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Development of Scalable Conditions for the Ugi Reaction – Application to the Synthesis of (*R*)-Lacosamide

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ABSTRACT: The Ugi reaction is applied for the preparation of (*R*)-lacosamide, an important drug for the treatment of epilepsy. To this end, key issues associated with the Ugi reaction, such as a practical preparation of the foul-smelling isocyanide as well as the efficient introduction of chirality via a cheap and easily removable chiral directing group were solved. Enantiomerically pure (>99.9% *ee*) drug substance meeting all required purity specifications is prepared in operationally simple four steps in 40% overall yield from the commodity chemical benzylamine.

INTRODUCTION

A number of reactions are very widely applied by the chemical community and are consequently assumed to have a high level of maturity in their development. However, a more critical assessment often reveals that key parameters required to perform the respective reaction

reliably on any scale are missing from the literature. One such reaction for which this holds is the Ugi reaction. Despite its industrial birth in 1959 in the Central Research laboratories of Bayer AG and its very wide adoption by the chemical community (over 3000 Scifinder hits), the authors are not aware of any large scale implementation of the Ugi reaction. Several reasons for this apparent discrepancy between its popularity and lack of utilization on large scale can be explained by three major challenges of the Ugi reaction:

- the preparation and handling of foul smelling isocyanides
- the need to find appropriate chiral auxiliaries for the introduction of chirality
- the need to remove these auxiliaries with high yield

This publication reports the solution to these problems using as an example a short, efficient and high-yielding preparation of lacosamide **1**.

Lacosamide **1** is a cornerstone of modern epilepsy treatment and has found widespread acceptance among patients and physicians.[2]

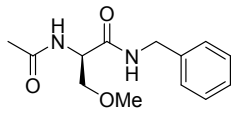

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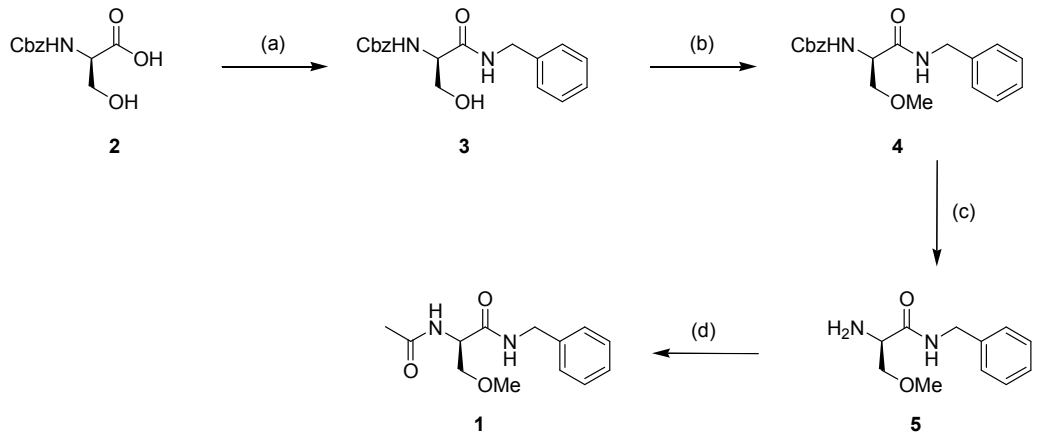
Figure 1. (*R*)-Lacosamide **1**.

RESULTS AND DISCUSSION

Despite its deceptively simple structure as a derivative of *D*-serine the reported syntheses are cumbersome.[3] Until recently the starting material, protected *D*-serine **2**, was expensive and difficult to obtain. The synthesis from *D*-serine requires a finicky *O*-methylation of compound **3** (reportedly requiring Ag_2O as base), the need to use a urethane protecting group such as Cbz to

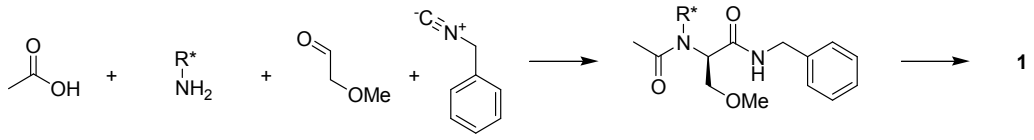
allow a racemization free formation of the *N*-benzyl amide **3**, and consequently an unproductive protection/deprotection prior to the installation of the *N*-acetamide of amine **5** in the final step (d), as shown in Scheme 1.[3a]



2 **3** **4** **5** **1**

Scheme 1. a) isobutyl chloroformate, *N*-methyl morpholine, $PhCH_2NH_2$, 84%; b) MeI, Ag_2O, 84%; c) H_2/Pd-C, 100%; d) Ac_2O, pyridine, DMAP, 90%.[3a]

