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Simple, versatile and highly diastereoselective synthesis of 1,3,4-trisubstituted-2-oxopiperazine-containing peptidomimetic precursors

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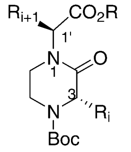
The selective *O*-deprotection of (1′*S*)-4-(*tert*-butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxopiperazine furnished an enantiomerically pure alcohol whose regio- and diastereoselective C$_3$-alkylation yielded either (3*R*)- or (3*S*)-1,3,4-trisubstituted-2-oxopiperazines in high diastereomeric purity. These derivatives were efficiently transformed into (1′*R*)- or (1′*S*)-peptide templates utilizable to prepare peptidomimetics. This method provides easy access to each 1,3,4-trisubstituted-2-oxopiperazine diastereomer and facilitates, through the large choice of substituents at the 3-position together with the chemistry that can be performed on the N1 substituent, the preparation of a large number of diastereomerically pure constrained peptidomimetics from a single precursor.

Introduction

(Aza)-lactams still receive much synthetic interest[1] because medicinal chemists used them to prepare peptidomimetics that provide prized structure–activity relationships.[2] Indeed, by allowing a better understanding of the peptide mechanism of action at a molecular level, peptidomimetics can permit the design of new, and more pharmacologically potent, molecules. At the same time, peptidomimetics can also be of higher stability towards physiological hydrolysis or enzymatic degradation than the parent peptide. Such improvement is of extreme importance from a therapeutic standpoint. Among all the useful aza-lactams, 1,3,4-trisubstituted-2-oxopiperazines whose 1-position is bonded to a chiral carbon atom (1*,3,4-trisubstituted-2-oxopiperazines) (general structure **1**) are of particular interest.



1

Such scaffolds, known to stabilize inverse γ-turns in small peptides,[3,4] result from the introduction of only two extra carbon atoms, compared to the parent peptide, linking N$_i$ and N$_{i+1}$. This ethylene bridge not only reduces the chances of "false negative" pharmacological responses consecutive to the introduction of excessive steric hindrance, although a correct conformational modification has been achieved, but also suppresses two NHs that could be part of a hydrogen bond network possibly stabilizing a undesirable conformer. Additionally, the pharmacologically relevant orientation and/or function of the *i*-amino-acid side chain (R$_i$) can possibly be probed from structure–activity data obtained by varying the 2-oxopiperazine 3-position substituent.

If the peptidomimetic **1** has a glycine residue at its $i + 1$ position (R$_{i+1}$ = H), its synthesis can be envisaged by direct N$_1$-alkylation of the readily available 3,4-disubstituted-2-oxopiperazine.[5] However, most 1,3,4-trisubstituted-2-oxopiperazines targetted by medicinal chemists have two stereogenic centers, one intracyclic (C$_3$) and one extracyclic (C$_{1'}$). This makes the N$_1$-alkylating method a poor choice. Four general methods have been reported for the synthesis of diastereomerically pure 1*,3,4-trisubstituted-2-oxopiperazines (Fig. 1). Lactamization of linear *N*,*N*′-bispeptides, prepared by reacting two optically pure amino acids and 1,2-dibromoethane, has yielded 1*,3-disubstituted-2-oxopiperazines whose 4-position could be easily substituted.[6] The best results were obtained with symmetrical bispeptides, meaning that the 2-oxopiperazine derivatives had necessarily similar substituents at their 3- and 1′-positions.[7] When two different amino acids were used to prepare the linear peptide dimer a mixture of 2-oxopiperazines is obtained, necessitating a subsequent inelegant resolution step.[8] 1*,3,4-Trisubstituted-2-oxopiperazines have been also synthesized by N$_4$–C$_5$ bond formation. For this, linear dipeptide analogues in which the nitrogen atom of the $i + 1$ residue was substituted with an α-aldehyde precursor have been prepared.[9] Reduction of the imine intermediate obtained by condensation of the unmasked aldehyde function and N$_i$ (the nascent 2-oxopiperazine N$_4$ atom) furnished the expected products. However, this method requires the preliminary preparation of a dipeptide whose accessibility can be limited if unusual side chains are desired at the 2-oxopiperazine 3-position. Furthermore, the whole synthesis has to be repeated if access to peptidomimetic diastereomers is desired. 1*,3,4-Trisubstituted-2-oxopiperazines have been also prepared by N$_1$–C$_6$ bond formation.[10] In this case, the ring formation was achieved by the alkylation of N$_1$ by a bromoethyl substituent at the nascent N$_4$ atom. This approach is thwarted by drawbacks similar to those depicted for the C$_5$–N$_4$ bond formation strategy.

Recently, we have reported the synthesis of 1*,3,4-trisubstituted-2-oxopiperazines by regio- and stereoselective C$_3$-alkylation of 1,4-disubstituted-2-oxopiperazines using various electrophiles.[11] Very high chiral induction (>95%) was achieved when simple electrophiles were used. A rigid intermediate that mandates approach of the electrophile from the face opposite to a lithium chelate involving N$_1$ and an alcohol appended to the 1′-substituent was proposed to be at the origin of the diastereoselectivity.[11–12] L-Leucinol[11] or D-phenylglycinol[13] have already been reported as chiral inductors, though almost any α-monosubstituted-β-amino alcohol could in principle be used.[14] In addition to its high diastereoselectivity, the C$_3$-alkylation method offers the enormous advantage of easy incorporation of a large diversity of substituents at the 2-oxopiperazine 3-position. However, as it is, two important drawbacks reduce its scope: 1) as the configuration of the 2-oxopiperazine 3-position

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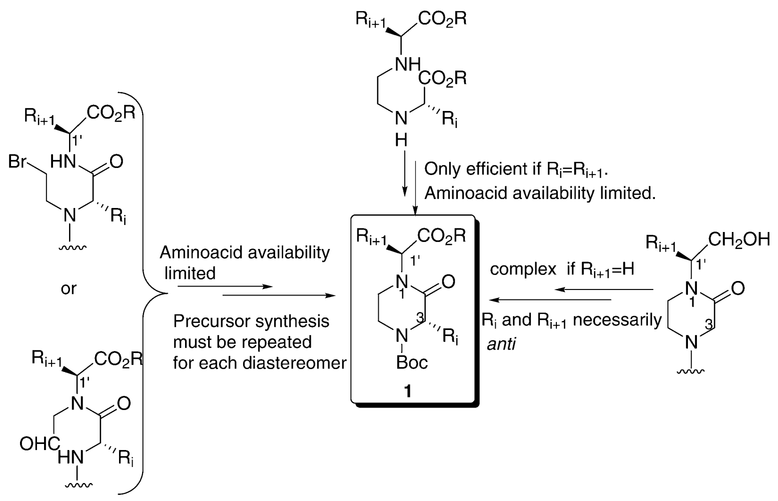


Fig. 1 Schematic representation of the current methods leading **1** and their main drawbacks.

