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Thermodynamic epimeric equilibration and crystallisation-induced dynamic resolution of lobelanine, norlobelanine and related analogues

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The step-economical synthesis of lobelanine implying a ring closing double aza-Michael (RCDAM) reaction is revisited and successfully extended to the synthesis of various configurationally more stable analogues. Owing to the presence of a configurationally labile β-aminoketone subunit, lobelanine is prone to self-catalyze mutarotation in solution. Through the synthesis of orginal lobelanine analogues, we studied the influence of (i) the size of central heterocycle, (ii) the bulkyness of nitrogen protecting group and, (iii) the phenacyl arm substituent, on the thermodynamic equilibrium and its displacement by crystallisation-induced dynamic resolution (CIDR). We demonstrated that fine structural tuning combined to optimized CIDR conditions favour the first efficient diastereoselective synthesis of lobelanine's analogues.

Introduction

(-)-Lobeline (Figure 1),[1] the most abundant alkaloid found in *Lobelia inflata*, was first characterised[2] and synthesized[3] in 1929. Since then, this natural product has been associated with a wide range of biological activities.[4] Despite this long and rich history of therapeutic uses and pharmacological properties, only a few analogues of (-)-lobeline, poorly functionalized, have been hemi-synthesized to date.[5]

Until now, the most convergent total syntheses of (-)-lobeline involved enantioselective desymmetrization of the *meso*-congeners lobelanidine[6] or lobelanine[7]. In both cases, the natural product, lobelanine, plays a pivotal role. Surprisingly, this key intermediate has never been fully characterised, and none of these convergent syntheses have been exploited to prepare *Lobelia* alkaloid analogues. However, one might be discouraged by the configurational instability exhibited by the β-aminoketone pattern borne by, among others, *Lobelia* or *Sedum* alkaloids (Figure 1).[8]

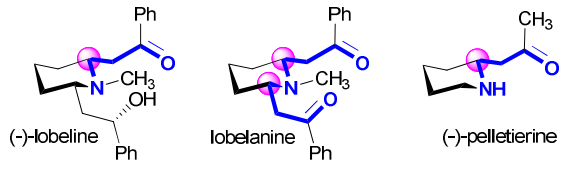
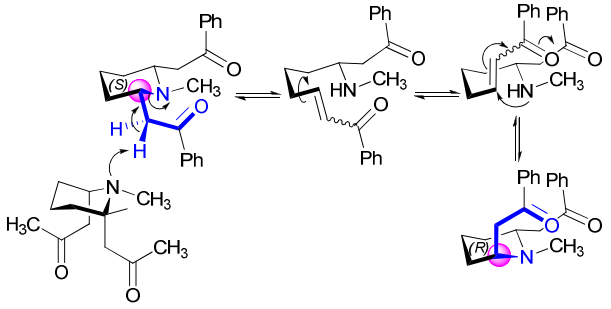


Figure 1. Examples of epimerisable *Lobelia* and *Sedum* alkaloids

During the development of the total synthesis of (-)-lobeline, today considered as the first biomimetic one, the pioneering chemists Schöpf and Lehmann demonstrated that the lobelanine stability was strikingly dependent on weak acidic conditions.[9] Later, in 1958, Ebnöther reported that lobeline congener free bases slowly epimerised in solution, but without providing any pertinent spectroscopic information except optical rotation.[10] More recently, the mutarotation phenomenon of (-)-lobeline free base in solution was clearly established by Marazano,[11] and the mechanism of self-catalyzed retro-Michael addition was confirmed by Crooks (Scheme 1).[12] Interestingly, Marazano also reported that a *cis/trans*-lobeline mixture could be converted to the sole thermodynamically stable *cis* epimer by treating the mixture with hydrochloric acid.[11] Based on this evidence, Stoltz and co-workers[13] recently developed an efficient crystallisation-induced dynamic resolution (CIDR) process[14,15] allowing the selective precipitation of the isomerically pure (-)-lobeline from the corresponding *cis*/*trans* mixture.

If the lobeline mutarotation seems to be deciphered, a big gap still remains in understanding of lobelanine epimerisation and of its dynamic diastereomeric enrichment by CIDR (Scheme 1). Moreover, consequences of the lobelanine mutarotation on the stereochemical outcome of a desymmetrizing process have not been studied so far. Surprisingly, the existence of a *cis/trans* diastereomeric mixture

of the lobelanine hydrochloride salts was only once mentioned by Birman and co-workers.[6b]



Scheme 1. Self-catalyzed epimerisation of lobelanine via a retro-Michael process.

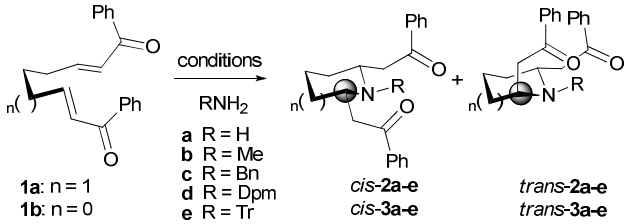
As part of a fundamental research program aiming at studying nAChRs allosteric rearrangements,[16] we draw particular attention on the development of a flexible series of structural lobeline analogues. In nAChRs, stereochemistry and ligand shape can affect the binding properties as well as the agonist versus antagonist activity. In this context, one of the key issues in designing new ligands relies on control of their three-dimensional geometry. Our continuing interest in developing "economical" asymmetric syntheses, focuses our attention on the preparation of series of ligands through stereoselective desymmetrizing reactions of *meso*-compounds such as lobelanine or related analogues. We recently reported[17] an solvent-free diastereoselective synthesis of pyrrolidine analogues of lobelanine *via* a ring closing double aza-Michael (RCDAM). RCDAM under more conventional conditions was first applied by W. Parker and coworkers to the synthesis of lobelanine.[18] Even though this RCDAM pathway could allow a direct and straightforward introduction of oriented molecular diversity to the lobelanine framework, its scope has never been studied and broadened until now.

In this particular context, we disclose herein a concise study as well as new aspects of this reversible RCDAM reaction to the preparation of diverse and original piperidine or pyrrolidine lobelanine analogues. Molecular determinants controlling the diastereomeric enrichment and inducing selective crystallisation have been highlighted permitting the first stereoselective access of lobelanine derivatives through a CIDR process.

Results and discussion

The nonadienedione **1a** was synthesized in a 9:1 diastereomeric ratio of, respectively, separable *E,E*[19] and *E,Z*[20] isomers. The lower homologue, octadienedione **1b**,[21] was obtained in its unique *E,E* configuration as previously described.[17] Table 1 summarizes the results of RCDAM reactions between both *bis*(enones) and diverse primary amines of increasing steric hindrance. In both series, tritylamine was too bulky to react with dienediones **1a** or **1b** even at elevated temperature (Table 1, entry 5). Piperidines **2a-d** and pyrrolidines **3a-d** were isolated, after thermodynamic equilibrium had been reached. The *cis*/*trans* ratio was measured by ^{1}H NMR experiments thanks to the shielding of the 2,5- or 2,6-proton signals of the *cis* compounds in the pyrrolidine or piperidine series, respectively.[22,23] Epimeric equilibrium was shown to be influenced by both the nature of nitrogen substituent and the ring size. However, we observed that the course of a reaction, which is under thermodynamic control, is independent on the dienedione configuration. Therefore, Michael acceptors can be used as single isomer or diastereomeric mixture.[24]

Table 1. RCDAM addition of primary amines to *bis*(enones) **1a** and **1b**



			Piperidine		*Pyrrolidine*	
Entry	R	conditions	Compd. (Yield)	*cis*:*trans* ratio (%)[a]	Compd. (Yield)	*cis*:*trans* ratio (%)[a]
1	H	MeOH/DCM 12h, rt	**2a** (96%)[b]	93:7	**3a** (92%)[b]	70:30
2	Me	THF, 15min, rt	**2b** (92%)	45:55	**3b** (98%)[b]	95:5
3	Bn	THF, 3h, rt	**2c** (96%)	23:67	**3c** (94%)	85:15
4	Dpm	THF, 72 h, rt	**2d** (68%)[b]	100:0	**3d** (97%)[b]	100:0
5	Tr	THF, 3h, reflux[c]	/	/	/	/

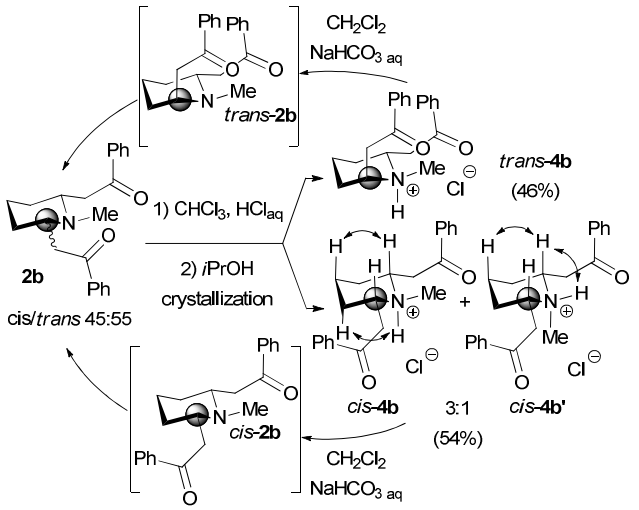
[a]Ratio were determined after equilibration of the crude reaction mixture in solution in deuterated solvent (benzene, acetone, chloroform or THF) by ^{1}H NMR experiment at room temperature. [b]Yield of the isolated sole *cis*-diastereomer after crystallisation-induced dynamic resolution. [c]No reaction were observed at room temperature and reflux.

