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**PAPER**

# Solvent-free double aza-Michael under ultrasound irradiation: diastereoselective sequential one-pot synthesis of pyrrolidine *Lobelia* alkaloids analogues†

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Novel 2,5-*meso*-pyrrolidines have been straightforwardly synthesized from readily available symmetrical double Michael acceptors. The key step rested on an aza-Michael addition of primary alkylamines to bis-enones. Competitive Rauhut–Currier and aza-Michael reactions have been highlighted in protic solvent. Ultrasound activation associated with solvent-free conditions led to the expected pyrrolidines in quantitative yields and excellent stereoselectivities. The optimized conditions have been extended to the sonochemical synthesis of pyrrolidine *Lobelia* alkaloids analogues in short sequences.

## Introduction

As the stereochemistry of chiral drugs determines their pharmacokinetic, pharmacodynamic and toxicological actions, 75% of new drugs introduced to the market are single enantiomers. Pfizer has shrewdly circumvented this constraint by launching in 2006 the smoking cessation agent varenicline **1**, a *meso*-analogue of (−)-cytisine **2** (Fig. 1).[1]

Similarly, lobelane **3**, one of 2,6-*meso*-piperidine *Lobelia inflata* alkaloids, has recently been described as an inhibitor of dopamine uptake into synaptic vesicles due to its high affinity for VMAT2 receptors (Fig. 2).[2] Starting from this natural *meso*-pharmacophore, Crooks and Dwoskin *et al.* have synthesized novel *meso*-pyrrolidine analogues **4** and **5** of *nor*-lobelane **3** as more potent VMAT2 inhibitors in order to develop potentially new efficacious treatments against drug-addictions or psychostimulants abuse (Fig. 2).[3,4]

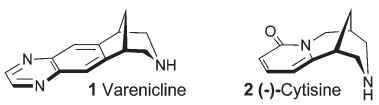


**Fig. 1** Varenicline, a smoking-cessation *meso*-therapeutic agent.

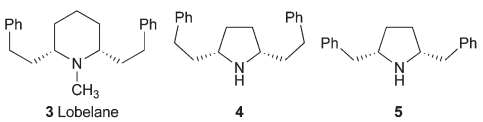


**Fig. 2** Lobelane and pyrrolidine-*nor*lobelane analogues.

If *meso*-derivatives can play a significant role in the development of therapeutics, they are also in a position of prominence as building blocks for the synthesis of chiral more complex compounds and have gained attention over the last decades.[5] Indeed, enantioselective processes for *meso*-compound desymmetrization are the most straightforward methods for the synthesis of enantioenriched products with formation of simultaneous multiple stereogenic centers in one reaction from simple substrates.[6] They allow step-economical syntheses and, *de facto*, more environmentally friendly reactions. Once more, *Lobelia* alkaloids illustrated well this concept of *meso*-compound desymmetrization: the pseudo-*meso* (−)-lobeline **6** has been elegantly synthesized by biomimetic approaches[9] *via* desymmetrizing acylation[7] of lobelanidine[9] **7** or *via* enantio- and stereoselective catalytic desymmetrizing reduction[10] of lobelanine **8** (Scheme 1). Taking advantage of the symmetry considerations, the asymmetric desymmetrization-based routes to (−)-lobeline **6** considerably reduce the step number (3 to 5 steps) compared to the stepwise construction of the three stereocenters as earlier reported by

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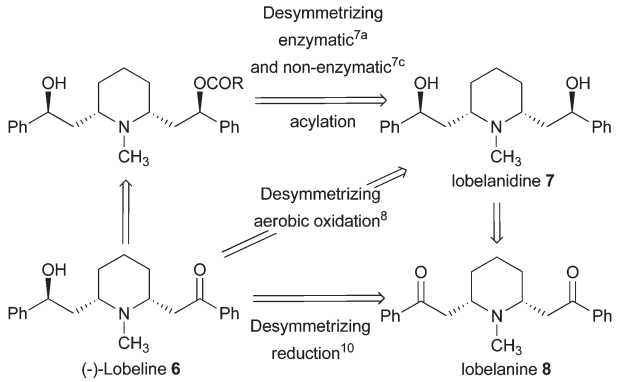
† Electronic supplementary information (ESI) available: X-ray structural data and crystallographic information files (CIF) of compounds **13d** and **17**. $^{1}$H, and $^{13}$C NMR spectra of the new compounds **13a–f**, **15a–c**, **16** and **17**. CCDC 854591 (**13d**) and 828848 (**17**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25963j




**Scheme 1** Biomimetic desymmetrization-based routes to (−)-lobeline.

Marazano *et al.* (18 steps)[11] and by Lebreton and Felpin (17 steps).[12] It is, therefore, easy to understand why both the development of new methods and the strategic deployment of known methods for the synthesis and the desymmetrization of *meso*-compounds continue to drive the field of synthetic organic chemistry.

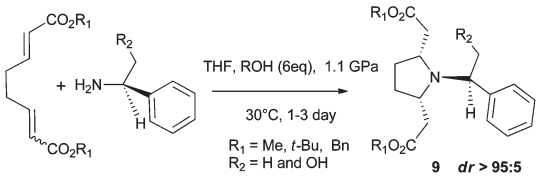
In addition to step-economical processes, high pressure[13] or ultrasound[14] promoted chemical transformations are also in agreement with the tendency and necessity of environmentally friendly approaches in organic chemistry by reducing energy consumption, using smaller quantities of hazardous chemicals and solvents and enhancing product selectivity.

In this context, we have recently described the efficient synthesis of pyrrolidines[15] and piperidines[16] using ultra-high pressure. Undeniably, 2,5-disubstituted pyrrolidines are known to be of great importance not only as a structural feature of natural alkaloids but also as fine chemicals.[17] While effort has been devoted to carrying out the synthesis of *trans*-pyrrolidines possessing a $C_2$ axis, which constitute an important class of chiral auxiliaries,[18] access to the *meso*-2,5-disubstituted pyrrolidine framework remains rather unexplored.[4a,19,20] That is why synthetic methods that give step-economical, easily-handled and sustainable accesses to aza-heterocyclic core-molecules ought to be developed.[21] In this context, the aza-Michael reaction is well-known to be a valuable strategy for the preparation of β-amino-carbonyl intermediates and has been efficiently applied to the preparation of nitrogen-containing heterocycles such as the pyrrolidine ring.[15,16,22] Recently discussed in several reviews,[23] this reaction remains an effusive subject in modern organic chemistry and, most of all, a current challenge in asymmetric catalysis.

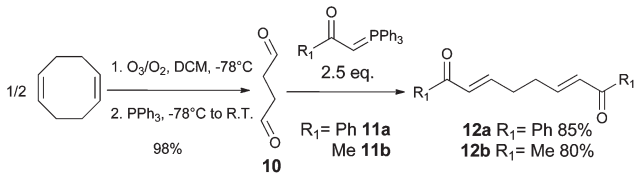
In our continuing effort towards the development of step-economical and environmentally friendly synthetic methodologies, we describe in this paper an efficient solvent-free protocol for the sonochemical synthesis of *meso*-2,5-disubstituted pyrrolidines using a double aza-Michael (DAM) strategy. We wish to report herein our methodological advance in this field and its application to the preparation of *Lobelia inflata* pyrrolidine alkaloids analogues.

