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Ring Contraction of Bridgehead Sultams by Photoinduced Di-π-methane Rearrangement

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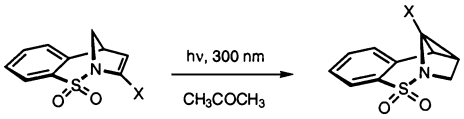
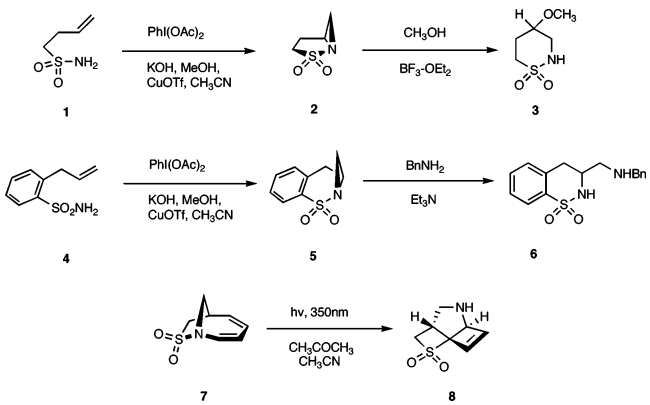


X = CH_3, CH_2Ph, $COC(CH_3)_3$, CO_2CH_2Ph
$SiMe_3$, $SnBu_3$, SePh, $-\equiv-(CH_2)_3CH_3$

Triplet-sensitized irradiation of 8-thia-9-azatricyclo[7.2.1.$0^{2,7}$]dodeca-2,4,6,10-tetraene (**16**) in acetone solution gives rise exclusively to tetracyclic sultam **20**. This strong preference for benzo-vinyl bridging distal to the sulfonamide functional group has also been observed in eight derivatives carrying chemically diverse functional groups at C-10. In none of these examples is regiospecificity eroded. This overall result suggests that the added substituents act in harmony with the electronic rebonding pathway found operative in the parent system. From the structural perspective, this transformation constitutes a facile means for accomplishing the ring contraction of a bridgehead sultam.

Introduction

Bridgehead sultams, constrained for structural reasons to deviate significantly from adoption of the normal orientation of the nitrogen lone pair in the bisector of the O−S−O internuclear angle,[1] hold interest from both the constitutional and reactivity perspectives. Particularly fascinating is the dichotomy surrounding whether diminished orbital interaction or conventional ring strain contributes more to the enhancement of chemical reactivity as ring size is diminished. To this date, attempts to shed light on these issues have been limited by the lack of availability of a sufficient number of probe systems. Nevertheless, the findings uncovered so far reveal an unusually divergent sensitivity to ring size.



Thus, the availability of **2** and **5** by intramolecular copper-catalyzed nitrene insertion within **1** and **4**[2] has resulted in the demonstration that these sultams are subject to preferential aziridine C−N bond cleavage by nucleophiles. However, while **3** results from exclusive attack at the more substituted three-membered ring site, **5** reacts at its less substituted carbon. In both examples, the sultam linkage is preserved. Along other lines, the bicyclo[4.2.1]nonadienyl framework resident in **7** experiences rupture of its SO_2N bond and conversion to **8** when irradiated at 350 nm.[3]

In this report, experiments defining a photochemical means for effecting the ring contraction of sulfonamides of general formula **9** are reported. Recourse to the di-π-methane rearrangement[4] was also intended to allow for variations in the nature of X on regioselectivity to be explored. Background information concerning the involvement of heterocyclic systems in related photochemistry is sparse. More than three decades ago, the response of **10** to triplet sensitization (acetone) was

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

(2) (a) Dauben, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327. (b) Liang, J.-L.; Yuan, S.-X.; Chang, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.

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

(4) Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065 and references therein.