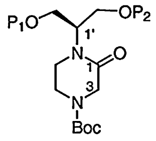
is totally governed by the configuration of the chiral inductor, only one diastereomer is accessible directly; and 2) since the N_1-substituting appendage must be chiral, peptidomimetics having a glycine residue at their $i + 1$ position are difficult to obtain.

Therefore, of all the methods reported so far to prepare 1*,3,4-trisubstituted-2-oxopiperazines, none is really satisfactory. General methods affording diastereomerically pure 1*,3,4-trisubstituted-2-oxopiperazines are still required.

Herein, we report an original and versatile method allowing, from a single precursor, the diastereoselective synthesis of each isomer of **1** and in which the choice of the C_3-substituent is not limited by the availability of the corresponding amino acid. This method also provides access to enantiomerically pure peptidomimetics having a glycine residue at the $i + 1$ position.

Results and discusion

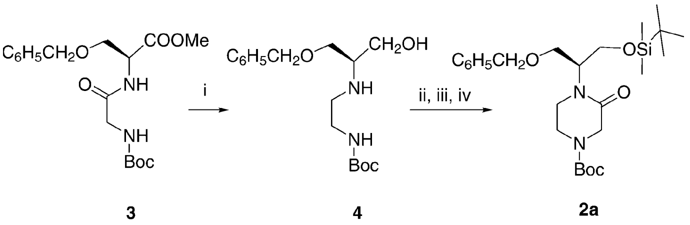
In our view, because of the large access to commercially available simple electrophiles the preparation of 1*,3,4-trisubstituted-2-oxopiperazines by the C_3-alkylation strategy is by far superior to the other reported methods. This strategy chosen, we had to design a 2-oxopiperazine substituted at N_1 with a chirality inductor whose 1′-configuration could be unambiguously achieved as desired. Thus, we considered serinol-based derivative **2**, in which P_1 and P_2 would be two orthogonal protective groups, as the best chemical entity to achieve our goal. We selected the benzyl (P_1) and *tert*-butyldimethylsilyl (P_2) groups as protective groups.



2a : $P_1=C_6H_5CH_2$, $P_2=SI(CH_3)_2C(CH_3)_3$
2b : $P_1=H$,$P_2=Si(CH_3)_2C(CH_3)_3$
2c : $P_1=C_6H_5CH_2$, $P_2=H$

Synthesis of 2-oxopiperazine 2a

Synthesis of **2a** could be readily achieved from dipeptide **3**. Concomitant amide and ester reduction of **3** (LAH in THF) afforded the expected amino alcohol **4** [80% yield, $[\alpha]_D^{17}$ +6 (*c* 0.1; EtOH)], whose hydroxyl function was protected by use of *tert*-butyl-dimethylsilyl chloride (*tert*-BDMSCl) in the presence of imidazole. The di-*O*-protected derivative was then reacted with bromoacetic acid in the presence of DCC to afford a linear intermediate whose cyclization (NaH, THF) afforded **2a** ($[\alpha]_D^{17}$ −1 (*c* 0.1; EtOH)) (70% yield from **3**) (Scheme 1).



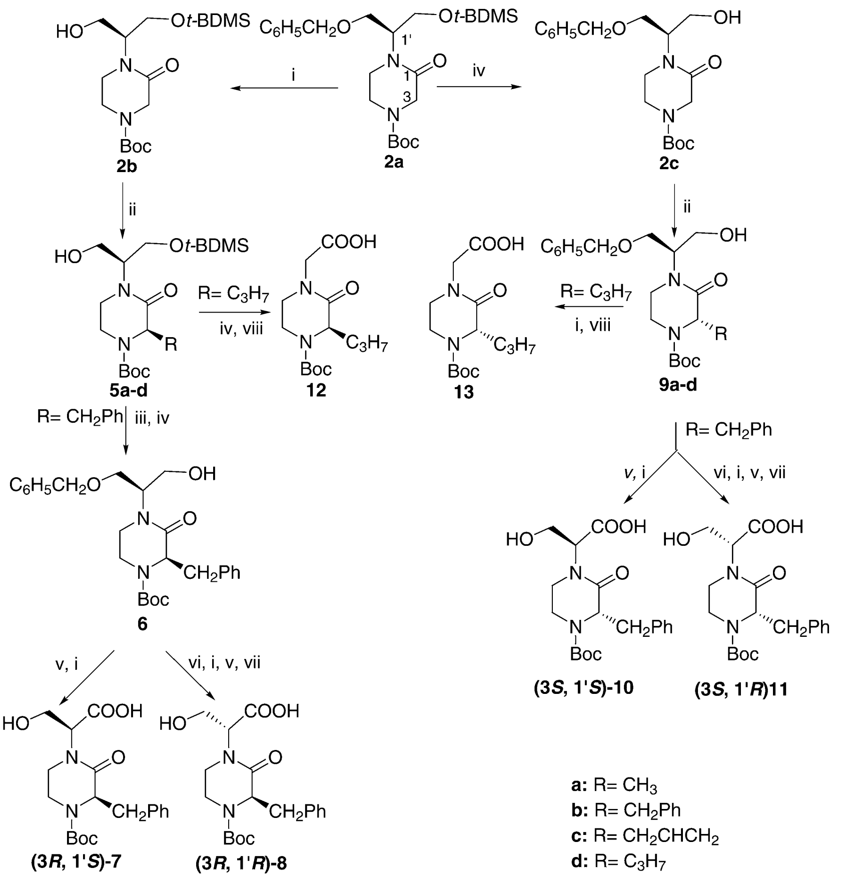
Scheme 1 *Reagents and yields*: i) LAH, THF (80%) ii) *tert*-BDMSCl, imidazole; iii) $BrCH_2COOH$, DCC, *N*-methylmporpholine, CH_2Cl_2; iv) NaH, THF (88%, 3 steps).

