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MULTICOMPONENT SYNTHESIS OF NOVEL 2- AND 3-SUBSTITUTED DIHYDROBENZO[1,4]OXAZEPINONES AND TETRAHYDRO-BENZO[1,4]DIAZEPIN-5-ONES AND THEIR CONFORMATIONAL ANALYSIS

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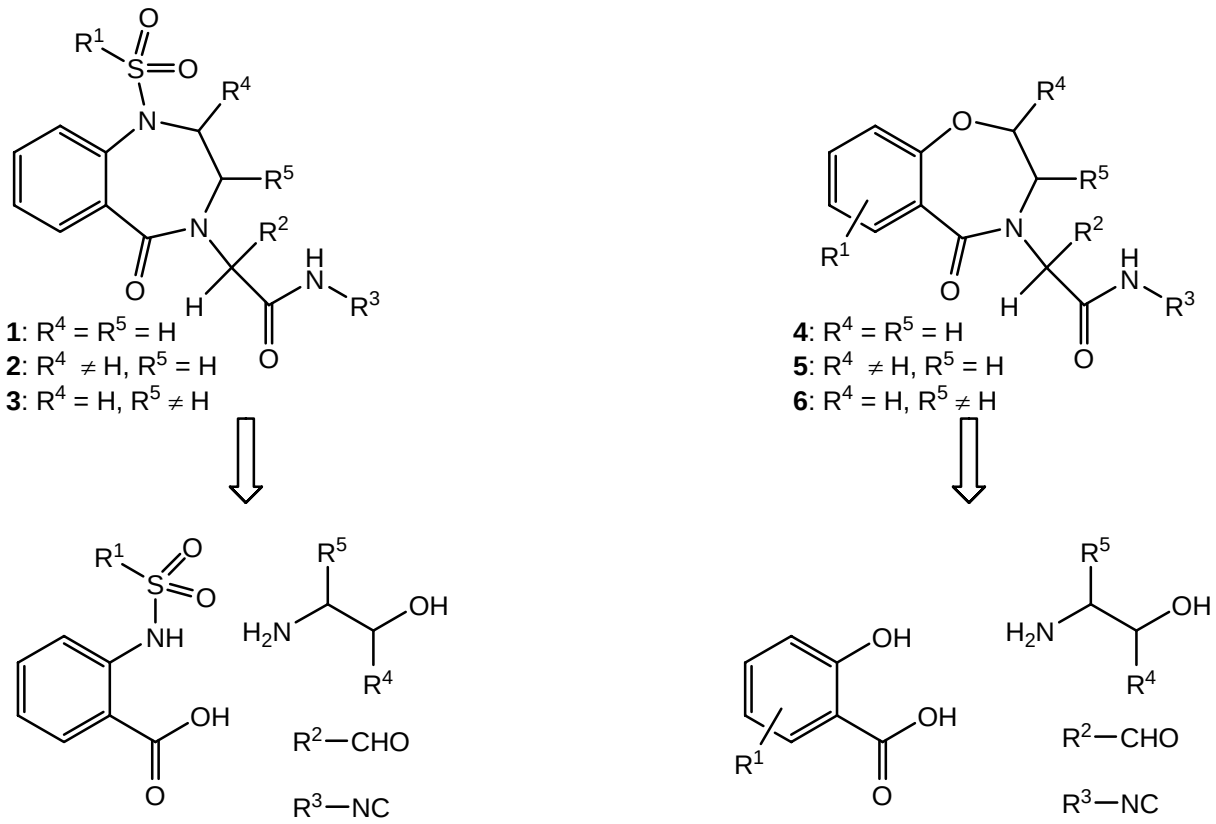
Abstract - By coupling an Ugi multicomponent condensation with a Mitsunobu reaction, a series of 2- and 3-substituted dihydrobenzo[1,4]oxazepinones and tetrahydrobenzo[1,4]diazepin-5-ones was synthesized in a very convergent manner. The strategy involves the use of substituted ethanolamines as amino components and of salicylic or *N*-methanesulphonyl anthranilic acid as carboxylic component. The general scope has been evaluated; in some cases better results have been obtained by reverting the order of the two reactions. A thorough conformational analysis on these products has been carried out through NMR, showing that in most cases a single conformation was strongly favoured.

INTRODUCTION

Isocyanide-based multicomponent reactions[1] represent a very powerful tool for diversity-oriented synthesis. They allow the highly convergent assembly, in just one step, of complex molecules, introducing, at the same time, 3 or more diversity inputs. Among them, the Ugi reaction[2] is by no doubt the most widely used, thanks to its operative simplicity and to the possibility to introduce 4 "real" diversity inputs. Apart from the isocyanides, the other three required components may be chosen among thousands of commercially available or easily synthesized compounds.

The only drawback of the classical Ugi and Passerini reactions is that they do not allow exploration of "scaffold diversity", since the products are always characterized by an acyclic, peptide- or depsipeptide-like, skeleton. In order to overcome this limitation, gaining access to drug-like heterocyclic scaffolds, several groups have successfully explored, during the last 10 years, various variants. Some of them take advantage of special components that induce a different mechanism (for example intramolecular attack by

an "internal" nucleophile).[3] Others rely on intramolecular modifications.[4] However, the most general approach involves coupling of the Ugi or Passerini MCRs with a post-condensation transformation, that takes advantage of one or two additional functionalities included in the starting components.[5] During the last years our research group has thoroughly explored this general methodology, developing new convergent routes to "non-classical" acyclic[6] or heterocyclic[7-10] scaffolds.



Scheme 1

In particular, we have recently reported a highly convergent two-step access to 1-sulphonyl-tetrahydrobenzo[1,4]diazepin-5-ones **1**[9] and dihydrobenzo[1,4]oxazepinones **4**,[10] based on coupling the Ugi MCR with a Mitsunobu intramolecular aliphatic substitution (Scheme 1). Towards this goal, two additional functionalities have been placed into two of the Ugi components, namely an alcoholic group in the amine component and a nucleophilic group (phenol or sulphonamide) into the carboxylic component. Interestingly these two groups do not need to be protected. After Ugi condensation, they are suitably placed to undergo the ensuing intramolecular Mitsunobu reaction. Small libriaries of drug-like heterocycles **1** and **4** have been obtained, taking advantage of three diversity points R^1, R^2 and R^3, whereas unsubstituted ethanolamine (R^4 = R^5 = H) was always used. In order to add a fourth diversity input, we have now studied the extension of the previously reported methodology to the use of substituted ethanolamines, leading to 2-substituted (**2**, **3**) or 3-substituted (**5**, **6**) compounds. Moreover, in view of the

potential biological applications of these compounds, we have carried out on them a conformational study by means of NMR.

SYNTHESIS

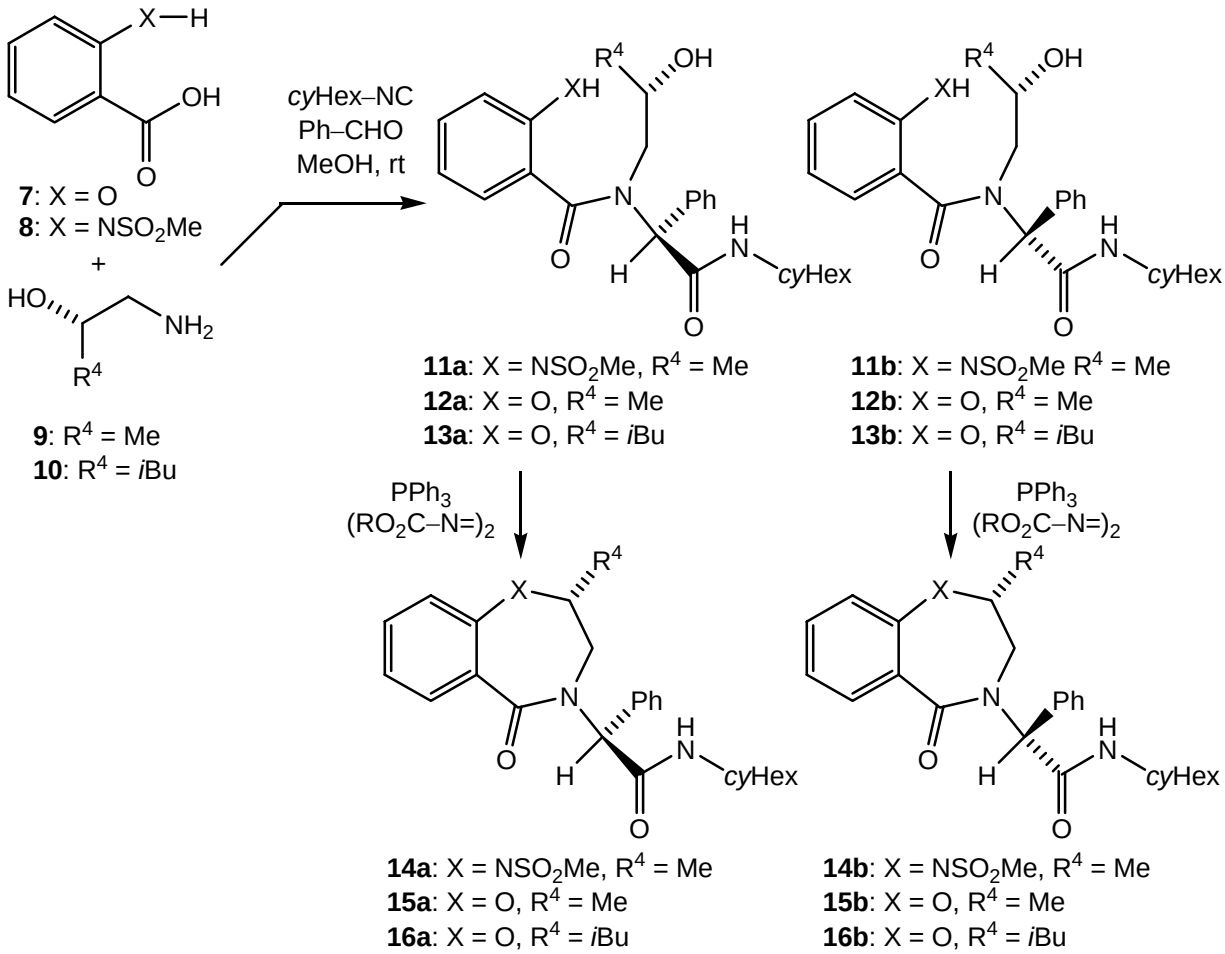
Since our primary aim was to assess the scope of the protocol on varying the substituted ethanolamine, we decided to keep the other three components constant. Therefore we always used benzaldehyde and cyclohexyl isocyanide. As for the carboxylic components, we employed either salicylic acid (for the synthesis of benzoxazepinones **5**,**6**) or *N*-methanesulphonyl anthranilic acid[9] (for the synthesis of benzodiazepinones **2**,**3**). The results are summarized in Table 1, whereas the formulas of the obtained products are depicted in Schemes 2 and 3. The choice of the azodicarboxylate reagent was mainly dictated by the easiness of chromatographic separation of the final products from the hydrazinodicarboxylate side-product. With less polar oxazepinones **5**,**6** we generally preferred DEAD (the products eluted before the hydrazinodicarboxylate), whereas with more polar sulphonyl diazepinones **2**,**3**, TBAD was more convenient (the products eluted after the hydrazinodicarboxylate). Obviously, the Ugi reaction affords in this case two diastereoisomeric products. Normally we did not separate them, but submitted instead the diastereoisomeric mixture to the following Mitsunobu step. The final heterocyclic adducts could be usually easily separated through chromatography into the two diastereoisomeric forms. This was especially true for 2-substituted compounds **14-16**. The only exception was represented by compounds **27a,b**, which resisted all attempts to separate the two diastereoisomers.

The relative configuration of all heterocyclic adducts obtained was unambigously established by NMR as described later in the section "Conformational and configurational analysis". The relative configuration of Ugi adducts **11-13** (when they were not reacted in mixture to afford the final products) was inferred from the reasonable assumption that the Mitsunobu reaction proceeds with inversion. We have indeed demonstrated that the Mitsunobu reaction is stereospecific. Finally, in the case of Ugi adducts **20-24** the configuration was expected to be maintained during the Mitsunobu step, since the two stereogenic centres are not involved.

For the synthesis of compounds **14a,b** and **15a,b** we employed 1-amino-2-propanol as starting ethanolamine. The synthesies were carried out on both (*S*) and (*R*) enantiomers. As shown in Table 1, the yields of the Ugi reaction were comparable to those obtained with unsubstituted ethanolamine.[9, 10] The Mitsunobu cyclizations proceeded uneventfully in good yields too. As expected, the Ugi reaction was poorly stereoselective and a nearly equal amount of the two diastereoisomers **a** and **b** was obtained. However the Mitsunobu reaction was demonstrated to be completely stereospecific. Actually, when the Ugi adducts were separated and reacted independently, only one isomer was obtained in each case. Moreover, having in hand all four stereoisomers (having used, as starting material, both (*S*) and (*R*)

ethanolamines), we were able to examine them in HPLC on a chiral column (Chiralpak AD (DAICEL)). This analysis showed that all four isomers were enantiomerically pure. We assume therefore that the Mitsunobu reaction proceeds with complete inversion of configuration and that (*S*) 1-amino-2-propanol furnishes (*R*) **14a,b** and **15a,b**. Interestingly, on the chiral HPLC column employed we found a remarkably large separation between the members of all enantiomer pairs. In particular, with **14b** we had to use a gradient from 9:1 to 50:50 hexane/*iso*-propanol in order to elute in reasonable times the slower eluting (*S*) enantiomer. Even under these conditions, it had R_t = 27.63 compared to 10.93 for the (*R*) isomer! This suggest a strong enantioselective interaction with the stationary phase.

We also prepared benzoxazepinones **16a,b**, using racemic 1-amino-4-methyl-2-pentanol,[11] prepared as described in the literature. In this case the yield of Ugi reaction was slightly lower.



