the American Chemical Society, for the support of this research.

**Registry No.** **6**, 42393-90-8; **7**, 105598-05-8; **8**, 90925-90-9; **9**, 105598-06-9; **10**, 105598-07-0; **11**, 1075-10-1; **12**, 105598-08-1; **13**, 105598-09-2; **14**, 17428-83-0; **15**, 13025-91-7; **16**, 1196-55-0; *cis*-**17**, 30983-79-0; *trans*-**17**, 2763-42-0; *cis*-**18**, 105598-10-5; *trans*-**18**, 105598-04-7; **19**, 105598-11-6; **20**, 105661-54-9; **21**, 105661-55-0; **22**, 826-56-2; **23**, 22241-35-6; **24**, 22241-36-7; **25**, 6432-30-0; **26**, 105598-12-7; **27**, 105598-13-8; **28**, 5164-37-4; **29**, 30538-57-9; **30**, 30538-58-0; **31**, 105661-56-1; $HSCH_2CH_2SH$, 540-63-6; bicyclo[4.4.0]dec-1(6)-en-3-one, 13837-12-2.

# Rapid Access to a Series of Highly Functionalized $\alpha,\beta$-Unsaturated Cyclopentenones. A Caveat on Aminospirocyclization[1]

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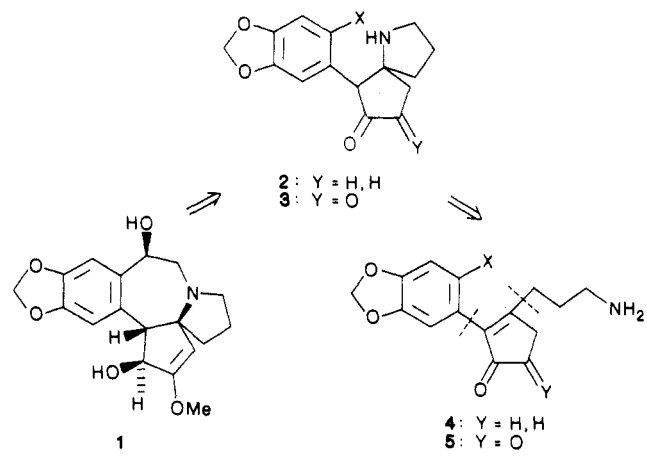
Conjugate addition of a series of functionalized aryllithium reagents to cyclopentenyl sulfones **9** and **17** results in $\alpha$-sulfonyl anion intermediates that are further alkylated to afford triply converged adducts **12a–c** and **19**. Refunctionalization of these adducts provides $\alpha,\beta$-unsaturated cyclopentenones **4a–c** and **21** in high overall yields. Attempted intramolecular Michael addition of these ($\gamma$-aminopropyl)cyclopentenones to produce the spiro [4.4] ring system was unsuccessful.

Several years ago we initiated a program directed toward the total synthesis of 11-hydroxycephalotaxine (**1**),[2] an alkaloid of the pharmacologically important harringtonine family.[3,4] The synthetic strategy adopted was envisaged to involve spirocyclization[5] of amino derivatives **4** and **5** (Scheme I).

Synthesis of the basic cyclopentenone system was smoothly accomplished in greater than 50% overall yield on the basis of our triply convergent (see dashed lines on structures **4** and **5**) cycloalkenone synthesis.[6] Preparation of the requisite aryllithium reagents **8a–c** was accomplished as follows: Treatment of 6-bromopiperonal (**6**) with methylenetriphenylphosphorane under phase-transfer conditions[7] afforded an 86% yield of bromostyrene **7b**. Conversion of **7b** to acetonide **7c**[8] involved catalytic osmylation[9] followed by treatment of the diol with 2,2-dimethoxypropane. Acetal **7a**[8] was synthesized from bromopiperonal (**6**). Reaction of **7a–c** with *tert*-butyllithium[10] afforded **8a–c**[8] in near quantitative yield as assayed by deuterium quenching studies.

