Organic Letters
Letter
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Modular Two-Step Approach for the Stereodivergent Synthesis of 1,3-Diamines with Three Continuous Stereocenters

Juliette Halli, Michael Bolte, Jan Bats, and Georg Manolikakes*

Department of Biochemistry, Chemistry and Pharmacy, Goethe-University, Max-von-Laue-Strasse 7, 60438 Frankfurt, Germany

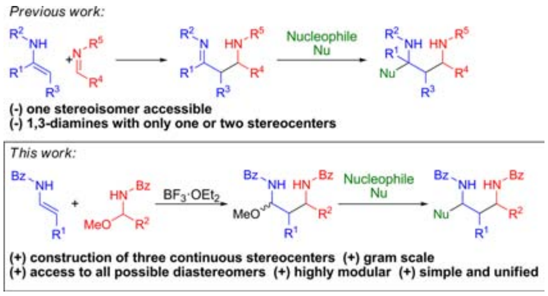
S *Supporting Information*

ABSTRACT: A two-step reaction sequence for the highly stereodivergent construction of 1,3-diamines with three continuous stereocenters is reported. This novel method enables the controlled synthesis of any given diastereomer of the 1,3-diamine scaffold from a simple set of starting materials in a highly modular manner. The disclosed approach is based on the reaction of an enamide with an in situ generated *N*-acylimine followed by a subsequent trapping of the generated intermediate with a suitable nucleophile. By careful choice of starting materials, reagents, and reaction conditions, each stereocenter can be constructed in a highly selective fashion.

The 1,3-diamine scaffold is an important structural feature in natural products, biologically active compounds, or chiral ligands. This motif can be found as backbone of the manzacidins,[1] a family of marine alkaloids, the phytotoxin ascaulitoxin,[2] and a whole class of HIV-protease inhibitors,[3] such as nelfinavir, saquinavir, or amprenavir.

The synthesis of such molecules, containing multiple, continuous stereocenters, represents a formidable challenge for synthetic organic chemists.[4] Contrary to the synthesis of 1,2-diamines,[5] only a few direct approaches for the stereoselective synthesis of 1,3-diamines[6] have been reported so far. Risch and co-workers developed a reaction sequence based on the aminoalkylation of enamines with iminium salts followed by reduction of the newly formed imine (Scheme 1).[7] Later, several groups reported similar transformations based on this imine−enamine−imine sequence.[8] Although these methods enable an efficient and stereoselective synthesis of 1,3-diamines, they only provide access to 1,3-diamines with one or two stereogenic centers and more importantly to only one stereoisomer. In general, the construction of a complete set of all possible stereoisomers of any given structure represents a formidable challenge and an important synthetic problem. Access to all stereoisomers is mandatory for the evaluation of new active pharmaceutical ingredients.[9] However, efficient and predictable methods to prepare all stereoisomers of a given target molecule bearing multiple stereogenic centers from readily available precursors are rare but would be highly desirable.[10] Herein, we disclose a two-step reaction sequence that enables the controlled and highly selective synthesis of all four possible diastereomers of 1,3-diamines with three continuous stereocenters from a simple set of starting materials.

Scheme 1. Enamide/Acylimine-Based Routes to 1,3-Diamines



Our approach is based on the reaction of an enamide[11a] with an in situ formed *N*-acylimine followed by trapping of the formed intermediate imine species with a terminal nucleophile (Scheme 1, this work). *N*-Acyl-*N*,*O*-acetals (**1**)[11b,12] were chosen as readily available and stable precursors for highly electrophilic *N*-acylimines. We began our studies by examining the controlled construction of the second stereocenter. We speculated that the relative configuration of the first two stereocenters C1 and C2 can be controlled by the configuration of the enamide.[8] Indeed, reaction of *N*-acylimine precursor **1a** with (*E*)-enamide **2a** in the presence of stoichiometric amounts of $BF_3{\cdot}OEt_2$ as Lewis acid and subsequent trapping with L-Selectride ($LiBH(sBu)_3$) furnished 1,2-*anti*-diamine **3a** in 97% yield as a single diastereomer (Scheme 2).[13]