## Results and discussion

Recently, we discovered a convenient method for preparing a series of orthogonally functionalized *meso*-2,5-disubstituted




**Scheme 2** Synthesis of *meso*-pyrrolidines under hyperbaric conditions.[15]




**Scheme 3** Synthesis of the bis(enones) **12a** and **12b**.

pyrrolidines **9** in high overall yield and excellent selectivity using a cyclising DAM reaction as a key step (Scheme 2).[15] Furthermore, as previously reported by our group, the aza-Michael addition of primary bulky chiral amines to crotonate derivatives requires a combination of high pressure activation and protic conditions to succeed.[15,16,24] Activation of aza-Michael reactions has been widely developed, mostly in protic solvents, using catalysts either with or without high temperature and/or high pressure.[25]

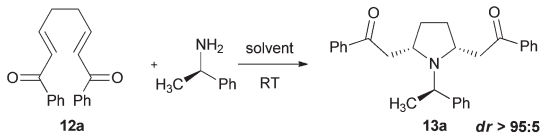
Recently, alternative energies such as microwave[27] and ultrasound[28] associated with the use of catalysts and/or solvent-free conditions have been developed, in agreement with the propensity and requirement of environmentally friendly synthetic procedures.

### Methodological development

As described in our previous work, the symmetrical double Michael acceptors **12** can be efficiently synthesized in a simple, high yielding, two-step procedure including an oxidative cleavage of diene followed by a double Wittig olefination (Scheme 3).[15] The double ozonolysis of 1,5-cyclooctadiene furnished quantitatively the succinaldehyde **10** which was treated with an excess of carbonyl-stabilized ylide **11a** ($R_1$ = Ph) or **11b** ($R_1$ = Me). The corresponding bis(enones) **12a**[29a] and **12b**[40] have been obtained as a single *E*,*E*-diastereoisomer in 85% and 80% yields respectively, and the physical data were in accordance with the literature.

Whilst this reaction sequence had the drawback that triphenylphosphine oxide was produced as a by-product, this process did allow us to produce multigram quantities of the doubly homologated compounds **12a** and **12b**. Unfortunately, attempts to develop a sequential oxidation–Wittig olefination one-pot procedure in order to reduce the number of purification operations remained unsuccessful. Indeed, symmetrical bis-α,β-unsaturated carbonyl compounds such as **12a** and **12b** are well-known to cycloisomerize with very high efficiency under the influence of a phosphine-based catalyst (*i.e.* $PPh_3$) *via* an intramolecular vinylogous Morita–Baylis–Hillman (MBH) reaction, also referred to as the Rauhut–Currier (RC) reaction.[30]

**Table 1** Double conjugate addition of (+)-phenylethylamine to **12a**[a]



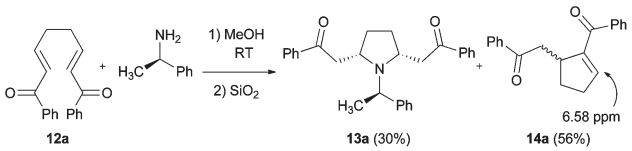

| Entry | Solvent | Yield (%) |
|---|---|---|
| 1 | *i*-PrOH | 63 |
| 2 | EtOH | 55 |
| 3 | MeOH | 36 |
| 4 | TFE | 62 |
| 5 | HFIP | 75 |
| 6 | Water, )))[b] | 47 |
| 7 | DCM | >98 |
| 8 | Toluene | >98 |
| 9 | THF | >98 |
| 10 | )))[b] | >98 |

[a] Reaction was carried out at room temperature by addition of **12a** (0.9 mmol) to a solution of (+)-phenylethylamine (1.1 mmol) in adequate solvent (90 μL). [b] Reaction was performed at room temperature in an ultrasonic stirring bath.

With dienone substrates **12** in hand, we next studied the DAM reaction at room temperature and atmospheric pressure. The model reaction involving the conjugate addition of a slight excess of (+)-phenylethylamine (1.1 eq.) to diphenyl-2,5-diene-1,8-dione (1 eq.) **12a** was performed (Table 1). As protic media proved its efficiency in the aza-Michael reaction thanks to external proton-transfer activation,[31] the effect of several protic solvents was first explored and the results are summarized in Table 1 (entries 1–6). The reaction was achieved in a very short reaction time, within one hour. In environmentally benign water as the reaction medium (Table 1, entry 6), ultrasonic stirring was necessary to increase solubility of the Michael bis(acceptor). The first assay was carried out in methanol (entry 3). Though a total conversion of the starting bis(enone) **12a** was observed by TLC and confirmed by $^1$H NMR experiments, the pyrrolidine adduct **13a** was isolated as the unique diastereomer in modest yield (36%) after purification by flash chromatography on alumina gel. In parallel, good yields were obtained using HFIP (entry 5), TFE (entry 4) and *i*-PrOH (entry 1) as solvents. The higher yield attained in the presence of HFIP (entry 5) undoubtedly confirmed that DAM addition is accelerated in proton-donating media but *a contrario* the similar results achieved in *i*-PrOH (entry 1) and in TFE (entry 4) did not permit us to establish a relationship between the reaction efficiency and solvent proton-donating ability.

DAM reaction of (+)-phenylethylamine to **12a** was, then, assayed in various aprotic solvents such as dichloromethane, toluene and THF (Table 1, entries 7–9). After a more prolonged reaction time (12 h) than in protic solvent (1 h), pyrrolidine **13a** was isolated in quantitative yield as the sole stereoisomer. This study revealed an increase in the reaction rate with protic solvent but that it gave rise to substantial quantities of cycloisomerized product. RC side reaction can be totally suppressed in aprotic media which promotes cleaner conversion.

Wiser for these experimental results, we were intrigued by the surprisingly poor yield obtained when MeOH was used as solvent (entry 3). The latter was corroborated by our initial attempt to purify the crude complex reaction mixture through chromatography on silica gel which allowed us to recover aza-Michael double adduct **13a** in lower yield (30%). In parallel, the well-characterized cyclopentene **14a** was isolated in 56% yield.




**Scheme 4** Competitive RC and DAM reactions in MeOH.

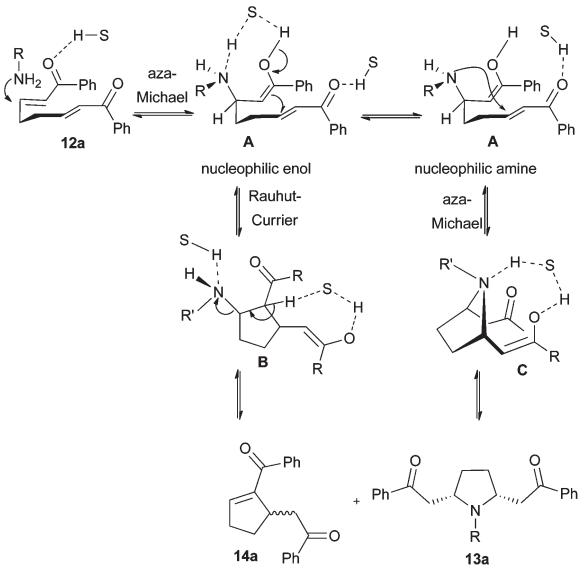
This by-product **14a** results from the electrophilic bis(enone) cycloisomerization (the so-called intramolecular RC reaction), which can be observed in the crude reaction mixture's $^1$H NMR spectrum by the characteristic chemical shift of its olefinic proton at 6.58 ppm (Scheme 4).[32]

