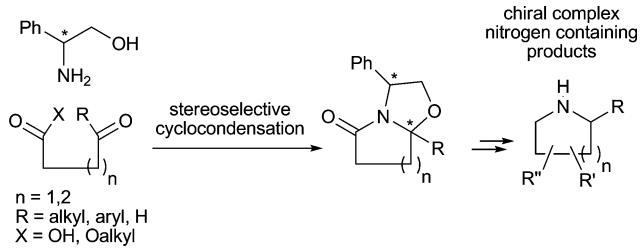
Nitrogen-containing heterocycles, including pyrrolidines and piperidines, are found in a myriad of natural products and biologically active compounds. For this reason, synthetic chemists continue to be interested in the construction and functionalization of these heterocyclic cores.[1]

In this context, the synthetic potential of phenylglycinol-derived oxazolopyrrolidone and oxazolopiperidone lactams as chiral synthons has been demonstrated.[2] They have been used in the enantioselective synthesis of a great structural variety of complex alkaloids and bioactive compounds embodying a pyrrolidine or a piperidine moiety with different substitution patterns.

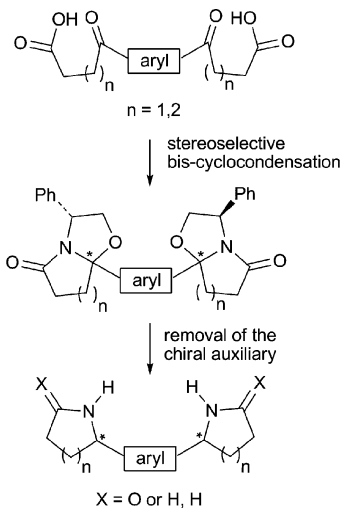
These lactams are readily available in both enantiomeric series by a cyclocondensation reaction of the (*R*)- or (*S*)-phenylglycinol with γ- or δ-oxoacid derivatives (Scheme 1).

Although this key reaction has received considerable attention over the years from several research groups,[3] to the best of our knowledge there are no references in the literature to double aminoalcohol-induced cyclocondensation reactions.

In this paper, we report cyclocondensation reactions of aryl bis(oxoacid) derivatives with (*R*)-phenylglycinol and the subsequent removal of the chiral auxiliary to gain access to enantiopure aryl bis-substituted nitrogen heterocycles (Scheme 2).



Scheme 1 Synthetic strategy for the enantioselective synthesis of saturated nitrogen heterocycles.



Scheme 2 General strategy.

Results and discussion

Synthesis of the starting aryl oxoacid and bis(oxoacid) derivatives 1–4

Ketoester **1a**[4] (Scheme 3) was prepared in 50% overall yield by a Negishi[5] coupling of picolinoyl chloride[6] and

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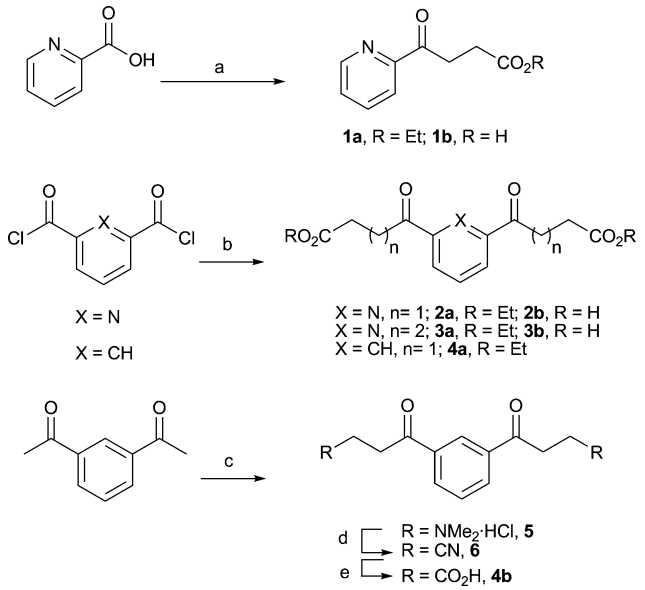
† Dedicated to Professor Pelayo Camps on the occasion of his 65th anniversary.

‡ Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of new products **1–7** and **9–22**. Cartesian coordinates and total energies for compounds **8** and **8**-stereoisomer. CCDC reference numbers 798251–798255. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00970a



Scheme 3 *Reagents and conditions*: (a) (i) $(COCl)_2$, rt; (ii) 3-ethoxy-3-oxopropylzinc bromide, $Pd(PPh_3)_4$, THF, 4 h, rt, 50%, **1a**; (iii) 4 N NaOH, MeOH, overnight, rt, 86%, **1b**; (b) (i) 3-ethoxy-3-oxopropylzinc bromide, $[Pd(PPh_3)_4]$, THF, 4 h, rt, 60%, **2a**; 39%, **4a**; 4-ethoxy-4-oxobutylzinc bromide, 68%, **3a**; (ii) 4 N NaOH, MeOH, overnight, rt, 98%, **2b**; 98%, **3b**; (c) $Me_2NH{\cdot}HCl$, CH_2O, conc HCl, EtOH, rfx, 15 h, 86%, **5**; (d) KCN, H_2O–AcOH, 80 °C, 5 h, 90%, **6**; (e) conc HCl/AcOH, rfx, 3 h, 69%, **4b**.

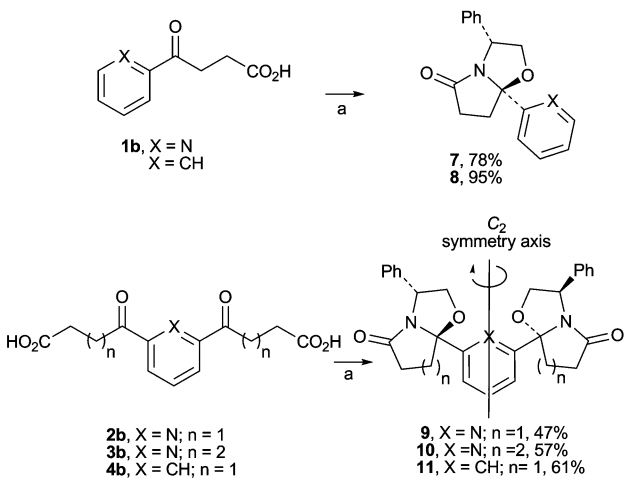
3-ethoxy-3-oxopropylzinc bromide in the presence of $[Pd(PPh_3)_4]$ as the catalyst.[7] A subsequent saponification led to acid **1b**.

The Negishi reaction was also used for the preparation of symmetric bis(oxoacids) **2b** and **3b**. Thus, reaction of the commercially available 2,6-pyridinedicarbonyl dichloride with the required zinc bromide derivative, followed by alkaline hydrolysis of the intermediate oxoesters **2a** and **3a**, led to **2b** and **3b** in 59% and 67% overall yield, respectively.

A similar reaction from isophthaloyl dichloride gave bis(oxoester) **4a** in low yield, probably as a consequence of the hygroscopicity of the starting material. However, the corresponding diacid **4b** was obtained in 53% overall yield using a three step procedure: a Mannich reaction between 1,3-diacetylbenzene, dimethylamine hydrochloride and paraformaldehyde, followed by treatment of the resulting hydrochloride salt **5** with potassium cyanide and acid hydrolysis of dinitrile **6**.[8] This sequence was successfully applied on a multigram scale.

Cyclocondensation reactions of oxoacids 1b–4b with (*R*)-phenylglycinol

Cyclocondensation of **1b** with (*R*)-phenylglycinol took place in good yield and excellent stereoselectivity to give the bicyclic lactam **7**, which bears a 2-pyridyl substituent at the angular position (Scheme 4).[9] Similarly, cyclocondensation of the commercially available 3-benzoylpropionic acid with (*R*)-phenylglycinol gave lactam **8** in 95% yield.[10] Gratifyingly, extrapolation of the reaction conditions to bis-γ-oxoacids **2b** and **4b**, and to bis-δ-oxoacid **3b**, led to the corresponding aryl bis-lactams **9**, **11** and **10** in acceptable yields. The reaction was highly stereoselective since only one diastereoisomer was produced.



Scheme 4 *Reagents and conditions*: (a) (*R*)-phenylglycinol, toluene, rfx, 7–24 h, 78%, **7**; 95%, **8**; 47%, **9**; 57%, **10**; 61%, **11**.

Stereochemical outcome of the cyclocondensation reactions

The relationship between the aryl substituent at the angular position and the C-3 phenyl substituent in the (*R*)-phenylglycinol moiety in lactams **7–11** was always *cis*.

Notably, the NMR spectra of aryl bis-cyclocondensed products **9** and **11** coincided with those of the mono-cyclocondensed analogues **7** and **8**, thus indicating that the stereochemical outcome in both groups of compounds was the same. Consequently, **9**, **10** and **11** present a C_2 symmetry axis. In the ^{13}C NMR spectrum of oxazolopiperidone **10**, the C-2 and the hemiaminal C are shielded as compared with oxazolopyrrolidones **7**, **8**, **9** and **11** (3–5 and 6–7 ppm, respectively; Table 1). Having a pyridyl or a phenyl group as linker between both oxazolopyrrolidone nuclei does not represent any significant change in the chemical shift or multiplicity.

