Tetrahedron 71 (2015) 8077–8084

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel chiral *N,N′*-dimethyl-1,4-piperazines with metal binding abilities

Christopher Bérubé, Sébastien Cardinal, Pierre-Luc Boudreault, Xavier Barbeau, Nicolas Delcey, Martin Giguère, Dave Gleeton, Normand Voyer *

Département de Chimie, PROTEO, Université Laval, Faculté des sciences et de génie, 1045 avenue de la Médecine, Québec, QC G1V OA6, Canada

ARTICLE INFO

Article history:
Received 10 June 2015
Received in revised form 18 August 2015
Accepted 20 August 2015
Available online 28 August 2015

Keywords:
N,N′-dimethyl-1,4-piperazines
2,5-Diketopiperazines
Picrate extraction
Chiral diamines
Metal diamino ligands

ABSTRACT

With the objective of developing novel chiral ligands, we report an efficient strategy to prepare chiral *N,N*-dimethyl-1,4-piperazines, six-member heterocyclic molecules that possess metal binding features. We prepared and characterized 18 piperazines, and evaluated their ability to complex different mono- and divalent metals, using a rapid picrate extraction technique. Some newly prepared diamine ligands were used in diethylzinc alkylation of aryl aldehydes. Yields increased significantly in the presence of the diamine ligands, though enantioselectivity was low. The results demonstrate the validity of the approach for preparing and identifying useful chiral diamine ligands.

1. Introduction

Developing new bio-inspired ligands continues to be a topic of great interest in asymmetric synthesis. Numerous applications using chiral tertiary diamines in asymmetric synthesis have been reported.[1] Among chiral diamines, many naturally occurring compounds are useful as chiral ligands, as exemplified by (−)-sparteine (**1**), a well known C_2-bidentate natural ligand (Fig. 1a).[2–4] Likewise, a series of reports demonstrated that 1,4-piperazines are efficient ligands, as exemplified by the Zn^{2+} complex in Fig. 1b.[5] Such ligands used in the addition of diethylzinc to aryl aldehydes, lead to as much as 98% enantiomeric excess (ee) of the resulting alcohols.[5–10] Also, chiral 1,4-piperazines were shown to be useful ligands in Cu^{2+} catalyzed Henry reactions.[11] Inspired by those reports and with the objective of developing novel bio-inspired chiral ligands, we explored a strategy to prepare chiral *N,N′*-dimethyl-1,4-piperazines, starting from readily available amino acids (Fig. 2).[11–16] In addition to the synthesis of 18 *N,N′*-dimethyl-1,4-piperazine ligands, we report here their ability to bind certain mono- and divalent metals ions using a convenient biphasic extraction assay, as well as preliminary results on the use of some of those compounds in the addition of diethylzinc to aryl aldehydes.

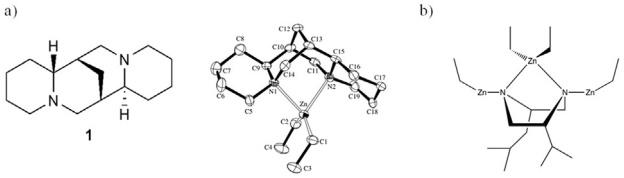


Fig. 1. Metal chelating features shown by a) (−)-sparteine[17] (**1**) and b) 1,4-piperazines[5] as determined by X-ray crystallography and NMR spectroscopy, respectively (Reproduced with the permission of the authors).

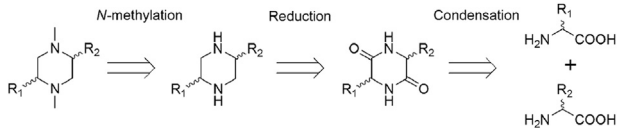


Fig. 2. Retrosynthetic approach towards the desired *N,N′*-dimethyl-1,4-piperazines.

2. Results and discussion

2.1. Preparation of *N,N′*-dimethyl-1,4-piperazines

We have developed a rapid synthesis to produce chiral *N,N′*-dimethyl-1,4-piperazines using natural and non-natural amino

* Corresponding author. Tel.: +1 418 656 3613; fax: +1 418 656 7916; e-mail address: normand.voyer@chm.ulaval.ca (N. Voyer).

http://dx.doi.org/10.1016/j.tet.2015.08.051
0040-4020/

acids. This retrosynthetic approach is depicted in Fig. 2. The diamino ligands can be obtained from the corresponding 1,4-piperazines, which in turn can be readily prepared from 2,5-diketopiperazines. The latters can be easily access from a variety of commercially available α-amino acids.

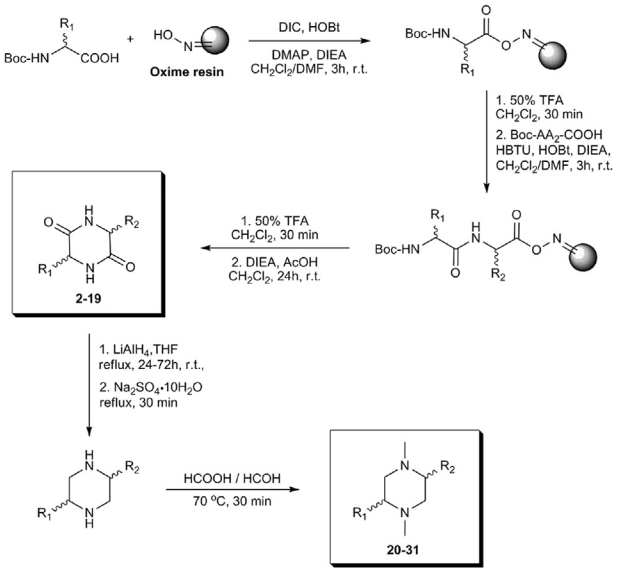
A noteworthy feature of our approach is the efficient solid-phase preparation of chiral 2,5-diketopiperazines from *N*-Boc protected amino acids. Taking advantage of the availability of natural and unnatural chiral amino acids as chiral synthons, a small library of 2,5-diketopiperazines were synthesized with a variety of substituents and stereochemistries (Table 1), which could be used to study the structural features required in a given process to obtain efficient conversion and enantioselectivities.

Table 1
2,5-diketopiperazines (DKPs) and *N,N′*-dimethyl-1,4-piperazines (DMPs) synthesized

Entry	R_1	R_2	DKPs	Yield (%)	DMPs	Yield (%)
1	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-CH_2Ph(*p*-OBn)	**2**	>90	**20a**	32
2	(*R*)-$CH_2CH(CH_3)_2$	(*R*)-CH_2Ph(*p*-OBn)	**3**	>90	**20b**	17
3	(*R*)-$CH(CH_3)_2$	(*R*)-CH_2OBn[a]	**4**	>90	**21**	44
4	(*S*)-CH_2Ph	(*S*)-CH_2OBn[b]	**5**	>90	**22**	50
5	(*S*)-CH_2Ph	(*S*)-CH_2Ph	**6**	>90	**23a**	87
6	(*R*)-CH_2Ph	(*R*)-CH_2Ph	**7**	>90	**23b**	84
7	(*R*)-CH_2Ph	(*S*)-CH_2Ph	**8**	54	**23c**	80
8	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-CH_2Ph	**9**	>90	**24**	45
9	(*R*)-$(CH_2)_2$ Ph	(*R*)-$CH_2CH(CH_3)_2$	**10**	78	**25**	35
10	(*R*)-$CH_2CH(CH_3)_2$	(*R*)-$CH_2CH(CH_3)_2$	**11**	>90	**26a**	43
11	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-$CH_2CH(CH_3)_2$	**12**	>90	**26b**	64
12	(*S*)-$CH_2CH(CH_3)_2$	(*R*)-$CH_2CH(CH_3)_2$	**13**	75	**26c**	15
13	(*S*)-CH_2Ph	(*S*)-CH_2Ph(*p*-OBn)	**14**	>90	**27**	57
14	(*R*)-CH_2Ph(*p*-OBn)	(*R*)-CH_2Ph(*p*-OBn)	**15**	>90	**28a**	11
15	(*S*)-CH_2Ph(*p*-OBn)	(*S*)-CH_2Ph(*p*-OBn)	**16**	>90	**28b**	40
16	(*S*)-CH_2Ph(*p*-OBn)	(*R*)-$CH(CH_3)_2$	**17**	>90	**29**	36
17	(*R*)-CH_2Ph	(*R*)-CH_3	**18**	>90	**30**	16
18	(*R*)-$CH_2CH(CH_3)_2$	(*R*)-$CH(CH_3)_2$	**19**	>90	**31**	12

[a] Becomes (*S*) after reduction.
[b] Becomes (*R*) after reduction.

