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FULL PAPER

Diversity-Oriented Synthesis of Various Enantiopure Heterocycles by Coupling Organocatalysis with Multicomponent Reactions

Samantha Caputo,[a] Luca Banfi,*[a] Andrea Basso,[a] Andrea Galatini,[a] Lisa Moni,[a] Renata Riva,[a] and Chiara Lambruschini[a]

Abstract: Chiral, enantiopure 1,3-aminoalcohols, obtained through an organocatalytic Mannich reaction, have been used as inputs in a concise sequence involving diastereoselective Ugi reaction followed by various types of S_N2 cyclization. In this way, different enantiopure heterocycles have been prepared, exploring both scaffold and decoration diversity (up to 4 diversity inputs).

Introduction

A very powerful method for synthesizing a variety of heterocycles in a diversity-oriented manner is represented by the combination of the Ugi multicomponent reaction with a post condensation cyclization step.[1] The Ugi reaction allows indeed the introduction, in a single step, of up to 4 diversity inputs, represented by easily available classes of molecules (carbonyl compounds, amines, carboxylic acids and isocyanides), thus granting an extraordinary rate of complexity increase per step, and hence a high step-economy. Then, the number of possible cyclization modes following the Ugi MCR is nearly limitless, allowing an ample exploration of scaffold diversity, and giving access to a wide range of nitrogen heterocycles, including unusual ones. Often it is also possible to obtain different scaffolds from a single Ugi adduct, making the MCR product a "pluripotent" intermediate.[2] Among the many cyclization modes, in the last decade, we have been particularly interested in nucleophilic aliphatic substitutions.[1c, 3]

During the Ugi reaction, generally a new stereogenic centre is formed. Therefore, unless some aromatization takes place, also the final heterocycles are chiral. However, in most cases reported in the literature, due to the lack of efficient asymmetric catalysts for the Ugi reaction, and to the use of achiral components, these heterocycles have been typically obtained in racemic form.

The use of chiral inputs for the Ugi reaction may also be troublesome. It is well known that chiral aldehydes with an α-stereogenic centre are prone to racemize,[4] whereas chiral isocyanides and carboxylic acids invariably lead to very poor diastereoselection.[5] The only way to obtain reasonable diastereomeric ratios is the use of chiral amines[6] or chiral cyclic imines.[7] The use of chiral auxiliaries in the amine component has also met some success, but the need to remove the auxiliary reduces the number of diversity inputs and increases the synthetic steps.

Thus, in our group, we chose to pursue an alternative strategy for the obtainment of chiral enantiopure heterocycles: the use of chiral components whose structure is retained in the final products thus contributing to their diversity.[8] In order to be realistically applicable, this approach requires a robust, and diversity-oriented method for obtaining the required chiral inputs. This may be done by using a 2-component organocatalyzed process that precedes the Ugi step. In this way, up to 5 diversity inputs may be introduced in the whole synthetic sequence. Recently this approach has been successfully employed by us and others.[9]

In this regard, we have been attracted by the very useful organocatalytic Mannich reaction of aromatic *N*-Boc-imines with aldehydes developed by List and coworkers (Scheme 1).[10] The products **2** of this reaction, that proceeds with high e.e. and d.r. using such a simple organocatalyst as proline, enclose two functional groups (a protected amine and an aldehyde), both of them exploitable in an Ugi MCR. In particular, we thought that 1,3-aminoalcohols derived from reduction and Boc cleavage could be ideal substrates for two reasons: a) the possibility to get good degrees of diastereoselectivity, also in view of a recent report by Nenajdenko, who used chiral 1,2-aminoalcohols;[6c] b) the presence of an additional alcohol, that could be precious for post-MCR cyclizations to afford heterocycles.

In a preliminary work,[11] we have already reported the Ugi reaction of aminoalcohols **4**, which allows a quite fast entry into adducts **5** with 5 points of diversity. Since aldehydes **2** and amines **4** are not isolated, the whole sequence involves just 2 steps from Boc-imines **1** (or, better, from their carbamoyl sulphone precursors).

In this paper, we extend the scope of this Ugi reaction, using other substrates (including functionalised ones), assign the relative configuration to the diastereomeric products, and, most of all, report the successful transformation of adducts **5** into a variety of heterocyclic structures, through S_N2 cyclizations, which take advantage of the presence of an alcohol, of a secondary amide, and of suitably placed additional functional groups.

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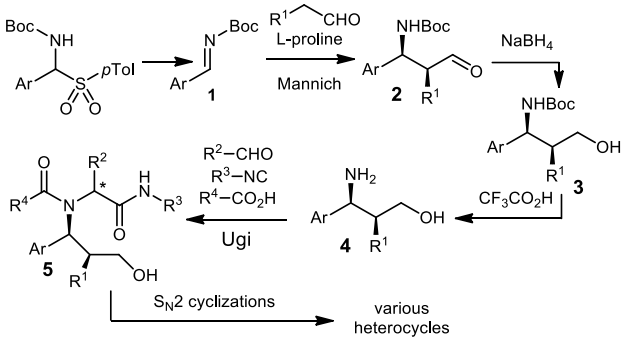


Scheme 1. General strategy.

Results and Discussion

For the synthesis of Ugi adducts **5** we used two general methodologies: a) a $ZnBr_2$ catalysed reaction in THF at -38°C (method A) and b) a classical reaction at r.t. in methanol (method B). Table 1 resumes the results of the Ugi reactions affording the intermediates discussed in this paper. Apart from compounds **5a** and **5i**, already described in our previous paper,[11] these Ugi adducts are all new. While in most cases the $ZnBr_2$ catalysed reaction proved to be more efficient in terms of diastereoselectivity, for some combinations of substrates, method B was found to be superior in terms of yield and/or diastereoselectivity. In all cases, using method A, the major diastereoisomer had always the *S* configuration (the same trend was found in our preliminary paper).

However, when using aromatic isocyanides with method B, an inversion of diastereoselection was observed (entries 2-4). This inversion was particularly pronounced when Ar = 3-BrC_6H_4 (entries 2 and 4). If one compares the results of entries 3 and 4 of Table 1, it is clear that the bromine atom has a remarkable effect, notwithstanding its remoteness from the reacting centre.

In the case of Ugi adduct **5b** (entry 2) also method A was poorly diastereoselective. Interestingly, by shifting from methanol to trifluoroethanol, the normal preference for the (*S*) isomer was restored.

Table 1. Table Caption. ((Note: Please do not include the table in a textbox or frame))

						method A		method B	
Entry	Ugi product	Ar	R^2	R^3	R^4	Yield[a]	d.r (*S*:*R*)[b]	Yield[a]	d.r (*S*:*R*)[b]
1	**5a**	Ph	*i*Pr	*cy*Hex	5-Cl-2-thienyl	82%[c]	91:9[c]	72%[c]	72:28[c]
2	**5b**	3-BrC_6H_4	*i*Pr	4-$AllOC_6H_4$	Et	54%	51:49	67% (68%)[d]	42:58 (64:36)[d]
3	**5c**	Ph	*i*Pr	4-$AllOC_6H_4$	$ClCH_2$	51%	67:33	64%	48:52
4	**5d**	3-BrC_6H_4	*i*Pr	4-$AllOC_6H_4$	$ClCH_2$	68%	66:34	69%	38:62
5	**5e**	Ph	$PhCH_2CH_2$	*t*Bu	$ClCH_2$	32%	69:31[e]		
6	**5f**	2-$AllOC_6H_4$	*i*Pr	*cy*Hex	$ClCH_2$	48%	85:15	51%	62:38
7	**5g**	Ph	*cy*Hex	*t*Bu	$ClCH_2$	43%	60:40[f]		
8	**5h**	2-$BnOC_6H_4$	*i*Pr	*n*Bu	Et	60%	69:31		
9	**5i**	2-$BnOC_6H_4$	*i*Pr	*cy*Hex	5-Cl-2-thienyl	31%[c]	82:18[c]	40%[c]	64:36[c]
10	**5j**	2-$BnOC_6H_4$	*i*Pr	*cy*Hex	$ClCH_2$	51%	88:12	67%	62:38
11	**5k**	2-$BnOC_6H_4$	*i*Pr	*n*Pent	$ClCH_2$	42%	75:25		
12	**5l**	2-$BnOC_6H_4$	$iPrCH_2$	*cy*Hex	$ClCH_2$	35%	76:24		

[a] Isolated yield of **5** from Boc aminoalcohols **9**, **15** or **16**. Method A: $ZnBr_2$, THF, −38°C. Method B: MeOH, r.t. [b] Determined by HPLC. [c] For compounds **5** and **5i** the yields are those already reported in our previous paper (ref. 11). [d] Reaction carried out in CF_3CH_2OH at 0°C. [e] Determined by weight of the isolated diastereomers. [f] Determined by weight of the isolated diastereomers only after conversion into diketopiperazines **17g**.

The two isomers could be in almost all cases separated at the level of Ugi adducts **5**. Only in one instance that was not possible and separation was carried out at the level of the final heterocycle (entry 7). Thus in all cases it has been possible to obtain the final heterocycles in enantio- and diastereoisomeric pure form.

The Ugi adducts **5c-g** and **5j-l**, derived from chloroacetic acid, proved to be somehow unstable on standing. Therefore, they

were not fully characterized, but submitted to the cyclization conditions soon after their chromatography.