Synthesis of the 3*R*,1′*S* and 3*R*,1′*R* diastereomers

3*R*-Diastereomers should then be prepared from (1′*S*)-**2b**. Hydrogenolysis (H_2, Pd–C) of **2a** afforded (1′*S*)-**2b** in 90% yield. Alkylation of its enolate (LDA, THF, HMPA, −78 °C then −50 °C) with methyl iodide, benzyl bromide, allyl bromide and propyl bromide afforded **5a–d** (75%, 82%, 72% and 77% yield, respectively). ^1H NMR analysis (500 MHz) of each compound confirmed the anticipated high diasteroselectivity (>95%) of the alkylation step, since only one diastereomer was observed in each case. The 1′*S*,3*R* configuration of **5a–d** was assigned by mechanistic analogy with our previous studies in the piperazine,[11–13] diazepinone[15] or thiomorpholine[16] fields. To obtain peptidomimetic precursors we then needed to oxidize the primary alcohol function of **5** and chose **5b** as an example. Unfortunately, the silyl protective group was found to be too unstable under oxidative conditions, precluding the regioselective oxidation of **5b** in good yields. Thus, we protected the alcohol function of **5b** as a benzyl ether (BnCl, NaH) and removed the *tert*-BDMS protective group (Bu_4NF) to obtain **6** (quantitative yield, two steps). Oxidation of the alcohol function of **6** (Jones' reagent) afforded the corresponding acid, whose benzyl group hydrogenolysis furnished (1′*S*,3*R*)-**7** in 70% yield (2 steps) ($[\alpha]_D^{17}$ −10 (*c* 0.1; EtOH)). To obtain the (1′*R*,3*R*)-derivative **8**, the alcohol function of **6** was esterified (BzCl–pyridine, quantitative) then, after hydrogenolysis (H_2, Pd–C 10%, 98% yield) the resulting ester could be oxidized (Jones' reagent) then saponified (2 N NaOH) to yield (1′*R*,3*R*)-**8** in 81% yield ($[\alpha]_D^{17}$ +4 (*c* 0.1; EtOH)) (Scheme 2).

Synthesis of the 3*S*,1′*R* and 3*S*,1′*S* diastereomers

For the synthesis of the 3*S* diastereomers, the preparation of (1′*R*)-**2c** was necessary. The latter was prepared quantitatively by reaction of **2a** with tetrabutylammonium fluoride. Diastereoselective C_3-alkylation of (1′*R*)-**2c** as described for the alkylation of **2b** afforded **9a–d** (89, 80, 84 and 85% yield, respectively). Oxidation of **9b** (Jones' reagent) afforded the corresponding



Scheme 2 *Reagents*: i) H_2, Pd–C MeOH; ii) LDA, HMPA, THF, −50 °C, then CH_3I or $PhCH_2Br$ or CH_2CHCH_2Br; iii) $PhCH_2Cl$, NaH; iv) *n*-Bu_4NF; v) Jones' reagent; vi) PhCOCl, pyridine; vii) 2 N NaOH; viii) Jones' reagent, then 90 °C.

acid, which was transformed into the peptidomimetic precursor (3*S*,1′*S*)-**10** after hydrogenolysis (H_2, MeOH, quantitative) ($[\alpha]_D^{17}$ −4 (*c* 0.1; EtOH)). To obtain (3*S*,1′*R*)-**11**, the primary hydroxyl group of **9b** was quantitatively esterified (BzCl, pyridine) and after hydrogenolysis and oxidation (Jones reagent, 62%), the resulting adduct was saponified (2 N NaOH), furnishing (3*S*,1′*R*)-**11** ($[\alpha]_D^{17}$ +10 (*c* 0.1; EtOH)) in 97% yield (Scheme 2).

Synthesis of 1′-unsubstituted peptidomimetics

In addition to the four 1*,3,4-trisubstituted-2-oxopiperazine diastereomers, **2a** also provided an efficient entry to enantiomerically pure peptidomimetics having a glycine residue at their $i + 1$ position. We decided to illustrate this ability from **5d** and **9d**, whose 3-position is substituted with a non-proteogenic side-chain. Treatment of **5d** with Bu_4NF afforded the corresponding diol in quantitative yield. Subsequent oxidation (Jones' reagent) and decarboxylation (heating at 90 °C) yielded (3*R*)-**12** ($[\alpha]_D^{17}$ −119 (*c* 0.1; EtOH)), in 62% overall yield (Scheme 2). Hydrogenolysis of **9d** afforded the corresponding diol (not isolated), whose subsequent oxidation (Jones' reagent) and decarboxylation (heating at 90 °C) afforded (3*S*)-**13** ($[\alpha]_D^{17}$ +113 (*c* 0.1; EtOH)), in 53% overall yield (Scheme 2).

Conclusion

The four diastereomers of 1*,3,4-trisubstituted-2-oxopiperazines are accessible in a concise, versatile and diastereoselective manner from **2a**. Our method provides also an entry to enantiomerically pure 1,3,4-trisubstituted-2-oxopiperazines. Because of the synthetic flexibility of the 1′-group hydroxymethyl substituent, particularly its transformation into other proteogenic or non-proteogenic amino acid side chains, and also of the chemistry that can be performed at C_3 (the allyl substituent provides an entry to a large diversity of other structures), a huge number of peptidomimetics can be easily prepared from the key intermediate **2a**. Since the preparation of the latter can be routinely performed on a multigram scale, our method should rapidly find its place in the peptidomimetic synthesis field. In addition, our strategy can easily be extended to the preparation of optically pure therapeutic agents.[17]

Experimental

THF was dried by distillation from sodium–benzophenone. Diisopropylamine was dired by distillation from calcium hydride. Thin-layer and column chromatography were carried out on silica gel $60F_{254}$ 60–15 µm and silica gel 6–35 µm, respectively, from SDS (Peypin, France). IR spectra were recorded on a Nicolet 210 spectrometer using KBr pellets. Optical rotations were measured on a Perkin-Elmer 241 polarimeter; values are given in 10^{-1}deg cm^2 g^{-1}. Melting points were determined on a Kofler plate and are given uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument. ^1H chemical shifts (δ) are reported in ppm relative to residual solvent peak ($CDCl_3$ δ 7.27). ^{13}C chemical shifts (δ) are reported in ppm relative to residual solvent peak ($CDCl_3$ δ 77.7). *J* values are given in Hertz. Mass spectra were recorded on a Micromass-Waters Q–TOF Ultima spectrometer. HPLC analyses were performed on a Shimadzu instrument using a Chirobiotic (18 mm) column.

