Multicomponent Reactions

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Short Synthesis of Skeletally and Stereochemically Diverse Small Molecules by Coupling Petasis Condensation Reactions to Cyclization Reactions**

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Herein, we report a short and efficient synthetic pathway that uses intramolecular cyclization reactions of readily synthesized and densely functionalized amino alcohols. The research illustrates the implementation of a strategy that enables the synthesis, in only three to five steps, of a diverse collection of single-isomer small molecules whose members have over 15 different types of skeleton. In the future, this research should also enable the consequences of the unique structural features of the compounds in small-molecule screens to be determined.[1,2]

We used the Petasis three-component, boronic acid Mannich reaction[3] followed by an amine propargylation to yield β-amino alcohols **1**. These compounds bear polar (amino, hydroxy, ester) and nonpolar (alkene, alkyne, cyclopropane) functionalities strategically placed as handles for subsequent skeletal diversification reactions (Scheme 1).

The Petasis reaction of (*S*)-lactol **2a** (from L-phenyllactic acid), L-phenylalanine methyl ester (**3a**), and (*E*)-2-cyclopropylvinylboronic acid (**4**) proceeded smoothly under ambient conditions in EtOH to afford the *anti* diastereomer **5aa** exclusively in 85% yield.[4] The same conditions but with (*R*)-lactol **2b** afforded the corresponding (2*R*,3*S*) isomer **5ba** exclusively (Scheme 2). These reactions indicate that the secondary hydroxy group adjacent to the intermediate imines directs the stereochemical outcome of the reaction, overriding any directing effects of the stereocenter in **3a**.[3b] These

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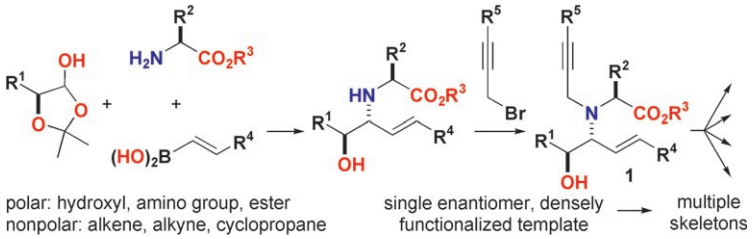
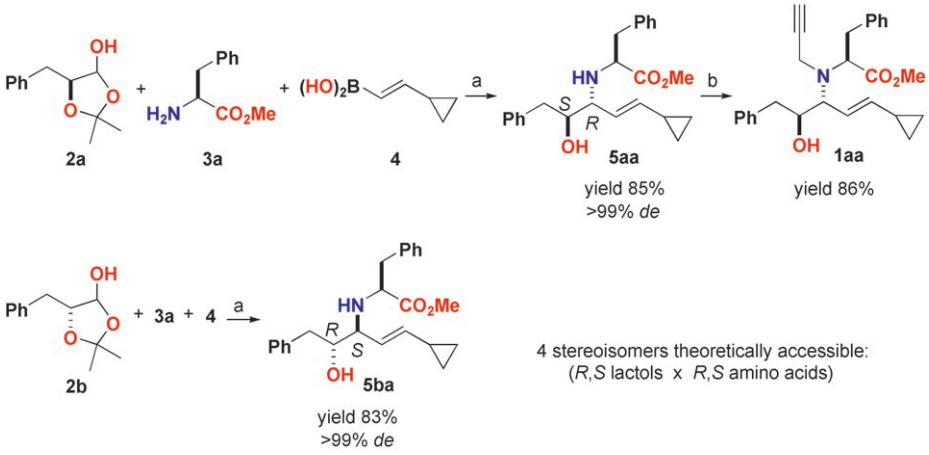
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. The Petasis reaction followed by amine propargylation to yield β-amino alcohols **1**.



Scheme 2. a) EtOH, RT; b) propargyl bromide, $NaHCO_3$, *N*,*N*,-dimethylformamide (DMF), 70 °C.

