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Stereo- and Regioselective Synthesis of Polysubstituted Chiral 1,4-Oxazepanes

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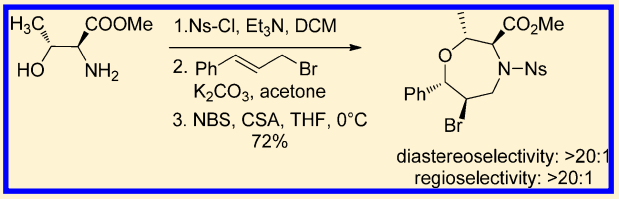
Supporting Information

ABSTRACT: The number of cyclic molecular scaffolds available to medicinal chemists remains limited, and simple structures such as oxazepanes are still made using multistep procedures, including a number of protection/deprotection steps and purifications. We report herein an expedient and efficient synthesis of chiral polysubstituted oxazepanes. The developed method relies on a regio- and stereoselective 7-*endo* cyclization through haloetherification. Mechanistic studies using a combination of computations and experiments confirmed the expected role of the asymmetry of the chiral bromonium intermediate on the haloetherification regioselectivity. Computations also suggested that the bromonium intermediate is formed with no transition state; hence, the stereoselectivity is controlled primarily by the conformation of the substrate. Applied to a set of 16 substrates, tetra- and pentasubstituted oxazepanes were prepared with good yields and moderate to excellent regio- and stereoselectivities.



INTRODUCTION

Molecular scaffolds such as mono- and bicyclic structures are of utmost interest in medicinal chemistry and more specifically in the preparation of geometrically constrained peptidomimetics or in the preparation of a focused library.[1] Thus, a number of potent enzyme inhibitors[2−4] and receptor antagonists[5,6] built around (bi)cyclic scaffolds have been reported. In parallel, a number of scaffolds inducing turns observed in proteins or peptides have been developed.[7,8] However, the number of readily available scaffolds remains limited or their lengthy synthesis remains to be improved. As a result, developing synthetic strategies to prepare molecular scaffolds is an active field.[9−12]

Despite the discovery of bioactive oxazepane derivatives such as **1**[13] and many reports on synthesis of oxazepinones (e.g., **2**[14]),[15] very little attention has been devoted to the synthesis of polysubtituted chiral oxazepane derivatives. In addition, most of these reports focus on benzoxazepines.[16] In fact, an exhaustive search of the literature revealed that very few syntheses of chiral polysubstituted oxazepanes have been reported. For example, Machetti and co-workers[17] and then Ley et al.[18] have reported efficient methods to prepare bridged oxazepanes around acetal functional groups (**3**; Figure 1).

In fact, most of the reported syntheses of oxazepanes rely on acetalization of ketones, intramolecular opening of epoxides, or ring expansion[13] (e.g., from carbohydrates[19]). A few other methods have been reported, such as the palladium-catalyzed cyclization of allenols.[20] Hsung and co-workers recently reported the application of halo-etherification of enamimes to the preparation of various cyclic structures, including one oxazepane.[21] As part of a medicinal chemistry program aiming to develop constrained enzyme inhibitors in a green fashion,[22] we developed a method to efficiently prepare polysubstituted oxazepanes, improving upon the aforementioned existing methods.

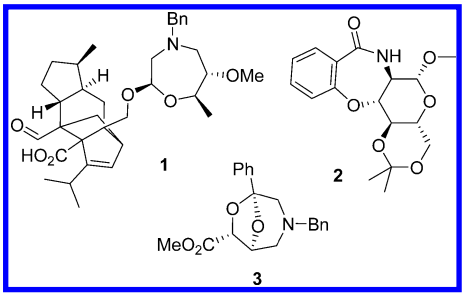


Figure 1. Reported synthetic oxazepanes.

We report herein our efforts to develop an efficient and expedient synthetic route to chiral oxazepanes, which are underinvestigated heterocycles. Additional computations and experiments were carried out to investigate the factors controlling the stereo- and regioselectivity of the key cyclization.

RESULTS AND DISCUSSION

Design of the Synthetic Strategy. Prior to the development of this synthetic methodology, we set the stringent criteria we wished to fulfill, considering that these molecular scaffolds should be easy to access and use by medical chemists and/or applicable to large-scale drug synthesis.[23] First, the synthesis should not exceed three to four steps and should be scalable.

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Second, the obtained cyclic scaffold should bear functionalizable groups. These first two criteria are essential for applicability to medicinal chemistry programs where diversification will follow. Third, it should not use toxic reagents (e.g., metal catalysts). Fourth, it should start from inexpensive, commercially available materials. Fifth, stereogenic centers should be formed in a controlled manner or taken from the chiral pool. This is a critical issue, as poor stereoselectivity renders the synthesis and isolation difficult. Sixth, atom economy should be considered (i.e., neither chiral auxiliaries nor excessive protection/deprotection steps). Finally, the number of tedious and non-green purifications should be limited. More specifically, simple workups requiring quantitative conversion or crystallization would be preferred over chromatography of complex mixtures. After extensive investigations, we developed the strategy outlined in Figure 2.

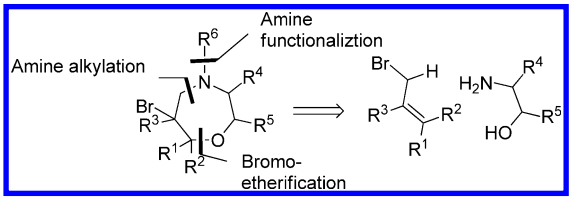


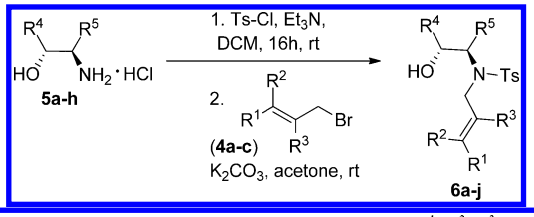
Figure 2. General synthetic strategy.

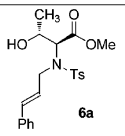
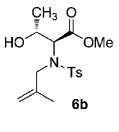
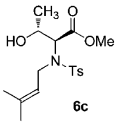
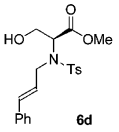
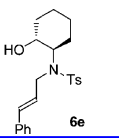
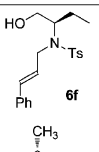
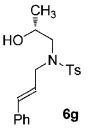
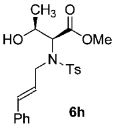
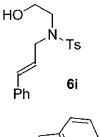
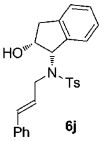
Preparation of the Unsaturated Alcohols. With this approach, the first or first two stereocenters bearing R^4 and R^5 are borrowed from the chiral pool, ensuring that the final molecule will be enantiopure. The other stereocenters will be introduced through substrate induction. Throughout the process, the alcohol will not be protected, thus reducing the number of steps and chemicals to be used (hence the waste) in comparison to existing methods.[21] Although this strategy may look straightforward, many issues had to be addressed. The first hurdle we met was the formation of the intermediate unsaturated amino alcohol that will be the substrate for the halo-etherification cyclization. After extensive optimization, the acyclic compounds were made following the strategy outlined in Table 1. Other approaches, such as reductive amination followed by further amine functionalization, proved less successful.

Thus, threonine methyl ester (**5a**), serine methyl ester (**5b**), and another six highly diverse amino alcohols (**5c**–**h**) were reacted sequentially with tosyl chloride and then cinnamyl bromide (**4a**) or other allyl bromides (**4b**,**c**), affording the corresponding secondary amines **6a**–**j** in reasonable to excellent yields. This approach does not require any protection of the primary alcohol.

Key Cyclization. With this set of subsrates in hand, the key cyclization was carried out (Table 2). Throughout the course of the cyclization reaction, one can expect the formation of

Table 1. Step 1: Amine Functionalization



Entry	R-Br	R^1 / R^2 / R^3	aa[a]	R^4 / R^5	Prod.	Yield (%)[b]
1	**4a**	Ph / H / H	**5a**	Me / CO_2Me	 **6a**	90
2	**4b**	H / H / Me	**5a**	Me / CO_2Me	 **6b**	30
3	**4c**	Me / Me / H	**5a**	Me / CO_2Me	 **6c**	98
4	**4a**	Ph / H / H	**5b**	H / CO_2Me	 **6d**	39
5	**4a**	Ph / H / H	**5c**	*trans*-c-Hex	 **6e**	84
6	**4a**	Ph / H / H	**5d**	H / Et	 **6f**	51
7	**4a**	Ph / H / H	**5e**	Me / H	 **6g**	46
8	**4a**	Ph / H / H	**5f**	Me / CO_2Me[c]	 **6h**	67
9	**4a**	Ph / H / H	**5g**	H/ H	 **6i**	62
10	**4a**	Ph / H / H	**5h**	*cis*-ind[d]	 **6j**	84

[a]Amino alcohol. [b]Over two steps. [c]*allo*-Threonine methyl ester. [d]*cis*-Indanolamine.

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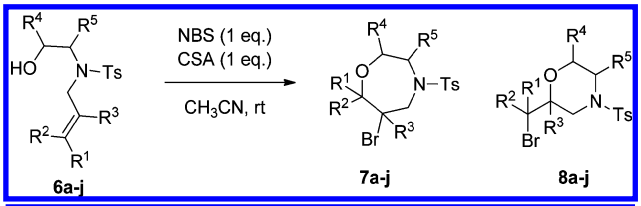
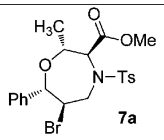
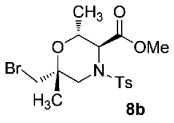
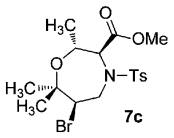
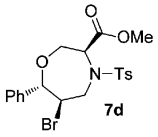
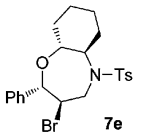
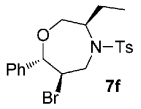
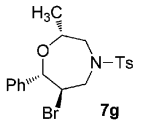
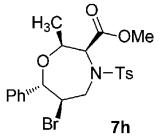
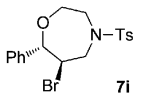
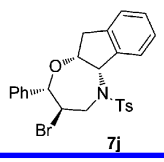
Table 2. Oxazepanes by Halo-Etherification



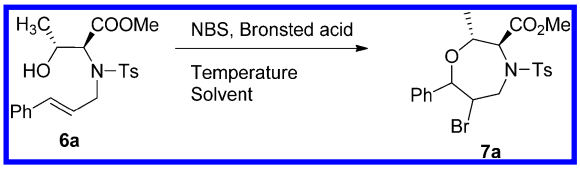
Entry	Product[a]	Yield (%)	7 : 8	d.r.[b]
1	 **7a**	95	> 20 : 1	1.3 : 1
2	 **8b**	77	> 1 : 20	2.0 : 1
3	 **7c**	37	> 20 : 1	1.5 : 1
4	 **7d**	69	> 20 : 1	2.0 : 1
5	 **7e**	83	> 20 : 1	1.1 : 1
6	 **7f**	> 99	> 20 : 1	2.0 : 1
7	 **7g**	80	> 20 : 1	1.5 : 1
8	 **7h**	78	> 20 : 1	1.4 : 1
9	 **7i**	99	> 20:1	-
10	 **7j**	85	> 20 : 1	1.5 : 1

[a]Major diastereomer shown. [b]As determined by ^{1}H NMR.

oxazepanes through a Markovnikov 7-*endo* cyclization or morpholines through an anti-Markovnikov 6-*exo* cyclization. In addition, two stereogenic centers are formed, leading to eight potential regio- and stereoisomers. In order to develop an efficient method, one has to significantly reduce this number of possible isomers. Halo-etherification is a stereospecific anti addition which reduces the number of potential isomers to four.

Although the cyclization was successful, the observed stereoselectivities were moderate (up to 2.0:1) and called for further optimization. The solvent, temperature, and additives were subsequently optimized (Table 3). For instance, the use of several different solvents showed excellent conversions although a wide variety of diastereoselectivities, with DMF and THF exhibiting the best results for both conversion and selectivity. For ease of utility, we opted to use THF for further experiments. We were pleased to see that, rather than a stoichiometric amount, the use of a catalytic amount of a Brønsted acid, such as CSA, activating the brominating reagent retained the significantly improved diastereomeric ratio (dr). This observation requires more investigations to be truly understood. Computational studies have been undertaken to investigate the complete mechanism and the role played by each partner and will be reported in due course. Lowering the reaction temperature showed increased diastereoselectivity below 0 °C. However, running the reaction at lower temperature reduces the applicability of this methodology to larger scales or large libraries. With these optimized conditions (NBS, THF, catalytic (±)-CSA, 0 °C), a variety of oxazepanes were obtainable.

Table 3. Condition Optimization



entry	solvent	temp (°C)	Brønsted acid	conversion (%)[a]	dr[a]
1	CH_3CN	0	(±)-CSA	100	2.1:1
2	CH_3CN	−20	(±)-CSA	97	3.4:1
3	CH_3CN	−78	(±)-CSA	97	4.0:1
4	DMF	0	(±)-CSA	100	>20:1
5	DCM	0	(±)-CSA	100	1.9:1
6	THF	0	(±)-CSA	100	8.6:1
7	MeOH	0	(±)-CSA	74	3.1:1
8	EtOH	0	(±)-CSA	100	7.7:1
9	^{i}PrOH	0	(±)-CSA	47	14.3:1
10	EtOAc	0	(±)-CSA	61	4.4:1
11	$CHCl_3$	0	(±)-CSA	95	2.9:1
12	acetone	0	(±)-CSA	96	1.2:1
13	1,4-dioxane	0	(±)-CSA	0	
14	benzene	0	(±)-CSA	95	7.1:1
15	toluene	0	(±)-CSA	96	7.3:1
16	THF	0	(+)-CSA	66	11.5:1
17	THF	0	(-)-CSA	63	10.0:1
18	THF	0	(±)-CSA (10 mol %)	51	10.0:1

[a]As determined by NMR of the crude mixtures.

