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ORIGINAL ARTICLE

Highly stable atropisomers by electrophilic amination of a chiral γ-lactam within the synthesis of an elusive conformationally restricted analogue of α-methylhomoserine

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Abstract Starting from chiral-protected 4-hydroxymethyl pyrrolidin-2-ones, the otherwise elusive 3,4-*trans*-3,3,4-trisubstituted isosteres of α-methyl homoserine, tethered on a γ-lactam ring, were prepared exploiting stereoselective electrophilic aminations. These reactions led to the isolation and characterization of a novel type of atropisomers, exceedingly stable at room temperature, that were directly converted to the desired products by a novel non-reductive N–N bond cleavage reaction.

Keywords Isosteres · γ-Lactams · Amination · Stereoselectivity · Atropisomers

Introduction

A promising approach in developing small useful peptidomimetics relies on restriction of either backbone or side chains of biologically active peptides, in order to obtain novel bioactive conformations (Al-Obeidi et al. 1998; Hruby and Balse 2000; Toniolo et al. 2001; Ahn et al. 2002; Bursavich and Rich 2002; Eguchi and Kahn 2002; Hruby 2002; Craik et al. 2002; Vagner et al. 2008; Wu and Gellman 2008; Grauer and Konig 2009; Zuckermann and Kodadek 2009; Matej et al. 2009; Hruby and Cai 2013; Avan et al. 2014). Within this topic, γ-lactams are of main concern and a lot of conformationally restricted analogues of amino acids tethered on this heterocyclic ring were introduced in bioactive peptides, often leading to isosteres displaying improved biological potency and selectivity with respect to the parent structures (Montaner et al. 2001; Freidinger 2003; Perdih and Kikelj 2006; Dolbeare et al. 2003; Galaud and Lubell 2005; Broadrup et al. 2005; Seufert et al. 2006; Otvos et al. 2007; Jamieson et al. 2009; Lesma et al. 2009; Virlouvet and Podlech 2010; St-Cyr et al. 2010; Boy et al. 2011). The γ-lactam core occurs in a variety of naturally occurring biologically active molecules (Bryskier 2005; Takao et al. 2007; Nay et al. 2009) such as Lactacystin (Gulder and Moore 2010) and Salinosporamide A (Shibasaki et al. 2007), potent inhibitors of the 20S proteasome and anticancer drug candidates. Moreover, γ-lactams are useful intermediates in the total synthesis of a number of biologically active non-peptidic compounds (Martelli et al. 2014a, b). Therefore, novel synthetic methodologies leading to highly substituted enantiopure analogues of amino acids tethered on γ-lactams, or to polyfunctionalised γ-lactams' backbones suitable for further transformations, deserve a large practical interest.

In the last years, we have synthesized conformationally constrained analogues of (*S*) and (*R*)-α-amino acids tethered on a pyrrolidin-2-one ring, having both a 3,4-*trans*- and a 3,4-*cis*-disubstitution (Galeazzi et al. 2003; 2005a, b; 2007), a 3,4,4-*trans*- and a 3,4,4-*cis*-trisubstitution,

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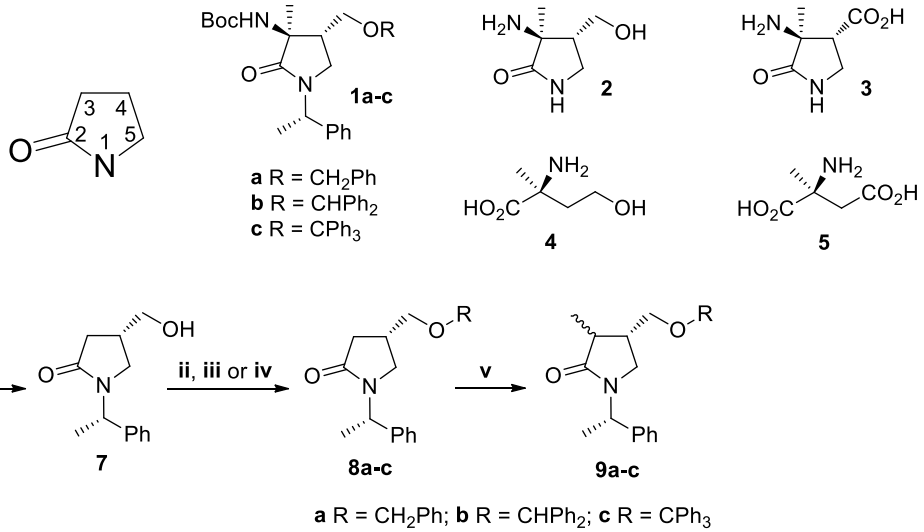


Fig. 1 Atom numbering for the generic γ-lactam cycle, target compounds **1**, conformationally constrained γ-lactam analogues **2** and **3**, (*S*)-α-methylhomoserine **4** and (*S*)-α-methylaspartic acid **5**

Scheme 1 **i** $LiAlH_4$, anhydrous THF, −23 °C: **7** 87 % yield. **ii** NaH, then BnBr, anhydrous DMF, rt: **8a** 82 % yield. **iii** Benzhydryl chloride, DIPEA, refluxing anhydrous DMF: **8b** 93 % yield. **iv** Trityl chloride, DIPEA, refluxing anhydrous DMF: **8c** 91 % yield. **v** TMP, *n*-BuLi, then MeI, anhydrous THF, −23 °C: **9a** 75 % yield (*trans*:*cis* = 81:19); **9b** 83 % yield (*trans*:*cis* = 80:20); **9c** 80 % yield (*trans*:*cis* = 70:30)

(Crucianelli et al. 2010) and a 3,3,4-*cis*-trisubstitution (Civitavecchia et al. 2014). Moreover, either foldamers displaying a stable secondary structure (Menegazzo et al. 2006; Galeazzi et al. 2011; Martelli et al. 2012) or a constrained analogue of dipeptide DG (Galeazzi et al. 2008) was prepared starting from β-amino acids tethered on γ-lactams, even in the β-peptoid form.

Results and discussion

Within a programme aimed to prepare isosteres of (*S*)-α-methylhomoserine, **4**, tethered on a γ-lactam ring, we report here the synthesis of **1**, the fully protected form of the 3,3,4-*trans*-trisubstituted analogue **2**. It is worth mentioning that other three diastereomeric analogues of this latter compound have already been obtained in our laboratory (Fig. 1). In fact, exploiting an alkylation–acylation–curtius rearrangement sequence (Civitavecchia et al. 2014), both the 3,3,4-*cis* diastereomers were easily prepared. In addition, an imine alkylation (Crucianelli et al. 2009) allowed to synthesize the protected compound **3**, a conformationally constrained analogue of (*S*)-α-methylaspartic acid **5**. However, since both approaches were ineffective for a practical and stereoselective synthesis of **1** that has remained so far elusive, a different synthetic strategy was planned.

Firstly, we devised **7** as a practical starting material, which was obtained in a more straightforward way with respect to the already-reported procedure (Galeazzi et al. 2003). Thus, by the reaction of itaconic acid and (*S*)-phenylethylamine according to a literature method (Nielsen et al. 1990), compound **6** was easily synthesized in a multigram scale, and subsequent reduction with lithium aluminium hydride afforded the hydroxymethyl derivative **7** in high yield (Scheme 1). Since problems arose when the dianion of **7** reacted with electrophiles (Galeazzi et al. 2003), we tested a homologous series of hydroxyl-protecting groups, with the aim of evaluating also the effect of the increasing steric hindrance at C-4 on the stereoselectivity of the following steps.

Thus, benzyl, benzhydryl and trityl ethers **8a–c** were prepared in very good yield by reaction with NaH and benzyl bromide in dry DMF for **8a** or with DIPEA (*N*,*N*-diisopropylethylamine) and the appropriate chloride in refluxing dry DMF for **8b** and **8c** (Scheme 1). Then, the methylation at C-3 of compounds **8a–c** was carried out by sequential addition of 0.5 equivalents of 2,2,6,6-tetramethylpiperidine (TMP) and 1.1 equivalents of n-BuLi and stoichiometric MeI to a solution of **8a–c** in anhydrous THF at −23 °C. The transient occurrence of a brownish colour during the n-BuLi dropwise addition, which persisted after one equivalent of added base, confirmed both the preliminary formation of LiTMP as the actual deprotonating reagent and its very rapid reaction with all the substrates **8a–c**.

The reactions proceeded in moderate to good yields to give, with low stereoselectivities, inseparable mixtures of 3,4-*trans* and 3,4-*cis* diastereomers **8a–c**, and the configuration of the main products was assigned as 3,4-*trans* by inspection of NOESY 1D spectra. We were not able to explain the anomalous small decrease in stereoselectivity with the increase in bulkiness of the ether-protecting group, which was in contrast with the previous data we obtained

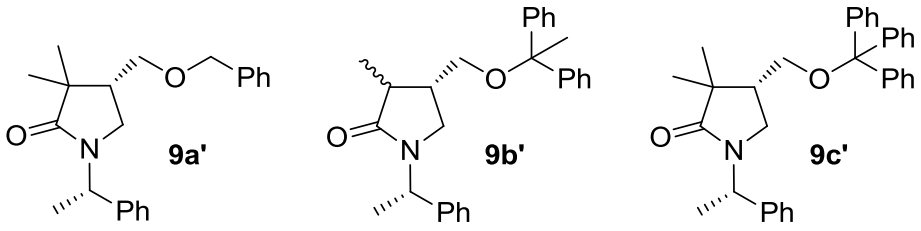


Fig. 2 By-products **9a′–c′** obtained in the methylation reactions of compounds **8a–c**

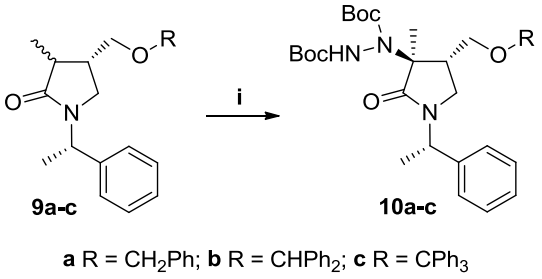
using silyl ethers having increasing bulkiness (Civitavecchia et al. 2014). However, either changes of reaction conditions, directed to attain a better stereoselectivity, or separation of the diastereomeric mixtures, were not required because the subsequent metalation step preceding the electrophilic amination leads to the same planar intermediate lithium enolate for both diastereomers.

An interesting and unexpected observation concerns the by-products arising from methylation of compounds **8a–c**. In fact, although only a stoichiometric amount of methyl iodide was used, dimethylated products were invariably isolated in low yield by chromatographic purification of the reaction mixtures (Fig. 2). However, while derivatives **9a′** (15 % yield) and **9c′** (11 % yield) were at some extent expected owing to further deprotonation of **9a** (or **9c**) by the unreacted Li-enolate or the excess LiTMP, followed by reaction with MeI, the formation of compound **9b′** (10 % yield, *trans*:*cis* = 62:38), due to reaction at benzhydrylic proton, was rather surprising. In addition, methylation of **8a** gave small traces of other not well-identified by-products, very probably having methyl groups added at the benzylic positions of the ether-protecting group or of the chiral auxiliary, as evidenced by the ^{1}H NMR spectra of less polar fractions after chromatographic separation. This preference, at least partial, for the generation of anions onto benzyl-type ethers with respect to a more acidic "expected" deprotonation site is quite rare in literature. In fact, some examples were reported only for the metalation of dithianes (Furuta et al. 2005, 2010) and for an attempted preparation of cyclopropane derivatives (van der Linden 1994). Eventually, the yields of by-products **9a′–c′** increased when the reactions were carried out at 0 °C (25, 18 and 21 % yields for **9a′**, **9b′** and **9c′**, respectively) with a concomitant decrease in the yields of the desired products (52, 66 and 61 % yields for **9a**, **9b** and **9c**, respectively). On the other hand, the addition of methyl iodide at −78 °C did not lead to any substantial improvement in comparison with the reaction at −23 °C.

Whereas the above-reported behaviour is not important *per se*, since practical amounts of the pure desired compounds could be anyway easily obtained, problems could arise in the subsequent electrophilic amination reactions carried out on the corresponding lithium enolates. In effect, in **9a–c** the 3,4-*trans* relative configuration is always predominating, so that protons on C-3 that must be abstracted by the base mainly lie on the same side of the substituent at C-4. This should slow down the enolate formation, thus favouring any other side reaction.

