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FULL PAPER

Diversity-oriented Synthesis of Bicyclic Heterocycles from Levulinic Acid through a Fast and Operationally Simple Multicomponent Approach

Chiara Lambruschini,[a] Andrea Basso,[a] Lisa Moni,[a] Alessandro Pinna,[a] Renata Riva,[b] and Luca Banfi*[a]

Abstract: Levulinic acid, which is one of the most important renewable building blocks derived from lignocellulosic biomass, has been converted, in a diversity-oriented manner, into two families of drug-like bicyclic nitrogen heterocycles. The methodology, endowed with high step economy and operational simplicity, is based on an Ugi multicomponent reaction, which employs aminoalcohols as components, followed by a S_N2 cyclization. Worth of noting is the successful synthesis of hexahydro pyrrolodiazepinediones, since the cyclization of the isocyanide-derived secondary amide onto an alcohol to give a seven-membered ring was unprecedented. Also enantiopure products have been prepared using chiral aminoalcohols.

Introduction

The production of chemicals, from commodities to specialties to highly valued products such as drugs, cosmetics, functional materials and so on, still heavily depends on conversion of fossil feedstock. Apart from the fact that these sources are destined to be depleted sooner or later, their use contributes to the unbalance of carbon cycle provoked by human activities. Thus, a whole new synthetic organic chemistry that starts from renewable sources should be developed.[1] This task is challenging, since the existing oil-based chemistry needed nearly two centuries to be fully progressed.

Lignoellulosic biomass is surely the most abundant and important one, but it typically provides polyoxygenated building blocks, whereas nitrogen containing ones are by far less common. According to a list recently published by the US Department of Energy (DOE),[2] only 2 out of the 12 most important building blocks that can be derived from lignocellulosic biomass contain nitrogen and they (aspartic and glutamic acids) are not heterocycles. Yet, heterocyclic compounds play a paramount role in many application fields, i.e. drugs or photoactive organic compounds. Thus, any sustainable synthetic methodology able to convert oxygenated renewable building blocks into complex heterocycles will be welcome.

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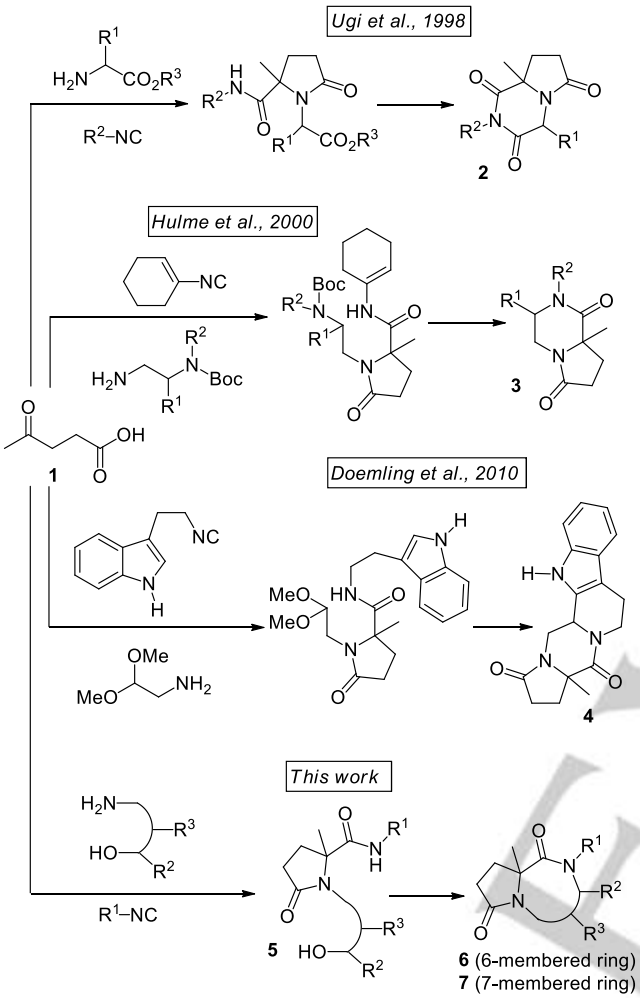
Multicomponent reactions are defined as processes where three or more substrates are combined in a single step, generating a product that contains all essential parts of the starting materials.[3] This highly convergent methodology allows molecular complexity to be created by the facile formation of several new covalent bonds in a one-pot transformation (step economy). At the same time, MCRs proceed with remarkably high atom economy, minimizing the number of functional group manipulations and the use of protective groups. Syntheses involving MCRs save time and energy (step and operational efficiency), reduce waste and quite closely approach the concept of the ideal eco-friendly synthesis, thus lowering the E factor.[4]

Among multicomponent reactions, those making use of isocyanides[5] have emerged as the most useful ones. They are quite flexible as the possible starting components and, with the aid of post-MCR cyclizations, can lead to a great variety of heterocycles, allowing a wide exploration of scaffold and decoration diversity. We thus believe that the application of isocyanide-based multicomponent reactions (IMCRS) to oxygenated renewable building blocks may be a very powerful strategy for the sustainable synthesis of bioactive heterocycles, especially if the experimental procedures are operationally simple and closer to the principles of green chemistry.[6]

In this paper we have focussed our attention to levulinic acid **1**, which belongs to the above quoted list of 12 most important lignocellulosic-derived compounds. In fact, it can be easily obtained by acid treatment of hexoses.[7] Production of levulinic acid on large scale is already a well assessed methodology. Its price is, at the moment, about 1 $ / kg, but it is expected to go further down, using waste sugar sources. Thus, the main problem now is not how to get it, but how to valorize it. Some applications in the polymer field are under study.[8] Far less investigated are transformations into nitrogen derivatives, with the exception of δ-aminolevulinic acid (DALA), used in photodynamic therapies, which again is not an heterocycle. Isocyanide-based MCRs can be a perfect tool to access levulinic derived heterocycles.

IMCRs and levulinic acid are old friends. Actually Passerini used levulinic acid in his famous reaction as early as in 1923.[9] More recently, several researchers have reported the synthesis of pyrrolidinones by the Ugi reaction of **1**.[10] However, we wanted to devise a fast approach to bicyclic systems applying post-MCR cyclizations. We found in the literature few examples regarding the obtainment of bicyclic systems through the Ugi reaction followed by a post-MCR cyclization (Scheme 1).[11] However, compounds **2**, obtained by Ugi *et al*,[11a] are imides, and thus less interesting for their hydrolytical instability. On the other hand, ketopiperazines **3**[11b] and **4**,[11c] synthesized by Hulme and Doemling, are limited from the point of view of the introduction of diversity: in **3** the isocyanide group is lost upon cyclization,

whereas the synthesis of **4** necessarily requires an indole containing isocyanide.



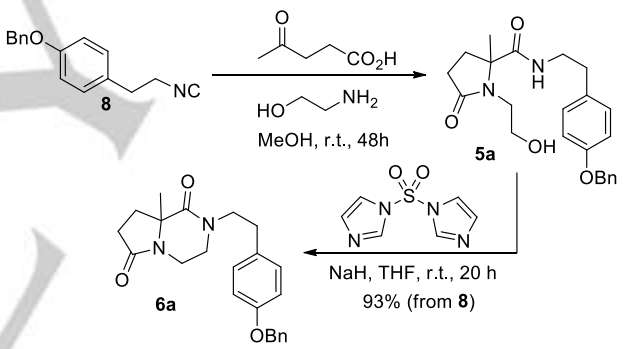
Scheme 1. Previous multicomponent synthesis of bicyclic heterocycles from levulinic acid compared to the here reported approach.

Our approach, depicted in Scheme 1 (bottom), seemed more flexible and diversity-oriented. Based on the thorough experience of our group,[12] and of other authors,[13] in Ugi reactions followed by intramolecular aliphatic substitutions, we planned to employ aminoalcohols as one of the two additional components in the Ugi reactions of **1**. Then, the isocyanide derived secondary amide can cyclize onto the alcohol through a Mitsunobu or Mitsunobu-like reaction. Two of the 3 components could be modified at will and different sizes of the diazalactam on the right can be achieved by varying the length of the spacer between the amino and the hydroxy groups. An added advantage of this strategy is that several aminoalcohols may be obtained from biomass as well, including chiral enantiopure ones. The products of this two-step approach are quite uncommon bicyclic systems that join two "privileged structures":[14] the pyrrolidinone[15] and the piperazine[16] or diazepine.

Results and Discussion

The planned two-step procedure was first optimized using ethanolamine and isocyanide **8** (Scheme 2). The latter was chosen because it is a solid, highly stable, and odorless isocyanide.[17] The best solvent for the Ugi reaction was found to be methanol, also according to the mechanism hypothesized by Harriman[10d] and shown in Scheme 3. For these authors, the reaction proceeds through the methyl ester **12**, and for this reason no pyrrolidinone is formed using *tert*-butanol instead. However, we can not completely rule out direct rearrangement of **11** into **13**, although difficult for steric reasons.

Using a 1.2/1.2/1.0 stoichiometry of levulinic acid, aminoalcohol and isocyanide, an excellent yield of the Ugi reaction was achieved. After a quick liquid-liquid extraction to remove the acid and the amine in excess, product **5a** was obtained in nearly quantitative yield without the need to perform any further purification.



Scheme 2. Optimized synthesis of tetrahydropyrrolopirazinedione **6a**

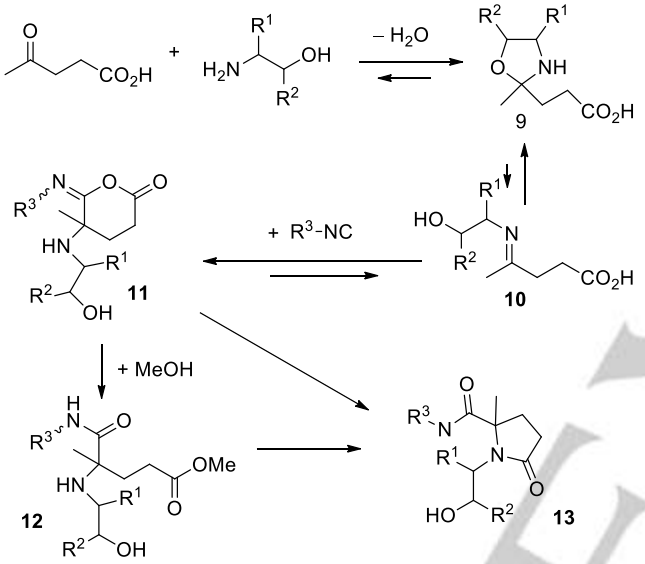
For the cyclization step we decided to rule out the classical Mitsunobu reaction, because of its poor atom economy. Moreover, a two-step procedure involving conversion of the alcohol into a sulfonate was less attracting from the point of view of operational simplicity.

Thus we chose to employ the combination of sulfonyl diimidazole (SDI) with NaH. This methodology was first introduced by Hanessian[18]. Although it is, surprisingly, seldom employed, it was already demonstrated by us[12b] to be an useful alternative to the classical Mitsunobu conditions. SDI is a relatively nontoxic and stable solid. The two reagents are simply added to the solution of the substrate at room temperature without special precautions.

The putative mechanism is shown in Scheme 4. The alkoxide formed by deprotonation with NaH reacts with SDI to form a sulfonate **15**. Then the amide is deprotonated by the imidazolide anion **14** and this anion promotes an S_N2 displacement of the sulfonate. On aqueous work-up, the leaving group **16** is hydrolysed to sulfate anion and imidazole. Both these side-

products are non toxic and easy removable by liquid-liquid extraction. Imidazole can be recycled and converted back into SDI by reaction with sulfuryl chloride.