A/ Lobelanine epimeric equilibrium study

We first turned our attention towards the piperidine series and access to lobelanine *cis*-**2b** and its epimer *trans*-**2b**. A commercial solution of methylamine in THF was added to the nonadienedione **1a**. Total conversion of the starting material was obtained in only 15 minutes at room temperature. In good agreement with results earlier described in pyrrolidine series,[17] the double aza-Michael adduct **2b** was isolated in excellent yield using aprotic conditions, improving radically the pioneering work of Parker *et al.* in protic solvent.[18] ^{1}H NMR analysis of the crude reaction mixture showed two sets of signals, reflecting the presence of two inseparable diastereomers *cis*-**2b** and *trans*-**2b**, in a nearly equimolar ratio (45:55) (Table 1, entry 2). This thermodynamic ratio proved to be identical whatever aprotic deuterated solvent was used (benzene, THF or chloroform). Moreover, the lobelanine *cis:trans* ratio was comparable to those measured by Crooks[12] for the pseudo-*meso* lobeline, showing the similar behaviour of these two congeners. Unpredictably, very slow crystallisation[25] of the neat diastereomeric mixture of **2b** occurred at room temperature. ^{1}H NMR determination of the diastereomeric ratio

revealed a noticeable enrichment (90:10) in favour of the natural *cis* epimer. Thanks to this unexpected spontaneous dynamic resolution, we anticipated that lobelanine might be produced in diastereomerically pure form through a selective crystallisation-induced disequilibration of the retro-aza-Michael/aza-Michael cascade. As solvent plays a crucial role in the success or failure of such a CIDR process, the RCDAM reaction was attempted in cyclohexane, ether, toluene, or dichloromethane and under solvent-free conditions in order to favour selective crystallisation of the *cis*-epimer. Unfortunately, we did not find any suitable conditions in which the solubility of the resultant lobelanine base permitted its dynamic resolution by crystallisation, neither in the course of the reaction nor after complete evaporation to dryness.

Inspired by the efficient late-stage CIDR of lobeline hydrochloride salt developed by Stoltz and co-workers,[13] we prepared the hydrochloride salt of lobelanine, anticipating that it might precipitate more easier from the reaction mixture due to its ionic character (Scheme 2). Washing a chloroform solution of *cis*-**2b** and *trans*-**2b** (45:55) with aqueous HCl gave a crude mixture of piperidinium salts **4b** whose ^{1}H NMR spectrum revealed three separate signals in accordance with symmetry considerations. From the diastereomer *cis*-**2b**, nitrogen quaternization generates two distinct *N*-invertomers with equatorial or axial orientation of the *N*-methyl group (Scheme 2). From *trans*-**2b**, only two enantiomeric hydrochloride salts are produced (Scheme 2).



Scheme 2. Synthesis of the lobelanine hydrochloride isomeric salts *cis*-**4b**, *cis*-**4b'** and *trans*-**4b** and characteristic nOesy correlations.

By selective crystallisation from *i*PrOH, an inseparable mixture of *cis*-**4b**(Me_{eq})/*cis*-**4b'**(Me_{ax}) (in a 3:1 ratio) was isolated from the compound *trans*-**4b** that remained in solution. All isomers *cis*-**4b**, *cis*-**4b'** and *trans*-**4b** were fully characterised by NMR spectroscopy and nOesy experiments (Scheme 2 and Supplementary Information). The general trend towards the preferential crystallisation of the *cis* over the *trans* lobelanine diastereomers, both under neutral and acidic forms, is in agreement with its behaviour reported by Ebnöther[10] and Birman[6b]. This observation might be explained by the ability of symmetrical *cis* epimers to crystallise as higher ordered structures than *trans* ones.

Subsequently, a solution of the 3:1 mixture of *cis*-**4b**/*cis*-**4b'** in dichloromethane was washed with aqueous sodium bicarbonate. The released lobelanine base *cis*-**2b** was obtained with a small amount of the epimer *trans*-**2b** (8%). Respectively, basic treatment of *trans*-**4b** produced a 4:1 mixture of *trans*-**2b** and *cis*-**2b**. For the first time, structures of lobelanine and *epi*-lobelanine were fully characterised by NMR. As expected, both basic solutions slowly equilibrated towards the starting thermodynamic 45:55 proportions of *cis*/*trans* isomers (Scheme 2 and Supplementary Information). As the stereoisomer *trans*-**2b** seems to interconvert faster than *cis*-**2b**, the equilibration process was monitored by ^{1}H NMR at various temperatures and concentrations using different solvents (Table 2 and Supplementary Information). As expected for a base self-catalyzed reaction involving an aza-Michael step, the interconversion rate was shown to be concentration-dependent (Table 2, entries 1 and 5). Similarly, an increase of the reaction temperature provoked the acceleration of the epimerisation process without modifying diastereomeric proportions (Table 2, entries 2 and 3). Eventually, more polar solvents also sped up the lobelanine epimerisation, similarly to those earlier observed for lobeline:[12] acetone-d_6 allowed a total return at thermodynamic equilibrium three times faster than for the same reaction performed in $CDCl_3$ (Table 2, entries 1 and 4). Once more, these results highlighted the similarity of lobelanine behaviour towards lobeline.

Table 2. ^{1}H NMR monitoring of equilibration of lobelanine *cis*-**2b**.

Entry	Concentration (M)	solvent	Time[a] (h)	Temperature (°C)	*cis*:*trans* ratio
1	0.085	$CDCl_3$	15	27	47:53
2	0.085	C_6D_6	10,5	27	46:54
3	0.085	C_6D_6	3,5	40	45:55
4	0.085	$(CD_3)_2CO$	7	27	46:54
5	1	$CDCl_3$	2	27	45:55

[a]Reaction time required to reach thermodynamic equilibrium.

B/ Effect of nitrogen substituents

In order to seek out the limitations of our methodology coupling RCDAM to CIDR, we studied the impact of the nitrogen substitution on both the thermodynamic RCDAM diastereomeric equilibration in solution and the dynamic resolution efficiency (Table 1). Our attention had been first focused on the reversible conjugate addition of ammonia as an unsubstituted source of nitrogen. RCDAM addition of aqueous ammonia to *E,E*- or *E,Z*-nonadienediones **1a** at room temperature gave the natural alkaloid norlobelanine **2a**, in excellent yield and a 4:1 *cis*/*trans* ratio. The RCDAM addition was also performed at -78°C using liquid ammonia as solvent. After removal of ammonia by overnight return to room temperature, the diastereomers **2a** were quantitatively obtained with similar thermodynamic proportions (77:23 *cis*/*trans* ratio). Selective crystallisation from diethylether led exclusively to the

isomerically pure natural norlobelanine, whose full characterisation had never been reported to date (Table 1, entry 1). We fully characterised *cis*-**2a** by NMR spectroscopy, and its relative configuration was confirmed by single crystal X-ray analysis (Figure 2A). In its crystal structure, norlobelanine adopts a classical chair conformation in which the proton of the central nitrogen forces both oxygen atoms of the phenacyl arms to face each other by the creation of stabilizing intramolecular hydrogen bonds ($d_{O...H}$ = 2.53 and 2.35 Å, Figure 2A). The driving force implied by this stabilized H-bonded conformation could explain the success of the dynamic resolution and the slow epimerisation of the norlobelanine *cis*-**2a**. Indeed, mutarotation was only complete after 12 hours of warming at 70°C in C_6D_6 giving a stable 93:7 *cis*/*trans* ratio (Table 1, entry 1).

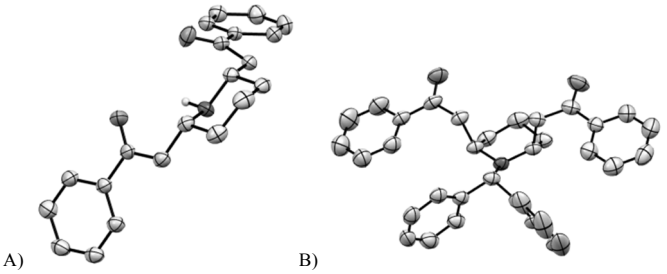
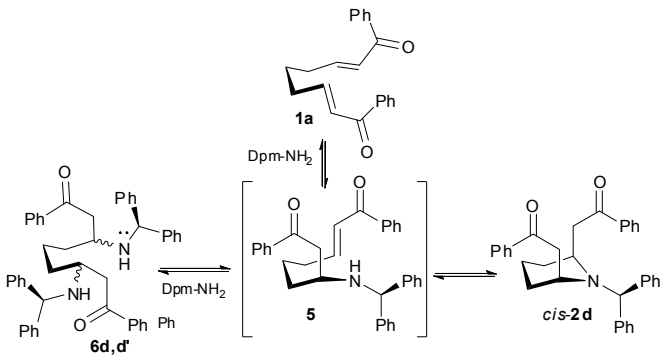


Figure 2. Thermal ellipsoid plots of molecular structure of A) norlobelanine *cis*-**2a** and B) *cis*-**2d** (35% probability thermal ellipsoids). H atoms have been omitted for clarity except the N*H* atom of *cis*-**2a**.[26]

We pursued our study by reacting successively the nonadienedione **1a** with benzylamine and diphenylmethylamine (benzhydryl amine) as *N*-nucleophiles having increasing steric hindrance. Moreover, these *N*-substituents could be easily cleaved, offering other possibilities for molecular modulation. With benzylamine, total disappearance of the starting material was observed after three hours at room temperature in THF (Table 1, entry 3). The *cis*/*trans* diastereomers **2c** were obtained in an unexpected reversed 23:67 *cis/trans* ratio. Despite many attempts, it was impossible neither to separate both diastereomers by chromatographic techniques nor to find optimal crystallisation solvent conditions. Nevertheless, the epimer characterisation was accomplished through ^{1}H NMR experiments made on the crude reaction mixture (see Supplementary Information).[27,28]

By contrast, the conjugate addition of the more hindered benzhydrylamine (Dpm-NH_2) gave the piperidine **2d** as the single *cis* diastereomer (Table 1, entry 4). *Cis*-**2d** was fully characterised and its stereochemistry confirmed by single crystal X-ray analysis (Figure 2B). In the crystal, the usual chair conformation of the piperidine ring is maintained with the bulky benzhydryl group in the equatorial position. The two phenacyl groups are placed in the unfavorable axial orientations, leading to a strong 1,3-diaxial steric interaction ($d_{C2...C6}$ = 2.52 Å and $d_{C7...C15}$ = 3.36 Å). Obviously, the conformation of **2d** is stabilized by two symmetrical perpendicular edge-to-face (T-shaped) π-stacking interactions,[29] favoured by a matched contribution of the aryl substituents. While the carbonyl electron-withdrawing group increases the *para*-hydrogen partial-positive charge, the π-donating aminophenylmethyl substituent increases the negative π-electron cloud density of the benzene ring below it.[30] Similarly to norlobelanine, diastereoselectivity of the RCDAM addition of benzhydrylamine could be justified by the formation of these stabilizing intramolecular noncovalent aryl-aryl interactions between phenacyl and benzhydryl groups.