**Scheme I**




Treatment of vinyl sulfone **9**[11] with aryllithium reagents **8a–c** afforded $\alpha$-sulfonyl anion intermediates **10a–c**, which were subsequently treated with iodide **11** in the same reaction vessel. The resulting intermediates were selectively cleaved at the primary isopropyldimethylsilyl (IPDMS) ether moiety by brief treatment with tetrabutylammonium fluoride (TBAF)[12] to afford adducts **12a–c**[8] in the indicated overall yields. The polarity change resulting from silyl ether cleavage makes purification of the triply converged adducts **12a–c** particularly efficacious since small amounts of residual vinyl sulfone **9**, quenched organometallic, and nonalkylated intermediates **10a–c** are easily removed by simple filtration through silica gel. Adducts **12a–c** were converted to enones **13a–c**[8] by sequential mesylation,[13] azide displacement, *tert*-butyldimethylsilyl ether (TBDMS) cleavage,[14] and Swern oxidation[15] followed by a diazabicycloundecene (DBU) workup to effect $\beta$-elimination of the resulting $\beta$-sulfonyl ketone intermediates.[6]

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(3) While 11-hydroxycephalotaxine has yet to be synthesized, the parent alkaloid has been prepared by three groups: (a) For a review see: Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1974**, *8*, 158. (b) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023.
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(8) The synthesis of intermediates in the **a** and **c** series is highly analogous to that reported in this paper for the **b** compounds. Detailed experimental conditions and spectral data can be found in: Conrad, P. C. Ph.D. Thesis Purdue University, 1980.
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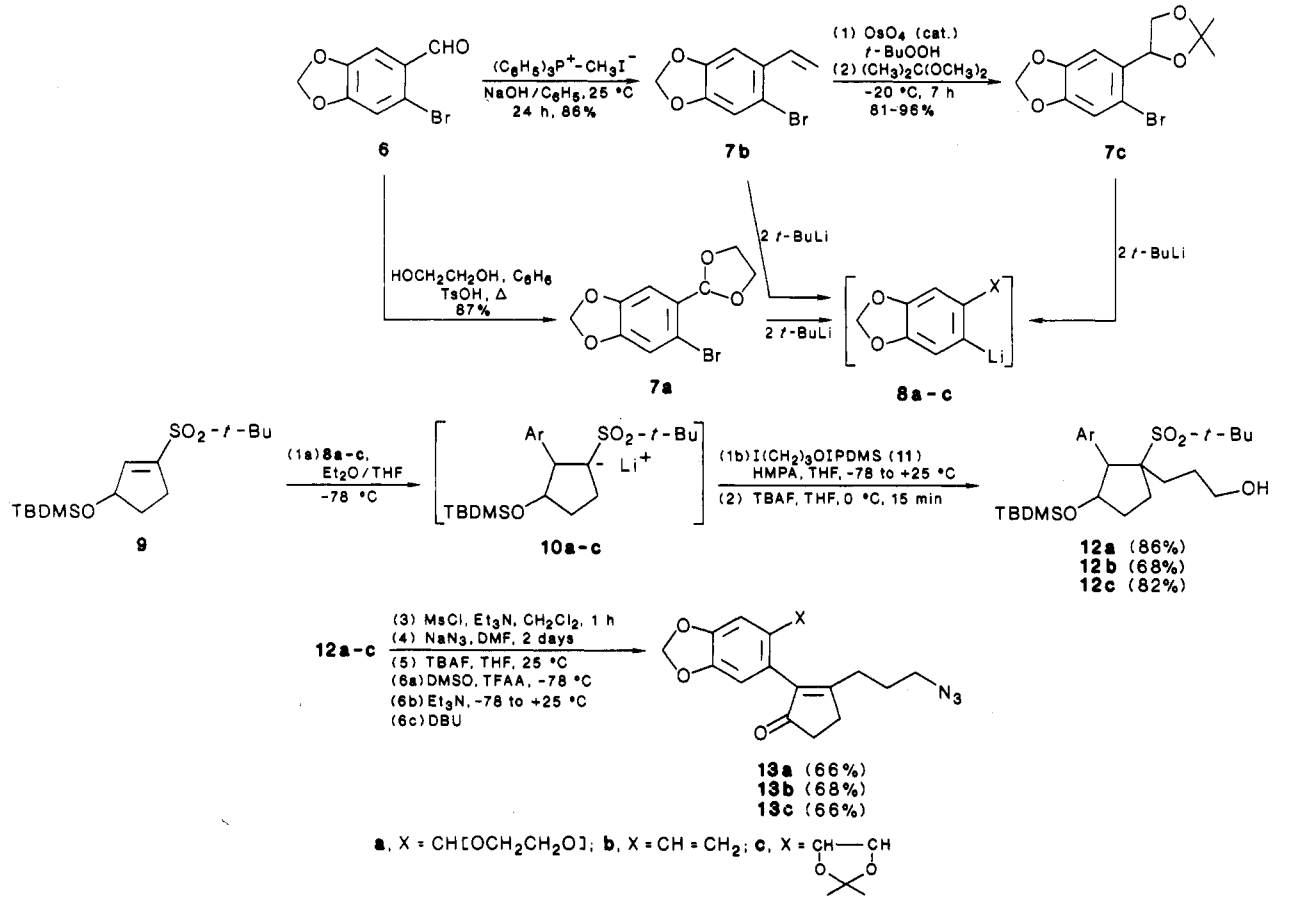
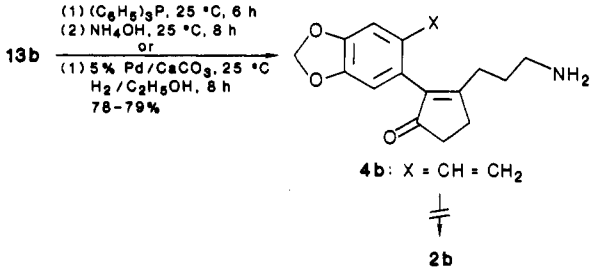
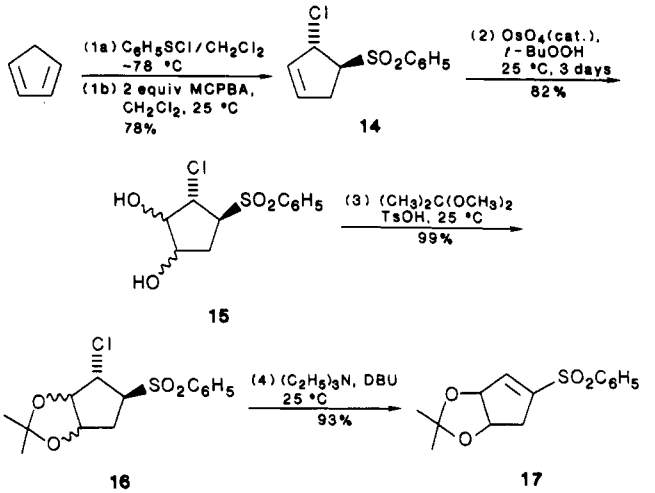
**Scheme II**