In fact, the amination reaction carried out with di-*tert*-butyl azodicarboxylate (DBAD) was unexpectedly challenging, since attempted deprotonation of **9a** with LiHMDS, followed by DBAD addition, resulted in no reaction at −78 °C and only in slow decomposition of starting material and DBAD when temperature was raised to 0 °C or room temperature. In addition, when the reported conditions were used (Evans et al. 1986; Trimble and Vederas 1986) and preformed LiTMP was added at −78 °C for 15 min, followed by dropwise addition of DBAD dissolved in THF, only traces of the desired compound **10a** were present in the reaction mixture and about 70 % of starting **9a** was recovered after chromatographic purification. Interestingly, from the TLC analysis of commercial DBAD and a comparative trial with LiTMP but without the starting compound, we ascertained that almost all the by-products observed in the reactions were already present in di-*tert*-butyl azodicarboxylate or were generated by the reaction with LiTMP and the following workup.

Thus, we purified the electrophile by flash chromatography on oven-dried silica gel and subsequent azeotropically drying with anhydrous THF (see "Experimental" section). Treatment at 0 °C for 15 min with either in situ generated or preformed LiTMP, followed by cooling at −78 °C and dropwise addition of pure DBAD dissolved in THF, led always to an almost complete conversion of **9a**. However, product **10a** was invariably obtained in only 23–25 % yield, together with a lot of unidentified by-products. We have already noted (Civitavecchia et al. 2014) this tendency to give an unsatisfying yield when a similar lithium enolate bearing a methyl group at C-3 was treated with another reactive and planar electrophile, methyl chloroformate, in striking contrast with the high yield obtained in the same reaction starting from the corresponding C-3 unmethylated analogue. All these observations are in agreement with the aforementioned tendency to the generation of by-products when the pyrrolidinonic C-3 already bears a methyl substituent. However, when the electrophilic amination was carried out metalating at −23 °C with in situ generated LiTMP, followed by slow addition at −78 °C of purified



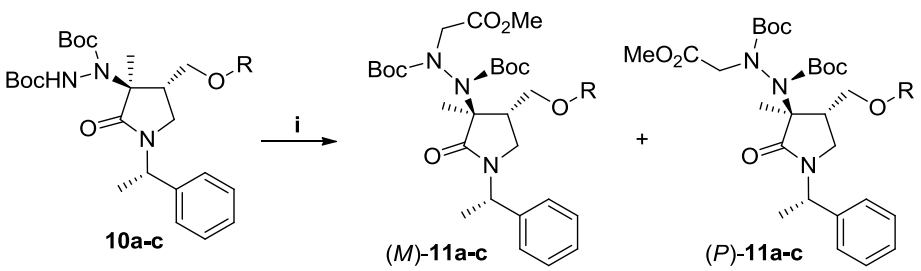
Scheme 2 **i** TMP, n-BuLi, anhydrous THF, −23 °C, then DBAD in anhydrous THF, −78 °C: **10a** 36 % yield; **10b** 41 % yield; **10c** 45 % yield

DBAD dissolved in THF, product **10a** was obtained in 36 % yield (Scheme 2). Unfortunately, when the metalation was performed at −78 °C, the yield was not further improved. Exploiting the preceding methodology, but starting from compounds **9b** and **9c**, the corresponding aminated products **10b** and **10c** were obtained in 41 and 45 % yields, respectively.

We wish to emphasize here that configurations of products **10a**–**c**, reported in Scheme 2, were definitively assigned after the derivatisation reported below. In fact, the presence in ^{1}H and ^{13}C NMR spectra of at least three sets of broad signals for most of the protons and carbons of pure products prevented to assign with certainty both stereochemistry and diastereomeric ratios. As an example, for **10a** the NH resonances at 6.66, 6.61, 6.31 and 6.15 ppm were about in a 1.18:4.45:1.55:1 ratio and were compatible both with four rotamers for a single diastereomer and with two or three rotamers for a diastereomer plus one or two rotamers for the other diastereomer. Due to the extremely broad signals, the uncertainty about diastereoselectivity remained also after the NOESY 1D and ROESY experiments, even if the major set of resonances seemed to be likely assigned to the expected 3,3,4-*trans* isomer. However, this behaviour was not unexpected, owing to the probably slow rotation around N–N, N–C-3 and N–C(=O) bonds due to either the high steric congestion and the partial double-bond character of N–C(=O) bonds in carbamate moieties. Eventually, HPLC elution on both an achiral reverse phase C18 column and a chiral OD-H column suggested the presence of a highly predominating (**10a**, ratio of areas $A_{trans\text{-}\mathbf{10a}}$:$A_{cis\text{-}\mathbf{10a}}$ = 92:8), or a sole (**10b** and **10c**), 3,3,4-*trans*-trisubstituted product. Although from a theoretical point of view a single HPLC peak could be ascribed either to a single diastereomer or to a completely unresolved mixture, this can hardly apply to the present case. Indeed, especially using the chiral OD-H column, the two peaks for **10a** were very well separated (see "Experimental" section). Thus, a perfect superimposition in the case of a diastereomeric mixture for both **10b** and **10c**, which differ from **10a** only in the dimension of protecting groups, seemed to be extremely unlikely. Moreover, the fact that two structurally different columns (achiral RP-C18 and chiral OD-H) gave the same results strongly strengthened our conclusions.

The subsequent cleavage of the N–N bond was chosen both to remove traces of the undesired 3,3,4-*cis* diastereomer from **10a** and to prepare fully protected compounds **1a**–**c**. In fact, from our previous experiences with *trans*/*cis* diastereomeric mixtures of a lot of 3,4-disubstituted and 3,3,4-trisubstituted compounds tethered on a γ-lactam ring reported above, we noted that in the presence of hydrogen bond donating functionalities the diastereomers were almost always chromatographically inseparable. This observation, together with the need for a chemoselective methodology not affecting protecting groups, led us to exclude traditional reductive methods (Feuer and Brown 1970; Mellor and Smith 1984; Jacobi et al. 1984; Brimble and Heathcock 1993; Alonso et al. 2000; Chandrasekhar et al. 2001; Ding and Friestad 2004; Sinha et al. 2006) and to use instead a modification of an already-reported eliminative N–N cleavage (Magnus et al. 2009).

Thus, at first compounds **10a**–**c** were treated with NaH in dry THF followed by *N*-alkylation with methyl bromoacetate, to give a smooth and clean reaction and a further unexpected result (Scheme 3). In fact, starting from **10b** and **10c**, we obtained two products with very different relative mobility (*Rf*) on silica gel TLC, whereas **10a** gave two highly predominating compounds accompanied by very small traces of two other species, again with notably different *Rf*. At first, these results seemed to be in whole contrast with the supposed diastereomeric purity of starting compounds **10b**–**c** and the high diastereomeric enrichment of **10a**, mainly because under the reaction conditions the



Scheme 3 **i** NaH, then $BrCH_2CO_2Me$, anhydrous THF, rt: (*M*)-**11a** 63 % yield, (*P*)-**11a** 26 % yield; (*M*)-**11b** 51 % yield, (*P*)-**11b** 40 % yield; (*M*)-**11c** 53 % yield, (*P*)-**11c** 44 % yield

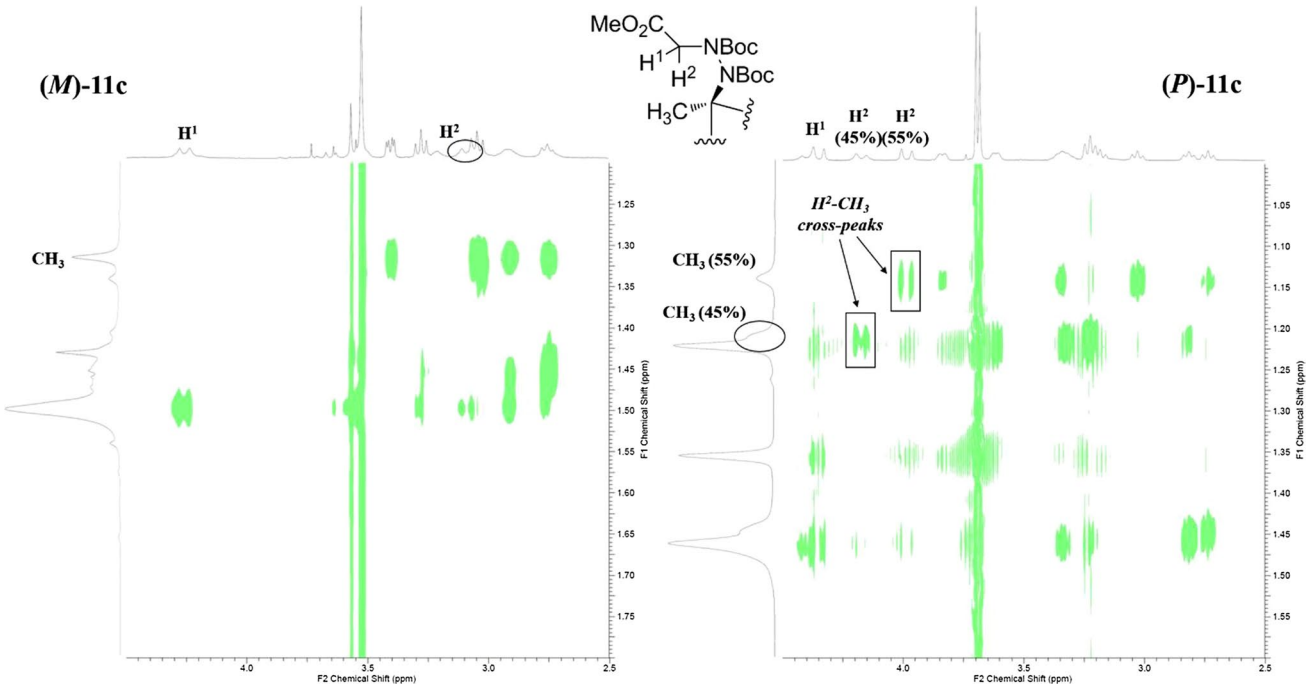


Fig. 3 Details of ROESY experiments for (*M*)-**11c** (*left*) and (*P*)-**11c** (*right*). *Circles* on ^{1}H spectra indicate peaks of interest that are superimposed with other peaks, and rectangles on the right ROESY *spectrum* indicate decisive cross-peaks. The assignment as H^1 and H^2 is arbitrary

epimerization should be impossible. However, this behaviour could be ascribed to the presence of stable atropisomers, as depicted in Scheme 3, where congestion due to changing from NH to N-alkyl group leads to a completely hindered rotation around the chirality axis (the N–N single bond), in (*M*)- and (*P*)-**11a–c**.

The axial chirality indicated in Scheme 3 and used throughout the article (*M* for all the first eluted and *P* for all the second eluted compounds) has been ascertained by the coupled NMR–computational approach described below, due to the fact that no crystalline compound suitable for crystallographic analysis has been obtained. From a synthetic point of view, the assignment of configuration around the chirality axis could be considered unimportant, because it will be lost after the eliminative cleavage. On the other hand, it deserves remarkable interest owing to both the novelty of this type of extremely stable atropisomers, having a hindered N–N bond between two non-heteroaromatic and in general non-heterocyclic moieties, and the possible future applications as chiral catalysts, after appropriate derivatisation.

Thus, after chromatographic separation, we have undertaken exhaustive mono- and bidimensional NMR analysis of all compounds **11a–c**, coupled with a computational approach. Inspection of ^{1}H and ^{13}C spectra highlighted very similar signals patterns among all the first eluted atropisomers ((*M*)-**11a–c**) that evidenced also the presence of two rotamers in about a 3:1 ratio, and the same occurred, but with about a 1.5:1 ratio, for all the second eluted (*P*)-**11a–c** atropisomers. However, only the atropisomers of **11c** furnished reliable ROESY spectra suitable for our goal, because in these cases the signals of methyl groups on the pyrrolidinonic C-3 atoms, critical to obtain the desired cross-peaks, were sufficiently deshielded and thus not completely covered by the methyl protons of Boc groups (Fig. 3). In fact, only for the minor rotamer of (*P*)-**11c** the methyl signal at about 1.21 ppm appeared as a shoulder, but its corresponding cross-peaks remained well distinguishable from the ones of the superimposed signal of the major rotamer of a Boc group.

