

1,3-Diazepanes of Natural Product-Like Complexity from Cyanamide-Induced Rearrangement of Epoxy- δ -lactams

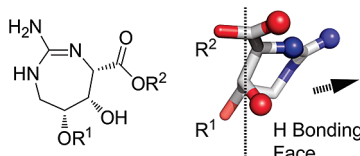
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ABSTRACT



A synthetic procedure toward 1,3-diazepane scaffolds of natural product-like complexity was developed for the construction of RNA-directed ligand libraries. A molecular building block was designed that combines the characteristics of RNA-binding natural products, including a high density of hydrogen bond donors and acceptors around a rigid, nonplanar scaffold with straightforward total-synthetic accessibility that permits extensive control over the chemical space. The synthesis of the 1,3-diazepane scaffold was achieved via an unprecedented cyanamide-induced rearrangement of epoxy- δ -lactams.

Seven-membered rings are largely unexplored in RNA-binding ligands despite the fact that they provide attractive scaffolds for the assembly of RNA-directed functional groups within a rigid nonplanar framework of high atom economy. The structural variety of natural product antibiotics that target the bacterial rRNA (rRNA), and thereby interfere with protein synthesis, has inspired synthetic approaches toward novel RNA binders, however, with emphasis on five- and six-membered rings, which are found in oxazolidinones, tetracyclins and aminoglycosides, as well as macrocycles, which occur in macrolides and their congeners.^{1–3} Dissection of the molecular properties that predispose antibacterial translation inhibitors for binding to RNA folds suggest that a dense arrangement of hydrogen bond donors and acceptors at the periphery of nonplanar and rigid molecular scaffolds provides the basis for both target affinity and selectivity in these natural products.⁴ A prime example for a privileged

scaffold for RNA recognition is the 2-deoxystreptamine ring (2-DOS) found in the aminoglycoside antibiotics (Figure 1).^{1,5}

While natural RNA-binding antibiotics often violate rules for druglike molecules,⁸ their structural complexity reflects an exquisite optimization of functional group density and arrangement for selective interaction with the RNA target. The structural complexity of the natural products is often limiting access to the chemical space around RNA-targeting scaffolds in antibiotics. For practical and economical reasons, semisynthetic procedures starting from the natural products dominate the medicinal chemistry of ribosome-directed antibiotics and thus bias the chemical diversity of RNA-

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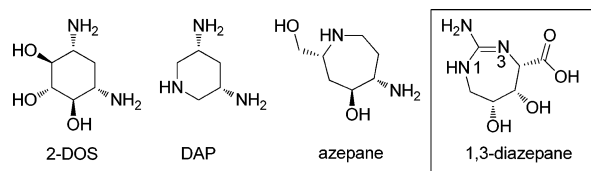


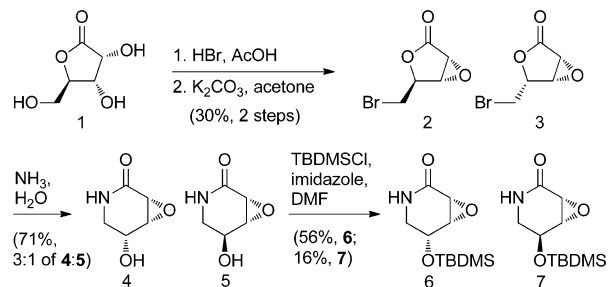
Figure 1. Scaffolds for RNA recognition and the novel 1,3-diazepane building block for the synthesis of RNA-targeted ligands. 2-Deoxystreptamine (2-DOS) is the pharmacophore of many natural aminoglycoside antibiotics.⁵ 3,5-Diaminopiperidine (DAP) has been designed as a 2-DOS mimetic.⁶ The azepane scaffold has been investigated as a replacement for 2-DOS in synthetic azepane-glycoside antibacterials.⁷ In this paper, we describe the synthesis of 1,3-diazepane scaffolds, including the carboxylic acid shown here, for the construction of RNA-targeting small molecule libraries.

