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Stereodivergent Access to *Cis*- and *Trans*-3,5-Disubstituted 1,4-Thiazane 1-Oxides by Cyclization of Homochiral β-Amino Sulfoxides and Sulfones. The Preparation of Isomeric Ant Venom Alkaloids

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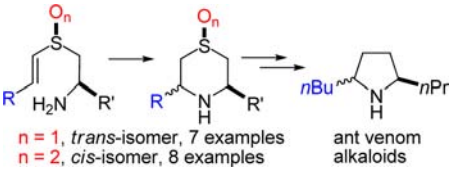
ABSTRACT



Intramolecular conjugate additions of homochiral (*E*)-1-alkenyl 2-aminoalkyl sulfoxides and sulfones were investigated. The relative position of the 3,5-substituents of the resulting 1,4-thiazane oxides was found to be dependent on the oxidation state of the sulfur atom, demonstrating a simple and highly stereodivergent synthetic protocol. Selected *cis*- and *trans*-3,5-disubstituted 1,4-thiazane dioxides were converted to *cis*- and *trans*-2,5-disubstituted pyrrolidines, known ant venom alkaloids.

Chiral 3,5-disubstituted 1,4-thiazane *S*-oxides represent an important class of biologically active heterocycles.[1−5] Cycloalliin (**2**), a natural product found in *Allium* plants, displays numerous medicinal benefits including antioxidant activity,[5] enhanced fibrinolysis in humans,[3] reduced serum triacylglycerol levels in rats,[4] and anticancer activity (Figure 1).[6,7] 3,5-Disubstituted thiazane *S*-oxide **3** (Figure 1) has antibiotic properties, inhibiting dihydrodipicolinate synthase in *E. coli*.[2,8]

Attempts to access 3,5-disubstituted 1,4-thiazane *S*-oxides by oxidation of thiomorpholine derivatives provide only single examples or low yielding mixtures of diastereomeric sulfoxides.[9,10] Sulfones are more readily accessible,[11] but cyclization protocols prior to the oxidation often fail to deliver ring substituents with good stereoselectivity.[9,12]

On the other hand, cyclization chemistry via conjugate addition to alkenyl sulfones and sulfoxides tends to hold more promise. In the sulfoxide manifold, cycloalliin[13] and homocycloalliin[14] were obtained as a single *cis*-3,5-disubstituted diastereomer by cyclization of the acyclic isomer, but reactions took at least four days. Low yields and isomeric mixtures were obtained when conditions were changed[15] or when *cis*-isoalliin[16] was cyclized. Sulfone

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analogs of isoalliin (**1**) delivered 3,5-disubstituted 1,4-thiazane *S,S*-dioxides in low yields with poor diastereoselection after five days.[17] More recently, a series of 3-substituted and 3,5-disubstituted 1,4-thiazane dioxides were prepared by the reaction of amines with divinyl sulfones,[18] which included a cyclization to create a second stereogenic center.

Overall, the stereoselective intramolecular cyclizations of vinylic β-amino sulfoxides and sulfones remain, in general, underexplored and sometimes inefficient reactions in organic chemistry. Herein we report the diastereoselective synthesis of *trans*-3,5-disubstituted thiazane *S*-monoxides and *cis*-3,5-disubstituted thiazane *S,S*-dioxides from an intramolecular asymmetric *aza*-Michael reaction of the corresponding enantiopure *trans*-1-alkenyl 2-aminoalkyl sulfoxides and sulfones, respectively. The value of the chemistry is demonstrated by the stereodivergent synthesis of *cis*- and *trans*-2,5-disubstituted pyrrolidine alkaloids isolated from the venom extract of *Myrmicaria melanogaster*.[19]

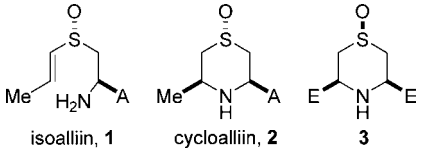
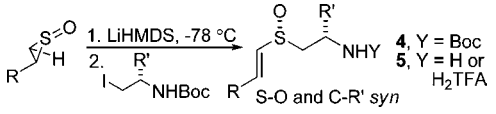


Figure 1. Bioactive β-amino sulfoxides (A = CO_2H; E = CO_2Me).