^{1}H NMR monitoring of the benzhydrylamine reaction allowed us to visualize the transient retroconjugate addition. In the case of benzhydrylamine, we observed the transient formation of diastereomeric double-adduct **6d,d'**, which evolved slowly towards the piperidine *cis*-**2d** through a tandem retro-Michael/ring-closing aza-Michael process (Scheme 3). To confirm the formation of the double-adducts, we effected the conjugate addition in the presence of two equivalents of benzhydrylamine. The double-adduct **6** was obtained as major product but its separation from the cyclized compound *cis*-**2d** and the starting primary amine proved impossible.[31] Spontaneously, the double-adducts **6d,d'** evolved towards the heterocycle *cis*-**2d**. The bulkiness of the benzhydryl group seems responsible for the decrease in the cyclization rate to benefit the double aza-conjugate addition. Its presence also favored the evolution of double-adducts **6d,d'** towards the cyclized species *cis*-**2d,** promoting the retro-Michael reaction in the tandem process.



Scheme 3. Plausible equilibria leading to *cis*-**2d**.

Interestingly, retro-Michael reaction has also been observed by ^{1}H NMR experiments when the piperidine *cis*-**2d** was heated at 70°C in deuterated benzene (Figure 3). After 12 hours (Figure 3, B), the ^{1}H NMR spectrum revealed the presence of a large amount of dienedione **1a** (1.18 and 1.82 ppm) and benzhydrylamine (4.87 ppm) accompanying the starting piperidine *cis*-**2d** (3.02, 3.38, 3.90 and 4.94 ppm). After one week at room temperature, this solution (Figure 3, C) evolved towards the diminution of both amine and dienedione **1a**, until the total disappearance of the free amine with concomitant production of *cis*-**2d** (Figure 3, D). These experiments proved the existence of the retro-aza-Michael/ring closing aza-Michael cascade through the sequential formation and consumption of both RCDAM reactants.

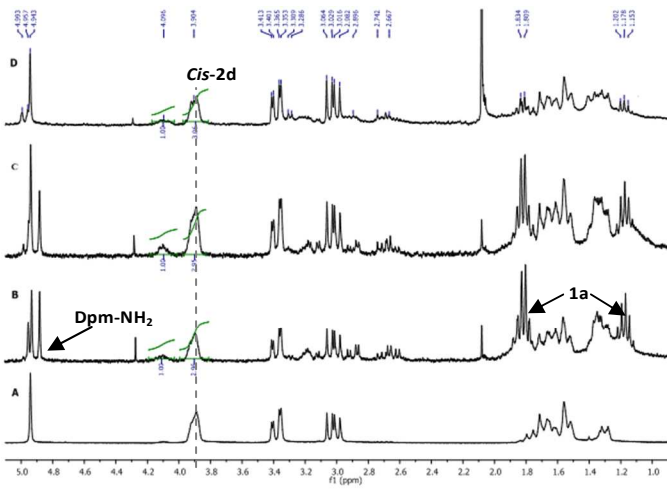


Figure 3. ^{1}H NMR spectra (C_6D_6; 300 MHz) of A) *cis*-**2d**. B) *cis*-**2d** after heating at 70°C for 12 hours. C) *cis*-**2d** after one week at room temperature. D) crude reaction mixture after slow evaporation of the solvent over an additional week.

C/ Effect of ring contraction

With the aim of developing more configurationally stable *Lobelia* alkaloid analogues,[17] we proceeded to synthesize pyrrolidine analogues. The latter were prepared under the same conditions mentioned above for the piperidine series (Table 1, compounds **3a-d**).

First, the pyrrolidine norlobelanine analogue **3a** was quantitatively obtained as a mixture of *cis*/*trans* diastereomers by RCDAM addition of ammonia. Selective crystallisation proceeds at low temperature in *i*PrOH, permitting the isolation of the single diastereomer *cis*-**3a** in more than 90% yield (Table 1, entry 1). *Cis*-**3a** was fully characterised and its *cis*-configuration confirmed by its X-ray analysis (Figure 4A). Similarly to norlobelanine **2a**, the X-ray structure shows that the configuration is maintained through stabilizing intramolecular hydrogen bonds between the nitrogen proton in a *pseudo*-equatorial position and both carbonyl oxygen atoms facing it ($d_{O\ldots H}$ = 2.47 Å and 2.48 Å respectively).

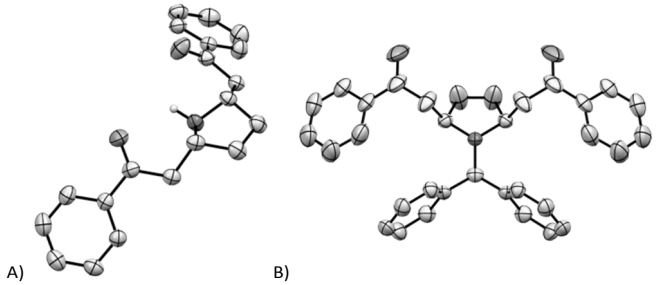


Figure 4. Thermal ellipsoid plots of molecular structure of A) *cis*-**3a** and B) *cis*-**3d**[17,32] (35% probability thermal ellipsoids). H atoms have been omitted for clarity except for the N*H* atom.[26]

The pyrrolidine lobelanine **3b** was prepared in a quantitative yield and excellent 95:5 *cis*/*trans* ratio, confirming the better configurational stability of pyrrolidine derivatives compared to piperidines (Table 1, entry 2). RCDAM addition of benzylamine to the *bis*(enone) **1b** gave the pyrrolidine **3c** in a 88% yield (Table 1, entry 3). Contrary to results observed for the piperidine homologue **2c**, the 85:15 *cis/trans* ratio of **3c** followed the general trend obtained for all 2,5-disubstituted pyrrolidines, in favour of the thermodynamic epimer c*is*-**3c**. Similarly to piperidine **2c**, no optimal conditions were found to induce crystallisation and thus to diastereomerically enrich the mixture by dynamic resolution.

Finally, the conjugate addition of benzhydrylamine to **1b** followed by recrystallisation in cyclohexane afforded the pyrrolidine *cis*-**3d** as the sole isomer in 95% yield (Table 1, entry 4). We demonstrated that *cis*-**3d** was much more stable than its higher homologue *cis*-**2d** in deuterated benzene solution even after one week at room temperature or 16 hours at 70°C. The pronounced stability of the *cis*-**3d** symmetrical configuration[17,32] is also insured by the presence of two stabilizing perpendicular edge-to-face (T-shaped) π-stacking interactions (Figure 4B).

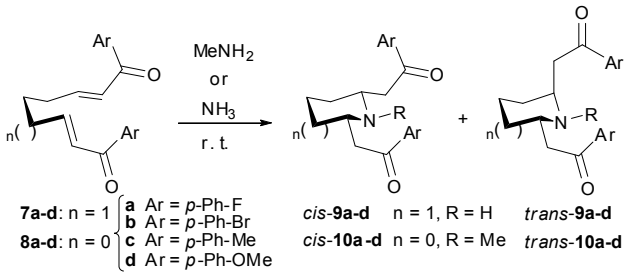
D/ Effect of phenyl substituents

Since even a slight modification in structure of the products might cause the target not to crystallise, we studied the robustness of our synthetic sequence through the synthesis of lobelanine analogues differing by the substitution of their phenacyl arms. In order to evaluate the contribution of phenyl substituents, we decided to prepare phenyl-substituted derivatives of norlobelanine **2a** and pyrrolidine lobelanine analogue **3b**, both identified as configurationally stable in solution. Results are summarized in table 3.

First, the required dienediones **7a-d** and **8a-d** were synthesized as reported in the literature, respectively, starting directly with a commercially available aqueous solution of glutaraldehyde[33,34] or starting with 1,5-cyclooctadiene according our two-step procedure.[24] Nonadienediones **7a-d** were reacted with ammonia and octadienediones **8b-d** with methylamine under conditions previously optimizedfor norlobelanine and lobelanine, respectively. The general trend observed in the case of the phenyl compounds **2a** and **3b** (Table 1) was verified for the synthesis of the diversely substituted phenyl analogues **9a-d** and **10a-d** (Table 3, entries 2-5). The latter were obtained in excellent yields and high diastereomeric ratio. Application of optimal solvent conditions for the CIDR allowed the isolation of the unique configurationally stable *cis*-epimer except for compounds **9c** (Table 1, entry 4) and **10d** (Table 1, entry 5), for which no suitable solvent or mixture of solvents has been found.

These results indicated that the electronic nature of the phenyl substituents did not dramatically influence the preferential crystallisation of *cis*-diastereomer.

Table 3. Influence of phenyl substituents on configuration stability of norlobelanine and pyrrolidine lobelanine derivatives.



		1H-piperidine		*N-methylpyrrolidine*	
Entry	Ar	Compd.[a] (Yield)	*cis*:*trans* ratio (%)[c]	Compd.[b] (Yield)	*cis*:*trans* ratio (%)[c]
1	Ph-H	**2a** (96%)[d]	93:7	**3b** (98%)[d]	95:5
2	*p*-Ph-F	**9a** (92%)[d]	89:11	**10a** (98%)[d]	93:7
3	*p*-Ph-Br	**9b** (95%)[d]	91:9	**10b** (88%)[d]	93:7
4	*p*-Ph-Me	**9c** (83%)	90:10	**10c** (97%)[d]	90:10
5	*p*-Ph-OMe	**9d** (85%)[d]	92:8	**10d** (99%)	93:7

The reaction was performed until completion at room temperature: [a]in $MeOH/CH_2Cl_2$ using a 28% ammonia solution (7 eq.); [b]in CH_2Cl_2 using methylamine (2M in THF, 2 eq.).[c]Ratio were determined on the crude reaction mixture by ^1H NMR experiment in C_6D_6 at room temperature. [d]Yield of isolated *cis*-diastereomer after dynamic resolution by crystallisation.