**Scheme III**




**Scheme IV**




The overall yield for the four-step sequence was between 66 and 68% (Scheme II).

Treatment of **13b** with either triphenylphosphine[16] or 5% palladium on calcium carbonate[5a] afforded primary amine **4b** in good yield. Unfortunately, neither **4b** nor the corresponding amines **4a,c**[8] could be made to cyclize to the desired spirocycles **2a–c**, even under a number of specialized conditions devised for this general purpose.[5b-d] Presumably this reluctance to undergo intramolecular Michael addition to generate spiro [4.4] ring system **2** is a consequence of severe eclipsing interactions between the aminopropyl group and the aryl moiety present in the α-position of enones **4a–c** (Scheme III).

Faced with this problem we elected to prepare cyclopentene-1,2-dione **5**, a "foiled cyclopentadienone"[17] that presumably would be much more reactive with respect to 1,4 addition to remove the unfavorable dipole–dipole interactions, of the 1,2-dione moiety.

Synthesis of the requisite vinyl sulfone precursor for this strategy was accomplished as follows: Treatment of cyclopentadiene with phenylsulfenyl chloride [generated in situ from thiophenol and *N*-chlorosuccinimide (NCS)[18]] yielded a 1,2 adduct that was immediately oxidized with *m*-chloroperoxybenzoic acid (MCPBA) to prevent rearrangement to the more stable 1,4 adduct. This procedure afforded β-chloro sulfone **14** in 78% yield. Catalytic os-

