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Iodine(III)-Catalyzed Cascade Reactions Enabling a Direct Access to β-Lactams and α-Hydroxy-β-amino Acids

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Supporting Information

ABSTRACT: In the presented method, a one-pot metal-free access to β-lactams is provided. The developed strategy employs a hypervalent iodine(III)-triggered bromination/rearrangement/cyclization cascade reaction that allows the straightforward synthesis of a broad range of structurally different lactams from cheap and easily available imides. This triple cascade reaction is furthermore extendable by an in situ ring-opening reaction, giving direct access to isoserine derivatives from simple imines in a four-step, one-pot reaction.

The impact of nitrogen-containing heterocycles on the well-being of mankind is impressively demonstrated by the β-lactams (azetidin-2-ones). With the discovery of the "magic" drug penicillin (**1**) in 1928 (Figure 1),[1] the golden age of antibiotic discovery was ignited. Many natural, synthetic, and semisynthetic antibacterial subclasses[2] within the β-lactam family have been identified since Fleming's landmark discovery, for example, the cephalosporins, clavulanates, penemes, carbapenems, or the monocyclic monobactams [aztreonam (**2**)[3]]. All of these family members make β-lactams the most frequently prescribed drugs to cure infections caused by both Gram-positive and Gram-negative bacteria. In general, the β-lactam nucleus constitutes a privileged structural motif in medicinal chemistry and drug development, with its applications reaching far beyond that of antibiotics, as shown, by the cholesterol-lowering ezetimibe (**3**).[4] Due to its overall importance, considerable efforts to introduce reliable and effective methods for the synthesis of the β-lactam core have been conducted, resulting in manifold versatile approaches available today,[5] spanning from classical methods, such as the Staudinger ketene cycloaddition[5c,f,h,6] or the cyclization of β-amino acids,[7] to the Kinugasa reaction,[8] intramolecular C−H insertions,[5a,i,9] and carbonylations of aziridines.[10] Nevertheless, the construction of such four-membered heterocycles remains a challenging task with still a lot of problems to be solved, such as complicated access to starting materials, nonpractical reaction conditions, low structural variability, etc. It is therefore not surprising that the majority of the commercially available β-lactams are still produced by biotechnological processes. To overcome the problems in azetidin-2-one synthesis, a perpetual exploration of new pathways toward these highly rewarding structures is necessary.

Within our research program dealing with the exploration of unusual reactivities and selectivities triggered by hypervalent λ^3-iodanes,[11] we recently reported the iodine(III)-catalyzed rearrangement of imides **5** using 10 mol % of *o*-iodobenzamide **6** as the catalyst with *N*-bromosuccinimide (NBS) as the oxidant (Table 1, entry 1).[12] This method provided access to a huge

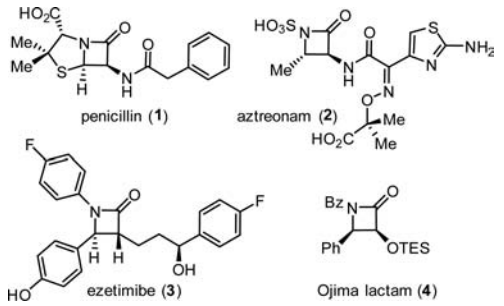

Figure 1. Examples of important drugs and synthetic building blocks bearing a β-lactam nucleus.

variety of structurally diverse α,α-disubstituted α-hydroxy carboxylamides **7** equipped with a methylene bromide side chain. The latter structural feature constitutes a versatile handle to introduce further structural complexity into these scaffolds, thus proving amides **7** as useful building blocks. Interestingly, upon treatment with sterically demanding non-nucleophilic bases, such as K-selectride, isolated **7a** was converted into lactam **8a** in 91% yield (Table 1, entry 2). Inspired by this observation, we were intrigued by the idea of developing a one-pot protocol for this two-step procedure, which would give straightforward access to the highly desired target structures **8**, directly from imides **5**.

