Expanding Stereochemical and Skeletal Diversity Using Petasis Reactions and 1,3-Dipolar Cycloadditions

Giovanni Muncipinto,† Taner Kaya,‡ J. Anthony Wilson,‡ Naoya Kumagai,§ Paul A. Clemons,‡ and Stuart L. Schreiber*,‡

Howard Hughes Medical Institute, Broad Institute of Harvard and MIT, 7 Cambridge Center, Cambridge, Massachusetts 02142, United States, and Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

stuart_schreiber@harvard.edu

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ABSTRACT

A short and modular synthetic pathway using intramolecular 1,3-dipolar cycloaddition reactions and yielding functionalized isoxazoles, isoxazolines, and isoxazolidines is described. The change in shape of previous compounds and those in this study is quantified and compared using principal moment-of-inertia shape analysis.

Small-molecule synthesis is enabling the testing of hypotheses concerning the structural properties that enable successful outcomes in probe and drug discovery. For example, diversity-oriented synthesis was used recently to illuminate roles for stereogenic elements and sp³ hybridization in the outcome of binding assays using a large panel of diverse proteins. Small molecules having these features showed increased specificity and hit frequency relative to those lacking these features.¹

Here, we report a short and modular synthetic pathway using the “build/couple/pair” strategy² with allylic alcohol rearrangements and intramolecular 1,3-dipolar cycloadditions of readily synthesized and densely functionalized amino alcohols. The pathway yields functionalized isoxazoles, isoxazolines, and isoxazolidines. As in a previous study,³ we used the Petasis three-component, boronic acid based Mannich reaction⁴ in the couple phase, where lactols and boronic acids are joined with high anti-selectivity. By using different functional groups incorporated in the build phase, we were able to perform intramolecular “pairing” reactions yielding novel skeletons (Figure 1). Using computational analyses, we demonstrate quantitatively how the new pathway expands the scope of the previous study and of screening candidates in general.

The Petasis reaction of (S)-lactol 2 (from L-phenyllactic acid), amino acetal 3 (from L-phenylalaninol), and 4-methoxyphenylboronic acid under ambient conditions in CH₂Cl₂ afforded the anti-diastereomer 4 with dr 94:6 in 79% yield. The N-selective alkylation of 4 with propargyl bromide 5

¹ Harvard University.
² Broad Institute of Harvard and MIT.
³ Current address: Graduate School of Pharmaceutical Sciences, The University of Tokyo.


using microwave radiation afforded the template 1a in 86% yield (Scheme 1). Standard conditions for the N-alkylation resulted in a poor yield or decomposition of propargyl bromide.

We next explored allylic alcohol rearrangements with the templates 6 and 7 (Scheme 2). Acetylation of 1a and selective deprotection of tert-butyldiphenylsilyl ether of 1b afforded 1c in 93% yield over two steps. Compound 1c was then subjected to stereoselective reductions of its alkyne moiety. The trans allylic alcohol 6 was obtained using LiAlH₄ in 86% yield, whereas the cis allylic alcohol 7 was obtained using hydrogenation with Lindlar’s catalyst6 in 90% yield. An Eschenmoser–Claisen rearrangement7 of 6 using N,N-dimethylacetamide dimethyl acetal gave amide 8 in 82% yield as single diastereomer. Compound 6 underwent an Overman rearrangement rapidly at room temperature8 affording allylic trichloroacetamide 9 as a single diastereomer with complete transfer of chirality. The reaction was performed in CH₂Cl₂ with trichloroacetone and DBU as base in slight excess.

Although not yet explored, the removal of the trichloroacetyl group should provide a versatile primary amino function. Palladium(II)-catalyzed rearrangement of allylic acetate9 in 90% yield. While standard acidic hydrolysis of the acetel failed, microwave-assisted conditions using catalytic pyridinium p-toluenesulfonate succeeded, generating the corresponding aldehydes of 1c and 6–11.

Intramolecular cycloadditions of the corresponding nitrile oxides of these aldehydes bearing alkene or alkyne groups provided bicyclic compounds 12–16 (oxime formation; N-bromosuccinimide, catalytic pyridine, triethylamine,12 and oximes derived from aldehyde derivatives of 1c and 6–11 with hydroxylamine hydrochloride (65–79%). While standard acidic hydrolysis of the acetel failed, microwave-assisted conditions using catalytic pyridinium p-toluenesulfonate succeeded, generating the corresponding aldehydes of 1c and 6–11.

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Reagents and conditions: (a) Ac-O, DMAP, py, rt; (a) MW, pyridinium p-toluenesulfonate (PPTS) (30 mol %), acetone, 10 min at 80 °C, 15 min at 100 °C. (b) N-hydroxylamine hydrochloride, NaHCO₃, dry MeOH; rt; (b) N-methylhydroxylamine hydrochloride, NaHCO₃, dry toluene, rt to 80 °C; (c) Et₃N, py (cat.), NBS, dry CH₂Cl₂, 100 °C; (d) -methyl hydroxylamine hydrochloride with heating at 80 °C.