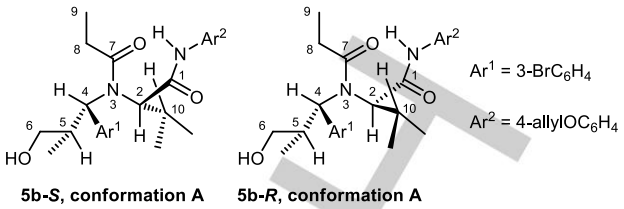
For all Ugi adducts **5**, both the ones described in this paper and those previously reported in our preliminary work,[11] strong HPLC, TLC and NMR analogies were found: **a**) the faster running isomer in HPLC (reverse-phase) was always the slower running isomer in TLC (petroleum ether/AcOEt). This was always the major isomer when the Ugi reaction was carried out in THF with $ZnBr_2$ as promoter (method A); **b**) ^{1}H NMR of the faster running isomer (HPLC) showed in all cases a strong upfield shift for the signals of the isocyanide derived secondary amide (namely the NH signals, and its neighbours). On the other hand, the slower running isomer (HPLC) showed in all cases a strong upfield shift for the isopropyl methyls (in particular for one of them the shift was around 1 ppm) or, when aldehydes different from isobutyraldehyde were used, for the signals of R^3 group.

These upfield shifts are due to the anisotropic effect of the aryl group present in the starting aminoalcohol. The use of anisotropic upfield shifts provoked by an aryl group is a well assessed methodology for the assignment of relative configuration.[12] However, in order to use this method, it is necessary to know the preferred conformation of the examined compounds.

Therefore, in the case of Ugi adducts **5b**, we have carried out a thorough conformational analysis with the aid of ^{1}H NMR experiments. More details are contained in the S.I., but, to be brief, the evidence coming from the vicinal coupling constants and from 2D-NOESY experiments, allowed to select, for both diastereoisomers, the conformations depicted in Scheme 2. Other three possible conformations (described in the S.I.) were ruled out, being in contrast with the experimental NMR evidence. In the preferred conformations shown in Scheme 2, H-4, C-4, N-3, C-2, H-2 lie approximately on a plane, and H-4 and H-2 are opposite each other. Therefore, the aryl group Ar^1 is near to the isocyanide derived secondary amide in isomer *S*, and near to the isopropyl in isomer *R*. The great difference in the above quoted chemical shifts is therefore due to the shielding effect of the Ar^1 group, demonstrating that the faster running isomer (HPLC) has an *S* configuration. We recall that this is the favoured isomer in all instances using method A and in most cases using method B, with the notable exception of compounds **5b**, **5c** and **5d** (employing aromatic isocyanides).

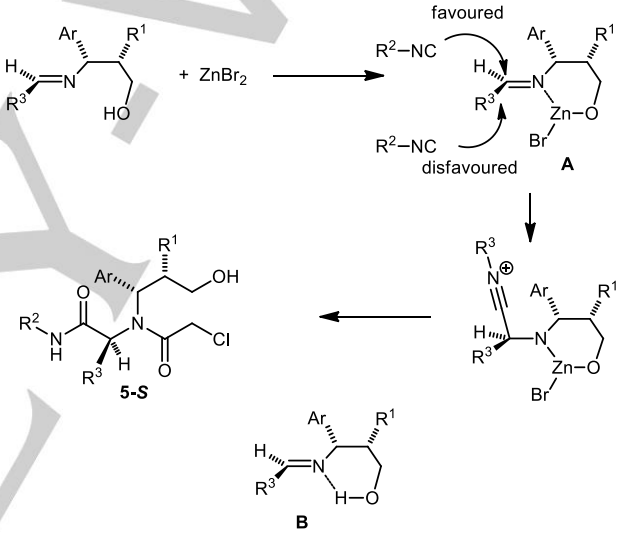
This assessment was further confirmed by ^{1}H NMR data on chromanyl diketopiperazines **20** (see S.I. for details).

Having established the relative configuration of Ugi adducts we can try to rationalise the results. As stated above, in all cases (including those previously reported), under $ZnBr_2$ catalysis, the (*S*) isomer is prevailing, usually with good d.r. (only in the case of **5b** we obtained a 1:1 mixture). This can be explained by a chelation model similar to the one proposed by Nenajdenko and coworkers[6c] for the $ZnBr_2$ catalysed Ugi reaction of 1,2-aminoalcohols (Scheme 3). An intramolecular imine activation by zinc would lead to a transition state **A** where the lower face is clearly more encumbered.



Scheme 2. Preferred conformations of Ugi adducts **5**.

It is less easy to explain the general preference for the (*S*) isomers also under standard Ugi conditions in methanol (method B). Maybe a similar preferred cyclic conformation of the chiral side chain is also in this case operating, thanks to a hydrogen bond between the OH and the imine (see formula **B**).



Scheme 3. Proposed models for rationalization of diastereoselectivity.

As stated above, with aromatic isocyanides the induction is lower with zinc bromide and even inverted in methanol. In this case, also taking into account the remarkable difference observed between **5c** and **5d**, by simply adding a *meta*-bromine to the aryl ring, we can suppose a cooperative effect, due to π bonding, between the aryl group and the incoming isocyanide, which may favour attack from the bottom face.

The first cyclization devised, which does not need any additional functionalities, involves an S_N2 where the alcoholic OH plays the role of leaving group and the isocyanide derived secondary amide acts as the nucleophile. This type of post-Ugi cyclization has been previously used mainly with halides as leaving groups,[13] but also with alcohols in Mitsunobu or Mitsunobu-like processes,[1c, 3a, 14] to afford 4-membered,[1c] 5-membered[3a] or 6-membered[13-14] lactams. No report on such type of cyclization to give 7-membered lactams is known so far.

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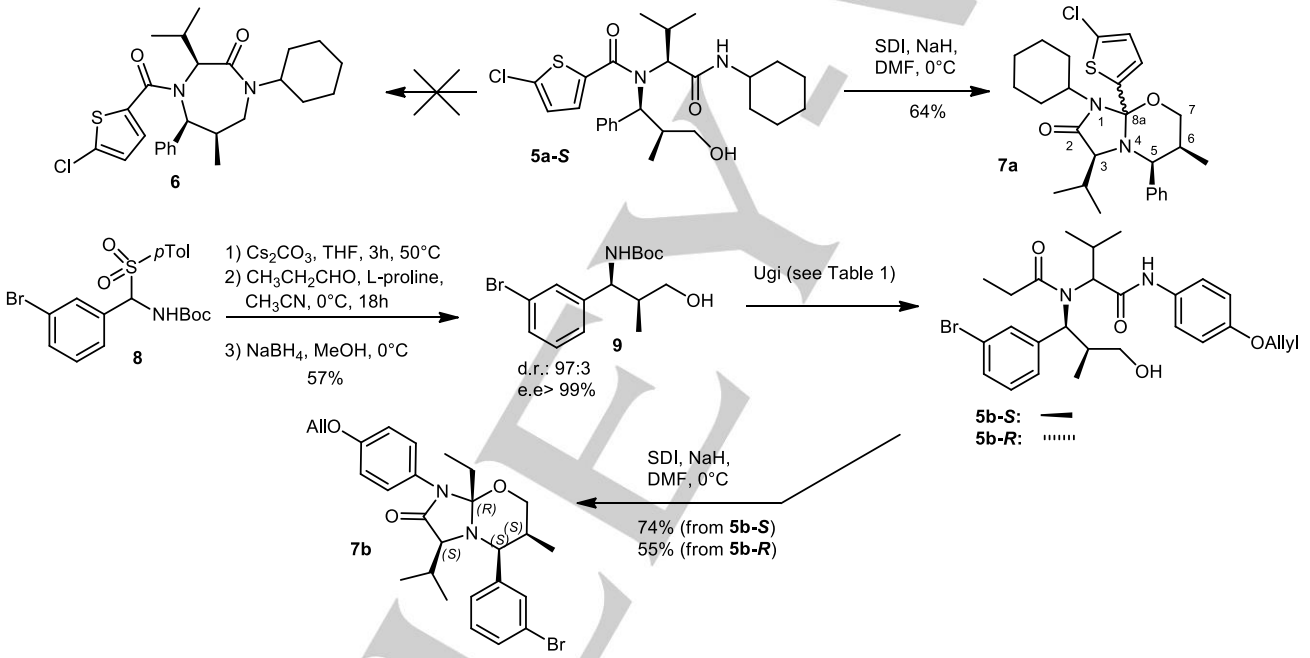
We explored this cyclization employing enantiomerically pure Ugi adduct **5a-*S*** expecting to obtain azepanone **6a** (Scheme 4). **5a-*S*** was obtained with 91:9 d.r. using Ugi method A (Table 1). Due to the high diastereoselectivity of the Ugi reaction, we performed these attempts only on the pure major (*S*) diastereomer.

We tested a variety of classical Mitsunobu conditions, with DEAD, TBAD or DIAD and PPh_3, but no cyclized product was obtained. On the other hand a clean reaction and a good yield was obtained by the Hanessian method,[15] that employs sulphonyl diimidazole (SDI) and NaH in DMF. Two new products (in a 60:40 ratio) were detected according to TLC and HPLC-MS analyses, and both had the expected nominal mass (472). However, a careful NMR investigation showed that the obtained products were not the diazepanone **6**, but, instead, the interesting imidazoxazinones **7**. This also explains the presence of two isomers, due to the newly generated stereogenic centre. In particular, ^{13}C NMR showed only one C=O signal, but two quaternary signals at 98.6-98.4 ppm, characteristic of the orthoaminal carbon 8a of the two isomers. HMBC bidimensional spectrum confirmed the connection of the various carbons. Interestingly, the two diastereomers easily interconvert on silica gel, making impossible their separation. Apart from this, they appear to be quite stable towards hydrolysis. A similar result, but with lower yield, was obtained in a two step sequence, converting **5a-*S*** into the mesylate followed by treatment with NaH in DMF.

