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Inverse electron-demand aza-[4+2] cycloaddition reactions of allenamides

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With the deepest gratitude and appreciation, this paper is dedicated to Professor Dieter Seebach on the special occasion of his receiving a Tetrahedron Prize for Creativity in Organic Chemistry

Abstract—An inverse electron-demand aza-[4+2] cycloaddition reaction of allenamides with 1-azadiene is described here. Effects of solvents on diastereoselectivity along with synthetic scopes and mechanistic insights are illustrated. Despite some synthetic limitations, this aza-[4+2] cycloaddition does provide a useful template for the synthesis of aza-glycoside related heterocycles.

1. Introduction

Allenamides have emerged as attractive building blocks in organic synthesis.[1–6] With vastly improved stability and comparable reactivity relative to traditional allenamines, allenamides can be utilized in a diverse array of stereoselective methodologies.[3–6] We reported [4+2] cycloadditions of chiral allenamide **1** with vinyl ketones **2** that led to pyrans **3** in a highly stereoselective manner,[3a] representing a rare account of an inverse demand hetero [4+2] cycloaddition involving a chiral enamide [Fig. 1].[7–9] We have also been focusing on applications of this cycloaddition method as a new approach for stereoselective constructions of *C*-glycoside derivatives **4** [W=O].[4,10] Given such synthetic potential, we examined [4+2] cycloadditions of 1-azadienes **5** with allenamides **6** to access nitrogen heterocycles **7**.

1-Azadienes are known to be poor dienes in Diels–Alder cycloadditions in general because of competing 1,2-additions to imines along with problems related to tautomerization to energetically favored enamines prior to cycloadditions.[7] However, elegant efforts from Boger[11–13] and Fowler,[14–15] by placing electron-withdrawing substituents on the nitrogen atom, have rendered 1-azadienes highly useful for inverse demand hetero [4+2]

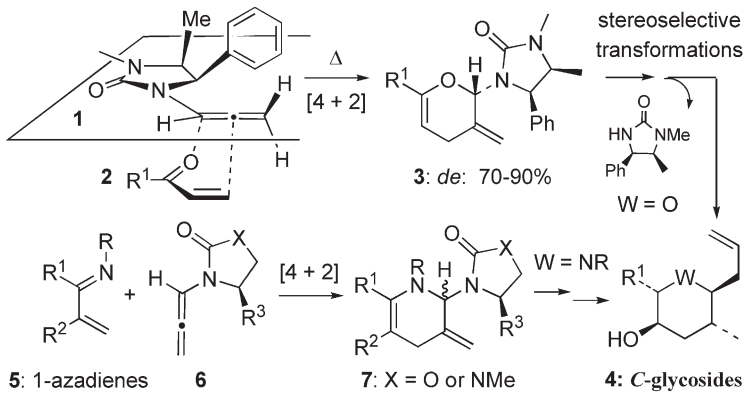

Figure 1.

Keywords: Allenamides; Diels–Alder; Cycloaddition; Inverse Demand; 1-Azadiene; Aza-glycoside.
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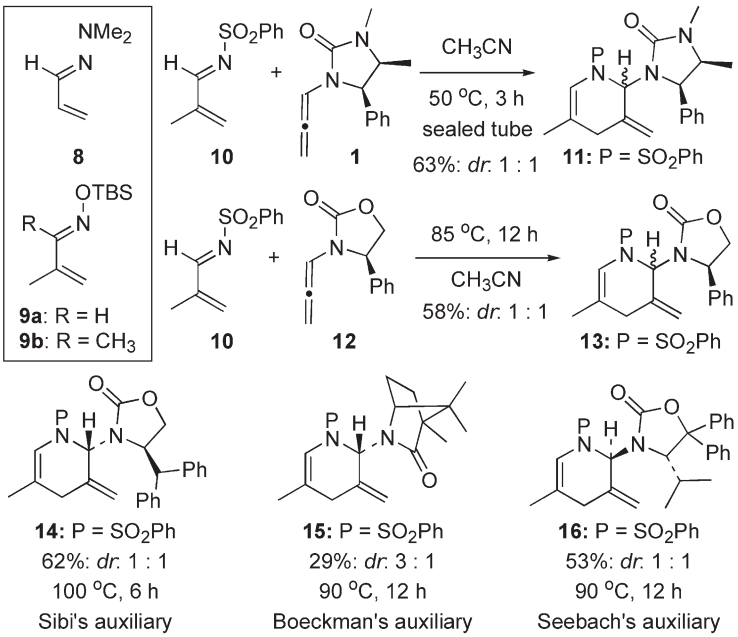


Scheme 1.

cycloadditions with electron rich dienophiles. While Boger[12] has demonstrated that allenol ethers can be used in such cycloadditions, nitrogen-substituted allenes have not been examined.[1,16] Success in this endeavor could provide an opportunity for constructing highly functionalized aza-sugars and related heterocycles [see also **4**: W=NR], a concept that we have already demonstrated using pyrans **3**.[4] We report here our findings in the feasibility and limitation of inverse electron-demand aza-[4+2] cycloadditions of allenamides with 1-azadienes.

2. Results and discussion

2.1. Feasibility of the aza-[4+2] cycloaddition

We quickly demonstrated that more electron-rich 1-azadeines,[17,18] such as **8** and **9a/b** [Scheme 1], did not match well electronically with an allenamide, leading to no observable hetero cycloadducts. On the other hand, 1-*N*-sulfonyl vinyl aldimine **10**[11] was a feasible 1-azadiene to give the desired hetero cycloadducts **11** and **13**[19] in good yields, respectively, from chiral allenamides **1** and **12**. However, the diastereoselectivity was not encouraging with chiral allenamides **1** and **12** substituted with the Close's auxiliary[20] and Evans' auxiliary,[21] respectively, providing virtually no stereoselectivity, although **1** appeared to be more reactive for the reaction could be carried out at a lower temperature.

