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Mette Ishoey,[a,†] Rico G. Petersen,[a,†] Michael A. Petersen,[a] Peng Wu,[a] Mads H. Clausen,[a,b*] and Thomas E. Nielsen[a,c,d*]

A high-yielding, stereoselective and extraordinarily complexity-generating Petasis 3-component/intramolecular Diels-Alder reaction has been developed. In combination with ROM-RCM, rapid access to complex sp^3-rich heterocyclic scaffolds amenable to subsequent functionalization and library synthesis is provided.

High-throughput screening (HTS) remains a preferred approach for the identification of novel starting points for chemical biology probe and drug discovery.[1] Hence, parameters such as size, design and quality of molecular screening collections are of crucial importance for the successful outcome of HTS campaigns. In recent years, it has become apparent that traditional screening collections, which are largely dominated by 'flat' (sp^2-rich), small molecules lack the structural complexity and diversity required to target more challenging biological targets such as protein-protein interactions, transcription factors and nucleic acid macromolecules.[2] Aiming for a better coverage of biologically relevant chemical space,[3] strategies relying on concise and efficient synthetic pathways for the generation of structurally diverse molecular libraries, featuring a higher content of sp^3-hybridization, scaffold complexity and functional group diversity have been developed.[4] Importantly, while providing access to molecular frameworks that mimic the structural complexity of natural products, these strategies focus on enabling the synthesis of structural analogs to allow for a smoother downstream optimization and advancement of screening hits.

In our continuing efforts to develop strategies for the generation of structurally diverse compound libraries,[5] we recently reported a build/couple/pair strategy[4e] combining the Petasis 3-component reaction (Petasis 3-CR) with Ru-alkylidene catalyzed ring-closing metathesis (RCM).[5b] To further develop this strategy, we employed 2-furylboronic acid in the Petasis 3-CR of masked α-hydroxy aldehyde **1** (racemic) and diallylamine, and we were delighted to observe that a consecutive intramolecular Diels-Alder (IMDA) reaction provided **2** in 68% yield as a single diastereomer (Figure 1A).

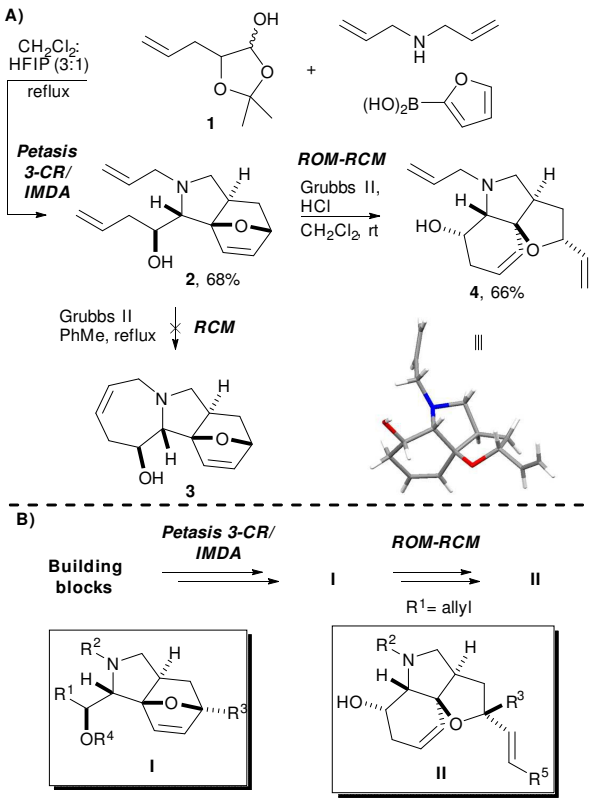

Figure 1: Tandem Petasis 3-CR/IMDA reaction combined with a ROM-RCM sequence: A) Reaction discovery and X-ray confirmation of structure; B) Strategy for utilization of the reaction sequence in the synthesis of libraries based on densely functionalized heterocyclic scaffolds.

In an attempt to promote RCM, **2** was subjected to Grubbs 2nd generation catalyst (Grubbs II), however, one equivalent of hydrochloric acid was required to promote full conversion.

