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PAPER

Development of a stereoselective Ugi reaction starting from an oxanorbornene β-amino acid derivative†

Luca Banfi,[a] Andrea Basso,*[a] Cinzia Chiappe,*[b] Fabio De Moliner,[c] Renata Riva[a] and Lorenzo Sonaglia[a]

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We have synthesised a novel oxanorbornene β-aminoacid derivative and employed it in a stereoselective Ugi reaction. Hypothesis regarding the mechanism taking place during the reaction have been made and validated through the determination of the relative and absolute configuration of the Ugi adducts. Use of the correct choice of solvents can increase stereoselection. The resulting bicyclic peptidomimetics can be used as a novel class of pluripotent substrates to be elaborated according to the synthetic strategies previously elaborated in our laboratories.

Introduction

Diversity oriented synthesis[1] has emerged as a very powerful tool for the discovery of biologically relevant, natural product like[2] molecular entities, especially in challenging fields such as protein–protein interactions.[3] We have recently applied this approach to the synthesis of norbornene derivative **1** and its elaboration to pluripotent substrate **2** (Scheme 1).[4] First of all we have elaborated a multicomponent approach to functionalise the core structure of **1** in a combinatorial fashion,[5] then we have devised an organocatalytic approach to prepare the adducts in an enantioselective manner.[6] Subsequently, exploiting the peculiar reactivity of the oxabicyclic system, we have elaborated products **2** from the multicomponent step *via* a number of transformations[7,8] leading to distinct classes of compounds, some of them showing activity towards proteins of the Bcl-2 family.[9]

We have now identified compound **3** (Fig. 1) as a new pluripotent substrate that, having opposite configurations of the carbons bearing the amine and carboxyl functionalities, could lead to novel classes of compounds similar to those obtained with **1** but with different spatial orientations. We wish to report in this paper the first results related to this novel derivative.

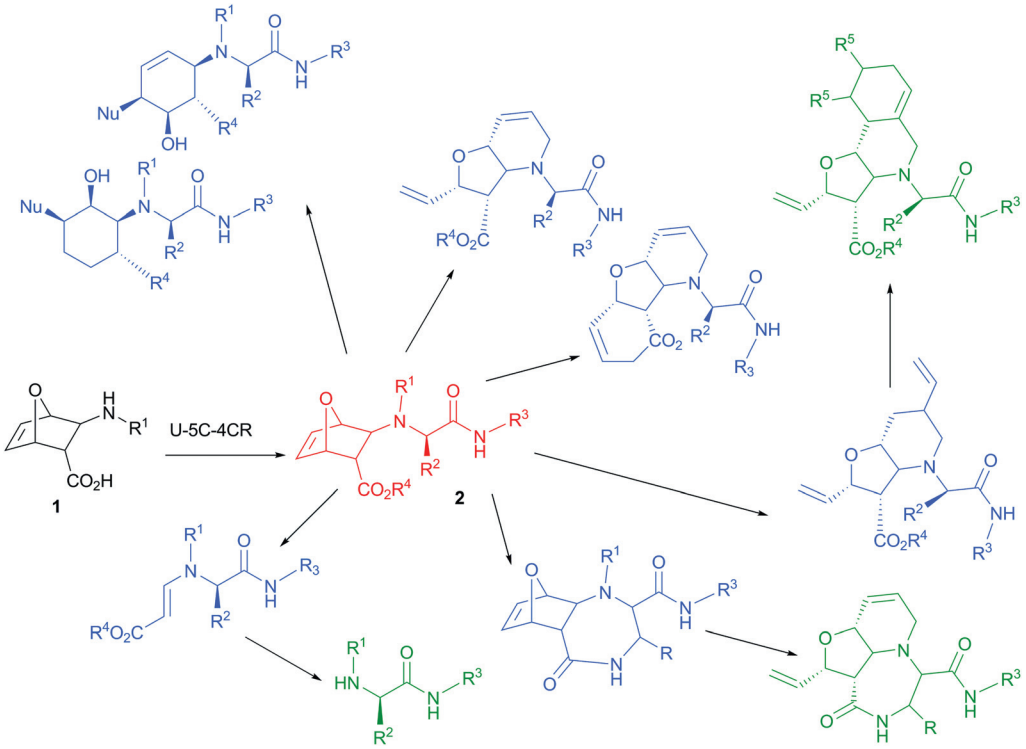
Results and discussion

With respect to compound **1**,[6] a completely different synthetic approach had to be planned for the elaboration of the bicyclic scaffold in order to obtain the desired *endo* amine substituent: we speculated that a Diels–Alder reaction between furan and *trans*-nitroacrylate **4** could be exploited to obtain an adduct having the correct spatial orientation of the two groups.[10] Indeed, by performing the cycloaddition reaction at low temperature, the desired *endo*-nitro adduct **5** could be obtained as the major isomer.[11] Various procedures are available to prepare nitroacrylate **4**: we first applied the Henry reaction with nitromethane and glyoxalate[12,13] and the CAN mediated nitrosation of ethyl acrylate[14] giving, however, variable results and yields of 2-hydroxy-3-nitropropanoate (always lower than 60%). In addition, the subsequent mesylation/elimination step was found to be troublesome due to the instability and low boiling point of the resulting nitroacrylate. On the other hand, the iodo nitrosation employed by Steel[15] was considered unsafe due to the use of highly toxic N_2O_4 gas. We eventually found that the procedure reported by Yuen,[16] starting from acrylate **7** and involving a nitromercuration, a bromination/demercuration and a final sodium acetate-mediated elimination, although not very eco-friendly and atom economical, allowed us to prepare up to 10 g of the desired nitroacrylate in 75% overall yield starting from cheap ethyl acrylate. Upon filtration of NaBr and excess sodium acetate, crude nitroacrylate was purified by flash chromatography (extractive work-up, as described in the original procedure, was avoided because partial decomposition was observed) and was immediately employed in the Diels–Alder cycloaddition.

For this purpose equal volumes of furan and chloroform were added to the reaction vessel; this was sealed and left standing (with occasional manual stirring) for two weeks in a refrigerator at −24 °C (Scheme 2). The two stereoisomers **5** and **6** were obtained in an overall 71% yield with a 3.6 : 1 ratio in favour of the desired isomer **5**; the two isomers could be separated by flash chromatography. Due to the high tendency of these adducts to give the retro Diels–Alder reaction, however, the desired *endo*-NO_2 adduct **5** was immediately reduced, soon after chromatography, with Zn/HCl to obtain the corresponding amine **8**.

[a]*Università degli Studi di Genova, Dipartimento di Chimica e Chimica Industriale, Genova, Italy. E-mail: andrea.basso@unige.it*
[b]*Università degli Studi di Pisa, Dipartimento di Chimica e Chimica Industriale, Pisa, Italy. E-mail: cinziac@farm.unipi.it*
[c]*University of Arizona, Department of Pharmacology and Toxicology, Tucson, Arizona, USA*

†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR of all new compounds and output files for intermediates **10** and **15**. See DOI: 10.1039/c2ob25060h



Scheme 1 A diversity-oriented approach employing an oxanorbornene pluripotent substrate.

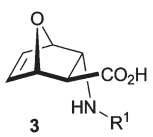


Fig. 1 General structure of a novel pluripotent substrate.

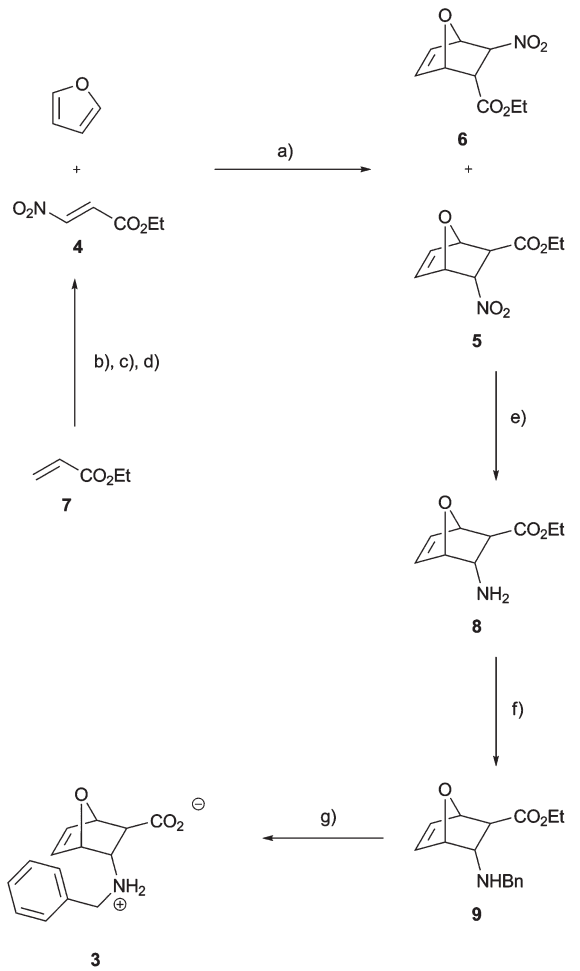
For our purposes a secondary amine was required and a reductive amination step was devised to introduce a benzyl substituent onto the amine functionality. Final hydrolysis of **9** afforded the amino acid derivative **3**, suitable for functionalisation *via* a multicomponent reaction.