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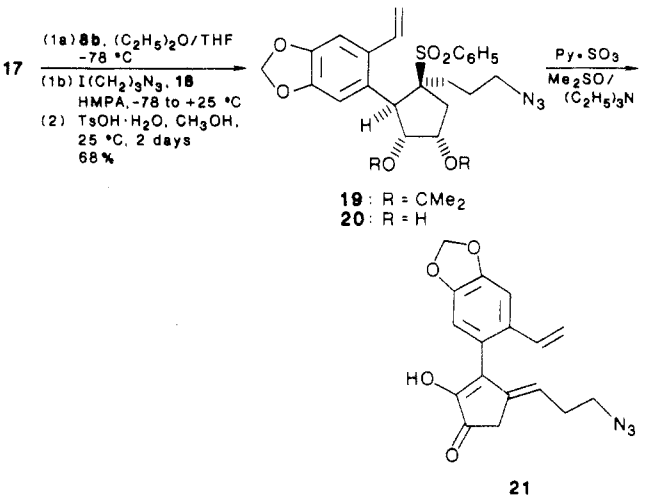
**Scheme V**




mylation[9] produced a diastereomeric mixture of diols **15** that were not separated but directly protected as acetonide **16** (80% from **14**). Treatment of this mixture with triethylamine and DBU gave the crystalline vinyl sulfone **17** in 93% yield (Scheme IV).

Reaction of aryllithium reagent **8b** with vinyl sulfone **17** afforded an $\alpha$-sulfonyl anion that was further alkylated with 3-iodopropyl azide **18** in the presence of HMPA to generate the triply converged adduct **19**.[19] It should be noted that in this instance it was deemed more efficient to directly employ azide-bearing alkylating agent **18**, thus avoiding the refunctionalizations that were necessary in the chemistry described in Scheme II. Although it was possible to isolate purified acetonide **19**[20] in 61% yield, it was operationally more efficient to delay the purification step until after acetonide removal, thus providing the more easily isolated diol **20**[19] in 68% overall yield. Oxidation of **20** with pyridine–sulfur trioxide in dimethyl sulfoxide ($Me_2SO$)[21] at 10 °C afforded dienol **21** in 76% yield. Careful examination of the spectral properties of **21** failed to reveal any evidence for an equilibrium with the azido analogue of **5**. Further efforts to convert **21** or earlier synthetic intermediates to **3** were completely unrewarding (Scheme V).

## Experimental Section

**General Procedures.** Melting points were taken on a Fisher-Johns melting point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded neat (NaCl) or were recorded in solution ($CHCl_3$; NaCl solution cells) on a Perkin-Elmer 710-B spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were determined in chloroform-$d_1$ solution unless otherwise stated. $^1H$ NMR spectra were recorded on a Perkin-Elmer R-32 or a Nicolet NT-470 spectrometer. Splitting patterns: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; c, complex. $^{13}C$ NMR spectra were recorded on a Varian CFT-20 or a XL-200 spectrometer to give either a full proton-decoupled/single-frequency off-resonance decoupled pair of spectra, a single full proton-decoupled spectrum, or a single APT[22] spectrum. Off-resonance splitting patterns are designated as for $^1H$ NMR splitting patterns. Mass spectra were recorded on a Finnigan 4000 mass spectrometer; exact mass determinations were obtained on a CEC-21-110-B high-resolution mass spectrometer.

All experiments were carried out under a positive pressure of nitrogen in a dry flask equipped with rubber stoppers for introduction of reagents via syringe. All solvents used for workup or recrystallization were distilled. Reactions were monitored by TLC on precoated thin-layer Sil G-25 $UV_{254}$ plates. The plates were visualized by immersing in either a *p*-anisaldehyde solution (1350 mL of EtOH, 50 mL of concentrated $H_2SO_4$, 15 mL of HOAc, 37 mL of *p*-anisaldehyde) or a cobalt(II) chloride solution (3 g of $NH_4SCN$, 1 g of $CoCl_2$, 20 mL of $H_2O$). Flash chromatography was carried out as described by Still[23] using silica gel 60 (230–400 mesh). All other chromatography was run on open columns of silica gel (60–200 mesh).

Reaction solvents were purified as follows: THF, $Et_2O$, distilled from sodium/benzophenone; benzene, toluene, methylene chloride, $Me_2SO$, HMPA, DMF, distilled from $CaH_2$ and stored over 4A molecular sieves. All other solvents and reagents were purified per ref 24. Stock solutions or organolithium reagents were titrated in benzene at 25 °C with menthol using 2,2′-bipyridyl as the indicator.[25]

IR data are reported in microns. $^{13}C$ NMR data are reported in parts per million with chloroform-$d_1$ as the internal standard. $^1H$ NMR data are reported in parts per million with tetramethylsilane as the internal standard.