As reported in Fig. 3, both the methyl signals at 1.14 ppm (major rotamer) and 1.21 ppm (minor rotamer) gave evident cross-peaks with the corresponding doublets at 3.99 ppm (major rotamer) and 4.18 ppm (minor rotamer) of one of the two protons of CH_2CO_2Me moiety, arbitrarily indicated as H^2. Conversely, neither H^1 nor H^2 of (*M*)-**11c** highlighted no cross-peaks, confirming the different positioning of this methylene group in the two atropisomers and thus the possibility to make the desired comparison between the experimental and computational results.

Our computational approach was chosen based on some simple observations. Firstly, the most obvious alternative, that is molecular dynamics, was not suitable since an *ad hoc* parametrization for the whole di-*tert*-butyl hydrazinedicarboxylate fragment is lacking in every force field. On the other hand, a complete conformational analysis

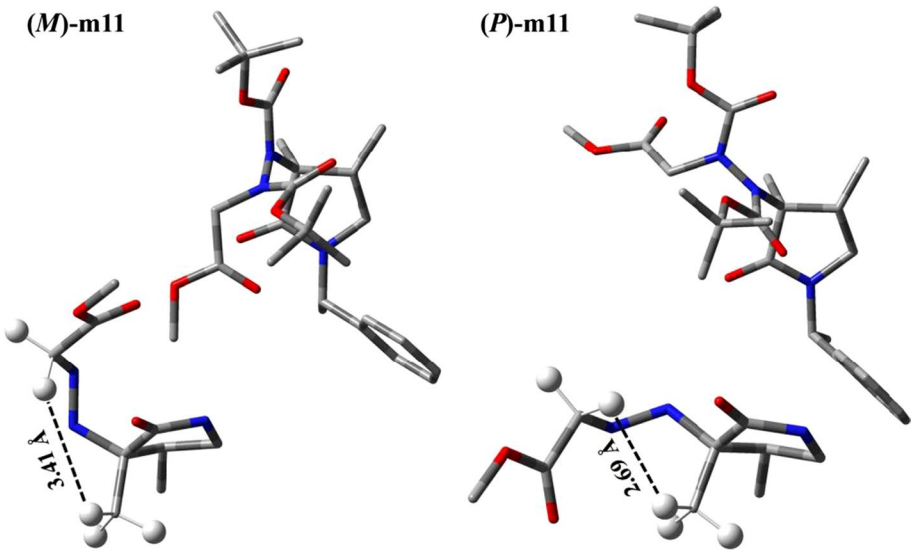


Fig. 4 Most stable conformers, computed at M06-2X/6-311G(d,p) level, for model (*M*)-**m11** (*left*) and (*P*)-**m11** (*right*) atropisomers (unnecessary hydrogens omitted for clarity), with details of distances relevant for comparisons with ROESY experiments

with ab initio and DFT techniques would have been tremendously time consuming, albeit energetically accurate, owing to both molecular size and number of rotatable bonds. Thus, in order to compare the experimentally obtained ROESYs with the ones expected from calculations, we decided to use PM3 semiempirical method (Stewart 1989a, b) for preliminary calculations on model (*M*) and (*P*)-**m11** atropisomers, where the alkoxymethyl substituent at C-4 was changed for a methyl group. All the minima were then submitted at B3LYP/6-31G(d) level calculations (Becke 1993; Lee et al. 1988), and the search for the most stable conformers was completed by the appropriate rotations of substituents (see the Supporting Material for a detailed methodological description and for optimized geometries and energies). Eventually, only the limited subsets of structures within 2 kcal/mol above the two global minima for both atropisomers were refined at M06-2X/6-311G(d,p) (Zhao and Truhlar 2006) level. All calculations were performed with Gaussian 09 (Gaussian 09, Revision E.01, Frisch et al. 2009).

The results obtained by DFT calculations clearly highlighted that, for both atropisomers, the substituents onto hydrazidic nitrogens have the expected approximate orthogonal arrangement in all conformers. However, there are two strikingly different dispositions of the hydrazidic moiety bonded to the pyrrolidinonic C-3 atom for the most stable conformers of *M* and *P* atropisomers (Fig. 4). In fact, in the global minimum for (*M*)-**m11** the N–N bond is roughly synperiplanar with the C(=O)–C-3 bond of γ-lactam ring, the dihedral angle being 35°, while in (*P*)-**m11** the N–N bond is almost perfectly synperiplanar with the C-3-Me bond and the relative dihedral is only 6°. The different distances between the nearest hydrogen atoms of CH_2CO_2Me and C-3-CH_3 groups, that are 3.41 Å and 2.69 Å for *M* and *P* isomers (Fig. 4), respectively, furnished an easy tool to discern the atropisomers on the basis of experimental ROESYs (Fig. 3).

In particular, for the computed most stable conformer of *P* atropisomer an evident cross-peak is expected even in the case of the quite broad signals in the experimental ^{1}H spectra, in perfect agreement with the observed ROESYs. On the contrary, the greater interproton distance in the case of *M* atropisomer should result in a complete lack of signal or, at the most, in a very low one, thus allowing the safe assignment of the *M* and *P* configurations to all the first and second eluted atropisomers, respectively (Fig. 3). It is noteworthy that the certainty of the reported assignment further increases considering the other conformers that follow the two global minima in the order of stability for both the M06-2X/6-311G(d,p) and B3LYP/6-31G(d) computations (see discussion and Cartesian coordinates in Supplementary Material).

With the aim of quantitatively determining the thermal stability of atropisomers, which is a crucial feature in view of a synthesis of chiral catalysts, we have undertaken simple kinetics experiments aimed to evaluate the possibility of interconversion between *M* and *P* isomers. It should be noted firstly that atropisomers generated by hindered rotation around an N–N single bond are relatively rare in literature, and mostly limited to nitrogen atoms tethered on heteroaromatics, or in general on heterocyclic compounds (Alkorta et al. 2012). In the few cases reported of structures similar to **11a–c**, they were metastable if compounds were not in the solid state, as already observed for various acyclic tetraacyl hydrazines (Platts and Coogan 2000; Coogan and Passey 2000; Arthur et al. 2009), and some stereostability occurred only when one or both nitrogen atoms were tethered on a planar cyclic fragment. For example, the most stable atropisomers were found among diacyl or acylphenyl derivatives of *N*-aminocamphorimides, for which

free energy barriers for N–N rotation of 96–100 kJ mol^{-1} were estimated (Verma and Prasad 1973), and in 3,3′-biquinazoline-4,4′-diones with an additional bridging ($t_{1/2} \approx 24$ h at 110 °C). Nevertheless, they were again completely labile at room temperature, with a barrier of about 85 kJ mol^{-1}, when the bridging was missing (Coogan et al. 1999; Coogan and Passey 2000). Even in the case of the sterically encumbered lactic acid derivative of tetraacyl hydrazine (Arthur et al. 2009), an experimental free energy barrier of merely 83 kJ mol^{-1} confirmed the theoretical findings about the simple tetraformylhydrazine (Platts and Coogan 2000). The computational analysis demonstrated that for unbridged compounds there is the possibility to circumvent the excessively high barrier for the direct rotation around the N–N bond in the most stable conformer. Indeed, starting from a value of more than 140 kJ mol^{-1}, found for the direct rotation of tetraformylhydrazine N–N bond, the barrier was calculated to be only 77 kJ mol^{-1} after preliminary rotations about two N–C amide bonds.

In striking contrast, since our compounds do not have nitrogen atoms tethered on heterocycles, at a first glance they appear unable to properly direct the carbonyl groups and the other substituents to give an extremely high rotational barrier. However, simple TLC controls evidenced that they were stable for more than 3 months at room temperature in their standard state (viscous oil or waxy solid) or in solution of dichloromethane or ethyl acetate. Thus, we performed preliminary experiments submitting (*M*)-**11a** to 24-h reflux in cyclohexane (81 °C) and toluene (111 °C) solutions, but no equilibration occurred in the former case, while only traces of epimerization were evidenced by TLC in the latter case. Then, we decided to use xylenes' mixture (boiling point 138–140 °C) as the solvent for kinetics on pure (*M*) and (*P*)-**11a** and to analyse by HPLC the samples, taken at the appropriate intervals, after previous determination of the response factor *F* on mixtures of known composition (see details in the "Experimental" section) (Scheme 4).

The most likely kinetic scheme for the interconversion of atropisomers is a reversible process where the reaction is simple first order in both directions, with rate constants k_1 and k_1' for the forward and backward reactions, respectively (Eq. 1). Species A and B are (*M*)-**11a** and (*P*)-**11a** in the kinetic experiment carried out starting from pure (*M*)-**11a**, with $k_{M\text{-}P} = k_1$ and $k_{P\text{-}M} = k_1'$ while the contrary apply starting from the pure *P* atropisomer.

$$\mathrm{A} \underset{k_1'}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \tag{1}$$

When the initial concentration of B at time $t = 0$ is null ($[\mathrm{B}]_0 = 0$), the concentration at every time t is given by Eq. 2, where $[\mathrm{A}]_0$ is the initial concentration of A, that is to say that [B] rises with exponential growth until its equilibrium value and the reaction behaves like a first order with $(k_1 + k_1')$ as the rate constant (Upadhyay 2006).

$$[\mathrm{B}] = \frac{k_1[\mathrm{A}]_0}{k_1 + k_1'}\left(1 - \mathrm{e}^{-(k_1 + k_1')t}\right) \tag{2}$$

An alternative way of writing Eq. 2, useful to directly obtain the equilibrium value $[\mathrm{B}]_{eq}$ and k_1 from the interpolation of experimental data by nonlinear regression, is given in Eq. 3.

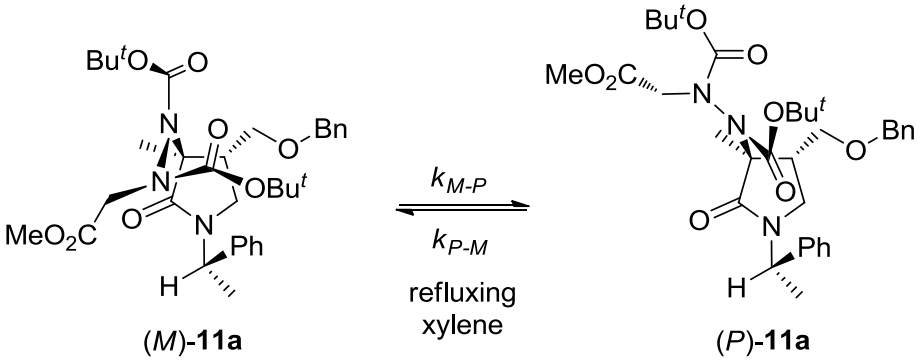
$$[\mathrm{B}] = [\mathrm{B}]_{eq}\left(1 - \mathrm{e}^{-\left(\frac{[\mathrm{A}]_0}{[\mathrm{B}]_{eq}}k_1\right)t}\right) \tag{3}$$

In the same way, the concentrations of [A] at various times follow an exponential decay to the equilibrium concentration $[\mathrm{A}]_{eq}$, with the same overall rate constant $(k_1 + k_1')$ (Szabo 1969).

$$[\mathrm{A}] = \frac{[\mathrm{A}]_0}{(k_1 + k_1')\left(k_1\mathrm{e}^{-(k_1 + k_1')\mathrm{t}} + k_1'\right)} \tag{4}$$

Eventually, the equilibrium constant K_{eq} can be easily computed exploiting Eq. 5, where either the extrapolated equilibrium concentrations or the rate constants can be used.