The same reaction sequence with the (*Z*)-enamide **2b** delivered the corresponding 1,2-*syn*-diastereomer **3b** in similar high yield and excellent stereoselectivity. Reaction of (*E*)-enamide **2a** and *N*-acylimine precursor **1a** in the presence of $BF_3{\cdot}OEt_2$ without subsequent reduction delivered *N*,*O*-acetal **4a** as a

Received: December 23, 2016
Published: January 18, 2017

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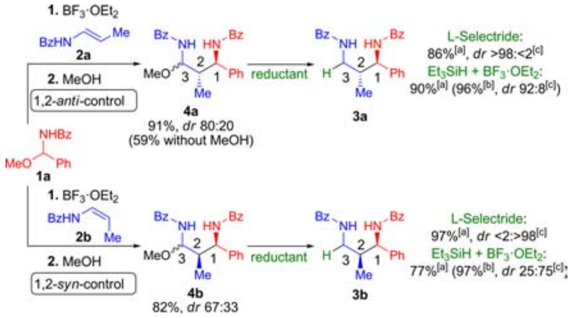
DOI: 10.1021/acs.orglett.6b03841

Scheme 2. Stereoselective One-Pot Synthesis of 1,3-Diamines 3a and 3b[a]

[a]Isolated yield of major diastereomer. [b]Ratio of **3a**:**3b**. The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture. In all cases, diastereomeric ratios in the same range were found in the isolated products. Bz = benzoyl.

Scheme 3. Two-Step Synthesis of 1,3-Diamines 3a and 3b with Formation of *N*-Acylimine Precursors 4a and 4b[a]

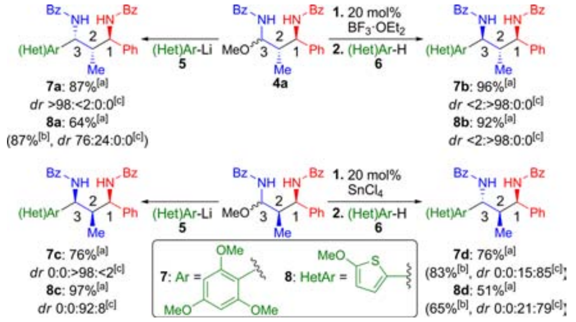


[a]Isolated yield of major diastereomer. [b]Values in parentheses represent the overall isolated yield of all diastereomers. [c]Ratio of **3a**:**3b**. The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture. In all cases, diastereomeric ratios in the same range were found in the isolated products. Bz = benzoyl.

stable solid in 59% yield and a diastereomeric ratio (dr) of 80:20 (Scheme 3). Addition of excess MeOH before workup led to an increased yield of 91%. After treatment of the newly formed *N*-acylimine precursor **4a** with L-Selectride, 1,2-*anti*-diamine **3a** was obtained in 86% yield as single stereoisomer.[14] These results indicate that an *N*,*O*-acetal of type **4** might serve as resting state for a more reactive *N*-acylimine species. In a similar manner, the reaction of **1a** with (*Z*)-enamide **2b** furnished **4b** in 82% yield and with a diastereomeric ratio (dr) of 67:33.

Reduction of **4b** with L-Selectride led to the formation of 1,2-*syn*-diamine **3b** in 97% yield and excellent stereoselectivity. Interestingly, reactions with weak nucleophiles in the presence of stoichiometric amounts of Lewis acids, for example, Et_3SiH with 2.0 equiv of $BF_3·OEt_2$, furnished the desired 1,3-diamines with lower stereoselectivities. For the reduction of **4a**, the selectivity was still very high (dr 92:8, **3a**/**3b**), but in the case of **4b** the selectivity dropped to 25:75 (**3a**/**3b**). These results show that the relative configuration of C1 and C2 can indeed be controlled by the enamide configuration. An (*E*)-configuration leads to the formation of the 1,2-*anti*-product, whereas the (*Z*)-enamide delivers the 1,2-*syn*-product. However, in the case of strong Lewis acids and weak nucleophiles, a subsequent isomerization can take place.[12] Since the products of type **4** proved to be stable and storable solids and are accessible in gram quantities, they were used for all further investigations. With ample amounts of **4a** and **4b** in hand, we embarked on the major challenge, the controlled synthesis of the last stereocenter at C3. As nucleophiles for our initial studies we chose electron-rich (hetero)arenes, such as 1,3,5-trimethoxybenzene (**6a**) or 2-methoxythiophene (**6b**) (Scheme 4).

