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Combining the Petasis 3-Component Reaction with Multiple Modes of Cyclization: A Build/Couple/Pair Strategy for the Synthesis of Densely Functionalized Small Molecules

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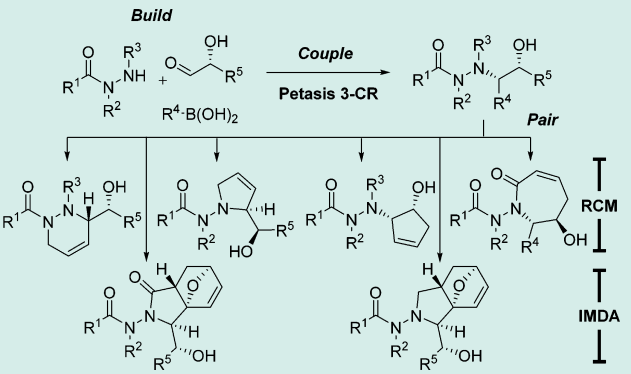
Supporting Information

ABSTRACT: A *build/couple/pair* strategy for the synthesis of complex and densely functionalized small molecules is presented. The strategy relies on synthetically tractable building blocks (build), that is, diversely substituted hydrazides, α-hydroxy aldehydes, and boronic acids, which undergo Petasis 3-component reactions (couple) to afford densely functionalized *anti*-hydrazido alcohols. The resulting scaffolds can subsequently be converted via chemoselective cyclization reactions (pair), including intramolecular Diels–Alder or Ru-alkylidene catalyzed ring-closing metathesis, into sets of structurally diverse heterocycles in good yields in only 3–4 steps.



KEYWORDS: *Petasis 3-component reaction, intramolecular Diels–Alder reaction, ring-closing metathesis, build/couple/pair, diversity-oriented synthesis*

In recent years, new synthetic concepts and methodologies have been proposed for the design and synthesis of molecular screening libraries.[1] Challenged by a tendency of traditional vendor libraries to incorporate simple and relatively "flat" molecules, as defined by their high content of sp^2-hybridized carbon,[2] evidence suggests that many available compound collections are not meeting the structural requirements of more demanding targets, such as protein–protein interactions, transcription factors and nucleic acid macromolecules.[1g] Some particularly successful strategies have heralded molecular diversity as a design parameter to access target-relevant chemical space. These strategies typically rely on short synthetic pathways yielding skeletally and stereochemically diverse molecular scaffolds, frequently drawing upon structural inspiration from natural products.[3] By maximizing the number of stereogenic carbon atoms in these scaffolds, emerging trends emphasize that spatially well-defined molecules more smoothly may be elaborated into selective modulators of biological targets.[4] In an effort to meet some of these challenging goals, diversity-oriented synthesis (DOS) tactics referred to as *build/couple/pair* (B/C/P) strategies have recently been proposed.[1e,5]

We herein report our efforts toward the development of a synthetic pathway that starts with readily available building blocks (build), comprising diverse mono-, di-, and trisubstituted hydrazides, α-hydroxy aldehydes and boronic acids, and combines the use of robust organic reactions, namely, Petasis 3-component (couple),[6] intramolecular Diels–Alder (IMDA),[7] and Ru-alkylidene catalyzed ring-closing metathesis (RCM) reactions (pair) (Figure 1).[8] We have previously reported the applicability of hydrazides in the Petasis 3-component reaction (3-CR), and the efficient and selective elaboration of hydrazido alcohols (**I**, Figure 1) into oxazolidinones and oxadiazolones by controlled carbonylation processes (**VI** and **VIII**, Figure 1).[9] We have also successfully combined Petasis 3-CRs with Ru-catalyzed cyclizations of simple amines to construct diverse 5- and 7-membered ring-systems.[5f]

In a continuous search for screening-relevant molecular entities, we desired to investigate if an elaboration of these strategies could further expand the array of accessible heterocycles from the Petasis 3-CR template, specifically via strategic positioning of functional groups, such as vinyl and furyl moieties, which would participate in RCM and IMDA reactions (**II**–**V** and **VII**, Figure 1).

