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Reductive Cyclization and Petasis-like Reaction for the Synthesis of Functionalized γ-Lactams

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Abstract: An efficient reductive cyclization strategy was employed for the synthesis of *N*-substituted β,γ-dihydroxy-γ-lactams. A subsequent Petasis-like reaction (PLR) through nucleophilic additions of boronic acids to intermediate *N*-acyliminium ions produced substituted γ-lactams. Overall, the application of this protocol provides β,γ-dihydroxy-γ-lactams and functionalized γ-lactams with potential interest for synthetic and bioorganic chemistry.

Introduction

The lactam is a structural motif that is present in a wide variety of bioactive natural compounds and synthetic molecules.[1] Specifically, functionalized γ-lactams are found in numerous biologically active compounds and several drug molecules, such as the anticonvulsant levetiracetam, the respiratory stimulant doxapram, and the antidiabetic agent glimepiride (Figure 1).[2]

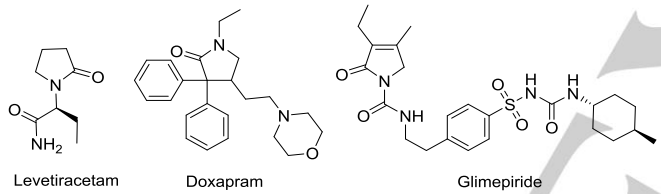

Figure 1. Examples of γ-lactams containing drugs.

Besides recently reported methods for the synthesis of functionalized lactams,[3] the addition of nucleophiles, such as allylsilanes, isonitriles, alkyl-, and aryl-metals, to *N*-acyliminium ions is one of the most widely used approaches.[4] Organoboronic acids or esters, which are readily available and stable toward air and water have been extensively used in syntheses of functionalized amines and *N*-heterocycles.[5] The nucleophilic addition of organoboronic acids and esters to *N*-acyliminium ions, which were derived from 3-hydroxypyrrolidines, was first reported by Batey and co-workers in 1999.[6] Morgan and co-workers then reported the addition of electron-rich boronic acids to *N*-acyliminium ions to synthesize substituted 4-hydroxypyrrolidin-2-ones and 5-hydroxypiperidin-2-ones.[7] Recently, Mizuta and co-workers have reported a Petasis-like reaction (PLR) for the synthesis of functionalized piperidines using hydroxypiperidines as the *N*-acyliminium precursors.[8] Besides these scattered examples of reactions between *N*-acyliminium precursors and electron-rich boronic acids or esters, a systematic study of the addition of boronic acids to various *N*-acyliminium ions has not yet been reported. Although dihydroxylactams are useful *N*-acyliminium ion precursors, only few synthetic examples, such as the reduction from the corresponding glutarimide or succiminide,[9] have been reported.[7, 10]

Herein, a novel versatile approach to *N*-substituted β,γ-dihydroxy-γ-lactams through reductive cyclization and a Petasis-like reaction to functionalized γ-lactams through nucleophilic addition of boronic acids to *N*-acyliminium ions are disclosed.

Results and Discussion

The acetal protected amides **1a-i** were synthesized through the formation of a mixed anhydride using isobutyl chloroformate starting from L-malic acid.[11] *N*-substituted β,γ-dihydroxy-γ-lactams **2a-h** were then obtained by a novel cyclization strategy through reduction of the dioxolanone carbonyl group of **1a-h** using $LiAlH_4$ in good to excellent yields. *N*-Pyridin-4-ylmethyl compound **2i** was isolated in low yield due to its high aqueous solubility (Figure 2). The compounds in Figure 2 were obtained as mixtures of diastereoisomers.

