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Synthesis and Selected Reactions of a Bicyclic Sultam Having Sulfur at the Apex Position

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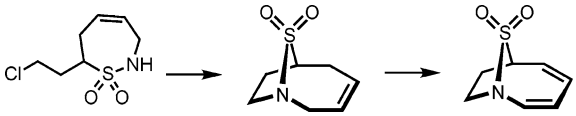
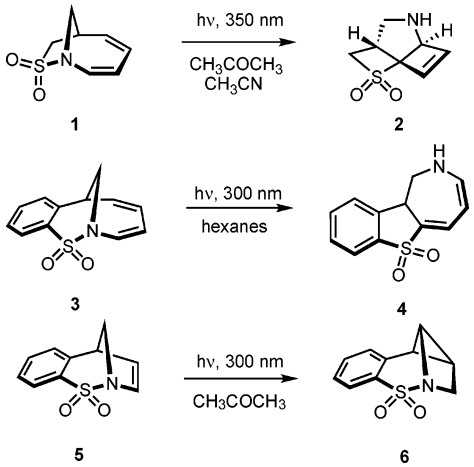


A practical synthesis of the bicyclic dienyl sultam **9** has been developed. The viable route involved several key steps. Of these, ring-closing metathesis represented by the conversion of **19** to **20** had to be implemented in advance of the assembly of other rings such as is present in **15**. Product **20** was used as the template for more advanced framework construction, as in **16**. The second double bond was best introduced by a bromination−dehydrobromination sequence, the 2-fold loss of HBr being achieved most reliably by the use of tetra-*n*-butylammonium fluoride in CH_2Cl_2 or DMSO. The direct irradiation of **9** gave rise to the endo-oriented cyclobutene derivative **30**. The title diene is not a ready participant in Diels−Alder reactions. When heated with *endo*-bornyltriazolinedione in ethyl acetate solution, conversion to a 1:1 mixture of **33** and its diastereomer occurred as confirmed by X-ray crystallographic analysis. From the mechanistic perspective, this transformation constitutes an interesting example of a stereocontrolled and regioselective [2+2] cycloaddition followed by a vinylcyclobutane−cyclohexene rearrangement. Products **30** and **33** constitute examples of strained sulfonamides featuring a norbornyl-like structural component.

Introduction

X-ray data relating to sulfonamides reveal that the lone electron pair on nitrogen is most often oriented to the bisector of the O−S−O internuclear angle notwithstanding substantial differences in hybridization at N.[1] Bridgehead sultams where a significant departure from this preferred stereoelectronic arrangement is amenable to incorporation hold interest from a structural and reactivity perspective. At the present time, few sultams of this general class have been reported. The system defined by **1** has been shown to experience unprecedented homolytic N−SO_2 bond cleavage with conversion to **2** when irradiated.[2] This transformation appears to hold generality in light of the recently discovered photoisomerization of **3** to **4**.[3] These features do not interfere with operation in **5** of the triplet-sensitized di-π-methane rearrangement.[4]



1 2 3 4 5 6

To our knowledge, no bridged sultam featuring the sulfur atom at the apex position as in **7** has as of yet been reported.

(1) (a) Beddoes, R. L.; Dalton, L.; Joule, J. A.; Miller, S. S.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans.* **1986**, *2*, 787. (b) For additional examples, see: Klug, H. P. *Acta Crystallogr.* **1968**, *24*, 792. Oppolzer, W.; Rodriguez, I.; Starkmann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*. 5019.

(2) Paquette, L. A.; Barton, W. R. S.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 1313.

(3) Paquette, L. A.; Dura, R. D.; Fosnaugh, N.; Stepanian, M. submitted for publication.

(4) Dura, R. D.; Paquette, L. A. *J. Org. Chem.* **2006**, *71*, 2456.

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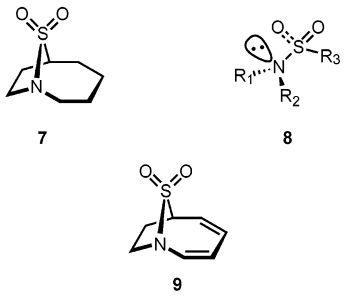
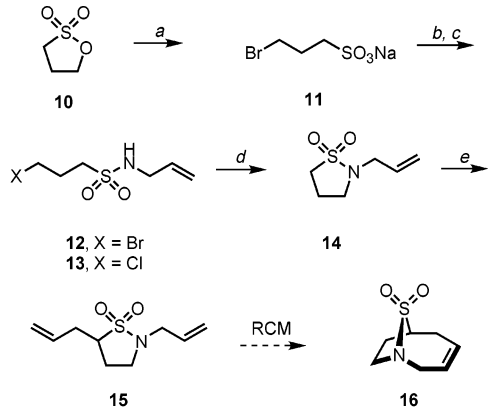
Molecular models of this sulfonamide subclass provide qualitative indication that little departure from ideal electronic interplay as in **8** is operational. To increase the opportunities for probing chemical reactivity patterns, we have in the present investigation synthesized the doubly unsaturated congener **9**, briefly assessed its capacity to enter into cycloaddition chemistry, and elucidated in a preliminary fashion its response to photoexcitation.



