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A new versatile and diastereoselective synthesis of polysubstituted 2-oxopiperazines from naturally occurring amino acids

Gianna Reginato,[a,*] Barbara Di Credico,[a] Daniele Andreotti,[b] Anna Mingardi,[b] Alfredo Paio[b] and Daniele Donati[b]

[a]*ICCOM—CNR, Dipartimento di Chimica Organica 'U. Schiff', Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy*
[b]*GlaxoSmithKline, Medicine Research Centre, Via A. Fleming 4, 37135 Verona, Italy*

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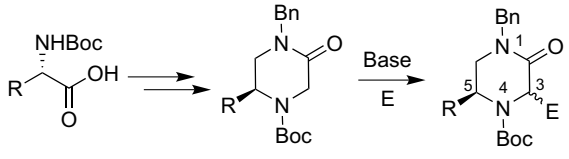
Abstract—A highly stereoselective approach to 1,3,4,5- and 1,3,3′,4,5-polysubstituted 2-oxopiperazines is reported. The method is based on the synthetic elaboration of naturally occurring amino acids to obtain enantiomerically enriched C-5 substituted oxopiperazines, which are further functionalized at C-3 via enolate formation and reaction with electrophiles. Notably, the two nitrogens of the ring can be orthogonally protected.

1. Introduction

Aza-lactams constitute a class of highly interesting molecules and have found widespread use as synthetic intermediates and in medicinal chemistry.[1] Substituted oxo-piperazines are components of a variety of bioactive compounds that include, amongst the others, constrained substance P analogues,[2] farnesyltransferase (FPTase), geranylgeranyltransferase-I (GGPTase-I),[3,4] elastase[5] and factor Xa inhibitors,[6] melanocortin receptors (MCR) agonists[7,8] and fibrinogen glycoprotein IIb–IIIa antagonists.[9] Thus, substituted oxopiperazines are not only found in central nervous system (CNS) active drugs but also might have significant potential as cancer chemotherapeutic agents,[3,4] or be promising candidates for the treatment and prevention of a range of diseases such as arthritis, asthma, depression,[2] obesity, sexual disfunctions,[8] emphysema, cystic fibrosis and rheumatoid arthritis.[5] In some cases, the oxopiperazine core is used as a conformationally constrained peptidomimetic[3,8–11] wherein the N_i and N_{i-1} positions of the peptide backbone fragments are linked by an ethylene bridge. This results in increasing the structural rigidity of the original peptide and has been found to modify the biological properties, occasionally enhancing affinity, specificity and enzymatic stability. Finally, such scaffolds have been found to stabilize inverse γ-turns in small peptides.[10] For all these reasons, the synthesis of a variety of piperazinones with substitution at different ring positions is of particular significance for medicinal chemists and many methods have been developed to achieve this goal.[12]

Stemming from our interest in the asymmetric synthesis of biologically interesting compounds, we have become interested in finding a general and highly stereoselective approach to 1,3,4,5-tetra-substituted- and 1,3,3′,4,5-penta-substituted 2-oxo-piperazines.

The method we designed, taking advantage of naturally occurring amino acids as starting materials, allows us to prepare some new oxopiperazinones, in which the substitution and the stereochemistry at C-5 can be pivoted by the choice of the starting amino acid and substitution at C-3 is accomplished via enolate formation and reaction with electrophiles (Scheme 1). In addition, we wanted to orthogonally protect the two nitrogens of the ring as it might be



Scheme 1.

* Corresponding author. Tel.: +39 0554573558; fax: +39 0554573580; e-mail: gianna.reginato@unifi.it

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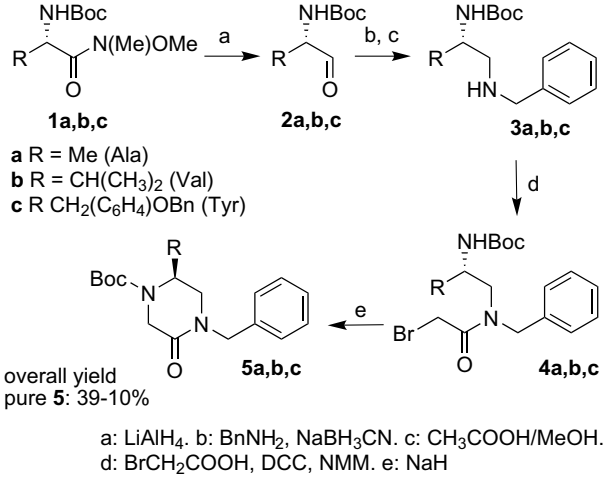
particularly valuable, allowing the stepwise positioning of substituents when the oxopiperazine core is used as a molecular scaffold.

2. Results and discussion

The key intermediates of our procedure were vicinal diamines **3**. This class of compounds, particularly in the chiral series, is commonly encountered as synthetic intermediates[13] and several methods have been developed for their synthesis.[14] For instance, α-amino aldehydes **2** are commonly used to prepare diamines via reductive amination with a primary amine.[15] Following this approach, we converted three different commercially available Boc protected L-amino acids into amino aldehydes **2** by $LiAlH_4$ reduction of the corresponding Weinreb amides **1**.[16,17] Reductive amination[18,19] with benzylamine gave orthogonally protected diamines **3**, which were purified by flash chromatography. Bromoacetylation of the diamines gave bromodiamides **4**, which provided 5-substituted 2-oxo piperazines **5** (Scheme 2) via base-promoted cyclization.

Although a similar approach has recently been reported on different substrates,[15,20,21] to the best of our knowledge the whole sequence has never been applied to the synthetic elaboration of naturally occurring amino acids. Thus, by using this reaction sequence, three new chiral 5-substituted oxopiperazines **5a**,**b**,**c**, respectively, derived from Boc protected L-alanine, L-valine and *O*-benzyl L-tyrosine, were obtained in reasonable overall yields and fully characterized after purification (Scheme 2).



Scheme 2.

To confirm the enantiomeric purity of the final compounds, oxopiperazine **5a** was deprotected in the presence of TFA. The corresponding Mosher's amide was prepared using (*S*)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride.[22] Unfortunately, the ^1H NMR analysis of the diastereomeric amide was complicated by the presence of two distinct rotamers in an approximate 2:1 ratio, which were observed when the spectrum was recorded at rt in C_6D_6. The two rotamers collapsed into broad signals when the spectrum was repeated at 70 °C. To exclude the presence of diastereoisomers, the (*S*,*R*)-amide was also prepared and a very similar behaviour was found, although the signals of the two rotamers showed different chemical shifts.

