On a Chemoenzymatic Desymmetrization–Ring Expansion Strategy towards Functionalized N-Heterocycles

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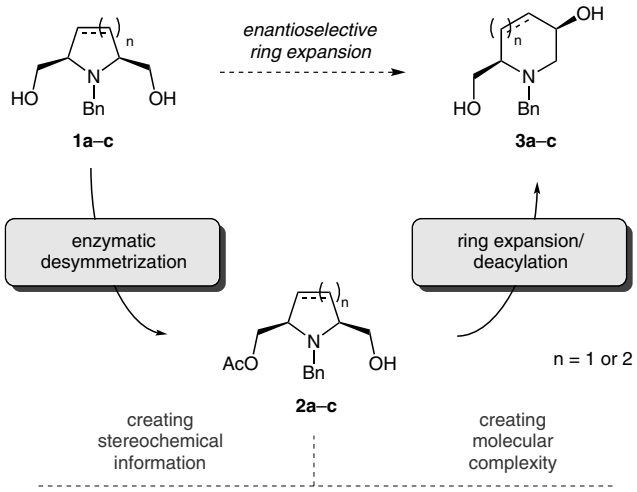
Abstract: The direct combination of the desymmetrization of N-heterocyclic *meso*-diols using lipase from *Mucor miehei* as biocatalyst and subsequent ring expansion of the optically active products by activation of the remaining hydroxy group gives rise to functionalized nonsymmetrical piperidines in a highly enantio- and diastereoselective manner.

Keywords: desymmetrization, biocatalysis, ring expansion, heterocycles, azasugars

Manipulations of hetero- and carbocyclic systems by means of either ring-expansion or ring-contraction reactions have gathered much attention over the past century, from the very early examples taking advantage of Beckmann-[1] or Faworsky-type[2] rearrangements, respectively, to modern transition-metal-catalyzed transformations such as ring rearrangement olefin metathesis.[3] From a synthetic point of view, the controlled alteration of ring sizes of cyclic compounds offers an elegant way to rapidly increase complexity of a given system and in some cases even allow for the preparation of otherwise troublesome medium-sized cyclic products.[4] In 1995, Cossy et al. presented a preparatively simple one-carbon ring-expansion procedure for the rearrangement of prolinols to give β-hydroxy piperidines with perfect transfer of chirality.[5] Upon treatment of the pyrrolidine-based amino alcohols with trifluoroacetic anhydride, reversible formation of aziridinium trifluoroacetates is proposed that are preferentially opened under thermodynamic control at the higher substituted position giving rise to ring-enlarged N-heterocycles. In succession, a number of variations have been developed that also allow for the stereocontrolled synthesis of 3-amino-, 3-azido-, and 3-fluoro-substituted piperidines based on this protocol.[6]

The enzymatic desymmetrization[7] of *meso*-dialcohols bearing N-heterocyclic core structures has been intensively studied and found numerous applications in the preparation of alkaloids and related synthetic motifs.[8] Offering a straightforward access to optically enriched pyrrolidine and piperidine building blocks in excellent enantiopurity, however, one limitation obviously lies in the remaining symmetric substructure of the desymmetrized products restricting their synthetic implementation to targets carrying this kind of subunits. We envisaged the aziridinium-mediated rearrangement of β-amino alcohols being a powerful tool for the preparation of nonsymmetrical N-heterocycles from symmetrical *meso*-diols. Thus, the initial step to create a nonracemic entity (**2a–c**) by enzymatic desymmetrization is ought to be directly combined with a subsequent ring-expansion reaction as second symmetry-breaking operation to substantially increase molecular complexity (Scheme 1). This proposed sequence would offer a very expeditious route towards entirely unsymmetric and highly functionalized N-heterocycles **3a–c** with excellent control of both enantio- and diastereomeric purity.



Scheme 1 Formal enantioselective ring expansion

Although being a well-studied transformation for the preparation of carbamate-protected N-heterocycles, there was no literature precedence describing lipase-catalyzed desymmetrizations of alkyl-protected N-heterocyclic *meso*-diols.[9] With the requirement of a nucleophilic nitrogen center for the subsequent ring expansion we started a thorough investigation on the lipase-mediated enantioselective transesterification of three different benzylamine-containing diols. With the piperidine-based diol **1a** as model substrate, a series of lipases were tested with regard to reactivity and enantioselectivity employing vinyl acetate as acyl donor in toluene at 35 °C.[10] Both lipases from *C. antarctica* suffered from low selectivity as indicated by the formation of undesired diacetate **4a** and only minor enantiomeric excess of **2a** (Table 1, entries 1 and 2). Good enantiomeric purity of **2a** was achieved by means of lipases from *C. rugosa*, *T. lanuginosa*, *P. cepacia*, and porcine