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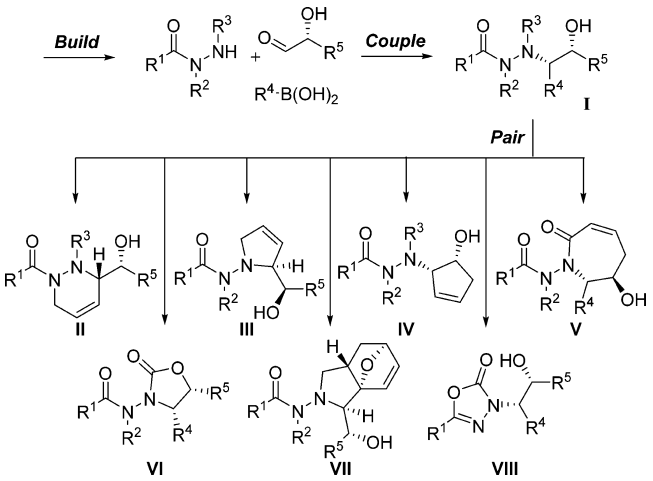


Figure 1. Build/couple/pair strategy utilizing the Petasis 3-component (couple) and cyclization (pair) reactions for the synthesis of densely functionalized compounds.

In accordance with our previous work,[9] the Petasis 3-CR of hydrazides (**1**), α-hydroxy aldehydes (**2**), and both vinyl and aryl boronic acids (**3**) proceeded smoothly in MeOH to provide an array of densely functionalized diastereomerically pure *anti*-hydrazido alcohols in good to excellent yields (**4**{*1*−*25*}, Scheme 1). When using electron-rich 2-furyl boronic acid yields were typically higher compared to the less electron-rich vinyl and phenyl boronic acids, and the reactions were generally promoted using 1,1,1,3,3,3-hexafluoro-propan-2-ol (HFIP) as a cosolvent.[10]

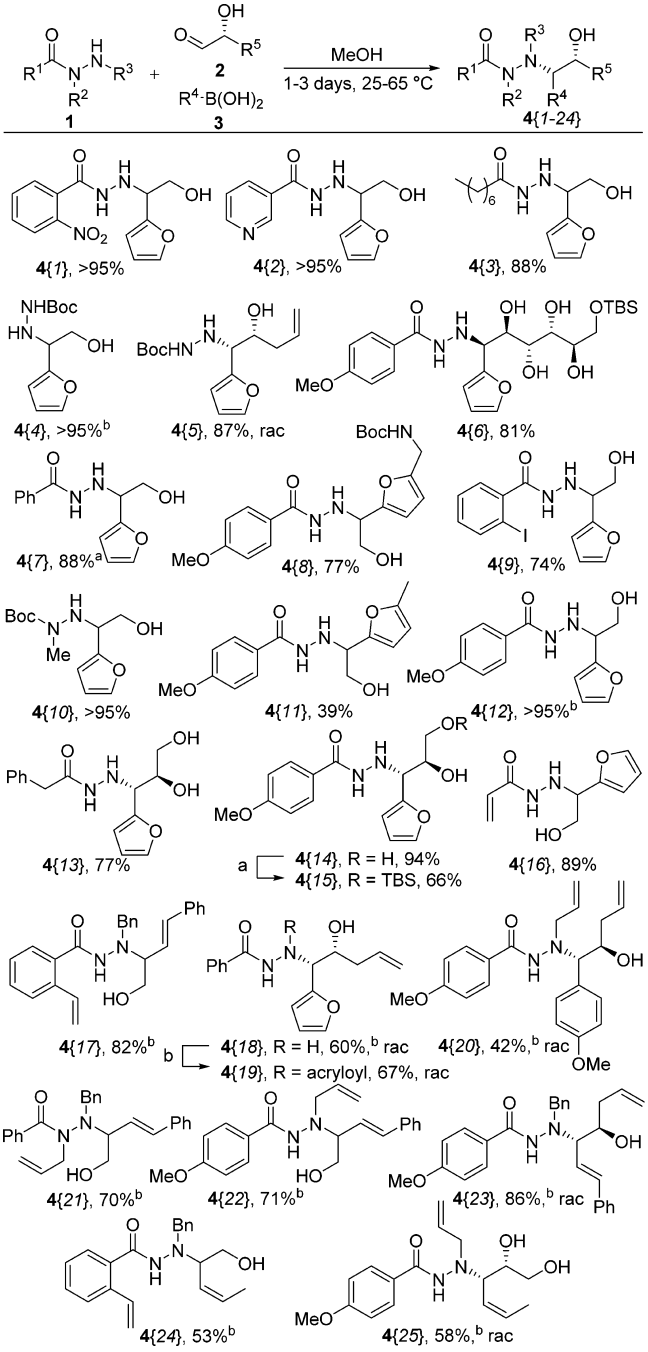
Interestingly, when *N*′-allylated hydrazides (**5**) were subjected to the Petasis 3-CR with 2-furyl boronic acid in refluxing MeOH, the expected Petasis 3-CR products (**6**) rapidly formed before a clean conversion (*albeit* more slowly) provided the diastereomerically pure IMDA adducts 7{*1*} and 7{*2*} (Scheme 2).

