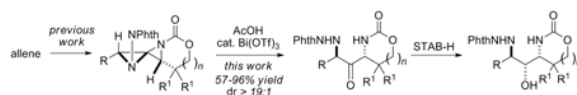# Synthesis of 1,3-Diaminated Stereotriads *via* Rearrangement of 1,4-Diazaspiro[2.2]pentanes

Cale D. Weatherly, **Jared W. Rigoli**, and **Jennifer M. Schomaker**

Department of Chemistry, University of Wisconsin, Madison, Wisconsin, 53706

Jennifer M. Schomaker: schomakerj@chem.wisc.edu

Abstract

The synthesis of 1,3-diaminated stereotriads *via* the bis-aziridination of allenes is reported. The reactive 1,4-diazaspiro[2.2]pentane intermediates undergo a mild Brønsted acid-promoted rearrangement to yield 1,3-diaminated ketones in good yields with excellent stereocontrol. Directed reduction of the ketone can be achieved to yield a C-N/C-O/C-N stereotriad in high *dr*. The ability to transfer the axial chirality of the substrates to the products allows for the facile preparation of enantioenriched stereotriads from allenes in two simple steps.

Compounds containing 1,3-diamino-2-ol stereotriads are prevalent in a number of biologically active natural products and pharmaceuticals. These include the potent HIV protease inhibitor palinavir, aminated cyclohexanes that constitute components of streptomycin and other antibiotics, the natural product manzacidin B and key components of the antibiotic mannopeptimycins known as the hydroxyenduracididines (Figure 1).[1]

Due to the priviledged nature of these motifs, a number of methods have been developed for the stereocontrolled synthesis of 1,3-diaminated compounds.[2-5] Typical approaches include the addition of enecarbamates to imines to yield *anti* 1,3-diamines,[2] the diastereoselective reduction of ketimines,[3] diastereoselective C-H amination[4] and the addition of the α-carbanion of imines to N-protected imines.[5] However, access to complex functionalized 1,3-diaminated compounds of the form C-N/C-X/C-N using well-established methodology is more limited. We hypothesized that a highly regio- and stereocontrolled allene oxidation could provide a new and convenient method to prepare C-N/C-O/C-N stereotriads in a few simple synthetic manipulations. Our previous work has already demonstrated the utility of allene bis-aziridination to 1,4-diazaspiro[2.2]pentanes (DASPs) **2** (Scheme 1) as a convenient scaffold to access vicinal diaminated synthetic motifs.[6] In this communication, we report a complementary reactivity that allows for the conversion of these reactive intermediates to **3** and stereotriads of the form **4**.

A DASP such as **2** can essentially be viewed as a 1,3-diaminated ketone intramolecularly "protected" as an *N,N*-aminal (Scheme 1). We initially envisaged that a simple hydrolysis would yield the desired 1,3-diaminated ketone **3** directly from **2**. However, this transformation was unsuccessful utilizing a variety of Lewis and Brønsted acids, irrespective of the presence or absence of water. In the case of mild acids, either no reaction was noted, or the DASP underwent ring-opening at C1 of **2**.[2a] The use of stronger acids generally resulted in intractable mixtures of products.

We postulated that the recalcitrance of the DASP to undergo hydrolysis might be due to the fact neither nitrogen atom is capable of resonance stabilization of an intermediate carbocation at C2. The relief of ring strain might render the heteroatoms better able to stabilize this carbocation, thus facilitating the desired reaction. In this vein, the acetate-opened DASP **5** was treated with a series of Lewis and Brønsted acids (Table 1). Weak Lewis acids, including $CeCl_3$, $Ti(O^iPr)_4$ and $ZnCl_2$ (entries 1-4), gave no reaction and the starting material was recovered unchanged. $InCl_3$ (entry 6) gave slow conversion to the desired product, while $Cu(OTf)_2$ and $Sc(OTf)_3$ (entries 5 and 7) yielded an unidentified mixture of products. BF_3OEt_2, TsOH and $Bi(OTf)_3$ (entries 8-12) all gave complete conversion of the starting material, with $Bi(OTf)_3$ resulting in a 96% isolated yield of **6**.