Scheme 2

The synthesis of the 3-substituted compounds (Scheme 3 and Table 1) proved to be in some cases more problematic, because of the formation, during the Mitsunobu reaction, of small to significant quantities of unexpected rearranged products, which have been identified as the esters **30**-**34** (Scheme 4). The structure of these side-products has been established by ^{1}H NMR and ^{13}C NMR spectra. Further evidence has been

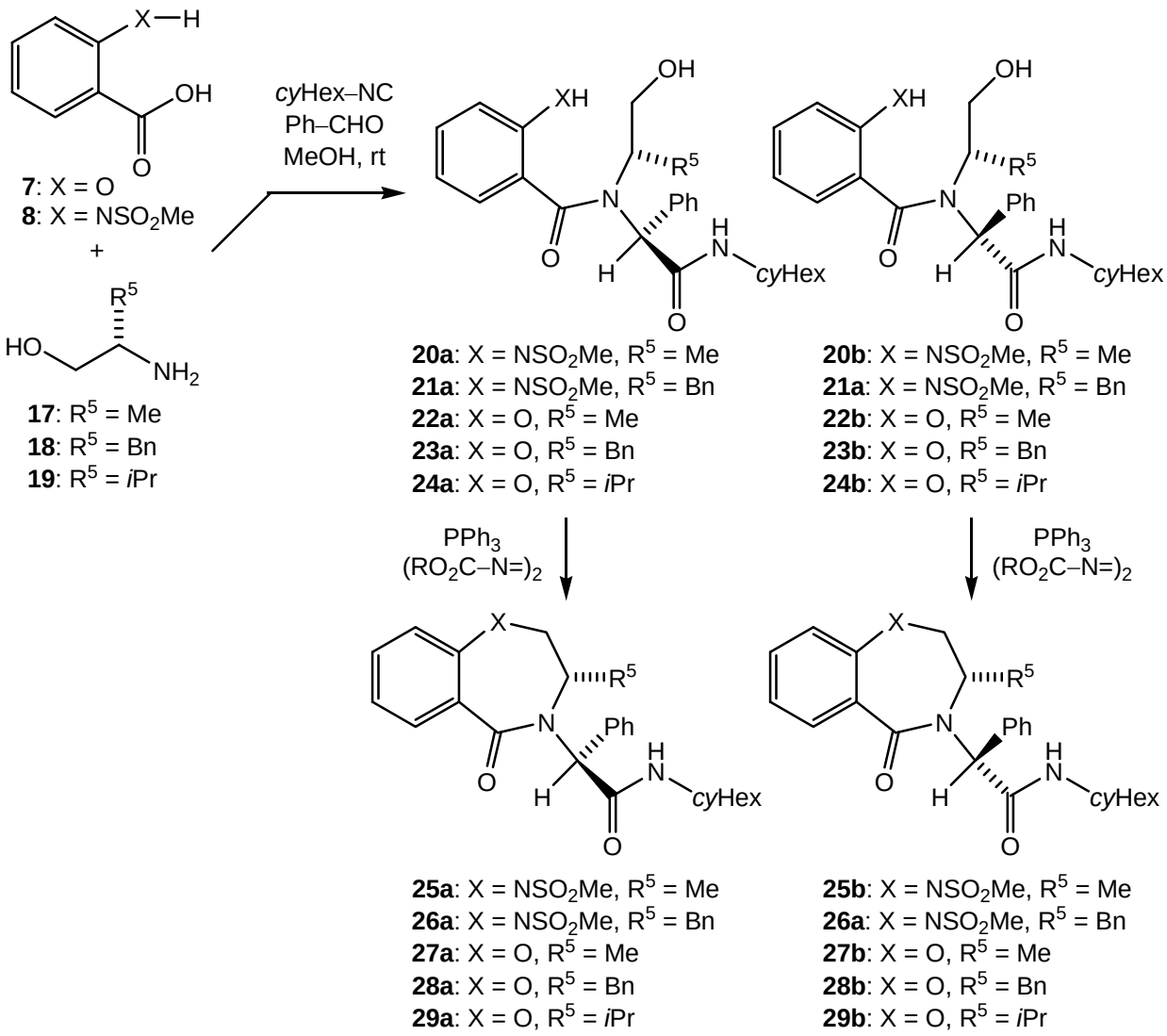
obtained, in the case of compounds **30b**, **31b** and **31a** by HPLC-MS analysis (see experimental). Finally, in the case of **30a** and **31b**, saponification with MeONa in MeOH led to the formation of the corresponding alcohols, that were identified at HPLC-MS. The formation of **30-34** seems at first sight in contrast with the know thermodinamic preference of amides compared to esters. However, we have already observed in a previous work, that when tertiary amides are highly encoumbered, the steric release can invert the usual equilibrium direction, making esters even more stable than amides.[8] Also in the present case we have seen that esters **30-34** do not convert back into Ugi adducts **20-24**, by prolonged treatment in the presence of triethylamine. On the contrary, Ugi adducts **21a** and **21b** are slowly converted into the isomeric esters **31a** and **31b** by simple standing in CH_3CN at 37°C. This conversion is configuration dependent: **21b** reacts much faster than **21a**. These side-products have not been observed in our previous work, using unsubstituted ethanolamine, nor when 1-amino-2-ols have been employed. Therefore it is the substitution α to nitrogen that provides a sufficient steric bias to promote this apparently "contra-thermodynamic" isomerization.

Table 1

TABLE 1. Synthesis of compounds **14-16a,b-25-29a,b** by tandem Ugi-Mitsunobu protocol[a]

Compound	Yield of Ugi reaction	**a**:**b** ratio after Ugi[b]	Mitsunobu conditions	Yield after Mitsunobu reaction	**a**:**b** ratio after Mitsunobu
14a,b	52%	*not det.*	TBAD / THF	86%	44:56[c,d]
15a,b	60%[f]	42:58[c]	DEAD / THF	82%	46:54[d]
16a,b	45%	*not det.*	DEAD / THF	75%	56:44[e]
25a,b	69%	46:54[c]	DEAD / THF	86%[g]	51:49[c]
25a,b			TBAD / THF	82%[g]	53:47[c]
26a,b	65%	55:45[d,e]	TBAD/THF	95% (**26a**)[h]	–
			DEAD/THF	76% (**26b**)[h]	–
27a,b	41%	12:88[c,d]	DEAD/THF	64%	21:79[e,i]
28a,b	57%	*not det.*	DEAD/THF	20%	51:49[d]
29a,b	45%	58:42	DEAD/THF	50%	> 90:10

Notes: [a] All Ugi reactions were carried out in MeOH at r.t. for 24-48h. Mitsunobu reactions were performed at r.t. in the indicated solvent using PPh_3 and the indicated azodicarboxylate: DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, TBAD = di-*tert*-butyl azodicarboxylate. Reactions were complete in 2-6 h. [b] The relative configuration was not determined at the level of Ugi products. Here we consider diast. **a** the one leading to diast. **a** of the final dihydrobenzoxazepinones or tetrahydrodiazepinones. [c] Determined by weight of isolated products. [d] Determined by HPLC. [e] Determined by NMR. [f] Reaction performed at 50°C. [g] These reaction were also carried out separately on **20a** (yield = 95% both with DEAD or TBAD) and **20b** (yield = 78% with DEAD and 71% with TBAD). [h] These reaction were carried out separately on **21a** and **21b.**. [i] It was not possible to separate these stereoisomers.

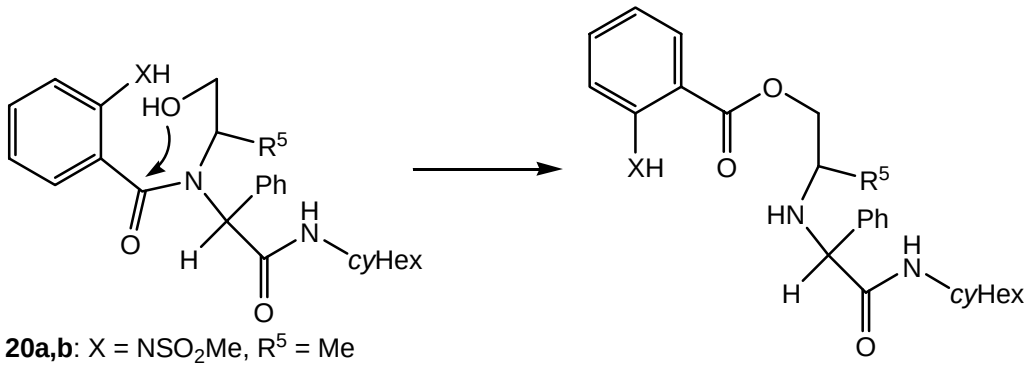


Scheme 3

3-Methyl substituted compounds **25a,b** were obtained from (*S*) alaninol. Performing the Mitsunobu reaction on the diastereoisomeric Ugi mixture, and employing TBAD as reagent, we observed the formation of small quantities of rearranged ester **30**. Surprisingly, it appeared to be, at NMR, a single diastereoisomer. Moreover the diastereoisomeric ratio after the Mitsunobu step was different than that determined after the Ugi reaction. By carrying out the reaction separately on Ugi adducts **20a** and **20b** we could see that only **20b** gave the rearranged ester **30b**. Therefore this isomerization is heavily dependent on the relative configuration of the starting alcohol. The ratio of **25b**:**30b** was found to be 75:25. The side reaction was in part suppressed using DEAD (**25b**:**30b** = 87:13). However in this case separation of **25b** from diethyl hydrazinodicarboxylate proved to be difficult.

A similar behaviour was found in the case of **26a,b**, obtained starting from (*S*) phenylalaninol. This time, however, a certain amount of rearranged ester **31b** was already present after the Ugi reaction. Together with a 65% yield of **21a,b**, we obtained indeed, in 14% yield, the rearranged ester **31b**, nearly

diastereoisomerically pure. Only traces of the diastereoisomer **31a** were present (**31b**:**31a** ratio = 95:5). After careful separation of **21a** and **21b**, we found that **21a** gave the expected product **26a** in better yield than **21b**, and with no formation of **31a**. On the contrary, **21b** gave a lower, albeit still good, yield, of the expected cyclized product **26b**, along with minor amounts of **31b** (ratio = 89:11 starting from a substrate already containing 5% of **31b**). Using DEAD instead of TBAD the amount of **31b** was lower (<10%) and the yield of **26b** slightly higher. Also in this case, the relative stereochemistry plays a decisive role in promoting the unwanted rearrangement. In any case, with sulphonamides this side reaction is not so pronounced, and the overall yields are still good.



20a,b: X = NSO_2Me, R^5 = Me
21a,b: X = NSO_2Me, R^5 = Bn
22a,b: X = O, R^5 = Me
23a,b: X = O, R^5 = Bn
24a,b: X = O, R^5 = *i*Pr

30a,b: X = NSO_2Me, R^5 = Me
31a,b: X = NSO_2Me, R^5 = Bn
32a,b: X = O, R^5 = Me
33a,b: X = O, R^5 = Bn
34a,b: X = O, R^5 = *i*Pr

Scheme 4

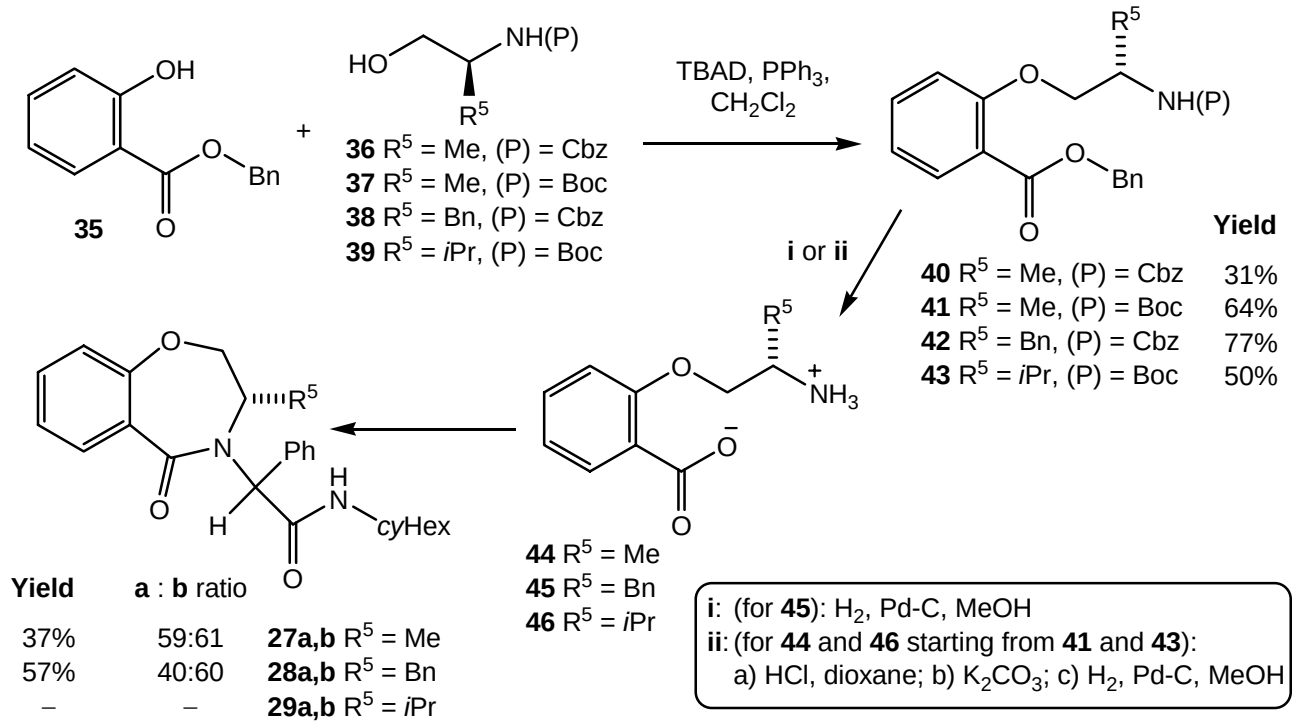
In the analogous phenol series, the importance of ester formation increases. Starting with alaninol, the Mitsunobu reaction gave an inseparable mixture of the expected products **27a,b** in 64% overall yield and 21:79 **a**:**b** ratio. We also isolated a second spot (31%), which was recognized as the rearranged ester **32**, as a single diastereoisomer. By performing the reaction on the isolated Ugi diastereoisomer, we could prove that it was **32b**. Also in this case the yield of the desired reaction is indeed higher for **22a**, causing a decrease of the **b**:**a** ratio from 88:12 to 79:21. What is somehow surprising in this entry is the high diastereoisomeric ratio obtained in the Ugi reaction (88:12 in favour of **22b**), which is in constrast with the generally low induction determined in all the other cases. Since the yield of Ugi reaction was only 41%, we cannot exclude that this ratio is due to selective decomposition of **22a** to give polar by-products (actually we did not detect side-products of similar polarity such as **32a,b**).

By increasing the bulkiness of the substituent, the stereochemical dependence of the rearrangement side-reaction was even more evident. Starting from (*S*) valinol, we observed that only diastereoisomer **24a** was able to give, in good yield, the expected desired adduct **29a**. On the contrary, **24b** furnished only the

rearranged ester **34b**. Finally in the case of phenylalaninol, both diastereoisomers gave the expected benzoxazepinones, but the yield of Mitsunobu reaction was only poor.

We do not have idea on how the DEADD/PPh_3 or TBAD/PPh_3 systems may catalyse amide-ester conversion. However, the addition of Et_3N to the reaction mixture or a change of solvent from THF to CH_2Cl_2 did not bring about any difference.

From the synthetic point of view, most of the products can be obtained efficiently, but the preparation of **27a** (because of the stereoselective Ugi reaction), of **28a,b** (because of low yield in the Mitsunobu step), and of **29b** (because of complete rearrangement to the ester) proved to be troublesome.