Results and Discussion

To achieve a directed synthesis of the appropriate molecular architecture, we envisioned the application of ring-closing metathesis (RCM) to the crafting of **16** from **15** as shown in Scheme 1. This intramolecular cyclization would establish a

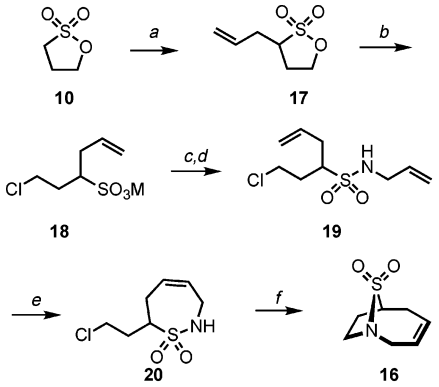
SCHEME 1



[a] NaBr, H_2O, 60 °C (51%). [b] $(COCl)_2$, DMF, 1:1 THF : CH_2Cl_2, 0 °C. [c] $H_2NCH_2CH{=}CH_2$, Et_3N, CH_2Cl_2, 0 °C (82% over two steps); 88% of **12**, 12% of **13**. [d] KOH, Et_3N, EtOH, reflux for 2 h (95%). [e] LDA, THF, $CH_2{=}CHCH_2Br$, -78 °C (60%).

needed carbon−carbon double bond and generate the [4.2.1] bicyclic framework in a single, simple operation. The evaluation of this plan of action began by heating commercially available 1,3-propanesultone (**10**) with sodium bromide in water at 60 °C.[6] The resulting sulfonate salt **11** was transformed into the sulfonyl chloride by reaction with oxalyl chloride. This activation step was followed by condensation with allylamine, thereby producing the bromo-substituted sulfonamide **12**. The chloro analogue **13** was also formed to a lesser degree (88:12) following the two-step sequence. This inseparable mixture of halogenated sulfonamides was conveniently cyclized through exposure to sodium hydroxide and triethylamine in refluxing ethanol to deliver **14** exclusively.[7] Allylation α to the sulfonyl

SCHEME 2



[a] *n*-BuLi, THF, $CH_2{=}CHCH_2Br$, -78 to 0 °C (58%). [b] NaCl, H_2O, 60 °C, 20 h. [c] $(COCl)_2$, DMF, THF-CH_2Cl_2, 0 °C, 4 h. [d] $CH_2{=}CHCH_2NH_2$, Et_3N, CH_2Cl_2, rt (40% over 3 steps). [e] Grubbs 1st generation catalyst (1 mol %), CH_2Cl_2, rt; $Pb(OAc)_4$ (98%). [f] NaOH, Et_3N, EtOH, reflux, 2 h (95%).

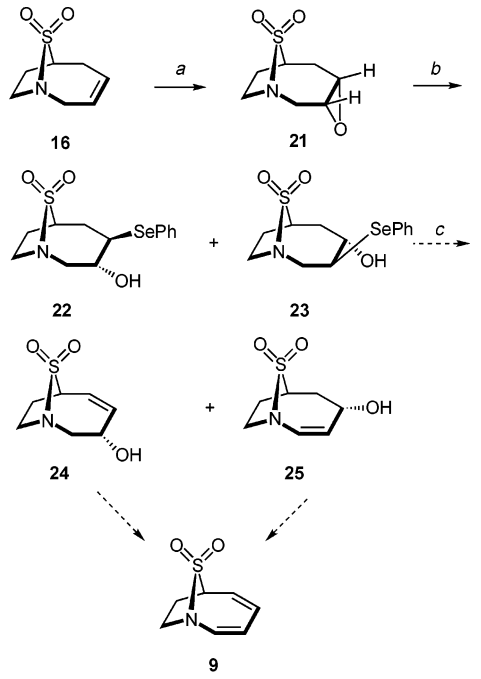
group was next achieved via carbanion generation with LDA and the controlled addition of an equivalent of allyl bromide. At this point, we soon discovered that all reactions carried out for the purpose of forming **16** by metathesis were to no avail. In the final analysis, we attributed this inability to achieve cyclization to a combination of ring strain and steric effects.

Our solution for remedying the lack of reactivity in **15** was to implement the RCM step on an acyclic intermediate prior to the formation of any other rings. Testing of the feasibility of this approach began by bringing the anion of propanesultone **10** into reaction with allyl bromide,[8] with resultant formation of **17** (Scheme 2). Nucleophilic ring opening was next undertaken with several different chloride salts (LiCl, NaCl, and KCl), of which sodium chloride proved to be the least scale-sensitive. The resulting sulfonate salt was used in unpurified form to generate the sulfonyl chloride and subsequently the sulfonamide **19**. As advertised by others for compounds of this class,[5,9] the exposure of **19** to the first-generation Grubbs catalyst proceeded smoothly to deliver **20** cleanly and in high yield (>90%) at catalyst loadings of 1 mol %. Subsequent base-promoted cyclization of **20** led readily and efficiently to **16** via intramolecular alkylation.

With a viable route to **16** in place, we were in a position to examine its transformation into the target diene **9**. The first attempts in this direction focused on a monoepoxide as the next intermediate. In proceeding to react **16** with *m*-chloroperbenzoic acid, we found that only one epoxide resulted despite the fact that both exo and endo isomers are possible. X-ray crystallographic analysis established that **21** had been formed (Scheme 3), presumably as a direct consequence of steric shielding on the exo face by that oxygen of the sulfonyl group that is projected over the four-carbon bridge. Treatment of **21** with the benzeneselenolate anion accomplished conversion to a 50:50 mixture of carbinols **22** and **23**, which, following exposure to hydrogen peroxide, did not give rise to either of the diastereomeric allylic alcohols **24** or **25**. For comparison purposes, we note that arrival at **24** or **25** could not be accomplished by other means including, for example, recourse