Surprisingly and, to our knowledge, the literature has never mentioned an intramolecular RC reaction catalysed by a primary amine. Most often, RC reaction is mediated by phosphines[32,33] or by tertiary amines mainly DABCO, DBU, DMAP or quinuclidine derivatives. Lithium amides and thiolates have been also used to initiate such cyclizations but the nucleophiles remain covalently attached in the cyclization products.[23c,29c,30,34] More astonishingly, if the cycloisomerized compound **14a** can be isolated in up to 56% yield after purification over silica gel, the crude reaction mixtures' $^1$H NMR spectra revealed its presence in lesser proportions regardless of the protic solvent used. As it is well-established that the solvent nature has dramatic effects on the RC reaction due to the highly polarized intermediates implicated,[35] NMR experiments have been undertaken respectively in protic ($CD_3OD$) and aprotic solvents ($CDCl_3$) in order to understand the mechanism involved and to increase the selectivity and efficiency of the desired pyrrolidine **13a** formation (see ESI†). Conjugate addition of phenylethylamine to the bis(enone) **12a** was carried out at room temperature. The reaction was monitored periodically by $^1$H NMR spectroscopy. In methanol-d$^4$, a complex mixture was observed owing to the formation of diastereomeric deuterated compounds by deuterium exchange between solvent and the starting amine and by deuterium transfer occurring in conjugate addition. Whereas the reaction kinetics were slowed down by dilution, $^1$H NMR spectra revealed the formation of the cycloisomerized by-product **14a** whose proportion increased over reaction time. $^1$H NMR experiments of DAM addition conducted in chloroform-d$^1$ allowed access to the desired pyrrolidine **13a** exclusively (see ESI†).

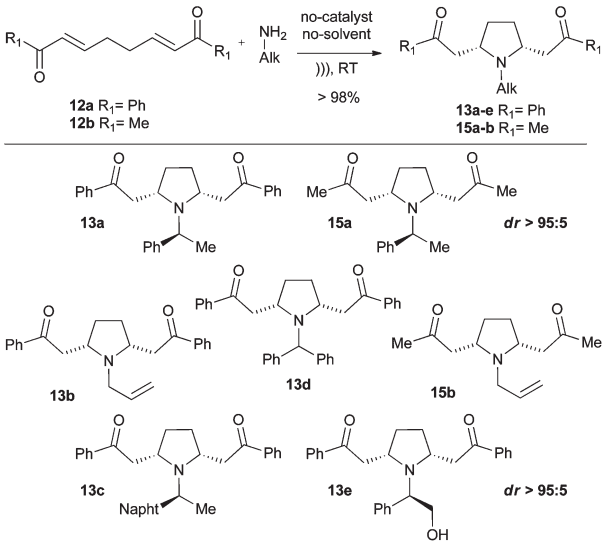
Concerning the mechanism involved, the ring closing reactions through RC or DAM strategy proceed *via* the common initial enol **A** resulting from the amine 1,4-addition to enone **12a** (Scheme 5). Subsequent conjugate addition to the second enone can follow two different pathways. In the RC reaction, the initial enol is added to the second Michael acceptor affording the cyclised intermediate **B** which, in a subsequent step, eliminates the nucleophilic amino-group. In the DAM pathway, the nucleophilic amino-group is added to the second enone acceptor affording the cyclised intermediate **C**. In addition, we have confirmed that the RC product was favoured in protic media (either in alcohol or over silica gel). In this particular case of primary






**Scheme 5** RC and DAM competitive reactions in protic solvents (S-H).




**Scheme 6** Sonochemical gram-scale preparation of pyrrolidines.

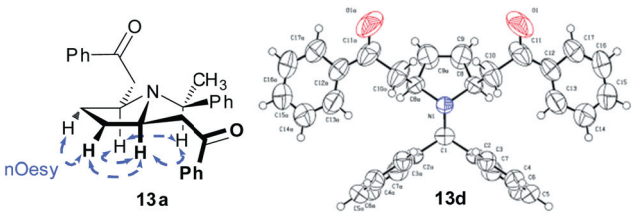



**Fig. 3** Relative configuration determined by nOesy experiments of compound **13a** and by X-ray crystal[41] structures of compound **13d**.

amine as a typical heteronucleophilic reagent, the increasing proportion of RC product could only be explained by a retro-Michael reaction applied to pyrrolidine compound accelerated by protic environment (Scheme 5). Indeed, NMR experiments based on aromatic protons' chemical shifts tend to demonstrate that, in methanol-d[4], the early formed DAM adduct **13a** evolved over time to the RC product **14a** while, in chloroform-d[1], **13a** remains much more stable.

As the DAM reaction rate has been shown to be dilution-dependent, the last assay was performed in solvent-free conditions (Table 1, entry 10). Pyrrolidine **13a** was isolated in quantitative yield in 1 h after ultrasonic irradiation. In solvent-free conditions, ultrasonic irradiation was crucial and accelerated the reaction by facilitating the solubility of reactant and the liberation of energy by cavitation.

To expand the scope of reaction substrates, various primary alkylamines were added onto dienone substrates **12a** and **12b** under ultrasonic solvent-free optimized conditions as shown in Scheme 6.

Pyrrolidines **13** and **15** can be rapidly synthesized in excellent purity and stereoselectivity and in quantitative yields. These results indicate that the DAM reaction applied to pyrrolidine preparation is not sensitive to steric hindrance in terms of efficiency and stereospecificity. In addition, this safe metal-free and easy to handle procedure is scalable, allowing pyrrolidine synthesis in multi-gram quantities. This route permits us to introduce a high level of molecular diversity under mild reaction conditions, including substitution and scaffold diversity. In the case of pyrrolidines **13a,c,e** and **15a** derived from the condensation of enantiopure amine, the relative configuration was unambiguously determined by virtue of two-dimensional nOesy correlations (Fig. 3 and ESI†): acyl arms are in the *syn* configuration in relation to each other, while they are in *anti* configuration in relation to the nitrogen substituent (Fig. 3). Indeed, as previously described,[15] only one conformer is characterized due to the absence of free-rotation around the N–C* bond. As a consequence, in the unique rotamer, the chemically equivalent $^{1}H$ and $^{13}C$ in the cyclic compound become magnetically different (diastereotopic) for the reason that the phenyl anisotropy effect only affects a part of the molecule. Gratifyingly, in this pyrrolidine series, only compound **13d** crystallized allowing the elucidation of its relative configuration by means of a single-crystal X-ray analysis (Fig. 3 and ESI†). The *syn*-configuration of the phenacyl arms and their *anti*-configuration in relation to the nitrogen substituent are confirmed. In addition, the conspicuous perfect harmonious symmetry of compound **13d** can be noted (Fig. 3).

This unique *syn*-configuration of the acyl arms can be explained by the thermodynamic control of the aza-annulation following the first conjugate addition of the primary alkylamine.