$Bi(OTf)_3$ was chosen to further optimize the conversion of the DASP **7** directly to **6** (Table 2). The addition of $Bi(OTf)_3$ alone (entry 1) did not promote the desired rearrangement. Treatment of **7** with AcOH, followed by addition of 5 mol % of $Bi(OTf)_3$ (entry 2) gave complete conversion of the DASP to **6**; however, the ring-opening with AcOH was slow. Interestingly, the ring-opening of **7** with TMSCl, followed by treatment with the Lewis acid (entry 3) gave only the ring-opened product and none of the desired rearrangement product. The same result was observed when thioacetic acid (entry 4) was employed as the nucleophile to open **7**. These results suggested that the ester was playing an important role in promoting the rearrangement, and indeed, treatment of **7** with chloroacetic acid and $Bi(OTf)_3$ also initiated the desired rearrangement to **6** (entry 5). We suspected that the role of $Bi(OTf)_3$ might be to simply generate small amounts of TfOH, and indeed, the addition of a catalytic amount of TfOH (entry 6) to a mixture of **7** and AcOH did promote the desired rearrangement. Ultimately, in order to decrease the reaction time, AcOH was added to **7** at 35 °C and the mixture heated for 8 h prior to addition of the $Bi(OTf)_3$ (entry 7) to give **6** in 88% isolated yield over the one-pot, two-step reaction.

A variety of DASPs were converted to the corresponding 1,3-diaminated ketone products (Table 3) using the optimized reaction conditions. There was only a slight difference in yield between the use of the DASP **7** or the ring-opened DASP **5** (entries 1-2). DASPs formed from *Z* bicyclic methylene aziridines also underwent the desired rearrangement with high stereoselectivity (entries 3 and 4). The stereospecific nature of the reaction is illustrated by a comparison of the 1,3-diaminated ketone **6**, obtained in 88% yield from the rearrangement of a DASP **7** derived from an *E* methylene aziridine, with the distinct product ketone **8c**, obtained in 90% yield from the rearrangement of a DASP formed from a *Z*-methylene aziridine (Table 3, entries 2 and 4, respectively). The rearrangement was not affected by the absence of alkyl substitution in the tether (entries 5-9) or limited to the formation of six-membered rings, as a five-membered ring-containing product (entry 8) was obtained in 78%

yield. The *dr* of the two nitrogen-bearing stereocenters was high in most cases (> 19:1) and none of the other diastereomer was detected by ^{1}H NMR spectroscopy. Not surprisingly, if the product was allowed to remain under the acidic conditions for extended periods of time, significant isomerization to a mixture of diastereomers did occur.

One convenient advantage of this methodology arises as a result of the ability to transfer the axial chirality of an enantioenriched allene to the 1,3-diaminated products.[7] The fidelity of this transfer was verified by subjecting an enantioenriched DASP **9** to the reaction conditions for the rearrangement to **10** (eq 1). No degradation of the enantiopurity was indicated by chiral HPLC (see the Supporting Information for further details).
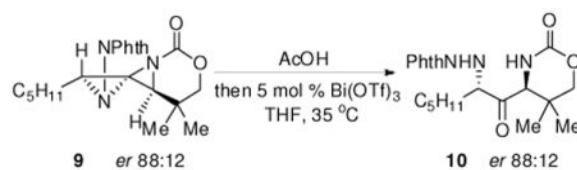
(1)