(2*R*)-6-(*tert*-Butoxycarbonyl)-2-phenylmethyloxymethyl-3,6-diazahexan-1-ol 4. To a solution of **3** (15 g) in dry THF at 0 °C, LAH (41 mmol) was added. The solution was stirred for 1 h at rt then 123 mmoles of LAH were added to the solution. After 30 h of stirring, 2 mL of a 15% aqueous solution of NaOH were slowly added. The suspension was stirred overnight at rt, then filtered and the cake washed with CH_2Cl_2. The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 10.6 g of a white solid (yield 80%). $[\alpha]_D^{17}$ +6 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3398 and 3333 (OH, N*H*), 2962, 1711 (CO), 1173; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (5H, m, Ar), 5.43 (1H, m, NH-Boc), 4.68 (2H, s, OCH_2), 3.85 (1H, m, OCH_2), 3.72 (2H, m, OCH_2), 3.71 (1H, m, OCH_2), 3.52 (1H, br s, OH), 3.39 (2H, m, NCH_2), 3.08 (1H, m, CH), 3.00 (1H, m, NCH_2), 2.95 (1H, m, NCH_2), 2.74 (1H, m, NH), 1.60 (9H, s, Boc). MS *m*/*z* 347 (M + Na)$^+$, 325 (M + H)$^+$, 269, 247.

(1′*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxopiperazine 2a. To a solution of **4** (10 g) in CH_2Cl_2 (20 mL), imidazole (46 mmol) then *tert*-butyldimethylsilyl chloride (46 mmol) were added. The solution was stirred overnight then a saturated aqueous solution of sodium carbonate (200 mL) was added. The organic phase was collected, the aqueous phase washed twice with Et_2O and the combined organic phases dried over sodium sulfate. Evaporation of the solvent furnished an oil sufficiently pure to be directly used for the next step and that was dissolved in a solution of CH_2Cl_2 (200 mL) and *N*-methylmorpholine (100 mL), then slowly poured into a CH_2Cl_2 solution of bromoacetic anhydride prepared by mixing bromoacetic acid (91 mmol) and DCC (45 mmol). The reaction was stirred overnight then extracted twice with a saturated solution of sodium carbonate (500 mL) then twice with a 1 N HCl aqueous solution (500 mL) and finally with brine (500 mL). The organic phase was dried over magnesium sulfate concentrated *in vacuo* to afford a yellow oil whose ^{1}H NMR spectrum displayed signals for an equimolar population of rotamers (MS *m*/*z* 581 (M + Na)$^+$, 559).

To a solution of the previously obtained yellow oil in dry THF (300 mL), at 0 °C, a 80% oily suspension of NaH (3 eq.) was added. After 5 h of stirring, the reaction was quenched by careful addition of H_2O (300 mL) and the solution was extracted with EtOAc (3 × 400 mL). The combined organic phases were washed with H_2O then dried ($MgSO_4$) and concentrated to afford a white powder, in 70% yield, that generally did not need the use of further purification procedures. $[\alpha]_D^{17}$ −1 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3125, 1729 (CO), 1651 (CO), 1248, 1159; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (5H, m, Ar), 4.84 (1H, m, CH), 4.70 (1H, d, *J* = 11.9, CH_2CO), 4.64 (1H, d, *J* = 11.9, CH_2CO), 4.25 (2H, s, CH_2Ar), 3.98 (2H, m, CH_2O), 3.90 (1H, dd, *J* = 10.2, 7.2, CH_2O), 3.81 (1H, dd, *J* = 10.2, 5.0, CH_2O), 3.73 (2H, m, CH_2N), 3.62 (2H, m, CH_2N), 1.64 (9H, s, $OC(CH_3)_3$), 1.04 (9H, s, $SiC(CH_3)_3$), 0.21 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 153.2 (CO), 138.6, 128.9, 128.3, 128.1 (Ar), 81.3 (O*C*$(CH_3)_3$), 73.5 (CH_2Ar), 68.0 (CH_2O), 61.7 (CH_2O), 55.4 (CH), 49.2 (CH_2N), 44.1 (CH_2N), 43.3 (CH_2CO), 28.7 ($OC(CH_3)$, 26.2 ($SiC(CH_3)_3$), 18.0 (Si*C*$(CH_3)_3$), 2.3 ($Si(CH_3)_2$); MS *m*/*z* 501 (M + Na)$^+$, 393, 301, 236, 220; HRMS (ES) (M + Na)$^+$ calc. for $C_{25}H_{42}N_2O_5SiNa$ 501.2761, found 501.2762.

(1′*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-oxopiperazine 2b. To a solution of **2a** (5 g) in MeOH (100 mL) placed under a nitrogen atmosphere, 0.1 g of 10% Pd–C was added. Nitrogen was slowly replaced by hydrogen and the suspension was stirred for 48 h then filtered over celite and concentrated *in vacuo*, affording **2b** as a white solid (3.7 g, 90% yield). $[\alpha]_D^{17}$ −3 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3410, 2945, 1707 (CO), 1641 (CO), 1259, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (1H, m, CH), 4.02 (2H, m, CH_2O), 3.82 (1H, m, CH_2CO), 3.75 (2H, m, CH_2N), 3.55 (4H, m, CH_2O, CH_2N), 3.41 (1H, m, OH), 1.41 (9H, s, $OC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.00 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 154.2 (CO), 81.3 (O*C*$(CH_3)_3$), 61.7 (OCH_2), 61.2 (NCH_2), 60.6 ($HOCH_2$), 59.8 (CH), 45.3 (NCH_2), 34.2 (CO*C*H_2), 28.7 (OC(*C*$H_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 18.4 (Si*C*$(CH_3)_3$), 1.1 ($Si(CH_3)_2$); MS *m*/*z* 411 (M + Na)$^+$, 355, 297, 236, 179; HRMS calc. for (M + Na)$^+$ 411.2291, found 411.2294.