In analogy with compound **1**, we thought that an intramolecular Ugi reaction could be employed to introduce the peptidomimetic chain onto the nitrogen atom, following the same Ugi 5 centre 4 component reaction (U-5C-4CR) mechanism[17] successfully employed before. Being interested to find whether this reaction outcome occurred, we reacted amino acid **3** with various aldehydes and isocyanides under classic Ugi conditions (in MeOH at room temperature). Such a reaction probably involves formation of a norbornene-fused 7-membered ring intermediate **10** as a consequence of interaction of **3** with one molecule of aldehyde and one of isocyanide, and subsequent displacement of the activated carboxy group by the alcohol employed as the solvent, to afford the final product **11** (Scheme 3).

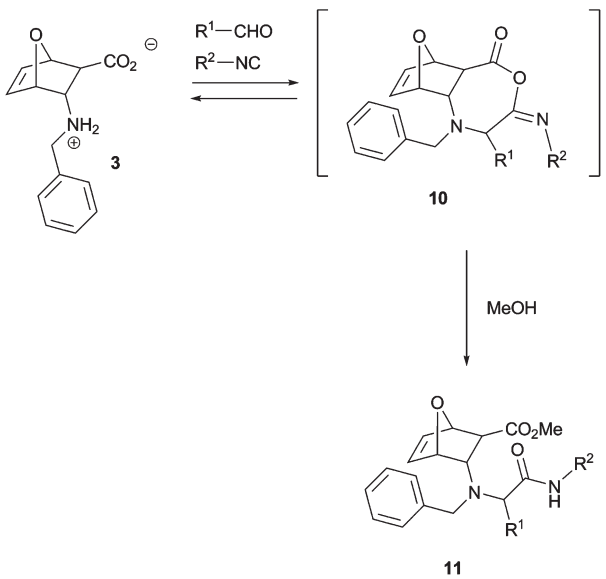
We were delighted to find that compounds **11a–j** could be all isolated in yields ranging from moderate to good. Moreover, crude materials showed in most cases the desired Ugi adducts as the main products present in the mixture. To our disappointment, however, the final compounds were in most cases mixtures of diastereoisomers (whereas with **1** complete diastereoselection was typically observed) with one prevailing in a d.r. > 3 : 1 (Table 1).

In addition, different levels of stereoselectivity were observed for the same reaction depending on the method employed for the isolation of the amino acid **3** after ester hydrolysis of **9**. In fact, three different methods were employed: (**a**) neutralisation of the reaction medium with HCl and collection of the precipitated product by filtration, (**b**) catching of the product on an acidic ion exchange resin and releasing in solution with aqueous ammonia and (**c**) neutralisation of the reaction medium with HCl and evaporation of the solvents. Out of these three methods the latter allowed for complete recovery of the amino acid, although it suffered from contamination by NaCl, whereas the first two, although affording pure product, allowed only its partial recovery (55–76%).

As outlined in Table 1, depending on the method employed (methods **a** and **b** gave the same results), the diastereomeric ratio varied, but a rationale could not be easily extrapolated, since in some cases the presence of NaCl seemed beneficial, in others not. It is worth noting that addition of NaCl to the amino acid **3** isolated with method **a**, resulted in an outcome similar to the one obtained with method **c**. We therefore speculated that NaCl could have a double effect, by increasing the polarity of the solvent (in our hypothesis this could facilitate direct formation of



Scheme 2 Reagents and conditions: (a) $CHCl_3$, −24 °C, 71%; (b) $HgCl_2$, $NaNO_2$, water; (c) bromine, water, Et_2O; (d) AcONa (an.), Et_2O, 75%; (e) Zn dust, HCl, EtOH, 78%; (f) benzaldehyde, $NaBH_3CN$, AcOH, MeOH, quant.; (g) NaOH, dioxane, see text.



Scheme 3 Mechanism for the Ugi 5 centre 4 component reaction.

Table 1 Outcome of the U-5C-4CR

			Method c		Method a or b	
Entry	R^1	R^2	Yield[a] (%)	d.r.	Yield[b]	d.r.
a	Et	*t*-Bu	75	>95 : 5	—	—
b	*i*-Bu	*t*-Bu	76	>95 : 5	—	—
c	*i*-Pr	Bn	79	75 : 25	45%	93 : 7
d	Bn	cHex	97	88 : 12	—	—
e	*i*-Bu	4-BnOPh	66	83 : 17	55%	82 : 18
f	Ph	*n*-Bu	67	79 : 21	—	—
g	Et	*n*-Bu	53	80 : 20	53%	75 : 25
h	*i*-Pr	4-BnOPh	74	82 : 18	—	—
i	Bn	Bn	68	74 : 26	65%	86 : 14
j	Ph	cHex	60	79 : 21	53%	84 : 16

[a] Yield is referred to **9**. [b] Yield is referred to **3**.

the 7-membered ring intermediate **10**, responsible for the stereoselection as it will be discussed below) but also by becoming an active part of the reaction, possibly with Cl^- acting as a nucleophile transiently competing with the carboxylate or the isocyanide, thus affecting the configuration of the newly generating stereogenic carbon. The fact that previous experiments showed that the stereoselectivity of the U-5C-4CR for amino acid **1** did not depend on the isolation method (and therefore on the presence or absence of NaCl) prompted us to investigate this effect more in detail. We therefore moved to use different salts, such as KCl or NaBr, and other alcohols as solvents. However, we could not find a general trend, although interesting results were obtained when trifluoroethanol (TFE) was employed with and without the presence of NaCl. In both cases the reaction was very sluggish, but in the absence of NaCl the stereoselectivity was complete and only one trifluoroethyl ester was isolated. On the other hand the presence of NaCl caused a marked decrease in stereoselection. It seemed reasonable that the poor nucleophilicity of TFE could render more difficult the displacement of the 7-member ring intermediate **10** and increase, when NaCl was employed, the extent of the Cl^- mediated side reactions. At the same time its higher polarity could favour the formation of the more stable diastereoisomer. A good compromise between the diminished reactivity and the increased polarity seemed to be the use of a mixture of methanol and trifluoroethanol, the first being the nucleophile becoming part of the U-5C-4CR and the latter modulating polarity. Indeed, by employing a 1 : 1 mixture of the two alcohols, the final compounds were obtained solely as the corresponding methyl esters and with very good diastereomeric ratios (Table 2); only in the case of benzaldehyde was more than 5% of the minor diastereoisomer isolated.

Having these results in hand we decided, in the case of entry j, to investigate further reaction conditions, including various solvent mixtures (*i.e.* ionic liquids (ILs)) and temperatures. As summarised in Tables 3 and 4, best results in terms of stereoselectivity were obtained with a 9 : 1 mixture of TFE–MeOH, although in this case also a certain amount of TFE ester was isolated. On the other hand, no reaction was observed when DMSO or water were used as co-solvent or solvent (when water was employed we were indeed expecting to isolate the corresponding carboxylic derivative). Also addition of benzaldehyde and cyclohexylisocyanide at different times was investigated, but no

Table 2 Outcome of the U-5C-4CR (**3→11**) performed in MeOH–TFE 1 : 1

Entry	R^1	R^2	d.r.	Yield (%)
a	Et	*t*-Bu	>95 : 5	50
b	*i*-Bu	*t*-Bu	>95 : 5	75
c	*i*-Pr	Bn	95 : 5	73
d	Bn	cHex	>95 : 5	74
e	*i*-Bu	4-BnOPh	95 : 5	77
f	Ph	*n*-Bu	83 : 17	97
g	Et	*n*-Bu	>95 : 5	80
h	*i*-Pr	4-BnOPh	>95 : 5	74
i	Bn	Bn	>95 : 5	93
j	Ph	cHex	83 : 17	98