We then examined chiral allenamides substituted with other well known chiral auxiliaries such as Sibi's[22] and Boeckman's auxiliaries,[23] but neither gave better selectivity as evident in their respective cycloadducts **14** and **15**. The allenamide substituted with the Boeckman's auxiliary was much less stable, and thus, under the same thermal conditions, much decomposition occurred to give **15** in a lower yield. Finally, the use of Seebach's chiral auxiliary[24] unfortunately also did not lead to any improvement in the diastereoselectivity, as evident with cycloadduct **16**.

2.2. Stereochemical and mechanistic issues

2.2.1. Solvent effect. We did observe some interesting solvent effect on the stereochemical outcome of the cycloaddition. As shown in Table 1, a very diverse range of different solvents could be used for the aza-[4+2] cycloaddition of allenamide **1** [entries 1–9]. The temperature could be lowered to 35 °C in some solvents [entries, 4, and 6–8]. More importantly, there is a small but noticeable increase in the diastereoselectivity with increasing in the

Table 1.

Entry	Allenamide[a]	Solvent	Temp (°C)	Time (h)	Cycloadd	Yield (%)[b]	Ratio[c]
1	**1**	Hexane	50	15	**11**	67	2.3:1
2	**1**	PhH	50	15	**11**	75	2.3:1
3	**1**	EtOAc	50	15	**11**	75	1.7:1
4	**1**	Et_2O	35	12	**11**	71	1.7:1
5	**1**	THF	50	15	**11**	75	2.4:1
6	**1**	CH_2Cl_2	35	12	**11**	70	3.5:1
7	**1**	$CHCl_3$	35	12	**11**	71	4.4:1
8	**1**	Acetone	35	12	**11**	67	1.4:1
9	**1**	MeOH	50	15	**11**	59	3.6:1
10	**12**	$CHCl_3$	35	50	**13**	53	1:1
11	**12**	$CHCl_3$	55	24	**13**	50	1:1
12	**12**	$CHCl_3$	65	24	**13**	52	1:1
13	**12**	CH_2Cl_2	35	50	**13**	52	1:1
14	**12**	CH_2Cl_2	55	24	**13**	60	1:1
15	**12**	MeOH	65	72	**13**	62	1:1
16	**12**	THF	65	72	**13**	25	1:1
17	**12**	EtOAc	65	72	**13**	34	1.5:1
18	**12**	PhH	65	72	**13**	52	1.5:1

[a] Reactions were carried out using anhydrous solvent in a sealed tube and 1.0 equiv. of 1-azadiene **10** were used.
[b] Isolated yields.
[c] Diastereomeric ratios [*dr*] were assigned by using ^{1}H NMR and represent ratios of **11/13a** : **11/13b** with **a** being the major isomer.

solvent polarity, with the best ratio being 4.4:1 when the reaction was run in $CHCl_3$ at 35 °C [entry 7]. This modest solvent effect suggests that the cycloaddition could proceed through a stepwise process that involves perhaps ionic intermediates. However, we are not clear how exactly the polarity of the solvent impacts the stereoselectivity of this cycloaddition, especially when the reaction in CH_3CN [see Scheme 1] did not give a good ratio. Stereochemistry of the major isomer **11a** was assigned using an X-ray structure [Fig. 2].

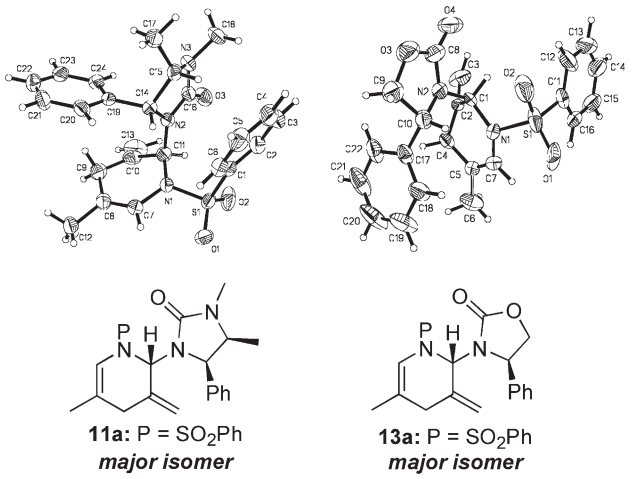


Figure 2. X-ray structures of **11a** [left] and **13a**.

For allenamide **12**, while a range of solvents could also be used [entries 10–18], in most cases, there was no observable increase in stereoselectivity [entries 10–16], even in $CHCl_3$ at various different temperatures [entries 10–13]. An exception would be that we did observe a very small but noticeable selectivity when the reaction was carried out in EtOAc and PhH. The major isomer **13a** was isolated with its stereochemistry being resolved using X-ray analysis [Fig. 2].

2.2.2. A mechanistic model. Although we did not observe any solvent effect on the stereoselectivity of *oxa*-[4+2] cycloadditions of allenamides with acrolein or various vinyl ketones,[3] the overall stereochemical outcome observed here in these aza-[4+2] cycloadditions illustrate a similar trend. That is, chiral allenamide **1** containing an imidazolidinone auxiliary provides better stereoselectivity than any of the oxazolidinone-based allenamides. This trend could be rationalized using the following proposed mechanistic model.