At this point we thought that formation of diazepanones could possibly be favoured by employing as starting component an aromatic isocyanide: the resulting aromatic secondary amide would be more acidic, favouring the normal course of cyclization. Thus, we used Ugi products **5b**, prepared from the new Boc-protected aminoalcohol **9**, in turn derived from known carbamoyl sulphone **8**,[16] through the organocatalytic Mannich reaction (Scheme 4).

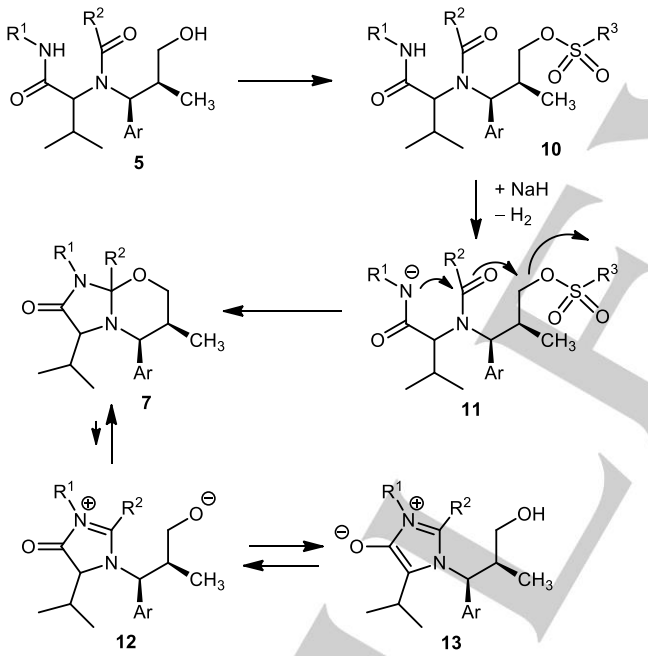


Scheme 4. Synthesis of imidazoxazinones through cyclization of Ugi adducts **5**.

As already described above, this reaction gave alternatively the (*S*) or (*R*) isomer depending on the method used. In all cases we separated the two diastereomers and submitted them independently to the cyclization conditions with SDI. Once again, we did not obtain a diazepanone **6**, but imidazooxazinones **7b** instead. The reaction was remarkably stereoselective (92:8), regarding the new stereogenic centre at C-8a, and surprisingly both Ugi adducts **5b-*S*** and **5b-*R*** afforded the same major diastereoisomer, as judged by TLC, HPLC, NMR and polarimetric analyses. The configuration of all centres was determined to be the one depicted in Scheme 2 by nOe experiments (see S.I.). Evidently, **5b-*R*** undergoes complete epimerization during the cyclization reaction. In this case, also because of the high diastereoselectivity regarding the stereogenic centre at C-8a, and because the two diastereomers were not separated in TLC, we could not assess if facile epimerization at C-8a takes place or not. However, compound **7b** was remarkably stable under acidic conditions (*p*TSA in H_2O-MeOH for several days).

To the best of our knowledge the imidazooxazinone scaffold **7** is quite unprecedented in the literature. We could find only an example of imidazooxazine,[17] although fused with two other rings and lacking the carbonyl, while the analogous imidazooxazolone motif, having 1 carbon atom less, has been previously synthesized by us.[18] Thus, despite its orthoaminal nature, this heterocycle may be, in our opinion, interesting in medicinal chemistry, thanks to its relative rigidity and non-flat structure. A

discussion on the conformations of this system is reported in the S.I. With this methodology, up to 5 diverse appendages can be positioned on it. The stereoconvergency of cyclization overcomes the possible low diastereoselectivity in the Ugi reaction, affording a complex product with 4 stereogenic centres in high e.e. and d.r. Scheme 5 shows a possible mechanism for the formation of imidazooxazinones. First of all the alcohol is transformed into sulphonate **10** either by reaction with MsCl or, *in situ*, by reaction with SDI. Then the base (NaH) deprotonates the secondary amide. At this stage, instead of direct S_N2 substitution of the sulphonate, the anionic nitrogen attacks first the carbonyl of the tertiary amide, that in turns attacks the sulphonate, resulting in compounds **7**. The complete epimerization and the easy equilibration on silica gel of the two epimers at C-8a observed for **7**, may be both explained by supposing that **7** is in equilibrium with an open zwitterion **12**. Although this equilibrium is probably shifted towards **7**, it can explain the facile interconversion of the epimers at C-8a observed for **7a**. Moreover, **12** may be in turn, through a simple proton transfer, in equilibrium with mesoionic compound **13**, stabilized by its aromatic character. This can explain the easy epimerization observed for **7b**.

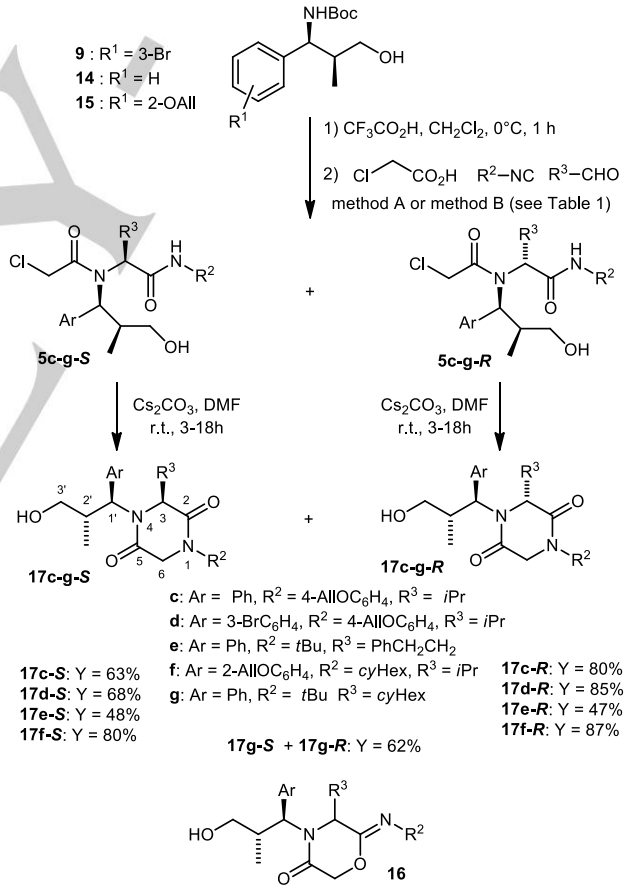


Scheme 5. Possible mechanism for imidazoxazinone formation.

Having set up a methodology to straightforwardly generate imidazooxazinones **7**, we moved to explore an alternative cyclative S_N2 process, employing Ugi adducts **5c-g**, displaying an additional alkyl halide in their structure. Preliminary attempts using glycolic acid as the acid component were unsatisfactory. While the Ugi reaction worked, attempted cyclization, again using SDI/NaH led to complex mixture of products. Thus we chose to use chloroacetic acid[13d] as carboxylic input for the Ugi, and were able to synthesize, in a straightforward manner, diketopiperazines **17** (Scheme 6).

The best conditions for cyclization involved the use of cesium carbonate, instead of KOH, previously employed by Marcaccini on other chloroacetic acid derived Ugi adducts.[13d] We typically preferred to separate the two diastereomers at the level of Ugi adducts **5**, with the exception of entry 5. Having performed the cyclization on the separated diastereomers of **5** allowed us to prove that this cyclization, contrary to the one leading to bicyclic **7**, was not epimerizing at all.

The cyclization yields are typically high, except when R^2 = *t*Bu. In the case of **17g** we indeed isolated a side product, that had the same molecular weight, by HPLC-MS, with the expected product, and whose structure, elucidated by ^{1}H, ^{13}C NMR and HMBC experiments, corresponds to a six-membered morpholin-3-one **16** derived from cyclization by the oxygen (instead of the nitrogen) of the secondary amide (see S.I. for details). The bulkiness of *tert*-butyl group may have favoured this side-reaction.



Scheme 6. Synthesis of diketopiperazines **17**. In the case of **17g**, cyclization was carried out on the unseparated diastereomeric mixture.

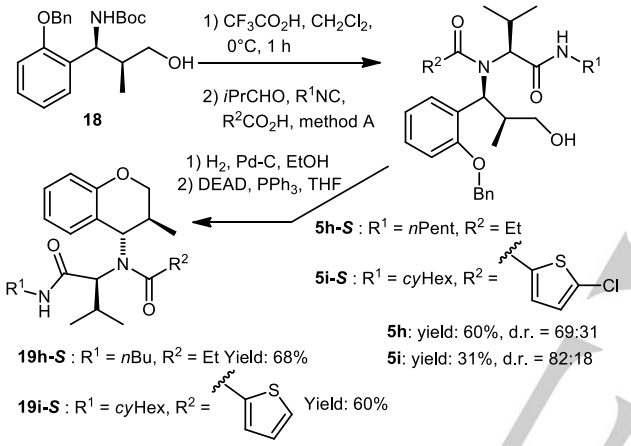
Ten different enantiopure diketopiperazines **17** have been prepared by this approach. Although the overall yield is only moderate, these complex compounds have been obtained

essentially in three steps from the starting carbamoyl sulphones, introducing three stereogenic centres. Thus the step-economy fully counterweighs the moderate yield from the "green synthesis" point of view.[19]

A third cyclative reaction was investigated with Ugi adducts **5h-i**, displaying an additional phenolic functionality (Scheme 7).