We next optimized the cyclization conditions and the selection of the group attached to the ring nitrogen (R^6 in Figure 2), which turned out to be critical. Preliminary investigations with nonfunctionalized secondary amines (R^6 = H) led to poor-yielding cyclization and bromination of the nitrogen, while the use of carbamates (R^6 = Boc, Cbz) led to

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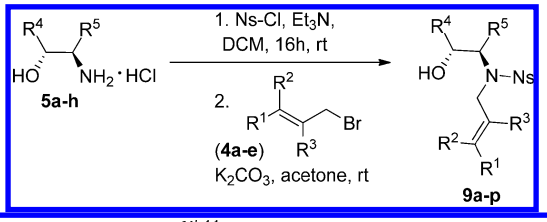
Table 4. Step 1: Amine Functionalization



Entry	R-Br	R^1 / R^2 / R^3	aa[a]	R^4 / R^5	Prod.	Yield (%)[b]
1	**4a**	Ph / H / H	**5a**	Me / CO_2Me	**9a**	> 99
2	**4b**	H / H /Me	**5a**	Me / CO_2Me	**9b**	74
3	**4c**	Me / Me / H	**5a**	Me / CO_2Me	**9c**	> 99
4	**4d**	Me / H / H	**5a**	Me / CO_2Me	**9d**	> 99
5	**4e**	Ph / H / Me	**5a**	Me / CO_2Me	**9e**	> 99
6	**4a**	Ph / H / H	**5b**	H / CO_2Me	**9f**	79
7	**4b**	H / H /Me	**5b**	H / CO_2Me	**9g**	42
8	**4c**	Me / Me / H	**5b**	H / CO_2Me	**9h**	97
9	**4d**	Me / H / H	**5b**	H / CO_2Me	**9i**	36
10	**4e**	Ph / H / Me	**5b**	H / CO_2Me	**9j**	38
11	**4a**	Ph / H / H	**5c**	*trans*-c-Hex	**9k**	>99
12	**4a**	Ph / H / H	**5d**	H / Et	**9l**	53
13	**4a**	Ph / H / H	**5e**	Me / H	**9m**	91
14	**4a**	Ph / H / H	**5f**	Me / CO_2Me[c]	**9n**	> 99
15	**4a**	Ph / H / H	**5g**	H/ H	**9o**	93
16	**4a**	Ph / H / H	**5h**	*cis*-ind[d]	**9p**	94

[a]Amino alcohol. [b]Over two steps. [c]*allo*-Threonine methyl ester. [d]*cis*-Indanolamine.

the formation of oxazolidinones, as reported by Guindon and co-workers.[24] The use of other protecting groups (R^6 = Bn, Ac, Bzl) also led to poor yields. Fortunately, nosyl derivatives (R^6 = Ns) led to higher yields during the alkylation step to afford **9** (Table 4) and also gave the desired cyclized products **10** with unexpectedly improved stereoselectivities (Table 5). While this paper was near completion, nosyl amide was used in the presence of NBS to open epoxides regioselectively, although no function was attributed to nosyl.[25]

At this stage the optimal conditions and nitrogen protecting group were applied to the combination of a variety of amino alcohols and alkene bromides. The set of nosylated derivatives was selected not only to probe the scope of this methodology but also to investigate the key elements for the observed high stereo- and regioselectivity (Table 5).

Mechanism. Throughout the cyclization process, the substrates induce the formation of given stereo- and regioisomers preferentially. By means of other substrates, we probed the scope of the reaction and further investigated the mechanism. As mentioned above, this reaction can potentially lead to a morpholine derivative through a 6-*exo* cyclization or to an oxazepane through a 7-*endo* cyclization. Haloetherification is believed to proceed through a bromonium ion (Figure 3a). The stereochemistry is set at this stage. However, it is well established that scrambling of the stereochemistry may occur by halogen transfer to another substrate molecule. Denmark has shown that this was a slow process that competed with intermolecular addition of alcohols[26] and that presence of a Lewis base shut down this undesired reaction and enabled asymmetric cyclization (Figure 3b).[27,28] Both the intra-

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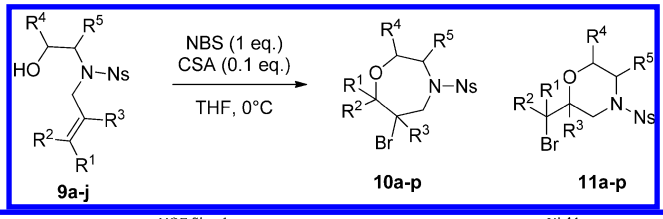
Table 5. Oxazepanes by Haloetherification



Entry	Product	Yield (%)	10 : 11	d.r.[a]	NOE Signals
1	**10a**	72	> 20 : 1	> 20 : 1	
2	**11b** / **11b'**	99	> 1 : 20	1.7 : 1	**11b**
3	**10c**	61	> 20 : 1	> 20 : 1	**10c**
4	**10d** / **11d**	> 99	2.9 : 1	> 20 : 1 > 20 : 1	**10d** **11d**
5	**10e** / **11e**	59	1.5 : 1	> 20 : 1 > 20 : 1	**10e** **11e**
6	**10f**	94	> 20 : 1	> 20 : 1	*J* = 7.2 Hz **10f**
7	**11g** / **11g'**	77	> 1 : 20	1.7 : 1	nd
8	**10h**	> 99	> 20 : 1	> 20 : 1	Stereochemistry assigned by analogy to **10c**
9	**10i** / **11i** / **11i'**	57	1.6 : 1	> 20 : 1 1.2 : 1	*J* = 6.6 Hz **10i** nd
10	**10j** / **11j**	42	1.8 : 1	> 20 : 1 > 20 : 1	*J* = 7.2 Hz **10j** *J* = 4 Hz **11j**
11	**10k** / **10k'**	73	> 20 : 1	2.0 : 1	**10k** nd
12	**10l**	> 99	> 20 : 1	> 20 : 1	**10l**
13	**10m** / **10m'**	78	> 20 : 1	1.2 : 1	**10m** nd
14	**10n** / **10n'**	42	> 20 : 1	2.1 : 1	**10n** **10n'**
15	**10o**	> 99	> 20 : 1	-	-[b]
16	**10p**	98	> 20 : 1	> 20 : 1	*J* = <1 Hz **10p**

[a]As determined by NMR for the major isomer. [b]Product is a mixture of enantiomers.

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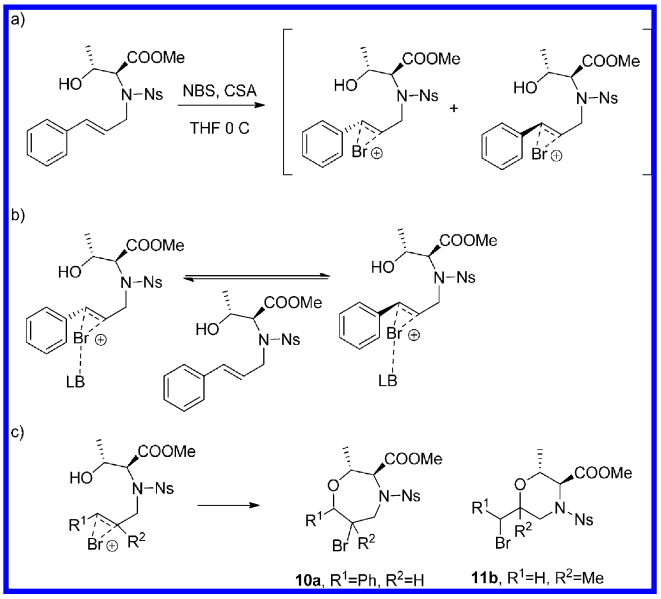

Figure 3. Mechanism and outcome (LB = Lewis base).

molecular nature of our process and the presence of the Lewis basic succinate originating from NBS and acting as Lewis base should preclude the undesired isomerization.

Regioselectivity. The regioselectivity (Figure 3c) was attributed on the basis of simple ^{13}C NMR shifts and confirmed by extensive heteronuclear multiple bond correlation (HMBC) experiments (Figure 4a) and a crystal structure (Figure 4c).

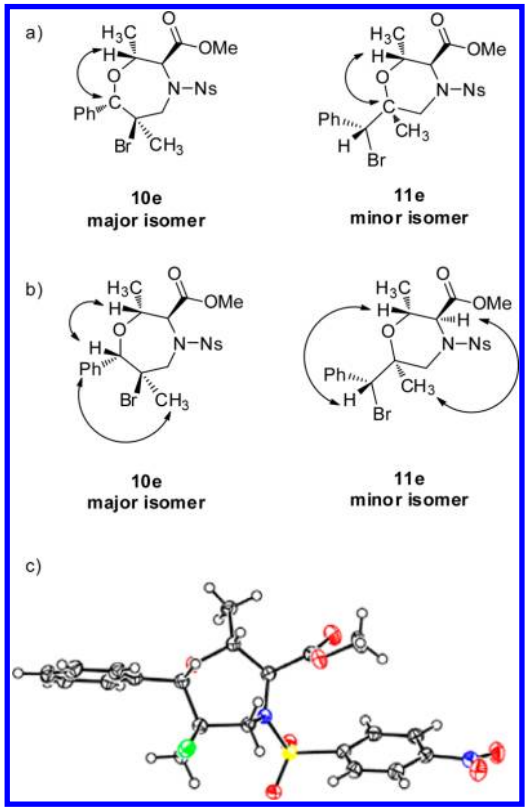

Figure 4. (a) HMBC signals confirming the regioselectivity. (b) NOESY signals used to ascertain the stereochemistry. (c) Crystal structure confirming the regio- and stereochemistry of the major product.

While this work was in progress, haloetherification has been found to favor the 6-*endo* over the 5-*exo* cyclization and the 7-*endo* over the 6-*exo* cyclization when an aromatic or an enamine group can stabilize the developing positive charge of the adjacent carbon through conjugation.[28] The presence of such groups controls the regioselectivity by desymmetrizing the bromonium intermediate. If no such group is found, then the exo cyclization was competitive. To further investigate this hypothesis, the reaction was carried out with **9a**,**f** and **9b**,**g**. In the case of **9a**,**f**, the most distant alkene carbon is adjacent to a phenyl ring favoring the 7-*endo* cyclization, while no stabilizing group are found at the same location in **9b**,**g**. Rather, a methyl group is branched on the internal alkene carbon, hence favoring the more entropically favored 6-*exo* cyclization. With **9e**,**j**, the regioselectivity is driven not just by the competition of stability between the tertiary carbocation and the benzylic-stabilized carbocation. If this were the case, we would expect to see predominantly the oxazepane product, but the observation of an approximately 2:1 ratio of oxazepane to morpholine implies that there is some entropic factor at play that is making the formation of the morpholine competitive.

Stereochemistry. The stereochemistry of the observed isomers was determined by NOESY experiments (Figure 4b) and when not possible (i.e., **10h**), by analogy with a similar substrate. First, we were pleased to see that the stereochemistry of the double bond is transferred to the product in all cases. This observation demonstrated that alkene to alkene transfer of the bromonium and scrambling of its stereochemistry does not occur. Although the rationalization of the regiochemical outcome and of the relative stereochemistry of the two stereocenters formed was somewhat straightforward, the preference for a given diastereoisomer induced by the amino alcohol stereocenters was more difficult. More specifically, investigating the mechanistic details of the stereochemistry of the reaction between NBS and **9** to form the observed oxazepanes was more challenging, as no obvious preference for one stereoisomer over the other can be predicted using simple models. For example, the role of each of the two stereogenic centers (i.e., methyl and methyl ester) of the threonine derivative **9a** in the observed stereoselectivity (>20:1, Table 5, entry 1) was evaluated. First, the methyl ester of **9a** was found to be critical, as removal of the methyl group (**9f**) retained the high level of selectivity (>20:1, entry 6). However, the methyl group is also important, as its inversion (**9n**) led to loss of stereoselectivity (2:1, entry 14) and poor yield (42%). To further investigate this observation, the derivative **9m**, in which only the methyl is kept, was prepared and cyclized. With this derivative (**9m**), poor selectivity was observed. Thus, we believe that the major factor impacting the stereoselectivity of **9a** is the methyl ester while the methyl group, if in the right configuration (matched case), is not essential. We initially postulated that the *cis* configuration of **9n** might cause distortion and disruption of the transition states (TS) conformation adopted by **9a**,**f**. However, the derivatives **9p**, although also in the *cis* configuration, led to high yield and stereoselectivity (98%, >20:1, entry 16). In addition, derivative **9k** in the *trans* configuration did not proceed with high selectivity (2.0:1, entry 11). The rigid nature of **9p**,**k** may explain their behavior in our cyclization reactions. It rapidly appeared that the flexible nature of seven-membered rings made the rationalization difficult.

In light of this, we turned to computational chemistry to guide the investigation into the mechanistic details of this

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reaction. We first investigated the addition of bromine to a model system. It was our initial hypothesis that the reaction involved two different TS's, one upon addition of bromine to the double bond and one upon formation of the ring by nucleophilic attack of the alcohol onto the bromonium. With this in mind, considering the first step, we modeled the reaction of NBS (protonated by (±)-CSA) and *trans*-butene. To our surprise, no TS was observed and the resulting structure was a cagelike system around the bromine and not a conventional bromonium ion (Figure 5). A lack of transition state has already

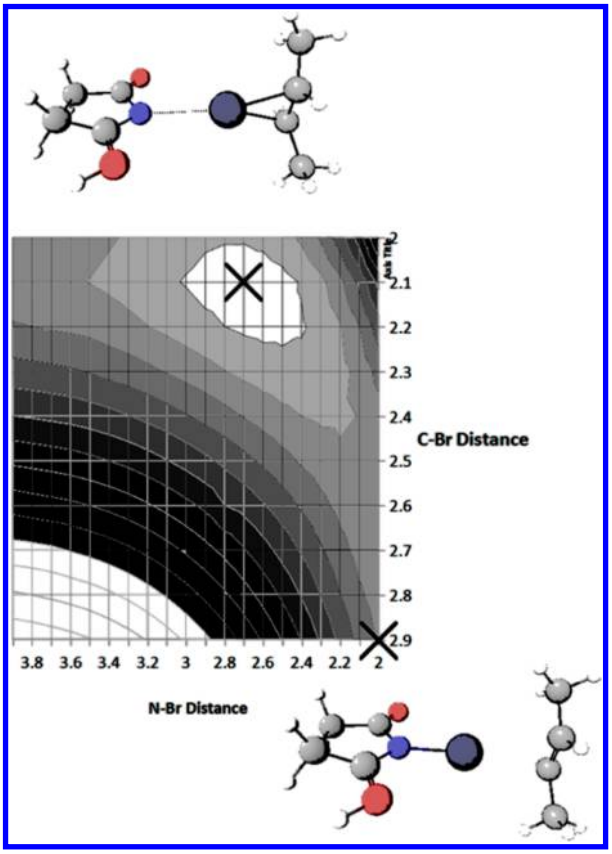

Figure 5. Potential energy surface of the reaction between NBS-H+ and *trans*-butene.

been observed for the hydroboration of alkenes.[29] We further confirmed this observation replacing butene with **9p**, indicating that this was not an artifact of the model.