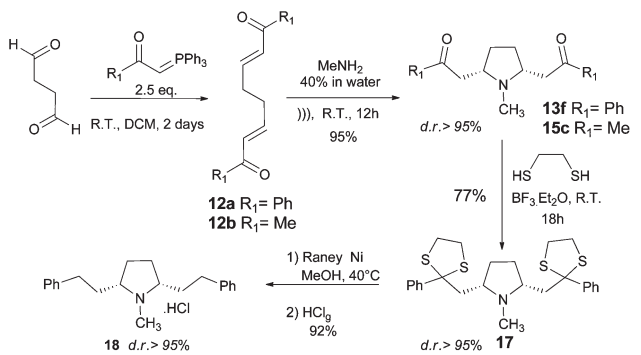
### Sequential one-pot synthesis of pyrrolidine *Lobelia* alkaloids analogues

Taking these interesting results into account, we envisaged extending the cyclising DAM strategy for the synthesis of pyrrolidine *Lobelia* alkaloids analogues. Crooks and co-workers[4] have recently described the synthesis of the pyrrolidine lobelane analogue **17** in a five-step sequence from succinaldehyde utilizing the elegant asymmetric Katritzky's benzotriazole-oxazolidine approach.[36] This strategy afforded a separable 2 : 1 diastereomeric mixture in favour of the *cis*(*meso*)-pyrrolidine norlobelane

analogue **4**. As mentioned in the introduction, the authors showed that the ring size reduction of the central piperidine of lobelane into pyrrolidine potentiated their ability to inhibit dopamine uptake with high affinity for VMAT2 receptors.

According to our strategy, the pyrrolidine lobelanine and lobelane analogues (**13f** and **17**) could be synthesized from succinaldehyde in a concise two- and three-step sequence respectively. Applying optimized double cyclising aza-Michael conditions, the pyrrolidine lobelanine analogue **13f** has been prepared in a quantitative yield as the single *meso*-isomer (d.r. >95%) by treatment of the solid dienone **12a** with a slight molar excess of a 40% aqueous methylamine solution under ultrasonic activation (Scheme 7). In the same way, starting from succinaldehyde, the open one-flask sequential double Wittig olefination–DAM addition led to the unique *meso*-pyrrolidine lobelanine analogue **13f** in an excellent 95% yield over two steps. Next, considerable efforts were made to develop a satisfactory procedure for reductive removal of the ketone groups in **13f** by general methods for converting ketone to methylene. Our attempts included standard Wolff–Kishner[37] or Clemmensen[38] deoxygenation and reduction of carbonyl tosylhydrazone intermediates[39] to hydrocarbons only furnished degradation of **13f**. More fruitfully, desulfurization of the dithioacetal **16** with RANEY® Ni[26d] led to pyrrolidine lobelane analogue which was isolated as the hydrochloride salt **17** in a very good 92% yield as the single *cis-meso* diastereoisomer (d.r. >95%) (Scheme 7).

As the $^1$H NMR data of **17** did not correspond to those described in the literature by Crooks,[4] we have performed X-ray analysis that has confirmed the stereochemical configuration of the *meso*-pyrrolidine lobelane hydrochloride **18** (Fig. 4 and ESI†).




**Scheme 7** Straightforward synthesis of pyrrolidine *Lobelia* alkaloids analogues.

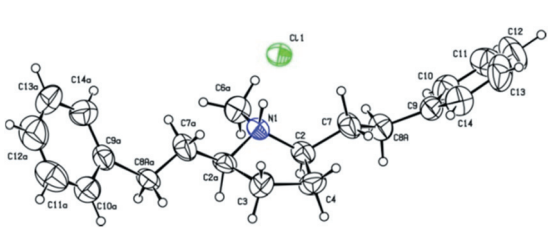


**Fig. 4** X-ray crystal[42] structure of *N*-methyl-2,5-*cis*-di-(2-phenethyl)-pyrrolidine hydrochloride **17**.

Furthermore, we have successfully simplified the synthetic processes by developing a rapid access to pyrrolidine lobelane hydrochloride analogue **17** using an only "open two-flask" procedure in high overall yield and excellent diastereoselectivity. Indeed, double Wittig olefination, DAM reaction and dithioacetalization have been handled consecutively in the same flask affording the dithioacetal **16** in excellent 72% overall yield. Due to the use of a large excess of 1,2-ethanedithiol for the dithioacetalization (20 eq.), the last reductive step by RANEY® Ni required the dithioacetal's isolation in pure form.

## Conclusions

We have successfully developed a safe, environmentally friendly, catalyst-free synthesis of 2,5-*meso*-pyrrolidines by double aza-Michael addition of primary amines to symmetrical (bis)-α,β-unsaturated compounds under solvent-free conditions. This environmentally sound double aza-Michael reaction was applied to the synthesis of a pyrrolidine lobelane hydrochloride analogue in high overall yield and excellent selectivity using two flask procedure only. In the context of the synthesis of bioactive compounds, our strategy offers a convergent synthetic pathway to introduce maximum chemical diversity elements with a limited number of chemical events and simple and powerful procedures.

## Experimental

### General experimental

Melting points were recorded on an electrothermal digital apparatus and were uncorrected. Infrared (IR) spectra were obtained as neat films on Bruker Vector22 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC 200, AC 300 or ARX 400 apparatus respectively at 300 or 400 MHz and 75 or 100 MHz unless otherwise specified. The chemical shifts for $^1$H 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 deuterochloroform (77.23 ppm) as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. NMR peak assignments have been made on the basis of HMBC, HMQC, nOesy, and $^1$H–$^1$H COSY spectra. Diastereomeric ratios (dr) were evaluated by $^1$H NMR spectroscopy. Specific rotations $[\alpha]_D^{20}$ were measured at 20 °C on a PolAAr32 polarimeter using a sodium lamp as the light source (589 nm) in a 1 dm cell and were given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$ and concentrations were quoted in g $10^{-2}$ mL. The electrospray impact (ESI) and the atmospheric pressure chemical ionisation (APCI) mass spectra were realized 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 ($\lambda$ = 0.71069 Å) or on a Rigaku MM007 HF copper ($\lambda$ = 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 by the Service de Microanalyse, Centre d'Etudes

Pharmaceutiques, Châtenay-Malabry, France. Sonication was performed in a Prolabo Transonic-TS540 ultrasonic cleaner with a frequency of 35 KHz and a power of 320 W.

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 (40–63 μm) or on Merck neutral activated Aluminiumoxid 90 (63–200 μm). Commercially available reagents such as phenyl- and methyl-carbonylmethylene-triphenylphosphane (**11a** and **11b**) were used throughout without further purification other than that detailed below. Prior to use, solvents were distilled according to *Purification of Laboratory Chemicals*, 4th Ed., W.L.F. Aramarego and D.D. Perrin, Butterworth Heinemann, 1996. Dienediones (**12a**, R = Ph)[29a] and (**12b**, R = Me)[40] were synthesized according to the procedures reported in the literature in 85% and 80% yield respectively. The physical data were in accordance with the literature.[32a,40]

### General procedure for the synthesis of pyrrolidines in solution (Method A)

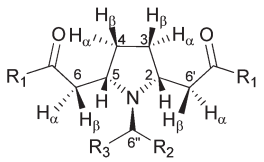
Primary amine (1.9 mmol) was added to a 1 M solution of freshly purified phenyldienedione **12a** (1.7 mmol) in the selected solvent. The solution was stirred at room temperature until completion of the reaction, which was monitored and measured by $^1$H NMR. Then, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on neutral alumina gel (90 : 10, *c*Hex–EtOAc) to yield the desired pyrrolidine (for results see Table 1).

