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New efficient enantioselective synthesis of 2-oxopiperazines: a practical access to chiral 3-substituted 2-oxopiperazines

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ABSTRACT

The development of efficient and stereoselective methods to produce 1,4-disubstituted-2-oxopiperazine in enantiomerically pure form, from a readily available starting material is crucial. Herein, we report a reduction modification to our previously described synthesis of 1,4-disubstituted-2-oxopiperazine and also two original shortly accessed pathways. These new pathways can be routinely performed on a multigram scale and should rapidly find a place in the preparation of the 3-substituted-2-oxopiperazine diastereomers. Stereoselective alkylation of 1,4-disubstituted-2-oxopiperazine led to the corresponding (3*S*)-diastereomer or (3*R*)-diastereomer from the corresponding 2-oxopiperazine enantiomer with the chiral inductor substituted at the N_1 (1^*) position, respectively, in good yield.

1. Introduction

Substituted oxopiperazines are highly interesting scaffolds that are found in a widespread variety of bioactive drugs used in central nervous system therapies.[1] Moreover, these azalactams have significant potential as cancer chemotherapeutic agents,[2,3] and are promising candidates for the treatment and prevention of diverse diseases such as rheumatoid arthritis,[4] depression,[5] sexual disfunctions[6] or venous and arterial thrombosis.[7] In some cases, the oxopiperazine core is used as a conformationally constrained peptidomimetic in which the N_i and N_{i+1} positions of the peptide backbone fragments are linked by an ethylene bridge. These peptidomimetics have been found to stabilize inverse γ-turn in small peptides[8] and allow biological property changes occasionally enhancing affinity, specificity and enzymatic stability. Amongst all of the useful azalactams, 1,3,4-trisubstituted-2-oxopiperazines, which possess two stereogenic centres, one intracyclic (C_3) and one extracyclic (C_1'), are of particular interest as medicinal chemistry tools. Many syntheses of diastereomerically pure 1,3,4-trisubstituted-2-oxopiperazine have been reported, such as the lactamization of linear *N*,*N*′-bispeptides,[9–11] N_4–C_5 bond formation[12] or N_1–C_6 bond formation.[13] However, in these methods, the whole synthesis has to be repeated if access to diastereomers is desired. In the majority of these cases, in absence of an asymmetric synthesis strategy, the final stereochemistry is dependant on the starting material configuration. Recently, several asymmetric syntheses of 3,5-disubstituted 2-oxopiperazine have been reported from the stereoselective alkylation of 2-oxopiperazine using a chiral auxiliary appended to the C-5 atom.[14–16] Husson et al.[17,18] have also developed a regio- and stereoselective C_3-alkylation of 1,4-disubstituted-2-oxopiperazines using various electrophiles. Very high chiral induction (>95%) has been described using a chiral alcohol as L-Leucinol[17] or D-phenylglycinol[18b] appended to N_1. A rigid intermediate that mandates the 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.[17–19] Moreover, as the configuration of the 2-oxopiperazine 3-position is totally governed by the configuration of the chiral inductor, only one diastereomer is directly accessible. Thereafter, we have reported an original, versatile and diastereoselective method allowing, from a single precursor, the synthesis of four diastereoisomers, in which the choice of the C_3-substituent is not limited by the availability of the corresponding aminoacid.[20] Indeed, the selected key intermediate **1** is substituted at N_1 with a chirality inductor, whose 1′-configuration could be unambiguously achieved as desired (Scheme 1). Indeed, these two hydroxymethyl potentially chiral inductors are selectively protected, at the 1′-position, by two orthogonal protective groups such as a benzyl group or *tert*-butyldimethylsilyl. A selective deprotection, Bu_4NF treatment or hydrogenolysis, of one of these two alcohols at C_1' followed by a diastereoselective alkylation leads to the two desired enantiomers (3*S*) and (3*R*).

Herein, we report a reduction modification in our previously described synthesis of 1,4-disubstituted-2-oxopiperazine **1** and also two new original shortly accessed pathways to 1,4-disubstituted-2-oxopiperazine **1**. Indeed, it was necessary to find another way due to low yields obtained in the reduction step of the key intermediate desilylated (1′*R*)-**2**. The development of efficient

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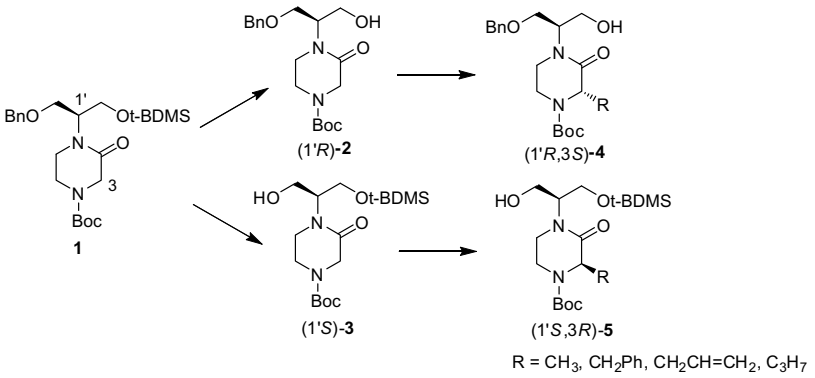


Scheme 1. Synthesis of two enantiomers (3*S*) and (3*R*) starting from the same key intermediate.

and stereoselective methods to produce such types of 1,4-disubstituted-2-oxopiperazine in enantiomerically pure form from readily available starting material is crucial. Our two short and original pathways can be performed on a multigram scale and should rapidly find a place in the preparation of the 3-substituted-2-oxopiperazine diastereomers (Scheme 1).

2. Results and discussion

In a previous work, we described the synthesis of 2-oxopiperazines (1′*R*)-**2** starting from *O*-benzyl-L-serine in an eight-step sequence with 49% overall yield (Scheme 2).[20] A peptide coupling reaction with glycine was followed by a concomitant amide and ester lithium aluminium hydride reduction to afford the aminoalcohol (*R*)-**7**. After four steps, (i) protection by use of *tert*-butyldimethylsilyl chloride; (ii) coupling with bromoacetic acid; (iii) cyclization with NaH and (iv) deprotection of silyl group, the 2-oxopiperazine (1′*R*)-**2** was obtained.

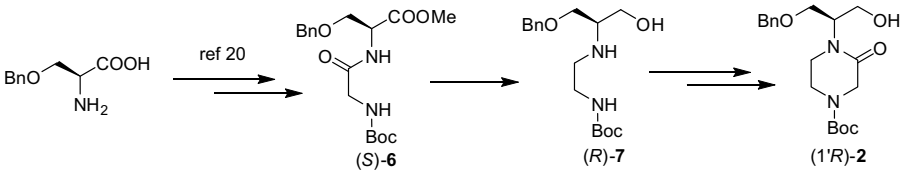
In a more recent work, many trials did not allow us to obtain (*R*)-**7** via the amide reduction with a satisfactory yield. To solve this problem, we used various experimental conditions for lithium aluminium hydride reduction such as (i) concentration and equivalent of aluminium powder; (ii) solvent and (iii) temperature (the most significant results are shown in Table 1). Unfortunately, despite extensive efforts, each experiment led to a mixture of three products (*R*)-**7**, (*R*)-**8** partially reduced and (*R*)-**9** Boc deprotected. The nature of the solvent seems to play an important role. Indeed, in THF, the amidoalcohol (*R*)-**8** is afforded exclusively (Table 1, entries 1 and 2). Whereas in Et_2O the desired compound (*R*)-**7** was obtained in 50% yield at best but always in mixture with (*R*)-**8** and/or (*R*)-**9** (Table 1, entries 3–5). The formation of (*R*)-**9** is observed with an increasing hydride equivalents (Table 1, entry 6). Smith and Williams have recently reported an identical reduction problem when they attempted to repeat the total synthesis of quinine previously originally published by Rabe and Kindler in 1918.[21] Thus, similar to Smith et al., we can speculate that the old lithium aluminium hydride powder that we had previously used could contain significant Al^{III} impurities to give good conversion of the amide substrate to the alcohol product without Boc deprotection.[20] Similar to Smith et al., we have used other reducing reagents, such as borane, DIBAL or silane catalyzed by ruthenium complex (Table 1, entries 7–10). Unfortunately, the best yield formation (42%) of (*R*)-**7** afforded other non-separable impurities, consequently not identified (Table 1, entry 8).

