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Asymmetric Sulfur Ylide Mediated Aziridination: Application in the Synthesis of the Side Chain of Taxol

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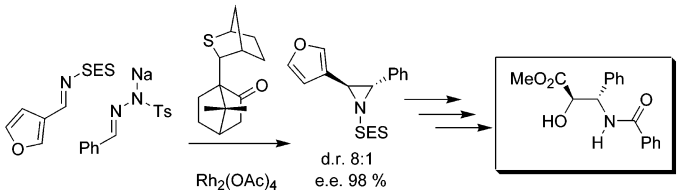
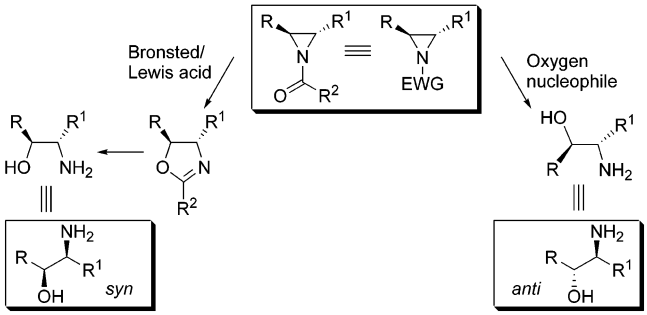
ABSTRACT



Sulfur ylide methodology has been used to construct the Taxol side chain with a high degree of enantioselectivity via a *trans*-aziridine followed by stereospecific rearrangement of the *trans*-benzoylaziridine into a *trans*-oxazoline.

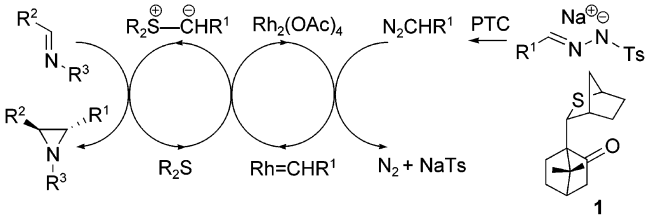
Aziridines are versatile synthetic intermediates[1] in the synthesis of α-amino alcohols.[2] *trans*-Aziridines, for example, can be converted into either *syn*- or *anti*-α-amino alcohols quite simply (Scheme 1): direct ring opening with an oxygen nucleophile furnishes the anti isomer, whereas stereospecific rearrangement of acylaziridines followed by hydrolysis gives the syn isomer.[3]

Scheme 1. Application of *trans*-Aziridines in the Synthesis of *syn*- or *anti*-α-Amino Alcohols



We recently described a powerful method for the asymmetric synthesis of *trans*-aziridines from imines and tosyl hydrazone salts, a process mediated by sulfur ylides (Scheme 2).[4] Key features of this process included (i) high conversion, (ii) high enantioselectivity, (iii) use of sulfide in substoichiometric amounts (20 mol %), (iv) sulfide quantitatively reisolated, (v) ready availability of both enantiomers of sulfide **1** in four steps, and (vi) efficient and user-friendly process.

Scheme 2. Catalytic Asymmetric Aziridination of Imines Using Tosylhydrazone Salts



(1) Reviews on applications and synthesis: (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (b) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519. (c) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 607. (d) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (e) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (f) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

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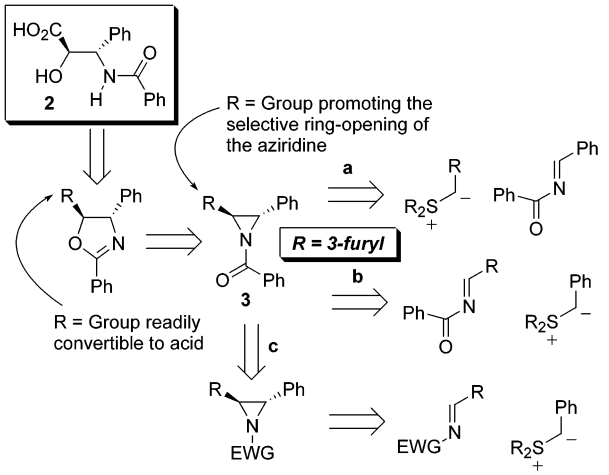
So far, the vast majority of asymmetric sulfur ylide studies have been directed at exploring the methodology[5] rather than exploiting their use in synthesis.[6] In this paper, we describe the first application of the asymmetric sulfur ylide mediated aziridination methodology in synthesis and, in particular, to the synthesis of the side chain of Taxol, a *syn*-α-amino alcohol.