Scheme 5

Thus we decided to explore, for these products, also an alternative methodology, based on an intermolecular Mitsunobu reaction followed by an intramolecular Ugi (Scheme 5). This strategy was previously used successfully for 2- and 3-unsubstituted benzoxazepinones.[10] This time it is necessary to have the carboxy and the amino moieities protected during the first reaction. Therefore also a deprotection step must be performed before the final intramolecular Ugi (Scheme 4).

This 3-step alternative route proved to be particularly useful for the synthesis of **28a,b**. Intermolecular Mitsunobu reaction with Cbz phenylalaninol worked well, provided that TBAD was used as the azodicarboxylate, in order to minimize substitution by the azo compound. Hydrogenolytic removal of the protections followed by intramolecular Ugi gave **28a,b** in good yield, and with moderate stereoselection favouring **28b**. This protocol is definitely better, in terms of yield, than the "normal" one.

However, with Cbz-alaninol or Cbz-valinol, the yield of intermolecular Mitsunobu reaction was modest (for alaninol) or very low (for valinol) because of concurrent intramolecular substitution by the urethane NH, to give an acylaziridine. This side reaction was mostly suppressed using the bulkier Boc protecting group, and compounds **41** and **43** were obtained in good or moderate yield. This time two successive deblocking steps had to be implemented, and the crude aminoacid was submitted to Ugi conditions. However, while **44** gave the expected adducts **27a,b**, **46** failed to afford **29a,b**. Therefore **29b** remains not accessible. In the case of **27**, this alternative method allows the obtainment of higher quantities of **27a**, that was formed only in small percentage through the "normal" protocol.

CONFORMATIONAL AND CONFIGURATIONAL ANALYSIS

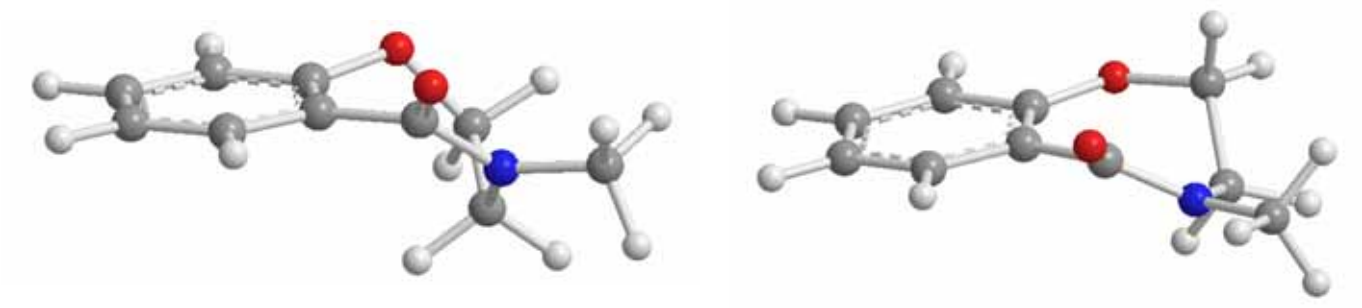
Computational analysis of the possible types of conformations

Compounds **2-3** and **5-6**, apart from possible substituents at the aromatic ring of the bicyclic system, contain 3 or 4 substituents that can be varied at will, that is R^4 (or R^5), R^2, R^3, and, only for **5-6**, the sulphonyl group. In view of possible biological applications it is important to have an idea of the conformational flexibility of these systems and on how these substituents are spatially oriented in the main(s) conformation(s). Therefore we decided to study their conformational behaviour exploiting relevant NMR data, namely NOEs, coupling constants, and anisotropic shifts. The presence of a phenyl ring in **14-16** and **25-29** was precious for these latter data. This analysis has also allowed to establish the relative configuration of the products synthesized.

In order to obtain models of the possible conformations, we did some minimization studies using the commercial software Chem3D from Cambridge Scientific, using both MM2 and MOPAC (AM1 or PM3) methods. To be sure to find all the local minima we carried out the minimizations starting from a series of initial conformations obtained by stepwise rotation of all rotatable bonds. For this task we took advantage of the "dihedral drive" function of the program. In most cases, minimization started from different initial conformations led to the same final structures. In other cases, for each type of the conformations discussed below, more than one local minimum was found. It should be stressed, however, that in this work, we did not use the results of calculation as a proof of the real conformations of our compounds. These minimization studies had only the goal to put in evidence all the possible structures that were then compared with the experimental NMR features in order to exclude those incompatible with the collected data. Although we have searched all the local minima for most of the real compounds synthesized by us, here, for the sake of briefness and clarity we will represent in the figures the various options using simplified models. Moreover we will depict only the benzoxazepinone systems, taking into account that the conformationally options for sulphonyl benzodiazepinones were found to be the same, apart from the added complication of the rotatable N—S bond, which leads, in some cases to more than one local

minimum.

First of all we studied the conformational behaviour of the parent dihydro benzoxazepinone (having just a methyl substituent at *N*-4). Here we do not have complications due to rotatable bonds outside the byciclyc system. In all cases, minimization afforded only two type of low energy conformations, shown in Figure 1 (**A** and **B**). Conformation **A** can be identified as "boat": its main feature is the fact that *C*-2, *C*-3 and *N*-4 are all placed on the same side of the aromatic plane. Conformation **B** can be identified as "half-chair": in it *C*-2 is nearly coplanar with *O*-1 and the aromatic ring, whereas *C*-3 and *N*-4 are on the same side of the plane. Obviously each of these two conformations possesses an enantiomeric conformer of the same energy.



A **B**

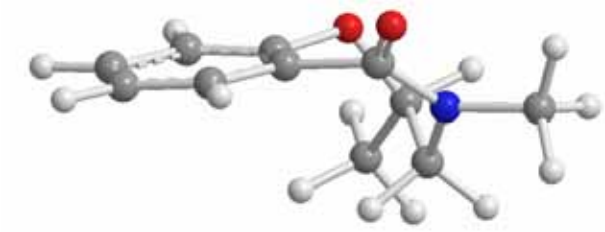
Figure 1

Minimizations (either with MM2, AM1 or PM3) suggest, for the parent compound, a higher stability for the "boat" conformation **A**. A similar situation is present in the analogous sulphonyl benzodiazepinone parent compound: here we have an additional degree of freedom due to the rotatable N−S bond. From our calculations, the methanesulphonyl group tends to stay, in the boat, on the opposite side than *C*-2, *C*-3, and *N*-4. The difference in energy between boat and half-chair is here more pronounced.

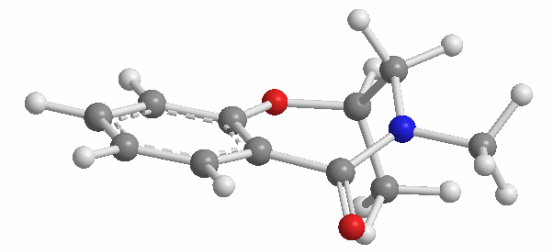
If we place a substituent at *C*-2 or *C*-3, the two enantiomeric conformations of **A** or **B** become diastereoisomeric. The result are four different possibilities for each type of substitution, depicted in Figure 2. Once again a simplified model is shown where *C*-2 (or *C*-3) and *N*-4 are both substituted with a methyl group. Note that the substituent at *C*-2 that is endo in the boat becomes exo in the half-chair and *vice-versa*. Once again, boat conformations are more stable. Among the boats, calculations suggest a higher stability for the *endo* conformers.

BOATS **HALF-CHAIRS**

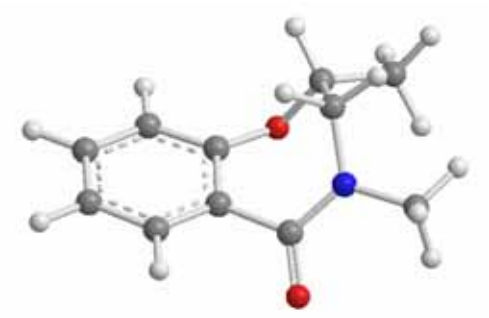
Substituent at *C*-2



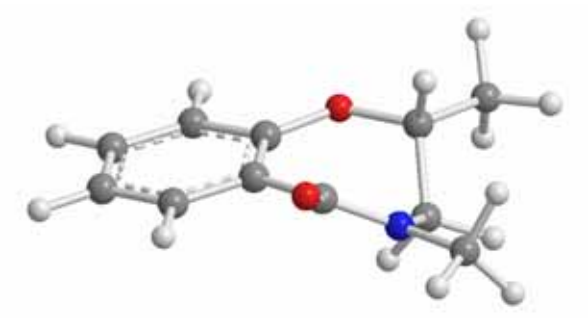
A2-endo



B2-endo

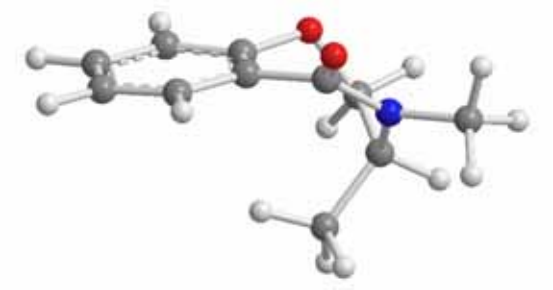


A2-exo

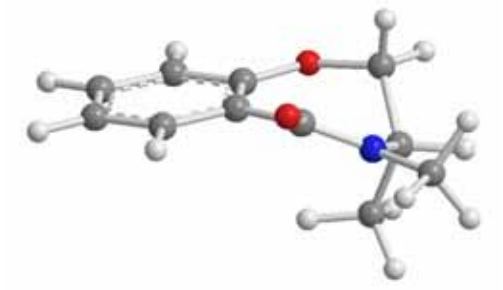


B2-exo

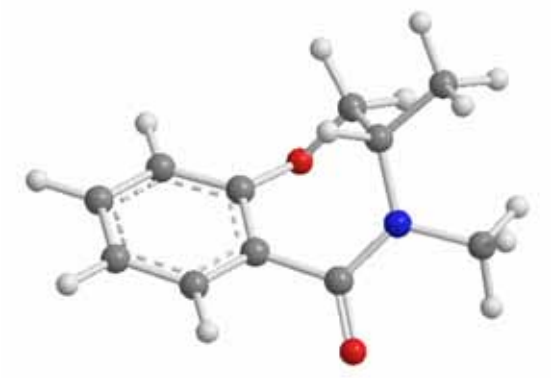
Substituent at *C*-3



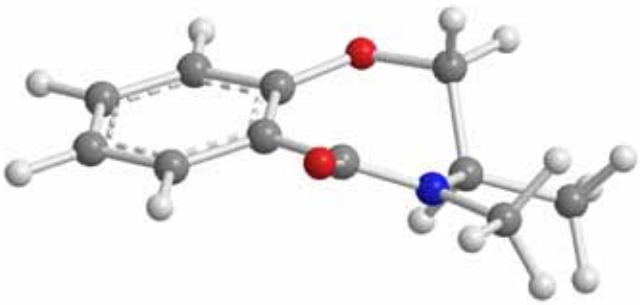
A3-endo



B3-endo



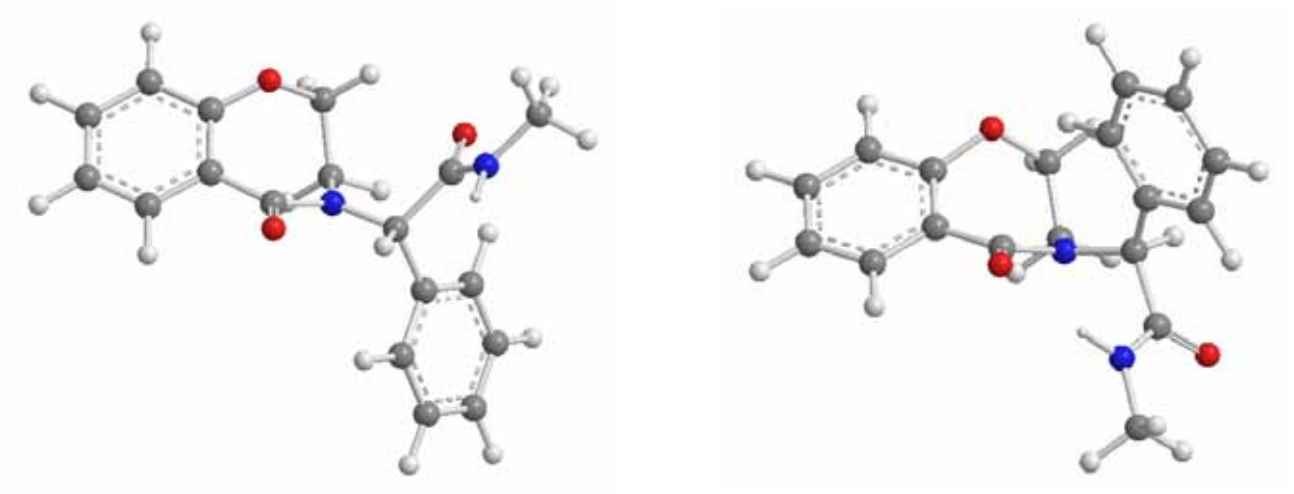
A3-exo



B3-exo

Figure 2

If we increase complexity, adding all the substituents of the real products, we have further degree of freedom, due to important rotatable bonds also outside the ring. Taking the likely assumption (strongly confirmed by NOE experiments) that the secondary amide prefers the *trans* (*anti*) arrangement, we found essentially two families of conformations, deriving from rotations around the *C*-3—(CHPh) and (CHPh)—(C=O) bonds. Here the possibility to form a hydrogen bond between the ring C=O and the N*H*, corresponding to a peptide γ-turn, is of great importance. Moreover, allylic strain arguments suggest that the PhC—H bond should be coplanar to the ring carbonyl. These logical arguments have been fully corroborated by our calculations, which have shown two families of minima conformations regarding these two rotatable bonds. Both imply the γ-turn hydrogen bond between N*H* and C=O and place the PhC—H bond nearly coplanar to the C=O. These two options are shown in Figure 3 for a boat conformation of a simplified model having a methyl instead of cyclohexyl, and with no substituents at *C*-2 and *C*-3. The difference is that in **C** the C*H*Ph hydrogen is directed towards the ring C=O ("H-inside"), whereas in **D** it is directed in the opposite direction ("H-outside"). In both types of conformation, the γ-turn hydrogen bond is present.



C ("H-inside") **D** ("H-outside")

Figure 3

In conclusion we can expect 8 different families of conformations for each compound, taking into account these three options: boat or half-chair, substituent in endo or exo, H inside or outside. For each of these types we found in some cases local minima due to rotation around the C−Ph bond, the N−cyclohexyl bond and (in the case of diazepinones only) of the N−S bond. Usually one of these local minima is definitely more stable and anyway these differences are less important for our following discussion.

Taking into account for each real compound these 8 possibilities we critically examined the NMR evidence, that allowed us to select the most compatible conformation type. Incidentally, these findings turned out to be essentially in line with the computational outcome.

First of all, the NMR evidence shows that in most cases one of these 8 conformations is strongly favoured over the others, whereas, only in few cases, a mixture of 2 conformations is present. Thus these systems, despite the possibility of 4 different ring conformations and of 2 rotatable bonds outside the ring, seems to be partially biased, being therefore promising for biological applications.