Our synthetic procedure involved the condensation of two *N*-Boc amino acids using oxime resin[18,19] and standard peptide solid-phase strategies (Scheme 1).[20] The first amino acid was coupled for three hours using diisopropylcarbodiimide and HOBt as coupling reagents. The *N*-Boc protecting group was removed using a mixture of 1:1 TFA/CH_2Cl_2. The second amino acid was activated with HOBt and HBTU and coupled for 3 h. After deprotection, the linear dipeptide was simultaneously cyclized and cleaved from the resin in the presence of diisopropylethylamine (2.5 equiv) and acetic acid (5 equiv) in dichloromethane, leading to 2,5-diketopiperazines **2**–**19** of high purity. Table 1 reports the isolated yields, which are all over 90% in cases when the two constituent amino acids have the same configuration. However, yields decreased when using two amino acids of different configurations (Table 1, entries 7 and 12). All 2,5-diketopiperazines synthesized were characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.



Scheme 1. Synthesis of 2,5-diketopiperazines (**2**–**19**) and *N,N′*-dimethyl-1,4-piperazines (**20**–**31**).

1,4-Piperazines are readily produced by the reduction of 2,5-diketopiperazines. From the amide reduction methods that we tested, we chose lithium aluminum hydride (1 M in THF) for 24–72 h in dry THF under an inert atmosphere. Once the reaction was completed, sodium sulfate decahydrate was added to neutralize residual lithium aluminum hydride and other active species, and the mixture was refluxed for 30 min.[21,22] A further simple filtration eliminated residual solids and led to the desired 1,4-piperazines, which were then *N*-methylated without purification using the Eschweiler-Clarke reaction[23] in the presence of formic acid (50 equiv) and formaldehyde (33 equiv), leading to 11–87% yields of *N,N′*-dimethyl-1,4-piperazines **20**–**31** listed in Table 1. All the *N,N′*-dimethyl-1,4-piperazines prepared were characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

The reduction/dimethylation reactions proceeded with variable yields from very good (87%, entry 5) to low (11%, entry 14). These variable yields are mostly due to solubility problems encountered during the reduction step. The lowest yields observed are those with **3**, **13**, **15**, **18** and **19** as substrates. Nevertheless, the synthetic ease and the rapidity of the procedure render it highly convenient to produce chiral piperazines. In addition, thorough NMR studies on **23a** and **23b** with comparison with their diastereoisomer **23c** showed a maximum of 5% epimerization during the overall synthetic process.

2.2. Metal binding ability evaluation

As we had access to a series of diverse *N,N′*-dimethyl-1,4-piperazines that could complex different metals, we explored their metal binding efficiency using a picrate extraction test.[24] This test consists of dissolving a potential ligand in chloroform, then adding an aqueous metal picrate solution. After stirring the biphasic system, aliquots of aqueous phase were analyzed by UV-Visible spectroscopy. If the ligand bound the metal, the metal was extracted into the organic phase, which turned yellow (Fig. 3). Extraction results are reported in Table 2.

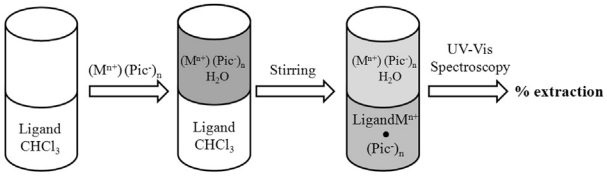


Fig. 3. Metal picrate extraction procedure to evaluate binding ability of potential ligands for different metal ions.

As a preliminary study, we used zinc, copper, manganese, lithium, nickel, and magnesium, which are useful monovalent and divalent metals in organic synthesis. As a control, we used (−)-sparteine **1** to optimize the extraction conditions. We examined different concentrations of picrate salts: 7×10^{-6} M, 7×10^{-5} M and 1.75×10^{-4} M. The lower concentration of picrate salts solution leads to lower extraction efficiency. To evaluate the binding ability

Table 2
Metal picrate extraction (%) results for **1** and *N,N′*-dimethyl-1,4-piperazines **20a**–**31**

Entry	Ligand	Picrate salts (1.75×10^{-4} M)					
		Zn^{2+}	Mn^{2+}	Cu^{2+}	Ni^{2+}	Mg^{2+}	Li^{+}
1	**1**	95	95	96	93	97	96
2	**20a**	89	92	94	84	85	83
3	**21**	78	72	90	50	47	39
4	**22**	70	61	90	43	38	32
5	**23b**	97	96	96	95	95	98
6	**23c**	65	31	95	18	25	8
7	**24**	86	82	93	63	57	46
8	**25**	91	74	97	64	57	40
9	**26a**	68	61	84	50	42	40
10	**26c**	17	0	21	0	2	8
11	**27**	81	56	97	45	33	28
12	**28a**	84	69	97	67	66	54
13	**29**	88	71	95	57	52	36
14	**30**	49	27	79	18	29	17
15	**31**	4	2	4	0	0	0

of (−)-sparteine **1** and *N,N′*-dimethyl-1,4-piperazines **20a**–**31**, we chose to use the highest concentration studied as it provided more reproducible results (Table 2).

At the optimal 1.75×10^{-4} M concentration of picrate salts, (−)-sparteine **1** had a very good affinity for all metal ions studied, and showed no ion selectivity (Table 2, entry 1). Under the same conditions, *N,N′*-dimethyl-1,4-piperazines showed variable extraction performances, in terms of binding ability and selectivity. This clearly illustrates the impact of the nature and the relative stereochemistry of the substituents on the coordinating character of the *N,N′*-dimethyl-1,4-piperazine scaffold.

First, ligand **20a**, which contains an isobutyl and *p*-benzyloxybenzyl groups on side chains, demonstrated good picrate salt extraction results (Table 2, entry 2). Use of compounds **21** (prepared from D-Val-D-Ser(OBzl)) and **22** (derived from (L-Phe-L-Ser(OBzl)) showed moderate to good extraction results, with a preference for Cu^{2+} (Table 2, entries 3 and 4). Ligand **23b**, which possesses *syn* benzyl side chains, demonstrated very high extraction efficiencies (over 95%) for all metal ions studied (Table 2, entry 5). However, analogous compound **23c**, which has *anti* benzyl side chains, demonstrated strikingly different extraction efficiencies, from low to moderate, except for Cu^{2+} (Table 2, entry 6). Therefore, the relative configuration of the chiral centers of the piperazine ligands is of crucial importance for their metal binding abilities. A similar result is obtained with ligands **26a** and **26c**, which have, respectively, a *syn* and an *anti* relationship for the two isobutyl groups (entries 9 and 10). In certain cases, it is possible to observe relatively good metal binding ability with ligands that have two different configurations at their chiral centers, as in the case of **29** (entry 13), although the metal affinity varies significantly. As expected, similar extraction results were obtained with ligands **24** and **25**, which both have an isobutyl group and a benzyl or a phenylethyl group in a *syn* relationship, respectively (Table 2, entries 7 and 8).

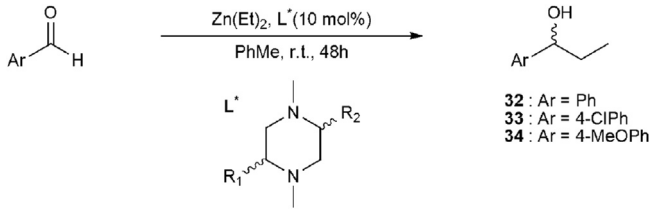
In general, ligands having two aromatic side chains demonstrate higher extraction ability then those with only one aromatic side chain, which in turn are better extractors than ligands with only alkyl substituents (entries 5, 14 and 15). The higher extraction level observed with copper in almost all cases could be due to enhanced lipophilicity of the Cu^{2+} picrate salt. It is therefore not possible to use the extraction results for identifying good Cu^{2+} ligands. Ligand **31** does not show any affinity for picrate salts (Table 2, entry 15). This is somewhat surprising, as its analog **26a** (entry 9) that has an isobutyl chain instead of an isopropyl chain show good extraction ability. These results demonstrate that subtle structural changes can affect the conformational behavior of *N,N′*-dimethyl-1,4-piperazine ligands, significantly impacting their metal binding affinities. Among all the ligands synthesized, ligand **23b** has the strongest binding ability, extracting over 95% of all metal ions studied. Not surprisingly, the enantiomer of **23b** (**23a**) demonstrated identical extraction results as **23b** within ±2%.