ChemDraw reproductions of the minimized structures of chiral allenamides **1**, **12**, and *ent*-**17** [containing the enantiomer of Seebach's auxiliary[24] for ease of comparison] using Spartan™ AM1-calculations are shown in Figure 3. The allene fragment is essentially co-planar with the imidazolidinone or oxazolidinone ring, thereby suggesting that the observed diastereoselectivity is likely due to a preferred addition of 1-azadienes from the less crowded bottom face of all allenamides.

The phenyl group of the imidazolidinone ring in allenamide **1** appears to be much closer to the allene fragment in the minimized model, thereby providing the best steric presence or facial differentiation and leading to the highest diastereoselectivity. The phenyl group in **12** actually tilts away from the allene moiety, thereby diminishing a significant amount of facial steric bias. This difference between **1** and **12**, however, is likely not a result of the methyl group present in the imidazolidinone ring of **1**, which could contribute toward pushing the phenyl ring closer to the allene fragment. However, if true, *ent*-allenamide **17** with Seebach's auxiliary would have provided an improved stereoselectivity relative to **12**.

Finally, although this mechanistic model accounts for the overall stereochemical outcome, it does not account at this time for the solvent effect that we have observed.

2.3. Synthetic limitations

An apparent limitation of this aza-[4+2] cycloaddition in this study is the accessibility of 1-*N*-sulfonyl vinyl imines. Although there are several accounts in describing their preparations,[11] we were only able to prepare a few,

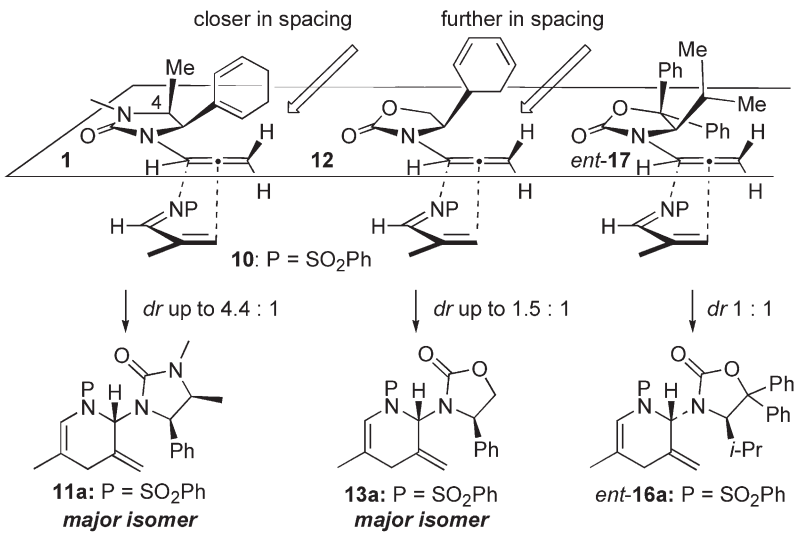
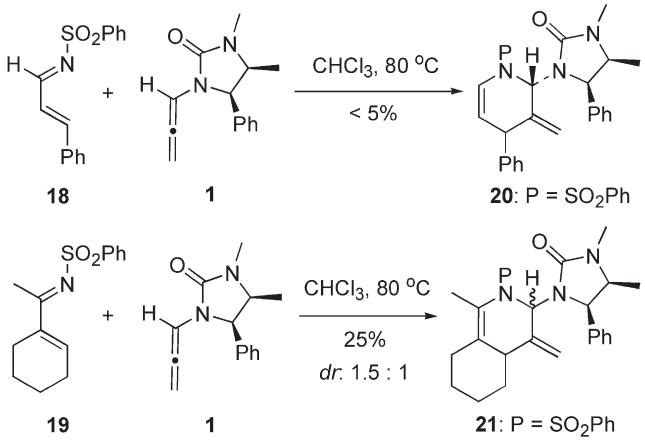


Figure 3.

including 1-azadiene **10**, consistently. The other two successful preparations afforded 1-*N*-sulfonyl vinyl aldimine **18** and ketimine **19** [Scheme 2]. However, cycloaddition of **18** with allenamide **1** did not produce the desired cycloadduct **20** in a synthetically useful manner, although we were able to isolate **21** in 25% yield from the reaction of **19** with **1**. In addition, **21** was isolated as a mixture of only two diastereomers [out of a possible four] with a moderate ratio of 1.5:1. Their relative stereochemistry was not assigned vigorously.



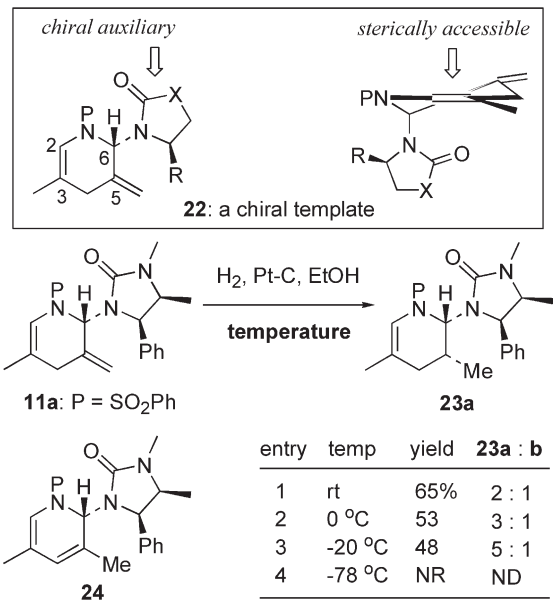
Scheme 2.

