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1,4-Diazaspiro[2.2]pentanes as a Flexible Platform for the Synthesis of Diamine-Bearing Stereotriads

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Abstract

Nitrogen-containing stereotriads occur in a number of biologically active compounds, but general and flexible methods to access these compounds are limited mainly to the manipulation of chiral olefins. An alternative approach is to employ a highly chemo-, regio-, and stereocontrolled allene oxidation that can install a new carbon–heteroatom bond at each of the three original allene carbons. In this paper, an intramolecular/intermolecular allene bis-aziridination is described that offers the potential to serve as a key step for the construction of stereotriads containing vicinal diaminated motifs. The resultant 1,4-diazaspiro[2.2]pentane (DASP) scaffolds contain two electronically differentiated aziridines that undergo highly regioselective ring-openings at C1 with a variety of heteroatom nucleophiles to give chiral *N,N*-aminals. Alternatively, the same DASP intermediate can be induced to undergo a double ring opening reaction at both C1 and C3 to yield vicinal diaminated products corresponding to formal ring opening at C3. The chirality of a propargyl alcohol is easily transferred to the DASP with good fidelity, providing a new paradigm for the construction of enantioenriched nitrogen-containing stereotriads.

INTRODUCTION

Diamines are privileged synthetic motifs found in a host of biologically active natural products and pharmaceuticals.^{1,2} These compounds can be prepared with varying levels of chemo-, regio-, and stereoselectivity, typically via diamination or aziridination of an olefin.¹ However, the generality of these methods in terms of the substrate scope has often been

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Supporting Information

¹H and ¹³C NMR spectra of all new compounds. X-ray crystal structure data tables for **7a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

problematic, as some approaches work well only for terminal olefins or those having a specific alkene geometry. In addition, the ring opening of aziridines with nitrogen nucleophiles to access vicinal diamines often suffers from reactivity and regioselectivity issues.³

Many diamine-containing molecules contain additional complexity that can be difficult to install using currently available synthetic methods. For example, several vicinal diamine-containing pharmaceuticals contain an additional contiguous oxygen-bearing chiral center (Figure 1).⁴ In order to employ standard olefin oxidation protocols to accomplish the construction of these stereotriads, the substrates are required to bear a suitably protected substituent at the allylic position. This can inhibit the reactivity of the olefin or lead to mixtures of regioisomers when two different heteroatoms are introduced. Even in cases when regiocontrol is not an issue, problems with stereochemical mismatching can lead to mixtures of diastereoisomers that can be inconvenient to separate. Thus, methods to directly oxidize all three carbons of an allene to generate these complex nitrogen-containing stereotriads with good levels of chemo-, regio- and diastereocontrol would be a valuable addition to methodology centered on hydrocarbon oxidation.

We hypothesized that allenic carbamates of the form **1** (Scheme 1) could serve as flexible substrates to develop a challenging, yet potentially powerful, approach to the rapid preparation of chiral nitrogen-containing stereotriads. Our group has demonstrated that the treatment of **1** with catalytic amounts of Rh₂esp₂ (esp = *α,α,α',α'*-tetramethyl-1,3-benzenedipropionic acid) or Rh₂TPA₄ (TPA = triphenylacetate) in the presence of a hypervalent iodine oxidant yields the bicyclic methyleneaziridines (MA) **E-2a** and **Z-2b**.^{5,6} The major isomer is generally **E-2a**, although greater amounts of **Z-2b** can be obtained if Rh₂(OAc)₄ is employed as the catalyst. Typically, the minor amounts of **Z-2b** are easily separated from the desired **E-2a**. If **E-2a** could be induced to undergo a second, metal-free aziridination with *N*-aminophthalimide (PhthNNH₂), the resulting 1,4-diazaspiro[2.2]pentane (DASP) **E-3a** could potentially undergo further ring opening at either C1 or C3 to elaborate these reactive intermediates to diamine-containing stereotriads of the form **4a** and **5a**. In addition, if the second aziridination and subsequent reactions of the DASP proved to be highly stereoselective, then transformation of the corresponding *Z* bicyclic MA **Z-3b** could be expected to yield motifs such as **4b** and **5b**.

The introduction of multiple carbon–heteroatom bonds into an allene is not a new concept, but it has been limited mainly to the installation of C–O bonds. Pioneering studies by the Crandall and Williams groups have demonstrated that bis-epoxidation of an allene to a spirodiepoxide (SDE) can be followed by elegant transformations of these highly reactive intermediates to 1,2,3-trioxygenated triads and other motifs.⁷ More recently, the Williams group has greatly expanded the usefulness of spirodiepoxides by showcasing how allene epoxidation can be used in the synthesis of a number of complex natural products, including epoxomicin, psymberin, pectenotoxin 4, and the erythronolides.^{7d–g} However, the corresponding aziridination chemistry was not explored, despite the potential for facile access to densely functionalized and enantioenriched vicinal diamines.

The additional valency of nitrogen as compared to oxygen imbues DASPs with several advantageous features not available to SDEs. Foremost is the potential to electronically differentiate between the two aziridines to control the reactivity independent of the substitution pattern of the allene. Regioselective ring opening at either C1 or C3 of a single DASP **E-3a** or **Z-3b** could then be achieved depending on the identity of these two activating groups. Another beneficial feature of substituting the oxygens of an SDE with nitrogen is that the additional valency of N allows DASPs to be prepared using an intra/intermolecular approach that enables excellent regiocontrol in the first aziridination.

RESULTS AND DISCUSSION

Treatment of the bicyclic methyleneaziridines **6–15** (Table 1)⁸ with PhthNNH₂ and PhIO induced formation of the desired DASPs **6a–15a** in moderate to good yields in most cases. Substitution in the carbamate linker did not greatly affect the second aziridination event, as both the unsubstituted **6** and the *gem*-dimethyl-substituted **7** gave similar yields of **6a** and **7a** (entries 1 and 2). However, the olefin geometry of the MA was crucial in determining the stereochemical outcome of the DASP formation. When the *E* isomer **7** (entry 2) was subjected to the reaction conditions, a 72% yield of the DASP **7a** was obtained. The structure of **7a** was determined unambiguously by X-ray crystallography (see Supporting Information for further details).

Examination of the X-ray crystal structure of **7a** indicated that the second aziridination occurred on the face of the methyleneaziridine opposite that of the first aziridine, as would be expected on steric grounds. The *E* configuration of **7** translated into a *syn* relationship between the C₅H₁₁ side chain and the central C1–C2 bond in **7a**. The reaction of the *Z*-MA **8** (entry 3) gave a different stereoisomeric product **8a** in a poor yield of 33%. The reason for the decreased reactivity of the *Z*-methyleneaziridine compared to the *E* is not completely clear. However, it is possible that the change from sp² to sp³ geometry at C2 and C3 in the second aziridination event forces unfavorable steric interactions between the proximal methylene of the side chain and the nitrogen of the C1–C2 aziridine. Nonetheless, the stereoselective nature of the reaction was illustrated.⁹

Methyleneaziridines bearing a ^tBu or Ph(CH₂)₂ group (entries 4 and 5) also gave even better yields of the desired DASPs **9a** and **10a**. The relative configuration was established based on analogy to the X-ray crystal structure of **7a**. Since it would be much more convenient to simply utilize the *E:Z* mixtures of bicyclic MAs for the DASP formation, a 3.5:1 *E:Z* mixture of **11** (entry 6) was attempted in the intermolecular aziridination. The desired product **11a** was obtained in 62% yield based on the amount of *E*-methyleneaziridine present in the mixture. No DASP product from the *Z* isomer was isolated. Similarly, the DASPs **13a** and **14a** (entries 8 and 9) were obtained as single stereoisomers when *E:Z* mixtures of the bicyclic methyleneaziridines were employed as the starting substrates. The much slower rate of DASP formation from the *Z* isomer compared to the *E* MA isomer proved helpful in this regard. However, if the DASP from the *Z*-methyleneaziridine (as in **12a**, entry 7) is desired, it was best to separate the two isomers prior to the second aziridination. In this manner, any unreacted *Z* MA could be recovered and resubjected to the reaction conditions. Finally, the trisubstituted bicyclic methyleneaziridine **15** (entry 10) gave

a lower yield of the DASP **15a**, likely due to steric hindrance. Nonetheless, this type of scaffold represents potential access to a quaternary nitrogen-bearing stereocenter.