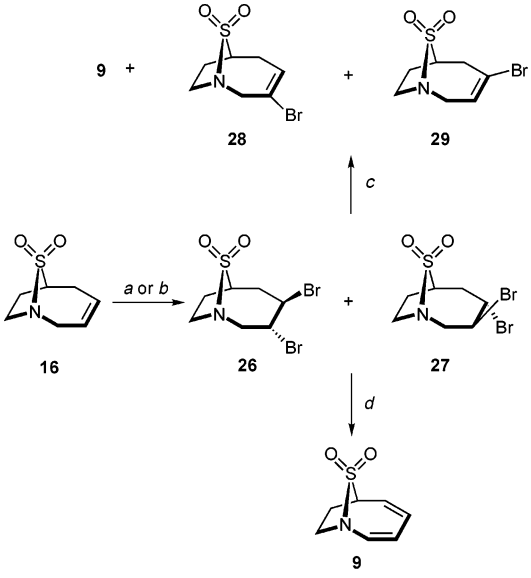
(5) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; You, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
(6) Helberger, J. H.; Sproviers, J. F. *Ann.* **1963**, *666*, 67.
(7) Erman, W. F.; Kretschmar, H. C. *J. Org. Chem.* **1961**, *26*, 4841.
(8) Smith, M. B.; Wolinsky, J. *J. Org. Chem.* **1981**, *46*, 101.
(9) (a) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, 1696. (b) Long, D. P.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743.

SCHEME 3



[a] MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 18 h (62%). [b] PhSeSePh, *n*-BuLi, THF, reflux, 48 h (60%, 1:1 ratio). [c] H_2O_2.

SCHEME 4

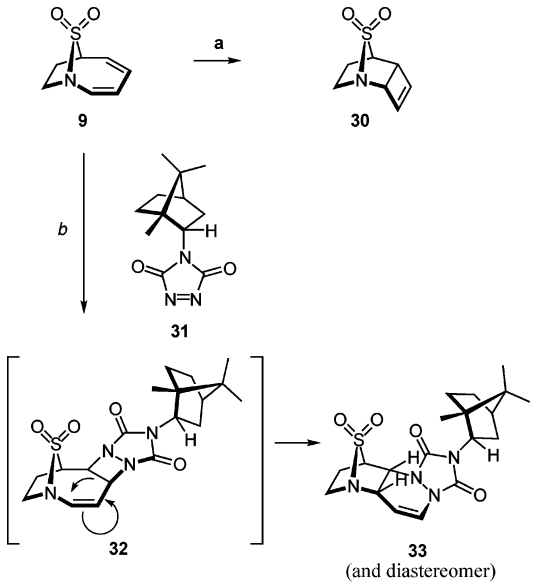


[a] Br_2, CH_2Cl_2, rt (90%). [b] Br_2, neat, rt (90%). [c] TBAF (1 M in THF), 50°C, 2 h (48% of **9**; lesser amounts of **28** and **29**). [d] TBAF/THF, DMSO, 110 °C (44%).

to the action on **21** of LDA in THF at the reflux temperature or its exposure to boron trifluoride etherate at −78 to 0 °C. No identifiable products again resulted under these circumstances.

In light of these developments, we set out to brominate **16**. The isomeric dibromides **26** and **27** were produced in high yield irrespective of whether Br_2 was utilized in neat form as the reaction medium or at the stoichiometric level in CH_2Cl_2 solution (Scheme 4). ^{1}H NMR analysis indicated that the dibromides were produced in different ratios. In the first instance, the distribution was 1:0.4 as compared to 1:0.7 when

SCHEME 5



[a] Hexane, hv, 300 nm (5%). [b] **31**, EtOAc, 80 °C/48 h and 90 °C/24 h (10%).

CH_2Cl_2 was the solvent. It is not known which specific dibromide is favored or if the differing reaction conditions are responsible for the dissimilar ratios. However, we recognize that the same product is favored in both cases.

We next set out to implement the conversion of **26**/**27** to diene **9**. The use of potassium *tert*-butoxide in either THF or DMF resulted in the generation of small amounts of **9** alongside the vinyl bromides **28** and **29**. Alternative exposure to DBU in acetonitrile improved the yield of **9** to the 30% level, while also providing **28** in comparable amounts. Ultimately, the involvement of TBAF as the base in THF or DMSO[10] proved in our hands to be most well suited to the acquisition of **9** (48%).

The photolability of **9** was established by performing irradiations at 300 or 350 nm in a Rayonet reactor at time intervals of 10 min to 2 h and in solvents ranging from pure acetone, CH_2Cl_2, ether, or hexane to mixed systems, e.g., CH_3CN in acetone or hexane. Polymerization was prevalent in every instance. Only at 300 nm in hexane was a sufficient amount (5%) of **30** isolated for characterization (Scheme 5). In **30**, the cyclobutene ring is considered to be projected endo, thereby avoiding nonbonded steric interactions involving the four-membered ring with the syn-oriented sultam oxygen atom.

Despite the recalcitrance of **9** to enter into Diels−Alder reactions with most dienophiles, the heightened ability of triazolinediones to function as 2π donors prompted the consideration of a reagent from this group. The selection of enantiopure **31**[11] held the added prospect of serving as a possible means for achieving the ultimate resolution of **9** should the [4+2] cycloaddition pathway be operational. Heating equimolar amounts of **9** and **31** in ethyl acetate at 80−90 °C for 48 h gave rise predominantly to a 1:1 mixture of **33** and its diastereomer. The material obtained by recrystallization from ethyl acetate indicated the presence of two independent molecules in the asymmetric unit (X-ray analysis). No Diels−Alder product was identified. In light of this key structural elucidation, it appears that **9** is most prone to [2+2] cycloaddition from the endo surface. This process is regioselective, with the double bond

(10) Dura, R. D.; Paquette, L. A. submitted for publication.

distal from the sulfonamide functionality being attacked preferentially. Arrival at **32** is followed by a thermally induced, strain-driven vinylcyclobutane to cyclohexene ring expansion.[12] It is noteworthy and relevant that the initial direction of attack on racemic **9** translates into providing the endo stereoisomer **33** and its diastereomer.