### General procedure for the sequential one-pot synthesis of pyrrolidines in solution (Method B)

To a 0.5 M solution of triphenylphosphane ylide **11a** (Ph) (30 g, 79 mmol, 2.5 eq.) or **11b** (Me) (25.1 g, 79 mmol, 2.5 eq.) in the selected solvent, was added freshly distilled succinaldehyde (2.7 g, 31 mmol, 1 eq.) by mean of a syringe pump. The reaction was stirred at room temperature for approximately two days. Completion of the reaction was monitored by $^{31}$P NMR of a crude evaporated aliquot. Then, primary amine (34 mmol, 1.1 eq.) was added to the crude reaction mixture, which was then allowed to stir at room temperature for an additional 12 h. The reaction mixture was concentrated under reduced pressure and purified by filtration on a pad of neutral alumina (90 : 10, *c*Hex–EtOAc) to give the desired pyrrolidine in >95% overall yield.

### General procedure for the solvent-free synthesis of pyrrolidines under ultrasonic irradiation (Method C)

Liquid primary amine (1.9 mmol, 1.1 eq.) was added to freshly purified solid dienedione (1.7 mmol, 1 eq.) **12a** (495 mg) or **12b** (285 mg). The mixture was irradiated under ultrasonic conditions during 1 h. Completion and conversion of the reaction was monitored and measured by $^1$H NMR. Pyrrolidines (**13** and **15**) were obtained quantitatively without further purification.



**(+)-2-[1-(1*R*-Phenylethyl)-5-(2-oxo-2-phenylethyl)pyrrolidin-2-yl]acetophenone (13a).** The reaction was carried out starting from 1-(*R*)-phenylethylamine (245 μL, 1.9 mmol) and the bis-(enone) **12a** (495 mg, 1.7 mmol).

Brown oil (Method C: ≥95% yield); de ≥95%; $[\alpha]_D^{20}$ +16° (*c* 0.5 in $CH_2Cl_2$); Found: C, 80.72; H, 7.10; N, 3.40. Calc. for $C_{28}H_{29}NO_2 \cdot 1/3H_2O$: C, 80.54; H, 7.16; N, 3.35%; IR $\nu_{max}/cm^{-1}$ 1675 (C═O), 1597 (C═C), 1580 (C═C); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.28 (3H, d, $J$ = 6.9 Hz, $H_{7''}$), 1.43 (2H, ddt, $J$ = 19.4 and 9.9 and 6.2 Hz, $H_{3\alpha}$–$H_{4\alpha}$), 1.78 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.63 (1H, dd, $J$ = 9.6 and 15.8 Hz, $H_{6\alpha}$), 2.74 (1H, dd, $J$ = 3.9 and 15.9 Hz, $H_{6\beta}$), 2.81 (1H, dd, $J$ = 9.1 and 15.6 Hz, $H_{6'\alpha}$), 3.10 (1H, dd, $J$ = 4.2 and 15.4 Hz, $H_{6'\beta}$), 3.48 (1H, m, $H_5$), 3.55 (1H, m, $H_2$), 3.88 (1H, q, $J$ = 6.7 Hz, $H_{6''}$), 7.11 (1H, t, $J$ = 7.7 Hz, $H_{Ar}$), 7.19 (2H, t, $J$ = 7.8 Hz, $H_{Ar}$), 7.29 (6H, m, $H_{Ar}$), 7.40 (2H, tt, $J$ = 7.44 and 1.9 Hz, $H_{Ar}$), 7.57 (2H, d, $J$ = 7.7 Hz, $H_{Ar}$), 7.68 (2H, d, $J$ = 7.7 Hz, $H_{Ar}$); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta$ 16.12 ($CH_3$), 30.46 ($C_3$), 31.01 ($C_4$), 47.03 ($C_{6'}$), 47.25 ($C_6$), 56.71 ($C_5$), 59.14 ($C_2$), 59.24 ($C_{6''}$), 126.98 ($CH_{ar}$), 128.11 ($CH_{ar}$), 128.15 ($CH_{ar}$), 128.20 ($CH_{ar}$), 128.28 ($CH_{ar}$), 128.48 ($CH_{ar}$), 128.59 ($CH_{ar}$), 132.87 ($CH_{ar}$), 132.98 ($CH_{ar}$), 137.20 ($C_{ar}$), 137.24 ($C_{ar}$), 144.28 ($C_{ar}$), 199.95 (C═O), 199.99 (C═O); Low resolution mass spectroscopy (CI) $m/z$ (%): 412.2 (100) $[M + H]^+$.

**(−)-2-[1-(1*R*-Phenylethyl)-5-(2-oxopropyl)pyrrolidin-2-yl]-acetone (15a).** The reaction was carried out starting from 1-(*R*)-phenylethylamine (245 μL, 1.9 mmol) and the bis(enone) **12b** (285 mg, 1.7 mmol).

Yellowish oil (Method C: ≥95% yield); de ≥95%; $[\alpha]_D^{20}$ −9° (*c* 0.45 in $CH_2Cl_2$); Found: C, 73.86; H, 8.59; N, 4.53. Calc. for $C_{18}H_{25}NO_2 \cdot 1/3H_2O$: C, 73.68; H, 8.82; N, 4.77%; IR $\nu_{max}/cm^{-1}$ 1707 (C═O), 1451 (C–N), 763 (═C–H); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 1.40 (5H, d, $J$ = 6.9 Hz, $H_{7''}$–$H_{3\alpha}$–$H_{4\alpha}$), 1.85 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 1.93 (3H, s, $H_8$), 2.07 (3H, s, $H_{8'}$), 2.14 (2H, dd, $J$ = 15 and 6 Hz, $H_{6\alpha}$–$H_{6'\beta}$), 2.33 (1H, dd, $J$ = 9 and 15.9 Hz, $H_{6\beta}$), 2.52 (1H, dd, $J$ = 4 and 16 Hz, $H_{6'\alpha}$), 3.36 (2H, m, $H_2$–$H_5$), 3.86 (1H, q, $J$ = 6.9 Hz, $H_{6''}$), 7.12–7.29 (5H, m, $H_{Ar}$); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 15.69 ($CH_3$), 30.61 ($C_3$), 30.83 ($C_8$), 31.00 ($C_{8'}$), 31.11 ($C_4$), 51.96 ($C_6$), 52.01 ($C_{6'}$), 55.61 ($C_5$), 58.14 ($C_2$), 58.83 ($C_{6''}$), 127.06 ($CH_{ar}$), 128.07 ($CH_{ar}$), 128.29 ($CH_{ar}$), 128.60 ($CH_{ar}$), 144.01 ($C_{ar}$), 208.41 (C═O); Low resolution mass spectroscopy (CI) $m/z$ (%): 288.2 (100) $[M + H]^+$.

**2-[1-Allyl-5-(2-oxo-2-phenylethyl)-pyrrolidin-2-yl]acetophenone (13b).** The reaction was carried out starting from allylamine (143 μL, 1.9 mmol) and the bis(enone) **12a** (495 mg, 1.7 mmol).