To avoid this crucial amide reduction step, the synthesis of (*R*)-**7** was performed in three steps via a thioamide reduction in 72% overall yield (Scheme 3). This method involves the conversion of amide (*S*)-**6** to thioamide (*S*)-**10** by using Lawesson's reagent.[22] Then, lithium aluminium reduction gives alcohol (*R*)-**11** in 99% yield. Finally, thioamide reduction using sodium borohydride in the presence of nickel chloride affords the aminoalcohol (*R*)-**7** in 93% yield.[23]

However, two additional steps are necessary to access to 2-oxopiperazine (1′*R*)-**2**, this modification of our previously described synthetic route is still so long. A shorter, more efficient route should be feasible. Thus, we have investigated a direct cyclization method, from dipeptide (*S*)-**6**, as previously mentioned by Pohlmann et al.[17] This method requires the use of the ethylene glycol bis-triflate as a dielectrophile (Scheme 4). Unfortunately, we were unable to obtain the desired cyclized product, but recovered a substantial amount of starting material and also some unidentified products. This is probably due to the fact that the hydrogen bound to the carbamate nitrogen is not acidic enough.

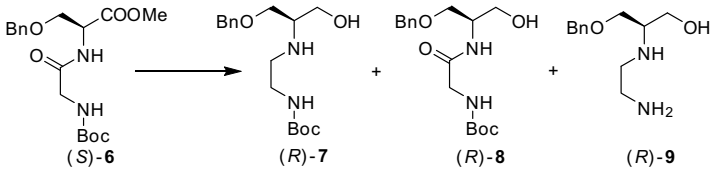
Due to the multi-steps and/or low yield of amide reduction, there remains a need for an easier and more practical method to obtain 1,4-disubstituted-2-oxopiperazine. We disclose now two new practical synthetic methods, which involves (i) the preparation of sulfonamide-2-oxopiperazine derivatives or; (ii) a regioselective ruthenium oxidation.

In this first synthesis strategy, to overcome the nitrogen acidity issue as described above, we decided to use a sulfonamide group instead of the carbamate group. The 2,4-dinitrosulfonamide group is also an excellent protective group due to its good stability under acidic, as well as basic conditions.[13,24] The sulfonamide dipeptide was prepared by the condensation of MeO-benzyl-L-serine **13** and *N*-nosyl-glycine **14** using 2-chloro-4,6-disubstituted-1,3,5-triazine (DMTMM) as a condensing agent (Scheme 5). The cyclization step was achieved under basic conditions in presence of an excess



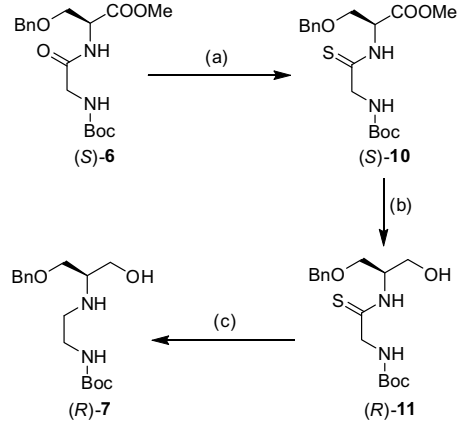
Scheme 2. First synthesis of 2-oxopiperazine (1′*R*)-**2**.

Table 1
Reduction of compound (*S*)-**6**

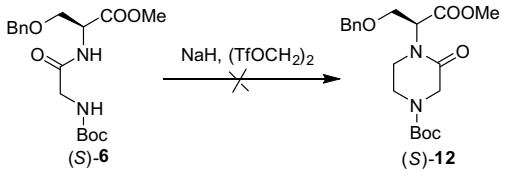


Entry	Reduction reagent (equiv)	Solvent	Temp. (°C)	Time (h)	Concentration[a]	Yield (%)		
						(*R*)-**7**	(*R*)-**8**	(*R*)-**9**
1	$LiAlH_4$ (2.1)	THF	Reflux	3	10	0	4	0
2	$LiAlH_4$ (4[b])	THF	TA	75	5	0	34	0
3	$LiAlH_4$ (2.1)	Et_2O	TA	5	5	35	60	0
4	$LiAlH_4$ (4[b])	Et_2O	TA	30	5	50	0	39
5	$LiAlH_4$ (2.1)	Et_2O	Reflux	3	10	10	60	0
6	$LiAlH_4$ (4.1)	Et_2O	Reflux	5	5	12	18	62
7	BH_3·DMS[c] (3)	THF	Reflux	6	6	41	36[d]	0
8	BH_3·DMS[c](4)	THF	Reflux	4	6	42[d]	0	0
9	DIBAL[e] (20)	THF	TA	24	10	16	60[d]	0
10	Et_3SiH, EtI[f] (4)	Toluene	110	4	1	10	80	0

[a] mL (solvent)/mmol ((*S*)-**6**).
[b] $t = 0$ h; addition of 1 equiv of reduction reagent, $t = 1$ h; three more equivalents are added.
[c] 2 M solution in THF.
[d] With non separable impurities.
[e] 1.5 M solution in toluene.
[f] Et_3SiH (4 equiv), $[RuCl_2(CO)_3]_2$ (1 mol %), EtI (5 mol %).



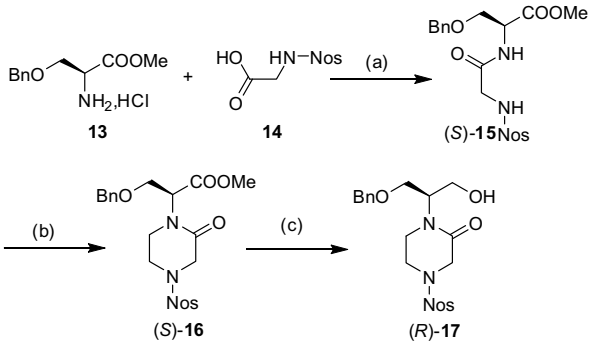
Scheme 3. Reduction of (*S*)-**6** via thioamide. Reagents and conditions: (a) Lawesson's reagent, THF, 78%; (b) $LiAlH_4$, THF, 99%; (c) $NiCl_2 \cdot 6H_2O/NaBH_4$, MeOH–THF, 93%.



Scheme 4. Assay of N,N-cyclization with ethylene glycol bis-triflate.

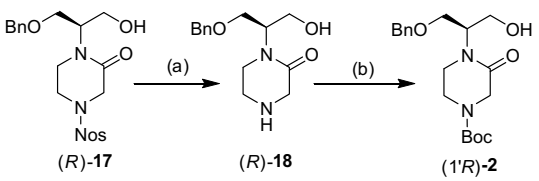
amount of 1,2-dibromoethane. Then, the expected 2-oxopiperazine $\{[\alpha]_D^{28} = -4$ (*c* 0.4, EtOH)} was isolated with an excellent yield (88%). Ester reduction of (*S*)-**16** with lithium borohydride afforded the ketoalcohol (*R*)-**17** $\{[\alpha]_D^{28} = +6$ (*c* 0.1, EtOH)} in 78% yield.