Scheme 4. Stereoselective Synthesis of 1,3-Diamines 7 and 8[a]

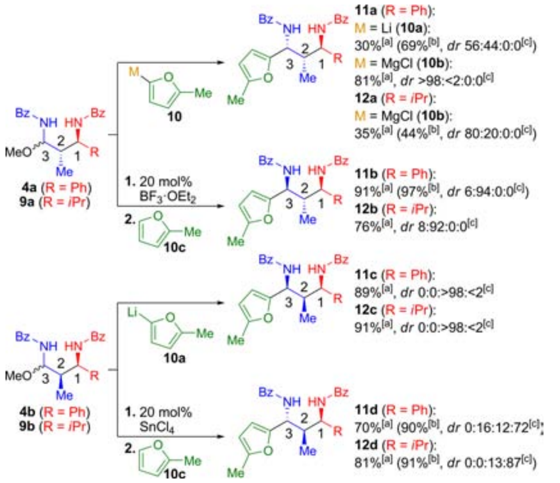


[a]Isolated yield of major diastereomer. [b]Values in parentheses represent the overall isolated yield of all diastereomers. [c]Ratio of **7a**:**7b**:**7c**:**7d**, respectively **8a**:**8b**:**8c**:**8d**. The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture. In all cases, diastereomeric ratios in the same range were found in the isolated products. Bz = benzoyl.

After extensive experimentation, we found that by careful choice of reagent and reaction conditions a controlled construction of the last stereocenter is indeed possible. Reaction of the 1,2-*anti*-intermediate **4a** with 1,3,5-trimethoxybenzene (**6a**) in the presence of 20 mol % of $BF_3·OEt_2$ furnished the 1,2-*anti*-2,3-*anti*-diamine **7b** in 96% as a single diastereomer. Treatment of **4a** with (2,4,6-trimethoxyphenyl)lithium (**5a**) delivered 1,2-*anti*-2,3-*syn*-diamine **7a** in 87% yield and excellent diastereoselectivity. In a similar manner, reaction of the 1,2-*syn*-intermediate **4b** with **5a** afforded the 1,2-*syn*-2,3-*syn*-diamine **7c** in 76% yield as single diastereomer. In the presence of catalytic amounts of $SnCl_4$ as Lewis acid, **4b** reacted with 1,3,5-trimethoxybenzene (**6a**) to give 1,2-*syn*-2,3-*anti*-diamine **7d** in 76% yield together with minor amounts of **7c** as side product. The reactions of **4a** and **4b** with 2-methoxythiophene-based nucleophiles proceed with comparable efficiency and stereoselectivities.[15] Treatment of the *N*,*O*-acetals **4a** and **4b** with (5-methoxythiophene-2-yl)lithium (**5b**) afforded the 2,3-*syn*-products **8a** and **8c**, whereas the reactions with 2-methoxythiophene (**6b**) in the presence of Lewis acids led to the formation of the 2,3-*anti*-products **8b** and **8d**. In all cases, high yields and stereoselectivities were obtained. These results show that the third stereocenter can be constructed in a divergent manner. A high degree of stereocontrol can be achieved by the appropriate choice of reagents and conditions. Reactions under (Lewis) acidic conditions deliver the 2,3-*anti*-product, while reactions with basic organometallic nucleophiles (basic conditions) furnish the 2,3-*syn*-products.

Next, we investigated the reactions of *N*,*O*-acetals **4a** and **4b** with 2-methylfuran-based nucleophiles (Scheme 5). Treatment of **4a** with 2-methylfuran (**10c**) in the presence of a Lewis acid and the reaction of **4b** with (5-methylfuran-2-yl)lithium (**10a**) proceeded as expected and furnished the desired 2,3-*anti*- and 2,3-*syn*-diamines **11b** and **11c** in high yields and essentially diastereomerically pure form. In the case of the Lewis acid catalyzed reaction of **4b** with 2-methylfuran (**10c**), the 2,3-*anti* product **11d** was isolated in 70% yield together with minor amounts of the 2,3-*syn*-product **11c** and the 1,2-*anti*-2,3-*anti*-diamine **11b**, presumably formed via the above-mentioned Lewis acid induced isomerization of intermediate **4b** (see Scheme 3). Interestingly, the reaction of **4a** with (5-methylfuran-2-yl)lithium (**10a**) proved to be completely unselective, furnishing an almost equimolar mixture of the 2,3-*syn*- and the 2,3-*anti*-1,3-diamines

