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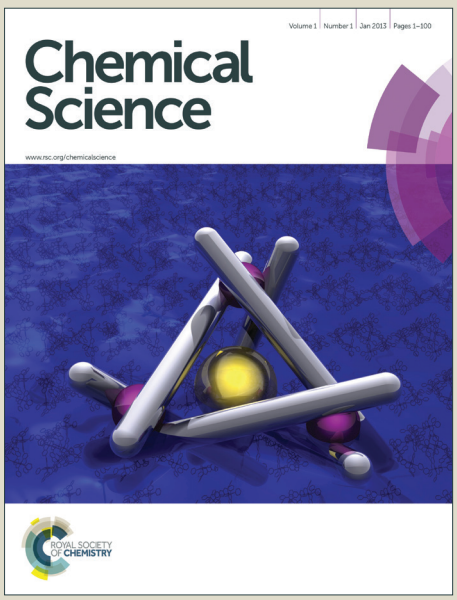

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Complete stereodivergence in the synthesis of 2-amino-1,3-diols from allenes

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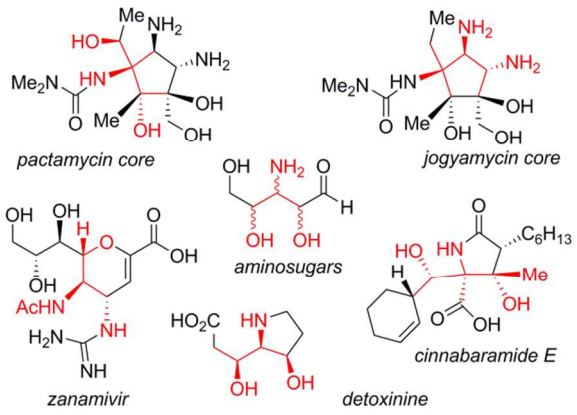
Amine-containing stereotriads ('triads'), where the nitrogen is embedded in an array of three contiguous, heteroatom-bearing chiral carbons, are key motifs in numerous bioactive natural products. Allene aziridination provides convenient access to amine triads where the position of the nitrogen and the identities of the accompanying heteroatoms can be readily manipulated. However, stereochemical flexibility, where a single allene can be selectively transformed into any possible diastereomer of a specific triad, has been elusive. Herein, we describe studies to understand how both reagent and substrate control can be effectively employed in the stereodivergent oxidative amination of allenes, with transfer of the axial chirality of an enantioenriched precursor to point chirality in each possible diastereomeric 2-amino-1,3-diol product. Application of this flexible strategy to the synthesis of all four stereoisomers of the natural product detoxinine is also presented.

Introduction

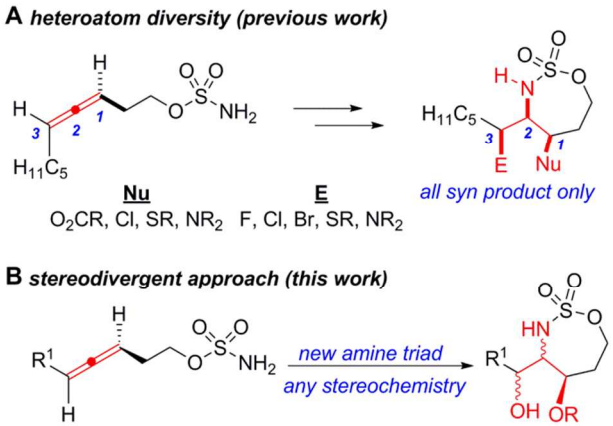
Compounds that display a stereodefined amine embedded in an array of three or more consecutive, chiral heteroatom-bearing carbons are common in natural products that exhibit potent and therapeutically useful biological activities (Figure 1). The efficient construction of this motif offers interesting synthetic challenges and opportunities for developing methods that complement alkene oxidation approaches, while enabling exploration of new chemical space inspired by complex amine-containing natural products.[1]

Our group has recently developed a suite of allene aziridination methods that enable the construction of diverse libraries of complex amine triads, where both the position of the nitrogen and the identity of the remaining two heteroatoms (Scheme 1, **A**) can be readily interchanged.[2-5] Key to our strategy is the formation of a highly strained bicyclic methylene aziridine intermediate that can be transformed into an array of triads by aziridine ring-opening and subsequent electrophilic substitution[3] or *via* functionalization of the exocyclic double bond.[4] In addition, the transfer of the axial chirality of the allene to point chirality in the products with excellent fidelity obviates the need for a different asymmetric catalyst for the synthesis of each diastereomeric triad.[5b,6]

Figure 1. Molecules containing complex amine stereotriads.



Scheme 1. Strategies for generating aminated stereotriads.



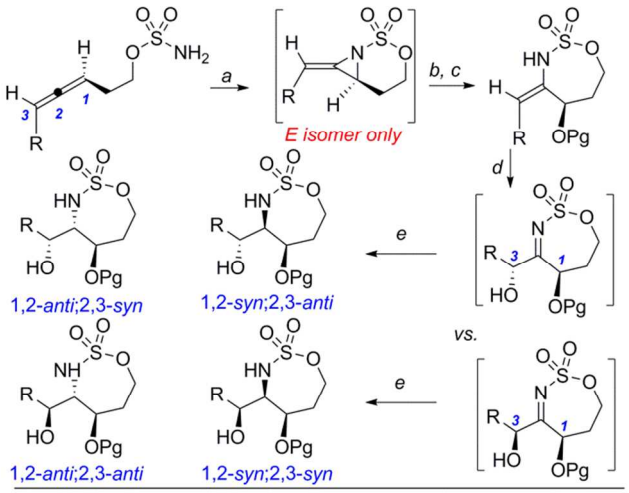
While our previous work was powerful in terms of the scope of the heteroatoms that could be introduced into the amine triads (Scheme 1, **A**), the stereochemical relationship amongst the three newly formed sp^3 carbons was always 1,2-*syn*:2,3-*syn*.[3c] We attributed this to inherent substrate control of the reaction, a feature that could potentially limit the utility of the oxidative amination of allenes. Thus, we wanted to explore the possibility of overriding substrate

control to generate amine triads with both *heteroatom* and *stereochemical* diversity from a single allene substrate (Scheme 1, **B**).[7,8] The successful realization of this goal would yield functional and stereochemically flexible methods as valuable tools for the construction of complex amine targets and libraries of closely related structures with useful biological activities.

