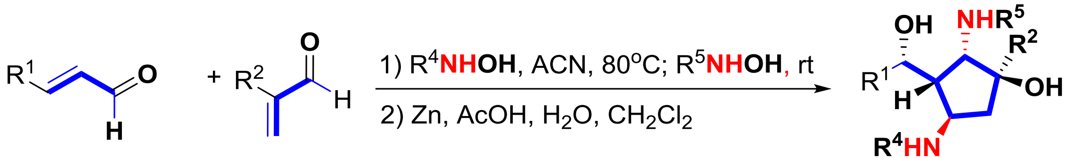
From Heterocycles to Carbacycles: Synthesis of Carbocyclic Nucleoside Analogues from Enals and Hydroxylamines

Pulakesh Das, David W. Almond, Lauren N. Tumbelty, Brooke E. Austin and Gustavo Moura-Letts*

Department of Chemistry and Biochemistry, Rowan University 201 Mullica Hill Rd, Glassboro, NJ, 08028



17 examples
51-82% yield
single purification
5 new stereocenters

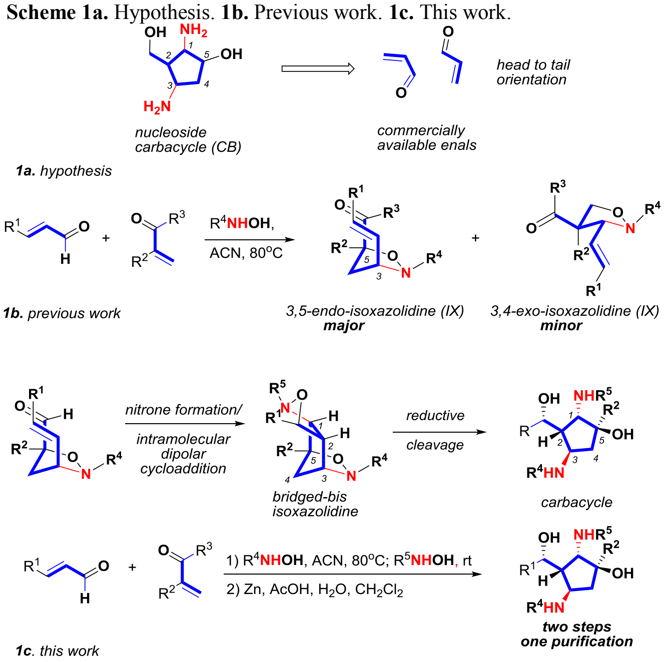
Supporting Information Placeholder

ABSTRACT: Substituted and stereochemically-dense carbacycles can be prepared by sequential dipolar cycloaddition and reductive cleavage from enals and hydroxylamines. The reaction sequence proceeds with high efficiency for a wide variety of enals and hydroxylamines. The reaction is regio- and diastereoselective for the initial formation of a bridged-bisisoxazolidine intermediate, which then undergoes quantitative double *N-O* cleavage to produce carbacycles as single diastereomers.

Substituted nucleoside carbacycles (**CB**) can activate or deactivate biological effects of secondary metabolites in cellular processes.[1] Carbacyclic nucleoside analogues possess significant pharmacological profiles and their specific efficiency as antivirals particularly enhances their value.[2] Thus developing methods for the efficient synthesis of stereochemically-dense carbacycles is of fundamental interest in chemistry. Approaches for the synthesis of carbacycles and carbasugars have mostly focused on the repurposing of pyranoses and furanoses carbon frameworks, ring-closing metathesis of functionalized dienes and modification of naturally-available carbacycles.[3] However, very few exploits the advantages of cycloaddition reactions to achieve the appropriate carbon skeleton with high stereochemical density.[4] This laboratory is focused on developing novel chemical reactions for the synthesis of *N*-containing heterocycles.[5] An extension of this hypothesis lies on using sequential heterocycle-forming reactions to produce highly substituted carbacycles. Thus, could we develop a process for the synthesis of substituted carbacycles through a series of heterocyclic forming/cleavage steps that produces the carbon framework and stereochemical density of nucleosides? We could envision a head to tail arrangement of substituted enals as a requirement to provide the correct regioselectivity and number of carbons (**Scheme 1a**). Our previous efforts have found that vinyl nitrones and α-substituted enals undergo a selective dipolar cycloaddition to form 3,5-endo-isoxazolidines (**IX**) as major products (**Scheme 1b**).[6] Therefore, we envision that a sequential dipolar cycloaddition/reductive cleavage would produce a highly substituted five membered ring carbacycle (**Scheme 1c**). To the best of our knowledge, this is the first report for such approach.