Cyclization of the β-halocarboxyl amides **7** by *N*,C3-bond assembly (step b, Table 1) is generally performed using metallic amides or hydrides, both bases requiring anhydrous conditions, as exemplified in our two-step synthesis of lactam **8a** (Table 1, entries 1 and 2). Such a reaction setup is not feasible in the planned reaction cascade, as at least 1 equiv of water is needed to trigger the ring opening of the oxazolidinonium intermediate during the rearrangement of imides **5** (step a, Table 1 and SI).[12] Based on this precondition, we set out to search for a suitable

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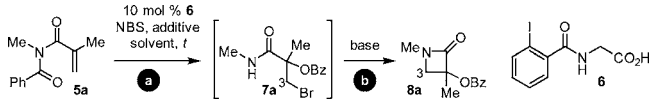
Table 1. Selected Conditions Applied during the Optimization for the Synthesis of Lactam 8a[a]



	base	additive	solvent	t	conversion, %	7a/8a[b]
1[12]			HFIP	rt	>99	100:0
					85[c]	
2[12]	K-selectride[e]		1. HFIP	rt	>99	0:100
			2. THF	0 °C	77[d,f]	
3	CsF[g]		HFIP	reflux	>99	100:0
4	CsF[g]	NH_4Cl	DCM	reflux	>99	100:0
5	CsF[g]	NH_4Cl	THF	reflux	85	9:91
6	CsF[g]	NH_4Cl, TEBA	THF	reflux	85	9:91
7	CsF	NH_4Cl, TEBA	THF	reflux	>99	9:91
					76[f]	
8	CsF	NH_4Cl, TEBA	THF/DCM[h]	reflux	>99	7:93
					85[f]	
9	CsF	TEBA	THF/DCM[h]	reflux	70	53:47
10	CsF	NH_4Cl	THF/DCM[h]	reflux	>99	55:45

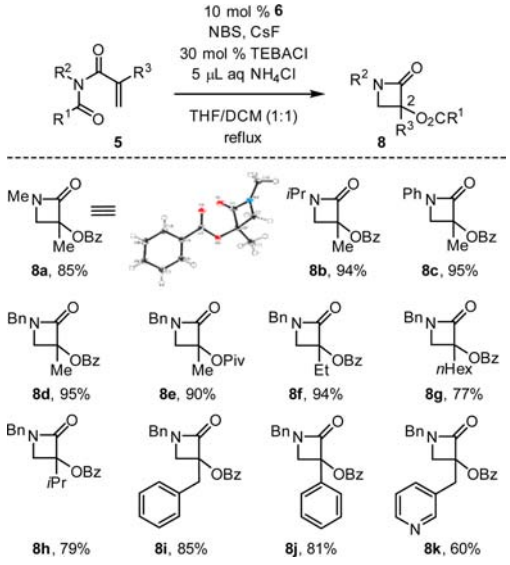
[a]Unless noted otherwise, the reactions were carried out using imide **5a** (20.3 mg, 0.10 mmol, 1.0 equiv), catalyst **6** (3.05 mg, 10.0 μmol, 0.1 equiv), NBS (19.5 mg, 0.11 mmol, 1.1 equiv), 5 μL aq saturated NH_4Cl solution, TEBA (6.83 mg, 30.0 μmol, 0.3 equiv), and CsF (106 mg, 0.07 mmol, 7 equiv) in a 0.10 M solution at reflux. [b]Determined by ^{1}H NMR spectroscopy of the crude mixture. [c]Isolated yield of **7a**. [d]Two-step procedure: **7a** was isolated and purified before base treatment. [e]1.2 equiv of base. [f]Isolated yield of **8a**. [g]5 equiv of base. [h]1:1 mixture. HFIP = hexafluoroisopropanol; TEBA = triethylbenzylammonium chloride.

base, which is compatible to the λ^3-iodane bromination/rearrangement conditions and additionally facilitates the cyclization event. Mild fluoride bases proved to be valuable in lactam formations in the past[7b,13] and should also be tolerated in step a of our protocol. To our delight, the addition of CsF did not affect the formation of amide **7a** at all using the standard solvents for this reaction: HFIP or DCM (>99%, entries 3 and 4).