Results and discussion

We focused our initial studies on the transformation of allenes to 2-amino-1,3-diols, as these motifs commonly occur in aminosugars and other bioactive natural products, but are not easily prepared *via* aminohydroxylation of allylic alcohols due to issues with regio- and stereocontrol.[1f,9] However, there were three major challenges we faced in applying allene aziridination to the stereodivergent syntheses of aminodiols (Scheme 2).[10-13] First, previous studies show that the Rh-catalyzed aziridination yields only (*E*) bicyclic methylene aziridines; the (*Z*) isomer cannot be obtained directly.[4] Second, irrespective of whether an (*E*) or (*Z*)-enesulfamate is employed as the substrate, the facial selectivity in its addition to a suitable electrophilic oxygen source must be controlled (Scheme 2, step *d*). This begs a detailed understanding of how the nature of the electrophile and the transition state of the nucleophilic addition influences the stereocontrol of the oxidation. Finally, the stereoselectivity in the reduction of the resulting *syn* and *anti* imines (step *e*) must be tunable, a task made difficult by the presence of both a protected and free alcohol flanking the imine. While the stereocontrolled reduction of cyclic imines with two adjacent oxygen-containing groups contained in the same ring are known, examples of high *dr* in the reduction of conformationally flexible 1,3-dioxo-2-imines are rare.[14,15]

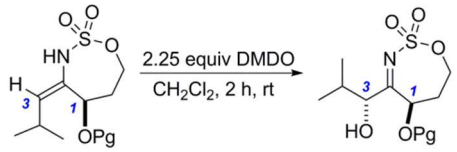
Scheme 2. Challenges in stereodivergent triad synthesis.



Optimization of the addition of (*E*)-enesulfamates to dimethyldioxirane (DMDO). The first challenge in developing a stereodivergent oxidative amination of allenes was to understand what factors control the *dr* in the addition of an enesulfamate, which results from a one-pot allene aziridination/ring-opening (Scheme 2, steps *a-c*), to a given electrophile. These attributes include, but are not limited to, the nature of the group at C1, the conformation of the exocyclic alkene (*E vs. Z*) and the identity of the electrophile.

To address how the nature of the group on C1 impacts the relative configuration and the *dr* of the resulting imine product, a series of (*E*)-enesulfamates were treated with DMDO as the electrophilic oxygen source (Table 1). A free hydroxyl group at C1 of **1** yielded the imine **6**[16], with the major isomer displaying a 1,3-*anti* stereo-

Table 1. Effect of the C1 group on the *dr* of the oxidation.



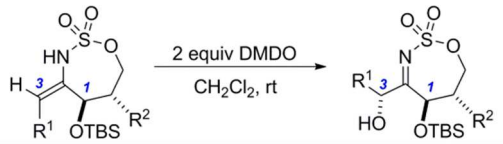
entry	OPg	substrate	*anti/syn*[a]	product
1	OH	**1**	2.5 : 1	**6**
2	OAc	**2**	1 : 1	**7**
3	4-MeOC$_6$H$_4$CO$_2$	**3**	2.7 : 1	**8**
4	9-phenCO$_2$	**4**	2.5 : 1	**9**
5	OTBS	**5**	> 9 : 1	**10**

[a] Determined by ^{1}H NMR of the crude imine.

chemistry, as determined by X-ray analysis (entry 1, see the SI for X-ray data).[17] This result was surprising, given that utilizing N-bromosuccinimide (NBS) as the electrophile in our previous studies gave the 1,2-*syn*:2,3-*syn* product upon reduction of the intermediate imine (Scheme 1A).[3c] The nature of the protecting group for the C1 hydroxyl also influenced the *dr* of the product imine (entries 2-4). Steric bulk at C1 was necessary to achieve good selectivity in the oxidation of the *E*-enesulfamate, with the OTBS group of **5** (entry 5) yielding the imine **10** with a *dr* of > 9:1. Other silyl protecting groups were explored, but none were superior to TBS. Attempts to open the methylene aziridine with TBSOH were not successful; thus, H_2O was used as the nucleophile and the crude alcohol protected using TBSOTf.

The scope of the DMDO oxidation was explored for a series of (*E*)-enesulfamates (Table 2). Substitution of the ^{i}Pr group of **5** with the *n*-pentyl chain of **11** (entry 2) resulted in a lowered *dr* of 3:1 in **16** when the reaction was carried out at rt. Lowering the temperature to -20 °C delivered a more satisfactory 5:1 *dr* (entry 3). Placement of

Table 2. Addition of (*E*)-enesulfamates to DMDO.



entry	R^1	R^2	substrate	°C	*anti:syn*[a]	product
1	^{i}Pr	H	**5**	25	> 9 : 1	**10**
2	C_5H_{11}	H	**11**	25	3 : 1	**16**
3	C_5H_{11}	H	**11**	-20	5 : 1	**16**
4	C_5H_{11}	Me	**12**	25	> 9 : 1	**17**
5	CH_2CH_2Ph	H	**13**	40	3 : 1	**18**
6	$CH_2CH_2SiMe_2Ph$	H	**14**	-20	3.5 : 1	**19**
7	Ph	H	**15**	0	1 : 10	**20**

[a] *anti:syn* ratios determined by crude ^{1}H NMR of the imine (not isolated due to its sensitivity to hydrolysis)