Having confirmed the viability of furyl-functionalized Petasis 3-CR products as IMDA precursors, we next decided to investigate if the *N*′-linked double bond could be introduced at a later synthetic stage, thereby providing a more divergent approach to the IMDA products. This would also allow for the use of unsubstituted hydrazides in the Petasis 3-CR. Gratifyingly, Petasis 3-CR product **4**{*12*} could be easily allylated with allyl bromide followed by refluxing in toluene to give IMDA product 7{*1*} in acceptable yield (41% over two steps, Scheme 3). Acrylic variants of the scaffold were obtained analogously by subjecting **4**{*12*} and **4**{*4*} to *O*-TBS-protection, *N*-acryloylation with acryloyl chloride and heating (refluxing toluene), providing IMDA adducts **11**{*1*} and **11**{*2*} in good yields over 3 steps (51% and 47%, respectively).

The scope of the acryloylation/IMDA sequence was investigated for a series of furyl-containing Petasis 3-CR products **4**{*1*−*13*} and **4**{*15*}. In general, the desired products (**12**{*1*−*6*} and **12**{*10*−*13*}) were obtained in decent to good yields (47−76%). The slightly lower yields observed for the formation of **12**{*7*−*9*} (25−44%) presumably reflect the low solubility of their corresponding starting materials during the acryloylation step.

Interestingly, when switching to methacryloyl chloride as the acryloylating agent (Scheme 5), the reaction of compound **9**{*2*} provided a mixture of anti diastereomers **13**{*1*} and **13**{*2*} after IMDA reaction (58% and 14% over 3 steps, respectively).

Scheme 1. Petasis 3-CR: Synthesis of Densely Functionalized *Anti*-Hydrazido Alcohols (Couple)[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) acryloyl chloride, Et_3N, THF, −78 °C. [b]10% HFIP added as a cosolvent.

Having established efficient protocols for IMDA reactions of vinyl and furyl moieties, pairwise reactive diene combinations were subjected to Ru-catalyzed RCM. For example, when subjecting the Petasis 3-CR products **4**{*21*−*23*} and **4**{*25*} to RCM conditions, three different ring systems (compounds **14**{*1*}, **14**{*3*−*4*}, and **14**{*5*}) were obtained in good yields (58−80%, Scheme 6). Unfortunately, despite the use of a range of different RCM conditions, Petasis 3-CR product **4**{20} could never be converted to the desired 7-membered ring **14**{*6*}. However, a related ring system could be obtained by

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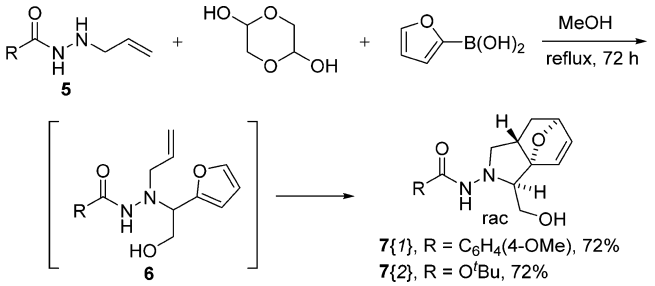
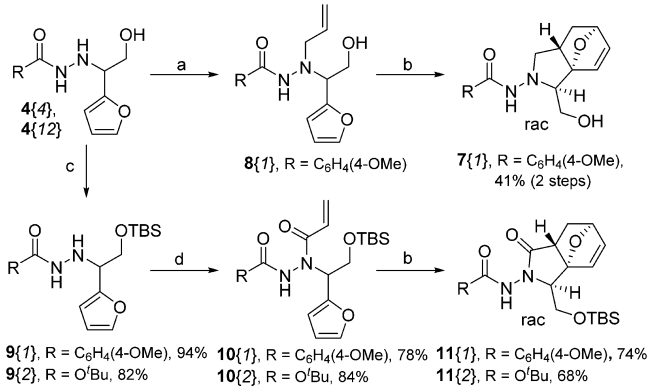
Scheme 2. Tandem Petasis 3-CR and Intramolecular IMDA Reaction (Couple−Pair)



Scheme 3. Functional Group Pairing via IMDA Reaction (Pair)[a]



[a]Reagents and conditions: (a) allyl bromide, Et_3N, DMF, 60 °C; (b) toluene, reflux; (c) TBSCl, imidazole, DMF, rt; (d) acryloyl chloride, Et_3N, CH_2Cl_2, −78 °C.