In the latter case, the activation of the in situ formed iodine(III)-bromo species was necessary using catalytic amounts of NH_4Cl to achieve sufficient conversion of **5a** (entry 4).[12,14] Unfortunately, in both cases, no ring closure to the desired heterocycle **8a** occurred. Only linear product **7a** was detectable in the crude mixture. More polar solvents, such as THF, however, led to the fluoride-assisted *N*,*C*-cyclization, predominantly giving rise to **8a** (entry 5). Interestingly, the corresponding imino oxetane (not shown) arising from the likewise possible *O*-cyclization of amide **7a** was never observed in the reaction mixture. Adding 30 mol % of phase-transfer catalyst TEBA (entry 6) together with increasing the amount of CsF (entry 7) further improved the synthesis of lactam **8a** (76% yield). By additionally changing the solvent from pure THF to a 1:1 mixture of THF and DCM, the optimum conditions for this reaction sequence were reached and product **8a** was furnished directly from starting material **5a** in 5 h and 85% yield (entry 8). The presence of both ammonium salts (NH_4Cl and TEBA) in the reaction mixture was inevitable for the success of this transformation. Omitting either of them significantly hampered the lactam formation (entries 9 and 10). This observation clearly showed that NH_4Cl played a decisive role in both parts of the cascade reaction.

With the optimized reaction conditions in hand, we started to evaluate the substrate scope of this triple cascade. In all cases, the conversion of imides **5** to the corresponding lactams **8** bearing a tertiary O-functionality at C-2 proceeded regio- and chemoselectively in excellent 60−95% yield (Scheme 1). Side reactions, such as aromatic bromination, O- instead of N-cyclization, or carbocyclization, were not observed. Besides structural alterations at the amide nitrogen (R^2 = alkyl, aryl, and benzyl

Scheme 1. Scope of the Iodine(III)-Catalyzed Triple Cascade Reaction to Lactams 8



groups),[15] alkyl and phenyl moieties at the second carboxyl fragment (R^1) were equally well-accepted. The same was true for variations at the alkene moiety (R^3). There, the range of tolerated substituents spans from simple linear and branched alkyl portions to benzyl and even heteroaryl fragments.

Even α,β-disubstituted Michael systems, such as in imide **5l**, were smoothly converted to the densely substituted lactam **8l** in 68% yield. This process occurred with complete stereoselectivity conserving the relative configuration of the starting material **5l** (Scheme 2).

Besides the unique utility of the β-lactam nucleus as a pharmacophore, its distinct applicability as a key building block in organic synthesis makes it even more valuable, as it gives access to most diverse, important nitrogen-containing compound

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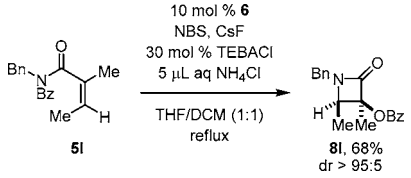
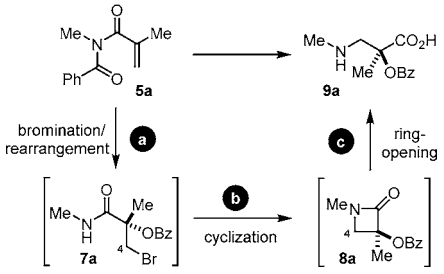
Scheme 2. Conversion of Trisubstituted Olefin 5l Using the Iodine(III)-Catalyzed Triple Cascade Reaction



classes of biological and medicinal interest.[5d,16] These reach from "simple" cyclic and linear molecules, such as amino acids and N-heterocycles, to structurally complex (macro)cyclic structures found in alkaloids, taxoids, and other types of natural products. One prominent example is the Ojima lactam (**4**, Figure 1),[17] which served as the precursor for the α-hydroxy-β-amino acid fragment in many total synthetic routes to the anticancer agent taxol.[18] As already observed in previous studies in our group, such α-hydroxy-β-amino acids are obtained in 94% yield by treating the isolated β-bromocarboxyl amide **7a** with NaH followed by an aqueous workup.[12] As this reaction has to involve the ring opening of the in situ formed lactam **8a** (Scheme 3, step

Scheme 3. Concept of the Four-Step, One-Pot Reaction Sequence to α-Hydroxy-β-amino Acids 9