2.3. Evaluation of *N,N′*-dimethyl-1,4-piperazines in diethylzinc addition reaction

We investigated the catalytic enantioselective addition of diethylzinc to benzaldehyde to examine the potential efficiency of *N,N′*-dimethyl-1,4-piperazine ligands in organic transformations. This alkylation to benzaldehyde using (−) sparteine **1** is known.[17] Initial optimization with **1** showed that 10% of the ligand provided the best performance in terms of both yield of (*R*)-1-phenyl-1-propanol (**32**) and chiral induction, confirming results reported by Johansson with **1**.[17] Using less ligand (2.5 mol %) **1** gave **32** with the same ee, but with a lower yield. Performing the reaction at a lower temperature led to approximately the same ee value. In all cases, using **1** as the chiral ligand provided the *R* enantiomer of **32**.

Preliminary results using 10 mol % of piperazines are reported in Table 3. First, control experiment without ligand led to very low conversions (15–30%, entries 1, 5 and 9). In all cases, using a *N,N′*-dimethyl-1,4-piperazine ligand, we observed more than 93% conversion of benzaldehyde to alcohol **32** after 48 h of reaction (Table 3, entries 2–4). With ligand **23a**, we obtained (*S*)-1-phenyl-1-propanol with a low 7% enantiomeric excess (Table 3, entry 2). As expected, we observed that ligand **23b** led also to 7% enantiomeric excess, but of (*R*)-1-phenyl-1-propanol (Table 3, entry 3). Comparable results were obtained with *p*-chlorobenzaldehyde, leading to high conversion and 6% enantiomeric excess of (*S*) and (*R*) alcohol **33** using ligands **23a** and **23b** (Table 3, entries 6 and 7), respectively. With *p*-methoxybenzaldehyde as substrate, lower yields of alcohol **34** were obtained due to carbonyl's lower electrophilicity. Also with this substrate, low enantiomeric excesses of 5% of (*S*) and (*R*) alcohol **34** were obtained with ligand **23a** and **23b** (Table 3, entries 10

Table 3
Diethylzinc addition to aryl aldehydes in the presence of *N,N′*-dimethyl-1,4-piperazine ligands[a]



Entry	Ligands	Ar	Product	Conversion (%)[b]	ee (%)[b]
1	**None**	Ph	**32**	20	0
2	**23a**	Ph	**32**	99 (81[c])	7(*S*)
3	**23b**	Ph	**32**	97	7(*R*)
4	**23c**	Ph	**32**	93	0
5	**None**	4-ClPh	**33**	30	0
6	**23a**	4-ClPh	**33**	98	6(*S*)
7	**23b**	4-ClPh	**33**	98	6(*R*)
8	**23c**	4-ClPh	**33**	99	0
9	**None**	4-MeOPh	**34**	15	0
10	**23a**	4-MeOPh	**34**	60[d]	5(*S*)
11	**23b**	4-MeOPh	**34**	61[d]	5(*R*)
12	**23c**	4-MeOPh	**34**	80[d]	0

[a] Unless otherwise noted, reactions were carried out with 0.1 mmol of aldehyde and 0.01 mmol of ligand.
[b] Determined by chiral GC analysis.
[c] Isolated yield.
[d] Reactions stopped after 72 h.

and 11), respectively. Furthermore, in all cases, the meso ligand **23c** led to racemic alcohols **32**–**34** (Table 3, entries 4, 8, 12), thus demonstrating the contribution of the chirality on the *N,N′*-dimethyl-1,4-piperazine scaffold in the chiral induction observed for **23a** and **23b** in the $ZnEt_2$ addition reaction.

Although the enantioselectivities observed are low in all studied cases, the results are as good as with (−)-sparteine **1**.[17] Most importantly, they demonstrate that the ligand is essential for enhanced conversion and to induce chirality. Indeed, using the different enantiomers of **23** led to addition products enriched with the two different enantiomers.

3. Conclusion

We have developed an efficient and rapid synthetic method for *N,N′*-dimethyl-1,4-piperazines that takes advantages of solid-phase peptide synthesis and the availability of a wide variety of natural or non-natural amino acids. We prepared and characterized 18 novel chiral *N,N′*-dimethyl-1,4-piperazines. We also demonstrated that the metal binding ability of these ligands for several metals of interest in organic synthesis could be rapidly assessed with a picrate salt extraction technique. In a test model reaction, we showed that a catalytic amount of *N,N′*-dimethyl-1,4-piperazines can significantly enhance conversion yields and induce chirality. Though the enantiomeric excesses obtained so far are low, these results validate the potential of the overall approach to prepare and rapidly identify efficient pairs of chiral diamine ligands for specific metals. Work is underway to assess the utility of *N,N′*-dimethyl-1,4-piperazine prepared in different metal-catalyzed transformations.

4. Experimental section

4.1. General information

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded using Varian Inova 400 MHz and Agilent DD2 500 MHz spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Splitting patterns are designated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), br (broad singlet) and m (multiplet). Mass spectra were obtained on an Agilent 6210 LC Time of Flight Mass Spectrometer in direct injection mode. Flash chromatography was performed with SiliaFlash® P60 silica gel. Optical rotations were measured at ambient temperature on a Jasco DIP-360 digital polarimeter, using a sodium lamp. UV–vis measurements were done on a using an HP 8452-A UV–vis spectrometer. GC data were recorded on a Thermo Scientific Focus instrument. Melting points were taken using a Stanford Research Systems OptiMelt MPA 100 instrument. IR spectrums were taken on Thermo Scientific Nicolet 380 FTIR using ZnSe crystal.

4.2. Preparation of 2,5-diketopiperazines (2–19)

4.2.1. General procedure

4.2.1.1. Coupling of the first Boc protected α-amino acid on oxime resin. A desired quantity of oxime resin (1.12 mmol/g) was added to a peptide synthesis vessel. The resin was treated three times with CH_2Cl_2. Amino acid (3.0 equiv) and HOBt (3.0 equiv) were dissolved in DMF in a 100 mL flask and the mixture was stirred for few minutes at 0 °C. DIC (3.0 equiv), DIEA (3.0 equiv) and DMAP (0.1 equiv) were introduced into the peptide synthesis vessel and the mixture was stirred mechanically for 3 h. The mixture was filtered under vacuum and the resin was washed [DMF (3×100 mL), MeOH (3×100 mL), DMF (3×100 mL), MeOH (3×100 mL)] and dried under reduced pressure.

4.2.1.2. Acetylation of unreacted sites on oxime resin. The resin was treated three times with CH_2Cl_2 (3×50 mL). A solution of 50% v/v DMF/acetic anhydride (80 mL) and DIEA (1 mL) were added to the peptide synthesis vessel and the mixture was shaken for 1 h. Then, the mixture was filtered under vacuum and the resin was washed [DMF (3×100 mL), MeOH (3×100 mL), DMF (3×100 mL), MeOH (3×100 mL)] and dried under reduced pressure.

4.2.1.3. Removal of the Boc protecting group. The resin was treated three times with CH_2Cl_2 (100 mL). A 50% v/v solution of trifluoroacetic acid (TFA) in CH_2Cl_2 was added to the peptide synthesis vessel, which was stirred for 30 min. Then, the mixture was filtered under vacuum and the resin was washed with DMF (3×100 mL), MeOH (3×100 mL), DMF (3×100 mL), MeOH (3×100 mL) and with a solution of 10% v/v DIEA in CH_2Cl_2 (100 mL).

4.2.1.4. Coupling of the second Boc protected α-amino acid. The amino acid (3.0 equiv) was dissolved in DMF in a 100 mL flask. The solution was cooled to 0 °C, then HBTU (3.0 equiv) and HOBt (3.0 equiv) were added. The mixture was poured into the peptide synthesis vessel in which the resin has been previously treated with CH_2Cl_2. DIEA (6.0 equiv) was also added to the vessel and the mixture was stirred for 3 h. After filtration under vacuum, the resin was washed [DMF (3×100 mL), MeOH (3×100 mL), DMF (3×100 mL) and MeOH (3×100 mL)] and dried reduced under pressure. The Kaiser nihydrin test was performed to monitor the efficiency of the coupling, and the coupling procedure was repeated if needed.