The ^1H NMR spectrum of a mixture of the two diastereomeric amides was recorded and an evident splitting of all the signals, owing to the four different rotamers which are present at rt, was observed, thus confirming the diastereomeric purity of the two amides. This is shown in Figure 1 where the ^1H NMR spectra of the two diastereomers and of the mixture, in the diagnostic distance $\delta = 5.50$–3.00 ppm, are reported.

Having fixed the substitution and the stereochemistry at C-5, we started to study if a stereoselective alkylation of C-3 could be achieved.

It is well known that glycine derived diketopiperazines (DKP) can be alkylated at the C-6 atom with high facial selectivity after enolate formation and the addition of electrophiles. This reaction, in which diastereoselectivity is efficiently controlled via 1,4 asymmetric induction, has been applied, for instance, to the synthesis of enantiomerically pure α-amino acids.[23–25] Likewise, the enantioselective synthesis of 3-substituted 2-oxo-piperazines has been reported via the stereoselective alkylation of achiral 2-oxopiperazine, by placing a chiral auxiliary at the N-1 atom[26] (Scheme 3).

Following a similar approach, compounds **5a**,**b**,**c** were deprotonated using a *t*-BuLi (2 equiv)/HMPA (4 equiv) mixture. The reaction was performed in THF at −78 °C and the enolate formed was reacted with allylbromide to quantitatively afford the corresponding 3-allylated 2-oxopiperazines **6a**,**b**,**c** which were purified by flash chromatography and fully characterized (Scheme 4). Remarkably, only one diastereoisomer was found in the final reaction mixture.

The stereochemistry of the newly formed stereogenic centre was deduced by NOE difference spectroscopy in $CDCl_3$. Selected NOE enhancements for **5a** are shown in Figure 2. Irradiation of the methyl protons ($\delta = 0.90$ ppm) produced an evident enhancement of the signal of Hd, according to a *syn* relationship; this was accompanied by the enhancement of the signals due to the Hb and to the benzylic protons. Irradiation at Hc ($\delta = 3.74$ ppm) produced an evident enhancement of the signals of Ha, Hb and of the methyl but had no effect on the Hd, which is in accordance with an *anti* relationship between these two protons.

Finally, irradiation at Hd ($\delta = 4.38$ ppm) produced the expected enhancement of the CH_3 signal and of the allylic CH_2 but had no effect on Hc, confirming that these hydrogen atoms lie on the opposite face of the oxopiperazine ring. These experiments were thus consistent with an *anti* relative stereochemistry between substituents at C-3 and C-5, which are in agreement with a conventional 1,3 asymmetric induction where the N-Boc protecting group plays no role in controlling the facial selectivity.[27] The absolute (3*S*,5*S*)-configuration thus follows from the known C-5

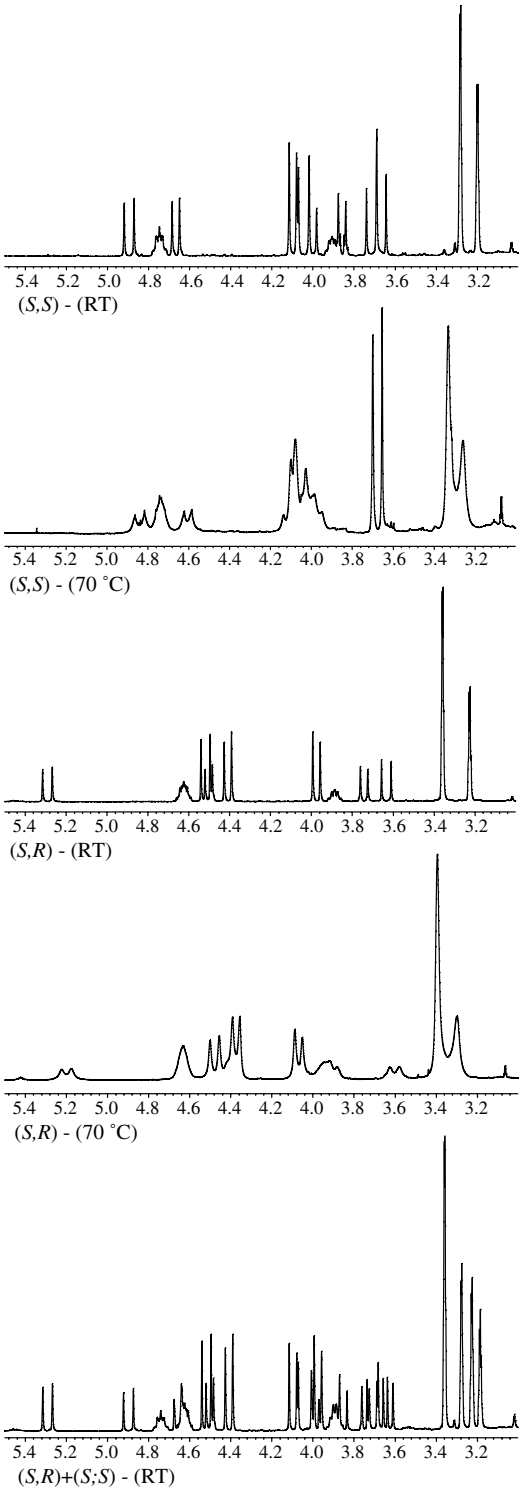
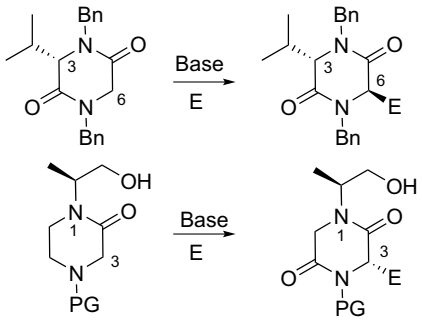


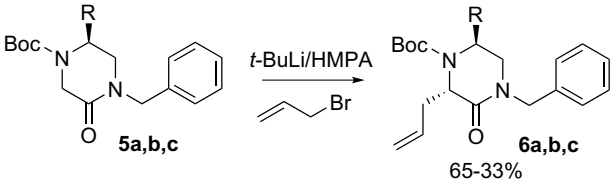
Figure 1. ^{1}H NMR (400 MHz, C_6D_6, $\delta = 5.50$–3.00 ppm) of Mosher's amides of compound **5a**.

stereogenic centre derived from the naturally occurring α-amino acid used as starting material.