NMR evidence: 2-Substituted compounds.

Let's start considering compounds **14** and **15**, with a methyl substituent at *C*-2. First of all the ^{1}H NMR spectra give quite sharp signals at r.t., showing that there are no slow conformational equilibria. An important evidence comes from NOEs. In all four compounds **14a,b** and **15a,b** there is a strong NOE (9.0 to 12.8%) between C*H*Ph and N*H*, whereas there is no NOE between C*H*Ph or N*H* and both *H*-3. This evidence unambigously proves these four facts: **a**) the secondary amide conformation is indeed *anti* (*trans*); **b**) the N*H* and C*H*Ph are close in space; **c**) the C*H*Ph is not directed "outside", than is towards *H*-3 (otherwise a strong NOE would have been present) and therefore it is directed "inside", that is towards the C=O; **d**) coupling **b** with **c**, also N*H* must be directed towards C=O (and therefore a hydrogen bond is operating). This outcome is perfectly in accord with the miminized conformation of type **C** (with H inside). The presence at the equilibrium of even a small percentage of a conformation of type **D** (H outside) would have caused an appreciable NOE between C*H*Ph and the *H*-3 exo (see below the discussion about **26a**). In this conformation the distance between these two hydrogens should be only 2.10 Å! Actually this NOE is completely absent in these compounds, apart from a very small value (0.9%) measured in **15a**. The absence of any NOE between N*H* and *H*-3 or the substituent at *C*-3 in all the compounds studied corroborates the presence of a γ-turn.

The second question regards the position of methyl (endo or exo). The presence, in all these four compounds, of a high vicinal J_{trans} (9-12.2 Hz.) between *H*-2 and the *H*-3 *cis* to methyl rules out the exo-boat or endo-half-chair compounds. Only in endo-boat or exo-chair there is a *trans* dihedral angle near to 180°.

The third question regards the half-chair/boat option. An important information comes from the J_{cis} between *H*-2 and *H*-3. They are (in Hertz): 4.8 (**14a**), 5.0 (**14b**), 3.6 (**15a**) and 3.9 (**15b**). Figure 4 (on the left) shows the expected dihedral angles. It is easy to see that J are more in agreement with the endo-boat. In the exo-half-chair J_{cis} should be indeed near to 0 Hz (dihedral angle is about 80°). Moreover, in the half-chair one should expect a higher NOE between Me and *H*-3 exo (*trans* to Me) and a smaller or no NOE between methyl and *H*-3 endo (*cis* to Me). On the contrary, in the boat, the methyl should have similar NOEs with the two *H*-3, and particularly a slightly higher NOE with cis H-3 is expected. As can be seen in the experimental part, NOEs data are more in accord with this last situation.

In conclusion, for 2-methyl-substituted compounds, the endo-boat-H-inside conformation seems strongly favoured among the others. Interestingly the experimental data are in accord with the MOPAC

minimizations, which indicated this as the lowest energy conformation for **14a,b** and **15a,b**.

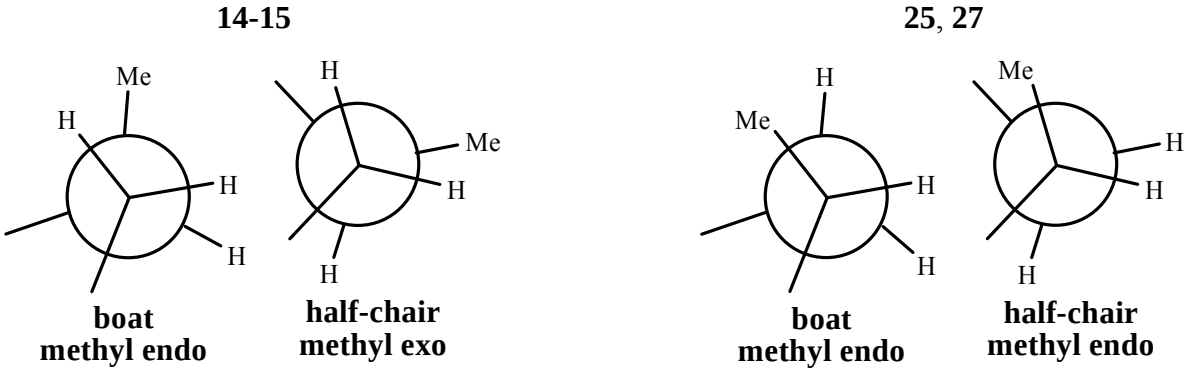


Figure 4. Newman projections of boats vs. half-chair conformations

Once the conformational preference has been elucidated, NOEs data and anisotropic shifts may be used for configurational assignment. In particular we took advantage from these informations:

1) There is a strong anisotropic shift upfield of *H*-2 in **b** isomers (3.67 vs. 5.27 ppm for **14** and 3.69 compared to 4.88 ppm for **15**). This is in complete agreement with the above discussed preferred conformation, that places this hydrogen near the center of the shielding field of the benzaldehyde derived phenyl group.

2) There is also (in **b** isomers) a remarkable NOE (9.8% in **14** and 6.7% in **15**) between the benzaldehyde derived phenyl ortho hydrogens and *H*-3 trans to Me, and a smaller NOE between *H*-2 and *H* ortho of phenyl (3.3% in **14** and 3.2% in **15**). This latter is particularly diagnostic, since it is not present at all in isomers **a** and is clearly possible only in compounds **b**.

Also other minor δ differences caused by anisotropic effects are in agreement with the proposed assignment.

Although we did not perform a thorough NOE study on **16a,b**, a series of close analogies with the ^{1}H and ^{13}C spectra of **15a,b** allowed to establish the relative configuration, and to prove that also in this case an endo-boat-H-inside conformation is preferred.

NMR evidence: 3-Substituted benzoxazepinones.

3-Methyl substituted benzoxazepinones **27a,b** produced very sharp lines in ^{1}H NMR as well. Also in this case, the evidence is definitely in favour of conformations with H inside. Actually, in both diastereoisomers, there is a strong NOE between C*H*Ph and N*H* (11.7-16.7), whereas, in **27a** there is nearly no NOE at all between C*H*Ph and *H*-3 or methyl in both diastereoisomers. However, the presence, in **27b**, of a small NOE between C*H*Ph and *H*-3 (2.6%) and of a smaller NOE (1.6%) between C*H*Ph and CH_3, suggests minor contributions of conformations with H outside. The coupling constants indicate a clear preference for an endo position of the methyl. With methyl exo, the *trans* $J_{2\text{-}3}$ should be quite high,

in both half-chair or boat. On the contrary, it is 5.4 Hz. in **27a** and 5.0 in **27b**. The *H*-2 *cis* to methyl and therefore *trans* to *H*-2 was easily recognized, because it is the only one that can give a NOE with methyl (see Figure 4, right).

In this case, decision among the boat and the half-chair is more difficult. From one side, for both diastereoisomers, the $J_{2\text{-}3}$ are more in agreement with a half-chair, because J_{trans} (5.4 for **27a** and 5.0 for **27b**) is higher than J_{cis} (0 and 1.5). As can be seen in Figure 4 the dihedral angles are expected to be higher (and hence J lower) for *trans* protons in the boat, whereas in the half-chair they are expected to be higher (and J lower) for *cis* proton. On the other hand, the strong difference in δ of *H*-2 *trans* to methyl (4.71 for **27a** and 3.76 for **27b**) suggests that in **27b** this hydrogen could fall in the shielding field of the phenyl. This is however consistent with the boat conformation. It is therefore difficult to decide unambigously which of these ring conformations is the most favoured one.

From calculations (AM1), the half-chair and boat conformations seem to have a similar energy. For **27a** the half-chair is even more stable, albeit by only 0.06 Kcal/mol, whereas for **27b** there was a difference of 1.1 Kcal/mol in favour of the boat conformation.

Talking about relative configuration, here the most important clues come from anisotropic effects. In **27a** the methyl group falls in the shielding field of phenyl (in both boats and half-chair). Therefore it appears at an unusually low value of 0.60 ppm (compared to 1.25 in **27b**). Moreover, a NOE between *H* ortho of phenyl and the methyl is present in **27a** and not in **27b**.

Compounds **28a,b** and **29a** show similar features. Without going too much in details, we can say that for the benzoxazepinones **28a,b** and **29a** the conformations with H inside and methyl endo are again strongly favoured. Also in these cases the half-chair is more in accord with the observed $J_{2\text{-}3}$.

NMR evidence: 3-Substituted benzodiazepinones.

Simply changing the oxygen at position 1 with the *N*-methanesulphonyl nitrogen brings about an important difference. Now, especially for **25a**, some signals at ^{1}H NMR are rather broad at r.t., and become sharper (although not completely sharp) only by warming to 45°C. These signals are those of the methyl, of C*H*Ph, and of *H*-2 *trans* to Me. The second important difference is that now C*H*Ph gives important NOEs not only with N*H* (5.7% for **25a** and 6.4% for **25b**), but also with CH_3 (3.9% for **25a** and 4.1% for **25b**). Interestingly, on the contrary, in **25a** there is no NOE between C*H*Ph and *H*-3, whereas in **25b** this NOE is present, albeit small (1.8%). As already pointed out above, conformations with methyl endo and H outside should give a strong NOE between C*H*Ph and *H*-3, and not at all with CH_3. Therefore these results suggest the presence of an equilibrium between the usual endo- H inside conformation and one with H outside and methyl in exo position. To gather further information on this point we performed a ^{1}H NMR of **25a** at −45°C. With our pleasure, two distinct sets of signals could be seen in a 60:40 ratio. The major conformation is in agreement with a boat with methyl endo and H-inside. Actually there is a

strong anisotropic shift of the methyl, which appears at 0.23 ppm. $J_{2\text{-}3}$ are consistent with methyl endo and boat, since J_{cis} = 6.9 Hz. and J_{trans} near to 0°C (the signal is however still broad).

In the other conformation there is no anisotropic shift for the methyl, which falls at 1.15 ppm. Moreover *H*-3 *cis* to methyl has a $J_{2\text{-}3}$ = 12.0 Hz. These data are consistent with a conformation with H outside and the methyl in the exo position. Moreover, the C*H*Ph falls at 5.02 ppm, that is at a much lower value than in the other compounds (and in the major conformation of the same compound), where it resonates at around 6.5-6.9 ppm. Actually, when this hydrogen is inside, it falls in the deshielding field of the carbonyl, whereas when it is outside, a more ordinary δ value (as in the starting Ugi products) is observed.

Compounds **26a,b** showed similar features. In the case of sulphonyl benzodiazepanone **26a**, broad signals are again observed at r.t., suggesting that also in this case an equilibrium between conformations may be present. Cooling to −30°C the two conformations splitted, but in this case the ratio was 95:5, favouring the usual one (boat-benzyl endo-H inside). The higher percentage of H-inside conformation is confirmed by NOE experiments. NOE between C*H*Ph and N*H* is actually 9.7%, whereas only small NOEs with *H*-3 (1.7) and CH_2Ph (1.9) are observed. For both **26a** and **26b** the $J_{2\text{-}3}$ are more consistent with a boat conformation.

The case of **26a** is very revealing, because it shows that the presence of only 5% of a conformation with *H*-outside can lead to signal broadening and to the presence of visible NOEs between C*H*Ph and *H*-3 or the substituent. Since in all other compounds (except **25a,b**) these NOEs were not observed or were rather small, and the signals were sharp, we can conclude that most of the here reported benzoxazepinones and benzodiazepinones strongly prefer a single conformation, characterized by having the C*H*Ph directed towards the ring carbonyl and the substituent in *endo* position. The only exception is represented by **25a,b**, where conformations with H-outside and methyl *exo* become important, although still minoritarian.

In conclusion, for 2-substituted compounds and 3-substituted benzodiazepinones **25-26** the NMR evidence is for a boat conformation, whereas some doubt remains about the preference for a boat or half-chair conformation for 3-substituted benzoxazepinones.

The fact that a single conformation is strongly favoured compared to the other ones, together with the strong differences in R_t observed for the two enantiomers of **14a,b** and **15a,b** on a chiral column, supports our initial hope that these compounds may possess a well defined tridimensional structure, making them promising as drug-like molecule for biological applications, where conformational biases are of great importance.

CONCLUSIONS

In the present paper we have reported on the very convergent and brief synthesis of rather complex heterocyclic compounds characterized by a rather original dihydrobenzo[1,4]oxazepinone or

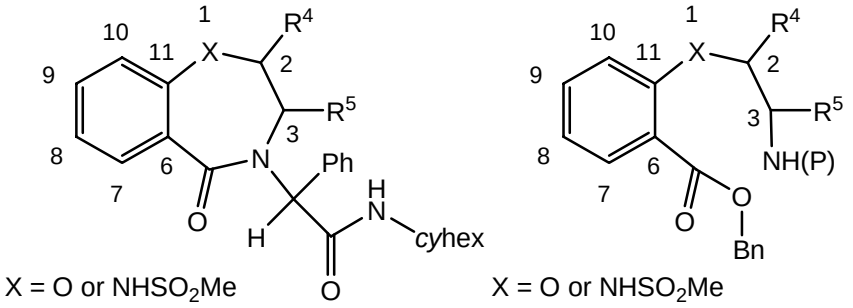
tetrahydrobenzo[1,4]diazepin-5-one scaffold and by substituents at the 2- or 3- position. The overall yield are in some cases good and in other instances acceptable anyway, considering the shortness of the synthetic pathway. For 3-substituted compounds, a side reaction, that is the formation of rearranged (uncyclized) esters was observed. Interestingly, this side-reaction is highly dependent on the relative stereochemistry of the starting alcohols. Actually, only one of the two diastereoisomers affords significant quantities of these side products. A thorough NMR conformatonal analysis has suggested a relatively rigid structure for these compounds, making them promising for rationally directed biological applications. In particular compounds **14-16** and **25-29** may be viewed as conformationally restricted peptidomimetics. The exploitation of these compounds, as well as of other analogues that can be easily prepared by the same protocol, in the inhibition of protein-protein interactions[12] is under study.