**3-(3-Aminopropyl)-2-[6-vinyl-3,4-(methylenedioxy)phenyl]-2-cyclopenten-1-one (4b). Method A.**[5a] Azo enone **13b** (0.2 g, 0.64 mmol) is dissolved in 6 mL of ethanol (100%) in the presence of 5% Pd/$CaCO_3$ (Lindlar catalyst, 80 mg) at 25 °C. The reaction vessel is fitted to a Brown hydrogenator and gassed with 1 atm hydrogen. After 8 h the reaction mixture is filtered through a plug of Celite and the ethanol removed in vacuo to leave crude **4b** as a light yellow oil. The crude product contains some nonpolar impurities that can be separated via an extractive type workup. The reaction mixture is taken up in 25 mL of $CH_2Cl_2$ and extracted 3× with 5% HCl. The $CH_2Cl_2$ phase is discarded. The combined acid phases are neutralized (10% NaOH) and extracted 3× with $CH_2Cl_2$. The second $CH_2Cl_2$ extracts are dried ($K_2CO_3$), and the solvent is removed in vacuo to afford essentially pure **4b**: 0.14 g, 0.5 mmol (78%); TLC ($SiO_2$, 2% concentrated $NH_4OH/CH_3OH$) $R_f$ 0.26; IR ($CDCl_3$) 2.95 ($NH_2$), 3.4 (CH), 5.83 (C=O) $\mu$m; $^1H$ NMR ($CDCl_3$) $\delta$ 7.15 (s, 1, arom), 6.5 (s, 1, arom), 6.4 (dd, $J$ = 17 Hz, 10 Hz, 1, styrene), 6.0 (sm, 2, methylenedioxy), 5.55 (dd, $J$ = 17 Hz, 2 Hz, 1, styrene), 5.1 (dd, $J$ = 10 Hz, 2 Hz, 1, styrene), 2.65 ($A_2B_2$, 4, 2 $CH_2$), 2.4 (t, $J$ = 8 Hz, 2, $CH_2$), 1.65 (m, $J$ = 8 Hz, $CH_2$), 1.2 (br s, 2, $NH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 207.58 (s, C=O), 176.94 (s, $\beta$-C=C), 148.06, 147.46, 140.79, 130.84, 124.87 (s, arom C and $\alpha$-C=C), 134.32 (d, CH=, styrene), 113.14 (t, $=CH_2$, styrene), 109.63 (d, CH aromatic ortho to cyclopentenone), 104.99 (d, CH aromatic ortho to side chain), 101.30 (t, $CH_2$, methylenedioxy), 41.92 (t, $CH_2NH_2$), 34.71 (t, $CH_2$ $\alpha$ to C=O), 29.34 (t, $CH_2$'s $\alpha$ to C=C); exact mass for $C_{17}H_{19}NO_3$, calcd 285.136, found 285.134. The major impurity (ca. 10%) was identified as the corresponding 3-ethoxypropyl enone: TLC ($SiO_2$, 10% EtOAc/$CH_2Cl_2$) $R_f$ 0.46.

**Method B.**[16] To a solution (15 mL of THF) of triphenylphosphine (2.3 g, 9.3 mmol) at 25 °C is added azo enone **13b** (1.44 g, 4.6 mmol) in 8 mL of THF. During the initial period of the reaction $N_{2(g)}$ can be seen bubbling out of the solution. The reaction mixture is stirred approximately 6 h and then treated with concentrated $NH_4OH$ (3 mL) at 25 °C for 8 h. The reaction mixture is poured into 50 mL of $CHCl_3$ and extracted 4× with 20 mL of 5% HCl. The chloroform phase is discarded. The combined acid extracts are neutralized with 50 mL of 10% NaOH and extracted 4× with 30 mL of $CHCl_3$. Drying ($K_2CO_3$) and evaporation in vacuo of the combined organic phases leaves amino enone **4b** [1.02 g, 3.6 mmol (77%)] in need of no further purification.

**6-Bromopiperonal (6).** To a vigorously stirred suspension of iron(0) fillings (29.3 g, 525 mmol) in 350 mL of glacial acetic

(19) The stereochemistry indicated at the quaternary center must be regarded as tentative at this point. This is based upon analogy with the addition of aryl anion **8a** to **17** followed by quenching with allyl bromide to provide an 82% yield of an adduct whose stereochemistry has been secured by X-ray analysis.[20]

(20) For further experimental details and spectral data, see: Kwiatkowski, P. L. Ph.D. Thesis, Purdue University, 1985.