Since the addition of bromine at this early stage determines the stereochemistry and no isomerization through intermolecular alkene-to-alkene transfer is expected, we concluded that the predominance of one stereoisomer should be determined by a conformational bias opening preferentially one face of the alkene to NBS. Thus, in practice this reduced our study to a simple conformational search rather than a TS analysis. Indeed, the computational prediction agreed, within error, with the experimentally observed products, predicting a 4:1 ratio of the *R* isomer of **10c** over the *S* isomer (Figure 6). Thus, the stereoselectivity can indeed be rationalized by simple conformational analysis of ground state reactants.

CONCLUSION

We have developed a strategy enabling the synthesis of chiral polysubstituted oxazepanes such as **10a**,**f**,**l**,**p** with excellent yields and regio- and diastereoselectivity in only three steps.

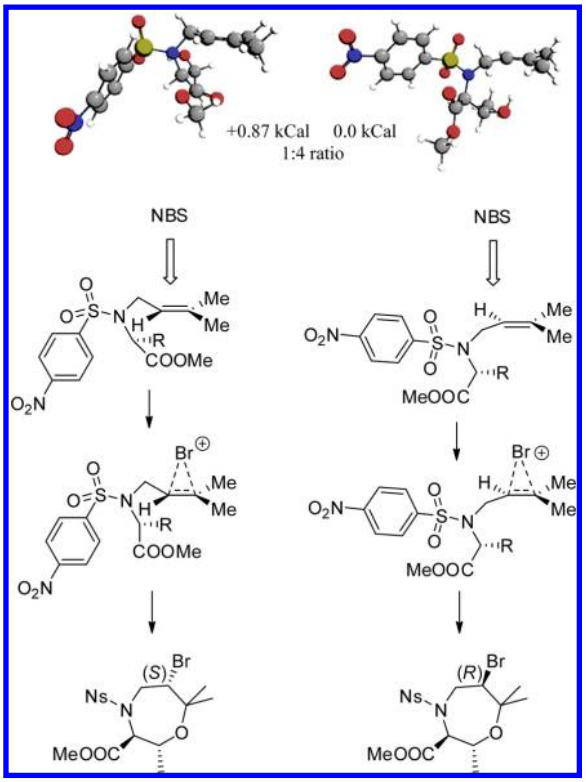

Figure 6. Stereochemical outcome from simple conformational analysis (**9c**).

10c features as many as five groups, while **10a** has four stereogenic centers. The strategy relies on the use of the chiral pool to introduce up to two stereogenic centers and a key stereo- and regioselective haloetherification to introduce up to two other stereogenic centers. This is a significant improvement over the rare existing (lengthy) approaches. The high regioselectivity observed was rationalized by the desymmetrization of the bromonium intermediate, while computational studies revealed that the stereochemistry is primarily controlled by conformational preferences of the substrates. Further computational investigations are in progress to explain the effects of CSA and the unexpected increase in selectivity offered by the nosyl protecting group. These results will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All commercially available reagents were used without further purification, unless otherwise stated. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$ (7.26 ppm for ^1H and 77.160 ppm for ^{13}C). ^1H and ^{13}C NMR assignments were confirmed by 2D COSY, HSQC, HMQC, and NOESY experiments. Chromatography was performed on silica gel 60 (230−40 mesh). Visualization was performed by UV or by development using ceric ammonim molybdate.

General Procedure for N-alkylation of N-protected Amino Alcohols. To a suspension of 200 mg (1.18 mmol) of threonine methyl ester hydrochloride salt in 40 mL of CH_2Cl_2 was added 330 μL (2.36 mmol) of NEt_3 via syringe, and the mixture was stirred for 0.5 h. The flask was then chilled to 0 °C, 288 mg (1.30 mmol) of solid nosyl chloride was added, and the resulting solution was warmed slowly to room temperature and stirred for 16 h. The product was washed with water (3 × 100 mL); the organic extract was then dried over Na_2SO_4, filtered, and concentrated in vacuo to give (2*S*,3*R*)-methyl 3-hydroxy-2-(4-nitrophenylsulfonamido)butanoate. The product was isolated and used in subsequent reactions without further purification. Then 260

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mg (0.82 mmol) of (2*S*,3*R*)-methyl 3-hydroxy-2-(4-nitrophenylsulfonamido)butanoate was dissolved in 40 mL of acetone and a large excess (>10 equiv) of solid K_2CO_3 was added to the flask. A 177 mg portion (1.01 mmol) of cinnamyl bromide was then added via syringe, and the resulting solution was stirred at room temperature for 16 h. The solvent was then removed in vacuo, and the remaining residue was partitioned between CH_2Cl_2 and water; the organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give **9a**. Products were purified by column chromatography (7/3 Hex/EtOAc eluent system).

*(2S,3R)-Methyl 2-(N-Cinnamyl-4-methylphenylsulfonamido)-3-hydroxybutanoate (**6a**).* White solid, mp 88−90 °C, isolated yield 8.68 g (90%). $[\alpha]^{22}_D$ = −57.3° (*c* 1.00, $CHCl_3$); R_f = 0.19 (1/99 MeOH/DCM). IR (film, cm^{-1}) 3531.3, 1737.7, 1335.3, 1153.2, 731.0. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.4 Hz, 3H), 2.39 (s, 3H), 2.56 (br s, 1H), 3.49 (s, 3H), 4.19 (ddd, *J* = 7.2, 16.0, 23.6 Hz, 2H), 4.36 (br s, 1H), 4.49 (d, *J* = 5.6 Hz, 1H), 6.20 (m, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 7.26 (m, 7H), 7.73 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 143.6, 136.8, 136.2, 133.4, 129.4, 128.5, 127.9, 127.7, 126.5, 125.9, 66.9, 64.6, 52.1, 49.0, 21.5, 19.9. HRMS: (M + H) for $C_{21}H_{25}NO_5SH$ calcd 404.15317, found 404.15253.

*(2S,3R)-Methyl 3-Hydroxy-2-(4-methyl-N-(2-methylallyl)-phenylsulfonamido)butanoate (**6b**).* Colorless oil, isolated yield 142 mg (30%). $[\alpha]^{22}_D$ = −44.5° (*c* 1.30, $CHCl_3$). R_f = 0.23 (1/99 MeOH/DCM). IR (film, cm^{-1}): 3526.6, 1738.7, 1338.2, 1156.1, 1091.3, 814.8, 661.3. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 5.8 Hz, 3H), 1.73 (s, 3H), 2.42 (s, 3H), 3.44 (s, 3H), 3.98 (s, 2H), 4.22 (s, 2H), 4.97 (s, 1H), 5.06 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.0, 169.7, 143.7, 142.2, 136.2, 129.3, 127.8, 114.5, 66.3, 65.4, 52.7, 51.8, 21.5, 20.3, 20.0 19.9. HRMS: (M + H) for $C_{16}H_{23}NO_5SH$ calcd 342.13752 found 342.13643.

*(2S,3R)-Methyl 3-Hydroxy-2-(4-methyl-N-(3-methylbut-2-en-1-yl)phenylsulfonamido)butanoate (**6c**).* Colorless oil, isolated yield 279 mg (98%). $[\alpha]^{22}_D$ = −91.8° (*c* 0.55, $CHCl_3$). R_f = 0.42 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3529.9, 2978.8, 1738.1, 1335.9, 1090.4, 667.9. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.3 Hz, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 2.42 (s, 3H), 3.52 (s, 3H), 4.01 (d, *J* = 7.5 Hz, 2H), 4.20 (m, 1H), 4.40 (d, *J* = 6.6 Hz, 1H), 5.23 (m, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 143.4, 136.5, 129.3, 127.6, 121.0, 66.4, 64.7, 51.9, 44.3, 25.8, 21.5, 19.7, 17.8. HRMS: (M + H) for $C_{17}H_{25}NO_5SH$ calcd 356.15317, found 356.15214.

*(S)-Methyl 2-(N-Cinnamyl-4-methylphenylsulfonamido)-3-hydroxypropanoate (**6d**).* Colorless oil, isolated yield 300 mg (39%). $[\alpha]^{22}_D$ = −28.9° (*c* 1.00, $CHCl_3$). R_f = 0.14 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3524.9, 1737.9, 1334.0, 1153.7, 908.9, 727.0. ^1H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.57 (s, 3H), 4.02 (m, 4H), 4.66 (t, *J* = 4.0 Hz, 1H), 6.12 (dt, *J* = 8.1, 16.2 Hz, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 7.26 (m, 7H), 7.76 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 143.7, 137.0, 136.1, 133.6, 129.6, 128.6, 128.0, 127.6, 126.5, 125.1 61.3, 60.9, 52.4, 48.9, 21.5. HRMS: (M + H) for $C_{20}H_{23}NO_5SH$ calcd 390.13752, found 390.13645.

*N-Cinnamyl-N-((1R,2R)-2-hydroxycyclohexyl)-4-methylbenzenesulfonamide (**6e**).* White solid, mp 121−123 °C, isolated yield 521 mg (84%). $[\alpha]^{22}_D$ = +10.4° (*c* 1.10, $CHCl_3$). R_f = 0.52 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3529.6, 1330.7, 1092.6, 735.1, 661.3. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (m, 3H), 1.48 (m, 2H), 1.66 (m, 2H), 2.10 (m, 1H), 2.31 (s, 1H), 2.41 (s, 3H), 3.53 (m, 2H), 4.06 (m, 2H), 6.15 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 7.29 (m, 7H), 7.74 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 138.0, 136.2, 132.9, 129.7, 128.6, 127.9, 127.2, 126.5, 70.1, 64.1, 46.2, 34.4, 29.3, 25.4, 24.0, 21.6. HRMS: (M + H) for $C_{22}H_{27}NO_3SH$ calcd 386.17899, found 386.17774.

*(R)-N-Cinnamyl-N-(1-hydroxybutan-2-yl)-4-methylbenzenesulfonamide (**6f**).* White solid, mp 70−72 °C, isolated yield 334 mg (51%). $[\alpha]^{22}_D$ = +30.4° (*c* 1.20, $CHCl_3$). R_f = 0.31 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3519.0, 1330.7, 1092.6, 657.9. ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (t, *J* = 7.6 Hz, 3H), 1.46 (m, 2H), 2.28 (br s, 1H), 2.41 (s, 3H), 3.62 (t, *J* = 6.4 Hz, 2H), 3.85 (m, 2H), 6.17 (m, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 7.27 (m, 7H), 7.75 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 138.0, 136.2, 132.7, 1296, 128.6, 127.9, 127.3, 126.6, 126.5, 63.5, 61.9, 46.0, 22.3, 21.5, 11.1. HRMS: (M + H) for $C_{20}H_{25}NO_3SH$ calcd 360.16334, found 360.16239.

*(R)-N-Cinnamyl-N-(2-hydroxypropyl)-4-methylbenzenesulfonamide (**6g**).* Colorless oil, isolated yield 292 mg (46%). $[\alpha]^{22}_D$ = +11.9° (*c* 1.15, $CHCl_3$). R_f = 0.31 (7/3 Hex/EtOAc). 3529.8, 1334.9, 1089.5, 736.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.0 Hz, 3H), 2.41 (s, 3H), 2.66 (br s, 1H), 3.10 (m, 2H), 4.02 (m, 3H), 5.94 (dt, *J* = 6.8, 15.6 Hz, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 7.25 (m, 7H), 7.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 136.3, 135.9, 134.3, 129.8, 127.4, 126.4, 123.7, 66.2, 55.1, 52.1, 21.5, 20.5. HRMS: (M + H) for $C_{19}H_{23}NO_3SH$ calcd 346.14769, found 346.14652.

*(2S,3S)-Methyl 2-(N-Cinnamyl-4-methylphenylsulfonamido)-3-hydroxybutanoate (**6h**).* Colorless oil, isolated yield 138 mg (67%). $[\alpha]^{22}_D$ = −31.3° (*c* 1.05, $CHCl_3$). R_f = 0.25 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3518.6, 1739.2, 1340.2, 1090.3, 743.7. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J* = 6.0 Hz, 3H), 2.42 (s, 3H), 3.49 (s, 3H), 4.00 (ddd, *J* = 1.2, 6.3, 9.3 Hz, 2H), 4.31 (m, 2H), 6.07 (dt, *J* = 6.6, 15.9 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 7.27 (m, 7H), 7.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 143.6, 137.1, 136.0, 134.0, 129.4, 128.6, 128.1, 127.7, 126.5, 124.8, 66.9, 64.3, 52.2, 49.3, 21.5, 19.9. HRMS: (M + H) for $C_{21}H_{25}NO_5SH$ calcd 404.15317, found 404.15233.

*N-Cinnamyl-N-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**6i**).* White solid, mp 54−58 °C, isolated yield 224 mg (62%). R_f = 0.15 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3518.4, 1332.0, 1153.3, 814.5, 719.5 ν. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.29 (t, *J* = 5.6 Hz, 2H), 3.75 (t, *J* = 5.2 Hz, 2H), 4.02 (dd, *J* = 0.8, 6.8 Hz, 2H), 5.98 (dt, *J* = 6.4, 16.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 7.28 (m, 7H), 7.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 136.3, 136.0, 134.2, 128.6, 127.3, 126.5, 123.8, 61.2, 51.7, 49.7, 21.5. HRMS: (M + H) for $C_{18}H_{21}NO_3SH$ calcd 332.13204, found 332.13094.