The concept, outlined in Scheme 2, makes use of the power of the Ugi reaction of compounds **6**-**9** to set up the complete skeleton of the molecule in a single step to yield compound **10**, followed by the removal of the chiral auxiliary R*.[4]



6 **7** **8** **9** **10**

Scheme 2. Synthesis of lacosamide via four component Ugi reaction.[4]

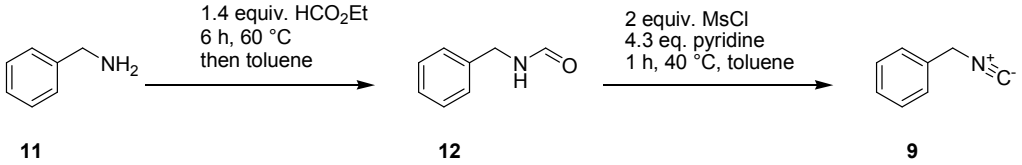
The chemistry was developed so that lacosamide **1** could be prepared using a very concise process from commodity chemicals in an overall yield of 40% with excellent chemical (>99.9 area %) and optical purity (>99.9% *ee*). The following describes the best solution and details the rationale for the choices.

The odor of isocyanides is repugnant. Benzyl isocyanide **9** is no exception and its foul smell is also very persistent. Detailed handling suggestions are described in the experimental section; it is expected that these will prove useful for other isocyanides as well. At this point it is appropriate to discuss some misconceptions about benzyl isocyanide. Commercially available benzyl isocyanide frequently appears to be partly decomposed, leading to the assumption that the compound is unstable. While contaminated benzyl isocyanide is indeed unstable when heated and can decompose rapidly to a black tar when a distillation is attempted, clean benzyl isocyanide is quite stable. Indeed, an accelerated reaction calorimetry (ARC) test indicated no decomposition after storage at 125 °C for 24 h.

However, preparation and isolation of the pure isocyanide is often unnecessarily burdensome. Among possible approaches, the dehydration of formamides is most attractive and $POCl_3$ is the most frequently used dehydrating agent.[5] Indeed, a recent publication demonstrates how $POCl_3$ can be used in combination with DIPEA in toluene to convert the formamide to the isocyanide in flow.[6] While this strategy might have been a viable solution, it was not pursued because of the problems associated with $POCl_3$ and the need to avoid the formation of precipitates in flow. Especially the second reason would have induced a very low volumetric productivity, which is a key driver for the economic viability of any process and is frequently ignored.

When the use of flow chemistry requires high dilutions and therefore high volumes of solvent, the purported advantages of a reaction in flow are essentially obviated. In addition, the benzyl formamide **12** is not readily commercially available and the frequently-used formylation procedure via formation of the mixed anhydride between acetic anhydride and formic acid is not attractive.[7] The alternative is a simple condensation between benzylamine **11** and ethyl formate, resulting in the quantitative formation of the highly crystalline *N*-benzyl formamide **12**.[8] Rather

than isolating the compound, a simple solvent switch into toluene set the stage for the dehydration, with the resulting formation of isocyanide after azeotropic distillation of toluene. Rather than resorting to the already-mentioned unattractive $POCl_3$, it was decided to explore alternative dehydrations of the formamide with the goal of finding a less cumbersome procedure. Using Corey's dehydration method[9] of formamides with tosylchloride/pyridine resulted in a non-stirrable mixture of precipitates at reasonable concentrations. Gratifyingly, the use of pyridine and mesyl chloride[10] in 4 volumes of toluene kept the mixture manageable at high concentrations and resulted in the rapid and quantitative dehydration of the formamide with the formation of crystalline pyridine salts (hydrochloride/methanesulfonate).



11 **12** **9**

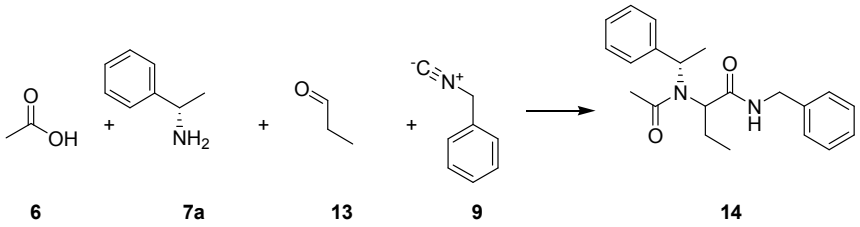
Scheme 3. One-pot procedure for benzyl isocyanide **9**.

Addition of water to the reaction vessel dissolved the salts and the isocyanide is obtained in essentially quantitative yield as solution in toluene. Thus the isocyanide could be prepared in an operationally simple one-pot procedure from benzylamine. The resulting isocyanide solution is approx. 2.5 molar and can be either used directly or be concentrated by a simple stripping of some toluene. This approach is very practical and it should be possible to extend it to isocyanides other than benzyl isocyanide. The one-pot preparation in a closed vessel minimizes manipulations and possible exposure to the odiferous compound.

