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Aziridines from Intramolecular Alkene Aziridination of Sulfamates: Reactivity toward Carbon Nucleophiles. Application to the Synthesis of Spisulosine and Its Fluoro Analogue

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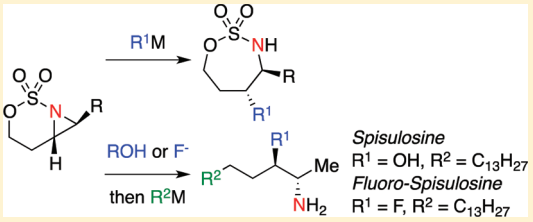
Supporting Information

ABSTRACT: Catalytic intramolecular alkene aziridination of sulfamate is an emerging methodology for the asymmetric synthesis of chiral functionalized amines involving the formation of bicyclic aziridines. This study demonstrates the ability of the latter to undergo ring-opening with various carbon nucleophiles: Grignard reagents, lithium salts of terminal alkynes, dithiane, malonate. These S_N2-type reactions occur with high levels of regio- and chemoselectivity to generally afford seven-membered cyclic sulfamidates in good yields. Carbon nucleophiles have also been found to react with these sulfamidates provided that the sulfamate ester has been previously activated by introduction of a tosyl substituent on the NH group. The versatility of this strategy has been illustrated with the syntheses of spisulosine and its fluoro analogue.



INTRODUCTION

The ability of aziridines to undergo ring-opening with a wide range of nucleophiles offers unique opportunities for the preparation of substituted nitrogen-containing products that are ubiquitous in nature or medicinal chemistry.[1] As a result, these heterocycles are receiving increasing attention, and among the various reactions available for their preparation, catalytic olefin aziridination stands as one of the most attractive methods. The simple insertion of a metallanitrene into a π-bond provides an efficient straightforward access to aziridines,[2] and the variety of alkenes which have been found to react makes this transformation a versatile tool to generate molecular diversity. Several nitrogen reagents such as azides, haloamines, and *N*-sulfonyloxycarbamates have proved to be efficient nitrene precursors,[3] but the most significant results have been reported with species produced with iodine(III) oxidants. Initially based on the use of preformed iminoiodanes ($PhI{=}NSO_2R$),[2a,4] the synthetic value of catalytic nitrene transfer has then been improved with the discovery of one-pot procedures allowing in situ formation of these reagents from sulfonamides, carbamates, and sulfamates.[5] In parallel, a growing number of metals[6] has been found suitable to catalyze alkene aziridination, with copper[7] and rhodium[8] complexes remaining the catalysts of choice in terms of enantioselective catalysis[9] and synthetic applications.[10]

The search for strategies involving intramolecular metallanitrene delivery has culminated in processes that occur with high levels of chemo- and stereocontrol. They give access to new heterocyclic scaffolds that offer unique opportunities as highlighted in several successful total syntheses of complex natural alkaloids achieved by the group of Du Bois.[11] We have been extensively involved in these methodological developments with initial studies devoted to the intramolecular catalytic aziridination of sulfonamides.[12] However, in comparison, the application of the reaction conditions to sulfamates affords much more versatile heterocycles. These are ambident synthetic intermediates that could undergo successive regioselective nucleophilic displacements leading, after acidic hydrolysis, to substituted deprotected amines (Scheme 1).[13,14]

Surprisingly, whereas the reactivity of bicyclic aziridines of type **1** and their corresponding sulfamidates **2** with heteroatom nucleophiles has been documented, the use of carbon reagents has been investigated very rarely.[15] Particularly, in the case of compounds **2**, the limited number of examples involving a C-nucleophile reported until now generally occur under rather harsh conditions and with low to moderate yields. In this context, Kumada coupling starting from a phenol-derived sulfamate appears to be the sole reaction of broad application described so far.[16] These observations prompted us to study the nucleophilic ring-opening of either sulfamate-derived aziridines or seven-membered cyclic sulfamidates, with various C-reagents in order to broaden the scope of the methodology. The results of our investigations as well as their application to the synthesis of spisulosine and its fluoro analogue are described therein.

RESULTS AND DISCUSSION

Intramolecular alkene aziridination of sulfamates, easily prepared by simple sulfamoylation of the corresponding alcohols using a combination of chlorosulfonyl isocyanate and formic acid,[17] is catalyzed by either copper(I) salts and iodosylbenzene[13] or rhodium(II) complexes in the presence of $PhI(OAc)_2$ and MgO.[14] Both metals efficiently mediate the intramolecular

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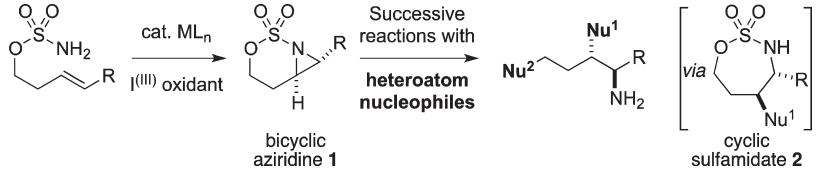
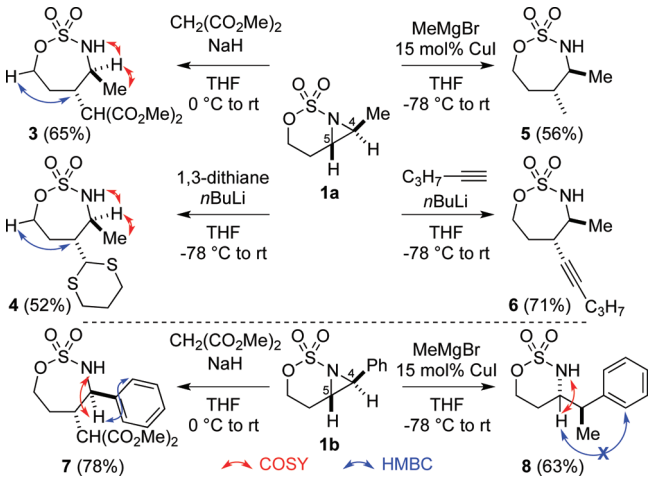
Scheme 1. Catalytic Aziridination of Sulfamates and Nucleophilic Ring-Opening



Scheme 2. Ring-Opening of Aziridines 1a and 1b with C-Nucleophiles



nitrene addition affording bicycle-[4.1.0] and -[5.1.0] systems in good yields (generally greater than 70%). The hallmark of this reaction, which tolerates the presence of various functional groups, is its stereospecificity with respect to olefin geometry, i.e., *trans*- and *cis*-alkenes give rise to *trans*- and *cis*-aziridines, respectively. Enantioselective processes have also been reported though only with chiral copper salts so far, allowing the formation of aziridines with ees of up to 84%.[13b] For the purpose of our study, application of the previously published procedure[13a] allowed us to isolate cyclic sulfamates **1a** and **1b** in 72% and 78% yield, respectively.

Reactivity with Carbon Nucleophiles. Heterocycles of type **1** display several electrophilic sites likely to react with a nucleophile: both carbon atoms of the aziridine, the carbon atom substituted by the sulfamoyl group, and the sulfur center. Fundamentally, Du Bois[14b] and our group[13a] have shown that nucleophilic displacement occurs chemo- and regioselectively at C5 position to afford seven-membered cyclic sulfamidates of type **2** with nitrogen-, oxygen-, and sulfur-derived reagents. On the basis of these results, we decided to document the reaction of **1** with carbon nucleophiles, particularly with nonstabilized reagents, for the formation of C−C bonds. We were thus very pleased to observe that heterocycles **1** react smoothly in the presence of various C-nucleophiles to afford the ring-opened products with yields in the 52−78% range (Scheme 2).

In the case of aziridine **1a**, addition of anions generated from dimethyl malonate, 1,3-dithiane, or pentyne proceeds with complete regio- and stereocontrol at C-5, and so does the reaction with methylmagnesium bromide. The regioselectivity, identical to that observed in previous work, was demonstrated by HMBC experiments, which show a correlation between H7 and the carbon atom bearing the incoming nucleophile hence C5.[18] However, contrary to what was initially reported, we have noticed that the substitution pattern on the sulfamate has an influence on the sense of the addition. A reversal of selectivity has thus been observed in the case of aziridine **1b**. Whereas addition of malonate provides the expected seven-membered cyclic sulfamidate **7**, methylmagnesium bromide attacks at the benzylic site, leading to oxathiazinane **8** in good yield. Evidence for this difference in reactivity was provided by NMR experiments: COSY spectra allowed us to unambiguously identify the hydrogen α to the NH for both compounds. But correlation between the latter and the ortho-carbons of the phenyl group was detected by HMBC only in the case of the seven-membered derivative **7**.[19] Formation of compounds **3**−**7** has been rationalized by Du Bois who has invoked a higher coefficient of the LUMO orbital at C5.[14b] Nucleophilic attack at C4 would also be disfavored by torsional strain in the transition state while X-ray studies and modeling calculations suggest a slightly shorter hence weaker C5−N bond in aziridines **1**. In the case of **1b**, introduction of a phenyl group did not reverse the regioselectivity with azide or thiophenol which can be considered as soft nucleophiles.[14b] Therefore, the result obtained with methylmagnesium bromide, a rather hard nucleophile, might be attributed to a ring-opening at the benzylic site which would be under charge control.[20]