*N-Cinnamyl-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-methylbenzenesulfonamide (**6j**).* Colorless oil, isolated yield 578 mg (84%). $[\alpha]^{22}_D$ = −74.9° (*c* 1.05, $CHCl_3$); R_f = 0.58 (7/3 Hex/EtOAc); IR (film, cm^{-1}): 3518.0, 1333.8, 1094.1, 815.3, 740.0. ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.93 (dd, *J* = 6.0, 16.8 Hz, 1H), 3.21 (dd, *J* = 7.2, 16.4 Hz, 1H), 3.85 (m, 2H), 4.68 (dq, *J* = 3.6, 7.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 6.03 (m, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 6.8 Hz, 1H), 7.22 (m, 8H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 141.4, 137.5, 137.0, 136.4, 132.8, 129.8, 129.2, 128.5, 127.7, 127.4, 126.9, 126.5, 126.3, 125.8, 125.5, 72.3, 64.8, 48.5, 39.5, 21.6. HRMS: (M + H) for $C_{25}H_{25}NO_3SH$ calcd 420.16334, found 420.16206.

*(2S,3R)-Methyl 2-(N-Cinnamyl-4-nitrophenylsulfonamido)-3-hydroxybutanoate (**9a**).* Colorless oil, isolated yield 356 mg (>99%). $[\alpha]^{22}_D$ = −57.9° (*c* 0.50, $CHCl_3$). R_f = 0.48 (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3540.7, 1741.3, 1530.0, 1311.1, 1162.3, 742.7. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, *J* = 6.3 Hz, 3H), 3.59 (s, 3H), 4.16 (dd, *J* = 0.9, 7.8 Hz, 1H), 4.23 (ddq, *J* = 1.5, 6.3, 15.9 Hz, 2H), 4.47 (sextet, *J* = 6 Hz, 1H), 4.59 (d, *J* = 5.7 Hz, 1H), 6.11 (ddd, *J* = 6.3, 7.8, 15.9 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 7.30 (m, 5H), 8.02 (d, *J* = 9 Hz, 2H), 8.27 (d, *J* = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.9, 146.0, 135.8, 134.4, 129.0, 128.7, 128.3, 126.7, 126.4, 124.7, 123.9, 67.2, 65.0, 52.5, 49.7, 20.1. HRMS: (M + Na) for $C_{20}H_{22}N_2O_7SNa$ calcd 457.10454, found 457.10383.

*(2S,3R)-Methyl 3-Hydroxy-2-(N-(2-methylallyl)-4-nitrophenylsulfonamido)butanoate (**9b**).* Colorless oil, isolated yield 226 mg (74%). $[\alpha]^{22}_D$ = −45.2° (*c* 1.55, $CHCl_3$). R_f = 0.26 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3545.8, 1739.3, 1529.5, 1309.5, 1161.4, 1090.3, 855.9, 734.7. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.0 Hz, 3H), 1.70 (s, 3H), 3.53 (s, 3H), 3.99 (br s, 2H), 4.32 (m, 2H), 4.99 (s, 1H), 5.03 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 8.34 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.4, 150.0, 145.2, 141.2, 129.1, 123.9, 115.5, 66.4, 65.5, 53.3, 52.2, 20.3. HRMS: (M + Na) for $C_{15}H_{20}N_2O_7SNa$ calcd 395.08889, found 395.08907.

*(2S,3R)-Methyl 3-Hydroxy-2-(N-(3-methylbut-2-en-1-yl)-4-nitrophenylsulfonamido)butanoate (**9c**).* Colorless oil, isolated

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yield 317 mg (>99%). $[\alpha]^{22}_{D} = -58.8°$ (*c* 1.35, $CHCl_3$). $R_f = 0.53$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3538.0, 1740.3, 1530.1, 1310.8, 1162.7, 1090.2, 855.3, 759.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, J = 6.3 Hz, 3H), 1.64 (s, 3H), 1.67 (s, 3H), 2.31 (d, J = 4.8 Hz, 1H), 3.59 (s, 3H), 4.06 (d, J = 6.9 Hz, 2H), 4.32 (q, J = 6.3 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 5.14 (m, 1H), 8.02 (d, J = 9.3 Hz, 2H), 8.33 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.9, 149.9, 146.1, 137.3, 128.9, 123.8, 120.1, 66.7, 64.9, 52.3, 45.1, 25.8, 20.0, 17.8. HRMS: (M + Na) for $C_{16}H_{22}N_2O_7SNa$ calcd 409.10454, found 409.10374.

(2S,3R)-Methyl 2-(N-((E)-But-2-en-1-yl)-4-nitrophenylsulfonamido)-3-hydroxybutanoate (**9d**). Colorless oil, isolated yield 305 mg (>99%). $[\alpha]^{22}_{D} = -40.7°$ (*c* 0.85, $CHCl_3$). $R_f = 0.54$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3538.1, 1740.7, 1530.4, 1311.4, 1163.5, 734.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, J = 6.0 Hz, 3H), 1.63 (dd, J = 1.2, 6.4 Hz, 3H), 3.56 (s, 3H), 3.97 (dq, J = 6.3, 17.4 Hz, 2H), 4.36 (q, J = 6.0 Hz, 1H), 4.47 (d, J = 5.6 Hz, 1H), 5.44 (qt, J = 1.6, 7.6 Hz, 1H), 5.66 (m, 1H), 8.01 (d, J = 9.2 Hz, 2H), 8.33 (d, J = 8.8 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.8, 145.9, 131.2, 129.0, 128.9, 126.6, 123.8, 66.7, 64.8, 52.2, 49.2, 19.9, 17.6. HRMS: (M + Na) for $C_{15}H_{20}N_2O_7SNa$ calcd 395.08889, found 395.08819.

(2S,3R)-Methyl 3-Hydroxy-2-(N-((Z)-2-methyl-3-phenylallyl)-4-nitrophenylsulfonamido)butanoate (**9e**). Colorless oil, isolated yield 368 mg (>99%). $[\alpha]^{22}_{D} = -63.4°$ (*c* 1.10, $CHCl_3$). $R_f = 0.62$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3544.1, 1740.5, 1530.5, 1310.7, 1162.9, 733.0. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, J = 69.0 Hz, 3H), 1.75 (s, 3H), 2.41 (d, J = 4.5 Hz, 1H), 3.58 (s, 3H), 4.14 (s, 2H), 4.42 (t, J = 7.2 Hz, 2H), 6.49 (s, 1H), 7.18 (m, 2H), 7.34 (m, 3H), 8.03 (d, J = 9.0 Hz, 2H), 8.31 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.5, 149.9, 145.7, 136.5, 132.8, 130.7, 129.2, 128.8, 128.3, 127.1, 123.8, 66.3, 65.4, 56.0, 52.3, 20.6, 16.0. HRMS: (M + Na) for $C_{21}H_{24}N_2O_7SNa$ calcd 471.12019, found 471.11926.

(S)-Methyl 2-(N-Cinnamyl-4-nitrophenylsulfonamido)-3-hydroxypropanoate (**9f**). White solid, mp 116–118 °C, isolated yield 306 mg (79%). $[\alpha]^{22}_{D} = +6.7°$ (*c* 0.55, $CHCl_3$). $R_f = 0.39$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3543.1, 1740.2, 1530.1, 1311.7, 1162.4, 741.4. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 3H), 4.02 (ddd, J = 1.2, 7.2, 15.9 Hz, 2H), 4.17 (m, 2H), 4.76 (dd, J = 5.7, 7.2 Hz, 1H), 6.09 (ddd, J = 6.6, 7.2, 22.5 Hz, 1H), 6.53 (d, J = 15.9 Hz, 1H), 7.31 (m, 5H), 8.07 (d, J = 9 Hz, 2H), 8.31 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.6, 146.0, 145.9, 135.6, 134.5, 128.9, 128.7, 128.4, 126.5, 124.1, 124.0, 61.4, 61.3, 52.7, 49.2. HRMS: (M + Na) for $C_{19}H_{20}N_2O_7SNa$ calcd 443.08889, found 443.08873.

(S)-Methyl 3-Hydroxy-2-(N-(2-methylallyl)-4-nitrophenylsulfonamido)propanoate (**9g**). Colorless oil, isolated yield 139 mg (42%). $[\alpha]^{22}_{D} = +2.4°$ (*c* 0.55, $CHCl_3$). $R_f = 0.59$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3545.6, 1736.5, 1530.9, 1311.4, 1163.5, 736.9. ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (s, 3H), 3.63 (s, 3H), 3.74 (d, J = 16.2 Hz, 1H), 3.95 (m, 2H), 4.14 (dd, J = 5.7, 11.7 Hz, 1H), 4.52 (t, J = 6.0 Hz, 1H), 4.98 (s, 1H), 5.02 (s, 1H), 8.05 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.5, 145.4, 140.9, 129.0, 124.4, 124.0, 115.2, 61.6, 61.5, 53.6, 52.5, 20.0. HRMS: (M + Na) for $C_{14}H_{18}N_2O_7SNa$ calcd 381.07324, found 381.07260.

(S)-Methyl 3-Hydroxy-2-(N-(3-methylbut-2-en-1-yl)-4-nitrophenylsulfonamido)propanoate (**9h**). Colorless oil, isolated yield 332 mg (97%). $[\alpha]^{22}_{D} = 3.2°$ (*c* 1.05, $CHCl_3$). $R_f = 0.41$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3548.7, 1736.2, 1530.1, 1311.0, 1162.1, 855.1, 743.7. ^1H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 3H), 1.67 (s, 3H), 3.65 (s, 3H), 3.86 (m, 2H), 3.97 (m, 1H), 4.08 (m, 1H), 4.66 (t, J = 7.2 Hz, 1H), 5.10 (dt, J = 1.5, 7.8 Hz, 1H), 8.05 (d, J = 9.0 Hz, 2H), 8.4 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.8, 146.1, 138.0, 128.8, 124.0, 119.4, 61.3, 61.2, 52.5, 44.8, 25.7, 17.8. HRMS: (M + Na) for $C_{15}H_{20}N_2O_7SNa$ calcd 395.08889, found 395.08796.

(S,E)-Methyl 2-(N-(But-2-en-1-yl)-4-nitrophenylsulfonamido)-3-hydroxypropanoate (**9i**). Colorless oil, isolated yield 119 mg (36%). $[\alpha]^{22}_{D} = -4.9°$ (*c* 0.90, $CHCl_3$). $R_f = 0.42$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3547.0, 1736.5, 1530.4, 1311.5, 1163.1, 741.5. ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (d, J = 6.6 Hz, 3H), 2.23 (br s, 1H), 3.64 (s, 3H), 3.78 (m, 1H), 3.92 (m, 2H), 4.10 (dd, J = 5.7, 11.7 Hz, 1H), 4.66 (t, J = 6.9 Hz, 1H), 5.41 (m, 1H), 5.67 (m, 1H), 8.05 (d, J = 9.0 Hz, 2H), 8.35 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.7, 145.9, 131.5, 128.8, 126.0, 124.1, 124.0, 61.2, 61.1, 52.5, 49.0, 17.7. HRMS: (M + Na) for $C_{14}H_{18}N_2O_7SNa$ calcd 381.07324, found 381.07244.

(S,Z)-Methyl 3-Hydroxy-2-(N-(2-methyl-3-phenylallyl)-4-nitrophenylsulfonamido)propanoate (**9j**). White solid, mp 113–116 °C, isolated yield 152 mg (38%). $[\alpha]^{22}_{D} = -10.2°$ (*c* 0.50, $CHCl_3$). $R_f = 0.52$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3548.9, 1736.2, 1530.3, 1311.3, 1162.3, 743.0. ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (d, J = 1.2 Hz, 3H), 3.64 (s, 3H), 3.93 (m, 2H), 4.15 (m, 2H), 4.59 (t, J = 6.6 Hz, 1H), 6.45 (s, 1H), 7.19 (m, 2H), 7.34 (m, 3H), 8.08 (d, J = 9.0 Hz, 2H), 8.35 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.6, 150.0, 145.6, 136.4, 132.6, 130.3, 129.0, 128.8, 128.3, 127.2, 124.0, 61.4, 61.2, 56.0, 52.6, 15.8. HRMS: (M + Na) for $C_{20}H_{22}N_2O_7SNa$ calcd 457.10454, found 457.10355.

N-Cinnamyl-N-((1R,2R)-2-hydroxycyclohexyl)-4-nitrobenzenesulfonamide (**9k**). White solid, mp 147–149 °C, isolated yield 500 mg (>99%). $[\alpha]^{22}_{D} = +8.8°$ (*c* 0.50, $CHCl_3$). $R_f = 0.61$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3548.6, 1528.0, 1347.8, 1162.5, 685.3. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (m, 4H), 1.61 (m, 3H), 1.80 (d, J = 2.7 Hz, 1H), 2.05 (br s, 1H), 3.54 (m, 2H), 4.04 (m, 2H), 6.01 (dt, J = 6.9, 15.9 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H), 7.25 (m, 5H), 7.97 (d, J = 8.7 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 147.1, 135.8, 133.7, 128.7, 128.6, 128.2, 126.7, 126.4, 125.5, 124.0, 70.1, 64.5, 46.4, 35.0 30.4, 25.3, 24.0. HRMS: (M + Na) for $C_{21}H_{24}N_2O_5SNa$ calcd 439.13036, found 439.13042.

(R)-N-Cinnamyl-N-(1-hydroxybutan-2-yl)-4-nitrobenzenesulfonamide (**9l**). Colorless oil, isolated yield 172 mg (53%). $[\alpha]^{22}_{D} = 234.8°$ (*c* 0.45, $CHCl_3$). $R_f = 0.56$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3537.4, 1527.2, 1346.9, 1157.8, 854.3, 691.7. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J = 7.5 Hz, 3H), 1.52 (m, 2H), 3.65 (d, 6.3 Hz, 2H), 3.96 (m, 2H), 4.11 (dd, J = 6.9, 15.9 Hz, 1H), 6.07 (dt, J = 6.6, 15.9 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 7.27 (m, 5H), 8.04 (d, J = 8.7 Hz, 2H), 8.24 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 149.7, 147.1, 135.8, 133.7, 128.7, 128.6, 128.2, 126.4, 125.4, 124.0, 63.3, 62.4, 46.1, 22.6, 11.1. HRMS: (M + Na) for $C_{19}H_{22}N_2O_5SNa$ calcd 413.11471, found 413.11482.