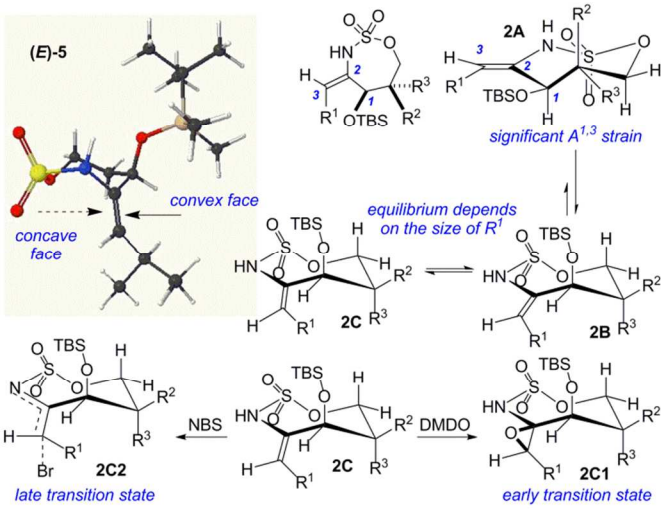
an *anti*-Me group on the carbon adjacent to the OTBS in **12** resulted in an improved *dr* of 9:1 (entry 4), while a phenethyl-substituted enesulfamate **13** (entry 5) and the PhMe$_2$Si-substituted **14** (entry 6)

gave lower *dr*. Surprisingly, placement of a Ph group in conjugation with the exocyclic double bond of **15** reversed the selectivity, giving a 10:1 *dr* in favor of the *syn* diastereomer **20** (entry 7).

These initial studies exploring the reaction of (*E*)-enesulfamates with DMDO provided an opportunity to establish design principles for achieving successful stereodivergent oxidative allene amination. In particular, the challenges in controlling the conformations of seven-membered heterocyclic rings[18], as compared to well-studied six-membered systems, prompted us to undertake a detailed analysis of the roles the specific nature of the electrophile and the substrate play in controlling the *dr* of the imine formation.

Figure 2 depicts the calculated optimized geometry for the (*E*)-enesulfamate **5** containing an OTBS group at C1. Comparison of two possible chair-like conformations, **2A** and **2B**, indicates relief of $A^{1,3}$ strain in **2A** may dispose the equilibrium towards conformer **2B**, despite the fact this places the OTBS group in a pseudoaxial position. This is reasonable, given that alkylidenecyclohexanes have been known to adopt conformations where an oxygen-containing group prefers to reside in an axial position.[19,20] In addition, the bulky OTBS group in the alkylidenecycloheptane **(*E*)-5** (Figure 2) may promote an additional perturbation of the exocyclic double bond to a pseudoaxial position to yield **2C**. This presents the electrophile with a choice between approaching the double bond from either the convex or concave face, with reaction at the more accessible convex face yielding the 1,3-*anti* stereochemistry.

Figure 2. Model for selective oxidation of (*E*)-enesulfamates.

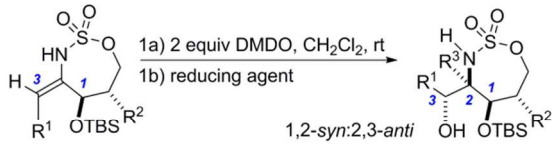


Conformers **2A-2C** also help to rationalize the impact of the size of the R^1 group on the *dr* of the DMDO oxidation. Substrates with larger R^1 groups experience enhanced $A^{1,3}$ strain in conformer **2A**, shifting the equilibrium further towards **2C** and improving the selectivity in the approach of the DMDO from the convex face of **2C**. While invoking **2C** as the preferred conformer explains the stereochemical outcome in the addition of **(*E*)-5** to DMDO, it does not explain the 1,3-*syn* geometry observed in our previous studies employing NBS as the electrophile.[3c] To rationalize these observations, we propose the nature of the transition state in the addition of an (*E*)-enesulfamate to the electrophile impacts the stereochemical outcome. For example, if the addition of **2C** to DMDO occurs in a concerted fashion with an early transition state that closely resembles the starting material, intermediate **2C1** would be produced and unravel to yield a 1,3-*anti* relationship in the imine product. In contrast, employing NBS in the reaction of **2C** may occur through a late transition state **2C2** that contains significant C=N double bond character. The bending of the C=C bond away from the pseudoaxial orientation in **2C** back to a more equatorial position in **2C2** may influence facial selectivity by precluding approach of NBS from the top face of the alkene due to effective shielding by the bulky OTBS group, resulting in the 1,3-*syn* imine.

The presence of the phenyl group at C3 in **15** (Table 2, entry 7) provides further insight into how the substrate can impact the facial selectivity in the addition of **15** to DMDO. Conjugation of the phenyl group of **15** with the enesulfamate double bond in the ground state may lead to significant C=N character in a transition state resembling **2C2** (Figure 2), resulting in a 1,3-*syn* stereochemistry in the imine product **20**. However, another possibility is that the Ph-bearing C3 hydroxyl stereocenter of a 1,3-*anti* imine may be more susceptible to epimerization to the thermodynamically favoured **20**.[21]

1,2-*Syn*:2,3-*anti* stereoisomers from (*E*)-enesulfamates. With a method in hand to form the 1,3-*anti* imines in good *dr*, hydride sources were investigated to set the C2 stereocenter (Table 3). An *a priori* prediction of the stereochemistry of imine reduction was difficult, due to the presence of two adjacent oxygen-containing groups. The bulky OTBS group at C1 could control reduction *via* steric effects, while the more conformationally flexible C3 hydroxyl might participate readily in chelation control. Ultimately, reductants providing chelation control, such as $Zn(BH_4)_2$ in non-coordinating solvents (CH_2Cl_2 or 1,2-dichloroethane), provided the 1,2-*syn*:2,3-*anti* triad products with high *dr*, as determined by X-ray analysis. The *anti* configuration between the C2 amine and C3 hydroxyl was consistent with a chelation-controlled Felkin-Anh addition of hydride and the *dr* of the 2-amino-1,3-diols closely matched the *dr* of the imine precursors, indicating that the reduction is highly stereoselective. Additional versatility was provided by employing Grignard reagents in place of a hydride reductant to yield the triad products **22-24** (entries 2-4). The pure amines were easily obtained by column chromatography or recrystallization.

Table 3. 1,2-*Syn*:2,3-*anti* triads from (*E*)-enesulfamates.