This study began with the discovery that upon reacting the product of cinnamaldehyde, methacrolein and benzylhydroxylamine with another equivalent of hydroxylamine, the resulting *3,5-endo-IX-nitrone* undergoes diastereoselective intramolecular cycloaddition at ambient temperature. The isolated bridged-bisisoxazolidine (**BIX**) **1a** upon reductive cleavage (Zn, AcOH) unveiled a highly substituted stereochemically-dense **CB 2a** as a single diastereomer (**Scheme 2**).[7]

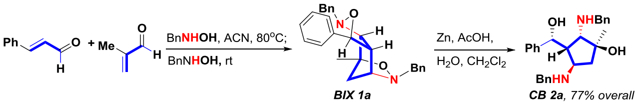
Scheme 1a. Hypothesis. **1b.** Previous work. **1c.** This work.



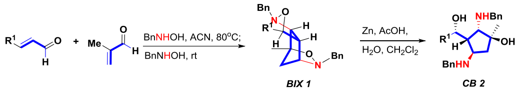
It was somehow serendipitous that the overlapping reaction conditions allowed for the initial crude *3,5-endo-IX* to selectively undergo the second intramolecular cycloaddition without purification. The obtained bicycle **BIX 1a** did require purification, but the following reductive cleavage went to full conversion only requiring a simple filtration to provide **CB 2a**. Thus, making this a two-step one-purification reaction. We were invested in developing a protocol that would allow the proposed overall transformation with minimal purification steps and in this search we tested a variety of conditions for the dipolar cycloaddition and reductive cleavage steps.[8]

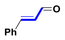
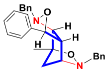
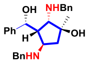
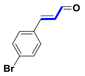
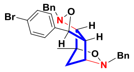
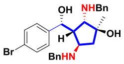
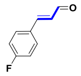
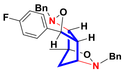
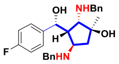
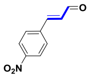
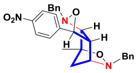
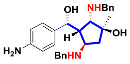
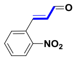
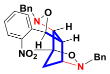
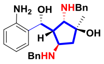
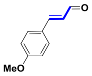
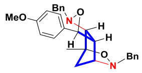
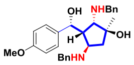
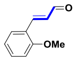
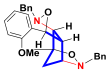
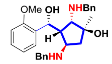
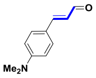
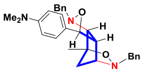
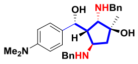
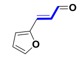
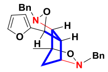
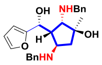
The initial discovery (**Scheme 2**) led us to study the scope of this reaction (**Figure 1**). The initial dipolar cycloaddition regioselectivity is controlled by the substitution pattern on the dipolarophile, thus we decided to use methacrolein and assess different substituted cinnamaldehydes. Para substituted halogenated cinnamaldehydes provided the expected CBs in great yields and as single diastereomers (Entries 2 and 3). Electronic changes around the aromatic ring of cinnamaldehyde may have an influence in the intramolecular dipolar cycloaddition reaction efficiency, but to our satisfaction NO_2 substituted (Entries 4 and 5) and OMe substituted (Entries 6 and 7) provided the expected CBs in equally high yields. As expected, 4- and 2-nitro substrates were exposed to further reduction under the reductive cleavage conditions to produce the corresponding 4- and 2-amino **CB 2d** and **2e**. Similar results were observed when using para dimethylamino cinnamaldehyde and heterosubstituted enal 3-furylpropenal (Entries 8 and 9). Substitution at the α or β positions of the enal did hinder the reaction productivity and complex mixtures were obtained.