Scheme 4 Equilibration of (*M*) and (*P*)-**11a** in refluxing xylene



$$K_{eq} = \frac{k_1}{k_1'} = \frac{[B]_{eq}}{[A]_{eq}} \quad (5)$$

The fitting of experimental data reported in Fig. 5 by nonlinear regression always gave correlation coefficients $R^2 > 0.99$, and the computed values for $k_{M\text{-}P}$, $k_{P\text{-}M}$ and K_{eq} were, respectively, $k_{M\text{-}P} = 0.116 \pm 0.002$ min^{-1}, $k_{P\text{-}M} = 0.021 \pm 0.001$ min^{-1} and $K_{eq} = 5.56$ from the equilibration of (*M*)-**11a** atropisomer and $k_{M\text{-}P} = 0.121 \pm 0.003$ min^{-1}, $k_{P\text{-}M} = 0.022 \pm 0.001$ min^{-1} and $K_{eq} = 5.59$ from the equilibration of (*P*)-**11a** atropisomer.

The rate constants for the interconversion of one atropisomer into the other, $k_{M\text{-}P}$ and $k_{P\text{-}M}$, and the overall constant for the equilibration process ($k_{M\text{-}P} + k_{P\text{-}M}$), allowed us to estimate the corresponding free energy barriers ($\Delta G^{\#}$) by means of the Eyring equation (Eyring 1935) (Eq. 6), where *R* is the gas constant, T is the reaction's temperature, *k* is the opportune rate constant, h is the Planck's constant, k_B is the Boltzmann's constant and a transmission coefficient of unity in the transition state theory was assumed.

$$\Delta G^{\#} = -RT \ln\left(\frac{kh}{k_B T}\right) \quad (6)$$

Using a temperature of 412.15 K (139 °C) and the mean values for $k_{M\text{-}P} = 0.1185$ min^{-1} (1.975×10^{-3} s^{-1}), $k_{P\text{-}M} = 0.0215$ min^{-1} (3.583×10^{-4} s^{-1}) and ($k_{M\text{-}P} + k_{P\text{-}M}$) = 0.140 min^{-1} ($2.333 \times 10^{-3}$ s^{-1}), the estimated barriers were 123.4 kJ/mol for the conversion from *M* to *P* atropisomer, 129.2 kJ/mol for the conversion from *P* to *M* atropisomer and 122.8 kJ/mol for the overall equilibration process. These values are quite impressive if compared to the ones reported above for other hydrazine derivatives with unbridged N atoms. In fact, they are more than 20 kJ/mol higher with respect to the largest values measured in literature, but in perfect agreement with the experimental stability of atropisomers **11a–c** for months, both as pure compounds and in solution. Assuming an approximate constancy of $\Delta G^{\#}$ with temperature and rearranging Eq. 6 to obtain the rate constants at room temperature, we found $k_{M\text{-}P298} = 4.717\ 10^{-2}$ year^{-1} (1.496×10^{-9} s^{-1}), $k_{P\text{-}M298} = 4.439 \times 10^{-3}$ year^{-1} (1.408×10^{-10} s^{-1}) and $(k_{M\text{-}P} + k_{P\text{-}M})_{298} = 5.161 \times 10^{-2}$ year^{-1} (1.637×10^{-9} s^{-1}). The corresponding estimated half-lives were then 14.69 years [from (*M*) to (*P*)-**11a**], 156.1 years [from (*P*) to (*M*)-**11a**] and 13.43 years for the overall equilibration process.

Having demonstrated that isomers of **11a–c** are undoubtedly two atropisomers with an unexpected, extreme stability at room temperature, we proceeded to the final N–N bond cleavage exploiting a variant of the Cs_2CO_3/refluxing MeCN methodology (Magnus et al. 2009). We preferred to avoid cesium carbonate because of its hygroscopicity and

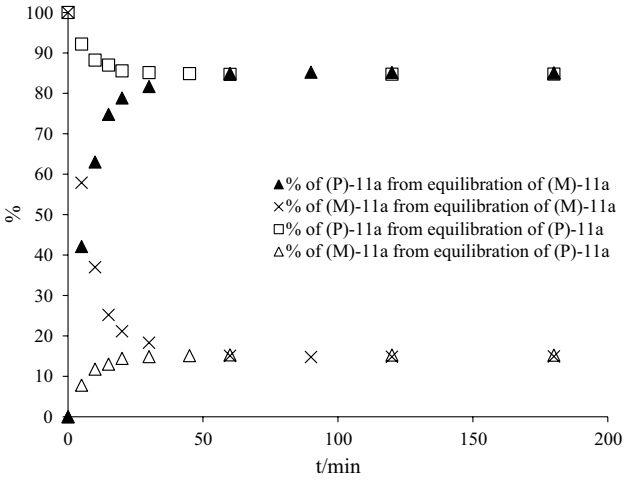


Fig. 5 Results of kinetic experiments on pure (*M*)-**11a** and (*P*)-**11a**

of the occurrence of a partial decomposition in preliminary trials on atropisomers of **11b**, which became extensive on the trityl-protected compounds **11c**.

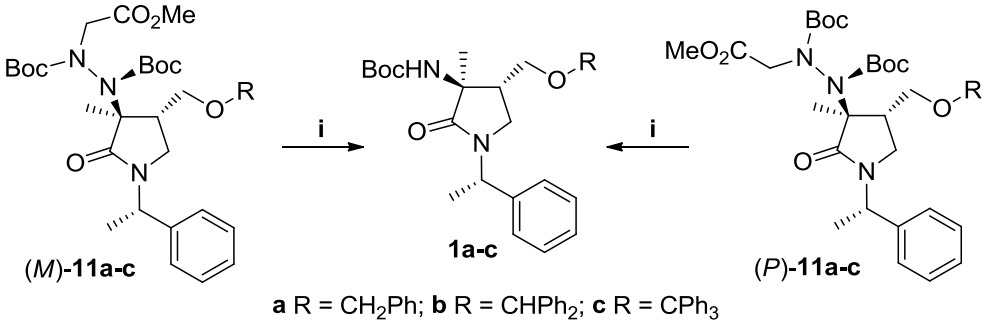
Then, by simple treatment with LiHMDS in anhydrous THF, diastereomerically pure compounds **1a-c**, the fully protected mimetics of (*S*)-β-methylhomoserine, were obtained in satisfying yield without a thorough optimization of reaction conditions (Scheme 5), and configuration at γ-lactam C-3 was definitely confirmed by means of NOESY 1D experiments.

Conclusions

We reported here the stereoselective synthesis of the otherwise elusive fully protected conformationally constrained isosteres of α-methyl homoserine, **1a–c**, tethered on a γ-lactam ring, exploiting the electrophilic amination reaction of a lithium enolate followed by eliminative N–N bond cleavage. Eventually, we observed the formation of atropisomers displaying an unprecedented stability around the N–N single bond, with completely hindered rotation due to the *N*-alkylation step preceding the eliminative cleavage. This last behaviour can be of great interest and will be the subject of future studies, directed towards the synthesis of other atropisomeric compounds based on a γ-lactam structure and, after a suitable derivatisation, of chiral catalysts exploiting this kind of axial chirality.

Experimental

Melting points were obtained on an Electrothermal apparatus IA 9000 and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined on a Varian MR400 spectrometer, at 400 and 100 MHz for ^{1}H and ^{13}C, respectively,



Scheme 5 (**i**) LiHMDS, anhydrous THF, 0 °C, then rt: **1a** 75 % yield from (*M*)-**11a**, 70 % yield from (*P*)-**11a**; **1b** 69 % yield from (*M*)-**11b**, 76 % yield from (*P*)-**11b**; **1c** 81 % yield from (*M*)-**11c**, 74 % yield from (*P*)-**11c**

in $CDCl_3$ unless otherwise reported. Chemical shifts are reported in ppm relative to residual solvent signals ($\delta = 7.26$ and 77.16 ppm for ^1H and ^{13}C NMR, respectively), and coupling constants (*J*) are given in Hz. Optical rotations, $[\alpha]_D$, were recorded at room temperature on a Perkin-Elmer Model 241 polarimeter at the sodium D line (concentration in g/100 mL). LC electrospray ionization mass spectra were obtained with a Finnigan Navigator LC/MS single-quadrupole mass spectrometer, cone voltage 25 V and capillary voltage 3.5 kV, injecting samples dissolved in methanol. Elemental analyses were performed with a Carlo Erba CHN Elemental Analyser. Column chromatography was performed using Kieselgel 60 Merck (230–400 mesh ASTM). The pure compounds for kinetic experiments ((*M*)-**11a** and (*P*)-**11a**) were obtained from a further chromatographic purification with cyclohexane and ethyl acetate distilled under vacuum. Tetrahydrofuran and DMF were distilled from sodium-benzophenone and P_4O_{10}, respectively, under an argon atmosphere. DBAD was purified by flash chromatography on oven-dried silica gel, using a 98:2 mixture of cyclohexane and ethyl acetate dried on anhydrous Na_2SO_4 as the eluent. After evaporation at reduced pressure and room temperature of eluents, pure DBAD was azeotropically dried for three times by dissolution in anhydrous THF followed by *in vacuo* evaporation, then the flask was filled with argon and stored at −18 °C. Xylenes' mixture was distilled from sodium under an argon atmosphere, and only the central fraction (boiling point 138–140 °C) was used for kinetics. Column chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM) unless otherwise specified. The TLC analysis was performed with sheets of silica gel Fluka TLC-PET, using exposure to UV light and immersion in aqueous $KMnO_4$, followed by heating and by possible immersion in H_2SO_4 9 M. The cooling baths at −23 °C were obtained using both ice and acetone precooled at −18 °C in a freezer. To eliminate traces of eluents from the pure chromatographed products, these were submitted for three times to the dissolution in a few millilitres of anhydrous dichloromethane, followed by *in vacuo* evaporation. Diastereomerically pure compound **6** was obtained according to Nielsen et al. (1990). The kinetics were performed by rapidly adding 0.5 mL of a stock 0.1 M solution of pure compounds [(*M*)-**11a** or (*P*)-**11a**] in xylenes to a refluxing 4.5 mL xylenes' mixture. At suitable times, 100 μL was rapidly taken, evaporated under vacuum at room temperature and dissolved in 1 mL of n-hexane:2-propanol 95:5 solution. The samples were injected in a Hewlett-Packard 1100 chromatograph equipped with a Daicel Chiralcel OD-H column and a diode-array UV detector ($\lambda = 210$ nm), eluting with n-hexane:2-propanol 99:1 with a flow rate of 0.5 mL/min [$t_R = 37.1$ [(*P*)-**11a**], 43.0 [(*M*)-**11a**] min]. The percentages of atropisomers at various times were obtained correcting the experimentally observed percent areas with the response factor $F = (A_{(M)\text{-}\mathbf{11a}}/M_{(M)\text{-}\mathbf{11a}})/(A_{(P)\text{-}\mathbf{11a}}/M_{(P)\text{-}\mathbf{11a}})$, where A and M are percent areas and molarities, respectively. The response factor $F = 1.47 \pm 0.03$ was formerly determined from the injection of 5 samples with known concentration ratios $M_{(M)\text{-}\mathbf{11a}}/M_{(P)\text{-}\mathbf{11a}}$ (0.1, 0.5, 1, 5, 10) for a total concentration $M_{(M)\text{-}\mathbf{11a}} + M_{(P)\text{-}\mathbf{11a}} = 1$ mM. The known samples were obtained by appropriate dilutions of the stock 0.1 M solutions of pure compounds [(*M*)-**11a** and (*P*)-**11a**) with an n-hexane:2-propanol 95:5 solution. Compounds **7**, **8a–c**, **9a′**, **9c′**, (*M*)-**11a–c**, (*P*)-**11a–c** and **1a-c** were characterized as diastereomerically pure by careful examination of their ^1H and ^{13}C NMR spectra, because no peaks ascribable to diastereomers were visible within the limits of detection. Compounds **10b** and **10c** were characterized as diastereomerically pure by careful examination of their HPLC traces relative to two different columns (chiral OD-H column and achiral RP-C18 column), where no peaks ascribable to diastereomers were visible within the limits of detection, and by subsequent derivatisation (see "Results and discussion" section).

