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Studies on the reduction and reductive alkylation of amino acid-derived spirocyclic 2,6-dioxopiperazines

Juan A. González-Vera, Pilar Ventosa-Andrés, Joanne Casey, M. Teresa García-López and Rosario Herranz*

Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain

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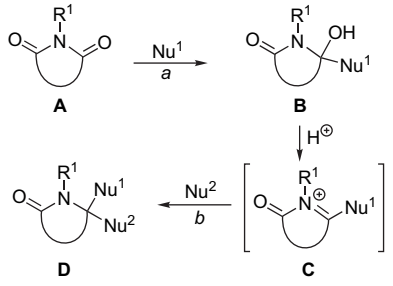
Abstract—The regio- and diastereoselective reduction and reductive alkylation of 3-spiro-2,6-dioxopiperazines are described via a two-step process, which involves addition of $NaBH_4$ or Grignard reagents, followed by TFA-mediated dehydration with a second $NaBH_4$ addition. The results show that the reactivity of 2,6-dioxopiperazines is limited by their steric hindrance and by the volume of the nucleophile, which preferably add to the C_6 carbonylic carbon with complete diastereoselectivity. The diastereoselectivity of the first step is mainly governed by electronic factors, which direct the addition of the nucleophile from the most hindered face, while in the second step, the $NaBH_4$ attacks from the less crowded face. This second step proceeds with partial or complete racemization.

1. Introduction

Piperazines and their spiro derivatives are included among the most frequently occurring privileged substructures found in compounds of therapeutic interest.[1] Amongst them, 1,4-disubstituted piperazine derivatives[1b,d] and 2,5-dioxopiperazines (cyclic dipeptides)[1c,2] have been the main focus of interest. However, 2,6-dioxopiperazine derivatives have received scarce attention, apart from certain antitumoral bis(2,6-dioxopiperazine) derivatives (topoisomerase II inhibitors),[2a,3] and some inhibitors of the influenza virus endonuclease, such as flutimide.[4] From the synthetic point of view, the 2,6-dioxopiperazine system could be considered as a versatile template for the synthesis of diversity of scaffolds, due to the presence of the reactive endocyclic imide group. This group is highly reactive toward nucleophiles,[5] and is a potential precursor of *N*-acyliminium ions,[6] which are very useful and versatile reactive species in organic synthesis. Perhaps, one of the most successful and versatile methods for obtaining *N*-acyliminium ion precursors has been the selective addition of hydride or organometallic reagent to one carbonyl group of a cyclic imide.[5,6] As shown in Scheme 1, most of the described methods for the reduction of cyclic imides (**A**) to lactam derivatives (**D**) involve a two-step process: a first step of addition of a nucleophile (a metal hydride[7] or an organometallic compound[8]) to give a hydroxylactam (**B**). In the second step, this hydroxylactam in acid media generates an unstable *N*-acyliminium ion intermediate (**C**), which adds a second nucleophile (Et_3SH[8b–d,9] or an organometallic compound[7a,c,8a,b]).



Scheme 1. General process of cyclic imide reduction to lactams.

In the course of a project focused on diversity-oriented synthesis, we have recently reported a general method for the synthesis of α-amino acid-derived spirocyclic 2,6-dioxopiperazines from α-quaternary-α-amino nitriles.[10] Now, having in mind the synthetic potential of cyclic imides, we have explored and reported herein our studies on reduction and reductive alkylation of 2,6-dioxopiperazine-3-spirocyclohexane derivatives as a source of diverse and highly substituted spirocyclic piperazines.

2. Results and discussion

Spirocyclic 2,6-dioxopiperazines **1a** and **1b**, derived from L-phenylalanine, and **1c**, derived from L-aspartic acid (Scheme 2),[10] were selected for the studies reported herein. First, we studied the reduction of these dioxopiperazines with $NaBH_4$. As shown in Scheme 2, treatment of **1a–c** with 3 equiv of $NaBH_4$ in MeOH at room temperature quantitatively led to a (6:1) mixture of the corresponding

* Corresponding author. Tel.: +34 91 5622900; fax: +34 91 5644853; e-mail: rosario@iqm.csic.es

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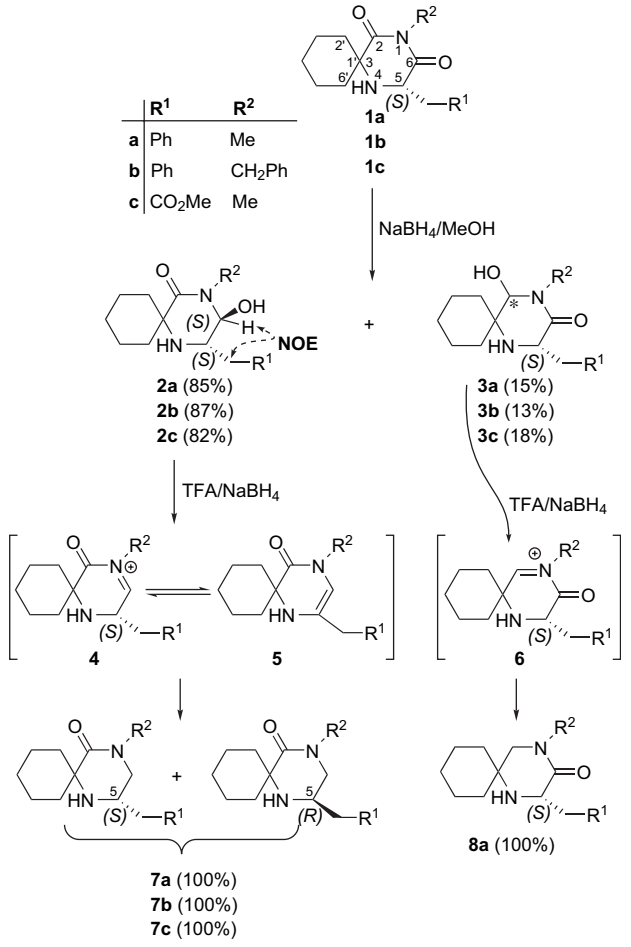
6-hydroxy- and 2-hydroxypiperazine derivatives **2a–c** and **3a–c**, respectively.