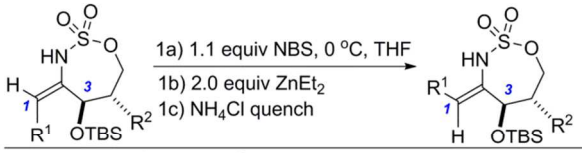
entry[a,b]	R^1	R^2	R^3	substrate	yield	*dr*[c]	product
1	^{i}Pr	H	H	**5**	80%	> 9 : 1	**21**
2	^{i}Pr	H	Ph	**5**	84%	> 9 : 1	**22**
3	^{i}Pr	H	$CHCH_2$	**5**	83%	8.2 : 1	**23**
4	^{i}Pr	H	CCH	**5**	81%	7.4 : 1	**24**
5	C_5H_{11}	H	H	**11**	82%	5 : 1	**25**
6	C_5H_{11}	Me	H	**12**	74%	> 9 : 1	**26**
7	CH_2CH_2Ph	H	H	**13**	80%	3.0 : 1	**27**
8	$CH_2CH_2SiMe_2Ph$	H	H	**14**	72%	3.5 : 1	**28**

[a] Entries 1, 5-8: 1 equiv $Zn(BH_4)_2$, $Cl(CH_2)_2Cl$, 0 °C *or* CH_2Cl_2, -78 °C. [b] Entries 2-4: 3.0 equiv Grignard reagent. [c] *anti:syn* ratios determined by ^{1}H NMR of the crude product.

Isomerization of (*E*)-enesulfamates and conversion to 1,2-*anti*:2,3-*anti* triads. Extension of the scope of allene aziridination to the synthesis of diastereomeric aminodiol triads required access to the (*Z*)-enesulfamate, as the facial selectivity in the addition of DMDO to the (*E*)-enesulfamates (Table 2) could not be readily reversed using reagent control. We were pleased to find that the (*E*)-enesulfamates could be cleanly isomerized to the corresponding (*Z*) isomers by simple sequential treatment with NBS and $ZnEt_2$

(Scheme 3 and Table 4). This isomerization method proved to be both selective and high-yielding, with no remaining (*E*) isomer observed. Since the (*Z*)-enesulfamates were more sensitive to hydrolysis than their (*E*)-counterparts, they were used as crude mixtures in subsequent functionalizations.

Table 4. Isomerization of (*E*)- to (*Z*)-enesulfamates.

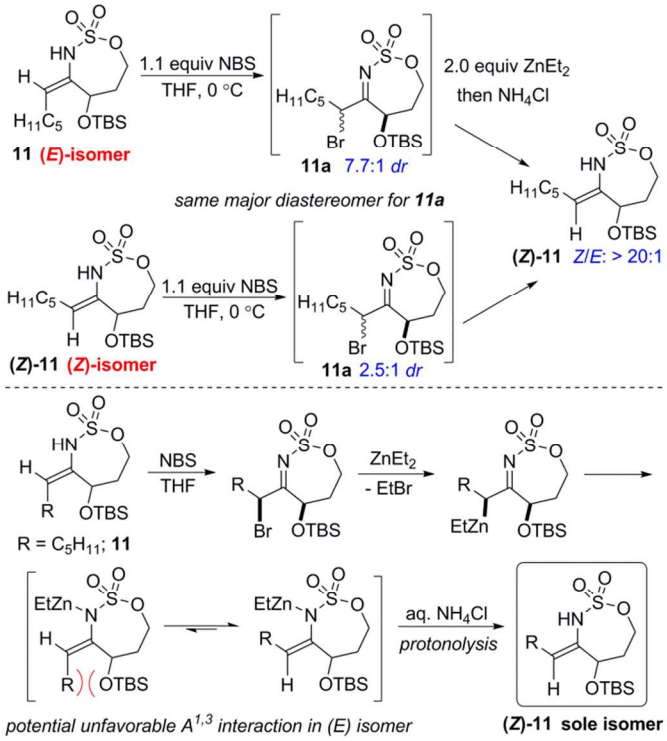


entry	R^1	R^2	substrate	yield	product	*Z*:*E*
1	^{i}Pr	H	**5**	97%	**(*Z*)-5**	> 20 : 1
2	C_5H_{11}	H	**11**	93%[a]	**(*Z*)-11**	> 20 : 1
3	C_5H_{11}	Me	**12**	79%	**(*Z*)-12**	> 20 : 1
4	CH_2CH_2Ph	H	**13**	89%[a]	**(*Z*)-13**	> 20 : 1
5	$CH_2CH_2SiMe_2Ph$	H	**14**	85%	**(*Z*)-14**	> 20 : 1
6	Ph	H	**15**	98%[a]	**(*Z*)-15**	> 20 : 1

[a] Crude NMR yield with mesitylene as an internal standard and used in subsequent steps without further purification.

The mechanism of the NBS/$ZnEt_2$-mediated isomerization reaction was briefly probed by correlating the *E*/*Z* ratio of the isomerized product to the *dr* of the intermediate α-Br imine **11a** (generated by reaction of **11** and **(*Z*)-11** with NBS). As illustrated in Scheme 3, there is no relationship between the *dr* of the α-Br imine and the final *E*/*Z* ratio for either the (*E*) or (*Z*)-enesulfamate. Importantly, the (*Z*)-enesulfamate does not undergo isomerization back to the (*E*)-isomer. Based on this data, the final *E*/*Z* ratio likely reflects a high thermodynamic preference for the (*Z*)-isomer of the intermediate

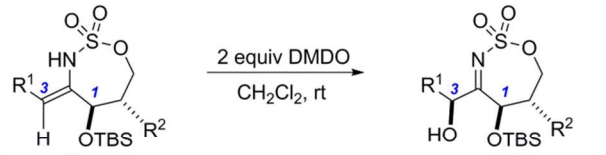
Scheme 3. Explorations of enesulfamate isomerization.



zinc-enamine that forms from insertion of $ZnEt_2$ into the C-Br bond and subsequent tautomerization (Scheme 3, bottom).[22] A facile *E*/*Z* interconversion of this intermediate explains why the *dr* of the α-Br imine **11a** is not reflected in the product **(*Z*)-11**. The (*Z*)-isomer may be favored due to $A^{1,3}$ interactions between the R group and the OTBS in the (*E*)-isomer. Protonolysis of the highly favored (*Z*)-zinc enamine then gives the (*Z*)-enesulfamate **(*Z*)-11** as the sole product.