Table 3 Outcome of the U-5C-4CR with benzaldehyde and cyclohexyl isocyanide (**3j→11j**) under various conditions

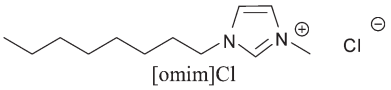
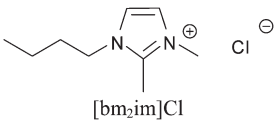
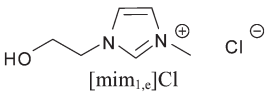
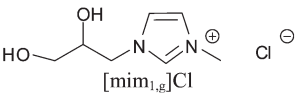
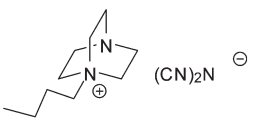
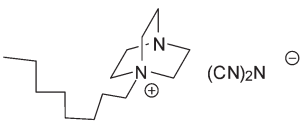
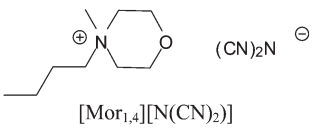
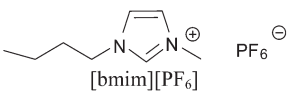
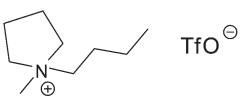
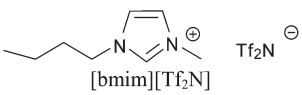
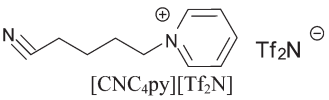
Conditions	d.r.	Yield
MeOH–CF_3CH_2OH 1 : 3 (0.2 M)	88 : 12	96%
MeOH–CF_3CH_2OH 1 : 3 (0.2 M) at 0 °C	83 : 17	84%
MeOH–CF_3CH_2OH 1 : 9 (0.2 M)	93 : 7	63%
H_2O (0.2 M)	—	—
MeOH–H_2O 1 : 1 (0.2 M)	—	—
MeOH–DMSO 1 : 1 (0.2 M)	—	—
MeOH–NMP 1 : 1 (0.2 M)	85 : 15	18%
MeOH–phenol 1 : 1 (0.2 M)	85 : 15	69%
MeOH (0.2 M) with tetrazole (2 eq)	79 : 21	81%

differences were observed. We also investigated if the lower stereoselectivities observed in the case of benzaldehyde were common to other aromatic aldehydes, and indeed aryl aldehydes with EW and ED groups behaved similarly, as outlined in Scheme 4.

Particularly interesting, is the use of ILs; in this investigation conventional ILs (differently substituted imidazolium, pyridinium and pyrrolidinium salts combined with anions such as chloride, hexafluorophosphate, bistriflimide and dicyanamide) and task-specific ILs, characterized by one or more functional groups on the cation, have been used in 1 : 1 (w/v) mixtures with methanol.[18] As evidenced in Table 4, depending on the IL employed the diastereoisomer ratio and reaction yield varied; although only in a few cases were selectivities higher than those obtained with pure methanol. This result is not completely surprising since IL polarities, at least as expressed by solvatochromic parameters, not only present some peculiarities,[19] but they are strongly affected by the presence of a molecular solvent, such as methanol, which is able to destroy the three-dimensional structure of the IL and modify significantly these parameters. Depending on concentration, polarity parameters can become practically identical to those of molecular solvents.[20] Consequently, under the employed conditions the polarity of the investigated media is probably not very different from that of methanol.

On the other hand, the specific interactions of methanol with the components of IL (in the case of protic solvents the interaction should be preferentially with the anion) can modify as observed the diastereoisomeric ratios and yields affecting the ability of the IL to interact with the species which should favor formation of intermediate **10**. For example, the high

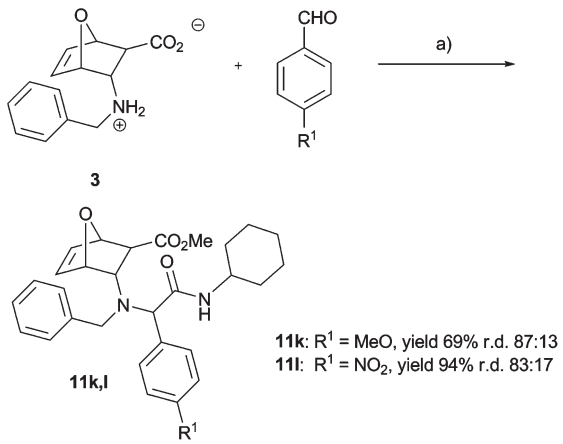
Table 4 Outcome of the U-5C-4CR with benzaldehyde and cyclohexyl isocyanide (**3j→11j**) with ionic liquids[a]

IL	d.r.	Yield (%)
 [omim]Cl	61 : 39	79
 [bm_2im]Cl	74 : 26	45
 [$mim_{1,e}$]Cl	73 : 27	56
 [$mim_{1,g}$]Cl	80 : 20	89
	71 : 29	18
 [C_4dabco][$N(CN)_2$]	83 : 17	40
 [C_8dabco][$N(CN)_2$],	80 : 20	42
 [$Mor_{1,4}$][$N(CN)_2$)]	85 : 15	45
 [bmim][PF_6]	73 : 27	68
 [bmpy][TfO]	75 : 25	96
 [bmim][Tf_2N]	77 : 23	77
 [CNC_4py][Tf_2N]	72 : 28	74

[a] Reactions were performed with IL–MeOH 1 : 1 at a 0.2 M concentration.

diastereoselectivity associated with a low yield observed in dicyanamide based ILs can be considered a consequence of the higher ability of this anion to interact with methanol. The anion–methanol interaction can reduce the amount of "free" and faster reacting methanol molecules. A similar explanation can be given for the moderate yields of the reaction in [bm_2im]Cl and

[$mim_{1,e}$]Cl, whereas the positive results obtained in the hydroxyl difunctionalized [$mim_{1,g}$]Cl can be attributed to the capability of this cation to compete efficiently with methanol in chloride coordination. On the other hand, in the case of [omim]Cl the presence on the cation of a long alkyl chain can favor the formation of polar and apolar domains which are able to determine a different methanol distribution and binding mode. Finally, it is necessary to consider that depending on the IL, cosolvent and substrate, the preferential solvation phenomena can also occur[20] in these media. Independent of the complexity of these systems, which can affect selectivity and reactivity through several different mechanisms, since in all the investigated ILs the diastereoisomer ratios are comparable or lower than those obtained in the 1 : 1 mixture methanol–TFE we can state that, although some combinations are more favorable than pure methanol, probably the specific interactions of IL cations and/or anions with the species which should favor the formation of intermediate **10** are never so efficient to give complete diastereospecificity.

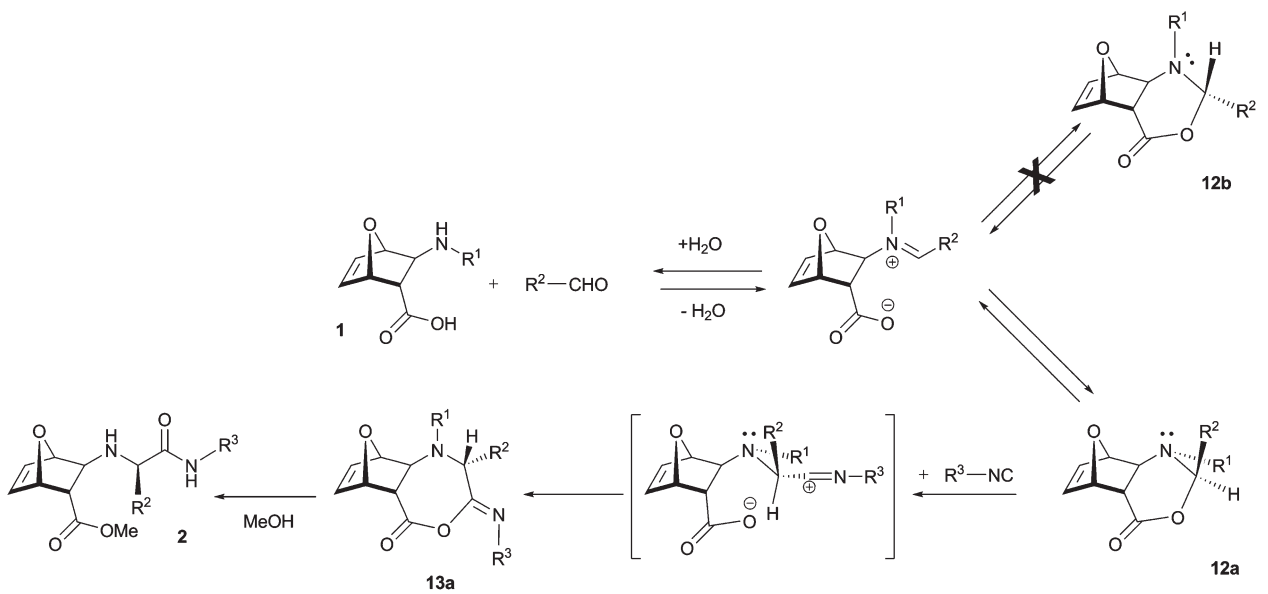


Scheme 4 Reagents and conditions: (a) cyclohexylisocyanide, MeOH–CF_3CH_2OH 1 : 1 (0.2 M).