To exploit the synthetic utility of such a reaction, compound **5a** was reacted, under the reported conditions, with a range of different electrophiles and the results are reported in Table 1. In almost all the cases, a high yielding



Scheme 3.



Scheme 4.

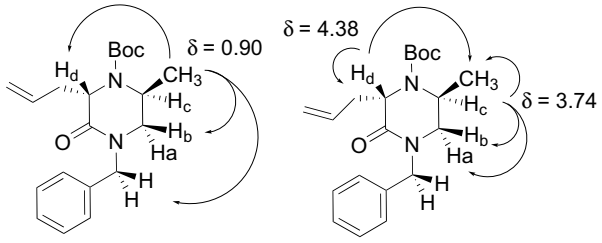


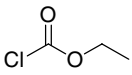
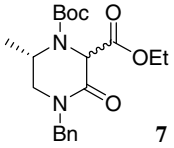
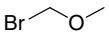
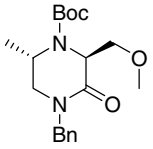
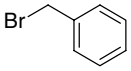
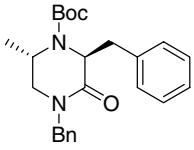
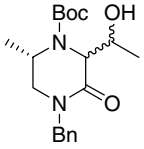
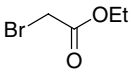
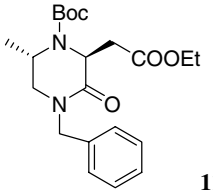
Figure 2. Selected NOE enhancements for **5a**.

conversion of the starting oxopiperazine into the corresponding 3-substituted derivatives **7**–**11** was obtained. In most cases only one diastereoisomer was formed, however reaction with chloroformate afforded compound **7** as a mixture of diastereoisomers, which could not be separated by chromatography. This might be due to the acidity of proton at C-3. Again, when acetaldehyde was used, the expected alcohol **10** was found but as a complex mixture of diastereoisomers.

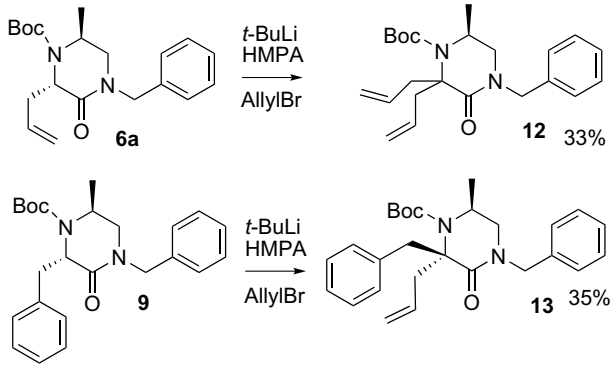
With the aim of achieving more decorated scaffolds, double functionalization at the 3-position was also attempted (see Scheme 5). Therefore, compounds **6a** and **9** were deprotonated under the same conditions and reacted with allylbromide to afford 3,3′-disubstituted oxopiperazines **12** and **13**, respectively. Once again compound **13** was recovered as a single diastereisomer in which an *anti* relative stereochemistry between the allyl group at C-3 and the methyl at C-5 was deduced by NOE difference spectroscopy in $CDCl_3$. This seems to show that the presence of a substituent at C-3 had no influence in directing the *anti* approach of the approaching electrophile.

Selected NOE enhancements for **13** are shown in Figure 3. Irradiation of the methyl protons ($\delta = -0.19$ ppm)

Table 1. Synthesis of 3,5-disubstituted oxopiperazines

Substrate	Electrophile	Final compound	Yield[a] (%)
5a		 **7**	70 (30%)
5a		 **8**	90 (30%)
5a		 **9**	90 (43%)
5a		 **10**	65 (27%)[b]
5a		 **11**	85 (40%)

[a] Yield of isolated compound is given in parentheses.
[b] A complex mixture of diastereoisomers.



Scheme 5.

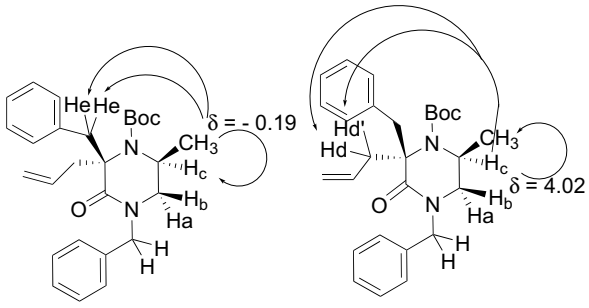


Figure 3. Selected NOE enhancements for **13**.

produced an evident enhancement of the signal of the benzylic CH_2He/He', which is in accordance with a *syn* relationship; this was accompanied by the enhancement of the signals of Hc. Irradiation at Hc ($\delta = 4.02$ ppm) produced an evident enhancement of the allylic CH_2 signals He/He′ and of the methyl but had no effect on He, according to an *anti* relationship.

The absolute (3*S*,5*S*)-configuration was thus inferred.

3. Conclusions

In conclusion, a stereoselective method for the synthesis of highly decorated and orthogonally protected 2-oxo-piperazines, from amino acids, has been reported. Further synthetic elaborations of the 2-oxopiperazine scaffold are currently in progress.

4. Experimental

4.1. General methods

Reactions were monitored by TLC on SiO_2, detection was made using a basic $KMnO_4$ solution. Flash column chromatography was performed using glass columns (10–50 mm wide) and SiO_2 (230–400 mesh). ^1H NMR were recorded at 200 or 400 MHz. For those compounds which are present as slowly interconverting rotamers, ^1H NMR experiments were performed at 50 °C and signals of the averaged spectrum are reported when possible. ^{13}C NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 ppm for ^1H NMR; $CHCl_3$, δ 77.00 ppm for ^{13}C NMR). Polarimetric measurements were performed at $\lambda = 589$ nm, and the temperature is specified case by case. All commercial reagents were used without further purification. Aldehydes **2a–c** were prepared according to the literature.[28,29] THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was dried over $CaCl_2$, and stored over 4 Å molecular sieves. DMF was distilled over $CaCl_2$, and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40–70 °C boiling fraction.

4.2. Synthesis of orthogonally protected diamines 3

Aldehydes **2a–c** (1 equiv) were dissolved in dry MeOH (10 mL) and benzylamine (1.5 equiv) was added, followed by an $NaCNBH_3$ solution in dry THF (1 M, 1.5 equiv) and acetic acid (2.5 equiv). The mixture was stirred overnight at room temperature, after which MeOH was evaporated and the crude was dissolved in ethyl acetate (20 mL). The organic phase was washed with a $NaHCO_3$ saturated solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated to afford diamines **3a–c** which were purified by flash chromatography.