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(25) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

acid is added $Br_2$ (132.6 g, 840 mmol) at a steady rate, care being taken to avoid an exotherm. Following addition, the solution is stirred 20 min before dropwise addition of piperonal (75.0 g, 500 mmol) in 350 mL of acetic acid. After the solution is stirred for 5 min, $Br_2$ (82.85 g, 525 mmol) is added dropwise and the reaction mixture stirred for several days until all starting material is reacted by TLC determination (periodic addition of 3–5% excess $Br_2$ may help maintain reaction rate). The reaction mixture is diluted with 2.5 L of $CHCl_3$ and filtered through Celite. The solution is washed with 750-mL portions of saturated $Na_2S_2O_3$ until all excess bromine is reduced (i.e., the aqueous layer remains colorless) followed by washes with 750 mL of 10% $Na_2CO_3$ and 750 mL of saturated NaCl. The solution is dried ($Na_2SO_4$) and decolorized (Darco) at 25 °C for 18 h. The solution is filtered and the solvent removed to give a tan solid. Recrystallization from 95% EtOH affords aryl bromide **6** [95.9 g, 420.5 mmol (84%)] as off-white needles: mp 131–132 °C; TLC ($SiO_2$, 5% $Et_2O/CHCl_3$) $R_f$ 0.66; $^1H$ NMR ($CDCl_3$) δ 10.2 (s, 1, aldehyde), 7.4 (s, 1, arom), 7.1 (s, 1, arom), 6.1 (s, 2, methylenedioxy).

Two reports have appeared in the literature concerning bromination of piperonal, both of which are modifications of the method developed by Parijs.[26] Raphael[27] has reported the bromination of piperonal in acetic acid (3.3 M) at 0 °C, followed by warming to 25 °C for 6 h to afford 6-bromopiperonal (**6**) in 48% yield after recrystallization. Fleming[28] has reported essentially the same reaction using chloroform at reflux in place of acetic acid as the solvent. The yield of 6-bromopiperonal was reported to be 54% after recrystallization. Attempts were made to repeat these reactions under the conditions reported. The reactions were convenient to carry out on large scales and afforded pure product but only in substantially lower yields (25%) after recrystallization. In one experiment it was determined by proton NMR that the reaction was only 40% complete, and only a 25% yield of pure product could be crystallized from the mother liquor. The only other detectable compound was found to be the starting aldehyde, piperonal.

**6-Bromo-3,4-(methylenedioxy)styrene (7b).** 6-Bromopiperonal (**6**); 16.0 g, 70 mmol) and methyltriphenylphosphonium iodide (42.5 g, 105 mmol) are combined in a two-phase reaction system composed of 200 mL of benzene and 600 mL of 5 N sodium hydroxide at 25 °C.[7] The reaction mixture is *vigorously* stirred for 48 h. The aqueous phase is separated and extracted 3× with 150 mL of benzene, the combined organic extracts are dried ($K_2CO_3$), and the radical inhibitor 4,4′-thio(bis-6-*tert*-butyl-m-cresol) (spatula tip) is added. Evaporation of the solvent leaves crude **7b** contaminated with triphenylphosphine oxide. Plug filtration ($SiO_2$, 60–200 mesh, 40:1, 20% THF/hexane) affords pure **7b** [13.6 g, 60.2 mmol (86%)] as a colorless oil: TLC ($SiO_2$, 20% THF/hexane) $R_f$ 0.49; $^1H$ NMR ($CDCl_3$) δ 7.0 (dd, $J$ = 17 Hz, 10 Hz, 1, styrene), 6.99 (s, 1, arom), 6.95 (s, 1, arom), 5.9 (s, 2, methylenedioxy), 5.54 (dd, $J$ = 17 Hz, 2 Hz, 1, styrene), 5.25 (dd, $J$ = 10 Hz, 2 Hz, 1, styrene).