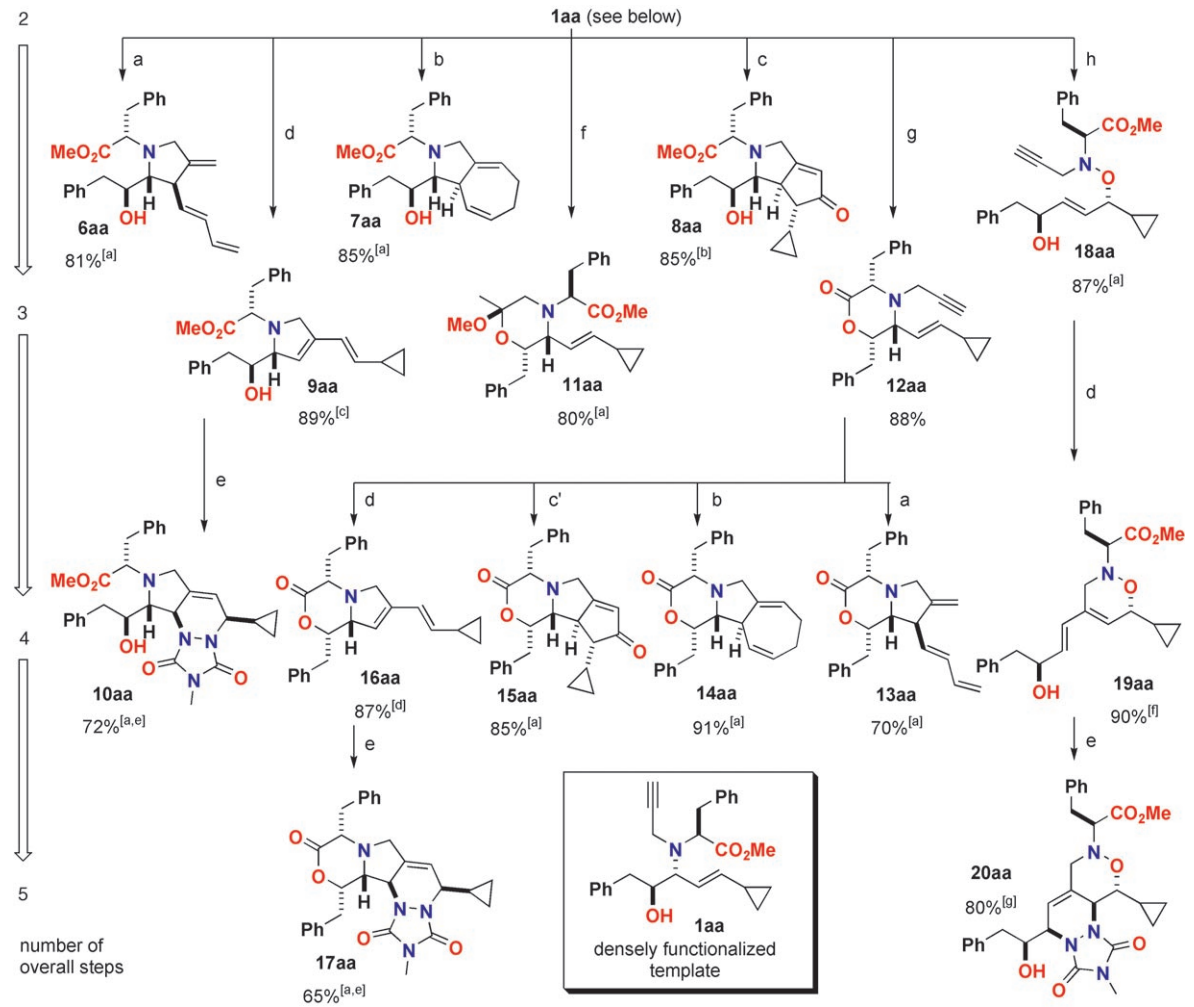
results suggest that all four of the possible *anti* amino alcohol stereoisomers can be generated by appropriate combination of stereoisomeric lactols and amino acids, thus leading to stereochemical diversity in the final products of this pathway. Although not explored herein, there is a reasonable assumption that appendage diversification may also be achieved by variation of the lactol building block; appendage diversification by varying the amino component is described below. To prepare a test substrate for subsequent skeletal diversification, the *N*-selective alkylation of **5aa** with propargyl bromide afforded the template **1aa** in 86% yield.