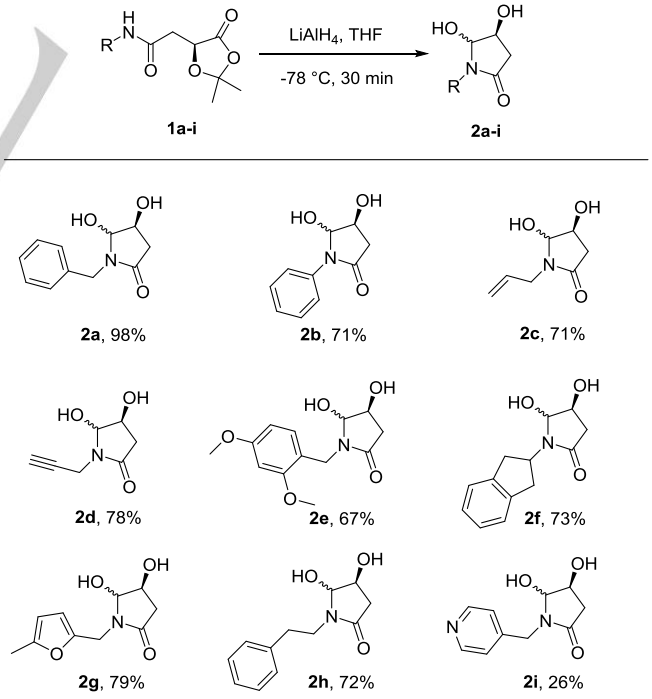

Figure 2. Synthesis of lactams **2a-i** through reductive cyclization.

Using *N*-benzyl-4,5-dihydroxylactam **2a** as the *N*-acyliminium ion precursor, initial experiments were performed under the Batey condition employing methylene chloride as the solvent in the presence

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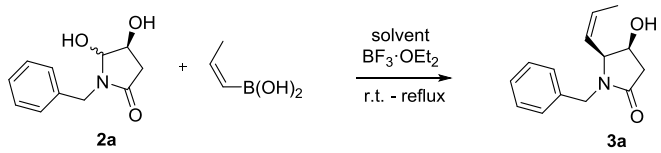
of boron trifluoride etherate.[6] The reaction of **2a** with *cis*-1-propen-1-ylboronic acid, phenylboronic acid, and 4-bromophenylboronic acid gave only traces of the expected product after refluxing for 3 days. 2-Furyl boronic acid, which has been successfully applied for various Petasis reactions,[7] gave the expected product in high yield but with poor diastereoselectivity.

Table 1. Optimization of conditions for the Petasis-like reaction.



2a **3a**

Entry	Solvent	Time	Conversion of **2a**, %[a]	Formation of **3a**, %[a]
1[b]	CH_2Cl_2	12 h	0	0
2[b]	HFIP	1 h	0	0
3	CH_2Cl_2	12 h	66	trace
4	HFIP	1 h	94	67
5	HFIP	5 h	100	67
6	methanol	1 h	100	0
7	2-propanol	1 h	100	0
8	methanol:HFIP (1:1)	1 h	100	0
9	THF	12 h	69	trace
10	acetone	12 h	73	11
11	acetonitrile	5 h	100	44
12	nitromethane	5 h	100	60[c]
13	1,4-dioxane	12 h	97	trace
14	CH_2Cl_2:HFIP (1:1)	12 h	100	53

[a] Determined by LC-MS. [b] Absence of $BF_3{\cdot}OEt_2$. [c] Both *cis*- and *trans*-isomers were detected on LC-MS with a dr ratio of 2:3.

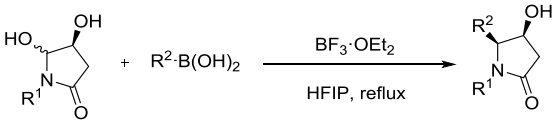
Based on the initial results and our previous experience with Petasis reactions,[5b, 12] optimization focused on solvent selection for the reaction between dihydroxylactam **2a** and *cis*-1-propen-1-ylboronic acid (Table 1). First of all, in the absence of $BF_3{\cdot}OEt_2$ (entries 1 and 2), no conversion of the starting dihydroxylactam **2a** was observed, indicating that a Lewis acid is indeed necessary for the formation of the *N*-acyliminium ion. Trace of the expected product **3a** was detected after refluxing in methylene chloride for 12 h (entry 3), while changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) sped up the reaction significantly (entries 4 and 5). The use of other protic solvent systems (entries 6-8) gave full conversion of **2a**, but unfortunately, none of the expected product was observed. A selection of other polar solvents were then tested (entries 9 to 13), where nitromethane gave the best formation of **3a** as judged from LC-MS, while the diastereoselectivity was poor. A mixture of CH_2Cl_2/HFIP (1:1, v:v) as solvent gave good conversion after 12 h (entry 14), but the formation of **3a** was lower than that in HFIP. Thus, HFIP in the presence of $BF_3{\cdot}OEt_2$ was chosen as the most efficient reaction condition for further experiments.