(*S*)-4-(Hydroxymethyl)-1-((*S*)-1-phenylethyl) pyrrolidin-2-one, 7

To a solution of compound **6** (16.1 g, 65 mmol) in anhydrous THF (300 mL) under inert atmosphere at -23 °C, $LiAlH_4$ (2 M in THF, 19.5 mL, 39 mmol) was slowly added under vigorous stirring. After 1 h, the reaction was quenched by sequential slow addition of methanol (10 mL) and HCl 6 M (25 mL), then all the volatiles were removed under vacuum. The residue was dissolved in ethyl acetate (500 mL) and HCl 0.5 M (300 mL) and then, after separation, the organic phase was washed with HCl 1 M (3 × 50 mL) and water (50 mL). The unified aqueous phases were newly extracted with ethyl acetate AcOEt (500 mL) and, after separation, the organic phase was washed with HCl 1 M (3 × 50 mL) and water (50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate) to give diastereomerically pure compound **7** in 87 % yield (12.5 g, 56.55 mmol) as a low melting white solid. The identity of compound **7** was confirmed by comparison of the ^{1}H NMR data with the ones of its enantiomer synthesized in Fava et al. (1999). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, J = 7.0 Hz, 3H), 2.21–2.28 (m, 1H), 2.33–2.56 (m, 3H), 3.05 (dd, J = 7.6 Hz, J = 9.8 Hz, 1H), 3.17 (dd, J = 5.4 Hz, J = 9.8 Hz, 1H), 3.55 (dd, J = 6.6 Hz, J = 10.8 Hz, 1H), 3.62 (dd, J = 5.6 Hz, J = 10.8 Hz, 1H), 5.47 (q, J = 7.0 Hz, 1H), 7.18–7.43 (m, 5ArH).

(*S*)-4-((Benzyloxy)methyl)-1-((*S*)-1-phenylethyl) pyrrolidin-2-one, 8a

To a solution of compound **7** (4.98 g, 22.6 mmol) in anhydrous DMF (68 mL) under inert atmosphere at room temperature, NaH (60 % dispersion in mineral oil, 1.36 g, 34 mmol) was added under vigorous stirring. After 10 min, benzyl bromide (4.14 mL, 34 mmol) was added and the mixture was stirred for 3 h, then the reaction was diluted with a 1:1 cyclohexane:ethyl acetate solution (400 mL) and water (400 mL). After separation, the organic phase was washed with water (3 × 50 mL), then the combined aqueous phases were newly extracted with a 1:1 cyclohexane:ethyl acetate solution (400 mL). After separation, the organic phase was washed with water (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, then the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30) to obtain diastereomerically pure compound **8a** in 82 % yield (5.76 g, 18.54 mmol) as a colourless oil. The identity of compound **8a** was confirmed by comparison of the ^{1}H NMR data with the ones of its enantiomer synthesized in Galeazzi et al. (2003). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J = 7.0 Hz, 3H), 2.20–2.28 (m, 1H), 2.47–2.58 (m, 2H), 3.08 (dd, J = 7.4 Hz, J = 9.8 Hz, 1H), 3.15 (dd, J = 5.1 Hz, J = 9.8 Hz, 1H), 3.37 (dd, J = 7.4 Hz, J = 9.0 Hz, 1H), 3.44 (dd, J = 5.1 Hz, J = 9.0 Hz, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 5.48 (q, J = 7.0 Hz, 1H), 7.24–7.37 (m, 10ArH).

(*S*)-4-((Benzhydryloxy)methyl)-1-((*S*)-1-phenylethyl) pyrrolidin-2-one, 8b

To a solution of compound **7** (3.3 g, 15 mmol) in dry DMF (15 mL) at room temperature, DIPEA (5.65 mL, 33 mmol) and benzhydryl chloride (6.08 g, 30 mmol) were sequentially added. The reaction mixture was stirred at reflux for 1 h, cooled at room temperature and diluted with an Na_2CO_3 saturated solution (20 mL), a cyclohexane:ethyl acetate 1:1 solution (400 mL) and water (200 mL). After separation, the organic phase was washed with water (3 × 100 mL). The unified aqueous phases were extracted with additional 400 mL of cyclohexane:ethyl acetate 1:1 solution and, after separation, the organic phase was washed with water (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, concentrated under vacuum and dissolved in 150 mL of cyclohexane:dichloromethane 9:1 solution. After addition of 3 g of activated charcoal, the mixture was gently stirred overnight, filtered through Celite and washed thoroughly with a cyclohexane:dichloromethane 9:1 solution (20 mL) and then with cyclohexane (3 × 20 mL). The solvents were eliminated under vacuum, and the crude product was purified by silica gel chromatography (cyclohexane:ethyl acetate 75:25) to afford diastereomerically pure compound **8b** in 93 % yield (5.38 g, 13.97 mmol) as a colourless viscous oil. NOTE: occasionally, the chromatographed product resulted brownish and susceptible to a very slow decomposition if stored at room temperature. In these cases, the product was submitted to another purification with activated charcoal. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, J = 7.0 Hz, 3H), 2.23–2.31 (m, 1H), 2.51–2.59 (m, 2H), 3.10 (dd, J = 7.8 Hz, J = 9.8 Hz, 1H), 3.18 (dd, J = 5.1 Hz, J = 9.8 Hz, 1H), 3.38 (dd, J = 7.0 Hz, J = 9.0 Hz, 1H), 3.43 (dd, J = 5.1 Hz, J = 9.0 Hz, 1H), 5.31 (s, 1H), 5.48 (q, J = 7.0 Hz, 1H), 7.22–7.36 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 31.6, 34.9, 45.5, 49.0, 71.2, 84.1, 127.0, 127.1, 127.2, 127.6, 127.7, 127.8, 128.55, 128.61, 128.67, 140.3, 142.0, 142.1, 173.5. $[\alpha]_D$ −72.9 (c 0.84, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{26}H_{27}NNaO_2$ $[M + Na]^+$ 408.2; found 408.1. Anal. calcd. for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.81; H, 6.89; N, 3.77.

(*S*)-1-((*S*)-1-Phenylethyl)-4-((trityloxy)methyl)pyrrolidin-2-one, 8c

To a solution of compound **7** (4.17 g, 19 mmol) in dry DMF (19 mL) at room temperature, DIPEA (4.88 mL,

28.5 mmol) and trityl chloride (10.60 g, 38 mmol) were sequentially added. The reaction mixture was stirred at reflux for 0.5 h, cooled at room temperature and diluted with an Na_2CO_3 saturated solution (30 mL), a cyclohexane:ethyl acetate 1:1 solution (500 mL) and water (250 mL). After separation, the organic phase was washed with water (3 × 100 mL). The unified aqueous phases were extracted with cyclohexane:ethyl acetate 1:1 solution (500 mL) and, after separation, the organic phase was washed with water (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, concentrated under vacuum and dissolved in 190 mL of cyclohexane:dichloromethane 95:5 solution. After addition of 4 g of activated charcoal, the mixture was gently stirred overnight, filtered through Celite and washed thoroughly with a cyclohexane:dichloromethane 95:5 solution (30 mL) and then with cyclohexane (3 × 30 mL). The solvents were eliminated under vacuum, and the crude product was purified by silica gel chromatography (cyclohexane:ethyl acetate 80:20) to give diastereomerically pure compound **8c** in 91 % yield (7.97 g, 17.27 mmol) as a pale yellow spongy solid. NOTE: occasionally, the chromatographed product resulted brownish and susceptible to a very slow decomposition if stored at room temperature. In these cases, the product was submitted to another purification with activated charcoal. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (d, J = 7.2 Hz, 3H), 2.18-2.26 (m, 1H), 2.48–2.58 (m, 2H), 3.04 (dd, J = 7.0 Hz, J = 9.0 Hz, 1H), 3.05–3.16 (m, 2H), 3.15 (dd, J = 5.1 Hz, J = 9.0 Hz, 1H), 5.47 (q, J = 7.2 Hz, 1H), 7.22–7.37 (m, 14ArH), 7.40–7.43 (m, 6ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 31.8, 35.1, 45.4, 48.9, 65.4, 86.6, 127.18, 127.22, 127.6, 128.0, 128.64, 128.71, 140.3, 143.9, 173.5. $[\alpha]_D$ −62.5 (c 1, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{32}H_{31}NNaO_2$ $[M+Na]^+$ 484.2; found 484.1. Anal. calcd. for $C_{32}H_{31}NO_2$: C, 83.26; H, 6.77; N, 3.03. Found: C, 83.06; H, 6.61; N, 3.17.

General procedure for the methylation reactions

To a solution of compound **8a**–**c** (10 mmol) dissolved in anhydrous THF (30 mL) under inert atmosphere at −23 °C, tetramethylpiperidine (0.843 mL, 5 mmol) and *n*-BuLi (2.5 M in hexanes, 4.4 mL, 11 mmol) were sequentially added; the mixture was stirred for 15 min and then methyl iodide (0.660 mL, 10.5 mmol) was added. After 30 min, the reaction mixture was quenched with water (20 mL) and the most part of THF was evaporated at reduced pressure and room temperature. After the addition of ethyl acetate (150 mL) and water (50 mL), the phases were separated and the organic one was washed with water (20 mL) and brine (5 mL). The combined aqueous phases were extracted with ethyl acetate (100 mL) and, after separation, the organic phase was washed with water (20 mL) and brine (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was eliminated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate) to give the inseparable diastereomeric mixture of products *trans* and *cis*-**9a**–**c** and the dimethylated by-products **9a**–**c′**.

(3*S*,4*S*)-4-((Benzyloxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *trans*-9a and (3*R*,4*S*)-4-((benzyloxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *cis*-9a

Starting from **8a** and following the general procedure, the title compounds were obtained in 75 % global yield (2.43 g, 7.52 mmol, *trans*-**9a**:*cis*-**9a** = 81:19) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 1.13 (d, J = 7.4 Hz, 3H, 19 %), 1.22 (d, J = 7.0 Hz, 3H, 81 %), 1.46 (d, J = 7.0 Hz, 3H, 19 %), 1.50 (d, J = 7.2 Hz, 3H, 81 %), 2.05–2.14 (m, 1H), 2.32 (dq, J = 7.0 Hz, J = 8.2 Hz, 1H, 81 %), 2.61–2.68 (m, 1H, 19 %), 3.00 (dd, J = 7.0 Hz, J = 9.8 Hz, 1H, 19 %), 3.06 (dd, J = 9.8 Hz, J = 11.7 Hz, 1H, 81 %), 3.08 (dd, J = 9.7 Hz, J = 11.7 Hz, 1H, 81 %), 3.16 (dd, J = 4.7 Hz, J = 9.8 Hz, 1H, 19 %), 3.33–3.37 (m, 1H, 19 %), 3.43 (dd, J = 7.4 Hz, J = 9.0 Hz, 1H, 81 %), 3.52 (dd, J = 5.5 Hz, J = 9.0 Hz, 1H, 19 %), 3.55 (dd, J = 4.7 Hz, J = 9.0 Hz, 1H, 81 %), 4.47 (d, J = 12.1 Hz, 1H, 19 %), 4.49 (d, J = 12.1 Hz, 1H, 81 %), 4.52 (d, J = 12.1 Hz, 1H, 19 %), 4.53 (d, J = 12.1 Hz, 1H, 81 %), 5.47 (q, J = 7.0 Hz, 1H, 19 %), 5.48 (q, J = 7.2 Hz, 1H, 81 %), 7.24–7.37 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ 10.5 (19 %), 15.4 (81 %), 15.9 (19 %), 16.0 (81 %), 35.6 (19 %), 39.1 (19 %), 40.0 (81 %), 40.8 (81 %), 43.7 (19 %), 43.9 (81 %), 48.9 (81 %), 48.9 (19 %), 68.8 (19 %), 71.1 (81 %), 73.2 (81 %), 73.3 (19 %), 126.9 (81 %), 127.0 (19 %), 127.3 (81 %), 127.4 (19 %), 127.56 (81 %), 127.69 (19 %), 127.70, 128.4, 128.5, 137.91 (19 %), 137.94 (81 %), 140.25 (19 %), 140.27 (81 %), 176.0 (81 %), 176.2 (19 %). $[\alpha]_D$ -86.6 (c 0.98, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{21}H_{25}NNaO_2$ $[M + Na]^+$ 346.2; found 346.1. Anal. calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.05; H, 7.90; N, 4.24.