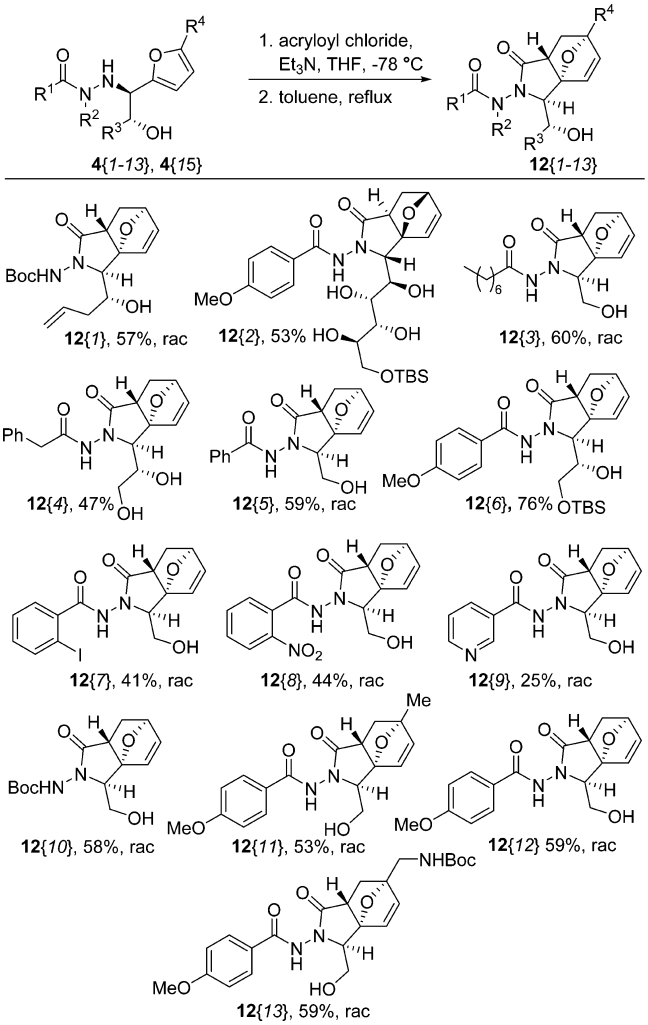
conversion of acryloylated compound **4**{*19*} to compound **14**{*2*} in good yield (70%), suggesting that the basic *N* of **4**{*20*} inactivates the metathesis catalyst. Attempts made to synthesize larger ring systems by RCM of the Petasis 3-CR products **4**{*17*} and **4**{*24*} were all unfruitful.

Finally, we envisioned that the exocyclic alcohol-moiety in the IMDA products (originating from the α-hydroxy aldehydes) could serve as an entry for further skeletalization reactions. Accordingly, compounds **12**{*12*} and **12**{*6*} were mesylated and subjected to NaH in a set of commonly used solvents at room temperature. However, under these conditions the mesylated compounds **15**{*1*−*2*} appeared completely unreactive. This issue was resolved by elevating the temperature, which resulted in the formation of different products depending on the nature of the solvent. For instance, complex reaction mixtures were observed when using THF and CH_2Cl_2, whereas reactions in toluene or DMF at 80 °C resulted in clean conversions to either eliminated product **16** (toluene) or cyclized product **17**{*1*} (DMF). In the same manner, subjection of mesylate **15**{*2*} to NaH in toluene provided compound **17**{*2*} as a single enantiomer in good yield (76%).

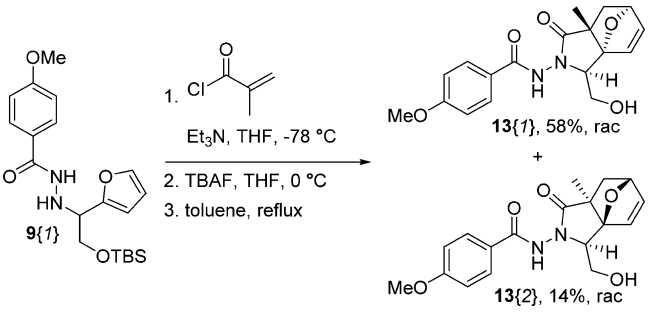
The stereochemistry of compound **17**{*2*} was assigned via X-ray crystallography (Figure 2), which provided unambiguous confirmation of the exo-anti selectivity of the IMDA reaction and proved that the NaH-mediated cyclization proceeds via S_N2-inversion.