[a] Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark. E-mail: ten@sund.ku.dk; mhc@kemi.dtu.dk
[b] Center for Nanomedicine and Theranostics, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark
[c] Singapore Centre on Environmental Life Sciences Engineering, Nanyang Technological University, Singapore 63755
[d] Costerton Biofilm Center, Department of Immunology and Microbiology, University of Copenhagen, Copenhagen DK-2200, Denmark.
† These authors contributed equally to this work.
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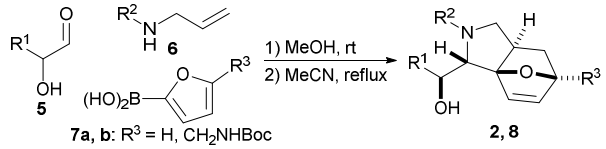
Interestingly, instead of the RCM product **3**, the tricyclic scaffold **4** resulting from a ring-opening ring-closing metathesis (ROM-RCM) reaction was isolated in 66% yield. The structure of **4** was verified by X-ray crystallography, which indirectly confirmed the diastereoselectivity assigned to the IMDA reaction.

Intrigued by the molecular complexity accessible in only two synthetic operations, we envisaged the synthesis of screening-relevant molecular libraries based on scaffolds **I** and **II** (Figure 1B). The multicomponent nature of the Petasis 3-CR would allow for variation of appendage diversity around the core scaffolds, and through appropriate incorporation of functional groups, additional downstream diversifications would be possible. We decided to probe the scope of the tandem Petasis 3-CR/IMDA reaction using glycolaldehyde (R^1 = H), as this would allow for the construction of a sub-library based on **I**, where diversification of the resulting primary alcohol would invoke no stereochemical consequences.

The Petasis 3-CR was conducted in methanol at room temperature (Table 1). Under these reaction conditions, subsequent IMDA reactions remained incomplete, and it proved more efficient to conduct this step in refluxing acetonitrile following removal of methanol *in vacuo*. Thus, the use of glycolaldehyde and 2-furylboronic acid in combination with diallylamine (entry 1) or benzyl allylamine (entry 2) afforded the products as single diastereomers in good yields. The stereochemistry of the products, resulting from an *exo* transition state with the dienophile approaching from the *Si* face, was determined by 2D NOESY correlations of **8b**.[§]

Table 1: Scope of the one-pot tandem Petasis 3-CR/IMDA reaction.



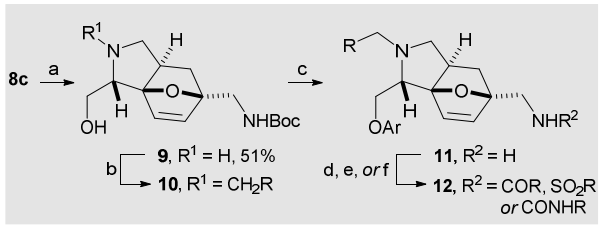
Entry	R^1	R^2	R^3	Product; yield (%)[a]
1	H[b]	allyl	H	**8a**, 65[c]
2	H[b]	Bn	H	**8b**, 77[c]
3	H[b]	allyl	CH_2NHBoc	**8c**, 97
4	allyl[d]	allyl	H	**2**, 91
5	allyl[d]	allyl	CH_2NHBoc	**8d**, 88
6	allyl[d]	Bn	CH_2NHBoc	**8e**, 84
7	allyl[d]	DMB[e]	CH_2NHBoc	**8f**, 72
8	allyl[d]	Me	CH_2NHBoc	**8g**, 47