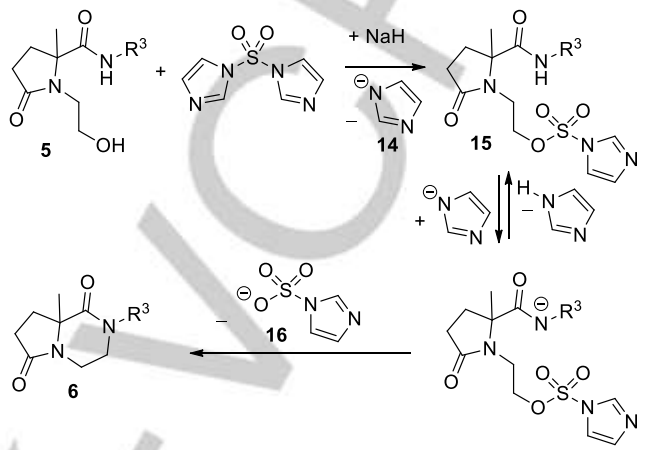
Initially we performed the cyclization of **5a** to **6a** in DMF as the solvent. However, we faced two problems. First of all, tetrahydropyrrolopirazinediones **6** are remarkably polar and thus relatively soluble in water. Thus, the usual tricks to remove DMF by extracting it in water (e.g. using aqueous LiCl solutions), caused also passage of some of the product in the aqueous phase, lowering the yield. On the other hand, extraction from saturated NH_4Cl was quantitative, but the crude was contaminated by DMF, that was difficult to remove under high vacuum.



Scheme 3. Presumed mechanism of the Ugi reaction with levulinic acid and 1,2-aminoalcohols

The second problem was that some of the excess of SDI used for the reaction was extracted into the organic phase, contaminating the product **6a**. Although in this particular case a chromatography was able to separate **6a** from SDI, for other products **6** shown in Figure 1 this was not so easy. Apart from that, we wanted a robust and operationally simple method that could avoid chromatography. Unfortunately, trituration of crude **6a** failed to removed SDI impurity.

The first problem was solved by replacing DMF with THF, that turned out to be equally effective. As far as it concerns the second issue, we implemented an easy procedure to destroy excess SDI at the end of the reaction, converting it into a water-soluble derivative, by addition of 0.5 equivalents of unexpensive *tris*(hydroxymethyl)aminomethane (TRIS). This compound, in the presence of excess NaH, reacts with SDI to form a water-soluble cyclic sulfate. In this way, extractive work-up afforded a very pure product, making chromatography unnecessary. The overall yield is quite high, and the methodology is operationally very simple: both steps are performed at room temperature, without particular precautions to avoid humidity. The slight excess of SDI can make up for the possible presence of trace of water. The work-up consists in just two liquid-liquid extractions after the Ugi and the cyclization steps, that removed all side-products or excess reagents.



Scheme 4. Presumed mechanism of the cyclization with SDI.

This procedure was extended to other pyrrolopirazinediones, again using ethanolamine, but varying the isocyanide. As shown in Figure 1, the overall yield was good to excellent. Compound **6b** was previously reported by Hulme et al.,[11b] using the approach depicted in Scheme 1 (R^1= H, R^2 = Bn). In that case the benzyl group (R^2) did not derive from the isocyanide, but from a Boc-protectedaminoalcohol instead, and the overall yields were lower. In the case of compound **6f**, in order to avoid the known instability problems of aromatic isocyanides and to make the method more operationally simple, we synthesized *in situ* the required isocyanide from the corresponding formamide using the Burgess reagent.[19] Thus the overall yield is calculated from the formamide (3 steps), which explains the apparent lower efficiency of this synthesis. Actually, the cyclization itself was again very efficient, proceeding in 95% yield. In the case of compounds **6d** and **6g**, the required benzyl isocyanides were obtained from the corresponding formamides ad purified by chromatography. However, due to their partial volatility, we did not dry them exhaustively, and thus also in this case the yield was calculated from the formamide.

Then, in order to further expand diversity, we explored the use of chiral 1,2-aminoalcohols derived from α-aminoacids, which can be deemed as renewable building blocks as well. Due to the fact that now the aminoalcohol was the most precious component, we chose to use a slight excess of the isocyanide. Initially, the Ugi reaction proved to be less clean than with ethanolamine, because of the concurrent formation of Passerini products. By shifting to trifluoroethanol as solvent, only the Passerini products were detected. Typically, this more polar solvent tends to favour Ugi adducts versus the Passerini ones, but in this case the role of methanol is probably essential to grant formation of the pyrrolidinone from intermediate **11** (Scheme 3). Eventually, we

found that the Passerini products may be completely suppressed by simply preforming the intermediate oxazolidine **9** (Scheme 3).[20] Thus, equimolar quantities of the chiral aminoalcohol and levulinic acid were mixed in methanol for 2 h in the presence of molecular sieves, before addition of the isocyanide. Using this modification the Ugi product yields were again good. On the other hand, the diastereoselectivity, as it often happens in isocyanide-based MCRs, was very poor. However, the two Ugi diastereomers could be separated and submitted independently to the next step.

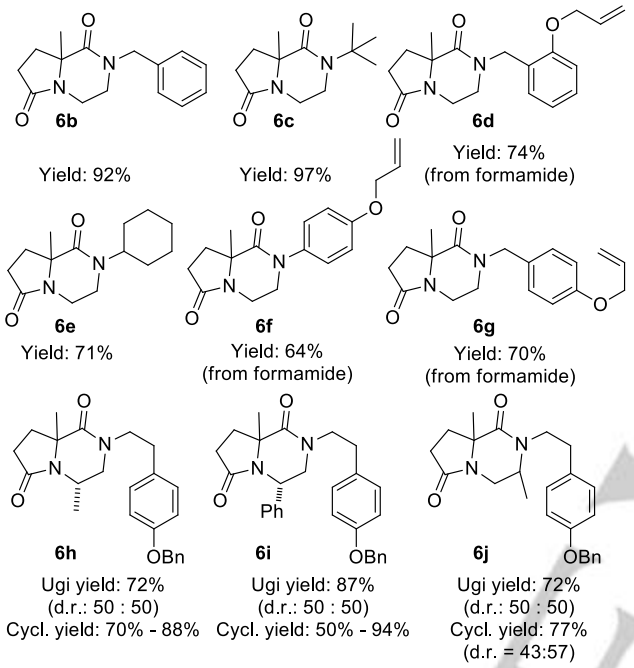


Figure 1. Tetrahydropyrrolopirazinediones prepared. For **6b**, **6d**, **6e**: overall yields of two steps from the isocyanide are reported. For **6d**, **6f** and **6g**: overall yields of three steps from the formamide are reported. For **6h**-**6j**: Ugi product yields are from the chiral aminoalcohol, after chromatoraphy. For **6h** and **6i**: the two diastereomers were separated after the Ugi step. Cyclization yields are for the upper and lower diast. (by TLC). In the case of **6j**, the diast. were separated only after cyclization.

Cyclization was slower and only low or moderate yields were obtained in THF. By shifting to DMF and, in some cases, by increasing the temperature, we succeeded to bring all reactions to completion. Interestingly, the rate of cyclization was remarkably lower for one of the two diastereomers. This is reflected in the different cyclization yields for the two diastereomers of **6h** and **6i**. In both cases the less polar diastereoisomer behaved poorly in this step.

We also employed, in racemic form, 1-amino-2-propanol. In this case the two Ugi diastereomers could not be separated at this stage, but only after cyclization. The different d.r. measured shows that also in this case cyclization is favoured for one of the two diastereoisomers.

Following our interest in the diversity-oriented synthesis of 7-membered nitrogen heterocycles,[12e] we then decided to extend this protocol to the obtainment of the hexahydro pyrrolodiazepinediones **7** depicted in Figure 2. The Ugi reactions using propanolamine as component proceeded without particular problems, but also in this case we obtained better yields by preforming the intermediate tetrahydrooxazine by premixing the aminoalcohol and levulinic acid.

The cyclization step was anticipated to be challenging. S_N2 reaction of the isocyanide-derived secondary amide of an Ugi adduct onto an alcohol or a halogen to afford seven-membered diazepinones was indeed unprecedented. In our own laboratory, we have previously tried this approach to monocyclic diazepinones, but without success. We observed, instead, other modes of cyclization, leading to bicyclic systems through attack of the anionic nitrogen onto the tertiary amidic carbonyl.[12b, 12f] However, in this case the attack onto the pyrrolidinone carbonyl would lead to an unfavored bridged bicyclic system, due to the inclusion of the tertiary amide in a 5-member ring.

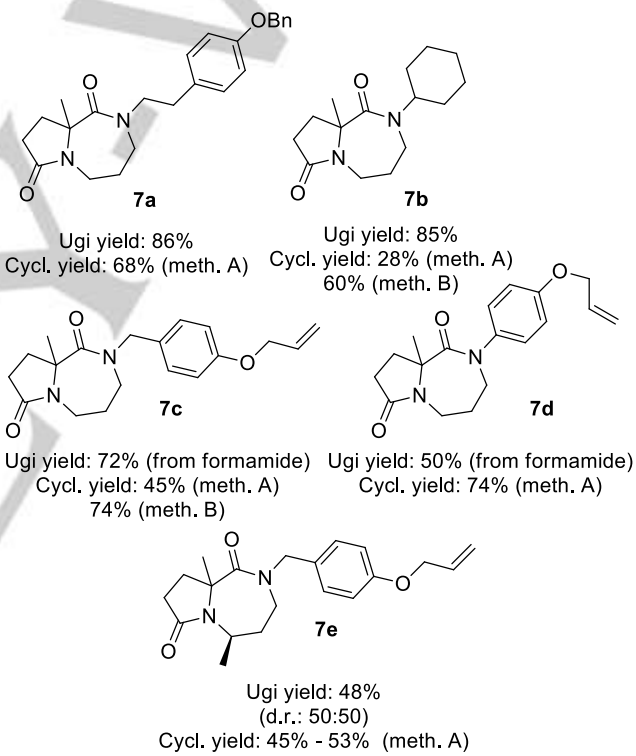


Figure 2. Hexahydropyrrolodiazepinediones prepared. Method A: SDI, NaH, DMF, 50 °C. Method B: 1) MsCl, Et_3N, CH_2Cl_2; 2) NaH, DMF, 50 °C. For **7c** and **7d** the Ugi yield is calculated from the formamide (precursor of the isocyanide). For **7e** the Ugi yield is calculated from the aminoalcohol. In the case of **7e** the two diastereomers were separated after the Ugi step and cyclized independently. Cyclization yields are for the upper and lower diast. (by TLC).

The cyclization was first tested on the Ugi adduct derived from isocyanide **8**, propanolamine and levulinic acid. Reaction in THF was sluggish and a very poor yield of the expected product **7a** was obtained. However, by simply shifting to DMF as the solvent, the reaction worked well, even at room temperature, though the yield was lower, compared to 6-membered adducts **6**. In this case

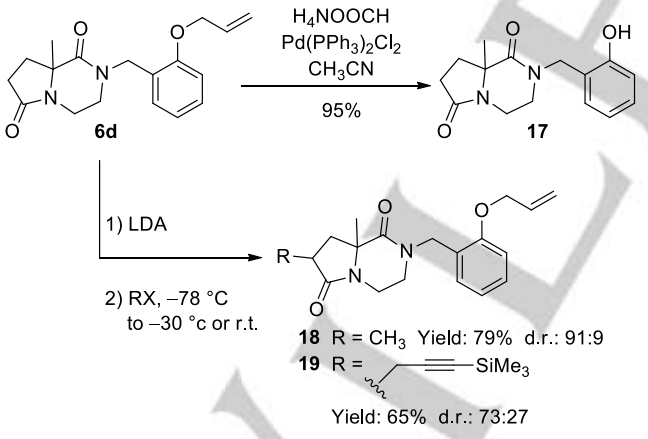
we detected very polar side-products containing the imidazole ring. We think that the intermediate sulfonate **15** (see the mechanism depicted in Scheme 4) may also be displaced by the imidazolide anion **14**.