(R)-N-Cinnamyl-N-(2-hydroxypropyl)-4-nitrobenzenesulfonamide (**9m**). White solid, mp 87–90 °C, isolated yield 723 mg (91%). $[\alpha]^{22}_{D} = +32.3°$ (*c* 0.60, $CHCl_3$). $R_f = 0.53$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3541.7, 1529.3, 1310.9, 1161.0 ,740.9. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, J = 6.3 Hz, 3H), 2.24 (br s, 1H), 3.329 (m, 2H), 4.14 (dd, J = 7.5, 14.1 Hz, 3H), 5.95 (dt, J = 6.9, 15.9 Hz, 1H), 6.49 (d, J = 15.9 Hz, 1H), 7.30 (m, 5H), 8.05 (d, J = 9 Hz, 2H), 8.33 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 145.7, 135.9, 135.6, 135.0, 128.7, 128.6, 128.4, 126.4, 124.3, 122.7, 66.4, 54.8, 51.8, 20.8. HRMS: (M + Na) for $C_{18}H_{20}N_2O_5SNa$ calcd 399.09906, found 399.09867.

(2S,3S)-Methyl 2-(N-Cinnamyl-4-nitrophenylsulfonamido)-3-hydroxybutanoate (**9n**). Colorless oil, isolated yield 348 mg (>99%). $[\alpha]^{22}_{D} = -30.8°$ (*c* 0.90, $CHCl_3$). $R_f = 0.47$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3537.4, 1740.0, 1530.6, 1311.5, 1164.7, 743.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, J = 6 Hz, 3H), 3.39 (s, 3H), 3.90 (ddq, J = 1.2, 7.5, 18.3 Hz, 2H), 4.02 (dd, J = 0.9, 7.5 Hz, 1H), 4.22 (m, 2H), 5.84 (ddd, J = 6.6, 7.8, 15.9 Hz, 1H), 6.35 (d, J = 15.9 Hz, 1H), 7.33 (m, 5H), 8.04 (d, J = 9 Hz, 2H), 8.31 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.6, 150.0, 145.9, 135.5, 134.9, 128.9, 128.7, 128.4, 126.4, 123.9, 123.5, 67.0, 64.7, 52.4, 49.5, 20.0. HRMS: (M + Na) for $C_{20}H_{22}N_2O_7SNa$ calcd 457.10454, found 457.10427.

N-Cinnamyl-N-(2-hydroxyethyl)-4-nitrobenzenesulfonamide (**9o**). White solid, mp 85–87 °C, isolated yield 245 mg (93%). $R_f = 0.35$ (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3536.9, 1528.5, 1348.0, 1159.9, 965.2, 692.0. ^1H NMR (300 MHz, $CDCl_3$): δ 3.41 (t, J = 5.4 Hz, 2H), 3.81 (q, J = 5.4 Hz, 2H), 4.11 (d, J = 6.6 Hz, 2H), 6.00 (ddt, J = 0.9, 6.9, 15.9 Hz, 1H), 6.51 (dd, J = 0.9, 15.9 Hz, 1H), 7.28 (m, 5H), 8.06 (d, J = 9 Hz, 2H), 8.35 (d, J = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 145.6, 135.5, 135.0, 128.7, 128.5, 128.4, 126.4, 124.4, 122.8, 61.0, 51.5, 49.6. HRMS: (M + Na) for $C_{17}H_{18}N_2O_5SNa$ calcd 385.08341, found 385.08321.

N-Cinnamyl-N-(2-hydroxy-2,3-dihydro-1H-inden-1-yl)-4-nitrobenzenesulfonamide (**9p**). Colorless oil, isolated yield 326 mg (94%).

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$[\alpha]^{22}_{D}$ = 75.5° (*c* 1.40, $CHCl_3$). R_f = 0.66 (6/4 Hex/EtOAc). IR (film, cm^{-1}): 3538.1, 1529.3, 1344.4, 1162.4, 1094.8, 692.5. ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (d, *J* = 2.4 Hz, 1H), 2.97 (dd, *J* = 4.0, 16.8 Hz, 1H), 3.27 (dd, *J* = 7.5, 16.8 Hz, 1H), 3.93 (dq, *J* = 8.1, 15.9 Hz, 2H), 4.16 (d, *J* = 7.5 Hz, 1H), 4.73 (dq, *J* = 4.2, 7.2 Hz, 1H), 5.89 (ddd, *J* = 6.0, 7.8, 15.9 Hz, 1H), 6.19 (d, *J* = 15.9 Hz, 1H), 7.25 (m, 9H), 8.06 (d, *J* = 9 Hz, 2H), 8.33 (d, *J* = 9 Hz, 2H). ^{13}C NMR (75 MHz): δ 146.9, 141.2, 136.6, 136.0, 133.9, 129.6, 128.6, 128.5, 128.1, 127.3, 126.7, 126.4, 125.7, 125.5, 125.1, 124.3, 72.3, 65.3, 49.1, 39.7. HRMS: (M + Na) for $C_{24}H_{22}N_2O_5SNa$ calcd 473.11471, found 473.11453.

General Procedure for Cyclization of N-alkylated Amino Alcohols. A 284 mg portion (0.65 mmol) of **9a** was dissolved in 10 mL of THF in a vial. A 15 mg portion of solid (±)-CSA (10 mol %, 0.06 mmol) was added, followed by 128 mg (0.72 mmol) of solid NBS. The mixture was then cooled to 0 °C and stirred for 12 h. The flask was warmed slowly to room temperature and was stirred for an additional 5 h. The reaction was quenched by adding 5 mL of saturated $NaHCO_3$ solution to the reaction mixture. The product was then extracted with EtOAc (2 × 40 mL), and the extract was dried over Na_2SO_4, filtered, and concentrated in vacuo to give **10a**. The crude product was purified by column chromatography (8/2 Hex/EtOAc eluent system).

*(2R,3S)-Methyl 6-Bromo-2-methyl-7-phenyl-4-tosyl-1,4-oxazepane-3-carboxylate (**7a**).* *Major diastereomer*: colorless oil, isolated yield 41 mg (11%). R_f = 0.40 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2923.6, 1740.3, 1454.5, 1355.6, 1157.1, 1090.9, 1009.3, 699.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, *J* = 4.5 Hz, 3H), 2.46 (s, 3H), 3.55 (s, 3H), 3.89 (dd, *J* = 8.7, 11.7 Hz, 1H), 3.94 (dd, *J* = 4.5, 7.2 Hz, 1H), 4.06–4.13 (m, 1H), 4.32 (dd, *J* = 2.7, 11.7 Hz, 1H), 4.37 (d, *J* = 7.8 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 7.20–7.22 (m, 2H), 7.31–7.35 (m, 5H), 7.73 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.9, 143.8, 139.4, 137.3, 129.8, 128.6, 128.2, 127.4, 127.1, 90.0, 64.6, 52.3, 51.8, 50.1, 21.6, 20.3. HRMS: (M + Na) for $C_{21}H_{24}BrNO_5SNa$ calcd 504.04563, found 504.04422. *Minor diastereomer*: colorless oil, isolated yield 234 mg (63%). R_f = 0.34 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2923.6, 2853.0, 1745.4, 1455.8, 1340.9, 1219.8, 1159.0, 1091.7, 699.8. ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, *J* = 5.1 Hz, 3H), 2.45 (s, 3H), 3.62 (s, 3H), 4.05 (dd, *J* = 3.9, 11.7 Hz, 1H), 4.24 (dd, *J* = 3.3, 11.7 Hz, 1H), 4.30–4.35 (m, 1H), 4.42 (d, *J* = 2.7 Hz, 1H), 4.72 (dq, *J* = 2.4, 5.1 Hz, 1H), 4.89 (d, *J* = 6.9 Hz, 1H), 7.30–7.34 (m, 7H), 7.77 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz): δ 166.9, 141.4, 167.6, 133.5, 127.1, 127.0, 126.0, 125.2, 124.3, 75.7, 70.5, 63.0, 50.5, 50.0, 49.7, 19.0. HRMS: (M + Na) for $C_{21}H_{24}BrNO_5SNa$ calcd 504.04563, found 504.04463.

*(2R,3S)-Methyl 6-(Bromomethyl)-2,6-dimethyl-4-tosylmorpholine-3-carboxylate (**8b**).* Characterized from a 2.0/1 mixture of diastereomers. Colorless oil, isolated yield 68 mg (77%). R_f = 0.43 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2983.0, 1743.3, 1348.0, 1126.5, 1091.2, 1039.7, 816.2, 663.5. ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (d, *J* = 4.5 Hz, 1H), 1.18 (d, *J* = 4.5 Hz, 2H), 1.24 (s, 1H), 1.39 (s, 2H), 2.43 (s, 2H), 2.44 (s, 1H), 2.60 (d, *J* = 9.3 Hz, 0.5H), 2.99 (d, *J* = 9.9 Hz, 0.5H), 3.17 (d, *J* = 6.9 Hz, 0.5H), 3.21 (s, 1H), 3.37 (d, *J* = 9.6 Hz, 0.5H), 3.44 (dd, *J* = 4.8, 8.4 Hz, 1H), 3.55 (d, *J* = 9.3 Hz, 0.5H), 3.71 (s, 2H), 3.76 (s, 1H), 3.79 (d, *J* = 8.1 Hz, 0.5H), 3.93–3.99 (m, 1H), 7.33–7.37 (m, 2H), 7.69 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.0, 169.7, 144.4, 144.2, 133.7, 132.3, 129.8, 129.7, 128.2, 127.9, 74.1, 72.6, 67.7, 67.6, 63.7, 63.6, 52.7, 52.6, 52.5, 49.8, 48.4, 38.5, 35.6, 24.4, 21.6, 20.2, 18.6, 18.3. HRMS: (M + K) for $C_{16}H_{22}BrNO_5SK$ calcd 458.0034, found 458.0008.

*(2R,3S)-Methyl 6-Bromo-2,7,7-trimethyl-4-tosyl-1,4-oxazepane-3-carboxylate (**7c**).* Characterized from a 1.5/1 mixture of diastereomers. Colorless oil, isolated yield 110 mg (47%). R_f = 0.36 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2981.7, 1739.8, 1351.8, 1334.0, 1195.9, 1089.8, 957.1, 771.2, 662.8. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20–1.25 (m, 3H), 1.30–1.34 (m, 6H), 2.40 (s, 3H), 3.47 (s, 2H), 3.63 (s, 1H), 3.73 (dd, *J* = 8.7, 12.0 Hz, 1H), 3.85–3.93 (m, 2H), 4.03 (m, 0.5H), 4.26 (d, *J* = 7.2 Hz, 1H), 4.41 (d, *J* = 5.1 Hz, 0.5H), 7.27–7.29 (m, 2H), 7.64 (d, *J* = 6.3 Hz, 1.5H), 7.68 (d, *J* = 6.0 Hz, 0.5H). ^{13}C NMR (75 MHz): δ 171.4, 171.1, 143.7, 143.6, 137.1, 135.9, 129.6, 129.5, 127.6, 127.0, 78.3, 78.0, 67.6, 66.8, 64.4, 63.9, 56.0, 52.5, 52.1, 51.7, 48.5, 48.1, 29.8, 24.9, 23.4, 23.2, 21.6, 21.5, 20.7, 19.8. HRMS: (2 M + K) for $2[C_{17}H_{24}BrNO_5S]K$ calcd 905.0749, found 905.0760.

*(3S)-Methyl 6-Bromo-7-phenyl-4-tosyl-1,4-oxazepane-3-carboxylate (**7d**).* Characterized from a 2.0:1 mixture of diastereomers. Colorless oil, isolated yield 74 mg (69%). R_f = 0.29 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3033.1, 2954.0, 1747.3, 1338.4, 1195.3, 1099.8, 1090.6, 1023.7, 757.5, 700.1, 662.2. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 1H), 2.47 (s, 2H), 3.63 (s, 2H), 3.69 (dd, *J* = 8.1, 9.9 Hz, 0.5H), 3.71 (s, 1H), 3.75 (dd, *J* = 8.7, 12.0 Hz, 1H), 3.96 (dd, *J* = 4.8, 11.7 Hz, 0.5H), 4.02–4.09 (m, 1H), 4.30–4.37 (m, 1.5H), 4.50 (dd, *J* = 5.1, 9.9 Hz, 1H), 4.54 (dd, *J* = 1.8, 10.2 Hz, 0.5H), 4.62 (d, *J* = 6.0 Hz, 0.5H), 4.69 (t, *J* = 1.8 Hz, 0.5H), 4.99 (dd, *J* = 5.1, 7.8 Hz, 1H), 7.17–7.19 (m, 1H), 7.30–7.37 (m, 5H), 7.77–7.80 (m, 2H). ^{13}C NMR (75 MHz): δ 169.8, 169.8, 144.0, 139.8, 138.8, 137.2, 136.1, 129.8, 129.7, 128.8, 128.6, 128.5, 128.4, 127.6, 127.3, 127.3, 126.7, 90.6, 88.9, 70.8, 69.8, 61.0, 59.2, 53.7, 52.7, 52.6, 52.5, 52.5, 50.8, 50.2, 49.7, 21.6. HRMS: (M + K) for $C_{20}H_{22}BrNO_5SK$ calcd 506.0034, found 506.0008.