The (*Z*)-enesulfamates (Table 5) underwent reaction with DMDO to afford the corresponding 1,3-*syn* imines **29-34** in moderate to high *dr*.[23] While the isopropyl-substituted enesulfamate **(*Z*)-5** gave a reduced *dr* of 4.3:1 (entry 1) compared to the analogous (*E*)-enesulfamates, several other substrates exhibited much improved selectivities (entries 2-5). Similar to **15** (see Table 2, entry 7), the Ph-substituted enesulfamate **(*Z*)-15** also delivered the *syn* diastereomer **34** in good *dr*.

Table 5. Addition of (*Z*)-enesulfamates to DMDO.

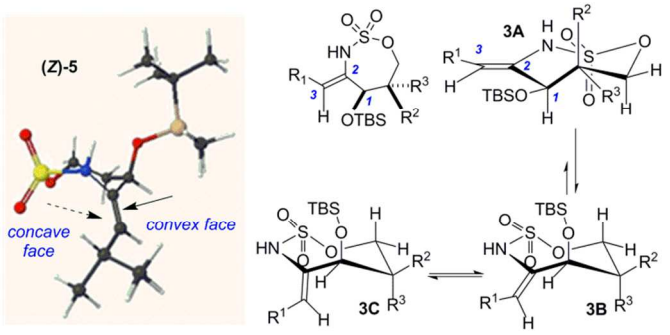


entry	R^1	R^2	substrate	°C	*syn*:*anti*[a]	product
1	^{i}Pr	H	**(*Z*)-5**	-20	4.3 : 1	**29**
2	C_5H_{11}	H	**(*Z*)-11**	0	9 : 1	**30**
3	C_5H_{11}	Me	**(*Z*)-12**	0	>9 : 1	**31**
4	CH_2CH_2Ph	H	**(*Z*)-13**	0	9 : 1	**32**
5	$CH_2CH_2SiMe_2Ph$	H	**(*Z*)-14**	0	>9 : 1	**33**
6	Ph	H	**(*Z*)-15**	0	7.7 : 1	**34**

[a] *anti*:*syn* ratios determined by ^{1}H NMR of the crude imine

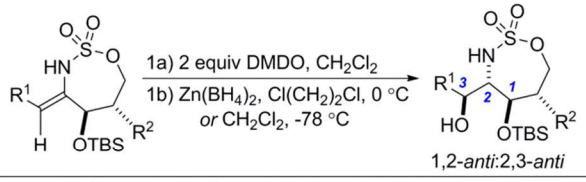
A calculated optimized geometry for the (*Z*)-enesulfamate **(*Z*)-5** (Figure 3) shows a similar conformation to the (*E*)-isomer **5**. Although conformer **3A** is not predicted to possess as much $A^{1,3}$ strain as the analogous (*E*)-isomer, conformers **3B** and **3C** do relieve some of this strain, and we cannot rule out stereoelectronic preferences for placing the oxygenated group in a pseudoaxial position.[19,20] Oxidation is again proposed to occur from the concave face of **(*Z*)-5** to give the 1,3-*anti* imine as the major stereoisomer. Bulkier groups at R^1, such as the isopropyl group of **(*Z*)-5**, may favour conformer **3B** due to a steric interaction between R^1 and the neighbouring sulfamate group, which would tilt the exocyclic alkene back into the plane of the ring and lower the selectivity of the oxidation, an observation borne out by the lower *dr* of 4.3:1 in **29**.

Figure 3. Model for selective oxidation of (*Z*)-enesulfamates.



The 1,3-*syn* imines in Table 5 were subjected to reduction with $Zn(BH_4)_2$, resulting in the desired 1,2-*anti*;2,3-*anti* stereotriads in high *dr* (Table 6), as confirmed by X-ray crystallographic analysis for **38** (see the SI for further details). Again, the *anti* relationship observed between the C2 amine and the C3 hydroxyl group suggest that chelation between the imine and the C3 OH group is the dominant mode of stereocontrol in this reduction. Products **36** and **38** were observed as mixtures of three stereoisomers, owing to imperfect diastereocontrol in the reduction step. However, the yields of isolated product were typically good to excellent, and the major diastereomers could be cleanly isolated by chromatography or recrystallization. Triad **40** was derived from the (*E*)-enesulfamate, due to the reversed selectivity observed in its reaction with DMDO (see Table 2, entry 7).

Table 6. 1,2-*Anti*-2,3-*anti* triads from (*Z*)-enesulfamates.



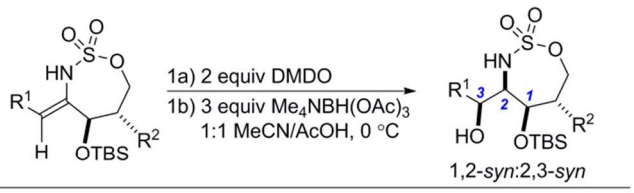
entry	R^1	R^2	substrate	yield	*dr*[a]	product
1	^{i}Pr	H	**(*Z*)-5**	89%	4.9 : 1	**35**
2	C_5H_{11}	H	**(*Z*)-11**	62%	11.7 : 1.7 : 1[b]	**36**
3	C_5H_{11}	Me	**(*Z*)-12**	61%	> 9 : 1	**37**
4	CH_2CH_2Ph	H	**(*Z*)-13**	85%	11.8 : 1.5 : 1[b]	**38**
5	$CH_2CH_2SiMe_2Ph$	H	**(*Z*)-14**	90%	9 : 1	**39**
6	Ph (*E*) isomer	H	**(*E*)-15**	85%	8.3 : 1	**40**

[a] *dr* determined by ^{1}H NMR of the product. [b] The major product is the 1,2-*syn*:2,3-*anti* stereoisomer.

Synthesis of 1,2-*syn*:2,3-*syn* triads. The synthesis of 1,2-*syn*:2,3-*syn* aminodiols required a reversal of the reduction facial selectivity of the 1,3-syn imines described in Table 5. The desired 2,3-*syn* reduction was achieved by preventing chelation between the C3 hydroxyl and the imine using $Me_4NBH(OAc)_3$ as the reductant in a polar protic solvent. The stereotriads **41-45** were obtained in good yields and moderate to good *dr* (Table 7). Fortunately, the products all had significantly different polarities and the major diastereomer could be obtained cleanly by column chromatography. Interestingly, the presence of an *anti*-Me group in **(*Z*)-12** biased the reaction towards the 2,3-*anti* reduction product **37** in good yield and *dr* (entry 3). This result points to the effects that small perturbations in the substrate can have on the reactive conformations in these seven-membered rings, thus prompting the development of alternate strategies to overcome cases of stereochemical mismatching.