In summary, we have developed a viable synthetic route to a doubly unsaturated bicyclo[4.2.1]nonanyl sultam featuring the nitrogen at the bridgehead site and the sulfonamide sulfur on the single atom bridge. The key steps in the pathway to **9** involve initial conversion of 1,3-propanesultone (**10**) to the functionalized diene **19**, ring-closing metathesis of the latter to provide **20**, and base-promoted cyclization of this advanced intermediate. The conjugated diene segment in the largest ring was next introduced by bromination followed by 2-fold dehydrobromination with TBAF in either CH_2Cl_2 or DMSO at elevated temperatures. Direct irradiation of **9** made available in this manner resulted in valence isomerization to provide the *endo*-cyclobutene **30**. Heating **9** with *endo*-bornyltriazolinedione in ethyl acetate solution gave rise to **33** and its diastereomer, the structural features of which were corroborated by crystallographic analysis. The stereocontrol associated with this pair of reactions is attributed to avoidance by the system of nonbonded steric interactions involving the "inside" sulfonyl oxygen. The formation of **33** is attributed to the sequential operation of a regioselective [2+2] cycloaddition and a heteroatomic variant of the vinylcyclobutane−cyclohexene rearrangement. Both **30** and **33** constitute products in which a strained norbornyl sultam unit has been embedded.

Experimental Section

Sodium 3-Bromopropane-1-sulfonate (11). To a solution of sodium bromide (47.6 g, 400 mmol) in water (70 mol) heated to 60 °C was added 1,3-propanesultone (35.1 mL, 400 mmol). After the sultone completely dissolved (about 10 min), the water was removed via distillation. The crude residue was washed with cold ethanol (2 × 50 mL). The crude solid was recrystallized from 3:1 EtOH/H_2O, giving **11** as a white crystalline solid (46.2 g, 51%): mp 255 °C dec (lit.[6] mp 256 °C dec); ^{1}H NMR (400 MHz, D_2O) δ 3.49 (t, J = 6.4 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.17 (m, 2H).

3-Bromopropane-1-sulfonic Acid Allylamide (12). To a suspension of **11** (11.3 g, 50.0 mmol) and DMF (10 drops) in 1:1 THF/CH_2Cl_2 (100 mL) cooled to 0 °C was slowly added oxalyl chloride (6.4 mL, 75 mmol). After the sulfonate completely dissolved, the reaction mixture was filtered to remove salts and the filtrate was concentrated under vacuum. The crude sulfonyl chloride was dissolved in CH_2Cl_2 (50 mL) and added to a solution of allylamine (4.5 mL, 60 mmol) and triethylamine (14 mL, 100 mmol) in CH_2Cl_2 (250 mL) over 4 Å molecular sieves and cooled to 0 °C. After 3 h, the reaction mixture was filtered and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water (50 mL), dried, filtered, and concentrated. The residual oil was chromatographed on silica gel (elution with 99:1 CH_2Cl_2/EtOAc) to give **12**/**13** as a colorless oil that solidified upon standing (9.9 g, 82%). The product was isolated as an 88:12 mixture of the 3-bromo and 3-chloro sulfonamides as determined by NMR: IR (film, cm^{-1}) 3279, 1646, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, J = 5.6, 10.4, 16.8 Hz, 1H), 5.31 (dq, J = 1.6, 17.2 Hz, 1H), 5.24 (dq, J = 1.2, 10.0 Hz, 1H), 4.51 (br s, 1H), 3.80−3.76 (m, 2 H), 3.54 (t, J = 6.4 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 2.41−2.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDC1_3$) δ 133.4, 118.0, 51.7, 45.7, 31.0, 26.9; HRMS m/z ($C_6H_{12}BrNO_2SNa^+$) calcd 263.9664, obsd 263.9674.

***N*-Allyl-1,3-propanesultam (14).** To a mixture of sodium hydroxide (1.7 g, 43 mmol) and triethylamine (6.0 mL, 43 mmol) in absolute ethanol (150 mL) was added the mixture of **12** and **13** (9.9 g, 43 mmol). The reaction mixture was heated to reflux for 2 h, cooled, and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and filtered through a plug of silica gel (elution with 9:1 CH_2Cl_2/EtOAc). Sultam **14** was isolated as a colorless oil (6.6 g, 95%): IR (neat, cm^{-1}) 1644, 1446, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 6.4, 10.0, 16.8 Hz, 1H), 5.32 (dq, J = 1.2, 16.8 Hz, 1H), 5.26 (dq, J = 1.2, 10.0 Hz, 1H), 3.65 (dt, J = 1.2, 6.4 Hz, 2H), 3.23 (t, J = 6.8 Hz, 2H), 3.17 (t, J = 7.8 Hz, 2H), 2.35 (dq, J = 6.8, 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 119.3, 47.2, 46.5, 46.0, 18.6; HRMS m/z ($C_6H_{11}NO_2SNa^+$) calcd 184.0403, obsd 184.0401.