4.2.1.5. Cyclization/cleavage from the resin. First, the Boc group was removed using procedure described in (4.2.1.3), but without the 10% v/v DIEA/CH_2Cl_2 washing step. After drying, CH_2Cl_2 and DIEA (2.5 equiv) were added to the peptide synthesis vessel and the mixture was stirred for 2 min. Acetic acid (5.0 equiv) was then added and the content was shaken for 24 h. Then the filtrate was collected and the resin was rinsed several times with CH_2Cl_2 and MeOH. All the filtrates were combined and evaporated, and the resulting solid was dissolved in CH_2Cl_2. Amberlite IR-120 was introduced to the solution to take off remaining traces of DIEA. The mixture was stirred for a few minutes and filtered. The filtrate was evaporated to give compounds **2** to **19**. Trituration in a minimum of cold ether was performed to obtain satisfying purity.

*4.2.1.6. (3S,6S)-3-(ρ-(Benzyloxy)benzyl)-6-isobutylpiperazine-2,5-dione (**2**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.08–0.15 (m, 1H), 0.58 (d, J=6.7 Hz, 3H), 0.60 (d, J=6.7 Hz, 3H), 0.70–0.77 (m, 1H), 1.32–1.45 (m, 1H), 2.71 (dd, J=13.6, 4.9 Hz, 1H), 3.03 (dd, J=13.6, 4.9 Hz, 2H), 3.38–3.42 (m, 1H) 4.04–4.08 (m, 1H), 4.97 (s, 2H), 6.87 (d, J=8.6 Hz, 2H), 7.00 (d, J=8.6 Hz, 2H), 7.23–7.38 (m, 5H), 8.04 (d, J=2.7 Hz, 1H), 8.02 (d, J=2.2 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=21.8, 23.4, 23.6, 38.3, 53.0, 56.3, 69.9, 115.0, 128.3, 128.5, 128.8, 129.1, 132.0, 137.8, 158.2, 166.8, 168.1; **HRMS** (ESI-TOF, m/z) calcd for $C_{22}H_{27}N_2O_3$ $(M+H)^+$=367.2016, found 367.2026.

*4.2.1.7. (3R,6R)-3-(ρ-(Benzyloxy)benzyl)-6-isobutylpiperazine-2,5-dione (**3**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.08–0.15 (m, 1H), 0.58 (d, J=6.7 Hz, 3H), 0.60 (d, J=6.7 Hz, 3H), 0.70–0.77 (m, 1H), 1.32–1.45 (m, 1H), 2.71 (dd, J=13.6, 4.9 Hz, 1H), 3.03 (dd, J=13.6, 4.9 Hz, 2H), 3.38–3.42 (m, 1H) 4.04–4.08 (m, 1H), 4.97 (s, 2H), 6.87 (d, J=8.6 Hz, 2H), 7.00 (d, J=8.6 Hz, 2H), 7.23–7.38 (m, 5H), 8.04 (d, J=2.7 Hz, 1H), 8.02 (d, J=2.2 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=21.8, 23.4, 23.6, 38.3, 52.9, 56.3, 69.9, 115.0,

128.3, 128.5, 128.8, 129.1, 132.0, 137.8, 158.2, 166.9, 168.1; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{22}H_{27}N_2O_3$ $(M+H)^+$=367.2016, found 367.2022.

*4.2.1.8. (3R,6R)-3-(Benzyloxymethyl)-6-isopropylpiperazine-2,5-dione (**4**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.78 (d, *J*=6.9 Hz, 3H), 0.89 (d, *J*=6.9 Hz, 3H), 2.08–2.17 (m, 1H), 3.53 (dd, *J*=9.7, 2.8 Hz, 1H), 3.58–3.60 (m, 1H), 3.76 (dd, *J*=9.7, 2.8 Hz, 1H), 3.89–3.92 (m, 1H), 4.45 (dd, *J*=5.5, 9.3 Hz, 1H), 7.20–7.32 (m, 5H), 8.06 (s, 1H), 8.07 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=17.3, 19.0, 55.6, 60.1, 71.8, 73.1, 128.0, 128.1, 128.9, 138.8; 167.4, 168.3; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{15}H_{21}N_2O_3$ $(M+H)^+$=277.1547, found 277.1567.

*4.2.1.9. (3S,6S)-3-Benzyl-6-(benzyloxymethyl)piperazine-2,5-dione (**5**).*[25] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.59 (dd, *J*=9.7, 6.4 Hz, 1H), 2.86 (dd, *J*=13.9, 5.0 Hz, 1H), 3.0 (dd, *J*=13.5, 5.7 Hz, 1H), 3.23 (dd, *J*=9.6, 3.0 Hz, 1H), 3.76–3.81 (m, 1H) 4.02–4.08 (m, 1H), 4.26 (s, 2H), 7.03 (d, *J*=6.9 Hz, 2H), 7.13–7.32 (m, 8H), 8.07 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=40.1, 55.6, 56.1, 72.2, 72.8, 127.2, 128.2, 128.3; 128.8, 128.9, 130.7, 137.1, 138.6, 165.7, 167.1; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{19}H_{21}N_2O_3$ $(M+H)^+$=325.1547, found 325.1555.

*4.2.1.10. (3S,6S)-3,6-Dibenzylpiperazine-2,5-dione (**6**).*[26–28] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.18 (dd, *J*=14.1, 6.1 Hz, 2H), 2.52 (dd, *J*=13.6, 4.9 Hz, 2H), 3.89–3.95 (m, 2H), 6.96–7.01 (m, 4H), 7.13–7.26 (m, 6H) 8.03 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=40.0, 56.1, 127.2, 128.9, 130.5, 137.2, 166.8; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{18}H_{19}N_2O_2$ $(M+H)^+$=295.1441, found 295.1445.

*4.2.1.11. (3R,6R)-3,6-Dibenzylpiperazine-2,5-dione (**7**).*[27] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.18 (dd, *J*=14.1, 6.1 Hz, 2H), 2.52 (dd, *J*=13.6, 4.9 Hz, 2H), 3.89–3.95 (m, 2H), 6.96–7.01 (m, 4H), 7.13–7.26 (m, 6H) 8.03 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=40.0, 56.1, 127.2, 128.9, 130.5, 137.2, 166.8; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{18}H_{19}N_2O_2$ $(M+H)^+$=295.1441, found 295.1450.

*4.2.1.12. (3R,6S)-3,6-Dibenzylpiperazine-2,5-dione (**8**).*[28] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.67 (dd, *J*=14.0, 8.0 Hz, 2H), 2.95 (dd, *J*=12.0, 4.0 Hz, 2H), 3.33 (br, 2H), 7.06–7.09 (m, 4H), 7.16–7.22 (m, 6H), 8.01 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=32.2, 55.0, 127.0, 128.4, 130.1, 136.3, 167.3, **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{18}H_{19}N_2O_2$ $(M+H)^+$=295.1441, found 295.1452.

*4.2.1.13. (3S,6S)-3-Benzyl-6-isobutylpiperazine-2,5-dione (**9**).*[29] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.01–0.08 (m, 1H), 0.54 (d, *J*=6.6 Hz, 3H), 0.58 (d, *J*=6.6 Hz, 3H), 0.65–0.83 (m, 3H), 1.28–1.41 (m, 1H), 3.08 (dd, *J*=13.6, 3.7 Hz, 1H), 3.38–3.45 (m, 1H) 4.09–4.15 (m, 1H), 7.05–7.25 (m, 5H), 8.04 (s, 1H), 8.02 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=22.0, 23.4, 23.5, 39.1, 44.3, 52.9, 56.1, 127.4, 128.7, 131.1, 136.7, 166.8, 168.1; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{15}H_{21}N_2O_2$ $(M+H)^+$=261.1598, found 261.1607.

*4.2.1.14. (3R,6R)-3-Isobutyl-6-phenethylpiperazine-2,5-dione (**10**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.81–0.85 (m, 6H) 1.40–1.47 (m, 1H) 1.55–1.62 (m, 1H) 1.76–1.97 (m, 3H) 2.60 (t, *J*=8.0 Hz, 2H), 3.74–3.76 (m, 2H) 7.13–7.18 (m, 3H), 7.22–7.26 (m, 2H), 8.18 (s, 1H), 8.25 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=22.3, 23.4, 24.0, 35.9, 43.4, 53.0, 54.1, 126.3, 128.8, 141.7, 168.2, 169.0; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{18}H_{31}N_2$ $(M+H)^+$=275.2482, found 275.1763.