We next explored a series of skeletal diversification reactions with **1aa** (Scheme 3).[4] Cycloisomerization catalyzed by $[Pd(PPh_3)_2(OAc)_2]$ resulted in opening of the cyclopropyl ring to afford triene **6aa** by a β-hydride elimination/reductive elimination sequence,[5] whereas cycloisomerization catalyzed by $[CpRu(CH_3CN)_3PF_6]$ (Cp = cyclopentadienyl) resulted in a [5+2] reaction to afford cyclic diene **7aa** by a cyclopropyl ring-opening/reductive elimination sequence.[6] Both reactions proceeded in a diastereoselective manner to afford single diastereomers. To the best of our knowledge, there have been no reports on palladium-catalyzed cycloisomerizations accompanied by opening of a cyclopropyl ring to furnish a triene. A Pauson–Khand reaction of **1aa** with $[Co_2(CO)_8]$ in the presence of trimethylamine *N*-oxide[7] proceeded efficiently to provide azabicyclo-[3.3.0] **8aa** diastereoselectively (>10:1 d.r.). Enyne metathesis of **1aa** using the Hoveyda–Grubbs catalyst[8] gave diene **9aa**, which, following Diels–Alder reaction with 4-methyl-1,2,4-triazolin-3,5-dione at room temperature, afforded tricyclic compound **10aa**. The stereochemistry of the only isolated isomer **10aa** results from the dienophile approaching the side opposite to the substituent on the pyrroline ring of **9aa**. Electrophilic activation of the alkyne functionality in **1aa** with $NaAuCl_4$ in MeOH led to the intramolecular cyclization of the hydroxy group followed by incorporation of MeOH to provide a morpholine skeleton **11aa** as a single diastereomer,[9] likely because of an anomeric effect. Treatment of **1aa** with NaH at room temperature gave lactone **12aa** in 88% yield without epimerization. Lactone **12aa** was subjected to the same reaction conditions as those for template **1aa** to furnish the corresponding bicyclic triene **13aa**, fused tricyclic [5+2] product **14aa**, fused tricyclic enone **15aa**, and bicyclic diene **16aa** in good yield. Diene **16aa** was further converted into fused tetracyclic compound **17aa** by a Diels–Alder reaction using the same conditions as before. Transformations of lactone **12aa** also proceeded with high diastereoselectivity to afford each product as a single detectable diastereomer.

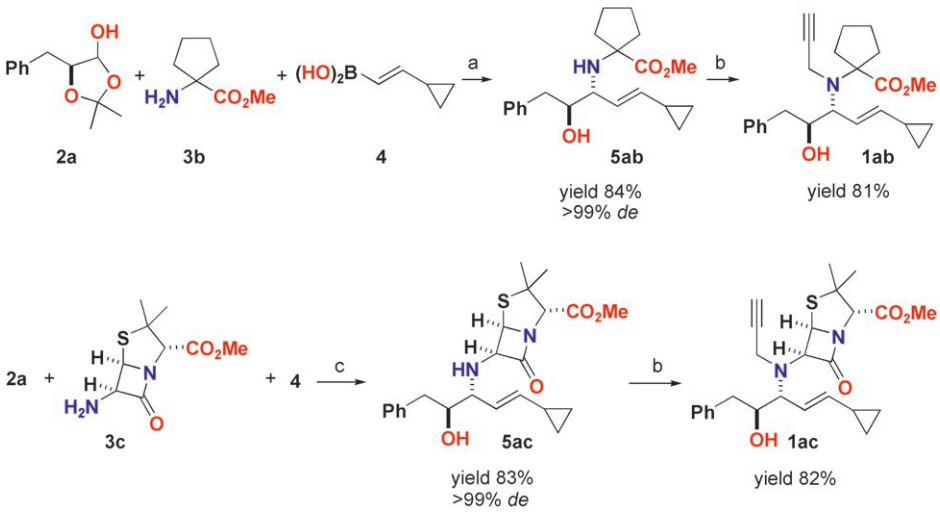
We next demonstrated this diversity-oriented synthesis (DOS) pathway using different starting building blocks. A Petasis reaction with methyl 1-amino-1-cyclopentanecarboxylate (**3b**) afforded *anti* amino alcohol **5ab** exclusively in 84% yield under modified conditions (solvent system: CH_2Cl_2/1,1,1,3,3,3-hexafluoroisopropanol).[4,10] Subsequent propargylation furnished **1ab** in 81% yield (Scheme 4).