The chemoselectivity of the aziridine ring-opening offers the opportunity to introduce a second nucleophile because the other electrophilic sites have been left intact. Nucleophilic ring-opening of five- and six-membered cyclic sulfamates is well documented,[15,21] but less attention has been paid to seven-membered analogues. As initially demonstrated by Du Bois and our group, such a process is facilitated by introduction of an electron-withdrawing substituent on the sulfamidate nitrogen prior to ring-opening. Cbz or Boc groups have thus been found appropriate to activate the sulfamate.[13a,14b] However, these protecting groups proved not to be robust enough in the presence of a carbon nucleophile because addition preferentially takes place at the carbamoyl center, affording the starting NH-free cyclic sulfamidates. This observation led us to consider *N*-(sulfonyl)sulfamates as a viable alternative. Nosyl derivatives were first investigated though unsuccessfully regardless of the reagents used (Grignard reagents, lithium alkynides, etc.). The reactions generally provide complex mixtures as a consequence of the preferred nucleophilic attack at the sulfur center. Introduction of the less electrophilic tosyl group thus allowed us to find suitable conditions to perform ring-opening of a cyclic sulfamate of type **2**. Within the aim of synthesizing spisulosine (vide infra), it was decided to carry out these studies with the *N*-(tosyl)sulfamate **9** (Scheme 3).

Nucleophilic substitution proceeds with the soft nucleophiles diethyl malonate or dithiane to afford the expected products **10** and **11** in 34% and 48% yield, respectively. Comparable yields of 28% and 32% are observed with reactions involving 3 equiv of

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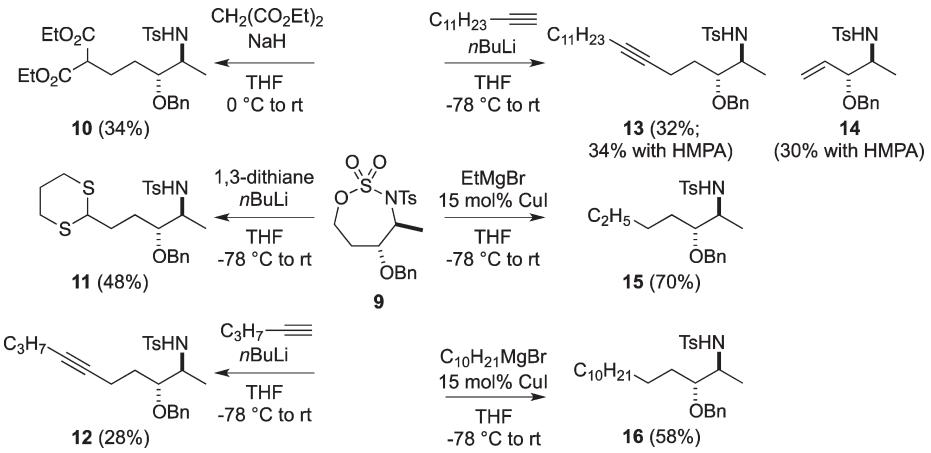
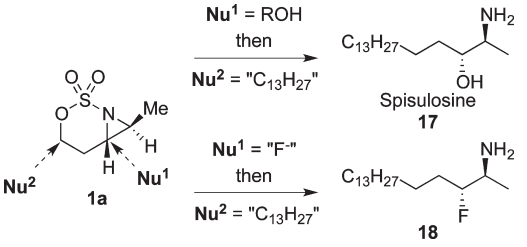
Scheme 3. Ring-Opening of Sulfamate 9 with C-Nucleophiles



lithiated pent-1-yne and tridecyne. Attempts to increase the reactivity of these reagents by addition of HMPA did not really improve the conversion though compound **13** was obtained with a similar yield of 34% using only 1.2 equiv of lithium tridecynide. This somewhat disappointing result can be explained by the formation of a side product, the unsaturated amino alcohol **14**, which is isolated in 30% yield. The latter would be generated by elimination of the sulfamate induced by the alkynide, the basicity of which would be exacerbated by HMPA. Finally, the best results were found with Grignard reagents in the presence of a substoichiometric amount of copper iodide. Good conversions are therefore achieved using commercially available ethyl- and decylmagnesium bromide, leading to the isolation of the expected products **15** and **16** in 70% and 58% yield, respectively.

Synthesis. Having demonstrated the capacity to transform aziridines **1** by sequential addition of various carbon and heteroatom nucleophiles into substituted amines, our studies were then aimed at applying the intramolecular aziridination of sulfamates to the total synthesis of natural bioactive compounds. Spisulosine [(2*S*,3*R*)-2-amino-3-octanedecanol **17**] was thus regarded as a relevant target in this context. This marine natural product was first isolated from the clam *Spisulosa polynyma* and displays potent antitumoral activities against several cancer cell lines and has entered clinical trials for the treatment of solid tumors.[22] Also worthy of note is the mechanism of action because spisulosine is a potent apoptotic inducer as a consequence of intracellular ceramide accumulation and PKCS activation.[23] Not surprisingly, its biological activity as well as its rather simple structure have triggered the interest of several synthetic chemists.[24] Various efficient strategies, generally relying on the use of the chiral pool, have therefore been reported and only recently has the first catalytic asymmetric synthesis of spisulosine, based on the application of Sharpless dihydroxylation, been described by Panda et al.[24g] By comparison, one of the features of our approach involving catalytic asymmetric aziridination of sulfamates is its versatility. In addition to the total synthesis, it provides the opportunity to carry out SAR studies by simple choice of the nucleophiles added sequentially to the aziridine **1a** (Scheme 4). Therefore, while we obviously planned to successively introduce an alcohol and then a C-nucleophile as part of the preparation of **17**, we also decided to target the fluoro analogue **18**.

Scheme 4. Synthetic Strategy for the Preparation of Spisulosine and Its Fluoro Analogue



Copper-catalyzed asymmetric alkene aziridination mediated by PhIO and applied to sulfamate **19** leads to aziridine **1a** in 78% yield and 80% ee (Scheme 5).[13b] The latter can then be transformed efficiently by reaction with benzyl alcohol in the presence of boron trifluoride etherate to afford the seven-membered sulfamidate **20** as a white solid, which can be recrystallized to give enantiomerically pure material. X-ray analysis thus allowed us to confirm the absolute configuration, namely 4*S*,5*R*, that matches the stereochemistry of the natural product. Installation of an *N*-tosyl group is finally carried out by simple protection in the presence of sodium *tert*-butylate in DME.

Similar results were obtained when aziridine **1a** was subjected to nucleophilic ring-opening with TBAF in THF: reaction takes place at C5 to give the fluoro derivative **21** isolated with a good yield of 75%. A subsequent tosylation step then leads to a solid, the recrystallization of which affords optically pure **22**. X-ray crystallography analysis, once again, allowed us to secure the regio- and stereochemistry of the aziridine ring-opening.

We next capitalized on the ability of cyclic sulfamates to undergo reactions with carbon nucleophiles to introduce the lipophilic alkyl chain. As previously demonstrated, the lithiated anion of tridecyne reacts with **9** to give the expected product **13** though with a modest yield of 34% (Scheme 6).[25] Removal of the *N*-tosyl group from nitrogen then proceeds via a two-step procedure involving carbamoylation with a Boc group prior to reductive cleavage using magnesium in methanol under sonication.[26] Hydrogenolysis of the resulting compound **23** with palladium on charcoal efficiently induces reduction of the triple bond and concomitant removal of the benzyl group. Finally, acidic hydrolysis of the Boc group affords the hydrochloride salt of

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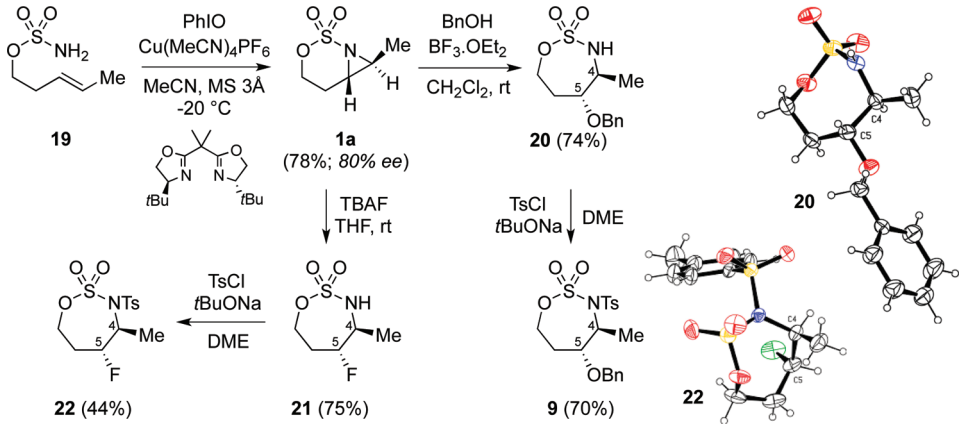
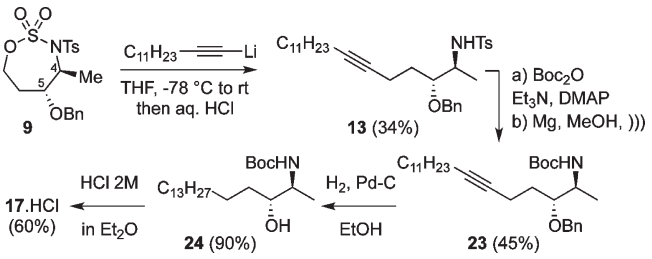
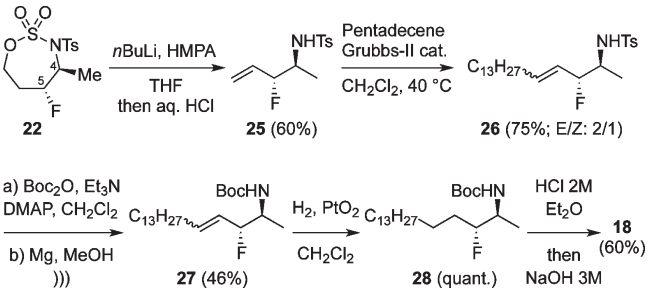
Scheme 5. Preparation of *N*-(Tosyl)sulfamidates 9 and 22