Brown oil (Method C: ≥95% yield); de ≥95%; Found: C, 78.77; H, 7.49; N, 3.85. Calc. for $C_{23}H_{25}NO_2 \cdot 1/4H_2O$: C, 78.49; H, 7.30; N, 3.98%; IR $\nu_{max}/cm^{-1}$ 1680 (C═O), 1597 (C═C), 1580 (C═C), 1448 (C–N); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.49

(2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 2.04 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.93 (2H, m, $H_{6\alpha}$–$H_{6'\alpha}$), 3.31 (6H, m, $H_{6''}$–$H_{6\beta}$–$H_{6'\beta}$–$H_2$–$H_5$), 5.10 (1H, d, $J_{cis}$ = 9.9 Hz, $H_{8''}$), 5.20 (1H, d, $J_{trans}$ = 17.1 Hz, $H_{8''}$), 5.91 (1H, m, $H_{7''}$), 7.42–7.54 (6H, m, $H_{Ar}$), 7.95 (4H, d, $J$ = 7.7 Hz, $H_{Ar}$); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$, 30.21 ($C_3$–$C_4$), 45.11 ($C_6$–$C_{6'}$), 55.55 ($C_{6''}$), 60.37 ($C_2$–$C_5$), 128.11 ($CH_{ar}$), 128.54 ($CH_{ar}$), 133.04 ($C_{7''}$), 137.13 ($C_{ar}$–$C_{8''}$), 199.27 (C═O).

**2-[1-Allyl-5-(2-oxopropyl)pyrrolidin-2-yl]acetone (15b).** The reaction was carried out starting from allylamine (143 μL, 1.9 mmol) and the bis(enone) **12b** (285 mg, 1.7 mmol).

Yellowish oil (Method C: ≥95% yield); de ≥95%; Found: C, 68.18; H, 9.53; N, 6.32. Calc. for $C_{13}H_{21}NO_2{\cdot}1/3H_2O$: C, 68.09; H, 9.52; N, 6.11%; IR $\nu_{max}$/cm$^{-1}$ 1708 (C═O), 1419 (C═C), 1357 (C–N); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.37 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 1.94 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.11 (6H, s, $H_8$–$H_{8'}$), 2.37 (2H, dd, $J$ = 16.0 and 8.7 Hz, $H_{6\alpha}$–$H_{6'\alpha}$), 2.69 (2H, dd, $J$ = 16.0 and 4.2 Hz, $H_{6\beta}$–$H_{6'\beta}$), 3.07 (2H, m, H, $H_2$–$H_5$), 3.19 (2H, d, $J$ = 6.6 Hz, $H_{6''}$), 5.12 (2H, m, $H_{8''}$) 5.85 (1H, m, $H_{7''}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 29.98 ($C_3$–$C_4$) 30.90 ($C_8$–$C_{8'}$), 50.19 ($C_6$–$C_{6'}$), 55.47 ($C_{6''}$), 59.63 ($C_2$–$C_5$), 117.42 ($C_{8''}$), 135.64 ($C_{7''}$), 208.27 (C═O); Low resolution mass spectroscopy (CI): $m/z$ (%) 224.1 (100).

**(+)-2-[1-(1*R*-Naphthylethyl)-5-(2-oxo-2-phenylethyl)-pyrrolidin-2-yl]acetophenone (13c).** The reaction was carried out starting from 1-(*R*)-naphthylethylamine (307 μL, 1.9 mmol) and the bis(enone) **12a** (495 mg, 1.7 mmol).

Brown oil (Method C: ≥95% yield); de ≥95%; $[\alpha]_D^{20}$ +45 ($c$ 0.75, $CH_2Cl_2$); Found: C, 82.33; H, 6.87; N, 3.20. Calc. for $C_{32}H_{31}NO_2{\cdot}1/3H_2O$: C, 82.19; H, 6.83; N, 3.00%; IR $\nu_{max}$/cm$^{-1}$ 1674(C═O), 1596 (C═C), 1448 (C–N); $^1$H NMR ($C_6D_6$, 300 MHz): $\delta$ 1.60 (5H, m, $H_{3\alpha}$–$H_{4\alpha}$–$H_{7''}$), 1.98 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.30 (1H, dd, $J$ = 16.6 and 2.3 Hz, $H_{6\beta}$), 2.49 (1H, dd, $J$ = 15.9 and 9.4 Hz, $H_{6\alpha}$), 2.96 (1H, dd, $J$ = 15.4 and 8.5 Hz, $H_{6'\alpha}$), 3.47 (1H, dd, $J$ = 15.5 and 4.9 Hz, $H_{6'\beta}$), 3.68 (m, 1H, $H_2$), 3.80 (m, 1H, $H_5$), 4.87 (1H, q, $J$ = 6.6 Hz, $H_{6''}$), 7.24–7.65 (m, 12H, $H_{Ar}$), 7.69–7.92 (m, 4H, $H_{Ar}$), 8.41 (1H, d, $J$ = 8.1 Hz, $H_{Ar}$); $^{13}$C NMR ($C_6D_6$, 75 MHz): $\delta$, 14.17 ($C_{7''}$), 30.91 ($C_3$), 31.15 ($C_4$), 46.16 ($C_6$), 47.31 ($C_{6'}$), 55.45 ($C_{6''}$), 56.11 ($C_2$), 59.70 ($C_5$), 125.01 ($CH_{ar}$), 125.32 ($CH_{ar}$), 125.64 ($CH_{ar}$), 125.79 ($CH_{ar}$), 125.96 ($CH_{ar}$), 125.53 ($CH_{ar}$), 125.96 ($CH_{ar}$), 128.48 ($CH_{ar}$), 128.73 ($CH_{ar}$), 128.93 ($CH_{ar}$), 132.41 ($CH_{ar}$), 132.73 ($CH_{ar}$), 134.41 ($C_{ar}$), 137.66 ($C_{ar}$), 137.87 ($C_{ar}$), 140.19 ($C_{ar}$), 198.44 (C═O); Low resolution mass spectroscopy (CI): $m/z$ (%) 462 (100) $[M + H]^+$.

**2-[1-Benzhydryl-5-(2-oxo-2-phenylethyl)pyrrolidin-2-yl]acetophenone (13d).** The reaction was carried out starting from benzhydrylamine (327 μL, 1.9 mmol) and the bis(enone) **12a** (495 mg, 1.7 mmol).

