Cycloaddition Reactions of Phthalimide Substituted Cyclic Polyenes with Heteroatom Dienophiles

Stephen S. Templin[a], Nathaniel J. Wallock[b], Dennis W. Bennett[c], Tasneem Siddiquee[c], Daniel T. Haworth[b], and William A. Donaldson[b]*

[a]Department of Chemistry, Cardinal Stritch University, 6801 N. Yates Road, Milwaukee, WI 53217 USA
[b]Department of Chemistry, Marquette University, P. O. Box 1881, Milwaukee, WI 53201-1881 USA
[c]Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, 3210 N. Cramer St., Milwaukee, WI 53211-3029 USA

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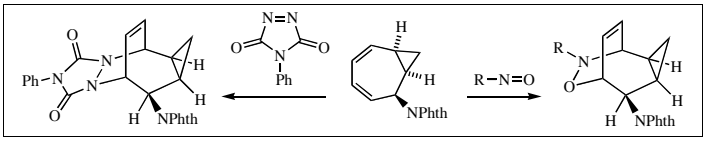

The cycloaddition of 6-phthalimidobicyclo[5.1.0]octa-2,4-diene and 7-phthalimido-1,3,5-cycloheptatriene with nitrosobenzene and with 4-phenyl-1,2,4-triazoline-3,5-dione each gave a single heterocyclic product. X-ray crystallographic analysis of **8a** indicated the regio- and stereoselectivity of this cycloaddition.

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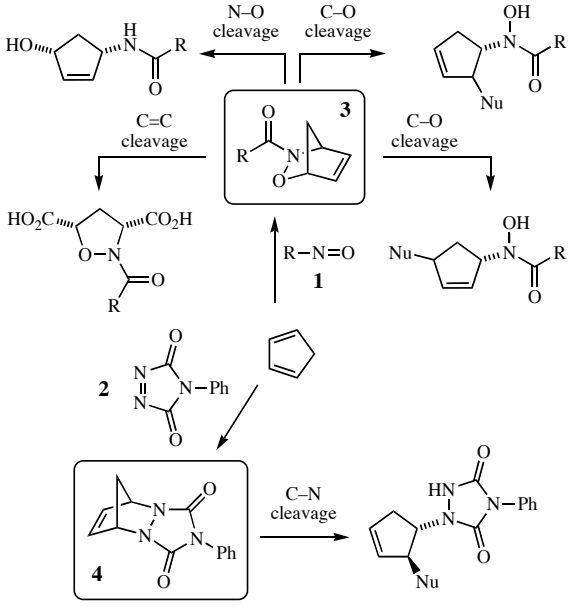
INTRODUCTION

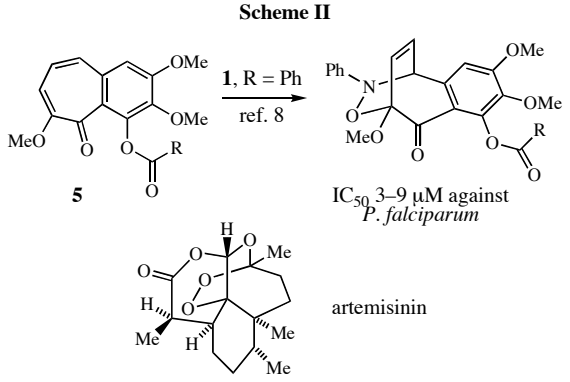
Cycloadditions of conjugated dienes such as cyclopentadiene with heteroatom dienophiles, such as nitroso compounds (**1**) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD, **2**) have been known for more than a half-century [1,2]. In particular, the derived 3-azo-2-oxabicyclo[2.2.1]heptenes (**3**) have great synthetic potential due to the versatile routes to open the bicyclic ring structure by either C=C, N–O, or C–O bond cleavage (Scheme I) [3, 4]. This methodology has been utilized for the preparation of 2-amino-6-hydroxy-1,7-heptanedioic acid [5a], 5-lipoxygenase inhibitors [4b], metabotropic glutamate receptor II (mGluR II) agonist analogues [5b], (+)-uracil polyoxin C [5c], and (+)-streptazoline [5d]. More recently, C–N bond cleavage of 2,4,6-triaza-3,5-dioxotricyclo[5.2.1.$0^{2,6}$]decenes (**4**) has been reported including asymmetric variants (Scheme I) [6].