Taxol (paclitaxel) is used in the treatment of various forms of cancer.[7] It can be isolated from the bark of *Taxus brevifolia* but is more economically prepared by semisynthesis through the coupling of the commercially synthesized side chain **2** with 10-deactylbaccatin, which itself is isolated from the tree's leaves. Thus, synthetic routes for the side chain of Taxol are important and indeed have attracted much attention.[8] A number of strategies have been used to prepare this intermediate but none have involved aziridine intermediates. Epoxide intermediates have been utilized, but cis stereochemistry is required to access the *syn*-α-amino alcohol.[9] On the basid of the above discussion, it was clear to us that *trans*-aziridines could be employed to prepare the *syn*-α-amino alcohol required for the Taxol side chain (Scheme 3).

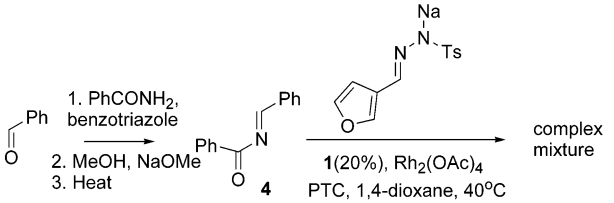
Key to the success of the strategy was to ensure that during rearrangement of the *trans*-aziridine **3** to the *trans*-oxazoline, cleavage of the C−N bond occurred adjacent to the R group rather than the Ph group. Thus, R had to be a group more capable of stabilizing a transient positive charge than a phenyl group and had to be readily converted into an acid. These requirements led us to propose the 3-furyl moiety as the R group. The disconnection of the benzoyl aziridine leads to two possible direct coupling partners (paths **a**/**b**). However, it was known that reactions of sulfur ylides with acyl imines furnish a mixture of aziridines and (the required) oxazolines.[10] This mixture could be utilized in path **a** but not in path **b** as the oxazoline would have the incorrect regiochemistry. However, a change of activating groups on nitrogen (path **c**) provides another solution to the problem. For example, it was known that phenyl-stabilized sulfur ylide reacts with *N*-sulfonylimines (EWG = sulfonyl group) cleanly to give aziridines only.[4] Both pathways **a** and **c** were therefore investigated in the synthesis of the Taxol side chain **2**.

Scheme 3. Retrosynthetic Analysis of the Taxol Side Chain



We initially explored pathway **a**. The *N*-benzoylimine **4** was prepared cleanly using Katritzky's benzotriazole method[11] (this was found to be cleaner than the method employing the *N*-trimethylsilylimine and reaction with benzoyl chloride[12]), but reaction of this substrate with the 3-furyl tosylhydrazone salt lead to a complex mixture of products (Scheme 4). This was disappointing as the 3-furyl tosylhydrazone salt had been successfully employed in catalytic asymmetric epoxidation with benzaldehyde[13] and *N*-benzoylimines had successfully been employed in catalytic asymmetric aziridination with benzaldehyde tosylhydrazone salt.[10] We therefore investigated the stoichiometric variant[6] of our ylide reaction and positive results ensued.

Scheme 4. Path **a**: Attempted Catalytic Aziridination of Benzoyl Imine



The 3-furyl sulfonium **5** salt was prepared by alkylation of sulfide **1** with the corresponding 3-furylmethyl bromide (Scheme 5).[14] The salt **5** was then deprotonated at low

(2) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

(3) (a) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574 (and references therein). (b) Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087.

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(6) Application of the asymmetric epoxidation process in the synthesis of CDP 840 was recently described: Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.

(7) For reviews, see: (a) Kingston, D. G. I. *Chem. Commun.* **2001**, 867. (b) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726. (c) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(8) The most direct route is attributed to Sharpless: Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.

(9) (a) Jacobsen, E. N. Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron Lett.* **1994**, *50*, 4323. (b) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.

(10) Aggarwal, V. K.; Alonso, E. Unpublished results.