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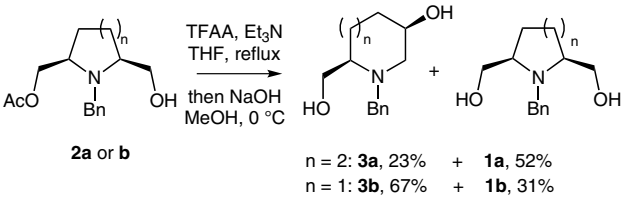
pancreas (Table 1, entries 3–6). However, best results were obtained employing either *P. fluorescens* lipase or *M. miehei* lipase with almost quantitative conversion into monoacetate **2a** in perfect optical purity (Table 1, entries 7 and 8). Changing from piperidine **1a** to pyrrolidine **1b**, the selectivity of all tested enzyme catalysts dropped more or less severely as exemplified for TLL, PCL, and PFL (Table 1, entries 9–11). Only lipase from *Mucor miehei* maintained synthetically useful enantiotopic differentiation and to the expense of a certain overacylation (21% diacetate **4b**) enantiomerically pure **2b** could be isolated in 74% yield (Table 1, entry 12). The same selectivity loss occurred in the desymmetrization of pyrrolin **1c** (Table 1, entries 13–15) and again, MML proved to be the catalyst of choice giving rise to the desired monoacetate **2c** in 67% yield and 95% enantiomeric excess.

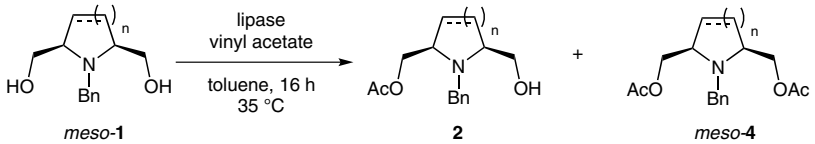
With a generally applicable method for the highly enantioselective synthesis of the cyclic benzylamines **1a**–**c** in hand we started our studies on the ring-expanding nucleophilic substitution reactions. First, we chose Cossy's original protocol exploiting the reversible aziridinium formation of initially generated trifluoroacetates under elevated temperature.[5d] To facilitate analysis, the reaction mixtures were saponified prior to isolation yielding ring-expanded diols **3a**,**b** alongside with the *meso*-diols **1a**,**b** (Scheme 2). Under thermodynamic control, the ring expansion from piperidine **2a** to azepane **3a** proceeded sluggishly resulting in the isolation of *meso*-**1a** as major product in 52% yield together with the desired azepane **3a** in only 23% yield after two days. Substantially higher regioselectivity towards the desired product was observed for the saturated five-membered heterocycle **2b** with a ratio of 2:1 in favor of the expanded product **3b** and an isolated yield of 67%.[11,12]



Scheme 2 Trifluoroacetate-mediated ring expansion

During the course of our studies, Charette et al. reported on a novel approach for the ring expansion of functionalized N-heterocycles employing trifluoromethanesulfonic anhydride as activating reagent.[13] Using 3-pyrolline derivatives as starting material, the intermediate aziridinium triflates were regioselectively and irreversably attacked at the higher substituted position thanks to the allylic activation. Due to the non-nucleophilic character of the leaving group, this protocol allows for the flexible use of different kinds of oxygen-, nitrogen-, sulfur-, and carbon-centered nucleophiles making this procedure a valuable complement to existing strategies. Hence, Charette's conditions

Table 1 Lipase-Screening for the Desymmetrization of *meso*-**1**[a]



Entry	Lipase	Diol	**2** (%)[b]	ee (%)	**4** (%)
1	CALA		34	19	28
2	CALB		26	–33	73
3	CRL		52	87	1
4	TLL		30	92	1
5	PCL		69	97	<1
6	PPL		5	89	<1
7	PFL	**1a**	95	>99	2
8	MML		>99 (85)	>99	<1
9	TLL		82	80	3
10	PCL		20	7	2
11	PFL		45	36	9
12	MML	**1b**	79 (74)	>99	21
13	TLL		56	76	2
14	PCL		9	8	<1
15	PFL		10	–13	<1
16[c]	MML	**1c**	74 (67)	95	26

[a] Reaction conditions: diol **1a**–**c** (0.50 mmol), vinyl acetate (5.0 mmol), lipase, toluene (0.5 mL) at 35 °C for 16 h. Conversion and ee was determined by HPLC on chiral phase from the crude mixture. For enzyme specifications see Supporting Information.
[b] Isolated yield of monoacetate **2** on 3 mmol scale given in parentheses.
[c] Reaction was performed at 22 °C.