Unfortunately, the acetal hydrolysis was not as successful as expected due to problems with the acetal hydrolysis. Moreover, when the unsubstituted hydroxylamine was replaced by the unstable 1c, the yield due to decomposition in the acetal hydrolysis step, but the final isoxazolines, albeit in poor yield, were isolated. Only 17 was obtained in appreciable yield (50%) over 3 steps. 17 Water reacted with the unstable azolidines 17–21 in 47–50% yield over 3 steps. Intra- molecular nitrone cycloadditions of 6 and 7 proceeded in poor yield due to problems with the acetal hydrolysis. Moreover, when the alkyl group in 1c was allowed to react with the nitrone under identical conditions, the expected isoxazoline was not isolated. Only 17 was obtained in appreciable yield (50%) over 3 steps. Water reacted with the unstable isoxazoline during the workup. Except for 18, all isoxazolines were obtained as stereomerically pure substances. The stereochemistry of the isoxazoline rings was assigned using ¹H NMR, COSY, and differential NOE and by comparing data from with similar compounds (Table 1).18,19

The stereochemistry was assigned by differential NOE spectroscopy and by comparing data from with similar compounds.14 Unfortunately, the acetal hydrolysis was not as successful with the scaffolds 6 and 7 due to decomposition in the acetal hydrolysis step, but the final isoxazolines, albeit in poor yield, were obtained (see Supporting Information).

When the unsubstituted hydroxylamine was replaced by N-methyl hydroxylamine hydrochloride with heating at 80 °C in toluene,15 the presumed (Z)-nitrones16 yielded isoxazolidines 17–21 in 47–50% yield over 3 steps. Intramolecular nitrone cycloadditions of 6 and 7 proceeded in poor yield due to problems with the acetal hydrolysis. Moreover, when the alkyl group in 1c was allowed to react with the nitrone under identical conditions, the expected isoxazoline was not isolated. Only 17 was obtained in appreciable yield (50%) over 3 steps.17 Water reacted with the unstable isoxazoline during the workup. Except for 18, all isoxazolines were obtained as stereomerically pure substances. The stereochemistry of the isoxazoline rings was assigned using ¹H NMR, COSY, and differential NOE and by comparing data from with similar compounds (Table 1).18,19

As illustrated in the proposed transition states (Figure 2), the approach of the allylic group to the nitrone from the re side having a minor steric interaction between nitrone oxygen and hydrogen at position 2 is more favorable than an attack from the si side having a major steric interaction between oxygen and benzyl group.20 The trans-orientation at positions 2 and 3 and cis-orientation at positions 3, 7, and 8 were assigned for 18–20 from coupling constants and NOE measurements. This conformation benefits from the favorable quasi-equatorial positions of the substituents at position 2...
and 8 that are quasi-axial in the si side attack. For 21, the two possible transition states show how the asymmetric induction by the intramolecular cycloaddition is primarily controlled by the stereogenic center next to the nitrone.

We performed a computational analysis of the molecular shape space spanned by the library described here (LIB1) and one described in our previous study (LIB2). We calculated normalized principal moment-of-inertia (PMI) ratios, which allow chemists to quantify molecular shapes in terms of intuitive geometric ideas of shape. Ratios of each of the two lower magnitude PMIs \( I_{\text{small}} \) and \( I_{\text{medium}} \) to the highest magnitude PMI \( I_{\text{large}} \) were plotted as characteristic coordinates \( I_{\text{small}}/I_{\text{large}}, I_{\text{medium}}/I_{\text{large}} \) of normalized PMI ratios for minimum-energy conformers of each compound (Figure 3).

Points in PMI plots occupy a triangle defined by the vertices (0,1), (0.5,0.5), and (1,1) and corresponding to the canonical shapes of rod, disk, and sphere, respectively. To quantify the change in shape of LIB2 (42 structures) relative to LIB1 (31 structures), we calculated distances for members of both libraries from the geometric center of LIB2. These two populations of distances differed significantly in location and spread in PMI space using a Kolomorgov–Smirnov (KS) test. To understand this difference in terms of shape, we tested whether one library was significantly closer to the rod, disk, or sphere vertices of PMI space than the other. We also used the disk and sphere canonical shapes as reference points for our recently reported \( \alpha \) shape-based descriptor. Differences in \( \alpha \) shape-based distances to the sphere shape were significant \( (p = 1.16 \times 10^{-4}) \), whereas those relative to the flat shape were not. In PMI space, we found that differences between libraries relative to the sphere shape were significant \( (p = 5.86 \times 10^{-4}) \). Both results indicate that LIB1 molecules tend more toward a spherical shape than do LIB2 molecules. Future studies of these libraries might entail more detailed examination of the relative roles of building blocks, skeletons, and stereochemistry on changes in shape.

We started this research with the hypothesis that densely substituted and skeletally diverse small molecules will facilitate successful outcomes in probe and drug discovery. This new DOS pathway should enable the further testing of this hypothesis following probe-development efforts. PMI shape analysis quantifies the differences between the two libraries and demonstrates how simple synthetic variations in functional groups, incorporated in the “build phase”, can yield significant changes in molecular shape.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Figure 3. Change in molecular shape introduced by new DOS library and PMI space comparison of LIB1 (this study) vs LIB2 (ref 3). (A) PMI space coverage for both libraries LIB1 (blue) and LIB2 (red). (B) Distance distributions for LIB1 (blue) vs LIB2 (red) relative to the canonical sphere; conceptual depiction of distances for two arbitrary data sets (inset). Point densities in binned PMI space for LIB2 (C) vs LIB1 (D).

References:


