Annulation

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The Use of Vinyl Sulfonium Salts in the Stereocontrolled Asymmetric Synthesis of Epoxide- and Aziridine-Fused Heterocycles: Application to the Synthesis of (−)-Balanol**

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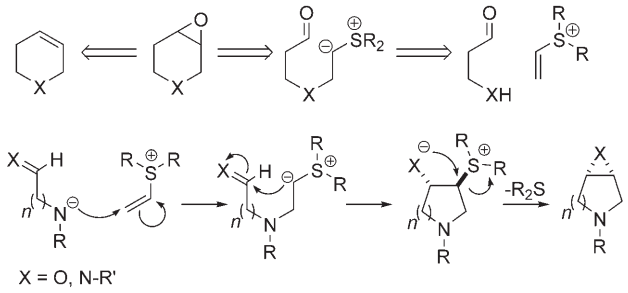
The asymmetric synthesis of epoxides fused to carbo- or heterocycles by epoxidation methods is inherently challenging because the two enantiotopic faces of the corresponding cyclic (*cis*) alkene are poorly differentiated. The use of chiral sulfur ylides offers a complementary method for preparing epoxides, but this method has essentially only been employed to make acyclic epoxides.[1] We considered the possibility of extending sulfur ylide reactions to make fused bicyclic epoxides, and in particular to the challenging substrates described above. We were particularly attracted by the possibility of designing a general asymmetric annulation process for the synthesis of N-heterocycles through the reaction of a bifunctional aminoaldehyde with a chiral vinyl sulfonium salt (Scheme 1). This type of reaction has been studied by Jimenez and co-workers in relation to the synthesis of mitomycins[2] but has not been explored beyond that.

If we could achieve such an annulation process, we envisaged that it could be employed in a short synthesis of the protein kinase C inhibitor balanol[3] from readily available



Scheme 1. An annulation reaction mediated by a vinyl sulfonium salt for the synthesis of fused bicyclic heterocycles.

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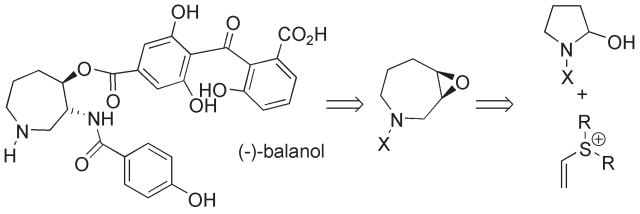
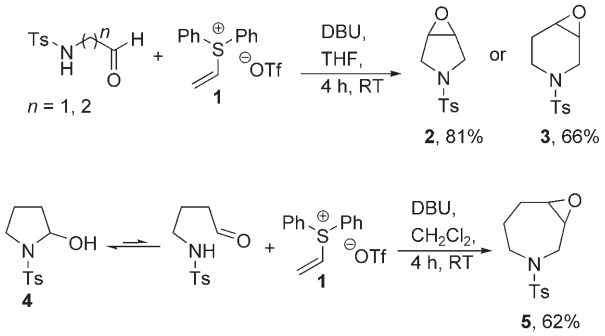
precursors (Scheme 2). We began our investigation with the diphenyl vinyl sulfonium salt[2b] **1** and α-,[4] β-,[5] and γ-[6] aminoaldehydes. Through extensive screening of solvents, bases and N-substituents, we found that the use of DBU in



Scheme 2. Proposed retrosynthesis of balanol.

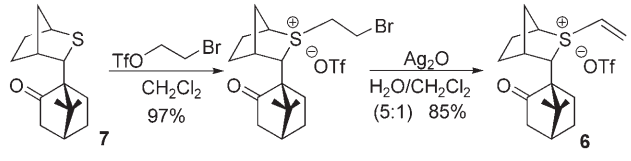
THF with sulfonamides was optimum, and the reaction gave the fused heterocyclic epoxides **2** and **3** in good yields (Scheme 3). The γ-aminoaldehyde substrate **4** proved to be a



Scheme 3. The synthesis of five-, six-, and seven-membered heterocyclic epoxides through an annulation reaction mediated by **1**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Ts = toluene-*p*-sulfonyl, Tf = triflate = trifluoromethanesulfonyl.

challenge, because: 1) the aldehyde exists predominantly in the ring-closed, hemiaminal form, which leads to a low concentration of the nucleophile, and 2) ring closure to form the seven-membered ring **5** is much more difficult. Nevertheless, after optimization, even this substrate participated in the annulation process, thus providing a new route to functionalized azepines from simple and readily available starting materials.