Table 1 shows diagnostic signals in the ^1H and ^{13}C NMR spectra of compounds **7–11** (H-2 and C-2, H-3 and C-3, and hemiaminal quaternary C).

The configuration of the stereogenic carbon atoms generated in the above cyclocondensation reactions was unambigously established by X-ray crystallographic analysis of bis-lactams **9**, **10**, and **11** (Fig. 1).

The stereochemical outcome of these reactions can be accounted for by considering that the two initially formed oxazolidines **A** and **B** are in equilibrium through the corresponding imine. The subsequent irreversible lactamization occurs preferentially from the oxazolidine that allows a less hindered approach of the carboxy group to the nitrogen atom, that is, *anti* with respect to both phenyl groups (Fig. 2).[11]

Notably, theoretical calculations using *ab initio* [HF/6-31G(d)] and DFT [B3LYP/6-31G(d)] methods predicted that **8** is 2.6 and 2.3 kcal mol^{-1}, respectively, more stable than its stereoisomer with the two phenyl rings in a *trans* relationship.

Removal of the chiral auxiliary

The removal of the chiral auxiliary from phenylglycinol-derived oxazolopyrrolidones involves two steps: the reductive cleavage of the C–O bond of the oxazolidine ring, and the removal of the 2-hydroxy-1-phenylethyl substituent (Scheme 5).

Table 1 ^{1}H and ^{13}C NMR representative signals of lactams **7–11**

	C-2 (ppm) H-2 (ppm, *J* Hz)	C-3 (ppm) H-3 (ppm, *J* Hz)	Hemiaminal C (ppm)
7	74.7 3.99 (dd, 8.8, 7.7) 4.73 (dd, 8.8, 8.0)	58.4 5.26 (t, 7.7)	102.4
9	75.1 4.03 (dd, 8.8, 7.5) 4.77 (dd, 8.8, 8.0)	57.8 5.26 (t, 7.5)	102.2
10	69.8 3.84 (dd, 9.1, 8.2) 4.48 (dd, 9.1, 8.2)	59.6 5.36 (t, 8.2)	95.7
8	73.6 3.87 (t, 8.8) 4.64 (dd, 8.8, 8.0)	59.1 5.14 (t, 8.0)	102.7
11	72.6 3.71 (t, 8.9) 4.56 (dd, 8.9, 8.0)	58.7 5.14 (t, 8.0)	102.6

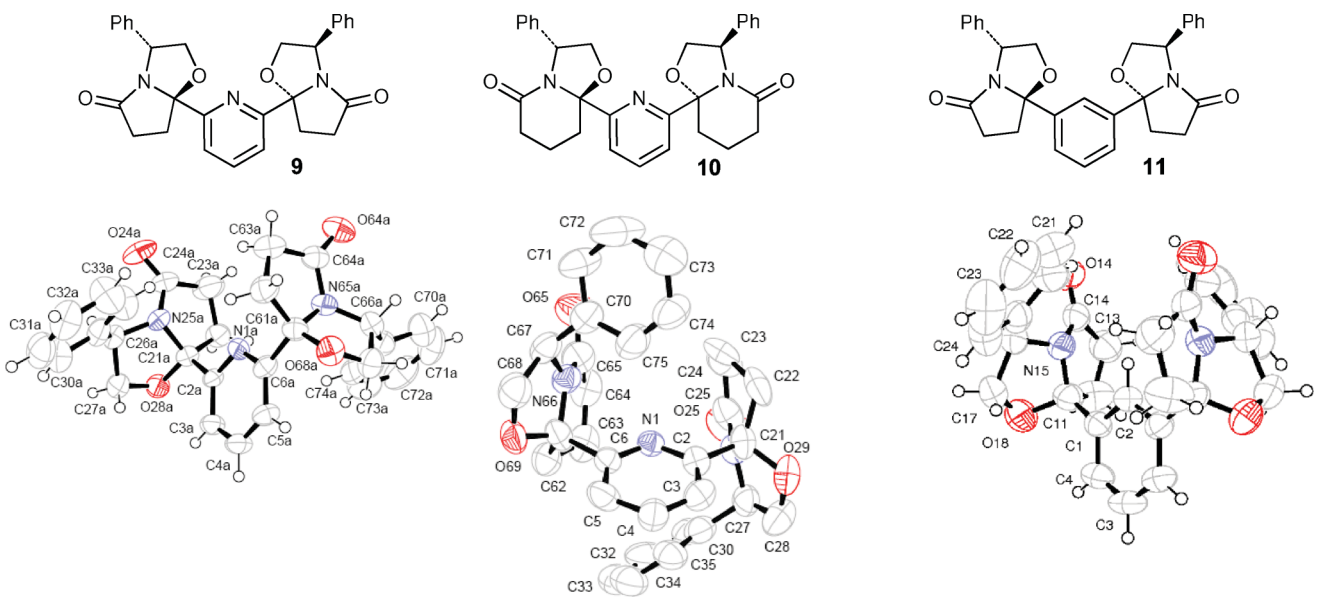
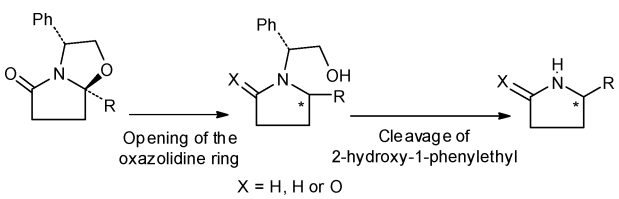
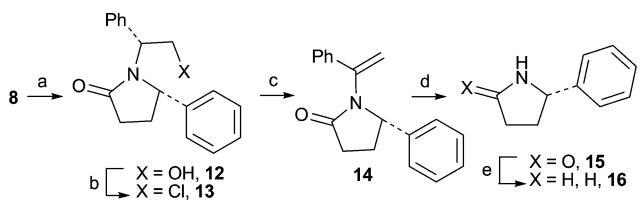


Fig. 1 ORTEP view of molecular structures of **9**, **10** and **11**.



Scheme 5 Removal of the chiral auxiliary.



Scheme 6 *Reagents and conditions*: (a) Et_3SiH, $TiCl_4$, CH_2Cl_2, rfx, 20 h, 71%, **12**; (b) $SOCl_2$, THF, 15 min 0 °C, rfx, 1.5 h, 93%, **13**; (c) DMF, DBU, 85 °C, 5 h, 70%, **14**; (d) 5 M H_2SO_4, Et_2O, rfx, 20 h, 96%, **15**; (e) $LiAlH_4$, THF, rt, 3 days, 81%, **16**.

First of all, model studies were carried out upon the simple oxazolopyrrolidone derivative **8** (Scheme 6). Titanium(IV) chloride/triethylsilane[12] mediated the ring opening of **8** and the reduction of the resulting *N*-acyliminium intermediate, stereoselectively providing lactam **12** in 71% yield, with retention of the configuration at C-5.

Attempts to remove the 2-hydroxy-1-phenylethyl moiety of **12** with sodium in liquid ammonia met with failure; the cleavage of the endocyclic benzylic bond occurred instead affording the corresponding linear amide **12a**.[13] However, the chiral auxiliary was successfully removed by an alternative procedure. Thus, conversion of the hydroxyl group of lactam **12** to its corresponding chloride **13** (93%) and subsequent β-elimination by treatment with DBU in DMF provided enamide **14** in 70% yield. Hydrolysis of the enamide was easily accomplished with H_2SO_4 to afford lactam **15** in nearly quantitative yield.[14] Finally, reduction of **15** with $LiAlH_4$ gave (*S*)-phenylpyrrolidine **16** in 81% yield.

The above procedure was then applied to bislactam **11** (Scheme 7). The chemoselective reductive opening of the oxazolidine rings of **11** by Et_3SiH and $TiCl_4$ led to a 2 : 1 mixture of **17** and

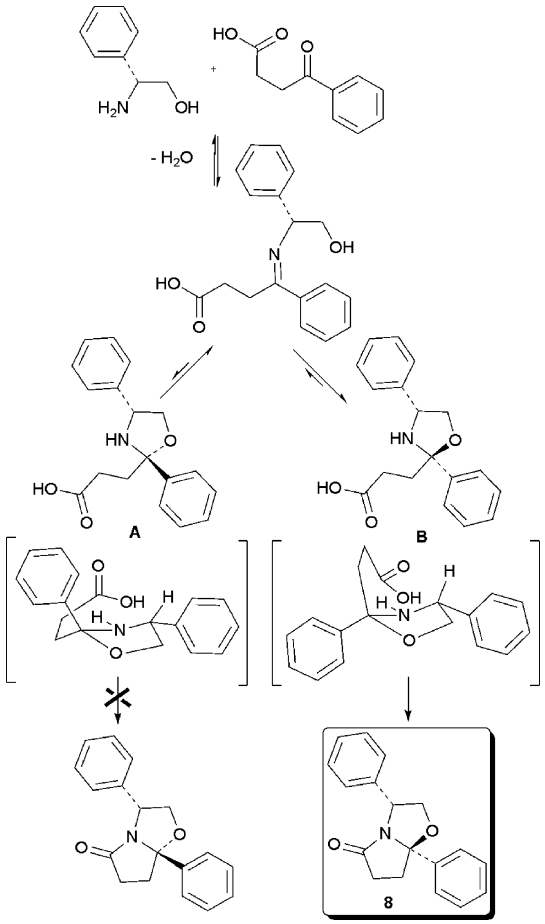


Fig. 2 Proposed mechanism for cyclocondensation reactions.