Scheme 2. $NaBH_4$ mediated reduction of spirocyclic 2,6-dioxopiperazines **1**.

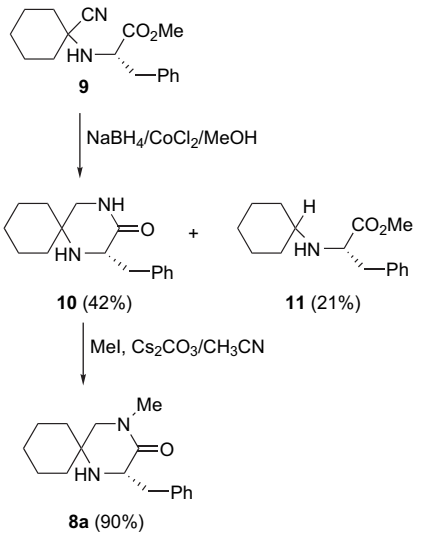
The ^1H NMR spectra of 6-hydroxy-2-oxopiperazines **2a–c** showed the presence of the 6-H proton as a doublet (**2a**,**b**), coupled to 5-H, or as a triplet (**2c**), coupled to 5-H and 6-OH, at δ 4.46–4.49 ppm, while the spectra of the 2-hydroxy isomers **3a–c** showed the presence of 2-H as a singlet at δ 4.40–4.44 ppm. The ^{13}C NMR spectra of these hydroxylactams showed the disappearance of one of the carbonylic carbons and the appearance of a new carbon in the aliphatic carbon region (83–87 ppm). The reduction position was confirmed by the ^1H–^{13}C correlations observed in the HMBC spectra. As indicated in Scheme 2, the stereochemistry at C_6 in the 6-hydroxy-2-oxopiperazines **2a–c** was assigned as 6*S* based on the NOE effect observed between 6-H and 5-CH_2 protons in their 1D NOESY spectra. These results showed that the nucleophilic attack of $NaBH_4$ at C_6 was completely diastereoselective, *syn* to the amino acid side chain. As it has been previously proposed for the addition of nucleophiles to cyclic ketones,[11] this high preference for the axial addition of the nucleophile on the most hindered face of the dioxopiperazine ring could be due to the higher electronic stabilizing *syn* interaction of the emerging σ^* orbital with the C_5–H bond than with the C_5–C bond. The addition of $NaBH_4$ to C_2 was also completely stereoselective, obtaining only one of the possible diastereoisomers **3a–c**, but, due to the absence of NOE effects on 2-H, we could not assign the configuration at C_2.

In most of the reported precedents of reduction of cyclic imides to lactams,[8b–d,9] the reduction of the hydroxylactam **B** in the second step of Scheme 1 is carried out with Et_3SiH, using $BF_3\cdot OEt_2$ as acid to generate the intermediate *N*-acyliminium ion **C**. However, taking into account our experience in the reduction of 5-hydroxypyrrolidin-2-ones with $NaBH_4$ in neat TFA,[12] we applied these reagents to the reduction of the major 6-hydroxypiperazines **2a–c** and the minor 2-regioisomer derived from phenylalanine **3a**. This reduction quantitatively yielded the oxopiperazines **7a–c** and **8a**. We also tried to transform directly 2,6-dioxopiperazines **1a–c** into the oxopiperazines **7a–c** and **8a–c** by using $NaBH_4$ in neat TFA. However, in contrast to the reactivity of **1a–c** toward $NaBH_4$ in MeOH, these dioxopiperazines were recovered unaltered. This different behavior depending on the solvent showed up the suggested participation of MeOH in the reduction of carbonyl groups by $NaBH_4$.[13]

Taking into account the potential tautomerization of the *N*-acyliminium intermediate **4** to the enamine **5**, and thereby the possible racemization,[14] the enantiomeric purity of the reaction products was investigated. Firstly, we attempted this objective by means of chiral HPLC, using a CHIRALPAK IA column (150×4.6 mm, 5 μm) for the analysis of the reduction products. For this purpose, the reactions shown in Scheme 2 were repeated starting from the enantiomeric (*R*)-form of the 2,6-dioxopiperazines **1a–c**, derived from the corresponding D-amino acid derivative. Then, all the reaction products were analyzed on chiral HPLC, and the results for each enantiomeric pair were compared. Unfortunately, only the phenylalanine-derived pair **7a** showed enough enantiomeric resolution to be able to quantify racemization (ee=76). As an alternative methodology, the racemization was indirectly determined by the measure of D-incorporation at position 5, replacing $NaBH_4$ with $NaBD_4$ and using deuterated solvents (CD_3OD and deuterated TFA) in the two steps of Scheme 2. Then, the D-incorporation was determined by the integral decrease for 5-H in the ^1H NMR spectra. As the racemization should be due to the hydride addition to the enamine intermediate **5**, the percentage of D-incorporation at C_5 should be twice the percentage of racemization. This study showed the absence of racemization in the first step of addition of hydride to the 2,6-dioxopiperazines **1a–c**, while a variable rate of racemization was determined for the reduction of the 6-hydroxy-2-oxopiperazines **2a–c** (ee=80 for **7a**, 60 for **7b**, and 0 for **7c**).