Scheme I



There are few examples of the reaction of **1** with cycloheptatrienes or cycloheptadienes [7,8]. For example, cycloadducts of nitrosobenzene with the benzannulated cycloheptatrienone, purpurogallin (**5**), have been examined as mimetics for the antimalarial agent artemisinin (Scheme II) [8]. While there are slightly more examples of the reaction of PTAD with cycloheptadienes [7b,9], the cycloaddition of **2** with cycloheptatrienes has been extensively studied [10].

Scheme II

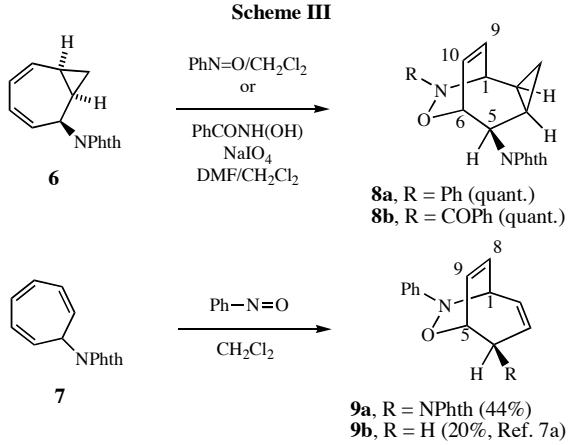


As part of our interest in the preparation of mGluR II ligands [11], we herein report on the cycloaddition of cyclic polyenes **6** and **7** with heteroatom dienophiles. The phthalimide substituted polyenes **6** and **7** were chosen since this protected nitrogen substitutent would provide a useful functionality for further elaboration.

RESULTS AND DISCUSSION

6-Phthalimidobicyclo[5.1.0]octa-2,4-diene (**6**) and 7-phthalimido-1,3,5-cycloheptatriene (**7**) were prepared by literature procedures [11a,12]. Reaction of **6** with nitrosobenzene gave **8a** (Scheme III). The ^{13}C NMR spectrum of **8a** indicated that this compound consisted of 10 sp^2 and 6 sp^3 hybridized carbons, while the ^1H NMR spectrum contained four signals due to cyclopropane protons. In order to determine the structure of **8a** unambiguously an X-ray diffraction analysis of this compound was undertaken. A drawing of the molecule and the crystallographic numbering is given in Figure 1, the experimental crystallographic data, and the structural parameters are given in Tables 1–3. This reveals the stereo- and regioselectivity of the cycloaddition product as indicated. The bond lengths and bond angles of **8a** are similar to those of other 7-oxa-8-aza-bicyclo[2.2.2]octa-2-enes and 8-oxa-9-aza-bicyclo[2.2.2]non-2-enes [13]. The reaction of **6** with PhC(O)NO gave **8b**, whose structure was assigned on the basis of similarity of its ^1H NMR spectral data [14] with that of **8a**.

Scheme III



In comparison, the reaction of **7** with an excess of **1** (12 mol equiv.) did not go to completion after 6 days (40 °C). Monitoring of the crude reaction mixture indicated the presence of **9a** (R = NPhth) and unreacted **7**. After purification **9a** was obtained in 44% isolated yield (58% BORSM). Notably, the reaction between **1** and the parent cycloheptadiene is reported to give **9b** (R = H) in low yield [7c]. The structure of **9a** was assigned by comparison of its NMR spectral data with that of **8a**. In particular, the signals for H-5, H-8 and H-9 of **8a** (δ 5.35, 5.94, 6.20 ppm) [15] match well with those of H-6, H-9 and H-10 of **8a** (δ, 5.28, 5.84, and 6.36 ppm), while the signals for C-1, C-4 and C-5 of (δ 73.6, 50.4, 64.1 ppm) of **9a** match well with those of C-1, C-5 and C-6 of **8a** (δ 73.8, 51.8, and 62.3 ppm).