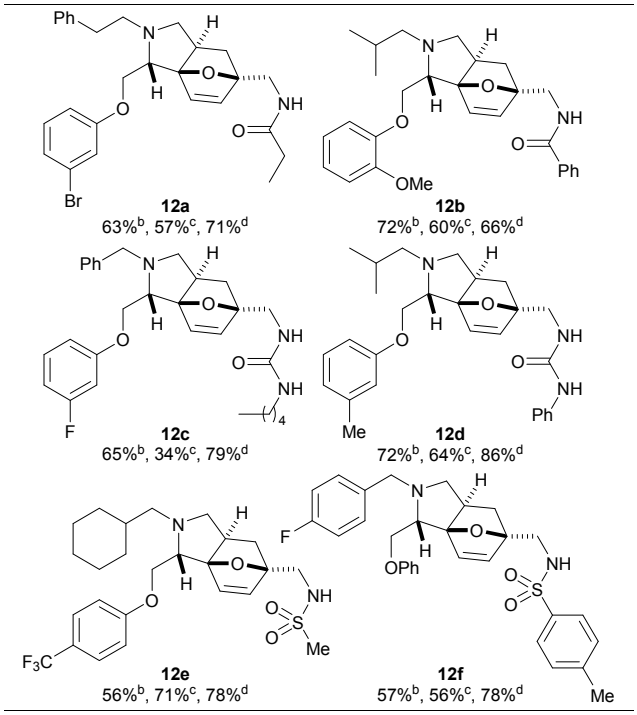
[a] Isolated yield after flash column chromatography. [b] Glycolaldehyde dimer was used as the aldehyde component. [c] Overall yield over two steps with isolation of the Petasis product (see ESI). [d] Masked α-hydroxy aldehyde **1** was used as the aldehyde component. [e] DMB = 2,4-dimethoxybenzyl.

Pleasingly, the use of the Boc-protected 5-aminomethyl-substituted 2-furylboronic acid **7b** gave the corresponding product **8c** in quantitative yield, thereby providing an additional handle for downstream diversification (entry 3). Importantly, these conditions minimized the formation of a by-product resulting from the reaction of masked α-hydroxy aldehyde **1** with the furyl boronic acid **7b** (see ESI), in contrast to when the reaction was carried out in a mixture of refluxing CH_2Cl_2 and HFIP (Figure 1). Consequently, the yield of **2** was improved from the original 68% to 91% (entry 4).Furthermore, the use of masked α-hydroxy aldehyde **1** in combination with furylboronic acid **7b** was well-tolerated for various allylamines (entries 5-8), although the yield of **8g** was slightly lower. The use of salicylaldehyde in the Petasis 3-CR/IMDA reaction with benzyl allylamine and 2-furylboronic acid gave the corresponding product in 84% yield (see ESI), and the X-ray structure unambiguously confirmed the diastereoselectivity of the transformation.

To allow for a more modular introduction of amine appendages, R^2, we investigated the possibility of deallylating **8c**, and then, through reductive amination, re-introduce amine substituents.

Table 2: Deallylation, reductive amination, *O*-arylation and primary amine functionalization for the synthesis of densely functionalized compounds **12**.[a]





[a] Reagents and conditions: a) $Pd(PPh_3)_4$, isopropylidene 2-methylmalonate, $CHCl_3$, reflux; b) R^1CHO, $NaBH(OAc)_3$, CH_2Cl_2, rt, 4 Å M.S; c) (i) ArOH, DEAD, PPh_3, THF, 0 °C to rt; (ii) TFA, CH_2Cl_2, 0 °C to rt; d) Carboxylic acid, PyBOP, $^iPr_2EtN$, CH_2Cl_2, rt; e) Isocyanate, $^iPr_2EtN$, CH_2Cl_2, rt; f) Sulfonyl chloride, $^iPr_2EtN$, CH_2Cl_2, rt. [b] Yield of **10**. [c] Yield of **11**. [d] Yield of **12**.

The use of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid in refluxing chloroform[6] gave full conversion of **8c** to **9**, but it proved challenging to remove the barbituric acid by-products during purification. However, the use of methyl Meldrum's acid (isopropylidene 2-methylmalonate)[7] effectively solved this

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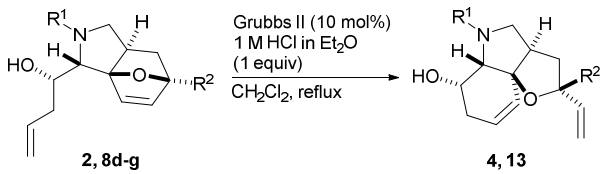
problem and **9** could be isolated in 51% yield (Table 2). We noted that the use of aqueous ammonium hydroxide as co-solvent for flash-column chromatography[8] was crucial, as triethylamine proved impossible to remove.