In this case the cyclization was carried out only on the major (*S*) adduct. Hydrogenolysis of the benzyl protecting group followed by Mitsunobu reaction with diethyl azodicarboxylate (DEAD) and triphenylphosphine, gave the two chromanes **19h** and **19i** in good yields. In the case of **19i** the chlorine on the thiophene ring underwent hydrogenolysis during removal of the benzyl.

Finally, we have performed in sequence two of the above described cyclizations, obtaining complex compounds containing two privileged structures, that is the chromane and the diketopiperazine (Scheme 8).

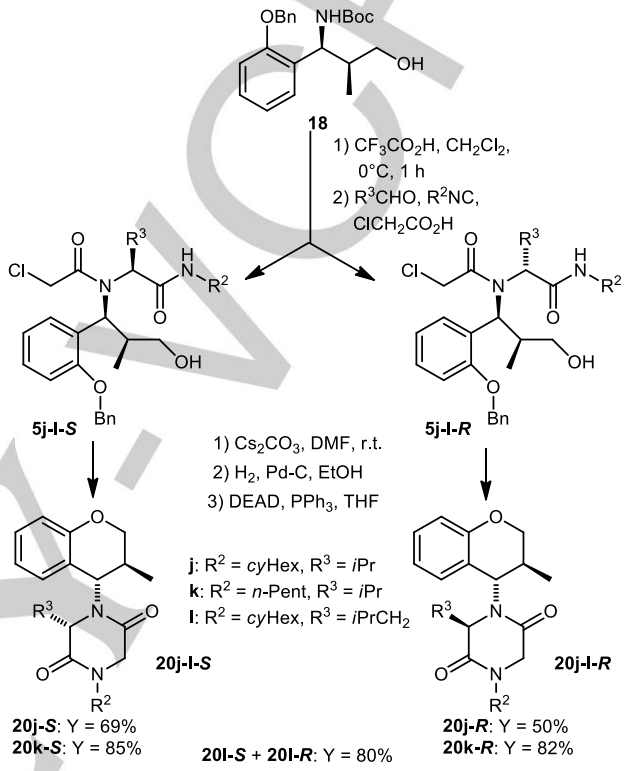


Scheme 7. Synthesis of chromanes **19**.

With aminoalcohol **18** and chloroacetic acid, the Ugi reactions were rather diastereoselective, using $ZnBr_2$ promoted conditions. Anyway, in this case we converted both isomers into the final products.

Conclusions

In conclusion we have been able to prepare, through a concise synthetic sequence, a small collection of complex heterocyclic systems (including the unprecedented ortho-aminals **7** and **10**). We have explored both scaffold and decoration diversity, reporting here 4 different scaffolds, and varying 4 diversity inputs (a fifth one can in principle be modified too, by using different aldehydes in the Mannich step). Most importantly, all the 13 final compounds are enantiomerically pure, and their optical isomers can be accessed simply using D-proline as the catalyst. Often, libraries of potential drug candidates are prepared in racemic form and, when a hit or lead is found, it is rather difficult to access the pure enantiomers without exploiting resolution methods or chiral auxiliaries. In this work we have employed only asymmetric catalysis to generate chirality, by the List's organocatalytic Mannich reaction. We think that we have added further value to this precious methodology by combing it with the Ugi multicomponent reaction and intramolecular S_N2 reactions, showing that List's adducts are really "pluripotent" intermediates.



Scheme 8. Synthesis of chromanyl diketopiperazines **20**. In the case of **20l**, cyclization was carried out on the unseparated diastereomeric mixture.

Experimental Section

General remarks. NMR spectra were taken at rt in $CDCl_3$ at 300 MHz (^1H), and 75 MHz (^{13}C), using, as internal standard, TMS (^1H NMR: 0.000 ppm) or the central peak of $CDCl_3$ (^{13}C: 77.02 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY, gHSQC and gHMBC experiments. GC-MS were carried out using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Only m/z > 33 were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 1.0 ml/min with initial temp. of 70 °C, init. time 1 min, rate 20 °C/min, final temp. 260 °C, inj. temp. 250 °C, det. temp. 280 °C. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in ESI positive or negative ionization mode. IR spectra were recorded with the ATR (attenuated total reflectance) technique. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) and developed with Hanessian stain (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) or with ninhydrin (in the case of Boc aminoalcohols). R_f were measured after an elution of 7-9 cm. Column chromatographies were done with the "flash" methodology using 220-400 mesh silica. Petroleum ether (40-60 °C) is abbreviated as PE. In extractive

work-up, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions using dry solvents were carried out under a nitrogen atmosphere.

(2*S*,3*S*)-3-(3-Bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-2-methylpropan-1-ol 9. Cs_2CO_3 (1.12 g, 3.44 mmol) was weighted in a flask, put under argon and heated with a heating gun for 5 minutes. After cooling, dry THF (17 mL), and carbamoyl sulfone **8**[16] (600 mg, 1.72 mmol) were added and the suspension heated at 50 °C for 3 h. After cooling, the white suspension was rapidly filtered through a sintered funnel filled with celite, dry Na_2SO_4, and celite layers,[10b] washing with THF. The filtrate was evaporated, dissolved in dry CH_3CN (17 mL), cooled to 0 °C, and treated with L-proline (40 mg, 0.344 mmol) and with freshly distilled propanal (247 µL, 1.67 mmol). The mixture was stirred at 0 °C for 18 h, and then quenched with water (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extract dried (Na_2SO_4), evaporated to dryness, dissolved in MeOH (9 mL), and cooled at 0°C. $NaBH_4$ (100 mg, 2.58 mmol) was added. After 5 min the cooling bath was removed and the reaction stirred for 1 h at rt and then quenched with a 10:2 mixture of 5% aqueous $NH_4H_2PO_4$ and 2M HCl. Extraction with EtOAc, evaporation and chromatography (PE/CH_2Cl_2/Diethyl ether 3:2:2) gave pure **9** as a solid (338 mg, 57%). The enantiomeric ratio was determined to be > 99% by HPLC on chiral stationary phase (Daicel Chiral Pak AD 250x4.6 mm column: 25 °C: hexane / *i*PrOH 90:10; flow of 0.8 mL/min; temp= 26°C, UV detection at 220 nm; R_t (*S*,*S*) = 10.2 min; R_t (*R*,*R*) = 11.9 min). In order to have a reference of the (2*R*,3*R*) enantiomer, the same procedure was repeated with D-proline as catalyst. The diastereomeric ratio was determined by ^{1}H NMR and was found to be = 97:3. The relative *syn* configuration was assigned on the basis of spectral analogies with other similar compounds. R_f = 0.18 ((PE/CH_2Cl_2/Diethyl ether 3:2:1). M.P.: 123.2-124.1 °C. $[\alpha]_D$ -26.1 (c 1, $CHCl_3$). ^{1}H NMR: (300 MHz, $CDCl_3$, 25 °C): δ = 7.43-7.36 (m, 2 H); 7.26-7.16 (m, 2 H); 5.29 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH); 5.04 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, ArCH); 3.58-3.28 (m, 2 H, C*H*$_2$OH); 3.10 (mc) (m, 1 H, OH); 2.19 (mc) (m, 1 H, C*H*CH$_3$); 1.46 (s, 9 H, (C*H*$_3$)$_3$CH); 0.69 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, C*H*$_3$CH). ^{13}C NMR (300 MHz, $CDCl_3$, 20 °C): δ = 156.3 (C=O), 143.0, 122.6 (quat.), 130.0, 129.9, 129.6, 125.3 (ArCH), 80.2 (*C*(CH$_3$)$_3$), 64.7 (CH$_2$OH), 54.2 (ArCH), 40.7 (*C*HCH$_3$), 28.3 ((CH$_3$)$_3$C), 10.9 (*C*H$_3$CH). GC-MS: R_t 10.11 min; *m/z* 286 (5.2) [M − CH(CH$_3$)CH$_2$OH (^{81}Br)]$^+$, 284 (4.9) [M − CH(CH$_3$)CH$_2$OH (^{79}Br)]$^+$, 230 (21), 228 (21), 186 (27), 184 (32), 77 (5.0), 59 (21), 58 (5.4), 57 (100), 56 (7.8), 41 (19), 39 (5.0). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{15}H_{23}BrNO_3$ 344.0861; Found 344.0861.