A convenient aspect of allene oxidation is that the axial chirality of the substrate can be potentially transferred to the products in a diastereoselective process.^{7c} The enantioenriched propargyl alcohol **16** was prepared according to literature procedure and converted to the allene **17** (Scheme 2).¹⁰ The synthesis of the DASP **19** from the alcohol **16a** resulted in no degradation in the enantiopurity, and a simple recrystallization enhanced the *er* to 96:4. The stereoselective nature of the DASP formation ensured that the axial chirality of the original allene could be transferred to the product with excellent fidelity. The number of methods available for the synthesis of enantio-enriched allenes, as well as the continued focus on the development of new approaches, should render allene oxidation a convenient alternative for the preparation of enantioenriched stereotriads.¹¹

With a suitable method in hand to prepare DASPs containing two electronically differentiated aziridines, we set about understanding how to induce regioselective ring opening at both C1 and C3 with heteroatom-containing nucleophiles. Ring opening at C1 to yield chiral *N,N*-aminals **4a,b** (Scheme 1) was examined first, as these motifs are found in a number of biologically active natural products and pharmaceuticals that exhibit promising anticancer, anti-inflammatory, antiparasitic, and anticholinesterase activities.¹² Treatment of a series of DASPs with weak nucleophiles gave exclusive ring opening at the internal aziridine (C1 of the original allene). For example, acetic acid opened the DASP **6a** in 95% yield to give one regioisomer **20** (Table 2, entry 1). The *gem*-dimethyl DASP **7a** gave only **21** (entry 2). For a DASP derived from the *Z*-methyleneaziridine **12a** (entry 4), reaction with acetic acid gave an 85% yield of the equivalent ring-opened product **23**. The bulky pivalic acid was also successful and delivered the *N,N*-aminal **24** in 80% yield (entry 5). The unsaturated tiglic acid (entry 6) gave **25** in moderate yield. A new C–S bond could be introduced into the *N,N*-aminal by treatment of **7a** with thioacetic acid to give **26** (entry 7) in 82% yield. Chloride was also a good nucleophile, opening both DASPs **6a** and **7a** in excellent yields using either LiCl or TMSCl as the halogen source (entries 8 and 9) to yield **27** and **28**. NaN₃ successfully opened the bicyclic methyleneaziridine, but a subsequent elimination event destroyed the newly formed chiral centers. Carbon-based nucleophiles, such as malonates, were not sufficiently nucleophilic to open the ring, while stronger Grignard reagents and cuprates preferred to attack the phthalimide group. These issues have been addressed by employing a sulfamate-based nitrene precursor, which will be described in a future communication.

We were pleased to find an allenic carbamate **29** could be converted directly to functionalized *N,N*-aminals in one flask as a single diastereomer (Table 3). Four new carbon–heteroatom bonds and three chiral centers are generated in a stereoselective fashion using operationally simple procedures under mild reaction conditions. The yields were also increased significantly in the one-pot reaction; for example, the yield of **21** (Table 3) improved to 46%, compared to 33% for the three-step process.

As part of our initial design of the DASP scaffold, we employed a Phth protected aziridine to promote ring opening at C1 and discourage competing ring opening at C3. However, it

would be desirable to be capable of manipulating the protecting groups on the two aziridines such that ring opening at either C1 or C3 could be accomplished. Unfortunately, all attempts to aziridinate a bicyclic methyleneaziridine with nitrene precursors other than *N*-aminophthalimide met with limited success. This precluded the intermolecular installation of an aziridine containing a more electron-withdrawing group to direct ring opening to C3 (**5a** in Scheme 1). While one possible solution would be to introduce additional substitution in the allene to minimize subsequent ring opening of the DASP at C1, this would limit the flexibility of the method. Thus, we opted to implement a double nucleophilic ring opening as the best way to achieve a formal ring opening at C3 (eq 1).

Treatment of **2a** (Table 4, entry 1) with 6 equiv of TMSBr, followed by direct loading of the reaction mixture onto a silica gel column, resulted in formation of the expected *N,N*-arinal product **30** in 89% yield. A minor amount of the desired stereotriad **31** was also observed. The second ring opening at C3 could be pushed to completion by slow concentration of the reaction mixture at 40 °C prior to purification, giving a 59% yield of a single diastereomer proposed as **31** (entry 2). Indeed, treatment of the likely intermediate **30** with additional TMSBr under more concentrated conditions also yielded **31** as the major product. Poorer leaving groups, including acetate (Table 4, entry 3), could also function for ring opening at C3, albeit with some epimerization at C3 to give **32a** and **32b**. This ability to control the regioselectivity of the ring opening of DASPs is a promising approach to access a range of diverse stereotriads from the same core allenic carbamate substrate.

CONCLUSION

The intra/intermolecular bis-aziridination of a series of allenic carbamates to an unusual heterocyclic ring system, the 1,4-diazaspiro[2.2]pentane, was demonstrated for the first time. The ability to electronically differentiate the two aziridine rings of the DASPs enabled regioselective ring opening at the terminal carbon of either aziridine depending on the reaction conditions. As the chirality from a propargyl alcohol could be transferred to all three of the new carbon–heteroatom bonds to yield an enantioenriched DASP, these strained rings represent useful scaffolds for the preparation of a diverse range of functionalized, enantioenriched vicinal diamines. Future work will focus on the expansion of the substrate scope, the identification of other nitrene precursors, and further manipulations of the ketones/imines resulting from ring opening at both C1 and C3 of the DASP.

EXPERIMENTAL SECTION

General Methods

All glassware were either oven-dried overnight at 130 °C or flame-dried under a stream of dry nitrogen prior to use. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and diethyl ether were freshly

distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile, and toluene were dried over CaH₂ and freshly distilled prior to use. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".¹³ Air- and moisture-sensitive reactions were performed either in a glovebox under an atmosphere of nitrogen or using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing precoated silica gel 60 F₂₅₄ plates containing a fluorescent indicator, while preparative chromatography was performed using silica gel (230–400 mesh) via Still's method.¹⁴ Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient method, beginning with 100 mL of 100% hexanes, then progressing to 100 mL of 9:1 hexane/EtOAc, 3:1 hexane/EtOAc, 2:1 hexane/EtOAc, and 1:1 hexane/EtOAc. If necessary, the column was continued using 1:2 hexane/EtOAc and then 100% EtOAc until all of the products had been eluted from the column. Various stains were used to visualize reaction products, including *p*-anisaldehyde, KMnO₄, ceric ammonium nitrate, and phosphomolybdic acid in ethanol stain. Unless otherwise stated, rt refers to temperatures between 21 and 23 °C. ¹H NMR and ¹³C NMR spectra were obtained using either 300 or 500 MHz NMR spectrometers. For ¹H NMR, chemical shifts are reported relative to residual protiated solvent peaks (δ 7.26, 2.49, 7.15, and 4.80 ppm for CDCl₃, (CD₃)₂SO, C₆D₆, and CD₃OD, respectively). ¹³C NMR spectra were measured at either 125 or 150 MHz on the same instruments noted above for recording ¹H NMR spectra. Chemical shifts were again reported in accordance to residual protiated solvent peaks (δ 77.0, 39.5, 128.0, and 49.0 ppm for CDCl₃, (CD₃)₂SO, C₆D₆, and CD₃OD, respectively). IR spectral data were obtained using either a thin film or an ATR adapter. High-pressure liquid chromatography (HPLC) analyses were performed at 224 and 254 nm using an AD-H column (4.6 μ m diameter $\times$ 258 mm) at a temperature of 40 °C, using a flow rate of 1 mL/min and a gradient starting at 10% isopropyl alcohol in hexanes for 10 min and increasing to 30% isopropyl alcohol in hexanes. The eluant was then held at 30% isopropyl alcohol in hexanes until the run was completed. Accurate mass measurements were acquired by high-resolution mass spectrometry utilizing electrospray ionization, time-of-flight analyzer, or electron impact methods.