*4.2.1.15. (3R,6R)-3,6-Diisobutylpiperazine-2,5-dione (**11**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.81 (d, *J*=6.5 Hz, 6H), 0.84 (d, *J*=6.5 Hz, 6H), 1.35–1.45 (m, 2H) 1.49–1.57 (m, 2H) 1.70–1.81 (m, 2H), 3.64–3.69 (m, 2H) 8.14 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=22.3, 23.7, 24.3, 44.3, 53.3, 169.2; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{12}H_{23}N_2O_2$ $(M+H)^+$=227.1754, found 227.1764.

*4.2.1.16. (3S,6S)-3,6-Diisobutylpiperazine-2,5-dione (**12**).*[30] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.81 (d, *J*=6.5 Hz, 6H), 0.84 (d, *J*=6.5 Hz, 6H), 1.35–1.45 (m, 2H) 1.49–1.57 (m, 2H) 1.70–1.81 (m, 2H), 3.64–3.69 (m, 2H) 8.14 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=22.3, 23.7, 24.3, 44.3, 53.3, 169.2; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{12}H_{23}N_2O_2$ $(M+H)^+$=227.1754, found 227.1762.

*4.2.1.17. (3R,6S)-3,6-Diisobutylpiperazine-2,5-dione (**13**).*[31] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.81 (d, *J*=6.3 Hz, 6H), 0.83 (d, *J*=6.3 Hz, 6H), 1.40–1.59 (m, 4H), 1.69–1.83 (m, 2H), 3.67–3.74 (m, 2H), 8.00 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=22.6, 23.5, 24.2, 42.0, 53.1, 169.4; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{12}H_{23}N_2O_2$ $(M+H)^+$=227.1754, found 227.1762.

*4.2.1.18. (3S,6S)-3-Benzyl-6-(ρ-(benzyloxy)benzyl)piperazine-2,5-dione (**14**).*[32] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.14 (dd, *J*=13.8, 6.1 Hz, 1H), 2.22 (dd, *J*=13.8, 6.1 Hz, 1H), 2.48–2.57 (m, 2H), 3.84–3.89 (m, 1H) 3.90–3.95 (m, 1H), 5,00 (s, 2H) 6.84–6.92 (m, 4H), 6.99 (d, *J*=6.7 Hz, 2H), 7.12–7.35 (m, 8H), 7.84 (m, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=39.1, 42.4, 56.1, 56.2, 69.8, 115.2, 127.1, 128.1, 128.4, 128.9, 129.0, 129.2, 130.5, 131.5, 137.3, 137.8, 157.8, 166.9, 166.9; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{25}H_{25}N_2O_3$ $(M+H)^+$=401.1860, found 401.1865.

*4.2.1.19. (3R,6R)-3,6-Bis(ρ-(benzyloxy)benzyl)piperazine-2,5-dione (**15**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.13 (dd, *J*=13.9, 6.0 Hz, 2H), 2.47 (dd, *J*=9.7, 4.7 Hz, 2H), 3.83–3.89 (m, 2H), 4.99 (s, 4H), 6.87 (d, *J*=9.3 Hz, 2H), 6.89 (d, *J*=9.3 Hz, 2H), 7.21–7.33 (m, 10H), 7.83 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=39.2, 56.2, 67.7, 115.2, 128.1, 128.4, 129.0, 129.3, 131.5, 137.8, 157.8, 167.0, **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{32}H_{31}N_2O_4$ $(M+H)^+$=507.2278, found 507.2286.

*4.2.1.20. (3S,6S)-3,6-Bis(ρ-(benzyloxy)benzyl)piperazine-2,5-dione (**16**).*[33] White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=2.13 (dd, *J*=13.9, 6.0 Hz, 2H), 2.47 (dd, *J*=9.7, 4.7 Hz, 2H), 3.83–3.89 (m, 2H), 4.99 (s, 4H), 6.87 (d, *J*=9.3 Hz, 2H), 6.89 (d, *J*=9.3 Hz, 2H), 7.21–7.33 (m, 10H), 7.83 (s, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=39.2, 56.2, 67.7, 115.2, 128.1, 128.4, 129.0, 129.3, 131.5, 137.8, 157.8, 167.0; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{32}H_{31}N_2O_4$ $(M+H)^+$=507.2278, found 507.2288.

*4.2.1.21. (3S,6R)-3-(ρ-(Benzyloxy)benzyl)-6-isopropylpiperazine-2,5-dione (**17**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.22 (d, *J*=7.0 Hz, 3H), 0.60 (d, *J*=7.0 Hz, 3H), 1.59–1.71 (m, 1H), 2.75 (dd, *J*=14.0, 4.8 Hz, 1H), 3.03 (dd, *J*=14.0, 4.8 Hz, 1H), 3.44–3.49 (m, 1H), 4.07–4.13 (m, 1H), 5.00 (s, 2H), 6.83 (d, *J*=8.5 Hz, 2H), 7.03 (d, *J*=8.5 Hz, 2H), 7.23–7.38 (m, 5H), 7.83 (s, 1H), 8.01 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=16.8, 18.9, 31.7, 37.6, 55.8, 59.8, 69.7, 115.1, 128.1, 128.3, 129.0, 129.1, 131.9, 137.9, 157.9, 167.1, 167.3; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{21}H_{25}N_2O_3$ $(M+H)^+$=353.1860, found 353.1867.

*4.2.1.22. (3R,6R)-3-Benzyl-6-methylpiperazine-2,5-dione (**18**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.40 (d, *J*=6.9 Hz, 3H), 2.80 (dd, *J*=13.7, 4.9 Hz, 1H), 3.08 (dd, *J*=13.5, 5.6 Hz, 1H), 3.53–3.60 (m, 1H), 4.10–4.15 (m, 1H), 7.07–7.15 (m, 2H), 7.14–7.26 (m, 3H), 7.97 (s, 1H), 8.07 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=20.4, 39.0, 50.4, 56.0, 127.3, 128.7, 131.0, 136.7, 166.5,

168.4; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{12}H_{15}N_2O_2$ $(M+H)^+$=219.1128, found 219.1138.

*4.2.1.23. (3R,6R)-3-Isobutyl-6-isopropylpiperazine-2,5-dione (**19**).* White powder; **^{1}H NMR** (400 MHz, DMSO-d_6): δ=0.79 (d, *J*=3.0 Hz, 3H), 0.80 (d, *J*=3.0 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H), 1.34–1.43 (m, 1H), 1.52–1.62 (m, 1H), 1.79–1.85 (m, 1H), 2.05–2.12 (m, 1H), 3.55–3.59 (m, 1H), 3.68–3.74 (m, 1H), 8.01 (s, 1H), 8.14 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ=18.0, 19.4, 22.4, 23.8, 24.2, 32.1, 44.6, 53.0, 60.2, 167.5, 169.1; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{11}H_{21}N_2O_2$ $(M+H)^+$=213.1598, found 213.1601.

4.3. Reduction of 2,5-diketopiperazines

4.3.1. General procedure. The 2,5-diketopiperazine was partially dissolved in anhydrous THF in an oven-dried three-neck flask under argon. The solution was cooled to 0 °C and $LiAlH_4$ (1.0 M THF, 12 equiv) was added dropwise. The mixture was allowed to warm at room temperature and the reaction was refluxed overnight. The mixture was then cooled to 0 °C and treated with Na_2SO_4 decahydrate. The suspension obtained was refluxed for 30 min and then filtered. The solvent was evaporated under reduced pressure and the crude product was dried under vacuum and used as in the next step.

4.4. Preparation of *N,N′*-dimethyl-1,4-piperazines (20a–31)

4.4.1. General procedure. Without purification, the 1,4-piperazine from previous step was dissolved in formic acid (50 equiv) in a regular round bottom flask and stirred for a few minutes. Formaldehyde (33 equiv, 37% v/v in water) was added and the mixture was stirred at 70 °C for 30 min. EtOAc was used to dilute the reaction mixture and a saturated $NaHCO_3$ solution was added dropwise until no further gas formation was observed. The reaction mixture was extracted three times with EtOAc. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo, giving compounds **20a** to **31**. When necessary, crude products were purified by flash chromatography using (90:5:5) CH_2Cl_2/MeOH/AcOH).