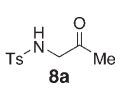
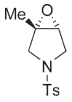
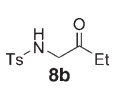
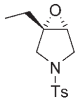
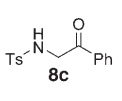
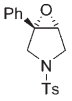
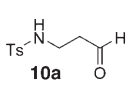
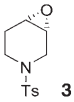
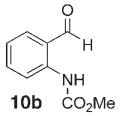
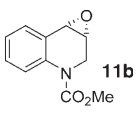
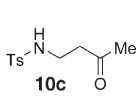
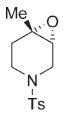
Having developed a new synthesis of fused heterocyclic epoxides, we sought to render the process asymmetric using the chiral vinyl sulfonium salt **6**. This was prepared in two steps from sulfide **7** (Scheme 4), which we had previously used in both our catalytic[7] and stoichiometric[8] epoxidations mediated by sulfur ylides.



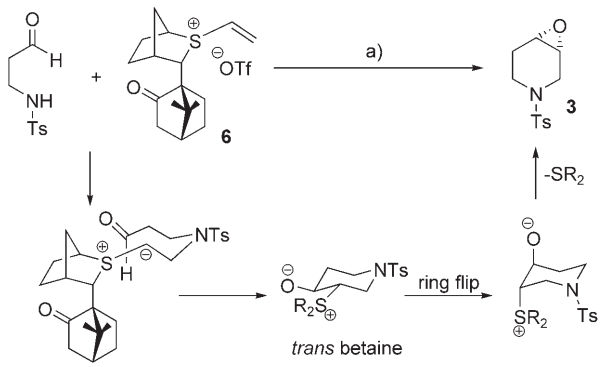
Scheme 4. The synthesis of the chiral vinyl sulfonium salt **6**.

We explored reactions with α-aminoketones, β-aminoaldehydes, and β-aminoketones (α-aminoaldehydes were not tested as they would give meso epoxides) (Table 1). Under optimized conditions (method B), the α-aminoketones **8a**–**c**[9,10] gave the desired epoxides **9a**–**c** in good yield and with very high enantioselectivity (Table 1, entries 1–3). Interestingly, we achieved even higher yields in the annulation process with the achiral, more robust diphenyl vinyl sulfonium salt **1** (Table 1, method A, entries 1–3). The β-aminoaldehydes[11] **10a**[5] and **10b**[12] were also effective and furnished the corresponding epoxides **3** and **11b**, again with high enantioselectivity (Table 1, entries 4 and 5). The absolute stereochemistry of epoxide **3** was determined by X-ray analysis[13] and is consistent with our established model for asymmetric induction; the remaining compounds are assigned by analogy (Scheme 5).[1b,14] The β-aminoketone **10c**[15] also provided good enantioselectivity, but yields were low because of a competing β elimination of the tosylamide[16] (Table 1, method B, entry 6). This elimination was not observed in the reaction with the achiral diphenyl vinyl sulfonium salt **1** (Table 1, method A, entry 6), which provided the epoxide **11c** in high yield. Interestingly, this methodology provides a class of enantiomerically pure epoxides (for example, **3**) that are very difficult to make by the well-established epoxidation methods, such as Jacobsen–Shi epoxidation of alkenes.[17] Although other methods exist for the synthesis of some of the other epoxides, for example, benzofused epoxides **11b**,[18] and trisubstituted epoxides **11c**,[19] our method offers a