We are currently exploring improved preparations of 1-*N*-sulfonyl vinyl imines to access a broader range of aza-cycles through this aza-[4+2] cycloaddition.

2.4. Functionalizations of the aza-[4+2] cycloadduct and removal of the auxiliary

With the aza-cycles **11**, **13**, and **14**–**16** in hand, we examined the concept of employing them as a template for constructing aza-glycoside related heterocycles. X-ray analysis of the major isomer of **11** [Fig. 2] reveals that the chiral imidazolidinone group at C6 is oriented *pseudo*-axially and situated beneath the two olefins: The electron-rich *endo*-cyclic at C2/C3, and the accessible *exo*-cyclic at C5. Based on this analysis, we envisioned that in a manner analogous to our work using pyran **3**,[4] azacycle **22** can also be utilized as a chiral template with the C6 imidazolidinone of **22** being the chiral auxiliary, and that transformations of the two well-differentiated olefins can proceed selectively from the sterically less congested top face [Scheme 3].

To support this concept, the C5 *exo*-cyclic olefin in **11a** was hydrogenated under standard conditions at rt to give **23a** as the major isomer with a modest ratio of 2:1 [entry 1]. The assignment of relative stereochemistry in **23a** using NOE confirmed that the addition of hydrogen occurred at the less congested top face. While the overall selectivity was not as high as we had expected, we did see a much better selectivity [entry 3] at lower temperature. In addition, we consistently isolated 10–15% of dihydropyridine **24**, resulting from isomerization of the *exo*-cyclic olefin. The formation of **24** could be related to the erosion of diastereoselectivity during the hydrogenation.

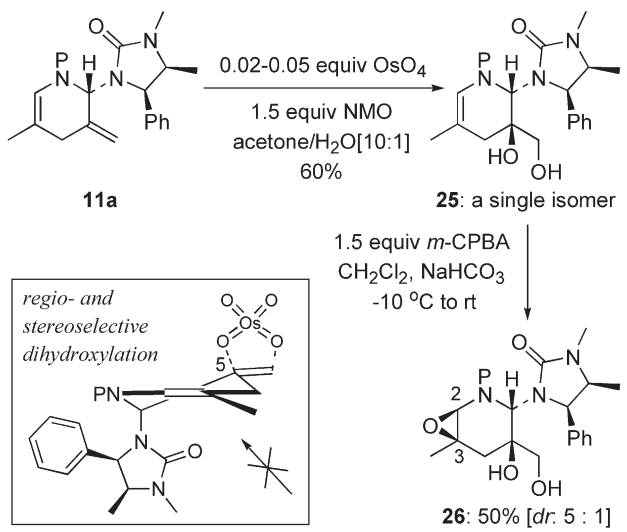


Scheme 3.

A more solid support of the template concept was obtained when azacycle **11a** was dihydroxylated in a highly regio- and stereoselective manner using cat OsO_4 to give diol **25** as a single isomer in 60% yield [Scheme 4]. NOE assignment of relative stereochemistry confirmed that the dihydroxylation occurred exclusively at the top less congested face of the more accessible C5 *exo*-cyclic olefin [lower left box]. An ensuing epoxidation of the C2-3 *endo*-cyclic olefin was also stereoselective, leading to a surprisingly stable epoxide **25** in 50% yield with an isomeric ratio of 5:1.

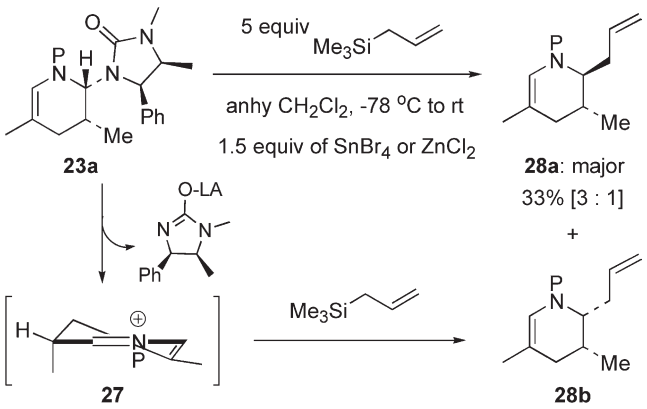
These studies suggest that the aza-[4+2] cycloadduct **22** can be employed as a template with the imidazolidinone group at C6 serving as a chiral auxiliary [or blocking one face] for constructing aza-glycoside related heterocycles.

2.4.1. Removal of the chiral auxiliary. To complete the concept of the C6 imidazolidinone of **22** serving as a chiral auxiliary, we carried out its removal and recovery using related conditions reported for *oxa*-[4+2] cycloadducts,[4a]



Scheme 4.

but it proved to be quite difficult. As shown in Scheme 5, after screening through a variety of Lewis acids, only $SnBr_4$ and $ZnCl_2$ appeared to be suitable Lewis acids that would facilitate a proper departure of the C6 imidazolidinone group in **23a**. An ensuing addition of allyltrimethylsilane to the presumed aza-carbenium intermediate **27** did give azacycle **28a/b** as an isomeric mixture in only 33% yield with a ratio of 3:1. The major isomer was again assigned using NOE experiments.



Scheme 5.