Scheme 2. Initial discovery



Attempts to expand the scope to enones as the initial nitrone forming substrate displayed conversions to the expected CB in moderate yields and additional purification steps were required.[9] On the other hand, we were successful at introducing alkyl groups on the enal substrate (**Figure 2**). Octenal provided the expected carbacycle in high yield with minimal purification and as a single diastereomer (Entry 1). Moreover, decenal and hexadienal were also successful and provided the respective carbacycles in high yields (Entries 2 and 3). Hexadienal is particularly important as it provides an extra chemical handle for further diversification on the final CB. We were also interested in testing the scope for the hydroxylamine component of this reaction. We decided to keep the initial hydroxylamine the same and change the second one and we were pleased to see that different substitution patterns (methyl, cyclohexyl, isopropyl and t-butyl) provided the respective carbacycle in high yields (Entries 4-7). Hydroxylamines with *N*-bound electron withdrawing groups failed at triggering the intramolecular cycloaddition due to poor nitrone condensation kinetics. We were also interested in testing the steric demands of the intramolecular cycloaddition by diversifying the group at the α position of the dipolarophile. We found that anything larger than ethyl hinders the intramolecular dipolar cycloaddition to almost no conversion (Entry 8, α-Ph and α-iPr did not work). Other substitution pattern proved not successful under the reaction conditions.

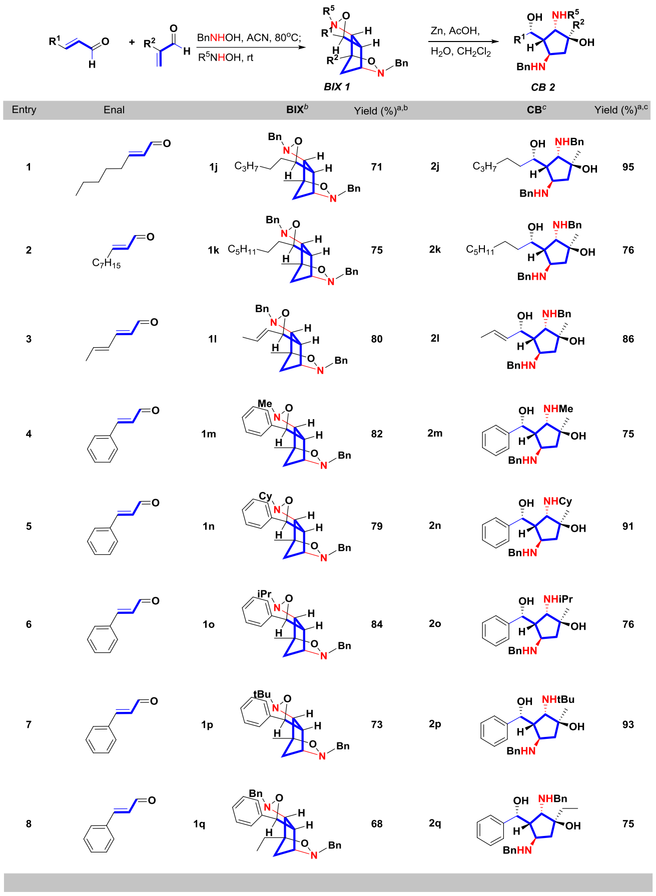


Entry	Enal		BIX^{b}	Yield (%)^{a,b}		CB^{c}	Yield (%)^{a,c}
1		1a		80	2a		96
2		1b		82	2b		96
3		1c		73	2c		86
4		1d		79	2d		92
5		1e		84	2e		98
6		1f		86	2f		78
7		1g		79	2g		88
8		1h		84	2h		87
9		1i		71	2i		87