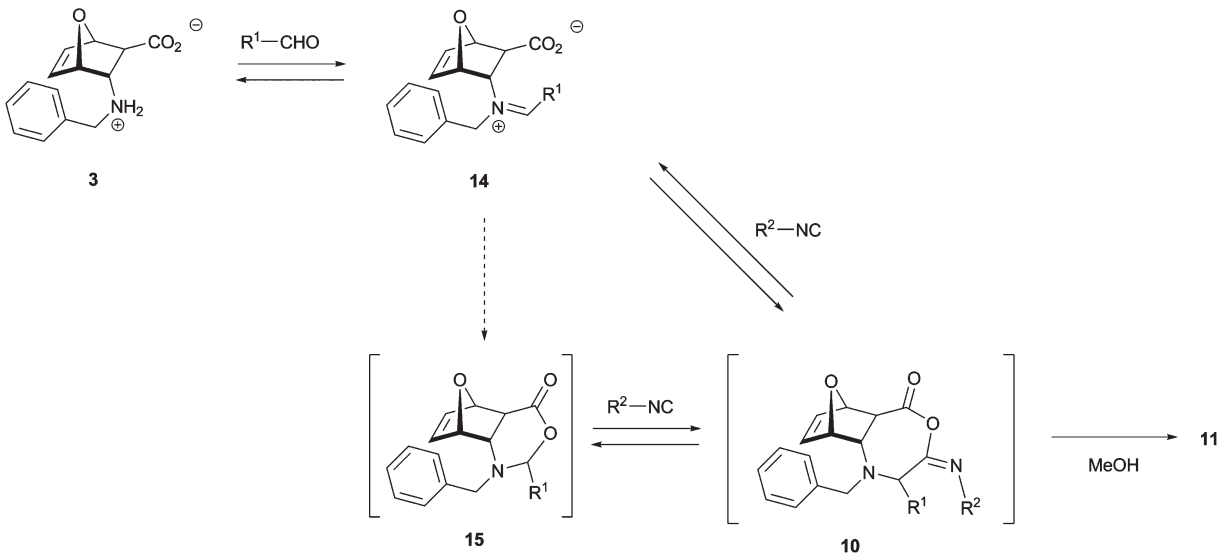
Although poor stereoselectivity is quite typical in isocyanide-based multicomponent reactions, we were surprised at such an outcome, on the basis of the results obtained with bicyclic amino acid **1**, where the Ugi reactions were found to be completely stereoselective, independently from the aldehyde and isocyanide employed. In the case of this bicyclic amino acid, it was postulated that the reaction proceeded through formation of a transient 6-member ring intermediate **12**, generated by intramolecular attack of the carboxylate onto the iminium ion. This hypothesis was taken into account to rationalise the unusually high diastereoselection observed in the multicomponent reaction.[4,6] Indeed, the small energy difference of the two diastereomeric 7-member ring intermediates **13** could not be sufficient to justify such an outcome. The more stable diastereoisomer **12a** would be then nucleophilically attacked by the isocyanide onto the Cα carbon with subsequent inversion of the configuration and formation of **13a** through the attack of the carboxylate onto the sp carbon derived from the isocyanide. Final methanolysis affords compound **2** with the correct configuration at the Cα carbon (Scheme 5). If a similar mechanism could be applied also in the case of **3**, intermediate **15** would be generated from iminium ion **14** prior to attack of the isocyanide (Scheme 6). We were therefore intrigued to find out if the same hypothesis could be applied also in this case.

Having established a method to generate the Ugi adducts in a stereoselective manner, it became evident that the relative configuration of the final products had to be determined, also to confirm that the major diastereoisomer was originating from the more stable 7-member ring intermediate. Being the final compounds foams rather than giving crystalline solids, methods other than crystallography had to be employed. It was therefore decided to exploit the bicyclic system as a chiral auxiliary and to remove it at the end of the Ugi condensation in order to determine the absolute configuration of the resulting α-aminoamide **17**,[21] as outlined in Scheme 7.

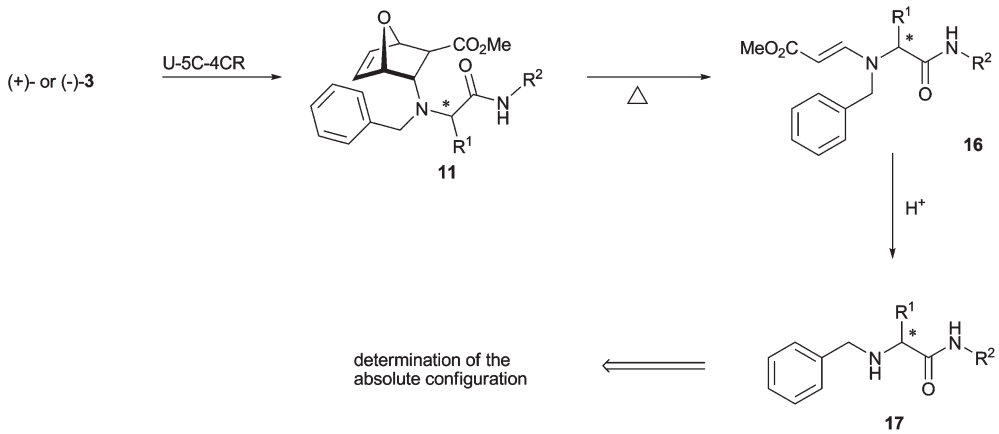
Removal of the bicyclic system had already been performed on compounds **2** and did not seem to be problematic at this



Scheme 5 Postulated mechanism occurring when amino acid **1** is employed in the U-5C-4CR.



Scheme 6 Postulated mechanism occurring when amino acid **3** is employed in the U-5C-4CR.

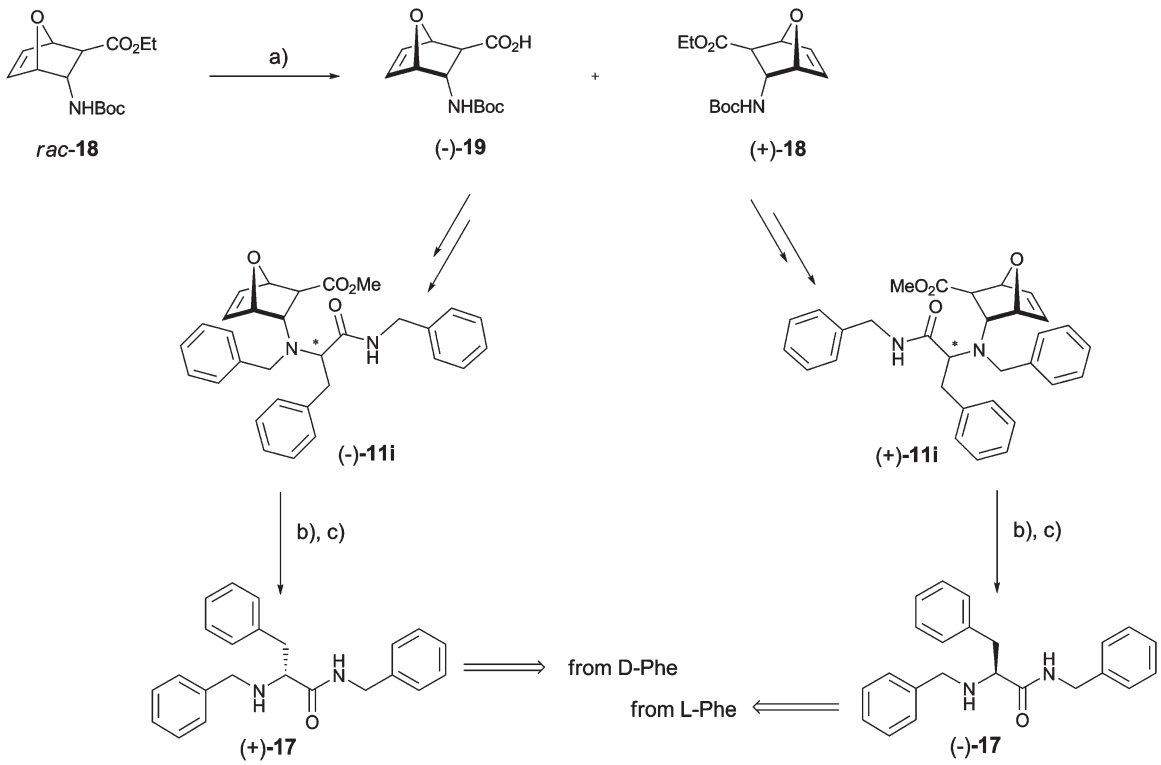


Scheme 7 Synthetic scheme for the determination of the configuration of **11**.

stage, while more concern regarded the preparation of the bicyclic aminoacid in an optically pure form.