General Procedure for Preparation of 1,4-Diazaspiro[2.2]-pentanes

The bicyclic methyleneaziridines **6–10** and **13–15** were prepared as described in the literature.^{5a,b} If necessary, the *E* and *Z* bicyclic methyleneaziridines were separated by column chromatography before initiating the DASP formation. The general procedure uses 1.0 mmol of substrate as a standard amount; however, reactions were run at many different scales, and the total amount of isolated product is reported for each compound. A solution of the methyleneaziridine (1.0 mmol, 1.0 equiv) in 10 mL of dry dichloromethane was cooled to 0 °C and treated with *N*-aminophthalimide (1.5 mmol, 1.5 equiv) and dry potassium carbonate (3.5 mmol, 3.5 equiv), followed by PhI(OAc)₂ or PhIO as the oxidant (1.6 mmol, 1.6 equiv). The resulting light yellow slurry was allowed to warm slowly to rt and monitored carefully by TLC. In some cases, the DASP product was sensitive to ring opening by acetate and it was best to stop the reaction when conversion of the methyleneaziridine to the DASP stalled. When reaction was complete, the dichloromethane was removed under reduced pressure on a vacuum line, the residue was diluted with *dry* Et₂O, and the organics were decanted. The residual salts were washed two more times with Et₂O and the volatiles

removed under reduced pressure on a vacuum line. A silica gel column was packed using 99.5:0.5 hexanes/triethylamine, followed by flushing with four column volumes of hexanes prior to loading the sample onto the column to improve the separation and prevent the decomposition of sensitive DASPs. The residue was loaded onto the column and eluted using a hexanes/ethyl acetate gradient (see General Information for amounts of solvent). Phenyl iodide eluted first from the column, followed by unreacted MA (if present), then the desired 1,4-diazaspiro[2.2]-pentane(s) and, finally, *N*-aminophthalimide/hydrolysis products and/or products arising from DASP ring opening. The DASPs were stored in a freezer at -20°C . It was best to run any NMRs in deuterated benzene if the sample was to be recovered, as any residual acid in the CDCl_3 caused decomposition of the product.

(E)-2-(2'-Oxo-3-pentyl-1H-spiro[aziridine-2,7'-[3]oxa[1]-azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (6a)—The *E*-methyleniaziridine **6** was utilized as the starting material.^{5a,b} The product **6a** (149.5 mg) was obtained in 58% yield after column chromatography as a single diastereomer, the yield based on recovered starting material was 65%. The material was obtained as a light yellow solid: mp 143–144 $^{\circ}\text{C}$; IR 2959, 2858, 1736, 1714, 1465, 1378, 1246, 1226, 1196, 1143 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.75–7.65 (Ar, 4H), 4.56 (dd, 1H, $J = 11.0, 1.2$ Hz), 4.46 (dd, 1H, $J = 5.4, 4.8$ Hz), 3.93 (2 overlapping signals, 2H), 2.46 (m, 1H), 2.03–1.08 (several signals, 9H), 0.86 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 165.3, 157.7, 134.3, 130.8, 123.5, 68.8, 66.9, 45.9, 42.2, 31.8, 29.6, 26.1, 22.8, 22.7, 14.2. The NMRs pictured in the Supporting Information were run in C_6D_6 : ^1H NMR (500 MHz, C_6D_6) δ 7.21, 7.20 (Ar, AA'BB' pattern, 2H), 6.62, 6.61 (Ar, AA'BB' pattern, 2H), 4.28 (dd, 1H, $J = 5.9, 5.9$ Hz), 3.52–3.46 (2 overlapping signals, 2H), 3.36 (ddd, 1H, $J = 10.9, 4.0, 1.9$ Hz), 1.66–1.60 (overlapping signals, 4H total), 1.39–1.28 (br m, 4H total), 1.05 (dd, 1H, $J = 14.0, 6.5$ Hz), 0.9 (t, 3H, $J = 6.5$ Hz), 0.8 (overlapping m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.1, 157.1, 133.4, 130.9, 122.8, 68.0, 67.0, 45.5, 41.9, 31.9, 29.5, 26.2, 22.8, 22.3, 14.2; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^{+}$ 378.1425, found 378.1421.

(E)-2-(3-Pentyl-5',5'-dimethyl-2'-oxo-1H-spiro[aziridine-2,7'-[3]-oxa[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (7a)—The product (582.4 mg) was obtained as a single diastereomer in 72% yield using PhIO as the oxidant and the *E*-methyleniaziridine **7** as the substrate. The compound was a white solid: mp 101–102 $^{\circ}\text{C}$; IR 2953, 2932, 2859, 1736, 1472, 1374, 1297, 1232, 1208, 1126, 1100 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 4.34 (d, 1H, $J = 10.6$ Hz), 4.11 (dd, 1H, $J = 9.2, 3.5$ Hz), 3.79 (d, 1H, $J = 11.3$ Hz), 3.66 (s, 1H), 1.92 (m, 1H), 1.86–1.79 (br m, 2H), 1.58–1.22 (overlapping signals, 5H total), 1.29 (s, 3H), 0.93 (s, 3H), 0.90 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 165.2, 157.5, 134.1, 130.5, 123.2, 78.0, 65.0, 51.1, 46.0, 31.6, 31.2, 29.6, 25.8, 24.0, 22.5, 21.0, 14.0; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_4$ [$\text{M} + \text{H}$] $^{+}$ 384.1918, found 384.1926.

(Z)-2-(3-Pentyl-5',5'-dimethyl-2'-oxo-1H-spiro[aziridine-2,7'-[3]-oxa[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (8a)—The compound was obtained as a white solid in 33% yield as a single diastereomer using PhIO

as the oxidant and the *Z*-methyleneaziridine **8** as the substrate. The remainder of the mass balance was unreacted starting material, but the addition of additional aliquots of PhthNNH₂ and PhIO did not push the reaction to completion: IR 2959, 2932, 2859, 1736, 1472, 1374, 1297, 1232, 1208, 1126, 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.82, 7.81 (Ar, AA'BB' pattern, 2H), 7.75, 7.74 (Ar, AA'BB' pattern, 2H), 4.31 (d, *J* = 12.0 Hz, 1H), 3.87–3.83 (m(overlapping signals), 2H), 3.33 (s, 1H), 2.18–1.99 (m, 2H), 1.77–1.59 (m, 2H), 1.43–1.33 (m, 3H), 1.26–1.22 (m(overlapping signals), 4H), 1.05 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.6, 155.8, 134.4, 130.2, 123.4, 77.6, 63.3, 48.7, 48.6, 31.5, 29.4, 29.2, 26.7, 24.0, 22.4, 19.9, 14.0; HRMS (ESI) *m/z* calcd for C₂₁H₂₅N₃O₄Na [M + Na]⁺ 406.1738, found 406.1744.

(E)-2-(3-tert-Butyl-2'-oxo-1H-spiro[aziridine-2,7'-[3]oxa[1]-azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (9a)—The product (158.8 mg) was obtained in 79% yield: mp 174–176 °C; IR 2964, 2927, 2856, 1776, 1718, 1470, 1367, 1251, 1218, 1189, 1148, 1134 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 4.60 (app td, *J* = 11.3, 2.1 Hz, 1H), 4.40 (ddd, *J* = 10.6, 4.7, 1.7 Hz, 1H), 3.97 (overlapping signals, 2H total), 2.50 (dddd, *J* = 14.9, 6.8, 2.6, 2.1 Hz, 1H), 1.72 (m, 1H), 1.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 157.5, 134.0, 130.5, 123.1, 68.4, 65.5, 53.6, 42.2, 31.3, 27.1, 23.8; HRMS (ESI) *m/z* calcd for C₁₈H₂₀N₃O₄ [M + H]⁺ 342.1449, found 342.1451.

(E)-2-[2'-Oxo-3-(2-phenylethyl)-1H-spiro[aziridine-2,7'-[3]oxa[1]-azabicyclo[4.1.0]heptan]-1-yl]-1H-isoindole-1,3(2H)-dione (10a)—The product (103.0 mg) was obtained in 75% yield as a yellow oil: IR 2955, 2926, 2857, 1737, 1716, 1372, 1251, 1147 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.79, 7.78 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 7.33–7.29 (Ar, m, 2H), 7.26–7.19 (Ar, m, 3H), 4.50 (app td, *J* = 11.6, 2.4 Hz, 1H), 4.25 (ddd, *J* = 11.6, 4.0, 2.2 Hz, 1H), 4.00 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.84 (dd, *J* = 8.7, 7.1 Hz, 1H), 3.05 (m, 2H), 2.19 (overlapping signals, 3H total), 1.09 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.1, 157.2, 141.0, 134.1, 130.5, 128.7, 128.5, 126.2, 123.2, 68.5, 66.5, 45.4, 41.8, 32.7, 31.8, 21.6; HRMS (ESI) *m/z* calcd for C₂₂H₂₀O₄N₃ [M + H]⁺ 390.1449, found 390.1463.