Scheme 6. Final Steps for the Synthesis of Spisulosine 17



Scheme 7. Final Steps for the Synthesis of the Fluoro Derivative 18



spisulosine **17**. Isolation of the latter was confirmed by physical and spectroscopic data that were comparable to those previously reported.[24]

In contrast, starting from the fluoro intermediate **22**, application of the same strategy proved unsuccessful. Thus, contrary to the previous case, reaction with lithium alkynides only affords the vinylic fluoro derivative **25** in 60% yield (Scheme 7). This result can be explained by the presence of the fluorine that increases the lability of the sulfamate, thereby favoring its elimination under basic conditions. This was confirmed by the reaction performed with *n*BuLi and HMPA that gives the same product with the same yield. Nevertheless, alkene **25** was considered as a useful intermediate. Inspired by the previous studies of the Chemla group,[24c] Grubbs-II-catalyzed cross-metathesis was found to proceed nicely to give the alkene **26** as a mixture of isomers in a 2:1 ratio in favor of the (*E*)-isomer. Finally, an identical sequence of deprotection reactions applied to **26** led us to isolate the fluoro analogue of spisulosine **18**. Cytotoxic properties were then evaluated on various cancer cell lines at the ICSN. While the potent biological activity of spisulosine has been confirmed on KB, HCT116, and HL60 cells (IC_{50} in the 100 nM range), the fluoro derivative **18** has been found completely inactive even at micromolar concentrations.

In conclusion, copper-catalyzed intramolecular asymmetric aziridination of sulfamates is a versatile method for the synthesis of optically pure substituted amines as highlighted by its application to spisulosine and its fluoro analogue. The methodology involves the formation of bicyclic aziridines displaying several electrophilic sites, the relative reactivity of which can be nicely controlled. Importantly, this work has demonstrated that chemoselective sequential addition of different carbon nucleophiles can be achieved. Application of this strategy to the asymmetric total synthesis of natural nitrogen-containing products is in progress in our group.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Bicyclic Aziridines 1a and 1b. A solution of $[Cu(MeCN)_4]PF_6$ (5 mol %) in MeCN was stirred under argon at room temperature for 30 min in the presence of 4 Å molecular sieves. The appropriate sulfamate (1 equiv) dissolved in MeCN and PhIO (1.5 equiv) were then sequentially added. The mixture was stirred for 48 h. After completion of the reaction (monitored by TLC), the mixture was filtered through a pad of Celite and concentrated. The products were purified by flash chromatography to afford the desired aziridine in racemic form.

*trans-7-Methyl-3-oxa-2-thia-1-azabicyclo[4.1.0]heptane 2,2-Dioxide (**1a**).* Prepared following the general procedure using $Cu(MeCN)_4PF_6$ (52 mg, 0.091 mmol), PhIO (600 mg, 2.7 mmol), the sulfamate (300 mg, 1.8 mmol), and MeCN (10 mL). Purification by flash chromatography with heptane/EtOAc (60/40) affords compound **1a** as an oil (72%). R_f = 0.15 (heptane/EtOAc 50/50); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.63 (ddd, 1H, J = 12.7, 6.4 and 6.1), 4.37 (ddd, 1H, J = 12.2, 6.4 and 6.3), 2.93 (m, 2H), 2.38 (m, 1H), 2.25 (m, 1H), 1.35 (d, 3H, J = 5); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 68.6 (CH_2), 48.8 (CH), 42.9 (CH), 19.0 (CH_2), 17.1 (CH_3); IR (Neat): ν = 2977, 2358, 1445, 1359, 1182, 780 cm^{-1}; HRMS (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z

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calculated for $C_5H_9NO_3S$: (M + Na) calcd = 186.0201, found = 186.0206.

The enantioenriched aziridine **1a** (78%, 80% ee) was prepared by using 5.5 mol % of (*S*,*S*)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) according to the procedure previously described in the literature.[13b] Enantiomeric excess was determined by chiral HPLC (chiral column AD, hexane/*i*-PrOH/Et_3N 95/5/0.1) after ring-opening of aziridine with $BnNH_2$.

*trans-7-Phenyl-3-oxa-2-thia-1-azabicyclo[4.1.0]heptane 2,2-Dioxide (**1b**).* Prepared following the general procedure using $Cu(MeCN)_4PF_6$ (52 mg, 0.091 mmol), PhIO (600 mg, 2.7 mmol), the sulfamate (405 mg, 1.8 mmol), and MeCN (10 mL). Purification by flash chromatography with heptane/EtOAc (60/40) affords compound **1b** as an oil (78%). R_f = 0.28 (heptane/EtOAc 60/40); mp 94−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.32−7.19 (m, 5H), 4.70 (dt, 1H, *J* = 11.6, and 6.8), 4.46 (dt, 1H, *J* = 11.5 and 6.4), 3.80 (d, 1H, *J* = 4.4), 3.18 (dq, 1H, *J* = 4.6 and 3.2), 2.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 134.2 (C quat), 128.8 (4 CHar), 126.3 (CHar), 68.8 (CH_2), 50.4 (CH), 47.8 (CH), 18.8 (CH_2); IR (Neat): ν = 2985, 1497, 1373, 1357, 1243, 1180, 1054, 955, 905, 693 cm^{-1}; HRMS (TOF MS ES$^+$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_{10}H_{11}NO_3S$: (M + Na) calcd = 248.0357, found = 248.0337.

(4R,5R*)-Dimethyl 2-(4-Methyl-2,2-dioxo-1,2,3-oxathiazepan-5-yl)malonate (**3**).* Dimethyl malonate (145 μL, 1.2 mmol, 2 equiv) was added to a suspension of NaH (50 mg, 1.2 mmol, 60% in oil, 2 equiv) in THF (2 mL) at 0 °C under argon. After 15 min of stirring, aziridine **1a** (100 mg, 0.6 mmol, 1 equiv) was added and the mixture was stirred 12 h at room temperature before being quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (60/40) to yield a colorless oil (65%). R_f = 0.5 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 5.30 (d,1H, *J* = 8.8), 4.28 (ddd, 2H, *J* = 5.6, 3.8 and 1.3), 3.72 (s, 6H), 3.59 (d, 1H, *J* = 4.3), 3.50−3.35 (m, 1H), 2.42 (ddd, 1H, *J* = 13.8, 8.8 and 3.7), 2.14−2.07 (m, 2H), 1.31 (d, 3H, *J* = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 168.8 (C quat), 168.1 (C quat), 69.3 (CH_2), 52.9 (CH), 52.8 (CH_3), 52.7 (CH_3), 51.3 (CH), 45.3 (CH), 30.3 (CH_2), 20.0 (CH_3); IR (Neat): ν = 3283, 2936, 1730, 1434, 1345, 1173, 1122, 1086, 974, 913, 746 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_{10}H_{17}NO_7S$: (M + H) calcd = 296.0804, found = 296.0811.

(4R,5S*)-5-(1,3-Dithian-2-yl)-4-methyl-1,2,3-oxathiazepane 2,2-Dioxide (**4**).* *n*-BuLi in hexane (770 μL, 1.2 mmol, 2 equiv) was added to a solution of dithiane (147 mg, 1.2 mmol, 2 equiv) in THF (2 mL) under argon at −78 °C. After 15 min, aziridine **1a** (100 mg, 0.6 mmol, 1 equiv) was added. The solution was stirred for 15 min at −78 °C, 15 min at 0 °C, and 45 min at room temperature. The mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (60/40) to yield an amorphous yellow solid (52%). R_f = 0.63 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 5.06 (d, 1H, *J* = 8.3), 4.38−4.24 (m, 2H), 4.21 (d, 1H, *J* = 3.8), 3.58 (qdd, 1H, *J* = 8.7, 6.7 and 4.1), 2.97 (ddd, 1H, *J* = 14.5, 12.3 and 2.6), 2.89−2.80 (m, 3H), 2.25−2.20 (m, 5H), 1.38 (d, 3H, *J* = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 69.4 (CH_2), 51.6 (CH), 50.9 (CH), 50.7 (CH), 31.4 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 25.9 (CH_2), 19.8 (CH_3); IR (Neat): ν = 3305, 3017, 2894, 1454, 1423, 1344, 1214, 1178, 907, 666 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_9H_{17}NO_3S_3$: (M + Na) calcd = 306.0279, found = 306.0283.