Desymmetrisation of a *meso* compound according to the method developed by Bolm[24] could not be applied in this case. It seemed more feasible to employ kinetic resolution through enzymatic hydrolysis of ester **18**, following the approach developed by Steel.[15] Compound **rac-18** was prepared from **8** *via* protection of the primary amine with Boc_2O, while hydrolysis was performed with horse liver acetone powder in TRIS buffer. At this stage the enzymatic reaction was not optimised, since the main aim was to be able to determine the configuration of aminoamide **17**. The unoptimised methodology afforded (−)-acid **19** in approximately 86% ee and (+)-ester **18** in 85% ee, as determined by absolute optical rotatory power. Both enriched enantiomeric mixtures were transformed into the corresponding *N*-benzyl aminoacid derivative **3** and reacted under the optimised Ugi conditions with phenylacetaldehyde and benzyl isocyanide, affording, as expected, only one diastereoisomer. Conversion of the Ugi adducts **11i** into the α-aminoamide was performed as previously described,[6] by heating the compound in refluxing toluene and by treating the resulting enamine with HCl in dioxane. Comparison of the sign of the optical rotatory power of products **17** with that of authentic samples derived from L- and D-phenylalanine confirmed that (−)-**19** afforded (*R*)-**17** and (+)-**18** afforded (*S*)-**17** (Scheme 8). Going backwards, we could therefore assign the relative configuration of the newly generated stereocenter of the major diastereoisomer of **11** during the Ugi reaction, as depicted in Fig. 2.

This is in accordance with the results obtained by preliminary molecular modelling calculations. Molecular modelling calculations on the postulated intermediates originating from the reaction of **3** with benzyl isocyanide and phenylacetaldehyde were carried out (conformational analysis was performed with CONFLEX[22] software using GB/SA calculation, while SCF energy of more stable conformers was calculated in methanol using GAUSSIAN (RB3LYP/6-31G SCRF = PCM).[23] Such preliminary calculations showed that diastereomeric 6-membered ring intermediates **15i_a** and **15i_b** had an energy difference of less than 0.06 kcal mol^{-1}, favouring **15i_a**.



Scheme 8 Reagents and conditions: (a) enzymatic hydrolysis, see text; (b) toluene, reflux, quant.; (c) HCl, dioxane, 87%.

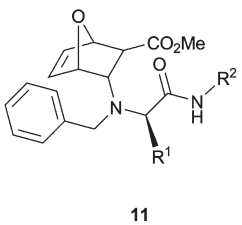


Fig. 2 The major diastereoisomer originating from the U-5C-4CR with amino acid **3**.

In contrast, diastereomeric 7-membered ring compounds **10i_a** and **10i_b**, have an energy difference of about 4.5 kcal mol^{-1}, favouring **10i_b**, (→ major diastereoisomer of **11i**; Fig. 3).

We had therefore to conclude that, in the case of compound **3**, differently from what observed in the case of **1**, the observed stereoselection was probably determined at the level of the 7-membered ring intermediate.

It is worth noting that, according to our postulated mechanism, the more stable 6-membered ring intermediate **15i_a** would lead to the minor diastereoisomer of **11** *via* formation of **10i_a** (the attack of the isocyanide proceeds with inversion of the configuration). One possible explanation of the different stereoselectivity observed in MeOH and trifluoroethanol could therefore be that in the former solvent the reaction proceeds to some extent *via* the formation of intermediate **15**, thus lowering diastereoselectivity as a consequence of the formation of a certain amount of **10i_a**, while the employment of the more polar trifluoroethanol could stabilise the iminium ion **14**, which could directly react with the isocyanide to afford solely **10i_b** (Scheme 6). According to this hypothesis, the detrimental effect of NaCl on stereoselection observed for **3** and not for **1** could be rationalised with a

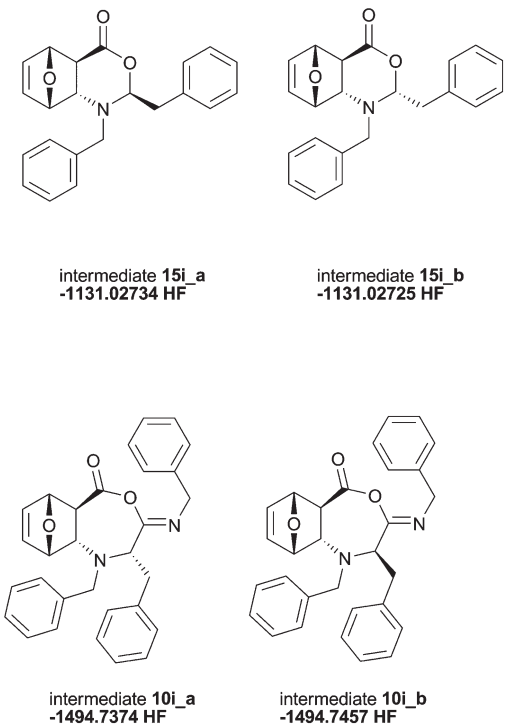


Fig. 3 SCF energies of diastereomeric 6- and 7-member ring intermediates.

higher tendency of chloride anions to interact (and thus giving transient nucleophilic addition to the iminium group) with the open intermediate **14** rather than with cyclic adduct **12**.

Experimental

General remarks

The reagents and solvents of the highest purity available were used as purchased or purified/dried by standard procedures when necessary. All ionic liquids, namely, 1-octyl-3-methylimidazolium chloride ([omim]Cl), 1-butyl-2,3-dimethylimidazolium chloride ([bm_2im]Cl), 1-hydroxyethyl-3-methylimidazolium chloride ([$mim_{1,e}$]Cl), 1-glyceryl-3-methylimidazolium chloride ([$mim_{1,g}$]Cl), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), 1-butyl-3-methylimidazolium bistriflimide ([bmim][Tf_2N]), 1-(1-cyanobutyl)pyridinium bistriflimide ([CNC_4py][Tf_2N]), 1-butylpyridinium dicyanamide ([BPy]-[$N(CN)_2$]), 1-butyl-4-aza-1-azaniabicyclo[2.2.2]octane dicyanamide ([C_4dabco][$N(CN)_2$]), 1-octyl-4-aza-1-azaniabicyclo[2.2.2] octane dicyanamide ([C_8dabco][$N(CN)_2$]), *N*-butyl-*N*-methylmorpholinium dicyanamide ([$Mor_{1,4}$][$N(CN)_2$]) and *N*-methyl-*N*-butylmorpholinium triflate ([bmpy][TfO]) were prepared according to well-established synthetic procedures[18] and confirmed by NMR analysis and electrospray ionization mass spectrometry (ESI-MS). All ILs were dried under vacuum (pressure 10^{-2} – 10^{-3} mbar) at 80 °C for 24 h prior spectral analysis.

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively in $CDCl_3$ if not specifically indicated, and calibrated to internal standard (TMS) or the residual peak of the solvent.

Synthesis of amino acid 3

Amino ester **8** has been prepared following the literature procedure.[15] Benzaldehyde (1.08 mmol, 110 μL) and acetic acid (1.5 mL) were added to a solution of **8** (0.72 mmol, 132 mg) in dry methanol and the reaction was stirred at room temperature over night. Sodium cyanoborohydride (1.3 mmol, 81 mg) was then added and the reaction stirred at room temperature for 4 h. Saturated aqueous $NaHCO_3$ and dichloromethane were added, the phases separated and the organic one was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (gradient: petroleum ether–ethyl acetate 70 : 30 up to 50 : 50) to afford **9** (0.53 mmol, 145 mg). Ester **9** (0.53 mmol) was then treated with aqueous NaOH 1.0 M (0.58 mmol) in dioxane (3.5 mL) at room temperature overnight. The reaction was quenched with aqueous HCl 1.0 M (0.58 mmol) and a precipitate was formed. The solid was filtered after cooling the flask with an ice bath and washed with cold water to give acid **3** (0.29 mmol, 71 mg) in 55% yield.