We then moved on to investigate the scope of the method. When we tried to prepare product **7b** starting from cyclohexyl isocyanide, the cyclization yield, under the usual conditions with SDI (method A) was only poor (27% at rt and 28% at 50 °C) and the polar side products became predominant, likely because of the higher steric bias of the nucleophilic nitrogen. We thus tried different conditions (method B), involving formation of the methanesulfonate followed by treatment with NaH in DMF. By avoiding the presence of imidazolide anion the yield was rised to a good 60%. Also for hexahydro pyrrolodiazepinedione **7c** method B was superior. On the other hand, in the case of **7d**, derived from an aromatic isocyanide, cyclization was quite fast and the yield turned out good also with method A.

Finally, we prepared also compounds **7e** starting from a chiral enantiopure propanolamine.

As can be seen in Figures 1 and 2, several of the adducts prepared contain a protected phenol. This follows our recent interest in the synthesis of artificial phenols from natural phenolic building blocks.[21] The allyl group was selected by us as an ideal protecting group for the phenolic moiety, since it can be deblocked under neutral conditions. As an example, in Scheme 5 we show the high yield deprotection of compound **6d** to give the free phenol **17**.

The pyrrolidinone ring can be further functionalised through enolate chemistry. Scheme 5 shows the α-alkylation of the lactam with two different electrophiles. These alkylations were found to be diastereoselective, especially in the case of methylation.



Scheme 5. Further reactions performed on pyrrolopiperazinedione **6d**. Yields for **17** and **18** are calculated from unrecovered **6d**.

Conclusions

In conclusion, we have developed an operationally simple and high yielding methodology to convert levulinic acid into tetrahydro pyrrolopiperazinediones, which contain two privileged scaffolds, the pyrrolidinone[15] and the piperazine. Although this bicyclic system is still poorly explored in medicinal chemistry, a recent patent has shown activity of tetrahydro pyrrolopiperazines as neurokinin 1 receptor antagonists.[15] Moreover, some natural alkaloids (e.g. paraherquamides and aspergillimides), that contains this scaffold, have antihelmintic or neuroprotective activity.[22] The procedure is endowed with operational simplicity and compliance to the green chemistry principles. Both reactions were performed by simply mixing the reagents at r.t. (no energy consumption). Atom economy is quite good: during the Ugi reaction only a molecule of water is lost, whereas cyclisation consumed just 1 equivalent of NaH and 1 equivalent of SDI. The unavoidable waste produced is untroublesome (imidazole and sulfate anion) and no heavy metal is used.

We have also succeeded in converting levulinic acid into hexahydro pyrrolodiazepinediones. Albeit the higher strain of the seven membered ring makes the cyclization less efficient, it is worth noting that this represents the first example of synthesis of seven-membered rings through S_N2 cyclization of an Ugi-derived secondary amide onto an alcohol (or halogen) leaving group.[12e] This bicyclic scaffold is nearly unexplored, but, due to its drug-likeness, it is expected to be promising in medicinal chemistry as well.[23]

Experimental Section

General remarks. NMR spectra were taken at rt in $CDCl_3$ or CD_3OD 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) (for spectra taken in $CDCl_3$) or the central peak of CD_3OD (^1H: 3.31 ppm, ^{13}C: 49.00 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 ionization mode. 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 in an iodine chamber. 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 three times 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.

(*R*,*S*)-2-(4-(Benzyloxy)phenethyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6a. Isocyanide **8**[17] (475 mg, 2.00 mmol) was dissolved in dry MeOH (10 mL) and treated with 3 Å powdered molecular sieves (200 mg), levulinic acid (246 µL, 2.40 mmol), and ethanolamine (145 µL, 2.40 mmol). The mixture was stirred at room temperature for 48 h. Then it was diluted with CH_2Cl_2, filtered and evaporated to dryness. It was taken up in AcOEt / MeOH 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, the crude Ugi product **5a**, as a white solid (784 mg). It resulted

quite pure at NMR. M.P.: 137.5-138.3 °C. R_f = 0.22 (AcOEt/MeOH 95:5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ = 7.46-7.27 (m, 5 H, aromatics of Bn); 7.11 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* meta to OBn); 7.08 (broad s, 1 H, N*H*), 6.91 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* ortho to OBn); 5.05 (s, 2 H, OCH_2); 3.96-3.86 (m, 1 H, C*H*HOH); 3.60-3-37 (m, 4 H, C*H*HN, C*H*HOH, CH_2NH); 3.09-2.96 (m, 1 H, C*H*HN); 2.78 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, ArCH_2); 2.34-2.18 (m, 3 H, 2 *H*-3, 1 *H*-4); 1.97-1.83 (m, 1 H, *H*-4); 1.46 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 178.0 (HN-*C*=O), 173.7 (*C*-2), 157.4, 136.9, 130.9 (quat,), 129.7 (*C* meta to OBn), 128.6 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 115.0 (*C* ortho to OBn), 70.0 (OCH_2Ph), 67.6 (*C*-5), 60.2 (*C*H_2OH), 43.5 (OCH_2CH_2N); 40.9 (CH_2NH); 34.2 (ArCH_2), 33.8 (*C*-4), 29.4 (*C*-3), 22.3 (CH_3). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{23}H_{28}N_2O_4$ 396.2049; Found 396.2055. This Ugi adduct was taken up in dry THF (10 mL) and treated with sulfonyl diimidazole (SDI) (595 mg, 3.00 mmol), and NaH (60% suspension in mineral oil) (120 mg, 3.00 mmol). The mixture was stirred for 20 h at rt. Then *tris*(hydroxymethyl)aminomethane (TRIS) (121 mg, 1.00 mmol) was added, followed by another aliquot of NaH (12 mg, 0.30 mmol). After 1 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. Evaporation afforded a nearly pure crude (750 mg) that was anyway chromatographed (from AcOEt to AcOEt/MeOH 95:5) to give analytically pure **6a** (703 mg). M.P.: 114.1-115.0 °C. R_f = 0.44 (AcOEt/MeOH 95:5).^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.45-7.27 (m, 5 H, aromatics of Bn); 7.09 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* meta to OBn); 6.91 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* ortho to OBn); 5.05 (s, 2 H, OCH_2); 4.10-3.97 (m, 1 H, *H*-4), 3.65 (dt, $^3J_{H,H}$ = 6.7 (t), $^2J_{H,H}$ = 13.5 (d), 1 H, ArCH_2C*H*H); 3.46 (dt, $^3J_{H,H}$ = 6.7 (t), $^2J_{H,H}$ = 13.5 (d), 1 H, ArCH_2C*H*H); 3.40-3.27 (m, 1 H, *H*-3); 3.10-2.92 (m, 2 H, *H*-3, *H*-4); 2.81 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, ArCH_2); 2.48 (dt, $^3J_{H,H}$ = 9.6 (t), $^2J_{H,H}$ = 17.4 (d), 1 H, *H*-8); 2.38-2.24 (m, 1 H, *H*-8); 2.20-2.02 (m, 2 H, *H*-7); 1.43 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.6, 171.4 (*C*=O), 157.5, 136.9, 130.6 (quat,), 129.7 (*C* meta to OBn), 128.5 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 114.9 (*C* ortho to OBn), 70.0 (OCH_2Ph), 62.4 (*C*-8a), 49.0 (*C*-CH_2Ar), 47.3 (*C*-3), 33.7 (*C*-4), 32.4 (CH_2Ar), 30.6 (*C*-7), 29.6 (*C*-8), 23.2 (CH_3). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{23}H_{27}N_2O_3$ 379.2022; Found 396.2030.

(*R*,*S*)-2-(Benzyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6b. It was prepared from benzyl isocyanide, ethanolammine, and levulinic acid, following the same procedure described for **6a**. M.P.: 98.5-100 °C. R_f = 0.42 (AcOEt/MeOH 95 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.38-7.19 (m, 5 H, aromatics); 4.78. 4.39 (AB system, $^2J_{H,H}$ = 14.5 Hz, 2 H, CH_2Ph); 4.18-4.08 (m, 1 H, *H*-4); 3.45-3.31 (m, 1 H, *H*-3); 3.20-3.07 (m, 2 H, *H*-4 and *H*-3); 2.60-2.15 (m, 4 H, *H*-8. *H*-7); 1.55 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.6, 171.6 (*C*=O), 136.3 (quat,), 128.8 (x 2), 128.0 (x 2), 127.8 (*C*H of Bn), 62.5 (*C*-8a), 50.1 (*C*H$_2$Ph), 45.9 (*C*-3); 33.6 (*C*-4), 30.8, 29.7 (*C*-7. *C*-8), 23.2 (CH_3). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{15}H_{19}N_2O_2$ 259.1447; Found 259.1442.

(*R*,*S*)-2-(*tert*-Butyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6c. It was prepared from *t*-butyl isocyanide, ethanolammine, and levulinic acid, following the same procedure described for **6a**. M.P.: 96.6-97.0 °C. R_f = 0.38 (AcOEt/CH_2Cl_2/MeOH 47.5 : 47.5 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 4.06 (dt, $^3J_{H,H}$ = 4.2 (t), $^2J_{H,H}$ = 13.5 (d), 1 H, *H*-4); 3.45-3.33 (m, 2 H, *H*-3); 3.16 (ddt, $^5J_{H,H}$ = 1.0, $^3J_{H,H}$ = 7.8 (t), $^2J_{H,H}$ = 13.5 (d), 1 H, *H*-4); 2.49 (ddt, $^5J_{H,H}$ = 1.2, $^3J_{H,H}$ = 9.7 (t), $^2J_{H,H}$ = 16.7 (d), 1 H, *H*-8), 2.34 (ddd, $^3J_{H,H}$ = 2.6, 9.0, $^2J_{H,H}$ = 16.7, 1 H, *H*-8), 2.26-2.06 (m, 2 H, *H*-7); 1.46 (s, 3 H, CH_3); 1.43 (s, 9 H, (CH_3)$_3$C). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 172.81, 172.78 (*C*=O), 63.2 (*C*-8a), 57.9 (*C*(CH$_3$)$_3$), 42.8 (*C*-3); 34.9 (*C*-4), 31.4 (*C*-7), 29.8 (*C*-8), 28.1 ((CH$_3$)$_3$C), 23.2 (CH_3). GC-MS: R_t 9.43 min. M/z: 224 (M$^+$. 16.9%), 196 (22.7), 181 (14.7), 167 (100.0), 153 (5.3), 139 (9.0), 127 (6.3), 125 (26.6), 124 (24.5), 123 (5.2), 111 (6.9), 98 (16.5), 97 (13.2), 86 (16.8), 84 (7.1), 83 (9.1), 82 (6.5), 70 (13.4), 68 (6.1), 57 (17.7), 56 (17.2), 55 (24.6), 54 (6.3), 42 (27.4), 41 (20.1), 39 (6.5). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{12}H_{21}N_2O_2$ 225.1603; Found 225.1603.