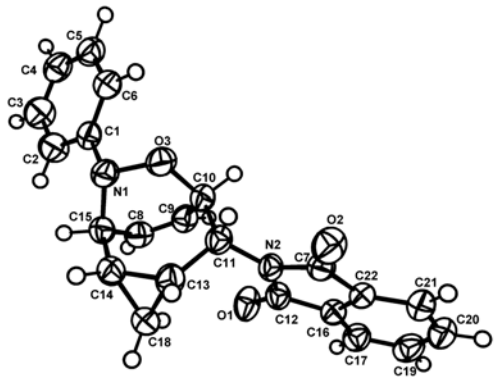


Figure 1. ORTEP diagram of **8a** with atomic numbering, showing 50% probability ellipsoids for non-hydrogen atoms.

Table 1

Crystal Data and Structure Refinement for **8a**

Empirical formula		$C_{22}H_{18}N_2O_3$
Formula weight		358.38
CCDC No.		239646
Wavelength (Å)		0.71069
Crystal system		Monoclinic
Space group		P21/c
Unit cell dimensions	a (Å)	9.426(5)
	b (Å)	10.753(5)
	c (Å)	17.161(5)
	β, deg	98.130(5)
Volume, Å^3		1721.9(13)
Z		4
Calculated (density), g cm^{-3}		1.382
Absorption coefficient, mm^{-1}		0.093
Crystal size, mm		0.3 x 0.2 x 0.15
θ range, deg		2.18 to 25.00
Reflections collected/unique		4035/3026 [R_{int} = 0.0298]
Range of *h, k, l*		–1 to 11, –1 to 12, –20 to 20
Data/restraints/parameters		3026/0/317
Goodness-of-fit on F^2		0.994
Final *R* indices [$I > 2s$ (I)]		$R1$ = 0.0434, $wR2$ = 0.0860
R indices (all data)		$R1$ = 0.0980, $wR2$ = 0.1089
Largest feature, e Å^{-3}		0.152 and –0.180

The products **8a** and **8b** represent cycloaddition of the N=O bond to **6** in a regioselective fashion. This selectivity is such that the oxygen adds to the diene carbon closest to the phthalimide substitutent. It is anticipated that the phthalimide group will act as an electron withdrawing substituent, and thus diene/triene carbons proximal to this group will bear a greater partial positive charge than those more distant. This is qualitatively supported by Hartree-Fock calculations of **6**. Notably, the observed regioselectivity is similar to that previously reported for cycloaddition of nitrosobenzene with a variety of substituted dienes [16]. Additionally, minimization of the

Table 2.

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **8a**

Atom	x	y	z	U_{eq}
O(1)	–3994(2)	–514(2)	8004(1)	63(1)
O(2)	–1155(2)	800(2)	10235(1)	57(1)
O(3)	564(3)	1150(2)	7815(1)	57(1)
N(1)	324(2)	1866(2)	7096(1)	45(1)
N(2)	–2271(2)	260(2)	8990(1)	39(1)
C(1)	1189(3)	1377(2)	6544(1)	42(1)
C(2)	811(4)	1522(3)	5739(2)	60(1)
C(3)	1716(4)	1113(3)	5223(2)	66(1)
C(4)	2997(3)	552(4)	5498(2)	58(1)
C(5)	3396(3)	427(3)	6291(2)	57(1)
C(6)	2511(3)	841(3)	6815(2)	51(1)
C(7)	–2033(3)	189(2)	9813(1)	42(1)
C(8)	–1825(3)	689(3)	6679(2)	49(1)
C(9)	–1476(3)	–134(3)	7237(2)	49(1)
C(10)	–597(3)	312(3)	7975(2)	46(1)
C(11)	–1368(3)	1050(2)	8559(1)	41(1)
C(12)	–3477(4)	–450(2)	8685(1)	44(1)
C(13)	–2070(3)	2248(3)	8238(2)	46(1)
C(14)	–1920(3)	2721(3)	7423(2)	50(1)
C(15)	–1232(3)	1977(3)	6829(2)	45(1)
C(16)	–3970(3)	–1077(2)	9371(2)	42(1)
C(17)	–5103(4)	–1871(3)	9406(2)	53(1)
C(18)	–3367(3)	2356(3)	7628(2)	55(1)
C(19)	–5313(4)	–2307(3)	10141(2)	60(1)
C(20)	–4401(4)	–1971(3)	10808(2)	62(1)
C(21)	–3271(3)	–1164(3)	10778(2)	55(1)
C(22)	–3084(3)	–719(2)	10042(1)	42(1)

steric interactions between the phenyl group of **1** and the phthalimide group of **6** in the cycloaddition transition state, may contribute to the observed regioselectivity [17]. For **9a** (cycloadduct of **7** with **1**), the regioselectivity is the same as that reported for **9b**, the cycloaddition product from unsubstituted cycloheptatriene and **1** [7c].