***C*-Allylation of 14.** To a solution of diisopropylamine (4.4 mL, 31 mmol) in THF (20 mL), cooled to −78 °C, was added a 1.59 M solution of *n*-butyllithium in hexanes (18 mL, 29 mmol). The reaction mixture was allowed to warm to 0 °C for 5 min, then recooled to −78 °C. A solution of **14** (4.2 g, 26 mmol) in THF (20 mL) was slowly introduced, and stirring was maintained at −78 °C for 45 min. Allyl bromide (2.9 mL, 34 mmol) was quickly added prior to stirring at −78 °C for 1 h, warming to 0 °C, and quenching with 1 N HCl (25 mL). The separated aqueous phase was extracted with ether (3 × 25 mL), and the organic phases were combined, dried, filtered, and concentrated. The residue was chromatographed on silica gel (elution with 85:15 hexanes/EtOAc). Product **15** was isolated as a colorless oil (3.2 g, 60%): IR (neat, cm^{-1}) 1643, 1441, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.77 (m, 2H), 5.32 (dd, J = 1.2, 17.2 Hz, 1H), 5.25 (d, J = 10.8 Hz, 1H), 5.21 (d, J = 19.2 Hz, 1H), 5.17 (d, J = 10.8 Hz, 1H), 3.72 (dd, J = 6.4, 14.8 Hz, 1H), 3.61 (dd, J = 6.8, 14.8 Hz, 1 H), 3.23−3.15 (m, 2H), 3.09 (dt, J = 7.6, 9.2 Hz, 1H), 2.76 (dt, J = 6.0, 14.0 Hz, 1H), 2.44−2.30 (m, 2H), 2.00 (dq, J = 8.0, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 132.6, 119.3, 118.7, 56.4, 47.5, 44.2, 33.2, 24.7; HRMS m/z ($C_9H_{15}NO_2SNa^+$) calcd 224.0716, obsd 224.0723.

1-Allyl-1,3-propanesultone (17). A solution of 1,3-propanesultone (6.1 g, 4.4 mL, 50 mmol) in THF (200 mL) was cooled to −78 °C, treated dropwise with 1.59 M *n*-butyllithium in hexane (34.6 mL, 55 mmol), and stirred for 5 min. Allyl bromide (4.3 mL, 50 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at −78 °C, warmed to 0 °C, then poured into H_2O (100 mL). The separated organic phase was washed with brine (100 mL), and the aqueous layers were back-extracted with CH_2Cl_2 (2 × 60 mL). The combined organic phases were dried, filtered, and concentrated to leave a colorless oil. The residue was purified by column chromatography over silica (elution with 75:25 hexanes/EtOAc) yielding 4.71 g (58%) of **17** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87−5.77 (m, 1H), 5.28−5.21 (m, 2H), 4.46−4.34 (m, 2H), 3.33 (dq, J = 6.4, 8.4 Hz, 1H), 2.80−2.73 (m, 1H), 2.69−2.61 (m, 1H), 2.47−2.40 (m, 1H), 2.37−2.28 (m, 1H).

6-Chloro-1-hexene-4-sulfonic Acid Allylamide (19). A. NaCl as Reactant. To a solution of sodium chloride (1.67 g, 28.6 mmol)

(11) (a) Paquette, L. A.; Doehner, R. F., Jr.; Jenkins, J. A.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 1188. (b) Gardlik, J. M.; Paquette, L. A. *Tetrahedron Lett.* **1979**, 3597. (c) Paquette, L. A.; Gardlik, J. M.; Johnson, J. L.; McCullough, K. J. *J. Am. Chem. Soc.* **1980**, *102*, 5026. (d) Jenkins, J. A.; Doehner, R. F., Jr.; Paquette, L. A. *J. Am. Chem. Soc.* **1980**, *102*, 2131. (e) Horn, K. A.; Browne, A. R.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 5381. (f) Paquette, L. A.; Doehner, R. F., Jr. *J. Org. Chem.* **1980**, *45*, 5105. (g) Paquette, L. A.; Hanzawa, Y.; McCullough, K. J.; Tagle, B.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 2262. (h) Klobucar, W. D.; Burson, R. L.; Paquette, L. A. *J. Org. Chem.* **1981**, *46*, 2680. (i) Klobucar, W. D.; Hanzawa, Y.; Hefferon, G. J.; Blount, J. F. *J. Org. Chem.* **1982**, *47*, 265. (j) Paquette, L. A.; Trova, M. P. *Tetrahedron Lett.* **1986**, *27*, 1895. (k) Paquette, L. A.; Wang, T. Z. *J. Am. Chem. Soc.* **1988**, *110*, 3663. (l) Paquette, L. A.; Trova, M. P.; Luo, J.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 228. (m) Paquette, L. A.; Bzowej, E. I.; Kreuzholz, R. *Organometallics* **1996**, *15*, 4857.

(12) It is known that *N*-phenyltriazolinedione undergoes thermal [2+2] cycloaddition to 1,3-butadiene and that the resulting vinyldiazetidine experiences a 1,3-shift at 50 °C with a half-life of a few minutes [Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376].