18 (90%). Attempts to exclusively prepare **17** using more drastic reaction conditions did not work,[15] but a subsequent treatment of **18** under the same $TiCl_4/Et_3SiH$ conditions led exclusively to **17**. Transformation of the hydroxyl group into a chloride (**19**), followed by elimination with DBU as the base led to bis-enamide **20** (50% overall yield). The hydrolysis of **20** was performed in the best reaction conditions found for the model compound **14** (5 M H_2SO_4/Et_2O), leading to aryl bis-pyrrolidone **21** (63%). Finally, the reduction of both amide groups gave the target enantiopure di(pyrrolidinyl)benzene **22** in good yield (74%).

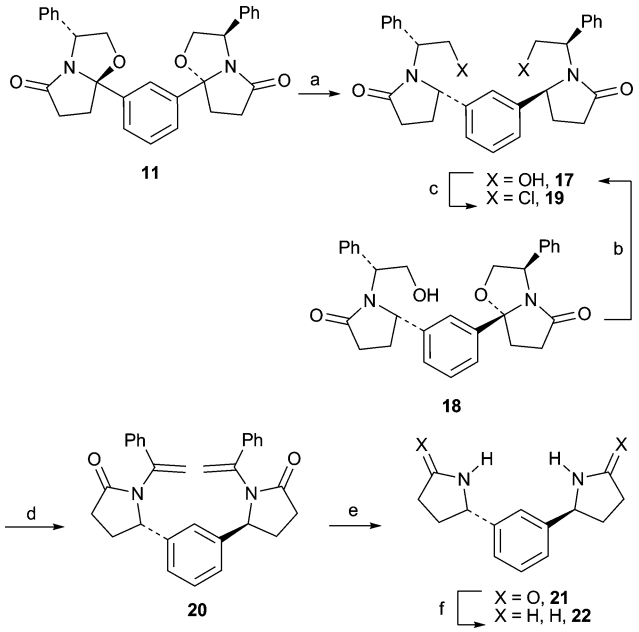
The stereochemistry of **18** and **21** was unequivocally confirmed by X-ray crystallographic analysis, which made it evident that the process occurs with retention of the configuration at the pyrrolidone 5-position (Fig. 3 and 4).

A comparison of the ^1H and ^{13}C NMR spectra of compounds **12–16** and their bis analogues **17** and **19–22** showed basically the same set of peaks, indicating the presence of a C_2 symmetry axis in the latter.

Structural considerations

The structural attractiveness of aryl bis derivatives **9–11**, **18** and **21** deserves a description on their molecular conformations and crystal packings.

Compound **9** crystallizes as two independent molecules in the monoclinic $P2_1$ space group (see Table 1 in the ESI for a summary of the crystal data and structure refinement parameters



Scheme 7 *Reagents and conditions*: (a) Et_3SiH, $TiCl_4$, CH_2Cl_2, rfx, 43 h, 60%, **17**, 30%, **18**; (b) Et_3SiH, $TiCl_4$, CH_2Cl_2, rfx, 24 h, 84%, **17**; (c) $SOCl_2$, THF, 15 min 0 °C, rfx, 2 h; (d) DMF, DBU, 85 °C, 5 h, 50% (from **17**), **20**; (e) 5 M H_2SO_4, Et_2O, rfx, 5 h, 63%, **21**; (f) $LiAlH_4$, THF, rfx, 24 h, 74%, **22**.

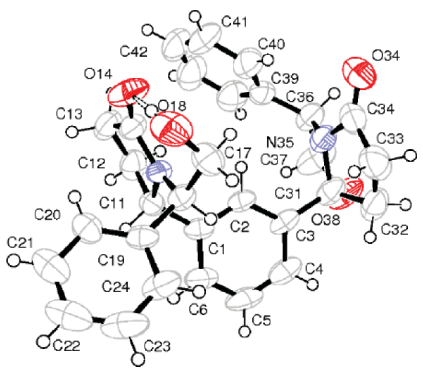


Fig. 3 ORTEP view of molecular structure of **18**.

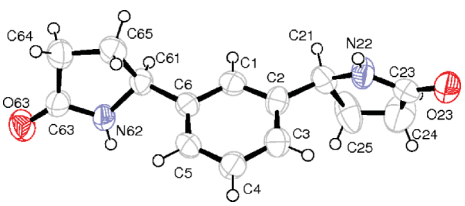


Fig. 4 ORTEP view of molecular structure of **21**.

of the five crystal structures described in this article‡). The two bicyclic lactams linked to the pyridine ring present opposed twisting orientations resulting in approximate binary axes for both independent molecules [τ(N1–C2–C21–C22) = 59.2(8), τ(N1–C6–C61–C62 = 65.0(8), τ(N1A–C2A–C21A–C22A) = 63.5(8), τ(N1A–C6A–C61A–C62A) = 59.1(8)°]. Assuming *R* chiralities for the C26 and C66 (and C26a and C66a) centres, C21 and C61 (and C21a and C61a) are also *R* centres.

Compound **10** also crystallizes as two independent molecules in the orthorhombic $P2_12_12_1$ space group but with a water molecule, thus constituting a hemihydrate form. The overall conformation and chiral centres are similar to those of compound **9** (τ(N1–C2–C21–C22) = 73.6(12), τ(N1–C6–C61–C62 = 80.7(10), τ(N1A–C2A–C21A–C22A) = 77.2(12), τ(N1A–C6A–C61A–C62A) = 80.4(11)°). The water molecule bridges the two independent molecules through the hydrogen bonds O1W–H1W···O69^{i} (i = −x + 1/2, −y + 1, z + 1/2; d(O···O) = 2.921(15) Å) and O1W–H2W···O25A (d(O···O) = 2.849(17) Å).

Compound **11** crystallizes in the tetragonal $P4_12_12$ space group, the asymmetric unit being a half a molecule, that becomes complete through a binary axis. The change of pyridine to benzene as a bridging group increases the twisting of the substituent bicyclic lactam (τ(C2–1–C11–C12) = 99.4(3)°). Chiral centres are as in **9** and **10**.

Compound **18** crystallizes in the orthorhombic $P2_12_12_1$ space group. In this case, the difference in the benzene substituent groups is also apparent in their different spatial orientation (τ(C2–C1–C11–C12) = 62.8(5), τ(C2–C3–C31–C32) = 110.9(5)°). C16, C31 and C36 are *R* centres while C11 is an *S* centre. An intramolecular hydrogen bond links the ethoxy group with a carbonyl (O18–H18···O14, d(O···O) = 2.631(6) Å).

Compound **21** crystallizes in the monoclinic $P2_1$ space group. Here, the benzene substituent groups are similarly oriented (τ(C1–C6–C61–C65) = −103.1(6), τ(C1–C2–C21–C25) = −105.7(7)°) and C21 and C61 centres have *S* chirality. The molecules pack in infinite one-dimensional chains along [110] and [1–10] directions through the N22–H22...O63^{ii} (ii = x − 1, y − 1, z; d(O···O) = 2.928(6) Å) and N62–H62···O23^{iii} (iii = x + 1, y + 1, z; d(O···O) = 2.952(6) Å) hydrogen bonds.

Summary

The bis-cyclocondensation reaction of (*R*)-phenylglycinol with aryl bis(oxoacid) compounds **2b**, **3b** and **4b** stereoselectively led to aryl bis-bicyclic lactams **9**, **10** and **11**. The stereochemical outcome of the cyclocondensation reactions has been rationalised taking into account that irreversible lactamization occurs from *cis*-diphenyl oxazolidine intermediate **B**. The absolute configuration of **9**, **10** and **11** was confirmed by X-ray crystallographic analysis. Finally, efficient cleavage of the phenylethanol moiety derived from phenylglycinol led to enantiopure di(pyrrolidinyl)benzene **22**.

These new bicyclic heterocycles are attractive candidates for organocatalysts or ligands in metal coordination chemistry.

Experimental

General

All non-aqueous reactions were performed under inert atmosphere with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Thin layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV or 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230–400 mesh). Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz (^{1}H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (J) in hertz (Hz), integrated intensity. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad signal.