*(5aR,9aR)-3-Bromo-2-phenyl-5-tosyldecahydrobenzo[b][1,4]-oxazepine (**7e**).* *Major diastereomer*: colorless oil, isolated yield 54 mg (24%). R_f = 0.16 (1/1 DCM/toluene). IR (film, cm^{-1}): 2927.1, 2856.8, 1454.8, 1328.3, 1130.0, 1101.4, 761.8, 728.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (tt, *J* = 2.7, 9.6 Hz, 2H), 1.32 (tq, *J* = 2.7, 9.9 Hz, 1H), 1.45 (dq, *J* = 2.7, 9.3 Hz, 1H) 1.75 (t, *J* = 9.6 Hz, 2H), 1.91 (t, *J* = 11.4 Hz, 2H), 2.14 (dq, *J* = 2.7, 9.3 Hz, 1H), 2.44 (s, 3H), 3.19 (dt, *J* = 2.4, 8.7 Hz, 1H), 3.31 (dd, *J* = 7.8, 10.8 Hz, 1H), 4.07 (dt, *J* = 3.0, 8.7 Hz, 1H), 4.33 (m, 2H), 4.63 (d, *J* = 7.2 Hz, 1H), 7.26–7.35 (m, 7H), 7.76 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz): δ 143.2, 141.0, 139.7, 129.7, 128.3, 128.2, 127.2, 126.7, 78.9, 77.7, 67.6, 58.2, 51.6, 31.4, 30.3, 26.2, 24.5, 21.5. HRMS: (M + Na) for $C_{22}H_{26}BrNO_3SNa$ calcd 486.07145, found 486.07080. *Minor diastereomer*: colorless oil, isolated yield 31 mg (14%). R_f = 0.24 (1/1 DCM/toluene). IR (film, cm^{-1}): 2937.8, 2860.5, 1335.9, 1180.0, 1087.2, 1000.0, 872.6, 776.6, 659.0. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.49 (m, 4H), 1.71–1.79 (m, 2H), 2.01 (d, *J* = 9.3 Hz, 1H), 2.14 (d, *J* = 5.4 Hz, 1H), 2.49 (s, 3H), 3.39(dt, *J* = 3.0, 7.8 Hz, 1H), 3.63 (dd, *J* = 9.0, 12.0 Hz, 1H), 3.78 (m, 2H), 4.31 (m, 2H), 6.90 (dd, *J* = 1.2, 6.0 Hz, 2H), 7.24 (m, 3H), 7.38 (d, *J* = 6.0 Hz, 2H), 7.84 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (75 MHz): δ 143.5, 139.7, 139.0, 130.0, 128.4, 128.1, 127.3, 127.2, 88.4, 82.4, 63.3, 51.4, 48.6, 33.9, 32.4, 24.8, 24.7, 21.6. HRMS: (M + Na) for $C_{22}H_{26}BrNO_3SNa$ calcd 486.07145, found 486.07201.

*(3R)-6-Bromo-3-ethyl-7-phenyl-4-tosyl-1,4-oxazepane (**7f**).* Characterized from a 2.0/1 mixture of diastereomers, Colorless oil, isolated yield 57 mg (>99%). R_f = 0.61 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3033.3, 2968.4, 2877.5, 1455.0, 1337.4, 1095.9, 1040.0, 760.87, 699.5. ^1H NMR (300 MHz, $CDCl_3$): δ 0.79 (t, *J* = 5.7 Hz, 1H), 0.94 (t, *J* = 5.7 Hz, 2H), 2.45 (s, 1H), 2.5 (s, 2H), 3.36 (dd, *J* = 9.9, 11.7 Hz, 1H), 3.51 (dd, *J* = 9.0, 12.0 Hz, 1H), 3.70 (dd, *J* = 2.4, 9.3 Hz, 0.5H), 3.77–3.84 (m, 1H), 3.93–4.00 (m, 1H), 4.18 (d, *J* = 7.5 Hz, 1H), 4.22–4.30 (m, 2H), 4.38 (dd, *J* = 2.4, 11.7 Hz, 1H), 5.54 (d, *J* = 6.9 Hz, 0.5H), 6.85 (dd, *J* = 1.2, 6.0 Hz, 2H), 7.22–7.26 (m, 1.5H), 7.33–7.35 (m, 2H), 7.38 (d, *J* = 6.0 Hz, 1.5H), 7.81 (d, *J* = 6.3 Hz, 0.5H), 7.84 (d, *J* = 6.3 Hz, 1.5H). ^{13}C NMR (75 MHz): δ 143.5, 140.0, 139.3, 139.2, 137.5, 130.0, 129.7, 128.5, 128.4, 128.1, 127.5, 127.3, 127.1, 126.9, 90.5, 88.6, 73.9, 73.0, 60.2, 58.7, 54.2, 50.2, 49.0, 58.4, 31.6, 24.7, 22.7, 22.3, 21.6, 14.1, 10.9, 10.1. HRMS: (M + Na) for $C_{20}H_{24}BrNO_3SNa$ calcd 460.05525, found 460.05520.

*(2R)-6-Bromo-2-methyl-7-phenyl-4-tosyl-1,4-oxazepane (**7g**).* *Major diastereomer*: colorless oil, isolated yield 22 mg (43%). R_f = 0.63 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2925.9, 1450.7, 1340.6, 1159.4, 1087.8, 699.4. ^1H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.4 Hz, 3H), 2.46 (s, 3H), 2.69 (dd, *J* = 10.0, 14.0 Hz, 1H), 3.29 (dd, *J* = 10.0, 14.0 Hz, 1H), 3.82 (ddd, *J* = 1.2, 3.2, 14.0 Hz, 1H), 3.93–3.98 (m, 1H), 4.31 (ddd, *J* = 1.2, 3.2, 14.0 Hz, 1H), 4.37 (dt, *J* = 3.6, 10.0 Hz, 1H), 4.81 (d, *J* = 9.2 Hz, 1H), 7.36 (m, 7H), 7.71 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$),: δ 143.8, 138.9, 136.2, 129.9, 128.5, 128.4, 127.4, 127.0, 80.3, 71.0, 54.9, 54.7, 49.7, 21.5, 18.4. HRMS: (M + H) for $C_{19}H_{22}BrNO_3SH$ calcd 424.0567, found 424.0558; *Minor diastereomer*: colorless oil, isolated yield 19 mg (37%). R_f = 0.56 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2925.8, 1450.4, 1342.2, 1161.5, 1088.8,

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771.6, 699.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, J = 6.0 Hz, 3H), 2.46 (s, 3H), 2.96 (dd, J = 10.4, 12.8 Hz, 1H), 3.57 (ddd, J = 0.8, 3.2, 12.8 Hz, 1H), 3.85 (dd, J = 4.4, 15.2 Hz, 1H), 3.91 (dd, J = 0.8, 5.2 Hz, 1H), 3.93−3.97 (m, 1H), 4.14 (ddd, J = 4.0, 5.2, 9.6 Hz, 1H), 4.60 (d, J = 9.6 Hz, 1H), 7.32−7.37 (m, 7H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 140.0, 135.8, 129.9, 128.3, 128.2, 127.3, 127.1, 87.6, 77,.2, 56.7, 54.0, 53.9, 21.5, 19.5. HRMS: (M + H) for $C_{19}H_{22}BrNO_3SH$ calcd 424.0567, found 424.0555.

*(2S,3S)-Methyl 6-Bromo-2-methyl-7-phenyl-4-tosyl-1,4-oxazepane-3-carboxylate (**7h**).* *Major diastereomer*: colorless oil, isolated yield 136 mg (31%). R_f = 0.29 (8/2 Hex/EtOAc). IR (film, cm^{-1}): 2925.0, 1745.9, 1340.7, 1091.2, 1050.5, 902.2, 736.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 6.8 Hz, 3H), 2.44 (s, 3H), 3.54 (s, 3H), 3.91 (dq, J = 2.4, 5.2 Hz, 1H), 4.32 (m, 2H), 4.54 (dt, J = 2.4, 9.6 Hz, 1H), 4.62 (d, J = 1.6 Hz, 1H), 4.97 (d, J = 9.2 Hz, 1H), 7.31−7.45 (m, 7H), 7.67 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.6, 143.9, 136.6, 136.5, 129.8, 128.7, 128.6, 127.8, 127.0, 83.0, 73.2, 61.6, 51.9, 50.1, 47.8, 21.6, 19.7. HRMS: (M + Na) for $C_{21}H_{24}BrNO_5SNa$ calcd 504.04563, found 504.04558. *Minor diastereomer*: colorless oil, isolated yield 70 mg (16%). R_f = 0.21 (8/2 Hex/EtOAc). IR (film, cm^{-1}): 2950.8, 1744.1, 1343.6, 1219.4, 1160.3, 731.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, J = 6.8 Hz, 3H), 2.44 (s, 3H). 3.64 (s, 3H), 3.91 (dd, J = 7.2, 15.2 Hz, 1H), 4.33 (dq, J = 2.4, 6.4 Hz, 1H), 4.39 (dt, J = 2.4, 7.2 Hz, 1H), 4.52 (d, J = 2.0 Hz, 1H), 4.60 (dd, J = 2.4, 15.2 Hz, 1H), 4.70 (d, J = 7.2 Hz, 1H), 7.32 (m, 7H), 7.72 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.3, 144.0, 140.4, 135.9, 129.7, 128.4, 127.5, 126.7, 87.9, 75.6, 69.6, 63.8, 54.7, 52.0, 49.3, 21.6, 19.6. HRMS: (M + Na) for $C_{21}H_{24}BrNO_5SNa$ calcd 504.04563, found 504.04408

*6-Bromo-7-phenyl-4-tosyl-1,4-oxazepane (**7i**).* White solid, mp 93−94 °C, isolated yield 1.65 g (>99%). R_f = 0.47 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2923.3, 1713.8, 1337.7, 1158.0, 1088.3, 906.1, 771.9, 698.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.40−5.56 (m, 2H), 3.71−3.81 (m, 2H), 4.01 (dd, J = 3.9, 15.3 Hz, 1H), 4.10−4.20 (m, 2H), 4.50 (d, J = 9.3 Hz, 1H), 7.27−7.37 (m, 7H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz): δ 143.9, 139.5, 135.9, 130.0, 128.5, 128.4, 127.2, 127.1, 88.7, 53.1, 21.6. HRMS: (M + Na) for $C_{18}H_{20}BrNO_3SNa$ calcd 432.02450, found 432.02502

*(5aS,10aR)-3-Bromo-2-phenyl-5-tosyl-3,4,5,5a,10,10a-hexahydro-2H-indeno[2,1-b][1,4]oxazepine (**7j**).* *Major diastereomer*: colorless oil, isolated yield 28 mg (18%). R_f = 0.24 (1/1 DMC/toluene). IR (film, cm^{-1}): 2923.4, 1339.7, 1219.7, 1162.0, 1092.1, 1062.6, 911.0 699.3, 673.0;. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.89−3.06 (m, 2H), 3.89 (dd, J = 5.1, 16.5 Hz, 1H), 4.01 (dd, J = 4.8, 10.2 Hz, 1H), 4.44−4.51 (m, 2H), 4.63 (d, J = 9.9 Hz, 1H), 5.47 (d, J = 3.9 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 7.15−7.20 (m, 3H), 7.25−7.30 (m, 5H), 7.40 (d, J = 7.8 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz): δ 141.3, 138.1, 136.6, 135.2, 134.3, 127.3, 125.8, 125.7, 125.6, 125.3, 124.8, 124.4, 122.9, 121.5, 81.9, 81.8, 64.2, 51.7, 45.9, 35.4, 19.0. HRMS: (M + Na) for $C_{25}H_{24}BrNO_3SNa$ calcd 520.05580, found 520.05545. *Minor diastereomer*: colorless oil, isolated yield 70 mg (45%), R_f = 0.14 (1:1 DMC/toluene). IR (film, cm^{-1}): 2924.5, 1598.0, 1456.9, 1337.0, 1157.5, 1093.0, 998.9, 809.3, 698.9, 660.9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.07−3.35 (m, 3H), 4.04−4.19 (m, 2H), 4.31 (dd, J = 4.2, 15.0 Hz, 1H), 4.94 (dt, J = 1.5, 7.8 Hz, 1H), 5.75 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 7.13−1.35 (m, 8H), 7.42 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz): δ 141.3, 138.2, 138.1, 135.5, 134.8, 127.4, 126.6, 125.9, 125.8, 125.1, 124.6, 124.3, 122.5, 122.4, 77.3, 74.8, 62.0, 47.9, 46.5, 34.2, 19.1. HRMS: (M + Na) for $C_{25}H_{24}BrNO_3SNa$ calcd 520.05580, found 520.05555.

*(3S)-Methyl 6-Bromo-7-phenyl-4-tosyl-1,4-oxazepane-3-carboxylate (**7k**).* Isolated yield 56%, complex mixture of isomers.

*(2R,3S)-Methyl 6-Bromo-2,7-dimethyl-4-((4-nitrophenyl)-sulfonyl)-1,4-oxazepane-3-carboxylate and (2R,3S)-Methyl 6-(1-Bromoethyl)-2-methyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate (**7l**).* Isolated yield 81%, complex mixture of isomers.

*(2R,3S,6R,7S)-Methyl 6-Bromo-2-methyl-4-((4-nitrophenyl)-sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10a**).* White solid, mp 138−141 °C, isolated yield 240 mg (72%). $[\alpha]^{22}_D$ = −22.1° (c 1.00, $CHCl_3$). R_f = 0.55 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2957.6, 1739.2, 1530.3, 1348.4, 1159.0, 1088.5, 1008.3, 699.0. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, J = 6.0 Hz, 3H), 3.57 (s, 3H), 3.92 (m, 2H), 4.15 (dt, J = 3.9, 11.4 Hz, 1H), 4.27 (dd, J = 3.6, 15.3 Hz, 1H), 4.40 (d, J = 10.2 Hz, 1H), 4.53 (d, J = 9.6 Hz, 1H), 7.31 (m, 5H), 8.04 (d, J = 8.7 Hz, 2H), 8.40 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.3, 150.1, 145.5, 139.0, 128.8, 128.4, 128.3, 127.3, 124.4, 90.1, 77.5, 64.7, 52.5, 51.5, 50.5, 20.5. HRMS: (M + Na) for $C_{20}H_{21}BrN_2O_7SNa$ calcd 535.01505, found 535.01620.

*(2R,3S,6S)-Methyl 6-(Bromomethyl)-2,6-dimethyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate (**11b**).* Colorless oil, isolated yield 69 mg (49%). $[\alpha]^{22}_D$ = −74.7° (c 0.15, $CHCl_3$). R_f = 0.55 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2926.4, 1743.6, 1532.1, 1350.8, 1165.3, 1089.8, 855.9, 737.9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.3 Hz, 3H), 1.32 (s, 3H), 3.00 (d, J = 12.9 Hz, 1H), 3.46 (d, J = 10.2 Hz, 1H), 3.53−3.60 (m, 2H), 3.72 (s, 3H), 3.98 (dd, J = 6.0, 9.0 Hz, 1H), 8.02 (d, J = 8.7 Hz, 2H), 8.41 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 164.0, 142.8, 142.0, 129.2, 124.3, 73.3, 67.6, 63.2, 52.8, 49.0, 35.6, 24.3, 18.6. HRMS: (M + H) for $C_{15}H_{19}BrN_2O_7SH$ calcd 451.0169, found 451.0170.