Two final steps are necessary to obtain the 2-oxopiperazine ring (1′*R*)-**2** (Scheme 5): (i) deprotection of the nosyl group to give (*R*)-**18** $\{[\alpha]_D^{20} = +25$ (*c* 0.05, EtOH)} and (ii) Boc protection of **18**

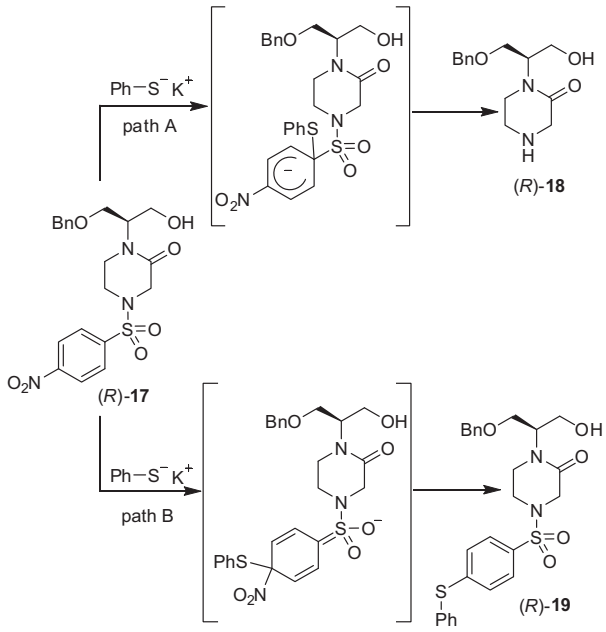


Scheme 5. Synthesis of 2-oxo piperazine (1′*R*)-**2** via a sulfonamide. Reagents and conditions: (a) DMTMM, NMM, THF, 77%; (b) dibromoethane, K_2CO_3, DMF, 88%; (c) $LiBH_4$, THF/MeOH, 78%.

to afford (1′*R*)-**2**. The Fukayama conditions were used initially for the deprotection of the nosyl group (PhSH, K_2CO_3, DMF, 23 °C); but only 40% of the desired product was isolated. The reaction between **17** and PhSH resulting in competitive N-deprotection to mainly give (60%) the 4-phenylthioether (*R*)-**19** (Scheme 6). The mechanism underlying the unsuccessful regioselectivity resulted in nucleophilic attack of the thiophenolate. Indeed, two pathways are possible: nucleophilic aromatic substitution via the Meisenmeisher complex (path A) or nucleophilic attack on the carbon



Scheme 6. Synthesis of 2-oxopiperazine (1′*R*)-*2* via a sulfonamide. Reagents and conditions: (a) method 1: PhSH, K_2CO_3, DMF, 23 °C, 40%; method 2: PhSH, K_2CO_3, AcCN/DMSO, 96%; (b) Boc_2O, MeOH, 100%.

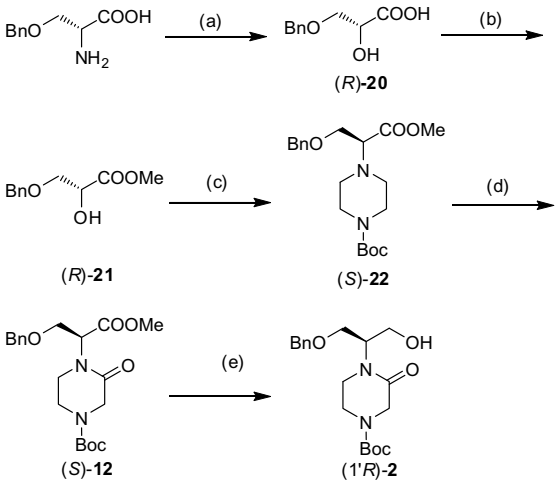


Scheme 7. Regioselectivity of the attack of the thiophenolate during the deprotection of the nosyl group.

bearing the nitro group (path B) to obtain the diphenylthioether (Scheme 7). This "path B" reaction had already been evoked by Wuts et al.[25] This lack of regioselectivity was overcome by heating at 50 °C a mixture of two solvents (AcCN/DMSO: 98:2) in which acetonitrile promotes the complete deprotection, whereas addition of DMSO shortens the reaction time. Under these conditions, the exclusive formation of the desired product (*R*)-**18** was observed in 96% yield.[26] The final step leads to the key 2-oxopiperazine (1′*R*)-**2** {$[\alpha]_D^{24} = +7$ (*c* 0.1, EtOH)} by carbamate formation with *tert*-butyldicarbonate.

This strategy of this synthesis gave 2-oxopiperazine in a seven-step sequence with 49% overall yield, starting from *O*-benzyl-L-serine, with excellent enantiomeric excesses (ees) of 95%. In this pathway, two steps in the (1′*R*,3*S*)-disubstituted-2-oxopiperazine synthesis can be gained by using the nosyl piperazine (*R*)-**17** instead of the boc compound (*R*)-**2** (not published).

In a continuation of our work regarding the structure–activity relationships of the segetalins,[27,28] there remains a need to reduce the number of steps to obtain the *N*-boc piperazine (1′*R*)-**2**. Thus, by taking note of the work of Watson et al.[29] and of Vetuschi et al.[30] we have developed a third strategy of synthesis starting from *O*-benzyl-D-serine (Scheme 8). The synthesis begins with a diazotation reaction in presence of sodium nitrite to give hydroxyacid (*R*)-**20** with retention of configuration {$[\alpha]_D^{22} = -2$ (*c* 0.5, EtOH)} which could be explained by the carbonyl assistance of the carboxylic group as shown in Figure 1. Thus, the two equilibrium oxiran cations are attacked by H_2O to afford the hydroxyacid (*R*)-**20**. Subsequently, this compound was converted to methyl ester (*R*)-**21** using methyl orthoformiate in acid conditions. The treatment of alcohol (*R*)-**21** with triflic anhydride, in toluene, furnished the corresponding triflate intermediate which immediately underwent an *N*-Boc-piperazine SN_2 substitution to afford piperazine (*S*)-**22** {$[\alpha]_D^{23} = -16$ (*c* 0.5, EtOH)} with a good yield of 98% and an ees superior to 95%. No epimerization at the stereogenic carbon was observed, as determined by chiral HPLC analysis, using the opposite enantiomer as a standard {(piperazine (*R*)-**22**: $[\alpha]_D^{23} = +16$ (*c* 0.5, EtOH)}. The next key step in our strategy involved a regioselective oxidation at the α-position to the nitrogen atom bearing the function methylester. Previous work was carried out by Petride



Scheme 8. Synthesis of 2-oxopiperazine (1′*R*)-**2** via regioselective ruthenium oxidation. Reagents and conditions: (a) $NaNO_2$, H_2SO_4 2 N, 90%; (b) $(MeO)_3CH$, MeOH, HCl 1 M, 87% ; (c) (i) Tf_2O, DIPEA, toluene; (ii) *N*-bocpiperazine, 98%; (d) $RuO_2{\cdot}xH_2O$, $NaIO_4$ 10% (H_2O), 58%; (e) $LiBH_4$, THF/MeOH, 73%; global yield: 32%.

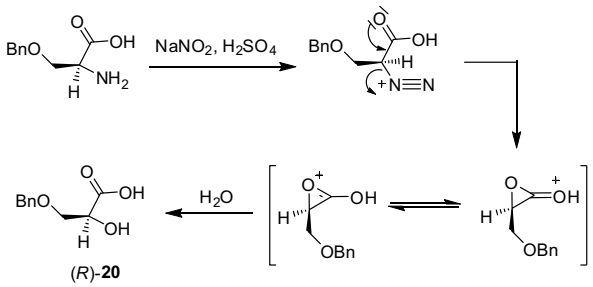
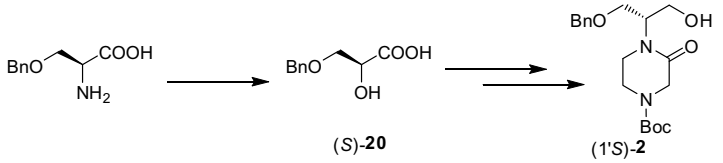


Figure 1. Synthesis of hydroxyacid (*R*)-**20** with retention of configuration.