A selection of boronic acids was tested for the PLR under the optimized condition. The results are summarized in Table 2. Similar to the reaction of **2a** with *cis*-1-propen-1-ylboronic acid, which gave only the *cis*-adduct **3a** (entry 1), reactions of **2a** with *trans*-2-chloromethylvinylboronic acid and vinyl boronic acid dibutyl ester gave only the corresponding *cis*-adducts **3b** and **3c** (entries 2 and 3). Phenylboronic acid and 4-bromophenylboronic acid, also yielded the corresponding *cis*-adducts **3d** and **3e** with excellent diastereoselectivity when reacted with **2a** (entries 4 and 5). The good *cis*-diastereoselectivity associated with the above results were lost when electron-rich 3,4-dimethoxyphenylboronic acid and 2,4-dimethoxyphenylboronic acid were used (entries 6-7). An expanded scope of the PLR was then investigated by using aromatic/heteroaromatic β,γ-dihydroxy-γ-lactams **2b**, **2e-h** and aliphatic dihydroxy-γ-lactams **2c**-**d**. *N*-Allyl-4,5-dihydroxylactam **2c** and *N*-propargyl-4,5-dihydroxylactam **2d** were reacted with *trans*-2-chloromethylvinylboronic acid to selectively afford the expected *cis*-products **3h** and **3i**, respectively (entries 8 and 9), so did the use of vinyl boronic acid dibutyl ester (entry 10). The use of 3- and 2-benzothienylboronic acids led to both isomers with a favored formation of the *cis*-products (entries 11-12). Reaction between *N*-(2,4-dimethoxybenzyl)-4,5-dihydroxylactam **2e** and thienyl-2-boronic acid did not proceed cleanly and only the major *cis*-isomer **3m** could be isolated in a low yield (entry 13), a compound formed through the intramolecular Friedel-Crafts alkylation was among byproducts detected by LC-MS. The reaction of *N*-(2-dihydroindene)-4,5-dihydroxylactam **2f** with furan-2-boronic acid was fast and similar to the result of using other electron-rich boronic acids, poor diastereoselectivity was observed with formation of the *cis*-product **3n** being favored (entry 14). Reaction of *N*-(5-methylfuran-2-yl)methyl-4,5-dihydroxylactam **2g** with either 4-bromophenylboronic acid or benzofuran-2-boronic acid was unsuccessful and the best result was obtained with the reactive furan-2-boronic acid, albeit affording both isomers in a low yield (entry 15). Poor diastereoselectivity was also observed for the reaction between *N*-phenethyl-4,5-dihydroxylactam **2h** and benzofuran-2-boronic acid (entry 16).