(E)-6-(Benzyloxy)-2,2-dimethylhexa-3,4-dien-1-yl carbamate—The precursor for compound **11** was prepared in the following manner. The corresponding homoallenlic alcohol (524.3 mg, 2.26 mmol, 1.0 equiv) was dissolved in 9.0 mL of CH₂Cl₂ and cooled to 0 °C. To this was added dropwise trichloroacetyl isocyanate (350 μL, 2.9 mmol, 1.3 equiv) at 0 °C and warmed to rt. After approximately 1 h, the solvent was removed via rotary evaporation and redissolved in 6 mL of MeOH. To this was added K₂CO₃ (78.0 mg, 0.56 mmol, 0.25 equiv) in one portion. After TLC indicated complete consumption of starting material, the reaction mixture was quenched with saturated NH₄Cl, extracted with three portions of CH₂Cl₂ washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford the carbamate in 91% yield (565.6 mg) as a thick, clear oil: IR 2973, 1963, 1708, 1601, 1405, 1380, 1331 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.34 (Ar, 4H), 7.29 (ddd, *J* = 8.5, 4.1, 1.0 Hz, 1H), 5.37 (dd, *J* = 13.2, 6.8 Hz, 1H), 5.21 (ddd, *J* = 6.3, 2.5, 2.2 Hz, 1H), 4.54

(overlapping signals, 4H), 4.06 (dd, $J = 6.8, 2.3$ Hz, 2H), 3.87 (AB quartet, $J = 10.4, 2$ H), 1.07 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 203.6, 156.9, 138.2, 128.4, 127.8, 127.6, 99.3, 90.8, 72.8, 71.8, 68.5, 35.5, 24.9, 24.8; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ [M^+] 276.1595, found 276.1606.

(E)-7-[2-(Benzyloxy)ethylidene]-5,5-dimethyl-3-oxa-1-azabicyclo-

[4.1.0]heptan-2-one (11)—Dry CH_2Cl_2 (12 mL) was added to a flask containing 3 Å molecular sieves (0.5 g) and Rh_2eSP_2 (0.022 g, 0.029 mmol, 0.027 equiv). The material prepared above (0.300 g, 1.08 mmol, 1.0 equiv) was added, and the reaction mixture was stirred for 10 min. PhIO (0.660 g, 3.0 mmol, 2.8 equiv) was then added in one portion, and the reaction was stirred vigorously until the starting material was consumed. The mixture was filtered through a silica gel pad and washed several times with EtOAc. The filtrate was concentrated under reduced pressure, and the crude material indicated a 1:1 ratio of the *E*:*Z* olefin isomers by ^1H NMR. The crude material was purified via flash column chromatography through silica gel pretreated with 0.5% triethylamine to obtain **11** in 80% yield (0.236 g) as a clear oil: IR 2882, 1731, 1472, 1454, 1373, 1309, 1208, 1118 cm^{-1} . The ^1H and ^{13}C NMR spectra in the Supporting Information reflect an *E*:*Z* isomer ratio of approximately 1:0.6 (isomer A = *E*, isomer B = *Z*): ^1H NMR (500 MHz, C_6D_6) δ 7.35–7.07 (isomer A + B, m, 8H), 5.66 (isomer A, ddd, $J = 6.7, 5.7, 0.9$ Hz, 1H), 5.39 (isomer B, ddd, $J = 8.2, 6.6, 0.5$ Hz, 0.6H), 4.72 (isomer B, dd, $J = 11.7, 7.9$ Hz, 0.6H), 4.51 (isomer B, dd, $J = 12.0, 6.1$ Hz, 0.6H), 4.45 (isomer B, AB quartet, $J = 11.8$ Hz, 1.2H), 4.21 (isomer A, AB quartet, $J = 11.8$ Hz, 2H), 3.73 (isomer A, d, $J = 5.5$ Hz, 2H), 3.54 (isomer A, d, $J = 10.7$ Hz, 1H), 3.47 (isomer B, d, $J = 10.5$ Hz, 0.6 H), 3.16 (isomer A, d, $J = 10.7$ Hz, 1H), 3.13 (isomer B, $J = 10.7$ Hz, 0.6H), 2.59 (isomer A, 1H), 2.50 (isomer B, 0.6H), 0.53 (isomer A, 3H), 0.44–0.39 (isomer A + B, m, 6.6H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.3, 154.0, 138.9, 138.3, 128.3, 128.2, 128.2, 128.0, 127.6, 127.3, 126.6, 126.1, 101.3, 99.8, 77.2, 76.7, 72.2, 72.1, 66.8, 66.3, 47.9, 47.7, 28.6, 28.2, 22.8, 22.8, 19.8, 19.7; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3$ [$\text{M} + \text{H}^+$] 274.1438, found 274.1426.

(E)-2-{3-[(Benzyloxy)methyl]-5',5'-dimethyl-2'-oxo-1H-spiro-[aziridine-2,7'-[3]oxa[1]azabicyclo[4.1.0]heptan-1-yl]}-1H-isoindole-1,3(2H)-dione (11a)—A

3.5:1 *E*:*Z* ratio of the methyleneaziridine **11** was utilized as the starting material. The product (36.2 mg) was obtained in 62% isolated yield (based on the amount of **11** present in the starting material) as a white solid: mp 105–107 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.74, 7.73 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 7.36–7.29 (m, 5H), 4.72 (d, $J = 11.8$ Hz, 1H), 4.61 (d, $J = 11.6$ Hz, 1H), 4.36 (d, $J = 10.4$ Hz, 1H), 4.25 (dd, $J = 3.8, 3.6$ Hz, 1H), 4.16 (dd, $J = 11.5, 3.1$ Hz, 1H), 3.93 (dd, $J = 11.7, 3.7$ Hz, 1H), 3.82 (d, $J = 10.5$ Hz, 1H), 3.70 (s, 1H), 1.23 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.1, 157.5, 137.4, 134.1, 130.6, 128.4, 127.9, 127.9, 123.3, 78.2, 73.6, 66.5, 63.0, 50.9, 44.9, 29.7, 23.7, 19.7; HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_5$ [$\text{M} + \text{H}^+$] 434.1711, found 434.1703.

Ethyl 7-(carbamoyloxy)-6,6-dimethylhepta-3,4-dienoate—The precursor for **12** was prepared in the following manner. Chlorosulfonyl isocyanate (10.8 mmol, 1.5 equiv) was dissolved in dry CH_2Cl_2 (25 mL) and placed in an ice bath. The homoallenlic alcohol (1.43

g, 7.2 mmol, 1.0 equiv) was then added slowly over 20 min. Once the addition was complete, the ice bath was removed and the reaction mixture was stirred at rt until the starting material was consumed by TLC. The reaction was then placed in an ice bath, and THF (6 mL) and water (3 mL) were added to the reaction. The vessel was fitted with a reflux condenser and refluxed until TLC indicated the reaction was complete. Brine (50 mL) was added to the reaction mixture, and the solution was extracted with CH₂Cl₂ (2 × 50 mL) and dried with Mg₂SO₄, and the solvents were removed under reduced pressure. The residue was subjected to silica gel chromatography (100 mL portions of 0–50% EtOAc in hexanes gradient increased in increments of 10%) to give the product in 87% yield (1.38 g) as a clear oil: IR 2978, 1723, 1604, 1404, 1379, 1330, 1259, 1161 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.34 (m, 1H), 5.17 (m, 1H), 4.83 (br, 2H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.86 (s, 2H), 3.02 (dd, *J* = 7.0, 2.8 Hz, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 203.8, 171.73, 157.3, 99.7, 86.5, 72.8, 61.0, 35.8, 35.4, 25.0, 24.8, 14.4; HRMS (ESI) *m/z* calcd for C₁₂H₁₉NO₄Na [M + Na]⁺ 264.1207, found 264.1214.