Reductive amination of the secondary amine with $NaBH(OAc)_3$ proceeded smoothly with both aromatic and aliphatic aldehydes to give **10** in good yields (Table 2). The primary hydroxyl group was then arylated with a set of phenols using the Mitsunobu reaction. Both electron-rich and electon-poor phenols, as well as more sterically demanding entities, were well-tolerated, and following Boc-deprotection, primary amines **11** were isolated in good yields over two steps. The concomitant Boc-deprotection was necessary in order to effectively remove by-products from the Mitsunobu reaction. A final diversification step consisting of acylation, carbamoylation and sulfonylation of the primary amines **11**, afforded the densely functionalized **12**. Hence, library members (**I**) were obtained in just five synthetic operations from commercially available starting materials, thereby validating the proposed library strategy.

Encouraged by these results, we investigated the scope of the ROM-RCM reaction (Table 3), with the goal of exploring a broader library design by utilizing the reaction to introduce scaffold diversity.

Table 3: Scope of the ROM-RCM reaction.



2, 8d-g **4, 13**

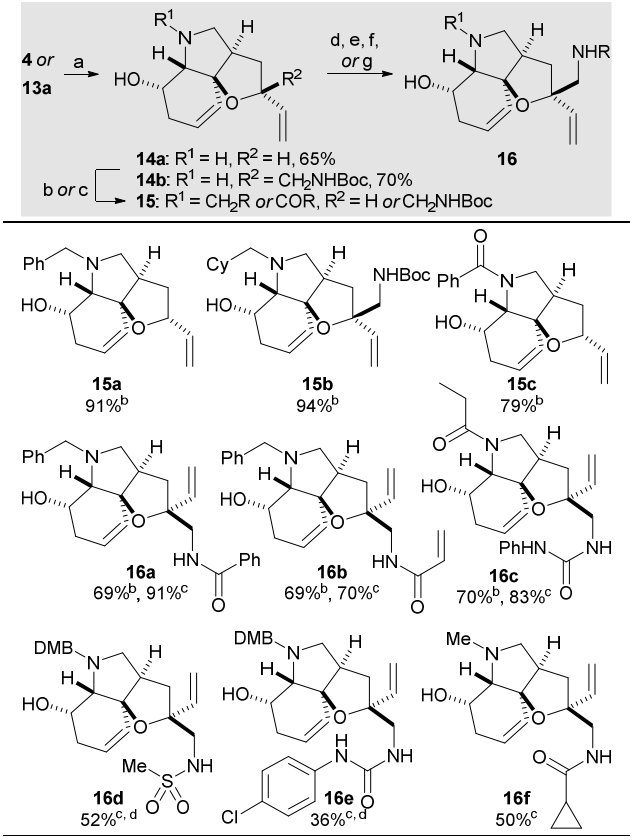
Entry	Substrate	R^1	R^2	Product, yield (%)[a]
1	**8d**	allyl	CH_2NHBoc	**13a**, 62
2	**2**	allyl	H	**4**, 76
3	**8e**	Bn	CH_2NHBoc	**13b**, 72, (80)[b]
4	**8f**	DMB[c]	CH_2NHBoc	**13c**, N.D.,[d] (76)[b]
5	**8g**	Me	CH_2NHBoc	**13d**, 65, (56)[b]

[a] Isolated yield after flash column chromatography. [b] Reaction conditions: Grubbs II (10 mol%), toluene, reflux. [c] DMB = 2,4-dimethoxybenzyl. [d] N.D. = not determined.