(1′*R*)-4-(*tert*-Butoxycarbonyl)-1-(1′-phenylmethyloxymethyl-2′-hydroxyethyl)-2-oxopiperazine 2c. To a solution of **2a** (5 g) in THF (130 mL), a 1M solution of Bu_4NF in THF (20 mL) was added. The solution was stirred overnight then 200 mL of H_2O were added. The solution was extracted twice with EtOAc (250 mL) and the combined organic phases washed with H_2O. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*, affording **2c** in quantitative yield. $[\alpha]_D^{17}$ +5 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3114, 2982, 2928, 1695 (CO), 1653 (CO), 1417, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3 (5H, m, Ar), 4.53 (1H, d, *J* = 12.7, CH_2CO), 4.49 (1H, d, *J* = 12.7, CH_2CO), 4.37 (1H, m, CH), 4.08 (2H, m, CH_2O), 3.85 (2H, s, CH_2Ar), 3.79 (1H, m, CH_2O), 3.69 (1H, m, CH_2O), 3.58 (2H, m, CH_2N), 3.50 (1H, m, CH_2N), 3.45 (1H, m, CH_2N), 3.02 (1H, m, OH), 1.48 (9H, s, $OC(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 153.3 (CO), 138.0, 128.9, 128.3, 128.1 (Ar), 81.4 (O*C*$(CH_3)_3$), 73.8 (*C*H_2Ar), 68.3 (CH_2N), 62.1 (CH_2OH), 60.8 (CH), 49.2 (CH_2O), 47.8 (CH_2CO), 40.3 (CH_2N), 28.7 (OC(*C*$H_3)_3$); MS *m*/*z* 387 (M + Na)$^+$, 242, 186; HRMS calc. for (M + Na)$^+$ 387.1896, found 387.1898.

(1′*S*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy] ethyl]-3-substituted-2-oxopiperazine (5). A solution of diisopropylamine (1 mL) in THF (20 mL) was cooled at −70 °C and kept under nitrogen atmosphere. A 1.6 M solution of *n*-BuLi in hexane (4 mL) was slowly added to the cold solution and the mixture was stirred for 15 min. A solution of **2b** (2.1 mmol) and HMPA (6.3 mmol) in THF was slowly poured into the cold solution and stirred for 15 min. A solution of electrophile (6.3 mmol) in THF was added and the mixture was stirred for 5 h at −50 °C, then for 30 min at −15 °C. The reaction was quenched by addition of an aqueous saturated solution of NH_4Cl (80 mL) then extracted three times with CH_2Cl_2. The combined organic phases were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Alkylation products were finally purified by column chromatography using cyclohexane–EtOAc (1 : 20) as an eluent.

(1′*S*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy] ethyl]-3-methyl-2-oxopiperazine 5a. Obtained in 75% yield using iodomethane as electrophile. $[\alpha]_D^{17}$ −53 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3334 (OH), 1752, 1640 (CO), 1250, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (1H, q, *J* = 6.9, C*H*CH_3), 4.11 (1H, m, CH), 3.89 (2H, m, CH_2OH), 3.79 (2H, m, CH_2O), 3.77 (1H, m, CH_2N), 3.53 (1H, m, CH_2N), 3.36 (1H, m, CH_2N), 3.19 (1H, m, CH_2N), 2.27 (1H, m, OH), 1.43 (9H, s, $OC(CH_3)_3$), 1.39 (3H, d, *J* = 6.9, CHCH_3), 0.84 (9H, s, $SiC(CH_3)_3$), 0.01 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 155.1 (CO), 80.9 (O*C*$(CH_3)_3$), 61.8 (CH_2O), 61.7 (CH_2OH), 60.7 (*C*HCH_3), 46.2 (CH_2N), 45.1 (CH_2N), 44.2(CHCO), 28.7 (OC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 18.4 (Si*C*$(CH_3)_3$), 18.1 (CHCH_3), −4.2 ($Si(CH_3)_2$); MS *m*/*z* 425 (M + Na)$^+$, 369, 325; HRMS calc. for (M + Na)$^+$ 425.2448, found 425.2461.

(1′*S*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy] ethyl]-3-phenylmethyl-2-oxopiperazine (5b). Obtained in 82% yield using benzyl bromide as electrophile. $[\alpha]_D^{20}$ −18 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3402 (OH), 1712, 1653 (CO), 1421, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4–7.1 (5H, m, Ar), 4.57 (1H, m, CHCO), 3.95 (1H, m, CH), 3.90 (1H, m, CH_2OH), 3.79 (2H, m, CH_2O), 3.72 (1H, m, CH_2OH), 3.45 (1H, m, CH_2N), 3.41 (1H, m, OH), 3.16 (2H, m, CH_2Ar), 3.08 (2H, m, N), 2.71 (1H, m, CH_2N), 1.40 (9H, s, $OC(CH_3)_3$), 0.79 (9H, s, $SiC(CH_3)_3$), 0.00 (6H, s, 6H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 153.9 (CO), 137.9, 130.2, 128.8, 127.1 (Ar), 80.9 (O*C*$(CH_3)_3$), 62.0 (CH_2OH), 61.8 (CH), 60.7 (CH_2O), 59.4 (*C*HCO), 47.2 (CH_2N), 38.1 (CH_2N), 30.5 (OC(*C*$H_3)_3$), 26.1 (SiC(*C*$H_3)_3$), 18.5 (Si*C*$(CH_3)_3$), −1.1 ($Si(CH_3)_2$); MS *m*/*z* 501 (M + Na)$^+$, 475, 445, 411, 255; HRMS calc. for (M + Na)$^+$ 501.2761, found 501.2737.

(1′*S*,3*R*)-3-Allyl-4-(*tert*-butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethyl silyl)oxy] ethyl]-2-oxopiperazine (5c). Obtained in 72% yield using allyl bromide as electrophile. $[\alpha]_D^{17}$ −42 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3422 (OH), 3086, 1707, 1637 (CO), 1255, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (1H, ddd, J = 17.1, 10.1, 4.4, CH olef), 5.06 (1H, d, J = 17.1, CH_2 olef), 5.03 (1H, d, J = 10.1 CH_2 olef), 4.51 (1H, m, CHCO), 4.18 (1H, m, CH), 4.05 (1H, m, CH_2N), 3.90 (2H, m, CH_2O), 3.81 (1H, br m, OH), 3.75 (1H, m, CH_2O), 3.73 (2H, m, CH_2O), 3.71 (1H, m, CH_2N), 3.50 (1H, m, CH_2N), 3.37 (1H, m CH_2N), 3.18 (1H, m, CH_2N), 2.64 (1H, ddd, J = 10.7, 7.7, 4.4, CH_2), 2.54 (1H, m, CH_2), 1.41 (9H, s OC$(CH_3)_3$), 0.83 (9H, s, SiC$(CH_3)_3$), 0.00 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 154.0 (CO), 134.4 (CH olef), 118.3 (CH_2 olef), 80.9 (O*C*$(CH_3)_3$), 61.8 (CH_2O), 61.3 (CH_2O), 60.5 (*C*HCO), 57.4 (CH), 45.9 (CH_2N), 37.7 (CH_2), 28.6 (OC$(CH_3)_3$), 27.2 (CH_2N), 26.1 (SiC$(CH_3)_3$), 18.4 (Si*C*$(CH_3)_3$), −5.3 (Si$(CH_3)_2$); MS *m*/*z* 451 (M + Na)$^+$, 395, 301; HRMS calc. for (M + Na)$^+$ 451.2604, found 451.2602.