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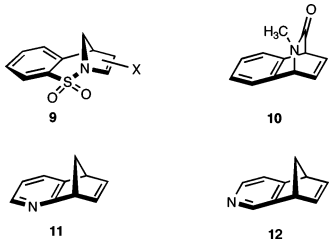
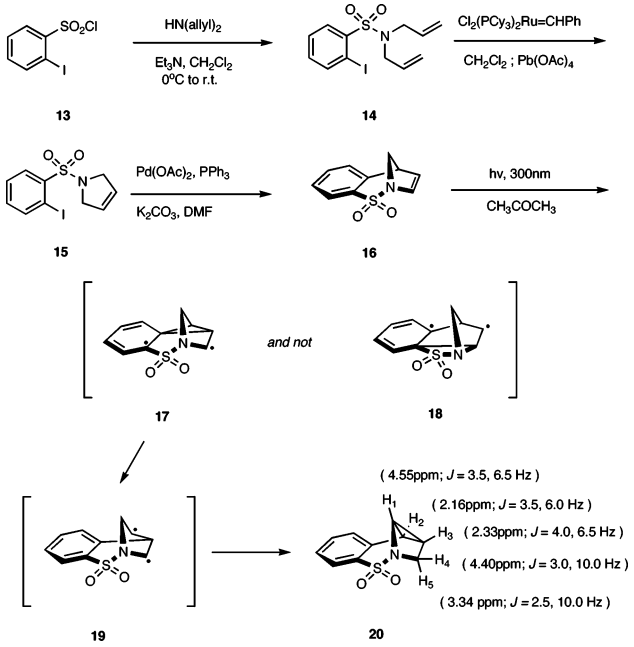
disclosed.[5] The resulting product distribution indicated that advancement via the biradical proximal to the amide nitrogen was favored by a factor of 3:1. In the intervening years, the influence of pyridine nitrogen as in **11** and **12** in controlling the course of the "dual-channeled" triplet state rearrangement was similarly accorded attention.[6]



Synthetic Considerations

The acquisition of parent sultam **16** was realized straightforwardly by adaptation of earlier work emanating from the Grigg[7] and Evans laboratories.[8] As shown in Scheme 1, the

SCHEME 1



transformation of sulfonyl chloride **13** to **14** set the stage for the implementation of ring-closing metathesis (workup with lead tetraacetate[9]) and ensuing intramolecular Heck reaction. Irradiation of dilute solutions of **16** in acetone at 3000 Å in a Rayonet reactor provided **20** in 48% yield. The proton assignments are based on a combination of COSY and NOE data. Evidently, the increased distance separating the reaction centers along the leading edge of **16** (as drawn) serves to impede rebonding in the manner defined by **18**.

The exclusive formation of **20** prompted investigation of the possibilities available for functionalization of one or both of the available vinyl sites as in **21** and **22**. These substrates hold the capability for revealing whether the X group will work cooperatively with the existing sulfonamide functionality to foster unidirectional structural organization or induce a change in the overall regioselectivity pattern.[10,11]

The bromination of **16** was expected to occur on the exo face of the isolated π-bond, with subsequent capture of the second halogen materializing competitively from either the cis or trans direction. In practice, treatment of the bridgehead sultam with bromine in a chlorinated solvent (CCl_4, $CHCl_3$, or CH_2Cl_2) afforded a mixture of **23** and **24** (Scheme 2). The use of neat bromine returned **23** exclusively. Proper distinction between these dibromides was realized on the basis of an X-ray crystallographic analysis of **23**. Subjection of equimolar mixtures of **23** and **24** or isomerically pure **23** to dehydrobromination with a variety of basic reagents (see Table 1) resulted in the production of **25** exclusively. Regrettably, no suggestion of a second vinyl bromide was seen under any circumstances. The unidirectional nature of these reactions is noteworthy. Also of interest is the notable efficiency with which tetra-*n*-butylammonium fluoride accomplishes this transformation.

Bromo sultam **25** readily undergoes halogen−metal exchange in the presence of methyl- or *tert*-butyllithium. The resulting organometallic is in turn amenable to C-alkylation (→ **26** and **27**), C-acylation (→ **28** and **29**), and conversion to silyl (e.g., **30**), stannyl (e.g., **31**), and selenyl derivatives (e.g., **32**, Scheme 2). Pd(0)-catalyzed Sonagashira coupling to a terminal alkyne (→ **33**) also proved possible, albeit inefficiently so.