in H_2O (18 mol) heated to 60 °C was added **17** (4.64 g, 28.6 mmol). The reaction mixture was stirred at 60 °C for 20 h, concentrated, and placed under high vacuum for 24 h. To the residue was added a 1:1 solution of THF/CH_2Cl_2 (72 mL), DMF (10 drops), and, after cooling to 0 °C, oxalyl chloride (3.1 mL, 35.8 mmol). After being stirred for 4 h, the reaction mixture was filtered and concentrated and the sulfonyl chloride was dissolved in CH_2Cl_2 (30 mL) and added to a 0 °C solution of allylamine (2.7 mL, 35.8 mmol) and triethylamine (8.0 mL, 57.2 mmol) in CH_2Cl_2 (150 mL) over 4 Å molecular sieves. The solution was stirred for 16 h while warming to room temperature. The reaction mixture was filtered, then washed with water (100 mL), saturated $NaHCO_3$, (100 mL) and brine (100 mL). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 50 mL), and the organic phases were combined, dried, and concentrated to leave a yellowish solid. The residue was purified via column chromatography on silica gel (elution with 99:1 CH_2Cl_2/EtOAc) to give **19** as a light yellow oil (3.0 g, 40%): IR (thin film, cm^{-1}) 1642, 1439, 1312; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94−5.78 (m, 2H), 5.31 (dq, J = 1.2, 16.8 Hz, 1H), 5.25−5.16 (m, 3H), 4.26 (bt, J = 5.6 Hz, 1H), 3.86−3.76 (m, 3H), 3.69 (dt, J = 6.4, 12.8 Hz, 1H), 3.32−3.25 (m, 1H), 2.75−2.68 (m, 1H), 2.49−2.33 (m, 2H), 2.19−2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 133.2, 119.0, 118.0, 58.8, 46.1, 42.1, 33.7, 31.4; HRMS *m*/*z* ($C_9H_{16}ClNO_2SNa^+$) calcd 260.0482, obsd 260.0489.

6-Chloro-1-hexene-4-sulfonic Acid Allylamide (19). B. LiCl as Reactant. To a solution of lithium chloride (3.19 g, 75.2 mmol) in THF (160 mL) heated to 60 °C was added **17** (10.2 g, 62.7 mmol). The reaction mixture was stirred at 60 °C for 20 h, then concentrated under vacuum. A portion of the crude sulfonate (1.02 g, 5.0 mmol) dissolved in a 1:1 solution of THF/CH_2Cl_2 (5 mL) and DMF (5 drops) was cooled to 0 °C and treated with oxalyl chloride (0.54 mL, 6.25 mmol). After 4 h of stirring, the crude sulfonyl chloride was added to a 0 °C solution of allylamine (1.5 mL, 20.0 mmol) and triethylamine (2.8 mL, 20.0 mmol) in CH_2Cl_2 (25 mL) over 4 Å molecular sieves. The solution was stirred for 16 h while warming to room temperature. The reaction mixture was filtered and washed with H_2O (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried and concentrated to leave a yellowish solid. The residue was purified via column chromatography over silica gel (elution with 99:1 CH_2Cl_2/EtOAc), and **19** was isolated as a light yellow oil (0.21 g, 18%).

6-Chloro-1-hexene-4-sulfonic Acid Allylamide (19). C. KCl as Reactant. To a solution of potassium chloride (2.90 g, 38.9 mmol) in H_2O (35 mL) heated to 60 °C was added **17** (5.73 g, 35.3 mmol). The reaction mixture was stirred at 60 °C for 16 h, concentrated, and freed of residual water by distillation from toluene. To the crude sulfonate was added a 1:1 solution of THF/CH_2Cl_2 (100 mL), DMF (10 drops), and, after cooling to 0 °C, oxalyl chloride (3.75 mL, 43.8 mmol). After being stirred for 4 h, the reaction mixture was filtered and concentrated to leave an oil. The sulfonyl chloride was dissolved in CH_2Cl_2 (10 mL) and added to a 0 °C solution of allylamine (5.3 mL, 70.0 mmol) and triethylamine (9.8 mL, 70.0 mmol) in CH_2Cl_2 (175 mL) over 4 Å molecular sieves. The solution was stirred for 16 h while warming to room temperature, filtered, and washed in turn with H_2O (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 50 mL), and the organic phases were combined, dried, and concentrated to leave a yellowish solid. The residue was purified via column chromatography on silica (elution with CH_2Cl_2), and **19** was isolated as a light yellow oil (4.14 g, 50%).

Ring-Closing Metathesis of 19. To a degassed solution of **19** (6.25 g, 26.3 mmol) in CH_2Cl_2 (500 mL) was added a solution of Grubbs first-generation catalyst (0.21 g, 0.26 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature with periodic purging of ethylene for 24 h. Lead tetraacetate (0.44 g, 1.0 mmol) was added, and after 24 h, the solvent was evaporated under vacuum and the product was purified over silica gel (elution with 70:30 hexanes/EtOAc) to leave **20** as a tan oil (5.4 g, 98%): IR (thin film, cm^{-1}) 3270, 1438, 1312; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07−5−96 (m, 2H), 4.41 (br s, 1H), 3.80 (dt, J = 6.4, 11.6 Hz, 1H), 3.72−3.63 (m, 3H), 3.52−3.32 (m, 1H), 2.60−2.57 (m, 1H), 2.48 (ddt, J = 6.0, 7.2, 14.8 Hz, 1H), 2.03−1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 130.6, 59.8, 41.7, 40.1, 31.9, 27.0; HRMS *m*/*z* ($C_7H_{12}ClNO_2SNa^+$) calcd 232.0169, obsd 232.0175.

Base-Promoted Cyclization of 20. 1-Aza-9-thiatricyclo[4.2.1]-non-3-ene 9,9-Dioxide (16). Sodium hydroxide (0.34 g, 8.5 mmol) in a solution of **20** (1.78 g, 8.49 mmol) and triethylamine (1.2 mL, 8.5 mmol) in absolute EtOH (32 mL) was heated to reflux for 2 h, cooled, concentrated under vacuum, redissolved in CH_2Cl_2, filtered, and reconcentrated. The residue was chromatographed on silica gel (elution with 50:48:2 hexanes/CH_2Cl_2/EtOAc) to deliver **16** as a white solid (1.4 g, 95%): mp 112−115 °C; IR (CH_2Cl_2, cm^{-1}) 1423, 1333, 1270; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73−5.68 (m, 1H), 5.60−5.54 (m, 1H), 4.04 (br d, J = 18.4 Hz, 1H), 3.57−3.48 (m, 3H), 2.97 (ddd, J = 5.2, 11.2, 12.4 Hz, 1H), 2.69 (br d, J = 18.0 Hz, 1H), 2.58−2.49 (m, 1H), 2.34 (ddd, J = 5.2, 6.8, 18.0 Hz, 1H), 2.05−1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.8, 126.7, 53.7, 50.5, 45.5, 29.4, 26.6; HRMS *m*/*z* ($C_7H_{11}NO_2SNa^+$) calcd 196.0403, obsd 196.0407.