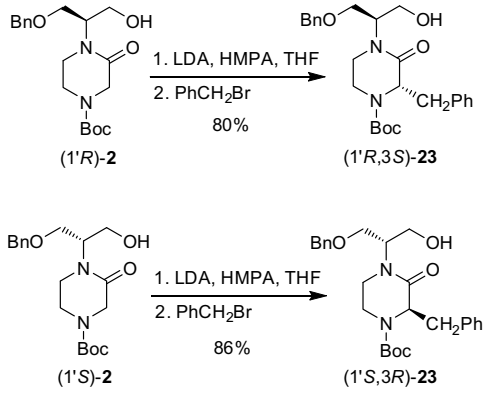
et al.[31] on a mechanistic study of the oxidation of 1,4-dibenzylpiperazine and 1-benzoyl-4-benzylpiperazine by ruthenium tetroxide. They proposed RuO_4 attack (generated in situ) at the endocyclic and exocyclic (benzylic) aminic N–α-C–H bonds resulting in endocyclic or exocyclic iminium cations. These react with water while further oxidation leads to various oxygenated derivatives. In our case, the regioselectivity could be obtained by two factors: (i) amides are less reactive than amines and (ii) there is no benzylic amine. In our synthesis, oxidation was accomplished in the presence of catalytic amounts of ruthenium dioxide in a double layer (ethyl acetate/water) with an additional oxidant, sodium periodate, to re-oxidize the transiently formed ruthenium dioxide and thus completing the catalytic cycle. This reaction led to the 2-oxopiperazine (*S*)-**12** {$[\alpha]_D^{23} = -12$ (*c* 0.3, EtOH)} with an excellent regioselectivity in 58% yield. The final ester reduction step of compound **12** gave the desired 2-oxopiperazine (1′*R*)-**2** in 73% yield. Thus, with only five steps, we are able to access to this first enantiomer with ees (>95%) in 32% global yield.

The same strategy of synthesis was used to obtain the 2-oxopiperazine (1′*S*)-**2** in a 40% global yield (Scheme 9). Also in this case, no epimerization has occurred, as observed by chiral HPLC analysis and, by determination of the specific rotation of compound (1′*S*)-**2**: $[\alpha]_D^{24} = -7$ (*c* 0.1, EtOH).This observed value was identically opposed to its enantiomer (1′*R*)-**2**.

Being able to prepare (1′*R*)-**2** and (1′*S*)-**2** in satisfactory yields and enantiomerically pure form, we then studied its C_3-substitution. Stereoselective alkylation of **2** was achieved in THF in the presence of HMPA as previously described,[20] using LDA as a strong



Scheme 9. Synthesis of 2-oxopiperazine (1′*S*)-**2**; global yield: 40%.



Scheme 10. Alkylation of 2-oxopiperazine (1′*R*)-**2** and (1′*S*)-**2**.

base and benzyl bromide as a model electrophile (Scheme 10). The (3*S*)-diastereomer **23** could then be prepared from (1′*R*)-**2** and the (3*R*)-diastereomer **23** from (1′*S*)-**2** respectively in 80% or 86% yield. Only one diastereomer was observed on the ^{1}H NMR spectrum (500 MHz) of the alkylation products demonstrating their high diastereomeric purity (above 96%).

3. Conclusion

In conclusion, we have proposed a new key-reduction amide pathway and as an alternative; we have developed two short practical syntheses of 1*, 2-oxopiperazine that allow the preparation of chiral 3-subsituted 2-oxopiperazine starting from inexpensive and readily starting materials. The reported methodology appears very suitable for the synthesis of a large number of piperazinone-based peptidomimetic. Studies directed at the utilization of these 3-substituted 2-oxopiperazines as chiral building blocks to obtain segetalins analogues are currently under investigation in our laboratory.

4. Experimental

4.1. General methods

THF and acetonitrile were dried by distillation from sodium-benzophenone. Diisopropylamine was dried by distillation from calcium hydride. DMF and DMSO were distilled. MeOH was dried by distillation using Magnesium–I_2. Column chromatography was performed on Kielselgel 60 (40–63 μm) ASTM (Merck). Reactions were analyzed on precoated Silica Gel 60 F_{254} plates (Merck) and the compounds were visualized with a UV lamp (254 nm) and by staining with phosphomolybdic acid (in EtOH). IR spectra were recorded on a Jasco FT/IR-4200 spectrometer. Optical rotations were measured with a Jasco P1010 polarimeter. Melting point (mp) was uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument. The residual signal of the solvent protons with the chemical shifts δ 7.27 ($CDCl_3$) or δ 2.54 (DMSO-d_6) was used as internal standards. *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.

4.2. Methyl (*2S*)-6-*tert*-butoxycarbonyl-2-benzyloxymethyl-3,6-diaza-4-thioxohexanoate (*S*)-10

To a solution of compound (*S*)-**6** (12 g, 33.8 mmol) in THF (180 mL), lawesson's reagent (14.6 g, 36.1 mmol) was added. The reaction mixture was stirred for 20 h at room temperature. The crude mixture was filtered on Celite® and the filtrate was evaporated under reduced pressure. The desired compound (*S*)-**10** (10.1 g, 78%), yellow oil, was achieved after silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 7:3). $[\alpha]_D^{28} = +32$ (*c* 0.3, EtOH). IR ν_{max}/cm^{-1}: 3342, 1742, 1718, 1520, 1162. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.82 (s, 3H), 3.94 (dd, 1H, ^2J = 10, ^3J = 2.7), 4.01 (dd, 1H, ^2J = 10, ^3J = 2.7), 4.26 (m, 2H), 4.51 (d, 1H, ^2J = 12.2), 4.59 (d, 1H, ^2J = 12.2), 5.37 (se, 1H), 6.9 (se, 1H), 7.30–7.40 (m, 5H), 8.9 (se, 1H). MS *m/z* 405 $[MNa]^+$ (100), 305, 236. HRMS calcd for $C_{18}H_{26}N_2NaO_5S$: 405.4636. Found: 405.4633.

4.3. (2*R*)-6-*tert*-Butoxycarbonyl-2-benzyloxymethyl-1-hydroxy-3,6-diazahexane-4-thione (*R*)-11

To a solution of ester (*S*)-**10** (11.0 g, 28.80 mmol) in THF (140 mL), at 0 °C, lithium aluminium hydride (2.13 g, 57.6 mmol) was added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by 1 M NaOH (4.65 mL) and then stirred for 1 h. After this time, H_2O (7 mL) was added and the suspension was stirred for a further 12 h. The precipitate was filtered and washed by Et_2O. The filtrate was dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure to yield the desired compound (10.2 g, 99%) as a yellow oil. $[\alpha]_D^{28} = +27$ (*c* 0.4, EtOH). IR ν_{max}/cm^{-1}: 3338, 1697, 1526, 1249, 1161. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.48 (s, 9H), 3.52 (se, 1H), 4.21 (m, 2H), 3.85 (m, 2H), 3.88 (m, 1H), 4.02 (dd, 1H, ^2J = 11.4, ^3J = 3.4), 4.60 (d, 1H, ^2J = 11.9), 4.65 (d, 1H, ^2J = 11.9), 4.80 (m, 1H), 5.30 (se, 1H), 7.40–7.50 (m, 5H), 8.70 (se, 1H). MS *m/z* 377 $[MNa]^+$ (100), 343.

4.4. (2*R*)-6-*tert*-Butoxycarbonyl-2-benzyloxymethyl-1-hydroxy-3,6-diazahexane (*R*)-7

To a solution of the thioamide (*R*)-**11** (10 g, 28.24 mmol) in a mixture of solvent THF/MeOH (136 mL, 1:3: v/v), hexahydrate nickel chloride (20 g, 98.8 mmol) was added. The reaction mixture was cooled to 0 °C and sodium borohydride (11.7 g, 310.6 mmol) was added in small portions. The mixture was stirred for 18 h at room temperature. Then, the solution was quenched with saturated solution of sodium bicarbonate (250 mL). The aqueous layer was extracted successively with Et_2O (3 × 100 mL) and with ethyl acetate (3 × 100 mL). The organic layers were combined and filtered on Celite®. The filtrate was concentrated under reduced pressure to afford compound (*R*)-**7** (8.5 g, 93%) as a yellow oil. $[\alpha]_D^{28} = +5$ (*c* 0.4, EtOH). IR ν_{max}/cm^{-1}: 3321, 1693, 1524, 1365,

1169. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (s, 9H), 2.76 (m, 1H), 2.82 (m, 1H), 2.90 (m, 1H), 3.23 (m, 2H), 3.53 (m, 1H), 3.55 (m, 1H), 3.59 (m, 1H), 3.69 (m, 1H), 4.54 (d, 1H, ^2J = 12), 4.55 (d, 1H, ^2J = 12), 5.20 (se, 1H), 7.4–7.5 (m, 5H). MS *m/z* 347 $[MNa]^+$ (100), 325. HRMS calcd for $C_{17}H_{28}N_2O_4Na$: 347.1947. Found: 347.1965.

