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# Remote Chiral Induction in Vinyl Sulfonium Salt-Mediated Ring Expansion of Hemiaminals into Epoxide-Fused Azepines

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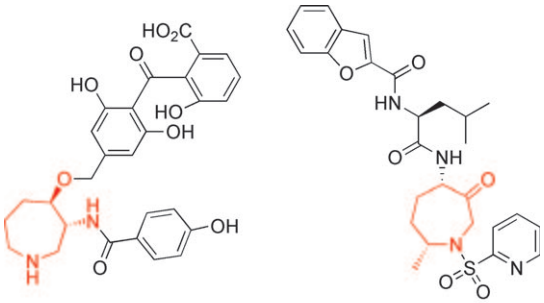
*Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday*

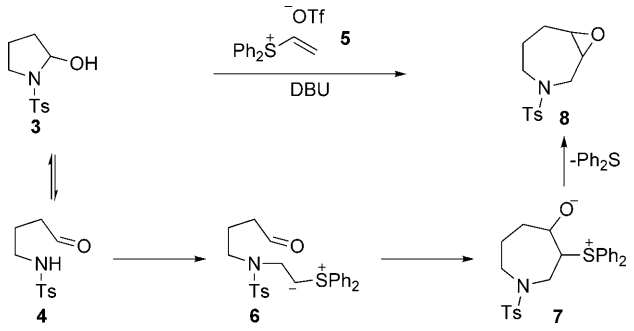
Perhydroazepines,[1] seven-membered ring nitrogen heterocycles, have attracted considerable attention from the synthetic community due to their significant biological activity. In particular, the discovery that (−)-balanol **1** was a potent protein kinase C inhibitor acted as a springboard to a broader study of related analogues.[2–5] For example, the seven-substituted azepine SB-462795 **2**[3,4] was found to be a potent cathepsin K inhibitor and so has potential application in the treatment of osteoporosis. Thus, there is considerable interest in the synthesis of substituted perhydroazepines bearing suitable functionality for further manipulation.[1,3–5]




(−)-balanol
**1**

SB-462795
**2**

As part of our ongoing research on the chemistry of vinyl sulfonium salts,[6,7] we recently reported a new route to perhydroazepines, which involves ring expansion of a hemiaminal (Scheme 1).[6a,8] The process involves ring opening of the




Scheme 1. Proposed pathway for a vinyl sulfonium salt mediated annulation reaction for the synthesis of epoxide-fused *N*-heterocycles from hemiaminals.

hemiaminal **3** to the aminoaldehyde **4**, conjugate addition of the amide to the vinyl sulfonium salt **5** to form a sulfur ylide **6**, followed by ring-closure to the betaine **7**, and finally cyclization to the epoxide. Due to the significant interest in substituted azepines, we investigated the effect of substituents on the hemiaminal ring on the course of the reaction. In this paper, we report that sterically encumbered substituents can lead to very high diastereocontrol in the formation of substituted epoxy azepines, thereby providing a rapid entry into substituted and functionalized azepines.

We began our studies with the 5-methyl-substituted hemiaminal **3a**, which was synthesized from commercially available 5-methyl-2-pyrrolidone in two steps.[9] The 5-methyl hemiaminal **3a** was then treated with an excess of diphenyl vinyl sulfonium salt **5** in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in a range of solvents, from non-

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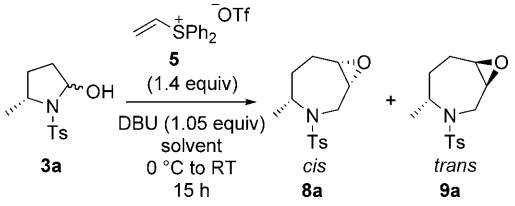
polar toluene to highly polar *N*,*N*-dimethylformamide (DMF), as shown in Table 1. The best diastereoselectivity was obtained using DMF as solvent, which produced the

Table 1. The optimization of reaction conditions for the synthesis of fused epoxy azepines **8a** and **9a**.