EXPERIMENTAL

NMR spectra were taken, unless otherwise stated, at rt in $CDCl_3$ at 300 MHz (^1H), and 75 MHz (^{13}C), using TMS as internal standard for ^1H NMR and the central peak of $CDCl_3$ (at 77.02 ppm) for ^{13}C NMR. When taken in DMSO-*d6*, the central peak of DMSO (at 2.506 for ^1H and at 39.429 ppm for ^{13}C) was taken as reference. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignments were made with the aid of DEPT, gCOSY and gHSQC experiments. In AB system, proton A is upfield. NOEDIFF experiments were carried out at about 80% saturation. The NOE is calculated by the integral ratio between of the enhanced peak and the irradiate peak. When irradiating a single proton, it is reported as such, without corrections calculated on the basis of the number of equivalent protons enhanced. On the contrary, when irradiating a peak corresponding to 2 or 3 H, the % enhancement is multiplied by 2 or 3 respectively.Only the most significant NOEs are reported. I.r. were taken as $CHCl_3$ solutions. HPLC-MS were carried out on an 1100 Series HPLC system from Agilent Technologies consisting of a 1100 Series binary pump, an autosampler provided with a 100μL loop and a Diode Array Detector. The column was an Atlantis RP C18 150x2.1 mm 3μm. The mass spectrometric instrumentation was an MSD-ion trap, model SL, from Agilent Technologies equipped with an orthogonal electrospray ionisation source operated in the positive ion mode. Nitrogen was used as both drying and nebulizing gas (drying gas flow rate 10 L/min; drying gas temperature 300° C; nebulizer pressure 30 psi). The parameters of the ESI source and the MS were optimised for HPLC-MS analysis: spray voltage was set at 3.2 kV; capillary exit voltage 79.6V; skimmer 13V; trap drive 44.2. Ion accumulation time was automatically set with ion charge control (ICC) with a target of 10,000 to avoid space charge effects. The experiments were performed in full scan condition (mass range of m/z 50–1300).

TLC analyses were carried out on silica gel plates and developed at U.V. or by dipping into a solution of

$(NH_4)_4MoO_4 \cdot 4\ H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4\ H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming. R_f were measured after an elution of 7-9 cm. Chromatographies were carried out on 220-400 mesh silica gel using the "flash" methodology. Petroleum ether (40-60°C) is abbreviated as PE. For atom numbering see Scheme 6.



Scheme 6

General procedure for the synthesis of Ugi adducts 11-13a,b and 20-24a,b

A solution of benzaldehyde (200 μL, 1.97 mmol) in dry diethyl ether (10 mL) was treated, at r.t., with the appropriate ethanolamine (1 eq.) and powdered 4 Å molecular sieves (500 mg). After 2 h the mixture was filtered and the filtrate evaporated at 20 mbar to give the crude imine as a colorless liquid. The freshly prepared imine is dissolved in dry MeOH (3 mL) and added with powdered 3 Å mol. sieves (90 mg). Acid **7** or **8** (1.1 eq.) and cyclohexyl isocyanide (1.2 eq) are then added in sequence. After 48h the solution is filtered and evaporated. The crude product is chromatographed on silica gel (220-400 mesh) with CH_2Cl_2/Me_2CO (about 85:15, for benzodiazepanones) or petroleum ether/Me_2CO (about 6:4 for benzodiazepanones and 75:25 for benzoxazepanones). Apart from the case of **21a,b**, in all the other cases, the Ugi adducts were the only compounds visible at U.V. after TLC of the crude product using these solvent systems. The side products were either much less polar (the remaining isocyanide) or much more polar (including the starting carboxylic acid). The NMR spectra of these Ugi products showed a double set of signals (for each diastereoisomer) due to conformational equilibria. Only at 115 °C did the coalescence occur. However, some signals were still broad. For this reason we preferred to carry out the complete characterization on the cyclized products. When determination of the diastereoisomeric ratio was needed, the chromatographed mixture was examined at ^{1}H NMR or HPLC. In few cases, the two diastereoisomer have been separated in order to study their behaviour in the ensuing Mitsunobu step.

HPLC-MS analysis of Ugi adducts 18a,b and their rearranged esters 31a,b

Starting from carboxylic acid **8** and (*S*) phenylalaninol, the TLC of the Ugi crude product showed three rather close spots. Analysis of the whole mixture was carried out both through HPLC-MS and NMR.

By NMR a **21a** : **21b** : **31a** : **31b** ratio of 45.3 : 37.0 : 0.9 : 16.8 was measured. A similar ratio was determined by HPLC with an UV detector (220 nm). Samples of nearly pure **21a** (higher R_f with PE/AcOEt) and **21b** (lower R_f) were obtained by careful chromatography (PE/CH_2Cl_2/acetone from

50:40:10 to 40:50:10). HPLC-MS was carried out both on the whole mixture and on isolated **21a** and **21b**. Flow: 350 μL/min, T=60°C, eluents: A: H_2O/HCO_2H (0.1%); B: MeCN. Gradient: time 0, A:B 50:50; time 25 min: A:B = 0:100. **21a**: R_t 12.50 min; m/z (positive): 602.3 (6, M + K^+); 586.1 (23, M + Na^+), 564.3 (100, M+H^+). **21b**: R_t 9.34 min.; m/z (positive): 602.3 (5, M + K^+), 586.3 (10, M + Na^+), 564.2 (100, M+H^+), 546.3 (10, M −18+H^+), 465.1 (19, M−98+H^+). **31a**: R_t 10.85; m/z (positive): 586.1 (2, M + Na^+), 564.3 (100, M+H^+). **31b**: R_t 10.24; m/z (positive): 586.1 (2, M + Na^+), 564.3 (100, M+H^+).

Interestingly, diluted solutions of **21a** and **21b** left at 37°C in CH_3CN for 16h, and then analysed at HPLC, showed the partial transformation of **21a** into **31a** and of **21b** into **31b**. This allowed to prove that **31b** had the same relative configuration of **21b** (the same obviously applies for **21a-31a**). However, this transformation was much faster for **21b**. From a 95:5 initial ratio (measured at 196 nm) of **21b** : **31b**, a final ratio of 20:80 was obtained. On the contrary, starting from a 72:28 mixture of **21a** and **31b** (no **31a** present), after 24h the % amount of **31b** remained identical, whereas a 7% (on the overall mixture) of **31a** was formed, with a corresponding decrease of the amount of **21a**.

The UV spectra of **21b** and **31b** were rather different. While **21b** presents only a maximum at 198 nm, **31b** has 4 maximums, in decreasing intensity order: 196, 215, 246, 310 nm. This behaviour is common to all the other rearranged esters examined. On the contrary, the cyclized products **25-26** give UV spectra very similar to that of **21b**.

HPLC-MS furnished also some evidence of the fact that **31a,b** are secondary amines. Actually a strong dependence of R_t on the pH of the eluent was observed (R_t were lower at lower pH). For example, **31b** has R_t = 14.16 at pH 7, 12.98 at pH 4, 9.97 at pH 2. On the other hand the R_t of **21a,b** did not change at all. Moreover **31a,b** gave peaks of Na^+ adducts of remarkably lower intensity.

HPLC analysis of other Ugi or Mitsunobu adducts.

Compounds **22a,b** were analysed on a Synergy Hydro 150 × 3mm 4 μ column at 30°C. Flow: 0.4 ml/min. Gradient: 0 min: H_2O 100%; 20 min.: MeCN 100%. R_t 14.71 min (**22b**), 15.37 min (**22a**). Compounds **28a,b** were analysed on an Eclypse Zorbax XDB 150×4.6 mm 5 μm column at 30°C. Flow: 1.0 ml/min. Gradient: 0 min: H_2O 100%; 20 min.: MeCN/H_2O 90:10. R_t 147.63 min (**28a**), 17.91 min (**28b**).

General procedure for the Mitsunobu reaction of 11-13a,b and 20-24a,b to give 14-16a,b and 25-29a,b. A solution of the Ugi adduct (as diastereoisomeric mixture) (0.5 mmol) in dry THF (5 mL) was cooled to 0°C, and treated with PPh_3 (197 mg, 0.75 mmol), and the appropriate azodicarboxylate (see the Table) (0.75 mmol). After 5 min the cooling bath was removed and the mixture stirred at r.t. for 1-8 h until disappearence of the substrate. The solvent was evaporated and the crude product chromatographed through 220-400 mesh silica gel (for the eluent used refer to the R_f of the various compounds) to give the pure diastereoisomeric products and, in some cases (see main text) the rearranged esters. Only in the case of **27a,b** it was not possible to separate the two diastereoisomers.

HPLC-MS analysis of Mitsunobu adduct 25b and of its rearranged ester 30b

The conditions were the same reported above for **21a,b** and **31a,b**. **25b**: R_t 5.68; m/z (positive): 508.2 (6.9, M + K^+), 492.2 (13, M + Na^+), 470.2 (100, M+H^+), 371.2 (11, M−98 + H^+). **30b**: R_t 2.47; m/z (positive): 510.2 (4, M + Na^+), 488.3 (100, M+H^+). Also in this case **30b** gave peaks of Na^+ adducts of remarkably lower intensity.

HPLC-MS analysis of Mitsunobu adduct 26b and of its rearranged ester 31b

The conditions were the same reported above for **21a,b** and **31a,b**. **26b**: R_t 11.69; m/z (positive): 584.3 (20, M + K^+), 568.3 (34, M + Na^+), 546.2 (100, M+H^+), 447.2 (11, M−98 + H^+). The data for **31b** were already reported above. It is worth noting that, starting from a 95:5 mixture of Ugi adduct **21b** and rearranged ester **31b**, the Mitsunobu reaction (TBAD) gave an 89:11 ratio, demonstrating that rearrangement occurs also under the Mitsunobu conditions. On the contrary, **21a** gave only traces (<2%) of **31a** under Mitsunobu conditions.

Saponification of rearranged esters 30b and 31b.

Samples containing mixtures of **25b/30b** and of **26b**/**31b** were subjected overnight to MeONa in MeOH at 37°C and the resulting solution analysed in HPLC-MS as described above. The analysis showed an increase of **25b/30b** and of **26b**/**31b** ratios and the appearance of a new, faster eluting, peak having respectively m/z 291 and 367 (M + H^+). These masses correspond to the alcohols deriving from saponification of **30b** and **31b**.

CHIRAL HPLC analysis of Mitsunobu adducts 14a,b and 15a,b

Column: Chiralpak AD (DAICEL), 250 x 4.6 mm. Flow: 1 ml/min. Temp.: 35°C. Time 0: *n*-hexane/*i*-PrOH 90:10. Time 25: *n*-hexane/*i*-PrOH 50:50 (linear gradient). From time= 25, isocratic conditions (50:50). These analyses indicated that all these adducts were always enantiomerically pure.

14a,b: R_t: **14a** (*S*) (that is from (*R*) 1-amino-2-propanol): 14.69. **14b** (*S*): 27.63. **14a** (*R*): 13.06. **14b** (*R*): 10.93.

15a,b. R_t: :**15a** (*S*) (that is from (*R*) 1-amino-2-propanol): 11.14; **15b** (*S*): 13.54; **15a** (*R*): 12.22; **15b** (*R*): 6.57.

Analytical data of 2- and 3-substituted dihydrobenzo[1,4]oxazepinones and tetrahydrobenzo[1,4]diazepin-5-ones.

14a (both enantiomers have been prepared): R*f*: 0.52 with PE / AcOEt 1:1. Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95%. Found: C, 64.2; H, 6.8; N, 9.0%. [(*S*) enantiomer, derived from (*R*) 1-amino-2-propanol]: $[\alpha]_D$ + 64.9 (c 2, $CHCl_3$). IR: ν_{max} 3413, 3003, 2929, 2855, 1675, 1635, 1600, 1491, 1450, 1406, 1341, 1192, 1152, 1115, 1030, 966 cm^{-1}. ^1H NMR: δ 7.72 [1 H, dd, *H*-7, J 1.8, 7.5]; 7.58-7.40 [3 H, m, *H*-9, *H*-8, *H*-10]; 7.40-7.30 [5 H, m, C*H* of Ph]; 6.57 [C*H*Ph]; 5.92 [1 H, d, N*H*, J 8.1]; 5.17 [1 H, d of quint. (apparent septuplet), *H*-2, J_d 12.0, J_q 6.0]; 3.89 [1 H, dtt, C*H*NH, J_d, 7.8, J_t 3.9, 11.1]; 3.28 [1 H, dd,

H-3 trans to Me, J 4.8, 15.0]; 2.92 [3 H, s, C*H*$_3$SO$_2$]; 2.68 [1 H, dd, *H*-3 cis to Me, J 11.7, 15.0]; 2.00-1.84 [2 H, m, cyclohexyl]; 1.82-1.58 [4 H, m, cyclohexyl]; 1.55-1.02 [4 H, m, cyclohexyl]; 1.09 [3 H, d, C*H*$_3$CH, J 6.6]. ^{13}C NMR: δ 170.0, 167.9 [*C*=O]; 135.6, 134.8, 132.6 [aromatic quat.]; 133.2 [*C*-8]; 132.2 [*C*-9]; 129.9 [*C*-7]; 129.2 and 128.6 [*C* ortho and meta of Ph]; 129.0 [*C*-10]; 128.8 [*C* para of Ph]; 60.5 [*C*HPh]; 59.7 [*C*-2]; 49.6 [*C*-3]; 48.8 [*C*HNH]; 38.5 [*C*H$_3$], 32.9, 32.8, 25.3, 24.8, 24.7 [*C*H$_2$ cyclohexyl]; 18.8 [*C*H$_3$CH]. NOEDIFF experiments: C*H*Ph → N*H*: 12; *H*-2 → *H*-3 *trans* to Me: 4.4; C*H*$_3$ → *H*-3 *cis* to Me: 3.4; C*H*$_3$ → *H*-3 *tran* to Me: 1.4; C*H*$_3$SO$_2$ → *H*-2: 6.1.

14b (both enantiomers have been prepared): R*f* : 0.27 (PE / AcOEt 1:1). Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95%. Found: C, 64.1; H, 6.7; N, 8.8%. [(*S*) enantiomer, derived from (*R*) 1-amino-2-propanol]: [α]$_D$ + 213.6 (c 2, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3418, 2933, 2855, 1677, 1641, 1600, 1501, 1450, 1405, 1341, 1239, 1152, 1115, 1093, 1029, 963 cm^{-1}. ^{1}H NMR: δ 7.81 [1 H, dd, *H*-7, J 2.1, 7.2]; 7.58-7.48 [2 H, m, *H*-9, *H*-8]; 7.48 [5 H, s, C*H* of Ph]; 7.41 [1 H, dd, *H*-10, J 1.8, 7.2]; 6.26 [C*H*Ph]; 5.61 [1 H, d, N*H*, J 8.1]; 3.81 [1 H, dtt, C*H*NH, J$_d$, 7.8, J$_t$ 4.2, 10.8]; 3.67 [1 H, d of quint. (apparent septuplet), *H*-2, J$_d$ 11.8, J$_q$ 5.9]; 3.55 [1 H, dd, *H*-3 trans to Me, J 5.0, 15.7]; 3.09 [1 H, dd, *H*-3 cis to Me, J 12.2, 15.7]; 2.71 [3 H, s, C*H*$_3$SO$_2$]; 1.98-1.86 [2 H, m, cyclohexyl]; 1.77-1.54 [4 H, m, cyclohexyl]; 1.43-1.00 [4 H, m, cyclohexyl]; 0.95 [3 H, d, C*H*$_3$CH, J 6.3]. ^{13}C NMR: δ 169.7, 168.0 [*C*=O]; 135.0, 134.7, 132.0 [aromatic quat.]; 132.4 [*C*-10]; 132.2 [*C*-9]; 130.6 [*C*-7]; 129.6, 129.3 [*C* para of Ph and *C*-8]; 129.5 [*C* ortho and meta of Ph]; 61.1 [*C*HPh]; 60.1 [*C*-2]; 49.7 [*C*-3]; 48.8 [*C*HNH]; 39.0 [*C*H$_3$], 32.79, 32.77, 25.4, 24.8, 24.7 [*C*H$_2$ cyclohexyl]; 18.6 [*C*H$_3$CH]. NOEDIFF experiments: C*H*Ph → N*H*: 11.1; *H*-3 *trans* to Me → *H* ortho of Phe: 9.8; C*H*$_3$ → *H*-3 *cis* to Me: 4.5; C*H*$_3$ → *H*-3 *trans* to Me: 2.0; *H*-2 → *H* ortho of Phe: 3.3; C*H*$_3$SO$_2$ → *H*-2: 3.0; C*H*$_3$SO$_2$ → *H* ortho of Phe: 1.5; C*H*$_3$SO$_2$ → C*H*Ph: 1.5.