*4.4.2. (2S,5S)-2-(ρ-(Benzyloxy)benzyl)-5-isobutyl-1,4-dimethylpiperazine (**20a**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.89 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 1.30–1.46 (m, 2H), 1.53–1.64 (m, 1H), 2.16 (dd, *J*=11.7, 3.2 Hz, 1H), 2.21 (s, 3H), 2.27–2.35 (m, 1H), 2.43 (s, 3H), 2.49–2.60 (m, 2H), 2.69 (dd, *J*=13.4, 9.9 Hz, 1H), 2.89 (dd, *J*=13.1, 3.3 Hz, 1H), 5.04 (s, 2H), 6.90 (d, *J*=8.3, 2H), 7.10 (d, *J*=8.3, 2H), 7.30–7.46 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.3, 24.2, 26.0, 36.3, 42.7, 43.2, 56.0, 56.6, 59.7, 62.9, 70,3, 114.9, 127.7, 128.2, 128.9, 130.5, 133.2, 137.4, 157.3; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{24}H_{35}N_2O$ $(M+H)^+$=367.2744, found 367.2752.

*4.4.3. (2R,5R)-2-(ρ-(Benzyloxy)benzyl)-5-isobutyl-1,4-dimethylpiperazine (**20b**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.89 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 1.30–1.46 (m, 2H), 1.53–1.64 (m, 1H), 2.16 (dd, *J*=11.7, 3.2 Hz, 1H), 2.21 (s, 3H), 2.27–2.35 (m, 1H), 2.43 (s, 3H), 2.49–2.60 (m, 2H), 2.69 (dd, *J*=13.4, 9.9 Hz, 1H), 2.89 (dd, *J*=13.1, 3.3 Hz, 1H), 5.04 (s, 2H), 6.90 (d, *J*=8.3 Hz, 2H), 7.10 (d, *J*=8.3, 2H), 7.30–7.46 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.3, 24.2, 26.0, 36.3, 42.7, 43.2, 56.0, 56.6, 59.7, 62.9, 70.3, 114.9, 127.7, 128.2, 128.8, 130.5, 133.2, 137.4, 157.3; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{24}H_{35}N_2O$ $(M+H)^+$=367.2744, found 367.2752.

*4.4.4. (2S,5R)-2-(Benzyloxymethyl)-5-isopropyl-1,4-dimethylpiperazine (**21**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.84 (d, *J*=7.1 Hz, 3H), 0.88 (d, *J*=7.1 Hz, 3H), 1.88–1.96 (m, 1H), 2.03–2.46 (m, 5H), 2.19 (s, 3H), 2.42 (s, 3H), 2.82–2.90 (m, 2H), 3.68 (dd, *J*=9.3, 6.4 Hz, 1H), 3.8 (dd, *J*=8.7, 4.7 Hz, 1H), 4.51 (s, 2H), 7.23–7.36 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=15.9, 19.9, 27.0, 42.9, 43.5, 48.2, 57.9, 58.7, 66.5, 66.7, 73.4, 127.7, 127.8, 128.6, 138.8; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{17}H_{29}N_2O$ $(M+H)^+$=277.2274, found 277.2276.

*4.4.5. (2S,5R)-2-Benzyl-5-(benzyloxymethyl)-1,4 dimethylpiperazine (**22**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.21 (dd, *J*=11.8, 2.8 Hz, 1H), 2.28 (s, 3H), 2.44 (s, 3H), 2.54–2.79 (m, 5H), 2.94 (dd, *J*=13.2, 3.6 Hz, 1H), 3.54 (dd, *J*=8.8, 5.9 Hz, 1H), 3.73 (dd, *J*=9.5, 4.4 Hz, 1H), 4.54 (dd, *J*=15.8, 12.0 Hz, 2H) 7.11–7.42 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=32.5, 43.3, 43.3, 55.0, 56.2, 61.0, 62.6, 69.3, 73.5, 126.1, 127.8, 128.5, 128.6, 138.7, 140.5; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{21}H_{29}N_2O$ $(M+H)^+$=325.2274, found 325.2286.

*4.4.6. (2S,5S)-2,5-Dibenzyl-1,4-dimethylpiperazine (**23a**).*[11,12] Yellow powder. **mp**=120 °C. $[a]_D^{20}$ +117.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.24 (dd, *J*=11.6, 3.1 Hz, 2H), 2.36 (s, 6H), 2.46–2.53 (m, 2H), 2.54–2.62 (m, 2H), 2.76 (dd, *J*=13.8, 10.1 Hz, 2H), 2.98 (dd, *J*=13.0, 6.7 Hz, 2H), 7.19–7.24 (m, 6H), 7.27–7.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=33.1, 43.0, 55.8, 63.1, 128.1, 128.6, 129.6, 129.7, 140.5; **IR** (ATR, ZnSe): 3059, 2950, 2790, 1597, 1453, 1353, 1058, 736, 696 cm^{-1}; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{20}H_{27}N_2$ $(M+H)^+$=295.2169, found 295.2173.

*4.4.7. (2R,5R)-2,5-Dibenzyl-1,4-dimethylpiperazine (**23b**).*[12] Pale yellow powder. **mp**=120 °C. $[\mathbf{a}]_D^{20}$ −117.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.24 (dd, *J*=11.6, 3.1 Hz, 2H), 2.36 (s, 6H), 2.46–2.53 (m, 2H), 2.54–2.62 (m, 2H), 2.76 (dd, *J*=13.8, 10.1 Hz, 2H), 2.98 (dd, *J*=13.0, 6.7 Hz, 2H), 7.19–7.24 (m, 6H), 7.27–7.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=33.1, 43.0, 55.8, 63.1, 128.1, 128.6, 129.6, 129.7, 140.5; **IR** (ATR, ZnSe): 3059, 2951, 2790, 1597, 1453, 1353, 1058, 736, 696 cm^{-1}; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{20}H_{27}N_2$ $(M+H)^+$=295.2169, found 295.2177.

*4.4.8. (2R,5S)-2,5-Dibenzyl-1,4-dimethylpiperazine (**23c**).*[12] White powder. **mp**=123.2 °C.$[\mathbf{a}]_D^{20}$ 0.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.26 (dd, *J*=11.8, 3.0 Hz, 2H), 2.41 (s, 3H), 2.43 (s, 3H), 2.42–2.51 (m, 2H), 2.54–2.59 (m, 2H), 2.83 (dd, *J*=13.2, 9.8 Hz, 2H), 3.01 (dd, *J*=13.1, 6.9 Hz, 2H), 7.18–7.24 (m, 6H), 7.23–7.33 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=32.1, 43.2, 56.8, 63.3, 128.1, 128.5, 129.6, 129.7, 140.5; **IR** (ATR, ZnSe): 3025, 2952, 2788, 1600, 1452, 1078, 751, 699 cm^{-1}; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{20}H_{27}N_2$ $(M+H)^+$=295.2169, found 295.2181.

*4.4.9. (2S,5S)-2-Benzyl-5-isobutyl-1,4-dimethylpiperazine (**24**).* Transparent oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.89 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 1.31–1.46 (m, 2H), 1.53–1.65 (m, 1H), 2.14–2.21 (m, 4H), 2.27–2.36 (m, 1H), 2.42–2.54 (m, 6H), 2.58–2.67 (m, 1H), 2.71–2.80 (m, 1H), 2.90–2.98 (m, 1H), 7.15–7.20 (m, 3H), 7.24–7.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.3, 24.2, 25.9, 32.3, 37.2, 42.6, 43.1, 56.0, 56.3, 59.7, 62.7, 126.1, 128.5, 129.6, 140.5; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{17}H_{29}N_2$ $(M+H)^+$=261.2325, found 261.2333.

*4.4.10. (2R,5R)-2-Isobutyl-1,4-dimethyl-5-phenethylpiperazine (**25**).* Transparent oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.89 (d, *J*=6.5, 3H), 0.94 (d, *J*=6.5 Hz, 3H), 1.33–1.48 (m, 2H), 1.52–1.63 (m, 1H), 1.82–1.91 (m, 2H), 2.30 (s, 3H) 2.34 (s, 3H), 2.40–2.56 (m, 6H), 2.59–2.76 (m, 2H), 7.15–7.23 (m, 3H), 7.25–7.31 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.2, 24.1, 25.9, 32.55, 32.56, 42.6, 42.6, 55.4, 56.5, 59.1, 60.5, 126.1, 128.5, 128.6, 142.4; **HRMS** (ESI-TOF, *m*/*z*) calcd for $C_{18}H_{31}N_2$ $(M+H)^+$=275.2482, found 275.2487.