Scheme 5. Controlled Synthesis of All Four Diastereomers of 1,3-Diamines 11 and 12[a]



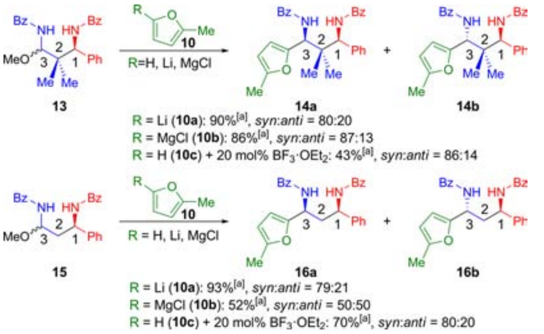
[a]Isolated yield of major diastereomer. [b]Values in parentheses represent the overall isolated yield of all diastereomers. [c]Ratio of **11a**:**11b**:**11c**:**11d**, respectively **12a**:**12b**:**12c**:**12d**. The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture. In all cases, diastereomeric ratios in the same range were found in the isolated products. For the synthesis of *N*,*O*-acetals **9a** and **9b**, see the Supporting Information. Bz = benzoyl.

11a and **11b**. However, if the corresponding magnesium reagent **10b** was used, the desired 2,3-*syn*-1,3-diamine **11a** was obtained in 81% yield and excellent diastereoselectivity. All transformations with the isobutyraldehyde-derived intermediates **9a** and **9b** proceeded as expected.[15] Reaction of 1,2-*anti*-intermediate **9a** with (5-methylfuran-2-yl)magnesium chloride (**10b**) afforded selectively the 1,2-*anti*-2,3-*syn*-1,3-diamine **12a**, albeit in a low yield of 35%. In the presence of a Lewis acid and 2-methylfuran (**10c**), the corresponding 2,3-*anti* derivative **12b** was obtained in 76% yield. In a similar manner 1,2-*syn*-intermediate **9b** could be transformed with high selectivity to either the 2,3-*syn* product **12c** using the organolithium-based nucleophile **10a** or the 2,3-*anti*-product **12d** under Lewis acidic reaction conditions.

As shown, our new method provides a modular route toward the complete tetrad of the 1,3-diamine scaffold. In all examples, the formation of the third stereocenter was controlled only by the second stereocenter (1,2-stereoinduction) and the combination of reagent and reaction conditions. No influence of the first stereocenter C1 (1,3-stereoinduction) was observed, at least at first glance. In most cases, the desired diastereomers were formed almost stereochemically pure, but in some cases, considerable amounts of undesired isomers were formed. In order to investigate any potential 1,3-stereoinduction and the influence on the outcome of the reactions, the two *N*,*O*-acetals **13** and **15**, bearing an achiral center at carbon C2, were synthesized (Scheme 6).[15] Interestingly, the reaction of intermediate **13** with 2-methylfuran-based nucleophiles furnished the 1,3-*syn*-diastereomer **14a** as a major product under acidic as well as basic reaction conditions.

These results indicate a substrate-specific 1,3-*syn*-induction, irrespective of the applied reagents and conditions. In addition, the treatment of *N*,*O*-acetal **15** with 2-methylfuran (**10c**) and a Lewis acid or with 2-methylfuryllithium (**10a**) afforded the 1,3-*syn*-diastereomer **16a** as the major product. However, reaction of **15** with the corresponding magnesiated 2-methylfuran (**10b**) led to the formation of an equimolar mixture of the 1,3-*syn*- and the 1,3-*anti*-products **16a** and **16b**. These results show that it is possible to modulate the substrate-induced 1,3-*syn*-control and might offer an explanation why reactions with organomagnesium reagents can lead to higher selectivities.