(*R*,*S*)-2-((2-Allyloxyphenyl)methyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6d. A solution of *N*-(2-allyloxybenzyl) formamide (for its preparation see the S.I.) (409.5 mg, 1.995 mmol) in dry CH_2Cl_2 (9.4 mL) was cooled to –30 °C and treated, in this order, with triethylamine (945 µL, 6.78 mmol) and $POCl_3$ (205 µL, 2.19 mmol). After stirring at –30 °C for 1 h, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. Evaporation and chromatography (PE / Et_2O 95:5 to 90:10) gave pure 2-(allyloxybenzyl)isocyanide (R_f = 0.69, PE/Et_2O 95:5), that was evaporated at 15 mbar only (because it was partly volatile) and used as such for the Ugi reaction and the subsequent cyclization as described for **6a**. The overall yield was 74% from the formamide (3 steps). Foam. R_f = 0.55 (AcOEt/CH_2Cl_2/MeOH 45 : 45 : 10). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.30-7.15 (m, 2 H, *H* meta to Oallyl), 6.93 (dt, $^4J_{H,H}$ = 1.0 (d), $^3J_{H,H}$ = 7.5 (t), 1 H, *H* para to Oallyl), 6.87 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, *H* ortho to Oallyl), 6.04 (ddt, $^3J_{H,H}$ = 10.4, 17.3 (d), 5.2 (t), 1 H, C*H*=CH$_2$), 5.40 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.3 (d), 1 H, CH=C*H*H), 5.28 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.4 (d), 1 H, CH=C*H*H), 4.72 and 4.61 (AB syst,. $^2J_{H,H}$ = 14.7, 2 H, CH_2Ar), 4.55 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.2 (d), 2 H, CH_2CH=), 4.11 (ddd, $^3J_{H,H}$ = 1.6, 5.0, 13.5, 1 H, *H*-4); 3.39 (m, 1 H, *H*-3), 3.27-3.09 (m, 2 H, *H*-3 and *H*-4), 2.51 (ddt, $^5J_{H,H}$ = 1.0, $^3J_{H,H}$ = 16.5 (d), 10.2 (t), 1 H, *H*-8), 2.44-2.13 (m, 3 H, *H*-7 and *H*-8), 1.53 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 172.7, 171.5 (*C*=O), 156.6, 124.6 (quat,), 133.1 (*C*H=CH$_2$), 129.7, 128.9 (*C* meta to Oallyl), 121.0 (*C* para to Oallyl), 117.5 (CH=*C*H$_2$), 111.7 (*C* ortho to Oallyl), 68.8 (OCH_2), 62.6 (*C*-8a), 46.2 (*C*-3); 44.9 (CH_2Ar), 33.8 (*C*-4), 30.8 (*C*-7), 29.7 (*C*-8), 23.3 (CH_3). GC-MS: R_t 10.41 min. M/z: 271 (M$^+$ - 43. 1.1), 257 (0.9), 245 (1.8), 176 (3.3), 167 (100.0), 147 (26.3), 146 (22.0), 145 (5.7), 139 (12.2), 132 (6.1), 131 (11.4), 125 (22.8), 124 (25.7), 123 (7.3), 119 (6.6), 111 (8.9), 107 (20.6), 98 (20.4), 97 (14.3), 96 (8.9), 91 (43.6), 83 (10.9), 82 (16.4), 78 (16.8), 77 (17.5), 70 (32.4), 69 (9.8), 68 (10.3), 65 (8.6), 56 (32.1), 55 (67.8), 54 (13.2), 53 (10.0), 51 (9.2), 44 (11.7), 43 (10.0), 423 (64.5), 41 (90.2), 39 (32.7). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{18}H_{23}N_2O_3$ 315.1709; Found 315.1706.

(*R*,*S*)-2-(Cyclohexyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6e. It was prepared from cyclohexyl isocyanide, ethanolammine, and levulinic acid, following the same procedure described for **6a**. Foam. R_f = 0.38 (AcOEt/CH_2Cl_2/MeOH 45 : 45 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.44 (tt, $^3J_{H,H}$ = 3.6, 11.7 Hz, 1 H, CyHex*C*HN), 4.06 (ddd, $^3J_{H,H}$ = 2.5, 4.6, 13.2 Hz, 1 H, *H*-4); 3.36-3.08 (m, 3 H, *H*-3, *H*-4); 2.53 (ddt, $^5J_{H,H}$ = 1.2, $^3J_{H,H}$ = 9.9 (t), $^2J_{H,H}$ = 16.7 (d) Hz, 1 H, *H*-8), 2.37 (ddd, $^3J_{H,H}$ = 3.5, 8.3, $^2J_{H,H}$ = 16.7 Hz, 1 H, *H*-8), 2.29-2.10 (m, 2 H, *H*-7); 1.87-1.72 (m, 2 H); 1.72-1.57 (m, 3 H); 1.48 (s, 3 H, CH_3); 1.46-1.30 (m, 4 H); 1.15-0.98 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.7, 170.9 (*C*=O), 62.5 (*C*-8a), 52.4 (*cy*Hex*C*HN), 40.6 (*C*-3); 34.2 (*C*-4), 31.0 (*C*-7), 29.7 (*C*-8), 29.6, 29.5, 25.6, 25.5, 25.4 (*C*H$_2$ of cyclohexyl), 23.3 (CH_3). GC-MS: R_t 8.71 min. M/z: 250 (M$^+$. 32.5), 235 (1.7), 222 (23.4), 207 (21.8), 179 (12.4), 169 (25.6), 167 (30.7), 165 (7.0), 153 (55.1), 140 (11.4), 139 (5.3), 125 (45.2), 124 (25.6), 123 (21.5), 112 (69.6), 111 (17.5), 110 (11.7), 98 (50.6), 97 (52.6), 96 (11.8), 83 (24.6), 82 (30.1), 81 (9.4), 72 (22.9), 70 (22.0), 69 (22.5), 68 (20.4), 56 (69.0), 55 (100.0), 54 (26.4), 44 (18.7), 42 (61.4), 41 (64.0), 39 (18.9). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{14}H_{23}N_2O_2$ 251.1760; Found 251.1757.

(*R*,*S*)-2-(2-Allyloxyphenyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6f. A solution of *N*-(4-allyloxyphenyl) formamide[21] (177.5 mg, 1.00 mmol) in dry CH_2Cl_2 (1.5 mL) was cooled to 0 °C, and treated with Burgess reagent ((Methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt) (286 mg, 1.20 mmol). After stirring for 2 h and 30 min at 0 °C, dry methanol (4.5 mL), 3 Å powdered molecular sieves (100 mg), levulinic acid (123 µL, 1.20

mmol), and ethanolamine (72 µL, 1.20 mmol) were added. The mixture was stirred at room temperature for 48 h. Then it was diluted with CH_2Cl_2, filtered and evaporated to dryness. It was taken up in AcOEt / MeOH 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, and chromatography, the Ugi product (221 mg, 69% from formamide). This intermediate was cyclized following the same procedure described for **6a**, to give pure **6f** as an oil (198 mg, 95%). R_f =0.42 (AcOEt/CH_2Cl_2 50:50).^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.12 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* meta to Oallyl); 6.93 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, *H* ortho to Oallyl); 6.04 (ddt, $^3J_{H,H}$ = 10.5, 17.2 (d), 5.3 (t) Hz, 1 H, C*H*=CH_2), 5.41 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.2 (d) Hz, 1 H, CH=C*H*H), 5.29 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.53 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.3 (d) Hz, 2 H, CH_2CH=), 4.25 (ddd, $^3J_{H,H}$ = 1.9, 5.2, $^2J_{H,H}$ = 13.5 Hz, 1 H, *H*-4); 3.85 (ddd, $^3J_{H,H}$ = 5.3, 11.4, $^2J_{H,H}$ = 12.0 Hz, 1 H, *H*-3), 3.54 (ddd, $^3J_{H,H}$ = 1.9, 4.7, $^2J_{H,H}$ = 12.1 Hz, 1 H, *H*-3), 3.37 (dddd, $^5J_{H,H}$ = 1.1, $^3J_{H,H}$ = 4.7, 11.2, $^2J_{H,H}$ = 13.5 Hz, 1 H, *H*-4), 2.65-2.15 (m, 4 H, *H*-7 and *H*-8), 1.61 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.8, 171.8 (*C*=O), 157.5, 134.6 (quat,), 132.9 (*C*H=CH_2), 127.0 (*C* meta to OAllyl), 117.8 (CH=CH_2), 115.4 (*C* ortho to Oallyl), 69.0 (OCH_2), 62.9 (*C*-8a), 50.5 (*C*-3); 34.2 (*C*-4), 30.7 (*C*-7), 29.7 (*C*-8), 23.5 (*C*H_3). GC-MS: R_t 10.68 min. M/z: 300 (M^+. 60.8), 272 (11.1), 231 (100.0), 175 (3.9), 162 (50.3), 134 (24.5), 124 (48.1), 121 (6.3), 120 (7.1), 111 (5.3), 110 (6.2), 82 (9.7), 80 (5.4), 79 (6.7), 77 (6.7), 68 (5.4), 65 (5.2), 56 (12.9), 55 (38.3), 54 (8.6), 53 (6.9), 42 (24.3), 41 (35.1), 42 (10.2), 41 (18.1). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{17}H_{21}N_2O_3$ 301.1552; Found 301.1545.

(*R*,*S*)-2-((4-Allyloxyphenyl)methyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-dione 6g. A solution of *N*-(4-allyloxybenzyl) formamide (for its preparation see the S.I.) (2.222 g, 11.62 mmol) was dissolved in dry CH_2Cl_2 (60 mL) and treated with *N*-methylmorpholine (3.83 mL, 34.86 mmol). Then a solution of triphosgene (*bis*(trichloromethyl) carbonate) (1.034 g, 5.23 mmol) in dry CH_2Cl_2 (10 ml) was added. After stirring for 2 h at room temperature, the mixture was poured into brine (50 mL) + saturated aqueous $NaHCO_3$ (50 mL) and extracted three times with Et_2O. The organic phase was washed with 1 M KH_2PO_4 + some 2 M HCl to adjust the pH to 5. Evaporation and chromatography (PE / Et_2O 8:2) gave pure 4-(allyloxybenzyl)isocyanide (R_f = 0.43, PE/Et_2O 8:2), that was evaporated at 15 mbar only (because it was partly volatile) and used as such for the Ugi reaction and the subsequent cyclization as described for **6a**. The yield of the Ugi reaction was 87% (from the formamide), whereas the yield of cyclization was 80 %. the overall yield was 70% the from formamide (3 steps). M.P. = 107.6-108.5 °C. R_f = 0.61 (AcOEt/CH_2Cl_2/MeOH 45 : 45 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.15 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* meta to OAll); 6.88 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* ortho to OAll); 6.05 (ddt, $^3J_{H,H}$ = 10.5, 17.3 (d), 5.3 (t) Hz, 1 H, C*H*=CH_2); 5.41 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.3 (d) Hz, 1 H, CH=C*H*H), 5.29 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.70 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, ArC*H*H), 4.53 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.3 (d) Hz, 2 H, CH_2CH=CH_2); 4.32 (d, $^2J_{H,H}$ = 14.4 Hz, 1 H, ArC*H*H), 4.16-4.08 (m, 1 H, *H*-4); 3.40-3.28 (m, 1 H, *H*-3); 3.19-3.05 (m, 2 H, *H*-4, *H*-3); 2.59-2.15 (m, 4 H, *H*-7, *H*-8); 1.53 (s, 3 H, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.6, 171.5 (*C*=O), 158.3, 128.5 (quat,), 133.1 (CH=CH_2), 129.4 (*C* meta to OAll), 117.8 (CH=CH_2), 115.0 (*C* ortho to OAll), 68.8 (=C-CH_2), 62.5 (*C*-8a), 49.5 (N-CH_2Ar), 45.6(*C*-3), 33.7 (*C*-4), 30.8 (*C*-8), 29.7 (*C*-7), 23.2 (*C*H_3). GC-MS: R_t 10.77 min. M/z: 314 (M^+, 66.8%), 273 (5.6), 167 (100.0), 147 (54.1), 139 (5.1), 125 (7.7), 124 (11.9), 107 (5.9), 42 (5.8), 41 (14.4). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{18}H_{23}N_2O_3$ 315.1709; Found 315.1708.