Ethyl 3-*endo*-(benzylamino)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate 9. ^{1}H NMR: δ 1.28 (t, J = 7.1 Hz, 3H), 2.05 (d, J = 3.4 Hz, 1H), 3.69 (dd, J = 4.3, 3.5 Hz, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 1H), 4.87–4.92 (m, 1H), 5.14 (dd, broad, J = 1.7, 0.7 Hz, 1H), 6.44 (d, J = 5.8, 1.6 Hz, 1H), 6.55 (dd, J = 5.8, 1.8 Hz, 1H), 7.20–7.35 (m, 5H). ^{13}C NMR: δ 14.4 (CH_3), 52.36 (CH), 53.1 (CH_2), 61.1 (CH_2), 62.1 (CH), 79.6 (CH), 82.0 (CH), 127.3 (CHAr), 128.2 (CHAr), 128.6 (CHAr), 134.5 (CH), 137.4 (CH), 140.0 (C), 173.0 (C). HRMS calculated for $C_{16}H_{19}NO_3$ 273.1365, found 273.1358.

3-*endo*-(Benzylamino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid 3. ^{1}H NMR (d_6-DMSO): δ 1.90 (d, J = 3.4 Hz, 1H), 3.40–3.44 (m, 1H), 3.66 (d, J = 13.6 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 4.73 (d, broad, J = 4.3 Hz, 1H), 4.95 (m, 1H), 6.35 (dd, J = 5.8, 1.5 Hz, 1H), 6.53 (dd, J = 5.8, 1.7 Hz, 1H), 7.17–7.38 (m, 5H). ^{13}C NMR (d_6-DMSO): δ 51.6 (CH), 51.9 (CH_2), 61.2 (CH), 78.8 (CH), 81.8 (CH), 126.6 (CHAr), 128.0 (CHAr), 128.1 (CHAr), 134.0 (CH), 136.9 (CH), 140.8 (C), 174.6 (C). HRMS calculated for $C_{14}H_{15}NO_3$ 245.1052, found 245.1050.

General procedure for the Ugi reaction

Amino acid **3** (0.20 mmol, 50 mg) was dissolved in the appropriate solvent (2 mL), then the aldehyde (1.5 eq) and the isocyanide (1.2 eq) were added in this order. The reaction mixture was stirred at room temperature for 48 h. Brine (10 mL) and dichloromethane (10 mL) were added and the phases separated. The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography.

Methyl 3-*endo*-(benzyl(1-(*tert*-butylamino)-1-oxobutan-2-yl) amino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 11a. Pale yellow oil, R_f = 0.48 (PE–EtOAc 7 : 3). ^{1}H NMR: δ 1.02 (t, J = 7.4 Hz, 3H), 1.32 (s, 9H), 1.45–1.72 (m, 1H), 1.74–1.96 (m, 1H), 2.26 (d, J = 4.2 Hz, 1H), 2.76–3.05 (m, 1H), 3.60 (d, J = 14.7 Hz, 1H), 3.74 (s, 3H), 3.86 (d, J = 14.7 Hz, 1H), 3.86 (d, J = 4.1 Hz, 1H), 4.95 (d, J = 3.9 Hz, 1H), 5.05 (d, J = 0.8 Hz, 1H), 5.98 (dd, J = 5.8, 1.2 Hz, 1H), 6.45 (dd, J = 5.8, 1.7 Hz, 1H), 6.81 (s, 1H), 7.27 (m, 5H). ^{13}C NMR: δ 12.9 (CH_3), 21.3 (CH_2), 28.9 ($3CH_3$), 49.1 (CH), 51.0 (C), 52.6 (CH_3), 54.5 (CH_2), 65.7 (CH), 66.1 (CH), 81.0 (CH), 82.3 (CH), 127.4 (CHAr), 128.5 (CHAr), 128.8 (CHAr), 135.4 (CH), 135.5 (CH), 140.2 (CAr), 171.4 (C), 174.3 (C). HRMS calculated for $C_{23}H_{32}N_2O_4$ 400.2362, found 400.2375.

Methyl 3-*endo*-(benzyl(1-(*tert*-butylamino)-4-methyl-1-oxopentan-2-yl)amino)-7-oxabicyclo [2.2.1]hept-5-ene-2-*exo*-carboxylate 11b. Colourless oil, R_f = 0.30 (PE–EtOAc 8 : 2). ^{1}H NMR: δ 0.90 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 1.30 (s, 9H), 1.36 (dd, J = 8.8, 4.0 Hz, 1H), 1.71–1.83 (m, 2H), 2.28 (d, J = 4.1 Hz, 1H), 3.04 (dd, J = 7.9, 4.7 Hz, 1H), 3.62 (d, J = 14.7 Hz, 1H), 3.75 (d, J = 14.7 Hz, 1H), 3.76 (s, 3H), 3.85 (t, J = 4.1 Hz, 1H), 4.98 (d, J = 3.9 Hz, 1H), 5.05 (d, J = 1.3 Hz, 1H), 6.09 (dd, J = 5.8, 1.5 Hz, 1H), 6.47 (dd, J = 5.8, 1.8 Hz, 1H), 6.75 (s, 1H), 7.19–7.35 (m, 5 H). ^{13}C NMR: δ 22.5 (CH_3), 23.5 (CH_3), 26.0 (CH), 28.8 ($3CH_3$), 37.0 (CH_2), 48.8 (CH_2), 51.0 (C), 52.6 (CH_3), 54.4 (CH_2), 62.3 (CH), 65.6 (CH), 81.2 (CH), 82.3 (CH), 127.5 (CHAr), 128.6 (CHAr), 128.6 (CHAr), 135.4 (CH), 135.5 (CH), 140.2 (CAr), 171.6 (C), 174.2 (C). HRMS calculated for $C_{25}H_{36}N_2O_4$ 428.2675, found 428.2679.

Methyl 3-*endo*-(benzyl(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)amino)-7-oxabicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylate 11c. Colourless oil, R_f = 0.22 (PE–Et_2O–EtOAc 6 : 3 : 1). ^{1}H NMR: δ 0.87 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.98–2.12 (m, 1H), 2.27 (d, J = 4.2 Hz, 1H), 2.64 (d, J = 10.5 Hz, 1H), 3.21 (d, J = 15.1 Hz, 1H), 3.67 (s, 3H), 3.83 (t, J = 4.1 Hz, 1H), 4.34 (d, J = 15.1 Hz, 1H), 4.46 (dd, J = 14.7, 5.6 Hz, 1H), 4.54 (dd, J = 14.7, 5.6 Hz, 1H), 4.79 (d, broad, J = 4.1 Hz, 1H), 5.07 (d, J = 1.1 Hz, 1H), 5.35 (dd, J = 5.8, 1.3 Hz, 1H), 6.28 (dd, J = 5.8, 1.8 Hz, 1H), 7.19–7.38 (m, 10H). ^{13}C NMR: δ 19.9 (CH_3), 20.6 (CH_3), 28.4 (CH), 43.4 (CH_2), 50.1 (CH), 52.9 (CH_3), 54.8 (CH_2), 67.3 (CH), 72.2 (CH), 81.5 (CH), 81.8 (CH), 127.2 (CHAr), 127.5 (CHAr), 128.1 (CHAr), 128.4 (CHAr), 128.8 (CHAr), 129.2 (CHAr), 134.6 (CH), 136.5 (CH), 139.0 (CAr), 140.9 (CAr), 170.4 (C), 175.7 (C). HRMS calculated for $C_{27}H_{32}N_2O_4$ 448.2362, found 448.2358.