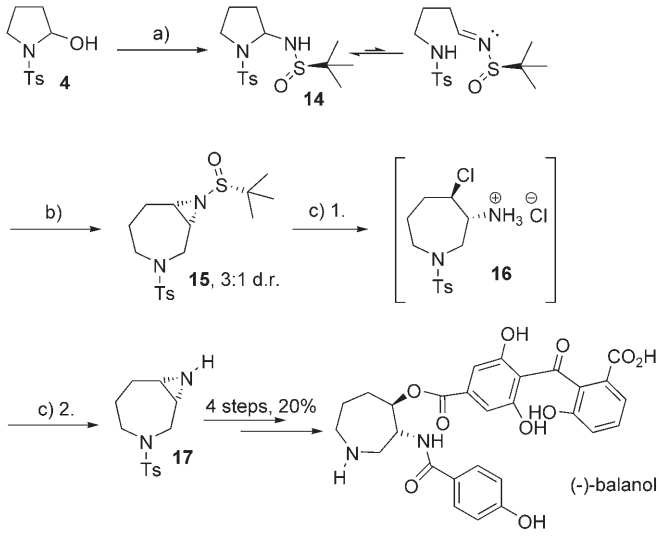
Table 1: The reaction of chiral and achiral vinyl sulfonium salts with aminoaldehydes and -ketones.

Entry	Substrate	Product	Method	Yield [%]	*ee* [%]
1	 **8a**	 **9a**	A	90	–
			B	76	97
2	 **8b**	 **9b**	A	90	–
			B	65	99
3	 **8c**	 **9c**	A	96	–
			B	80	92
4	 **10a**	 **3**	A	67	–
			B	67	98
5	 **10b**	 **11b**	A	50%	–
			B	50	88
6	 **10c**	 **11c**	A	77	–
			B	30	86

Method A: Diphenyl vinyl sulfonium salt **1** (1.2 equiv), DBU (2 equiv), CH_2Cl_2 (0.09 M), 2–4 h, 0 °C. Method B: Chiral vinyl sulfonium salt **6** (1.0 equiv), DBU (2 equiv), CH_2Cl_2 (0.015 M), 2–5 days, −20 °C.



Scheme 5. Model for asymmetric induction in the epoxy-annulation reaction of β-aminoaldehyde **10a** with chiral vinyl sulfonium salt **6**. a) Chiral vinyl sulfonium salt **6** (1.0 equiv), DBU (2 equiv), CH_2Cl_2 (0.015 M), −20 °C, 3 days, 66% yield, 98% *ee*.



Scheme 7. Formal synthesis of (−)-balanol through an asymmetric aziridine-annulation reaction mediated by vinyl sulfonium salt. a) Ti(OEt)$_4$, *tert*-butylsulfinimine, CH_2Cl_2, 7 days, reflux, 95%; b) **1**, NaH (1.2 equiv), DMF (0.018 M), 4 h, 0 °C, 68%; c) 1. HCl (3 equiv) in dioxane, 20 min; 2. aq NH_3, 42 h, 80%.

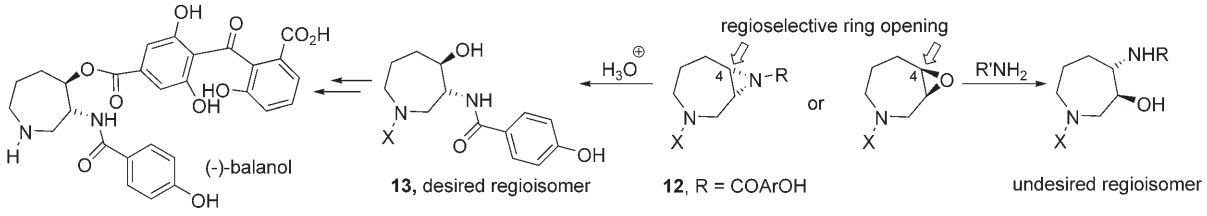
completely different disconnection and requires very different starting materials, so is a complementary route.