(Z)-Ethyl 3-(5,5-dimethyl-2-oxo-3-oxa-1-azabicyclo[4.1.0]hept-7-ylidene)propanoate (12)—Dry CH₂Cl₂ (20 mL) was added to a flask that containing 4 Å molecular sieves (1.5 g) and Rh₂(esp)₂ (0.062 mmol, 0.03 equiv). The material prepared above (0.46 g, 2.07 mmol, 1 equiv) was added, and the reaction mixture was stirred for 10 min. PhIO (4.14 mmol, 2 equiv) was then added in one portion, and the reaction was stirred vigorously until the starting material was consumed by TLC. The mixture was filtered through a silica gel pad and washed several times with EtOAc. The filtrate was then concentrated under reduced pressure. Crude NMR indicated a ratio of 1:2.8 of the *E*:*Z* olefin isomers. The crude material was purified by silica gel chromatography (the column was pretreated with 1% triethylamine in hexanes). A gradient of 0–20% EtOAc in hexanes was used, increasing the more polar component by increments of 10%. The column was eluted with 80/20 hexanes/ethyl acetate until the green band corresponding to Rh₂(esp)₂ was collected. The polarity of the eluant was then increased to 20% ethyl acetate and slowly increased to 50% EtOAc in hexanes to give **12** in 86% yield (0.39 g) as a 36% yield of a mixture of *E*:*Z* and 50% isolated as the pure *Z* isomer as a thick oil: IR 2981, 1726, 1376, 1336, 1296, 1209, 1184, 1128, 1108 cm⁻¹. *Z* isomer: ¹H NMR (300 MHz, C₆D₆) δ 5.40 (t, *J* = 7.4 Hz, 1H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.65 (dd, *J* = 18.1, 7.2 Hz, 1H), 3.55 (dd *J* = 18.1 Hz, 1H), 3.42 (d, *J* = 10.6 Hz, 1H), 3.13 (d, *J* = 10.6 Hz, 1H), 2.47 (s, 1H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.49 (s, 3H), 0.37 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 171.3, 154.8, 126.9, 97.3, 60.9, 49.0, 33.1, 28.9, 23.5, 20.6, 14.5; HRMS (ESI) *m/z* calcd for C₁₂H₁₇NO₄Na [M + Na]⁺ 262.1050, found 262.1050.

(Z)-Ethyl-[1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5',5'-dimethyl-2'-oxospiro[aziridine-2,7' [3]oxa[1]azabicyclo[4.1.0]heptan]-3-yl]acetate (12a)—The compound was obtained in 42% yield (70.1 mg) as a single diastereomer using PhIO as the oxidant and the *Z*-methyleneamidine **12** as the substrate (there was a small amount of contamination from remaining PhtNNH₂). The remainder of the mass balance was unreacted starting material, and the yield based on recovered starting material was 58%. The material was an off-white solid: mp 51–52 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.82, 7.81 (Ar, AA'BB' pattern, 2H), 7.75, 7.74 (Ar, AA'BB' pattern, 2H), 4.33 (d, *J* = 10.5 Hz, 1H), 4.26 (t, *J* =

6.6 Hz, 1H), 4.19 (q, $J = 7.0$ Hz, 2H), 3.88 (d, $J = 10.5$ Hz, 1H), 3.38 (s, 1H), 3.35 (dd, $J = 18.0$, 6.6 Hz, 1H), 3.12 (dd, $J = 18.0$, 6.6 Hz, 1H), 1.27 (s, 3H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 165.7, 156.3, 134.7, 130.3, 123.7, 78.1, 62.2, 61.3, 49.5, 43.4, 34.8, 29.8, 24.4, 20.1, 14.3; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{21}\text{O}_6\text{N}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 422.1323, found 422.1323.

**(E)-2-(4'-Methyl-2'-oxo-3-pentyl-1H-spiro[aziridine-2,7'-[3]oxa-
[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (13a)**—The product was obtained in 79% yield (120.5 mg) based on the amount of **13** present in the starting material as a white solid: mp 143–144 °C; IR 2914, 1720, 1352, 1283, 1245, 1143 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 4.77 (m, 1H), 3.94 (dd, $J = 7.0$, 4.4 Hz, 1H), 3.86 (dd, $J = 9.3$, 7.0 Hz, 1H), 2.45 (ddd, $J = 14.4$, 6.0, 2.1 Hz, 1H), 1.95–1.88 (m, 1H), 1.78–1.67 (overlapping signals, 3H total), 1.42–1.27 (m, 8H), 0.92 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.0, 157.9, 134.0, 130.5, 123.1, 76.7, 66.9, 45.5, 41.4, 31.5, 29.4, 29.2, 25.8, 22.4, 20.6, 13.9; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{20}\text{H}_{23}\text{N}_3\text{O}_4\text{Na}$ [$\text{M} + \text{Na}^+$] 392.1581, found 392.1586.

**(E)-2-(4',4'-Dimethyl-2'-oxo-3-pentyl-1H-spiro[aziridine-2,7'-[3]-
oxa[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (14a)**—The product was obtained in 58% yield (125.3 mg) based on the amount of **14** present in the starting material as a white solid: mp 125–126 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 3.93 (dd, $J = 7.8$, 4.2 Hz, 1H), 3.83 (dd, $J = 9.1$, 6.8 Hz, 1H), 2.31 (dd, $J = 14.9$, 7.1 Hz, 1H), 1.94–1.89 (m, 1H), 1.73–1.67 (m, 3H), 1.64 (s, 3H), 1.58–1.20 (m, 8H), 0.92 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 160.5, 136.7, 133.3, 125.9, 87.2, 70.8, 48.2, 42.7, 35.6, 34.3, 32.4, 32.0, 32.0, 28.6, 27.8, 25.1, 16.7; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4\text{Na}$ [$\text{M} + \text{Na}^+$] 406.1738, found 406.1730.

**(E)-2-(6'-Methyl-2'-oxo-3-pentyl-1H-spiro[aziridine-2,7'-[3]oxa-
[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (15a)**—The product was obtained in 46% yield (53.5 mg) as an off-white, mushy solid: mp 27–30 °C; IR 2955, 2930, 2859, 1719, 1467, 1374, 1277, 1246, 1185, 1158 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 7.69, 7.68 (Ar, AA'BB' pattern, 2H), 4.59 (ddd, $J = 14.2$, 11.4, 1.8 Hz, 1H), 4.38 (ddd, $J = 11.4$, 3.8, 2.6 Hz, 1H), 3.96 (dd, $J = 7.0$, 4.6 Hz, 1H), 2.14 (ddd, $J = 15.0$, 3.4, 2.0 Hz, 1H), 2.00 (s, 3H), 1.95–1.90 (m, 1H), 1.74–1.65 (m, 4H), 1.42–1.34 (m, 4H), 0.92 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.3, 158.0, 134.0, 130.4, 123.1, 71.3, 67.4, 48.8, 46.1, 31.6, 29.3, 29.3, 25.7, 22.4, 18.2, 13.9; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4\text{Na}$ [$\text{M} + \text{Na}^+$] 392.1581, found 392.1570.

**(E)-2-(3-Pentyl-5',5'-dimethyl-2'-oxo-1H-spiro[aziridine-2,7'-[3]-
oxa[1]azabicyclo[4.1.0]heptan]-1-yl)-1H-isoindole-1,3(2H)-dione (19)**—The enantioenriched propargyl alcohol **16** was prepared according to literature procedure.⁹ The same procedure previously reported for the synthesis of racemic **17** was used to prepare the enantioenriched sample. High-pressure liquid chromatography (HPLC) analyses were performed at 224 and 254 nm. An AD-H column (4.6 μm diameter $\times$ 258 mm) at a

temperature of 40 °C was employed, using a flow rate of 1 mL/min and a gradient starting at 10% isopropyl alcohol in hexanes for 10 min and increasing to 30% isopropyl alcohol in hexanes. The eluant was then held at 30% isopropyl alcohol in hexanes until the run was completed. For the recrystallized **19**, the HPLC run was started at 5% isopropyl alcohol in hexanes. The er of **16a** was determined to be 88:12 by synthesizing the ester using (*S*)-(-)- α -methoxy- α -(trifluoromethyl)phenyl acetic acid and measuring the ratio of the resulting diastereomers.

General Procedure for Acetic Acid DASP Ring Openings

The DASP was dissolved in enough THF to prepare a 0.1 M solution and cooled to 0 °C. Glacial acetic acid (50.0 equiv) was added dropwise to the reaction mixture over 2 min, ensuring that the reaction temperature remained at 0 °C. The reaction was warmed to room temperature and monitored by TLC until complete (3–10 h). After consumption of the starting material, the reaction mixture was concentrated under reduced pressure and purified via column chromatography (hexanes/ethyl acetate gradient; see General Information for the amounts) to afford the desired ring-opened DASPs.

(E)-1-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-9-yl acetate (20)—The ring-opened DASP **20** was obtained in 95% yield as an off-white solid (86.9 mg): ¹H NMR (500 MHz, C₆D₆) δ 7.83, 7.82 (Ar, AA'BB' pattern, 2H), 7.76, 7.75 (Ar, AA'BB' pattern, 2H), 7.28 (NH, 1H), 4.35 (dt, *J* = 11.1, 4.3 Hz, 1H), 4.22 (app t, *J* = 11.9 Hz, 1H), 3.64 (dd, *J* = 11.9, 5.1 Hz, 1H), 3.59 (dd, *J* = 6.0, 6.0 Hz, 1H), 2.09–2.04 (m, 1H), 1.98 (s, 3H), 1.93–1.68 (m, 5H), 1.43–1.36 (m, 4H), 0.93 (t, *J* = 7.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.0, 165.9, 153.7, 134.5, 130.0, 123.5, 74.9, 65.1, 53.9, 53.6, 31.5, 28.6, 26.2, 23.9, 22.4, 20.8, 14.0; HRMS (ESI) *m/z* calcd for C₂₁H₂₆N₃O₆ [M + H⁺] 416.1817, found 416.1821.