D/ Computational studies

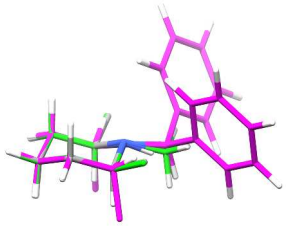
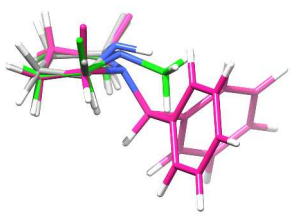
With the aim of understanding the origin of the thermodynamic equilibration and the observed stereoselectivity of the CIDR process, DFT calculations at the B3LYP/6-31G* level[35,36,37,38,39] were conducted (Table 4 and Supplementary Information). For isolated structures, we have experimentally demonstrated that the sterically hindered environment of nitrogen atom is necessary but not sufficient to induce stereo-discrimination in RCDAM reaction. In contrast, the ability of the thermodynamic adduct to precipitate was shown to be highly dependent on structural modification. Steric interactions in RCDAM adducts seem to thermodynamically govern conformational and configurational swap-over that predisposes the equilibrium shift towards the diastereomer presenting the more favourable shape to crystallise.

First, DFT calculations broadly corroborate the experimental findings, showing unambiguously that RCDAM *trans*-adducts are kinetically produced and the more stable *cis*-adducts are thermodynamically favoured in both pyrrolidine and piperidine series (Table 4 and Supporting Information).[40] They also suggest that epimeric barrier increases on passing from the piperidine to the pyrrolidine series, confirming that pyrrolidine analogues are configurationally more stable than related piperidines.

In the piperidine series, calculated global thermodynamic trends were correctly predicted. The clear energetic drop in calculated *cis* form predominance between norlobelanine **2a** (NH) and both lobelanine **2b** (NMe) and benzhydrylpiperidine **2d** (NDpm) is consistent with experimental findings, highlighting the crucial role played by the stabilizing intramolecular hydrogen bond in the epimerisation process (Table 4, entries 1 and 2). Concerning benzhydrylpiperidine **2d** (NDpm), the difference between calculated relative enthalpies of *cis* and *trans* diastereomers is not sufficient to satisfactorily explain the experimentally observed diastereoselectivity (Table 4, entry 3). This could find an explanation in the particular mechanism followed in the course of RCDAM addition of benzhydrylamine, which was proved to proceed according to a double intermolecular aza-Michael / retro-Michael / intramolecular aza-Michael cascade. This complex mechanism could directly favour the *cis* diastereomer because of steric hindrance and stabilizing π-stacking interactions avoiding the equilibration step.

By comparison, the calculated energetic profile for the pyrrolidine series is more satisfactory (Table 4, entries 4 to 6). As the pyrrolidine system is less floppy than the corresponding six-membered ring, steric interactions in pyrrolidine system can be strong enough to be considered as crucial factor in the dynamic thermodynamic resolution (Table 4, pyrrolidines superimposition). Diastereomeric species possess significantly different thermodynamic stabilities to provide highly diastereoenriched products under convenient CIDR conditions.

Table 4. Difference of DFT calculated energies between *cis* and *trans* diastereomers and superimposition of calculated more stable *cis*-structures.

		Piperidines		*Pyrrolidines*
				
Entry	R	$\Delta\Delta G^0_{rel} = \Delta G^0_{trans} - \Delta G^0_{cis}$ (kcal/mol)	Entry	$\Delta\Delta G^0_{rel} = \Delta G^0_{transs} - \Delta G^0_{cis}$ (kcal/mol)
1	H	2.96	4	2.58
2	Me	0.64	5	2.19
3	Dpm	0.99	6	2.54

The results obtained by calculation also suggest that the difference in intrinsic geometries for five and six-membered ring gives rise to distinct, well-characterised and substituent-controllable conformation families, which are of great importance in the application of CIDR (Table 4, superimpositions). In addition, conformations highly similar to the X-ray crystallographic structures were produced by DFT calculations: details of these comparisons are given in the supplementary data. In order to rationalize the molecular factors stabilizing preferred shapes and influencing the epimeric equilibrium shift, distances between the α-carbons of the phenacyl arm and the nitrogen substituent (R) were

measured on our theoretical models or on X-ray structures when available (Figure 5). Calculations show that major conformational effects are involved mainly through steric effects of the nitrogen substituent.

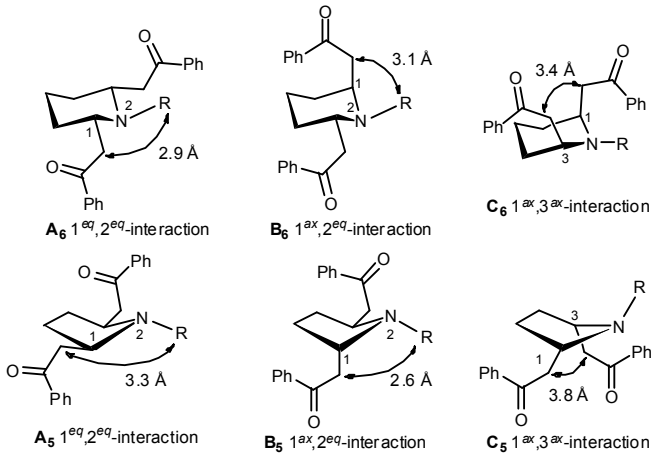


Figure 5. Relative distances measured on theoretical models or on X-ray structures between substituents in 1,2- or 1,3-interaction in both piperidine and pyrrolidine families.

In the piperidine series, the 1,2-diequatorial distance (Figure 5, $\mathbf{A_6}$) is shorter than the 1,2-axial-equatorial one (Figure 5, $\mathbf{B_6}$). Consistently, the more the R substituent bulkiness increases (R=H→Bn), the more the proportion of *trans* diastereomer in conformation $\mathbf{B_6}$ is preferentially formed in the course of the RCDAM reaction. In the case of *cis* norlobelanine (R=H), the classical conformation $\mathbf{A_6}$ with both phenacyl arms in equatorial positions is preferred. This *cis*-configuration is accentuated by the existence of two strong intramolecular hydrogen bonds, which favour the epimeric equilibrium towards this double highly stabilized *cis*-diastereomer. For the hindered benzhydryl substituent, 1,2-diequatorial interactions become so important that phenacyl arms are shifted from their ideal equatorial positions to the *pseudo*-axial ones, showing the loss of the expected equatorial chair shape (Figure 5, $\mathbf{C_6}$). Moreover, this repulsion of the 1,3-diaxial substituents is accompanied by flattening of the nitrogen pyramidal arrangement.

In the pyrrolidine series, the ring strain shortens the 1,2-interaction distances between the phenacyl arm in *pseudo*-axial orientation and the *N*-substituent (Figure 5, $\mathbf{B_5}$). In contrast, the 1,3-interaction distance between both phenacyl arms in *pseudo*-axial position is enhanced (Figure 5, $\mathbf{C_5}$). Thus, for methyl and benzyl groups, the conformations $\mathbf{A_5}$ for *cis* diastereomers are favoured. In the case of hydrogen-substituted nitrogen, diminished steric hindrance allows the formation of a significant amount (30%) of *trans* diastereomers in conformation $\mathbf{B_5}$. For the bulky benzhydryl group, detrimental 1,2-interactions induce the *anti*-relative configuration between *N*-substituent and phenacyl arms, the *pseudo*-axial orientation of phenacyl arms and the flattening of the five-membered azacycle (Figure 5, $\mathbf{C_5}$).

In summary, calculations undoubtedly confirm that in both analogous series, the *cis* diasteromers are thermodynamically the most stable epimers. *Cis* diastereomers were produced with enhanced diastereoselectivity by increasing the contribution of steric interactions of the *N*-substituents and by associating stabilizing intramolecular bonds or stackings. Furthermore, calculations revealed some structural features: minimizing steric effects enforces *N*-substituents to adopt a restricted orientation (equatorial in piperidines and axial in pyrrolidines) for which the distance between the α-carbons of the *N*-substituents and phenacyl arms is maximal. For similar reasons, piperidine ring prefers a classical chair conformation while pyrrolidine chooses a planar conformation. If the 1,2-*anti*/1,5-*anti* configuration is highly conserved in the smaller azacycle pyrrolidine, it is not the case for piperidine derivatives. Indeed, floppy six-membered azacycles are able to counterbalance *N*-substituent steric hindrance by inversion of the chair conformation or the pyramidal nitrogen.

Conclusions

This work confirms the efficiency of the RCDAM reaction to synthesize α,α'-disubstituted piperidines and pyrrolidines under mild conditions. We highlight its high flexibility to introduce molecular diversity. RCDAM addition was successfully applied to the straightforward preparation of a series of structural analogues of lobelanine, differing by the size of the heterocycle core and the nature of substituents borne by the central nitrogen atom or the phenacyl arms. With respect to our interest in the synthesis of *Lobelia* alkaloid analogues targeting nAChRs, this easy-to-handle method of pharmacomodulation could offer new avenues in terms of structure-activity relationship studies and of pharmacokinetic, pharmacodynamic, and safety properties optimization of lead compounds.

Arguably, our study demonstrates through the synthesis of these novel lobelanine analogues that the mutarotation in solution of the β-aminoketone motif can be thermodynamically controlled. CIDR conditions in conjunction with the formation of privileged constrained symmetric conformations through intramolecular H-bond, intramolecular π-stacking interaction, and/or heterocycle contraction allow the selective crystallisation of the thermodynamic *cis*-lobelanine analogues in high diastereomeric excess and excellent yield. The noticeable advantages of this synthetic approach are that no external chiral agents are required and that it can be scaled-up and experimentally set up easily.

These compounds constitute good candidates for the stereoselective synthesis of pharmacologically relevant lobeline analogues and open new opportunities for the development of stereocontrolled desymmetrizing process through crystallisation-induced asymmetric transformation (CIAT).