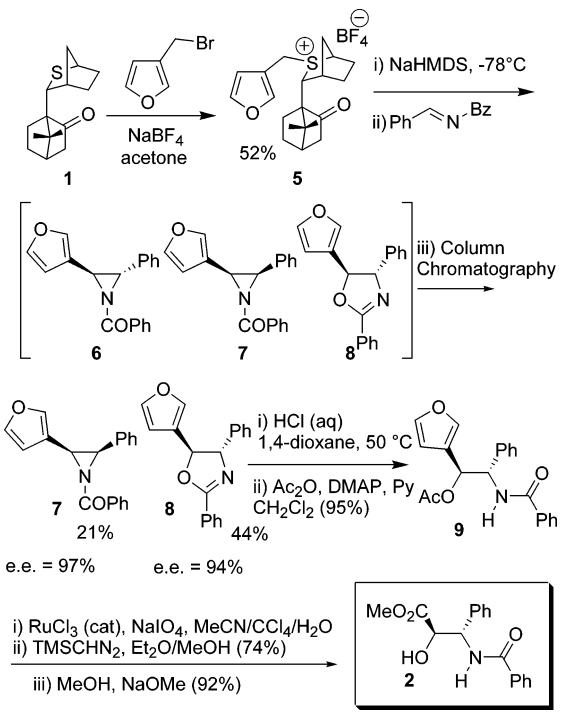
(11) Katritzky, A. R.; Fan, W.-Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547.

(12) Kupfer, R.; Meier, S.; Würthwein, E.-U. *Synthesis* **1984**, 688.

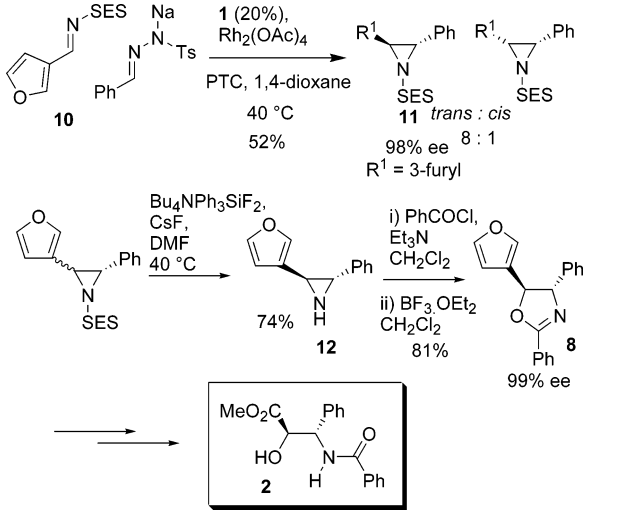
(13) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Richardson, J.; Stenson, R. A.; Studley, J.; Vasse, J.-L.; Winn, C. *J. Am. Chem. Soc.* **2003**, *125*, 10926.

(14) Aggarwal, V. K.; Thompson, A.;. Jones, R. V. H. *Tetrahedron Lett.* **1994**, 8659. This method was more successful than reaction of the sulfide with 3-furylmethanol and HBF_4 (see ref 6).

Scheme 5. Stoichiometric Sulfur Ylide Route to Taxol Side Chain.



Scheme 6. Catalytic Sulfur Ylide Route to Taxol Side Chain.



temperature with NaHMDS in THF[6] and the *N*-benzoylimine **4** added giving a 2:1:0.2 mixture of *trans*-aziridine **6**/*cis*-aziridine **7**/*trans*-oxazoline **8**. During purification by column chromatography, the *trans*-aziridine **6** was converted into *trans*-oxazoline **8** while the *cis*-aziridine **7** was largely untouched.[15] The two isolated compounds **7** and **8** had enantiomeric excesses of 94% and 97%, respectively. We believe that the small reduction in enantioselectivity for the *trans*-oxazoline **8** originates from partial isomerization of the *cis*-aziridine **7** into *ent-trans*-oxazoline **8**.[16]

We attempted oxidative cleavage of the furyl group on substrate **8** as the corresponding acid had previously been coupled with 10-deactylbaccatin and the oxazoline subsequently cleaved to give Taxol.[17] However, all attempts at this oxidation led to a complex mixture of products. We believed that the oxazoline moiety was interfering with the oxidative cleavage and so this group had to be modified. Thus, hydrolysis of the oxazoline **8** with dilute HCl followed by treatment with acetic anhydride led to the amide ester **9**. Oxidation of the furyl group using Sharpless' conditions[18] was now no longer problematic, furnishing the carboxylic acid, which was esterified with trimethylsilyldiazomethane[19] in 74% yield over two steps. Finally, hydrolysis of the acetate gave the Taxol side chain **2** in six steps and 16% overall yield. This material was identical by NMR spectroscopy[9b] and optical rotation[20] to that reported in the literature.