Ethyl γ-oxo-2-pyridinebutanoate (1a)

Tetrakis(triphenylphosphine)palladium(0) (250 mg, 0.18 mmol) was added at r.t. to a solution of 3-ethoxy-3-oxopropylzinc bromide (36 mL of a 0.5 M solution in THF, 18 mmol) in THF (40 mL). Then, a solution of picolinoyl chloride[6] (2.5 g, 18 mmol) in THF (40 mL) was added over a period of 5 min, and stirring was continued for 4 h at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4 : 1 hexane–Et_2O) to afford **1a** (1.8 g, 50%) as a yellowish oil: IR (film) 1700, 1734, 2800–3000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.1 Hz, 3H, CH_3), 2.76 (t, J = 6.7 Hz, 2H, CH_2CO$_2$), 3.56 (t, J = 6.7 Hz, 2H, CH_2CO), 4.16 (q, J = 7.1 Hz, 2H, OCH_2), 7.48 (ddd, J = 7.8, 4.7, 1.2 Hz, 1H, H-5), 7.84 (td, J = 7.8, 1.7 Hz, 1H, H-4), 8.05 (dt, J = 7.8, 1.2 Hz, 1H, H-3), 8.70 (dm, J = 4.7 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2 (CH_3), 28.3 (CH_2, CH$_2$CO$_2$), 32.8 (CH_2, CH$_2$CO), 60.5 (CH_2, OCH_2), 121.7 (CH, C-3), 127.2 (CH, C-5), 136.8 (CH, C-4), 148.9 (CH, C-6), 153.0 (C, C-2), 172.8 (C, COO), 200.0 (C, CO); HRMS $C_{11}H_{14}NO_3$ (M + H$^+$), 208.0968; found, 208.0971.

γ-Oxo-2-pyridinebutanoic acid (1b)

A solution of oxoester **1a** (1.5 g, 7.2 mmol) in MeOH (30 mL) and 4 N aqueous NaOH (20 mL) was stirred at rt overnight. The solvent was evaporated, and the resulting residue was dissolved in H_2O. The solution was acidified with 5 N aqueous HCl (pH = 3–4) and extracted with EtOAc and CH_2Cl_2. The combined organic extracts were dried and concentrated to give **1b** (1.2 g, 86%) as a white solid: IR (KBr) 1711, 2900–3100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (t, J = 6.6 Hz, 2H, CH_2CO$_2$), 3.56 (t, J = 6.6 Hz, 2H, CH_2CO), 7.49 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H, H-5), 7.84 (td, J = 7.7, 1.7 Hz, 1H, H-4), 8.05 (dt, J = 7.7, 1.1 Hz, 1H, H-3), 8.70 (ddd, J = 4.8, 1.7, 1.1 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.0 (CH_2, CH$_2$COO), 32.7 (CH_2, CH$_2$CO), 121.9 (CH, C-3), 127.3 (CH, C-5), 136.9 (CH, C-4), 148.9 (CH, C-6), 152.8 (C, C-2), 178.3 (C, CO$_2$), 199.6 (C, CO); HRMS $C_9H_{10}NO_3$ (M + H$^+$), 180.0655; found, 180.0656.

Diethyl γ,γ′-dioxo-2,6-pyridinedibutanoate (2a)

Following the procedure described for the preparation of **1a**, tetrakis(triphenylphosphine)palladium(0) (850 mg, 0.74 mmol), 3-ethoxy-3-oxopropylzinc bromide (32 mL of a 0.5 M solution in THF, 16 mmol), and a solution of 2,6-pyridinedicarbonyl dichloride (1.5 g, 7.35 mmol) in THF (30 mL) afforded **2a** (1.45 g, 60%) as a yellowish solid after column chromatography (9 : 1 to 7 : 3 hexane–EtOAc): IR (film) 1701, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$,

300 MHz) δ 1.28 (t, J = 7.0 Hz, 6H, CH_3), 2.79 (t, J = 7.0 Hz, 4H, CH_2CO$_2$), 3.63 (t, J = 7.0 Hz, 4H, CH_2CO), 4.16 (q, J = 7.0 Hz, 4H, OCH_2), 8.00 (dd, J = 8.0, 7.0 Hz, 1H, H-4), 8.21 (d, J = 8.0 Hz, 2H, H-3 and H-5); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.2 (2 CH_3), 28.1 (2 CH_2, 2 CH_2CO_2), 32.7 (2 CH_2, 2 CH_2CO), 60.6 (2 CH_2, 2 OCH_2), 125.0 (2 CH, C-3 and C-5), 138.0 (CH, C-4), 152.1 (2 C, C-2 and C-6), 172.8 (2 C, 2 CO_2), 199.2 (2 C, 2 CO); mp 78-80 °C (EtOAc–hexane); MS-EI m/z 335 (M^+, 46), 290 (100), 262 (83), 216 (64), 188 (75), 161 (43), 101 (40); HRMS $C_{17}H_{22}NO_6$ (M + H^+), 336.1441; found, 336.1444. Anal. calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.86; H, 6.35; N, 4.11.

γ,γ′-Dioxo-2,6-pyridinedibutanoic acid (2b)

Following the procedure described for the preparation of **1b**, a solution of **2a** (1.5 g, 4.48 mmol) in MeOH (20 mL) and 4 N aqueous NaOH (11 mL) afforded **2b** (1.1 g, 98%) as a yellowish solid: IR (film) 1702, 2900–3500 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 2.76 (t, J = 6.5 Hz, 4H, CH_2CO$_2$), 3.61 (t, J = 6.5 Hz, 4H, CH_2CO), 8.11 (dd, J = 8.5, 6.6 Hz, 1H, H-4), 8.21 (dm, J = 8.5 Hz, 2H, H-3 and H-5); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 28.7 (2 CH_2, CH_2CO_2), 33.7 (2 CH_2, CH_2CO), 125.8 (2 CH, C-3 and C-5), 139.6 (CH, C-4), 153.4 (2 C, C-2 and C-6), 176.6 (2 C, 2 CO_2), 200.7 (2 C, 2 CO); MS-EI m/z 279 (M^+, 5), 278 (35), 277 (100), 199 (16), 183 (17), 77 (18). Anal. calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 56.35; H, 4.82; N, 4.93.

Diethyl δ,δ'-dioxo-2,6-pyridinedipentanoate (3a)

Following the procedure described for the preparation of **1a**, tetrakis(triphenylphosphine)palladium(0) (2 g, 1.7 mmol), 4-ethoxy-4-oxobutylzinc bromide (100 mL of a 0.5 M solution in THF, 50 mmol), and a solution of 2,6-pyridinedicarbonyl dichloride (5 g, 24.5 mmol) in THF (100 mL) afforded **3a** (6.1 g, 68%) as a yellowish oil after column chromatography (1 : 1 Et_2O–hexane): IR (film) 1698, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.5 Hz, 6H, CH_3), 2.11 (m, 4H, H-3′), 2.47 (t, J = 7.0 Hz, 4H, H-4′), 3.34 (t, J = 7.0 Hz, 4H, H-2′), 4.14 (q, J = 7.5 Hz, 4H, OCH_2), 7.99 (tm, J = 7.8 Hz, 1H, H-4), 8.20 (d, J = 7.8 Hz, 2H, H-3 and H-5); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2 (2 CH_3), 19.2 (2 CH_2, 2 C-3′), 33.5 (2 CH_2, 2 C-4′), 36.6 (2 CH_2, 2 C-2′), 60.3 (2 CH_2, 2 OCH_2), 124.8 (2 CH, C-3 and C-5), 138.0 (CH, C-4), 152.3 (2 C, C-2 and C-6), 173.1 (2 C, 2 CO_2), 200.4 (2 C, 2 CO); MS-EI m/z 363 (M^+, 37), 318 (100), 262 (69), 230 (81), 93 (43); HRMS $C_{19}H_{26}NO_6$ (M + H^+), 364.1754; found, 364.1756. Anal. calcd for $C_{19}H_{25}NO_6 \cdot {}^1/_4H_2O$: C, 62.03; H, 6.99; N, 3.81. Found: C, 62.18; H, 7.12; N, 3.88.

δ,δ'-Dioxo-2,6-pyridinedipentanoic acid (3b)

Following the procedure described for the preparation of **1b**, a solution of **3a** (6 g, 16.5 mmol) in MeOH (70 mL) and 4 N aqueous NaOH (83 mL) afforded **3b** (5 g, 98%) as a white solid: IR (film) 1706, 1708, 2500-3200 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 2.04 (m, J = 7.0 Hz, 4H, H-3′), 2.44 (t, J = 7.0 Hz, 4H, H-4′), 3.36 (t, J = 7.0 Hz, 4H, H-2′), 8.09 (dd, J = 8.0, 6.8 Hz, 1H, H-4), 8.18 (dm, J = 8.0 Hz, 2H, H-3 and H-5); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 20.5 (2 CH_2, 2 C-3′), 34.2 (2 CH_2, 2 C-4′), 37.7 (2 CH_2, 2 C-1′), 125.8 (2 CH, C-3 and C-5), 139.7 (CH, C-4), 153.8 (2 C, C-2 and C-6), 177.1 (2 C, 2 CO_2), 202.0 (2 C, 2 CO); mp 126-127 °C (EtOAc–Et_2O–MeOH); MS-EI m/z 307 (M^+, 40), 279 (50), 248 (56), 230 (66), 193 (100), 175 (98), 55 (37); HRMS $C_{15}H_{18}NO_6$ (M + H^+), 308.1134; found, 308.1125. Anal. calcd for $C_{15}H_{17}NO_6 \cdot {}^1/_4H_2O$: C, 57.78; H, 5.66; N, 4.49. Found: C, 57.85; H, 5.51; N, 4.47.