4.2.1. (*S*)-*tert*-Butyl-1-(benzylamino)-propan-2-yl-carbamate 3a. To amide **1a** (1.0 g, 4.3 mmol) in THF (45 mL) $LiAlH_4$ (205 mg, 5.4 mmol) was added. After workup aldehyde **2a** (771 mg, 4.5 mmol) was obtained and reacted with benzylamine (0.73 mL, 6.7 mmol), $NaCNBH_3$ solution (7.0 mL) and acetic acid (0.63 mL) in dry MeOH (45.0 mL). Purification [petroleum ether/ethyl acetate = 1:8] gave **3a** as a colourless oil (856 mg, 73%). R_f: 0.8. Compound **3a**: ^1H NMR (200 MHz) δ: 7.37–7.28 [m, 5H]; 4.84 [br s, 1H]; 3.97–3.79 [m, 1H+2H]; 2.77–2.70 [m, 2H]; 1.44 [s, 9H]; 1.16 [d, $J = 7.0$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 156.15; 137.04; 128.56 (×2); 128.47 (×2); 127.7; 79.96; 53.96; 52.93; 45.77; 28.44; 19.17. $[\alpha]_D^{24} = -1.8$ (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.21; H, 9.16; N, 10.57.

4.2.2. (*S*)-*tert*-Butyl-1-(benzylamino)-3-methylbutan-2-yl-carbamate 3b. To amide **1b** (2.0 g, 7.7 mmol) in THF (75.0 mL), $LiAlH_4$ (365 mg, 9.6 mmol) was added. After workup aldehyde **2b** (2.223 g, 11.1 mmol) was obtained and reacted with benzylamine (1.8 mL, 16.6 mmol), $NaCNBH_3$ solution (16.6 mL) and acetic acid (1.57 mL) in dry MeOH (100.0 mL). Purification [petroleum ether/ethyl acetate = 1:4] gave **3b** as a yellow oil (2.620 g, 81%). R_f: 0.6. Compound **3b**: ^1H NMR (200 MHz) δ: 7.40–7.32 [m, 5H]; 4.82 [d, $J = 7.6$ Hz, 1H]; 3.95–3.85 [m, 2H]; 3.66–3.53 [m, 1H]; 2.98–2.73 [m, 2H]; 1.92–1.71 [m, 1H]; 1.44 [s, 9H]; 0.91 [d, $J = 6.4$ Hz, 6H]. ^{13}C NMR (50.3 MHz) δ: 157.05; 133.22; 128.78; 128.72; 128.58; 128.52; 127.85; 80.40; 60.32; 53.95; 51.81; 30.84; 28.29; 19.03; 18.00. $[\alpha]_D^{24} = +1.2$ (*c* 0.94, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83; H, 9.65; N, 9.58. Found: C, 69.87; H, 9.61; N, 9.60.

4.2.3. (*S*)-*tert*-Butyl-1-(benzylamino)-3-(4-(benzyloxy)-phenyl)propan-2-ylcarbamate 3c. To amide **1c** (2.0 g, 4.83 mmol) in THF (45 mL) $LiAlH_4$ (228 mg, 6.0 mmol) was added. After workup 1706 mg (99%) of crude aldehyde **2c** was obtained and reacted with benzylamine (0.6 mL, 5.9 mmol), $NaCNBH_3$ solution (7.08 mL) and acetic acid (0.6 mL) in dry MeOH (42 mL). After workup and purification [petroleum ether/ethyl acetate = 1:4], 1.815 g (83%) of **3c** were obtained. R_f: 0.2. Compound **3c**: ^1H NMR (200 MHz) δ: δ ($CDCl_3$, 200 MHz): 7.42–7.30 [m, 10H]; 7.08 [d, $J = 8.8$ Hz, 2H]; 6.89 [d, $J = 8.8$ Hz, 2H]; 5.04 [m, 1H]; 4.80 [d, $J = 7.8$ Hz, 1H]; 3.90–3.72 [m, 2H+1H]; 2.99 [br s, 1H]; 2.79–2.68 [m, 2H+2H]; 1.42 [s, 9H]. ^{13}C NMR (100.6 MHz) δ: 157.42; 155.66; 140.14; 137.11; 130.58; 130.29 (×2); 128.53 (×2); 128.36 (×2); 128.11 (×2); 127.88; 127.42 (×2); 126.98; 114.77 (×2); 79.18; 70.04; 64.18; 53.75; 51.34; 38.11; 28.39. $[\alpha]_D^{24} = -1.4$ (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27. Found: C, 75.26; H, 7.64; N, 6.23.

4.3. Synthesis of 2-oxopiperazines 5

Synthesis of (2-bromoacetyl)-amides **4a–c**: A solution of bromoacetic acid (4.23 equiv) and DCC (2 equiv) in dry CH_2Cl_2 (4 mL) was stirred at rt for 1 h. To this mixture, after cooling at −15 °C, a solution of **3a–c** (1 equiv) in dry CH_2Cl_2 (4 mL) and NMM (2.85 equiv) was added. The mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2 (5 mL) and quenched by the addition of H_2O (10 mL). The organic phases were collected and the aqueous phase was extracted with DCM. The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The crude was filtered over a silica gel column to afford compounds **4a–c**, which were used without further purification.

Cyclization to oxopiperazines **5a–c**: Bromides **4a–c** (1 equiv) were dissolved in dry THF/DMF (1/1, 10 mL)) and cooled at 0 °C. NaH (3 equiv) was added and the mixture was stirred at room temperature for 2 h, after which it was quenched by the careful addition of H_2O (50 mL). The solution was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with H_2O (30 × 20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated to afford oxopiperazines **5a–c** which were purified by flash chromatography.