To the authors' best knowledge, and in line with the mechanism of the Ugi reaction, there is no totally satisfactory solution to using the Ugi reaction for the preparation of enantiomerically pure compounds.[11] Enantioselective catalysts are not known, thus necessitating the utilization of a chiral primary amine as inducer. High diastereoselectivity, crystalline products and efficient and

high-yielding removal of the chiral auxiliary are necessary prerequisites for a successful implementation of an Ugi reaction.

Having secured a viable access to the benzyl isocyanide, chiral amines[12] could then be assessed. As the Ugi reaction is a four-component reaction, the order of addition of the components must be defined. The Ugi reaction between acetic acid (**6**), benzyl isocyanide **9**, propionaldehyde **13** and phenethylamine **7a** (Scheme 4) was studied as a model reaction.



Scheme 4. Components of a model Ugi reaction.

Despite the fact that four different components are combined in an Ugi reaction, the order of addition has not received much attention in the literature. A common description is "mixed together", or in more detailed protocols the imine is preformed from aldehyde, amine and carboxylic acid followed by the addition of the isocyanide last.[13] This order appears logical from the mechanism of the Ugi reaction and the sensitivity of isocyanides in acidic medium (hydration of **9** to formamide **12**); it should also avoid the competing direct addition of the isocyanide into the aldehyde, known as the Passerini three component reaction.[14] However, application of the standard protocol to our model system resulted in a complex mixture with less than 10 area % of the desired product **14**.

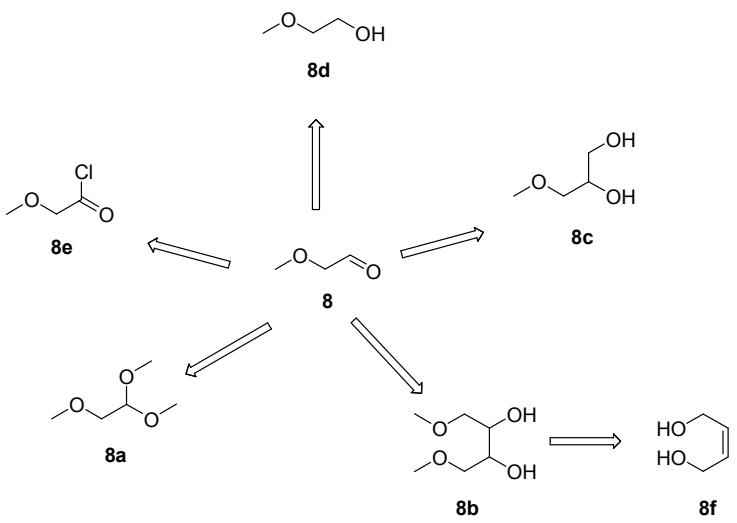
Apparently the enolizable aldehyde suffered degradation when the isocyanide is absent – caused by aldol addition/condensation reactions – leading to diverse Ugi by-products.

A search for alternative procedures revealed a description of the amine added as the last component[15] and application of this concept formed product **14** almost quantitatively. Gratifyingly, the competing Passerini reaction is much slower, so that at most, traces of the corresponding product can be detected.

We found that the aldehyde can be added last, leading also to a clean conversion to product **14**. This order should be even preferred when scaling-up the reaction (*vide infra*) due to a highly exothermic salt formation in addition to the reaction heat produced in the Ugi reaction.

It is remarkable that by changing the order of addition a clean and rapid transformation can be essentially completed in less than 30 min. It appears that this critical information is not fully recognized by the community applying the Ugi reaction. As even traces of residual isocyanide impart a strong smell to the reaction mixture, it is advisable to keep the essentially completed reaction closed for an additional 10 h, when the amount of residual isocyanide is below 0.1% and is no longer detectable by its odor.

A strong rationale for the choice of the Ugi route for the preparation of lacosamide is the desire to use methoxyacetaldehyde **8**, which avoids an alcohol methylation in the synthesis. However methoxyacetaldehyde is an unstable, volatile (bp. 90 °C),[16a] highly water soluble, colorless liquid which cannot be obtained on scale and a commercial sample turned out to be entirely decomposed. Methoxyacetaldehyde **8** is described in the older literature, but without a full experimental procedure, and its preparation was a struggle. Several conceivable approaches were examined, but failed to lead to viable solutions (Scheme 5). As an example, the oxidative cleavage of 1-*O*-methyl glycerol **8c** with sodium periodate furnished **8** in 46% yield.[16b]