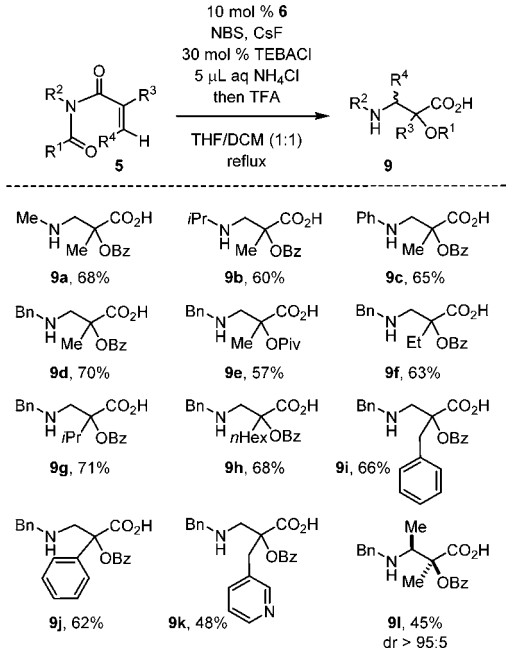


c), we were curious if this heterocycle cleavage can be added on top of the λ^3-iodane-catalyzed halogenation/rearrangement/cyclization sequence. If so, our protocol can be further extended to a one-pot, four-step procedure yielding isoserines **9** with a quaternary center in the α-position, right from the corresponding imides **5**.

Therefore, we adjusted the reaction conditions of the lactam synthesis described above (Scheme 1). Conversion of lactams to β-amino acids is typically accomplished by a nucleophilic attack to the carbonyl group under basic conditions. Unfortunately, this is not compatible with the rearrangement process of imide **5** (step a), as the formation of the iodine(III)-bromo species is completely abolished under such conditions.[14a] Because of this, ring opening under acidic conditions was envisaged. The best results for the preparation of **9a** were obtained by adding TFA to the reaction mixture (for details, see SI). All imides **5** employed in the β-lactam synthesis were easily converted to the corresponding β-amino acids **9** in good yields of up to 71% and under complete stereocontrol (dr > 95:5; Scheme 4).

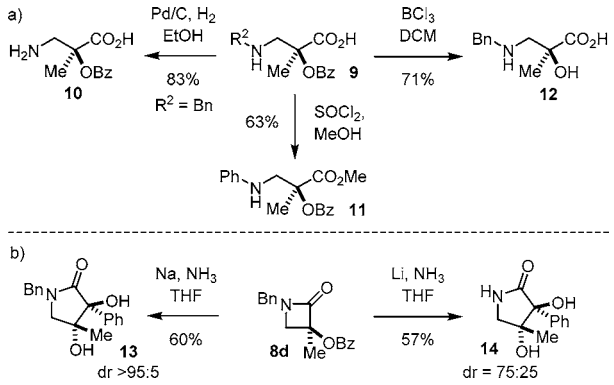
Obtained products **8** and **9** show a quaternary carbon center in the α-position bearing a hydroxy function, a structural feature that is difficult to install otherwise. There, the products **10**−**12** were obtained in good 63−83% yield (Scheme 5a). More interestingly, treating **8d** with alkali metals in liquid ammonia did not result in the expected reductive debenzylation of β-lactam **8d**. Instead, the ring-extended γ-lactams **13** and **14** having a α,β-*trans*-diol functionality were obtained with good diastereose-

Scheme 4. Scope of the Iodine(III)-Catalyzed Four-Step, One-Pot Reaction to α-Hydroxy-β-amino Acids 9[a]



[a]Poducts **9** were all isolated as the corresponding TFA salts.

Scheme 5. Further Transformations of the Obtained Lactams 8 and Isoserines 9



lectivities and yields (Scheme 5b). Formation of these intriguing structures possibly involves a rearrangement reaction with concomitant ring enlargement, followed by ring opening. Subsequent reductive ring closure by an intramolecular Pinacol coupling finalized the five-membered ring formation (see SI).

In summary, we established an as yet unprecedented and efficient synthetic strategy to highly desirable targets, the β-lactams **8** and α,α-disubstituted α-hydroxy-β-amino acids **9**. To realize our goal, we combined the unusual reactivity triggered by hypervalent iodine(III)-catalyzed halogenations with a variety of other transformations, leading to three-step and even four-step conversions that can now be conducted in one pot. The broad compatibility of λ^3-iodane chemistry demonstrated here opens completely new opportunities for the introduction of benign and straightforward synthetic pathways to interesting structural scaffolds with novel architectures.

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■ ASSOCIATED CONTENT

Supporting Information

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X-ray data of lactam **8a** (CIF)

Experimental procedures, characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) The CIF files of lactam **8a** has been deposited with Cambridge Crystallographic Data Centre (no. CCDC 1483038). The data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif.

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