(*S*)-4-((Benzyloxy)methyl)-3,3-dimethyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, 9a′

Starting from **8a** and following the general procedure, the diastereomerically pure title compound was obtained in 15 % yield (503 mg, 1.49 mmol) as a pale yellow solid. Colourless crystals were obtained after recrystallization from cyclohexane. Mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.21 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H), 2.16-2.24 (m, 1H), 2.97 (dd, J = 7.8 Hz, J = 9.8 Hz, 1H), 3.02 (dd, J = 7.8 Hz, J = 9.8 Hz, 1H), 3.39 (dd, J = 7.8 Hz,

J = 9.0 Hz, 1H), 3.55 (dd, J = 5.8 Hz, J = 9.0 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 5.45 (q, J = 7.0 Hz, 1H), 7.21–7.36 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 18.7, 24.8, 42.8, 42.9, 43.2, 48.8, 69.4, 73.4, 127.0, 127.4, 127.7, 127.8, 128.5, 128.6, 138.0, 140.4, 178.8. $[\alpha]_D$ −87.7 (c 1.83, $CHCl_3$). ESI–MS: m/z calcd. for $C_{22}H_{27}NNaO_2$ $[M + Na]^+$ 360.2; found 360.1. Anal. calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.42; H, 8.19; N, 4.08.

(3*S*,4*S*)-4-((Benzhydryloxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *trans*-9b and (3*R*,4*S*)-4-((benzhydryloxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *cis*-9b

Starting from **8b** and following the general procedure, the title compounds were obtained in 83 % global yield (3.321 g, 8.31 mmol, *trans*-**9b**:*cis*-**9b** = 80:20) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 1.11 (d, J = 7.0 Hz, 3H, 20 %), 1.22 (d, J = 7.0 Hz, 3H, 80 %), 1.43 (d, J = 7.0 Hz, 3H, 20 %), 1.48 (d, J = 7.0 Hz, 3H, 80 %), 2.08–2.17 (m, 1H, 80 %), 2.37 (dq, J = 7.0 Hz, J = 8.4 Hz, 1H, 80 %), 2.54–2.68 (m, 2H, 20 %), 3.00 (dd, J = 7.0 Hz, J = 9.8 Hz, 1H, 20 %), 3.03–3.11 (m, 2H, 80 %), 3.18 (dd, J = 4.3 Hz, J = 9.8 Hz, 1H, 20 %), 3.33 (dd, J = 8.0 Hz, J = 9.2 Hz, 1H, 20 %), 3.42 (dd, J = 7.0 Hz, J = 9.3 Hz, 1H, 80 %), 3.49 (dd, J = 4.7 Hz, J = 9.2 Hz, 1H, 20 %), 3.51 (dd, J = 5.1 Hz, J = 9.3 Hz, 1H, 80 %), 5.30 (s, 1H, 20 %), 5.31 (s, 1H, 80 %), 5.44–5.50 (m, 1H), 7.22–7.36 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ 10.7 (20 %), 15.7 (80 %), 16.2, 35.9 (20 %), 39.3 (20 %), 40.3 (80 %), 41.0 (80 %), 43.9 (80 %), 44.0 (80 %), 49.0, 68.0 (20 %), 70.2 (80 %), 84.2 (80 %), 84.3 (20 %), 126.9 (80 %), 127.00 (20 %), 127.02 (80 %), 127.08 (80 %), 127.16 (20 %), 127.23 (20 %), 127.50 (80 %), 127.53 (20 %), 127.6, 127.7, 128.52 (20 %), 128.55 (80 %), 128.59, 128.7, 140.4 (20 %), 140.5 (80 %), 142.01 (20 %), 142.09 (80 %), 142.16, 176.2 (80 %), 176.3 (20 %). $[\alpha]_D$ −82.0 (c 1.34, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{21}H_{25}NNaO_2$ $[M + Na]^+$ 422.2; found 422.0. Anal. calcd. for $C_{21}H_{25}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.30; H, 7.49; N, 3.38.

(3*S*,4*S*)-4-((1,1-Diphenylethoxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *trans*-9b′ and (3*R*,4*S*)-4-((1,1-diphenylethoxy)methyl)-3-methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one, *cis*-9b′

Starting from **8b** and following the general procedure, the title compounds were obtained in 10 % global yield (409 mg, 0.99 mmol, *trans*-**9b′**:*cis*-**9b′** = 62:38) as a pale yellow waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 1.13 (d, J = 7.4 Hz, 3H, 38 %), 1.22 (d, J = 7.4 Hz, 3H, 62 %), 1.46 (d, J = 7.4 Hz, 3H, 38 %), 1.51 (d, J = 7.4 Hz, 3H, 62 %), 1.86 (s, 3H), 2.03–2.12 (m, 1H, 62 %), 2.25–2.33 (m, 1H, 38 %), 2.39 (dq, J = 7.4 Hz, J = 8.6 Hz, 1H, 62 %), 2.66 (dq, J = 7.4 Hz, J = 8.2 Hz, 1H, 38 %), 3.01 (dd, J = 7.2 Hz, J = 10.0 Hz, 1H, 38 %), 3.05-3.18 (m, 2H), 3.21 (dd, J = 6.8 Hz, J = 9.2 Hz, 1H, 62 %), 3.29 (dd, J = 5.1 Hz, J = 8.6 Hz, 1H, 38 %), 3.32 (dd, J = 5.1 Hz, J = 9.0 Hz, 1H, 62 %), 5.50 (q, J = 7.4 Hz, 1H), 7.21–7.38 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ 10.7 (38 %), 15.7 (62 %), 16.18 (62 %), 16.23 (38 %), 25.56 (38 %), 25.63 (62 %), 36.0 (38 %), 39.3 (38 %), 40.3 (62 %), 41.1 (38 %), 43.9, 49.0, 61.0 (38 %), 63.3 (62 %), 80.52 (62 %), 80.58 (38 %), 126.65 (62 %), 126.74 (38 %), 126.83 (62 %), 126.99 (38 %), 127.04 (62 %), 127.2 (38 %), 128.08, 128.09, 128.6, 140.4 (38 %), 140.5 (62 %), 146.4 (38 %), 146.5 (62 %), 146.6 (62 %), 146.7 (38 %), 176.3 (62 %), 176.4 (38 %). $[\alpha]_D$ −68.6 (c 1.42, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{28}H_{31}NNaO_2$ $[M + Na]^+$ 436.2; found 436.0. Anal. calcd. for $C_{28}H_{31}NO_2$: C, 81.32; H, 7.56; N, 3.39. Found: C, 81.49; H, 7.72; N, 3.27.

(3*S*,4*S*)-3-Methyl-1-((*S*)-1-phenylethyl)-4-((trityloxy)methyl)pyrrolidin-2-one, *trans*-9c and (3*R*,4*S*)-3-methyl-1-((*S*)-1-phenylethyl)-4-((trityloxy)methyl)pyrrolidin-2-one, *cis*-9c

Starting from **8c** and following the general procedure, the title compounds were obtained in 80 % global yield (3.82 g, 8.03 mmol, *trans*-**9c**:*cis*-**9c** = 70:30) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 1.19 (d, J = 7.0 Hz, 3H, 70 %), 1.24 (d, J = 7.0 Hz, 3H, 30 %), 1.46 (d, J = 7.0 Hz, 3H, 70 %), 1.52 (d, J = 7.0 Hz, 3H, 30 %), 1.95–2.08 (m, 1H), 2.27–2.35 (m, 1H), 2.96–3.18 (m, 3H, 70 % + 2H, 30 %), 3.21 (dd, J = 5.5 Hz, J = 9.4 Hz, 1H, 70 %), 3.63 (dd, J = 7.0 Hz, J = 10.5 Hz, 1H, 30 %), 3.76 (dd, J = 5.1 Hz, J = 10.5 Hz, 1H, 30 %), 5.45 (q, J = 7.0 Hz, 1H, 70 %), 5.49 (q, J = 7.0 Hz, 1H, 30 %), 7.21–7.41 (m, 20ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers): δ 10.5 (30 %), 15.7 (70 %), 16.10 (30 %), 16.14 (70 %), 36.1 (30 %), 39.3 (30 %), 40.4 (70 %), 41.0 (70 %), 43.6 (30 %), 43.8 (70 %), 48.8 (30 %), 48.9 (70 %), 61.9 (30 %), 64.5 (70 %), 86.68 (30 %), 86.70 (70 %), 126.99 (70 %), 127.02 (30 %), 127.14 (30 %), 127.16 (70 %), 127.42 (70 %), 127.46 (30 %), 127.9, 128.6 (30 %), 128.7 (70 %), 140.5 (30 %), 143.9 (70 %), 176.2. $[\alpha]_D$ −26.3 (c 0.36, $CHCl_3$). ESI–MS: *m/z* calcd. for $C_{33}H_{33}NNaO_2$ $[M + Na]^+$ 498.2; found 498.1. Anal. calcd. for $C_{33}H_{33}NO_2$: C, 83.33; H, 6.99; N, 2.94. Found: C, 83.55; H, 7.17; N, 2.86.

(*S*)-3,3-Dimethyl-1-((*S*)-1-phenylethyl)-4-((trityloxy) methyl)pyrrolidin-2-one, 9c′

Starting from **8c** and following the general procedure, the diastereomerically pure title compound was obtained in 11 % yield (524 mg, 1.07 mmol) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 3H), 1.22 (s, 3H), 1.40 (d, J = 7.0 Hz, 3H), 2.19–2.26 (m, 1H), 2.82 (dd, J = 8.2 Hz, J = 9.8 Hz, 1H), 2.97 (dd, J = 7.4 Hz, J = 9.8 Hz, 1H), 3.06 (dd, J = 7.6 Hz, J = 9.4 Hz, 1H), 3.15 (dd, J = 6.6 Hz, J = 9.4 Hz, 1H), 5.41 (q, J = 7.0 Hz, 1H), 7.21–7.41 (m, 20ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 16.2, 28.4, 39.8, 43.0, 43.7, 49.2, 64.0, 86.4, 127.13, 127.17, 127.27, 127.29, 127.4, 127.6, 127.87, 127.91, 128.00, 128.03, 128.08, 128.12, 128.7, 128.8, 129.9, 140.4, 143.8, 147.1, 176.3. $[\alpha]_D$ −18.6 (c 0.39, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{34}H_{35}NNaO_2$ $[M + Na]^+$ 512.3; found 512.2. Anal. calcd. for $C_{34}H_{35}NO_2$: C, 83.40; H, 7.20; N, 2.86. Found: C, 83.56; H, 7.37; N, 2.80.

General procedure for the electrophilic amination reactions

To a solution of diastereomeric mixtures of compounds *trans*-**9a–c** and *cis*-**9a–c** (6 mmol) in anhydrous THF (18 mL) at -23 °C under inert atmosphere, tetramethylpiperidine (1.62 mL, 9.6 mmol) and n-BuLi (2.5 M in hexanes, 3.84 mL, 9.6 mmol) were sequentially added. After 30 min at −23 °C, the reaction was thermostated at −78 °C, then DBAD (2.21 g, 9.6 mmol) dissolved in 4 mL of anhydrous THF was slowly added under vigorous stirring. After 30 min, the reaction mixture was quenched with 1 M HCl (15 mL) and diluted with ethyl acetate (300 mL) and water (300 mL); then the phases were separated and the organic one was washed with water (100 mL) and brine (10 mL). The combined aqueous phases were extracted with 200 mL of ethyl acetate and, after separation, the organic phase was washed with water (50 mL) and brine (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was eliminated under reduced pressure. Eventual purification of crude products by silica gel chromatography (cyclohexane:ethyl acetate 70:30) gave products **10a**–**c**.