Our second strategy, path **c**, was also explored. We decided to employ the *N*-trimethylsilylethylsulfonyl (SES) imine as we had previously found that *N*-sulfonylimines were more stable than *N*-carbonylimines to the catalytic aziridination conditions[10] and that this group could be readily removed. Thus, the *N*-SES imine **10** was prepared[4] and reacted with the tosylhydrazone salt derived from benzaldehyde in the presence of a phase transfer catalyst (PTC), $Rh_2(OAc)_4$ and catalytic quantities of chiral sulfide **1** (Scheme 6).[4] After optimization of the reaction conditions, aziridine **11** was obtained in 57% yield as an 8:1 *trans*/*cis* diastereoisomeric ratio. The trans isomer was obtained with an enantiomeric excess of 98%. The inseparable mixture of aziridines **11** was then deprotected using a mixture of CsF and tetrabutylammonium triphenyldifluorosilicate (TBAT)[21] in a DMF/THF mixture at 40 °C providing the N-H aziridines in 91% which could be easily separated by column chromatography to afford **12** in diastereoisomeric pure form (74%). The *trans*-aziridine was then quantitatively converted into benzoyl aziridine and subsequent treatment with $BF_3 \cdot Et_2O$ resulted in regioselective ring-expansion/isomerization[22] furnishing the *trans*-oxazoline **8** in 81% yield over two steps with complete retention of stereochemical integrity. The same final steps as shown in Scheme 5 furnished the Taxol side chain in a total of seven steps and 20% overall yield.

Our key sulfur ylide reactions in both routes gave aziridines/oxazolines with very high enantioselectivity. We believe this is because (Figure 1) (i) a single diastereomeric

(15) Silica gel has been reported to effect rearrangement of unsaturated acyl aziridines into oxazolines: Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc*. **1997**, *119*, 8385.

(16) Treatment of the pure *cis*-aziridine with acetic acid resulted in a 3/1 mixture of *trans*/*cis* oxazoline, whereas pure *trans*-aziridine gave *trans*-oxazoline only. This showed that rearrangement of the *cis*-aziridine is not stereospecific.

(17) Cabri, W.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett*. **1996**, *37*, 4785−4786.

(18) (a) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Boger, D. L.; Lee, R. J.; Bournaud, P.-Y.; Meier, P. *J. Org. Chem*. **2000**, *65*, 6770−6772.

(19) Murakami, N.; Tamura, S.; Wang, W.; Takagi, T.; Kobayashi, M. *Tetrahedron* **2001**, 57, 4323−4336.

(20) Hamamoto, H.; Mamedov, V. A.; Kitamoto, M.; Hayashi, N.; Tsuboi, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4485−4497.

(21) The use of CsF or TBAT on their own were much less effective than the combination.

(22) Papa, C.; Tomasini, C. *Eur. J. Org. Chem.* **2000**, 1569.

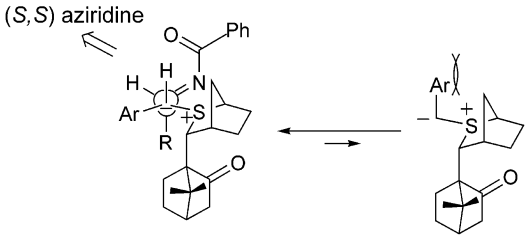


Figure 1. Origin of high enantioselectivity in ylide reactions with imines.

sulfonium ylide is formed, (ii) high levels of control in ylide conformation result from steric interactions of the aryl group with the methylene bridge, (iii) high levels of control in face selectivity of the ylide result from the bulky camphor moiety blocking one face, and (iv) betaine formation is nonreversible (proven by crossover experiments[23]).

In conclusion, we have described two routes to the *syn*-α-amino alcohol found in the side chain of Taxol. The first route involved a stoichiometric sulfur ylide mediated reaction with an *N*-benzoylimine which furnished the required oxazoline directly. In this route, the benzoyl group serves multiple purposes: it activates the imine toward nucleophilic attack by the ylide, promotes rearrangement of the intermediate aziridine to the oxazoline, and is required in the final product. The second route utilizes our catalytic asymmetric aziridination process of *N*-sulfonylimines. Although our syntheses do not compete with the shortest synthesis of the Taxol side chain,[8] they are nevertheless efficient and highly enantioselective and demonstrate the application of asymmetric sulfur ylide technology in the synthesis of *syn*-*β*-amino alcohols, a common motif in natural products.

Acknowledgment. We thank EPSRC for support of this work.

Supporting Information Available: Experimental procedures, characterization data, and methods for determination of enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035554W

(23) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159.