Compared to the initial reaction conditions used for R^2 = H (Figure 1A), substrates with $R^2 = CH_2NHBoc$ (Table 3), required elevated temperatures to bring about full conversion of starting materials. Pleasingly, **13a** was obtained from **8d** in a good yield of 62% (entry 1). By employing these conditions to the original substrate (**2**) the yield of **4** was improved from 66% to 76% (entry 2). Satisfyingly, also the benzyl- and methyl-substituted amines (**8e** and **8g**, respectively) readily underwent ROM-RCM to give the corresponding products **13b** and **13d** in 72% and 65% yield (entries 3 and 5), respectively. Interestingly, the ROM-RCM reaction of benzyl-, 2,4-dimethoxybenzyl (DMB)- and methyl-substituted amines took place in the absence of hydrochloric acid when the reaction was conducted in refluxing toluene (entries 3-5). Under these conditions the yield of **13b** was improved to 80%, **13c** was isolated in 76% yield (entries 4 and 5, respectively), while **13d** was isolated in slightly lower yield (56%) (entry 5). Attempts to bring about the ROM-RCM reaction of **8d** in the absence of hydrochloric acid were unsuccessful. Altogether these findings suggested that the nucleophilicity as well as steric hindrance of the amine were determining factors for the ROM-RCM reaction.

Implementing the same modular approach for installation of amine appendages as before, **4** and **13a** were deallylated (Table 4). Pleasingly, only the most accessible allylic olefin reacted to provide secondary amines **14a** and **14b i**n good yields of 65% and 70%, respectively (Table 4). The versatility of this approach was further demonstrated through both reductive amination and PyBOP-mediated acylation with carboxylic acids, to afford tertiary amines and amides **15.** For example, amide **15c** would otherwise be inaccessible through the Petasis 3-CR. Functionalizations of the primary amine were subsequently realized through Boc-deprotection followed by acylation, carbamoylation or sulfonylation to afford final library members **16**.

Table 4: Deallylation, reductive amination and acylation, followed by primary amine functionalization for the synthesis of novel scaffolds **16**.[a]



[a] Reagents and conditions: a) $Pd(PPh_3)_4$, isopropylidene 2-methylmalonate, $CHCl_3$, reflux; b) R^1CHO, $NaBH(OAc)_3$, CH_2Cl_2, rt, 4 Å mol sieves; c) Carboxylic acid, PyBOP, Et_3N, CH_2Cl_2, rt; d) (i) TFA, CH_2Cl_2, rt; (ii) Carboxylic acid, PyBOP, Et_3N, CH_2Cl_2, rt; e) (i) TFA, CH_2Cl_2, rt; (ii) Acid chloride, Et_3N, CH_2Cl_2, 0 °C to rt; f) (i) TFA, CH_2Cl_2, rt; (ii) Isocyanate, Et_3N, CH_2Cl_2, rt; g) (i) TFA, CH_2Cl_2, rt; (ii) Sulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt. [b] Yield of **15**. [c] Yield of **16**. [d] DMB = 2,4-dimethoxybenzyl.

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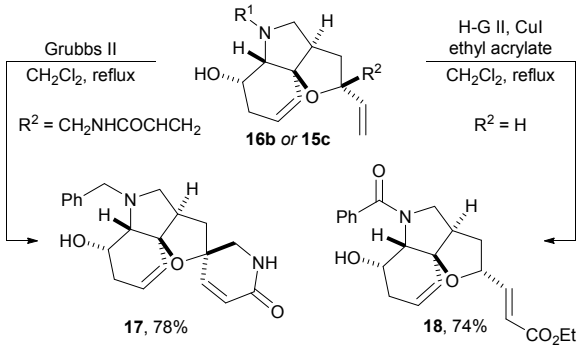
The introduction of the acryl amide moiety in **16b** provided the opportunity for further diversification through RCM of the terminal olefin, and the spirocyclic product **17** was isolated in 78% yield (Scheme 1). Cross-metathesis (CM) reactions were also investigated as a means of olefin functionalization, and while substrates with $R^3 = CH_2NHBoc$ only resulted in traces of product, Hoveyda-Grubbs 2nd generation catalyst (H-G II) in combination with copper(I)iodide[9] efficiently promoted the CM of **16e** with ethyl acrylate to afford **18** in 74% yield.



Scheme 1: Functionalizaton of the terminal olefin via RCM and CM.

In summary, we have developed a concise strategy for the synthesis of complex heterocyclic scaffolds utilizing a highly diastereoselective tandem Petasis 3-CR/IMDA reaction in combination with a ROM-RCM sequence. Through the incorporation of strategically positioned functional groups, we have synthesized a library of densely diversified small molecules that mimic the structural complexity of natural products.

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Notes and references

§ See NOESY assignments for **8b** in ESI.

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