The next issue was to determine if stereocontrolled reduction of the ketone could be achieved. The use of Na(OAc)$_3$BH (STAB-H) for the reduction of **6** gave the C-N/C-O/C-N stereotriad **11** in 3:1 *dr* when THF was employed as the solvent and in 9:1 *dr* in 70% yield when CH$_2$Cl$_2$ was utilized for the reaction (Scheme 2).[8] Treatment of **11** with an excess of *p*-nitrobenzoyl chloride gave a crystalline derivative **12** (Scheme 2), containing the three heteroatoms in a 1,2-*syn*:2,3-*anti* relationship. This indicates that the reduction could be controlled either by chelation involving the NNPhth group, or by Felkin-Ahn control *via* the carbamate. Changing the bulk of the side chain (Scheme 2, compounds **13-14**) did not affect the *dr*. Removing the steric bulk in the carbamate ring, as in **15**, gave decreased stereoselectivity, indicating that Felkin-Ahn control is likely operative.

We were pleased to find that the conversion of allenic carbamates **16** and **17** to the resulting 1,3-diaminated ketones **6** and **8d** could be achieved in a single pot (Scheme 3). Although the yields were only moderate (approximately 80% per chemical step), the reaction introduces significant complexity into a simple, readily available substrate. The major loss in yield occurs in the first allene aziridination, where the formation of the *Z* methylene aziridine competes with that of the desired *E* methylene aziridine. Our ongoing work in the design of new catalysts with improved selectivity in the allene aziridination should alleviate this issue. Regardless, the *Z* methylene aziridine reacts much more slowly in the subsequent reactions and can be easily separated from the final desired product. The diastereoselectivity of the isolated products was greater than 19:1, comparable to the *dr* observed in the step-wise conversion of the isolated DASPs to **6** and **8d**.

We did not carry out detailed mechanistic studies on this unusual rearrangement. However, the stereoselective nature of the reaction, the necessity for an ester moiety at C1 and the relative stereochemistry of the 1,3-diaminated chiral centers suggests that a mechanism similar to that illustrated in Scheme 4 may be operative. A double displacement at C1 of the

DASP *via* anchimeric assistance would yield retention of the stereochemistry at this carbon, while promoting the desired hydrolysis at C2.

In conclusion, allene bis-aziridination to 1,4-diazaspiro[2.2]pentanes can serve as a key step in the stereoselective syntheses of 1,3-diaminated ketones and their corresponding C-N/C-O/C-N stereotriads *via* stereoselective reduction with STAB-H. The factors that control the stereoselective reductions of these 1,3-diaminated ketones will be further investigated to provide access to other C-N/C-X/C-N stereoisomers. Studies to apply allene oxidation methods to the total synthesis of biologically active molecules, including manzacidin B and (2*R*,3*S*,4′*S*)-hydroxyenduracididine (Figure 1) are underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