(E)-1-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-8,8-trimethyl-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-9-yl acetate (21)—The product was obtained in 65% yield (354.1 mg) as a white solid: mp 115–117 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.84, 7.83 (Ar, AA'BB' pattern, 2H), 7.75, 7.74 (Ar, AA'BB' pattern, 2H), 7.72 (br, 1H), 4.06 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.93 (d, *J* = 10.9 Hz, 1H), 3.78 (d, *J* = 10.9 Hz, 1H), 3.30 (s, 1H), 2.01 (m, 1H), 1.90 (s, 3H), 1.76 (m, 2H), 1.39 (m, 5H), 1.16 (s, 3H), 1.15 (s, 3H), 0.93 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 166.3, 153.4, 134.8, 129.9, 123.7, 77.6, 75.3, 61.8, 54.6, 31.8, 31.2, 30.2, 26.3, 22.6, 21.6, 18.6, 14.2; HRMS (ESI) *m/z* calcd for C₂₃H₂₉N₃O₆Na [M + Na]⁺ 466.1949, found 466.1937.

(E)-2-tert-Butyl-1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-5-oxo-6-oxa-1,4-diazaspiro[2.6]non-9-yl acetate (22)—The product was obtained in 68% yield (47.4 mg) as a white solid: mp 134–136 °C; IR 2957, 2926, 2854, 1767, 1713, 1467, 1376, 1188 cm⁻¹ ¹H NMR (500 MHz, CDCl₃) δ 7.83, 7.82 (Ar, AA'BB' pattern, 2H), 7.76, 7.75 (Ar, AA'BB' pattern, 2H), 7.54 (NH, 1H), 4.30 (ddd, *J* = 11.1, 4.6, 2.3 Hz, 1H), 4.18 (app td, *J* = 11.7, 2.6 Hz, 1H), 3.86 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.70 (s, 1H), 2.13–2.08 (m, 1H), 1.97–1.92 (overlapping signals, 4H total), 1.20 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 169.9,

165.9, 153.8, 134.6, 129.8, 123.5, 75.6, 64.8, 60.8, 53.7, 32.1, 29.6, 28.4, 24.4, 20.9; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_3O_6Na$ [$M + Na^+$] 424.1480, found 424.1488.

(Z)-Ethyl-[9-(acetyloxy)-1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-8,8-dimethyl-5-oxo-6-oxa-1,4-diazaspiro[2.6]non-2-yl]acetate (23)—The product was obtained in 85% yield (52.8 mg) as a light yellow solid: mp 175–176 °C; 1H NMR (300 MHz, $CDCl_3$) δ 7.85, 7.84 (Ar, AA'BB' pattern, 2H), 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 6.77 (s, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.89 (d, $J = 10.9$ Hz, 1H), 3.81 (d, $J = 10.9$ Hz, 1H), 3.70 (dd, $J = 7.4, 4.6$ Hz, 1H), 3.28 (d, $J = 0.7$ Hz, 1H), 3.18 (dd, $J = 17.3, 4.6$ Hz, 1H), 2.64 (dd, $J = 17.3, 7.4$ Hz, 1H), 2.16 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 168.7, 152.6, 135.0, 130.3, 123.9, 76.3, 61.4, 61.1, 44.5, 33.1, 32.3, 23.7, 21.5, 20.2, 14.4; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_3O_8Na$ [$M + Na$] $^+$ 482.1534, found 482.1519.

(E)-1-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-8,8-trimethyl-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-9-yl pivalate (24)—The DASP **7a** (50.0 mg, 0.13 mmol, 1 equiv) was dissolved in dry THF (1.5 mL), and pivalic acid (1.3 mmol, 10 equiv) was added. The reaction was stirred until complete by TLC (~72 h). The reaction was quenched with a saturated solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (3×15 mL), dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 0–100% EtOAc in hexanes in increments of 20%) to give **24** in 80% yield (62.9 mg) as a white solid: mp 165–166 °C; 1H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.83, 7.82 (Ar, AA'BB' pattern, 2H), 7.76, 7.75 (Ar, AA'BB' pattern, 2H), 3.92 (d, $J = 10.9$ Hz, 1H), 3.87 (dd, $J = 9.6, 3.3$ Hz, 1H), 3.76 (d, $J = 10.9$ Hz, 1H), 3.32 (s, 1H), 2.03 (m, 1H), 1.78 (m, 2H), 1.42 (m, 5H), 1.19 (s, 3H), 1.13 (s, 3H), 0.93 (overlapping signals, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 166.0, 153.4, 134.8, 129.9, 123.6, 77.4, 75.5, 62.3, 55.1, 39.4, 31.2, 30.5, 26.7, 26.4, 23.0, 22.6, 19.1, 14.2. (line broadening set at 10 to observe the quaternary carbons); HRMS (ESI) m/z calcd for $C_{26}H_{35}N_3O_6Na$ [$M + Na$] $^+$ 508.2419, found 508.2413.

(E)-1-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-8,8-trimethyl-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-9-yl tiglate (25)—The DASP **7a** (31.2 mg, 0.081 mmol, 1.0 equiv) was dissolved in 2.0 mL of CH_2Cl_2 and cooled to 0 °C. Tiglic acid (51.0 mg, 0.51 mmol, 6.3 equiv) was added to this solution in one portion and warmed to rt, followed by sonication for 5 h. After TLC indicated complete consumption of starting material, the reaction mixture was quenched with $NaHCO_3$, extracted with three portions of CH_2Cl_2 , washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude material was purified via flash column chromatography to afford **25** as a white solid in 74% yield (28.8 mg): 1H NMR (500 MHz, C_6D_6) δ 8.05 (NH, 1H), 7.32, 7.31 (Ar, AA'BB' pattern, 2H), 6.84, 6.82 (Ar, AA'BB' pattern, 2H), 6.72 (qq, $J = 7.0, 1.5$ Hz, 1H), 4.37 (dd, $J = 9.7, 3.7$ Hz, 1H), 3.42 (d, $J = 10.6$ Hz, 1H), 3.40 (d, $J = 11.0$ Hz, 1H), 3.15 (s, 1H), 1.93–1.87 (m, 3H), 1.50–1.37 (m, 5H), 1.07 (s, 3H), 0.96 (overlapping signals, 6H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.9, 152.4, 141.0, 133.7, 129.9, 128.0, 127.4, 122.7, 76.7, 76.1, 61.7, 54.6, 31.7, 30.7, 30.2, 26.4, 22.7, 22.2, 18.4, 14.0, 13.8, 11.3; HRMS (ESI) m/z calcd for $C_{26}H_{34}N_3O_6$ [$M + H^+$] 484.2443, found 484.2419.

(E)-(S)-[1-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-pentyl-8,8-dimethyl-5-oxo-6-oxa-1,4-diazaspiro[2.6]non-9-yl] ethanethioate (26)—Thioacetic acid (600 μ L, 8.4 mmol, 105 equiv) was dissolved in 1.5 mL of THF and cooled to -78°C . The DASP **7a** (30.5 mg, 0.080 mmol, 1.0 equiv) dissolved in 2.5 mL of THF was added dropwise to the solution over 2 min. The reaction mixture was maintained at -78°C for an additional 15 min, warmed to 0°C for 2 h, and then left to warm to rt overnight. After TLC indicated complete consumption of the starting materials, the volatiles were removed under reduced pressure and the crude material was purified via column chromatography (hexanes/ethyl acetate gradient) to afford **26** in 82% yield (29.9 mg) as an off-white solid. The reaction was repeated on a larger scale to give an 84% yield of **26** (275.9 mg): mp $185\text{--}186^{\circ}\text{C}$; IR 2930, 1704, 1479, 1374, 1279, 1262, 1120 cm^{-1} ^1H NMR (500 MHz, CDCl_3) δ 7.86 (br signal, 2H), 7.75, 7.74 (Ar, AA'BB' pattern, 2H), 7.25 (NH, 1H), 4.07 (d, $J = 10.5$ Hz, 1H), 3.88 (dd, $J = 10.1, 3.8$ Hz, 1H), 3.80 (d, $J = 11.4$ Hz, 1H), 3.35 (s, 1H), 2.27 (s, 3H), 2.19–2.12 (m, 1H), 1.89–1.75 (m, 2H), 1.62–1.53 (m, 1H), 1.46–1.37 (m, 4H), 1.17 (s, 3H), 1.14 (s, 3H), 0.94 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 193.3, 167.0, 165.1, 153.2, 134.6, 130.4, 129.3, 123.7, 123.5, 76.1, 63.4, 60.9, 56.8, 31.8, 31.5, 31.2, 31.1, 26.7, 24.6, 22.5, 19.7, 14.1 (line broadening set at 5 in order to observe quaternary carbons); HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_5\text{S}$ [$\text{M} + \text{H}^+$] 460.1901, found 460.1897.