(1′*S*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-[(*tert*-butyldimethylsilyl)oxy] ethyl]-3-propyl-2-oxopiperazine (5d). Obtained in 77% yield using 1-bromopropane as electrophile. $[\alpha]_D^{17}$ +43 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3438, 1760, 1632 (CO), 1259, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, m, C*H*Pr), 4.21 (1H, m, CH), 3.99 (1H, m, CH_2O), 3.80 (1H, m, CH_2O), 3.70 (2H, m, CH_2O), 3.61 (1H, m, CH_2N), 3.38 (1H, m, CH_2N), 3.28 (1H, m, CH_2N), 3.12 (1H, m, CH_2N), 2.01 (1H, m, CH_2C), 1.61 (1H, m, CH_2C), 1.41 (9H, s, OC$(CH_3)_3$), 1.31 (2H, m, CH_2CH_3), 0.88 (3H, t, J = 6, CH_3), 0.86 (9H, s, SiC$(CH_3)_3$), 0.00 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 154.7 (CO), 81.4 (O*C*$(CH_3)_3$), 61.3 (CH_2O), 61.1 (CH_2O), 60.0 (*C*HCO), 57.1 (CH), 45.9 (CH_2N), 33.4 (CH_2), 29.3 (CH_2), 27.9 (SiC$(CH_3)_3$), 26.0 (SiC$(CH_3)_3$), 20.4 (CH_2), 19.4 (Si*C*$(CH_3)_3$), 14.7 (CHCH_3), −4.2 (Si$(CH_3)_2$); MS *m*/*z* 453 (M + Na)$^+$, 397, 369, 353; HRMS calc. for (M + Na)$^+$ 453.2761, found 453.2782.

(1′*R*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-hydroxyethyl]-3-phenylmethyl-2-oxopiperazine 6. To a solution of **5b** (1 mmol) in dry THF (5 mL), NaH (3 mmol) was slowly added at 0 °C. The solution was stirred for 15 min then benzyl bromide (1.1 mmol) was added. The solution was stirred for 6 h then H_2O (3 mL) was added. The solution was extracted twice with CH_2Cl_2 (15 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. A slightly orange oil of diprotected derivative was quantitatively obtained. This was dissolved in dry THF (1.3 mL) and 2 mL of a 1 M solution of *n*-Bu_4NF in THF added. The solution was stirred at rt overnight, then 20 mL of H_2O was poured into the solution. After extraction (CH_2Cl_2 30mL) of the aqueous phase, the dried ($MgSO_4$) and concentrated *in vacuo* organic phases furnish **6** as an orange oil in quantitative yield. $[\alpha]_D^{17}$ −7 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3360 (OH), 2979, 2866, 1687 (CO), 1642, 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5–7.2 (10H, m, Ar), 4.71 (1H, m, C*H*$(CH_2)_2$), 4.40 (1H, d, J = 12, OCH_2Ar), 4.36 (1H, d, J = 12, OCH_2Ar), 4.31 (1H, t, J = 6.5, CHCO),4.10 (1H, br t, J = 6.8, OH), 3.70 (2H, d, J = 6.5, CH_2Ar), 3.55 (2H, m, J = 6.5, CH_2O), 3.34 (2H, m, CH_2O), 3.32 (2H, m, CH_2N), 3.09 (2H, m, CH_2N), 2.96 (2H, m, CH_2N), 1.2 (9H, s, OC$(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 154.6 (CO), 138.4, 137.5, 130.8, 129.8, 129.4, 128.9, 128.8, 128.1 (Ar), 81.7 (O*C*$(CH_3)_3$), 71.6 (OCH_2Ar), 67.1 (OCH_2), 62.6 (OCH_2), 62.4 (CH*C*H_2Ar), 56.3 (CH), 55.3 (*C*HCO), 45.2 (CH_2N), 38.0 (CH_2N), 27.5 (OC$(CH_3)_3$); MS *m*/*z* 477 (M + Na)$^+$, 417, 381, 367, 342, 239, 234, 121.

(2*S*)-((3′*R*)-4′-(*tert*-Butoxycarbonyl)-3′-phenylmethyl-2′-oxo-piperazin-1′-yl)-3-hydroxypropanoic acid 7. To a solution of **6** (0.3 mmol) in acetone (1.5 mL) at 0 °C, Jones' reagent (0.45 mL) was slowly added. The solution was stirred for 30 min then *i*-propanol (6 mL) was added and the solution stirred for 30 min. The solution was extracted three times with EtOAc (8 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated affording an orange oil that was rapidly and directly used in the next step without purification. The previously obtained orange oil was dissolved in MeOH under a nitrogen atmosphere and Pd–C 10% was carefully added. The nitrogen atmosphere was replaced by a hydrogen atmosphere and the suspension was stirred overnight. The suspension was filtered over celite and the solution was concentrated *in vacuo*. Final purification was achieved by means of SiO_2 chromatography using cyclohexane–EtOAc (1 : 2) as an eluent. $[\alpha]_D^{17}$ −10 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3352 (OH), 1758, 1684 (CO), 1156; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.3 (2H, s, OH), 7.0–7.3 (5H, m, Ar), 4.84 (1H, m, C*H*COOH), 4.74 (1H, m, CHCO), 4.12 (2H, m, CH_2O), 3.99 (1H, m, CH_2N), 3.53 (1H, m, CH_2N), 3.18 (2H, m, CH_2Ar), 2.92 (1H, m, CH_2N), 2.78 (1H, m, CH_2N), 1.3 (9H, br s, OC$(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.8, 154.2 (CO), 137.1, 133.7, 131.5, 127.4 (Ar), 81.4 (OC$(CH_3)_3$), 61.4 (CH_2Ar), 61.0 (CH_2O), 59.0 (*C*HCOOH), 53.5 (*C*HCO), 46.1 (CH_2N), 41.8 (CH_2N), 38.2 (OC$(CH_3)_3$); MS *m*/*z* 378 (M + H)$^+$, 377, 349, 257, 171; HRMS calc. for M$^+$ 377.1713, found 377.1717.