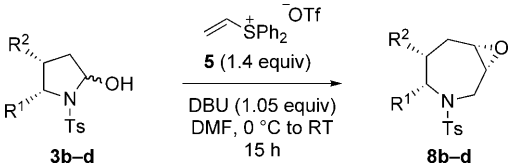

| Entry | Solvent | *cis*/*trans*[a] | Yield [%][b] |
|---|---|---|---|
| 1 | DMF | 6:1 | 61 |
| 2 | THF | 2:1 | 54 |
| 3 | $CH_3CN$ | 2:1 | 70 |
| 4 | $CHCl_3$ | 1.2:1 | 51 |
| 5 | $CH_2Cl_2$ | 3:1 | 50 |
| 6 | toluene | 2:1 | 31 |

[a] d.r. was measured by GC on crude samples before purification-see the Supporting Information for details. [b] Isolated yields after column chromatography.

epoxy azepine with good diastereoselectivity (6:1) and in good yield (60%). The two diastereoisomers were separable and it was determined by X-ray crystallography that the *cis*-isomer **8a** was the major product (see the Supporting Information for X-ray data). Dichloromethane, tetrahydrofuran (THF), acetonitrile, and toluene gave moderate diastereoselectivity (*cis*/*trans*, 3:1 to 2:1), while chloroform showed poor diastereoselectivity (*cis*/*trans*, 1.2:1).

Under the optimized conditions, a range of substituted hemiaminals were explored bearing different groups at both the four- and five-position (Table 2). The methoxyester-substituted hemiaminal **3b** gave the azepines **8b/9b** in good diastereoselectivity 4:1 and 62% yield (Table 2, entry 1). To our delight, the *tert*-butoxyester-substituted hemiaminal **3c** and *tert*-butyldiphenylsilyl (TBDPS)-substituted hemiaminal **3d**[10] generated the azepines **8c** and **8d**, respectively, with essentially complete diastereoselectivity and good yield (61–69%; Table 2, entries 2 and 3). In all cases the *cis* diastereoisomer was found to be the major azepine and no epimerization of the carbon bearing the ester substituent was detected. The absolute stereochemistry of both **8c** and **8d** was confirmed by X-ray crystallography (see Supporting Information for X-ray data).

Table 2. Synthesis of azepines using diphenyl vinyl sulfonium salt **5**.

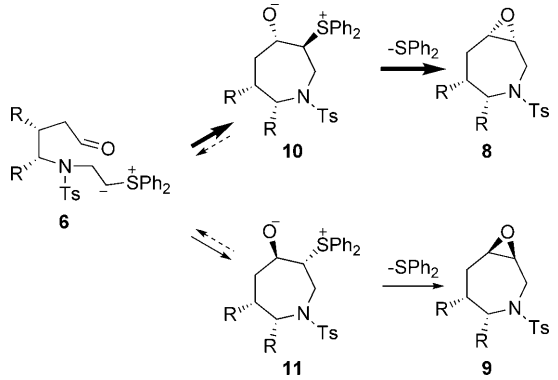



| Entry | | $R^1$ | $R^2$ | *cis*/*trans* | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | **b** | $MeCO_2$ | H | 4:1 | 62 |
| 2 | **c** | $t$BuCO$_2$ | H | >19:1 | 61 |
| 3 | **d** | TBDPSOCH$_2$ | H | >19:1 | 69[b] |
| 4 | **e** | H | TBSO | 4:1 | 70[b] |

[a] Isolated yields after column chromatography. [b] 3 equiv of DBU and 4 equiv of **5** were used. TBDPS = *tert*-butyldiphenylsilyl.

To explore the effect of substituents at C-4 on the diastereoselectivity, the hemiaminal **3e** bearing a *tert*-butyldimethylsilyl (TBS)-ether substituent was prepared from commercially available pyrrolidin-2-one. Hemiaminal **3e** afforded the azepine **8e/9e** in good diastereoselectivity (4:1) and good yield (70%; Table 2, entry 4). Once again the *cis* epoxide **8e** was the major diastereoisomer.