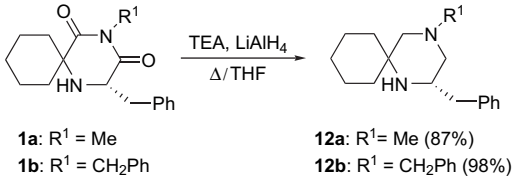
As an alternative for the regioselective synthesis of the 6-oxopiperazine **8a**, we studied its preparation by reduction of the L-phenylalanine-derived α-amino nitrile **9**[10] (Scheme 3). Initially, the reduction of the cyano group was unsuccessfully attempted by catalytic hydrogenation. Thus, using 10% Pd(C) or Raney Ni as catalyst at room temperature and 1–3 atm of H_2 pressure, conditions previously used for the reduction of other α-amino-nitriles,[15] the starting material was recovered unaltered after 2 days. Similarly, the attempts of cyano-reduction by hydrogen transfer from hydrazine monohydrate[16] or formate[17] were also unsuccessful. Finally, the cyano-reduction was achieved using $NaBH_4$ in the presence of $CoCl_2$.[18] As shown in Scheme 3, the treatment of **9** with 10 equiv of $NaBH_4$ and 2 equiv of $CoCl_2$ in MeOH led to a 42% of the *N*-unsubstituted-6-oxopiperazine **10**, along with a 21% of the *N*-cyclohexyl-L-phenylalanine derivative

11, resulting from the removal of HCN, followed by reduction of the intermediate imine. Alkylation of **10** by treatment with MeI in the presence of Cs_2CO_3 gave a 90% of **8a**.



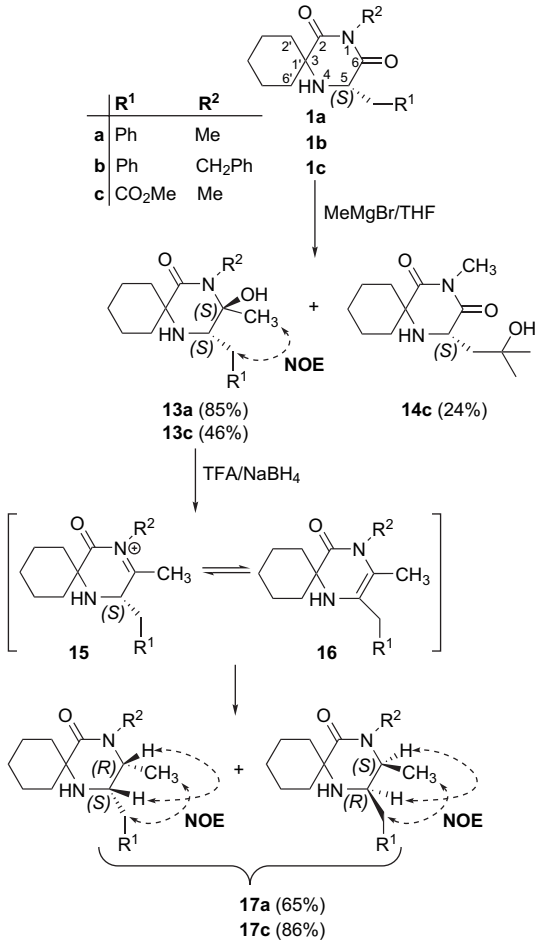
Scheme 3. Regioselective synthesis of 6-oxopiperazine derivatives.

Having in mind the recently reported regioselective reduction of glutarimide derivatives to δ-lactams by treatment with Et_3N, followed by reaction with $LiAlH_4$ in refluxing THF,[19] we also studied the application of these reaction conditions to the L-phenylalanine-derived dioxopiperazines **1a**,**b**. In this case, $LiAlH_4$ reduced both carbonyl groups at C_2 and C_6 to give the respective piperazines **12a** and **12b** (Scheme 4).



Scheme 4. $LiAlH_4$ mediated reduction of 2,6-dioxopiperazines.

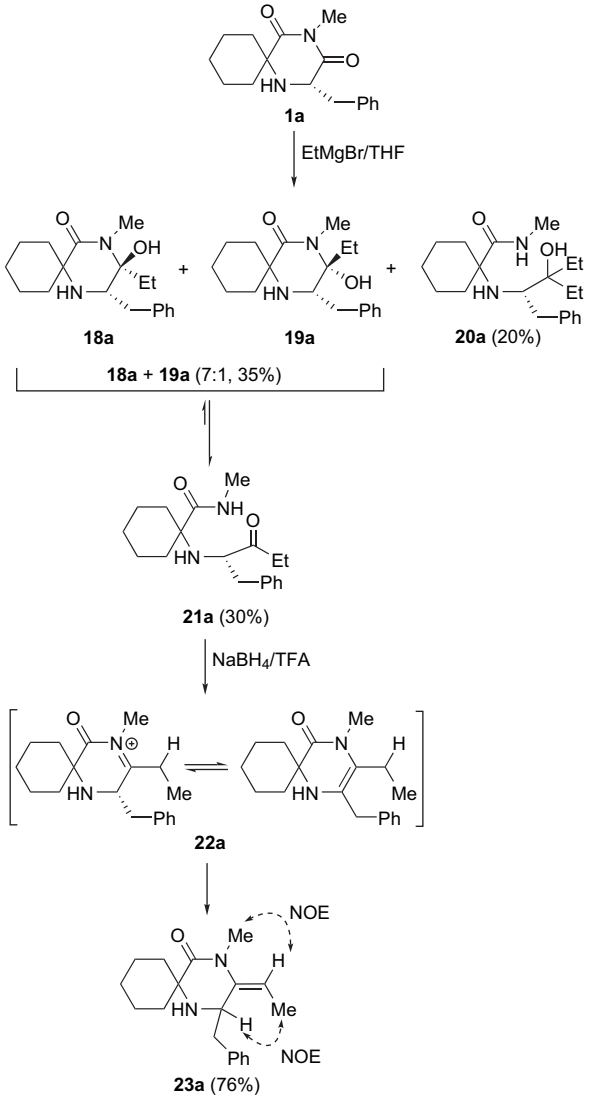
In parallel to the reduction studies, the reductive alkylation of 2,6-dioxopiperazines **1a–c** was studied via reaction with Grignard reagents, such as MeMgBr, EtMgBr, and $PhCH_2MgCl$. As shown in Scheme 5, the reactivity of 1-methyl-2,6-dioxopiperazines **1a** and **1c** toward MeMgBr was, in part, similar to that commented above for their reduction with $NaBH_4$ in MeOH, however, the 1-benzyl analog **1b** was unreactive. The addition of MeMgBr to **1a** and **1c** was completely regioselective at C_6, and, as in the case of the reduction, also completely diastereoselective for the *syn* addition with respect to the amino acid side chain, to give the 6-hydroxy-2-oxopiperazine derivatives **13a** and **13c**, respectively. In the case of the aspartic acid derivative **1c**, the alcohol **14c**, resulting from a double addition of MeMgBr to the methyl ester of the side chain, was obtained as side product. The assignment of the nucleophilic addition position was based on the ^1H–^{13}C correlations observed in the HMBC spectra of **13a** and **13c**. Particularly, those of C_2 with 2′-H or 6′-H, and 5-H with C_6 and 6-CH_3. In a second reaction step, the treatment of the 6-hydroxy-2-oxopiperazines **13a** and **13c** with $NaBH_4$ in neat TFA led, via the intermediates **15** and **16**, to the 2-oxopiperazines **17a** and **17b**. The assignment of relative configuration at C_6 was based on the NOE effects indicated in Scheme 5. According to this assignment, and contrary to the commented addition of $NaBH_4$ and MeMgBr to 2,6-dioxopiperazines, the addition of hydride to the *N*-acyliminium ions was mainly governed by steric factors, thus, the nucleophile attacked the intermediate **15** from the less hindered face, *anti* to the amino acid side chain.