Diethyl δ,δ'-dioxo-1,3-benzenedibutanoate (4a)

Tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.12 mmol) was added to a solution of isophthaloyl dichloride (2.5 g, 12.3 mmol) in THF (60 mL). The mixture was heated at 60 °C, stirred over 5 min, and cooled to rt. Then, 3-ethoxy-3-oxopropylzinc bromide (50 mL of a 0.5 M solution in THF, 25 mmol) was added, and stirring was continued for 5 h at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the aqueous solution was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (9 : 1 to 1 : 1 hexane–Et_2O) to afford **4a** (1.6 g, 39%) as a yellowish oil: IR (film) 1687, 1732, 2983 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, J = 7.1 Hz, 6H, CH_3), 2.79 (t, J = 6.5 Hz, 4H, CH_2CO$_2$), 3.35 (t, J = 6.5 Hz, 4H, CH_2CO), 4.16 (q, J = 7.1 Hz, 4H, OCH_2), 7.60 (t, J = 7.8 Hz, 1H, H-5), 8.19 (dd, J = 7.8, 1.7 Hz, 2H, H-4 and H-6), 8.58 (t, J = 1.7 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2 (2 CH_3), 28.2 (2 CH_2, CH_2CO_2), 33.5 (2 CH_2, CH_2CO), 60.7 (2 CH_2, OCH_2), 127.5 (CH, Ar), 129.1 (CH, Ar), 132.3 (2 CH, Ar), 136.9 (2 C, Ar), 172.7 (2 C, CO_2), 197.4 (2 C, CO). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.36; H, 6.51.

1,3-Bis[1-oxo-3-(dimethylamino)propyl]benzene dihydrochloride (5)

A mixture of 1,3-diacetylbenzene (20 g, 124 mmol), paraformaldehyde (11 g, 370 mmol), dimethylamine hydrochloride (30 g, 370 mmol), and concentrated HCl (0.5 mL, 6 mmol) in absolute EtOH (125 mL) was refluxed for 15 h. The mixture was poured into dry acetone (200 mL), and the crude product was filtered affording **5** (37.2 g, 86%) as a white solid: IR (KBr) 1692, 2667 cm^{-1}; ^{1}H NMR (D_2O, 400 MHz) δ 3.02 (s, 12H, CH_3), 3.66 (t, J = 6.1 Hz, 4H, CH_2CO), 3.77 (t, J = 6.1 Hz, 4H, CH_2N), 7.78 (t, J = 7.8 Hz, 1H, H-5), 8.33 (dd, J = 7.8, 1.7 Hz, 2H, H-4 and H-6), 8.59 (t, J = 1.7 Hz, 1H, H-2); ^{13}C NMR (D_2O, 100.6 MHz) δ 33.2 (2 CH_2, CH_2CO), 43.0 (4 CH_3), 52.7 (2 CH_2, CH_2N), 127.6 (CH, Ar), 129.6 (CH, Ar), 133.5 (2 CH, Ar), 135.8 (2 C, Ar), 198.9 (2 C, CO); HRMS $C_{16}H_{25}N_2O_2$ (M + H^+), 277.1911; found, 277.1912.

γ,γ′-Dioxo-1,3-benzenedibutanenitrile (6)

A solution of KCN (15 g, 230 mmol) in H_2O (50 mL) was added dropwise to a solution of **5** (20 g, 57 mmol) in H_2O (100 mL) and AcOH (7 mL). The mixture was heated at 80 °C for 5 h. The precipitate was filtered and washed with water to give **6** (12.4 g, 90%) as a dark brown solid: IR (film) 1691, 2250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.82 (t, J = 7.1 Hz, 4H, CH_2CN), 3.44 (t, J = 7.1 Hz, 4H, CH_2CO), 7.67 (t, J = 7.8 Hz, 1H, H-5), 8.2 (dd, J = 7.8, 1.7 Hz, 2H, H-4 and H-6), 8.53 (t, J = 1.7 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.8 (2 CH_2, CH_2CN), 34.5 (2 CH_2, CH_2CO), 118.9 (2 CN), 127.4 (CH, Ar), 129.7 (CH, Ar), 132.8 (2 CH, Ar), 136.1 (2 C, Ar), 194.5 (2 C, CO); HRMS $C_{14}H_{12}N_2NaO_2$ (M + Na^+), 263.0791; found, 263.0793.

γ,γ′-Dioxo-1,3-benzenedibutanoic acid (4b)

A suspension of **6** (12 g, 50 mmol) in a solution of 1 : 1 conc AcOH–HCl (125 mL) was refluxed for 3 h. The solution was concentrated to dryness, and the resulting black solid was taken up with 4 N aqueous NaOH and extracted with EtOAc. The aqueous solution was acidified to pH = 1 with 5 N aqueous HCl and extracted with EtOAc. The organic extracts were dried and concentrated to afford **4b** (9.6 g, 69%) as a brown solid: IR (KBr) 1685, 2800–3200 cm^{-1}; ^1H NMR (DMSO, 400 MHz) δ 2.61 (t, J = 7.8 Hz, 4H, CH_2CO_2), 3.33 (t, J = 7.8 Hz, 4H, CH_2CO), 7.7 (t, J = 7.8 Hz, 1H, H-5), 8.23 (dd, J = 7.8, 1.7 Hz, 2H, H-4 and H-6), 8.48 (t, J = 1.7 Hz, 1H, H-2), 12.19 (br s, 2H, CO_2H); ^{13}C NMR (DMSO, 100.6 MHz) δ 27.9 (2 CH_2, CH_2CO_2), 33.3 (2 CH_2, CH_2CO), 126.9 (CH, Ar), 129.4 (CH, Ar), 132.2 (2 CH, Ar), 136.8 (2 C, Ar), 173.8 (2 C, CO_2), 198.2 (2 C, CO); HRMS $C_{14}H_{13}O_6$ ($M\text{-}H^+$), 277.0718; found, 277.0718.

(3*R*,7a*R*)-3-Phenyl-7a-(2-pyridyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one (7)

(*R*)-Phenylglycinol (410 mg, 3 mmol) was added to a solution of **1b** (510 mg, 2.9 mmol) in toluene (25 mL), and the mixture was heated at reflux temperature for 7 h with azeotropic elimination of water produced by a Dean–Stark apparatus. Then, the solution was concentrated under reduced pressure to give a residue, which was purified by flash chromatography (4 : 1 to 3 : 2 hexane–EtOAc) to afford **7** (620 mg, 78%) as a yellow solid: IR (film) 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 2.49–2.56 (m, 2H, H-7), 2.68 (ddd, J = 16.7, 7.5, 4.8 Hz, 1H, H-6), 3.21 (dt, J = 16.7, 9.9 Hz, 1H, H-6), 3.99 (dd, J = 8.8, 7.7 Hz, 1H, H-2), 4.73 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 5.26 (t_{ap}, J = 7.7 Hz, 1H, H-3), 6.96–7.03 (m, 2H, ArH), 7.09–7.22 (m, 4H, ArH), 7.41 (dt, J = 7.8, 1.1 Hz, 1H, PyrH), 7.58 (td, J = 7.8, 1.8 Hz, 1H, PyrH), 8.67 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, PyrH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.8 (CH_2, C-6), 34.8 (CH_2, C-7), 58.4 (CH, C-3), 74.7 (CH_2, C-2), 102.4 (C, C-7a), 119.2 (CH, Ar), 123.0 (CH, Ar), 126.0 (2 CH, Ar), 127.2 (CH, Ar), 128.3 (2 CH, Ar), 136.6 (CH, Ar), 138.9 (C, *i*-Ar), 150.0 (CH, Ar), 160.3 (C, *i*-Ar), 179.6 (C, C-5); $[\alpha]_D^{22}$ −79.0 (*c* 1.0, MeOH); mp 81–83 °C (EtOAc–hexane); MS-EI *m/z* 280 (M^+, 3), 202 (100), 161 (48), 120 (21); HRMS $C_{17}H_{17}N_2O_2$ (M + H^+), 281.1271; found, 281.1277. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.74; H, 5.82; N, 9.90.