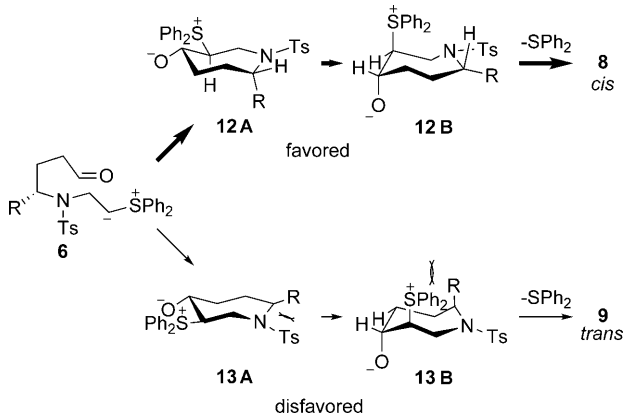
The factors affecting diastereocontrol in this reaction are worthy of further consideration. If betaine formation is reversible, the diastereoselectivity will be dependent on the relative stability of the *anti*-betaines **10** and **11** that lead to *cis*- and *trans*-azepines, and their relative rates of ring closure to form the corresponding epoxides (Scheme 2). However, betaine formation is not usually considered to be reversible for nonstabilized ylides.




Scheme 2. Pathways for epoxide formation in the azepine synthesis.

If betaine formation is nonreversible (which is suspected as a nonstabilized ylide is involved), the diastereoselectivity will be determined in the betaine formation step. Reaction of the ylide with the aldehyde can lead to betaines **12** and **13** (Scheme 3). Electrostatic interactions between the sulfonium group and the developing alkoxide group are expected to lower the energy of the transition states, thus leading to conformers **12A** and **13A**.[11] We propose that formation of betaine **12A** is favored over **13A** as the transition state leading to the latter betaine will suffer from a steric clash between the pseudo-equatorial R substituent and the bulky tosyl group. Similarly, conformer **13B** would suffer from a clash between the pseudo-axial R substituent and the sulfonium groups. We propose that conformer **12B** is formed from **12A** and leads to epoxide **8** by ring closure. Based on this proposal, one would expect that the larger the substituent, the greater the steric clash and hence the higher the diastereoselectivity. A similar line of argument can be advanced for the formation of **8e** as the major product from **3e**. In this case, the *tert*-butyldimethylsiloxy (TBSO)-group

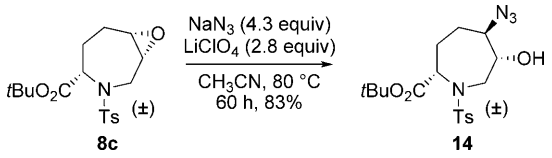



Scheme 3. Proposed rationale for the selectivity observed in azepine synthesis.

can sit in either a pseudo-equatorial (**12 A**) or pseudo-axial (**12 B**) position depending on which betaine is formed. Lower selectivity is observed as there is no steric clash with the tosyl (Ts) group.

The synthetic utility of the products is further illustrated by a completely regioselective ring opening of the epoxy azepine **8 c** with $NaN_3$.[2j,k,3,4c,12] The regiochemistry was established from the 2D NMR spectra of the product, and is in line with expectations based on reports on the ring opening of the parent (unsubstituted) epoxy azepine with a range of nucleophiles.[2j,k] Tanner and co-workers attributed the excellent regioselectivity to a combination of charge and conformational effects.

Scheme 4




Scheme 4. Regioselective ring-opening of epoxide **8 c**.

In conclusion, the synthesis of seven-membered epoxide-fused azepines has been achieved from hemiaminals and the vinyl sulfonium salt **5** in good-to-excellent diastereoselectivity and good yield. It has been observed that both the size and position of substituents play an important role in controlling the diastereoselectivity, and a rationale for the selectivity has been proposed. Our substrate-controlled methodology enables the rapid construction of functionalized azepines from simple precursors. This will enable a greater diversity of azepine structures to be prepared to further probe the potential biological applications of this important class of compound.

## Experimental Section

The supporting information (SI) for this paper provides full experimental details, characterization data, and NMR spectra. CCDC 800707, CCDC 800708, CCDC 800709, CCDC 800710 contain the supplementary crystallographic data for **8 a**, **9 a**, **8 c**, and **8 d** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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**Keywords:** azepine · epoxidation · medium-ring compounds · nitrogen heterocycles · sulfur ylide

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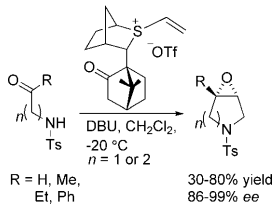
[8] Related reactions of α-aminoaldehydes and β-aminoaldehydes were also reported which gave five- and six-membered epoxide-fused *N*-heterocycles. In those cases the use of our chiral vinyl sulfonium salt furnished the epoxides with high *ee* (86–99%). See reference 6a.

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