***tert*-Butyl ((2-(allyloxy)phenyl)(tosyl)methyl)carbamate**. 2-allyloxybenzaldehyde[20] (3.06 g, 18.85 mmol, 1 equiv) was dissolved in methanol (11 mL) and treated at rt with *tert*-butyl carbamate (2.21 g, 18.85 mmol, 1 equiv) and a solution of sodium *p*-toluenesulphinate (6.72 g, 37.7 mmol, 2 equiv) in H_2O (22 mL). The resulting cloudy solution was treated with HCO_2H (1.56 mL, 41.47 mmol, 2.2 equiv) and vigorously stirred overnight, during which time the desired product precipitates. The resulting white solid was filtered through a Büchner funnel and washed with distilled H_2O (75 mL). The product was suspended in diisopropyl ether (10 mL) and stirred for 2 hours. The product was collected by filtration and washed with diisopropyl ether (40 mL) to give a white solid (4.94 g, 63%). M.p. 119.3 - 120.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *H ortho* to SO_2); 7.45 – 7.30 (m, 2 H, *H*-4, *H*-6); 7.29 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *H meta* to SO_2); 7.00 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, *H*-5); 6.86 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, *H*-3); 6.42–6.21 (m, 2 H, CHAr and NH); 6.01 (ddt, $^3J_{H,H}$ = 17.2, 10.4, 5.2 (t) Hz, 1 H, C*H*=CH$_2$); 5.42 (1 H, dq, $^3J_{H,H}$ = 17.3, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.4 Hz, 1 H, C*H*H=CH); 5.30 (1 H, dq, $^3J_{H,H}$ = 10.4, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.3 Hz, 1 H, C*H*H=CH); 4.57-4.40 (m, 2 H, ArC*H*$_2$CH= CH$_2$), 2.40 (s, 3 H, CH$_3$Ar), 1.31 (s, 9 H, (C*H*$_3$)$_3$C). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.9, 153.7 (C=O, C-OAll), 144.5, 134.4, 119.1 (quat.), 132.7 (*C*H=CH$_2$), 130.9, 130.1, 129.40 (x2), 129.37 (x2), 121.0, 112.7 (ArCH), 117.8 (CH=*C*H$_2$), 80.7 (*C*(CH$_3$)$_3$), 70.7 (ArCH), 69.5 (OCH$_2$), 28.0 (C(*C*H$_3$)$_3$), 21.6 (ArCH$_3$). I.R.: ῡ 3259, 3150, 3008, 2970, 2933, 2867, 1699, 1606, 1592, 1491, 1456, 1449, 1423, 1411, 1366, 1333, 1316, 1300, 1288, 1258, 1182, 1146, 1115, 1100, 1085, 1046, 1012, 985, 936, 925, 916, 873, 846, 821, 799, 773, 747, 719, 705, 692, 660, 630, 614 cm^{-1}) = HRMS (ESI+) m/z [M + H$^+$]: Calcd for $C_{22}H_{28}NO_5S$ 418.1683; Found 418.1688.

(2*S*,3*S*)-3-(2-Allyloxyphenyl)-3-((*tert*-butoxycarbonyl)amino)-2-methylpropan-1-ol 15. It was prepared in 48% (from the carbamoyl sulphone of 2-allyloxybenzaldehyde described above) using the same methodology employed for **9**. White foam. *Syn*:*anti* ratio (^{1}H NMR): > 95:5. The e.e. was demonstrated to be > 95% by Mosher's ester analysis. R_f = 0.18 (PE / AcOEt 5:1 + 2% MeOH). $[\alpha]_D$: -19.5 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ = 7.26-7.13 (m, 2 H, *H*-4 and *H*-6); 6.95 (td, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.0 Hz, 1 H, *H*-5); 6.89 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, *H*-3); 6.08 (ddt, $^3J_{H,H}$ = 17.2, 10.5, 5.2 (t) Hz, 1 H, C*H*=CH$_2$); 5.94 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H, NH); 5.48 (1 H, dq, $^3J_{H,H}$ = 17.2, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.3 Hz, 1 H, C*H*H=CH); 5.32 (1 H, dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*H=CH); 5.17 (dd, $^3J_{H,H}$ = 4.8 9.7 Hz, 1 H, ArCH); 4.65-4.52 (m, 2 H, CH$_2$OAr), 3.48-3.30 (m, 3 H, C*H*$_2$O*H*); 2.10 (mc) (m, 1 H, C*H*-CH$_3$); 1.44 (s, 9 H, (CH$_3$)$_3$C); 0.77 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, C*H*$_3$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ = 156.6, 155.8 (C=O and C-OAll), 132.7 (*C*H=CH$_2$), 128.9 (quat.), 128.7, 128.1, 121.0, 112.3 (ArCH), 117.9 (CH=*C*H$_2$), 79.6 (*C*(CH$_3$)$_3$), 69.0 (CH$_2$OAr), 65.2 (CH$_2$OH), 52.6 (ArCH), 41.7 (*C*H-CH$_3$), 28.3 (C(*C*H$_3$)$_3$), 11.3 (*C*H$_3$CH). I.R.: ῡ 3442, 3064, 2974, 2942, 2854, 1661, 1605, 1555, 1496, 1455, 1413, 1381, 1364, 1325, 1295, 1284, 1248, 1165, 1136, 1100, 1079, 1038, 1024, 997, 929, 916, 886, 864, 823, 756, 732, 704, 668, 643, 616 cm^{-1}. HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{18}H_{28}NO_4$ 322.2018; Found 322.2015.

Typical procedures for the Ugi reactions: (*S*) and (*R*) *N*-(4-(Allyloxy)phenyl)-2-(*N*-((1*S*,2*S*)-1-(3-bromophenyl)-3-hydroxy-2-methylpropyl)propionamido)-3-methylbutanamide 5b. *Preparation of aminoalcohol*. A solution of Boc aminoalcohol **9** (172 mg, 0.50 mmol) in dry CH_2Cl_2 (8 mL), was cooled to 0 °C, and treated with trifluoroacetic acid (4 mL). After stirring for 1 h at 0 °C, the solution was evaporated to dryness, and taken up with AcOEt and 1 M aqueous NaOH so that pH = 9-10. The phases were separated, and the organic extracts washed with saturated aqueous NaCl and evaporated to dryness to give the crude aminoalcohol as an oil.

Method A. The crude aminoalcohol was taken up in dry THF (5 mL), cooled to −38 °C, and treated, in this order, with isobutyraldehyde (48 µL, 0.525 mmol, 1.05 equiv), 3 Å powdered molecular sieves (50 mg), zinc dibromide (113 mg, 0.50 mmol, 1 equiv), propionic acid (45 µL, 0.600 mmol, 1.2 equiv), and 4-allyloxyphenyl isocyanide (see S.I. for its preparation) (96 mg, 0.600 mmol, 1.2 equiv). The mixture was stirred for 48 h at −38 °C. Then it was evaporated to dryness and chromatographed (CH_2Cl_2 / PE / Et_2O from 8:2:1 to 8:2:2) to give first the (*R*) diastereomer (70 mg) and then the (*S*) one (73 mg) (54% overall yield). The diastereomeric ratio (*S*) : (*R*) was determined to be 51:49 by HPLC on the crude product (Column Phenyl C6 150 x 3 mm, 3 µ, conc.: 200µg/ml; flow=0,34ml/min; Vinj 5µl; Temp: 25°C detection : 220nm; gradient (H_2O+0,1% formic acid) / CH_3CN from 60:40 to 0:100 in 20 min. R_t (*S*): 12.7 min; R_t (*R*): 13.9 min).

Method B. The crude aminoalcohol was taken up in dry MeOH (5 mL), and treated, in this order, with isobutyraldehyde (48 µL, 0.525 mmol, 1.05 equiv), 3 Å powdered molecular sieves (50 mg), propionic acid (45 µL, 0.600 mmol, 1.2 equiv), and 4-allyloxyphenyl isocyanide (96 mg, 0.600 mmol, 1.2 equiv). The mixture was stirred for 48 h at r.t.. Then it was evaporated to dryness and chromatographed as for method A (67% overall

yield). The diastereomeric ratio (*S*) : (*R*) was determined to be 42:58 by HPLC on the crude product.

Method C. Exactly as method B, but using trifluoroethanol instead of methanol as the solvent (68% overall yield). The diastereomeric ratio (*S*) : (*R*) was determined to be 64 : 36 by HPLC on the crude product.

5b-(*R*). R_f 0.34 (CH_2Cl_2 / PE / Et_2O 8:2:2). $[\alpha]_D$ -37.3 (c 2.13, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) (for numbering see Scheme 2): δ = 10.47 (s, 1 H, N*H*), 7.56-7.47 (m, 2 H, *H* 2' and *H*-5'), 7.46 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* meta to O-allyl), 7.38 (broad d, $^3J_{H,H}$ = 7.8 Hz, *H*-6'); 7.30 (d, $^3J_{H,H}$ = 7.8 Hz, *H*-4'), 6.87 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* ortho to O-allyl), 6.04 (ddt, $^3J_{H,H}$ = 5.3 (t), 10.5, 17.2 Hz, 1 H, C*H*=CH_2), 5.40 (dq, $^3J_{H,H}$ = 17.1 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 Hz), 5.40 (dq, $^3J_{H,H}$ = 17.1 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 Hz, 1 H, CH=C*H*H), 5.27 (dq, $^3J_{H,H}$ = 10.5 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 Hz, 1 H, CH=C*H*H), 5.02 (d, $^3J_{H,H}$ = 11.7 Hz, 1 H, *H*-4), 4.51 (dt, $^3J_{H,H}$ = 5.3 Hz, $^4J_{H,H}$ = 1.4 Hz, 2 H, CH_2O), 3.59 and 3.44 (slightly broad AB syst., $^3J_{H,H}$ = 10.0 Hz, 2 H, CH_2OH), 3.29 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, *H*-2), 2.92-2.63 (m, 4 H, *H*-5, *H*-8, C*H*$(CH_3)_3$), 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, C$H_3$$CH_2$), 1.05 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3CH-5), 0.79 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3 isopropyl), -0.05 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3 isopropyl) ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 176.2, 170.3 (C=O), 155.1, 139.3, 131.6, 122.8 (quat.), 133.3 (*C*H=CH_2), 132.8, 131.8, 130.2, 128.0, 121.4 (x2), 115.0 (x2) (ArCH), 117.6 (CH=*C*H_2), 70.0 (*C*-2), 69.1 (CH_2OAr), 63.9 (*C*-6), 63.4 (*C*-4), 35.0 (*C*-5), 28.5 (*C*-8), 27.2 (*C*H$(CH_3)_2$), 19.8, 18.6 ((CH_3)$_2$CH), 14.0 (*C*H_3-C5), 9.6 (*C*-9). I.R.: ū = 3413, 3250, 3132, 3063, 2969, 2934, 2874, 1657, 1594, 1545, 1509, 1461, 1425, 1389, 1370, 1331, 1271, 1232, 1172, 1156, 1113, 1075, 1024, 988, 923, 871, 828, 777, 681, 634 cm^{-1}. HRMS (ESI-) m/z [M - H^+]: Calcd. For $C_{27}H_{34}BrN_2O_4$ 529.1702; Found 529.1710.