binding ligands.⁹ Novel chemical classes of RNA binders may emerge from the screening of synthetic compounds and from de novo or structure-guided ligand design. For example, the 3,5-diaminopiperidine ring (DAP) has been described as a structural mimetic of the RNA-recognizing pharmacophore of the 2-DOS scaffold (Figure 1).⁶ For RNA-directed small molecules that contain a seven-membered heterocycle as a central motif, only few examples have been described, including micromolar binders of the ribosomal decoding site which were discovered by screening or structure-guided design (Figure 1).^{7,10,11} Seven-membered rings, however, are conspicuously absent from a recently reported fragment library directed at RNA targets.¹²

Here, we report a novel synthetic approach to substituted 1,3-diazepane scaffolds of natural product-like complexity for the construction of small molecules directed at RNA targets (Figure 1). We sought to develop a versatile molecular building block that combines the characteristics of RNA-binding natural products, including a high density of hydrogen bond donors and acceptors around a rigid, non-planar scaffold with straightforward total-synthetic accessibility that permits extensive control over the chemical space around the central scaffold. Ideally, this would be achieved within a compact molecular architecture of high atom economy. This paper describes the synthesis of such building blocks via an unprecedented cyanamide-induced rearrangement of epoxy- δ -lactams (**6** and **7**), which are readily prepared from commercially available sugars (Scheme 1).

The starting material for the rearrangement, silyl-protected epoxy- δ -lactams **6** and **7**, was prepared from D-ribo-1,4-lactone (**1**) through bromination¹³ and epoxide formation,¹⁴ followed by opening of the epoxy- γ -lactones and cyclization

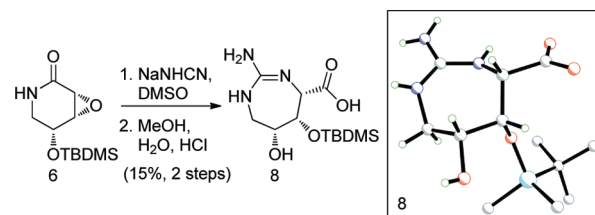
Scheme 1. Preparation of Epoxy- δ -lactams **6** and **7**



to the lactams which were then silyl protected.¹⁵ Bromination of **1** and epoxidation furnished two diastereomers¹³ which were carried forward as a mixture. Silyl protection gave the less polar diastereomers **6** and **7** which were readily separated by flash chromatography.

Treatment of the silyl-protected epoxy- δ -lactam **6** with sodium cyanamide in dry DMSO for 24 h at room temperature followed by addition of aqueous methanol and acidic workup furnished the highly substituted 1,3-diazepane carboxylic acid **8** as a major product (Scheme 2 and Supporting Information).

Scheme 2. One-Pot Synthesis of the Silyl-Protected 1,3-Diazepane Carboxylic Acid **8**



To gain insight into this intriguing synthetic transformation, which formally corresponds to an insertion of the cyanamide nitrile group into the δ -lactam, we investigated the mechanism and intermediates of the reaction (Figure 2). When a solution of **6** and sodium cyanamide in dry DMSO was quenched with aqueous acid after 24 h at room temperature, a mixture of three compounds, **9**, **10**, and **11**, was isolated with the cyanamides being the major products (7:10 ratio of **9**:**11**). Eventually, a modified procedure was devised to produce **10** as the major product of the reaction of **6** with cyanamide (see the Supporting Information). The intermediates **9**–**11** were sufficiently stable to allow for their purification and spectroscopic characterization at room temperature (Supplementary Figure 1, Supporting Information). Crystallization and X-ray structure determination succeeded for **9** and **10**, which established their constitution unequivocally (Figure 2). Compound **11** was isolated as a green oil that resisted crystallization.