(E)-2-(9-Chloro-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-1-yl)-1H-isoindole-1,3(2H)-dione (27)—DASP **6a** (50.0 mg, 0.14 mmol, 1 equiv) was dissolved in acetone (1.4 mL), and dry, powdered LiCl (1.4 mmol, 10 equiv) was added to the reaction mixture. The suspension was stirred at rt until TLC indicated complete consumption of **6a**. Water (15 mL) was added and the reaction mixture extracted with EtOAc (3×15 mL), dried with Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient 0–100% EtOAc in hexanes in increments of 20%) to give **27** in 84% yield (45.9 mg) as a white solid: mp $133\text{--}135^{\circ}\text{C}$; IR 2995, 2929, 1721, 1467, 1376, $1300, 1249\text{ cm}^{-1}$ ^1H NMR (300 MHz, CDCl_3) δ 8.01–7.80 (overlapping signals, Ar, 4H), 7.10 (s, 1H), 4.41 (m, 1H), 4.26 (m, 1H), 3.71 (m, 2H), 2.22 (m, 1H), 1.99 (m, 1H), 1.70–1.10 (m, 8H), 0.93 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.0 (indirectly observed by HMBC), 153.9, 134.8, 130.0 (indirectly observed by HMBC), 124.0, 71.0, 64.7, 55.1, 54.3, 31.8, 29.0, 26.5, 24.4, 22.6, 14.2; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{ClO}_4$ [$\text{M} + \text{H}^+$] 392.1372, found 392.1376.

(E)-2-(9-Chloro-8,8-dimethyl-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-1-yl)-1H-isoindole-1,3(2H)-dione (28)—Chlorotrimethylsilane (150 μ L, 1.18 mmol, 14 equiv) was dissolved in 1 mL of THF and cooled to -78°C . The DASP **7a** (33.2 mg, 0.086 mmol, 1.0 equiv) in 2.5 mL of THF was added dropwise over 2 min. After the addition was complete, the reaction mixture was warmed to 0°C for 2 h and then to room temperature for an additional 2 h. The reaction mixture was concentrated under reduced pressure and the residue purified via column chromatography (hexanes/ethyl acetate gradient) to afford **28** in 93% yield (33.5 mg) as a white solid: mp $122\text{--}124^{\circ}\text{C}$; IR 2954, 1715, 1480, 1467, 1375, $1261, 1120\text{ cm}^{-1}$ ^1H NMR (500 MHz, CDCl_3) δ 7.87 (br s, Ar, 1H), 7.79 (br s, Ar, 1H), 7.75, 7.74 (Ar, AA'BB' pattern, 2H), 7.00 (NH, 1H), 4.39 (d, $J = 11.2$ Hz, 1H), 4.12 (dd, $J = 11.2, 3.9$ Hz, 1H), 3.74 (d, $J = 10.8$ Hz, 1H), 3.32 (s, 1H), 2.00–1.94 (m, 1H), 1.76–1.67 (m,

2H), 1.43–1.34 (m, 5H), 1.25 (s, 3H), 1.22 (s, 3H), 0.93 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 165.0, 153.2, 134.6, 130.4, 129.1, 123.8, 123.3, 73.9, 70.8, 62.8, 54.2, 31.6, 31.0, 30.5, 26.5, 26.4, 22.5, 20.5, 14.0; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_4\text{Cl}$ $[\text{M} + \text{H}]^+$ 420.1685, found 420.1666.

General Procedure for Tandem Reactions

A 50 mL flame-dried round-bottom flask was charged with 3 Å molecular sieves (500 mg), followed by $\text{Rh}_2(\text{esp})_2$ (0.041 mmol, 0.025 equiv). The allenic carbamate (1.6 mmol, 1.0 equiv) in 15 mL of dry CH_2Cl_2 was added to the reaction flask. The resulting blue-green mixture was stirred for 10 min at rt under a flow of nitrogen, then iodosobenzene (4.1 mmol, 2.5 equiv) was added in one portion. The reaction was monitored by TLC until it was complete, then cooled to 0 °C in an ice bath. A portion of *N* aminophthalimide (3.1 mmol, 1.9 equiv) and dry potassium carbonate (6.4 mmol, 4.0 equiv), followed by additional oxidant (3.0 mmol, 1.9 equiv), was added, and the resulting light yellow slurry was allowed to warm slowly to rt. The reaction mixture was monitored by TLC, and additional portions of PhthNNH₂ and oxidant were added until no further conversion to the 1,4-diazaspiro[2.2]pentane was noted. The desired nucleophile was then added (3.0–15.0 equiv) and the reaction stirred at rt until complete. The reaction mixture was passed through a plug of silica gel to remove solids using first Et_2O , then EtOAc to flush the plug. The solvents were removed under reduced pressure, and the residue was purified via silica gel column chromatography (hexanes/ethyl acetate gradient). Phenyl iodide eluted first from the column, followed by the Rh catalyst, unreacted methyleneaziridine (if present), unreacted 1,4-diazaspiro[2.2]pentane(s) (if present), products of the hydrolysis of the excess *N*-aminophthalimide and, finally, the desired *N,N*-aminal product as a single diastereomer. The following amounts of material were obtained: **21** (315.1 mg) for a 46% yield; **26** (328.1 mg) for a 48% yield; and **28** (345.0 mg) for a 53% yield.

(E)-2-(9-Bromo-8,8-dimethyl-5-oxo-2-pentyl-6-oxa-1,4-diazaspiro[2.6]non-1-yl)-1H-isoindole-1,3(2H)-dione (30)—DASP **7a** (44.8 mg, 0.117 mmol, 1.0 equiv) was dissolved in 3.0 mL of THF and cooled to 0 °C. Bromotrimethylsilane (90 μL , 0.682 mmol, 5.8 equiv) was added to the solution in one portion. The reaction was maintained at 0 °C for 2 h until complete consumption of starting material was observed by TLC. The reaction mixture was loaded directly onto the column without removal of the solvent and purified via flash column chromatography to afford the desired compound **30** and a byproduct **31** (see below) in a 6.7:1.0 ratio in 89% overall yield (48.2 mg, 77% yield **30**) as a white solid. The ^1H and ^{13}C NMR spectra of the ring-opened DASP were obtained on a sample further purified by recrystallization: mp 88–90 °C; ^1H NMR (500 MHz, CDCl_3) δ 7.90–7.87 (m, 1H), 7.81–7.74 (m, 3H), 7.01 (NH, 1H), 4.55 (d, $J = 11.2$ Hz, 1H), 4.26 (dd, $J = 10.8, 3.2$ Hz, 1H), 3.69 (d, $J = 11.3$ Hz, 1H), 3.24 (d, $J = 3.24$ Hz, 1H), 2.03–1.96 (m, 1H), 1.77–1.67 (m, 1H), 1.44–1.33 (m, 6H), 1.25 (s, 3H), 1.22 (s, 3H), 0.93 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.5, 164.7, 153.1, 134.6, 134.5, 130.3, 129.1, 123.9, 123.4, 73.4, 66.8, 63.3, 54.5, 31.6, 31.0, 30.7, 27.2, 26.4, 22.5, 20.4, 14.0; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_4\text{Br}$ $[\text{M} + \text{H}^+]$ 464.1180, found 464.1161.