4.5. *O*-Benzyl-L-serine methyl ester hydrochloride 13

To a solution of carboxylic acid (10 g, 51 mmol) in MeOH (200 mL), under a nitrogen atmosphere, $SOCl_2$ (7.3 mL, 100 mmol) was carefully added. The reaction mixture was stirred for 18 h at room temperature. The solution was evaporated and the excess HCl eliminated by successive addition/evaporation of diethyl ether. The ester **13** (12.7 g, quantitative yield) is obtained as a white solid. Mp = 143 °C. $[\alpha]_D^{26} = +9$ (*c* 0.3, EtOH). IR ν_{max}/cm^{-1}: 2847, 1742, 1500, 1251, 1105. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.78 (s, 3H), 3.92 (m, 2H), 4.51 (m, 1H), 4.60 (d, 1H, ^2J = 12.6), 4.63 (d, 1H, ^2J = 12.6), 7.3–7.4 (m, 5H), 8.67 (se, 3H).

4.6. *N*-4-Nitrobenzylsulfonyl-glycine 14

To a cold solution (0 °C) of the amino acid (3 g, 40.2 mmol) in 1 M NaOH (42 mL) was added 4-nitrobenzylsulfonyl chloride (8.9 g, 40.2 mmol). The reaction mixture was stirred for 2 h at room temperature. The pH was kept at 9. The crude mixture was then washed with ethyl acetate (3 × 100 mL). The pH of the aqueous phase was adjusted to 2 by the addition of 1 N hydrochloric acid. This solution was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with H_2O and saturated aqueous solution of sodium chloride. The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure. The peptide (8.2 g, 79%) was afforded as a yellow solid. Mp: 154–155 °C. IR ν_{max}/cm^{-1}: 3412, 3285, 1728, 1524, 1350, 1160, 1084. ^{1} H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 2H), 8.08 (d, 2H, ^3J = 8.3), 8.43 (d, 2H, ^3J = 8.3), 8.52 (se, 1H), 12.61 (se, 1H). MS *m/z* 283 $[MNa]^+$ (100), 271.

4.7. Methyl (2*S*)-6-(4-nitrobenzenesulfonyl)-2-(benzyloxymethyl)-3,6-diaza-4-oxohexanoate (*S*)-15

To a solution of sulfonamide **14** (8 g, 30.8 mmol) in dry tetrahydrofuran was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, DMTMM (12.6 g, 46.2 mmol). The reaction mixture was stirred for 1.5 h, after which amino acid methyl ester hydrochloride (8.3 g, 33.8 mmol) and *N*-methyl morpholine, NMM (5.4 mL, 50.7 mmol), were added. The reaction mixture was stirred for 18 h at room temperature. The crude mixture was filtered and washed with citric acid solution (5% w/v), water and sodium bicarbonate (5% w/v) successively. The organic layer was further concentrated to give compound (*S*)-**15** (10.4 g, 77%) as a yellow solid. Mp: 110–111 °C. $[\alpha]_D^{24} = +7$ (*c* 0.1, EtOH). IR ν_{max}/cm^{-1}: 3321, 3279, 1741, 1656, 1522, 1347, 1147. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (dd, 2H, ^2J = 10, ^3J = 3), 3.72 (s, 3H), 3.81 (dd, 2H, ^2J = 10, ^3J = 6), 3.82 (dd, 2H, ^2J = 10, ^3J = 6), 3.87 (dd, 2H, ^2J = 10, ^3J = 3), 4.45 (d, ^2J = 12.1), 4.54 (d, ^2J = 12.1), 4.70 (se, 1H), 6.60 (m, 1H), 7.35 (se, 1H), 8.04 (d, 2H, ^3J = 8.7), 8.3 (d, 2H, ^3J = 8.7). MS *m/z* 474 $[MNa]^+$ (100). HRMS calcd for $C_{19}H_{21}N_3O_8NaS$: 474.0947. Found: 474.0950.

4.8. Methyl (2*S*)-3-benzyloxy-2-[4′-(4-nitrobenzenesulfonyl)-2′-oxopiperazin-1′-yl]propanoate (*S*)-16

To a solution of 4-nitrobenzenesulfonyl dipeptide (8 g, 16.8 mmol) in dry dimethylformamide (DMF) was added potassium carbonate (23.2 g, 168 mmol). The reaction mixture was allowed to stir at 60 °C for 30 min; 1,2-dibromoethane (14.4 mL, 168 mmol) was added to the above solution which was left to stir at 60 °C for 24 h. The DMF was removed in vacuo and the residue dissolved in ethyl acetate. This organic layer was then washed with hydrochloric acid (10% v/v) and brine successively. The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure to yield the desired compound (7.1 g, 88%) as a yellow oil. $[\alpha]_D^{28} = -4$ (*c* 0.4, EtOH). IR ν_{max}/cm^{-1}: 1743, 1656, 1530, 1350, 1169. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.29 (m, 1H), 3.58 (m, 1H), 3.59 (m, 1H), 3.67 (m, 5H), 3.72 (m, 5H), 3.76 (m, 5H), 3.81 (dd, 1H, ^2J = 10.5, ^3J = 3.5), 3.96 (dd, 1H, ^2J = 10.5, ^3J = 3.5), 4.00 (m, 2H), 4.47 (d, 1H, ^2J = 11.9), 4.50 (d, 1H, ^2J = 11.9), 5.25 (se, 1H), 7.20–7.39 (m, 5H), 8.02 (d, 2H, ^3J = 7.9), 8.41 (d, 2H, ^3J = 7.9). MS *m/z* 500 $[MNa]^+$ (100). HRMS calcd for $C_{21}H_{23}N_3O_8NaS$: 500.1104. Found: 500.1124.

4.9. (1′*R*)-4-(4-Nitrobenzenesulfonyl)-1-[1′-benzyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine (*R*)-17

A solution of ester (5 g, 10.48 mmol) in anhydrous THF (70 mL) was cooled to 0 °C. Then, $LiBH_4$ (0.5 g, 21 mmol) was carefully added in absolute MeOH (280 mL) and the reaction mixture was adjusted to pH 4 by the addition of a 10% (w/v) aqueous solution of citric acid. This solution was extracted with ethyl acetate (3 × 40 mL). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated to obtain the desired alcohol (3.8 g, 78%) as a transparent oil. $[\alpha]_D^{28} = +6$ (*c* 0.1, EtOH). IR ν_{max}/cm^{-1}: 3460, 1633, 1524, 1348, 1172. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 (m, 1H), 3.38 (m, 1H), 3.60 (m, 1H), 3.65 (m, 1H), 3.67 (m, 1H), 3.73 (m, 1H), 3.80 (m, 2H), 3.82 (m, 2H), 4.46 (se, 1H), 4.49 (d, 1H, ^2J = 12), 4.51 (d, 1H, ^2J = 12), 7.28–7.39 (m, 5H), 8.03 (d, 2H, ^3J = 8.6), 8.45 (d, 2H, ^3J = 8.6). MS *m/z* 472 $[MNa]^+$ (100). HRMS calcd for $C_{20}H_{23}N_3O_7NaS$: 472.1154. Found: 472.1177.