4.3.1. (*S*)-1-Benzyl,4-*tert*-butoxycarbonyl,5-methyl-2-oxo-piperazine 5a. To a solution of bromoacetic acid (1.59 g, 11.4 mmol) and DCC (1.11 g, 5.4 mmol) in dry CH_2Cl_2 (8 mL) a solution of **3a** (712 mg, 2.7 mmol) in dry CH_2Cl_2

(8 mL) was added, together with NMM (0.8 mL, 7.7 mmol). Filtration [petroleum ether/ethyl acetate (4:1)] gave **4a** as a yellow oil (894 mg, 86%). Compound **4a** (2.2 mmol) was reacted with NaH (264 mg, 6.6 mmol) in THF/DMF (1/1) (30 mL). Purification [petroleum ether/ethyl acetate = 1:4] gave **5a** as a yellow solid (509 mg, 76%). R_f: 0.6. Compound **5a**: ^{1}H NMR (400 MHz) δ: 7.35–7.25 [m, 5H]; 4.83 [d, $J = 14.5$ Hz, 1H]; 4.41–4.32 [m, 1H+1H+1H]; 3.85 [d, $J = 18.4$ Hz, 1H]; 3.51 [dd, $J = 12.4$, 4.4 Hz, 1H]; 2.92 [dd, $J = 12.4$, 1.6 Hz, 1H]; 1.45 [s, 9H]; 1.07 [d, $J = 6.8$ Hz, 3H]. ^{13}C NMR (100.6 MHz) δ: 165.54; 153.52; 136.08; 128.67 (×2); 128.42; 127.77 (×2); 80.60; 50.21; 49.92; 44.69; 28.32; 15.75. $[\alpha]_D^{24} = +0.7$ (c 0.81, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.12; H, 7.92; N, 9.23.

4.3.2. (*S*)-1-Benzyl,4-*tert*-butoxycarbonyl,5-isopropyl-2-oxopiperazine 5b. To a solution of bromoacetic acid (2.60 g, 18.7 mmol) and DCC (1.82 g, 8.8 mmol) in dry CH_2Cl_2 (12 mL) a solution of **3b** (1293 mg, 4.4 mmol) in dry CH_2Cl_2 (12 mL) was added together with NMM (1.38 mL, 12.6 mmol). Filtration [petroleum ether/ethyl acetate (4:1)] gave **4b** as a yellow oil (894 mg, 86%). Compound **4b** (700 mg, 1.7 mmol) was reacted with NaH (72 mg, 5.1 mmol) in dry THF/DMF (1/1) (22 mL). Purification [petroleum ether/ethyl acetate = 1:3] gave **5b** as a yellow oil (290 mg, 53%). R_f: 0.4. Compound **5b**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.35–7.26 [m, 5H]; 4.95 [d, $J = 14.0$ Hz, 1H]; 4.46 [br d, $J = 18.6$ Hz, 1H]; 4.22 [d, $J = 14.0$ Hz, 1H]; 3.89–3.77 [m, 1H]; 3.72 [d, $J = 18.6$ Hz, 1H]; 3.42 [dd, $J = 12.6$, 4.6 Hz, 1H]; 3.20 [dd, $J = 12.6$, 1.4, 1H]; 1.85–1.69 [m, 1H]; 1.46 [s, 9H]; 0.85 [d, $J = 6.6$ Hz, 3H]; 0.59 [d, $J = 6.6$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 165.09; 153.62; 136.05; 128.43 (×2); 128.32 (×2); 127.56; 80.29; 55.65; 53.84; 49.64; 46.21; 45.06; 28.27; 26.57; 19.51. $[\alpha]_D^{24} = +0.9$ (c 0.45, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.61; H, 8.46; N, 8.47.

4.3.3. (*S*)-(1-Benzyl)-4-*tert*-butoxycarbonyl,5-[(4-benzyloxy)-benzyl]-2-oxopiperazine 5c. To a solution of bromoacetic acid (1.320 g, 9.5 mmol) and DCC (910 mg, 4.4 mmol) in dry CH_2Cl_2 (20 mL) a solution of **3c** (1.00 g, 2.2 mmol) in dry CH_2Cl_2 (20 mL) was added together with NMM (6.9 mL, 6.2 mmol). After workup 640 mg (70%) of crude **4c** was obtained as a white solid and used without further purification. Compound **4c** (300 mg, 0.5 mmol) was reacted with NaH (38 mg, 1.59 mmol) in dry THF/DMF (1/1)(7mL). Purification [petroleum ether/ethyl acetate = 3:1] gave **5c** as a yellow oil (81 mg, 31%). R_f: 0.3. Compound **5c**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.32–7.23 [m, 10H]; 6.71 [d, $J = 8.4$, 2H]; 6.65 [d, $J = 8.8$, 2H]; 4.95–4.93 [m, 2H]; 4.80 [d, $J = 14.4$, 1H]; 4.34–4.21 [m, 1H+1H+1H]; 3. 84 [d, $J = 18.8$, 1H]; 3.30 [dd, $J = 12.4$, 4.4, 1H]; 2.92 [dd, $J = 12.4$, 1.6 Hz, 1H]; 2.64 [dd, $J = 13.6$, 6.0 Hz, 1H]; 2.49–2.43 [dd, $J = 13.6$, 9.2 Hz, 1H]; 1.33 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 165.04; 157.11; 153.11; 136.62; 136.02; 129.70; 129.25; 128.61 (×2); 128.50 (×2); 128.20 (×2); 127.55 (×2); 127.58; 127.05; 114.60 (×2); 80.41; 69.75; 53.66; 49.76; 46.47; 45.011; 28.15. $[\alpha]_D^{24} = -62.9$ (c 1.00, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}N_2O_4$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.10; H, 7.05; N, 5.71.

4.4. Alkylation of 2-oxopiperazines

Oxopiperazines **5a–c** (1 equiv) were dissolved in dry THF (10 mL) and HMPA (3.3 equiv), then the solution was cooled at −78 °C and carefully reacted with a solution of *t*-BuLi (1.7 M, pentane, 2 equiv). After 15 min, the suitable electrophile (3.3 equiv) was added. The reaction mixture was stirred at −78 °C for 3–5 h, then treated with a saturated aqueous solution of ammonium chloride (10 mL). The two phases were separated, extracted with CH_2Cl_2 (3 × 10 mL), dried and concentrated to afford a crude which was purified by flash chromatography.

4.4.1. (3*S*,5*S*)-1-Benzyl,3-allyl,4-*tert*-butoxycarbonyl,5-methyl-2-oxopiperazine 6a. Oxopiperazine **5a** (100 mg, 0.3 mmol) was reacted with HMPA (197 μL, 1.12 mmol), *t*-BuLi (400 μL, 0.7 mmol) and allylbromide (93 μL, 1.12 mmol) in dry THF (6 mL) for 3 h. Purification [hexane/ethyl acetate = 2:1] gave **6a** as a yellow oil (76 mg, 65%). R_f: 0.8. Compound **6a**: ^{1}H NMR (200 MHz) δ: 7.26–7.19 [m, 5H]; 5.81–5.62 [m, 1H]; 5.04–4.95 [m, 1H+1H]; 4.64 [d, $J_{xy} = 14.3$ Hz, 1H]; 4.42 [d, $J_{xy} = 14.3$ Hz, 1H]; 4.32 [t, $J = 6.6$ Hz, 1H]; 4.01 [m, 1H]; 3.54 [dd, $J = 13.3$, 3.6 Hz, 1H]; 2.81 [dd, $J = 13.3$, 1.8 Hz, 1H]; 2.57 [m, 1H+1H]; 1.40 [s, 9H]; 0.90 [d, $J = 6.6$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 168.10; 153.44; 135.97; 133.12; 128.64 (×2); 128.50 (×2); 127.72; 118.11; 80.42; 57.44, 50.57; 48.99; 46.73; 38.67, 28.44, 17.48. $[\alpha]_D^{24} = 11.1$ (c 1.26, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8,13. Found: C, 69.70; H, 8.22; N, 8.12.