5b-(*S*). R_f 0.21 (CH_2Cl_2 / PE / Et_2O 8:2:2). $[\alpha]_D$ +146.3 (c 2.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) (for numbering see Scheme 2): δ = 9.55 (s, 1 H, N*H*), 7.42-7.30 (m, 2 H, *H* 2' and *H*-4'), 7.24 (broad d, $^3J_{H,H}$ = 7.5 Hz, *H*-6'); 7.11 (t, $^3J_{H,H}$ = 7.8 Hz, *H*-5'), 6.99 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* meta to O-allyl), 6.75 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* ortho to O-allyl), 6.02 (ddt, $^3J_{H,H}$ = 5.3 (t), 10.5, 17.2 Hz, 1 H, C*H*=CH_2), 5.38 (dq, $^3J_{H,H}$ = 17.2 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 Hz), 5.40 (dq, $^3J_{H,H}$ = 17.1 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 Hz, 1 H, CH=C*H*H), 5.26 (dq, $^3J_{H,H}$ = 10.5 Hz, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 Hz, 1 H, CH=C*H*H), 4.93 (d, $^3J_{H,H}$ = 11.2 Hz, 1 H, *H*-4), 4.47 (dt, $^3J_{H,H}$ = 5.3 Hz, $^4J_{H,H}$ = 1.4 Hz, 2 H, CH_2O), 3.64 (broad d, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*HOH), 3.48 (broad dd, $^3J_{H,H}$ = 3.9, 10.5 Hz, 1 H, C*H*HOH), 3.22 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H, *H*-2), 3.03-2.85 (m, 1 H, C*H*$(CH_3)_3$), 2.76-2.60 (m, 2 H, C$H_2$$CH_3$), 2.60-2.43 (m, 1 H, *H*-5), 1.28 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, CH_3CH-5), 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, C$H_3$$CH_2$), 0.99 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3 isopropyl), 0.97 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3 isopropyl).^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 177.5, 169.9 (C=O), 154.9, 138.6, 131.2, 122.6 (quat.), 133.3 (*C*H=CH_2), 132.4, 131.4, 130.1, 127.7, 121.5 (x2), 114.7 (x2) (ArCH), 117.5 (CH=*C*H_2), 72.0 (*C*-2), 69.1 (CH_2OAr), 64.2 (*C*-6), 63.7 (*C*-4), 34.5 (*C*-5), 28.7 (*C*-8), 28.6 (*C*H$(CH_3)_2$), 22.0, 20.5 ((CH_3)$_2$CH), 14.9 (*C*H_3-C5), 9.9 (*C*-9). I.R.: ū = 3274, 3133, 3067, 2971, 2935, 2875, 1658, 1595, 1541, 1509, 1462, 1420, 1388, 1369, 1224, 1172, 1157, 1107, 1074, 1022, 989, 925, 870, 827, 802, 775, 680, 634 cm^{-1}. HRMS (ESI-) m/z [M - H^+]: Calcd. For $C_{27}H_{34}BrN_2O_4$ 529.1702; Found 529.1700.

(3*S*,5*S*,6*S*,8a*R*) and (3*S*,5*S*,6*S*,8a*S*) 8a-(5-chlorothiophen-2-yl)-1-cyclohexyl-3-isopropyl-6-methyl-5-phenyltetrahydro-1*H*-imidazo[2,1-b][1,3]oxazin-2(3*H*)-ones 7a. Compound **5a-*S***[11] (100 mg, 204 µmol) was dissolved in dry DMF (2 mL), cooled to 0°C, and treated with 1,1'-sulfonyldiimidazole (SDI) (101 mg, 520 µmol). After 10 min, NaH (60% in mineral oil) (24.5 mg, 612 µmol) was added. After 10 min the cooling bath was removed and the mixture stirred at r.t. for 8 h, and then poured into a 10:2 mixture of 5% aqueous $NH_4H_2PO_4$ and 2M HCl. Extraction (AcOEt) was followed by washing with 5% aqueous LiCl (to remove DMF), and brine. Evaporation and chromatography (PE / AcOEt 95 : 5) gave pure **7a** as a yellow oil (62 mg, 64%). Note: although two well separated spots are well visible at TLC (R_f = 0.74 and 0.50 with PE / AcOEt 9:1), chromatography fails to separate them. A simple two-dimensional TLC showed that the two spots interconverts on silica gel. The diastereomeric ratio between isomers A and B was 60:40 as determined by NMR. The relative configuration was not established. ^1H NMR: (300 MHz, $CDCl_3$, 25 °C): δ = 7.40-7.25 (m, 3 H); 7.15-7.05 (m, 1.2 H, diast. A); 7.02-6.95 (m, 0.8 H, diast. B); 7.00 (d, $^3J_{H,H}$ = 3.9 Hz, 0.6 H, *H*-3' of A); 6.88 (d, $^3J_{H,H}$ = 3.9 Hz, 0.4 H, *H*-3' of B); 6.84 (d, $^3J_{H,H}$ = 3.9 Hz, 0.6 H, *H*-4' of A); 6.64 (d, $^3J_{H,H}$ = 3.9 Hz, 0.4 H, *H*-4' of B); 4.43 (d, $^3J_{H,H}$ = 4.5 Hz, 0.6 H, *H*-5 of A); 4.21 (t, $^3J_{H,H}$ = $^2J_{H,H}$ = 10.9 Hz, 0.4 H, *H*-7 of B); 4.01 (d, $^3J_{H,H}$ = 6.3 Hz, 0.4 H, *H*-5 of B); 3.90 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 5.4 Hz, 0.4 H, *H*-7 of B); 3.84 (dd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 6.9 Hz, 0.6 H, *H*-7 of A); 3.56 (d, $^3J_{H,H}$ = 3.0 Hz, 0.4 H, *H*-3 of B); 3.41 (t, $^2J_{H,H}$ = $^3J_{H,H}$ = 10.9 Hz, 0.6 H, *H*-7 of A); 3.28 (d, $^3J_{H,H}$ = 5.4 Hz, 0.6 H, *H*-3 of A); 3.20 (tt, $^3J_{H,H}$ = 3.6, 12.1 Hz, 0.6 H, C*H* cyclohexyl of A); 2.97 (tt, $^3J_{H,H}$ = 3.6, 12.1 Hz, 0.4 H, C*H* cyclohexyl of A); 2.65-2.15 (m, 1 H, *H*-6); 2.08-1.85 (m, 1 H, C*H*$(CH_3)_2$); 1.85-1.45 (m, m); 1.35-0.80 (m, 6 H); 1.25 (d, $^3J_{H,H}$ = 7.2 Hz, 1.2 H, CH_3CHCH$_3$ of B); 1.07 (d, $^3J_{H,H}$ = 6.9 Hz, 1.2 H, CH_3CHCH$_3$ of B); 1.02 (d, $^3J_{H,H}$ = 6.9 Hz, 1.8 H, CH_3CHCH$_3$ of A); 0.96 (d, $^3J_{H,H}$ = 6.9 Hz, 1.8 H, CH_3CHCH$_3$ of A); 0.80 (d, $^3J_{H,H}$ = 7.2 Hz, 1.2 H, CH_3CH of B); 0.53 (d, $^3J_{H,H}$ = 6.6 Hz, 1.8 H, CH_3CH of A). ^{13}C NMR (300 MHz, $CDCl_3$, 20 °C): δ = 171.5 (A), 170.9 (B) (*C*=O); 147.5 (A) (*C*-2'), 143.4 (B) (*C*-2'), 139.2 (B), 135.5 (A) (quat. Ph); 132.3 (B), 131.4 (A), 130.1 (A), 129.4 (B), 128.6 (A), 127.6 (B) (*C*H Ph), 127.1 (B) (*C*-3'), 126.7 (A+B) (*C*-5'), 126.1 (A) (*C*-3'), 124.6 (B) (*C*-4'); 124.5 (A) (*C*-4'), 98.6 (B), 98.4 (A) (*C*-9); 67.91 (A), 67.9 (B) (*C*-3), 66.3 (A) (*C*-5); 65.51 (A), 65.47 (B) (*C*-7); 64.8 (A) (*C*-3); 61.9 (B) (*C*-5); 53.4 (A), 53.3 (B) (*C*H cyclohexyl); 32.3 (A), 30.4 (B) (*C*H$(CH_3)_2$), 29.9 (A), 29.4 (B) (*C*-6), 29.7, 29.6, 29.5, 28.8, 27.3, 26.5, 26.32, 26.28, 26.2 (CH_2 cyclohexyl), 19.4 (A), 19.2 (A), 18.7 (B), 16.7 (B) (CH_3CHCH_3), 15.3 (A), 14.4 (B) (CH_3CH). At gHMBC, the signal at 98.4 (diast. A) is coupled with the doublet at 3.28 (*H*-3), with the doublet at 4.43 (*H*-5), and with the two signals of *H*-7. The signal at 98.6 (diast. B) is coupled with the doublet at 3.56 (*H*-3), with the doublet at 4.01 (*H*-5), and with the two signals of *H*-7. I.R.: ū = 3425, 2962, 2252, 1701, 1424, 1370, 1322, 1258, 1213, 1051, 1023, 1005, 865, 819, 791, 762, 702, 661, 625 cm^{-1}. HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{26}H_{34}ClN_2O_2S$ 473.2030; Found 473.2032.