(*4S,8aR*) and (*4S,8aS*)-2-(4-(Benzyloxy)phenethyl)-4,8a-dimethyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-diones 6h. Levulinic acid (153 µL, 1.50 mmol) was dissolved in dry MeOH (7.5 mL), and treated with 3 Å powdered molecular sieves (150 mg), and (*S*)-2-amino-1-propanol (117 µl, 1.50 mmol) was added. After 2 h, isocyanide **8** (427 mg, 1.80 mmol) was added, and the mixture stirred for 48 h at room temperature. Then it was diluted with CH_2Cl_2, filtered and evaporated to dryness. It was taken up in AcOEt / MeOH 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, the crude Ugi diastereomeric products. The diastereomeric ratio was 50:50 as determined by ^{1}H NMR of the crude. The two diastereomers were separated by chromatography (CH_2Cl_2 : AcOEt 1:1 to CH_2Cl_2 : AcOEt : MeOH 47.5 : 47.5 : 5). Here we refer to them as "upper" and "lower" on the basis of their R_f at TLC. R_f = 0.52 (upper), 0.40 (lower) (CH_2Cl_2 : AcOEt : MeOH 45 : 45 : 10). The overall yield was 615 mg (72%). These Ugi adducts were cyclized independently to the two isomers of **6h**. They were taken up in dry DMF (2 mL/mmol) and treated with sulfonyl diimidazole (SDI) (1.5 equiv.), and NaH (60% suspension in mineral oil) (1.5 equiv.). The mixture was stirred for 20 h at rt. Then *tris*(hydroxymethyl)aminomethane (TRIS) (0.5 mmol) was added, followed by another aliquot of NaH (12 mg, 0.15 equiv.). After 1 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. Evaporation afforded a crude product that was chromatographed (from AcOEt to AcOEt/MeOH 95:5) to give analytically pure **6h-upper** (61%) and **6h-lower** (88%), as foams (upper and lower refers to the TLC behavior of intermediate Ugi adducts, because, after cyclization, the diastereomers coelute at TLC. R_f = 0.34 (AcOEt/CH_2Cl_2/MeOH 45 : 45 : 5).

6h-upper. Foam. $[\alpha]_D$ = +49.8 (c 1.52, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.26 (m, 5 H, aromatics of Bn); 7.12 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* meta to OBn); 6.91 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* ortho to OBn); 5.05 (s, 2 H, OCH_2); 3.96 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 7.5, 6.0 Hz, 1 H, ArCH_2C*H*H), 3.93-3.83 (m, 1 H, *H*-4); 3.46 (dd, $^3J_{H,H}$ = 4.2, $^2J_{H,H}$ = 13.2, 1 H, *H*-3); 3.35 (ddd, $^3J_{H,H}$ = 7.9, 6.9, $^2J_{H,H}$ = 13.5 Hz, 1 H, ArCH_2C*H*H), 3.03 (dd, $^3J_{H,H}$ = 3.8, $^2J_{H,H}$ = 13.4 Hz, 1 H, *H*-3); 2.93-2.72 (m, 2 H, ArCH_2); 2.55-2.44 (m, 1 H, *H*-8); 2.33-2.15 (m, 2 H, *H*-7. *H*-8); 2.07-1.96 (m, 1 H, *H*-7); 1.35 (d, $^3J_{H,H}$ = 6.5, 3 H, CH_3CH); 1.32 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 173.8, 171.7 (*C*=O), 157.5, 136.9, 130.5 (quat,), 129.8 (*C* meta to OBn), 128.5 (x 2), 127.9. 127.4 (x 2) (*C*H of Bn), 115.0 (*C* ortho to OBn), 70.0 (OCH_2Ph), 63.3 (*C*-8a), 52.0 (*C*-3), 49.2 (*C*-CH_2Ar), 45.6 (*C*-4), 33.0 (CH_2Ar), 31.4 (*C*-7), 30.3 (*C*-8), 23.6 (C-CH_3), 17.1 (CH-CH_3). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{24}H_{29}N_2O_3$ 393.2178; Found 393.2184.

6h-lower. Foam. $[\alpha]_D$ = –25.2 (c 0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.26 (m, 5 H, aromatics of Bn); 7.11 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* meta to OBn); 6.91 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* ortho to OBn); 5.05 (s, 2 H, OCH_2); 4.16 (hexuplet, $^3J_{H,H}$ = 6.9 Hz, 1 H, *H*-4); 3.68 (dt, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.1 Hz, 1 H, ArCH_2C*H*H), 3.54 (dt, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.1 (t) Hz, 1 H, ArCH_2C*H*H), 3.34 (dd, $^3J_{H,H}$ = 6.7, $^2J_{H,H}$ = 13.1, 1 H, *H*-3); 3.13 (dd, $^3J_{H,H}$ = 7.7, $^2J_{H,H}$ = 13.1 Hz., 1 H, *H*-3); 2.81 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, ArCH_2), 2.56-2.20 (m, 3 H, *H*-8 (2), *H*-7 (1)), 2.00-1.90 (m, 1 H, *H*-7), 1.43 (s, 3 H, CH_3); 1.23 (d, $^3J_{H,H}$ = 6.6, 3 H, CH_3CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C) δ 174.1, 172.0 (*C*=O), 157.5, 137.0, 130.6 (quat,), 129.8 (*C* meta to OBn), 128.5 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 115.0 (*C* ortho to OBn), 70.0 (OCH_2Ph), 62.8 (*C*-8a), 51.7 (*C*-3), 49.2 (*C*-CH_2Ar), 43.9 (*C*-4), 32.9 (CH_2Ar), 31.3 (*C*-7), 29.7 (*C*-8), 25.0 (C-CH_3), 18.8 (CH-CH_3). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{24}H_{29}N_2O_3$ 393.2178; Found 393.2180.

(*4S,8aR*) and (*4S,8aS*)-2-(4-(Benzyloxy)phenethyl)-8a-methyl-4-phenyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-diones 6i. They were prepared with the same procedure employed for **6h**. However, in this case, cyclization of the upper (higher R_f) Ugi adduct was carried out at 80 °C. R_f of intermediate Ugi adducts: 0.64 (upper), 0.48 (lower) (CH_2Cl_2 / AcOEt / MeOH 48.5 : 48.5 : 3). The diastereomeric ratio, determined by ^{1}H NMR on the crude was 50:50. Chromatography after cyclization (from AcOEt to AcOEt/MeOH 95:5) gave analytically pure **6i-upper** (61%) and **6i-lower** (88%), as foams (upper and lower refers to the TLC behavior of intermediate Ugi adducts), because, after cyclization, the diastereomers coelute at TLC. R_f = 0.34 (AcOEt/CH_2Cl_2/MeOH 45 : 45 : 5).

6i-upper. Oil. R_f = 0.46 (PE / AcOEt / MeOH 19: 76 : 5). $[\alpha]_D$ = –103.4 (c 0.64, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.20 (m, 8 H); 7.04 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H); 6.98 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* meta to OBn); 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* ortho to OBn); 5.02 (s, 2 H, OC*H*$_2$); 4.94 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, *H*-4); 3.94 (dd, $^2J_{H,H}$ = 4.6, $^3J_{H,H}$ = 13.7 Hz, 1 H, *H*-3); 3.76 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 8.8, 6.0 Hz, 1 H, ArCH$_2$C*H*H); 3.13 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 1.2 Hz, 1 H, *H*-3); 2.99 (ddd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 8.5, 6.9 Hz, 1 H, ArCH$_2$C*H*H); 2.67-2.51 (m, 3 H, ArC*H*H, *H*-8, *H*-7); 2.45-2.13 (m, 3 H, ArC*H*H, *H*-8, *H*-7); 1.44 (s, 3 H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.4, 172.1 (*C*=O), 157.5, 140.2, 136.9, 130.6 (quat,), 129.7 (*C* meta to OBn), 128.8 (x 2), 128.6 (x2), 128.0, 127.8, 127.4 (x 2), 125.5 (x2) (CH of benzyl and phenyl), 115.0 (*C* ortho to OBn), 70.0 (O*C*H$_2$Ph), 63.1 (*C*-8a), 53.3 (*C*-4), 52.7 (*C*-3), 49.4 (*C*-CH$_2$Ar), 32.6 (*C*H$_2$Ar), 31.4 (*C*-7), 29.9 (*C*-8), 23.9 (C-*C*H$_3$). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{29}H_{31}N_2O_3$ 455.2335; Found 455.2337

6i-lower. Oil. R_f = 0.51 (PE / AcOEt / MeOH 19: 76 : 5).. $[\alpha]_D$ = –10.5 (c 0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.25 (m, 8 H); 7.22-7.15 (m, 2 H); 7.14 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* meta to OBn); 6.93 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* ortho to OBn); 5.07 (d, *J* = not measurable, 1 H, *H*-4); 5.05 (s, 2 H, OC*H*$_2$); 3.83 (dt, $^2J_{H,H}$ = 13.8 (d), $^3J_{H,H}$ = 7.0 (t) Hz, 1 H, ArCH$_2$C*H*H); 3.66-3.54 (m, 2 H, *H*-3. ArCH$_2$C*H*H); 3.48 (dd, $^3J_{H,H}$ = 3.8, $^2J_{H,H}$ = 13.5, 1 H, *H*-3); 2.95-2.79 (m, 2 H, ArC*H*$_2$); 2.63-2.40 (m, 2 H, *H*-8, *H*-7); 2.38-2.25 (m, 1 H, *H*-7); 2.09-1.95 (m, 1 H, *H*-8); 1.30 (s, 3 H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.6, 172.1 (*C*=O), 157.6, 138.4, 137.0, 130.5 (quat,), 129.8 (*C* meta to OBn), 128.8 (x 2), 128.6 (x2), 127.93, 127.87, 127.4 (x 2), 126.2 (x2) (CH of benzyl and phenyl), 115.1 (*C* ortho to OBn), 70.0 (O*C*H$_2$Ph), 63.0 (*C*-8a), 51.9 (*C*-4), 50.7 (*C*-3), 49.3 (*C*-CH$_2$Ar), 33.1 (*C*H$_2$Ar), 31.4 (*C*-7), 29.4 (*C*-8), 25.5 (C-*C*H$_3$). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{29}H_{31}N_2O_3$ 455.2335; Found 455.2331

(*3R*,8aR) and (*3R*,8aS**)-2-(4-(Benzyloxy)phenethyl)-3,8a-dimethyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H*,*7H*)-diones 6j**. They were prepared starting from isocyanide **8**, racemic 1-amino-2-propanol, and levulinic acisd following the same procedure employed for **6h**. The diastereomeric ratio after the Ugi step was 50:50 as determined by NMR. The two Ugi diastereomeric adducts were not separable. After cyclization, a diastereomeric ratio of 43 : 57 (upper / lower) was determined by ^{1}H NMR of the crude. Chromatography (from CH_2Cl_2 / AcOEt 1:1 to CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5) gave analytically pure **6j-upper** (61%) and **6j-lower** (88%), as oils (upper and lower refers to the TLC behavior of the cyclized products) in 77% overall yield.

6j-upper. Oil. R_f = 0.47 (CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.45-7.27 (m, 5 H, aromatics of Bn); 7.12 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, *H* meta to OBn); 6.90 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, *H* ortho to OBn); 5.04 (s, 2 H, OC*H*$_2$); 4.18 (dd, $^3J_{H,H}$ = 5.3, $^2J_{H,H}$ = 13.8 Hz, 1 H, *H*-4); 3.99 (ddd, $^3J_{H,H}$ = 7.7, 8.8, $^2J_{H,H}$ = 13.7 Hz, 1 H, ArCH$_2$C*H*H); 3.60 (dquint, 1 H, $^3J_{H,H}$ = 5.7, $^2J_{H,H}$ = 11.4 Hz, 1 H, *H*-3); 3.31 (ddd, $^3J_{H,H}$ = 4.8, 8.9, $^2J_{H,H}$ = 13.7 Hz, 1 H, ArCH$_2$C*H*H); 2.90-2.74 (m, 2 H, ArC*H*H, *H*-4); 2.67 (dt, $^3J_{H,H}$ = 8.1, $^3J_{H,H}$ = 13.5 Hz, 1 H, ArC*H*H); 2.42 (dt, $^3J_{H,H}$ = 9.9, $^2J_{H,H}$ = 17.0 Hz, *H*-8); 2.21 (ddd, $^3J_{H,H}$ = 3.4, 9.5, $^3J_{H,H}$ = 17.0 Hz, 1 H, *H*-8); 2.09-1.90 (m, 2 H, *H*-7); 1.45 (s, 3 H, C*H*$_3$); 1.24 (d, $^3J_{H,H}$ = 5.7 Hz, 3 H, C*H*$_3$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 172.5, 172.4 (*C*=O), 157.5, 137.0, 130.6 (quat,), 129.8 (*C* meta to OBn), 128.5 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 114.8 (*C* ortho to OBn), 69.9 (O*C*H$_2$Ph), 62.1 (*C*-8a), 51.1 (*C*-3), 44.0 (*C*-CH$_2$Ar), 40.2 (*C*-4), 32.8 (*C*H$_2$Ar), 30.8 (*C*-7), 29.4 (*C*-8), 22.9 (C-*C*H$_3$), 18.3 (CH-*C*H$_3$). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{24}H_{29}N_2O_3$ 393.2178; Found 393.2185.