Scheme 5. Reaction of 2,6-dioxopiperazines **1a–c** with MeMgBr.

Steric factors were also responsible for the different reactivity of these spirocyclic 2,6-dioxopiperazines with Grignard reagents more voluminous than MeMgBr. Thus, as shown in Scheme 6, the reaction of **1a** with EtMgBr gave a complex mixture, which was chromatographically resolved into the (≈7:1) diastereoisomeric mixture of 6-hydroxy-2-oxopiperazines **18a** and **19a** (35%), their ketone tautomer **21a** (30%), and the tertiary alcohol **20a** (20%), resulting from the attack of EtMgBr to **21a**. Interestingly, the diastereoisomeric mixture of **18a** and **19a** was unstable due to their transformation into the ketone **21a**. In view of this transformation,[8c] the second step of $NaBH_4$ mediated reduction was carried out with the **18a**+**19a**+**21a** mixture, which gave the 6-ethylidene-2-oxopiperazine derivative **23a** (76%) as the only reaction product. The NOE effects observed in the ^1H 1D NOESY spectrum of **23a**, between the N–Me and the olefinic proton, and between 5-H and the allylic protons, allowed the assignment of *E* configuration to the double bond. The preference

for the deprotonation to the reduction reaction due to the slight increase in volume from the Me to the Et group showed that the entrance of hydride was strongly limited by the high steric crowding in the *N*-acyliminium ion. Similarly, the steric hindrance to the entrance of the nucleophile could be the reason for the unreactivity of the 2,6-dioxopiperazines **1a–c** toward $PhCH_2MgCl$.



Scheme 6. Reaction of the 2,6-dioxopiperazine **1a** with EtMgBr.

The racemization rate in the two steps of the reductive alkylations of Schemes 5 and 6 was also determined by chiral HPLC and by the measure of D-incorporation at C_5. Both methodologies showed a complete racemization (ee=0) for the second reaction step in the synthesis of **17a**, **17c**, and **23a**.

3. Conclusion

In conclusion, the overall results herein disclosed show the potential of spirocyclic 2,6-dioxopiperazine as a source of diverse piperazine derivatives, via regio- and diastereoselective reduction and reductive alkylation. The addition of $NaBH_4$ or Grignard reagents to the 2,6-dioxopiperazine ring is mainly governed by electronic factors, which determine the preferential entrance of the nucleophile to C_6 from the most hindered face, *syn* to the amino acid side chain. However, in the resulting 6-hydroxypiperazines, the diastereoselectivity of the acid-mediated dehydration/$NaBH_4$ addition is determined by steric factors, to give the product of nucleophilic attack from the less hindered face, *anti* to the amino acid side chain. This second reduction step produces partial or total racemization. The steric crowding of the 3-spiro-2,6-dioxopiperazine skeleton limits its reactivity to hydride and low volume Grignard reagents.

4. Experimental

4.1. General

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}. Silica gel 60 (230–400 mesh) was used for flash chromatography. Preparative circular chromatography was performed on 20 cm diameter glass plates coated with a 1-mm layer of silica gel PF_{254}. Analytical RP-HPLC was performed on a Novapak C_{18} (3.9×150 mm, 4 μm) column, with a flow rate of 1 mL/min, and using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phases. Analytical chiral HPLC was carried out on a CHIRALPAK IA (150×4.6 mm, 5 μm) column of Daicel Chemical Industries Ltd., with a flow rate of 1 mL/min. EtOH of 10–1% in hexane was tried as mobile phase, although the best enantiomer resolution was obtained with 1% of EtOH. ^1H NMR spectra were recorded at 300 or 400 MHz, using TMS as reference, and ^{13}C NMR spectra were recorded at 75 or 100 MHz. The NMR spectral assignment was based on COSY, HSQC, and HMBC spectra. ES-MS spectra were performed, in positive mode, using MeOH as solvent.

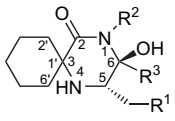
4.2. General procedure for the $NaBH_4$ mediated reduction of 2,6-dioxopiperazine-3-spirocyclohexanes 1a–c. Synthesis of the hydroxypiperazines 2a–c and 3a–c

$NaBH_4$ (28.4 mg, 0.75 mmol) was slowly added to a 0 °C cooled solution of the corresponding 2,6-dioxopiperazines **1a–c**[10] (0.25 mmol) in MeOH (4 mL). After reaching room temperature, the reaction mixture was stirred for 2 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). This solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 6–35% gradient of MeOH in CH_2Cl_2 as eluant. In this purification the 6-hydroxy-2-oxopiperazines **2a–c**, of higher R_f, were separated from their regioisomers **3a–c**. Significant analytical and spectroscopic data of these hydroxypiperazines are summarized in Tables 1 and 2.