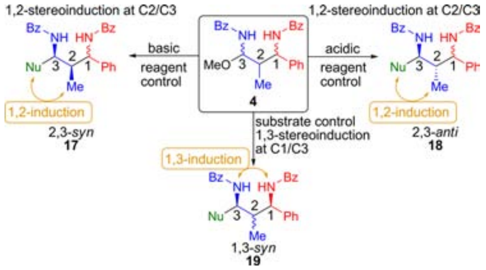
Scheme 6. Investigations on Potential 1,3-Stereoinductions[a]



[a]Isolated yield of both diastereomers. The diastereomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture. in all cases, diastereomeric ratios in the same range were found in the isolated products. For the synthesis of *N*,*O*-acetals **13** and **15**, see the Supporting Information. Bz = benzoyl.

Based on these findings, we can deduce some general rules for the observed stereoselectivities (Scheme 7).[16] Reactions under (Lewis) acidic conditions lead to the selective formation of the 2,3-*anti*-product, whereas under basic conditions the 2,3-*syn*-product is formed preferentially. At the same time, the *N*,*O*-acetal **4** itself exhibits a substrate specific 1,3-*syn*-stereoinduction, unaffected by the reagent and the reaction conditions. In all cases, the 1,2-induction seems to be dominant. A closer look at the shown examples (Schemes 4–6) reveals an interesting fact.

Scheme 7. General Rules for the Observed Stereoselectivities



In all transformations where reagent and substrate control will lead to the same stereoisomer (stereoreinforcing or "matched" case), excellent selectivities are observed. On the other hand, when 1,2- and 1,3-induction should lead to two different stereoisomers (nonstereoreinforcing or "mismatched" case), lower selectivities are obtained. For most examples, the 1,2-induction predominates and the desired diastereomers are formed with high selectivity (dr ≥ 75:25). In addition, it seems to be possible to decrease the influence of the 1,3-*syn*-induction by modulation of the reaction conditions. So far, we do not have a conclusive mechanistic rational which could explain all these facts.[16] It is obvious that two distinct reaction pathways should be operative under acidic or basic reaction conditions. However, by following these two simple set of rules, (i) (*E*)-enamide for 1,2-*anti* and (*Z*)-enamide for 1,2-*syn* and (ii) acidic conditions for 2,3-*anti* and basic conditions for 2,3-*syn*, an organic chemist can now plan and conduct the synthesis of any desired diastereomer of a 1,3-diamine.

In summary, we have developed a highly modular, stereoconvergent two-step enamide/acylimine-based approach for the synthesis of 1,3-diamines with three continuous stereocenters. Our procedure provides simple access to the complete tetrad of stereoisomers of a 1,3-diamine structure from a small set of readily available starting materials. The construction of the individual stereocenters can be controlled by the enamide configuration for the second stereocenter and a variation of the reaction conditions for the third stereocenter. Hence, our procedure provides a versatile platform for a unified and stereoconvergent preparation of synthetically challenging 1,3-diamines. Further investigations on the reaction mechanism, the use of chiral catalysts and other nucleophiles, as well as application in the synthesis of natural products are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03841.

Syntheses, NMR spectra, and X-ray crystal structures (PDF)

X-ray data for compounds **3b**, **7a**,**b**,**d**, **8a**,**c**,**d**, **11a**−**d**, **12a**−**d**, **14a**, and **16b** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g.manolikakes@chemie.uni-frankfurt.de.

ORCID

Georg Manolikakes: 0000-0002-4013-5757

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Fonds der Chemischen Industrie (Liebig fellowship to G.M.) and the Evonik Stiftung (Ph.D. fellowship to J.H.). We thank Prof. Michael Göbel (Frankfurt) for his support and Prof. Günter Helmchen (Heidelberg) for helpful discussions. We also thank Rockwood Lithium GmbH, Evonik Industries AG, and BASF SE for the generous donation of chemicals.

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(13) Relative configurations of all reported stereoisomers were unambiguously assigned via single-crystal X-ray-diffraction. CCDC files 1507284−1507300 contain the supplementary crystallographic data for this paper and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) The dr of **3a** is not dependent on the dr of **4a**.

(15) See the Supporting Information for experimental details.

(16) Models for merged 1,2- and 1,3-asymmetric inductions are very rare, e.g.: Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322 and fail in our case.