(4R,5S*)-4,5-Dimethyl-1,2,3-oxathiazepane 2,2-Dioxide (**5**).* MeMgBr in ether (410 μL, 1.2 mmol, 2 equiv) was added to a suspension of CuI (18 mg, 0.09 mmol, 0.15 equiv) in THF (2 mL) under an atmosphere of argon at −78 °C. After 20 min of stirring, aziridine **1a** (100 mg, 0.6 mmol, 1 equiv) was added and the solution was stirred for 15 min at −78 °C and 45 min at 0 °C. The mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (60/40) to yield a white solid (56%). R_f = 0.54 (heptane/EtOAc 60/40); mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.78 (d, 1H, *J* = 9.5), 4.33−4.24 (m, 1H), 4.21 (tt, 1H, *J* = 11.6 and 3.2), 3.10 (ddt, 1H, *J* = 15.8, 9.5 and 6.6), 1.92−1.74 (m, 2H), 1.73−1.59 (m, 1H), 1.21 (d, 3H, *J* = 6.8), 0.89 (d, 3H, *J* = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 69.6 (CH_2), 54.5 (CH), 41.3 (CH), 37.1 (CH_2), 20.2 (CH_3), 19.4 (CH_3); IR (Nujol): ν = 3266, 2958, 1334, 1168, 1121, 971, 746 cm^{-1}; HRMS: (TOF MS ES$^-$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_6H_{13}NO_3S$: (M − H) calcd = 178.0538, found = 178.0538.

(4R,5R*)-4-Methyl-5-(pent-1-yn-1-yl)-1,2,3-oxathiazepane 2,2-Dioxide (**6**).* *n*-BuLi in hexane (770 μL, 1.2 mmol, 2 equiv) was added to a solution of 1-pentyne (121 μL, 1.2 mmol, 2 equiv) in THF (2 mL) under an atmosphere of argon at −78 °C. After 20 min of stirring, azridine **1a** (100 mg, 0.6 mmol, 2 equiv) was added and the solution was stirred for 15 min at −78 °C, 45 min at 0 °C, and 12 h at room temperature. The mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (60/40) to yield a yellow solid (71%). R_f = 0.79 (heptane/EtOAc 60/40); mp 76−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.91 (d,1H, *J* = 8), 4.24−4.11 (m, 2H), 3.29 (ddt, 1H, *J* = 13.9, 6.9 and 8.2), 2.47−2.38 (m, 1H), 2.15−1.90 (m, 2H), 1.99 (dt, 2H, *J* = 6.9 and 2.1), 1.35 (q, 2H, *J* = 7.2), 1.29 (d, 3H, *J* = 6.8), 0.81 (t, 3H, *J* = 7.3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 84.5 (C quat), 79.4 (C quat), 68.4 (CH_2), 53.0 (CH), 39.1 (CH), 34.5 (CH_2), 22.2 (CH_2), 20.6 (CH_2), 19.6 (CH_3), 13.4 (CH_3); IR (Neat): ν = 3263, 2964, 1437, 1341, 1170, 964, 912, 752 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_{10}H_{17}NO_3S$: (M + Na) calcd = 254.0827, found = 254.0839.

(4R,5S*)-Dimethyl 2-(2,2-Dioxo-4-phenyl-1,2,3-oxathiazepan-5-yl)malonate (**7**).* Dimethyl malonate (47 μL, 0.4 mmol, 2 equiv) was added to a suspension of NaH (20 mg, 0.5 mmol, 60% in oil, 2.5 equiv) in THF (1 mL) at 0 °C under an atmosphere of argon. After 15 min of stirring, aziridine **1b** (45 mg, 0.2 mmol, 1 equiv) was added and the mixture was stirred for 12 h at room temperature before being quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (60/40) to yield an amorphous white foam (78%). R_f = 0.24 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.41−7.25 (m, 5H), 5.41 (d, 1H, *J* = 8.1), 4.52−4.41 (m, 2H), 4.36 (dt, 1H, *J* = 12.9 and 3.4), 3.69 (s, 3H), 3.63 (s, 3H), 3.08 (d, 1H, *J* = 3.1), 2.90 (tt, 1H, *J* = 10.6 and 3.2), 2.45−2.30 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 168.8 (C quat), 167.9 (C quat), 138.3 (C quat), 129.5 (CH ar), 129.0 (CH ar), 127.2 (CH ar), 70.0 (CH_2), 59.9 (CH), 52.8 (CH), 52.5 (CH_3), 52.4 (CH_3), 44.5 (CH), 30.7 (CH_2); IR (Neat): ν = 3281, 2954, 2922, 1727, 1434, 1346, 1169, 1050, 701 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): *m*/*z* calculated for $C_{15}H_{19}NO_7S$: (M + Na) calcd = 380.0780, found = 380.0747.

(4R,5R*)-5-Methyl-4-phenyl-1,2,3-oxathiazepane 2,2-Dioxide (**8**).* MeMgBr in ether (300 μL, 0.9 mmol, 2 equiv) was added to a suspension of

CuI (13 mg, 0.07 mmol, 0.15 equiv) in THF (2 mL) under an atmosphere of argon at −78 °C. After 20 min of stirring, aziridine **1b** (100 mg, 0.45 mmol, 1 equiv) was added and the solution was stirred for 15 min at −78 °C and 45 min at 0 °C. The mixture was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/AcOEt (60/40) to yield compound **8** (69%). R_f = 0.50 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.40−7.16 (m, 5H), 4.70 (dt, 1H, J = 11 and 4.5), 4.50 (dt, 1H, J = 10.9 and 3.0), 3.99 (d, 1H, J = 9), 3.93−3.82 (m, 1H), 2.91 (qd, 1H, J = 7.3 and 6.4), 1.83−1.69 (m, 2H), 1.38 (d, 3H, J = 7.3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 140.3 (C quat), 129.1 (CH ar), 128.0 (CH ar), 127.6 (5 CH ar), 71.9 (CH_2), 60.3 (CH), 43.7 (CH), 27.9 (CH_2), 17.6 (CH_3); IR (Neat): ν = 3230, 2958, 1463, 1318, 1197, 1160, 1045, 932, 777, 684 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{11}H_{15}NO_3S$: (M + Na) calcd = 264.0670, found = 264.0668.

(4R,5S*)-Ethyl 5-Benzyloxy-2-ethoxycarbonyl-6-N-(tosyl)aminoheptanoate (**10**).* Diethyl malonate (53 μL, 0.35 mmol, 2 equiv) was dissolved in THF (1.5 mL) under an atmosphere of argon at 0 °C. NaH (17 mg, 60% in oil, 0.42 mmol, 2.5 equiv) was added, and the mixture was stirred for 15 min. Oxathiazepane **9** (75 mg, 0.17 mmol, 1 equiv) in THF (1 mL) was then added. After overnight stirring at room temperature, the reaction was quenched with water and concentrated. The residue was taken up in EtOAc and 1 M HCl. The solution was stirred for 1 h and then treated with 5 M NaOH (pH = 11). The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc, 85/15 then 70/30) to yield a colorless oil (34%). R_f = 0.29 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.67 (d, 2H, J_o = 8.3), 7.40−7.20 (m, 7H), 4.68 (d, 1H, J = 7.4), 4.45 (d, 1H, J = 11.3), 4.29 (d, 1H, J = 11.3), 4.19 (q, 4H, J = 6.7), 3.44 (m, 1H), 3.29 (m, 1H), 3.22 (t, 1H, J = 7.4), 2.41 (s, 3H), 1.85 (m, 2H), 1.60−1.37 (m, 2H), 1.26 (t, 6H, J = 7.3), 1.03 (d, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 169.2 (C quat), 143.4 (C quat), 138.1 (C quat), 138.0 (C quat), 129.8 (CH ar), 128.6 (CH ar), 128.0 (CH ar), 127.8 (CH ar), 127.2 (CH ar), 80.8 (CH), 72.1 (CH_2), 61.6 (CH_2), 51.8 (CH), 51.2 (CH), 27.9 (CH_2), 24.9 (CH_2), 21.6 (CH_3), 15.7 (CH_3), 14.2 (CH_3); IR (Neat): ν = 3291, 2982, 1730, 1454, 1370, 1331, 1163, 1093, 671 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{26}H_{35}NO_7S$: (M + Na) calcd = 528.2032, found = 528.2038.