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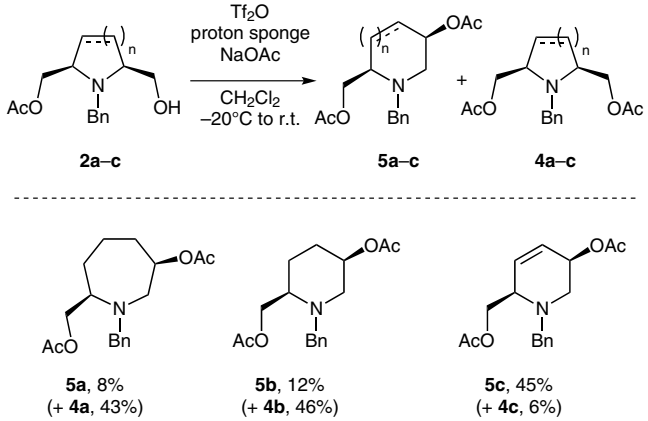
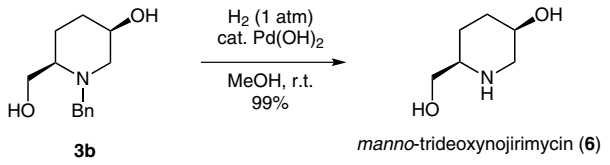
were also tested for the ring expansion of the *meso*-diol-derived amino alcohols **2a**–**c**, employing sodium acetate as O-nucleophile and proton sponge [1,8-bis(dimethylamino)naphthalin] as a base. Not surprisingly, at low temperature the lack of allylic activation of the saturated substrates **2a** and **2b** resulted in the preferential attack of the nucleophile at the less hindered position and thus, the desired ring-expanded compounds were obtained only as minor side products in 8% (**5a**) and 12% yield (**5b**), respectively (Scheme 3). The product selectivity changed dramatically by switching to unsaturated amino alcohol **2c**. Under identical conditions, the ring-expanded diacetate **5c** was now accessible as major product with a selectivity of 8:1 over the competing *meso*-diacetate **4c**.[11]



Scheme 3 Triflate-mediated ring expansion

While selective azepane formation still represents an unsolved issue in our desymmetrization–ring-expansion strategy, the enantio- and diastereoselective synthesis of saturated and unsaturated six-membered N-heterocycles opens up great opportunities for implementations into more complex synthetic strategies of this preparatively simple reaction sequence. In particular, the multifunctional dehydropiperidine **5c** with four orthogonally modifiable groups will thus be studied in detail as synthetic building block in our future investigations. Nonetheless, also saturated ring-expanded diols such as piperidine **3b** have the potential to be employed as valuable precursors for the synthesis of truncated azasugars as demonstrated with the preparation of the unnatural *manno*-configured epimer **6** of the alkaloid 1,3,4-trideoxynojirimycin (from *Angylocalyx pynaertii*)[14] which is easily obtained in quantitative yield by hydrogenative debenzylation (Scheme 4).



Scheme 4 Synthesis of *manno*-trideoxynojirimycin

In conclusion, we have successfully developed a novel protocol for the preparation of optically enriched, functionalized piperidines based on the combination of enzymatic desymmetrization, and subsequent ring-expanding rearrangement reactions. Currently, extension of the triflate-mediated substitution to other, more functionalized nucleophiles is ongoing work. In continuation, application of this method in the context of alkaloid synthesis as well as in the preparation of substituted cyclic amino acids will be studied in detail.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988. (b) Wallach, O. *Justus Liebigs Ann. Chem.* **1900**, *312*, 171.
(2) Faworsky, A.; Boshowski, W. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1097; *Chem. Zentralbl.* **1915**, 984.
(3) For a review, see: Holub, N.; Blechert, S. *Chem. Asian J.* **2007**, *2*, 1064.
(4) For recent examples in natural product synthesis, see: (a) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954. (b) Matovic, R.; Ivkovic, A.; Manojlovic, M.; Tokic-Vujosevic, Z.; Sicic, R. N. *J. Org. Chem.* **2006**, *71*, 9411.
(5) (a) Cossy, J.; Dumas, C.; Michel, P.; Gomez Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549. (b) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Synlett* **1997**, 905. (c) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *ARKIVOC* **1997**, *(v)*, 38. (d) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693.
(6) (a) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224. (b) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 2023.
(7) For a review, see: García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2011**, *111*, PR110.
(8) Selected examples: (a) Chênevert, R.; Dickman, M. *J. Org. Chem.* **1996**, *61*, 3332. (b) Lesma, G.; Colombo, A.; Landoni, N.; Sacchetti, A.; Silvani, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1948. (c) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298. (d) Chênevert, R.; Jacques, F.; Giguère, P.; Dasser, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1333. (e) Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615.
(9) Kawanami et al. described the enzymatic kinetic resolution of corresponding *trans*-2,5-disubstituted pyrrolidines: Kawanami, Y.; Moriya, H.; Goto, Y.; Tsukao, K.; Hashimoto, M. *Tetrahedron* **1996**, *52*, 565.
(10) Literature based on our recent studies on lipase-catalyzed transformations of primary alcohols: (a) Deska, J.; Bäckvall, J.-E. *Org. Biomol. Chem.* **2009**, *7*, 3379. (b) Manzuna Sapu, C.; Bäckvall, J.-E.; Deska, J. *Angew. Chem. Int. Ed.* **2011**,

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50, 9731; *Angew. Chem.* **2011**, *123*, 9905. (c) Hammel, M.; Deska, J. *Synthesis* **2012**, *44*, 3789.
(11) Formation of undesired *trans*-diastereomers was not observed, neither for diols **1** and **3** nor for diacetates **4** and **5**.
(12) Unfortunately, this protocol proved to be not suitable for the ring expansion of unsaturated monoacetate **2c**, as decomposition was observed under these conditions.
(13) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830.
(14) Yasuda, K.; Kizu, H.; Yamashita, T.; Kameda, Y.; Kato, A.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 198.

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