(3*S*,5*S*,6*S*,8a*R*)-1-(4-(Allyloxy)phenyl)-5-(3-bromophenyl)-8a-ethyl-3-isopropyl-6-methyltetrahydro-1*H*-imidazo[2,1-b][1,3]oxazin-2(3*H*)-one 7b. It was prepared either starting from 50 mg of **5b-*S*** or from 50 mg of **5b-*R*** in 55% and 74% yields respectively, using the same method used for preparation of **7a**. Chromatography was carried out with PE/AcOEt 80:20. R_f 0.34 (PE/AcOEt 80:20). $[\alpha]_D$ -53.5 (c 1.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) (this compound contains an inseparable 8% of the diastereomer at C-8a; only the signals of major diast. are reported): δ = 7.62 (t, $^4J_{H,H}$ = 1.5 Hz, 1 H, H ortho to Br and C); 7.44-7.35 (m, 2 H, H of Br-Ar); 7.27-7.17 (m, 1 H, H of Br-Ar); 7.23 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H meta to O); 76.92 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H ortho to O); 6.05 (ddt, $^3J_{H,H}$ = 5.3 (t), 10.5 (d), 17.2 (d) Hz, 1 H, C*H*=CH_2); 5.41 (dq, $^3J_{H,H}$ = 17.2, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, CH=C*H*H)); 5.29 (dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.2, 1 H, CH=C*H*H); 4.53 (dt, $^3J_{H,H}$ = 5.4, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.4, 2 H, CH_2O); 4.11 (dd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 4.7 Hz, 1 H, *H*-7); 3.96 (d, $^3J_{H,H}$ = 5.6 Hz, 1 H, *H*-5); 3.89 (dd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 5.7 Hz, 1 H, *H*-7); 3.30 (d, $^3J_{H,H}$ = 6.8 Hz, 1 H, *H*-3); 2.39 (dtq, $^3J_{H,H}$ = 6.6 (q), 5.7 (t), 4.7 (d) Hz, 1 H, *H*-6); 2.10 (octuplet $^3J_{H,H}$ = 6.9 Hz, 1 H, C*H*$(CH_3)_2$); 1.72 (dq, $^3J_{H,H}$ = 5.3 (q), $^2J_{H,H}$ = 10.6 (d) Hz, 1 H, C*H*HCH$_3$); 1.55 (dq, $^3J_{H,H}$ = 5.3 (q), $^2J_{H,H}$ = 10.6 (d) Hz, 1 H, C*H*HCH$_3$); 1.12 (d, $^3J_{H,H}$ = 6. Hz, 3 H, CH_3 isopropyl), 1.09 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3 isopropyl); 1.04 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH-5), 0.70 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, C$H_3$$CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ = 173.2 (C=O), 157.6, 142.8, 127.9, 122.0 (quat.), 133.05 (*C* ortho to Br and C), 132.99 (*C*H=CH_2), 130.3, 129.5, 128.4, 128.3 (x2), 115.0 (x2) (ArCH), 117.8 (CH=*C*H_2), 104.0 (C-8a), 70.4 (*C*-3), 69.0 (CH_2OAr), 64.7, 64.6 (*C*-7, *C*-5), 31.7 (*C*H$(CH_3)_2$), 30.8 ($CH_2$$CH_3$), 29.8 (*C*-6), 20.2, 19.1 ((CH_3)$_2$CH), 14.4

(CH_3-C-6), 8.3 (CH_3CH_2). At gHMBC, the signal at 104.0 is coupled with the doublet at 3.30 (*H*-6), with the doublet at 3.96 (*H*-5), with the two signals of *H*-7, and finally with CH_2CH_3 and CH_2CH_3 signals. I.R.: ῡ = 2963, 2933, 2876, 1703, 1608, 1593, 1568, 1509, 1463, 1425, 1394, 1382, 1350, 1294, 1241, 1189, 1170, 1068, 1020, 997, 925, 902, 884, 826, 790, 733, 700, 665, 606 cm^{-1} HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{27}H_{34}BrN_2O_3$ 513.1753; Found 513.1740.

(*S*)-1-(4-(Allyloxy)phenyl)-4-((*1S,2S*)-3-hydroxy-2-methyl-1-phenylpropyl)-3-isopropylpiperazine-2,5-dione 17c-*S*. Boc-protected aminoalcohol **14** was converted, according to method A or method B (see preparation of **5b**), by reaction with 4-allyloxyphenyl isocyanide, isobutyraldehyde and chloroacetic acid, into the diastereomeric mixture of **5c**. The two isomers **5c-*S***, and **5c-*R*** where separated by chromatography, and recognized by ^{1}H NMR (selected data are reported in the S.I.). The slower running (major) isomer (60 mg, 127 µmol) was dissolved in dry DMF (2 mL), and treated, at r.t., with cesium carbonate (82.7 mg, 250 µmol). After 6 h the reaction was complete, as judged by TLC. The mixture was quenched with 5% aqueous $NH_4H_2PO_4$ (final pH = 7) and extracted with EtOAc. The organic layer was washed with 5% aqueous LiCl and then with brine, and evaporated under reduced pressure. The crude was purified by column cromatography to afford pure 2,5-diketopiperazine **17c-*S*** (34.8 mg, 63%) as an oil. R_f = 0.39 (PE / AcOEt 50:50 + 1% MeOH). $[\alpha]_D$ = +37.7 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)(for numbering see Scheme 6) δ = 7.61 (dd, $^3J_{H,H}$ = 7.9, $^4J_{H,H}$ = 1.5 Hz, 2 H, H ortho of Ph); 7.39-7.29 (m, 3 H, other CH of Ph); 7.14 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H meta to OAll); 6.93 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H ortho to OAll); 6.03 (ddt, $^3J_{H,H}$ = 17.3, 10.5, 5.3 (t) Hz, 1 H, C*H*=CH_2); 5.40 (1 H, dq, $^3J_{H,H}$ = 17.3, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.6 Hz, 1 H, C*H*H=CH); 5.29 (1 H, dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.4 Hz, 1 H, C*H*H=CH); 4.53 (dt, $^3J_{H,H}$ = 5.4 (d), $^4J_{H,H}$ = 1.5 Hz, 2 H, CH_2OAr); 4.51 (d, $^2J_{H,H}$ = 17.1 Hz, 1 H, H-6); 4.48 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, H-1'); 4.12 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, H-6); 3.93 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, H-3); 3.51 (dd, $^3J_{H,H}$ = 3.9, $^2J_{H,H}$ = 10.8 Hz, 1 H, H-3'); 3.27 (dd, $^3J_{H,H}$ = 4.7, $^2J_{H,H}$ = 10.8 Hz, 1 H, H-3'); 3.04 (mc) (m, 1 H, H-2'); 2.22 (d of heptuplet, $^3J_{H,H}$ = 6.9, 4.5 (d) Hz, 1 H, C*H*(CH_3)$_2$); 1.21 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, C*H*$_3$CH); 1.04 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, (CH_3)$_2$CH); 0.92 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, (CH_3)$_2$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ = 165.0, 164.9 (C=O), 157.6 (C-OAll), 139.2 (quat.), 132.9, 132.8 (quat. and *C*H=CH_2), 129.4 (x2), 128.8 (x2), 128.2, 126.6 (x2), 115.5 (x2) (ArCH), 117.9 (CH=*C*H_2), 70.2 (C-3), 69.0 (CH_2OAr and C-1'), 64.8 (CH_2OH), 54.1 (C-6), 37.4 (*C*H-CH_3), 33.3 (*C*H(CH_3)$_3$), 20.6, 17.0 (CH(*C*H_3)$_2$, 15.0 (*C*H_3CH). I.R.: ῡ 3432, 2967, 2933, 2878, 1656, 1607, 1587, 1509, 1449, 1425, 1390, 1368, 1326, 1293, 1244, 1221, 1187, 1151, 1109, 1062, 1028, 986, 924, 866, 830, 804, 746, 702, 666, 632 cm^{-1}. HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{26}H_{33}N_2O_4$ 437.2440; Found 437.2444.

(*R*)-1-(4-(Allyloxy)phenyl)-4-((*1S,2S*)-3-hydroxy-2-methyl-1-phenylpropyl)-3-isopropylpiperazine-2,5-dione 17c-*R*. It was prepared as described above from the faster running (minor) isomer **5c-*R*** (36 mg, 76 µmol) to give pure **17c-*R*** as an oil (26.8 mg, 80%). R_f = 0.50 (PE / AcOEt 50:50 + 1% MeOH). $[\alpha]_D$ = -35.1 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$)(for numbering see Scheme 6) δ = 7.54-7.47 (m, 2 H, H ortho of Ph); 7.41-7.30 (m, 3 H, other CH of Ph); 7.13 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H meta to OAll); 6.93 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, H ortho to OAll); 6.03 (ddt, $^3J_{H,H}$ = 17.3, 10.5, 5.2 (t) Hz, 1 H, C*H*=CH_2); 5.40 (1 H, dq, $^3J_{H,H}$ = 17.3, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*H=CH); 5.29 (1 H, dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = $^4J_{H,H}$ = 1.5 Hz, 1 H, C*H*H=CH); 5.22 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, H-1'); 4.55 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, H-6); 4.52 (dt, $^3J_{H,H}$ = 5.4 (d), $^4J_{H,H}$ = 1.5 Hz, 2 H, CH_2OAr); 4.12 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, H-6); 3.89 (d, $^3J_{H,H}$ = 4.2 Hz, 1 H, H-3); 3.59 (dd, $^3J_{H,H}$ = 3.0, $^2J_{H,H}$ = 10.8 Hz, 1 H, H-3'); 3.37 (dd, $^3J_{H,H}$ = 5.3, $^2J_{H,H}$ = 10.8 Hz, 1 H, H-3'); 2.93 (mc) (m, 1 H, H-2'); 1.66-1.42 (m, 1 H, C*H*(CH_3)$_2$); 1.17 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, C*H*$_3$CH); 0.94 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, (CH_3)$_2$CH); 0.85 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, (CH_3)$_2$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ = 165.30, 165.27 (C=O), 157.6 (C-OAll), 138.3 (quat.), 132.9 (quat. and *C*H=CH_2), 129.0 (x2), 128.9 (x2), 128.6, 126.6 (x2), 115.5 (x2) (ArCH), 117.9 (CH=*C*H_2), 69.0 (CH_2OAr), 65.0 (CH_2OH), 64.3 (C-3), 61.5 (C-1'), 54.0 (C-6), 36.0 (*C*H-CH_3), 33.1 (*C*H(CH_3)$_3$), 20.2, 17.2 (CH(*C*H_3)$_2$, 14.6 (*C*H_3CH). I.R.: ῡ 3429, 2967, 2934, 2878, 1652, 1608, 1588, 1509, 1449, 1390, 1369, 1349, 1325, 1293, 1245, 1220, 1179, 1146, 1107, 1029, 990, 923, 865, 830, 801, 743, 702, 667, 628 cm^{-1}. HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{26}H_{33}N_2O_4$ 437.2440; Found 437.2451.