**3-Iodopropyl Isopropyldimethylsilyl Ether (11).** To a solution (200 mL of $CH_2Cl_2$) composed of 3-bromopropanol (13.9 g, 100 mmol), 4-(dimethylamino)pyridine (DAP; 1.22 g, 10 mmol), and triethylamine (12.14 g, 120 mmol) at 0 °C is added dropwise isopropyldimethylsilyl chloride (16.32 g, 120 mmol). An immediate precipitate is formed, and the reaction is stirred for 12 h. The reaction mixture is filtered. The organic phase is diluted with an additional 100 mL of $CH_2Cl_2$, extracted 2× with 5% HCl (0 °C), 1× with saturated $NaHCO_3$, and 1× with saturated NaCl, and dried ($K_2CO_3$). Removal of the solvent in vacuo leaves the corresponding bromosilyl ether as a near-colorless liquid. The halide is taken up in 20 mL of acetone and the resultant mixture added to a solution (100 mL of acetone) of sodium iodide (16.5 g, 110 mmol) at 25 °C, followed by stirring for 24 h. The reaction mixture is filtered to remove the salts, and the filtrate is washed with acetone. After removal of the acetone in vacuo, the remaining liquid is taken up in 200 mL of $Et_2O$, washed 1× with saturated $Na_2S_2O_3$ and 1× with $H_2O$, and dried ($K_2CO_3$) and the solvent removed in vacuo to afford crude **11**. The crude product is distilled from $K_2CO_3$ onto finely ground Cu metal to give pure **11**: 24.4 g, 84.7 mmol (85% from 3-bromo-1-propanol); 75–77 °C (2.2 mm); $^1H$ NMR ($CDCl_3$) δ 3.6 (t, $J$ = 7 Hz, $CH_2$), 3.2 (t, $J$ = 7 Hz, $CH_2$), 1.9 (tt, $J$ = 7 Hz, $CH_2$), 1.85 (sm, 7, CH, 2 $CH_3$), −0.05 (s, 6, dimethylsilyl); $^{13}C$ NMR ($CDCl_3$) δ 62.06 (t, $CH_2$), 36.20 (t, $CH_2$), 16.91 (q, 2 $CH_3$), 14.50 (d, CH), 3.34 (t, $CH_2$), −4.41 (q, 2 $CH_3$); exact mass for $C_8H_{19}IOSi$, calcd 286.021, found 286.021.

**3-[(*tert*-Butyldimethylsilyl)oxy]-2-[6-vinyl-3,4-(methylenedioxy)phenyl]-1-(3-hydroxypropyl)cyclopentyl *tert*-Butyl Sulfone (12b).** Addition of a solution (85 mL of $Et_2O$) of vinyl sulfone **9** (15.9 g, 50 mmol) with LiH (to ensure anhydrous conditions) to organolithium reagent **8b** [prepared in situ by the dropwise addition of *tert*-butyllithium (1.3 M pentane, 123 mmol) to a solution (0.25 M, 200 mL of $Et_2O$) of bromostyrene **7b** (13.6 g, 60 mmol) at −78 °C and stirring for 30 min] generates α-sulfonyl anion **10b**. To the reaction mixture of **10b** is added a solution composed of iodide **11** (17.2 g, 60 mmol), HMPA (22% of total reaction volume, 81.5 mL) THF (15% of total reaction volume, 50 mL), and LiH (to ensure anhydrous conditions) at −78 °C, followed by immediate warming to 25 °C. The alkylation reaction is characterized by the bright red color produced by the addition of HMPA, which gradually fades to pale yellow as the alkylation takes place over 30–45 min. The reaction mixture is quenched with saturated $NH_4Cl$ and 250 mL of $Et_2O$. The organic phase is washed 3× with $H_2O$, dried ($Na_2SO_4$), and concentrated in vacuo to leave a brown oil. After workup, the brown oil is taken up in THF (200 mL), treated with tetrabutylammonium fluoride (0.84 M THF, 65 mL, 55 mmol) at −20 °C for 15 min, and immediately quenched by the addition of 50 mL of $H_2O$. The reaction mixture is diluted with 240 mL of $Et_2O$, washed 3× with $H_2O$, and dried ($Na_2SO_4$) and the solvent evaporated *in vacuo* to leave crude **12b** as a brown oil. Plug filtration [$SiO_2$; 60–200 mesh; 30:1 (1) 5% $EtOAc/CH_2Cl_2$, (2) EtOAc] affords essentially pure **12b** [16.8 g, 32 mmol (68%)] as a yellow-tinted oil: TLC ($SiO_2$, 5% $EtOAc/CH_2Cl_2$) $R_f$ 0.23; IR ($CDCl_3$) 2.8 (OH), 3.38 (CH), 6.65 (C=C), 7.8, 8.9 ($SO_2$) μm; $^1H$ NMR ($CDCl_3$) δ 7.45 (dd, $J$ = 17 Hz, $J$ = 10 Hz, 1, sytrene), 7.05 (s, 1, arom), 6.8 (s, 1, arom), 5.98 (s, 2, methylenedioxy), 5.45 (dd, $J$ = 17 Hz, $J$ = 2 Hz, 1, styrene), 5.28 (dd, $J$ = 10 Hz, $J$ = 2 Hz, 1, styrene), 4.3 (m, 1, α-silyloxy), 3.65 (m, 2, $CH_2$), 2.75 (brm, 1, α-aryl), 1.6–2.3 (brm, 8, 4 $CH_2$), 1.4 (s, 9, *tert*-butyl), 1.75 (s, 9, *tert*-butylsilyl), −0.15 (s, 3, $CH_3Si$), −0.35 (s, 3, $CH_3Si$); exact mass for $C_{27}H_{44}O_6SSi$, calcd 524.263, found 409.169 (−TBDMS, −115.094).