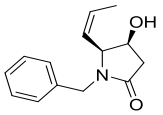
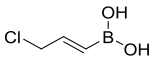
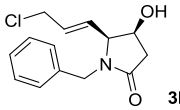
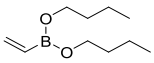
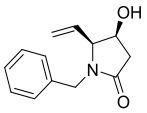
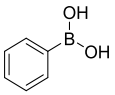
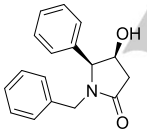
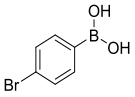
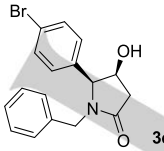
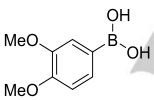
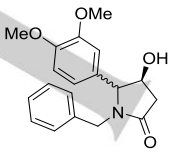
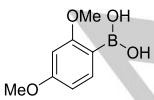
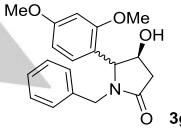
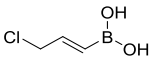
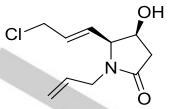
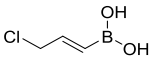
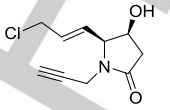
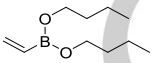
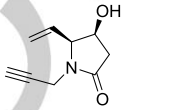
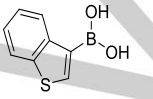
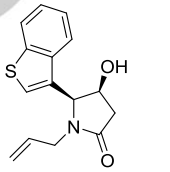
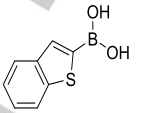
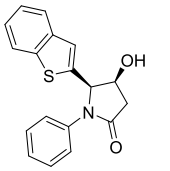
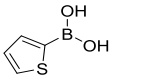
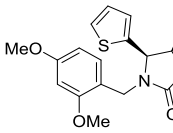
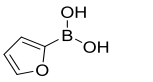
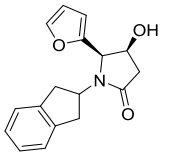
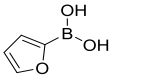
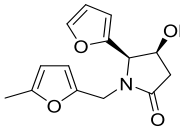
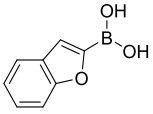
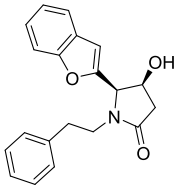
Based on the above results, it was clearly demonstrated that under the optimal reaction condition of using HFIP as the solvent together with of $BF_3{\cdot}OEt_2$, high *cis*-diastereoselectivity was achieved by using less reactive boronic acids. In contrast, the use of electron-rich boronic acids significantly shortened the reaction time and gave products of poor diastereomeric purity. Thus, it was proposed that the *N*-acyliminium ion, derived from the corresponding β,γ-dihydroxy-γ-lactam through BF_3 coordination in the presence of HFIP, could follow two reaction pathways with boronic acids: 1) a pathway of direct nucleophilic addition of electron-rich boronic ligand to the electrophilic 5-position of the *N*-acyliminium ion to give both isomers with favored formation of the *trans*-products; 2) a slow chelation pathway that involved Petasis-like nucleophilic addition of boronic acids that were activated through the formation of an initial boronate intermediate, followed by the intramolecular addition of R^2 to the same

face of the iminium ion intermediate, leading exclusively to the corresponding *cis*-product. Electron-deficient boronic acids, such as 4-bromophenyl and chloromethylvinyl boronic acids, proceeded through the chelation pathway exclusively to give the Petasis-like *cis*-products; more reactive boronic acids, such as 2-furyl and benzothienylboronic acids, reacted with the *N*-acyliminium ion through both pathways to give a mixture of *cis*- and *trans*-isomers (Scheme 1).

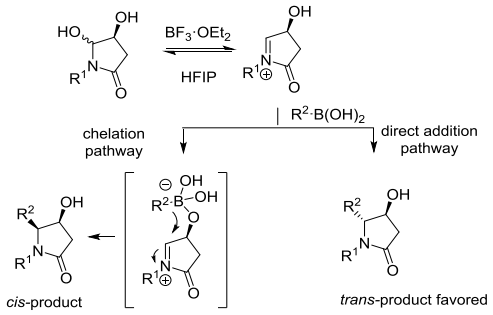
Table 2. Petasis-like reactions between γ-lactam **2a-h** and boronic acids.



2a-h **3a-p**

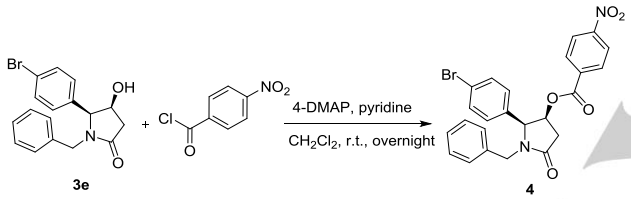
Entry	Boronic acid/ester	Time	Product[a]	Yield,%[b] (dr)[c]
1		5 h	 **3a**	31 (>20:1)
2		4 d	 **3b**	46 (>20:1)
3		12 h	 **3c**	50 (>20:1)
4		4 d	 **3d**	13 (>20:1)
5		7 d	 **3e**	23 (>20:1)
6		1 h	 **3f**	72 (1:1)
7		0.5 h	 **3g**	48 (1:1)
8		1 d	 **3h**	17 (>20:1)
9		7 d	 **3i**	17 (>20:1)
10		12 h	 **3j**	50 (>20:1)
11		12 h	 **3k**	39 (3:2)
12		1 h	 **3l**	90 (3:2)
13		1h	 **3m**	11[d](7:3)
14		0.5 h[e]	 **3n**	72 (3:2)
15		1 h[e]	 **3o**	20 (3:2)
16		1h	 **3p**	56 (3:2)

[a] Major diastereoisomer shown. [b] Isolated yields of both isomers after column chromatography. [c] Crude mixture, determined by LC-MS, *cis*:*trans*. [d] Isolated yield of the *cis*-isomer only. [e] Performed at room temperature.