The stereochemical outcomes of the reductions in Table 7 were surprising. Binding of the C3 OH group to the borohydride might shut down chelation control and result in the C3 group acting as the bulky group in a sterically-controlled, 2,3-*syn* selective Felkin-Anh reduction. However, this explanation is complicated by the fact that reductions mediated by $Me_4NBH(OAc)_3$ are typically thought to proceed *via* internal delivery of hydride, which should result in the production of the 1,2-*anti*:2,3-*anti* product instead of the observed 1,2-*syn*:2,3-*syn* stereoisomer.[24] We propose the steric bulk of the C1 OTBS group forces the imine into a conformation that requires the hydride to be delivered (in either an intra- or intermolecular fashion) *anti* to the OTBS group (see the Supporting Information for details). Thus, the observed relationship between the C1 OTBS and the C2 amine is always *syn*.

Table 7. 1,2-*Syn*-2,3-*syn* stereotriads from (*Z*)-enesulfamates.

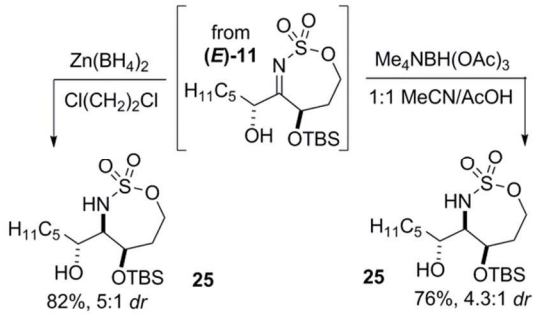


entry	R^1	R^2	substrate	yield	*dr*[a]	product
1	^{i}Pr	H	**(*Z*)-5**	82%	3.6 : 1.3[b] : 1[c]	**41**
2	C_5H_{11}	H	**(*Z*)-11**	73%	10.1 : 1.4 : 1[d]	**42**
3	C_5H_{11}	Me	**(*Z*)-12**	70%	< 1 : 9[e]	**37**
4	CH_2CH_2Ph	H	**(*Z*)-13**	73%	10.2 : 1.8 : 1[d]	**43**
5	$CH_2CH_2SiMe_2Ph$	H	**(*Z*)-14**	74%	3.1 : 1	**44**
6	Ph (from *E* isomer)	H	**(*E*)-15**	67%	8.7 : 1	**45**

[a] *dr* determined by ^{1}H NMR. [b] 1,2-*anti*:2,3-*anti* isomer. [c] 1,2-*syn*:2,3-*anti* isomer. [d] minor diastereomers not identified. [e] 1,2-*anti*:2,3-*anti* isomer.

1,2-*Anti*:2,3-*syn* stereoisomers from (*Z*)-enesulfamates. We anticipated reduction of (***E*)-11** (Scheme 4) with $Me_4NBH(OAc)_3$, which had previously yielded the 1,2-*syn*:2,3:*anti* triad **25** with $Zn(BH_4)_2$, might reverse the selectivity of imine reduction to provide the final 1,2-*anti*:2,3-*syn* diastereomer. However, we were disappointed to discover that multiple substrates supplied the 1,2-*syn*:2,3-*anti* triads using both $Me_4NBH(OAc)_3$ and $Zn(BH_4)_2$. This result was quite unexpected, given the outcomes that had been observed in Table 7. We suspect the OTBS group at C1 dictates the stereochemical outcome of imine reduction with $Me_4NBH(OAc)_3$ irrespective of the C3 stereochemistry, while the C3 group dictates the outcome when $Zn(BH_4)_2$ is employed as the reductant.

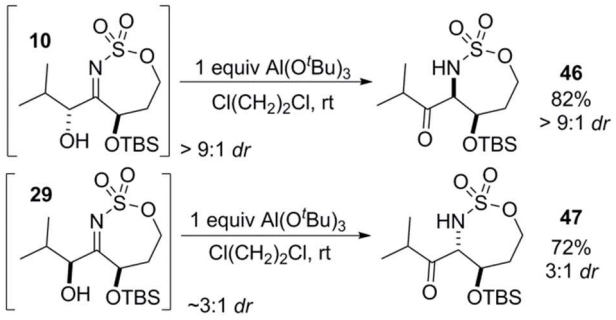
Scheme 4. Lack of complementary reduction for the 1,3-*anti* imine.



Since complementary imine reduction was not possible for 1,3-*anti* imines, alternative routes for accessing the final 1,2-*anti*:2,3-*syn* diastereomer were examined. We hypothesized isomerization of the α-hydroxyimine to a α-aminoketone might provide a way to carry out the intramolecular delivery of a hydride to the desired face of the imine (Scheme 5).[26] In addition, reducing ketones **46** or **47** instead of the imines **10** and **29** would curtail the problem of the two flanking heteroatom groups competing for stereocontrol. A variety of Lewis acids were explored for the Amadori-type rearrangement, with $Al(O^tBu)_3$ giving the best yields.[27] The isomerization was stereospecific, delivering either diastereomer of the α-aminoketone depending on the initial stereochemistry of the imine, with no noticeable epimerization observed under the reaction conditions.

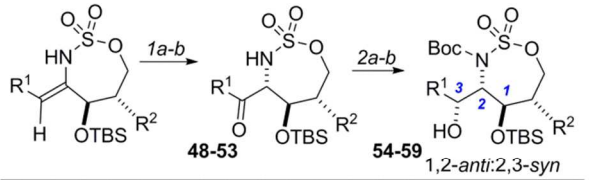
Success in obtaining the final 1,2-*anti*:2,3-*syn* 2-amino-1,3-diol triad was achieved through reduction of the 1,2-*anti* α-aminoketones (Table 8) with $NaBH_4$ in MeOH, provided the nitrogen of the sulfamate was Boc-protected. In the absence of Boc protection, the

Scheme 5. Isomerization of α-hydroxyimines to α-aminoketones.



reduction proceeded under chelation control to give the 1,2-*anti*:2,3-*anti* triad, providing an alternative route to this stereoisomer. This protocol was carried out in two steps, with isolation of the aminoketone intermediate prior to the Boc protection/reduction steps. As illustrated in Table 8, step 2, the *dr* for the $NaBH_4$ reductions ranged from 4:1 to > 20:1, with moderate to good yields.