Experimental section

General experimental procedures

Commercial reagents were used without purification. Prior to use, THF, toluene and CH_2Cl_2 were purified by passage through a drying column. Melting points were recorded on an electrothermal digital apparatus and were uncorrected. ^1H (respectively ^{13}C) NMR spectra were recorded at 300 or 400 MHz (respectively 75 or 100 MHz). The chemical shifts for ^1H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of deuterated solvent as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. NMR peak assignments have been made on the basis of HMBC, HMQC, nOesy, and ^1H-^1H COSY spectra. Diastereomeric ratios (*dr*) were evaluated by ^1H NMR spectroscopy of the crude reaction mixtures. The electrospray ionisation (ESI) and the atmospheric pressure chemical ionisation (APCI) mass spectra were performed on an Esquire-LC Brucker spectrometer. The X-ray crystallographic data were measured at ambient temperature (293°K) on an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å) or on a Rigaku MM007 HF copper (λ = 1.54187 Å) rotating-anode generator equipped with Osmic confocal optics and a rapid II Curved Image Plate at 200°K. Elemental analyses were performed with Perkin-Elmer 2400 analyser. IR spectra were recorded as neat films on Bruker Vector22 spectrophotometer. HRMS spectra were obtained by the FAB method. Analytical thin layer chromatography was performed on Merck 60F-254 precoated silica (0.2 mm) on glass and was revealed by UV light or Kägi-Misher or Dragendorf reagent. Flash chromatography separations were performed on Merck Kieselgel (40-63µm).
Dienediones **1a,**[19,20] **1b**,[21] and **7a** to **7d**[19,20] were synthesized according to the procedures reported in the literature and physical data were in accordance with the literature.

General procedures for the synthesis of norlobelanine 2a and its analogues 3a and 9a-d.

The appropriate dienedione (**1a**, **1b**, **7a-d**) was dissolved in a DCM/MeOH mixture. An ammonia solution (28% in H_2O) was added at room temperature and the reaction mixture was allowed to stir for 12 hours. The crude reaction mixture was dissolved in CH_2Cl_2 and washed with brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under vacuum.

Norlobelanine or 2,2'-(piperidine-2,6-*cis*-diyl)bis(1-phenylethanone) *cis*-2a. The reaction was carried out starting with **1a** (1.04 g, 3.4 mmol) and an ammonia solution (3.4 mL, 24.5 mmol) in CH_2Cl_2/MeOH (3 mL /3 mL). Crystallisation of the crude reaction mixture in diethylether allowed the isolation of *cis*-**2a** (1.05 g, 96%). Orange solid. mp 119°C (from Et_2O) (Litt: 115-121°C)[21]; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J* = 7.7 Hz, 4H); 7.52 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 4H), 3.27 (m, 2H), 3.06 (dd, *J* = 16.7, 5.1 Hz, 2H), 3.03 (dd, *J* = 16.8, 7.3 Hz, 2H), 1.82 (dtt, *J* = 13.1, 6.0, 3.1 Hz, 1H), 1.71 (dtd, *J* = 12.2, 6.0, 2.3 Hz, 2H), 1.49 (dtt, *J* = 13.1, 13.1, 3.7 Hz, 1H), 1.24 (ddd, *J* = 12.5, 12.5, 3.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.0, 137.5, 132.9, 128.5, 128.1, 53.1, 45.8, 32.3, 24.5; Elemental anal. Found: C 77.87 H 7.10, N 4.2. Calcd for $C_{21}H_{23}NO_2.1/5H_2O$.: C 77.60, H 7.26, N 4.31%; IR (neat) υ_{max}/cm^{-1} 1689, 1677, 1285, 1223, 1001, 803, 758, 750, 689; HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}NO_2$ 322.1807, found 322.1810.
NMR spectra of the minor diastereomer *trans*-**2a** are partially described, some of the signals being hidden by the major product *cis*-**2a**. ^1H NMR (C_6D_6, 300 MHz): δ 7.95 (d, *J* = 8.1, 1.2 Hz, 4H); 3.71 (m, 2H), 3.08 (dd, *J* = 16.8, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.4, 129.5, 128.5, 47.8, 43.0, 31.0, 19.9.

2,2'-(piperidine-2,6-*cis*-diyl)bis(1-(4-fluoro-phenyl)-ethanone) *cis*-9a. The reaction was carried out starting with **7a** (154 mg, 0.45 mmol) and an ammonia solution (0.4 mL, 2.9 mmol) in CH_2Cl_2/MeOH (0.4 mL/0.4 mL). Compound *cis*-**9a** was obtained by crystallisation of the crude reaction mixture in ethylacetate (148 mg, 92%) as a white solid. mp 131.3 °C (from AcOEt); ^1H NMR (C_6D_6, 300 MHz): δ 7.57 (dd, *J* = 8.7, 5.4 Hz, 4H); 6.63 (t, *J* = 8.7 Hz, 4H), 3.25 (m, 2H), 2.66 (dd, *J* = 17.1, 7.5 Hz, 2H), 2.55 (dd, *J* = 17.1, 4.8 Hz, 2H), 1.70 (dt, *J* = 12.6, 3.3 Hz, 1H), 1.54 (dd, *J* = 12.3, 2.7 Hz, 2H), 1.36 (qt, *J* = 12.9, 3.6 Hz, 1H), 1.17 (qd, *J* = 12.0, 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.4, 165.7 (d, *J* = 1014 Hz), 133.48 (d, *J* = 9 Hz), 130.6 (d, *J* = 36 Hz), 115.6 (d, *J* = 87 Hz), 52.5, 45.5, 32.1, 24.3; IR (neat) υ_{max}/cm^{-1} 2926, 2910, 2890, 2805, 1689, 1683, 1677, 1594, 1505, 1226, 1204, 1194, 1164, 1156, 848, 841, 828; MS (ESI) *m/z* 358 $[M+H]^+$; Elemental anal. Found: C 70.10, H 5.94, N 3.85. Calcd for $C_{21}H_{21}F_2NO_2.1/8$ H_2O: C 70.13, H 5.96, N 3.89%. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{21}H_{22}F_2NO_2$ 358.1619, found 358.1620.
The diastereomer *trans*-**9a** was detected by the presence of two characteristic signals (3.60 (m, 2H, C*H*N) and 2.68 (dd, *J* = 17.1, 8.1 Hz, 2H, CH*H*CO)).

2,2'-(piperidine-2,6-*cis*-diyl)bis(1-(4-bromophenyl)-ethanone) *cis*-9b. The reaction was carried out starting with **7b** (46 mg, 0.1 mmol) and an ammonia solution (0.1 mL, 0.72 mmol) in CH_2Cl_2./MeOH (0.4 mL/0.4 mL). Compound *cis*-**9b** was obtained by precipitation of the crude reaction mixture in AcOEt (45 mg, 95%) as a white solid. mp 226°C (from AcOEt); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, *J* = 8.5 Hz, 4H); 7.59 (d, *J* = 8.5 Hz, 4H), 3.27 (m, 2H), 3.05 (dd, *J* = 17.4, 4.8 Hz, 2H), 2.98 (dd, *J* = 17.4, 7.5 Hz, 2H), 1.83 (dt, *J* = 12.9, 3.0 Hz, 1H), 1.69 (dd, *J* = 12.3, 2.4 Hz, 2H), 1.48 (qt, *J* = 12.9, 3.6 Hz, 1H), 1.25 (qd, *J* = 11.7, 3.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 135.7, 131.8, 129.5, 128.3, 52.5, 45.4, 32.0, 24.3; IR (neat) υ_{max}/cm^{-1} 2903 (broad), 1682, 1678, 1584, 1399, 1074, 1066, 985, 806, 798, 788; MS (ESI) *m/z* 480 $[M+H]^+$; Elemental anal. Found: C 52.64, H 4.39, N 2.89. Calcd for $C_{21}H_{21}Br_2NO_2$: C 52.63, H 4.42, N 2.92%.

The minor diastereomer *trans*-**9b** was detected by the presence of two characteristic signals (^{1}H NMR (C_6D_6, 300 MHz): δ 3.51 (m, 2H), 2.85 (dd, *J* = 14.1, 5.7 Hz, 2H)).

2,2'-(piperidine-2,6-*cis*-diyl)bis(1-(*p*-tolyl)ethanone) *cis*-9c. The reaction was carried out starting with **7c** (202 mg, 0.6 mmol) and ammonia (1 mL, 7.2 mmol) in CH_2Cl_2./MeOH (1 mL/3 mL). A 90/10 mixture of *cis*-**9c**/*trans*-**9c** was obtained by evaporation of the crude reaction mixture (171 mg, 83%). mp 103.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, *J* = 8.2 Hz, 4H); 7.23 (d, *J* = 8.2 Hz, 4H), 3.27 (m, 2H), 3.07 (dd, *J* = 17.4, 4.8 Hz, 2H), 3.02 (dd, *J* = 17.4, 7.5 Hz, 2H), 2.40 (s, 3H), 1.80 (dt, *J* = 12.9, 3.0, Hz, 1H), 1.68 (dd, *J* = 12.6, 2.4 Hz, 2H), 1.48 (qt, *J* = 12.9, 3.6 Hz, 1H), 1.27 (qd, *J* = 11.7, 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.7, 143.9, 134.6, 129.2, 128.2, 52.8, 45.3, 31.9, 24.3, 21.6; IR (neat) υ_{max}/cm^{-1} 2930 (broad), 1684, 1673, 1607, 1292, 1284, 1228, 1196, 1177, 821, 811; MS (ESI) *m/z* 350 $[M+H]^+$; Elemental anal. Found: C 77.17, H 7.54, N 3.99. Calcd for $C_{23}H_{27}NO_2.1/2H_2O$: C 77.06, H 7.87, N 3.91%. HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2120, found 350.2123.

The minor diastereomer *trans*-**9c** was detected by the presence of two characteristic signals (^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.60 (m, 2H), 3.20 (dd, *J* = 14.3, 5.8 Hz, 2H)).

2,2'-(piperidine-2,6-*cis*-diyl)bis(1-(4-methoxyphenyl)-ethanone) *cis*-9d. The reaction was carried out starting with **7d** (729 mg, 2.0 mmol) and ammonia (2 mL, 14.4 mmol) in CH_2Cl_2./MeOH (2 mL/2 mL). Compound *cis*-**9d** was obtained by evaporation of the crude reaction mixture (648 mg, 85%) as a yellow solid. mp 93.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, *J* = 9.0 Hz, 4H); 6.91 (d, *J* = 9.0 Hz, 4H), 3.86 (s, 3H), 3.26 (m, 2H), 3.05 (dd, *J* = 16.8, 5.1 Hz, 2H), 2.98 (dd, *J* = 16.8, 8.4 Hz, 2H), 1.82 (dt, *J* = 12.9, 3.0, Hz, 1H), 1.69 (dd, *J* = 11.7, 2.1 Hz, 2H), 1.47 (qt, *J* = 12.9, 3.6 Hz, 1H), 1.27 (bq, *J* = 9.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 163.5, 130.4, 130.2, 113.7, 55.4, 53.0, 45.1, 32.0, 24.4; IR (neat) υ_{max}/cm^{-1} 2944 (broad), 2839 (broad), 1673, 1666, 1597, 1260, 1228, 1166, 830, 810, 733; GC-MS (ESI) *m/z* 404 $[M+Na]^+$; Elemental anal. Found: C 71.32, H 7.45, N 3.31. Calcd for $C_{23}H_{27}NO_4.1/3H_2O$: C 71.29, H 7.20, N 3.61%.