4.4.2. (3*S*,5*S*)-1-Benzyl,3-allyl,4-*tert*-butoxycarbonyl,5-isopropyl-2-oxopiperazine 6b. Oxopiperazine **5b** (541 mg, 1.62 mmol) was reacted with HMPA (776 μL, 4.42 mmol), *t*-BuLi (296 μL, 2.68 mmol) and allylbromide (373 μL, 4.42 mmol) in dry THF (23 mL) for 2 h. Purification [hexane/ethyl acetate = 3:1] gave **6b** as a white solid (203 mg, 33%). R_f: 0.5. Compound **6b**: ^{1}H NMR (200 MHz) δ: 7.26–7.21 [m, 5H]; 5.80–5.59 [m, 1H]; 5.02–4.95 [m, 1H+1H]; 4.64 [d, $J_{xy} = 14.2$ Hz, 1H]; 4.36–4.26 [m, 1H+1H]; 3.68 [m, 1H]; 3.37 [dd, $J = 13.2$, 3.8 Hz, 1H]; 3.08 [dd, $J = 13.2$, 2.2 Hz, 1H]; 2.68–2.50 [m, 2H]; 1.79–1.61 [m, 1H]; 1.40 [s, 9H]; 0.77 [d, $J = 6.6$ Hz, 3H]; 0.56 [d, $J = 6.6$ Hz, 6H]. ^{13}C NMR (50.3 MHz) δ: 168.49; 154.04; 136.05; 128.69 (×2); 128.52 (×2); 127.72, 132.90; 118.23; 80.35; 58.12; 56.03; 50.52; 45.54, 38.00; 29.82; 28.41; 19.64; 19.38. $[\alpha]_D^{24} = +1.0$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.88; H, 8.63; N, 7.55.

4.4.3. (3*S*,5*S*)-1-Benzyl,3-allyl,4-*tert*-butoxycarbonyl,5-[4-(benzyloxy)-benzyl]-2-oxopiperazine 6c. Oxopiperazine **6c** (162 mg, 0.33 mmol) was reacted with HMPA (195 μL, 1.1 mmol), *t*-BuLi (65 μL, 0.66 mmol) and allylbromide (93 μL, 1.1 mmol) in dry THF (5 mL) for 5 h. Purification [hexane/ethyl acetate = 3:1] gave **6c** as a white solid (56 mg, 32%). R_f: 0.6. Compound **6c**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.34–7.17 [m, 10H]; 6.74 [d, $J = 8.6$ Hz, 2H]; 6.67 [d,

$J = 8.6$ Hz, 2H]; 5.75–5.65 [m, 1H]; 4.99–4.94 [m, 1H+1H+2H]; 4.68 [d, $J = 14.4$ Hz, 1H]; 4.38 [t, $J = 5.6$ Hz, 1H]; 4.30 [d, $J = 14.4$ Hz, 1H]; 3.98 [m, 1H]; 3.29 [dd, $J = 3.6$, 1.2 Hz, 1H]; 2.84–2.28 [m, 2H+2H+1H]; 1.44 [s, 9H]. ^{13}C NMR (100.6 MHz) δ: 168.61; 157.46; 153.63, 136.96; 136.39; 133.12; 130.10; 128.96 (×2); 128.77 (×2); 128.55 (×2); 127.94; 127.43 (×2); 127.33 (×2); 114.88 (×2); 118.38; 80.75; 69.97; 60.35; 57.48; 53.32; 50.51; 44.65; 36.13; 28.40. $[\alpha]_D^{24} = -31.8$ (c 1.31, $CHCl_3$). Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.26; H, 7.27; N, 5.32. Found: C, 75.24; H, 7.25; N, 5.30.

4.4.4. (3*S*,5*S*)-1-Benzyl,3-carboxyethyl,4-*tert*-butoxy-carbonyl,5-methyl-2-oxopiperazine 7. Oxopiperazine **5a** (30 mg, 0.1 mmol) was reacted with HMPA (58 μL, 0.33 mmol), *t*-BuLi (118 μL, 0.2 mmol) and ethyl chloroformate (31 μL, 0.33 mmol) in dry THF (1.5 mL) for 3 h. Purification [hexane/ethyl acetate = 2:1] gave **7** as a diastereomeric mixture (10 mg, 30%). R_f: 0.4. Compound **7**, major diastereoisomer: ^{1}H NMR (400 MHz, 50 °C) δ: 7.40–7.25 [m, 5H]; 5.06 [br s, 1H]; 4.74 [d, $J = 14.4$ Hz, 1H]; 4.50 [d, $J = 14.4$ Hz, 1H]; 4.35–4.24 [m, 1H+2H]; 3.43 [dd, $J = 12.6$, 4.6 Hz, 1H]; 3.02 [dd, $J = 13.0$, 4.6 Hz, 1H]; 1.40 [s, 9H]; 1.34 [t, $J = 7.2$ Hz, 3H]; 0.90 [d, $J = 6.4$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 170.0; 168.43; 157.61; 135.75; 128.76 (×2); 128.45 (×2); 127.95; 81.39; 61.95; 60.32; 50.46; 50.11, 49.17; 28.22; 17.46; 14.09.