Methyl 3-*endo*-(benzyl(1-(cyclohexylamino)-1-oxo-3-phenylpropan-2-yl)amino)-7-oxabicyclo [2.2.1]hept-5-ene-2-*exo*-carboxylate 11d. Pale yellow oil, R_f = 0.42 (PE–EtOAc 7 : 3). ^{1}H-NMR: δ 0.98–1.76 (m, 10H), 1.84–1.94 (m, 1H), 2.28 (d, J = 4.0 Hz, 1H), 2.87 (dd, J = 13.4, 5.8 Hz, 1H), 3.28–3.43 (m, 2H), 3.64 (d, J = 14.6 Hz, 1H), 3.76 (s, 3H), 3.81 (d, J = 14.6 Hz, 1 H), 3.98 (t, J = 4.0 Hz, 1H), 4.93–4.99 (m, 1 H), 5.06 (m, 1H), 6.06 (dd, J = 5.8, 1.5 Hz, 1H), 6.43 (dd, J = 5.8, 1.8 Hz, 1H), 6.69 (m, 1H), 7.12–7.51 (m, 10H). ^{13}C NMR: δ 25.0, 25.7, 33.0, 33.4, 34.3 (CH_2), 48.6 (CH), 48.8 (CH), 52.7 (CH_3), 54.9 (CH_2), 65.7 (CH), 66.3 (CH), 81.1 (CH), 82.5 (CH), 126.3 (CHAr), 127.5 (CHAr), 128.5 (CHAr), 128.6 (CHAr), 128.7 (CHAr), 129.6 (CHAr), 135.4 (CH), 135.5 (CH), 139.7 (CAr), 140.2 (CAr), 170.5 (C), 174.2 (C). HRMS calculated for $C_{30}H_{36}N_2O_4$ 488.2675, found 488.2661.

Methyl 3-*endo*-(benzyl(1-(4-(benzyloxy)phenylamino)-4-methyl-1-oxopentan-2-yl)amino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 11e. Colourless oil, R_f = 0.50 (PE–EtOAc 75 : 25). ^{1}H NMR: δ 0.92 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H), 1.35–1.47 (m, 1H), 1.77–1. 95 (m, 2H), 2.34 (d, J = 4.3 Hz, 1H), 3.27 (dd, J = 8.0, 4.6 Hz, 1H), 3.65 (s, 3H), 3.73 (s, 2H), 3.88 (t, J = 4.1 Hz, 1H), 4.97 (d, J = 3.9 Hz, 1H), 5.04 (s, 2H), 5.08 (d, J = 1.3 Hz, 1H), 6.11 (dd, J = 5.8, 1.3 Hz, 1H), 6.46 (dd, J = 5.8, 1.8 Hz, 1H), 6.88–6.98 (m, 2H), 7.21–7.50 (m, 12H), 8.85 (s, 1H). ^{13}C NMR: δ 22.5 (CH_3), 23.6 (CH_3), 26.1 (CH), 37.3 (CH_2), 48.8 (CH), 52.9 (CH_3), 54.2 (CH_2), 62.2 (CH), 65.7 (CH), 70.5 (CH_2), 81.2 (CH), 82.0 (CH), 115.4 (CHAr), 120.9 (CHAr), 127.7 (CHAr), 127.8 (CHAr), 128.1 (CHAr), 128.75 (CHAr), 128.81 (CHAr), 128.84 (CHAr), 131.7 (CAr), 135.4 (CH), 135.7 (CH), 137.2 (CAr), 139.7 (CAr), 155.4 (CAr), 170.5 (C), 174.5 (C). HRMS calculated for $C_{34}H_{38}N_2O_5$ 554.2781, found 554.2781.

Methyl 3-*endo*-(benzyl(2-(butylamino)-2-oxo-1-phenylethyl) amino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 11f. Pale yellow oil, R_f = 0.28 (PE–Et_2O–EtOAc 7 : 2 : 1). ^{1}H NMR: δ 0.93 (t, J = 7.3 Hz, 3H),1.28–1.38 (m, 2H), 1.43–1.56 (m, 2H), 2.43 (m, 1H), 3.10–3.22 (m, 1H), 3.38–3.46 (m, 1H), 3.46 (d, J = 14.5 Hz, 1H), 3.64 (m, 1H), 3.79–3.89 (m, 5H), 4.46 (s, 1H), 5.02 (d, J = 1.4 Hz, 1H), 6.05 (dd, J = 5.8, 1.6 Hz, 1H), 6.39 (dd, J = 5.8, 1.8 Hz, 1H), 7.20–7.49 (m, 11H). ^{13}C NMR: δ 14.3 (CH_3), 20.1 (CH_2), 31.7 (CH_2), 39.0 (CH_2), 46.8 (CH), 52.6 (CH_3), 52.8 (CH_2), 64.1 (CH), 67.5 (CH), 79.4 (CH), 80.3 (CH), 127.6 (CHAr), 128.2 (CHAr), 128.5 (CHAr), 128.7 (CHAr), 128.8 (CHAr), 129.8 (CHAr), 134.9 (CH), 135.1 (CH), 137.3 (CAr), 138.9 (CAr), 170.5 (C), 174.5 (C). HRMS calculated for $C_{27}H_{32}N_2O_4$ 448.2362, found 448.2363.

Methyl 3-*endo*-(benzyl(1-(butylamino)-1-oxobutan-2-yl) amino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 11g. Colourless oil, R_f = 0.33 (PE–EtOAc 7 : 3). ^{1}H NMR: δ 0.93 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 1.28–1.38 (m, 2H), 1.38–1.53 (m, 2H), 1.66 (m, H), 1.82–2.01 (m, 1H), 2.27 (d, J = 4.3 Hz, 1H), 2.99 (dd, J = 7.5, 6.0 Hz, 1H), 3.07–3.19 (m, 1H), 3.26 (td, J = 13.3, 7.0 Hz, 1H), 3.58 (d, J = 14.7 Hz, 1H), 3.76 (s, 3H), 3.85 (d, J = 14.7 Hz, 1H), 3.85 (d, J = 4.2 Hz, 1H), 4.87– 4.95 (m, 1H), 5.07 (dd, J = 1.8, 0.7 Hz, 1H), 5.95 (dd, J = 5.8, 1.5 Hz, 1H), 6.44 (dd, J = 5.8, 1.8 Hz, 1H), 6.94–7.07 (m, 1H), 7.17–7.40 (m, 5H). ^{13}C NMR: δ 12.7 (CH_3), 13.8 (CH_3), 20.2 (CH_2), 21.7 (CH_2), 31.7 (CH_2), 38.9 (CH_2), 49.0 (CH), 52.6 (CH_3), 54.1 (CH_2), 65.6 (CH), 80.9 (CH), 81.8 (CH), 127.3 (CHAr), 128.4 (CHAr), 128.6 (CHAr), 135.2 (CH), 135.3 (CH), 139.9 (CAr), 171.8 (C), 174.4(C). HRMS calculated for $C_{23}H_{32}N_2O_4$ 400.2362, found 400.2368.

Methyl 3-*endo*-(benzyl(1-(4-(benzyloxy)phenylamino)-3-methyl-1-oxobutan-2-yl)amino)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate 11h. Pale yellow oil, R_f = 0.53 (PE–EtOAc 7 : 3). ^{1}H NMR: δ 0.92 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H), 1.99–2.15 (m, 1H), 2.33 (d, J = 4.1 Hz, 1H), 2.72 (d, J = 10.5 Hz, 1H), 3.31 (d, J = 15.1 Hz, 1H), 3.76 (s, 3H), 3.91 (t, J = 4.1 Hz, 1H), 4.41 (d, J = 15.1 Hz, 1H), 4.80 (d, J = 4.1 Hz, 1H), 5.13 (s, 2H), 5.17 (d, J = 1.1 Hz, 1H), 5.23 (dd, J = 5.9, 1.4 Hz, 1H), 6.30 (dd, J = 5.9, 1.9 Hz, 1H), 6.92–6.99 (m, 2H), 7.23–7.48 (m, 10H), 7.59–7.68 (m, 2H), 9.30 (s, 1H). ^{13}C NMR: δ 20.0 (CH_3), 20.5 (CH_3), 28.4 (CH), 51.2 (CH), 53.3 (CH_3), 54.9 (CH_2), 67.8 (CH), 70.5 (CH_2), 73.4 (CH_3), 81.8 (CH), 115.4 (CHAr), 121.3 (CHAr), 127.3 (CHAr), 127.6 (CHAr), 128.1 (CHAr), 128.4 (CHAr), 128.8 (CHAr), 129.4 (CHAr), 132.1 (CAr), 134.3 (CH), 136.6 (CH), 137.3 (CAr), 140.9 (CAr), 155.4 (CAr), 168.4 (C), 176.2 (C). HRMS calculated for $C_{33}H_{36}N_2O_5$ 540.2624, found 540.2636.