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We suggest that, in the absence of a proton source that would stabilize the end products, the equilibration of **9** to **10** and **11** is slow. The crystal structure of **9** reveals the bulky TBDMS group in an axial conformation which fixes the neighboring alkoxide and cyanamide substituents in a trans-equatorial orientation with the nitrile functionality directed away from the alkoxide nucleophile and disfavoring the cyclization toward the oxazole **10** (route 1 in Figure 2). Migration of the axial TBDMS group to the equatorial neighboring alcohol, which leads to the interconversion of **9** to **11**, seems to be slow as well (route 2 in Figure 2). Treatment of pure **11** with aqueous hydroxide for 45 min followed by quenching with acid (see the Supporting Information) furnished the regioisomer **9**, through re-equilibration, along with the oxazoles **12** and **13**.

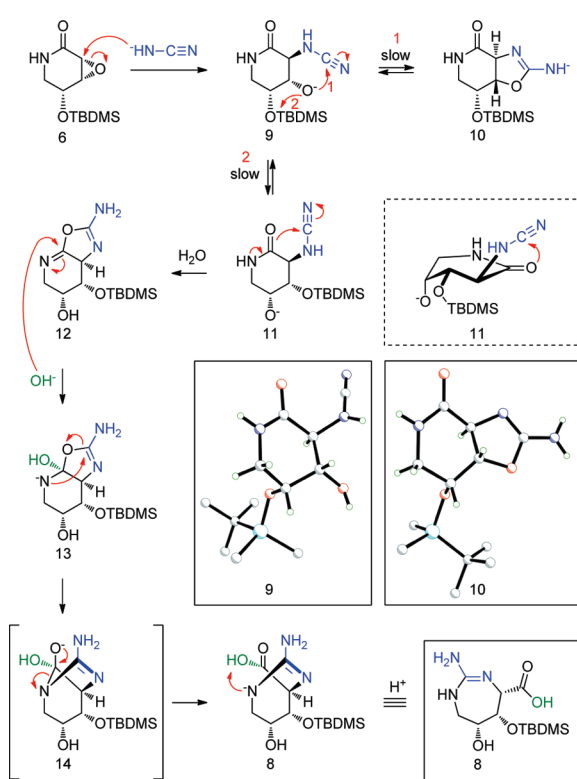


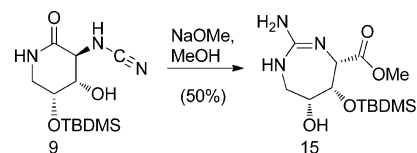
Figure 2. Proposed mechanism for the formation of the 1,3-diazepane carboxylic acid **8** from epoxy- δ -lactam **6**. Crystal structures are shown for the isolated key intermediates **9** and **10** (boxed). All intermediates, except **14**, have been isolated and characterized by MS and NMR spectroscopy. For clarity, the corresponding bases (deprotonated forms) are shown for compounds **8–11** and **13**. Hydrogen atoms for the TBDMS protection group are omitted in the crystal structures. The conformation of **11** (dashed box) is proposed on the basis of sterical considerations.

While the alkoxide in **11** adopts an unfavorable orientation for an intramolecular attack, the carbonyl oxygen of the lactam is in an optimal position for a nucleophilic addition at the nitrile of the cyanamide group. The ensuing ring closure to the amino-oxazole **12** might be facilitated by concurrent deprotonation of the lactam nitrogen when aqueous hydroxide is added to the reaction (step b in Scheme 2). Following cyclization, a

hydroxide nucleophile adds to the electrophilic carbon center in **12** which furnishes the nitrogen analog of an orthoester (**13**). The intermediate **13** undergoes further rearrangement to the 1,3-diazepane final product **8**, perhaps via the bicyclo[3.2.1] derivative **14**, which we have not been able to isolate. The intermediates **12** and **13** could not be crystallized but were isolated and are supported by spectroscopic evidence (see the Supporting Information).