6j-lower. Oil. R_f = 0.38 (CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.27 (m, 5 H, aromatics of Bn); 7.11 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *H* meta to OBn); 6.92 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *H* ortho to OBn); 5.05 (s, 2 H, OC*H*$_2$); 4.17-4.04 (m, 1 H, ArCH$_2$C*H*H); 3.77 (d, $^2J_{H,H}$ = 13.4 Hz, *H*-4); 3.10 (quintuplet, $^3J_{H,H}$ = 6.3 Hz, 1 H, *H*-3); 2.98-2.74 (m, 4 H, ArCH$_2$C*H*H, *H*-4, ArC*H*$_2$); 2.60-2.35 (m, 2 H, *H*-8); 2.25-2.02 (m, 2 H, *H*-7); 1.42 (s, 3 H, C*H*$_3$); 1.09 (d, $^3J_{H,H}$ = 6.3 Hz, 3 H, C*H*$_3$CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.1, 171.1 (*C*=O), 157.4, 136.9, 131.0 (quat,), 129.8 (*C* meta to OBn), 128.5 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 114.9 (*C* ortho to OBn), 70.0 (O*C*H$_2$Ph), 62.1 (*C*-8a), 53.6 (*C*-3), 47.7 (*C*-CH$_2$Ar), 39.1 (*C*-4), 32.8 (*C*H$_2$Ar), 30.7 (*C*-7), 29.6 (*C*-8), 22.9 (C-CH$_3$), 18.6 (CH-*C*H$_3$). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{24}H_{29}N_2O_3$ 393.2178; Found 393.2174.

(*R,S*)-2-(4-(Benzyloxy)phenethyl)-9a-methylhexahydro-*1H*-pyrrolo[1,2-*a*][1,4]diazepine-1,7(*8H*)-dione 7a.

Levulinic acid (306 µL, 3.00 mmol) was dissolved in dry MeOH (15 mL), and treated with 3 Å powdered molecular sieves (300 mg), and propanolammine (230 µl, 3.00 mmol) was added. After 2 h, isocyanide **8** (593 mg, 2.5 mmol) was added, and the mixture stirred for 48 h at room temperature. Then it was diluted with CH_2Cl_2, filtered and evaporated to dryness. It was taken up in AcOEt / MeOH 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, and chromatography (AcOEt to AcOEt / MeOH 9:1) the pure Ugi adduct (895 mg, 86%). It was taken up in dry DMF (4 mL) and treated with sulfonyl diimidazole (SDI) (649 mg, 3.27 mmol), and NaH (60% suspension in mineral oil) (131 mg, 3.27 mmol). The mixture was stirred for 20 h at rt. Then *tris*(hydroxymethyl)aminomethane (TRIS) (198 mg, 1.63 mmol) was added, followed by another aliquot of NaH (20 mg, 0.5 mmol). After 1 h, the mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. Chromatography (AcOEt / CH_2Cl_2 1:1 to CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5) gave pure **7a** as an oil (583 mg, 68%). R_f = 0.47 (CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.45-7.27 (m, 5 H, aromatics of Bn); 7.10 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* meta to OBn); 6.90 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, *H* ortho to OBn); 5.04 (s, 2 H, OC*H*$_2$); 4.12 (dt, $^3J_{H,H}$ = 7.0, $^2J_{H,H}$ = 14.0 Hz, 1 H, *H*-5), 3.70 (dt, $^3J_{H,H}$ = 7.6, $^2J_{H,H}$ = 13.4, 1 H, ArCH$_2$C*H*H); 3.49 (dt, $^3J_{H,H}$ = 6.8, $^2J_{H,H}$ = 13.4 Hz, 1 H, ArCH$_2$C*H*H); 3.29 (ddd, $^3J_{H,H}$ = 2.1, 9.4, $^2J_{H,H}$ = 14.7 Hz, 1 H, *H*-3), 3.12 (ddd, $^3J_{H,H}$ = 2.3, 6.9, $^2J_{H,H}$ = 14.7, 1 H, *H*-3), 2.85 (dt, $^3J_{H,H}$ = 6.3, $^2J_{H,H}$ = 14.0 Hz, 1 H, *H*-5), 2.78 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, ArC*H*$_2$); 2.66 (ddd, $^3J_{H,H}$ = 4.6, 8.6, $^2J_{H,H}$ = 12.9 Hz, 1 H, *H*-9); 2.38-2.14 (m, 2 H, *H*-8); 1.95-1.62 (m, 3 H, *H*-9, *H*-4); 1.50 (s, 3 H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.8, 173.9 (*C*=O), 157.4, 137.0, 130.9 (quat,), 129.8 (*C* meta to OBn), 128.5 (x 2), 127.9, 127.4 (x 2) (*C*H of Bn), 114.9 (*C* ortho to OBn), 70.0 (O*C*H$_2$Ph), 67.5 (*C*-9a), 53.1 (*C*-CH$_2$Ar), 47.7 (*C*-3), 36.5 (*C*-5), 33.6 (*C*-9) 33.1 (*C*H$_2$Ar), 29.5 (*C*-8), 26.9 (*C*-4), 23.3 (*C*H$_3$). GC-MS (initial temp = 100 °C for 2 min. then 20 °C min up to 270 °C. After 4 min. at 270 °C the temp. was raised to 280 °C in 30 sec): R_t 16.93 min. M/z: 392 (M$^+$. 1.0), 210 (66.8), 204 (2.5), 167 (13.4), 138 (10.5), 124 (7.3), 111 (5.1), 110 (7.1), 91 (100.0), 82 (4.3), 70 (10.9), 65 (5.9), 56 (6.2), 55 (6.4), 44 (7.4), 42 (9.1), 41 (5.4). HRMS (ESI+) m/z [M + H$^+$]: Calcd. For $C_{24}H_{29}N_2O_3$ 393.2178; Found 393.2180.

(*R,S*)-2-Cyclohexyl-9a-methylhexahydro-*1H*-pyrrolo[1,2-*a*][1,4]diazepine-1,7(*8H*)-dione 7b.

The Ugi reaction of levulinic acid, propanolamine, and cyclohexyl isocyanide was carried out as described for **7a** and gave, after chromatography, a yield of 85%. Then, cyclization was carried out with two different methodologies. Method A. The same procedure described for **7a** was followed, but the reaction was performed at 50 °C. The yield of pure **7b** after chromatography (AcOEt to AcOEt/MeOH 95:5) was 28%. Method B. A solution of Ugi adduct (300 mg, 1.06 µmol) in dry CH_2Cl_2 (10 mL) was cooled to – 18 °C, and treated with triethylamine .(326 µL, 2.34 mmol) and with methanesulfonyl chloride (100 µL, 1.28 mmol). After 40 min the reaction was complete by TLC. The mixture was poured into a 3:1 mixture of saturated aqueous NH_4Cl and 5% aqueous $(NH_4)_2PO_4$, and extracted

with AcOEt (pH of aqueous phase = 4). After evaporation to dryness, the crude mesylate was taken up in dry DMF (1 mL), and treated with NaH (60% in mineral oil, 64 mg, 1.59 mmol). The solution was stirred at 50 °C for 6 h. Then it was poured into saturated NH_4Cl and extracted with AcOEt. Evaporation and chromatography gave pure **7b** (167 mg, 60%). M.P. = 109.2-110.9. R_f 0.21 (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 4.42 (tt, $^3J_{H,H}$ = 3.6, 11.1 Hz, 1 H, C*H*N); 4.17 (ddd, $^3J_{H,H}$ = 7.5, 6.0, $^2J_{H,H}$ = 13.8 Hz, 1 H, *H*-5), 3.30-3.15 (m, 2 H, *H*-3), 2.94 (dt, $^3J_{H,H}$ = 6.9, $^2J_{H,H}$ = 13.8 Hz, 1 H, *H*-5); 2.68 (ddd, $^3J_{H,H}$ = 8.1, 6.0, $^2J_{H,H}$ = 12.3 Hz, 1 H, *H*-9); 2.48-2.29 (m, 2 H, *H*-8); 2.06-1.88 (m, 2 H, *H*-9, *H*-4); 1.85-1.55 (m, 6 H, *H*-4 and CH_2 cyclohexyl); 1.55 (s, 3 H, CH_3); 1.48-1.23 (4 H, m, CH_2 cyclohexyl); 1.16-0.97 (m, 1 H, CH_2 cyclohexyl). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.6, 173.6 (*C*=O), 67.8 (*C*-9a), 54.9 (*C*HN), 39.9 (*C*-3), 36.5 (*C*-5), 33.5 (*C*-9), 30.2, 29.6, 25.6, 25.5, 25.4 (*C*H_2 cyclohexyl), 29.5 (*C*-8), 27.6 (*C*-4), 23.4 (*C*H_3). GC-MS: R_f 9.07 min. M/z: 264 (M^+. 30.1), 236 (4.8), 235 (5.3), 221 (31.5), 193 (9.5), 181 (23.4), 167 (7.5), 153 (6.0), 139 (15.0), 138 (24.8), 137 (8.4), 124 (48.8), 111 (100.0), 110 (13.8), 98 (28.6), 96 (11.4), 83 (11.9), 82 (12.0), 70 (6.4), 69 (5.5), 68 (6.9), 56 (39.1), 55 (42.5), 54 (9.0), 42 (19.7), 41 (34.7), 39 (8.4). Calcd. For $C_{15}H_{25}N_2O_2$ 265.1916; Found 265.1912.

(*R,S*)-2-((4-Allyloxyphenyl)methyl)-9a-methylhexahydro-*1H*-pyrrolo[1,2-*a*][1,4]diazepine-1,7(*8H*)-dione 7c. It was prepared from levulinic acid, propanolamine and 4-allyloxybenzyl isocyanide (for its preparation see the synthesis of **6g**), following the same procedures described for **7b**. The yield of the Ugi step was 72% (from the formamide). The isolated yield of cyclization was 45% (method A) or 74% (method B), after chromatography (AcOET to AcOEt / MeOH 95:5). Oil. R_f = 0.24 (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.13 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* meta to OAll); 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* ortho to OAll); 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, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.2 (d) Hz, 1 H, CH=C*H*H), 5.28 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.56 and 4.48 (AB syst,. $^2J_{H,H}$ = 14.4 Hz, 2 H, ArCH_2), 4.52 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.3 (d) Hz, 2 H, CH_2CH=CH_2); 4.16 (dt, $^3J_{H,H}$ = 6.8 (t), $^2J_{H,H}$ = 13.8 (d) Hz, 1 H, *H*-5), 3.32 and 3.23 (ABXY syst,.$^2J_{H,H}$ = 14.7, $^3J_{H,H}$ = 6.4 (ax), 9.5 (bx), 2.4 (ay=by) Hz, 2 H, *H*-3), 2.97-2.77 (m, 2 H, *H*-5 and *H*-9); 2.39 (dd, $^3J_{H,H}$ = 6.7, 8.7 Hz, 2 H, *H*-8); 2.00-1.63 (m, 3 H, *H*-9 and *H*-4), 1.59 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.7, 174.2 (*C*=O), 158.1, 129.4 (quat,), 133.1 (*C*H=CH_2), 129.2 (*C* meta to OAll), 117.7 (CH=*C*H_2), 114.9 (*C* ortho to OAll), 68.8 (=C-*C*H_2), 67.6 (*C*-9a), 52.9 (N-*C*H_2Ar), 46.1 (*C*-3), 36.6 (*C*-5), 33.7 (*C*-9) 29.6 (*C*-8), 26.9 (*C*-4), 23.3 (*C*H_3). GC-MS: R_f 11.08 min. M/z: 328 (M^+. 10.6), 287 (5.7), 181 (100.0), 162 (6.4), 147 (62.9), 138 (10.3), 124 (12.1), 111 (16.7), 110 (12.7), 107 (9.9), 98 (17.8), 82 (8.4), 78 (5.7), 56 (42.3), 55 (23.2), 42 (17.3), 41 (65.2). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{19}H_{25}N_2O_3$ 329.1865; Found 329.1862.