Table 8. 1,2-*Anti*-2,3-*syn* triads from (*Z*)-enesulfamates.

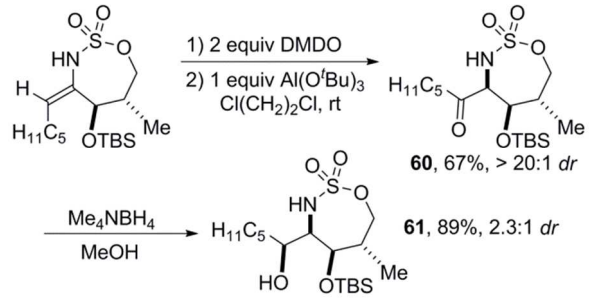


entry	substrate	R^1	R^2	yield	*dr* product[c]	
1	**(*Z*)-5**	^{i}Pr	H	72%[a]	3 : 1	**48**
				88%[b]	5.3 : 1	**54**
2	**(*Z*)-11**	C_5H_{11}	H	72%	10.6 : 1	**49**
				77%	> 20 : 1	**55**
3	**(*Z*)-12**	C_5H_{11}	Me	60%	> 20 : 1	**50**
				79%	6.2 : 1	**56**
4	**(*Z*)-13**	CH_2CH_2Ph	H	63%	11 : 1	**51**
				78%	> 20 : 1	**57**
5	**(*Z*)-14**	$CH_2CH_2SiMe_2Ph$	H	58%	7.3 : 1	**52**
				76%	> 20 : 1	**58**
6	**(*Z*)-15**	Ph	H	60%	20 : 1	**53**
				48%	4 : 1	**59**

Conditions: 1a) DMDO, CH_2Cl_2, rt; 1b) $Al(O^tBu)_3$, $Cl_2(CH_2)_2Cl_2$, rt; 2a) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt; 2b) $NaBH_4$, MeOH, 0 °C. [a]Yield of the ketone. [b]Yield of the reduction. [c]*dr* determined by ^1H NMR.

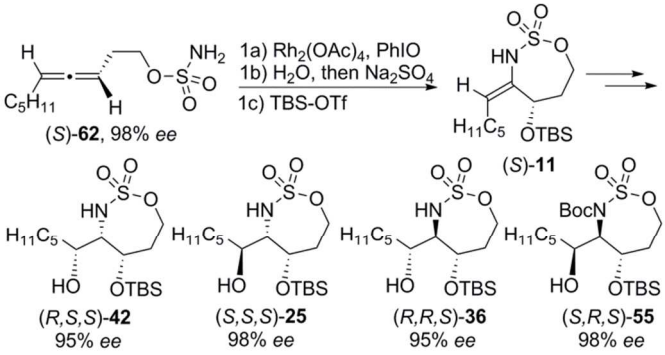
The strategy described in Table 8 could be used to obtain the 1,2-*syn*:2,3-*syn* stereotriad **61** (Scheme 6), which was inaccessible *via* direct imine reduction. The 1,2-*syn* α-aminoketone **60** was prepared from the (*E*)-enesulfamate **12**, followed by a *syn*-selective reduction with Me_4NBH_4. Taken together, the paths in Table 8 and Scheme 6 represent a convenient alternative for obtaining stereotriads from precursors where the imine reduction proves problematic.

Scheme 6. 1,2-*Syn*:2,3-*syn* diastereomers by a different route.



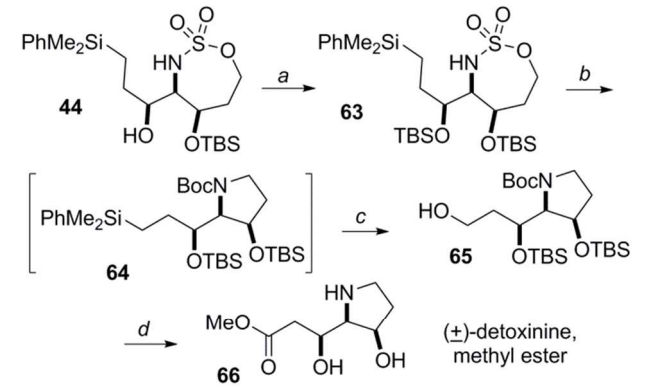
Transfer of axial to point chirality. With routes to all four possible diastereomers in hand, we wanted to clearly demonstrate that oxidative amination of an enantioenriched homoallenic sulfamate could be used to prepare enantioenriched 2-amino-1,3-diol triads. The homoallenic sulfamate (*S*)-**62** was prepared in three steps from the corresponding propargylic alcohol and converted to the enesulfamate (*S*)-**11** in 98% *ee*. Subsequent transformation of (*S*)-**11** to each of the four possible diastereomers occurred as expected, and no significant erosion in the stereochemical fidelity in the axial to point chirality transfer (Scheme 7) was noted.

Scheme 7. Effective transfer of axial to point chirality.

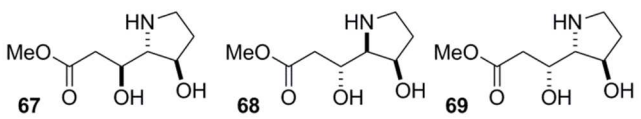


Total synthesis of (±)-detoxinine methyl ester and stereoisomers. The potential of our methods to enable rapid access to all possible stereoisomers of an aminodiol-containing bioactive molecule from a single allene substrate was demonstrated in the syntheses of the methyl ester of (±)-detoxinine and its three stereoisomers (Scheme 8).[13b,28] Detoxinine is an unusual bis-hydroxylated α-amino acid that

Scheme 8. Total synthesis of (±)-detoxinine from triad **44**.



a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 85%. b) NaHMDS, Boc_2O, cat. DMAP, CH_2Cl_2, 0 °C, then NaI, NaH, DMF, 60 °C. c) KBr, NaOAc, CH_3CO_3H, AcOH, rt, 67%, 2 steps. d) cat. TEMPO, $PhI(OAc)_2$, $NaHCO_3$, cat. Bu_4NCl, 1:1 MeCN:H_2O, then HCl/MeOH, 78%.