The cyclopentyl template **1ab** was next subjected to the same skeletal diversification reactions described above to provide the corresponding products with a spiro ring system (Scheme 5).[4] The reactions afforded skeletally distinct compounds **6ab**–**20ab** in good yield with high diastereoselectivity, whereas **8ab** cyclized under reaction conditions to form lactone **15ab**. The mild and chemoselective nature of these diversification reactions allows the use of chemically complex building blocks, such as 6-aminopenicillanic acid methyl ester (**3c**). The two-step preparation of the common template **1ac** with **3c** proceeded with excellent diastereoselectivity (Scheme 4).[4] The transition-metal-catalyzed diversification reactions worked well under the same conditions described for the L-Phe series despite the sulfur atom in the penam skeleton, whereas basic treatment resulted in ring opening of β-lactam to afford lactone **21ac** bearing a thiazolidine ring (Scheme 5).

We initiated this research with the hypothesis that densely substituted small molecules with diverse skeletons and stereochemistries will be especially effective in small-molecule screens. This new DOS pathway should enable the further testing of this hypothesis in an effective way owing to its ability to yield remarkably diverse, rigid, and complex small molecules with considerable efficiency. We are encouraged by preliminary results that have assigned, among others, high-feature signatures to a cluster of compounds that result from this pathway using multidimensional, cell-based screen-



Scheme 3. a) $[Pd(PPh_3)_2(OAc)_2]$ (10 mol%), benzene, 80°C; b) $[CpRu(CH_3CN)_3PF_6]$ (10 mol%), acetone, RT; c′) $[Co_2(CO)_8]$, trimethylamine *N*-oxide, NH_4Cl (for conditions c), benzene, RT; d) Hoveyda–Grubbs second-generation catalyst (10 mol%), CH_2Cl_2, reflux; e) 4-methyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2, RT; f) $NaAuCl_4$ (10 mol%), MeOH, RT; g) NaH, toluene, RT; h) *m*CPBA, THF, −78→0°C. [a] Single diastereomer; [b] >10:1 d.r.; [c] *trans*/*cis* = 6.7:1; [d] *trans*/*cis* = 6.4:1; [e] from *trans* diene; [f] *trans*/*cis* = 3:1; [g] combined yield from the *trans* and *cis* dienes. *m*CPBA = *m*-chloroperbenzoic acid.



Scheme 4. a) CH_2Cl_2/1,1,1,3,3,3-hexafluoroisopropanol = 9:1, RT; b) propargyl bromide, $NaHCO_3$, DMF, 70°C; c) EtOH/1,1,1,3,3,3-hexafluoroisopropanol (9:1), RT.

ing.[11] Small molecules prepared by this pathway are being included in a public effort to assess comparatively the role of structural features in assay measurements.[12] Such studies are hoped to illuminate the variation of assay outcomes that result from small molecules distinct in both their origins (natural and non-natural) and structural features.