4.4.5. (3*S*,5*S*)-1-Benzyl,3-methoxymethyl,4-*tert*-butoxy-carbonyl,5-methyl-2-oxopiperazine 8. Oxopiperazine **5a** (30 mg, 0.1 mmol) was reacted with HMPA (58 μL, 0.33 mmol), *t*-BuLi (118 μL, 0.2 mmol) and bromomethyl methyl ether (30 μL, 0.33 mmol) in dry THF (1.5 mL) for 3 h. Purification [hexane/ethyl acetate = 2:1] gave **8** as a white oil (10 mg, 30%). R_f: 0.4. Compound **8**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.40–7.25 [m, 5H]; 4.79 [d, $J = 14.4$ Hz, 1H]; 4.50 [d, $J = 14.4$ Hz, 1H]; 4.39–4.37 [m, 1H]; 4.08–4.05 [m, 1H]; 3.94–3.88 [m, 1H]; 3.85 [dd, $J = 9.4$, $J = 2.0$ Hz, 1H]; 3.80 [dd, $J = 9.4$, $J = 2.4$ Hz, 1H]; 3.32 [s, 3H]; 2.79 [dd, $J = 12.4$, $J = 2.0$ Hz, 1H]; 1.47 [s, 9H]; 1.02 [d, $J = 6.4$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 167.66; 159.49; 135.92; 128.34 (×2); 128.20 (×2); 127.47; 80.55; 67.65, 62.00; 59.22; 50.66, 49.26; 46.59; 28.50; 17.13. $[\alpha]_D^{24} = +14.4$ (c 0.61, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.43; H, 8.13; N, 8.01.

4.4.6. (3*S*,5*S*)-1,3-Dibenzyl,4-*tert*-butoxycarbonyl,5-methyl-2-oxopiperazine 9. Oxopiperazine **5a** (65 mg, 0.22 mmol) was reacted with HMPA (109 μL, 0.73 mmol), *t*-BuLi (259 μL, 0.44 mmol) and benzyl bromide (87 μL, 0.73 mmol) in dry THF (1.5 mL) for 3 h. Purification [hexane/ethyl acetate = 2:1] gave **9** as a white solid (37 mg, 43%). R_f: 0.5. Compound **9**: ^{1}H NMR (100.6 MHz, 50 °C) δ: 7.30–7.04 [m, 10H]; 4.73 [d, $J = 14.2$ Hz, 1H]; 4.60–4.57 [m, 1H]; 4.09 [d, $J = 14.2$ Hz, 1H]; 3.86 [m, 1H]; 3.45 [m, 1H]; 3.14 [dd, $J = 13.6$, 3.2 Hz, 1H]; 2.8 [d, $J = 12.8$ Hz, 1H]; 2.08 [dd, $J = 12.4$, 2.0 Hz, 1H]; 1.62 [s, 9H]; 0.88 [d, $J = 6.4$ Hz, 3H]. ^{13}C NMR (100.6 MHz) δ: 168.12; 153.78; 135.86; 135.78; 130.07 (×2); 129.10 (×2); 128.49 (×2); 128.04 (×2); 127.79; 126.85; 78.24; 58.58; 50.17; 47.75; 46.10; 39.36; 28.40; 17.08. $[\alpha]_D^{24} = +15.1$ (c 1.00, $CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.02; H, 7.62; N, 7.13.

4.4.7. (3*S*,5*S*)-1-Benzyl,3-(1-hydroxyethyl)-4-*tert*-butoxy-carbonyl,5-methyl-2-oxopiperazine 10. Oxopiperazine **5a** (45 mg, 0.15 mmol) was reacted with HMPA (75 μL, 0.50 mmol), *t*-BuLi (182 μL, 0.30 mmol) and acetaldehyde (25 μL, 0.50 mmol) in dry THF (2.0 mL) for 5 h. Purification [hexane/ethyl acetate (1:1)] gave **10** as a complex mixture of diastereoisomers which have not been separated (15 mg, 27%). R_f: 0.2. Compound **10**, major diastereoisomer: ^{1}H NMR (200 MHz) δ: 7.32–7.28 [m, 5H]; 4.63 [br s, 1H]; 4.41 [d, $J = 6.2$ Hz, 1H]; 4.19–4.07 [m, 1H+1H]; 3.60 [dd, $J = 13.4$, 3.6 Hz, 1H]; 2.96 [dd, $J = 13.4$, 2.0 Hz, 1H]; 1.47 [s, 9H]; 1.17 [d, $J = 6.8$ Hz, 3H]; 0.98 [d, $J = 6.4$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 167.51; 154.82; 135.77; 128.78 (×2); 128.66 (×2); 128.06; 81.31; 69.78; 62.40; 50.48; 49.19; 47.09; 28.28; 19.86; 17.13.

4.4.8. (3*S*,5*S*)-1-Benzyl,3-(ethoxycarbonylmethyl)-4-*tert*-butoxycarbonyl,5-methyl-2-oxopiperazine 11. Oxopiperazine **5a** (45 mg, 0.15 mmol) was reacted with HMPA (0.75 mL, 0.50 mmol), *t*-BuLi (0.182 mL, 0.30 mmol) and ethylbromoacetate (0.55 mL, 0.50 mmol) in dry THF (2.0 mL) for 3 h. Purification [hexane/ethyl acetate = 2:1] afforded 21 mg (40%) of compound **11** as an oil. R_f: 0.3. Compound **11**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.35–7.27 [m, 5H]; 4.74 [d, 1H, $J = 14.4$ Hz]; 4.58–4.54 [m, 1H]; 4.49 [d, 1H, $J = 14.4$ Hz]; 4.16–4.09 [m, 2H+1H]; 3.68 [dd, $J = 13.0$ Hz, $J = 3.8$ Hz, 1H]; 2.98 [d, $J = 5.6$ Hz, 1H]; 2.91 [dd, $J = 12.8$ Hz, $J = 2.4$ Hz, 1H]; 1.47 [s, 9H]; 1.25 [t, $J = 7.2$ Hz 3H]; 0.98 [d, $J = 6.8$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 167.41; 153.75; 135.82; 128.66 (×2); 128.52 (×2); 127.70; 80.90; 60.70; 54.47; 50.46; 48.70; 46.82; 39.05; 28.40; 17.15; 14.30 $[\alpha]_D^{24} = +9.4$ (c 0.93, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.63; H, 7.71; N, 7.14.