Scheme 1. Doubly Diastereoselective Preparation of Chiral *syn*-(*E*)-1-Alkenyl 2-Aminoalkyl Sulfoxides (ref 20)



Our recently disseminated doubly diastereoselective sulfenate alkylation chemistry permits facile access to *syn* oriented Boc-protected (*E*)-1-alkenyl 2-aminoalkyl sulfoxides **4** (Scheme 1).[20] Numerous cyclization attempts of sulfoxide **4a** (R = Me, R′ = Bn)[20] failed to provide any cyclic products, likely due to the electronic and steric hindrance of the Boc group.[21] Therefore cyclizations of the deprotected free amine were pursued. Amine **5a** could be cyclized to the corresponding *trans*-3,5-substituted thiazane **6a** as a single diastereomer by treatment with Et_3N in MeOH at reflux.[22] The stereochemistry of **6a** contrasts with that of the *cis*-disubstituted thiazane obtained from the cyclization of isoalliin (**1**), which possesses *anti* S−O/C−R′ stereochemistry. A selection of other sulfoxides **5** with *syn* stereochemistry also provided *trans*-3,5-disubstituted heterocycles as single diastereomers in excellent yields, whether the starting material was introduced as an amine (Table 1, entries 5, 7, 8) or as the ammonium trifluoroacetate salt (Table 1, entries 2−4, 6). To the best of our knowledge these are the first examples of an intramolecular *aza*-Michael reaction of an (*E*)-1-alkenyl 2-aminoalkyl sulfoxide with *syn* stereochemistry. In contrast, a β-amino sulfoxide (**5h**, Table 1, entry 9) with *anti* stereochemistry provided the complementary *trans*-3,5-disubstituted heterocycle over an extended reaction time, consistent with isoalliin and its analog.[13,14] The data in Table 1 suggest the sulfinyl configuration alone directs the stereochemistry of the R group.

β-Amino sulfoxides **5** with *t*-Bu, *c*-hexenyl, or phenylethyl R groups failed to cyclize after prolonged heating under various reaction conditions. Therefore, we prepared several (*E*)-1-alkenyl 2-aminoalkyl sulfones (**7**), anticipating them to be superior Michael acceptors.[23,24] Using similar conditions, sulfones **7** were converted to *cis*-3,5-disubstituted thiazanes **8**, possessing substituent stereochemistry different from that of *trans*-3,5-thiazane sulfoxides **6a**−**g**. Entry 1 of Table 2 displays near-complete reversal in selectivity from that of entries 1 and 2 of Table 1; a similar relationship is seen for entries 7 of the tables. Simply oxidizing the sulfoxides **5** to the corresponding sulfone **6** prior to cyclization can shift the 3,5-substituent orientation of the thiazanes from *trans* to *cis*!

Sulfones **7** with sterically demanding phenylethyl and *t*-Bu substituents at the electrophilic carbon cyclized efficiently to give *cis*-3,5-disubstituted thiazane dioxides in good yields with dr's ≈ 9:1 (Table 2, entries 2−3, 6). Ph and *t*-Bu substituted thiazane **8e** was formed as a single diastereomer, likely owing to the large steric bulk of the substituents (Table 2, entry 5). 1-Cyclohexenyl sulfone **7d** cyclized to bicyclic thiazane **8d** with its tertiary hydrogens in an all-*cis* orientation (Table 2, entry 4).[25]