(3*R*,3'*R*,7a*R*,7a'*R*)-2,6-Bis(5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazol-7a-yl)pyridine (9)

Following the procedure described for the preparation of **7**, from (*R*)-phenylglycinol (600 mg, 4.4 mmol) and **2b** (600 mg, 2.15 mmol) in toluene (25 mL) for 18 h, lactam **9** (520 mg, 47%) was obtained as a white solid after flash chromatography (1 : 1 hexane–EtOAc to EtOAc): IR (film) 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 2.36–2.55 (m, 4H, H-7), 2.68 (ddd, J = 16.6, 10.0, 2.1 Hz, 2H, H-6), 3.24 (dt, J = 16.6, 10.0 Hz, 2H, H-6), 4.03 (dd, J = 8.8, 7.5 Hz, 2H, H-2), 4.77 (dd, J = 8.8, 8.0 Hz, 2H, H-2), 5.26 (t_{ap}, J = 7.5 Hz, 2H, H-3), 6.89–6.95 (m, 4H, PhH), 7.06–7.13 (m, 6H, PhH), 7.35 (d, J = 8.0 Hz, 2H, H-3′ and H-5′), 7.54 (t, J = 8.0 Hz, 1H, H-4′); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.2 (2 CH_2, C-6), 35.4 (2 CH_2, C-7), 57.8 (2 CH, C-3), 75.1 (2 CH_2, C-2), 102.2 (2 C, C-7a), 118.0 (2 CH, C-3′ and C-5′), 125.7 (4 CH, Ph), 127.3 (2 CH, Ph), 128.3 (4 CH, Ph), 137.8 (CH, C-4′), 139.1 (2 C, *i*-Ph), 161.2 (2 C, C-2′ and C-6′), 178.6 (2 C, C-5); $[\alpha]_D^{22}$ −291.5 (*c* 0.95, MeOH); mp 178–182 °C (EtOAc–hexane); MS-EI *m/z* 481 (M^+, 22), 281 (16), 202 (100), 120 (15); HRMS $C_{29}H_{28}N_3O_4$ (M + H^+), 482.2074; found, 482.2072. Anal. Calcd for $C_{29}H_{27}N_3O_4 \cdot {}^1/_3H_2O$: C, 71.45; H, 5.72; N, 8.62. Found: C, 71.46; H, 5.72; N, 8.55.

(3*R*,3′*R*,8a*R*,8a'*R*)-2,6-Bis(5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyrid-8a-yl)pyridine (10)

Following the procedure described for the preparation of **7**, from (*R*)-phenylglycinol (550 mg, 4 mmol) and **3b** (550 mg, 1.79 mmol) in toluene (25 mL) for 18 h, lactam **10** (520 mg, 57%) was obtained as a white solid after flash chromatography (SiO_2 previously washed with 8 : 2 Et_3N–EtOAc; gradient from 7 : 3 EtOAc–hexane to EtOAc): IR (film) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.39 (m, 2H, H-7), 1.53 (m, 2H, H-7), 1.92 (td, J = 13.0, 4.3 Hz, 2H, H-8), 2.16 (dt, J = 13.0, 4.3 Hz, 2H, H-8), 2.33 (ddd, J = 18.0, 9.6, 8.0 Hz, 2H, H-6), 2.49 (ddd, J = 18.0, 6.8, 1.5 Hz, 2H, H-6), 3.84 (dd, J = 9.1, 8.2 Hz, 2H, H-2), 4.48 (dd, J = 9.1, 8.2 Hz, 2H, H-2), 5.36 (t, J = 8.2 Hz, 2H, H-3), 6.81-6.88 (m, 4H, PhH), 7.03-7.12 (m, 6H, PhH), 7.60 (d, J = 8.0 Hz, 2H, H-3′ and H-5′), 7.78 (t, J = 8.0 Hz, 1H, H-4′); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.3 (2 CH_2, C-7), 30.8 (2 CH_2, C-6), 35.2 (2 CH_2, C-8), 59.6 (2 CH, C-3), 69.8 (2 CH_2, C-2), 95.7 (2 C, C-8a), 119.3 (2 CH, C-3′ and C-5′), 127.3 (2 CH, Ph), 127.5 (4 CH, Ph), 128.0 (4 CH, Ph), 138.0 (CH, C-4′), 138.5 (2 C, *i*-Ph), 160.4 (2 C, C-2′ and C-6′), 170.5 (2 C, C-5); $[\alpha]_D^{22}$ −42.1 (*c* 1.5, MeOH); mp 129–132 °C (EtOAc–hexane); MS-EI *m/z* 509 (M^+, 9), 295 (11), 216 (100), 120 (23); HRMS $C_{31}H_{32}N_3O_4$ (M + H^+), 510.2387; found, 510.2385. Anal. Calcd for $C_{31}H_{31}N_3O_4$: C, 73.06; H, 6.13; N, 8.25. Found: C, 72.74; H, 6.45; N, 7.89.

(3*R*,3'*R*,7a*R*,7a'*R*)-1,3-Bis(5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazol-7a-yl)benzene (11)

Following the procedure described for the preparation of **7**, from (*R*)-phenylglycinol (4.9 g, 36 mmol) and **4b** (4.5 g, 16 mmol) in toluene (270 mL) for 24 h, lactam **11** (4.7 g, 61%) was obtained as a brown solid after flash chromatography (4 : 1 to 1 : 1 hexane–EtOAc): IR (KBr) 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 2.02–2.12 (m, 2H, H-7), 2.47–2.61 (m, 4H, H-7 and H-6), 2.62–2.75 (m, 2H, H-6), 3.71 (t, J = 8.9 Hz, 2H, H-2), 4.56 (dd, J = 8.9, 8.0 Hz, 2H, H-2), 5.14 (t, J = 8.0 Hz, 2H, H-3), 7.00–7.06 (m, 4H, PhH), 7.12–7.17 (m, 6H, PhH), 7.31–7.35 (m, 2H, PhH), 7.38–7.43 (m, 2H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.6 (2 CH_2, C-6), 35.3 (2 CH_2, C-7), 58.7 (2 CH, C-3), 72.6 (2 CH_2, C-2), 102.6 (2 C, C-7a), 122.5 (CH, Ph), 125.0 (2 CH, Ph), 126.5 (4 CH, Ph), 127.4 (2 CH, Ph), 128.4 (4 CH, Ph), 129.3 (CH, Ph), 138.7 (2 C, *i*-Ph), 142.4 (2 C, C-1′ and C-3′), 180.3 (2 C, C-5); $[\alpha]_D^{22}$ −126.9 (*c* 1.0, $CHCl_3$); mp 198-200 °C (EtOAc–hexane); MS-EI *m/z* 480 (M^+, 57), 423 (50), 306 (44), 202 (100), 120 (60), 104 (73), 91 (93), 55 (49); Anal. Calcd for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83. Found: C, 75.08; H, 5.74; N, 5.62.

(5*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-phenyl-2-pyrrolidone (12)[16]

Triethylsilane (1 mL, 6.3 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) were added to a solution of lactam **8** (700 mg, 2.5 mmol) in CH_2Cl_2

(20 mL). The mixture was refluxed for 20 h, quenched by the cautious addition of saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (4 : 1 hexane–EtOAc to EtOAc) to afford pyrrolidone **12** (500 mg, 71%) as a white solid: IR (film) 1686, 3200–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.95 (m, 1H, H-4), 2.44 (m, 1H, H-4), 2.58 (ddd, J = 16.8, 9.5, 6.5 Hz, 1H, H-3), 2.72 (ddd, J = 16.8, 9.5, 6.5 Hz, 1H, H-3), 3.93 (dd, J = 12.3, 3.2 Hz, 1H, H-2′), 4.06 (dd, J = 7.4, 3.2 Hz, 1H, H-1′), 4.19 (dd, J = 12.3, 7.4 Hz, 1H, H-2′), 4.40 (dd, J = 8.2, 5.2 Hz, 1H, H-5), 4.81 (br s, 1H, OH), 7.05–7.21 (m, 4H, PhH), 7.27–7.41 (m, 6H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.7 (CH_2, C-4), 31.3 (CH_2, C-3), 63.2 (CH, C-1′), 64.0 (CH, C-5), 64.4 (CH_2, C-2′), 126.6 (2 CH, Ph), 127.4 (2 CH, Ph), 127.9 (CH, Ph), 128.2 (CH, Ph), 128.7 (2 CH, Ph), 129.1 (2 CH, Ph), 137.2 (C, Ph), 140.5 (C, Ph), 177.4 (C, C-2); $[\alpha]_D^{22}$ +12.3 (c 0.7, CH_2Cl_2) {lit.[16] $[\alpha]_D^{22}$ +11 (c 0.7, CH_2Cl_2)}; mp 85–88 °C (EtOAc–hexane); MS-EI m/z 281 (M^+, 0.2), 250 (57), 162 (29), 117 (53), 106 (100), 91 (63), 77 (32); HRMS $C_{18}H_{20}NO_2$ (M + H^+), 282.1489; found, 282.1485.