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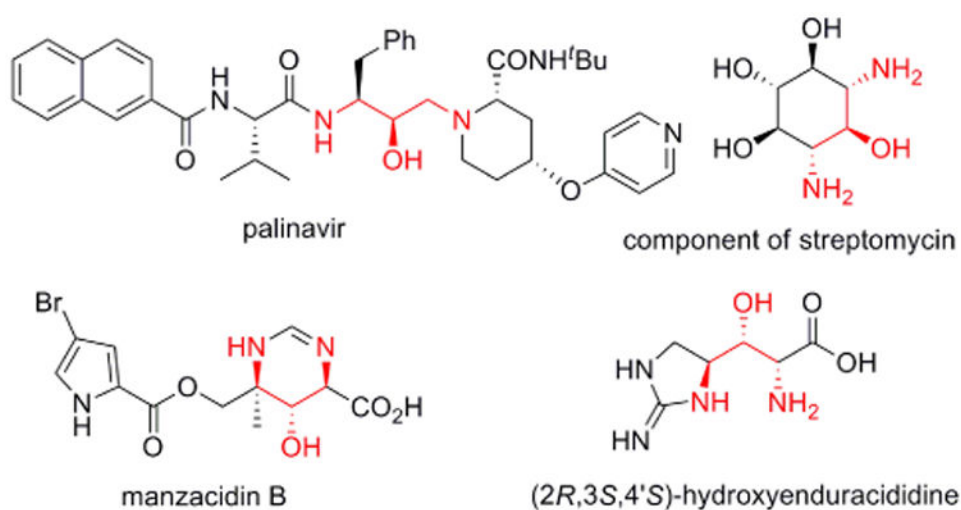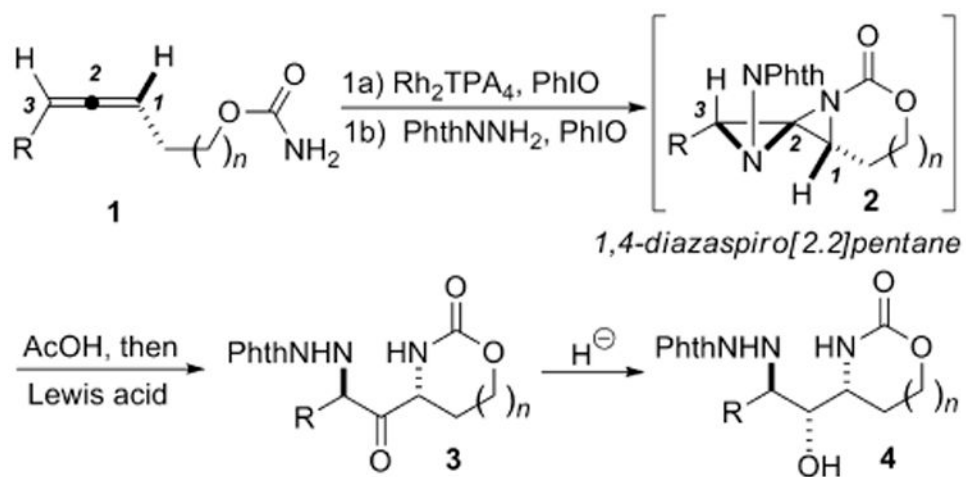