The proposed mechanism of the rearrangement suggested that instead of aqueous hydroxide other nucleophiles and proton sources might be added after the reaction with cyanamide to furnish synthetically useful derivatives of **8**. Indeed, when the isolated intermediate **9**, or a mixture of the regioisomers **9** and **11**, was treated with sodium methoxide in methanol the 1,3-diazepane methyl ester **15** was obtained in good yield (Scheme 3 and the Supporting Information). Though the methyl ester could also be formed in the one-pot version of the transformation, by adding methoxide to the reaction of **6** with cyanamide (compare Scheme 2 and the Supporting Information), purification of the product from DMSO was difficult due to facile hydrolysis of the ester to the carboxylic acid **8** and better yields are obtained in the two-step route via the isolation of intermediate **9** (Scheme 3).

Scheme 3. Synthesis of the 1,3-Diazepane Methyl Ester **15**



When higher alcohols and alkoxides were used in the reaction with cyanamide **9** the esters were not obtained but racemisation occurred, furnishing a diastereomer (**17**) of the oxazole **10** as the major product (Supplementary Figure 3, Supporting Information). We speculate that the sterical requirements for higher alkoxides hinder the nucleophilic attack on **12** which may favor base-catalyzed epimerization of the cyanamide or another intermediate. In contrast, the oxazole diastereomer **17** was isolated only as a minor side product from the reaction with methoxide.

The methyl ester **15** is a useful building block that contains orthogonal functional groups for the construction of RNA-targeted compound libraries (Figure 3). The 1,3-diazepane is an ideal scaffold for the rigid spatial orientation of hydrogen bonding groups and substituents for interactions with RNA targets. A cluster of hydrogen bond donors on the heterocycle provides an interface for molecular recognition of unpaired bases in RNA loops and bulges^{4,16} while the carboxylic acid and hydroxyl groups provide handles for the attachment of additional RNA-interacting moieties. The distinct reactivity of the functional groups in the ester **15** allows straightforward derivatization toward RNA-targeted libraries (Figure 3).

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Substitution at the carboxylic acid (R1) followed by substitution at the free alcohol (R2) and final removal of the silyl protection group will provide entry into a wide chemical diversity space around the diazepane scaffold. We are currently exploring the synthesis of such libraries.

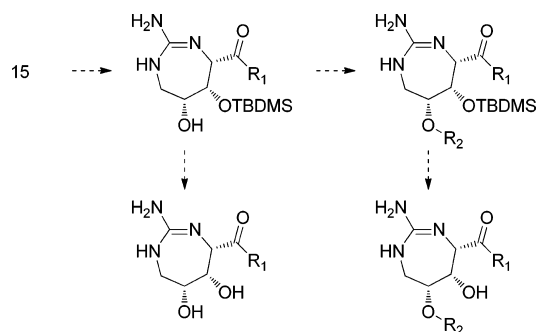


Figure 3. Methyl ester **15** is a versatile advanced intermediate for the synthesis of RNA-targeted compound libraries. The structure of the 1,3-diazepane ring (bottom, from the crystal structure of **8**) highlights the clustering of hydrogen bond donors and acceptors on one face of the seven-membered scaffold as well as the spatial separation of the attachment points for R¹ and R² as handles for additional RNA-interacting substituents.

In summary, we have developed an effective synthetic approach toward substituted 1,3-diazepane scaffolds of

natural product-like complexity for the construction of RNA-directed small molecule libraries. While the one-pot procedure described here leads from a readily accessible epoxy- δ -lactam, via an unprecedented rearrangement, directly to the 1,3-diazepane in 15% yield, improved syntheses for the preparation of the diazepamines can be envisaged. For example, isolation of the cyanamide intermediate **9** followed by reaction with a nucleophile (as outlined in Scheme 3) gave increased yields over the one pot procedure. The novel 1,3-diazepane building block contains a surface made from a cluster of hydrogen bond donors and acceptors in an ideal orientation for interaction with RNA as well as spatially separated handles for further synthetic diversification. The facile synthesis of substituted diazepane scaffolds described here is a first step toward unlocking the potential of rigid seven-membered heterocycles as frameworks of high atom economy for RNA targeting by small molecule ligands.

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Supporting Information Available: Experimental procedures for transformations and spectroscopic as well as crystallographic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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