(2R,3S*)-3-Benzyloxy-5-(1,3-dithian-2-yl)-2-N-(tosyl)aminopentane (**11**).* Dithiane (43 mg, 0.35 mmol, 2 equiv) was dissolved in THF (1 mL) at −78 °C under an atmosphere of argon then *n*-BuLi in hexane (350 μL, 0.35 mmol, 2 equiv), was added. After 20 min of stirring, the oxathiazepane **9** (75 mg, 0.17 mmol, 1 equiv) in THF (1 mL) was added. After 1 h of stirring at 0 °C and 2 h at room temperature, the mixture was quenched with water and concentrated. The residue was taken up in EtOAc and 1 M HCl. After 30 min of stirring, the mixture was basified with 5 M NaOH (pH = 11). The aqueous layer was extracted with EtOAc three times. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (80/20) to yield a yellow oil (48%). R_f = 0.59 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.67 (d, 2H, J_o = 8.5), 7.38−7.28 (m, 5H), 7.25 (d, 2H, J_o = 8.5), 4.68 (d, 1H, J = 7.5), 4.45 (d, 1H, J = 11.6), 4.31 (d, 1H, J = 11.6), 3.89 (t, 1H, J = 6.6), 3.44−3.36 (m, 1H), 3.30−3.25 (m, 1H), 2.85−2.63 (m, 4H), 2.41 (s, 3H), 2.16−1.98 (m, 2H), 1.80−1.55 (m, 4H), 1.05 (d, 3H, J = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.4 (C quat), 138.1 (C quat), 137.9 (C quat), 129.8 (CH ar), 128.6 (CH ar), 128.0 (CH ar), 127.9 (CH ar), 127.2 (CH ar), 80.5 (CH), 72.0 (CH_2), 51.2 (CH), 47.2 (CH), 31.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 21.7 (CH_3), 15.8 (CH_3); IR (Neat): ν = 3276, 2929, 1725, 1598, 1496, 1454, 1423, 1325, 1161, 1090, 908, 815, 738, 699, 667 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{23}H_{31}NO_3S_3$: (M + Na) calcd = 488.1364; found = 488.1382.

(2R,3S*)-3-Benzyloxy-2-N-(tosyl)aminodec-6-yne (**12**).* *n*-BuLi in hexane (530 μL, 0.51 mmol, 3 equiv) was added to a solution of *n*-pentyne (52 μL, 0.51 mmol, 3 equiv) in THF (0.75 mL) at −78 °C under an atmosphere of argon. The mixture was stirred 1 h, and the oxathiazepane **9** (75 mg, 0.17 mmol, 1 equiv) in THF (0.75 mL) was added at −78 °C. The mixture was allowed to warm to room temperature. After 16 h of stirring, the mixture was hydrolyzed and concentrated. The residue was taken up in EtOAc and treated with 1 M HCl. After 30 min, the aqueous layer was basified with 3 M NaOH (pH = 11). The aqueous layer was extracted three times with EtOAc, and the organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc 80/20) to yield a colorless oil (28%). R_f = 0.43 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.69 (d, 2H, J_o = 8.5), 7.38−7.20 (m, 7H), 4.62 (d, 1H, J = 7), 4.46 (d, 1H, J = 11.8), 4.31 (d, 1H, J = 11.8), 3.49 (m, 2H), 2.41 (s, 3H), 2.19 (m, 2H), 2.09 (m, 2H), 1.77−1.43 (m, 4H), 1.07 (d, 3H, J = 6.5), 0.96 (t, 3H, J = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.3 (C quat), 138.2 (C quat), 138.0 (C quat), 129.8 (CH ar), 128.6 (CH ar), 128.0 (CH ar), 127.8 (CH ar), 127.2 (CH ar), 81.2 (C quat), 80.4 (CH), 79.1 (C quat), 72.4 (CH_2), 51.3 (CH), 29.8 (CH_2), 22.6 (CH_2), 21.7 (CH_3), 20.9 (CH_2), 16.1 (CH_3), 15.4 (CH_2), 13.7 (CH_3); IR (Neat): ν = 3279, 2961, 2932, 2872, 1599, 1497, 1455, 1379, 1328, 1163, 1092, 815, 737, 699, 669 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{24}H_{31}NO_3S$: (M + Na) calcd = 436.1922, found = 436.1942.

(2R,3S*)-3-Benzyloxy-2-N-(tosyl)aminooctadec-6-yne (**13**).* *n*-BuLi in hexane (411 μL, 0.66 mmol, 1.4 equiv) was added to a solution of tridecyne (153 μL, 0.66 mmol, 1.4 equiv) in a mixture THF/HMPA (5/1, 6 mL) at −78 °C under an atmosphere of argon. The mixture was stirred for 1 h, and the oxathiazepane **9** (200 mg, 0.47 mmol, 1 equiv) in THF (4 mL) was added at −78 °C. The mixture was allowed to warm to room temperature. After 16 h of stirring, the mixture was hydrolyzed and concentrated. The residue was taken up in EtOAc and treated with 1 M HCl. After 30 min of stirring, the aqueous layer was basified with 3 M NaOH (pH = 11). The aqueous layer was extracted three times with EtOAc, and the organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc 90/10) to yield compound **13** as a colorless oil (34%) and the side product **14** (30%). Analysis for compound **13**. R_f = 0.50 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.69 (d, 2H, J = 8.2), 7.34−7.21 (m, 7H), 4.64 (d, 1H, J = 7), 4.45 (d, 1H, J = 11.6), 4.3 (d, 1H, J = 11.6), 3.47 (m, 2H), 2.41 (s, 3H), 2.18 (m, 2H), 2.10 (m, 2H), 1.76−1.52 (m, 2H), 1.50−1.2 (m, 18H), 1.07 (d, 3H, J = 6.2), 0.88 (t, 3H, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.3 (C quat), 138.2 (C quat), 138.0 (C quat), 129.8 (CH ar), 128.6 (CH ar), 127.9 (CH ar), 127.8 (CH ar), 127.2 (CH ar), 81.4 (C quat), 80.4 (CH), 78.9 (C quat), 72.4 (CH_2), 51.3 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 22.8 (CH_2), 21.7 (CH_3), 18.9 (CH_2), 16.2 (CH_3), 15.4 (CH_2), 14.3 (CH_3); IR (Neat): ν = 3280, 2923, 2852, 1599, 1454, 1326, 1163, 1090, 1027, 813, 735, 697, 668 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{32}H_{47}NO_3S$: (M + Na) calcd = 548.3174, found = 548.3183. Analysis for compound **14**. R_f = 0.41 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.67 (d, 2H, J_o = 8.6 Hz,), 7.39−7.20 (m, 7H), 5.71−5.56 (m, 1H), 5.34−5.15 (m, 2H), 4.88 (d, 1H, J = 8.4), 4.5 (d, 1H, J = 12.5 Hz), 4.17 (d, 1H, J = 12.5 Hz), 3, 70−3.63 (m, 1H), 3.43−3.34 (m, 1H), 2.40 (s, 3H), 1.07 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,

δ $CDCl_3$ = 77.16 for the central peak): δ = 143.3 (C quat), 138.2 (C quat), 138.1 (C quat), 134.8 (CH), 129.7 (CH ar), 128.6 (CH ar), 127.9 (CH ar), 127.8 (CH ar), 127.2 (CH ar), 119.7 (CH_2), 82.2 (CH), 70.6 (CH_2), 53.0 (CH), 21.6 (CH_3), 15.9 (CH_3); IR (Neat): ν = 3283, 2981, 2925, 2857, 1599, 1497, 1454, 1421, 1329, 1161, 1090, 995, 934, 815, 665 cm^{-1}; HRMS: (TOF MS ES^+; $MeOH/CH_2Cl_2$): m/z calculated for $C_{19}H_{23}NO_3S$: (M + Na) calcd = 368.1296, found = 368.1298.

(2R,3S*)-3-Benzyloxy-2-N-(tosyl)aminoheptane (**15**).* EtMgBr in ether (235 μL, 0.35 mmol, 2 equiv) was added to a suspension of CuI (10 mg, 0.053 mmol, 0.3 equiv) in THF (0.75 mL) at −78 °C under an atmosphere of argon. After 20 min of stirring, the oxathiazepane **9** (75 mg, 0.17 mmol, 1 equiv) in THF (0.75 mL) was added and the mixture was allowed to warm to room temperature overnight. The mixture was quenched with a saturated solution of NH_4Cl and concentrated. The residue was taken up in EtOAc and 1 M HCl and stirred for 1 h. The solution was then basified with a solution of 5 M NaOH (pH = 11). The aqueous layer was extracted with EtOAc three times. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (80/20) to yield a colorless oil (78%). R_f = 0.63 (heptane/EtOAc 60/40); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.66 (d, 2H, J_o = 7.9), 7.40−7.28 (m, 5H), 7.24 (d, 2H, J_o = 7.9), 4.75 (d, 1H, J = 7.9), 4.47 (d, 1H, J = 12.0), 4.26 (d, 1H, J = 12.0), 3.41 (td, 1H, J = 7.4 and 3.6), 3.23 (td, 1H, J = 6.7 and 3.6), 2.41 (s, 3H), 1.60−1.14 (m, 6H), 1.05 (d, 3H, J = 6.7), 0.86 (t, 3H, J = 6.7); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.1 (C quat), 138.3 (C quat), 138.0 (C quat), 129.6 (CH ar), 128.4 (CH ar), 127.7 (CH ar), 127.6 (CH ar), 127.0 (CH ar), 81.2 (CH), 71.8 (CH_2), 51.2 (CH), 29.8 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 21.5 (CH_3), 15.4 (CH_3), 13.9 (CH_3); IR (Neat): ν = 3281, 2955, 2870, 1599, 1496, 1454, 1324, 1159, 1092, 1066, 1028, 814, 735, 697, 666 cm^{-1}; HRMS: (TOF MS ES^+; $MeOH/CH_2Cl_2$): m/z calculated for $C_{21}H_{29}NO_3S$: (M + Na) calcd = 398.1766; found = 398.1784.