15a (both enantiomers have been prepared). R*f*: 0.36 (PE/Acetone/AcOEt 8:1:1). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14%. Found: C, 73.55; H, 7.3; N, 7.2%. [(*S*) enantiomer, derived from (*R*) 1-amino-2-propanol]: [α]$_D$ −2.8 (c 1, $CHCl_3$). ^{1}H NMR: δ 7.81 [1 H, dd, *H*-7, J 1.8, 7.8]; 7.41 [1 H, dt, *H*-9, J$_d$ 2.1, J$_t$ 8.1]; 7.40-7.30 [5 H, m, C*H* of Ph]; 7.l6 [1 H, dt, *H*-8, J$_d$ 1.2, J$_t$ 7.5]; 6.97 [1 H, dd, *H*-10, J 1.0, 7.9]; 6.53 [1 H, s, C*H*Ph]; 6.22 [1 H, d, N*H*, J 7.8]; 4.88 [1 H, ddq, *H*-2, J$_d$ 3.6, 9.7, J$_q$ 6.5]; 3.86 [1 H, dtt, C*H*NH, J$_d$ 7.8, J$_t$ 4.1, 10.8]; 3.49 [1 H, dd, *H*-3 exo, J 3.6, 15.3]; 3.04 [1 H, dd, *H*-3 endo, J 9.0, 15.3]; 2.02-1.90 [2 H, m, cyclohexyl]; 1.76-1.54 [4 H, m, cyclohexyl]; 1.44-1.10 [4 H, m, cyclohexyl]; 1.11 [3 H, d, C*H*$_3$, J 6.6]. ^{13}C NMR: δ 169.8, 168.3 [*C*=O]; 153.0 [*C*-11]; 135.7 [quat. of PhCH]; 132.8 [*C*-9]; 131.1 [*C*-7]; 128.9, 128.7 [*C* ortho and meta of PhCH]; 128.3 [*C* para of PhCH]; 127.1 [*C*-6]; 123.3 [*C*-8]; 122.7 [*C*-10]; 80.1 [*C*-2]; 60.3 [*C*HPh]; 49.1 [*C*-3]; 48.7 [*C*HNH]; 32.9, 32.7, 25.4, 24.82, 24.79 [*C*H$_2$ cyclohexyl]; 17.9 [*C*H$_3$]. NOEDIFF experiments: C*H*Ph → N*H*: 9.0; *H*-2 → *H*-3 *trans* to Me: 3.9; C*H*$_3$ → *H*-3 *cis* to Me: 1.5; C*H*$_3$ → *H*-3 *trans* to Me: 2.0; *H*-3 *trans* to Me → *H* ortho of Ph: 3.2.

15b (both enantiomers have been prepared). R*f*: 0.26 (PE/Acetone/AcOEt 8:1:1). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14%. Found: C, 73.65; H, 7.25; N, 7.25%. [(*S*) enantiomer, derived from (*R*) 1-amino-2-propanol]: $[\alpha]_D$ +108.9 (c 1, $CHCl_3$). ^{1}H NMR: δ 7.80 [1 H, dd, *H*-7, J 1.5, 7.8]; 7.54-7.46 [2 H, *H* ortho of Ph]; 7.46-7.34 [4 H, m, *H* ortho and para of Ph, *H*-9]; 7.l9 [1 H, dt, *H*-8, J_d 1.2, J_t 7.5]; 6.91 [1 H, dd, *H*-10, J 0.9, 8.1]; 6.38 [1 H, s, C*H*Ph]; 5.89 [1 H, d, N*H*, J 7.5]; 3.85 [1 H, dtt, C*H*NH, J_d 7.8, J_t 3.9, 10.8]; 3.69 [1 H, ddq, *H*-2, J_d 4.2, 11.1, J_q 6.3]; 3.57 [1 H, dd, *H*-3 exo, J 3.9, 15.9]; 3.27 [1 H, dd, *H*-3 endo, J 11.1, 15.9]; 2.02-1.90 [2 H, m, cyclohexyl]; 1.77-1.54 [4 H, m, cyclohexyl]; 1.44-1.06 [4 H, m, cyclohexyl]; 0.93 [3 H, d, CH_3, J 6.3]. ^{13}C NMR: δ 169.6, 168.5 [*C*=O]; 151.9 [*C*-11]; 135.4 [quat. of PhCH]; 132.7 [*C*-9]; 131.0 [*C*-7]; 129.3 [*C* ortho of PhCH], 129.0 [*C* meta of PhCH]; 128.7 [*C* para of PhCH]; 128.4 [*C*-6]; 124.0 [*C*-8]; 123.2 [*C*-10]; 80.5 [*C*-2]; 60.1 [*C*HPh]; 49.0 [*C*-3]; 48.7 [*C*HNH]; 32.9, 32.8, 25.4, 24.8, 24.7 [*C*H_2 cyclohexyl]; 17.4 [*C*H_3]. NOEDIFF experiments: C*H*Ph → N*H*: 0.5; *H*-2 → *H*-3 *trans* to Me: 4.0; CH_3 → *H*-3 *cis* to Me: 2.8; CH_3 → *H*-3 *trans* to Me: 1.4; *H*-3 *trans* to Me → *H* ortho of Ph: 6.7; *H*-2 → *H* ortho of Ph: 4.0.

16a (prepared in racemic form). R*f*: 0.44 (PE/AcOEt 8:2). Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45;%. Found (analysis performed on the diast. mixture of **16a,b**): C, 74.8; H, 7.9; N, 6.5%. ^{1}H NMR: δ 7.81 [1 H, dd, *H*-7, J 1.8, 7.8]; 7.42 [1 H, dt, *H*-9, J_d 1.8, J_t 7.7]; 7.40-7.30 [5 H, m, C*H* of Ph]; 7.17 [1 H, dt, *H*-8, J_d 1.2, J_t 7.5]; 6.96 [1 H, dd, *H*-10, J 0.9, 8.4]; 6.49 [1 H, s, C*H*Ph]; 6.25 [1 H, d, N*H*, J 7.8]; 4.76 [1 H, tt, *H*-2, J 3.9, 9.5]; 3.87 [1 H, dtt, C*H*NH, J_d 8.1, J_t 4.0, 10.8]; 3.45 [1 H, dd, *H*-3 exo, J 3.6, 15.3]; 3.03 [1 H, dd, *H*-3 endo, J 9.3, 15.3]; 2.02-1.90 [2 H, m, cyclohexyl]; 1.90-1.78 [1 H, m, C*H*$(CH_3)_2$, mc = 1.84]; 1.76-1.52 [4 H, m, cyclohexyl]; 1.47-1.07 [6 H, m, cyclohexyl and CH_2*i*Pr]]; 0.93 and 0.92 [2 x 3 H, 2 d, CH_3, J 6.6]. ^{13}C NMR: δ 169.9, 168.2 [*C*=O]; 153.0 [*C*-11]; 135.6 [quat. of PhCH]; 132.8 [*C*-9]; 130.9 [*C*-7]; 128.8, 128.7 [*C* ortho and meta of PhCH]; 128.3 [*C* para of PhCH]; 127.7 [*C*-6]; 123.5 [*C*-8]; 122.8 [*C*-10]; 82.4 [*C*-2]; 60.6 [*C*HPh]; 48.5 [*C*HNH]; 48.2 [*C*-3]; 40.6 [*C*H_2*i*Pr]; 32.9, 32.7, 25.4, 24.7 (x2) [*C*H_2 cyclohexyl]; 24.5 [*C*H$(CH_3)_2$]; 23.2, 22.0 [*C*H_3].

16b (prepared in racemic form). R*f*: 0.25 (PE/AcOEt 8:2). Found: see above. ^{1}H NMR: δ 7.76 [1 H, dd, *H*-7, J 1.6, 7.7]; 7.56-7.48 [2 H, *H* ortho of Ph]; 7.46-7.32 [4 H, m, *H* meta and para of Ph, *H*-9]; 7.16 [1 H, dt, *H*-8, J_d 1.2, J_t 7.5]; 6.87 [1 H, dd, *H*-10, J 0.9, 8.1]; 6.42 [1 H, s, C*H*Ph]; 5.99 [1 H, d, N*H*, J 7.8]; 3.85 [1 H, dtt, C*H*NH, J_d 8.0, J_t 3.9, 10.5]; 3.62-3.47 [2 H, m, *H*-2 and *H*-3 exo]; 3.31-3.19 [1 H, m, *H*-3 endo]; 2.02-1.90 [2 H, m, cyclohexyl]; 1.75-1.47 [5 H, m, cyclohexyl and C*H*$(CH_3)_2$ (from COSY, *C*H$(CH_3)_2$ is centered at 1.57]; 1.43-1.03 [6 H, m, cyclohexyl and CH_2*i*Pr]; 0.65 and 0.65 [2 x 3 H, 2 d, CH_3, J 6.6]. ^{13}C NMR: δ 169.5, 168.5 [*C*=O]; 152.2 [*C*-11]; 135.4 [quat. of PhCH]; 132.7 [*C*-9]; 131.0 [*C*-7]; 129.5 [*C* ortho of PhCH], 128.9 [*C* meta of PhCH]; 128.7 [*C* para of PhCH]; 128.4 [*C*-6]; 123.8

[*C*-8]; 123.1 [*C*-10]; 80.5 [*C*-2]; 60.1 [*C*HPh]; 48.6 [*C*HNH]; 48.0 [*C*-3]; 40.5 [*C*H$_2$*i*Pr]; 32.8, 32.7, 25.4, 24.8, 24.7 [*C*H$_2$ cyclohexyl]; 24.2 [*C*H(CH$_3$)$_2$]; 22.4, 22.1 [*C*H$_3$].

25a (prepared from (*S*) alaninol). R*f*: 0.35 (CH_2Cl_2/acetone 9:1), 0.53 (PE/AcOEt 50:50). Anal. Calcd for $C_{25}H_{31}N_3O_4S$: C, 63.94; H, 6.65; N, 8.95%. Found: C, 64.2; H, 6.75; N, 8.9%. $[\alpha]_D$ -37.6 (c 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 45°C): δ 7.73-7.68 [1 H, m, *H*-7]; 7.57-7.47 [2 H, m, *H*-9 and *H*-10]; 7.46-7.34 [6 H, m, *H* of Ph and *H*-8]; 6.19 [1 H, broad s, C*H*Ph]; 5.50 [1 H, d, N*H*, J 8.1]; 4.68 [1 H, broad s, *H*-2 trans to methyl]; 3.95 [1 H, ddq, *H*-3, J_d 4.2 and 5.7, J_q 7.2]; 3.90-3.78 [1 H, m, C*H*NH]; 3.80-3.70 [1 H, broad doublet, *H*-2 cis to methyl]; 3.02 [3 H, s, C*H*$_3$S]; 1.96-1.80 [2 H, m, cyclohexyl]; 1.70-1.52 [4 H, m, cyclohexyl]; 1.40-1.24 [2 H, m, cyclohexyl]; 1.20-1.10 [2 H, m, cyclohexyl]; 0.55 [3 H, d, C*H*$_3$CH, J 7.5]. ^{13}C NMR ($CDCl_3$, r.t.): 169.4, 168.1 [*C*=O]; 135.9, 135.8, 134.8 [aromatic quat.]; 132.2 and 131.5 [*C*-9 and *C*-10]; 129.9 [*C*-7]; 129.2, 129.0, 128.9 [*C*H of Ph + *C*-8]; 61.7 [*C*HPh]; 57.7 [*C*-2]; 50.4 (broad) [*C*-3]; 48.8 [*C*HNH]; 38.6 [*C*H$_3$S]; 32.8 (x2), 25.4, 24.74, 24.66 [*C*H$_2$ cyclohexyl]; 18.9 (broad) [*C*H$_3$]. ^{1}H NMR ($CDCl_3$, −45°C)(two conformations were clearly visible in 60:40 ratio): δ of selected peaks: major conformation: 6.94 [1 H, s, C*H*Ph]; 5.32 [1 H, slightly broad doublet, N*H*]; 5.26 [1 H, dd, *H*-2 trans to Me, J 6.9, 12.9]; 3.03 [3 H, s, C*H*$_3$SO$_2$]; 0.23 [3 H, d, Me]; minor conformation: 6.12 [1 H, slightly broad doublet, N*H*]; 5.02 [1 H, s, C*H*Ph]; 4.50 [1 H, t, *H*-2 *cis* to Me, J 12.0]; 3.18 [3 H, s, C*H*$_3$SO$_2$]; 1.15 [3 H, d, Me]. NOEDIFF: C*H*Ph → N*H* : 5.7; C*H*Ph → C*H*$_3$: 3.9; *H*-3 → *H* ortho of Ph: 5.9; C*H*$_3$ → *H* ortho of Ph: 3.4; *H*-2 *cis* to Me → C*H*$_3$: 4.8; *H*-2 *trans* to Me → C*H*$_3$SO$_2$: 1.3; *H*-2 → C*H*$_3$SO$_2$: 1.0.