a. Conditions: Conjugated aldehyde (0.1 mmol) and BnNHOH (1.1 equiv) reacted in ACN at rt for 2h, then methacrolein (5 equiv) was added and mixture was heated at 80 °C for 6h. The solvent and excess methacrolein was then removed under vacuum and BnNHOH (2.5 equiv.) was added in ACN and then reacted at rt. Purified **BIX 1** is then dissolved in $H_2O/CH_2Cl_2/AcOH$ and reacted with Zn (40 equiv.) to provide **CB 2** through filtration and a pentane wash. b. Isolated yields, only **BIX 1** was purified by standard silica gel chromatography. c. Obtained by filtration.

Figure 1. Reaction scope

Thus, we had successfully developed a two-step/one purification protocol for the synthesis of substituted stereochemically-dense carbacycles from simple enals. The reaction stereochemistry is initially determined by a highly regio- and diastereoselective dipolar cycloaddition that arranges the *endo* spatial relationship between the *C3-C5* positions. The stereochemical relationship between *C3* and *C5* then allows for the intramolecular dipolar cycloaddition to set the *syn C1-C2* and *anti C2-C3* protons. Substrates with substitution patterns around the alkene (C2-C6) disrupt the orbital alignment for the intramolecular cycloaddition thus providing considerably lower yields. Careful analysis of the ground-state available conformations for the *3,5-endo-IX* revealed two available diastereoselective pathways (**Figure 3**).



Entry	Enal	BIX[b]	Yield (%)[a,b]	CB[c]	Yield (%)[a,c]
1		1j	71	2j	95
2	C_7H_{15}	1k	75	2k	76
3		1l	80	2l	86
4		1m	82	2m	75
5		1n	79	2n	91
6		1o	84	2o	76
7		1p	73	2p	93
8		1q	68	2q	75

a. Conditions: Conjugated aldehyde (0.1 mmol) and BnNHOH (1.1 equiv) reacted in ACN at rt for 2h, then methacrolein (5 equiv) was added and mixture was heated at 80 °C for 6h. The solvent and excess methacrolein was then removed under vacuum and R^5NHOH (2.5 equiv.) was added in ACN and then reacted at rt. Purified **BIX 1** is then dissolved in $H_2O/CH_2Cl_2/AcOH$ and reacted with Zn (40 equiv.) to provide carbacycle **2** through filtration and a pentane wash. b. Isolated yields, only **BIX** was purified by standard silica gel chromatography. c. Obtained by filtration.

Figure 2. Reaction scope

An *endo-endo* nitrone conformer-1 that would lead to *endo-endo-BIX* and an *endo-exo* nitrone conformer-2 that would lead to *endo-exo-BIX*. All the reaction substrates proved to be diastereoselective for the *endo-exo-BIX* products based on stereochemical analysis. We hypothesized that the preferred *endo-exo* ground state conformation would selectively provide the observed *endo-exo-BIX*, with the isoxazolidine heteroatom pairs away from each other rather than on the same face.[10] B3LYP-D3/6-31++G** calculations corroborated that the relative stabilities of the nitrone conformers allowed for the lower energy *endo-exo* conformer to conserved the required orbital alignment.[11] These results were verified by NOE experiments and corroborated by X-Ray crystallography of **1f** and **2e**.

Further efforts to demonstrate the robustness of this reaction focused on testing the scalability of transformation. We were concerned that the observed results for the reductive cleavage step may not correlate well in large scale, but Zn/AcOH remained superior to other methods .[12] In a large scale experiment, 5 mmols of cinnamaldehyde were used and we found that the corresponding CB **2a** was obtained in 80% overall yield as a single diastereomer, thus providing further evidence for the reaction robustness and highlighting the scalability and simplicity of the reductive cleavage conditions.