*(2R,3S,6R)-Methyl 6-(Bromomethyl)-2,6-dimethyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate (**11b′**).* Characterized from a 1.7/1 mixture of diastereomers. Yellow oil. R_f = 0.48 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.3, 1984.4, 2954.3, 1741.7, 1530.5, 1345.0, 1163.3, 911.6, 855.7, 819.3, 736.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.0 Hz, 1.5H), 1.26 (d, J = 6.0 Hz, 1.5H), 1.31 (s, 1.5H), 1.36 (s, 1.5H), 2.99 (d, J = 12.9 Hz, 0.5H), 3.25 (s, 1H), 3.37 (d, J = 8.1 Hz, 0.5H), 3.46 (d, J = 10.8 Hz, 0.5H), 3.52−3.58 (m, 1.5H), 3.69 (s, 1.5H), 3.71 (s, 1.5H), 3.75 (d, J = 9.0 Hz, 0.5H), 3.93−4.00 (m, 1H), 8.02 (d, J = 8.7 Hz, 2H), 8.39 (m, 2H). ^{13}C NMR (75 MHz): δ 169.6, 169.4, 150.4, 150.3, 143.6, 142.8, 129.1, 128.9, 124.3, 74.7, 73.3, 67.6, 67.5, 63.3, 63.2, 52.8, 52.7, 49.0, 47.5, 37.9, 35.6, 24.3, 20.7, 19.0, 18.6. HRMS: (M + H) for $C_{15}H_{19}BrN_2O_7SH$ calcd 451.0169, found 451.0173.

*(2R,3S,6R)-Methyl 6-Bromo-2,7,7-trimethyl-4-((4-nitrophenyl)-sulfonyl)-1,4-oxazepane-3-carboxylate (**10c**).* White solid, mp 119−122 °C, isolated yield 148 mg (61%). $[\alpha]^{22}_D$ = −35.0° (c 0.60, $CHCl_3$). R_f = 0.56 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2982.7, 1739.6, 1531.3, 1349.6, 1157.7, 1088.4, 684.9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, J = 6.3 Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 3.52 (s, 3H), 3.73 (dd, J = 4.3, 15.6 Hz, 1H), 3.94 (m, 2H), 4.05 (dd, J = 1.8, 15.6 Hz, 1H), 4.33 (d, J = 9.9 Hz, 1H), 7.98 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.8, 150.1, 145.5, 128.3, 124.3, 78.2, 67.6, 64.6, 55.6, 52.4, 48.5, 29.8, 20.9, 19.7. HRMS: (M + Na) for $C_{16}H_{21}BrN_2O_7SNa$ calcd 487.01505, found 487.01370.

*(2R,3S,6R,7S)-Methyl 6-Bromo-2,7-dimethyl-4-((4-nitrophenyl)-sulfonyl)-1,4-oxazepane-3-carboxylate (**10d**).* Colorless oil, isolated yield 128 mg (66%). $[\alpha]^{22}_D$ = −29.3° (c 0.90, $CHCl_3$). R_f = 0.55 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2926.6, 1739.4, 1530.8, 1348.2, 1160.9, 1089.9, 1024.5, 684.9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, J = 6.3 Hz, 3H), 1.74 (s, 3H), 3.29 (s, 3H), 3.88 (dt, J = 6.0, 15.3 Hz, 1H), 4.24 (d, J = 15.6 Hz, 1H), 4.42 (d, J = 9.6 Hz, 1H), 4.49 (d, J = 15.3 Hz, 1H), 4.69 (s, 1H), 7.34 (m, 3H), 7.45 (m, 2H), 7.98 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.2, 150.1, 145.1, 137.2, 128.8, 128.7, 128.1, 127.3, 124.1, 92.7, 79.2, 66.9, 65.2, 56.9, 52.1, 22.8, 20.7. HRMS: (M + Na) for $C_{15}H_{19}BrN_2O_7SNa$ calcd 472.99940, found 472.99854.

*(2R,3S,6S)-Methyl 6-((R)-1-Bromoethyl)-2-methyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate (**11d**).* Colorless oil, isolated yield 62 mg (32%). $[\alpha]^{22}_D$ = −48.9° (c 0.70, $CHCl_3$). R_f = 0.47 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.1, 2955.4, 1745.2, 1530.7, 1312.8, 1168.8, 995.4, 855.6, 762.8, 736.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (d, J = 6.6 Hz, 3H), 1.65 (d, J = 6.9 Hz, 3H), 3.27 (t, J = 13.2 Hz, 1H), 3.59 (s, 3H), 3.75 (dd, J = 3.0, 12.3 Hz, 1H), 3.93 (m, 2H), 4.35 (s, 1H), 4.69 (q, J = 6.9 Hz, 1H), 7.96 (d, J = 8.7 Hz, 2H), 8.37 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.8, 150.1, 144.7, 128.5, 124.2, 70.5, 69.7, 58.4, 52.6, 47.7, 43.9, 21.2, 16.5. HRMS: (M + Na) for $C_{15}H_{19}BrN_2O_7SNa$ calcd 472.99940, found 472.99850.

*(2R,3S,6R,7S)-Methyl 6-Bromo-2,6-dimethyl-4-((4-nitrophenyl)-sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10e**).* White solid,

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mp 213-217 °C, isolated yield 49 mg (39%). $[\alpha]^{22}_{D}$ = +17.1° (*c* 0.50, $CHCl_3$). R_f = 0.58 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2926.4, 1740.5, 1531.3, 1344.5, 1161.1, 1023.5, 910.1, 701.8. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.3 Hz, 3H), 1.74 (s, 3H), 3.29 (s, 3H), 3.88 (dt, *J* = 6.0, 15.3 Hz, 1H), 4.24 (d, *J* = 15.6 Hz, 1H), 4.42 (d, *J* = 9.6 Hz, 1H), 4.49 (d, *J* = 15.3 Hz, 1H), 4.69 (s, 1H), 7.34 (m, 3H), 7.45 (m, 2H), 7.98 (d, *J* = 9.0 Hz, 2H), 8.36 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 170.2, 150.1, 145.1, 137.2, 128.8, 128.7, 128.1, 127.3, 124.1, 92.7, 79.2, 66.9, 65.2, 56.9, 52.1, 22.8, 20.7. HRMS: (M + Na) for $C_{21}H_{23}BrN_2O_7SNa$ calcd 549.03070, found 549.03051.

*(2R,3S,6S)-Methyl 6-((S)-Bromo(phenyl)methyl)-2,6-dimethyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate (**11e**).* Colorless oil, isolated yield 25 mg (20%). $[\alpha]^{22}_{D}$ = −78.6° (*c* 1.55, $CHCl_3$). R_f = 0.48 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3105.6, 2937.3, 1741.8, 1530.5, 1311.8, 1161.5, 1090.3, 1039.3, 852.7, 746.2, 736.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.27 (s, 3H), 3.59 (s, 3H), 3.75 (s, 2H), 4.12 (m, 2H), 5.04 (s, 1H), 7.33 (m, 5H), 7.99 (d, *J* = 8.7 Hz, 2H), 8.37 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.6, 150.1, 145.0, 136.6, 129.5, 128.6, 128.5, 128.0, 124.2, 77.9, 67.3, 62.3, 57.4, 52.5, 48.7, 21.3, 18.9. HRMS: (M + H) for $C_{21}H_{23}BrN_2O_7SH$ calcd 527.0482, found 527.0458.

*(3S,6R,7S)-Methyl 6-Bromo-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10f**).* White solid, mp 148−150 °C, isolated yield 235 mg (94%). $[\alpha]^{22}_{D}$ = −21.1° (*c* 0.75, $CHCl_3$). R_f = 0.45 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2955.5, 1745.6, 1530.5, 1349.3, 1100.9, 739.0. ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H), 3.72 (m, 2H), 4.21 (m, 2H), 4.37 (d, *J* = 10.2 Hz, 1H), 4.55 (dd, *J* = 7.2, 13.2 Hz, 1H), 5.06 (dd, *J* = 7.2, 10.5 Hz, 1H), 7.28 (m, 2H), 7.36 (m, 3H), 8.09 (d, *J* = 9.0 Hz, 2H), 8.40 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.3, 150.2, 145.3, 138.4, 129.0, 128.7, 128.5, 127.3, 124.4, 90.7, 69.6, 59.2, 52.7, 50.7, 50.1. HRMS: (M + Na) for $C_{19}H_{19}BrN_2O_7SNa$ calcd 520.99940, found 521.00099.

*(3S)-Methyl 6-Bromo-6-methyl-4-((4-nitrophenyl)sulfonyl)-1,4-oxazepane-3-carboxylate (**11g**).* Characterized from a 1.7:1 mixture of diastereomers. Yellow oil, isolated yield 77%. R_f = 0.40 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2956.0, 1745.4, 1529.9, 1348.9, 1162.6, 1090.9, 855.4, 768.8, 731.2. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 3H), 3.28 (m, 1.5H), 3.46 (d, *J* = 11.4 Hz, 1H), 3.59 (s, 1H), 3.62 (s, 2H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.99 (dd, *J* = 4.2, 12.6 Hz, 1H), 4.08−4.14 (m, 0.5H), 4.54−5.57 (m, 1H), 7.7.95 (d, *J* = 8.7 Hz, 2H), 8.36 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.7, 168.6, 150.2, 150.1, 144.7, 144.5, 128.6, 128.5, 124.2, 124.1, 72.1, 71.4, 62.8, 62.3, 54.6, 54.2, 52.8, 52.7, 48.5, 47.4, 38.7, 33.8, 24.2, 17.9. HRMS: (M + H) for $C_{14}H_{17}BrN_2O_7SH$ calcd 437.0013, found 436.9996.

*(3S)-Methyl 6-Bromo-7,7-dimethyl-4-((4-nitrophenyl)sulfonyl)-1,4-oxazepane-3-carboxylate (**10h**).* White solid, mp 113−115 °C, isolated yield 158 mg (>99%). $[\alpha]^{22}_{D}$ = −22.1° (*c* 0.95, $CHCl_3$). R_f = 0.44 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2957.2, 1747.0, 1530.3, 1349.0, 1158.2, 1088.0, 706.8. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.37 (s, 3H), 3.66 (s, 3H), 3.74 (dd, *J* = 10.2, 15.6 Hz, 1H), 3.97 (m, 3H), 4.11 (dd, *J* = 3.9, 13.2 Hz, 1H), 4.84 (t, *J* = 3.6 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 2H), 8.37 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.1, 145.2, 128.7, 128.6, 124.3, 78.7, 63.9, 59.4, 54.9, 52.7, 48.9, 25.4, 24.0. HRMS: (M + Na) for $C_{15}H_{19}BrN_2O_7SNa$ calcd 472.99940, found 472.99955.

*(3S,6S,7R)-Methyl 6-Bromo-7-methyl-4-((4-nitrophenyl)sulfonyl)-1,4-oxazepane-3-carboxylate (**10i**).* Colorless oil, isolated yield 48 mg (46%). $[\alpha]^{22}_{D}$ = −35.2° (*c* 1.65, $CHCl_3$). R_f = 0.42 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.8, 2925.4, 1745.2, 1530.3, 1313.8, 1160.9, 1103.9, 1089.8, 1008.2, 855.5, 738.7. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, *J* = 6.0 Hz, 3H), 3.55 (m, 3H), 3.60 (s, 3H), 3.80 (m, 1H), 4.10 (dd, *J* = 3.0, 15.6 Hz, 1H), 4.44 (dd, *J* = 6.6, 13.2 Hz, 1H), 4.93 (dd, *J* = 7.2, 10.2 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 8.37 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.3, 150.1, 145.3, 128.6, 124.2, 84.6, 68.9, 59.2, 52.6, 51.7, 59.9, 20.2. HRMS: (M + H) for $C_{14}H_{17}BrN_2O_7SH$ calcd 437.0013, found 437.0002.

*(3S)-Methyl 6-(1-Bromoethyl)-4-((4-nitrophenyl)sulfonyl)-morpholine-3-carboxylate (**11i**).* Characterized from a 1.2/1 mixture of diastereomers. Yellow oil. R_f = 0.35 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.5, 2956.1, 1745.2, 1530.4, 1349.2, 1104.0, 1090.0, 855.4, 773.4, 738.1. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, *J* = 6.0 Hz, 2H), 1.67−1.74 (m, 1H), 3.52−3.57 (m, 1.5H), 3.61 (s, 3H), 3.68 (s, 1H), 3.7−3.89 (m, 2H), 4.10 (dd, *J* = 2.7, 15.9 Hz, 1H), 4.44 (dd, *J* = 6.9, 13.2 Hz, 1H), 4.93 (dd, *J* = 6.9, 939 Hz, 0.5H), 7.94−8.04 (m, 2H), 8.36 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.3, 168.6, 150.7, 150.2, 145.3, 144.8, 128.9, 128.6, 124.3, 124.2, 84.6, 79.2, 78.5, 77.2, 68.9, 59.2, 54.8, 54.7, 52.8, 52.6, 51.7, 49.9, 46.8, 46.8, 21.9, 20.2. HRMS: (M + H) for $C_{14}H_{17}BrN_2O_7SH$ calcd 437.0013, found 436.9992.

*(3S,6R,7R)-Methyl 6-Bromo-6-methyl-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10j**).* Colorless oil, isolated yield 30 mg (25%). $[\alpha]^{22}_{D}$ = +7.9° (*c* 3.15, $CHCl_3$). R_f = 0.66 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.0, 2953.9, 1743.5, 1530.3, 1348.5, 1160.1, 1112.1 1021.6, 1011.5, 895.3, 855.1, 701.9. ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H), 3.38 (s, 3H), 3.64 (d, *J* = 10.8 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 4.53 (dd, *J* = 0.9, 15.6 Hz, 1H), 4.55 (d, *J* = 7.5 Hz, 1H), 4.59 (t, *J* = 7.5 Hz, 1H), 4.91 (dd, *J* = 7.5, 10.8 Hz, 1H), 7.35 (m, 3H), 7.43 (m, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 8.36 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 169.2, 150.1, 145.3, 136.7, 128.8, 128.7, 128.3, 127.5, 124.1, 94.1, 71.8, 66.5, 59.6, 56.5, 52.4, 22.8. HRMS: (M + NH_4) for $C_{20}H_{21}BrN_2O_7SNH_4$ calcd 530.0591, found 530.0567.