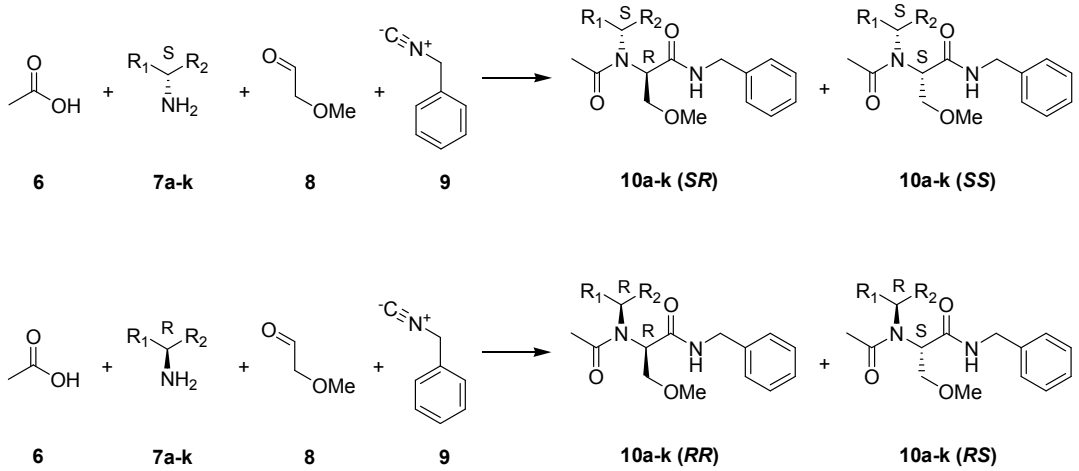


Scheme 5. Synthetic approaches towards methoxyacetaldehyde **8**.

Methoxyacetaldehyde dimethylacetal **8a** would appear to be an attractive starting material as it is commercially available on scale and would require only a simple acetal deprotection. However, the use of various acidic catalysts in aqueous medium for the deprotection, as described in the literature[17] resulted in complex reaction mixtures and a low yield of the desired product, presumably a result of acid catalyzed methyl ether cleavage[17]. Fortunately, the simple heating of the acetal in water[18] for 6-10 h leads to almost complete conversion obtaining the aldehyde as an approx. 2 M solution in water. This aqueous solution is stable, presumably in the form of its hydrate, for at least two years in the refrigerator. This route provided the first convenient and easy access to this interesting aldehyde building block.

With a viable access to the aldehyde and the isocyanide at hand, a systematic screen of commercially available chiral amines for reactivity and selectivity was performed. The resulting diastereomers were not separable by simple flash-chromatography; the use of chiral stationary phases was required in order to obtain preparative quantities of the respective diastereomers for assessment of their crystalline properties. The need to prepare a high purity drug requires

purification by crystallization and so a crystallization of the resulting diastereomers was attempted. The results are summarized in Table 1.



Scheme 6. Possible diastereomers obtained from a chiral amine in the presented Ugi reaction.

In line with observations from the literature,[11,12] the diastereoselectivity of the Ugi reaction is poor: approx. 3:2 for most chiral amines (Table 1), with some amines being slightly better (entry 11) or slightly worse (entry 10). There is a clear temperature dependence of the diastereoselectivity, improving to about 69:31 at -10 °C and eroding almost totally at 60 °C (entry 7 and 13). Having separated the diastereomers on a preparative scale, it was consistent that in the case of the amines **7** and **13** the minor (*R,R*) and (*S,S*) diastereomers were highly crystalline.

Table 1. Selectivity of Ugi reaction with various chiral amines. a: -10 °C, b: 60 °C.

Entry	Amine 7	R1	R2	10*SR*:10*SS*	10*RS*:10*RR*
1	(*S*)-1-Phenethylamine **7a**	Ph	Me	65:35	--
2	(*S*)-1-Phenpropylamine **7b**	Ph	Et	65:35	--
3	(*S*)-1-Naphtylethylamine **7c**	1-Naphthyl	Me	55:45	--
4	(*S*)-2-Naphtylethylamine **7d**	2-Naphthyl	Me	60:40	--
5	(*R*)-2-Methoxyphenethyl-amine **7e**	2-$MeOC_6H_4$	Me	--	60:40
6	(*S*)-4-Methoxyphenethyl-amine **7f**	4-$MeOC_6H_4$	Me	65:35	--
7	(*S*)-4-Methoxyphenethyl-amine **7f**	4-$MeOC_6H_4$	Me	69:31[a]	--
8	(*S*)-4-Nitrophenethyl-amine **7g**	4-$NO_2C_6H_4$	Me	65:35	--
9	(*S*)-1-Aminoindane **7h**	1-Indanyl		55:45	--
10	(*S*)-1-Aminotetraline **7i**	1-Tetralinyl		50:50	--
11	(*S*)-1-Phenyl-2-cyanoethyl-amine **7j**	Ph	CH_2CN	70:30	--
12	(*R*)-4-Methoxyphenethyl-amine **7k**	4-$MeOC_6H_4$	Me	--	65:35
13	(*R*)-4-Methoxyphenethyl-amine **7k**	4-$MeOC_6H_4$	Me	--	55:45[b]