25b (prepared from (*S*) alaninol). R*f*: 0.18 (CH_2Cl_2/acetone 9:1), 0.32 (PE/AcOEt 50:50). This compound was obtained contaminated by 14% of rearranged ester **30b** and we did not succeeded in separating it from it. Therefore elemental analysis was not carried out, and the $[\alpha]_D$ was measured on this 86:14 mixture. $[\alpha]_D$ −61.7 (c 1.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 45°C): δ 7.77-7.70 [1 H, m, *H*-7]; 7.60-7.38 [8 H, m, *H*-9, *H*-10, *H*-8 and C*H* of Ph]; 6.08 [1 H, s, C*H*Ph]; 5.80 [1 H, d, N*H*, J 7.8]; 4.02 [1 H, ddq, *H*-3, J_d 3.9 and 6.0, J_q 7.2]; 3.85 [1 H, dtt, C*H*NH, J_d, 7.8, J_t 3.9, 10.5]; 3.68 [1 H, dd, *H*-2 trans to methyl, J 6.0, 12.6]; 3.51 [1 H, dd, *H*-2 cis to methyl, J 3.6, 12.6]; 2.61 [3 H, s, C*H*$_3$S]; 1.98-1.86 [2 H, m, cyclohexyl]; 1.76-1.54 [4 H, m, cyclohexyl]; 1.42-1.08 [4 H, m, cyclohexyl]; 1.06 [3 H, d, C*H*$_3$CH, J 7.2]. ^{13}C NMR ($CDCl_3$, 45°C): δ 169.3, 168.0 [*C*=O]; 135.6, 135.1, 134.8 [aromatic quat.]; 132.2 and 130.5 [*C*-9 and *C*-7]; 130.2, 129.7(x2), 129.3 (x2), 129.1, 127.3[*C*H of Ph + *C*-8 + *C*-10]; 62.3 [*C*HPh]; 58.0 [*C*-2]; 50.4 (slightly broad) [*C*-3]; 48.8 [*C*HNH]; 38.9 [*C*H$_3$S]; 32.8 (x2), 25.5, 24.8, 24.7 [*C*H$_2$ cyclohexyl]; 19.3 (slightly broad) [*C*H$_3$]. NOEDIFF: C*H*Ph → N*H* : 6.4; C*H*Ph → C*H*$_3$: 4.1; C*H*Ph → *H*-3: 1.8; *H*-3 → *H* ortho of Ph: 5.6; *H*-2 *cis* to Me → C*H*$_3$: 2.4; *H*-2 *trans* to Me → C*H*$_3$: 1.4; *H*-2 → C*H*$_3$SO$_2$: 3.7.

26a (prepared from (*S*) phenylalaninol. R_f: 0.60 (PE/AcOEt 50:50). Anal. Calcd for $C_{31}H_{35}N_3O_4S$: C, 68.23; H, 6.46; N, 7.70%. Found: C, 68.5; H, 6.55; N, 7.7%. $[\alpha]_D$ −53.2 (c 1.34, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 50°C): δ 7.81 [1 H, dt, *H*-7, J_d 7.8, J_t 0.9]; 7.61-7.56 [2 H, m, *H* ortho of phenyl]; 7.52-7.41 [6 H, m, *H*-8, *H*-9, *H*-10, *H* meta and para of phenyl]; 7.09-7.00 [3 H, m, *H* meta and para of benzyl]; 6.64 [1 H, broad s, C*H*Ph]; 6.23 [2 H, broad s, *H* ortho of benzyl]; 5.63 [1 H, broad d, N*H*, J not det.]; 4.81 [1 H, broad s, *H*-2 trans to Bn]; 3.93-3.80 [2 H, m, *H*-3 and C*H*NH]; 3.57 [1 H, broad d, *H*-2 cis, J 16.2]; 2.97 [3 H, s, C*H*SO_2]; 1.97-1.75 [4 H, m, CH_2 cyclohexyl + CH_2Ph]; *(thanks to NOE it is possible to see that CH_2Ph is a multiplet centered at 1.86 ppm)* 1.75-1.54 [4 H, m, CH_2 cyclohexyl]; 1.48-1.06 [4 H, m, cyclohexyl]. ^{13}C NMR ($CDCl_3$, 35 °C): δ 169.3, 168.2 [*C*=O]; 137.0, 136.3 (broad), 135.4 [quat.] (*note: 1 quat. carbon is probably very broad or covered by the* C*H*); 132.3, 131.8, 130.1, 129.8 (x2), 129.3 (x 2), 129.2, 129.2 (x 2), 129.1, 128.6 (x 2), 126.7 [aromatic *C*H]; 61.7 [*C*HPh]; 55.5 (broad) [*C*-3]; 53.0 [*C*-2]; 48.8 [*C*HNH]; 40.0 (broad) [*C*H_2Ph]; 38.3 [*C*H_3]; 32.94, 32.86, 25.4, 24.8, 24.7 [*C*H_2 cyclohexyl]. ^{1}H NMR (d6-DMSO, 70°C): δ 8.31 [1 H, broad d, N*H*, J 6.6]; 7.76 [1 H, dd, *H*-7, J 1.6, 7.7]; 7.68 [1 H, dt, *H*-9, J_d 1.8, J_t 7.5]; 7.59 [1 H, dt, *H*-8, J_d 1.2, J_d 7.5]; 7.53-7.40 [6 H, m, Ph C*H* and *H*-10]; 7.12-7.05 [3 H, m, *H* meta and para of PhCH_2]; 6.72 [1 H, s, C*H*Ph]; 6.20-6.12 [2 H, m, *H* ortho of PhCH_2]; 4.72 [1 H, dd, *H*-2 trans to Bn, J 6.9, 12.9]; 3.92 [1 H, dt, J_t 6.0, J_d 12.0]; 3.71 (mc) [1 H, C*H*NH, m]; 3.34 [1 H, d, *H*-2 cis to Bn, J 13.2]; 2.91 [CH_3]; 1.86-1.50 [6 H, m, cyclohexyl CH_2 and CH_2Ph (from gCOSY and gHSQC, CH_2Ph is centered at 1.75 ppm)]; 1.40-1.07 [6 H, m, cyclohexyl CH_2]. ^{13}C NMR (d6-DMSO, 70°C): δ 167.73, 167.70 [*C*=O]; 136.8, 136.1, 135.8, 134.6 [quat. aromatics]; 131.6 [*C*-8]; 130.8 [*C*-10]; 129.5 [*C*-7]; 128.9 (x2), 128.7, 128.5 (x2), 128.1 [*C* of Ph + *C*-9]; 128.3 [*C* ortho of Bn]; 128.1 [*C* meta of Bn]; 126.1 [*C* para of Bn]; 59.6 [*C*HPh]; 54.3 [*C*-3]; 51.8 [*C*-2]; 47.6 [*C*HNH]; 39.3 [*C*H_2Ph]; 37.7 [*C*H_3SO_2]; 31.7, 31.6, 24.7, 24.03, 24.95 [cyclohexyl *C*H_2]. NOEDIFF: C*H*Ph →N*H*: 9.7; C*H*Ph → C*H*HPh: 1.9; C*H*Ph → *H*-3: 1.7; *H*-2 *cis* to Bn → *H* ortho of Bn: 4.2; *H*-2 *cis* to Bn → CH_2Ph: 0.8; *H*-3 → *H* ortho of Bn: 2.4.

26b (prepared from (*S*) phenylalaninol). R_f: 0.47 (PE/AcOEt 50:50). Anal. Calcd for $C_{31}H_{35}N_3O_4S$: C, 68.23; H, 6.46; N, 7.70%. Found: C, 68.35; H, 6.35; N, 7.6%. $[\alpha]_D$ −89.0 (c 4.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 45°C):δ 7.81 [1 H, dd, *H*-7, J 7.5, 1.5]; 7.64-7.56 [4 H, m, *H*-9 and other aromatics]; 7.48-7.56 [1 H, m, *H*-8]; 7.46-7.36 [2 H, m, aromatics]; 7.30-7.08 [3 H, m, aromatics]; 6.92 [2 H, d, aromatics, J 7.2]; 6.32 [1 H, s, C*H*Ph]; 5.78 [1 H, broad d, N*H*, J 6.6]; 4.06-3.96 (mc = 4.02) [1 H, m, *H*-3]; 3.88 [1 H, dtt, C*H*NH, J_d 7.8, J_t 3.9, 10.5]; 3.46 [1 H, dd, *H*-2, J 6.6, 12.9]; 3.32 [1 H, slightly broad d, *H*-2, J 13.2]; 3.15 [1 H, dd, C*H*HPh, J 3.6, 13.2]; 2.70 [3 H, s, CH_3]; 2.03-1.87 [3 H, m, C*H*HPh and cyclohexyl]*(thanks to NOE it is possible to see that CHHPh is a triplet at 1.95 with J 12.3)*; 1.77-1.50 [4 H, m, cyclohexyl]; 1.48-1.06 [4 H, m, cyclohexyl]. ^{13}C NMR ($CDCl_3$, 45°C): δ 169.1, 168.1 [*C*=O]; 138.1, 136.3, 135.3,

135.0 [quat.]; 132.5 [*C*-9]; 130.8 [*C*-7]; 130.1 [*C*-8]; 129.7 (x2), 129.6 (x 2), 129.4 (x2), 129.31, 129.28, 128.7 (x 2) [other aromatic *C*H]; 126.7 [*C*-10]; 62.5 [*C*HPh]; 56.0 [*C*-3]; 53.1 [*C*-2]; 48.7 [*C*HNH]; 39.4 [CH_2Ph]; 39.1 [CH_3]; 32.9 (x2), 25.5, 24.8, 24.7 [CH_2 cyclohexyl].
NOEDIFF: C*H*Ph →N*H*: 9.2; C*H*Ph → *H*-3: 1.5; *H*-2 *cis* to Bn → *H* ortho of Bn: 1.1.

27a,b. (prepared from (*S*) phenylalaninol). The two diastereoisomers could not be separated in this case However, a small sample of pure **27b** could be obtained starting from diastereoisomerically pure **23b**. R_f: 0.33 (PE/AcOEt/acetone 80:10:10). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14%. Found (analysis carried out of the diast. mixture): C, 73.3; H, 7.3; N, 7.0%. ^{1}H NMR: **27a**: δ 8.17 [1 H, dd, *H*-7, J 8.1, 1.8]; 7.50-7.30 [6 H, m, *H*-9 and *H* of PhCHN]; 7.02-6.94 [2 H, m, *H*-8 and *H*-10]; 6.38 [1 H, s, C*H*Ph]; 5.82 [1 H, d, N*H*, J 8.1]; 4.61 [1 H, d, *H*-2 trans to Bn, J 12.6]; 4.42 [1 H, dd, *H*-2 cis to Bn, J 12.6, 5.4]; 4.07 [1 H, dq, *H*-3, J_d 5.4, J_q 6.9]; 3.90-3.80 [1 H, m, C*H*NH]; 2.00-1.90 [2 H, m, cyclohexyl]; 1.77-1.55 [4 H, m, cyclohexyl]; 1.50-1.10 [4 H, m, cyclohexyl]; 0.60 [3 H, d, CH_3, J 6.9]. **27b**: δ 8.11 [1 H, dd, *H*-7, J 8.1, 1.8]; 7.50-7.30 [6 H, m, *H*-9 and *H* of PhCHN]; 7.06 [1 H, ddd, *H*-8, J 1.2, 7.4, 7.8]; 6.97 [1 H, dd, *H*-10, J 0.9, 8.1]; 6.36 [1 H, s, C*H*Ph]; 6.21 [1 H, d, N*H*, J 7.8]; 4.10 [1 H, dd, *H*-2 cis to Me, J 11.8, 5.0]; 3.97 [1 H, ddq, *H*-3, J_d 1.5, 5.1, 6.9]; 3.90-3.80 [1 H, m, C*H*NH]; 3.76 [1 H, dd, *H*-2 trans to Me, J 1.5, 12.0]; 2.00-1.90 [2 H, m, cyclohexyl]; 1.77-1.55 [4 H, m, cyclohexyl]; 1.50-1.10 [4 H, m, cyclohexyl]; 1.25 [3 H, d, CH_3, J 7.2].
^{13}C NMR: **27a**: δ 169.1, 167.5 [*C*=O]; 155.9 [*C*-11]; 135.2 [quat. of PhCH]; 133.9 [*C*-7]; 132.8 [*C*-9]; 130.3 (x2), 128.8 (x2), 128.7 [*C*H of PhCH]; 120.5 [*C*-8]; 120.3 [*C*-6]; 119.1 [*C*-10]; 73.7 [*C*-2]; 62.8 [*C*HPh]; 52.0 [*C*-3]; 48.7 [*C*HNH]; 32.8 (x2), 25.5, 24.8 (x2) [CH_2 cyclohexyl]; 15.2 [CH_3]. **27b**: δ 168.4, 167.8 [*C*=O]; 155.6 [*C*-11]; 135.2 [quat. of PhCH]; 133.5 [*C*-7]; 133.1 [*C*-9]; 128.9 (x2), 128.7 (x2), 128.3 [*C*H of PhCH]; 122.4 [*C*-6]; 121.6 [*C*-8]; 119.7 [*C*-10]; 75.1 [*C*-2]; 63.0 [*C*HPh]; 51.3 [*C*-3]; 48.5 [*C*HNH]; 32.8, 32.7 25.5, 24.8 (x2) [CH_2 cyclohexyl]; 15.9 [CH_3].
NOEDIFF: **27a**: C*H*Ph → N*H*: 16.7; CH_3 → *H* ortho of Ph: 3.0; CH_3 → *H*-2 *cis* to Me: 3.5. **27b**: C*H*Ph → N*H*: 11.7; C*H*Ph → CH_3: 1.5; CH_3 → *H*-2 *cis* to Me: 2.0; *H*-2 *trans* to Me →*H* ortho of Ph: 2.4.

28a (prepared from (*S*) phenylalaninol). R_f 0.48 (PE/Et_2O/acetone 75:15:10). Anal. Calcd. for $C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98%. Found: C, 76.8; H, 6.85; N, 5.9%. $[\alpha]_D$ + 62.3 (c 1.88, $CHCl_3$). ^{1}H NMR: δ 8.20 [1 H, broad d, *H*-7, J 8.4]; 7.58-7.46 [5 H, m, *H* of PhCHN group]; 7.42 [1 H, ddd, *H*-9, J 2.0, 6.9, 8.4]; 7.18-7.10 [3 H, m, *H* meta and para of $PhCH_2$,]; 7.07 [1 H, dd, *H*-10 O, J 1.2, 8.4]; 7.03 (mc) [1 H, m, *H*-8]; 6.57 (mc) [2 H, m, *H* ortho of $PhCH_2$]; 6.44 [1 H, s, C*H*Ph]; 5.81 [1 H, broad s, N*H*]; 4.55 [1 H, d, *H*-2 trans to benzyl, J 12.6]; 4.25 [1 H, dd, *H*-2 cis to benzyl, J 5.2, 12.6]; 4.02 [1 H, dt, *H*-3, J_d 12.9, J_t 4.5]; 3.81 [1 H, dtt, C*H*NH, J_t 3.6, 10.8, J_d 7.8]; 2.56 [1 H, t, C*H*HPh, J 12.7]; 2.02-1.88 [2 H, m,

cyclohexyl]; 1.84 [1 H, dd, C*H*HPh, J 3.6, 13.2]; 1.74-1.50 [4 H, m, cyclohexyl]; 1.44-1.00 [4 H, m, cyclohexyl]. ^{13}C NMR: δ 169.2, 167.6 [*C*=O]; 156.0 [*C*-11]; 137.4, 135.1 [quat. of $PhCH_2$ and PhCH]; 134.1 [*C*-7]; 133.0 [*C*-9]; 130.6 [*C* ortho of PhCH]; 129.1 [*C* ortho of $PhCH_2$, *C* meta and para of PhCH]; 128.3 [*C* meta of $PhCH_2$]; 126.4 [*C* para of $PhCH_2$]; 120.6 [*C*-8]; 120.3 [*C*-6]; 119.2 [*C*-10]; 69.9 [*C*-2]; 63.2 [*C*HPh]; 58.0 [*C*-3]; 48.7 [*C*HNH]; 36.2 [*C*H_2Ph]; 32.8 (x2), 25.4, 24.8, 24.7 [*C*H_2 cyclohexyl]. NOEDIFF: C*H*Ph → N*H*: 11.0; *H*-3 → *H* ortho of Ph: 7.8; *H* of CH_2Ph gauche to *H*-3 → *H*-3: 4.9; *H* of CH_2Ph gauche to *H*-3 → *H* ortho of Ph: 1.8; *H*-3 → *H* ortho of benzyl: 5.7.