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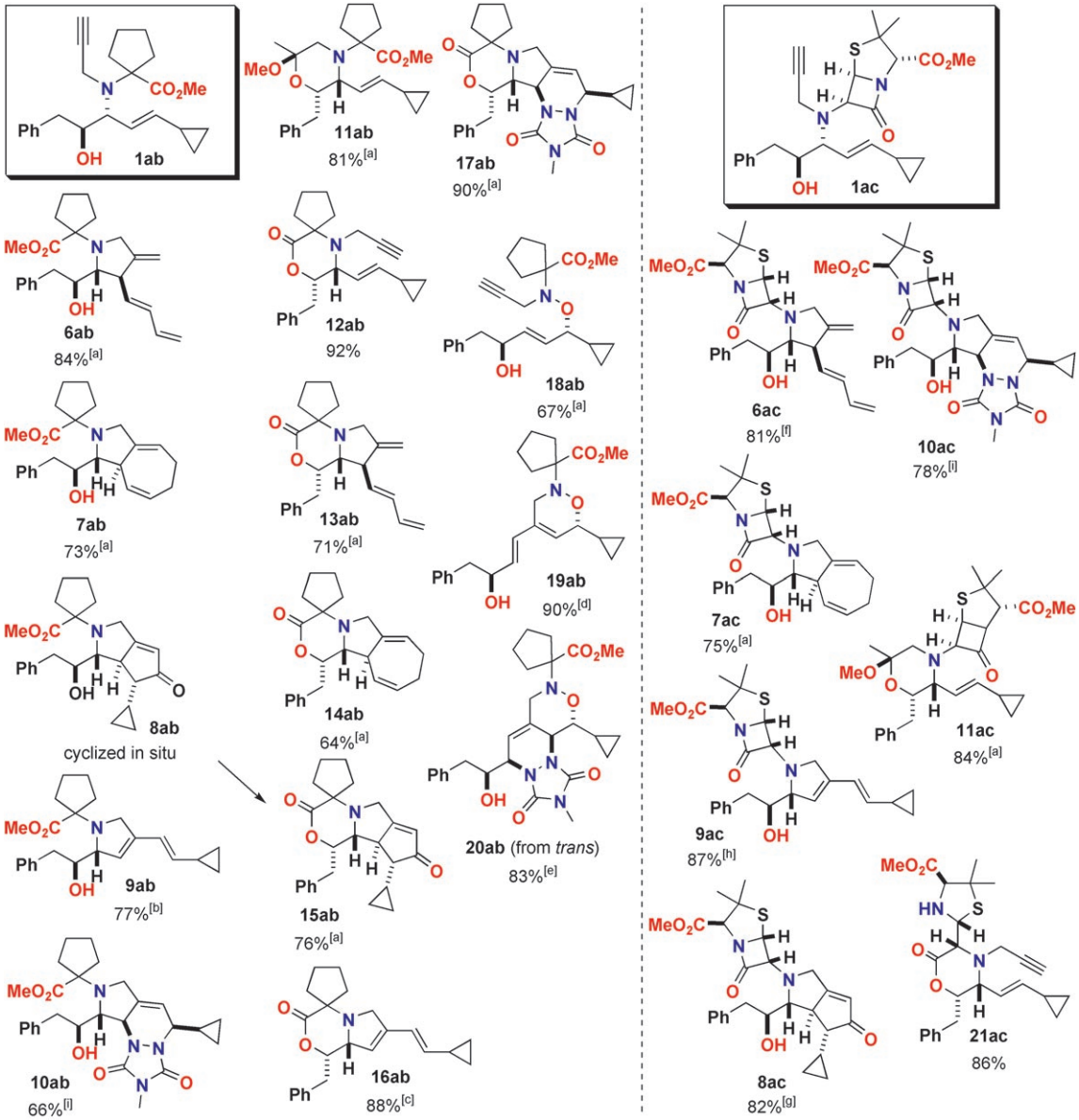

Scheme 5. [a] Obtained as a single diastereomer; [b] *trans*/*cis* = 3:1; [c] *trans*/*cis* > 13:1; [d] *trans*/*cis* = 5:1; [e] combined yield from the *cis* and *trans* dienes; [f] 3:1 d.r.; [g] > 12:1 d.r.; [h] *trans*/*cis* = 5.6:1; [i] from the *trans* diene.

[1] S. L. Schreiber, *Chem. Eng. News* **2003**, *81*, 51.

[2] R. L. Strausberg, S. L. Schreiber, *Science* **2003**, *300*, 294.

[3] a) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445; b) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1998**, *120*, 11798.

[4] The structures and stereochemistry of all the reported compounds were determined by detailed spectroscopic analyses, including an X-ray structure of a diastereomer of **10aa** prepared from **5ba** (see the Supporting Information).

[5] For a review of cycloisomerization of 1,6-enynes, see: a) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813; c) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215.

[6] a) B. M. Trost, F. D. Toste, H. Shen, *J. Am. Chem. Soc.* **2000**, *122*, 2379; for pioneering studies of [5+2] cycloadditions, see: b) P. A. Wender, H. Takahashi, B. Witulski, *J. Am. Chem. Soc.* **1995**, *117*, 4720.

[7] a) I. U. Khand, G. R. Knox, P. L. Pauson, *J. Chem. Soc. Perkin Trans. 1* **1977**, 977; b) P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855; c) S. Shambayati, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, *31*, 5289.

[8] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[9] Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729.

[10] K. K. Nanda, B. W. Trotter, *Tetrahedron Lett.* **2005**, *46*, 2025.

[11] P. A. Clemons, unpublished results; such signatures reflect both the activity and selectivity of these compounds in a panel of 16 cell-based assays. These preliminaries studies follow the concepts reported in: Y.-K. Kim, M. A. Arai, T. Arai, J. O. Lamenzo, E. F. Dean III, N. Patterson, P. A. Clemons, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 14740–14745.

[12] This public effort ("The Forma Project") is sponsored by the NCI Initiative for Chemical Genetics, see: http://www.broad.harvard.edu/chembio; all assay measurements will be made publicly available in ChemBank.[2]