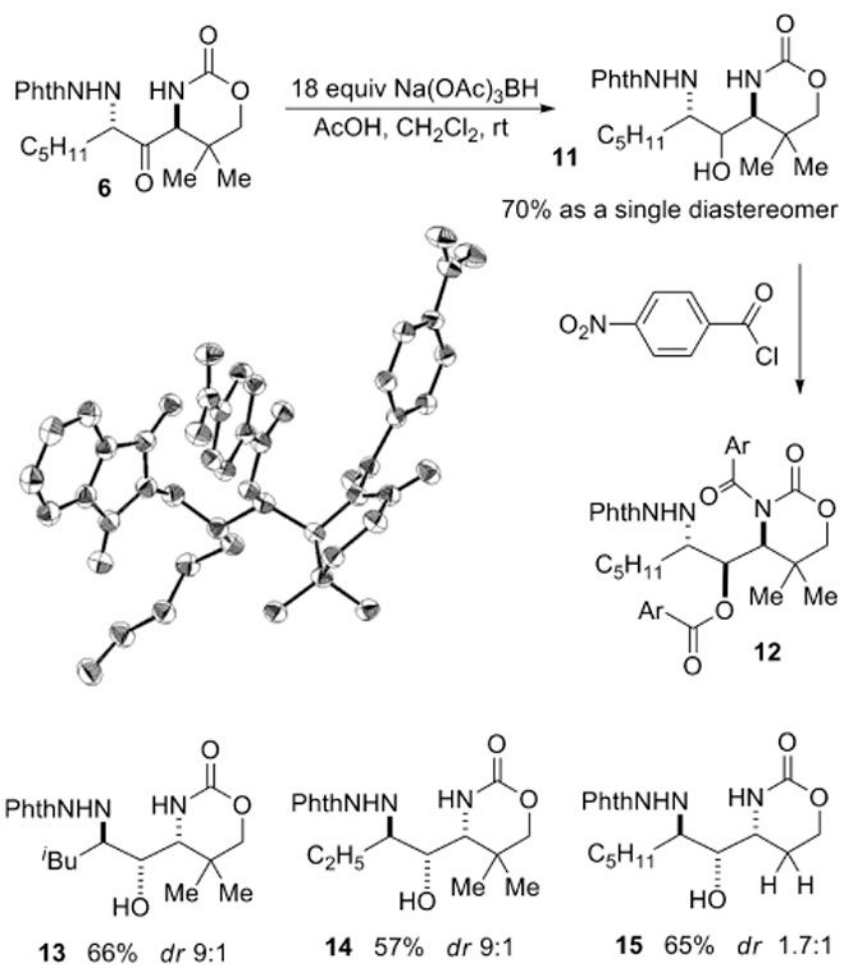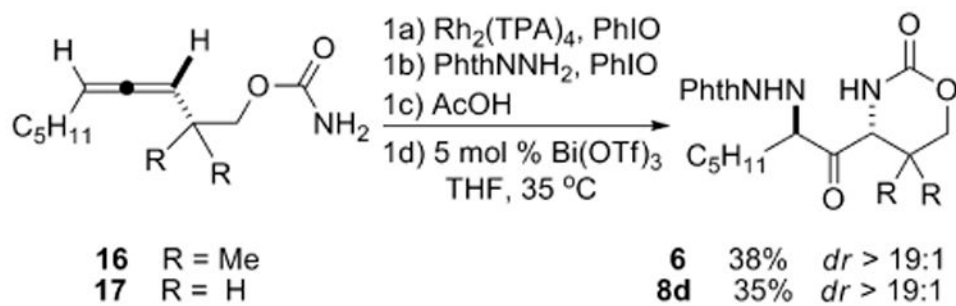
Figure 1.
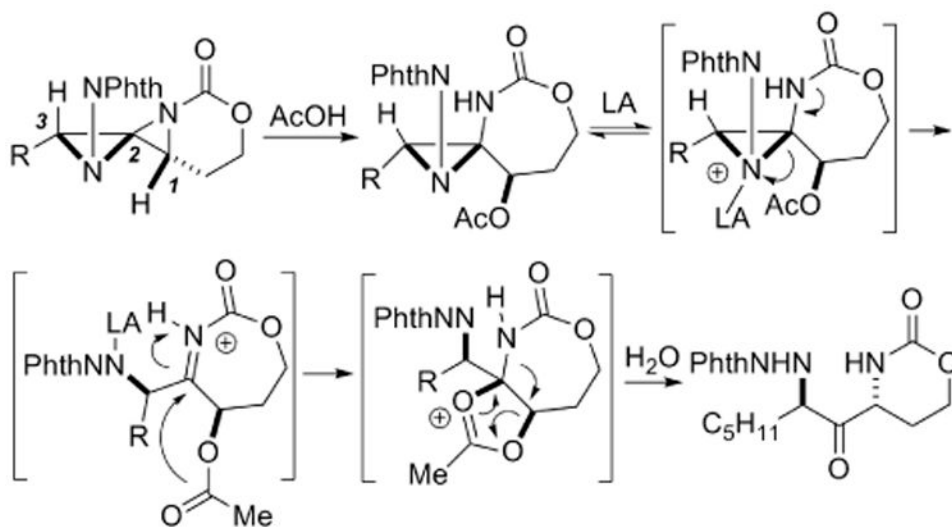Biologically active 1,3-diamino-2-ols.