*4.4.11. (2R,5R)-2,5-Diisobutyl-1,4-dimethylpiperazine (**26a**).* Transparent oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.87 (d,

J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H), 1.31–1.41 (m, 4H), 1.49–1.61 (m, 2H), 2.27 (s, 6H), 2.29–2.50 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.2, 24.2, 26.0, 36.2, 42.8, 56.8, 59.2; **HRMS** (ESI-TOF, m/z) calcd for $C_{14}H_{31}N_2$ $(M+H)^+$=227.2482, found 227.2486.

*4.4.12. (2S,5S)-2,5-Diisobutyl-1,4-dimethylpiperazine (**26b**).* Red oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.87 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H), 1.31–1.41 (m, 4H), 1.49–1.61 (m, 2H), 2.27 (s, 6H), 2.29–2.50 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.2, 24.2, 26.0, 36.2, 42.8, 56.8, 59.2; **HRMS** (ESI-TOF, m/z) calcd for $C_{14}H_{31}N_2$ $(M+H)^+$=227.2482, found 227.2490.

*4.4.13. (2S,5R)-2,5-Diisobutyl-1,4-dimethylpiperazine (**26c**).* Transparent oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.88 (d, J=6.4, 3H), 0.90 (d, J=6.4, 3H), 1.13–1.21 (m, 4H), 1.60–1.69 (m, 2H), 2.36 (s, 3H), 2.39 (dd, J=12.3, 10.1 Hz, 2H) 2.43 (s, 3H), 2.61–2.69 (m, 2H), 2.96 (dd, J=11.6, 2.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.8, 23.3, 24.6, 42.5, 43.8, 53.3, 54.0; **HRMS** (ESI-TOF, m/z) calcd for $C_{14}H_{31}N_2$ $(M+H)^+$=227.2482, found 227.2482.

*4.4.14. (2S,5S)-2-Benzyl-5-(ρ-(benzyloxy)benzyl)-1,4-dimethylpiperazine (**27**).* White powder. **mp**=111 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.20–2.28 (m, 2H), 2.35 (s, 3H), 2.36 (s, 3H), 2.44–2.63 (m, 4H), 2.65–2.81 (m, 2H), 2.90–3.01 (m, 2H), 5.06 (s, 2H), 6.91 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 7.19–7.47 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=34.2, 43.0, 43.1, 55.6, 55.9, 63.0, 63.2, 70.3, 114.9, 126.1, 127.8, 128.2, 128.6, 128.8, 129.7, 130.5, 132.6, 137.4, 140.5, 157.4; **IR** (ATR, ZnSe): 2953, 2489, 1513, 1452, 1252, 1161, 992, 729, 695 cm^{-1}; **HRMS** (ESI-TOF, m/z) calcd for $C_{27}H_{33}N_2O$ $(M+H)^+$=401.2587, found 401.2593.

*4.4.15. (2R,5R)-2,5-Bis(ρ-(benzyloxy)benzyl)-1,4-dimethylpiperazine (**28a**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.23 (dd, J=11.6, 2.6 Hz, 2H), 2.35 (s, 6H), 2.44–2.58 (m, 4H), 2.65–2.74 (m, 2H), 2.91 (dd, J=13.1, 3.2 Hz, 2H), 2.89 (dd, J=13.1, 3.2 Hz, 1H), 5.05 (s, 4H), 6.90 (d, J=8.3 Hz, 4H), 7.12 (d, J=8.3 Hz, 4H), 7.30–7.46 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=32.2, 43.0, 55.7, 63.1, 114.9, 127.8, 128.2, 128.8, 130.5, 132.7, 137.4, 157.3; **HRMS** (ESI-TOF, m/z) calcd for $C_{34}H_{39}N_2O_2$ $(M+H)^+$=507.3006, found 507.3015.

*4.4.16. (2S,5S)-2,5-Bis(ρ-(benzyloxy)benzyl)-1,4-dimethylpiperazine (**28b**).* White powder. **mp**=158 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ=2.23 (dd, J=11.6, 2.6 Hz, 2H), 2.35 (s, 6H), 2.44–2.58 (m, 4H), 2.65–2.74 (m, 2H), 2.91 (dd, J=13.1, 3.2 Hz, 2H), 2.89 (dd, J=13.1, 3.2 Hz, 1H), 5.05 (s, 4H), 6.90 (d, J=8.3 Hz, 4H), 7.12 (d, J=8.3 Hz, 4H), 7.30–7.46 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=32.2, 43.0, 55.7, 63.1, 114.9, 127.8, 128.2, 128.8, 130.5, 132.7, 137.4, 157.3; **IR** (ATR, ZnSe): 2949, 2788, 1511, 1452, 1247, 1045, 806, 728, 693 cm^{-1}. **HRMS** (ESI-TOF, m/z) calcd for $C_{34}H_{39}N_2O_2$ $(M+H)^+$=507.3006, found 507.3011.

*4.4.17. (2S,5R)-2-(4-(Benzyloxy)benzyl)-5-isopropyl-1,4-dimethylpiperazine (**29**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.93 (d, J=7.0 Hz, 3H), 0.97 (d, J=7.0 Hz, 3H), 1.95–2.03 (m, 1H), 2.09–2.23 (m, 5H), 2.42–2.59 (m, 5H), 2.53–2.59 (m, 1H), 2.70–2.81 (m, 2H), 2.92–3.01 (m, 1H), 5.05 (s, 2H), 6.91 (d, J=8.7 Hz, 2H), 7.10 (d, J=8.7 Hz, 2H), 7.30–7.47 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=15.6, 19.8, 27.1, 27.9, 42.6, 43.0, 47.6, 57.6, 61.7, 66.7, 70.3, 115.0, 127.7, 128.2, 128.8, 130.6, 133.4, 137.4, 157.3; **HRMS** (ESI-TOF, m/z) calcd for $C_{23}H_{33}N_2O$ $(M+H)^+$=353.2587, found 353.2601.

*4.4.18. (2R,5R)-2-Benzyl-1,4,5-trimethylpiperazine (**30**).* White powder; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=1.05 (d, J=6.3 Hz, 3H), 2.14 (dd, J=11.5, 3.3 Hz, 2H), 2.17 (s, 3H), 2.27–2.35 (m, 1H), 3.20 (s, 3H), 2.44–2.50 (m, 3H), 2.66–2.75 (m, 1H), 2.83–2.91 (m, 2H), 7.13–7.19 (m, 3H), 7.23–7.29 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=15.3, 31.2, 43.7, 42.9, 56.2, 56.9, 57.9, 62.8, 126.0, 128.5, 129.6, 140.9; **HRMS** (ESI-TOF, m/z) calcd for $C_{13}H_{23}N_2$ $(M+H)^+$=219.1856, found 219.1867.

*4.4.19. (2R,5R)-2-Isobutyl-5-isopropyl-1,4-dimethylpiperazine (**31**).* Transparent oil; **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.86 (d, J=3.8 Hz, 3H), 0.87 (d, J=3.8 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H), 0.92 (d, J=6.9 Hz, 3H), 1.18–1.32 (m, 2H), 1.45–1.67 (m, 2H), 1.91–2.13 (m, 2H), 2.19 (s, 2H), 2.31 (s, 3H), 2.34–2.43 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=19.9, 21.4, 22.2, 24.9, 27.0, 34.5, 42.5, 43.0, 47.5, 56.1, 57.2, 58.9, 66.6; **HRMS** (ESI-TOF, m/z) calcd for $C_{13}H_{29}N_2$ $(M+H)^+$=213.2325, found 213.2339.