The cyclic polyenes **6** and **7** were treated dropwise with a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (**2**), to afford **10** and **11** as crystalline solids (Scheme IV). The structure of **10** was assigned by comparison of its NMR spectral data with that for **8a**. In particular, the signals for H-7, H-11, H-12, H-13 and H-14 of **10** (δ 5.19, 5.50, 4.88, 6.13, 6.54 ppm) are similar to those of H-1, H-5, H-6, H-10 and H-9 of **8a** (δ 4.97, 5.28, 4.58, 5.84, and 6.36 ppm). Additionally the NMR spectral data for **10** may be compared to **12**, the cycloadduct of homofulvene (**13**) and **2** (Equation I) [9d]. The signals for H-7, H-12, and H-13/H-14 of **12** (δ 5.07, 5.39, 6.04/6.26 ppm) are similar to those of **10**.

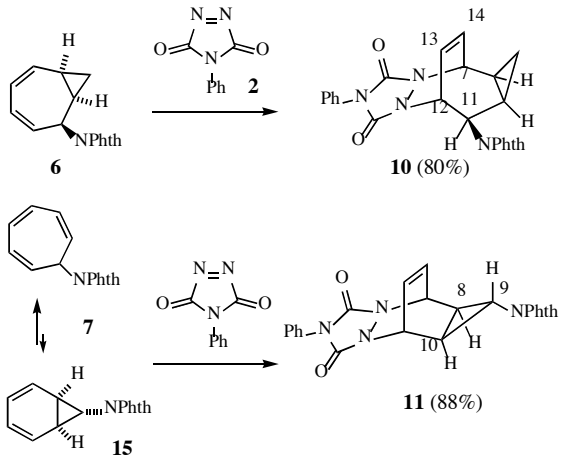
The symmetrical structure of **11** was assigned on the basis of its NMR spectral data. In particular, the ^{1}H NMR spectrum of **11** consisted of four non-aromatic signals while the ^{13}C NMR spectrum consisted of 13 total signals, three of which corresponded to sp^3 hybridized carbons. The relative stereochemistry about the cyclopropane ring was assigned on the basis of the magnitude of H-H

Table 3.

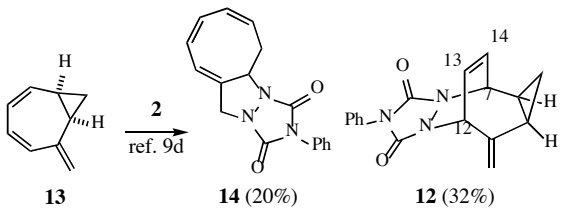
Selected bond lengths (Å) and bond angles (deg) for **8a**