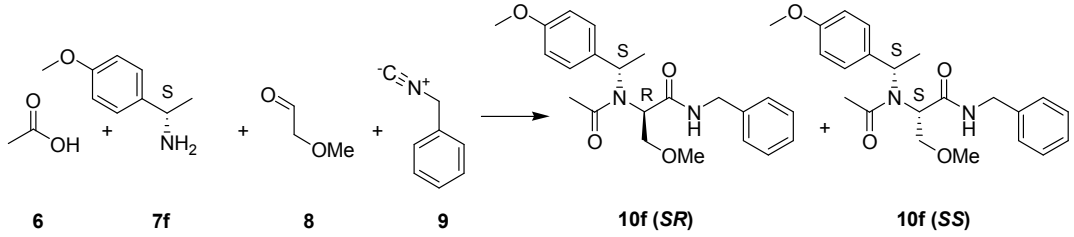
Given these data, it is clear that the choice of chiral amine directing group will be dictated by commercial availability of the amine and by the ease of the final deprotection. Attempted

hydrogenolytic deprotection of either 1- or 2-naphthylethylamine (**10c,d-*SR***) could not be accomplished despite screening several reaction conditions and Pd/C catalysts. In line with expectations, the use of the commercially available phenethylamine (**10a-*SR***) failed to be amenable to hydrogenolytic deprotection.

The application of the amine **7j** in Ugi reactions (entry 11) should be explained. To the best of our knowledge, amines with an electron-withdrawing group in beta-position have unique properties, which was recognized by Ugi in a seminal publication in 1964, as a deprotection of **10j** is possible under basic conditions by elimination.[19] Only one reference to this highly attractive chiral ammonia equivalent was found: Ugi examined the reaction, albeit with racemic material only, and subsequently, this chiral ammonia equivalent does not appear to have found any application in diastereoselective Ugi reactions. While the obtained diastereoselectivities are in the expected 2:1 range, the facile and efficient subsequent deprotection under basic (THF, KOtBu) conditions is a very useful addition to the repertoire of chiral directing groups. This is even more valuable as the amine **7j** is commercially available – at least on small scale – thus significantly extending the scope of synthetic opportunities afforded by the Ugi condensation. It should be noted that attempts to achieve similar results with derivatives of the cheaply available aspartic acid failed to give satisfactory results in the Ugi condensation, so that the work then focused on other available amines.

These results led to the choice of (*S*)-4-methoxyphenethylamine **7f**, a chiral ammonia equivalent that is commercially available in both enantiomeric forms on scale and that is removed under mild acidic conditions (*vide infra*).[20] According to entry 6 and 7 (Table 1), the diastereoselectivity is approx. 65:35 and almost 70:30 under optimized conditions in favor of the desired (*S,R*)-diastereomer. Consequently, the chemistry was developed using (*S*)-4-

methoxyphenethylamine and the strategy on how to utilize the properties of the product to circumvent the poor diastereoselectivity of the Ugi reaction will be described next (scheme 7).



Scheme 7. Ugi reaction employing (*S*)-4-methoxyphenethylamine.

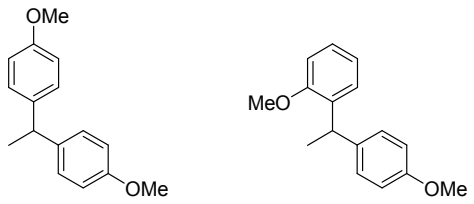
For the optimized Ugi condensation, an approx. 33% by weight solution of 4-methoxy phenethylamine **7f** (1.03 equiv) was neutralized in an exothermic reaction in EtOH with AcOH (1.07 equiv). After cooling to about 5 °C, the suspension was added to a concentrated benzyl isocyanide **9** solution in 1 volume of toluene (1.0 equiv) at 10 °C, followed by the final addition of the methoxyacetaldehyde **8** solution (1.1 equiv) at -10 °C. By using this order of addition it is possible to remove the heat of reaction resulting from the reaction of the carboxylic acid and the amine, before adding the isocyanide and the aldehyde, thus making it possible to conveniently perform the reaction at low temperature on scale. In order to assure the better stereocontrol and a complete reaction of the isocyanide (minimization of the associated pungent odor), the reaction was left first for 2 h at -10 °C, then for 2 h at 0 °C and was then reacted for about 18 h at ambient temperature, even though the reaction is essentially complete after 1 h stirring at room temperature.