(E)-2-([2-Bromo-1-(5,5-dimethyl-2-oxo-1,3-oxazinan-4-yl)-heptylidene]amino)-1H-isoindole-1,3(2H)-dione (31)—The DASP **7a** (42.1 mg, 0.11 mmol, 1.0 equiv) was dissolved in 4 mL of THF and cooled to 4 °C. Bromotrimethylsilane (60 μ L, 0.46 mmol, 4.2 equiv) was added to the solution in one portion. The reaction was stirred for 2 h at 4 °C until TLC indicated complete consumption of the starting material. The volatiles were removed under reduced pressure, and the crude reaction mixture was purified via column chromatography to afford **31** in 59% yield (30.0 mg) as a white solid: mp 101–103°C; ¹H NMR (500 MHz, CDCl₃) δ 7.89, 7.88 (Ar, AA'BB' pattern, 2H), 7.77, 7.76 (Ar, AA'BB' pattern, 2H), 5.99 (d, NH, J = 3.2 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.62 (dd, J = 11.3, 3.3 Hz, 1H), 4.32 (dd, J = 4.3, 1.2 Hz, 1H), 3.85 (dd, J = 11.0, 1.6 Hz, 1H), 2.31–2.24 (m, 1H), 1.87–1.79 (m, 1H), 1.38–1.26 (m, 12H), 0.88 (t, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.9, 163.6, 152.6, 134.7, 131.0, 124.0, 74.7, 58.1, 48.5, 33.9, 31.7, 30.7, 27.0, 26.3, 22.4, 21.0, 13.9; HRMS (ESI) m/z calcd for C₂₁H₂₆N₃O₄BrNa [M + Na⁺] 486.0999, found 486.0996

(E)-2-([2-Methoxy-1-(5,5-dimethyl-2-oxo-1,3-oxazinan-4-yl)-heptylidene]amino)-¹H-isoindole-1,3(2H)-dione (32a,b)—The DASP **7a** (100.0 mg, 0.261 mmol, 1 equiv) was dissolved in 3 mL of methanol, and acetic acid (0.261 mmol, 1 equiv) was added to the reaction. The mixture was stirred at rt until the starting material was consumed as indicated by TLC. The reaction mixture was quenched with saturated sodium bicarbonate (10 mL) and extracted with 2 $\times$ 10 mL of ethyl acetate. The combined organics were washed with brine and dried over sodium sulfate, and the volatiles were removed under reduced pressure. The product ratio was determined by ¹H NMR analysis of the crude reaction mixture. The two diastereomers were difficult to separate by conventional column chromatography (obtained as a mixture in 61% yield (65.9 mg) using a gradient of 0–1% MeOH in CHCl₃, increasing in 0.2% increments), and preparative TLC (75% ethyl acetate/hexane) was used to obtain samples for analysis. The mixture was a white solid, but due to the small amounts of material separated for analysis, no mp was obtained. Minor diastereomer: ¹H NMR (300 MHz, CDCl₃) δ 7.88 (Ar, AA'BB' pattern, 2H), 7.77 (Ar, AA'BB' pattern, 2H), 5.38 (br d, J = 3.1 Hz, 1H), 4.37 (t, J = 6.2 Hz, 1H), 4.33 (d, J = 11.4 Hz, 1H), 4.18 (dd, J = 3.1, 1H), 3.79 (dd, J = 10.9, 1H), 3.45 (s, 3H), 1.92 (m, 2H), 1.36–0.86 (several overlapping signals, 15H); ¹³C NMR (125 MHz, CDCl₃) δ 177.8, 164.1, 152.3, 134.8, 131.0, 124.0, 77.2, 74.1, 60.1, 54.6, 31.7, 31.6, 29.7, 26.7, 24.7, 22.5, 20.1, 14.0; HRMS (ESI) m/z calcd for C₂₂H₃₀N₃O₅ [M + H⁺] 416.2180, found 416.2179. Major diastereomer (containing some of the minor diastereomer): ¹H NMR (300 MHz, CDCl₃) δ 7.90 (Ar, AA'BB' pattern, 2H), 7.80 (Ar, AA'BB' pattern, 2H), 6.10 (br s, 1H), 4.47 (dd, J = 8.2, 6.4 Hz, 1H), 4.44 (d, J = 0.9 Hz, 1H), 3.93 (d, J = 11.2 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.35 (s, 3H), 2.04 (m, 1H), 1.88 (m, 1H), 1.38 (m, 6H), 1.10 (s, 3H), 0.94 (6H); ¹³C NMR (125 MHz, CDCl₃) δ 174.9, 164.1, 152.6, 135.0, 131.2, 124.3, 78.2, 76.1, 60.9, 52.8, 32.9, 31.9, 28.1, 25.5, 23.7, 22.7, 19.6, 14.2; HRMS (ESI) m/z calcd for C₂₂H₂₉N₃O₅Na [M + Na⁺] 438.2000, found 438.2000.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of biologically active molecules containing a C–N/C–N/C–O stereotriad.

Scheme 1.

Table 1

Synthesis of 1,4-Diazaspiro[2.2]pentanes

$ \begin{array}{c} \text{R}^1 \\ \\ \text{C}=\text{C} \\ \quad \\ \text{R}^2 \quad \text{R}^3 \\ \quad \\ \text{N} \quad \text{O} \\ \quad \\ \text{R}^4 \quad \text{R}^5 \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C to rt}]{1.5 \text{ equiv PhthNNH}_2, 1.6 \text{ equiv PhIO}, 3.5 \text{ equiv K}_2\text{CO}_3} \begin{array}{c} \text{R}^1 \\ \\ \text{C}=\text{C} \\ \quad \\ \text{R}^2 \quad \text{R}^3 \\ \quad \\ \text{N} \quad \text{O} \\ \quad \\ \text{R}^4 \quad \text{R}^5 \end{array} \quad \text{6a-15a} $							
entry	R, R ¹ , R ² , R ³ , R ⁴ , R ⁵	product	yield	entry	R, R ¹ , R ² , R ³ , R ⁴ , R ⁵	product	yield
1	C ₆ H ₁₁ , H, H, H, H, H		58% (65%) ^a	6	BnOCH ₂ , H, H, Me, H, H		62% ^c
2	C ₆ H ₁₁ , H, H, Me, H, H		72%	7	H, CH ₂ CO ₂ Et, H, Me, H, H		42% (58%) ^{b,d}
3	H, C ₆ H ₁₁ , H, Me, H, H		33% ^b	8	C ₆ H ₁₁ , H, H, H, Me, H		79% ^c
4	^t Bu, H, H, Me, H, H		79%	9	C ₆ H ₁₁ , H, H, H, Me, Me		58% ^c
5	Ph(CH ₂) ₂ , H, H, H, H, H		75%	10	C ₆ H ₁₁ , H, Me, H, H, H		46%

^aYield based on recovered *E*-methyleneaziridine. ^bThe starting material was the *Z*-methyleneaziridine. ^cYield based on the amount of *E*-methyleneaziridine present in the mixture. ^dYield based on recovered *Z*-methyleneaziridine.

^aYield based on recovered *E*-methyleneaziridine. ^bThe starting material was the *Z*-methyleneaziridine. ^cYield based on the amount of *E*-methyleneaziridine present in the mixture. ^dYield based on recovered *Z*-methyleneaziridine.

Table 2

Synthesis of N,N-Aminals via Ring Opening at C1 of a 1,4-Diazaspiro[2.2]pentane

entry	R, R ¹ , R ² , R ³	nucleophile	product	yield	entry	R, R ¹ , R ² , R ³	nucleophile	product	yield
1	C ₅ H ₁₁ , H, H, H 6a	AcOH		95% 20	6	C ₅ H ₁₁ , H, H, Me 7a	tiglic acid		74% 25
2	C ₅ H ₁₁ , H, H, Me 7a	AcOH		65% 21	7	C ₅ H ₁₁ , H, H, Me 7a	AcSH		82% 26
3	^t Bu, H, H, H 9a	AcOH		68% 22	8	C ₅ H ₁₁ , H, H, H 6a	LiCl		84% 27
4	H, CH ₂ CO ₂ Et, H, Me 12a	AcOH		85% 23	9	C ₅ H ₁₁ , H, H, Me 7a	TMSCl		93% 28
5	C ₅ H ₁₁ , H, H, Me 7a	PivOH		80% 24					

Table 3**One-Pot Synthesis of N,N-Spiroaminals from an Allenic Carbamate** ^aCombined yield of the three individual steps.

Table 4

Directing the Nucleophilic Ring Opening of the DASP to C3

entry	conditions	products	yield
1	6 equiv TMSBr		30:31 6.7:1 89%
2	4 equiv TMSBr mixture concentrated before purification		31 59%
3	1 equiv AcOH MeOH ^a		32a:32b 1.6:1 61%

^aMethanol was substituted for THF as the solvent for the reaction.