The observed stereochemical dependence of the cyclization on the sulfur oxidation state can be attributed to differences in conjugate addition reactivity and to the dissimilar H-bonding propensities between sulfoxides and sulfones.[26] Sulfoxides are among the strongest H-bond accepting functional groups, while sulfones are comparatively weak.[26,27] Sulfoxides exhibit strong intramolecular H-bonds with hydroxyl groups even at temperatures > 170 °C,[28−30] while the analogous sulfones do not.[29,30] It is suggested here

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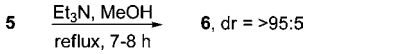
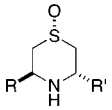
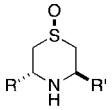
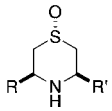
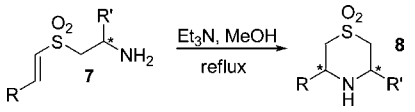
Table 1. *Trans*-Selective Cyclizations of (*E*)-1-Alkenyl 2-Aminoalkyl Sulfoxides

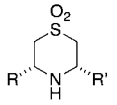
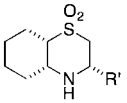
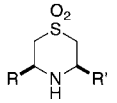


no.	R, R'	Y	Et_3N (equiv)	product,	yield (%)[a]
1	Me, Bn	H	1		**6a**, 95
2	Me, Bn	H_2TFA	2		**6a**, 95
3	Me, Me	H_2TFA	2		**6b**, 91
4	Me, *i*-Pr	H_2TFA	2		**6c**, 97
5	*n*-Bu, Me	H	1		**6d**, 93
6	Me, Bn	H_2TFA	2		**6e**, 93
7	*n*-Bu, *n*-Pr	H	5		**6f**, 96
8	*n*-Bu, Bn	H	1		**6g**, 84[b,c]
9	*n*-Bu, *n*-Pr	H	10		**6h**, 75[b,d,e]

[a] All dr's assigned by NMR analysis of the crude reaction mixture. No minor isomers were evident. The relative stereochemistry of ring substituents was determined by analysis of ^1H NMR coupling constants and 2D NMR acquisitions and NOE experiments. [b] Reaction did not go to completion. Yield reported is of isolated material based on 100% consumption of **5**. [c] Yield is 91% based on consumed **5g**. [d] Yield is 94% based on consumed **5h**. [e] Reaction mixture was refluxed for 42 h.

Table 2. *Cis*-Selective Cyclizations of (*E*)-1-Alkenyl 2-Aminoalkyl Sulfones



no.	R, R'	conditions[a]	major isomer	yield (%)	dr[b]
1[c]	Me, Bn	1 h, rt		**8a**, 97	92:8
2	$Ph(CH_2)_2$, Bn	7 h, reflux		**8b**, 94	91:9
3	*t*-Bu, Bn	8 h, reflux		**8c**, 99	92:8
4	*c*-C_6H_{11}, Bn	7 h, reflux		**8d**, 79[d]	>95:5
5	*t*-Bu, Ph	10 h, reflux		**8e**, 79[d]	>95:5
6	*t*-Bu, Et[e]	8 h, reflux		**8f**, 70	91:9
7	*n*-Bu, *n*-Pr	1 h, 40 °C		**8g**, 99	92:8

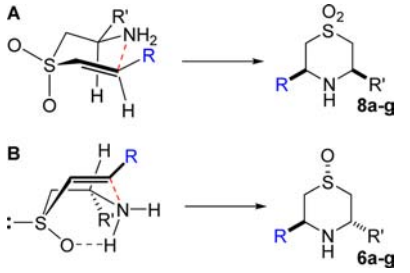
[a] 1 equiv of Et_3N was used unless otherwise noted. [b] All dr's assigned as indicated for Table 1. [c] Cyclization reaction was done on an ~5:1 (uncyclized/cyclized) mixture, because partial cyclization was observed following Boc removal. [d] Product was isolated from unreacted **7** (~5%). Yield based on consumed **7** ~83%. [e] Compound was reacted as the TFA salt. 2 equiv of Et_3N were employed.

that the cyclization reactions of the sulfones proceed by way of a six-membered transition state (labeled **A**, Scheme 2) wherein both R and R′ assume pseudoequatorial positions.