(2R,3S*)-3-Benzyloxy-2-N-(tosyl)aminopentadecane (**16**).* $C_{10}H_{21}MgBr$ in ether (700 μL, 0.35 mmol, 2 equiv) was added to a suspension of CuI (10 mg, 0.053 mmol, 0.3 equiv) in THF (0.75 mL) at −78 °C under an atmosphere of argon. After 20 min of stirring, the oxathiazepane **9** (75 mg, 0.17 mmol, 1 equiv) in THF (0.75 mL) was added and the mixture was allowed to warm to room temperature overnight. The mixture was quenched with a saturated solution of NH_4Cl and concentrated. The residue was taken up in EtOAc and 1 M HCl and stirred for 1 h. The solution was then basified with a solution of 5 M NaOH (pH = 11). The aqueous layer was extracted with EtOAc three times. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/AcOEt (80/20) to yield an orange oil (57%). R_f = 0.73 (heptane/EtOAc 60/40); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.59 (d, 2H, J_o = 8.3), 7.32−7.11 (m, 7H), 4.62 (d, 1H, J = 7.6), 4.39 (d, 1H, J = 11.9), 4.19 (d, 1H, J = 11.9), 3.34 (td, 1H, J = 7.3 and 3.7), 3.16 (td, 1H, J = 6.6 and 3.0), 2.34 (s, 3H), 1.30−1.05 (m, 22H), 0.98 (d, 3H, J = 6.6), 0.81 (t, 3H, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.3 (C quat), 138.4 (C quat), 138.2 (C quat), 129.7 (CH ar), 128.6 (CH ar), 127.9 (CH ar), 127.8 (CH ar), 127.2 (CH ar), 81.3 (CH), 71.9 (CH_2), 51.3 (CH), 32.1, 30.3, 29.9, 29.8, 29.7, 29.6, 29.5, 25.7, 22.8 (11 CH_2), 21.7 (CH_3), 15.6 (CH_3), 14.3 (CH_3); IR (Neat): ν = 3279, 2923, 2853, 1599, 1497, 1455, 1327, 1161, 1092, 814, 734, 697, 668 cm^{-1}; HRMS: (TOF MS ES^+; $MeOH/CH_2Cl_2$): m/z calculated for $C_{29}H_{45}NO_3S$: (M + Na) calcd = 510.3018; found = 510.3030.

*(4S,5R)-5-Benzyloxy-4-methyl-1,2,3-oxathiazepane 2,2-Dioxide (**20**).* Benzyl alcohol (640 μL, 6.0 mmol) and $BF_3 \cdot Et_2O$ (40 μL, 0.30 mmol) were added to a solution of aziridine **1a** (500 mg, 3.0 mmol) in DCM (7 mL) at 0 °C. The reaction was stirred overnight at room temperature and quenched with a saturated solution of $NaHCO_3$. The aqueous layer was extracted three times with DCM, and all the organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc 70/30) to yield a white solid (77%). This solid can be crystallized from cold toluene to furnish enantioenriched compound (ee = 97%). R_f = 0.51 (heptane/EtOAc 50:50); mp 88−89 °C; $[\alpha]^{24}_D$ = −20.0 (c = 1.14 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.42−7.27 (5H, m), 5.05 (1H, br), 4.62 (1H, d, J = 11.9), 4.5 (1H, ddd, J = 12,8, 9.1 and 2,1), 4.5 (1H, d, J = 11.9), 4.19 (1H, ddd, J = 13.1, 6.7 and 2.1), 3.48 (2H, m), 2.27 (1H, ddt, J = 16.1, 9.2, 2.3), 2.06 (1 H, m), 1.43 (3H, d, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 137.5 (C quat), 128.8 (CH ar), 128.3 (CH ar), 127.9 (CH ar), 79.5 (CH), 71.6 (CH_2), 65.7 (CH), 52.9 (CH), 30.9 (CH), 15.9 (CH_3); IR (Neat): ν = 3289, 2873, 1454, 1428, 1347, 1176, 1176, 1072, 976, 916, 746 cm^{-1}; HRMS: (TOF MS ES^+; $MeOH/CH_2Cl_2$): m/z calculated for $C_{12}H_{17}NO_4S$: (M + Na) calcd = 294.0776, found = 294.0768; Chiral HPLC: IC column 5 μm, Hept/i-prOH 80/20, t_{R1}: 19.07 min, t_{R2}: 20.515 min.

*(4S,5R)-5-(Benzyloxy)-4-methyl-3-N-tosyl-1,2,3-oxathiazepane 2,2-Dioxide (**9**).* The oxathiazepane **20** (215 mg, 0.80 mmol, 1 equiv) in DME (3 mL) was added to a suspension of ^tBuONa (115 mg, 1.2 mmol, 1.5 equiv) in DME (5 mL). After 1 h 30 min of stirring, TsCl (380 mg, 2 mmol, 2.5 equiv) was added and the mixture was stirred for 3 h. The reaction was quenched with water. The aqueous layer was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (90/10 and then 70/30) to yield a white solid (70%). R_f = 0.44 (heptane/EtOAc 60/40); mp 121−123 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.88 (d, 2H, J_o = 8.5), 7.40−7.27(m, 7H,), 4.70−4.20 (m, 5H), 3.80 (t, 1H, J = 7.1), 2.43 (s, 3H), 2.32−2.12 (m, 2H), 1.41 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 145.3 (C quat), 137.5 (C quat), 129.7 (CH ar), 128.7 (CH ar), 128.6 (CH ar), 128.2 (CH ar), 128.0 (CH ar), 116.9 (C quat), 82.4 (CH), 72.2 (CH_2), 70.2 (CH_2), 59.4 (CH), 32.0 (CH_2), 21.8 (CH_3), 18.0 (CH_3); IR (Neat): ν = 2924, 1596, 1487, 1454, 1404, 1357, 1194, 1186, 1172, 1069, 1039, 990, 964, 890, 866, 815, 781, 736, 705, 653 cm^{-1}; HRMS: (TOF MS ES^+; $MeOH/CH_2Cl_2$): m/z calculated for $C_{19}H_{23}NO_6S_2$: (M + Na) calcd = 448.0865, found = 448.0848.

*(4S,5R)-5-Fluoro-4-methyl-1,2,3-oxathiazepane 2,2-Dioxide (**21**).* Aziridine **1a** (600 mg, 3.7 mmol, 1 equiv) was dissolved in THF (50 mL), and TBAF (5.5 mL, 1 M in THF, 5.5 mmol, 1.5 equiv) was added under an atmosphere of argon. The mixture was stirred for 1 h 30 min, and the solvent was evaporated. The product was purified by flash chromatography (DCM/MeOH 100/0 and 90/10) to yield a brownish oil (75%). R_f = 0.30 (heptane/EtOAc 50/50); ^1H NMR (300 MHz, acetone-d_6, 25 °C, δ acetone-d_6 = 2.05): δ = 4.52 (dtd, 1H, J = 45.8, 8.9 and 4.7), 4.4−4.12 (m, 2H), 3.45 (m, 1H), 2.92 (br, 1H), 2.44 (ttd, 1H, J = 14.9, 4.7 and 1.7), 2.25−2.10 (m, 1H), 1.32 (dd, 3H, J = 6.6 and 2.3); ^{13}C NMR (75 MHz, acetone-d_6, 25 °C, δ acetone-d_6 = 29.84 for the central peak): δ = 94.1 (d, J = 175.6, CH), 66.1 (d, J = 11.6, CH), 52.5 (d, J = 27.2, CH_2), 34.9 (d, J = 24.5, CH_2), 17.8 (d, J = 2.2, CH_3); ^{19}F NMR decoupling (300 MHz, acetone-d_6, δ TFA = 100.5): δ = 2.75; IR (Neat): ν = 3425, 3064, 1561, 1493, 1483, 1430, 1407, 1331, 1190, 1136, 1066, 920, 877, 817, 781, 722 cm^{-1}; HRMS: (TOF MS ES^-; $MeOH/CH_2Cl_2$): m/z calculated for $C_5H_{10}FNO_3S$: (M − H) calcd = 182.0287; found = 182.0283.