Photochemical Results

All of the di-π-methane reactants of interest have chromophores absorbing at wavelengths above 270 nm. This feature allowed acetone to be used as the triplet sensitizer. Operationally, the reaction vessel was a large-size quartz tube which was irradiated with a bank of low-pressure lamps emitting 3000 Å

(5) Paquette, L. A.; Meisinger, R. H. *Tetrahedron Lett.* **1970**, 1469.

(6) (a) Paquette, L. A.; Coghlan, M. J.; Cottrell, C. E.; Irie, T.; Tanida, H. *J. Org. Chem.* **1986**, *51*, 696. (b) Paquette, L. A.; Burke, L. D.; Irie, T.; Tanida, H. *J. Org. Chem.* **1987**, *52*, 3246.

(7) (a) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T. *Tetrahedron* **1991**, *49*, 9703. (b) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139. (c) Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255.

(8) Evans, P.; McCabe, T.; Morgon, B.; Reau, S. *Org. Lett.* **2005**, *7*, 43.

(9) Paquette, L. A.; Schloss, J.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259.

(10) The triplet-sensitized photoisomerization of benzonorbornadienes carrying substituents at the bridgehead positions and vinyl segments has been thoroughly scrutinized: (a) Paquette, L. A.; Ku, A. Y.; Santiago, C.; Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 5972. (b) Ku, A. Y.; Paquette, L. A.; Rozeboom, M. D.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 5981. (c) Paquette, L. A.; Bay, E.; Ku, A. Y.; Rondan, N. G.; Houk, N. K. *J. Org. Chem.* **1982**, *47*, 422. (d) Paquette, L. A.; Bay, E. *J. Org. Chem.* **1982**, *47*, 4597. (e) Paquette, L. A.; Bay, E. *J. Am. Chem. Soc.* **1984**, *106*, 6693. (f) Paquette, L. A.; Varadarajan, A.; Bay, E. *J. Am. Chem. Soc.* **1984**, *106*, 6702.

(11) Full consideration has also been given to the control of benzo-vinyl bonding options by aryl-bound functionality: (a) Paquette, L. A.; Cottrell, D. M.; Snow, R. A.; Gifkins, K. B.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 3275. (b) Santiago, C.; Houk, K. N.; Snow, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 7443. (c) Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 3723. (d) Snow, R. A.; Cottrell, D. M.; Paquette, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 3734. (e) Santiago, C.; McAlduff, E. J.; Houk, K. N.; Snow, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1978**, *100*, 6149. (f) Paquette, L. A.; Burke, L. D. *J. Org. Chem.* **1987**, *52*, 2674.

(12) Lane, J. W.; Holcomb, R. L. *Org. Lett.* **2003**, *5*, 4017.

