Skeletally Diverse Small Molecules Using a Build/Couple/Pair Strategy

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ABSTRACT

Intermolecular couplings of simple building blocks using catalytic, stereoselective cross-Mannich reactions followed by intramolecular functional group-pairing reactions of easily accessed variants of the Mannich products are explored as a route to skeletally diverse small molecules. The synthetic pathway yields products having 12 different skeletons using only three steps and has the potential to enable substantial stereochemical diversification in the future.

Small molecules are widely used as probes in biology and drugs in medicine.† One approach to their discovery involves, in part, an upfront investment in chemistry; specifically, the complete synthesis of a transformative small-molecule screening collection.‡ The properties of compounds in such a collection should possess have been discussed elsewhere, as has a synthesis strategy that might facilitate their production.³ We describe an application of this “build/couple/pair” strategy here, illustrating how intramolecular, functional group-pairing reactions can facilitate the synthesis of skeletally diverse small molecules. A recent application of this strategy proved effective in generating stereochemically and skeletally diverse small molecules, but the requirement for a pre-existing stereogenic center in aldehyde-containing building blocks, which imparted face selectivity during a Petasis reaction, limited the diversity of stereoisomers. In this case, only one face of the imine was accessible to the nucleophile, resulting in anti-diastereoselectivity.⁴ We reasoned that organocatalytic enantioselective additions to electrophilic imines might increase the degree of stereocchemical diversity.⁵ Here, we explore the use of catalytic, enantioselective Mannich reactions using achiral aldehydes as the nucleophile in cross-coupling reactions of highly electrophilic imines derived from primary amines and ethyl glyoxylate.⁶ Although, in principle, recent advances in this area would provide access to all four stereoisomeric products, we have in this study focused on the syn-diastereomeric

products. Our initial aim was to establish conditions that permit (1) the attachment of functional groups to the amine and aldehyde functionalities and (2) intramolecular, functional group-pairing reactions that would result in products having diverse skeletons (Scheme 1).

We initiated the current research with commercially available achiral reagents 1, 2, and 3 to minimize the overall number of synthetic steps (Scheme 2). Stereochemical control of the coupling step was achieved by using an organocatalytic asymmetric cross-Mannich reaction.5b (As noted, extensions of this chemistry should exploit the full potential of analogous enantio- and diastereoselective Mannich reactions coupled to analogous derivatization and cyclization reactions. Such reactions would enable the synthesis of both stereochemically and skeletally diverse products, provided that the cyclization reactions proceed with both diastereomeric Mannich products.)

The first reaction was a three-component, cross-Mannich reaction using a simple aldehyde to afford the syn-product 4 stereoselectively in 72% yield. A one-pot Wittig reaction proceeded at room temperature and gave E-alkene 5 with high stereoselectivity in 69% yield. The E-alkene 5 was also alkylated to give 6, 8, and 11. Benzyl compound 6 was cyclized by using a Heck reaction to give 6/7-fused bicyclic compound 7 in 79% yield. Allyl compound 8 was cyclized by using another Heck reaction to give diene 9 in 42% yield6 or a one-pot Heck/Diels–Alder-cascade sequence to give tricyclic compound 10 with a 5/6/6-fused ring system.

The structure of 10 was confirmed by X-ray crystallographic analysis. A Pauson–Khand reaction of propargyl compound 11 proceeded diastereoselectively to give azabicyclic compound 12.7

The E-alkene 5 was further transformed via one-pot acylations to give 13 and 14 in 57% and 50% yields, respectively (Scheme 3). Attempts to achieve microwave-assisted intramolecular Diels–Alder reactions using furans 13 and 14 gave poor results when performed below 200 °C. Above this temperature only diesters 15 and 16, resulting

from cyclization, olefin isomerization, and epimerization, were isolated. The stereochemistry of tricyclic compound 15 was confirmed by X-ray crystallographic analysis.

Next, we examined a sequence where the amine moiety of aminoaldehyde 4 was acylated in the second step (Scheme 4). A hydrazone of 17 was transformed to give lactam 18 presumably via either an intramolecular Michael addition or an ene reaction. A nitrene derived from 17 underwent an intramolecular 1,3-dipolar cycloaddition to give the fused isoxazolidine 19 in 65% yield. Compound 19 was obtained as a single isomer, and the assignment of its stereochemistry was based on NOESY experiments.

We next investigated a reaction sequence where the aminoaldehyde 4 was acylated to form a urea in the second step (Scheme 5).

Following urea formation and mild acidic treatment, aminoaldehyde 4 was converted into cyclic compounds 20 and 21. The hemiaminal 20 was obtained as an inseparable mixture of α-OH and β-OH (α/β = 4.9) and was converted into compound 21 following treatment with aqueous TFA. The hemiaminal 20 was also converted into the bridged bicycle 22 by Weinreb amidation and in situ cyclization.

Compound 21 was converted into the tricycle 23 by a Pictet–Spengler reaction under conditions more acidic than those required to form 21. After column chromatography, 23 was obtained as a single isomer in 67% yield. This structure was confirmed by X-ray crystallographic analysis.

Furthermore, a hydrazone of 17 underwent intramolecular 1,3-dipolar cycloaddition reaction via hydrazone-azoimine isomerization to afford the fused pyrazolidine 18b in 9% yield.
In conclusion, using a syn-selective cross-Mannich reaction in the context of the build/couple/pair strategy, we obtained skeletally diverse small molecules with 12 different skeletons within three steps starting from commercially available reagents. In addition to incorporating the compounds now available by the pathway described here into the Broad Institute screening collection, we aim to use this strategy with enantio- and diastereomeric products resulting from syn- and anti-selective Mannich reactions.\textsuperscript{5} Results of small-molecule screens using the compounds synthesized here and in the future will be made available on the public database ChemBank.\textsuperscript{13}

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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.

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