*(4S,5R)-5-Fluoro-4-methyl-3-N-tosyl-1,2,3-oxathiazepane 2,2-Dioxide (**22**).* Oxathiazepane **21** (500 mg, 2.7 mmol, 1 equiv) in DME (10 mL) was added to a suspension of ^tBuONa (415 mg, 4.1 mmol, 1.5 equiv) in DME (20 mL). After 1 h 30 min of stirring, TsCl (1.3 g, 6.8 mmol, 2.5 equiv) was added and the mixture was stirred for 5 h. The reaction was quenched with water and poured into a H_2O/EtOAc mixture (1/2.5). The aqueous layer

was extracted twice with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/AcOEt (90/10 and then 70/30) to yield a white solid (44%) that can be crystallized from toluene to yield enantioenriched compound (97% ee). R_f = 0.62 (heptane/EtOAc 50/50); mp 127−132 °C; $[\alpha]^{24}_D$ = 68.2 (c = 0.29 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.89 (d, 2H, J_o = 8.4), 7.35 (d, 2H, J_o = 8.4), 4.83 (d, 1H, J = 50.7), 4.72 (m, 1H), 4.48−4.40 (m, 1H), 4.38−4.30 (m, 1H), 2.46 (s, 3H), 2.31−2.34 (m, 2H), 1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 145.6 (C quat), 129.8 (C quat and CH ar), 128.7 (CH ar), 93.8 (d, J = 175.0, CH), 68.5 (d, J = 9.1, CH), 58.5 (d, J = 35.8, CH_2), 33.5 (d, J = 23.6, CH_2), 21.9 (CH_3), 17.3 (CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, δ TFA = −75.69): δ = −169.55; IR (Neat): ν = 2983, 1718, 1597, 1409, 1395, 1366, 1198, 1174, 1031, 997, 868 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{12}H_{16}FNO_5S_2$: (M + Na) calcd = 360.0302, found = 360.0351, Chiral HPLC: IC column 5 μm, Hept/i-prOH 80/20, t_{R1}: 15.98 min, t_{R2}: 27.55 min.

(2S,3R)-3-Benzyloxy-2-N-(tert-butylcarbamate)aminooctadec-6-yne (***23***). Tosylamine **13** (85 mg, 0.16 mmol, 1 equiv) was dissolved in DCM under an atmosphere of argon at room temperature, and then di-*tert*-butyl dicarbonate (70 mg, 0.32 mmol, 2 equiv), DMAP (4 mg, 0.032 mmol, 0.2 equiv), and triethylamine (68 μL, 0.48 mmol, 3 equiv) were added. The mixture was stirred for 24 h and quenched with water. The aqueous layer was extracted with DCM three times. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (95/5) to yield a colorless oil (55%). R_f = 0.71 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.82 (d, 2H, J = 8.2), 7.36−7.27 (m, 7H), 4.73 (d, 1H, J = 11), 4.62 (d, 1H, J = 11), 4.53−4.43 (m, 1H), 4.14 (td, 1H, J = 8.9 and 3.7), 2.43 (s, 3H), 2.40−2.32 (m, 2H), 2.20−2.10 (m, 2H), 1.52 (d, 3H, J = 6.7), 1.55−1.20 (large, m, 20 H), 1.40 (s, 9H), 0.88 (t, 3H, J = 6.8); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 150.8 (C quat), 144.1 (C quat), 138.6 (C quat), 137.7 (C quat), 129.3 (CH ar), 128.5 (CH ar), 128.3 (CH ar), 128.0 (CH ar), 127.8 (CH ar), 84.5 (C quat), 81.0 (C quat), 79.9 (CH), 79.7 (C quat), 74.0 (CH_2), 57.7 (CH), 32.1 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.1 (CH_3), 22.8 (CH_2), 21.8 (CH_3), 19.0 (CH_2), 17.3 (CH_3), 14.8 (CH_2), 14.3 (CH_3); IR (Neat): ν = 2924, 2853, 1732, 1455, 1371, 1352, 1263, 1170, 1089, 1067, 989, 672 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{37}H_{55}NO_5S$: (M + Na) calcd = 648.3699, found = 648.3692. The protected amine (55 mg, 0.088 mmol, 1 equiv) was dissolved in MeOH (0.75 mL), and magnesium powder (21 mg, 0.88 mmol, 10 equiv) was added. The mixture was stirred at room temperature under sonication for 30 min. The solution was then hydrolyzed with a saturated solution of NH_4Cl and extracted three times with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc 90/10) to yield a colorless oil (82%). R_f = 0.72 (heptane/EtOAc 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.35 (m, 4H,), 7.28 (m, 1H,), 4.62 (d, 1H, J = 11.8), 4.57 (d, 1H, J = 11.8), 3.85 (br, 1H), 3.58 (q, 1H, J = 3.9 Hz), 2.27 (m, 2H), 2.14 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.47 (m, 1H), 1.43 (s, 9H), 1.36 (m, 2H), 1.26 (br, 16H), 1.11 (d, 3H, J = 7.3), 0.88 (t, 3H, J = 7.1); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 155.5 (C quat), 138.8, (C quat), 128.6 (CH ar), 128.0 (CH ar), 127.8 (CH ar), 81.2 (C quat), 80.5 (CH and C quat), 79.3 (C quat), 72.8 (CH_2), 48.2 (CH), 32.1 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.6 (CH_3), 22.8 (CH_2), 18.9 (CH_2), 15.6 (CH_3), 15.5 (CH_2), 14.2 (CH_3); IR (Neat): ν = 2927, 2855, 1717, 1498, 1366, 1170, 1061 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{30}H_{49}NO_3$: (M + Na) calcd = 494.3610; found = 494.3623.

(2S,3R)-3-Hydroxy-2-N-(tert-butylcarbamate)aminooctadecane (***24***). *N*-Boc protected alkyne **23** (34 mg, 0.072 mmol, 1 equiv) was dissolved in EtOH (0.5 mL), and Pd/C (3 mg) was added. The flask was purged with argon and placed under an atmosphere of H_2 (P = 1 bar). The mixture was stirred for 24 h, filtered through a pad of Celite, and concentrated to afford a clean crude product (90% yield). R_f = 0.52 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.43 (m, 1H), 3.77−3.55 (m, 2H), 1.44 (s, 9H), 1.41−1.21 (br, 29H), 1.08 (d, 3H, J = 6.8), 0.88 (t, 3H, J = 6.8); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 156.0 (C quat), 79.6 (C quat), 74.6 (CH), 50.7 (CH), 33.6, 32.1, 29.8, 29.7, 29.5, 28.6, 26.2, 22.8 (14 CH_2 and 1 CH_3), 14.5 (CH_3), 14.3 (CH_3); IR (Neat): ν = 2927, 2855, 1717, 1498, 1366, 1170, 1061 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{23}H_{47}NO_3$: (M + Na) calcd = 408.3454; found = 408.3468.

Spisulosine HCl (***17***). *N*-Boc protected spisulosine **24** (20 mg, 0.052 mmol, 1 equiv) was dissolved in a solution of HCl in ether (2M, 1 mL) and stirred for 1 h. The mixture was concentrated, taken up in ether, and filtered to yield a white solid (60%). R_f = 0.60 (heptane/EtOAc 60/40); $[\alpha]^{24}_D$ = +7.15 (c = 0.42 in MeOH); ^{1}H NMR (300 MHz, CD_3OD, 25 °C, δ CD_3OD = 3.31): δ = 4.84 (br, 4H), 3.69 (td, 1H, J = 6.5 and 3.0), 3.27 (qd, 1H, J = 7.0 and 3.4), 1.56−1.25 (br, 28H), 1.21 (d, 3H, J = 6.8), 0.90 (t, 3H, J = 6.8); ^{13}C NMR (75 MHz, CD_3OD, 25 °C, δ CD_3OD = 49.0 for the central peak): δ = 71.7 (CH), 52.6 (CH), 34.0, 33.1, 30.8, 30.7, 30.65, 30.6, 30.5, 27.0, 23.7 (11 CH_2), 14.4 (CH_3), 12.1 (CH_3); IR (Neat): ν = 3392, 2920, 2851, 1501, 1051 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{18}H_{39}NO$: (M + H) calcd = 286.3110; found = 286.3121.

(2S,3R)-3-Fluoro-2-N-(tosyl)aminopent-4-ene (***25***). A solution of fluorooxathiazepane **22** (58 mg, 0.17 mmol, 1 equiv) in THF (0.5 mL) was added to a solution of *n*-BuLi in hexane (215 μL, 0.26 mmol, 1.5 equiv) in a THF/HMPA mixture (0.5 mL/0.2 mL) under argon at −78 °C. After being stirred overnight at room temperature, the reaction was quenched with water and concentrated. The residue was taken up in EtOAc and 1 M HCl, stirred for 30 min, and then basified with 3 M NaOH (pH = 11). The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography with heptane/EtOAc (90/10) to yield a colorless oil (60%). R_f = 0.33 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.76 (d, 2H, J_o = 8.4), 7.30 (d, 2H, J_o = 8.4), 5.73 (tq, 1H, J = 17.4 and 5.3), 5.36−5.26 (m, 2H), 4.92−4.88 and 4.77−4.72 (2 m, 1H), 4.80 (d, 1H, J = 9.1), 3.64−3.40 (m, 1H), 2.42 (s, 3H), 1.03 (d, 3H, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.6 (C quat), 138.1 (C quat), 132.4 (d, J = 19.9, CH), 128.6 (CH ar), 127.1 (CH ar), 119.0 (d, J = 11.1, CH_2), 94.7 (d, J = 177.4, CH), 52.6 (d, J = 20.6, CH), 21.6 (CH_3), 15.0 (d, J = 5.2, CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, 25 °C, δ TFA = −75.69): δ = −195.5; IR (Neat): ν = 3279, 2986, 1599, 1431, 1331, 1160, 1092, 942, 815, 666 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{12}H_{16}FNO_2S$: (M + Na) calcd = 280.0883, found = 280.0773.