(2*R*)-((3′*R*)-4′-(*tert*-Butoxycarbonyl)-3′-phenylmethyl-2′-oxo-piperazin-1′-yl)-3-hydroxypropanoic acid 8. To a solution of **6** (0.9 mmol) in pyridine (10 mL) at 0 °C, benzoyl chloride (0.1 mL) was slowly added. The solution was stirred for 3 h at rt. Then 20 mL of 2 N aqueous HCl was added into the solution that was extracted with Et_2OAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated. The resulting oil was oxidized then hydrogenolyzed using the conditions depicted for the preparation of **7**. Final saponification was carried out in a 8% aqueous solution of NaOH. The solution was stirred for 2 h then concentrated *in vacuo*. The obtained residue was dissolved in H_2O (20 mL) and the solution was extracted twice with EtOAc (20 mL). The combined organic phases were dried and concentrated, affording **8** as an oil (90% yield from **6**).

$[\alpha]_D^{17}$ −4 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3354, 2952, 1758, 1714, 1684, 1156; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.3 (2H, br s, OH), 7.0–7.3 (5H, m, Ar), 4.70 (1H, m, C*H*COOH), 4.58 (1H, m, CHCO), 4.05 (1H, m, CH_2N), 3.93 (2H, m, CH_2O), 3.33 (1H, m, CH_2N), 2.90 (2H, m, CH_2Ar), 2.79 (1H, m, CH_2N), 2.57 (1H, m, CH_2N), 1.3 (9H, br s, OC$(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.2, 154.2 (CO), 137.5, 134.0, 130.6, 128.8 (Ar), 81.2 ((O*C*$(CH_3)_3$), 61.8 (*C*H_2Ar), 61.1 (CH_2OH), 59.3 (*C*HCOOH), 52.6 (*C*HCO), 46.4 (CH_2N), 41.8 (CH_2N), 38.3 ((OC$(CH_3)_3$); MS *m*/*z* 377 (M)$^+$, 283, 277; HRMS calc. for M$^+$ 377.1713, found 377.1701.

(1′*R*,3*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-hydroxy ethyl]-3-substituted-2-oxopiperazine 9. Compound **9** was prepared from **2c** using the procedure reported for the preparation of **5**.

(1′*R*,3*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-hydroxyethyl]-3-methyl-2-oxopiperazine 9a. Obtained in 89% yield using iodomethane as electrophile. $[\alpha]_D^{17}$ +48 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3220 (OH), 2964, 1704, 1655 (CO), 1183; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (5H, m, Ar), 4.44 (1H, d, 1H, J = 11.9, CH_2Ar), 4.40 (1H, q, J = 7.0, CHCO), 4.38 (1H, d, J = 11.9, CH_2Ar), 3.85 (2H, m, CH_2O), 3.70 (2H, m, CH_2OH), 3.65 (1H, m, CH_2N), 3.55 (1H, m, CH_2N), 3.49 (1H, m, CH$(CH_2)_2$), 3.43 (1H, m, CH_2N), 3.26 (1H, m, CH_2N), 3.10 (1H, br m, OH), 1.37 (9H, s, OC$(CH_3)_3$), 1.32 (3H, d, J = 7.0, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 153.9 (CO), 138.2, 128.8, 128.2, 127.4 (Ar), 80.9 (O*C*$(CH_3)_3$), 73.5 (*C*H_2Ar), 68.4 (CH_2N), 61.4 (CH_2OH), 57.5 ($CHCH_3$), 53.7 (CH_2O), 45.1 (CH_2N), 45.0 (*C*HCO), 28.7 (OC$(CH_3)_3$), 18.1 (OC$(CH_3)_3$); MS *m*/*z* 401 (M + Na)$^+$, 345, 301, 184; HRMS calc. for (M + Na)$^+$ 401.2052, found 401.2041.

(1′*R*,3*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-[hydroxyethyl]-3-phenylmethyl-2-oxopiperazine 9b. Obtained in 80% yield using benzyl bromide as electrophile. $[\alpha]_D^{17}$ +16 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3364 (OH), 2974, 1687, 1641 (CO), 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.0–7.3 (10H, m, Ar), 4.60 (1H, m, C*H*(CH_2)$_2$), 4.44 (1H, d, *J* = 11.6, ArC*H*$_2$O), 4.40 (1H, d, *J* = 11.6, ArC*H*$_2$O), 4.37 (1H, t, *J* = 8.3, CHCO)), 3.89 (1H, br m, OH), 3.71 (2H, d, *J* = 8.3, CHC*H*$_2$Ar), 3.62 (2H, m, CH_2OH), 3.51 (2H, m, CH_2O), 3.32 (2H, m, CH_2N), 3.16 (1H, m, CH_2N), 3.10 (1H, m, CH_2N), 3.00 (1H, m, CH_2N), 1.20 (9H, s, OC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 154.0 (CO), 138.2, 130.3, 129.4, 128.8, 128.2, 128.0, 127.1 (Ar), 80.9 (O*C*(CH_3)$_{3)}$, 73.6 (CH_2O), 68.6 (CH_2O), 61.6 (CH_2OH), 61.5 (CH*C*H$_2$Ar), 59.3 (CH(CH_2)$_2$), 58.1 (CHCO), 45.1 (CH_2N), 38.3 (CH_2N), 28.5 (OC(*C*H$_3$); MS *m*/*z* 477 (M + Na)$^+$, 421, 377, 345; HRMS calc. for (M + Na)$^+$ 477.2349, found 477.2343.