4.5. Typical procedure for picrate salts extraction

The extraction efficiency of the ligands was investigated by liquid-liquid phase extraction using the following metals: Zn^{2+}, Mn^{2+}, Mg^{2+}, Li^+, Ni^{2+}, Cu^{2+}. The picrate salts were prepared by dissolving metal nitrates (0.01 M) and picric acid (7×10^{-5} M) in distilled water and by stirring the resulting mixtures for 2 h. The *N*,*N*′-dimethyl-1,4-piperazine solutions were prepared in chloroform stabilized with amylene. 1 mL of picrate solution and 1 mL of ligand solution were mixed together using a magnetic stirrer for two hours at room temperature. 250 μL of the aqueous solution was removed and measured. The absorbance was measured at 350 nm. For each metal-ligand combination, the tests were repeated three times and the average extraction values were calculated using Eq. 1.

$$\text{extraction}(\%) = \left(1 - \frac{A_{350\ \text{extracted}}}{A_{350\ \text{initial}}}\right) \times 100 \quad (1)$$

4.6. Addition of diethylzinc on aryldehydes

4.6.1. General procedure. In an oven-dried 5 mL flask under argon atmosphere, the ligand (0.1 equiv, 0.1 mmol) was dissolved in 2.5 mL of anhydrous toluene and diethylzinc (1.5 M in toluene, 2 mmol) was added dropwise. The solution was cooled to 0 °C for 15 min and the aldehyde (1 equiv, 1 mmol) was added as a single portion. The mixture was then warmed to room temperature and stirred for 48 h before 1 N HCl was added. The resulting alcohol was extracted with three portions of EtOAc. The organic layers were then combined, washed with brine, dried with Na_2SO_4, and concentrated in vacuo, giving an oil from which conversion and enantiomeric excess were determined by GC. In one case involving benzaldehyde and ligand **23a** (Table 3, entry 1), the crude product was purified by flash chromatography (5:95 EtOAc/hexanes), giving 81% isolated yield of **32**. Commercially available (*S*)-1-phenyl-1-propanol was used for enantiomer identification on the GC chromatograms. Products **33** and **35**, as control experiments, were also prepared from Grignard addition reactions and analyzed by GC.

4.6.2. GC general conditions. Column: Beta Dex™ 120 (30 m×0.25 mm×0.25 μm film thickness); Detector: FID (250 °C); Inlet temperature: 230 °C; Gas saver: 10 mL/min; Split flow 100 mL/min; Carrier gas: H_2/air; Injection volume: 1 μL.

*4.6.3. 1-Phenyl-1-propanol (**32**).*[34,35] **^{1}H NMR** (400 MHz, $CDCl_3$): δ=1.25 (d, J=6.2 Hz, 3H), 1.84 (s, 1H), 2.75 (qd, J=13.4, 6.4, 1H), 3.97–4.06 (m, 1H), 7.20–7.27 (m, 3H), 7.30–7.35 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=22.8, 45.8, 68.7, 126.5, 128.5, 129.4, 138.6; **GC** (Oven temperature: 40 °C–125 °C (4.3 °C/min) then 125 °C–220 °C (10 °C/min); Total run time: 29.27 min): Retention times=21.87 min [(*R*)-**32**] and 22.60 min [(*S*)-**32**].

*4.6.4. 1-(4-Chloro)phenyl-1-propanol (**33**).*[34] **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.87 (t, J=7.4 Hz, 3H), 1.60–1.83 (m, 2H), 2.42 (s, 1H), 4.52

(t, J=6.6 Hz, 1H), 7.21–7.24 (m, 2H), 7.27–7.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=9.97, 31.9, 75.2, 127.3, 128.5, 133.0, 143.0; **GC** (Oven temperature: 40 °C–125 °C (4.3 °C/min) then 125 °C–220 °C (10 °C/min); Total run time: 29.27 min): Retention times=25.53 min [(*R*)-**33**] and 25.67 min [(*S*)-**33**].

*4.6.5. 1-(4-Methoxy)phenyl-1-propanol (**34**).*[34,35] **^{1}H NMR** (400 MHz, $CDCl_3$): δ=0.89 (t, J=7.4 Hz, 3H), 1.65–1.88 (m, 2H), 2.05 (br s, 1H), 3.79 (s, 3H), 4.53 (t, J=6.7 Hz, 1H), 6.87 (d, J=8.8 Hz, 2H), 7.25 (d, J=8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=10.2, 31.8, 55.2, 75.6, 113.6, 127.2, 130.8, 136.8, 159.0; **GC** (Oven temperature: 40 °C–125 °C (4.3 °C/min) then 125 °C–220 °C (5 °C/min); Total run time: 38.33 min): Retention times=28.73 min [(*R*)-**35**] and 28.89 min [(*S*)-**35**].

Acknowledgements

The authors thank Raphaël Lafleur-Lambert for his technical assistance with gas chromatography and the assistance of François Otis in peptide synthesis. This work was supported by the NSERC of Canada, the FQRNT of Quebec, PROTEO, and Université Laval. C.B. is also indebted to PROTEO for a postgraduate scholarship.

References and notes

1. Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140.
2. Breuning, M.; Steiner, M. *Synthesis* **2008**, 2841.
3. Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.
4. Chuzel, O.; Riant, O. *Top. Organomet. Chem.* **2005**, *15*, 59.
5. Eriksson, J.; Arvidsson, P. I.; Davidsson, O. *Chem.—Eur. J.* **1999**, *5*, 2356.
6. Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717.
7. Falorni, M.; Satta, M.; Conti, S.; Giacomelli, G. *Tetrahedron : Asymmetry* **1993**, *4*, 2389.
8. Fuji, K.; Tanaka, K.; Miyamoto, H. *Chem. Pharm. Bull.* **1993**, *41*, 1557.
9. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063.
10. Soai, K.; Soai, S.; Niwa, Y.; Yamada, H. *Tetrahedron Lett.* **1987**, *28*, 4841.
11. Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156.
12. Ohta, A.; Okuwaki, Y.; Komaru, T.; Hisatome, M.; Yoshida, Y.; Aizawa, J.; Nakano, Y.; Shibata, H.; Miyazaki, T.; Watanabe, T. *Heterocycles* **1987**, *26*, 2691.
13. Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.
14. Grina, J. A.; Ratcliff, M. R.; Stermitz, F. R. *J. Org. Chem.* **1982**, *47*, 2648.
15. Grina, J. A.; Stermitz, F. R. *Tetrahedron Lett.* **1981**, *22*, 5257.
16. Takeuchi, S.; Ohgo, Y.; Miyoshi, N.; Shin, C.-G.; Yonezawa, Y. *Heterocycles* **1990**, *31*, 2073.
17. Johansson, A.; Johansson, E.; Wingstrand, M. *J. Organomet. Chem.* **2005**, *690*, 3846.
18. Degrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1980**, *45*, 1295.
19. Degrado, W. F.; Kaiser, E. T. *J. Org. Chem.* **1982**, *47*, 3258.
20. Smith, R.; Smith, M.; Bobko, W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2369.
21. Kopac, D. S.; Hall, D. G. *J. Comb. Chem.* **2002**, *4*, 251.
22. Nystrom, R. F. *J. Am. Chem. Soc.* **1948**, *70*, 3738.
23. Eschweiler, W. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 880.
24. Voyer, N.; Roby, J.; Deschênes, D.; Bernier, J. *Supramol. Chem.* **1995**, *5*, 61.
25. Kleinsmann, A. J.; Nachtsheim, B. J. *Chem. Commun.* **2013**, 7818.
26. Guo, C.-J.; Yeh, H.-H.; Chiang, Y.-M.; Sanchez, J. F.; Chang, S.-L.; Bruno, K. S.; Wang, C. C. C. *J. Am. Chem. Soc.* **2013**, *135*, 7205.
27. Govindaraju, T. *Supramol. Chem.* **2011**, *23*, 759.
28. Donkor, I. O.; Sanders, M. L. *Bioorg. Med. Chem.* **2001**, *11*, 2647.
29. Sun, X.; Ray, R.; Rachita; MacKerell, A. D.; Faden, A. I.; Xue, F. *Tetrahedron Lett.* **2014**, *55*, 1905.
30. Huang, H.; She, Z.; Lin, Y.; Vrijmoed, L. L. P.; Lin, W. *J. Nat. Prod.* **2007**, *70*, 1696.
31. Tanihara, M.; Hiza, T.; Imanishi, Y.; Higashimura, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1155.
32. Zeng, Y.; Li, Q.; Hanzlik, R. P.; Aubé, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3034.
33. Cochrane, J. R.; White, J.; Wille, U.; Hutton, C. *Org. Lett.* **2012**, *14*, 2402.
34. Zong, H.; Huang, H.; Bian, G.; Song, L. *Tetrahedron Lett.* **2013**, *54*, 2722.
35. Faigl, F.; Deák, S.; Erdélyi, Z.; Holczbauer, T.; Czugler, M.; Nyerges, M.; Mátravölgyi, B. *Chirality* **2015**, *27*, 216.