White crystal (Method C: ≥95% yield); de ≥95%; mp 138 °C (from *c*-hexane); Found: C, 83.54; H, 6.68; N, 3.14. Calc. for $C_{33}H_{31}NO_2$: C, 83.69; H, 6.60; N, 2.96%; IR $\nu_{max}$/cm$^{-1}$ 1669 (C═O), 1593 (C═C), 1447 (C–N), 1270 (C–N), 713 (═C–H); Crystal data: thin colourless plate of dimensions 0.60 × 0.46 × 0.10 mm, $C_{33}H_{29}NO_2$, $M$ = 471.57, orthorhombic system, space group *Pbcm*, $Z$ = 4, $a$ = 8.806 (4), $b$ = 11.377 (5) Å, $c$ = 26.118 (8) Å, $V$ = 2616.7(2) Å$^3$, $D_{calcd}$ = 1.197 g cm$^{-3}$, $F$(000) = 1000, $\mu$ = 0.074 mm$^{-1}$, 11 516 collected reflections (1.98° ≤ $\theta$ ≤ 46.58°), $-9 \le h \le 9$, $-12 \le k \le 12$, $-28 \le l \le 28$), 1920 independent reflections ($R_{int}$ = 0.0245), goodness-of-fit on $F^2$: $S$ = 1.050, $R_1$ = 0.0885 and w$R_2$ = 0.1925 for all 1919 reflections, $R_1$ = 0.0635 and w$R_2$ = 0.1708 for 1361 observed reflections [$I > 2\sigma(I)$], refining 167 parameters, semi-empirical absorption correction from multi-scans ($T_{min}$ = 0.89, $T_{max}$ = 0.99), final electron density between −0.180 and 0.385 e Å$^{-3}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.60 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 1.87 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.74 (2H, dd, $J$ = 10.4 and 14.7 Hz, $H_{6\alpha}$–$H_{6'\alpha}$), 3.18 (2H, dd, $J$ = 3.8 and 14.6 Hz, $H_{6\beta}$–$H_{6'\beta}$), 3.54 (2H, m, $H_2$–$H_5$), 4.88 (1H, s, $H_{6''}$), 7.20 (2H, m, $H_{Ar}$), 7.26 (8H, m, $H_{Ar}$), 7.45 (10H, m, $H_{Ar}$); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta$ 29.74 ($C_3$–$C_4$), 47.11 ($C_6$–$C_{6'}$), 60.23 ($C_2$–$C_5$), 73.16 ($C_{6''}$), 127.24 ($CH_{ar}$), 128.15 ($CH_{ar}$), 128.44 ($CH_{ar}$), 128.55 ($CH_{ar}$), 128.76 ($CH_{ar}$), 132.80 ($CH_{ar}$), 136.70 ($C_{ar}$), 142.93 ($C_{ar}$), 199.55 (C═O); Low resolution mass spectroscopy (APCI) $m/z$: 474 ($[M + H]^+$, 100%).

**(−)-2-[1-(2-Hydroxy-1*R*-phenylethyl)-5-(2-oxo-2-phenylethyl)-pyrrolidin-2-yl]acetophenone (13e).** The reaction was carried out starting from 1-(*R*)-phenylglycinol (260 mg, 1.9 mmol) and the bis(enone) **12a** (495 mg, 1.7 mmol).

Brown oil (Method C: ≥95% yield); de ≥95%; $[\alpha]_D^{20}$ −26° ($c$ 1 in $CH_2Cl_2$); Found: C, 77.12; H, 7.23; N, 3.25. Calc. for $C_{28}H_{29}NO_3{\cdot}1/2H_2O$: C, 77.04; H, 6.93; N, 3.21%; IR $\nu_{max}$/cm$^{-1}$ 3440 (O–H), 1674 (C═O), 1597 (C═C), 1579 (C═C); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.47 (3H, m, $H_{3\alpha}$–$H_{4\alpha}$–$H_{3\beta}$), 1.97 (1H, m, $H_{4\beta}$), 2.99 (1H, dd, $J$ = 9.2 and 15.7 Hz, $H_{6\alpha}$), 3.11 (1H, dd, $J$ = 8.0 and 16.0 Hz, $H_{6'\alpha}$), 3.22 (1H, dd, $J$ = 4.0 and 15.8 Hz, $H_{6\beta}$), 3.49 (1H, dd, $J$ = 4.5 and 16.0 Hz, $H_{6\beta'}$), 3.78 (1H, dd, $J$ = 4.7 and 10.0 Hz, $H_{7''}$), 3.79 (2H, m, $J$ = 4.5 and 8–10 Hz, $H_2$–$H_5$), 3.95 (1H, t, $J$ = 10.0 Hz, $H_{7''}$), 4.04 (1H, dd, $J$ = 4.7 and 10 Hz, $H_{6''}$), 7.32 (3H, m, $J$ = 7.4 and 1.4 Hz, $H_{Ar}$), 7.36 (2H, td, $J$ = 7.2 and 2.0 Hz, $H_{Ar}$), 7.44 (2H, t, 7.5 Hz, $H_{Ar}$), 7.48 (2H, t, $J$ = 7.6 Hz, $H_{Ar}$), 7.56 (1H, tt, $J$ = 7.5 and 1.6 Hz, $H_{Ar}$), 7.60 (1H, tt, $J$ = 7.3 and 1.6 Hz, $H_{Ar}$), 7.93 (2H, d, $J$ = 7.3 Hz, $H_{Ar}$), 8.04 (2H, d, $J$ = 7.6 Hz, $H_{Ar}$). $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta$ 30.53 ($C_3$), 30.81 ($C_4$), 45.26 ($C_6$), 46.88 ($C_{6'}$), 54.77 ($C_5$), 60.03 ($C_2$), 62.12 ($C_{7''}$), 65.51 ($C_{6''}$), 127.87 ($CH_{ar}$), 128.09 ($CH_{ar}$), 128.13 ($CH_{ar}$), 128.48 ($CH_{ar}$), 128.60 ($CH_{ar}$), 128.61 ($CH_{ar}$), 128.70 ($CH_{ar}$), 133.11 ($CH_{ar}$), 133.16 ($CH_{ar}$), 136.96 ($C_{ar}$), 137.12 ($C_{ar}$), 137.20 ($C_{ar}$), 199.34 (C═O), 199.54 (C═O); Low resolution mass spectroscopy (ESI) $m/z$ (%): 428.3 (100) $[M + H]^+$, 308.1 (4).

**2[1-Methyl-5-(2-oxo-2-phenylethyl)-pyrrolidin-2-yl]acetophenone (13f).** The reaction was carried out starting from a 40% aqueous methylamine solution (160 μL, 1.9 mmol) and the bis(enone) **12a** (495 mg, 1.7 mmol).

Brown oil (Method C: ≥95% yield); de ≥95%; Found: C, 76.98; H, 7.20; N, 4.17. Calc. for $C_{21}H_{23}NO_2{\cdot}1/3H_2O$: C, 77.03; H, 7.29; N, 4.28%; IR $\nu_{max}$/cm$^{-1}$ 1679 (C═O), 1597 (C═C), 1448 (C–N); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.46 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 2.11 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.36 (3H, s, $H_{6''}$), 2.98 (4H, m, $H_6$–$H_{6'}$), 2.33 (2H, dd, $J$ = 12.6 and 8.4 Hz, $H_2$–$H_5$), 7.45 (4H, t, $J$ = 7.4 Hz, $H_{ar}$), 7.55 (2H t, $J$ = 7.3 Hz, $H_{ar}$), 7.96 (4H, d, $J$ = 7.2 Hz, $H_{ar}$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 29.91 ($C_3$–$C_4$), 39.31 ($C_{6''}$), 44.20 ($C_6$–$C_{6'}$), 63.00 ($C_2$–$C_5$), 128.04 ($CH_{ar}$), 128.58 ($CH_{ar}$), 133.05 ($CH_{ar}$), 137.19 ($C_{ar}$), 199.16 (C═O);

Low resolution mass spectroscopy (CI): *m*/*z* (%) 322.2 (100) $[M + H]^+$, 202.3 (30).

**2-[1-Methyl-5-(2-oxopropyl)pyrrolidin-2-yl]acetone (15c).** The reaction was carried out starting from a 40% aqueous methylamine solution (160 µL, 1.9 mmol) and the bis(enone) **12b** (285 mg, 1.7 mmol).