(*R,S*)-2-(4-Allyloxyphenyl)-9a-methylhexahydro-*1H*-pyrrolo[1,2-*a*][1,4]diazepine-1,7(*8H*)-dione 7d. The isocyanide was prepared *in situ* from *N*-(4-Allyloxyphenyl)formamide,[21] as described for the synthesis of **6f**. Then, the crude isocyanide (as CH_2Cl_2) solution was treated with the premixed levulinic acid and propanolamine mixture (see the synthesis of **7a**). Chromatography gave the Ugi product in 50% yield from formamide. Cyclization was carried out with method A, as described for **7a**, but at 50 °C. Reaction was complete after 1 h. Chromatography (AcOEt to AcOEt : MeOH 99:1) gave pure **7d**, as an oil (74%). R_f: 0.37 (AcOEt : MeOH 99:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.01 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, *H* meta to OAll); 6.90 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, *H* ortho to OAll); 6.03 (ddt, $^3J_{H,H}$ = 5. (t), 10.5 (d), 17.2 (d) Hz, 1 H, C*H*=CH_2), 5.40 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 (q), $^3J_{H,H}$ = 17.3 (d) Hz, 1 H, CH=C*H*H), 5.28 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.52 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.2 (d) Hz, 2 H, CH_2CH=CH_2); 4.31 (dt, $^3J_{H,H}$ = 6.4 (t), $^2J_{H,H}$ = 13.9 (d) Hz, 1 H, *H*-5), 3.74 and 3.65 (ABXY syst,.$^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 6.6 (ax), 8.7 (bx), 3.0 (ay=by) Hz, 2 H, *H*-3), 3.07 (dt, $^3J_{H,H}$ = 6.7 (t), $^2J_{H,H}$ = 13.8 (d) Hz, 1 H, *H*-5), 2.88 (ddd, $^3J_{H,H}$ = 5.1, 7.7, $^2J_{H,H}$ = 12.8 Hz, 1 H, *H*-9), 2.55-2.35 (m, 2 H, *H*-8), 2.18-1.93 (m, 2 H, *H*-4), 1.92 (dt, $^3J_{H,H}$ = 9.0 (t), $^2J_{H,H}$ = 12.8 (d) Hz, 1 H, *H*-9), 1.65 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.8, 174.4 (*C*=O), 157.2, 138.9 (quat,), 133.0 (*C*H=CH_2), 127.3 (*C* meta to OAll), 117.7 (CH=*C*H_2), 115.4 (*C* ortho to OAll), 69.0 (=C-CH_2), 67.6 (*C*-9a), 50.9 (*C*-3), 36.9 (*C*-5), 33.7 (*C*-9) 29.6 (*C*-8), 27.5 (*C*-4), 23.1 (CH_3). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{18}H_{23}N_2O_3$ 315.1709; Found 315.1715.

(*5R,9aR*) and (*5R,9aS*)-2-((4-Allyloxyphenyl)methyl)-5,9a-dimethylhexahydro-*1H*-pyrrolo[1,2-*a*][1,4]diazepine-1,7(*8H*)-diones 7e. They were prepared with the same procedure employed for **7b** (method A). However, in this case, the isocyanide was used in excess (1.2 equivalents) whereas (*R*)-3-amino-1-butanol and levulinic acid were used in equimolar quantities. R_f of intermediate Ugi adducts: 0.50 (upper), 0.43 (lower) (CH_2Cl_2 / AcOEt / MeOH 45 : 45 : 10). The diastereomeric ratio, determined by ^{1}H NMR on the crude, was 50:50. The two diastereomers were separated after the Ugi and cyclized independently using method A. **Upper** and **lower** refers to the TLC behavior of intermediate Ugi adducts, since, after cyclization, they had the same R_f. Chromatography after cyclization (from AcOEt to AcOEt/MeOH 95:5) gave analytically pure **7e-upper** (45%) and **7e-lower** (53%), as oils. R_f = 0.54 (AcOEt / MeOH 95 : 5).

7e-upper. $[\alpha]_D$ = −12.6 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz $CDCl_3$, 25°C) δ 7.17 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* meta to OAll); 6.87 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, *H* ortho to OAll); 6.05 (ddt, $^3J_{H,H}$ = 10.5, 17.2 (d), 5.3 (t) Hz, 1 H, C*H*=CH_2); 5.41 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.2 (d) Hz, 1 H, CH=C*H*H), 5.29 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.56 and 4.47 (AB syst,. $^2J_{H,H}$ = 14.3 Hz, 2 H, ArCH_2), 4.52 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ =5.4 (d) Hz, 2 H, CH_2CH=CH_2); 3.44 (ddd, $^3J_{H,H}$ =4.4, 12.4, $^2J_{H,H}$ = 15.1 Hz, 1 H, *H*-3), 3.26 (dquint, $^3J_{H,H}$ = 6.7, $^2J_{H,H}$ = 11.4 Hz, 1 H, *H*-5), 3.14 (ddd, $^3J_{H,H}$ =1.2, 5.1, $^2J_{H,H}$ = 15.1 Hz, 1 H, *H*-3), 2.68-2.51 (m, 1 H, *H*-9), 2.36-2.22 (m, 2 H, *H*-8); 2.19-2.07 (m, 1 H, *H*-9), 1.91 (1 H, dddd, $^3J_{H,H}$ = 1.5, 4.5, 11.7, $^2J_{H,H}$ = 13.2 Hz, 1 H, *H*-4); 1.67-1.53 (m, 1 H, *H*-4), 1.60 (d,$^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3CH), 1.59 (s, 3 H, CH_3C). ^{13}C NMR (75 MHz $CDCl_3$, 25°C) δ 174.9, 173.7 (*C*=O), 158.1, 129.7 (quat,), 133.1 (*C*H=CH_2), 129.3 (*C* meta to OAll), 117.7 (CH=*C*H_2), 114.9 (*C* ortho to OAll), 69.3 (=C-*C*H_2), 68.8 (*C*-9a), 52.2 (N-*C*H_2Ar), 48.5 (*C*-5), 45.3 (*C*-3), 31.7 (*C*-9) 31.6 (*C*-4), 30.6 (*C*-8), 24.4 (C-*C*H_3), 17.4 (CH*C*H_3). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{20}H_{27}N_2O_3$ 342.2022; Found 343.2019.

7e-lower. $[\alpha]_D$ = + 136.2 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz $CDCl_3$, 25°C) δ 7.13 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* meta to OAll); 6.86 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *H* ortho to OAll); 6.05 (ddt, $^3J_{H,H}$ = 10.5, 17.2 (d), 5.3 (t) Hz, 1 H, C*H*=CH_2); 5.41 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.3 (d) Hz, 1 H, CH=C*H*H), 5.29 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.62 and 4.41 (AB syst,. $^2J_{H,H}$ = 14.4 Hz, 2 H, ArCH_2), 4.52 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.3 (d) Hz, 2 H, CH_2CH=CH_2); 4.50-4.35 (m, 1 H, *H*-5), 3.30-3.12 (m,. 2 H, *H*-3), 2.79 (ddd, $^3J_{H,H}$ = 8.2, 4.7, $^2J_{H,H}$ = 12.9 Hz, 1 H, *H*-9), 2.45-2.25 (m, 2 H, *H*-8); 2.16-1.72 (m, 3 H, *H*-9, *H*-4), 1.71 (s, 3 H, CH_3C), 1.26 (d,$^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3CH). ^{13}C NMR (75 MHz $CDCl_3$, 25°C) δ 175.6, 174.8 (*C*=O), 158.1, 129.3 (quat,), 133.2 (*C*H=CH_2), 129.2 (*C* meta to OAll), 117.7 (CH=CH_2), 114.9 (*C* ortho to OAll), 68.8 (=C-*C*H_2), 68.6 (*C*-9a), 53.0 (N-*C*H_2Ar), 47.6 (*C*-5), 46.6 (*C*-3), 35.6 (*C*-9) 34.0 (*C*-4), 29.4 (*C*-8), 28.0 (C-*C*H_3), 20.5 (CH*C*H_3). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{20}H_{27}N_2O_3$ 342.2022; Found 343.2017.

2-(2-Hydroxybenzyl)-8a-methyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H,7H*)-dione 17. A solution of compound **6d** (103 mg, 328 µmol) in dry acetonitrile (3.1 mL) was treated with ammonium formate (136.2 mg, 2.16 mmol) and $Pd(PPh_3)_2Cl_2$ (18.4 mg, 26.2 µmol). The solution was heated at 80 °C in a closed vessel for 3 h. Then it was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. Evaporation and chromatography (CH_2Cl_2 / AcOEt 1 : 1 to CH_2Cl_2 / AcOEt / MeOH 45 : 45 :

10) gave pure **17** as a foam (85 mg, 95%). R_f = 0.44 (CH_2Cl_2 / AcOEt / MeOH 47.5 : 47.5 : 5). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.05 (s, 1 H, O*H*), 7.26 (dt, $^4J_{H,H}$ = 1.7 (d), $^3J_{H,H}$ = 7.7 (t) Hz, 1 H, *H meta* to OH and *para* to CH_2), 7.09 (dd, $^4J_{H,H}$ =1.7, $^3J_{H,H}$ = 7.5 Hz, 1 H, *H* ortho to CH_2), 6.95 (dd, $^4J_{H,H}$ = 1.2, $^3J_{H,H}$ = 8.0 Hz, 1 H, *H* ortho to OH), 6.83 (dt, $^4J_{H,H}$ = 1.2 (d), $^3J_{H,H}$ = 7.4 (t) Hz, 1 H, *H para* to OH), 4.66 and 4.26 (AB syst., $^2J_{H,H}$ = 14.6 Hz, 2 H, CH_2Ar), 4.21 (ddd, $^3J_{H,H}$ = 1.0, 5.4, $^2J_{H,H}$ = 14.4 Hz, 1 H, *H*-4); 3.55 (dt, $^3J_{H,H}$ = 11.9, 5.5, $^2J_{H,H}$ = 11.9, 1 H, *H*-3), 3.39 (ddd, $^3J_{H,H}$ = 1.0, 4.9, $^2J_{H,H}$ = 12.1 Hz, 1 H, *H*-3), 3.13 (dddd, $^3J_{H,H}$ = 1.2, 5.0, 12.0, $^2J_{H,H}$ = 14.4 Hz, 1 H, *H*-4), 2.53 (ddt, $^3J_{H,H}$ = 1.2, 9.8 (t), $^2J_{H,H}$ = 16.7 Hz, 1 H, *H*-8), 2.38 (ddd, $^3J_{H,H}$ = 3.8, 8.1, $^2J_{H,H}$ = 16.6 Hz, 1 H, *H*-8), 2.32-2-13 (m, 2 H, *H*-7), 1.50 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 173.8, 172.5 (*C*=O), 156.0, 120.7 (quat,), 131.3 (*C* ortho to CH_2), 130.7 (*C meta* to OH and *para* to CH_2), 119.5 (*C para* to OH), 117.8 (*C ortho* to OH), 62.3 (*C*-8a), 48.7 (CH_2Ar), 46.6 (*C*-3); 33.1 (*C*-4), 30.6 (*C*-7), 29.6 (*C*-8), 23.1 (CH_3). GC-MS: R_t 9.70. M/z: 274 (M^+. 71.1), 246 (4.2), 231 (8.3), 167 (100.0), 149 (8.6), 139 (11.6), 136 (38.7), 125 (33.8), 124 (20.4), 123 (7.6), 122 (11.9), 111 (7.6), 107 (83.6), 98 (26.8), 97 (16.0), 83 (11.2), 78 (11.5), 77 (29.8), 70 (21.5), 56 (23.0), 55 (41.5), 51 (7.8), 42 (37.2), 41 (11.5), 39 (10.2). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{15}H_{19}N_2O_3$ 275.1396; Found 275.1398.