(1′*R*,3*S*)-3-Allyl-4-(*tert*-butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine 9c. Obtained in 84% yield using allyl bromide as electrophile. $[\alpha]_D^{17}$ +38 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3114 (OH), 2972, 1721, 1655 (CO), 1172; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (5H, m, Ar), 5.74 (1H, m, CH olef), 4.98 (1H, dd, *J* = 17.2, 0.5, C*H*$_2$ olef), 4.93 (1H, dd, *J* = 10.0, 0.5, C*H*$_2$ olef), 4.63 (2H, m, CHCO), 4.09 (1H, m, CH(CH_2)$_2$), 3.95 (1H, m, C*H*$_2$N), 3.79 (1H, m, C*H*$_2$O), 3.75 (1H, m, C*H*$_2$O), 3.70 (2H, m, CH_2OH), 3.51 (1H, m, C*H*$_2$N), 3.48 (1H, m, C*H*$_2$N), 3.04 (2H, m, CH_2N), 2.59 (1H, m, CHC*H*$_2$CH), 2.48 (1H, m, CHC*H*$_2$CH), 1.39 (9H, s, OC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 153.8 (CO), 134.2 (*C*H = CH_2), 138.3, 129.3, 128.2, 127.5 (Ar), 118.2 (CH = *C*H$_2$), 81.3 (O*C*(CH_3)$_3$), 61.8 (OCH_2), 60.2 ($HOCH_2$), 57.4 (*C*HCO), 56.3 (CH(CH_2)$_2$), 45.6 (NCH_2), 38.4 (CH*C*H$_2$CH), 29.2 (OC(*C*H$_3$)$_3$), 27.6 (NCH_2); MS *m*/*z* 427 (M + Na)$^+$, 345, 301, 154; HRMS calc. for (M + Na)$^+$ 404.2311, found 404.2297.

(1′*R*,3*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-phenylmethyloxymethyl-2′-hydroxyethyl]-3-propyl-2-oxopiperazine 9d. Obtained in 80% yield using 1-bromopropane as electrophile. $[\alpha]_D^{17}$ +45 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 3114 (OH), 1650 (CO), 1164 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.1–7.4 (5H, m, Ar), 4.67 (2H, m, CHCO), 4.11 (1H,m, C*H*(CH_2)$_2$), 4.01 (2H, s, CH_2Ar), 3.87 (1H, m, CH_2O), 3.71 (1H, m, CH_2O), 3.58 (2H, m, CH_2OH), 3.50 (1H, m, CH_2N), 3.24 (1H, m, CH_2N), 3.02 (2H, m, CH_2N), 1.87 (1H, m, CHC*H*$_2$$CH_2$), 1.48 (2H, m, CHC*H*$_2$$CH_2$), 1.42 (9H, s, OC($CH_3$)$_3$), 1.24 (2H, m, C*H*$_2$$CH_3$), 0.78 (3H, t, *J* = 6, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 154.5 (CO), 139.0, 129.6, 129.1, 128.2 (Ar), 82.4 (O*C*(CH_3)$_3$), 61.8 (CH_2O), 60.0 (CH_2OH), 56.9 (CHCO), 55.8 (*C*H(CH_2)$_2$), 45.9 (CH_2N), 33.2 (CH_2), 29.1 (OC(*C*H$_3$)$_3$), 28.4 (CH_2N), 21.3 (CH_2CH_3), 14.5 (CH_3); MS *m*/*z* 429 (M + Na)$^+$, 397, 345, 154; HRMS calc. for (M + Na)$^+$ 429.2365, found 429.2339.

(2*S*)-((3′*S*)-4′-(*tert*-Butoxycarbonyl)-3′-phenylmethyl-2′-oxopiperazin-1′-yl)-3-hydroxypropanoic acid 10. Oxidation of **9** performed in the conditions depicted for the preparation of **7** followed by hydrogenolysis afforded **10** as a white solid in 74% yield (2 steps).

$[\alpha]_D^{17}$ +5 (*c* 0.1; EtOH). For other characteristics see **8**.

(2*R*)-((3′*S*)-4′-(*tert*-Butoxycarbonyl)-3′-phenylmethyl-2′-oxopiperazin-1′-yl)-3-hydroxypropanoic acid 11. The procedure reported for the preparation of **8** was repeated using **9** as starting material. Compound **11** was obtained in 62% yield.

$[\alpha]_D^{17}$ +10 (*c* 0.1; EtOH). For other characteristics see **7**.

((3′*R*)-4′-(*tert*-Butoxycarbonyl)-3′-propyl-2′-oxopiperazin-1′-yl)-3-acetic acid 12. Deprotection of **5d** was carried out using the procedure depicted for the preparation of **2c**. Oxidation/decarboxylation was achieved using Jones' reagent and according to the procedure depicted for the preparation of **7**, followed by heating at 90 °C for 2 h. Reaction work up was as indicated for the preparation of **7**. Compound **12** was obtained in 62% yield from **5d**.

$[\alpha]_D^{17}$ −119 (*c* 0.1; EtOH); IR ν_{max}/cm^{-1} 1855, 1680, 1637, 1157; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (1H, br s, OH), 5.23 (2H, m, CH_2CO), 3.55 (1H, m, CH_2N), 3.48 (1H, m, CHCO), 3.38 (2H, m, CH_2N), 2.61 (1H, m, C*H*$_2$N), 2.35 (1H, m, C*H*$_2$N), 1.93 (1H, m, C*H*$_2$CH), 1.53 (1H, m, C*H*$_2$CH), 1.36 (2H, m, C*H*$_2$$CH_3$), 1.26 (9H, s, OC($CH_3$)$_3$), 0.89 (3H, t, *J* = 6, C*H*$_2$$CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 168.4, 155.1 (CO), 79.2 (O*C*(CH_3)$_3$), 68.4 (CH_2COOH), 59.1 (*C*HCO), 46.6 (CH_2N), 33.4 (CH*C*H$_2$), 28.0 (CH_2N), 25.4 (OC(*C*H$_3$)$_3$), 21.5 (*C*H$_2$$CH_3$), 14.0 ($CH_2$*C*H$_3$); MS *m*/*z* 323 (M + Na)$^+$ 263, 215; HRMS calc. for (M + Na)$^+$ 323.1583, found 323.1587.

((3′*S*)-4′-(*tert*-Butoxycarbonyl)-3′-propyl-2′-oxopiperazin-1′-yl)-3-acetic acid 13. Hydrogenolysis of **9d** was carried out using the conditions used for the preparation of **2b**. Oxidation/decarboxylation was achieved using Jones' reagent and according to the procedure depicted for the preparation of **7**, followed by heating at 90 °C for 2 h. Reaction work up was as indicated for the preparation of **7**. Compound **13** was obtained in 53% yield (from **9d**).

$[\alpha]_D^{17}$ +113 (*c* 0.1; EtOH). For other characteristics see **12**.

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