In conclusion, we have shown the feasibility of forming a collection of structurally diverse heterocycles through a build/couple/pair pathway that combines the Petasis 3-CR reaction

Scheme 4. Sequential Acryloylation and IMDA Reactions (Pair)



Scheme 5. Intramolecular Diels−Alder Reactions (Pair)



of diverse hydrazides with regio- and stereoselective cyclization reactions, including ring-closing metathesis and intramolecular Diels−Alder reactions. Using this strategy, 10 structurally distinct scaffolds were synthesized in good yields in only 3−4 steps. Functionalized hydrazido alcohols accessed through the Petasis 3-CR are synthetically versatile templates for subsequent cyclization reactions at several positions, thus constituting valuable compounds of modular and synthetically programmable pathways. The presented key cyclization steps of the pathway take advantage of pairwise reactive functional groups of a densely functionalized hydrazido alcohol template,

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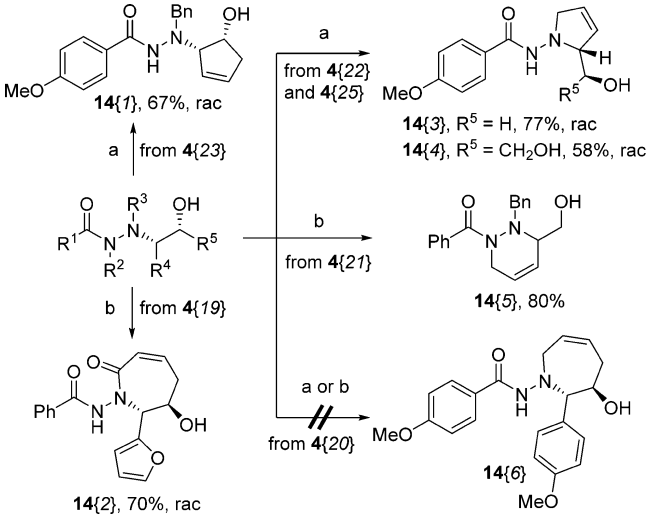
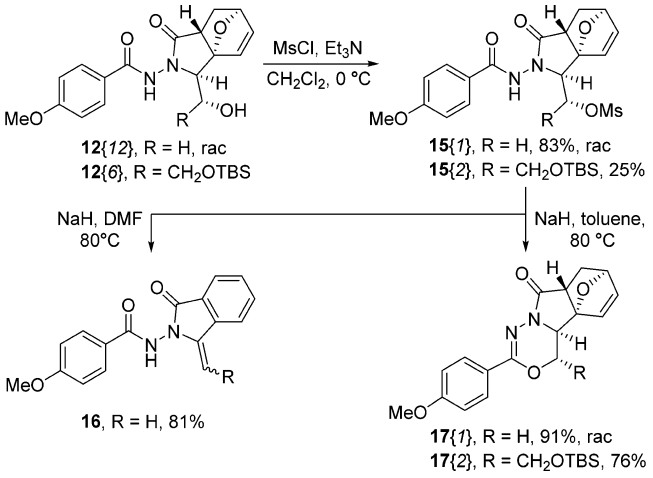
Scheme 6. Ring-Closing Metathesis of Diene-Containing Hydrazido Alcohols (*Pair*)[a]



[a]Reagents and conditions: (a) Grubbs II (10 mol %), toluene, 65 °C, 2 h; (b) Grubbs II (10 mol %), CH_2Cl_2, rt, overnight.

Scheme 7. Solvent-Dependent Cyclization and Elimination of Mesylates



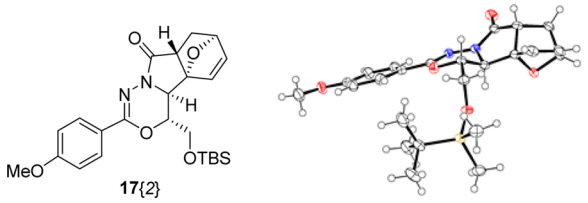


Figure 2. Crystal Structure of Compound **17**{2}.

leaving any remaining handle amenable to additional diversification, including secondary cyclization processes, and appendage decoration.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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