The resulting reaction mixture contained **10f-(*SR*)** and **10f-(*SS*)** in a combined assay yield of about 95% in a diastereomeric ratio of 69 to 31. Gratifyingly, the amount of isocyanide in the reaction mixture – and thus the pungent smell – was reduced to a level that allows normal manipulation of the reaction mixture. As mentioned above, the (*S,S*)-diastereomer is a highly

crystalline compound that crystallizes directly from the reaction mixture after removal of solvent and replacement by a defined EtOH/water mixture. After filtering off the (*S,S*)-diastereomer in high purity, the diasteromeric ratio of the mother liquor was increased to 92:8. The mother liquor was concentrated and the crude product was obtained after a standard aqueous work-up and a solvent switch to isopropyl acetate (IPAC). It was possible to crystallize the desired (*S,R*)-diastereomer from IPAC/MCH (methylcyclohexane) and **10f-(*SR*)** was obtained in 34% yield (based on isocyanide) with a satisfactory diastereomeric purity of >99.7%. After concentrating the resulting mother liquor, a second crop of desired (*S,R*)-diastereomer contaminated with about 20% of the (*S,S*)-diastereomer was obtained. Combining several batches of the second crop and repeating the sequence of removal of the undesired (*S,S*)-diastereomer followed by the crystallization of the desired diastereomer from IPAC resulted in a 52 to 55% yield from isocyanide **9** of **10f-(*SR*)** diastereomer with excellent chemical and diastereromeric purity as a white crystalline product.

The high crystallinity of one of the diastereomers could enable a crystallization-driven asymmetric transformation and thus a, in theory, quantitative yield of the desired diastereomer, if the chiral center of the amino acid could be epimerized. While this would appear to be quite easy, in reality all attempts to achieve an epimerization of this chiral center in **10** using a plethora of reaction conditions failed. Forcing conditions led to decomposition, presumably by elimination of methanol and the subsequent degradation of the resulting acrylate system. As this decomposition mode is specific to this compound, substrates lacking the leaving group are likely to function successfully in a crystallization-driven asymmetric transformation, thus expanding the utility of the Ugi reaction.

Having established an efficient access to the required diastereomer in crystalline form in a gratifying 52-55% overall yield from isocyanide **9**, the subsequent removal of the chiral directing group remained the outstanding challenge. A screen of various acidic and hydrogenolytic conditions quickly revealed that the use of formic acid resulted in a rapid and clean deprotection at 80 °C, with the formation of a fairly nonpolar and undefined oligomer resulting from the polymerization of the intermediate 4-methoxybenzyl cation. While the removal of this by-product was readily achieved by extractions with toluene or MCH, a better-defined product from the deprotection was clearly preferable considering that the drug substance stage had been reached. To this end, the deprotection was performed in the presence of anisole, which generated cleanly and in quantitative yield the corresponding mixture of para and ortho bis-4-methoxyphenyl ethane isomers **15** and **16** (Figure 2).[21]



15 **16**

Figure 2. Para and ortho bis-4-methoxyphenyl ethane isomers.

These nonpolar side products could be readily removed by extraction using MCH. After removal of the bulk of the formic acid by distillation, the remaining formic acid was neutralized by the addition of an aqueous solution of trisodium citrate. Lacosamide **1** is extracted into isopropyl acetate and crystallized from the same solvent resulting in 82% yield, >99.9% purity and 99.9% *ee*.

CONCLUSIONS

In summary, an Ugi four component condensation approach was utilized to synthesize lacosamide **1** in an overall yield of 40% starting from benzylamine **11**. The resulting API met the required quality specification. The synthesis is scalable; a less developed version of the Ugi reaction described here has been used to prepare 50 kg of in-specification lacosamide. The preparation method of isocyanide **9** and the optimization of the Ugi condensation using an easily-removable and inexpensive chiral auxiliary holds promise for applications beyond lacosamide.

EXPERIMENTAL SECTION

Methoxyacetaldehyde 8. A mixture of 100 mL (93 g, 0.77 mol) methoxyacetaldehyde dimethylacetal **8a** and 280 ml (15.5 mol) of water was refluxed for 8 h under argon atmosphere. The reaction was followed by GC and the response factor was 3:2 for an equimolar acetal/aldehyde mixture (Agilent HP-5MS, 30 m x 0.25 mm x 0.25 µm, 50 °C/3 min – 30 °C/min to 290 °C – 290 °C/5 min, FID, Rt acetal **8a**: 4.85 min, aldehyde **8**: 2.86 min). At the end of the reflux, about 5-10 area % of the acetal remained, but are inconsequential for the subsequent reaction. The mixture was cooled to 20 °C and methoxyacetaldehyde **8** was used directly or stored in a refrigerator or freezer. GC: R_t = 2.86 min.