Scheme 1. Proposed mechanism.

Besides, comparing the results using 3,4-dimethoxyphenyl and 2,4-dimethoxyphenyl boronic acids (entries 6 and 7, Table 2) revealed that steric hindrance had a significant impact on the yield of the reaction.



Scheme 2. Preparation of compound **4**.

The stereochemistry of the compounds discussed in this study was assigned based on the magnitude of the vicinal *J*-coupling constant between the 4- and 5-protons: $J_{4,5}$ around 6 Hz for 4,5-*cis*-stereochemistry and $J_{4,5}$ value ranging from 0 to 3 Hz for 4,5-*trans*-stereochemistry.[13] To confirm the assignment, compound **3e** bearing a 4-bromophenyl group was reacted with 4-nitrobenzoyl chloride to form the nitrobenzoate **4** for X-ray crystallographic analysis (Scheme 2). The 4,5-*cis*-stereochemistry of **4** was confirmed by inspection of the crystal structure (Figure 3).

Conclusions

A highly efficient reductive cyclization strategy for the synthesis of *N*-substituted β,γ-dihydroxy-γ-lactams starting from L-malic acid has been developed. A wide range of novel *N*-substituted β,γ-dihydroxy-γ-lactams were convenient substrates for Petasis-like reactions with boronic acids promoted by boron trifluoride etherate. Under optimized conditions in HFIP, both electron-rich and electron-deficient boronic acids were successfully employed for the nucleophilic additions to cyclic *N*-acyliminium ions derived from β,γ-dihydroxy-γ-lactams. *cis*-Diastereoselectivity was observed in the Petasis-like reactions when using electron-deficient boronic acids, while electron-rich boronic acids resulted in no or poor selectivity, a phenomenon that we explain by chelation controlled addition and direct addition of boronic acids to *N*-acyliminium ions, respectively. A series of functionalized γ-lactams were successfully synthesized employing this method.

Supporting Information (see footnote on the first page of this article): General methods; all experimental procedures and characterization data; copies of the ^{1}H NMR, ^{13}C NMR, RP-HPLC and/or LC-MS spectra, Dept135 and 2D NMR spectra whenever applicable, for all new compounds. CCDC-1033851 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

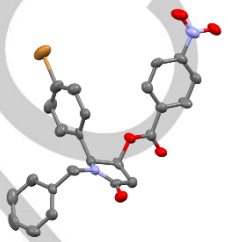


Figure 3. Crystal structure of compound **4**.

Acknowledgements

The Lundbeck Foundation (R141-2013-13835) and the Technical University of Denmark are gratefully acknowledged for financial support.

Keywords: Reductive cyclization • Petasis-like reaction • Lactams • Nucleophilic addition • Synthetic methods

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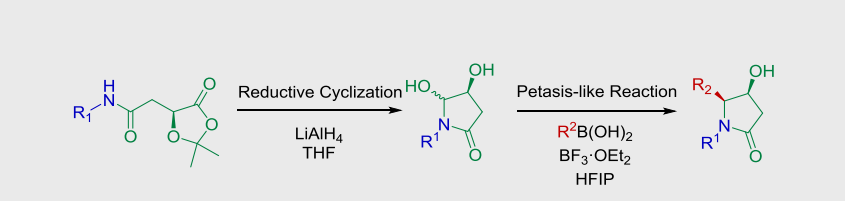
SHORT COMMUNICATION



A novel approach to *N*-substituted β,γ-dihydroxy-γ-lactams through reductive cyclization and a Lewis acid mediated Petasis-like reaction to functionalized γ-lactams through nucleophilic addition of both electron-rich and electron-deficient boronic acids to *N*-acyliminium ions are disclosed.

Peng Wu, Michael Åxman Petersen, A. Emil Cohrt, Rico Petersen, Mads H. Clausen and Thomas E. Nielsen**

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Reductive Cyclization and Petasis-like Reaction for the Synthesis of Functionalized γ-Lactams