A similar chair transition state for the cyclizations of *syn* β-amino sulfoxides (Table 1, entries 1−8) would not deliver the observed *trans*-3,5-disubstituted thiazanes **6**. However, if pseudotwist-boat conformation **B** is adopted in the transition state, the *trans*-3,5-disubstituted heterocycles **6** can be accessed. Twist-boat **B** features a stabilizing hydrogen bond interaction between the sulfinyl oxygen and amine functionalities, which precludes the unfavorable 1,4-flagpole interaction present in the twist-boat conformation of related ring systems, while the R′ and R substituents remain remote from one another. The sluggish cyclization of sulfoxide **5h** (e.g., Table 1, entry 9) can be explained by the weaker activating sulfoxide group if geometry **A** is operable. Alternatively, the R and R′ groups of **6h** are expected to undergo a steric clash if **B** is part of the reaction pathway. MeOH is also anticipated to be involved; further investigations are underway.

Jones et al. isolated 14 alkaloids from venom extracts of the ant *Myrmicaria melanogaster*,[19] two of which include chiral *trans*- and *cis*-2,5-disubstituted pyrrolidines **15** and **20** (Scheme 3). The authors did not elucidate the absolute configuration at either stereocenter. Alkaloids of the same structural family have been isolated from frog skin extracts[31] and extracts of the venoms from other ant species.[32] In Nature, alkaloids **15** and **20** are sprayed from a venom gland of *M. melanogaster* to ward off predators.[19]

Scheme 2. Possible Transition State Geomteries for Cyclization Reactions



Structurally similar 2,5-substituted pyrrolidines have shown potent insecticidal activity toward arthropods[32] while other such compounds have demonstrated high biological activity.[33] The biological study of insect venoms has led to the discovery of new therapeutic agents.[34]

Coldham and Leonori have prepared venom alkaloids **15** and **20** in good optical purity using a sequence of stereoselective Cu(I)-promoted allylation and crotylation reactions as key steps.[35] However, the crotylation provides a disubstituted pyrrolidine intermediate in low yield (32%) and poor dr (1.8:1 = *cis*/*trans*). Further, (−)-sparteine, the ligand used for the allylation reaction, is no longer available from major suppliers[36] and is a preparative challenge.[37,38]

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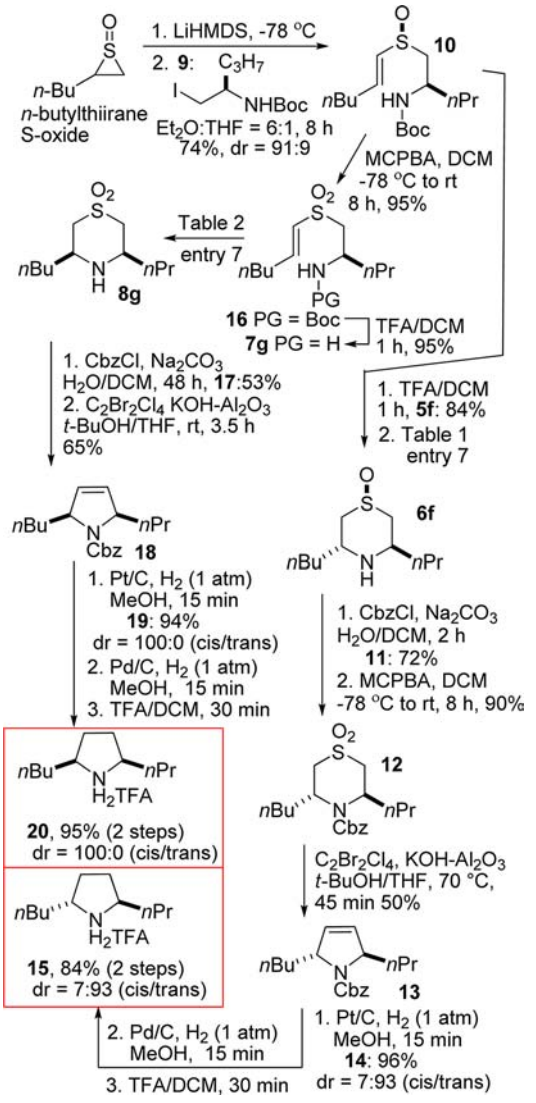
Scheme 3. Stereodivergent Synthesis of *Trans* and *Cis* Isomeric Ant Venom Alkaloids