For a further characterization, 10 mL of this solution were extracted with 3 x 10 mL dichloromethane. The combined organic layers were dried with $MgSO_4$ and carefully concentrated (40 °C, 250 mbar) yielding about 1 g of crude methoxyacetaldehyde **8** with some DCM and MeOH. 1H-NMR ($CDCl_3$, 400 MHz): 3.47 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 9.73 (s, CHO).

Benzyl isocyanide 9. Ethyl formate (192 g, 2.60 mol, 1.3 equiv) was heated to 50 °C and benzylamine **11** (214 g, 2.00 mol, 1.0 equiv) was added over 30 min. After completion of the addition, the mixture was refluxed for 10 h resulting in an almost complete consumption of the benzylamine (<1 area %) The resulting solution of **12** (>98 area %) was solvent-switched into toluene by twice distilling off 150 mL toluene (50 °C, 65 mbar). Additional toluene (270 mL) and pyridine (160 g) were added at 50 °C to result in an about 40 wt % solution of **12** that could be cooled to 17 °C without precipitating product. HPLC (Merck Chromolith Performance RP18e, A. H_2O/0.05% TFA, B: MeCN/0.05% TFA, 10->70% B 10 min, 4 mL/min, 40 °C): R_t = 1.28 min.

An additional 120 mL toluene and 77 g pyridine (4.3 equiv pyridine) were added to the solution of **12** (97 g, 290 mmol, 1.0 equiv) before the subsequent addition of mesyl chloride (70.7 g, 617 mmol, 2.1 equiv) over 10 min (temperature below 40 °C). After stirring for 1 h at 35-40 °C the mixture was cooled to 0-5 °C and water (200 mL) was added while maintaining the temperature below 20 °C. After stirring for 1 h at 0 °C the phases were separated and the organic layer was washed with 70 mL water (residues of isocyanide in the aqueous layer were decomposed by 10% v/v conc. sulfuric acid, 30 min at rt). The content of isocyanide **9** in the light brown organic layer was analyzed by GC (81% toluene, 17% isocyanide about 32 g, 0.27 mol 93-94% yield of isocyanide). The organic layer was distilled at 35 °C/60 mbar to a total volume of about 60 mL yielding an approx. 50 vol % solution of **9** in toluene (the distilled toluene fraction was treated with 0.3 volume *i*PrOH containing 30% of a 40% H_2SO_4 to destroy the isocyanide odor). GC: (Agilent HP-5MS, 30 m x 0.25 mm x 0.25 µm, 50 °C/3 min – 30 °C/min to 290 °C – 290 °C/5 min, FID) R_t = 8.80 min.

(*R*)-2-{Acetyl-[(*S*)-1-(4-methoxy-phenyl)-ethyl]-amino}-*N*-benzyl-3-methoxy-propionamide 10f-(*SR*). To a solution of (*S*)-1-(4-Methoxy-phenyl) ethylamine **7f** (43.0 g, 284 mmol, 1.0 equiv) in EtOH (110 mL) and H_2O (20 mL) was added AcOH **6** (17.4 g, 290 mmol, 1.02 equiv) over 30 min maintaining the temperature at 15 °C. The resulting suspension was transferred to the 0 °C isocyanide/toluene (about 270 mmol, 0.95 equiv) solution with a 20 mL EtOH rinse. While maintaining the temperature at -10 °C, the aqueous methoxyacetaldehyde **8** (162 mL, ~1.85 M, ~300 mmol, 1.06 equiv) solution was slowly added to the 3-component mixture. After 2 h at -10 °C the mixture was stirred for 2 h at 0 °C and then for 18 h at 20 °C, at which point the residual **9** was below 0.1 area %. The minor (*S,S*)-diastereomer was removed by a solvent switch from toluene/EtOH/water to 250 mL of EtOH/water 3:2. After filtration and wash of the filter cake with cold 100 mL of EtOH/water 1:1, 23 g of **10f-(*SS*)** were obtained in 99.7% purity. The resulting mother liquors were enriched in the desired diastereomer **10f-(*SR*)** (90:10). After distillative removal of the EtOH and addition of 400 mL IPAC, the organic phase was washed successively with 90 mL 1 M $NaHSO_4$ and 50 mL water. The solution was concentrated to about 300 mL and addition of about 85 mL of MCH precipitated the desired diastereomer **10f-(*SR*)** which was obtained after filtration and wash of the filter cake with cold 40 mL of MCH/IPAC 1:1 (32 g, 84 mmol, 31% yield based on isocyanide, 99.8% purity).

The mother liquor (approx. 450 mL containing about 45 g of **10f-(*SS*)** and **10f-(*SR*)** with about 20:80 was concentrated to approx. 350 mL and addition of 100 mL of MCH precipitated a second crop (27.4 g) with high purity as a mixture of diastereomers with a ratio of 17:83 (*S,S*):(*S,R*).