Extension of this asymmetric process to the challenging seven-membered azepine ring **5**, the starting point of our proposed asymmetric synthesis of balanol, was unsuccessful. The hemiaminal was recovered, but the vinyl sulfonium salt **6** decomposed. Presumably the slower rate of addition of the amide nucleophile to the vinyl sulfonium salt allowed competing side reactions (decomposition pathways) of the more sensitive dialkyl vinyl sulfonium salt to dominate. However, even though the epoxide **5** has been used as an intermediate in the synthesis of balanol,[20a] it is not ideal, since the epoxide is opened regioselectively at the C4 position[19] (Scheme 6). Thus, the epoxide is first converted to the corresponding aziridine **12**, which undergoes selective ring opening, again at C4, to furnish the required 3-amino-4-hydroxyhexahydroazepine **13**.

We therefore considered the direct formation of the required aziridine, in which the identical annulation strategy would be used. For this we would need an aminal, and in order to induce asymmetry, we elected to use the Davis–Ellman *tert*-butyl sulfinimine.[21] Aminal **14** was prepared by condensation of the hemiaminal **4** with (*R*)-*tert*-butyl sulfinamide, and reaction with diphenyl vinyl sulfonium salt **1** under the optimized reaction conditions (NaH in DMF) furnished the desired hexahydroazepine **15** in 68% yield as a 3:1 mixture of diastereomers, which were separated by flash chromatography (Scheme 7).[22] The stereochemistry of the minor diastereomer was determined by X-ray analysis,[13] thus establishing the stereochemistry of the major isomer.

Deprotection of aziridine **15** was achieved on treatment with anhydrous HCl (3 equiv), which resulted in the unavoidable formation of the ring-opened product **16**. Monitoring of this reaction using LC-MS showed that the protected aziridine was very susceptible to ring opening under these conditions. In fact, it is likely that the protected aziridine **15** first underwent ring opening with HCl and the resulting 1,2-chlorosulfinamide was then deprotected to yield the intermediate **16**. Upon workup with saturated aqueous ammonia solution, the known chiral aziridine **17**[19] was obtained, thus completing a formal synthesis of balanol.

In conclusion, we have developed a new epoxy-annulation method for converting α-, β-, and γ-aminoaldehydes and -ketones into racemic five-, six-, and seven-membered epoxide-fused heterocycles. The reaction has been rendered asymmetric in the synthesis of five- and six-membered rings, using the chiral vinyl sulfonium salt **6**, and practical levels of asymmetric induction were achieved. The new process creates one new C–C bond and two C–X bonds with control over both relative and absolute stereochemistry. The methodology has been extended to an asymmetric aziridine-annulation process for the construction of the most challenging seven-membered hexahydroazepine ring **15**. This methodology now



Scheme 6. The regioselective ring opening of the hexahydroazepine core of balanol.

provides the shortest route (nine steps)[23] to the important protein kinase C inhibitor, balanol.

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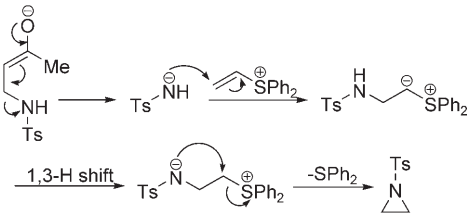

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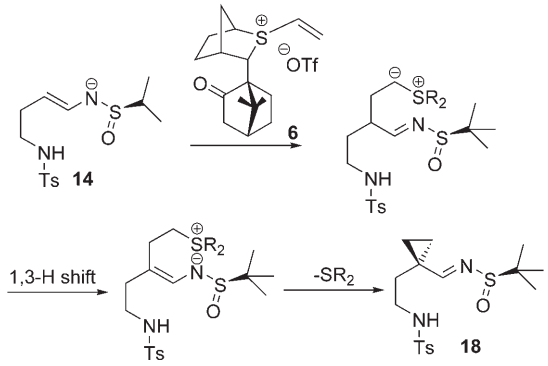
[22] Attempts to improve the diastereoselectivity through the reaction of aminal **14** with the chiral vinyl sulfonium salt **6** did not result in the formation of the desired aziridine **15**. Enolization α to the imine **14** and subsequent conjugate addition of the enolate to the chiral vinyl sulfonium salt **6** gave an ylide, which underwent 1,3-proton shift and ring closure to form the α-cyclopropylimine **18**.



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