Epoxidation of 16. A mixture of $NaHCO_3$ (0.39 g, 4.6 mmol), *m*-chloroperbenzoic acid (0.79 g, 4.6 mmol), and **16** (0.40 g, 2.3 mmol) in CH_2Cl_2 (45 mL) was heated to reflux for 18 h. The reaction mixture was purified via column chromatography over silica gel (elution with 50:48:2 hexanes/CH_2Cl_2/EtOAc) to furnish **21** as a white solid (0.27 g, 62%): mp 197−199 °C; IR (CH_2Cl_2, cm^{-1}) 1421, 1335, 1184; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (dd, J = 1.2, 17.2 Hz, 1H), 3.56−3.35 (m, 3H), 3.30 (br s, 1H), 3.16−3.15 (m, 1H), 2.55 (ddd, J = 2.0, 3.2, 16.4 Hz, 1H), 2.50−2.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3, 56.5, 53.0, 46.2, 45.9, 26.5, 26.3.

Phenylselenation of 21. To a solution of diphenyl diselenide (0.47 g, 1.5 mmol) in THF (4 mL) was added 1.59 M *n*-butyllithium (0.95 mL, 1.5 mmol). After 5 min, a solution of **21** (0.095 g, 0.5 mmol) in THF (4 mL) was added, and the reaction mixture was stirred at reflux for 48 h, diluted with CH_2Cl_2 (20 mL), and washed with 0.2 M HCl (25 mL) and brine (25 mL). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were dried and concentrated to leave a yellow residue. The crude product was purified over silica gel (elution with 90:10 CH_2Cl_2/EtOAc) to provide the isomeric selenides as a white waxy solid in a 50:50 ratio (0.10 g, 60%).

For the less polar alcohol: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.42−7.32 (m, 3H), 4.23−4.16 (m, 1H), 4.04 (dd, J = 6.8, 15.2 Hz, 1H), 3.77 (ddd, J = 3.6, 10.4, 13.6 Hz, 1H), 3.31−3.24 (m, 2H), 3.15 (ddd, J = 6.0, 10.8, 12.8 Hz, 1H), 3.08 (s, 1H), 2.75 (dd, J = 8.4, 14.8 Hz, 1H), 2.56−2.47 (m, 1H), 2.35 (ddd, J = 3.2, 5.6, 15.2 Hz, 1H), 2.28−2.20 (m, 1H), 2.09−2.02 (m, 1H); HRMS *m*/*z* ($C_{13}H_{17}NO_3SSeNa^+$) calcd 369.9987, obsd 369.9985.

For the more polar alcohol: IR (CH_2Cl_2, cm^{-1}) 3684, 1338, 1280; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.60 (m, 2H), 7.41−7.32 (m, 3H), 4.28−4.21 (m, 1H), 3.59−3.45 (m, 4H), 3.34 (dt, J = 4.4, 11.2 Hz, 1H), 3.20 (d, J = 2.0 Hz, 1H), 3.05 (ddd, J = 4.0, 10.8, 12.3 Hz, 1H), 2.84 (pent, J = 7.2 Hz, 1H), 2.79−2.70 (m, 1H), 2.14−2.06 (m, 1H), 1.56 (ddd, J = 0.8, 8.4, 14.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 129.6, 129.0, 125.5, 69.8, 54.6, 49.8, 49.8, 43.1, 37.0, 32.2; HRMS *m*/*z* ($C_{13}H_{17}NO_3SSeNa^+$) calcd 369.9987, obsd 369.9971.

Bromination of 16. A solution of **16** (0.17 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was treated dropwise with bromine until an orange color persisted. The solvent was evaporated under vacuum, and the residue was purified by column chromatography on silica gel (elution with 70:30 hexanes/EtOAc) to provide a mixture of the isomeric dibromides **26** and **27** (0.30 g, 90%): IR (CH_2Cl_2,cm^{-1}) 1342, 1170, 1140; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (ddd, J =

6.8, 10.4, 11.6 Hz, 1H (L)), 4.78 (ddd, J = 6.8, 9.6, 11.6 Hz, 1H (M)), 4.37−4.28 (m, 1H (L), 1H (M)), 4.17 (dd, J = 6.8, 15.2 Hz, 1H (M)), 3.95 (dd, J = 11.6, 15.2 Hz, 1H (L)), 3.87−3.80 (m, 1H (M)), 3.72 (dd, J = 3.6, 15.2 Hz, 1H (L)), 3.62−3.50 (m, 2H (L)), 3.36−3.28 (m, 2H (M)), 3.22−3.12 (m, 2H (L), 1H (M)), 2.87−2.72 (m, 1H (L), 2H (M)), 2.63−2.54 (m, 1H (M)), 2.30−2.24 (m, 1H (L)), 2.22−2.11 (m, 1H (L), 1H (M)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.0, 56.1, 54.3, 53.5, 52.9, 52.7, 51.9, 50.4, 49.4, 43.0, 41.2, 39.9, 32.0, 24.5 (M = more dominant; L = less dominant).