Scheme 1.
Bis-aziridination as a key step in the conversion of allenes to 1,3-diamino-2-ols *via* DASP intermediates.

Scheme 2.
Reduction of aminoketones and determination of the relative stereochemistry of the C-N/C-O/C-N stereotriad.
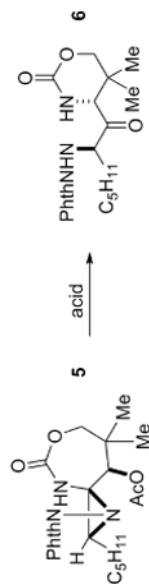
Scheme 3.
One-pot conversion of allenic carbamates to 1,3-diaminated ketones.

Scheme 4.
Possible mechanism for the rearrangement.

Table 1

Optimizing the rearrangement of an *N,N*-spiroaminal to a 1,3-diaminated ketone.

| entry	additives[a]	conversion	entry	additives[a]	conversion
1	$CeCl_3 \cdot 7H_2O$	0%	7	$Sc(OTf)_3$	100%[b]
2	$NiCl_2 \cdot 6H_2O$	0%	8	BF_3OEt_2	100%
3	$Ti(O^iPr)_4$	0%	9	TsOH	100%
4	$ZnCl_2$	0%	10	$Bi(OTf)_3$	96%[c]
5	$Cu(OTf)_2$	100%[b]	11	$Bi(OTf)_3$ (0.2 equiv)	100%
6	$InCl_3$	33%	12	$Bi(OTf)_3$ (0.05 equiv)	100%

[a]1.0 equiv unless otherwise indicated.

[b]Complete conversion, several side products observed.

[c]Isolated yield.

Table 2

Investigation of the rearrangement reaction.
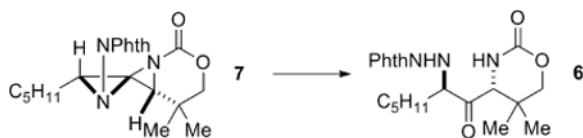
entry	conditions	conversion
1	Bi(OTf)$_3$(1.0 equiv)	0%
2	AcOH, then Bi(OTf)$_3$ (0.05 equiv)[a]	100%
3	TMSCl, then Bi(OTf)$_3$ (0.05 equiv)[b]	0%
4	AcSH, then Bi(OTf)$_3$ (0.05 equiv)[b]	0%
5	ClCH$_2$CO$_2$H, then Bi(OTf)$_3$ (0.05 equiv)	100%
6	AcOH, then cat. TfOH	100%
7	AcOH at 35 °C, then Bi(OTf)$_3$ (0.05 equiv)	100%(88%)[c,d]

[a] 40 h reaction time.

[b] The product was the ring-opened DASP.

[c] 12 h reaction time.

[d] Isolated yield with a *dr* > 19:1.

Table 3

Rearrangement of DASPs to 1,3-diaminated ketones.
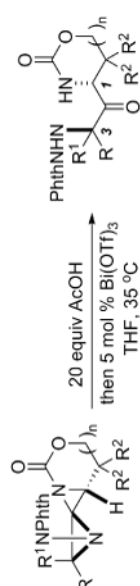
entry[a]	R, R^1	R^2	E/Z[c]	n	yield	dr
1[b]	**5** C$_5$H$_{11}$, H	Me	E	1	96% **6**	> 19:1
2	**7a** C$_5$H$_{11}$, H	Me	E	1	88% **6**	> 19:1
3[b]	**7b** H, CH$_2$CO$_2$Et	Me	Z	1	65% **8b**	86:12
4	**7c** H, C$_5$H$_{11}$	Me	Z	1	90% **8c**	> 19:1
5[b]	**7d** C$_5$H$_{11}$, H	H	E	1	89% **8d**	> 19:1
6	**7d** C$_5$H$_{11}$, H	H	E	1	81% **8d**	> 19:1
7	**7e** Ph(CH$_2$)$_2$, H	H	E	1	60% **8e**	> 19:1
8[b]	**7f** C$_5$H$_{11}$, H	H	E	0	78% **8f**	> 19:1
9	**7g** ^{t}Bu, H	H	E	1	57% **8g**	> 19:1
10	**7h** ^{t}Bu, H	Me	E	1	77% **8h**	> 19:1

[a] The dr of the starting DASPs was > 19:1 in all cases.

[b] The starting material was the acetate-opened DASP with a dr > 19:1.

[c] Stereochemistry of the methylene aziridine used to form the DASP.