3. Conclusions

We have described here an inverse electron-demand aza-[4+2] cycloaddition reaction of allenamides with 1-aza-dienes. Effect of solvents on diastereoselectivity, along with synthetic scopes and mechanistic insights are reported. Despite some of the current synthetic limitations, this aza-[4+2] cycloaddition does provide cycloadducts that can be employed as a template for the synthesis of aza-glycoside related hetereocycles.

4. Experimental

All reactions performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separation were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VX-300, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and vanillin or $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses performed at Department of Chemistry Mass Spectrometry Laboratory, University of Minnesota. X-ray analyses performed at University of Minnesota Department of Chemistry X-ray facility. All spectral data obtained for new compounds are reported here.

4.1. General procedure for the aza-[4+2] cycloadditions

To a solution of 0.83 g of allenamide **1** (3.6 mmol, 1.0 equiv.) in freshly distilled CH_3CN (36 mL, 0.10 M) was added 0.76 g of sulfonyl imine **10** (3.6 mmol, 1.0 equiv.). The reaction mixture was sealed under a blanket of nitrogen, and the mixture was stirred for 3 h at 50 °C. After which, the solution was allowed to cool to room temperature, and solvent was removed under reduced pressure. Silica gel flash column chromatography (gradient eluent: 0–25% EtOAc in hexanes) afforded both the major and minor cycloadduct **11a** and **11b** in 63% yield (1.00 g) of as a foamy solid. The two isomers could be separated via subsequent column chromatography.

4.1.1. Major isomer 11a. R_f=0.35 [50% EtOAc/hexane]; mp 148–150 °C; $[\alpha]_D^{20}$ −66.3° [*c* 4.1, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 0.65 (d, 3H, *J*=6 Hz), 1.22 (d, 1H, *J*=20.5 Hz), 1.31 (s, 3H), 1.94 (d, 1H, 20.5 Hz), 2.69 (s, 3H), 3.52 (dq, 1H, *J*=6, 9 Hz), 4.59 (s, 1H), 4.60 (d, 1H, *J*=9 Hz), 5.04 (s, 1H), 6.24 (s, 1H), 6.44 (s, 1H), 7.20–7.24 (m, 4H), 7.47–7.56 (m, 4H), 7.82 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 19.8, 28.7, 32.0, 56.8, 59.1, 65.4, 114.9, 116.5, 117.9, 126.4, 127.0, 127.9, 128.6, 129.1, 132.9, 138.1, 138.3, 138.9, 161.1; IR (film) cm^{-1} 3212m, 3063s, 2933s, 2882s, 1712s, 1168s; mass spectrum (LRMS): *m/e* (% relative intensity) 438 (100) M^++H, 296 (50), 248 (100), 203 (80), 191 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1664.

4.1.2. Minor isomer 11b. R_f=0.30 [50% EtOAc/hexane]; mp 84–87 °C; $[\alpha]_D^{20}$ +29.8° [*c* 1.7, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 0.74 (d, 3H, *J*=6 Hz), 1.60 (s, 3H), 2.35 (d, 1H, *J*=20 Hz), 2.71 (s, 3H), 3.01 (d, 1H, *J*=20 Hz), 3.69 (dq, 1H, *J*=6, 9 Hz), 4.67–4.70 (m, 3H), 5.80 (s, 1H), 5.93 (s, 1H), 7.31–7.42 (m, 4H), 7.46–7.51 (m, 4H), 7.63 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9, 20.0, 28.7, 33.8, 56.1, 61.7, 66.2, 114.0, 118.5, 120.2, 126.9, 127.0, 127.9, 128.0, 128.7, 132.5, 136.5, 138.0, 138.7, 159.7; IR (film) cm^{-1} 3190m, 3090s, 2915s, 2930m, 1722s, 1209m; mass spectrum (LRMS): *m/e* (% relative intensity) 438 (100) M^++H, 296 (50), 248 (100), 203 (80), 191 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1678.

4.1.3. Cycloadduct 13a. R_f=0.30 [50% EtOAc/hexane]; mp 105–108 °C; $[\alpha]_D^{20}$ −88.1° [*c* 5.1, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.40 (d, 1H, *J*=20 Hz), 1.99 (d, 1H, *J*=20 Hz), 4.07 (dd, 1H, *J*=6, 9 Hz), 4.51 (t, 1H, *J*=9 Hz), 4.08 (d, 1H, *J*=2.5 Hz), 4.88 (dd, 1H, *J*=6, 9 Hz), 5.07 (d, 1H, *J*=2.5 Hz), 5.98 (s, 1H), 6.28 (s, 1H), 7.24–7.36 (m, 4H), 7.48–7.54 (m, 4H), 7.81 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 31.6, 57.6, 67.0, 71.2, 116.1, 116.7, 117.6, 127.0, 127.3, 128.6, 128.7, 129.2, 133.2, 136.8, 138.2, 140.0, 158.5; IR (film) cm^{-1} 3010s, 2905s, 2877m, 1709s, 1552m; mass spectrum (LRMS): *m/e* (% relative intensity) 411 (100) M^++H, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1198, found 433.1193.

4.1.4. Cycloadduct 13b. R_f=0.22 [50% EtOAc/hexane]; mp 121–123 °C; $[\alpha]_D^{20}$ +59.0° [*c* 2.7, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 2.36 (d, 1H, *J*=20 Hz), 2.96 (d, 1H, *J*=20 Hz), 4.10 (dd, 1H, *J*=6, 8.5 Hz), 4.56 (t, 1H, *J*=9 Hz), 4.71 (d, 1H, *J*=2.5 Hz), 4.77 (d, 1H, *J*=2.5 Hz), 4.93 (dd,

1H, *J*=6.5, 9 Hz), 5.67 (s, 1H), 5.95 (s, 1H), 7.36–7.44 (m, 6H), 7.50–7.54 (m, 2H), 7.48 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.0, 59.6, 66.4, 67.1, 70.3, 112.4, 115.4, 118.0, 127.0, 127.2, 128.8, 128.9, 129.0, 132.9, 136.7, 138.6, 148.0, 156.6; IR (film) cm^{-1} 2997m, 2912m, 2815m, 1689s, 1541m; mass spectrum (LRMS): *m/e* (% relative intensity) 411 (100) M^++H, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1198, found 433.1190.