4.10. (1′*R*)-1-[1′-Benzyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine (*R*)-18

4.10.1. Path A

To a mixture of potassium carbonate (0.46 g, 3.3 mmol) in dry DMF (5.6 mL) was added thiophenol (0.14 mL, 1.33 mmol). This mixture was left to stir under nitrogen for 30 min. The sulfonamide compound (0.5 g, 1.1 mmol) in dry DMF (5.6 mL) was slowly injected into the above reaction mixture which was left to stir for an additional six hours. The DMF was removed in vacuo and the residue dissolved in ethyl acetate (50 mL). This organic layer was washed with sodium bicarbonate (10% w/v). The organic layer was dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure. The desired compound (*R*)-**18** (0.13 g, 40%) was obtained after silica gel column chromatography (eluent: cyclohexane/ethyl acetate, 1:1, then ethyl acetate 100%).

4.10.2. Path B

To a mixture of potassium carbonate (0.06 g, 0.4 mmol) in dry acetonitrile/dimethyl sulfoxide (49:1 v/v, 0.8 mL) at 50 °C was added thiophenol (0.035 mL, 0.3 mmol). The reaction mixture was stirred for 30 min. The sulfonamide compound (*R*)-**17** (0.05 g, 0.11 mmol) in dry acetonitrile/dimethyl sulfoxide (49:1 v/v, 0.1 mL) was slowly injected into the above reaction mixture which was left to stir for an additional 1.5 h. The solvent was removed in vacuo and the residue dissolved in ethyl acetate (5 mL). This organic layer was washed with sodium bicarbonate (10% w/v). The organic phase was dried over anhydrous sodium sulfate and concentrated. Purification was achieved by column chromatography (eluent: cyclohexane/ethyl acetate, 1:1, then ethyl acetate 100%) to result compound (*R*)-**18** (0.027 g, 95%) as a yellow oil. $[\alpha]_D^{20} = +25$ (*c* 0.05, EtOH). IR ν_{max}/cm^{-1}: 2925, 1725,

1269. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.27 (m, 1H), 3.29 (m, 1H), 3.51 (m, 1H), 3.60 (m, 1H), 3.68 (m, 1H), 3.71 (m, 2H), 3.79 (m, 2H), 3.80 (m, 1H), 3.83 (m, 2H), 4.30 (se, 1H), 4.53 (d, 2H, ^2J = 12), 4.57 (d, 2H, ^2J = 12), 7.28–7.39 (m, 5H). MS *m/z*: 287 $[MNa]^+$ (100). HRMS calcd for $C_{14}H_{20}N_2O_3Na$: 287.3094. Found: 287.3089.

4.11. (1′*R*)-4-(4-Thiophenylbenzenesulfonyl)-1-[1′-benzyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine (*R*)-19

Following the same procedure (path A) of (*R*)-**18**, the compound (*R*)-**19** was prepared (0.68 g, 60%) as a yellow oil. $[\alpha]_D^{23} = -26$ (*c* 0.01, EtOH). IR ν_{max}/cm^{-1}: 3398, 1644, 1349, 1167. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.23 (m, 1H), 3.28 (m, 1H), 3.45 (m, 1H), 3.52 (m, 1H), 3.60 (m, 1H), 3.73 (m, 1H), 3.75 (m, 1H), 3.77 (m, 1H), 3.85 (m, 2H), 4.32 (se, 1H), 4.49 (d, 1H, ^2J = 12), 4.51 (d, 1H, ^2J = 12), 7.27–7.63 (m, 14H).

4.12. (2*R*)-3-Benzyloxy-2-hydroxypropanoic acid (*R*)-20

A mixture of *O*-benzyl-D-serine (4 g, 20.5 mmol) in 2 N H_2SO_4 (24 mL) was cooled to 0 °C. A solution of $NaNO_2$ (2.56 g, 36.96 mmol) in H_2O was added over 2 h while the temperature was maintained between 0 °C and 5 °C. After complete addition, the reaction mixture was stirred at this temperature for 10 h followed by stirring at ambient temperature for 2 h. The reaction mixture was adjusted to pH 4 with 50% NaOH. EtOAc (3 × 20 mL) was added, and the layers were vigorously stirred while the aqueous layer was adjusted to a pH of 2 with 2 N H_2SO_4. The aqueous layer was extracted further with EtOAc (3 × 20 mL) and the combined extracts were dried over Na_2SO_4. The drying agent was filtered off and washed with EtOAc, and the filtrate was concentrated. The compound (3.62 g, 90%) was obtained as a yellow oil. $[\alpha]_D^{22} = -2$ (*c* 0.5, EtOH). IR ν_{max}/cm^{-1}: 3439, 1725, 1096, 696. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.65 (m, 1H), 3.66 (m, 1H), 4.20 (se, 1H), 4.51 (d, 1H, ^2J = 11.6), 4.57 (d, 1H, ^2J = 11.6), 7.31–7.35 (m, 5H). MS *m/z* 677 $[M_3Na_4]^+$, 241 $[MNa_2]^+$ (100). HRMS calcd for $C_{10}H_{11}O_4Na_2$: 241.0453. Found: 241.0426.

4.13. (2*S*)-3-Benzyloxy-2-hydroxypropanoic acid (*S*)-20

Following the same procedure for (*R*)-**20** starting from *O*-benzyl-L-serine (4 g, 20.5 mmol), the compound (*S*)-**20** was prepared (3.62 g, 90%) as yellow oil. $[\alpha]_D^{22} = +2$ (*c* 0.5, EtOH). Spectroscopic data of (*S*)-**20** were identical with those of (*R*)-**20**.

4.14. Methyl (3*R*)-3-benzyloxy-2-hydroxypropanoate (*R*)-21

A mixture of acid (*R*)-**20** (3 g, 13.7 mmol), MeOH and freshly prepared methanolic HCl 1 M (5.4 mL) was stirred at ambient temperature for 1.5 h. Trimethyl orthoformate (2.98 mL, 27.4 mmol) was added, and the mixture was stirred at ambient temperature for 18 h. The solution was concentrated with vacuo and the crude product was purified by column chromatography using cyclohexane/ethyl acetate (1:1: v/v). The compound (2.8 g, 87%) was afforded as a transparent liquid. $[\alpha]_D^{23} = -6$ (*c* 0.5, EtOH). IR ν_{max}/cm^{-1}: 3480, 1738, 1208, 1104. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (se, 3H), 3.75 (m, 1H), 3.76 (m, 1H), 4.40 (se, 1H), 4.55 (m, 1H), 4.62 (d, 1H, ^2J = 12), 4.62 (d, 1H, ^2J = 12), 7.32–7.36 (m, 5H). MS *m/z* 233 $[MNa]^+$ (100). HRMS calcd for $C_{11}H_{14}O_4Na$: 233.0790. Found: 233.0789.

4.15. Methyl (3*S*)-3-benzyloxy-2-hydroxypropanoate (*S*)-21

Following the same procedure for (*R*)-**21**, = compound (*S*)-**21** was prepared (2.8 g, 87%) as a transparent liquid. $[\alpha]_D^{23} = +6$ (*c* 0.5, EtOH). Spectroscopic data of (*S*)-**21** were identical with those of (*R*)-**21**.