28b (prepared from (*S*) phenylalaninol). R_f 0.55 (PE/Et_2O/acetone 75:15:10). Anal. Calcd for $C_{30}H_{32}N_2O_3$: C, 76.90; H, 6.88; N, 5.98%. Found: C, 76.8; H, 6.85; N, 5.9%. $[\alpha]_D$ −31.4 (c 1.95, $CHCl_3$). ^{1}H NMR: δ 8.22 [1 H, dd, *H*-7, J 8.0, 1.6]; 7.56-7.47 [2 H, m, *H* ortho of PhCHN group]; 7.46 [1 H, ddd, *H*-9, J 1.5, 6.9, 7.8]; 7.40-7.30 [3 H, m, *H* meta and para of PhCHN group]; 7.27-7.15 [5 H, m, *H* of $PhCH_2$]; 7.10 [1 H, ddd, *H*-8, J 1.2, 7.2, 8.1]; 7.07 [1 H, dd, *H*-10, J 0.9, 8.1]; 6.51 [1 H, s, C*H*Ph]; 6.11 [1 H, d, N*H*, J 7.5]; 4.10 [3 H, m, *H*-3, C*H*NH, *H*-2 cis to benzyl]; 3.59 [1 H, d, *H*-2 trans to benzyl, J 11.4]; 3.20 [1 H, dd, C*H*HPh, J 3.3, 12.9]; 2.67 [1 H, dd, C*H*HPh, J 12.0 and 12.6]; 2.03-1.93 [2 H, m, cyclohexyl]; 1.77-1.55 [4 H, m, cyclohexyl]; 1.50-1.10 [4 H, m, cyclohexyl]. ^{13}C NMR: 168.1, 167.7 [*C*=O]; 155.8 [*C*-11]; 138.1, 135.0 [quat. of $PhCH_2$ and PhCH]; 133.9 [*C*-7]; 133.4 [*C*-9]; 129.5 (x2), 129.0 (x2), 128.9 (x2), 128.5, 128.4 (x2), 126.5 [*H* of PhCh and $PhCH_2$]; 121.8 [*C*-6]; 121.4 [*C*-8]; 119.7 [*C*-10]; 71.1 [*C*-2]; 62.6 [*C*HPh]; 57.3 [*C*-3]; 48.6 [*C*HNH]; 35.9 [*C*H_2Ph]; 32.9, 32.8 25.5, 24.8 (x2) [*C*H_2 cyclohexyl]. NOEDIFF: C*H*Ph → N*H*: 11.0; N*H* → *H*-3: 2.4.

Note: in the cases of **28a,b**, the attribution of *H*-2 (*cis* to Bn or *trans* to Bn) is not completely sure. Actually in this case there is no NOE between the benzyl CH_2 and *H*-2, because the phenyl group is in *anti* position (relative to the ring C-N bond) and hence directed towards *H*-2, as demostrated by the coupling constants.. This attribution is therefore based on analogies with the methyl derivatives **27a,b**.

29a (prepared from (S*)* valinol). R_f 0.31 (PE / Et_2O / acetone 75: 15: 10). Anal. Calcd. for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66%. Found: C, 74.2; H, 7.7; N, 6.6%. $[\alpha]_D$ +15.4 (c 1.71, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.00 [1 H, dd, *H*-7, J 1.5, 8.1]; 7.55-7.46 [2 H, m, aromatics]; 7.42-7.34 [3 H, m, aromatics]; 7.34 [1 H, ddd, *H*-9, J_d 1.8, 6.9, 8.7]; 6.98-6.89 [2 H, m, *H*-8 and *H*-10]; 6.12 [1 H, s, C*H*Ph]; 6.02 [1 H, d, N*H*]; 4.68 [2 H, d, *H*-2, J 3.0]; 3.76 [1 H, dtt, C*H*NH, J_d, 8.0, J_t 4.2, 10.5]; 3.56 [1 H, dt, *H*-3, J_d 10.5, J_t 3.0]; 1.95-1.78 [2 H, m, cyclohexyl CH_2]; 1.70-1.50 [3 H, m, cyclohexyl CH_2 + C$H(CH_3)_2$]; 1.40-1.00 [6 H, m, cyclohexyl CH_2]; 0.75 [3 H, d, CH_3, J 6.6]; 0.27 [3 H, d, CH_3, J 6.9]. ^{13}C ($CDCl_3$): δ 169.1, 168.5 [*C*=O]; 155.9 [*C*-11]; 135.0 [quat.]; 133.7 [*C*-7]; 132.7 [*C*-9]; 130.8 (x2), 130.0, 128.8 (x2) [Ph *C*H];

121.0 [*C*-11]; 120.5 [*C*-8]; 118.9 [*C*-10]; 71.8 [*C*H_2O]; 65.7 [Ph*C*H]; 61.7 [*C*-3]; 48.6 [*C*HNH]; 32.7, 32.6, 25.4, 24.8, 24.7 [*C*H_2 cyclohexyl]; 27.7 [*C*H(CH_3)$_2$]; 20.0, 19.4 [*C*H_3].

Selected NMR data of rearranged esters.

30b: ^{1}H NMR ($CDCl_3$, 45°C): 10.35 [1 H, s, N*H*SO_2]; 8.05 [1 H, dd, *H*-7, J 1.5, 8.1]; 7.60-7.38 [7 H, m, *H*-9, *H*-10 and C*H* of Ph]; 7.13 [1 H, dt, *H*-8, J_d 1.2, J_t 7.8]; 6.84 [1 H, d, N*H*cyclohexyl, J 8.1]; 4.31 [1 H, s, C*H*Ph]; 4.27 and 4.25 [2 H, AB part of ABX syst., C*H*$_2$O, J_{AB} 11.0, J_{BX} 4.1, J_{AX} 5.4]; 3.80-3.66 [1 H, m, C*H*NH]; 3.11 [1 H, quintuplet, C*H*CH_3, J 6.0]; 3.06 [3 H, s, C*H*$_3$$SO_2$]; 1.98-1.86 [2 H, m, cyclohexyl]; 1.76-1.54 [4 H, m, cyclohexyl]; 1.42-1.08 [4 H, m, cyclohexyl]; 1.21 [3 H, d, C*H*$_3$CH, J 6.6].

^{13}C NMR ($CDCl_3$, 45°C): 171.0, 167.8 [*C*=O]; 141.1, 140.1, 136.0 [aromatic quat.]; 131.5 [*C*-7]; 129.1, 129.0, 128.2, [*C*H of Ph + *C*-9]; 122.9 [*C*-8]; 118.3 [*C*-10]; 68.8 [*C*H_2O]; 65.3 [*C*HPh]; 51.3 [*C*HCH_3]; 47.9 [*C*HNH]; 40.2 [*C*H_3S]; 33.0 (x2), 25.5, 24.8, 24.7 [*C*H_2 cyclohexyl]; 18.0 [*C*H_3].

34b: R_f 0.57 (PE / Et_2O / acetone 75: 15: 10). ^{1}H NMR ($CDCl_3$): δ 9.08 [1 H, s, O*H*]; 7.66-7.60 [1 H, m, C*H* ortho to CO_2]; 7.50-7.40 [5 H, m, aromatic C*H*]; 7.27 [1 H, dt, C*H* para to C=O, J_d 1.5, J_t 7.8]; 6.97 [1 H, dd, C*H* ortho to O, J 0.9, 8.1]; 6.89 [1 H, dt, C*H* para to O, J_d 0.9, J_t 7.5]; 5.44 [1 H, d, amidic N*H*, J 8.1]; 4.64 [1 H, s, C*H*Ph]; 3.92-3.60 [4 H, m, C*H*(*i*Pr), C*H*NH, C*H*$_2$O]; 2.00-1.90 [2 H, m, cyclohexyl]; 1.80-1.44 [4 H, m, cyclohexyl]; 1.40-1.05 [5 H, m, cyclohexyl and C*H*(CH_3)$_2$]; 0.72 [3 H, d, C*H*$_3$, J 6.6]; 0.42 [3 H, d, C*H*$_3$, J 6.3]; ^{13}C NMR: δ 172.8, 170.9 [*C*=O]; 152.6 [aromatic *C*-O]; 136.2, 123.7 [quat.]; 130.9, 129.6 (x2), 129.35 (x2), 129.28, 128.1, 119.8, 119.0 [aromatic *C*H]; 68.1 [*C*H_2O]; 62.1, 59.7 [*C*HPh and *C*HN]; 49.2 [*C*HN cyclohexyl]; 28.9 [*C*H(CH_3)$_2$]; 32.3, 32.1, 25.3, 24.5, 24.3 [*C*H_2 cyclohexyl]; 20.4, 18.8 [*C*H_3].

Synthesis of compound 41 through intermolecular Mitsunobu reaction.

A solution of (Boc)(*S*)-alaninol (234 mg, 1.60 mmol) in dry CH_2Cl_2 (1 mL), was treated at 0°C with benzyl salycilate (246 mg, 1.07 mmol), PPh_3 (476 mg, 1.80 mmol) and di-*tert*-butyl azodicarboxylate (414 mg, 1.80 mmol). After 2 h at 0°C, the mixture was evaporated to dryness and chromatographed (PE / AcOEt 85:15) to give pure **41** (262 mg, 64%).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63%. Found: C, 68.0; H, 7.2; N, 3.8%.

^{1}H NMR ($CDCl_3$): δ 7.88 [1 H, dd, *H*-7, J 1.8, 7.8]; 7.49-7.30 [6 H, m, other aromatics]; 6.99 [1 H, dt, *H*-8, J_d 0.9, J_t 7.6]; 6.92 [1 H, d, *H*-10, J 7.6]; 5.38 and 5.34 [2 H, AB system, OC*H*$_2$Ph, J 12.0]; 5.12 [1 H, broad s, N*H*]; 4.06-3.95 [3 H, m, *H*-3, *H*-2]; 1.45 [9 H, s, C(C*H*$_3$)$_3$]; 1.18 [3 H, d, C*h*$_3$CH, J 6.6].

^{13}C NMR ($CDCl_3$): δ 166.1, 158.7 [*C*=O]; 155.3 [*C*-11]; 136.1 [aromatic quat.]; 133.8 [*C*-9]; 132.2 [*C*-7 + (probably) 1 aromatic quat.]; 128.7 (x2), 128.6 (x2), 128.3 [benzyl *C*H]; 120.6 [*C*-8]; 113.4 [*C*-10]; 79.2 [*C*(CH_3)$_3$]; 72.0 [*C*-2]; 66.7 [Ph*C*H_2O]; 45.7 [*C*-3]; 28.4 [C(*C*H_3)$_3$]; 17.9 [*C*H_3CH].

Synthesis of compound 42 through intermolecular Mitsunobu reaction.

It was prepared in 77% yield from 200 mg of Cbz-Phenylalaninol (0.70 mmol), 240 mg of benzyl salycilate (1.05 mmol), 272 mg of PPh_3 (1.04 mmol), 164 μL of DEAD (1.04 mmol) in 500 μL of THF following the same procedure employed above for **41**.

Anal. Calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83%. Found: C, 75.4; H, 6.0; N, 2.9%.

^{1}H NMR ($CDCl_3$): δ 7.91 [1 H, dd, *H*-7, J 1.8, 7.5]; 7.48-7.12 [11 H, m, other aromatics]; 7.00 [1 H, dt, *H*-8, J_d 1.2, J_t 7.5]; 6.81 [1 H, d, *H*-10, J 8.1]; 5.72 [1 H, d, N*H*, J 9.0]; 5.37 [2 H, s, OCH_2Ph]; 5.12 and 5.09 [2 H, AB system, OCH_2Ph, J 12.3]; 4.16 (mc) [1 H, m, *H*-3], 3.96 and 3.88 [2 H, AB part of ABX system, *H*-2, J_{AB} 9.1, J_{AX} 3.3, J_{BX} 2.2]; 2.96-2.80 [2 H, m, CH_2Ph].

^{13}C NMR ($CDCl_3$): δ 165.9, 158.6 [*C*=O]; 155.9 [*C*-11]; 137.9 (x2), 136.6, 136.0 [aromatic quat.]; 133.9 [*C*-9]; 132.2 [*C*-7]; 129.38 (x2), 128.7 (x2), 128.53 (x4), 128.47 (x2), 128.35, 128.00, 127.98 (x2), 126.5 [aromatic *C*H]; 120.7 [*C*-8]; 113.5 [*C*-10]; 68.4 [*C*-2]; 66.8, 66.6 [Ph*C*H_2O]; 51.9 [*C*HNH]; 37.6 [*C*H_2Ph].

Synthesis of compounds 27a,b from 41 through intramolecular Ugi reaction

A solution of **41** (172 mg, 0.446 mmol) in dioxane (2 mL) was treated with a 1.25 M solution of HCl in *i*PrOH. After 48 h at rt the deblocking of Boc group was complete. The solution was diluted with AcOEt (20 ml) and 1 M NaOH (15 ml). The phase were separated and the aqueous phase reextracted twice with AcOEt. After evaporation the residue was taken up in MeOH (5 mL) and H_2O (200 μL) and hydrogenated for 4 h over 10% Pd-C (30 mg). After filtration of the catalyst and evaporation to dryness the residue was taken up in trifluoroethanol (2.4 mL) and treated with benzaldehyde (48 μl, 0.472 mmol) and cyclohexyl isocyanide (60 μL, 0.480 mmol). The solution was stirred for 24 h, evaporated to dryness and chromatographed (PE/acetone) to give the pure inseparable mixture of **27a,b** in 41:59 **a**:**b** ratio (65 mg, 37%).

Synthesis of compounds 28a,b from 42 through intramolecular Ugi reaction

A solution of **42** (270 mg, 0.545 mmol) in MeOH (5 mL) and H_2O (200 μL) and hydrogenated overnight over 10% Pd-C (30 mg). After filtration of the catalyst and evaporation to dryness the residue was taken up in trifluoroethanol (2.8 mL) and treated with benzaldehyde (57 μl, 0.56 mmol) and cyclohexyl isocyanide (70 μL, 0.56 mmol). The solution was stirred for 24 h, evaporated to dryness and chromatographed (PE/Et_2O/acetone 75:15:10) to give pure **28b** (eluting first)(89 mg) **and 28a** (56 mg) in (overall yield: 57%). HPLC analysis on the crude product indicates a **28b** : **28a** ratio of 61:39.

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