4.1.5. Cycloadducts 14a/b as a mixture. R_f=0.22 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **14a** δ 1.23 (s, 3H), 2.35 (d, 1H, *J*=20 Hz), 2.55 (d, 1H, *J*=20 Hz), 4.05 (s, 1H), 4.26–4.31 (m, 2H), 4.45 (d, 1H, *J*=5 Hz), 4.52 (s, 1H), 4.79 (m, 1H), 5.86 (s, 1H), 6.38 (s, 1H), 7.22–7.38 (m, 8H), 7.49–7.62 (m, 4H), 7.86 (d, 2H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); **14b**: δ 1.63 (s, 3H), 2.14 (d, 1H, *J*=21 Hz), 3.04 (d, 1H, *J*=21 Hz), 4.15 (dd, 1H, *J*=2, 8 Hz), 4.24 (dd, 1H, *J*=2, 8 Hz), 4.57 (d, 1H, *J*=8 Hz), 4.86 (s, 1H), 4.90 (dt, 1H, *J*=2, 8 Hz), 5.03 (s, 1H), 6.27 (s, 1H), 6.42 (s, 1H), 7.22–7.38 (m, 8H), 7.49–7.62 (m, 4H), 7.86 (d, 2H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); IR (film) cm^{-1} 3060m, 2914m, 1755s, 1347s, 1166s; mass spectrum (LRMS): *m/e* (% relative intensity) 501 (20) M^++H, 359 (50), 266 (100), 193 (10); *m/e* calcd for $C_{29}H_{28}N_2O_4SNa$ 523.1668, found 523.1640.

4.1.6. Cycloadducts 15a/b as a mixture. R_f=0.25 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **15a**: δ 0.83 (s, 3H), 0.86 (s, 3H), 1.00 (s, 3H), 1.48–1.60 (m, 2H), 1.72 (s, 3H), 1.86–1.96 (m, 2H), 2.43 (d, 1H, *J*=20 Hz), 2.77 (d, 1H, *J*=20 Hz), 3.40 (d, 1H, *J*=2 Hz), 4.68 (d, 1H, *J*=2 Hz), 4.80 (d, 1H, *J*=2 Hz), 5.89 (s, 1H), 6.49 (s, 1H), 7.47–7.60 (m, 3H), 7.77 (d, 2H, *J*=7 Hz); **15b**: δ 0.97 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.21–1.29 (m, 2H), 1.58–1.62 (m, 2H), 1.65 (s, 3H), 3.45 (d, 1H, *J*=2 Hz), 3.76 (d, 1H, *J*=13 Hz), 4.01 (d, 1H, *J*=13 Hz), 4.68 (d, 1H, *J*=2 Hz), 4.80 (d, 1H, *J*=2 Hz), 6.08 (s, 1H), 6.40 (s, 1H), 7.47–7.60 (m, 3H), 7.77 (d, 2H, *J*=7 Hz); IR (film) cm^{-1} 3045m, 2905m, 2900m, 1710s, 1600m; mass spectrum (LRMS): *m/e* (% relative intensity) 400 (100) M^+, 273 (20), 154 (15); *m/e* calcd for $C_{22}H_{28}N_2O_3SNa$ 423.1718, found 423.1725.

4.1.7. Cycloadducts 16a/b as a mixture. R_f=0.30 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **16a**: δ 0.73 (d, 6H, *J*=6.5 Hz), 1.32 (d, 1H, *J*=11.5 Hz), 1.62 (s, 3H), 1.81–1.95 (m, 1H), 2.32 (d, 1H, *J*=15 Hz), 2.43 (d, 1H, *J*=15 Hz), 4.57 (d, 1H, *J*=2.5 Hz), 4.60 (d, 1H, *J*=2.5 Hz), 6.15 (t, 1H, *J*=2 Hz), 6.41 (s, 1H), 7.22–7.38 (m, 5H), 7.41–7.59 (m, 6H), 7.82 (d, 2H, *J*=8 Hz), 9.62 (d, 2H, *J*=9 Hz); **16b**: δ 0.69 (d, 6H, *J*=6 Hz), 1.32 (d, 1H, *J*=11.5 Hz), 1.66 (s, 3H), 1.81–1.95 (m, 1H), 3.72 (d, 1H, *J*=15 Hz), 3.86 (d, 1H, *J*=15 Hz), 4.60 (d, 1H, *J*=1 Hz), 4.89 (d, 1H, *J*=1 Hz), 6.07 (t, 1H, *J*=2 Hz), 6.12 (s, 1H), 7.22–7.38 (m, 5H), 7.41–7.59 (m, 6H), 7.82 (d, 2H, *J*=8 Hz), 9.62 (d, 2H, *J*=9 Hz); IR (film) cm^{-1} 3034m, 2945m, 2815m, 1708s, 1514m; mass spectrum (LRMS): *m/e* (% relative intensity) 529 (100) M^++H, 485 (22), 387 (60), 248 (32); *m/e* calcd for $C_{31}H_{32}N_2O_4SNa$ 551.1980, found 551.1988.