O(1)-C(12)	1.203(3)	O(1)-C(12)-N(2)	126.0(2)
O(2)-C(7)	1.213(3)	O(1)-C(12)-C(16)	127.9(2)
O(3)-N(1)	1.446(2)	O(2)-C(7)-N(2)	124.8(2)
O(3)-C(10)	1.472(3)	O(2)-C(7)-C(22)	128.6(2)
N(1)-C(1)	1.434(3)	O(3)-N(1)-C(1)	109.43(18)
N(1)-C(15)	1.478(3)	O(3)-N(1)-C(15)	109.63(18)
N(2)-C(7)	1.402(3)	O(3)-C(10)-C(9)	112.2(2)
N(2)-C(12)	1.407(3)	O(3)-C(10)-C(11)	103.7(2)
N(2)-C(11)	1.473(3)	N(1)-O(3)-C(10)	117.02(17)
C(7)-C(22)	1.482(3)	N(1)-C(15)-C(8)	107.9(2)
C(8)-C(9)	1.311(4)	N(1)-C(15)-C(14)	109.6(2)
C(8)-C(15)	1.502(4)	N(2)-C(11)-C(13)	114.8(2)
C(9)-C(10)	1.490(4)	N(2)-C(11)-C(10)	112.9(2)
C(10)-C(11)	1.539(3)	C(1)-N(1)-C(15)	117.2(2)
C(11)-C(13)	1.516(3)	C(8)-C(9)-C(10)	117.1(3)
C(12)-C(16)	1.487(3)	C(8)-C(15)-C(14)	114.7(2)
C(13)-C(14)	1.512(3)	C(9)-C(8)-C(15)	116.7(3)
C(13)-C(18)	1.498(4)	C(9)-C(10)-C(11)	117.5(2)
C(14)-C(15)	1.513(4)	C(10)-C(11)-C(13)	115.0(2)
C(14)-C(18)	1.507(4)	C(11)-C(13)-C(14)	121.9(2)
C(16)-C(17)	1.375(4)	C(11)-C(13)-C(18)	126.2(3)
C(16)-C(22)	1.378(3)	C(13)-C(14)-C(15)	123.4(2)
C(17)-C(19)	1.386(4)	C(13)-C(14)-C(18)	59.47(17)
C(19)-C(20)	1.380(4)	C(13)-C(18)-C(14)	60.43(18)
C(20)-C(21)	1.381(4)	C(14)-C(13)-C(18)	60.10(18)
C(21)-C(22)	1.385(3)	C(15)-C(14)-C(18)	120.5(3)

Scheme IV



Equation I



coupling for these protons; the 2.3 Hz coupling between the signals at δ 2.55 (1H) and 2.42 (2H) are consistent with their *trans*-disposition about the three-membered ring. Product **11** arises *via* equilibration of **7** with its

bicyclo[4.1.0]heptadiene isomer **15** *via* 3,3-sigmatropic rearrangement. Typical barriers for cycloheptatriene-norcaradiene interconversion ($\Delta G^{\ddagger}$ ~ 2–12 kcal mol^{-1}) [18] are considerably lower than activation parameters for cycloaddition with PTAD ($\Delta G^{\ddagger}$ ~ 17–20 kcal mol^{-1}) [10e]. Thus, while the equilibrium between **7** ↔ **15** lies far toward **7** (no **15** detected by NMR spectroscopy), apparently reaction of PTAD with **15** is more rapid than with **7**, and the dynamic equilibrium is siphoned off by this cycloaddition.

In summary, the cycloaddition of **6** or **7** with hetero dienophiles proceeded in a selective fashion to generate polycyclic heterocycles **8**-**11**. These structures provide a rich variety of structural diversity, which could be of further use in synthesis.

EXPERIMENTAL

All ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were obtained from Midwest Microlabs, Ltd., Indianapolis, IN.

Bicyclic diene **6** and cycloheptatrienyl phthalimide **7** were prepared according to the literature methods [10a,11].

General Procedure for the Reaction of Phthalimide substituted polyenes with Nitrosobenzene. To a solution of nitrosobenzene (215 mg, 2.01 mmol) in freshly distilled CH_2Cl_2 (2 mL), under N_2 at room temperature, was added bicyclic diene **5** (252 mg, 1.00 mmol). The green solution was stirred for 6 h and then concentrated. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 4:1 to 2:1 gradient) (362 mg, 100%).