Di-*t*-butyl 1-((3*S*,4*R*)-4-((benzyloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 10a

According to the general procedure and starting from the diastereomeric mixture of compounds *trans* and *cis*-**9a**, product **10a** was obtained as an inseparable diastereomerically enriched mixture in 36 % yield (1.19 g, 2.15 mmol) as a colourless oil. The exact diastereomeric ratio *trans*-**10a**:*cis*-**10a** could not be determined by HPLC due to the lack of the relative response factor, while the ratio of areas was determined to be $A_{trans\text{-}\mathbf{10a}}$:$A_{cis\text{-}\mathbf{10a}}$ = 92:8 by elution with a Chiralcel OD-H column (*n*-hexane:2-propanol 9:1, flow rate 1.0 mL/min, λ = 210 nm, $t_{trans\text{-}\mathbf{10a}}$ = 12.8 min, $t_{cis\text{-}\mathbf{10a}}$ = 16.1 min). ^{1}H NMR (400 MHz, $CDCl_3$, complex mixture of diastereomers and rotamers): δ 1.23–1.26 (m, 3H, 86 %), 1.34 (s, 3H, 14 %), 1.42–1.51 (m, 21H), 2.83–3.88 (m, 5H), 4.39–4.53 (m, 2H), 5.41–5.52 (m, 1H), 6.15 (bs, 1H, 12 %), 6.31 (bs, 1H, 19 %), 6.61 (bs, 1H, 55 %), 6.66 (bs, 1H, 14 %), 7.24–7.46 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer of major diastereomer): δ 16.2, 17.2, 28.3, 39.2, 43.5, 49.6, 67.4, 69.6, 73.3, 81.0, 81.7, 127.4, 127.5, 127.6, 127.7, 127.9, 128.39, 128.45, 128.6, 138.5, 139.7, 156.0, 174.2. $[\alpha]_D$ −68.2 (c 3.93, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{31}H_{43}N_3NaO_6$ $[M + Na]^+$ 576.3; found 576.2. Anal. calcd. for $C_{31}H_{43}N_3O_6$: C, 67.25; H, 7.83; N, 7.59. Found: C, 67.30; H, 7.87; N, 7.53.

Di-*t*-butyl 1-((3*S*,4*R*)-4-((benzhydryloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 10b

According to the general procedure and starting from the diastereomeric mixture of compounds *trans* and *cis*-**9b**, diastereomerically pure compound **10b** was obtained in 41 % yield (1.56 g, 2.48 mmol) as a white spongy solid. The diastereomeric purity of **10b** was determined by HPLC (Chiralcel OD-H column, n-hexane:2-propanol 9:1, flow rate 1.0 mL/min, λ = 210 nm, $t_{\mathbf{10b}}$ = 10.9 min). ^{1}H NMR (400 MHz, $CDCl_3$, complex mixture of rotamers): δ 1.22–1.53 (m, 24H), 2.43–2.99 (m, 1H), 3.02-3.15 (m, 1H), 3.17–3.35 (m, 1H), 3.38–3.56 (m, 1H), 3.59–3.84 (m, 1H), 5.26–5.37 (m, 1H), 5.44–5.54 (m, 1H), 6.00 (bs, 1H, 11 %), 6.35–6.38 (m, 1H, 18 %), 6.59–6.61 (m, 1H, 71 %), 7.18–7.49 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer): δ 16.3, 17.5, 28.26, 28.31, 39.3, 43.2, 49.4, 67.4, 68.2, 80.9, 81.6, 84.2, 126.8, 127.02, 127.17, 127.27, 127.45, 127.47, 127.7, 128.29, 128.38, 128.42, 128.53, 139.8, 142.38, 142.41, 153.6, 155.9, 174.2. $[\alpha]_D$ −62.84 (c 1.09, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{37}H_{47}N_3NaO_6$ $[M + Na]^+$ 652.3; found 652.2. Anal. calcd. for $C_{37}H_{47}N_3O_6$: C, 70.56; H, 7.52; N, 6.67. Found: C, 70.72; H, 7.77; N, 6.49.

Di-tert-butyl 1-((3*S*,4*R*)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-((trityloxy)methyl)pyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 10c

According to the general procedure and starting from the diastereomeric mixture of compounds *trans* and *cis*-**9c**, diastereomerically pure compound **10c** was obtained in 45 % yield (1.90 g, 2.69 mmol) as a pale yellow spongy solid. The diastereomeric purity of **10c** was determined by HPLC

(Chiralcel OD-H column, n-hexane:2-propanol 93:7, flow rate 1.0 mL/min, λ = 210 nm, $t_{\mathbf{10c}}$ = 15.1 min). ^{1}H NMR (400 MHz, $CDCl_3$, complex mixture of rotamers): δ 1.05 (s, 3H, 75 %), 1.26–1.57 (m, 21H + 3H, 25 %), 2.39–2.62 (m, 1H, 60 %), 2.70–2.75 (m, 1H, 40 %), 2.79–3.32 (m, 3H + 1H, 60 %), 3.72–3.75 (m, 1H, 40 %), 5.38–5.44 (m, 1H), 6.08 (bs, 1H, 17 %), 6.15 (bs, 1H, 12 %), 6.35–6.38 (m, 1H, 42 %), 6.69–6.73 (m, 1H, 29 %), 7.16–7.47 (m, 20ArH). ^{13}C NMR (100 MHz, $CDCl_3$, complex mixture of rotamers): δ 15.7, 16.2, 17.4, 28.17, 28.24, 28.34, 39.2, 43.1, 49.3, 62.4, 67.2, 80.7, 81.4, 86.9, 87.4, 126.9, 127.25, 127.31, 127.41, 127.7, 128.07, 128.15, 128.3, 128.4, 128.8, 139.8, 143.4, 144.1, 153.6, 155.6, 174.0. $[\alpha]_D$ −58.8 (c 1.14, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{43}H_{51}N_3NaO_6$ $[M + Na]^+$ 728.4; found 728.2. Anal. calcd. for $C_{43}H_{51}N_3O_6$: C, 73.17; H, 7.28; N, 5.95. Found: C, 73.32; H, 7.40; N, 5.86.

General procedure for the preparation of atropisomers

The thorough elimination of residual traces of eluents and moisture from the pure starting compounds **10a–c** has been proven to be essential for obtaining high yields, and thus these were submitted for three times to additional dissolutions in a few millilitres of anhydrous dichloromethane, followed by *in vacuo* evaporation.

To a solution of compounds **10a–c** (1.75 mmol) in anhydrous THF (5.25 mL) under inert atmosphere at room temperature, sodium hydride (60 % dispersion in mineral oil, 105 mg, 2.63 mmol) was added slowly under vigorous stirring. After 15 min, methyl bromoacetate (0.25 mL, 2.63 mmol) was added and the reaction mixture was stirred for 3 h, then ethyl acetate (5 mL) and water (5 mL) were sequentially added. After evaporation under vacuum at room temperature of volatiles, the mixture was diluted with ethyl acetate (50 mL) and water (10 mL), the phases were separated and the organic one was washed with water (3 × 5 mL) and brine (5 mL). The combined aqueous phases were extracted with 50 mL of ethyl acetate and, after separation, the organic phase was washed with water (3 × 5 mL) and brine (5 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was eliminated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate) to give the pure *M* and *P* atropisomers of compounds **11a–c**.

Di-*t*-butyl 1-((3*S*,4*R*)-4-((benzyloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate, (*M*) and (*P*)-11a

Starting from compound **10a** and following the general procedure, the diastereomerically and atropisomerically pure atropisomers (*M*)-**11a** and (*P*)-**11a** were obtained in 63 % (690 mg, 1.10 mmol) and in 26 % (285 mg, 0.46 mmol) yields, respectively, as colourless oils. (*M*)-**11a**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.43–1.47 (m, 15H), 1.53 (s, 9H), 2.64–2.69 (m, 1H, 75 %), 2.75–2.80 (m, 1H, 25 %), 2.86–2.96 (m, 1H, 75 %), 3.00–3.09 (m, 1H, 75 % + 1H, 25 %), 3.12–3.20 (m, 1H, 25 %), 3.30 (dd, *J* = 6.6 Hz, *J* = 9.4 Hz, 1H, 75 %), 3.44–3.48 (m, 1H, 25 %), 3.52 (dd, *J* = 7.4 Hz, *J* = 9.4 Hz, 1H, 75 %), 3.62 (s, 3H, 25 %), 3.65 (s, 3H, 75 %), 3.70–3.75 (m, 1H, 75 % + 1H, 25 %), 3.99–4.04 (m, 1H, 25 %), 4.22–4.29 (m, 1H, 25 %), 4.35–4.47 (m, 2H + 1H, 75 %), 5.36–5.41 (m, 1H, 25 %), 5.45–5.53 (m, 1H, 75 %), 7.22–7.34 (m, 8ArH), 7.40–7.48 (m, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer): δ 15.9, 28.1, 28.4, 28.5, 40.4, 41.8, 48.8, 51.8, 55.4, 69.0, 73.3, 82.3, 127.7, 127.9, 128.39, 128.40, 128.5, 137.7, 139.9, 156.6, 169.6, 172.7. $[\alpha]_D$ −41.1 (c 0.96, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{34}H_{47}N_3NaO_8$ $[M + Na]^+$ 648.3; found 648.2. Anal. calcd. for $C_{34}H_{47}N_3O_8$: C, 65.26; H, 7.57; N, 6.72. Found: C, 65.47; H, 7.71; N, 6.59. (*P*)-**11a**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.33 (s, 3H, 40 %), 1.35 (s, 3H, 60 %), 1.41–1.46 (m, 18H), 1.51 (d, *J* = 7.0 Hz, 6H), 2.97–3.06 (m, 1H), 3.19–3.30 (m, 1H), 3.42–3.63 (m, 2H), 3.67–3.75 (m, 1H), 3.72 (s, 3H, 40 %), 3.73 (s, 3H, 60 %), 3.87–3.96 (m, 1H), 4.37–4.54 (m, 3H), 5.38–5.45 (m, 1H), 7.24–7.35 (m, 8ArH), 7.42–7.45 (m, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 16.2, 16.8 (60 %), 17.0 (40 %), 28.1 (60 %), 28.3 (40 %), 28.4, 38.5 (40 %), 38.8 (60 %), 43.9 (40 %), 44.4 (60 %), 49.4, 51.8 (40 %), 51.9 (60 %), 55.4 (60 %), 56.0 (40 %), 68.4 (60 %), 68.6 (40 %), 69.9 (40 %), 70.4 (60 %), 73.3 (40 %), 73.8 (60 %), 81.7 (40 %), 82.0 (60 %), 82.2, 127.2, 127.4, 127.5, 127.7, 127.8, 127.9, 128.36, 128.43, 128.6, 138.1 (60 %), 138.7 (40 %), 139.8 (60 %), 139.9 (40 %), 156.5, 168.8 (40 %), 169.3 (60 %), 174.0 (60 %), 174.2 (40 %). $[\alpha]_D$ −44.3 (c 1.09, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{34}H_{47}N_3NaO_8$ $[M + Na]^+$ 648.3; found 648.2. Anal. calcd. for $C_{34}H_{47}N_3O_8$: C, 65.26; H, 7.57; N, 6.72. Found: C, 65.46; H, 7.66; N, 6.63.