The minor diastereomer *trans*-**9d** was detected by the presence of three characteristic signals (^{1}H NMR (C_6D_6, 300 MHz): δ 3.69 (m, 2H), 3.19 (s, 3H), 3.00 (dd, *J* = 16.2, 7.2 Hz, 2H)).

2,2'-(pyrrolidine-2,5-*cis*-diyl)bis(1-phenylethanone) *cis*-3a. The reaction was carried out starting with **1b** (870 mg, 3.0 mmol) and an ammonia solution (3.0 mL, 21.6 mmol) in CH_2Cl_2/MeOH (10 mL/3 mL). Crystallisation of the crude reaction mixture in *iso*-propanol (-30°C) allowed the isolation of *cis*-**3a** (848 mg, 92%). Red brick solid. mp 103°C (from *i*PrOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, *J* = 8.0 Hz, 4H), 7.56 (td, *J* = 7.6, 2.5 Hz, 2H), 7.44 (td, *J* = 6.9, 1.7 Hz, 4H), 3.71 (Q, *J* = 6 Hz, 2H), 3.21 (d, *J* = 6 Hz, 4H), 2.42 (bs, 1H), 2.05 (m, 2H), 1.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 136.9, 132.9, 128.4, 127.9, 53.9, 45.7, 30.1; IR (neat) υ_{max}/cm^{-1} 2941, 1682-1678 (large), 1449, 1211, 1002, 753, 690; MS (ESI) *m/z* 308 $[M+H]^+$; HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}NO_2$ 308.1651, found 308.1649.

NMR spectra of the minor diastereomer *trans*-**3a** are partially described, most of the signals being hidden by the major product *cis*-**3a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (q, *J* = 6.3 Hz, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.2, 133.0, 128.4, 127.9, 53.4, 45.2, 31.5.

General procedure for the synthesis of lobelanine 2b and its analogues 2c-d, 3b-d and 10a-d.

Primary amine was added to a solution of the appropriate dienedione (**1a**, **1b** or **8a-b**) dissolved in a round bottom flask capped with a rubber septum. The mixture was stirred at room temperature to afford the corresponding diastereomeric mixture of nitrogen-containing heterocycles after removal of the volatiles under reduced pressure. For lobelanine, this mixture was acidified (HCl) in order to isolate the corresponding hydrochloride salts.

Compounds *cis*-2b, *trans*-2b and their hydrochloride salts *cis*-4b, *cis*-4b' and *trans*-4b. The reaction was carried out in 15 minutes at room temperature starting with **1a** (1.7 g, 5.6 mmol) and methylamine (2M in THF, 4 mL, 8 mmol) in THF (11 mL). The ratio *cis*-**2b**:*trans*-**2b** (45/55) was measured by integration of the methyl signals of the brick red syrup obtained after evaporation of the crude reaction mixture. This mixture was dissolved in $CHCl_3$ (200 mL) and washed with HCl 1M (100 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 50 mL) and the organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in *iso*-propanol and cooled at -30°C. After two weeks at that temperature, a solid 3:1 mixture of the inseparable lobelanine salts *cis*-**4b** and *cis*-**4b'** (1.078 g, 52%) was filtered off and removal of solvent affords exclusively the salt *trans*-**4b** (0.920 g, 44%). A 0.03M solution of 3:1 *cis*-**4b**/*cis*-**4b'** (respectively *trans*-**4b**) in CH_2Cl_2 were washed with saturated $NaHCO_3$, dried with $MgSO_4$ and concentrated under reduced pressure to afford lobelanine *cis*-**2b** (containing 8% of *trans*-**2b**) (respectively *trans*-**2b** containing 20% of *cis*-**2b**). These mixtures both equilibrate at room temperature to afford the initial ratio *cis*-**2b**:*trans*-**2b** (45/55).

2,2'-(1-methylpiperidine-2,6-*cis*-diyl)bis(1-phenylethanone) hydrochloride *cis*-4b and *cis*-4b'. White solid. mp 189°C (from *i*PrOH) (Litt: 193-196°C)[10]. ^{1}H NMR (C_6D_6, 400 MHz): δ 12.88 (*cis*-**4b'**, bs, 1H), 12.35 (*cis*-**4b**, bs,1H), 8.02 (*cis*-**4b** + *cis*-**4b'**, d, *J* = 7.2 Hz, 4H), 7.65-7.55 (*cis*-**4b** + *cis*-**4b'**, m, 2H), 7.49 (*cis*-**4b** + *cis*-**4b'**, t, *J* = 7.5 Hz, 4H), 4.23 (*cis*-**4b'**, bd, *J* = 16.1 Hz, 2H), 4.13-4.10 (*cis*-**4b'**, m, 2H), 4.06 (*cis*-**4b**, dd, *J* = 18.9, 5.4 Hz, 2H), 3.91 (*cis*-**4b**, m, 2H), 3.36 (*cis*-**4b**, dd, *J* = 18.9, 4.5 Hz, 2H), 3.03 (*cis*-**4b'**, dd, *J* = 16.3, 11.4 Hz, 2H), 2.80 (*cis*-**4b'**, d, *J*= 4.9 Hz, 3H), 2.57 (*cis*-**4b**, d, *J* = 4.8 Hz, 3H), 2.27 (*cis*-**4b**, qd, *J* = 14.5, 3.0 Hz, 2H), 2.10 (*cis*-**4b'**, bd, *J* = 15.0 Hz, 2H), 2.00-1.50 (*cis*-**4b** + *cis*-**4b'**, m, 4H); ^{13}C NMR (C_6D_6, 100 MHz): δ major compound *cis*-**4b** 196.0, 135.4, 134.3, 129.0, 128.4, 61.8, 41.6, 38.4, 31.1, 22.9 minor compound *cis*-**4b'**, 194.9, 135.8, 133.9, 128.9, 128.4, 61.0, 40.2, 27.9, 23.7, 22.4; IR (neat) υ_{max}/cm^{-1} 2279, 1679, 1293, 1220, 758, 689; Elemental anal. Found: C 70.10, H 7.00, N

3.61. Calcd for $C_{22}H_{26}ClNO_2.1/3H_2O$: C 69.92, H 7.11, N 3.71%.

2,2'-((2*R,6*R**)-1-methylpiperidine-2,6-diyl)bis(1-phenylethanone) hydrochloride *trans*-4b.** mp 177.9 (Litt = 175-178°C)[10]. ^{1}H NMR (C_6D_6, 300 MHz) δ 12.64 (bs, 1H), 8.10-7.95 (m, 4H), 7.65-7.50 (m, 2H), 7.52-7.40 (m, 4H), 4.33-4.20 (m, 1H), 4.21 (dd, *J* = 18.0, 6.0 Hz, 1H), 4.05-3.95 (m, 1H), 3.81 (dd, *J* = 17.1, 2.4 Hz, 1H), 3.46 (dd, *J* = 17.9, 7.8 Hz, 1H), 3.27 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.78 (d, *J* = 5.0 Hz, 3H), 2.40-2.25 (m, 1H), 2.15-1.55 (m, 5H);); ^{13}C NMR (C_6D_6, 75 MHz) δ 195.8, 194.7, 135.8, 135.6, 134.0, 128.8, 128.3, 128.1, 57.5, 55.9, 38.6, 37.0, 36.9, 25.5, 25.2, 17.6; Elemental anal. Found: C 67.65, H 6.98, N 3.57. Calcd for $C_{22}H_{26}ClNO_2.H_2O$: C 67.77, H 7.24, N 3.59%.

Lobelanine or 2,2'-(1-methylpiperidine-2,6-*cis*-diyl)bis(1-phenylethanone) *cis*-2b. ^{1}H NMR (C_6D_6, 400 MHz) δ 8.00-7.90 (m, 4H), 7.60-7.50 (m, 2H), 7.50-7.35 (m, 4H), 3.35 (dd, *J* = 16.0, 4.4 Hz, 2H), 3.10-3.00 (m, 2H), 2.92 (dd, *J* = 16.0, 7.6 Hz, 2H), 2.24 (s, 3H), 1.75-1.55 (m, 4H), 1.55-1.25 (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz): δ 198.9, 137.1, 133.1, 128.6, 128.1, 59.8, 44.6, 36.6, 30.3, 24.0.

2,2'-((2*R,6*R**)-1-methylpiperidine-2,6-diyl)bis(1-phenylethanone) *trans*-2b.** ^{1}H NMR (C_6D_6, 300 MHz) δ 7.90-7.70 (m, 4H), 7.20-7.00 (m, 6H), 3.60-3.50 (m, 2H), 3.04 (dd, *J* = 15.9, 4.8 Hz, 2H), 2.73 (dd, *J* = 15.9, 7.8 Hz, 2H), 2.15 (s, 3H), 1.70-1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.3, 137.0, 133.1, 128.5, 128.0, 54.8, 44.3, 38.8, 29.3, 19.4.

***cis*-2b and *trans*-2b.** MS (CI) *m/z* 336 $[M+H]^+$; IR (neat) υ_{max}/cm^{-1} 2929, 1680, 1448, 1208, 7538, 690.

2,2'-(1-methylpyrrolidine-2,5-*cis*-diyl)bis(1-phenylethanone) *cis*-3b. The reaction was carried out starting with **1b** (875 mg, 3.0 mmol) and a 2M solution of methylamine in THF (2 mL, 4 mmol). Evaporation of the crude reaction mixture after 15 min. gave an orange oil which was precipitated in Et_2O/pentane to afford a creamy solid (951 mg, 98%) *cis*-**3b** containing 5% of the corresponding racemic compound *trans*-**3b**. Proton and carbon NMR spectra are in accordance with those previously reported using another method.[17] NMR spectra of the minor diastereomer *trans*-**3b** is partially described, most of the signals being hidden by the major product *cis*-**3b**. ^{1}H NMR (C_6D_6, 300 MHz): δ 3.61 (m, 2H), 2.57 (dd, *J* = 15.9, 8.7 Hz, 2H), 2.16 (s, 3H), 1.25-1.05 (m, 2H).