5-Phthalimido-8-phenyl-8-aza-7-oxatricyclo[4.2.2.0^{2,4}]dec-9-ene (8a). To a solution of nitrosobenzene (215 mg, 2.01 mmol) in freshly distilled CH_2Cl_2 (2 mL), under N_2 at room temperature, was added bicyclic diene **6** (252 mg, 1.00 mmol). The green solution was stirred for 6 h and then concentrated. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 4:1 to 2:1 gradient) to give an off-white solid (362 mg, 100%). Recrystallization from hexanes–ethyl acetate afforded crystals suitable for X-ray diffraction, mp 128-129°; ir (KBr): 3061, 3032, CO 1708, 1594, 1375 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.68 (ddd, 1H, 3-H, J = 5.2, 7.9, 9.5 Hz), 1.39 (pent, 1H, H-cyclopropyl, J = 8.5 Hz), 1.46-1.33 (m, 1H, H-cyclopropyl), 1.65-1.57 (m, 1H, H-cyclopropyl), 1.79-1.68 (m, 1H, H-cyclopropyl), 4.62-4.55 (m, 1H, 6-H), 4.97 (ddd, 1H, 1-H, J = 1.2, 6.1, 7.4 Hz), 5.28 (dd, 1H, 5-H, J = 4.4, 8.3 Hz), 5.84 (ddd, 1H, 9-H, J = 0.6, 7.3, 9.4 Hz), 6.36 (ddd, 1H, 10-H, J = 1.4, 6.6, 9.3 Hz), 7.00-6.92 (m, 1H, phenyl proton), 7.11-7.04 (m, 2H, phenyl protons), 7.29-7.21 (m, 2H, phenyl protons), 7.78-7.71 (m, 2H, phthalimide protons), 7.89-7.82 (m, 2H, phthalimide protons); ^{13}C nmr (deuteriochloroform): δ 9.6, 13.8, 15.8, 51.8, 62.3, 73.8, 117.6, 122.3, 123.4, 126.2, 128.6, 128.7, 131.9, 134.2, 152.5, 168.5. *Anal.* Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.85; H, 5.20; N, 7.75.

8-Benzoyl-5-phthalimido-8-aza-7-oxatricyclo[4.2.2.0^{2,4}]dec-9-ene (8b). To a rapidly stirring solution of **5** (754 mg, 3.00 mmol) and $NaIO_4$ (1.96 g, 8.98 mmol) in CH_2Cl_2 (7.2 mL), DMF (7.2 mL) and water (3.6 mL) was added, over a period of 80 min, a solution of benzohydroxamic acid (1.23 g, 8.97 mmol) in DMF (3.6 mL). The reaction mixture was stirred for an additional 2 h, then poured into water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried and concentrated. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 2:1 gradient) to afford **8b** as a cream colored solid (1.168 g, ~100%)(recrystallized from CH_3CN), mp 202-203°; ir (KBr): 3100, 3071, CO 1769, 1713, 1650, 1387 cm^{-1}; ^{1}H nmr (deuteriochloroform, 60°): δ 0.69 (ddd, 1H, J = 5.2, 7.9, 9.7 Hz), 1.39 (br pent, 1H, J = 8.5 Hz), 1.80-1.66 (m, 2H), 4.53-4.50 (m, 1H), 5.21 (dd, 1H, J = 3.6, 7.8 Hz), 5.81 (br m, 1H), 6.23 (br t, 1H, J = 8.4 Hz), 6.46 (ddd, 1H, J = 1.2, 6.6, 9.0 Hz), 7.50-7.39 (m, 3H), 7.78-7.72 (m, 4H), 7.86 (d, *J* = 3.0, 5.4 Hz, 2H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 9.6, 13.6, 16.1, 51.6, 76.7, 77.1, 123.5, 128.0, 128.5, 128.9, 129.7, 130.3, 130.8, 132.1, 134.3, 168.2. *Anal.* Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.22; H, 4.70; N, 6.87.

4-Phthalimido-7-phenyl-7-azo-6-oxabicyclo[3.2.2]nona-2,8-diene (9a). To a solution of nitrosobenzene (70 mg, 0.65 mmol) in freshly distilled CH_2Cl_2 (2 mL), under N_2 at room temperature, was added cycloheptatriene **7** (120 mg, 0.51 mmol). The green solution was heated at reflux for 20 h, at which time analysis of an aliquot by ^{1}H NMR spectroscopy indicated the reaction was ~25% complete. Additional nitrosobenzene (600 mg, 5.6 mmol) was added and the reaction mixture was heated at reflux for an additional 5 days. The mixture was cooled and concentrated, and ^{1}H NMR spectroscopy indicated **9a** and unreacted **7**. The residue was purified by column chromatography (SiO_2, hexanes–ethyl acetate = 4:1 –> pure ethyl acetate gradient) to give a tan solid (77 mg, 44%). Recrystallization from hexanes–ethyl acetate gave an analytically pure sample, mp 145.5-147°; ir (nujol): CO 1711, 1770 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.23 (dd, 1H, 5-H, J = 5.1, 7.7 Hz), 5.35 (dd, 1H, 4-H, J = 5.3, 7.7 Hz), 5.75-5.68 (m, 1H, 1-H), 5.99-5.88 (m, 3H, H-olefinic), 6.23-6.17 (m, 1H, 9-H), 7.04-6.98 (m, 1H, phenyl proton), 7.16-7.13 (m, 2H, phenyl proton), 7.34-7.27 (m, 2H, phenyl proton), 7.72-7.69 (AA'BB', 2H, phthalimide protons), 7.80-7.77 (AA'BB', 2H, phthalimide protons); ^{13}C nmr (deuteriochloroform): δ 50.4, 64.1, 73.6, 115.2, 123.0, 123.5, 126.7, 128.8, 129.1, 129.4, 130.3, 132.0, 134.4, 151.4, 168.2. *Anal.* Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.12; H, 4.82; N, 7.95.