4.1.8. Cycloadducts 21a/b as a mixture. R_f=0.28 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **21a**: δ 0.67 (d, 3H, *J*=7 Hz), 0.80–1.08 (m, 4H), 1.31–1.54 (m, 4H), 2.04 (s, 3H), 2.32 (m, 1H), 2.78 (s, 3H), 3.76 (dq, 1H, *J*=7, 9 Hz), 4.64 (s, 1H), 4.75 (d, 1H, *J*=9 Hz), 5.01 (s, 1H), 6.56 (s, 1H), 7.02–7.26 (m, 3H), 7.38–7.58 (m, 3H), 7.61 (d, 2H, *J*=8 Hz), 7.67 (d, 2H, *J*=8 Hz); **21b**: δ 0.64 (d, 3H, *J*=7 Hz), 0.80–1.08 (m, 4H), 1.31–1.54 (m, 4H), 1.81 (s, 3H), 2.28 (m, 1H), 2.73 (s, 3H), 3.76 (dq, 1H, *J*=7, 9 Hz), 4.54 (s, 1H), 4.64 (s, 1H), 4.75 (d, 1H, *J*=9 Hz), 6.43 (s, 1H), 7.02–7.26 (m, 3H), 7.38–7.58 (m, 3H), 7.61 (d, 2H, *J*=8 Hz), 7.67 (d, 2H, *J*=8 Hz); IR (film) cm^{-1} 3354m, 3024m, 2912m, 1715s, 1498m; mass spectrum (LRMS): *m/e* (% relative intensity) 492 (100) M^++H, 351 (20), 302 (15); *m/e* calcd for $C_{28}H_{33}N_3O_3SNa$ 514.2140, found 514.2124.

4.2. Synthesis of mono-hydrogenated product 23a

To a solution of 130.0 mg of cycloadduct **11a** (0.29 mmol) in EtOH (3.0 mL, 0.01 *M*) was added 10% Pt–C (25 mg). After purging the system with H_2 gas, the mixture was allowed to stir at rt for 2 h. Filtration through celite and removal of the solvent under reduced pressure provided the crude mono-hydrogenated product. Silica gel flash column chromatography (gradient eluent: 0–25% EtOAc in hexanes) provided the pure mono-hydrogenated **23a** [ratio of **a/b**: 2:1 at rt] in 65% yield (82.0 mg) along with 10–15% of the byproduct **24**.

4.2.1. Compound 23a. R_f=0.41 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −116.2° [*c* 2.6, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.19–0.25 (m, 1H), 0.71 (d, 3H, *J*=7 Hz), 0.84 (d, 3H, *J*=7 Hz), 1.22–1.31 (m, 1H), 1.38–1.45 (m, 1H), 1.40 (s, 3H), 2.74 (s, 3H), 3.73 (dq, 1H, *J*=7, 10 Hz), 4.50 (d, 1H, *J*=10 Hz), 5.70 (d, 1H, *J*=4 Hz), 6.62 (s, 1H), 6.95 (d, 1H, *J*=9 Hz), 7.21–7.31 (m, 4H), 7.53–7.62 (m, 3H), 7.87 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2, 16.6, 20.4, 29.0, 30.9, 32.1, 57.6, 59.1, 65.8, 116.2, 117.6, 127.1, 127.9, 128.3, 128.6, 129.1, 129.3, 132.9, 138.8, 163.5; IR (film) cm^{-1} 3478w, 3061m, 2931s, 2877s, 1715s, 1288s; mass spectrum (LRMS): *m/e* (% relative intensity) 440 (100) M^++H, 310 (10), 250 (10), 191 (15); *m/e* calcd for $C_{24}H_{29}N_3O_3SNa$ 462.1827, found 462.1835.

4.2.2. Byproduct dihydropyridine 24. R_f=0.37 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −420.7° [*c* 2.1, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.60 (d, 3H, *J*=6.5 Hz), 1.50 (m, 3H), 1.60 (s, 3H), 2.69 (s, 3H), 3.09 (dq, 1H, *J*=6.5, 9 Hz), 4.20 (d, 1H, *J*=9 Hz), 4.94 (s, 1H), 6.44 (s, 1H), 6.58 (s, 1H), 7.17–7.23 (m, 4H), 7.51–7.65 (m, 4H), 7.94 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 17.6, 19.8, 28.6, 55.9, 59.5, 63.1, 66.9, 115.1, 116.9, 123.3, 126.0, 127.1, 127.8, 129.1, 132.9, 137.3, 139.8, 146.3, 160.0; IR (film) cm^{-1} 3063w, 2969m, 2872w, 1699s, 1353m, 1165s; mass spectrum (LRMS): *m/e* (% relative intensity) 437 (100) M^+, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1701.

4.3. Synthesis of diol 25

To a solution of 0.47 g of cycloadduct **11a** (1.1 mmol, 1 equiv.) in 10:1 acetone/water mixture (22 mL, 0.05 M) was added NMO (0.19 g, 1.6 mmol, 1.5 equiv.) followed by addition of a solution of OsO_4 (5.0–13 mg, 0.02–0.05 mmol, 0.02–0.05 equiv.) in *t*-BuOH (1.5 mL). The mixture was allowed to stir for 3 h at rt after which sodium

bisulfite (1.0 g) and sodium *meta*-bisulfite (1.0 g) were added in large excess. The mixture was allowed to stir for an additional 5 h, after which gravity filtration followed by removal of solvent under reduced pressure provided crude diol **25**. Silica gel flash column chromatography (gradient eluent: 0–40% EtOAc in hexanes) provided the pure diol **25** in 60% yield (303.0 mg).