4.3. General procedure for the $NaBH_4$ mediated reduction of hydroxypiperazines. Synthesis of the oxopiperazines 7a–c, 8a, and 17a,c

$NaBH_4$ (23.8 mg, 0.63 mmol) was slowly added to a 0 °C cooled solution of the corresponding hydroxypiperazines

Table 1. Significant analytical and spectroscopic data of 6-hydroxy-2-oxopiperazines



	2a	2b	2c	13a	13c	18a+19a
R^1	Ph	Ph	CO_2Me	Ph	CO_2Me	Ph
R^2	Me	CH_2Ph	Me	Me	Me	Me
R^3	H	H	H	Me	Me	Et
Formula[a]	$C_{17}H_{24}N_2O_2$	$C_{23}H_{28}N_2O_2$	$C_{13}H_{22}N_2O_4$	$C_{18}H_{26}N_2O_2$	$C_{14}H_{24}N_2O_4$	$C_{19}H_{28}N_2O_2$
Yield (%)	85	87	82	85	46	35
ES-MS $[M+1]^+$	289.2	365.1	271.2	303.2	285.1	317.1
Mp (°C)	169–171 (Benzene)	156–157 (Benzene)	Syrup	Syrup	Syrup	Syrup
t_R (min) (A:B)[b]	2.31 (30:70)	3.84 (40:60)	1.59 (25:75)	2.11 (50:50)	1.89 (25:75)	7.79 (14%) and 8.39 (86%) (25:75)
^{1}H NMR[c]						
5-H	2.94	3.00	3.21	2.92	3.23	3.09, 3.23
5-CH_2	2.51, 3.25	2.49, 3.15	2.52, 2.87	2.45, 3.20	2.34, 2.80	2.50, 2.56, 2.62
2′-H^{ax}	1.94	2.09	2.09	1.95	2.04	1.10–1.98
Cyclohexyl	1.01–1.71	1.11–1.80	1.25–1.93	1.06–1.58	1.24–1.90	1.10–1.98
R^1	7.23	7.14–7.33	3.72	7.30	3.72	7.13–7.77
R^2	2.85	4.38, 5.11, 7.14–7.33	2.92	2.91	2.89	2.89, 2.92
R^3	4.46	4.49	4.46	1.46	1.32	0.90, 1.04, 1.87, 1.91
$J_{5,6}$ (Hz)	7.5	7.5	7.5	—	—	—-
OH	ND[d]	2.74	ND[d]	ND[d]	2.49	ND[d]
^{13}C NMR[e]						
C_2	175.0	174.5	174.9	174.2	174.5	ND[d]
C_3	58.1	58.1	58.3	58.6	58.9	ND[d]
C_5	55.7	56.1	51.9	60.0	56.0	ND[d]
C_6	84.4	81.9	83.8	86.6	85.9	ND[d]
5-CH_2	38.3	38.2	36.7	35.9	35.2	ND[d]
R^1	126.9, 128.7, 129.0, 137.8	126.6, 128.4, 128.7, 137.2	52.0, 172.4	127.0, 128.7, 128.9, 138.5	52.0, 173.1	ND[d]
R^2	30.1	44.84, 127.0, 128.6, 129.1 137.5	30.1	26.8	26.7	ND[d]
R^3	—	—	—	19.1	18.9	ND[d]
Cyclohexyl	19.8, 20.6, 24.8, 29.4, 35.6	19.7, 20.5, 24.6, 30.1, 35.7	20.3, 20.7, 25.1, 30.1, 35.6	19.7, 20.7, 24.7, 29.1, 36.2	20.5, 20.9, 25.1, 30.3, 36.3	ND[d]

[a] Satisfactory analysis for C, H, and N.
[b] Novapak C_{18} (3.9×150 mm, 4 μm). A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 300 or 400 MHz, in $CDCl_3$, assigned with the help of COSY spectra.
[d] ND=not determined.
[e] Spectra registered at 75 or 100 MHz, in $CDCl_3$, assigned with the help of HSQC and HMBC spectra.

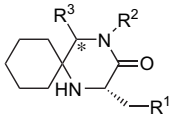
2a–c, **3a**, and **13a**,**c** (0.21 mmol) in TFA (3 mL). After reaching room temperature, the reaction mixture was stirred for 3 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). This solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 10–40% gradient of MeOH in CH_2Cl_2 as eluant. The significant analytical and spectroscopic data of the 6-oxopiperazine **8a** are summarized in Table 2, while those of the 2-oxopiperazines **7a–c** and **17a**,**c** are summarized in Table 3.

4.4. Synthesis of (5*S*)-5-phenylmethyl-6-oxopiperazine-3-spirocyclohexane (10) and *N*-cyclohexyl-L-phenylalanine methyl ester (11)

$NaBH_4$ (171.7 mg, 4.5 mmol) and $CoCl_2$ (118 mg, 0.9 mmol) were slowly added to a 0 °C cooled solution of *N*-(1-cyanocyclohexyl)-L-phenylalanine methyl ester (**9**)[10] (128.7 mg, 0.45 mmol) in MeOH (7 mL). After reaching room temperature, the reaction mixture was stirred for 1 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL). This solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 10–50% gradient of EtOAc in hexane as eluant. In this purification the 6-oxopiperazine **10** (49.2 mg, 42%), whose significant analytical and spectroscopic data are summarized in Table 2, was separated from *N*-cyclohexyl-L-phenylalanine methyl ester (**11**).

4.4.1. *N*-Cyclohexyl-L-phenylalanine methyl ester (11). Syrup (25.7 mg, 21%); HPLC [Novapak C_{18} (3.9× 150 mm, 4 μm) (A:B, 25:75)] t_R 5.46 min; ^{1}H NMR (300 MHz, $CDCl_3$) 1.00–1.76 (m, 10H, cyclohexyl), 2.27 (m, 1H, 1′-H), 2.79 (dd, 1H, *J*=7 and 13.5 Hz, 3-H), 2.89 (dd, 1H, *J*=7 and 13.5 Hz, 3-H), 3.54 (s, 3H, OCH_3), 3.58 (t, 1H, *J*=7 Hz, 2-H), 7.17 (m, 5H, Ph); ES-MS *m*/*z* 262.0 $[M+1]^+$. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.74; H, 8.92; N, 5.16.