General Procedure for the Reaction of Phthalimide substituted polyenes with 4-Phenyl-1,2,4-triazoline-3,5-dione. A solution containing a slight excess of 4-phenyl-1,2,4-triazoline-3,5-dione (**2**) dissolved in a minimal amount of ethyl acetate/hexanes (1:1, ~1 mL) was added, dropwise with stirring, to a solution of the bicyclic diene **5** (90 mg, 0.36 mmol), also dissolved in a minimal amount of ethyl acetate/hexanes (1:1, ~3 mL), just until the red color of the triazolinedione persisted. During the addition a white to off-white precipitate formed. The mixture was stirred for an additional 30 min, then cooled to 0 °C (ice/water bath). The precipitate was isolated by vacuum filtration and washed with ice-cold ethyl acetate/hexanes (1:1) to give the product **10** as colorless crystals (120 mg, 80%).

4-Phenyl-11-phthalimido-2,4,6-triaza-3,5-dioxotetracyclo-[5.4.2.0^{2,6}.0^{8,10}]tridec-12-ene (10). This compound was obtained as small needle-like white crystals, mp 129-129.5°; ir (nujol): CO 1707, 1766 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.74 (ddd,

1H, J = 5.1, 7.8, 11.3), 1.43 (br pent, 1H, J = 8.0 Hz), 1.78-1.63 (m, 2H), 4.88 (dd, 1H, J = 3.0, 6.7 Hz), 5.19 (dd, 1H, J = 3.0, 7.8 Hz), 5.50 (t, 1H, J = 6.7 Hz), 6.13 (dd, 1H, J = 7.8, 8.4 Hz), 6.54 (dd, 1H, J = 7.2, 8.7 Hz), 7.54-7.35 (m, 5H, phenyl protons), 7.91-7.76 (AA'BB'q, 4H, phthalimide protons); ^{13}C nmr (deuteriochloroform): δ 10.0, 15.0, 16.5, 50.3, 51.4, 54.1, 123.7, 125.9, 126.4, 128.4, 129.8, 131.7, 131.8, 134.6, 152.2, 168.2. *Anal*. Calcd. for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found: C, 67.51; H, 4.19; N, 13.12.

4-Phenyl-9-phthalimido-2,4,6-triaza-3,5-dioxotetracyclo-[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene (11). This compound was obtained as colorless crystals (ethanol), mp 215-217°; ir (nujol): CO 1713, 1779 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.42 (td, 2H, 8- and 10-H, *J* = 2.3, 3.2, Hz), 2.55 (t, 9-H, 1H, *J* = 2.3 Hz), 5.45 (m, 1- and 7-H, 2H), 6.29 (dd, 2H, 11- and 12-H, *J* = 3.2, 3.8), 7.54-7.33 (m, phenyl protons, 5H), 7.75-7.72 (AA'BB', 2H, phthalimide protons), 7.86-7.83 ppm (AA'BB', phthalimide protons, 2H); ^{13}C nmr (deuteriochloroform): δ 12.8, 29.8, 52.1, 123.6, 125.7, 126.3, 128.5, 129.3, 131.3, 131.6, 134.5, 156.7, 168.1 ppm. *Anal*. Calcd. for $C_{23}H_{16}N_4O_4$: C, 66.99; H, 3.91; N, 13.58. Found: C, 66.73; H, 3.92; N, 13.25.

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