Di-*t*-butyl 1-((3*S*,4*R*)-4-((benzhydryloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)-2-(2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate, (*M*) and (*P*)-11b

Starting from compound **10b** and following the general procedure, the diastereomerically and atropisomerically pure atropisomers (*M*)-**11b** and (*P*)-**11b** were obtained in 51 % (623 mg, 0.89 mmol) and in 40 % (494 mg, 0.70 mmol) yields, respectively, as white waxy solids. (*M*)-**11b**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.42–1.50 (m, 24H), 2.79–2.87 (m, 1H), 2.93–3.02 (m, 1H, 75 %), 3.10–3.24 (m, 1H + 1H, 25 %), 3.32–3.41 (m,

2H, 75 %), 3.45–3.49 (m, 1H, 25 %), 3.56–3.62 (m, 4H), 3.82–3.87 (m, 1H, 25 %), 4.14–4.30 (m, 1H), 5.27 (s, 1H, 75 %), 5.32 (s, 1H, 25 %), 5.36–5.42 (m, 1H, 25 %), 5.46–5.53 (m, 1H, 75 %), 7.21–7.38 (m, 13ArH), 7.43–7.49 (m, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 16.0 (75 %), 16.1 (25 %), 28.3 (75 %), 28.4 (25 %), 28.50 (25 %), 28.54 (75 %), 38.7 (75 %), 40.6 (25 %), 42.9, 50.4, 51.88 (75 %), 51.94 (25 %), 55.2 (75 %), 55.7 (25 %), 67.2, 68.4, 69.1, 82.4 (75 %), 83.8 (25 %), 84.5 (25 %), 85.1 (75 %), 126.8 (25 %), 126.9 (75 %), 127.0 (25 %), 127.1 (75 %), 127.4 (75 %), 127.6 (25 %), 127.8 (25 %), 128.0 (75 %), 128.49 (25 %), 128.54 (75 %), 128.58 (25 %), 128.63 (75 %), 128.69 (75 %), 128.74 (25 %), 138.5 (75 %), 140.0 (25 %), 141.3 (75 %), 141.4 (75 %), 141.8 (25 %), 141.9 (25 %), 153.3 (75 %), 153.4 (25 %), 156.5 (25 %), 156.8 (75 %), 169.0 (75 %), 169.3 (25 %), 172.5. $[\alpha]_D$ −44.0 (c 2.76, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{40}H_{51}N_3NaO_8$ $[M + Na]^+$ 724.4; found 724.2. Anal. calcd. for $C_{40}H_{51}N_3O_8$: C, 68.45; H, 7.32; N, 5.99. Found: C, 68.60; H, 7.49; N, 5.89. (***P***)-**11b**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.26 (s, 3H, 40 %), 1.29 (s, 3H, 60 %), 1.31–1.52 (m, 21H), 2.99–3.12 (m, 1H), 3.22–3.41 (m, 2H), 3.42–3.52 (m, 1H), 3.70 (s, 3H, 60 %), 3.71 (s, 3H, 40 %), 3.80-3.90 (m, 1H), 4.06–4.11 (m, 1H), 4.35–4.46 (m, 1H), 5.25 (s, 1H, 60 %), 5.31 (s, 1H, 40 %), 5.38–5.46 (m, 1H), 7.16–7.46 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer): δ 16.2 (60 %), 16.3 (40 %), 17.1 (40 %), 17.2 (60 %), 28.0 (60 %), 28.2 (40 %), 28.4, 38.7 (60 %), 38.9 (40 %), 43.8 (40 %), 44.2 (60 %), 49.4, 51.8 (40 %), 52.0 (60 %), 55.3 (60 %), 56.1 (40 %), 68.4 (40 %), 68.5 (60 %), 69.1, 81.7 (45 %), 82.0 (60 %), 82.1 (40 %), 84.1, 84.7 (60 %), 126.9 (40 %), 127.0 (60 %), 127.1 (60 %), 127.3 (40 %), 127.4 (60 %), 127.5 (40 %), 127.6 (60 %), 127.7 (40 %), 128.3 (40 %), 128.4 (60 %), 128.5, 128.6 (40 %), 139.8 (60 %), 140.0 (40 %), 142.2, 142.5 (40 %), 142.6 (60 %), 152.8 (60 %), 153.0 (40 %), 155.3 (60 %), 156.2 (40 %), 168.8 (60 %), 169.2 (40 %), 174.1 (60 %),174.3 (40 %). $[\alpha]_D$ −51.0 (c 0.60, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{40}H_{51}N_3NaO_8$ $[M + Na]^+$ 724.4; found 724.2. Anal. calcd. for $C_{40}H_{51}N_3O_8$: C, 68.45; H, 7.32; N, 5.99. Found: C, 68.64; H, 7.51; N, 5.87.

Di-*t*-butyl 1-(2-methoxy-2-oxoethyl)-2-((3*S*,4*R*)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-((trityloxy)methyl) pyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, (*M*) and (*P*)-11c

Starting from compound **10c** and following the general procedure, the diastereomerically and atropisomerically pure atropisomers (***M***)-**11c** and (***P***)-**11c** were obtained in 53 % (725 mg, 0.93 mmol) and in 44 % (597 mg, 0.77 mmol) yields, respectively, as colourless waxy solids. (***M***)-**11c**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.31 (s, 3H), 1.40–1.50 (m, 21H), 2.68–2.77 (m, 1H), 2.85-2.95 (m, 1H), 3.00–3.11 (m, 2H), 3.25–3.29 (m, 1H), 3.39 (dd, $J = 3.9$ Hz, $J = 9.4$ Hz, 1H), 3.52 (s, 3H, 80 %), 3.56 (s, 3H, 20 %), 4.16–4.29 (m, 1H), 5.33–5.42 (m, 1H, 20 %), 5.45–5.54 (m, 1H, 80 %), 7.20–7.41 (m, 18ArH), 7.44–7.52 (m, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer): δ 16.1, 28.0, 28.3, 28.5, 40.8, 43.4, 48.6, 51.8, 55.8, 63.9, 67.2, 81.6, 82.3, 87.2, 127.0, 127.2, 127.8, 127.9, 128.4, 128.6, 128.7, 140.1, 143.7, 152.1, 156.3, 169.0, 172.4. $[\alpha]_D$ −30.1 (c 1.12, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{46}H_{55}N_3NaO_8$ $[M + Na]^+$ 800.4; found 800.2. Anal. calcd. for $C_{46}H_{55}N_3O_8$: C, 71.02; H, 7.13; N, 5.40. Found: C, 71.26; H, 7.30; N, 5.29. (***P***)-**11c**: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 1.15 (s, 3H, 55 %), 1.21–1.25 (m, 9H, 45 % + 3H, 45 %), 1.36 (s, 9H, 55 %), 1.44–1.50 (m, 12H), 2.74 (t, $J = 9.0$ Hz, 1H, 45 %), 2.82 (t, $J = 8.6$ Hz, 1H, 55 %), 3.03 (t, $J = 8.6$ Hz, 1H, 45 %), 3.17–3.25 (m, 1H + 1H, 55 %), 3.29–3.39 (m, 1H), 3.61–3.64 (m, 1H, 55 %), 3.69 (s, 3H, 45 %), 3.70 (s, 3H, 55 %), 3.83–3.86 (m, 1H, 45 %), 3.99 (d, $J = 17.2$ Hz, 1H, 55 %), 4.18 (d, $J = 16.4$ Hz, 1H, 45 %), 4.34–4.43 (m, 1H), 5.36–5.41 (m, 1H), 7.18–7.32 (m, 10ArH), 7.36–7.47 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ 16.2 (55 %), 17.1 (45 %), 27.9 (55 %), 28.1 (45 %), 28.4, 38.5 (55 %), 38.7 (45 %), 43.7 (45 %), 43.9 (55 %), 49.3 (55 %), 49.4 (45 %), 51.7 (45 %), 51.8 (55 %), 54.9 (55 %), 56.0 (45 %), 62.7 (45 %), 62.9 (55 %), 68.4 (45 %), 68.6 (55 %), 81.5 (45 %), 81.69, 81.72 (55 %), 86.85 (45 %), 86.90 (55 %), 126.8 (45 %), 127.1, 127.2, 127.3 (55 %), 127.7 (45 %), 127.8 (55 %), 128.3 (45 %), 128.4 (55 %), 128.8 (45 %), 128.9 (55 %), 139.7 (55 %), 139.9 (45 %), 143.9 (45 %), 144.2 (55 %), 152.97 (55 %), 153.05 (45 %), 154.9 (55 %), 156.1 (45 %), 168.8 (45 %), 169.1 (55 %), 174.0 (45 %),174.2 (55 %). $[\alpha]_D$ −59.8 (c 1.13, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{46}H_{55}N_3NaO_8$ $[M + Na]^+$ 800.4; found 800.2. Anal. calcd. for $C_{46}H_{55}N_3O_8$: C, 71.02; H, 7.13; N, 5.40. Found: C, 71.22; H, 7.27; N, 5.31.

General procedure for the cleavage of N–N bond

To a solution containing compounds (***M***) or (***P***)-**11a–c** (350 μmol) in anhydrous THF (1.75 mL) under inert atmosphere at 0 °C, LiHMDS (1.06 M in THF, 695 μL, 735 μmol) was added. The reaction mixture was kept at room temperature and stirred for 3 h, then was quenched with water (5 mL). After evaporation under vacuum of THF, the mixture was diluted with ethyl acetate (20 mL). After separation, the organic phase was washed with a saturated sodium carbonate aqueous solution (2 × 3 mL) and brine (3 mL). The combined aqueous phases were extracted with ethyl acetate (20 mL) and, after separation, the organic phase was washed with a saturated sodium carbonate aqueous solution (2 × 3 mL) and brine (3 mL). The combined organic

layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure, then the obtained crude product was purified by silica gel chromatography (cyclohexane:ethyl acetate) to give pure products **1a-c**.

t-Butyl ((3*S*,4*R*)-4-((benzyloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl) carbamate, 1a

Starting from (***M***) or (***P***)-**11a** and following the general procedure, diastereomerically pure compound **1a** was obtained in 75 % yield (115 mg, 262 μmol) or 70 % yield (108 mg, 246 μmol), respectively, as a colourless waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.43 (s, 9H), 1.51 (d, J = 7.0 Hz, 3H), 2.94 (t, J = 9.0 Hz, 1H), 2.98-3.06 (m, 1H), 3.13-3.17 (m, 1H), 3.52 (t, J = 8.6 Hz, 1H), 3.88–3.95 (m, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.99 (bs, 1H), 5.46 (q, J = 7.0 Hz, 1H), 7.24–7.38 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 17.6, 28.5, 40.7, 42.8, 49.4, 59.8, 69.2, 73.3, 79.7, 127.1, 127.5, 127.6, 127.7, 128.5, 128.6, 138.2, 139.7, 154.6, 174.3. $[\alpha]_D$ −66.4 (c 1.22, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{26}H_{34}N_2NaO_4$ $[M + Na]^+$ 461.2; found 461.1. Anal. calcd. for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.33; H, 7.90; N, 6.30.

t-Butyl ((3*S*,4*R*)-4-((benzhydryloxy)methyl)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)pyrrolidin-3-yl)carbamate, 1b

Starting from (***M***) or (***P***)-**11b** and following the general procedure, diastereomerically pure compound **1b** was obtained in 69 % yield (124 mg, 241 μmol) or 76 % yield (137 mg, 266 μmol), respectively, as a colourless waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.44 (s, 9H), 1.50 (d, J = 7.0 Hz, 3H), 2.88–2.94 (m, 1H), 3.11–3.17 (m, 2H), 3.48 (dd, J = 7.4 Hz, J = 9.4 Hz, 1H), 3.79 (dd, J = 5.1 Hz, J = 9.4 Hz, 1H), 4.91 (bs, 1H), 5.30 (s, 1H), 5.47 (q, J = 7.0 Hz, 1H), 7.21–7.40 (m, 15ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 17.7, 28.5, 40.4, 42.5, 49.4, 59.9, 67.8, 79.7, 84.1, 126.9, 127.0, 127.2, 127.5, 127.6, 128.5, 128.7, 139.8, 142.19, 142.21, 154.5, 174.4. $[\alpha]_D$ −82.3 (c 1, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{32}H_{38}N_2NaO_4$ $[M + Na]^+$ 537.3; found 537.2. Anal. calcd. for $C_{32}H_{38}N_2O_4$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.82; H, 7.55; N, 5.35.

t-Butyl ((3*S*,4*R*)-3-methyl-2-oxo-1-((*S*)-1-phenylethyl)-4-((trityloxy)methyl)pyrrolidin-3-yl)carbamate, 1c

Starting from (***M***) or (***P***)-**11c** and following the general procedure, diastereomerically pure compound **1c** was obtained in 81 % yield (167 mg, 283 μmol) or 74 % yield (156 mg, 260 μmol), respectively, as a colourless waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.49 (s, 9H), 2.62 (t, J = 9.4 Hz, 1H), 3.05 (t, J = 9.0 Hz, 1H), 3.14–3.23 (m, 2H), 3.29–3.38 (m, 1H), 4.85 (bs, 1H), 5.45 (q, J = 7.0 Hz, 1H), 7.20–7.30 (m, 10ArH), 7.36–7.42 (m, 10ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 17.4, 28.6, 39.3, 41.7, 49.3, 59.9, 62.2, 79.6, 86.9, 127.1, 127.2, 127.4, 127.9, 128.58, 128.61, 139.7, 143.9, 154.3, 174.3. $[\alpha]_D$ −54.8 (c 1.30, $CHCl_3$). ESI–MS: *m*/*z* calcd. for $C_{38}H_{42}N_2NaO_4$ $[M + Na]^+$ 613.3; found 613.1. Anal. calcd. for $C_{38}H_{42}N_2O_4$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.40; H, 7.29; N, 4.67.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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