4.16. Methyl (2*S*)-3-benzyloxy-2-[4′-(*tert*-butoxycarbonyl)-1′-piperazinyl]propanoate (*S*)-22

To a solution of alcohol (*R*)-**21** (1.5 g, 7.14 mmol) in dry toluene at 0 °C was added *N*,*N*-diisopropylethylamine (DIPEA) (1.18 mL, 7.14 mmol). The solution was stirred while triflic anhydride (1.20 mL, 7.14 mmol) was added slowly and the temperature was maintained at <5 °C. The reaction mixture was warmed to 20 °C. After 1 h, the mixture was cooled to −78 °C and a solution of *N*-Boc piperazine (1.33 g, 7.14 mmol) and DIPEA (1.18 mL, 7.14 mmol) in dry toluene (19 mL) was added. The mixture was stirred for 18 h after which the insoluble material was removed by filtration and washed with toluene. The filtrate was concentrated in vacuo and the crude product was purified by chromatography using cyclohexane/ethyl acetate (6:4: v/v). The product (2.65 g, 98%) was afforded as orange oil. $[\alpha]_D^{23} = -16$ (*c* 0.5, EtOH). IR ν_{max}/cm^{-1}: 1733, 1689, 1164, 1116. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.58 (se, 2H), 2.59 (se, 2H), 3.42 (m, 1H), 3.43 (m, 1H), 3.53 (t, 1H, ^3J = 6.5), 3.71 (s, 3H), 3.77 (m, 1H), 3.79 (m, 1H), 4.53 (d, 1H, ^2J = 12), 4.55 (d, 1H, ^2J = 12), 7.3–7.4 (m, 5H). MS *m/z* 401 $[MNa]^+$ (100). HRMS calcd for $C_{20}H_{30}N_2O_5Na$: 401.2052. Found: 401.2072.

4.17. Methyl (2*R*)-3-benzyloxy-2-[4′-(*tert*-butoxycarbonyl)-1′-piperazinyl]propanoate (*R*)-22

Following the same procedure for (*S*)-**22**, the compound (*R*)-**22** was prepared (2.65 g, 98% of yield) as orange oil. $[\alpha]_D^{23} = +16$ (*c* 0.5, EtOH). Spectroscopic data of (*R*)-**16** were identical with those of (*S*)-**16**.

4.18. Methyl (2*S*)-3-benzyloxy-2-[4′-(*tert*-butoxycarbonyl)-2′-oxopiperazin-1′-yl]propanoate (*S*)-12

A solution of (*S*)-**22** (1.53 g, 4.04 mmol) in ethyl acetate (12 mL) was added to a mixture of $RuO_2{\cdot}xH_2O$ (0.053 g, 0.40 mmol) and 10% aqueous $NaIO_4$ (18.7 mL). The solution was stirred vigorously for 16 h at room temperature. The layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The extract was treated with 2-propanol (30 μL). Black-coloured RuO_2, which precipitated from the solution, was filtered off and the filtrate was washed with brine. The organic layer was dried over Na_2SO_4. The drying agent was filtered off and washed with EtOAc, and the filtrate was concentrated. The crude product was purified by column chromatography using as eluent cyclohexane/ethyl acetate (6:4: v/v). The product (0.93 g, 58%) was afforded as a yellow oil. $[\alpha]_D^{23} = -12$ (*c* 0.3, EtOH). IR ν_{max}/cm^{-1}: 1744, 1694, 1657, 1166. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 3.53 (m, 1H), 3.55 (m, 2H), 3.80 (m, 1H), 3.76 (s, 3H), 3.89 (dd, 1H, ^2J = 10.5, ^3J = 3.6), 4.00 (dd, 1H, ^2J = 10.5, ^3J = 3.6), 4.12 (d, 1H, ^2J = 18.3), 4.21 (d, 1H, ^2J = 18.3), 4.51 (d, 1H, ^2J = 12), 4.53 (d, 1H, ^2J = 12), 5.36 (se, 1H), 7.3–7.4 (m, 5H). MS *m/z* 807 $[M_2Na]^+$, 415 $[MNa]^+$ (100). HRMS calcd for $C_{20}H_{28}N_2O_6Na$: 415.1845. Found: 415.1849.

4.19. Methyl (2*R*)-3-benzyloxy-2-[4′-(*tert*-butoxycarbonyl)-2′-oxopiperazin-1′-yl]propanoate (*R*)-12

Following the same procedure for (*S*)-**12**, the compound (*R*)-**12** was prepared (0.93 g, 58%) and was afforded as a yellow oil. $[\alpha]_D^{23} = +12$ (*c* 0.3, EtOH). Spectroscopic data of (*R*)-**12** were identical with those of (*S*)-**12**.

4.20. (1′*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-benzyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine (1′*R*)-2

From (*R*)-**18**: To a solution of amine (*R*)-**18** (0.287 g, 1 mmol) in dry MeOH (3.4 mL) at 0 °C was slowly dropped a solution of di-*tert*-butyldicarbonate (0.13 g, 0.6 mmol) in dry MeOH (1.7 mL). The reaction mixture was stirred for 36 h at room temperature. The solvent was eliminated under reduced pressure and the residue dissolved in diethyl ether (1.7 mL). This solution was filtered and then washed with citric acid solution (5% w/v). The aqueous phases were combined and pH adjusted to 9 by addition of NaOH (50% w/v) and extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give compound (1′*R*)-**2** (0.387 g, 100%). $[\alpha]_D^{24} = +7$ (*c* 0.1, EtOH). IR ν_{max}/cm^{-1}: 3348, 1696, 1644, 1168. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H); 3.00 (se, 1H); 3.50 (m, 1H); 3.56 (m, 1H); 3.64 (m, 2H); 3.74 (m, 1H); 3.84 (m, 1H); 3.90 (m, 2H); 4.13 (d, 1H, ^2J = 17.8); 4.22 (d, 1H, ^2J = 17.8); 4.42 (m, 1H); 4.55 (d, 1H, ^2J = 12.0); 4.59 (d, 1H, ^2J = 12.0); 7.31–7.42 (m, 5H). MS *m*/*z*: 387 $[MNa]^+$ (100), 331. HRMS calcd for $C_{19}H_{28}N_2O_5Na$: 387.1896. Found: 387.1897.

4.21. Starting from (*R*)-12

Following the same procedure for (*R*)-**17**, compound (1′*R*)-**2** was prepared (0.282 g, 73%) starting from (*R*)-**12** (0.392 g, 1 mmol).

4.22. (1′*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-benzyloxymethyl-2′-hydroxyethyl]-2-oxopiperazine (1′*S*)-2

Following the same procedure for (*R*)-**17**, the compound (1′*S*)-**2** was prepared (0.42 g, 75%) as a transparent oil. $[\alpha]_D^{24} = -7$ (*c* 0.1, EtOH). Spectroscopic data of (1′*S*)-**2** were identical with those of (1′*R*)-**2**.

4.23. (1*R*,3*S*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-hydroxyethyl]-3-benzyl-2-oxopiperazine (1*R*,3*S*)-23

A solution of diisopropylamine (1 mL, 7.35 mmol) in THF (20 mL) was cooled to −78 °C and kept under a nitrogen atmosphere. A 1.6 M solution of *n*-BuLi in hexane (4 mL, 6.3 mmol) was slowly added to the cold solution and the mixture was stirred for 15 min. A solution of (1′*R*)-**2** (813 mg, 2.1 mmol) and HMPA (6.3 mmol) in THF (5 mL) was slowly poured into the cold solution and stirred for 15 min. A solution of benzyl bromide (1.07 g, 6.3 mmol) in THF (5 mL) was added and the mixture was stirred for 5 h at −50 °C, then for 30 min at −15 °C. The reaction mixture was quenched by the 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 over Na_2SO_4, filtered and concentrated in vacuo. The crude product was finally purified by column chromatography using cyclohexane/EtOAc (1:20) as an eluent to give diastereoisomer (1*R*,3*S*) (761 mg, 76%). $[\alpha]_D^{18} = +16$ (*c* 0.1, EtOH). IR ν_{max}/cm^{-1}: 3364, 2974, 1687, 1641, 1172. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.0–7.3 (10H, m), 4.60 (1H, m), 4.44 (1H, d, *J* = 11.6), 4.40 (1H, d, *J* = 11.6), 4.37 (1H, t, *J* = 8.3), 3.89 (1H, br m), 3.71 (2H, d, *J* = 8.3), 3.62 (2H, m), 3.51 (2H, m), 3.32 (2H, m), 3.16 (1H, m), 3.10 (1H, m), 3.00 (1H, m), 1.20 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 154.0, 138.2, 130.3, 129.4, 128.8, 128.2, 128.0, 127.1, 80.9, 73.6, 68.6, 61.6, 61.5, 59.3, 58.1, 45.1, 38.3, 28.5. MS *m*/*z* 477 $(M+Na)^+$, 421, 377, 345. HRMS calcd for $(M+Na)^+$ 477.2349, found 477.2343.