SCHEME 2

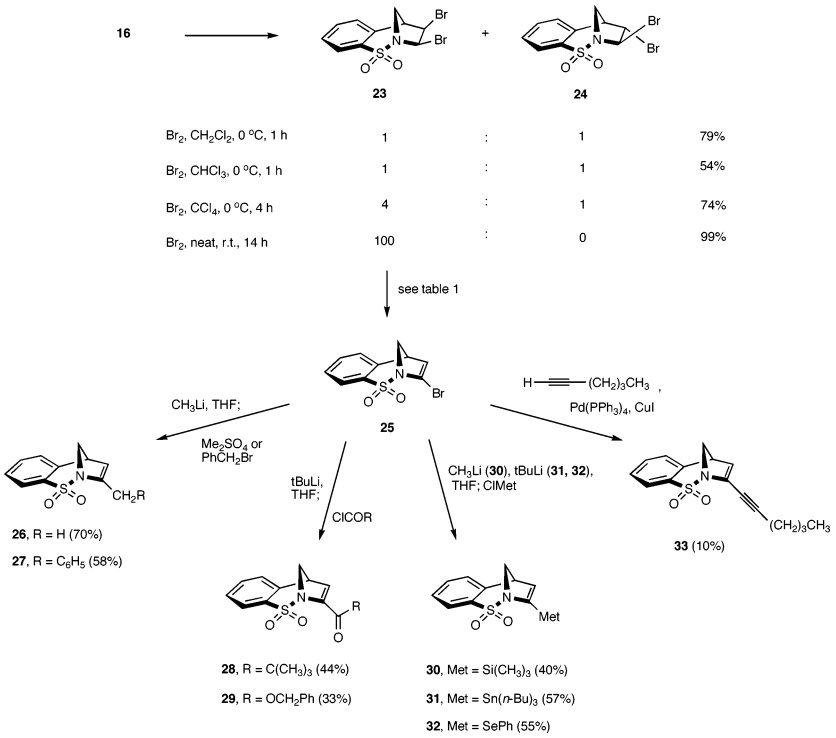


TABLE 1. Dehydrobromination of 23 and 24

reactant[a]	reaction conditions	**23**:**24**	yield, %
23/24	KO*t*-Bu, THF, reflux, 3 h[b]	100:0	77
23/24	DBU, CH_3CN, reflux, 24 h	100:0	60
23/24	NaH, THF, reflux, 24 h	100:0	70
23/24	1 M TBAF, THF, rt, 24 h[c]	100:0	98
23	NaH, THF, 0 °C → rt, 16 h	100:0	83
23	1 M TBAF, THF, rt, 16 h	100:0	82

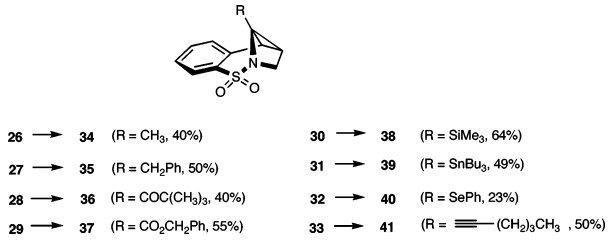
[a] 1:1 mixtures of **23** and **24**. [b] See ref 11f. [c] Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

light. Each experiment was carried out under an argon atmosphere for 1 h in the manner defined earlier for **16**.

In each instance, isomerization materialized to generate a single photoproduct despite the inherent capacity for bifurcate reactivity in every instance. The uniformity of the reaction conditions revealed no substantial differences in the individual rates of starting material disappearance or product formation. The salient feature of the photoreaction is that the new C−C bond forms part of a five-membered sultam. Overall, this new bonding arrangement represents a formal ring contraction relative to the connectivity present in the reactants. The resulting distorted structure clearly is more strained, with fused azetidine and cyclopropane subunits also incorporated therein.

Summary

We have developed a general route to strained bridgehead sultams that allows for the regiospecific incorporation of an additional functional group. The protocol consists of early steps involving olefin metathesis and an intramolecular Heck reaction and is capped by a bromination−dehydrobromination sequence and functional group manipulation in advance of di-π-methane photorearrangement. The strongly favored electronic rebonding that operates occurs distal to the sulfonamide component and eventuates in its direct ring contraction. That the same reaction pathway is followed when chemically diverse substituents are placed at C-10 is construed to be an indication of a cooperative effect. The reactivity pattern reveals that the bridgehead sultam group totally controls the pivotal bridging step.



Experimental Section

Photoisomerization of 16. Prototypical Procedure. A solution of **16** (50 mg, 0.24 mmol) in acetone (75 mL) was carefully deoxygenated with argon for 10 min after being placed in a quartz test tube and fitted with an appropriate septum. Irradiation for 1 h in a Rayonet reactor equipped with a bank of 3000 Å bulbs was followed by solvent evaporation and chromatography on silica gel. Elution with 7:3 hexanes/ethyl acetate furnished 24 mg (48%) of **20** as a colorless oil; IR (neat, cm^{-1}) 1479, 1382, 1339, 1176; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83−7.81 (m, 1H), 7.56 (dt, J = 1.0, 7.5 Hz, 1H), 7.48−7.42 (m, 2H), 4.54 (dd, J = 3.5, 6.5 Hz, 1H), 4.40 (dd, J = 3.0, 10.0 Hz, 1H), 3.34 (dd, J = 2.5, 10.0 Hz, 1H), 2.33 (dt, J = 3.5, 6.5 Hz, 1H), 2.16 (dd, J = 3.5, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 132.7, 132.4, 130.2, 128.4, 125.1, 51.1, 48.3, 18.0, 16.4; HRMS ES m/z $(M + Na)^+$ calcd 230.0246, obsd 230.0256.