2-(2-Allyloxybenzyl)-7,8a-dimethyltetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H,7H*)-dione 18. A 0.4 M solution of LDA was prepared at ─20 °C by adding *n*BuLi (1.6 M in hexanes, 5.0 mL, 8.0 mmol) to a solution of diisopropylamine (1.24 mL, 8.8 mmol) in dry THF (12.3 mL) containing few crystals of 2,2'-bipyridyl and stirring for 20 min. Part of this deep red solution (3.10 mL corresponding to 1.24 mmol)) was transferred via syringe into another flask, again cooled to ─20 °C. To this flask, a solution of compound **6d** (257 mg, 818 µmol) dissolved in dry THF (2 mL + 0.5 mL + 0.5 mL for washing) was added. After 20 min (the solution lose its deep red color) the flask was cooled to ─78 °C, and methyl iodide (77 µL, 1.24 mmol) was added. The temperature was allowed to rise slowly to ─30 °C during 3 h. Then the reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. Evaporation and chromatography (CH_2Cl_2 : AcOEt 1:1 + 1.5% MeOH) gave pure **18** as a foam (180 mg, 67%). Also 40 mg of starting **6d** were recovered. Thus, the yield from unrecovered substrate was 79%. R_f = 0.56 (CH_2Cl_2 : AcOEt 1:1 + 5% MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) (note: two diastereomers, in a 91: 9 ratio are detected. The diastereomeric ratio was calculated by integration of the CH_3CH signals (minor diast. resonates at 1.27. Here, only the signals of major diastereomer are reported) δ 7.30-7.15 (m, 2 H, *H* meta to Oallyl), 6.93 (dt, $^4J_{H,H}$ = 0.9 (d), $^3J_{H,H}$ = 7.5 (t) Hz, 1 H, *H* para to Oallyl), 6.87 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, *H* ortho to Oallyl), 6.04 (ddt, $^3J_{H,H}$ = 10.4, 17.2 (d), 5.1 (t) Hz, 1 H, C*H*=CH_2), 5.40 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.6 (q), $^3J_{H,H}$ = 17.3 (d) Hz, 1 H, CH=C*H*H), 5.28 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.73 and 4.60 (AB syst, $^2J_{H,H}$ = 14.7 Hz, 2 H, CH_2Ar), 4.55 (dt, $^4J_{H,H}$ = 1.5 (t), $^3J_{H,H}$ = 5.1 (d) Hz., 2 H, CH_2CH=), 4.09 (ddd, $^3J_{H,H}$ = 1.4, 5.0, 13.4 Hz, 1 H, *H*-4), 3.38 (dt, $^3J_{H,H}$ =5.0, 11.7, $^3J_{H,H}$ = 11.7 Hz, 1 H, *H*-3), 3.28-3.08 (m, 2 H, *H*-3 and *H*-4), 2.69-2.52 (m, 1 H, *H*-7), 2.44 (dd, $^3J_{H,H}$ = 8.1, $^2J_{H,H}$ = 12.9 Hz., 1 H, *H*-8), 1.82 (dd, $^3J_{H,H}$ = 11.0, $^2J_{H,H}$ = 12.9 Hz., 1 H, *H*-8), 1.51 (s, 3 H, CH_3), 1.19 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 174.7, 171.5 (*C*=O), 156.6, 124.6 (quat,), 133.0 (CH=CH_2), 129.7, 128.9 (*C* meta to Oallyl), 121.0 (*C* para to Oallyl), 117.5 (CH=CH_2), 111.6 (*C* ortho to Oallyl), 68.8 (OCH_2), 60.5 (*C*-8a), 46.2 (*C*-3); 44.8 (CH_2Ar), 40.1 (*C*-8), 35.1 (*C*-7), 33.8 (*C*-4), 22.7 (CH_3C), 15.3 (CH_3CH). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{19}H_{25}N_2O_3$ 329.1865; Found 329.1858.

2-(2-Allyloxybenzyl)-8a-methyl-7-(3-trimethylsilylprop-2-ynyl)tetrahydropyrrolo[1,2-*a*]pyrazine-1,6(*2H,7H*)-dione 19. It was prepared from **6d** (300 mg), using 1-bromo-3-(trimethylsilyl)propyne, following the same procedure employed for **18**. However, in this case, the temperature was allowed to rise to 0 °C, and the reaction mixture stirred overnight. The diastereomeric ratio was determined on the crude product abd was found to be 27: 73 by HPLC.The two diastereomers and recovered **6d** were separated by chromatography (PE / AcOEt 3:2). Yields: upper diastereomer (R_f = 0.46): 55 mg (13.6%). Lower diastereomer (R_f = 0.31): 127 mg (31.3%) Overall yield: 45%. Recovered substrate **6d**: 93 mg. Yield calculated form unrecovered substrate: 65%.

19-upper. Oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 7.27-7.14 (m, 2 H, *H* meta to Oallyl), 6.92 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, *H* para to Oallyl), 6.86 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, *H* ortho to Oallyl), 6.04 (ddt, $^3J_{H,H}$ = 10.4, 17.2 (d), 5.2 (t) Hz, 1 H, C*H*=CH_2), 5.40 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 (q), $^3J_{H,H}$ = 17.4 (d) Hz, 1 H, CH=C*H*H), 5.28 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.74 and 4.54 (AB syst, $^2J_{H,H}$ = 14.7 Hz, 2 H, CH_2Ar), 4.54-4.49 (m, 2 H, CH_2CH=), 4.18-4.07 (m, 1 H, *H*-4),3.50-3.15 (m, 3 H, *H*-3, *H*-4), 2.88 (dd, $^3J_{H,H}$ = 9.9, $^2J_{H,H}$ = 13.9 Hz., 1 H, *H*-8), 2.70-2.46 (m, 3 H, *H*-7, C≡C-CH_2), 2.05 (dd, $^3J_{H,H}$ = 6.3, $^2J_{H,H}$ = 13.9 Hz., 1 H, *H*-8), 1.63 (s, 3 H, CH_3), 0.14 (s, 9 H, (CH_3)$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 174.1, 171.7 (*C*=O), 156.6, 124.6 (quat,), 133.1 (CH=CH_2), 129.6, 128.9 (*C* meta to Oallyl), 121.0 (*C* para to Oallyl), 117.5 (CH=CH_2), 111.7 (*C* ortho to Oallyl), 103.4, 86.9 (*C*≡*C*), 68.8 (OCH_2), 62.0 (*C*-8a), 45.7 (*C*-3); 45.0 (CH_2Ar), 40.6 (*C*-7), 34.8 (*C*-8), 34.4 (*C*-4), 26.1 (CH_3C), 22.3 (C≡C-CH_2), 0.0 ((CH_3)$_3$Si). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{24}H_{33}N_2O_3Si$ 425.2260; Found 425.2263.

19-lower. White solid. M.P.: 143.4-145.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.28-7.20 (m, 2 H, *H* meta to Oallyl), 6.94 (dt, $^4J_{H,H}$ = 0.6 (d), $^3J_{H,H}$ = 7.5 (t) Hz, 1 H, *H* para to Oallyl), 6.87 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, *H* ortho to Oallyl), 6.04 (ddt, $^3J_{H,H}$ = 10.5, 17.3 (d), 5.1 (t) Hz, 1 H, C*H*=CH_2), 5.40 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.5 (q), $^3J_{H,H}$ = 17.3 (d) Hz, 1 H, CH=C*H*H), 5.29 (dq, $^2J_{H,H}$ and $^4J_{H,H}$ = 1.4 (q), $^3J_{H,H}$ = 10.5 (d) Hz, 1 H, CH=C*H*H), 4.84 and 4.50 (AB syst, $^2J_{H,H}$ = 14.7 Hz, 2 H, CH_2Ar), 4.55 (dt, $^4J_{H,H}$ = 1.4 (t), $^3J_{H,H}$ = 5.2 (d) Hz., 2 H, CH_2CH=), 4.09 (ddd, $^3J_{H,H}$ = 1.4, 4.8, 13.4 Hz, 1 H, *H*-4), 3.41-3.20 (m, 2 H, *H*-3), 3.14 (dt, $^3J_{H,H}$ = 4.5 (d), $^3J_{H,H}$ and $^2J_{H,H}$ =12.3 (t) Hz, 1 H, *H*-4), 2.82-2.66 (m, 2 H, C≡C-C*H*H and *H*-7), 2.55-2.32 (2 H, m, *H*-8), 2.50 (dd, $^3J_{H,H}$ = 7.9, $^2J_{H,H}$ = 13.1 Hz., 1 H, *H*-8), 2.40 (dd, $^3J_{H,H}$ = 9.4, $^2J_{H,H}$ = 17.8 Hz., 1 H, C≡C-C*H*H), 2.12 (dd, $^3J_{H,H}$ = 11.1, $^2J_{H,H}$ = 13.1 Hz., 1 H, *H*-8), 1.53 (s, 3 H, CH_3), 0.13 (s, 9 H, (CH_3)$_3$Si). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 172.1, 171.2 (*C*=O), 156.6, 124.6 (quat,), 133.0 (CH=CH_2), 129.7, 128.9 (*C* meta to Oallyl), 121.0 (*C* para to Oallyl), 117.5 (CH=CH_2), 111.7 (*C* ortho to Oallyl), 103.3, 86.6 (*C*≡*C*), 68.8 (OCH_2), 60.6 (*C*-8a), 46.4 (*C*-3); 44.7 (CH_2Ar), 39.6 (*C*-7), 37.3 (*C*-8), 34.1 (*C*-4), 23.1 (CH_3C), 21.0 (C≡C-CH_2), 0.1 ((CH_3)$_3$Si). HRMS (ESI+) m/z [M + H^+]: Calcd. For $C_{24}H_{33}N_2O_3Si$ 425.2260; Found 425.2255.

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Keywords: multicomponent reactions • nucleophilic substitution • isocyanides • renewable resources • heterocycles

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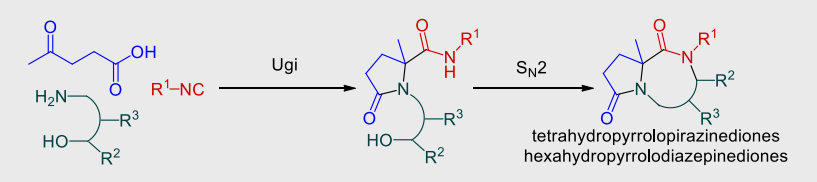

Operationally simple, 2-step conversion of levulinic acid into bicyclic drug-like heterocyclic systems.

*Chiara Lambruschini, Andrea Basso, Lisa Moni, Alessandro Pinna, Renata Riva, and Luca Banfi**

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