4.24. (1*S*,3*R*)-4-(*tert*-Butoxycarbonyl)-1-[1′-hydroxymethyl-2′-hydroxyethyl]-3-benzyl-2-oxopiperazine (1*S*,3*R*)-23

Following the same procedure for (1*R*,3*S*)-**23**, the compound (1*S*,3*R*)-**23** was prepared (0.4 g, 86%) as a transparent oil. $[\alpha]_D^{18} = -16$ (*c* 0.1, EtOH). IR ν_{max}/cm^{-1}: 3364, 2974, 1687, 1641, 1172. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.0–7.3 (10H, m), 4.62 (1H, m), 4.45 (1H, d, *J* = 11.6), 4.41 (1H, d, *J* = 11.6), 4.36 (1H, t, *J* = 8.3), 3.90 (1H, br m), 3.70 (2H, d, *J* = 8.3), 3.62 (2H, m), 3.50 (2H, m), 3.31 (2H, m), 3.16 (1H, m), 3.09 (1H, m), 3.02 (1H, m), 1.20 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 153.6, 137.7, 129.9, 128.5, 128.4, 127.9, 126.8, 80.6, 73.3, 68.2, 61.7, 61.6, 58.7, 58.1, 44.9, 38.7, 28.2. MS *m*/*z* 477 $(M+Na)^+$, 421, 377. HRMS calc. for $(M+Na)^+$ 477.2349, found 477.2367.

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References

1. For example see: Prisinzano, T.; Rice, K. C.; Baumann, M. H.; Rothman, R. B. *Curr. Med. Chem.: Central Nervous System Agents* **2004**, *4*, 47–59.
2. Dinsmore, J. C.; Bergman, J. M.; Wei, D. D.; Zartman, C. B.; Davide, J. P.; Greenberg, I. B.; Liu, D.; O'Neill, T. J.; Gibbs, J. B.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Chen, I.-W.; McLoughlin, D. A.; Olah, T. V.; Graham, S. L.; Hartman, G. D.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 537.
3. Bergman, J. M.; Abrams, M. T.; Davide, J. P.; Greenberg, I. B.; Robinson, R. G.; Buser, C. A.; Huber, H. E.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Graham, S. L.; Hartman, G. D.; Williams, T. M.; Dinsmore, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1411.
4. Seibel, J.; Brown, D.; Amour, A.; Macdonald, S. J.; Oldham, N. J.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 387.
5. Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484.
6. Tian, X.; Mishra, R. K.; Switzer, A. G.; Hu, X. E.; Kim, N.; Mazur, A. W.; Ebetino, F. H.; Wos, J. A.; Crossdoersen, D.; Pinney, B. B.; Farmer, J. A.; Sheldon, R. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4668.
7. Su, T.; Yang, H.; Volkots, D.; Woolfrey, J.; Dam, S.; Wong, P.; Sinha, U.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 729–732.
8. Pohlmann, A. R.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P. *J. Pept. Res.* **1997**, *51*, 116.
9. Schoenberg, L. N.; Cooke, D. W.; Liu, C. F. *Inorg. Chem.* **1968**, *7*, 2386–2393.
10. (a) Yamashita, T.; Kojima, Y.; Hirotsu, K.; Ohsuka, A. *Int. J. Pept. Protein Res.* **1989**, *33*, 110–114; (b) Lammek, B.; Czaja, M.; Derdowska, I.; Lempicka, E.; Sikora, P.; Szkrobka, W.; Trzeciak, H. I. *J. Pept. Res.* **1998**, *51*, 149–154; (c) Lempicka, E.; Derdowska, I.; Jastrzebska, B.; Kuncarova, P.; Slaninova, J.; Lammek, B. *J. Pept. Res.* **2001**, *57*, 162–167; (d) Yamashita, T.; Hatamoto, E.; Takenada, H.; Kojima, Y.; Inoue, Y.; Gemba, M.; Yasuda, M. *Chem. Pharm. Bull.* **1996**, *44*, 856–859.
11. Yamashita, T.; Tsuru, E.; Banjyo, D.; Shibata, K.; Yasuda, M.; Gemba, M. *Chem. Pharm. Bull.* **1997**, *45*, 1940–1944.
12. (a) Bhatt, U.; Mohamed, N.; Just, G. *Tetrahedron Lett.* **1997**, *38*, 3679–3682; (b) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679–1682; (c) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484–2493; (d) DiMaio, J.; Belleau, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1687–1689; (e) Sugihara, H.; Fukushi, H.; Miyawaki, T.; Imai, Y.; Terashita, Z. I.; Kawamura, M.; Fujisawa, Y.; Kita, S. *J. Med. Chem.* **1998**, *41*, 489–502; (f) Kitamura, S.; Fukushi, H.; Miyawaki, T.; Kawamura, M.; Konishi, N.; Terashita, Z. I.; Naka, T. *J. Med. Chem.* **2001**, *44*, 2438–2450; (g) Su, T.; Yang, H.; Volkots, D.; Woolfrey, J.; Dam, S.; Wong, P.; Sinha, U.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 729–732.
13. Mohamed, N.; Bhatt, U.; Just, G. *Tetrahedron Lett.* **1998**, *39*, 8213–8216.
14. Chen, Z.; Kende, A. S. *Synth. Commun.* **2006**, *36*, 473–479.
15. Viso, A.; Pradilla, R. F.; Flores, A.; Garcia, A.; Tortosa, M.; Lopez-Rodrigues, M. L. *J. Org. Chem.* **2006**, *71*, 1442–1448.
16. Reginato, G.; Di Credico, B.; Andreotti, D.; Mingardi, A.; Paio, A.; Donati, D. *Tetrahedron: Asymmetry* **2007**, *18*, 2680–2688.
17. Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J. C.; Husson, H. P. *J. Org. Chem.* **1997**, *62*, 1016–1022.

18. (a) Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J. C.; Husson, H. P. *Tetrahedron Lett.* **1994**, *35*, 2533–2536; (b) Schanen, V.; Cherrier, M. P.; Melo, S. J.; Quirion, J. C.; Husson, H. P. *Synthesis* **1996**, *7*, 833–869.
19. (a) Micouin, L.; Jullian, V.; Quirion, J. C.; Husson, H. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839–2846; (b) Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J. C.; Husson, H. P. *Tetrahedron Lett.* **1994**, *35*, 2529–2532.
20. Franceschini, N.; Sonnet, P.; Guillaume, D. *Org. Biomol. Chem.* **2005**, *3*, 787–793.
21. Smith, A. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1736–1740.
22. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061–5087.
23. Guziec, F. S.; Wasmund, L. M. *Tetrahedron Lett.* **1990**, *31*, 23–26.
24. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
25. Wuts, P. G. M.; Northuis, J. M. *Tetrahedron Lett.* **1998**, *39*, 3889–3890.
26. Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253–5256.
27. Sonnet, P.; Petit, L.; Marty, D.; Guillon, J.; Rochette, J.; Brion, J. D. *Tetrahedron Lett.* **2001**, *42*, 1681–1683.
28. Sonnet, P.; Da Nascimento, S.; Marty, D.; Franceschini, N.; Guillon, J.; Brion, J. D.; Rochette, J. *Tetrahedron Lett.* **2003**, *44*, 3293–3296.
29. Watson, T. J.; Ayers, T. A.; Shah, N.; Wenstrup, D.; Webster, M.; Freund, D.; Horgan, S.; Carey, J. P. *Org. Process Res. Dev.* **2003**, *7*, 521–532.
30. Vetuschi, C.; Tangari, N.; Giovine, M.; Franchini, C.; Tortorella, V. *Il Farm* **1992**, *47*, 599–605.
31. Petride, H.; Drăghici, C.; Florea, C.; Petride, A. *Cent. Eur. J. Chem.* **2006**, *4*, 674–694.