2,2'-(1-methylpyrrolidine-2,5-*cis*-diyl)bis(1-(4-fluorophenyl)ethanone) *cis*-10a. The reaction was carried out starting with **8a** (147 mg, 0.45 mmol) and a 2M solution of methylamine in THF (0.5 mL, 1 mmol,) in CH_2Cl_2 (2 mL). Evaporation of the crude reaction mixture after 15 min. gave a creamy solid (157 mg, 98%) *cis*-**10a** containing 7% of the corresponding diastereomer *trans*-**10a**. Crystallisation in AcOEt gave *cis*-**10a** as a creamy solid. mp 85.5°C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.65 (dd, *J* = 9.0, 5.7 Hz, 4H), 6.66 (dd, *J* = 9.0, 8.7 Hz, 4H), 3.00-2.80 (m, 4H), 2.61 (dd, *J* = 17.4, 9.0 Hz, 2H), 2.12 (s, 3H), 2.01-1.95 (m, 2H), 1.38-1.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 167.5, 133.6, 130.8 (d, *J* = 30 Hz), 115.7 (d, *J* = 90 Hz), 63.1, 43.9, 39.3, 29.9; IR (neat) υmax/cm-1 1686, 1592, 1502, 1410, 1365, 1341, 1296, 1209, 1195, 1159, 990, 837, 822, 802; MS (ESI) *m/z* 358 $[M+H]^+$, Elemental anal. Found: C 70.21, H 5.71, N 3.72. Calcd for $C_{21}H_{21}F_2NO_2$: C 70.57, H 5.92, N 3.92%.

NMR spectra of the minor diastereomer *trans*-**10a** are partially described, most of the signals being hidden by the major product *cis*-**10a**. ^{1}H NMR (C_6D_6, 300 MHz): δ 3.58 (m, 2H), 2.48 (dd, *J* = 16.2, 8.7 Hz, 2H), 2.16 (s, 3H).

2,2'-(1-methylpyrrolidine-2,5-*cis*-diyl)bis(1-(4-bromophenyl)ethanone) *cis*-10b. The reaction was carried out starting with **8b** (218 mg, 0.5 mmol) and a 2M solution of methylamine in THF (0.5 mL, 1 mmol) in CH_2Cl_2 (2 mL). Crystallisation in CH_2Cl_2/cyclohexane gave *cis*-**10b** as a creamy solid (210 mg, 88%). mp 125.7°C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.46 (d, *J* = 10.8 Hz, 4H), 6.90 (d, *J* = 9.0 Hz, 4H), 3.09 (dd, *J* = 15.7, 4.2 Hz, 2H), 3.05-2.90 (m, 2H), 2.76 (dd, *J* = 15.7, 8.4 Hz, 2H), 2.16 (s, 3H), 2.02 (s, 3H), 2.05-1.96 (m, 2H), 1.45-1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 136.5, 131.9, 129.9, 127.2, 63.3, 44.3, 39.5, 30.2; IR (neat) υ_{max}/cm^{-1} 1686, 1583, 1395, 1365, 1340, 1174, 1067, 1010, 988, 814, 804; MS (ESI); *m/z* 480 $[M+H]^+$, Elemental anal. Found: C 52.42, H 4.41, N 2.89. Calcd for $C_{21}H_{21}Br_2NO_2$: C 52.63, H 4.42, N 2.92%.

The minor diastereomer *trans*-**10b** can be detected by the presence of three characteristic signals: ^{1}H NMR (C_6D_6, 300 MHz): δ 3.54 (m, 2H), 2.42 (dd, *J* = 15.0, 7.5 Hz, 2H), 2.12 (s, 3H).

2,2'-(1-methylpyrrolidine-2,5-*cis*-diyl)bis(1-(*p*-tolyl)-ethanone) *cis*-10c. The reaction was carried out starting with **8c** (160 mg, 0.5 mmol) and a 2M solution of methylamine in THF (0.5 mL, 1 mmol) in CH_2Cl_2 (2 mL). Evaporation of the crude reaction mixture gave a 90/10 mixture of *cis*-**10c** and *trans*-**10c** Crystallisation in AcOEt gave *cis*-**10c** as a creamy solid (170 mg, 97%). mp 66.7 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.86 (d, *J* = 9.0 Hz, 4H), 7.19 (d, *J* = 10.8 Hz, 4H), 2.9-2.8 (m, 4H), 2.57 (dd, *J* = 18.9, 9.0 Hz, 2H), 2.08 (s, 3H), 2.05-1.80 (m, 2H), 1.40-1.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 143.3, 135.8, 129.4, 128.6, 63.5, 44.5, 39.5, 30.4, 21.4; IR (neat) υ_{max}/cm^{-1} 1675, 1604, 1408, 1364, 1339, 1297, 1183, 1115, 1041, 971, 803, 773; *m/z* 350 $[M+H]^+$; Elemental anal. Found: C 78.98, H 7.73, N 3.93. Calcd for $C_{23}H_{27}NO_2$: C 79.05, H 7.79, N 4.01%.

NMR spectra of the minor diastereomer *trans*-**10c** are partially described, most of the signals being hidden by the major product *cis*-**10c**. ^{1}H NMR (C_6D_6, 300 MHz): δ 3.67 (m, 2H), 2.62 (dd, *J* = 15.9, 8.7 Hz, 2H), 2.06 (s, 3H).

2,2'-(1-methylpyrrolidine-2,5-*cis*-diyl)bis(1-(4-methoxyphenyl)ethanone) *cis*-10d. The reaction was carried out starting with **8d** (100 mg, 0.28 mmol) and a 2M solution of methylamine in THF (0.25 mL, 0.5 mmol) in CH_2Cl_2 (1 mL). The evaporation of the crude reaction mixture gave an oil (105 mg, 99%) containing a 93/7 proportion of compounds *cis*-**10d** and *trans*-**10d**. ^{1}H NMR (300 MHz, C_6D_6) δ 7.92 (d, *J* = 7.1 Hz, 4H), 6.65 (d, *J* = 7.1 Hz, 4H), 3.19 (s, 3H), 3.12 (dd, *J* = 15.3, 4.5 Hz, 2H), 3.1-2.9 (m, 2H), 2.80 (dd, *J* = 15.3, 8.1 Hz, 2H), 2.20 (s, 3H), 2.19 (m, 2H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 163.5, 130.4, 130.1, 113.7, 63.3, 55.4,

43.2, 39.1, 29.7; IR (neat) υ_{max}/cm^{-1} 1673, 1597, 1575, 1509, 1258, 1166, 1030, 827; MS (ESI) 382 $[M+H]^+$; HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{23}H_{28}NO_4$ 382.2028; found, 382.2021.

The minor diastereomer *trans*-**10d** was detected by the presence of four characteristic signals (^{1}H NMR (C_6D_6, 300 MHz): δ 3.71 (m, 2H), 3.21 (s, 3H), 2.64 (dd, *J* = 15.6, 8.7 Hz, 2H), 2.45 (s, 3H)).

2,2'-(1-benzylpiperidine-2,6-*cis*-diyl)bis(1-phenyl-ethanone) *cis*-2c and **2,2'-((2*R**,6*R**)-1-benzylpiperidine-2,6-diyl)bis(1-phenylethanone) *trans*-2c**. The reaction was carried out starting with dienedione **1a** (152 mg, 0.5 mmol) and benzylamine (0.06 mL, 0.55 mmol,) in THF (1 mL). After 5 hours at room temperature, an inseparable mixture of *cis*-**2c** and *trans*-**2c** (23/67) (198 mg, 96%) was obtained. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz): δ 8.10-7.90 (*cis*-**2c** + *trans*-**2c**, m, 8H), 7.70-7.00 (*cis*-**2c** + *trans*-**2c**, m, 22H), 3.94 (*cis*-***2c***, s, 2H), 3.87 (*trans*-**2c**, d, *J* = 14.3 Hz, 1H), 3.80 (*trans*-**2c**, d, *J* = 14.3 Hz, 1H), 3.61-3.50 (*cis*-**2c** + *trans*-**2c**, m, 4H), 3.31 (*cis*-**2c**, dd, *J* = 16.0, 3.6 Hz, 2H), 3.10-3.05 (*trans*-**2c**, m, 4H), 3.10 (*cis*-**2c**, dd, *J* = 16.0, 9.3 Hz, 2H), 1.75-1.30 (*cis*-**2c** + *trans*-**2c**, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 199.1, 142.0, 140.5, 137.0, 132.9, 128.5, 128.3, 128.2, 128.1, 127;4, 126.9, 126.7, 126.5, 58.3, 53.1, 52.7, 43.8, 41.2, 40.9, 28.2, 26.6, 21.8, 19.8; IR (neat) υ_{max}/cm^{-1} 2962, 2852, 1673, 1528, 1012, 798, 790, 687; GC-MS (ESI) *m/z* 434 $[M+Na]^+$; Elemental anal. Found: C 80.56, H 7.47, N 3.48. Calcd for $C_{28}H_{29}NO_2.1/3H_2O$: C 80.54, H 7.16, N 3.35%.

2,2'-(1-benzylpyrrolidine-2,5-*cis*-diyl)bis(1-phenyl-ethanone) *cis*-3c. The reaction was carried out starting with **1b** (164 mg, 0.56 mmol) and benzylamine (0.06 mL, 0.55 mmol) in THF (1 mL). Evaporation of the crude reaction mixture after 3 hours gave a yellow oil (206 mg, 94%) as a mixture of *cis*-***3c*** (85%) and the epimer *trans*-***3c*** (15%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, *J* = 7.4 Hz, 4H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.4-7.0 (m, 9H), 3.75 (s, 2H), 3.29 (m, 2H), 3.04 (dd, *J* = 15.9, 3.0 Hz, 2H), 2.80 (dd, *J* = 15.9, 10.2 Hz, 2H), 2.00 (m, 2H), 1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.5, 137.1, 132.9, 129.1, 128.5, 128.3, 128.2, 127.9, 127.1, 61.9, 58.6, 45.6, 30.2; IR (neat) υ_{max}/cm^{-1} 3100-2750,1682 , 1597, 1579, 1494, 1448, 1275, 771, 688; HRMS (ESI): *m/z*: $[M+H]^+$ calcd for $C_{27}H_{27}NO_2$ 398.2120 found, 398.2118.