Dehydrobromination of the Dibromides 26 and 27. A solution of **26**/**27** (0.17 g, 0.50 mmol) in THF (2.5 mL) was treated with a 1 M solution of TBAF in THF (2.5 mL, 2.5 mmol). The reaction mixture was stirred at 50 °C for 2 h, concentrated under vacuum, and purified over silica gel (elution with 70:30 hexanes/EtOAc) to give **9** as a white crystalline solid (0.042 g, 48%): mp (CH_2Cl_2) 82−84 °C; IR (thin film, cm^{-1}) 1632, 1503, 1339; ^{1}H NMR ($CDCl_3$) δ 5.96−5.85 (m, 3H), 5.77 (t, J = 8.0 Hz, 1H), 3.87−3.83 (m, 1H), 3.75−3.68 (m, 1H), 3.65−3.58 (m, 1H), 2.78−2.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 133.4, 127.3, 126.7, 122.8, 56.6, 56.2, 39.9; HRMS m/z ($C_7H_9NO_2SNa^+$) calcd 194.0252, obsd 194.0250.

For **28**: mp 164−165 °C; IR (thin film, cm^{-1}) 1643, 1320, 1184; ^{1}H NMR ($CDCl_3$) δ 6.11 (dt, J = 2.8, 5.6 Hz, 1H), 4.08−4.02 (m, 1H), 3.57 (ddd, J = 5.2, 10.0, 12.8 Hz, 1H), 3.50 (dd, J = 1.2, 6.0 Hz, 1H), 3.48−3.44 (m, 1H), 3.25 (br dd, J = 3.2, 18.4 Hz, 1H), 3.03 (ddd, J = 4.4, 10.8, 12.4 Hz, 1H), 2.82 (ddd, J = 1.2, 5.2, 18.4 Hz, 1H), 2.65−2.55 (m, 1H), 2.18 (ddd, J = 4.8, 7.6, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 130.1, 120.6, 52.8, 51.6, 45.4, 40.1, 26.4.

For **29**: mp 123−126 °C; IR (thin film, cm^{-1}) 1646, 1331, 1178; ^{1}H NMR ($CDCl_3$) δ 6.22−6.18 (m, 1H), 4.32−4.25 (m, 1H), 3.77 (dd, J = 1.2, 18.4 Hz, 1H), 3.63−3.52 (m, 2H), 3.09 (ddd, J = 5.2, 11.8, 12.4 Hz, 1H), 2.71 (br d, J = 18.0 Hz, 1H), 2.59−2.50 (m, 1H), 2.35 (ddd, J = 4.8, 7.6, 17.6 Hz, 1H), 2.06 (ddd, J = 4.8, 7.6, 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 128.3, 121.0, 57.4, 53.8, 45.3, 31.3, 26.1.

Photoisomerization of 9. A deoxygenated solution of **9** (17 mg, 0.10 mmol) in hexanes (50 mL) was irradiated at 300 nm for 30 min, concentrated under vacuum, and purified over silica gel (elution with 70:30 hexanes/EtOAc) to provide **30** (1 mg, 5%) as a white solid: IR (thin film, cm^{-1}) 1336, 1226, 1168; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, J = 3 Hz, 1H), 6.34 (d, J = 3 Hz, 1H), 4.01 (d, J = 4 Hz, 1H), 3.59 (ddd, J = 4.5, 10.0, 12.5 Hz, 1H), 3.49 (d, J = 4 Hz, 1H), 3.16 (d, J = 4 Hz, 1H), 2.76 (ddd, J = 5.0, 10.5, 12.5 Hz, 1H), 2.43 (ddd, J = 4.5, 9.5, 12.5 Hz, 1H), 1.60 (ddd, J = 4.5, 10.0, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 140.8, 66.7, 55.2, 51.0, 49.3, 26.5; HRMS m/z ($C_7H_9NO_2SH^+$) calcd 172.0432, obsd 172.0428.

Cycloaddition of *endo*-Bornyltriazolinedione (31) to 9. A solution of **9** (86 mg, 0.50 mmol) and **31** (120 mg, 0.50 mmol) in EtOAc (5.0 mL) was heated at 80 °C for 48 h and at 90 °C for 24 h. After cooling and solvent evaporation, chromatography of the residue on silica gel (elution with 70:30 hexanes/EtOAc), and crystallization from ethyl acetate, 20 mg (10%) of **33** and its diastereomer (1:1) was isolated as a colorless solid: mp 202−203 °C; IR (film, cm^{-1}) 1769, 1709, 1425; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.17 (m, 1H), 5.22−5.17 (m, 1H), 4.87−4.83 (m, 1H), 4.60−4.55 (m, 1H), 4.37−4.31 (m, 1H), 4.10−4.07 (m, 1H), 3.43−3.33 (m, 1H), 3.27−3.16 (m, 1H), 2.44−2.38 (m, 2H), 2.08−1.93 (m, 2H), 1.83−1.72 (m, 3H), 1.65−1.52 (m, 1H), 1.42−1.32 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.85−0.84 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 147.9, 121.7, 99.9, 59.8, 55.9, 53.8, 51.6, 47.83, 47.80, 45.3, 29.7, 29.5, 27.1, 20.0, 18.7, 18.6, 14.0; HRMS m/z ($C_{19}H_{26}NO_4SNa^+$) calcd 429.1572, obsd 429.1574.

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Supporting Information Available: High-field ^{1}H and ^{13}C NMR spectra of all new compounds reported herein and X-ray crystallographic data for **21** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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