*(3S)-Methyl 6-(Bromo(phenyl)methyl)-6-methyl-4-((4-nitrophenyl)sulfonyl)morpholine-3-carboxylate(**11j**).* Colorless oil, isolated yield 20 mg (17%). $[\alpha]^{22}_{D}$ = −9.8° (*c* 1.50, $CHCl_3$). R_f = 0.53 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3106.0, 2953.7, 1746.9, 1530.5, 1311.9, 1164.3, 1089.3, 855.6, 759.4, 734.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 3H), 3.24 (d, *J* = 13.2 Hz, 1H), 3.62 (s, 3H), 4.01 (dd, *J* = 1.5, 12.3 Hz, 1H), 4.16 (dt, *J* = 4.2, 12.3 Hz, 1H), 4.31 (d, *J* = 13.5 Hz, 1H), 4.58 (d, *J* = 3.9 Hz, 1H), 5.53 (s, 1H), 7.32−7.49 (m, 5H), 7.057 (d, *J* = 8.7 Hz, 2H), 8.39 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.6, 150.2, 144.5, 136.9, 129.2, 128.9, 128.7, 128.3, 124.2, 75.9, 62.4, 54.6, 52.7, 52.5, 48.7, 21.8. HRMS: (M + H) for $C_{20}H_{21}BrN_2O_7SH$ calcd 513.0323, found 513.0294.

*(5a*R*,9a*R*)-3-Bromo-5-((4-nitrophenyl)sulfonyl)-2-phenyldecahydrobenzo[b][1,4]oxazepine (**10k**).* Characterized from a 2.0/1 mixture of diastereomers. *Major diastereomer*: colorless oil, isolated yield 267 mg (49%). R_f = 0.78 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2940, 1529.2, 1311.1, 1157.2, 1086.8, 1000.0, 728.2. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (m, 4H), 1.79 (m, 2H), 2.05 (m, 2H), 3.43 (dt, *J* = 3.9, 10.8 Hz, 1H), 3.66 (m, 3H), 4.26 (m, 2H), 6.95 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.26 (m, 3H), 8.14 (d, *J* = 9.0 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 150.0, 147.4, 139.3, 128.7, 128.4, 128.2, 127.1, 124.7, 88.4, 82.3, 77.4, 77.0, 76.6, 63.7, 51.4, 48.8, 33.8, 32.0, 24.7, 24.6. HRMS: (M + Na) for $C_{21}H_{23}BrN_2O_5SNa$ calcd 517.04087, found 517.04134. *Minor diastereomer*: characterized as a 2.0/1 mixture of diastereomers; yellow oil. R_f = 0.67 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2940.2, 1530.0, 1348.7, 1219.7, 1158.7, 1088.4, 855.3, 772.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.16−1.37 (br m, 4H), 1.74−1.82 (br m, 3H), 2.05 (m, 1.5H), 3.21−3.45 (br m, 2H), 3.67 (m, 0.5H), 3.74−3.82 (m, 1H), 4.03−4.11 (M, 0.5H), 4.28−4.39 (M, 2H), 4.66 (d, *J* = 9.6 Hz, 0.5H, 6.95 (m, 1H), 7.30−7.35 (m, 3H), 8.05 (d, *J* = 8.7 Hz, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 8.43 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 150.0, 149.8, 148.2, 147.4, 140.6, 139.3, 129.3, 128.7, 128.4, 128.3, 128.2, 128.2, 127.1, 127.1, 124.7, 124.5, 88.3, 82.3, 79.1, 77.7, 63.7, 58.5, 51.4, 51.3, 48.8, 42.2, 33.7, 32.0, 31.3, 30.0, 26.1, 24.7, 24.6, 24.4. HRMS: (M + K) for $C_{21}H_{23}BrN_2O_5SK$ calcd 533.0143, found 533.0118.

*(3R,6R,7S)-6-Bromo-3-ethyl-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane (**10l**).* Colorless oil, isolated yield 160 mg (>99%). $[\alpha]^{22}_{D}$ = +54.0° (*c* 0.80, $CHCl_3$). R_f = 0.60 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2968.0, 1529.2, 1347.7, 1155.6, 1087.8, 907.8, 678.9. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J* = 9.0 Hz, 3H), 1.57 (br m, 2H), 3.39 (dd, *J* = 9.3, 12.0 Hz, 1 H), 3.55 (dd, *J* = 12.0, 15.6 Hz, 1H), 3.81 (dt, *J* = 3.6, 10.2 Hz, 1H), 4.23 (d, *J* = 9.9 Hz, 1H), 4.29 (m, 2H), 4.38 (dd, *J* = 3.3, 13.2 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 2H), 7.25 (m, 3H), 8.14 (d, *J* = 8.7 Hz, 2H), 8.42 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (75 MHz): δ 150.0, 147.5, 138.8, 128.8, 128.6, 128.3, 126.8, 124.6, 90.5, 72.9, 59.1,

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50.0, 48.5, 24.5, 10.1. HRMS: (M + Na) for $C_{19}H_{21}BrN_2O_5SNa$ calcd 491.02522, found 491.02551.

*(2R,6S,7R)-6-Bromo-2-methyl-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane (**10m**).* White solid, mp 167−171 °C, isolated yield 400 mg (47%). $[\alpha]^{22}_D = -29.4°$ (*c* 0.85, $CHCl_3$). R_f = 0.62 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2926.7, 1530.0, 1311.3, 1163.6, 1087.0, 736.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.3 Hz, 3H), 2.78 (dd, *J* = 9.9, 13.8 Hz, 1H), 3.36 (dd, *J* = 9.6, 13.8 Hz, 1H), 3.85 (dd, *J* = 3.6, 14.1 Hz, 1H), 3.99 (m, 1H), 4.35 (m, 2H), 4.81 (d, *J* = 9.3 Hz, 1H), 7.37 (m, 5H), 8.03 (d, *J* = 9.0 Hz, 2H), 8.41 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 150.2, 145.1, 138.6, 138.5, 128.6, 128.2, 127.3, 124.6, 80.0, 71.1, 54.9, 54.8, 49.4, 18.2. HRMS: (M + H) for $C_{18}H_{19}BrN_2O_5SH$ calcd 454.0198, found 454.0174.

*(2R,6R,7S)-6-Bromo-2-methyl-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane (**10m′**).* Characterized as a 1.2/1 mixture of diastereomers. Yellow oil. R_f = 0.56 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 3105.5, 2927.4, 1541.1, 1347.7, 1160.9, 1084.7, 907.1, 775.0, 731.3, 696.0. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.3 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 1H), 2.78 (dd, *J* = 10.2, 14.1 Hz, 0.7H), 3.08 (dd, *J* = 10.5, 12.6 Hz, 0.3H), 3.37 (dd, *J* = 9.9, 13.8 Hz, 1H), 3.59 (dd, *J* = 3.6, 12.6 Hz, 0.3H). 3.85 (dd, *J* = 3.6, 14.7 Hz, 0.7H), 3.94 (d, *J* = 5.1 Hz, 0.7H), 3.97−4.04 (M, 0.6H), 4.16 (m, 0.3H), 4.29−4.42 (m, 1.4H), 4.59 (d, *J* = 9.6 Hz, 0.3H), 4.81 (d, *J* = 9.3 Hz, 0.7H), 1.33−7.37 (m, 5H), 8.02−8.08 (m, 2H), 8.39−8.43 (m, 2H). ^{13}C NMR (75 MHz): δ 150.2, 150.2, 145.1, 144.7, 139.6, 138.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.3, 127.0, 124.6, 87.8, 79.9, 71.1, 56.5, 54.9, 54.8, 53.8, 53.5, 49.5, 19.5, 18.2. HRMS: (M + H) for $C_{18}H_{19}BrN_2O_5SH$ calcd 454.0198, found 454.0181.

*(2S,3S,6R,7S)-Methyl 6-Bromo-2-methyl-4-((4-nitrophenyl)-sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10n**).* White solid, mp 156−159 °C, isolated yield 71 mg (25%). $[\alpha]^{22}_D$ = −48.2° (*c* 0.75, $CHCl_3$). R_f = 0.66 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2954.3, 1742.5, 1530.4, 1347.7, 1154.6, 1050.0, 901.8, 698.6. ^1H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.6 Hz, 3H), 3.59 (s, 3H), 3.97 (dq, *J* = 2.1, 6.6 Hz, 1H), 4.30 (m, 2H), 4.60 (dt, *J* = 2.4, 9.6 Hz, 1H), 4.64 (d, *J* = 2.1 Hz, 1H), 4.98 (d, *J* = 9.6 Hz, 1H), 7.45 (m, 5H), 7.98 (d, *J* = 8.7 Hz, 2H), 8.38 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 161.3, 145.0, 136.2, 128.9, 128.7, 128.6, 128.3, 127.8, 124.4, 83.0, 73.4, 62.0, 52.2, 50.5, 47.5, 19.8. HRMS: (M + Na) for $C_{20}H_{21}BrN_2O_7SNa$ calcd 535.01505, found 535.01630.

*(2S,3S,6S,7R)-Methyl 6-Bromo-2-methyl-4-((4-nitrophenyl)-sulfonyl)-7-phenyl-1,4-oxazepane-3-carboxylate (**10n′**).* White solid, mp 174−177 °C, isolated yield 48 mg (17%). $[\alpha]^{22}_D$ = −29.2° (*c* 0.65, $CHCl_3$). R_f = 0.57 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2953.6, 1743.2, 1531.3, 1311.0, 1166.0, 737.7. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, *J* = 6.9 Hz, 3H), 3.66 (s, 3H), 4.01 (dd, *J* = 6.9, 15.3 Hz, 1H), 4.38 (dt, *J* = 2.1, 6.6 Hz, 1H), 4.44 (dq, *J* = 2.4, 6.6 Hz, 1H), 4.60 (m, 2H), 4.79 (d, *J* = 6.6 Hz, 1H), 7.31 (m, 5H), 8.03 (d, *J* = 9.0 Hz, 2H), 8.38 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 168.9, 144.8, 140.1, 128.7, 128.6, 128.5, 126.4, 124.4, 124.3, 87.8, 75.6, 64.1, 54.4, 52.2, 49.2, 19.6. HRMS: (M + Na) for $C_{20}H_{21}BrN_2O_7SNa$ calcd 535.01505, found 535.01629

*6-Bromo-4-((4-nitrophenyl)sulfonyl)-7-phenyl-1,4-oxazepane (**10o**).* White solid, mp 157−159 °C, isolated yield 119 mg (>99%). R_f = 0.42 (7/3 Hex/EtOAc). IR (film, cm^{-1}): 2926.6, 1529.0, 1309.5, 1163.4, 1087.2, 1025.7, 855.0, 737.1. ^1H NMR (300 MHz, $CDCl_3$): δ 3.46 (dt, *J* = 2.7, 12.6 Hz, 1H), 3.63 (dt, *J* = 5.1, 10.8 Hz, 1H), 3.79 (m, 2H), 4.09 (dd, *J* = 3.9, 15.0 Hz, 1H), 4.19 (m, 2H), 4.50 (d, *J* = 9.3 Hz, 1H), 7.33 (m, 5H), 8.07 (d, *J* = 9.0 Hz, 2H), 8.42 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 150.2, 144.8, 139.1, 128.7, 128.5, 128.4, 127.0, 124.6, 88.8, 69.6, 53.3, 52.5, 50.1. HRMS: (M + Na) for $C_{17}H_{17}BrN_2O_5SNa$ calcd 462.99392, found 462.99495.

*(2R,3S,5aS,10aR)-3-Bromo-5-((4-nitrophenyl)sulfonyl)-2-phenyl-3,4,5,5a,10,10a-hexahydro-2H-indeno[2,1-b][1,4]oxazepine (**10p**).* White solid, mp 158−161 °C, isolated yield 244 mg (98%). $[\alpha]^{22}_D$ = −45.2° (*c* 0.55, $CHCl_3$). R_f = 0.68 (7/3 Hex/EtOAc). IR (neat, cm^{-1}): 2935.5, 1529.9, 1349.0, 1164.1, 1090.9, 999.0, 906.9, 808.9, 678.9. ^1H NMR (300 MHz, $CDCl_3$): δ 3.21 (m, 3H), 4.03 (d, *J* = 9.9 Hz, 1H), 4.10 (dq, *J* = 4.2, 10.8 Hz, 1H), 4.26 (dd, *J* = 4.2, 15.0 Hz, 1H), 4.93 (t, *J* = 7.5 Hz, 1H), 5.73 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 1.5, 6.6 Hz, 2H), 7.30 (m, 6H), 8.22 (d, *J* = 9.0 Hz, 2H), 8.47 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (75 MHz): δ 146.7, 140.8, 140.3, 136.5, 129.6, 128.6, 128.5, 128.3, 128.0, 126.7, 125.2, 124.7, 124.6, 79.8, 77.3, 65.0, 49.9, 49.3, 36.7. HRMS: (M + Na) for $C_{24}H_{21}BrN_2O_5SNa$ calcd 551.02522, found 551.02607.

Computational Methods. *General Considerations.* The quantum mechanical calculations were performed using density functional theory (DFT), more specifically the M06 functional (restricted Hartree−Fock) and the diffuse 6-31G(d,p) basis set. Certain convergence parameters were loosened slightly, due to the degrees of freedom in the molecules and difficulties acquiring a minimum state. No frequency analysis was required for this work. All calculations were carried out in a PCM (polarizable continuum model) solvent model of tetrahydrofuran. The M06 calculations were performed using GAMESS-US v.Aug2011-64bit.

Butene NBS Study. The modeling of the reaction of NBS with *trans*-butene involved the exploration of two reaction coordinates. We systematically varied the length of the C−Br forming bonds along with the length of the N−Br breaking bonds. The energies of these systems were compared to the sum of the reactants and plotted in 3D.

*Conformational Analysis of **9c**.* The conformational search was done in a stepwise fashion. First, molecular mechanics (MM3* as a forcefield, MacroModel, Schrödinger) was used to generate a set of over 50 stable conformations. Then, the semiempirical function PM3 (MOPAC) was used to minimize the energy of all generated conformations. Upon sorting these more accurate energies, we selected the top 5 structures for the formation of each of the *R* and the *S* conformers and finally optimized their structure by DFT (basis set/functional mentioned above).

■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, and a CIF file giving ^1H and ^{13}C NMR spectra for all compounds, COSY, NOESY, HMBC, HSQC 2D spectra for compound **10a**, crystallographic data for compound **10e**, and Cartesian coordinates of the strucures in Figures 5 and 6 (butene/NBS and compounds **9c**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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