NMR spectra of the minor diastereomer *trans*-**3c** are partially described, most of the signals being hidden by the major product *cis*-**3c**. ^{1}H NMR (C_6D_6, 300 MHz): δ 3.94 (d, *J* = 14.7 Hz, 1H), 3.69 (d, *J* = 14.7 Hz, 1H), 3.53 (m, 2H), 3.20 (dd, *J* = 15.6, 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.0, 139.6, 128.1, 57.6, 40.8, 28.7.

2,2'-(1-benzhydrylpiperidine-2,6-*cis*-diyl)bis(1-phenylethanone) *cis*-2d. Benzhydrylamine (200 µL, 1.2 mmol) was added in one portion into dienedione **1a** (360 mg, 1.2 mmol) dissolved in THF. The mixture was magnetically stirred at room temperature for 72 h. Compound *cis*-**2d** (392 mg, 68%) was obtained as a white crystals by slow evaporation of the solvent. mp 146°C; ^{1}H NMR (C_6D_6, 300 MHz): δ 7.74 (d, *J*= 7.2 Hz, 4H), 7.34 (d, *J*= 7.2 Hz, 4H), 7.2 (m, 12H), 5.04 (s, 1H), 3.89 (m, 2H), 3.38 (dd, *J*= 14.7, 3.6Hz, 2H), 3.02 (dd, *J*= 14.7, 10.5Hz, 2H), 1.80-1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.8, 142.7, 136.8, 132.8, 128.7, 128.6, 128.1, 128.0, 127.1, 71.1, 50.1, 40.2, 28.0, 14.3; IR (neat) υ_{max}/cm^{-1} 1669, 1596, 1579, 1456, 1446, 1281, 1269, 1080, 762, 748, 688; GC-MS (ESI) *m/z* 488 $[M+H]^+$; Elemental anal. Found: C 83.61, H 6.64, N 2.84. Calcd for $C_{34}H_{33}NO_2$: C 83.74, H 6.82, N 2.87%.

3,7-Bis(benzhydrylamino)-1,9-diphenylnonane-1,9-dione 6d,d'. Benzhydrylamine (200 µL, 1.2 mmol) was added in one portion into dienedione **1a** (180 mg, 0.6 mmol) dissolved in C_6D_6. The mixture was magnetically stirred at room temperature for 2 h and was analyzed without further purification. The ^{1}H NMR spectra showed the presence of unreacted benzhydrylamine, small amounts of *cis*-**2d** and one major mixture of diastereomers **6d,d'**: Amber oil; ^{1}H NMR (300 MHz, C_6D_6) δ 7.82 (m, 4H), 7.44 (m, 8H), 7.16-7.11 (m, 8H), 7.10-7.00 (m, 10H), 4.99 (s, 2H), 3.22 (m, 2H), 2.92 (dd, *J* = 5.3, 4.6, Hz, 1H), 2.87 (dd, *J* = 5.3, 4.6, Hz, 1H), 2.71 (dd, *J* = 6.0, 4.5, Hz, 1H), 2.67 (dd, *J* = 6.0, 4.5, Hz, 2H), 1.42-1.34 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 199.0, 144.8, 137.8, 132.6, 126.9-128.8 , 64.6, 52.4, 52.3, 43.2, 43.1, 35.0, 34.9, 22.2, 21.96; IR (neat) υ_{max}/cm^{-1} 1683, 1447, 744, 704; GC-MS (CI) *m/z* 671 $[M+H]^+$.

2,2'-(1-benzhydrylpyrrolidine-2,5-*cis*-diyl)bis(1-phenylethanone) *cis*-3d. Benzhydrylamine (110 µL, 0.6 mmol) was added in one portion into dienedione **1b** (190 mg, 0.6 mmol) dissolved in THF (0.6 mL). The mixture was magnetically stirred at room temperature for 72 h. Compound *cis*-**3d** (290 mg, 97%) was obtained as a white crystals by slow evaporation of the solvent. The ^{1}H NMR spectrum was in accordance with the previously published description of this compound.[17]

General procedure for the synthesis of dienediones 8a-d.

These compounds were synthesized according to a slightly modified procedure of a reported synthesis of ester analogues.[24] A solution of the appropriate phosphorous ylide in dichloromethane was added to freshly distilled succinic aldehyde obtained by ozonolysis of 1,5-cyclooctadiene. The reaction mixture was stirred at room temperature for 4 days, evaporated and the crude residue was purified by flash chromatography using a mixture of cyclohexane/AcOEt varying from 90/10 to 80/20.

(2*E*,6*E*)-1,8-bis(4-fluorophenyl)octa-2,6-diene-1,8-dione 8a.[33] The reaction was carried out starting with the phosphorous ylide (5.4 g, 13.5 mmol) and succinaldehyde (0.5 g, 5.8 mmol) in CH_2Cl_2 (30 mL). Compound **8a** was obtained as a yellow solid (1.28 g, 67%). mp 139.1°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (dd, *J* = 8.1, 5.4 Hz, 4H), 7.12 (t, *J* = 8.4 Hz, 4H), 7.05 (dt, *J* = 15.7, 5.7 Hz, 2H), 6.90 (d, *J* = 15.7 Hz, 2H), 2.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 165.6 (d, *J* = 1020 Hz), 147.4, 134.0 (d, *J* = 10 Hz), 131.1 (d, *J* = 40 Hz), 126.4, 115.7 (d, *J* = 87 Hz), 31.2; IR (neat) υ_{max}/cm^{-1} 1670, 1619, 1596, 1506, 1225, 984, 838, 819; MS (ESI) *m/z* 349 $[M+Na]^+$; Elemental anal. Found: C 73.18, H 4.96. Calcd for $C_{20}H_{16}F_2O_2.1/6H_2O$: C 72.94, H 5.00%.

(2*E*,6*E*)-1,8-bis(4-bromophenyl)octa-2,6-diene-1,8-dione 8b.[34] The reaction was carried out starting with the

phosphorous ylide (4.9 g, 10.6 mmol) and succinaldehyde (0.398 g, 4.6 mmol) in CH_2Cl_2 (15 mL). Compound **8b** was obtained as a yellow solid (893 mg, 43%). mp 179.2°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (d, *J* = 8.4 Hz, 4H), 7.59 (d, *J* = 8.4 Hz, 4H), 7.04 (dt, *J* = 15.3, 6.3 Hz, 2H), 6.89 (d, *J* = 15.3 Hz, 2H), 2.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 147.7, 136.4, 131.9, 130.0, 128.0, 126.4, 31.2; IR (neat) υ_{max}/cm^{-1} 1661, 1605, 1581, 1421, 1398, 1270, 1068, 1009, 980, 824, 746; MS (ESI) *m/z* 471 $[M+Na]^+$; Elemental anal. Found: C 53.44, H 3.57. Calcd for $C_{20}H_{16}Br_2O_2$: C 53.60, H 3.60%.

(2*E*,6*E*)-1,8-di-*p*-tolylocta-2,6-diene-1,8-dione 8c.[34] The reaction was carried out starting with the phosphorous ylide (4.63 g, 14.5 mmol) and succinaldehyde (0.500 g, 5.8 mmol) in CH_2Cl_2 (30 mL). Compound **8c** was obtained as a yellow solid (810 mg, 44%). mp 116.1°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, *J* = 8.4 Hz, 4H), 7.26 (d, *J* = 8.4 Hz, 4H), 7.06 (dt, *J* = 15.3, 6.0 Hz, 2H), 6.95 (d, *J* = 15.3 Hz, 2H), 2.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 146.8, 143.6, 135.1, 129.2, 128.6, 126.7, 31.2, 21.6; IR (neat) υ_{max}/cm^{-1} 1663, 1600, 1273, 1186, 981, 819, 747, 732; MS (ESI) 341 $[M+Na]^+$; Elemental anal. Found: C 82.69, H 6.72. Calcd for $C_{22}H_{22}O_2$: C 82.99, H 6.96%.

(2*E*,6*E*)-1,8-bis(4-methoxyphenyl)octa-2,6-diene-1,8-dione 8d.[34] The reaction was carried out starting with the phosphorous ylide (2.4 g, 5.8 mmol) and succinaldehyde (0.200 g, 2.3 mmol) in CH_2Cl_2 (15 mL). Compound **8d** was obtained as a yellow solid (250 mg, 31%). mp 151.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, *J* = 9.0 Hz, 4H), 7.01-6.93 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 4H), 3.86 (s, 6H), 2.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 163.4, 145.4, 130.8, 130.6, 126.5, 113.8, 55.5, 31.3; IR (neat) υ_{max}/cm^{-1} 1650, 1614, 1593, 1509, 1342, 1308, 1262, 1246, 1170, 1008, 998, 632; MS (ESI) 373 $[M+Na]^+$; Elemental anal. Found: C 71.56, H 6.26. Calcd for $C_{22}H_{22}O_4.H_2O$: C 71.72, H 6.57%.

Computational methods

Conformations of reactants and products were fully optimized without constraint using DFT[35,36] method with the hybrid Becke3LYP functional[37,38] and the 6-31G* base[39] as implemented in the Gaussian 09 software package.[41]
Vibrational analysis within the harmonic approximation was performed at the same level of theory upon geometrical optimization convergence and local minima were characterised by the absence of imaginary frequency. Thermodynamic quantities at 298.15 K were calculated using the zero-point and thermal energy corrections derived from unscaled frequencies.

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR data for all new compounds, 2D NMR experiments for *cis*-**2a**, *cis*-**4a**/*cis*-**4b** and *cis*-**2d**; X-ray structural data and crystallographic information files (CIF) for compounds *cis*-**2a**, *cis*-**2d** and *cis*-**3d;** calculation details for theoretical models. See DOI: 10.1039/b000000x/

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