Yellowish oil (Method C: ≥95% yield); de ≥95%; Found: C, 64.80; H, 9.62; N, 6.80. Calc. for $C_{11}H_{19}NO_2 \cdot 1/3H_2O$: C, 64.99; H, 9.75; N, 6.89%; IR $\nu_{max}/cm^{-1}$ 1709 (C═O), 1361(C–N); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.34 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 1.99 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.14 (6H, s, $H_8$–$H_{8'}$), 2.21 (3H, s, $H_{6''}$), 2.40 (4H, m, $H_6$–$H_{6'}$), 2.68 (2H, m, $H_2$–$H_5$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$, 29.45 ($C_3$–$C_4$), 30.89 ($C_8$–$C_{8'}$), 39.03 ($C_{6''}$), 48.91 ($C_6$–$C_{6'}$), 62.41 ($C_2$–$C_5$), 207.90 (C═O); Low resolution mass spectroscopy (ESI): *m*/*z* (%) 198.3 (100), 140.2 (42).

**1-Methyl-2,5-bis[(2-phenyl-1,3-dithiolan-2-yl)methyl]pyrrolidine (16).** To a 0.5 M solution of phenylcarbonylmethylene-triphenylphosphane (838 mg, 2.2 mmol) in dichloromethane, was added freshly distilled succinaldehyde (86 mg, 1 mmol) by mean of syringe pump. The reaction was magnetically stirred at room temperature for approximately two days. Then, the 40% aqueous methylamine (1.1 mmol, 92 µL) was added to the reaction mixture, which was stirred at room temperature for an additional 12 h. The mixture was next stirred at room temperature for 18 h after addition of 1,2-ethanedithiol (1.7 mL, 20 mmol) and borontrifluoride etherate (1.7 mL, 13.3 mmol). The mixture was washed twice with a 2 M sodium hydroxide solution (2 × 50 mL) and extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude mixture was then purified by silica gel column chromatography (80 : 20 cyclohexane–ethyl acetate) to give the desired pyrrolidine.

White solid (364 mg, 77%); mp 118 °C; Found: C, 63.54; H, 6.61; N, 2.91. Calc. for $C_{25}H_{31}NS_4$: C, 63.38; H, 6.60; N, 2.96%; IR $\nu_{max}/cm^{-1}$ 1443 (C–N), 1032 (C–N); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.99 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 1.25 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 1.93 (2H, m, $H_2$–$H_5$), 2.10 (3H, s, $H_{6''}$), 2.35 (2H, dd, $J$ = 9.2 and 14.0 Hz, $H_{6\alpha}$–$H_{6'\alpha}$), 2.73 (2H, d, $J$ = 14.0 Hz, $H_{6\beta}$–$H_{6'\beta}$), 3.12–3.17 (4H, m, $CH_2$–S), 3.32–3.38 (4H, m, $CH_2$–S), 7.22 (6H, m, $H_{Ar}$), 7.65 (4H, d, $J$ = 7.2 Hz, $H_{Ar}$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 30.62 ($C_3$–$C_4$), 38.48 ($CH_2$–S), 38.65 ($C_{6''}$), 38.75 ($CH_2$–S), 50.54 ($C_6$–$C_{6'}$), 65.45 ($C_2$–$C_{5'}$), 72.93 ($C_7$–$C_{7'}$), 126.94 ($CH_{ar}$), 127.26 ($CH_{ar}$), 127.69 ($CH_{ar}$), 145.07 ($C_{ar}$); Low resolution mass spectroscopy (CI): *m*/*z* (%) 474.2 (100) $[M + H]^+$.

**1-Methyl-2,5-bis(2-phenethyl)pyrrolidine hydrochloride (17).** To a suspension of RANEY® Nickel (1 g) in MeOH (30 mL), was added a solution of pyrrolidine **16** (200 mg, 0.42 mmol). The reaction mixture was heated at 40 °C and monitored by TLC. After completion, the crude was filtered through a thin pad of celite®, and rinsed with dichloromethane (25 mL) followed by ethyl acetate (25 mL). Prior to evaporation of the solvents, HCl gas was bubbled into the solution. The crude chlorhydrate was then triturated in diethyl ether to afford the pure compound as a white solid (127 mg, 92%).

White solid; mp 93–95 °C (from $Et_2O$) (lit.,[4] 94 °C); Found: C, 76.45; H, 8.55; N, 4.25. Calc. for $C_{28}H_{28}ClN$: C, 76.35; H, 8.60; N, 4.23%; IR $\nu_{max}/cm^{-1}$ 2960 ($^+$N–H), 1590 (N–H), 1445 (C–N), 1032 (C–N); Crystal data: elongated rectangular cuboid of dimensions 0.59 × 0.18 × 0.16 mm, $C_{21}H_{28}N^+$, $Cl^-$, $M$ = 329.89, orthorhombic system, space group *Aba* 2, $Z$ = 4, $a$ = 25.438(2), $b$ = 10.6710 (5) Å, $c$ = 7.1250 (2) Å, $V$ = 1934.07 (19) Å$^3$, $D_{calcd}$ = 1.133 g cm$^{-3}$, $F(000)$ = 712, $\mu$ = 1.721 mm$^{-1}$, 12 865 collected reflections ($6.96° \leq \theta \leq 73.14°$), $-31 \leq h \leq 31$, $-12 \leq k \leq 8$, $-8 \leq l \leq 8$), 1894 independent reflections ($R_{int}$ = 0.0375), goodness-of-fit on $F^2$: $S$ = 1.136, $R_1$ = 0.0718 and w$R_2$ = 0.1763 for all 1891 reflections, $R_1$ = 0.0544 and w$R_2$ = 0.1467 for 1405 observed reflections [$I > 2\sigma(I)$], refining 131 parameters and 4 restraints on bond lengths with respect the pyrrolidine group, semi-empirical absorption correction from multi ω-scans ($T_{min}$ = 0.680, $T_{max}$ = 1.000), final electron density between −0.312 and 0.205 e Å$^{-3}$; $^1H$ NMR (400 MHz, $CDCl_3$) 2.08 (2H, m, $H_{3\alpha}$–$H_{4\alpha}$), 2.19 (2H, m, $H_{3\beta}$–$H_{4\beta}$), 2.26 (2H, m, $H_{6\beta}$–$H_{6'\beta}$), 2.52 (2H, m, $H_{7\beta}$–$H_{7'\beta}$), 2.58 (2H, m, $H_{6\alpha}$–$H_{6'\alpha}$), 2.63 (3H, s, $H_{6''}$), 2.79 (2H, m, $H_2$–$H_5$), 2.88 (2H, m, $H_{7\alpha}$–$H_{7'\alpha}$), 7.14–7.29 (10H, m, $H_{ar}$), 11.99 (1H, br, s, NH); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 27.10 ($C_3$–$C_4$), 30.90 ($C_6$–$C_{6'}$), 32.30 ($C_7$–$C_{7'}$), 36.65 ($C_{6''}$), 69.02 ($C_2$–$C_5$), 126.53 ($CH_{ar}$), 128.21 ($CH_{ar}$), 128.69 ($CH_{ar}$), 139.45 ($C_{ar}$); Low resolution mass spectroscopy (CI): *m*/*z* (%) 294.3 (100) $[M + H - Cl]^+$.

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