4.4.9. (*S*)-1-Benzyl,3,3′-diallyl,4-*tert*-butoxycarbonyl,5-methyl-2-oxopiperazine 12. Oxo-piperazine **6a** (27 mg, 0.07 mmol) was reacted with HMPA (40 μL, 0.23 mmol), *t*-BuLi (80 μL, 0.14 mmol) and allylbromide (19 μL, 0.23 mmol) in dry THF (2.5 mL) for 2 h. Purification [hexane/ethyl acetate = 9:1] gave **12** as a colourless oil (10 mg, 33%). R_f: 0.3. Compound **12**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.30–7.26 [m, 5H]; 5.76–5.62 [m, 1H+1H]; 5.11–4.97 [m, 2H+2H]; 4.71 [d, $J = 14.0$ Hz, 1H]; 4.45 [d, $J = 14.0$ Hz, 1H]; 4.35–4.26 [m, 1H]; 3.59 [dd, $J = 12.6$, $J = 3.8$ Hz, 1H]; 3.24–3.18 [m, 1H]; 3.10–3.08 [m, 1H+1H]; 2.77 [dd, $J = 12.6$, 1.8 Hz, 1H]; 2.64–2.58 [m, 1H]; 1.49 [s, 9H]; 0.94 [d, $J = 6.4$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 169.66; 154.72; 136.30; 135.30; 133.37; 128.94 (×2); 128.57 (×2); 127.79; 118.80; 118.12; 79.90; 67.57; 51.39; 48.96; 46.10; 42.89; 29.69; 28.50; 19.23; 14.19. $[\alpha]_D^{24} = -3.3$ (c 0.25, $CHCl_3$). Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.89; H, 8.42; N, 7.16.

4.4.10. (3*S*,5*S*)-1-Benzyl,3-allyl,3′benzyl,4-*tert*-butoxy-carbonyl,5-methyl-2-oxopiperazine 13. Oxo-piperazine **9** (37 mg, 0.09 mmol) was reacted with HMPA (54 μL,

0.31 mmol), *t*-BuLi (112 μL, 0.19 mmol) and allylbromide (26 μL, 0.31 mmol) in dry THF (2 mL) for 3 h. Purification [hexane/ethyl acetate = 7:1] gave **13** as a yellow oil (16 mg, 35%). R_f: 0.5. Compound **13**: ^{1}H NMR (400 MHz, 50 °C) δ: 7.19–7.17 [m, 10H]; 5.69–5.57 [m, 1H]; 5.05–4.91 [m, 2H]; 4.79 [d, $J = 14.2$ Hz, 1H]; 4.15 [d, $J = 14.2$ Hz, 1H]; 4.05–3.95 [m, 1H]; 3.69 [d, $J = 13.2$ Hz, 1H]; 3.56 [m, 1H]; 3.42 [dd, $J = 12.4$, 4.0 Hz, 1H]; 3.39–3.35 [m, 1H]; 2.67–2.61 [m, 1H]; 2.49 [dd, $J = 12.4$, 0.8 Hz, 1H]; 1.47 [s, 9H]; −0.19 [d, $J = 6.8$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 169.44; 153.56; 138.72; 136.12; 133.33; 131.19 (×2); 128.78 (×2); 128.36 (×2); 127.89 (×2); 127.65; 126.58; 118.90; 80.17; 69.79; 51.18; 48.87; 46.07; 43.94; 39.82; 28.62; 16.37. $[\alpha]_D^{24} = +0.4$ (*c* 0.65, $CHCl_3$). Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.66; H, 7.86; N, 6.42.

4.5. Synthesis of the Mosher's amides

Oxopiperazine **5a** (100 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled at 0 °C and reacted with an excess of TFA (1.00 mL). The mixture was stirred at rt overnight then hydrolyzed with water (10 mL), extracted with CH_2Cl_2 (10 mL) and washed with Na_2CO_3 saturated solution (10 mL) and brine (10 mL). Evaporation of the solvent gave the deprotected oxopiperazine which was used without further purification (70 mg, 98%).

1-Benzyl-5-methyl-2-oxo-piperazine: ^{1}H NMR (200 MHz) δ: 7.38–7.16 [m, 10H]; 4.63 [d, 1H, $J = 14.6$ Hz]; 4.39 [d, 1H, $J = 14.6$ Hz]; 3.66–3.48 [m, 2H]; 3.07–2.82 [m, 2H+1H]; 2.21 [br s, 1H]; 1.03 [d, $J = 5.8$ Hz, 3H]. ^{13}C NMR (50.3 MHz) δ: 167.26; 136.35; 128.47 (×2); 127.97 (×2); 127.35; 53.57; 49.88; 49.77; 48.51; 19.00.

Deprotected oxopiperazine (50 mg, 0.2 mmol) was dissolved into pyridine (2 mL) and cooled to 0 °C. A solution of MTPA-Cl (100 mg, 0.4 mmol) in pyridine (1 mL). The reaction mixture was stirred overnight, then added with water (5 mL), extracted with diethyl ether and washed with Na_2CO_3 solution (5 mL) and brine (5 mL). Evaporation gave a crude which was filtered on silica gel.

(*S*,*S*)-*Mosher's amide, major rotamer*: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.56 [d, $J = 7.4$ Hz H]; 7.21–6.82 [m, 8H]; 4.89 [d, 1H, $J = 19.1$ Hz]; 4.79–4.70 [m, 1H]; 4.09 [d, 1H, $J = 14.4$ Hz]; 3.71 [d, 1H, $J = 14.4$ Hz]; 3.28 [d, 3H, $J = 1.6$ Hz]; 2.75 [dd, $J = 11.2$, 3.6 Hz, 1H]; 2.11 [dd, $J = 12.6$, 2.1 Hz, 1H]; 0.65 [d, 3H, $J = 6.6$]. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 164.38; 163.67; 136.66; 132.94; 129.62; 128.71 (×2); 128.45 (×2); 128.25 (×2); 127.89 (×2); 126.33; 120.05; 84.01; 55.15; 49.90; 49.16; 45.06; 43.16; 24.91; 15.50. ^{19}F NMR (200 MHz, $CDCl_3$) δ: 70.44.

(*S*,*R*)-*Mosher's amide, major rotamer*: ^{1}H NMR (400 MHz, C_6D_6) δ: 7.51 [d, $J = 7.4$ Hz, 2H]; 7.06–6.87 [m, 8H]; 4.68–4.58 [m, 1H]; 4.52 [d, 1H, $J = 18.0$ Hz]; 4.41 [d, 1H, $J = 14.4$ Hz]; 3.97 [d, 1H, $J = 14.4$ Hz]; 3.35 [d, 3H, $J = 1.6$ Hz]; 2.82 [d, $J = 18.0$, 1H]; 2.13 [dd, $J = 12.9$, 3.1 Hz, 1H]; 0.56 [d, 3H, $J = 7.0$]. ^{13}C NMR (50.3 MHz) δ: 170.89; 163.77; 135.60; 132.40; 129.47; 128.62 (×2); 128.50 (×2), 128.31 (×2); 128.14 (×2); 127.82; 126.32; 83.92; 55.51; 49.87; 49.67; 44.81; 43.20; 21.14; 14.30. ^{19}F NMR (200 MHz) δ: 70.59.

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