Several batches of second crops were combined to obtain further additional product: the resulting 98.5 g were dissolved in 300 mL of IPAC at reflux. On cooling to 50 °C, the undesired

(*S,S*)-diastereomer precipitated after seeding and was removed by filtration (14 g). Further concentration of the mother liquor to 240 mL and seeding resulted in the precipitation of 34.6 g of **10f-(*SR*)** in comparable purity (>99.5 %). The cycle was repeated several times so that the yield of the (*S,R*)-diastereomer was approx. 52-55% (based on isocyanide).

Major diastereomer **10f-(*S,R*)**: Mp.: 82 °C (IPAC/MCH); chiral HPLC (Chiralpak AD-H/120 (250x4.6 mm), Heptane:EtOH:MeOH 2:1:1 +0.1% TFA, 30 °C, 1 mL/min): R_t = 5.96 min; HPLC (Merck Chromolith Performance RP18e, A. H_2O/0.05% TFA, B: MeCN/0.05% TFA, 10->70% B 10 min, 4 mL/min, 40 °C): R_t = 3.65 min; NMR (250 MHz, 390 K): 1.55 (d, 3H, CH_3), 2.07 (s, 3H, Ac), 3.03 (s, 3H, OMe), 3.28 (dd, 1H, CH or CH_2OMe), 3.79 (s, 3H, OMe), 3.92-410 (m, 2H, CH or CH_2-OMe), 4.28 -4.46 (m, 2H, CH_2Ph), 5.18 (q, 1H, ArCH), 6.88-6.96 (m, 2H, Ar-H), 7.20-7.38 (m, 7H, Ar-H), 7.71 (bs, 1H, NH); LC-MS: MH+ 385 (250, 135).

Minor diastereomer **10f-(*S,S*)**: Mp.: 128 °C (EtOH/water); chiral HPLC (*vide supra*): R_t = 5.73 min; HPLC (*vide supra*): R_t = 3.53 min; NMR (250 MHz, 390 K): 1.62 (d, 3H, CH_3), 2.06 (s, 3H, Ac), 3.32 (s, 3H, OMe), 3.73 (dd, 1H, CH or CH_2-OMe), 3.94 (dd, 1H, CH or CH_2OMe), 4.12-4.25 (m, 3H, CH, CH_2Ph), 5.27 (q, 1H, CH), 7.07-7.44 (m, 10H, Ar-H); LC-MS: MH+ 385.

(*R*)-Lacosamide 1. (*S,R*)-diasteromer **10f** (50 g, 0.13 mol, 1.0 equiv) was dissolved in 50 mL anisole and formic acid (95 mL, 16 equiv, 85% solution) was added. The mixture was heated one hour at 82 °C. After cooling to 25 °C, water (100 mL) was added and the mixture was extracted twice with 100 mL MCH. To remove the formic acid, the aqueous layer was first concentrated under reduced pressure (60 mbar, 45 °C), before adding an additional 100 mL water and repeating the concentration. After addition of IPAC (160 mL), the bi-phasic mixture was heated to 40 °C and the pH was adjusted to 4 using an aqueous trisodium citrate solution (400g/L). The

phases were separated, the aqueous layer was extracted twice with 100 mL IPAC and the combined organic layers were washed with 10 mL water. The organic phase was concentrated to approx. 300 mL, at which point seeding resulted in crystallization of **1** (27 g, 0.11 mol, 83%, >99.9% purity, >99.9% *ee*) as colorless crystals. Mp.: 146 °C (IPAC); chiral HPLC (Chiralpak AD-H/91 (250x4.6 mm), EtOH, 30 °C, 1 mL/min): R_t = 13.7 min; HPLC (Merck Chromolith Performance RP18e, A. H_2O/0.05% TFA, B: MeCN/0.05% TFA, 10->70% B 10 min, 4 mL/min, 40 °C): R_t = 1.15 min; NMR (500 MHz, 300 K): 1.87 (s, 3H, Ac), 3.25 (s, 3H, OMe), 3.49 (dd, 1H, CH_2OMe), 3.53 (dd, 1H, CH_2OMe), 4.29 (d, 2H, CH_2Ph), 4.46-4.53 (m, 1H, CH), 72.20-7.35 (m, 5H, Ar-H), 8.09 (d, 1H, NH), 8.49 (t, 1H, NH); LC-MS: MH+ 251.

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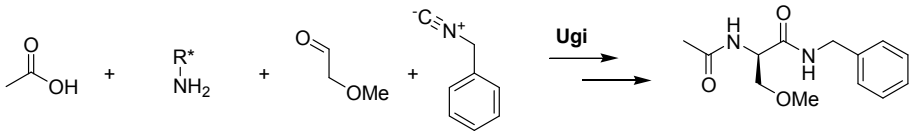

LACOSAMIDE