(2S,3R)-3-Fluoro-2-N-(tosyl)aminooctadec-4-ene (***26***). Grubbs II catalyst (24 mg, 0.028 mmol, 0.08 equiv) was placed in a flame-dried 50 mL flask, and degassed DCM (4 mL) was added. The tosyl amine **25** (90 mg, 0.35 mmol, 1 equiv) in degassed DCM (4 mL) and pentadecene (285 μL, 1.1 mmol, 3 equiv) in degassed DCM (4 mL) were then added, and the mixture was refluxed overnight. The mixture was concentrated and purified by flash chromatography (heptane/EtOAc 90/10) to yield a brownish oil (75%, mixture of *E* and *Z* olefin). R_f = 0.50 (heptane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 7.76 (d, 2H, J_o = 8.4 Hz), 7.30 (d, 2H, J_o = 8.4), 5.81−5.20 (m, ethylenic H of *Z* and *E* configuration), 4.84−4.60 (m, 2H, NH and CHF_E), 4.33 (2 m, J = 47.9, CHF_Z) 3.58−3.37 (m, 1H), 2.43 (s, 3H),

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2.06−1.89 (m, 2H), 1.40−1.17 (br, 22H), 1.06 (d, 3H, J = 6.9), 0.88 (t, 3H, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 143.6 (C quat), 138.3 (C quat), 133.7 (d, J = 10.8, CH), 128.9 (CH ar), 127.1 (CH ar), 123.9 (d, J = 19.9, CH), 95.2 (d, J = 174.6, CH), 53.0 (d, J = 23.4, CH), 32.7 (CH_2), 32.4 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.6(CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.35 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 22.8 (CH_2), 21.7 (CH_3), 15.4 (d, J = 6.1, CH_3), 14.3 (CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, δ TFA = −75.69): δ = −188.3 and −196.1; IR (Neat): ν = 3281, 2924, 2854, 1463, 1332, 1163, 1093, 942, 970, 814, 668 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{25}H_{42}FNO_2S$: (M + Na) calcd = 462.2818, found = 462.2820.

(2S,3R)-3-Fluoro-2-N-(tert-butylcarbamate)aminooctadec-4-ene (***27***). The *N*-tosyl protected amine **26** (110 mg, 0.25 mmol, 1 equiv) was dissolved in DCM (5 mL) under argon at room temperature. Boc_2O (163 mg, 0.75 mmol, 3 equiv) and DMAP (15 mg, 0.13 mmol, 0.5 equiv) were then added. The mixture was stirred overnight, concentrated, and purified by flash chromatography (heptane/EtOAc 90/10). Isolated product (125 mg, 0.23 mmol, 1 equiv) was dissolved in MeOH (2 mL), and then Mg (56 mg, 2.3 mmol, 10 equiv) was added. The mixture was submitted to sonic bath for 20 min and concentrated under vacuum. The residue was taken up in ether and quenched with saturated ammonium chloride solution. The aqueous layer was extracted three times with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography (heptane/EtOAc 95/5) to yield a colorless oil (46% overall yield, mixture of *E* and *Z* olefins). R_f = 0.30 (heptane/EtOAc 95/5); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 5.89−5.30 (m, ethylenic H of *Z* and *E* configuration), 5.01−4.65 (m, 2H, NH and CHF_E), 4.60−4.35 (2 m, CHF_Z), 3.89−3.64 (m, 1H), 2.12−1.93 (m, 2H), 1.44 (s, 9H), 1.40−1.19 (br, 22H), 1.13 (d, 3H, J = 6.8), 0.87 (t, 3H, J = 6.8); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 155.3 (C quat), 136.8 (d, J = 11.2, CH), 123.0 (d, J = 20.1, CH), 95.5 (d, J = 170.5, CH), 79.6 (C quat), 49.8 (d, J = 25.8, CH), 32.7 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.5 (CH_3), 22.8 (CH_2), 14.2 (2 CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, 25 °C, δ TFA = −75.69): δ = −190.3 and −197.3; IR (Neat): ν = 3351, 2921, 2851, 1686, 1535, 1468, 1367, 1252, 1181 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{23}H_{44}FNO_2$: (M + Na) calcd = 408.3264, found = 408.3243.

(2S,3R)-3-Fluoro-2-N-(tert-butylcarbamate)aminooctadecane (***28***). Olefin **27** (38 mg, 0.1 mmol, 1 equiv) was dissolved under an atmosphere of argon in degassed DCM (2 mL). PtO_2 (4.5 mg, 0.02 mmol, 0.2 equiv) was then added. The flask was flushed with argon before being placed under an atmosphere of H_2 (1 bar) for 1 h 30 min (monitored by NMR). The mixture was filtered through a pad of Celite and concentrated to afford a white solid (quantitative yield). R_f = 0.43 (heptane/EtOAc 90/10); mp: 41−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.76 (d, 1H, J = 8.1), 4.47 (d, 1H, J = 49.3), 3.88−3.58 (m, 1H), 1.44 (s, 9H), 1.37−1.17 (br, 28 H), 1.12 (d, 3H, J = 7.0), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 155.3 (C quat), 96.4 (d, J = 170.9 Hz, CH), 79.6 (C quat), 49.1 (d, J = 19.8 Hz, CH), 32.1 (CH_2), 32.05 (CH_2), 31.9 (CH_2), 29.85 (CH_2), 29.8 (CH_2), 29.75 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 28.5 (CH_3), 25.5 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.03 (d, J = 5.6, CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, δ TFA = −75.69): δ = −198.0; IR (Neat): ν = 3341, 2924, 2854, 1704, 1501, 1456, 1391, 1366, 1246, 1172, 1055, 967 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{23}H_{46}FNO_2$: (M + Na) calcd = 410.3410, found = 410.3424.

(2S,3R)-3-Fluorooctadecan-2-amine (***18***). *N*-Boc protected fluoro spisulosine **28** (38 mg, 0.1 mmol, 1 equiv) was dissolved in 2 M HCl in ether (2 mL) and stirred at room temperature for 2 h. The mixture was concentrated, taken up in DCM, and treated with a 3 M solution of NaOH for 30 min. The aqueous layer was then extracted with DCM three times, and all organic layers were combined, washed with water, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography to yield a colorless oil (60%). R_f = 0.31 (heptane/EtOAc 95:5); $[\alpha]^{24}_D$ = −10 (c = 1.15 in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 7.26): δ = 4.28 (d, 1H, J = 50.3), 3.07−2.95 (m, 1H), 1.67−1.41 (m, 4H), 1.38−1.18 (br, 26H,) 1.09 (d, 3H, J = 6.5), 0.88 (t, 3H, J = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ $CDCl_3$ = 77.16 for the central peak): δ = 98.3 (d, J = 171.3, CH), 49.9 (d, J = 20.7, CH), 32.1 (CH_2), 30.9 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 25.5 (d, J = 3.2), 22.8, 18.1 (CH_3), 14.2 (CH_3); ^{19}F NMR decoupling (300 MHz, $CDCl_3$, δ TFA = −75.69): δ = −191.9; IR (Neat): ν = 3335, 2917, 2850, 1583, 1485, 1469, 1356, 1328 cm^{-1}; HRMS: (TOF MS ES$^+$; MeOH/CH_2Cl_2): m/z calculated for $C_{18}H_{38}FN$: (M + H) calcd = 288.3067, found = 288.3061.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra of all compounds. HMBC, HSQC, and COSY experiments for compounds **3**, **4**, **7**, and **8**. Crystallographic data for **20** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) An identical result was obtained when aziridine **1b** was reacted with methanol in the presence of $BF_3 \cdot OEt_2$. Ring-opening exclusively occurs at C4 position, allowing isolation of the same regioisomer in 86% yield. HMBC spectrum points out the absence of correlation between H4 and the ortho-carbon atoms of the phenyl moiety. The reversed regioselectivity was then confirmed by X-ray crystallography.

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(25) On the basis of the observation made with Grignard reagents in the presence of CuI (see results in Scheme 3), ring-opening of cyclic sulfamidate **9** has also been performed with $C_{13}H_{27}MgBr$ which, contrary to its lower and higher homologues, is not commercially available. Whereas reactions with ethyl- or decylmagnesium bromide have proved to be efficient, use of freshly prepared tridecylmagnesium bromide affords the expected product albeit with a lower yield of 35−40%, a result attributed to the nonoptimized preparation of the Grignard reagent. We have therefore decided to use alkynides as C-nucleophiles because the triple bond could afford additional opportunities in the context of SAR studies.

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