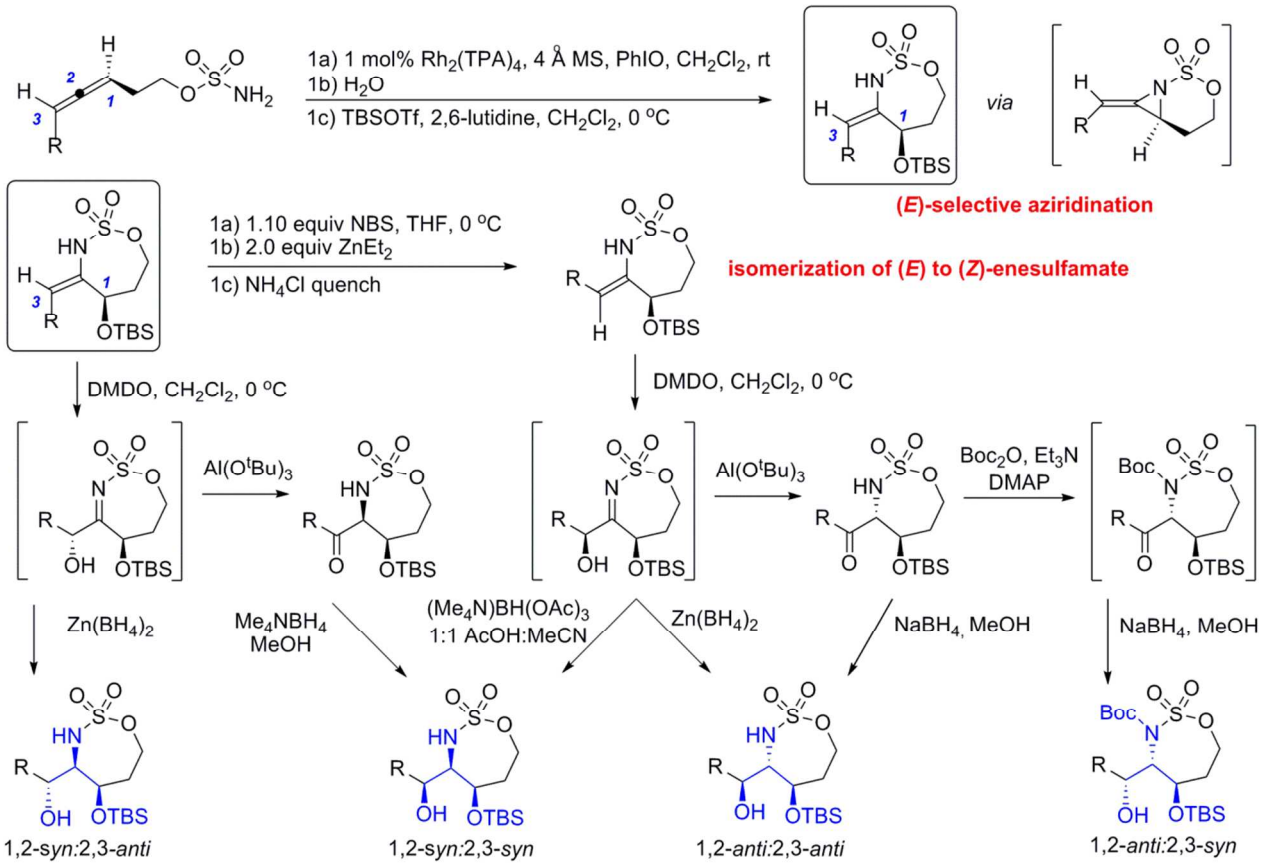
constitutes the core of the detoxifying agent detoxin, which is co-administered in combination with blasticidin S for the treatment of rice blast disease.[29] The synthesis of detoxinine itself is relatively straight-forward, but the flexibility of our methodology permits the same homoallenic sulfamate to be employed to access any possible stereoisomer. Application of this same strategy to other complex amines could prove very useful for exploration of structure-activity relationships.

In the synthesis, the free alcohol of the all-*syn* stereotriad **44** was silyl protected to give the sulfamate **63** in 85% yield. Boc protection of the amine, followed by NaI-mediated ring contraction, gave **64**.[30] This intermediate was subjected to Tamao-Fleming oxidation to furnish **65** in 67% yield over the two steps.[31] A two-step oxidation sequence yielded the terminal carboxylic acid, which upon acidic workup afforded (±)-detoxinine methyl ester **66**.[32] The same sequence of reactions was applied to the three remaining diastereomers of **44** to yield the non-natural stereoisomers of detoxinine, **67**, **68** and **69** (see the SI for additional details).[33]

Conclusion

In conclusion, Scheme 9 summarizes our demonstration of the versatility of allene aziridination for the flexible and fully stereodivergent syntheses of all four possible diastereomers of a 2-amino-1,3-diol motif. The ability to obtain stereochemically diverse outcomes from a single precursor, in addition to the heteroatom diversity we have previously demonstrated, further expands the scope of allene oxidation as a powerful tool for the construction of libraries of bioactive amines.[3,4] Current efforts are focused on the extension of this strategy to the synthesis of other amine motifs, including diaminoalcohol and triaminated triads. The utility of these methods is also being investigated for applications to the syntheses of jogyamycin and analogues (Figure 1) for structure-activity relationships. More importantly, the ability to introduce heteroatom and stereoisomeric diversity using a single, unified allene aziridination strategy will be of great utility in diversity-oriented synthesis and the exploration of novel chemical space.

Scheme 9. Overall 'roadmap' for the stereodivergent synthesis of 2-amino-1,3-diols from homoallenic sulfamates.



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Notes and references

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Electronic Supplementary Information (ESI) is available describing the characterization of all new compounds, as well as X-ray crystallographic information for **27**, **38** and **43**. See DOI: 10.1039/b000000x/

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