(5*S*)-1-[(1*R*)-2-Chloro-1-phenylethyl]-5-phenyl-2-pyrrolidone (13)

$SOCl_2$ (0.5 ml, 7 mmol) was added to a cooled (0 °C) solution of **12** (1 g, 3.55 mmol) in THF (70 mL), and resulting mixture was stirred for 15 min at 0 °C and then refluxed for 1.5 h. After evaporation of the solvent, the crude residue was taken up with EtOAc, washed with a saturated $NaHCO_3$ solution, dried, and concentrated to yield **13** (930 mg, 93%) as a yellowish solid: IR (film) 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.95 (m, 1H, H-4), 2.33–2.50 (m, 2H, H-4 and H-3), 2.65 (m, 1H, H-3), 3.99 (dd, J = 11.1, 6.3 Hz, 1H, H-2′), 4.38 (dd, J = 9.3, 6.3 Hz, 1H, H-1′), 4.48 (t, J = 7.0 Hz, 1H, H-5), 4.72 (dd, J = 11.1, 9.3 Hz, 1H, H-2′), 7.17–7.27 (m, 7H, ArH), 7.28–7.34 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.3 (CH_2, C-4), 31.1 C-3), 44.1 (C-2′), 60.3 (C-1′), 62.9 (C-5), 127.2 (2CHAr), 127.8 (2CHAr), 128.2 (CHAr), 128.2 (CHAr), 128.6 (2CHAr), 128.8 (2CHAr), 137.8 (C-i), 140.5 (C-i), 176.7 (CON); $[\alpha]_D^{22}$ − 8.0 (c 1.0, MeOH); mp 102-105 °C (EtOAc–hexane); MS-EI m/z 299 (M^+, 1), 263 (100), 250 (80), 106 (55); HRMS $C_{18}H_{19}ClNO$ (M + H^+), 300.1149; found, 300.1136. Anal. calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 72.09; H, 6.09; N, 4.59.

(*S*)-5-Phenyl-1-(1-phenylvinyl)-2-pyrrolidone (14)

DBU (0.85 mL, 5.6 mmol) was added at rt to a solution of **13** (850 mg, 2.8 mmol) in DMF (9.5 mL), and the mixture was heated at 85 °C for 5 h, cooled, poured into ice and water, and extracted with Et_2O. The combined organic extracts were washed with saturated $NaHCO_3$ solution, brine, and water, dried and concentrated. Flash chromatography (1 : 1 hexane–EtOAc) afforded **14** (530 mg, 70%) as a yellow oil: IR (film) 1693, 2800–3000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 2.02 (m, 1H, H-4), 2.50–2.82 (m, 3H, H-4 and H-3), 4.77 (dd, J = 7.8, 5.8 Hz, 1H, H-5), 5.21 (s, 1H, H-2′), 5.34 (s, 1H, H-2′), 7.01–7.10 (m, 2H, ArH), 7.11–7.19 (m, 2H, ArH), 7.20–7.36 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.6 (CH_2, C-4), 31.1 (CH_2, C-3), 63.4 (CH, C-5), 112.6 (CH_2, C-2′), 126.5 (2 CH, Ph), 126.7 (2 CH, Ph), 127.8 (CH, Ph), 128.2 (2 CH, Ph), 128.4 (CH, Ph), 128.6 (2 CH, Ph), 136.2 (C, C-1′), 140.9 (C, Ph), 142.0 (C, Ph), 174.9 (C, C-2); $[\alpha]_D^{22}$ −15.3 (c 0.9, MeOH); MS-EI m/z 263 (M^+, 75), 159 (73), 144 (100), 119 (51), 104 (40), 91 (34), 77 (27); HRMS $C_{18}H_{18}NO$ (M + H^+), 264.1382; found, 264.1391.

(*S*)-5-Phenyl-2-pyrrolidone (15)[17]

5 M aqueous H_2SO_4 (15 mL) was added to a solution of **14** (400 mg, 1.5 mmol) in Et_2O (60 mL). Then, the resulting mixture was stirred at reflux temperature until no more starting material was observed by TLC (20 h). The mixture was washed with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic phases were dried and evaporated. Flash chromatography (1 : 1 hexane–EtOAc to EtOAc) provided **15** (234 mg, 96%) as a white solid: IR (film) 1656, 1693, 3100–3200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.98 (m, 1H, H-4), 2.36–2.50 (m, 2H, H-4 and H-3), 2.56 (m, 1H, H-3), 4.75 (t, J = 7.1 Hz, 1H, H-5), 6.23 (br s, 1H, NH), 7.27–7.33 (m, 3H, ArH), 7.34–7.40 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.3 (CH_2, C-4), 31.2 (CH_2, C-3), 58.1 (CH, C-5), 125.6 (2 CH, Ph), 127.8 (CH, Ph), 128.8 (2 CH, Ph), 128.8 (CH, Ph), 142.5 (C, Ph), 178.6 (C, CON); $[\alpha]_D^{22}$ −58.7 (c 1.0, $CHCl_3$) {lit.[17] $[\alpha]_D^{22}$ −51.0 (c 0.97, CH_2Cl_2)}.

(*S*)-2-Phenylpyrrolidine (16)[10b]

$LiAlH_4$ (118 mg, 3.1 mmol) was added to a solution of **15** (100 mg, 0.62 mmol) in THF (12 mL), and the mixture was stirred at rt for 3 days. Then, the mixture was carefully poured into 2 N aqueous NaOH and extracted with EtOAc. The organic phase was washed with 2 N aqueous HCl, and the aqueous phase was then basified to pH = 14 with 4 N aqueous NaOH and extracted with EtOAc. The organic extracts were dried and concentrated to afford **16** (74 mg, 81%) as a colourless oil. ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.67 (m, 1H, H-3), 1.79–1.96 (m, 3H, H-4 and NH masked), 2.19 (m, 1H, H-3), 3.01 (m, 1H, H-5), 3.21 (ddd, J = 10.1, 7.7, 5.3 Hz, 1H, H-5), 4.11 (t, J = 7.7 Hz, 1H, H-2), 7.22 (m, 1H, ArH), 7.28–7.38 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.6 (CH_2, C-4), 34.3 (CH_2, C-3), 47.0 (CH_2, C-5), 62.6 (CH, C-2), 126.5 (2 CH, Ph), 126.7 (CH, Ph), 128.3 (2 CH, Ph), 144.8 (C, Ph); $[\alpha]_D^{22}$ −26.8 (c 0.3, MeOH) {lit.[10b] $[\alpha]_D^{22}$ −22.0 (c 0.3, MeOH).

(5*S*,5′*S*)-1,3-Bis{1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-5-pyrrolidinyl}benzene (17)

Following the procedure described for the preparation of **12**, lactam **11** (4 g, 8.32 mmol) in CH_2Cl_2 (80 mL), Et_3SiH (6.6 mL, 41.6 mmol) and $TiCl_4$ (7.3 mL, 66.6 mmol) for 43 h afforded **17** (2.4 g, 60%) as a white solid and **18** (1.4 g 30%) as a white solid after flash chromatography (1 : 1 hexane–EtOAc to 95 : 5 EtOAc–methanol). **17**: IR (film) 1669, 3200–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.84–1.98 (m, 2H, H-4), 2.39–2.51 (m, 2H, H-4), 2.52–2.78 (m, 4H, H-3), 3.87 (ddd, J = 12.3, 6.4, 3.6 Hz, 2H, H-2′), 4.05 (dd, J = 8.0, 3.6 Hz, 2H, H-1′), 4.30 (dt, J = 12.3, 8.0 Hz, 2H, H-2′), 4.40 (dt, J = 12.3, 6.1 Hz, 2H, H-5), 4.55 (dt, J = 14.4, 7.1 Hz, 2H, OH), 6.91–7.43 (m, 14H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.7 (2 CH_2, C-4), 31.2 (2 CH_2, C-3), 63.1 (2 CH, C-1′), 63.6 (2 CH, C-5), 64.1 (2 CH_2, C-2′), 124.8 (CH, Ph), 126.6 (2 CH, Ph), 127.4 (4 CH, Ph), 128.0 (2 CH, Ph), 128.7 (4 CH, Ph), 129.9 (CH, Ph), 137.1 (2 C, Ph), 141.9