Table 2. Significant analytical and spectroscopic data of 6-oxopiperazines



	3a	3b	3c	8a	10
R^1	Ph	Ph	CO_2Me	Ph	Ph
R^2	Me	CH_2Ph	Me	Me	H
R^3	OH	OH	OH	H	H
Formula[a]	$C_{17}H_{24}N_2O_2$	$C_{23}H_{28}N_2O_2$	$C_{13}H_{22}N_2O_4$	$C_{17}H_{24}N_2O$	$C_{16}H_{22}N_2O$
Yield (%)	15	13	18	100	42
ES-MS $[M+1]^+$	289.2	365.2	271.2	273.2	259.3
t_R (min) (A:B)[b]	2.32 (30:70)	3.50 (40:60)	2.77 (25:75)	2.83 (25:75)	2.06 (25:75)
^1H NMR[c]					
2-H	4.42	4.40	4.44	3.02, 3.07	2.94, 3.04
5-H	3.66	3.80	3.88	3.52	3.63
5-CH_2	2.67, 3.52	2.75, 3.59	2.57, 3.11	2.77, 3.28	2.88, 3.29
Cyclohexyl	1.11–1.67	1.02–1.62	1.15–1.62	1.29–1.70	1.19–1.64
R^1	7.27	7.12–7.38	3.70	7.27	7.21
R^2	3.01	4.22, 5.22, 7.12–7.38	3.00	2.91	6.12
^{13}C NMR[d]					
C_2	86.3	83.1	87.0	60.7	51.9
C_3	54.0	58.4	55.6	50.7	49.6
C_5	56.0	56.5	51.0	56.2	54.6
C_6	170.5	170.3	173.0	170.3	171.8
5-CH_2	39.9	40.3	38.7	39.9	38.0
R^1	126.6, 128.7, 129.2, 138.6	126.7, 128.5, 129.4, 137.4	51.6, 172.6	127.3, 129.3, 130.2, 140.6	126.6, 128.5, 129.2, 138.1
R^2	32.1	47.3, 127.5, 128.7, 129.4, 137.6	33.8	36.7	—
Cyclohexyl	20.9, 21.6, 25.6, 29.8, 34.4	21.2, 21.3, 25.5, 31.8, 34.6	20.8, 21.2, 25.7, 29.9, 33.8	22.5, 27.1, 32.1, 38.1	21.5, 21.6, 25.9, 30.6, 37.1

[a] Syrups, satisfactory analysis for C, H, and N.
[b] Novapak C_{18} (3.9×150 mm, 4 μm). A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 300 or 400 MHz, in $CDCl_3$, assigned with the help of COSY spectra.
[d] Spectra registered at 75 or 100 MHz, in $CDCl_3$, assigned with the help of HSQC and HMBC spectra.

4.5. Regioselective synthesis of (5*S*)-1-methyl-5-phenylmethyl-6-oxopiperazine-3-spirocyclohexane (8a)

MeI (16.3 μL, 0.26 mmol) and Cs_2CO_3 (85.2 mg, 0.26 mmol) were successively added under argon to a solution of the 6-oxopiperazine **10** in dry CH_3CN (2.5 mL). This reaction mixture was stirred at 50 °C for 2 h. Then, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 15–25% gradient of EtOAc in hexane as eluant, to obtain the 1-methyl-6-oxopiperazine **8a** (43 mg, 90%).

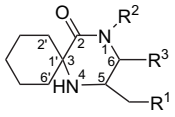
4.6. General procedure for the synthesis of piperazines 12a and 12b

TEA (25.1 μL, 0.18 mmol) was added under argon to a solution of the corresponding 2,6-dioxopiperazines **1a** and **1b** (0.15 mmol) in dry THF (4 mL). After 30 min of stirring at room temperature, $LiAlH_4$ (17.1 mg, 0.45 mmol) was added to the reaction mixture, and it was heated at reflux temperature for 3 h. Then, the reaction mixture was cooled at room temperature and saturated solution of NH_4Cl (1 mL) was added to destroy the excess of $LiAlH_4$. The precipitated $Al(OH)_3$ was filtered off and washed with THF. The combined filtrates were evaporated to dryness and the residue was dissolved in EtOAc (20 mL). This solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 20–45% gradient of EtOAc in hexane as eluant.

4.6.1. (5*S*)-1-Methyl-5-phenylmethylpiperazine-3-spirocyclohexane (12a). Syrup (33.7 mg, 87%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 25:75)] t_R 1.79 min; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08–1.57 (m, 10H, cyclohexyl), 1.62 (t, 1H, J=10.5 Hz, 6-H), 1.64 (d, 1H, J=11 Hz, 2-H), 2.18 (s, 3H, 1-CH_3), 2.55 (dd, 1H, J=8 and 13 Hz, 5-CH_2), 2.64 (dd, 1H, J=6 and 13 Hz, 5-CH_2), 2.67 (d, 1H, J=11 Hz, 2-H), 2.73 (dd, 1H, J=2.5 and 10.5 Hz, 6-H), 3.26 (m, 1H, J=2.5, 6, and 8 Hz, 5-H), 7.23 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 and 21.8 ($C_{3'}$ and $C_{5'}$), 26.2 ($C_{4'}$), 31.8 and 38.5 ($C_{2'}$ and $C_{6'}$), 41.0 (5-CH_2), 46.6 (CH_3), 50.2 (C_5), 51.4 (C_3), 62.1 (C_6), 64.7 (C_2), 126.3, 128.4, 129.0, and 138.5 (Ph); ES-MS *m*/*z* 259.3 $[M+1]^+$. Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 79.22; H, 10.24; N, 10.72.