(*S*)-3-Methyl-2-(*N*-((*3S,4S*)-3-methylchroman-4-yl)propionamido)-*N*-pentylbutanamide 19h. The mixture of Ugi adducts **5h-*S*** and **5h-*R*** was prepared in 60% overall yield from Boc-aminoalcohol **18** according to method A (see the synthesis of **5b**). After separation of the two diastereomers, the major one (slower running) **5h-*S*** (150 mg, 311 µmol) was dissolved in 96% EtOH (10 mL) and hydrogenated over 10% Pd-C (45 mg) at r.t. and under the slight overpressure of an inflated balloon. After stirring overnight, the suspension was filtered through a celite cake, washing with CH_2Cl_2, and evaporated to dryness. The residue was taken up in dry THF (10 mL), cooled to 0°C, and treated with triphenylphosphine (122 mg, 466 µmol) and diethyl azodicarboxylate (40% solution in toluene) (212 µL, 466 µmol). The solution was stirred for 5 h at 0°C. Evaporation and chromatography afforded pure **19h** as an oil. R_f = 0.28 (AcOEt/PE 1:4 + 1% MeOH). $[\alpha]_D$ = + 68.4 (c 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (broad s, 1 H, NH); 7.16 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H); 6.97 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H); 6.86-6.77 (m, 2 H); 4.84 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, H-4); 4.27-4-13 (m, 2 H, H-6 and CH*i*Pr); 3.75 (t, $^2J_{H,H}$ = $^3J_{H,H}$ = 11.1 Hz, 1 H, H-6); 3.05 (q, $^3J_{H,H}$ = 6.2 Hz, 2 H, C*H*$_2$NH); 2.97-2.80 (m, 1 H, C*H*(CH_3)$_2$); 2.65-2.45 (m, 2 H, CH_2CO); 2.46-2.28 (m, 1 H, H-3); 1.55-1.17 (m, 9 H, CH_2 of pentyl and CH_3CH_2); 1.11 (d, $^3J_{H,H}$ = 6.6 Hz, C*H*$_3$CH); 0.97-0.84 (m, 9 H, other CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ = 176.8, 171.3 (C=O), 156.4 (quat.)(the other quat. carbon is not visible, probably because of its broadiness), 129.3, 128.1, 121.1, 117.6 (Ar CH), 71.6 (CH*i*Pr), 70.6 (*C*-2), 60.9 (*C*-4), 39.1 (CH_2NH), 31.7 (C-3), 29.2, 28.9 (CH_2 pentyl), 28.6 (CO*C*H_2CH$_3$), 28.2 (*C*H(CH_3)$_2$), 22.4 (CH_2 pentyl), 20.8, 20.1 (CH(*C*H_3)$_2$, 15.4, 14.0 (*C*H_3CH and *C*H_3 of pentyl), 9.9 (CH_3CH_2CO). I.R.: ῡ 3299, 2961, 2932, 2873, 1716, 1656, 1623, 1585, 1542, 1489, 1451, 1368, 1314, 1260, 1227, 1173, 1102, 1072, 1049, 1024, 960, 930, 892, 852, 799, 752, 723, 698, 667, 643, 604 cm^{-1}. HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{23}H_{37}N_2O_3$ 389.2804; Found 389.2815.

(*S*)-1-Cyclohexyl-3-isopropyl-4-((*3S,4S*)-3-methylchroman-4-yl)piperazine-2,5-dione 20j-*S*. The mixture of Ugi adducts **5j-*S*** and **5j-*R*** was prepared in 51% overall yield from Boc-aminoalcohol **18**[11] according to method A (see the synthesis of **5b**). The two isomers **5j-*S***, and **5j-*R*** where separated by chromatography, and recognized by ^{1}H NMR (selected data are reported in the S.I.). The slower running (major) isomer (75 mg, 142 µmol) was dissolved in dry DMF (1.5 mL), and treated, at r.t., with cesium carbonate (92.5 mg, 284 µmol). After 4 h the reaction was complete, as judged by TLC. The mixture was quenched with 5% aqueous $NH_4H_2PO_4$ (final pH = 7) and extracted with EtOAc. The organic layer was washed with 5% aqueous LiCl and then with brine, and evaporated under reduced pressure. The crude was dissolved in 96% EtOH (5 mL) and hydrogenated over 10% Pd-C (22 mg) at r.t. and under the slight overpressure of an inflated balloon. After stirring overnight, the suspension was filtered through a celite cake, washing with CH_2Cl_2, and evaporated to dryness. The residue was taken up in dry THF (5 mL), cooled to 0°C, and treated with triphenylphosphine (56 mg, 213 µmol) and diethyl azodicarboxylate (40% solution in toluene) (97 µL, 466 µmol). The solution was stirred for 1 h at 0°C. Evaporation and chromatography afforded pure **20j-*S*** as an oil (38 mg, 69%). R_f = 0.33 (AcOEt/PE 1:3 + 1% MeOH). $[\alpha]_D$ = + 30.5 (c 0.52, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.14 (ddt, $^3J_{H,H}$ = 8.1 Hz (t), $^2J_{H,H}$ = 0.6, 1.8 Hz, 1 H); 6.90-6.81 (m, 2 H); 6.72 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H); 5.45 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, H-4); 4.50-4.36 (mc = 4.43) (m, 1 H, CHN); 4.23 (dd, $^3J_{H,H}$ = 3.8 Hz, $^2J_{H,H}$ = 11.2 Hz, 1 H, H-2); 4.08, 4.01 (AB syst., $^3J_{H,H}$ = 17.7 Hz, 2 H, CH_2N); 3.85 (t, $^3J_{H,H}$ = $^2J_{H,H}$ = 11.0 Hz, 1 H,

H-2); 3.56 (d, $^3J_{H,H}$ = 11.4 Hz, 1 H, CH*i*Pr); 2.41-2.24 (m, 1 H, H-3); 2.22-2.09 (m, 1 H, C*H*(CH_3)$_2$); 1.90-1.80 (m, 2 H); 1.75-1.65 (m, 2 H); 1.60-1.00 (m, 6 H); 1.09 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3); 1.08 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3); 1.07 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ = 167.4, 164.2 (C=O), 156.0, 119.9 (quat.), 129.0, 126.0, 121.5, 117.3 (Ar CH), 71.0 (*C*-2), 63.7 (CH*i*Pr), 57.8 (*C*-4), 52.3 (CHN), 45.9 (CH_2N); 34.7 (*C*H(CH_3)$_2$), 31.4 (C-3), 30.1, 29.3, 25.5, 25.4, 25.3 (CH_2 cyclohexyl), 20.9, 17.5 (CH(CH_3)$_2$, 14.3 (CH_3CH). I.R.: ῡ 2984, 2937, 2885, 2857, 1656, 1643, 1605, 1580, 1488, 1469, 1450, 1391, 1380, 1364, 1346, 1327, 1318, 1298, 1282, 1232, 1207, 1182, 1153, 1125, 1112, 1102, 1045, 1023, 994, 968, 923, 893, 882, 843, 829, 815, 794, 755, 743, 664, 651, 624, 608 cm^{-1}. HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{23}H_{33}N_2O_3$ 385.2491; Found 385.2495.

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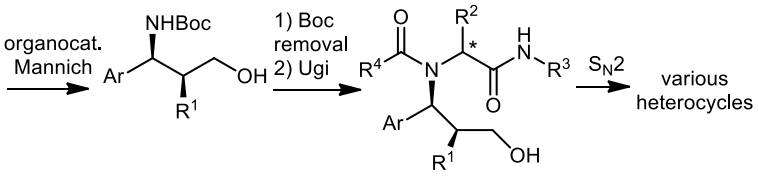

Different enantiopure heterocycles have been prepared, exploring both scaffold and decoration diversity, by a sequence of an enantioselective Mannich reaction, a diastereoselective U-4CR, and various cyclizations.

Multicomponent Reactions

S. Caputo, L. Banfi, A. Basso, A. Galatini, L. Moni, R. Riva, C. Lambruschini*

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Diversity-Oriented Synthesis of Various Enantiopure Heterocycles by Coupling Organocatalysis with Multicomponent Reactions