Bromination of 6. A. In Neat Bromine. A 2.0-g (9.6 mmol) sample of **16** was placed in neat bromine (4 mL) and allowed to stand overnight in a sealed flask. The excess bromine was evaporated in a stream of air to leave **23** (3.5 g, 99%), which was isolated as an off-white solid, mp 185−188 °C after dissolution in CH_2Cl_2, washing with $NaHSO_3$ solution, and drying; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83−7.81 (m, 1H), 7.57−7.54 (m, 2H), 7.37−

7.35 (m, 1H), 6.48 (d, J = 6.5 Hz, 1H), 4.67 (dd, J = 2.0, 6.5 Hz, 1H), 4.31 (d, J = 13.0 Hz, 1H), 4.13 (dd, J = 3.0, 13.0 Hz, 1H), 3.63 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 134.8 133.6, 130.5, 128.6, 126.5, 67.5, 57.8, 52.7, 52.3; HRMS ES m/z $(M + Na)^+$ calcd 389.8598, obsd 389.8594.

The structural assignment to **23** was corroborated by X-ray crystallography (see Supporting Information).

B. In a Chlorinated Solvent. A solution of **16** (25 mg, 0.12 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated dropwise with bromine until a red color persisted during 1 h. After the addition of sodium bisulfite solution, the separated organic layer was dried and evaporated. The residue was purified over silica gel (elution with 4:1 hexanes/ethyl acetate) to give a 1:1 mixture of **23** and **24** as a white solid (37 mg, 87%). For **24**: ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 136.0, 133.7, 129.9, 128.9, 126.1, 65.0, 58.2, 55.8, 50.2.

10-Bromo-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6,10-tetraene 8,8-Dioxide (25). A. Dehydrobromination with Potassium *tert*-Butoxide. Potassium metal (61 mg, 1.58 mmol) was added to *tert*-butyl alcohol with stirring. After 2 h, a solution of **23** (480 mg, 1.31 mmol) in 2:1 THF/*tert*-butyl alcohol (15 mL) was introduced, and the mixture was heated at reflux for 3 h prior to cooling and solvent evaporation. The residue was partitioned between ethyl acetate and water, and the separated organic phase was dried and concentrated. Purification over silica gel (4:1 hexanes/ethyl acetate) yielded 350 mg (77%) of **25** as a white solid, mp 179 °C dec; IR ($CHCl_3$, cm^{-1}) 1592, 1473, 1446, 1352; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 1.0, 7.5 Hz, 1H), 7.51 (dt, J = 1.5, 7.3 Hz, 1H), 7.43 (dt, J = 1.5, 7.3 Hz, 1H), 7.14 (dd, J = 1.0, 7.5 Hz, 1H), 6.67 (d, J = 3.5 Hz, 1H), 4.60 (d, J = 0.5, 12.0 Hz, 1H), 4.38 (dd, J = 4.0, 12.0 Hz, 1H), 3.30 (t, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 135.9, 134.5, 132.0, 130.1, 127.3, 125.4, 124.9, 65.4, 42.8; HRMS ES m/z $(M + Na)^+$ calcd 307.9357, obsd 307.9365.

B. Use of Tetrabutylammonium Fluoride. A 1:1 mixture of **23** and **24** (2.0 g, 5.4 mmol) was dissolved in 1 M TBAF in THF (27.2 mL, 27.2 mmol), stirred overnight, and freed of solvent. The residue was taken up in CH_2Cl_2 (100 mL), washed with $NaHSO_3$ solution (2 × 50 mL), dried, evaporated, and chromatographed on silica gel (4:1 hexanes/ethyl acetate) to give 1.54 g (99%) of **25**.