4.6.2. (5*S*)-1,5-Di(phenylmethyl)piperazine-3-spirocyclohexane (12b). Syrup (50.1 mg, 98%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 40:60)] t_R 8.42 min; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04–1.53 (m, 10H, cyclohexyl), 1.59

Table 3. Significant analytical and spectroscopic data of 2-oxopiperazines



	7a	7b	7c	17a	17c
R^1	Ph	Ph	CO_2Me	Ph	CO_2Me
R^2	Me	CH_2Ph	Me	Me	Me
R^3	H	H	H	Me	Me
Formula[a]	$C_{17}H_{24}N_2O$	$C_{23}H_{28}N_2O$	$C_{13}H_{22}N_2O_3$	$C_{18}H_{26}N_2O$	$C_{14}H_{24}N_2O_3$
Yield (%)	100	100	100	70	90
ES-MS $[M+1]^+$	273.2	349.2	255.1	287.3	269.2
t_R (min) (A:B)[b]	3.47 (25:75)	17.20 (25:75)	1.64 (25:75)	1.78 (50:50)	1.82 (25:75)
^1H NMR[c]					
5-H	4.38	3.80	4.35	3.34	3.63
6-H	3.28, 3.79	3.18, 3.50	3.58, 3.89	3.15	3.22
5-CH_2	3.06, 3.56	2.94, 3.18	2.98, 3.24	2.58, 2.69	2.37, 2.46
2′-H^{ax}	2.28	2.23	2.19–2.30	1.97	2.05
Cyclohexyl	1.49–2.24	1.34–2.09	1.35–2.30	1.10–1.65	1.15–1.87
R^1	7.32	7.22–7.33	3.73	7.22–7.33	3.71
R^2	2.85	4.38, 5.11, 7.14–7.33	2.92	2.91	2.89
R^3	—	—	—	1.23	1.16
$J_{5,6}$ (Hz)	4.5 and 11.5	4 and 11.5	4.5 and 11.5	3.5	3.5
^{13}C NMR[d]					
C_2	167.1	172.3	172.6	174.0	172.4
C_3	62.2	61.6	63.7	58.8	59.9
C_5	49.7	50.6	47.6	52.4	48.7
C_6	49.9	51.4	50.7	58.2	57.7
5-CH_2	36.4	239.2	34.5	38.3	36.2
R^1	127.7, 129.1, 129.5, 135.1	128.7, 130.0, 130.6, 138.7	53.4, 168.4	126.7, 128.7, 128.8, 138.2	52.6, 172.4
R^2	32.9	51.4, 128.7, 130.0, 130.6, 138.7	35.7	34.2	31.3
R^3	—	—	—	12.6	13.1
Cyclohexyl	20.4, 20.8, 24.3, 31.1, 34.4	21.6, 22.2, 26.3 32.4, 35.7	21.3, 21.5, 25.6, 31.9, 33.7	20.2, 20.9, 24.9, 30.3, 36.2	20.9, 21.2, 25.4, 30.1, 34.7

[a] Satisfactory analysis for C, H, and N.
[b] Novapak C_{18} (3.9×150 mm, 4 μm). A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 300 or 400 MHz, in $CDCl_3$, assigned with the help of COSY spectra.
[d] Spectra registered at 75 or 100 MHz, in $CDCl_3$, assigned with the help of HSQC and HMBC spectra.

(d, 1H, J=11 Hz, 2-H), 1.74 (t, 1H, J=10.5 Hz, 6-H), 2.47 (dd, 1H, J=8.5 and 13.5 Hz, 5-CH_2), 2.58 (d, 1H, J=11 Hz, 2-H), 2.60 (dd, 1H, J=5.5 and 13.5 Hz, 5-CH_2), 2.75 (dd, 1H, J=2.5 and 10.5 Hz, 6-H), 3.21 (m, 1H, J=2.5, 5.5, and 8.5 Hz, 5-H), 3.25 (d, 1H, J=13.5 Hz, 1-CH_2), 3.50 (d, 1H, J=13.5 Hz, 1-CH_2), 7.11–7.29 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 and 21.7 ($C_{3'}$ and $C_{5'}$), 26.2 ($C_{4'}$), 31.8 and 38.4 ($C_{2'}$ and $C_{6'}$), 41.0 (5-CH_2), 50.5 (C_5), 51.6 (C_3), 60.6 (C_6), 61.9 (C_2), 62.9 (1-CH_2), 126.3, 126.8, 128.1, 128.4, 128.6, 129.0, 138.8, and 138.9 (Ph); ES-MS m/z 335.2 $[M+1]^+$. Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.59; H, 9.04; N, 8.37. Found C, 82.43; H, 9.24; N, 8.57.

4.7. General procedure for the reaction of 2,6-dioxopiperazines 1a–c with Grignard reagents. Synthesis of hydroxypiperazines 13a,c, 18a, and 19a

The corresponding Grignard reagent, MeMgBr, EtMgBr (3 M solution in diethyl ether, 200 μL, 0.6 mmol), or $PhCH_2MgCl$ (1 M solution in diethyl ether, 600 μL, 0.6 mmol), was added under argon to a −40 °C cooled solution of the 2,6-dioxopiperazines **1a–c** (0.2 mmol) in dry THF (3 mL), and the reaction mixture was stirred at this temperature for 3 h. Afterward, the reaction mixture was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by circular chromatography, using 15–40% gradient of EtOAc in hexane as eluant, to give the compounds shown in Schemes 5 and 6. Significant analytical and spectroscopic data of the 6-hydroxy-2-oxopiperazines **13a**, **13c**, and **18a+19a** are summarized in Table 1.

4.7.1. (5*S*)-5-(2-Hydroxy-2-methyl)propyl-1-methyl-2,6-dioxopiperazine-3-spirocyclohexane (14c). Syrup (12.9 mg, 24%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 25:75)] t_R 4.03 min; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 and 1.33 [2s, 6H, Me (isopropyl)], 1.25–1.62 (m, 8H, cyclohexyl), 1.69 (dd, 1H, J=10.5 and 14.5 Hz, 5-CH_2), 2.03 (m, 1H, 2′-H^{ec}), 2.21 (m, 1H, 6′-H^{ax}), 2.44 (dd, 1H, J=2.5 and 14.5 Hz, 5-CH_2), 3.12 (s, 3H, 1-Me), 3.86 (dd, 1H, J=2.5 and 10.5 Hz, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 ($C_{3'}$ and $C_{5'}$), 24.3 ($C_{4'}$), 26.7 (1-Me), 28.2 and 31.1 [Me (isopropyl)], 29.2 and 34.6 ($C_{2'}$ and $C_{6'}$), 42.2 (5-CH_2), 51.3 (C_5), 58.9 (C_3), 70.5 (isopropyl), 173.1 (C_6), 176.1 (C_2); ES-MS m/z 269.2 $[M+1]^+$.

Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 62.46; H, 8.79; N, 10.62.

4.7.2. *N*-Methyl-1-[(2*S*)-3-ethyl-3-hydroxy-1-phenylpentan-2-yl]aminocyclohexylcarboxamide (20a). Syrup (24.2 mg, 20%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 25:75)] t_R 9.95 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 and 0.90 [2t, 6H, J=7.5 Hz, CH_3 (Et)], 0.95–1.82 (m, 10H, cyclohexyl), 1.45 and 1.49 [2q, 4H, CH_2 (Et)], 2.61 (dd, 1H, J=7.5 and 14.5 Hz, *CH*$_2$–Ph), 2.68 (dd, 1H, J=6.5 and 14.5 Hz, *CH*$_2$–Ph), 2.74 (d, 3H, J=5 Hz, NH–*CH*$_3$), 3.17 (dd, 1H, J=6.5 and 7.5 Hz, NH–*CH*), 6.37 (br s, 1H, *NH*–CH_3), 7.23 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.2 and 7.3 [CH_3 (Et)], 22.0, 22.1, 25.4, 33.2, 35.2, and 60.5 (cyclohexyl), 26.3 (NH–CH_3), 28.3 and 28.6 [CH_2 (Et)], 38.6 (*CH*$_2$–Ph), 57.6 (NH–*CH*), 74.7 (C–OH), 126.1, 128.3, 129.1, and 140.1 (Ph), 177.3 (CONH); ES-MS m/z 347.1 $[M+1]^+$. Anal. Calcd for $C_{21}H_{34}N_2O_2$: C, 72.79; H, 9.89; N, 8.08. Found: C, 73.12; H, 10.04; N, 7.96.

4.7.3. *N*-Methyl-1-[(2*S*)-3-oxo-1-phenylpentan-2-yl]-aminocyclohexylcarboxamide (21a). Syrup (33.2 mg, 30%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 25:75)] t_R 17.27 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 [(t, 3H, J=7.5 Hz, CH_3 (Et)], 1.02–1.92 (m, 10H, cyclohexyl), 2.18 (d, 3H, J=5 Hz, NH–*CH*$_3$), 2.36 (dd, 1H, J=9.5 and 13.5 Hz, *CH*$_2$–Ph), 2.39 [q, 2H, J=7.5 Hz, CH_2 (Et)], 2.71 (dd, 1H, J=4.5 and 13.5 Hz, *CH*$_2$–Ph), 3.29 (dd, 1H, J=4.5 and 9.5 Hz, NH–*CH*), 6.05 (br s, 1H, *NH*–CH_3), 7.22 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 7.5 [CH_3 (Et)], 21.6, 22.0, 25.2, 31.8, 36.8, and 61.5 (cyclohexyl), 25.8 (NH–CH_3), 35.3 [CH_2 (Et)], 41.9 (*CH*$_2$–Ph), 63.6 (NH–*CH*), 126.9, 128.6, 129.6, and 138.0 (Ph), 176.7 (CONH), 214.9 (COEt); ES-MS m/z 317.1 $[M+1]^+$. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.22; H, 8.75; N, 9.11.

4.8. Synthesis of 6-[(*E*)-ethylidene-1-methyl-5-phenylmethyl-2-oxopiperazine-3-spirocyclohexane (23a)

$NaBH_4$ (18.7 mg, 0.49 mmol) was slowly added to a 0 °C cooled solution of a mixture of the 6-hydroxypiperazines **18a+19a** and their ketone epimer **21a** (52.0 mg, 0.16 mmol) in TFA (3 mL). After reaching room temperature, the reaction mixture was stirred for 3 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). This solution was successively washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using 10–40% gradient of MeOH in CH_2Cl_2 as eluant, to give **23a** (37.2 mg, 76%); HPLC [Novapak C_{18} (3.9×150 mm, 4 μm) (A:B, 25:75)] t_R 9.01 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24–1.65 (m, 9H, cyclohexyl), 1.51 [d, 3H, J=7 Hz, CH_3 (ethylidene)], 2.03 (m, 1H, 2′-H^{ax}), 2.87 (dd, 1H, J=6 and 13.5 Hz, 5-CH_2), 2.91 (dd, 1H, J=6 and 13.5 Hz, 5-CH_2), 2.98 (s, 3H, 1-CH_3), 4.19 (t, 1H, J=6 Hz, 5-H), 4.96 [q, 1H, J=7 Hz, CH (ethylidene)], 7.23 (m, 5H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0 [CH_3 (ethylidene)], 21.1, 21.3, 25.6 (C_9), 31.6 and 33.7 (cyclohexyl), 32.0 (1-CH_3), 40.6 (5-CH_2), 51.4 (C_5), 57.0 (C_3), 104.6 [CH (ethylidene)], 126.7, 128.3, 129.4, and 137.5 (Ph), 139.7 (C_6), 175.0 (C_2); ES-MS m/z 299.3 $[M+1]^+$. Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.59; H, 8.48; N, 9.17.

4.9. Determination of the racemization ratio by the measure of deuterium incorporation

The procedures described above for the synthesis of oxopiperazines **7a–c**, **8a**, **17a**, **17c**, and **23a** were carried out replacing $NaBH_4$ by $NaBD_4$ and the corresponding solvents MeOH and TFA by CD_3OD and deuterated TFA. The resulting products were chromatographically (TLC and HPLC) identical to the respective nondeuterated compounds, as well as their ^{1}H NMR data, except for the commented decrease in the signals corresponding to the protons, which have been partial or completely replaced by deuterium. The 50% decrease in the integral of 5-H was used as a measure for the percentage of configuration inversion at C_5 for the calculation of the enantiomer excesses.

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