(2 C, Ph), 177.3 (2 C, C-2); $[\alpha]_D^{22}$ −3.0 (*c* 1.0, $CHCl_3$); MS-EI *m/z* 484 (M^+, 0.03), 454 (100), 436 (35), 347 (99), 106 (87), 91 (36); HRMS $C_{30}H_{33}N_2O_4$ (M + H^+), 485.2435; found, 485.2430. **18**: IR (KBr) 1657, 1701, 3200–3300 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.66–1.78 (m, 1H, H-7), 2.28–2.42 (m, 2H, H-4 and H-7), 2.45–2.75 (m, 4H, H-3, H-4 and H-6), 2.93–3.09 (m, 1H, H-3), 3.78 (ddd, *J* = 12.2, 6.5, 3.8 Hz, 1H, H-2′), 3.86 (dd, *J* = 8.1, 3.8 Hz, 1H, H-1′), 3.91–4.00 (m, 1H, H-2), 4.23 (dt, *J* = 12.2, 8.1 Hz, 1H, H-2′), 4.33 (dd, *J* = 8.2, 5.5 Hz, 1H, H-5), 4.39 (dd, *J* = 8.1, 6.5 Hz, 1H, OH), 4.64-4.72 (m, 1H, H-2), 5.22 (t, *J* = 8.0 Hz, 1H, H-3′), 6.97–7.09 (m, 5H, PhH), 7.14–7.22 (m, 3H, PhH), 7.23–7.36 (m, 5H, PhH), 7.43–7.48 (m, 1H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.6 (CH_2, C-7), 31.3 (CH_2, C-6), 32.8 (CH_2, C-3), 35.5 (CH_2, C-4), 58.7 (CH, C-3′), 63.0 (CH, C-1′), 63.6 (CH, C-5), 64.1 (CH_2, C-2′), 73.2 (CH_2, C-2), 102.5 (C, C-7a), 123.2 (CH, Ph), 125.3 (CH, Ph), 126.5 (2 CH, Ph), 126.9 (CH, Ph), 127.4 (2 CH, Ph), 127.4 (CH, Ph), 128.0 (CH, Ph), 128.4 (2 CH, Ph), 128.7 (2 CH, Ph), 129.4 (CH, Ph), 137.1 (C, Ph), 138.8 (C, Ph), 141.2 (C, Ph), 143.4 (C, Ph), 177.3 (C, C-2), 180.1 (C, C-5); $[\alpha]_D^{22}$ −62.4 (*c* 1.0, $CHCl_3$); mp 140–142 °C (EtOAc); MS-EI *m/z* 482 (M^+, 0.1), 451 (100), 331 (40), 243 (39), 106 (58); HRMS $C_{30}H_{31}N_2O_4$ (M + H^+), 483.2278; found, 483.2282.

(5*S*,5′*S*)-1,3-Bis{1-[(1*R*)-2-chloro-1-phenylethyl]-2-oxo-5-pyrrolidinyl}benzene (19)

Following the procedure described for the preparation of **13**, a solution of **17** (1.4 g, 2.9 mmol) in THF (55 mL) and $SOCl_2$ (0.9 ml, 11.5 mmol) afforded **19** (1.5 g) as a yellow solid. Dichlorinated compound **19** was used without further purification in next reaction. An analytical sample was purified by column chromatography (4 : 1 hexane–EtOAc) to afford **19** as yellowish solid. ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.84–1.96 (m, 2H, H-4), 2.35–2.50 (m, 4H, H-3 and H-4), 2.55–2.68 (m, 2H, H-3), 3.95 (dd, *J* = 11.2, 6.0 Hz, 2H, H-2′), 4.34 (dd, *J* = 10.0, 6.0 Hz, 2H, H′1′), 4.47 (t, *J* = 7.2 Hz, 2H, H-5), 4.82 (dd, *J* = 11.2, 10.0 Hz, 2H, H-2′), 7.11 (dd, *J* = 7.6, 1.6 Hz, 2H, PhH), 7.16–7.28 (m, 2H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 29.1 (2 CH_2, C-4), 31.1 (2 CH_2, C-3), 44.2 (2 CH_2, C-2′), 61.0 (2 CH, C-1′), 62.7 (2 CH, C-5), 125.2 (CH, Ph), 127.5 (2 CH, Ph), 127.8 (4 CH, Ph), 128.4 (2 CH, Ph), 128.8 (4 CH, Ph), 129.2 (CH, Ph), 137.7 (2 C, Ph), 141.9 (2 C, Ph), 176.8 (2 C, C-5); HRMS $C_{30}H_{31}Cl_2N_2O_2$ (M + H^+), 521.1757; found, 521.1762.

(5*S*,5′*S*)-1,3-Bis[1-(1-phenylvinyl)-2-oxo-5-pyrrolidinyl]benzene (20)

Following the procedure described for the preparation of **14**, a solution of **19** (1.5 g, 2.9 mmol) in DMF (12 mL) and DBU (1.75 mL, 11.5 mmol) afforded **20** (650 mg, 50% from **17**) as a yellowish foam after flash chromatography (1 : 1 hexane–EtOAc to EtOAc): IR (KBr) 1686, 2900–3400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.81–1.95 (m, 2H, H-4), 2.43–2.56 (m, 2H, H-4), 2.57–2.76 (m, 4H, H-3), 4.70 (dd, *J* = 7.6, 6.3 Hz, 2H, H-5), 5.11 (s, 2H, H-2′), 5.29 (s, 2H, H-2′), 6.60–6.98 (m, 3H, PhH), 7.07–7.32 (m, 11H, PhH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.6 (2 CH_2, C-4), 31.0 (2 CH_2, C-3), 63.2 (2 CH, C-5), 112.3 (2 CH_2, C-2′), 124.9 (CH, Ph), 126.1 (2 CH, Ph), 126.4 (4 CH, Ph), 128.2 (4 CH, Ph), 128.4 (2 CH, Ph), 128.9 (CH, Ph), 136.0 (2 C, C-1′), 141.3 (2 C, Ph), 141.9 (2 C, Ph), 174.7 (2 C, C-2); $[\alpha]_D^{22}$ +6.6 (*c* 1.0, $CHCl_3$); HRMS $C_{30}H_{29}N_2O_2$ (M + H^+), 449.2223; found, 449.2227.

(5*S*,5′*S*)-1,3-Bis(2-oxo-5-pyrrolidinyl)benzene (21)

5 M aqueous H_2SO_4 (20 mL) was added to a solution of **20** (500 mg, 1.1 mmol) in Et_2O (20 mL). Then, the resulting mixture was stirred at reflux temperature until no more starting material was observed by TLC (5 h). The mixture was extracted with EtOAc. The aqueous layer was basified to pH = 14 with 4 N aqueous NaOH and extracted with EtOAc. The combined organic phases were dried and concentrated to afford **21** (170 mg, 63%) as a white solid: IR (KBr) 1679, 3221 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.85–1.98 (m, 2H, H-4), 2.42 (dd, *J* = 9.1, 6.7 Hz, 4H, H-3), 2.53–2.65 (m, 2H, H-4), 4.78–4.83 (m, 2H, H-5), 7.23–7.31 (m, 3H, PhH), 7.34–7.41 (m, 1H, PhH); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 33.5 (2 CH_2, C-3), 32.2 (2 CH_2, C-4), 59.7 (2 CH, C-5), 124.1 (CH, Ph), 126.2 (2 CH, Ph), 130.3 (CH, Ph), 145.0 (2 C, Ph), 181.3 (2 C, C-2); $[\alpha]_D^{22}$ −59.1 (*c* 0.5, MeOH); mp 260–261 °C decomp (MeOH); HRMS $C_{14}H_{17}N_2O_2$ (M + H^+), 245.1285; found, 245.1288; Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.61; H, 6.68; N, 11.34.

(*S*)-1,3-Di[2-pyrrolidinyl]benzene (22)

$LiAlH_4$ (93 mg, 2.5 mmol) was added to a solution of **19** (60 mg, 0.25 mmol) in THF (5 mL), and the mixture was stirred at reflux temperature for 1 day. The mixture was carefully poured into 2 N aqueous NaOH and extracted with EtOAc. The organic phase was washed with 2 N aqueous HCl, and the aqueous solution was then basified to pH = 12 with 4 N aqueous NaOH and extracted with EtOAc. The organic extracts were dried and concentrated to afford **22** (40 mg, 74%) as a yellow oil: IR (film) 1630, 2961 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HSQC) δ 1.61–1.73 (m, 2H, H-3), 1.78–1.95 (m, 4H, H-4), 2.11–2.28 (m, 4H, H-3 and NH masked), 2.95–3.04 (m, 2H, H-5), 3.14–3.25 (m, 2H, H-5), 4.08 (t, *J* = 8.2 Hz, 2H, H-2), 7.20–7.25 (m, 3H, ArH), 7.35 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.6 (2 CH_2, C-4), 34.3 (2 CH_2, C-3), 46.9 (2 CH_2, C-5), 62.7 (2 CH, C-2), 124.7 (CH, Ph), 125.0 (2 CH, Ph), 128.3 (CH, Ph), 144.7 (2 C, Ph); $[\alpha]_D^{22}$ −83.5 (*c* 1.0, $CHCl_3$); HRMS $C_{14}H_{21}N_2$ (M + H^+), 217.1699; found, 217.1705.

Theoretical calculations

Initial geometries were obtained using the PCMODEL program.[18] Further geometry optimizations were carried out using the Gaussian 03 suite of programs on a Compaq HPC320 computer,[19] at the Hartree–Fock (HF) level,[20] and at the Becke's three-parameter hybrid functional with the Lee, Yang and Parr correlation functional (B3LYP) level,[21] using the 6-31G(d) basis set.[22] Analytical energy second derivatives were calculated at all optimized structures to confirm that these were minima.

Acknowledgements

Financial support from the Ministry of Science and Innovation, Spain (Project CTQ2009-07021/BQU), and the AGAUR, Generalitat de Catalunya (Grant 2009-SGR-111) is gratefully

acknowledged. Thanks are also due to the Ministry of Education and Science for a fellowship for C. A.

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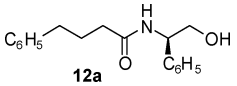

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