10-Methyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6,10-tetraene 8,8-Dioxide (26). Prototypical Procedure for CH_3Li. Bromo sultam **25** (500 mg, 1.75 mmol) was dissolved in dry THF (17.5 mL), cooled to −78 °C under argon, and treated with methyllithium (1.86 mL, 2.98 mmol) while being stirred. After 30 min, the reaction mixture was warmed quickly to 0 °C in an ice bath, treated immediately with dimethyl sulfate (0.215 mL, 2.27 mmol), and maintained at room temperature during 4 h. Ethyl acetate (50 mL) and water (50 mL) were introduced, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel. Elution with 4:1 hexanes/ethyl acetate gave 270 mg (70%) of **26** as a white solid, mp 118−121 °C; IR (neat, cm^{-1}) 1652, 1597, 1471; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.44 (dt, J = 1.2, 9.0 Hz, 1H), 7.37 (dt, J = 1.2, 9.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.13 (dd, J = 4.0, 10.0 Hz, 1H), 3.21 (t, J = 3.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 141.7, 134.6, 131.5, 129.7, 129.5, 127.7, 125.2, 64.5, 42.8, 16.3; HRMS ES m/z $(M + Na)^+$ calcd 244.0408, obsd 244.0406.

1-(8,8-Dioxo-8λ^6-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6,10-tetraen-1-yl)-2,2-dimethylpropan-1-one (28). Prototypical Procedure for tBuLi. A 100-mg (0.35 mmol) sample of **25** was dissolved in dry THF (3.5 mL), cooled to −78 °C under an argon atmosphere, and treated dropwise over 10 min with *tert*-butyllithium (0.56 mL of 1.26 M in hexanes, 0.70 mmol). After 30 min, pivalolyl chloride (0.043 mL, 0.35 mmol) was introduced in one portion, and the reaction mixture was allowed to warm to room temperature. After 2 h, the product was taken up in ethyl acetate (25 mL), and the organic solution was washed with NH_4Cl solution, water, and brine. The organic layer was dried and evaporated to leave a residue that was chromatographed on silica gel (7:3 hexanes/ethyl acetate) to furnish 45 mg (44%) of **28** as a colorless oil; IR (film, cm^{-1}) 1682, 1593, 1477; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 0.5, 7.5 Hz, 1H), 7.48 (dt, J = 1.0, 7.5 Hz, 1H), 7.43−7.40 (m, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 3.5 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.27 (dd, J = 4.1, 12.0 Hz, 1H), 3.45 (t, J = 4.1 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 145.1, 139.5, 137.7, 131.9, 130.4, 127.4, 125.7, 64.5, 44.0, 42.9, 27.0; HRMS ES m/z $(M + Na)^+$ calcd 314.0827, obsd 314.0814.

10-Hex-1-ynyl-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6,10-tetraene 8,8-Dioxide (33). Sonagashira Protocol. Sultam **25** (100 mg, 0.35 mmol), tetrakistriphenylphosphinepalladium (40 mg, 0.035 mmol), copper(I) iodide (13 mg, 0.07 mmol), and 1-hexyne (0.04 mL, 0.35 mmol) were added to a 0.8:1 mixture of DMF and triethylamine (1.8 mL). The reaction vessel was flushed with argon for 20 min, stirred overnight, diluted with ethyl acetate, and filtered through Celite. The filtrate was washed with saturated NH_4Cl solution, water, and brine prior to drying and solvent evaporation. Chromatography of the residue on silica gel (4:1 hexanes/ethyl acetate) afforded 10 mg (10%) of **33** as a yellowish oil; IR (neat, cm^{-1}) 2232, 1343; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.0 Hz, 1H), 7.40−7.37 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 4.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.15 (dd, J = 4.0, 12.0 Hz, 1H), 3.32 (t, J = 3.5 Hz, 1H), 2.39 (t, J = 7.1 Hz, 1H), 1.58−1.52 (m, 2H), 1.47−1.41 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 136.9, 134.6, 131.7, 129.9, 129.8, 127.4, 125.3, 98.0, 72.9, 63.5, 43.0, 30.1, 21.9, 19.3, 13.5; HRMS ES m/z $(M + Na)^+$ calcd 310.0878, obsd 310.0875.

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Supporting Information Available: Details of the X-ray crystallographic analysis of **23** in addition to ^{1}H and ^{13}C NMR spectra for all compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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