Our synthesis of alkaloids **15** and **20** commenced with the diastereoselective alkylation of lithium (*E*)-1-hexenesulfenate (from butylthiirane *S*-oxide) with amino iodide **9** derived from D-norvaline, to give *β*-amino sulfoxide **10** in good yield and diastereoselectivity (Scheme 3).[20,39,40] For the synthesis of **15**, the major isomer of sulfoxide **10** was deprotected with TFA to provide free amine **5f** in good yield and subsequent cyclization provided thiazane **6f** (entry 7, Table 1). The Cbz group was chosen to protect the **6f** so that hydrogenation/hydrogenolysis of **13** could be later performed in a single step. MCPBA oxidation of Cbz protected thiazane **11** afforded sulfone **12** which was then converted to pyrroline **13** in acceptable yield using newly developed Ramberg–Bäcklund conditions.[41] Initial hydrogenation/hydrogenolysis attempts on **13** with a $Pd/C/H_2$ catalyst system resulted in pyrrolidine formation with a large erosion of diastereoselectivity.[42] The use of a $Pt/C/H_2$ catalyst system converted **13** to pyrrolidine **14** in excellent yield with only a slight erosion of dr to the *cis* diastereomer. The *trans* pyrrolidine **14** could not be separated from the minor *cis* isomer so it was carried on to the next step. Cbz protected pyrrolidine **14** was deblocked with $Pd/C/H_2$ and then converted to the TFA salt **15** in excellent yield for the two steps without any change of the dr. Optical rotation of the free amine (2*R*,5*R*)-2-butyl-5-propylpyrrolidine (**15**) suggested it was obtained in high optical purity.[35]

The synthesis of **20** required immediate MCPBA oxidation of the original ~9:1 mixture of **10** which delivered an excellent yield of sulfone **16**. Subsequent deprotection of **16** with TFA to give free amine **7g** proceeded efficiently. The cyclization of **7g** occurred as per Table 2 (entry 7). The major *cis* diastereomer was separated from the *trans* isomer by flash chromatography. Protection of **8g** with Cbz affording **17** was followed by Ramberg–Bäcklund treatment to give an acceptable yield of pyrroline **18**. For hydrogenation/hydrogenolysis, the $Pt/C/H_2$ catalyst system converted **18** to pyrrolidine **19** with no loss of dr. Pyrrolidine **19** was deblocked with the Pd catalyst and isolated (2*S*,5*R*)-2-butyl-5-propylpyrrolidine (**20**) as its TFA salt in excellent overall yield. The success of the two syntheses and the data of Tables 1 and 2 indicate that the enantiomers of **15** and **20** can also be prepared if one employs L-norvaline as a source of the homochiral iodide.

To summarize, this investigation demonstrates a novel stereodivergent synthesis of *trans*- or *cis*-3,5-disubstituted 1,4-thiazane oxides achieved by *simply changing the oxidation state of the sulfur atom*. Transition states are offered to account for the observed selectivity. The utility of this chemistry permitted the stereodivergent diastereoselective synthesis of two isomeric ant venom alkaloids from identical starting materials. The mechanistic origins of the experimentally observed cyclization stereoselectivities are currently under investigation.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds, including selected NOESY data and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.