Methyl 3-*endo*-(benzyl(1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)amino)-7-oxabicyclo [2.2.1]hept-5-ene-2-*exo*-carboxylate 11i. Colourless oil, R_f = 0.36 (PE–EtOAc 7 : 3). ^{1}H NMR: δ 2.26 (d, J = 4.0 Hz, 1H), 2.90 (dd, J = 13.8, 6.2 Hz, 1H), 3.36–3.46 (m, 1H), 3.48–4.54 (m, 1H), 3.66 (m, 5H), 3.98 (t, J = 4.0 Hz, 1H), 4.28 (dd, J = 14.7, 5.5 Hz, 1H), 4.37 (dd, J = 14.7, 6.1 Hz, 1H), 4.93–4.96 (m, 1H), 4.97–4.99 (m, 1H), 6.06 (dd, J = 5.8, 1.5 Hz, 1H), 6.17 (dd, J = 5.8, 1.8 Hz, 1H), 7.05–7.36 (m, 16H). ^{13}C NMR: δ 34.1 (CH_2), 43.5 (CH_2), 48.4 (CH), 52.7 (CH_3), 54.9 (CH_2), 65.4 (CH), 65.8 (CH), 81.0 (CH), 82.4 (CH), 126.5 (CHAr), 127.6 (CHAr), 127.6 (CHAr), 128.0 (CHAr), 128.6 (CHAr), 128.7 (CHAr), 128.8 (CHAr), 129.6 (CHAr), 135.3 (CH), 135.5 (CH), 138.5 (CAr), 139.2 (CAr), 140.0 (CAr), 171.7 (C), 174.1 (C). HRMS calculated for $C_{31}H_{32}N_2O_4$ 496.2362, found 496.2363.

Methyl 3-*endo*-(benzyl(2-(cyclohexylamino)-2-oxo-1-phenylethyl)amino)-7-oxabicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylate 11j. Pale yellow oil, R_f = 0.20 (PE–Et_2O–EtOAc 4 : 5 : 1). ^{1}H

NMR: δ 1.10–1. 45 (m, 5H), 1.61–1.97 (m, 5H), 2.44 (d, J = 4.9 Hz, 1H), 3.52 (d, J = 14.9 Hz, 1H), 3.71–3.75 (d, broad, 1H), 3.79–3.84 (m, 4H), 3.86 (m, 1H), 4.44 (s, 1H), 4.98–5.00 (m, 1H), 6.08 (dd, J = 5.8, 1.6 Hz, 1H), 6.40 (dd, J = 5.8, 1.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.21–7.42 (m, 10H). ^{13}C NMR: δ 25.4 (CH_2), 25.8 (CH_2), 32.8 (CH_2), 33.5(CH_2), 47.1 (CH), 48.5 (CH), 52.7 (CH_3), 53.5 (CH_2), 64.3 (CH), 67.9 (CH), 79.8 (CH), 80.9 (CH), 127.7 (CHAr), 128.3 (CHAr), 128.7 (CHAr), 128.8 (CHAr), 129.0 (CHAr), 130.0 (CHAr), 135.1 (CH), 135.3 (CH), 137.7 (CAr), 139.3 (CAr), 169.8 (C), 174.5 (C). HRMS calculated for $C_{29}H_{34}N_2O_4$ 474.2519, found 474.2532.

Methyl 3-*endo*-(benzyl(2-(cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl)amino)-7-oxabicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylate 11k. Pale yellow oil, inseparable mixture of diastereoisomers. R_f = 0.22 (PE–EtOAc 7 : 3). ^{1}H NMR: major diastereoisomer δ 1.10–1. 45 (m, 5H), 1.50–1.90 (m, 5H), 2.40–2.45 (m, 1H), 3.49 (d, J = 14.7 Hz, 1H), 3.61 (d, J = 5.1 Hz, 1H), 3.76–3.86 (m, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.39 (s, 1H), 4.99 (d, J = 1.8 Hz, 1H), 6.09 (d, J = 5.7 Hz, 1H), 6.40 (dd, J = 5.7, 1.8 Hz, 1H), 6.90 (d, broad, J = 8.7 Hz, 2H), 7.20–7.34 (m, 8H). ^{13}C NMR: major diastereoisomer δ 25.3 (CH_2), 25.7 (CH_2), 32.8 (CH_2), 33.5(CH_2), 47.1 (CH), 48.4 (CH), 52.6 (CH_3), 53.4 (CH_2), 55.4 (CH_3), 64.2 (CH), 67.3 (CH), 79.9 (CH), 81.0 (CH), 114.3 (CHAr), 127.6 (CHAr), 128.6 (CHAr), 128.7 (CHAr), 129.6 (CAr), 131.1 (CHAr), 135.1 (CH), 135.3 (CH), 139.4 (CAr), 159.5 (CAr), 170.0 (C), 174.4 (C). HRMS calculated for $C_{30}H_{36}N_2O_5$ 504.2624, found 504.2622.

Methyl 3-*endo*-(benzyl(2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl)amino)-7-oxabicyclo[2.2.1] hept-5-ene-2-*exo*-carboxylate 11l. Pale yellow oil, inseparable mixture of diastereoisomers. R_f = 0.14 (PE–EtOAc 75 : 25). ^{1}H NMR: major diastereoisomer δ 1.10–1. 45 (m, 5H), 1.60–2.00 (m, 5H), 2.44 (d, J = 4.5 Hz, 1H), 3.60 (d, J = 14.7 Hz, 1H), 3.62–3.64 (m, 1H), 3.70–3.90 (m, 3H), 3.79 (s, 3H), 4.50 (s, 1H), 5.02–5.04 (m, 1H), 6.09 (dd, J = 5.7, 1.5 Hz, 1H), 6.47 (dd, J = 5.7, 1.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.15–7.35 (m, 5H), 7.53 (d, broad, J = 8.7, 2H), 8.22 (d, broad, J = 8.7, 2H). ^{13}C NMR: major diastereoisomer δ 25.2 (CH_2), 25.7 (CH_2), 32.8 (CH_2), 33.4 (CH_2), 47.7 (CH), 48.7 (CH), 52.8 (CH_3), 53.9 (CH_2), 64.6 (CH), 67.2 (CH), 79.8 (CH), 81.3 (CH), 123.8 (CHAr), 128.0 (CHAr), 128.6 (CHAr), 128.9 (CHAr), 130.9 (CHAr), 134.9 (CH), 135.9 (CH), 138.6 (CAr), 145.1 (CAr), 147.6 (CAr), 168.5 (C), 174.1 (C). HRMS calculated for $C_{29}H_{33}N_3O_6$ 519.2369, found 519.2373.

Enzymatic resolution of rac-18 to (−)-19 and (+)-18

HLPA (880 mg) was added to a vigorously stirred suspension of ester **rac-19** (1.7 mmol, 500 mg) in TRIS buffer (43 mL) and the reaction mixture stirred for 23 h at room temperature. To the mixture were then added ethyl acetate (10 mL) and HCl 0.5 M until pH was 3/4 and the suspension was saturated with solid NaCl, then filtered. The solid filtrate was washed in sequence with a mixture of ethyl acetate–methanol 9 : 1, brine and ethyl acetate–methanol 9 : 1 again. The phases were separated and the aqueous one was extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography, mobile phase petroleum ether–diethyl ether 50 : 50 for the ester (+)**-18** (0.85 mmol, 243 mg) and petroleum ether–diethyl ether 50 : 50 + 1% acetic acid for the acid (−)**-19** (0.73 mmol, 187 mg). NMR data were in accordance with those reported in the literature.[15] (+)**-18** $[\alpha]_D$ = +116.9 ($CHCl_3$, C 0.78), lit. +136;[15] (−)**-19** $[\alpha]_D$ = −50.9 ($CHCl_3$, C 1.06), lit. −58.[15]

Conclusions

In conclusion we have demonstrated that a novel oxabicyclic system can be efficiently prepared and employed in a stereoselective Ugi reaction to prepare collection of compounds with very high value. Hypothesis regarding the mechanism taking place during the reaction have been made and validated through the determination of the relative and absolute configuration of the Ugi adducts. Use of the correct choice of solvents can sensibly increase stereoselection. ILs, analogously to polar solvents, can stabilize the zwitterionic species through specific interactions of cation and anion with opposite charged moieties of intermediate **14**. Although no IL among the presently tested was able to give a complete diastereoselection the variability of the data suggests that it should be possible to design and synthesise a more efficient IL.

Studies are now carried out in our laboratories to increase the selectivity of the enzymatic hydrolysis and to have access to enantiomerically pure bicyclic aminoacids to be used as a novel class of pluripotent substrates to be elaborated according to the synthetic strategies previously employed for compounds **2**.

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