4.3.1. Compound 25. R_f=0.20 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −149.2° [*c* 0.7, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.32 (d, 1H, *J*=18 Hz), 0.78 (d, 3H, *J*=7 Hz), 1.13 (d, 1H, *J*=18 Hz), 1.31 (s, 3H), 2.40 (brs, 1H, –O*H*), 2.80 (s, 3H), 3.67 (dd, 1H, *J*=5, 12 Hz), 4.02 (dq, 1H, *J*=7, 9 Hz), 4.64 (d, 1H, *J*=9 Hz), 4.86 (brs, 1H, –O*H*), 5.13 (dd, 1H, *J*=5, 12 Hz), 5.32 (s, 1H), 6.93 (s, 1H), 7.01 (d, 1H, *J*=7 Hz), 7.24–7.38 (m, 4H), 7.48–7.61 (m, 3H), 7.89 (d, 1H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 20.1, 28.6, 31.3, 57.9, 59.2, 65.5, 67.4, 71.4, 112.7, 117.0, 127.1, 127.4, 128.1, 129.0, 129.2, 133.2, 138.1, 138.5, 164.1; IR (film) cm^{-1} 3507m, 3354m, 3062m, 2932m, 1679s, 1433s; mass spectrum (LRMS): *m/e* (% relative intensity) 472 (100) M^++H, 331 (58), 282 (50), 191 (20); *m/e* calcd for $C_{24}H_{29}N_3O_5SNa$ 494.1726, found 494.1724.

4.4. Preparation of epoxide 26

To solution of diol **25** (95.0 mg, 0.20 mmol, 1.0 equiv.) in freshly distilled CH_2Cl_2 (20 mL, 0.01 M) was added 51.0 mg $NaHCO_3$ (0.60 mmol, 3.0 equiv.). The mixture was cooled to −10 °C after which 1.5 equiv. of *m*-CPBA (52.0 mg, 0.30 mmol) was added. The mixture was allowed to stir under N_2 for 8 h. Gravity filtration followed by removal of solvent under reduced pressure and silica gel flash column flash chromatography (gradient eluent: 0–10% EtOAc in hexanes) afforded epoxide **26** in a 50% yield (49.0 mg).

4.4.1. Compound 26. R_f=0.62 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 1H, *J*=15 Hz), 0.91 (d, 3H, *J*=8 Hz), 1.10 (s, 3H), 1.14 (d, 1H, *J*=15 Hz), 2.86 (s, 3H), 2.90 (d, 1H, *J*=8.5 Hz), 3.65 (d, 1H, *J*=12 Hz), 4.26 (dq, 1H, *J*=8, 12 Hz), 5.18 (brm, 1H, –O*H*), 5.31 (t, 1H, *J*=5 Hz), 5.65 (d, 1H, *J*=1 Hz), 5.70 (d, 1H, *J*=8.5 Hz), 6.91 (s, 1H), 7.39–7.64 (m, 6H), 7.97–8.11 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2, 25.1, 28.3, 33.9, 58.0, 66.7, 69.9, 70.6, 73.9, 84.7, 105.3, 127.8, 128.0, 128.1, 128.6, 129.0, 129.7, 133.6, 133.7, 169.6; IR (film) cm^{-1} 3522m, 3317m, 3117m, 2958m, 1684s, 1421s; mass spectrum (LRMS): *m/e* (% relative intensity) 488 (100) M^++H, 191 (10); *m/e* calcd for $C_{24}H_{29}N_3O_6SNa$ 510.1675, found 510.1661.

4.5. Removal of the chiral auxiliary

To a solution of 35.0 mg of **23a** (0.08 mmol, 1.0 equiv.) in freshly distilled CH_2Cl_2 (8.4 mL, 0.01 M) was added at −78 °C 52.0 mg of $SnBr_4$ (0.12 mmol, 1.5 equiv.) followed by allyltrimethylsilane (0.05 mL, 4.0 equiv.) in dropwise manner via a syringe. The reaction mixture was allowed to gradually warm up to rt over 12 h under N_2 to give the crude mixture **28a/b** after removal of solvent under reduced pressure. Silica gel flash column chromatography (gradient eluent: 0–10% EtOAc in hexanes) provided the isomeric mixture **28a/b** in 33% yield (8.0 mg) as clear oil.

4.5.1. Compound 28a. R_f=0.45 [15% ethyl acetate/hexane]; ^{1}H NMR ($CDCl_3$) δ 0.85–0.91 (m, 1H), 1.01 (d, 3H, *J*=6.5 Hz), 1.24–1.36 (m, 1H), 1.72–1.79 (m, 1H), 2.05 (s, 3H), 2.61–2.79 (m, 2H), 3.70–3.82 (m, 1H), 4.99–5.18 (m, 2H), 5.91–6.11 (m, 1H), 6.42 (s, 1H), 7.40–7.61 (m, 3H), 7.87 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 31.8, 36.9, 37.5, 53.8, 57.3, 112.2, 115.7, 126.9, 127.8, 129.0, 132.4, 134.3, 138.1; IR (film) cm^{-1} 3190m, 3022m, 2952m, 1274m; mass spectrum (LRMS): *m/e* (% relative intensity) 292 (100) M^++H, 250 (20), 151 (30), 110 (10); *m/e* calcd for $C_{16}H_{21}NO_2SNa$ 314.1191, found 314.1218.

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