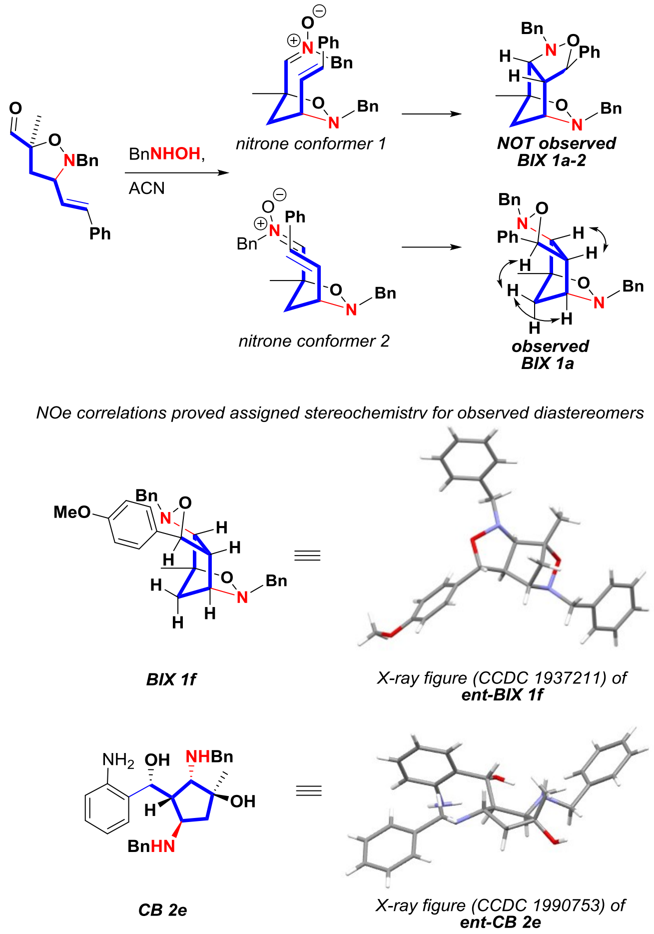


Figure 3. Stereochemical analysis by NOE and X-Ray crystallography

In conclusion we have developed a novel approach for the synthesis of nucleoside carbacycles from simple enals and hydroxylamines. The reaction is highly chemo-, regio- and diastereoselective for the formation of the proposed stereochemically-dense carbacycles. More importantly, the reaction is highly stereospecific and sets five chiral centers with high productivity. The obtained carbacycles are poised to provide access to better understand the pharmacology of such molecular scaffolds. Efforts for an enantioselective version of this method are underway.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Reactions protocol and characterization data (PDF)

Crystallography data (PDF)

AUTHOR INFORMATION

Corresponding Author

Gustavo Moura-Letts – Rowan University, Glassboro, New Jersey; Email: moura-letts@rowan.edu

Notes

The authors declare no competing financial interest.

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7. The isolated CB was characterized by 1D and 2D ^{1}H NMR. The correct relative stereochemistry was assigned based on coupling constant and NOE analysis.

8. The proposed reaction sequence requires for some substrates the scavenging of the corresponding 3,4-endo-IX minor isomer by acetal formation with 1,2-ethanediol and pTSA.

9. The success of this reaction lies heavily on the efficiency of the initial condensation/dipolar cycloaddition operation. Many other enals and enones with different substitution patterns do undergo the proposed dipolar cycloaddition, but the resulting isomeric ratios are not optimal, thus were excluded (SI).

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11. In order to determine the relative stability of the conformers, the geometry of each conformer was optimized by replacing all phenyl rings with methyl groups and using B3LYP-D3/6-31++G**. The calculations were performed using the Jaguar electronic structure package within the Schrödinger platform. These calculations predicted nitrone conformer 2 was more stable. In addition, the optimized conformer 2 maintained the necessary vertical bridging structure while the vertical carbon chains in the conformer 1 separated. Bochevarov, A.D.; Harder, E.; Hughes, T.F.; Greenwood, J.R.; Braden, D.A.; Philipp, D.M.; Rinaldo, D.; Halls, M.D.; Zhang, J.; Friesner, R.A. *Int. J. Quantum Chem.* **2013**, 113, 2110.

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