**3-(3-Azidopropyl)-2-[6-vinyl-3,4-(methylenedioxy)phenyl]-2-cyclopenten-1-one (13b).** To a solution (60 mL of $CH_2Cl_2$) at 0 °C composed of alcohol **12b** (10.5 g, 20 mmol) and triethylamine (4.05 g, 40 mmol) is added methanesulfonyl chloride (3.44 g, 30 mmol) maintaining the temperature at ≤5 °C. After 30 min the reaction is warmed to 25 °C, diluted with 240 mL of $CH_2Cl_2$, extracted 2× with 5% HCl, 1× with saturated $NaHCO_3$, and 1× with $H_2O$, and dried ($MgSO_4$). Removal of the solvent leaves essentially pure mesylate as a yellowish foam: TLC ($SiO_2$, 50% $EtOAc/CH_2Cl_2$) $R_f$ 0.54. The crude mesylate is treated with sodium azide (2.6 g, 40 mmol) in 80 mL of DMF (0.25 M) for 36 h at 25 °C. The reaction mixture is diluted with 200 mL of 50% $Et_2O$/toluene, washed 4× with $H_2O$, and dried ($Na_2SO_4$). Removal of the solvent in vacuo affords essentially pure azide as a slightly yellow foam: TLC ($SiO_2$, 5% $EtOAc/CH_2Cl_2$) $R_f$ 0.58; $^1H$ NMR ($CDCl_3$) δ 7.4 (dd, $J$ = 17 Hz, 10 Hz, 1, styrene), 6.97 (s, 1, arom), 6.7 (s, 1, arom), 5.95 (s, 2, methylenedioxy), 5.4 (dd, $J$ = 17 Hz, 2 Hz, 1, styrene), 5.25 (dd, $J$ = 10 Hz, 2 Hz, 1, styrene), 4.3 (brm, 1, α-silyloxy), 3.2 (t, $J$ = 7 Hz, $CH_2N_3$), 2.7–3.0 (brm, 1, α-aryl), 1.7–2.2 (brm, 8, 4 $CH_2$), 1.4 (s, 9, *tert*-butyl), .75 (s, 9, *tert*-butylsilyl), −0.15 (s, 3, $CH_3Si$), −0.35 (s, 3, $CH_3Si$). Uptake of the crude azide in 60 mL of THF followed by treatment with tetrabutylammonium fluoride (0.84 M THF, 40 mmol) at 25 °C for 6 h affords the azido alcohol as a yellow foam after workup [diluted with 180 mL of $Et_2O$, washed 3× with $H_2O$, dried ($MgSO_4$); solvent removed in vacuo]: TLC ($SiO_2$, 5% $EtOAc/CH_2Cl_2$) $R_f$ 0.29. Oxidation is readily achieved by dimethyl sulfoxide "activated" by oxalyl chloride.[15] To 50 mL of $CH_2Cl_2$ at 25 °C is added oxalyl chloride (3.81 g, 30 mmol), and the solution is cooled to −78 °C. Dimethyl sulfoxide (3.13 g, 40 mmol) is slowly added (≤−70 °C) at which time vigorous bubbling is observed ($-CO_2$, CO), and the homogeneous solution is stirred approximately 15 min. The azido alcohol is taken up in 20 mL of $CH_2Cl_2$ and added dropwise (−70

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°C) to the above Swern reagent, whereupon an immediate precipitate is formed. The mixture is kept at −78 °C for 30 min, followed by the addition of triethylamine (8.1 g, 80 mmol) at −78 °C, and finally warmed to 25 °C after 15 min. After 1 h at 25 °C, DBU (6.08 g, 40 mmol) is added and the reaction mixture is stirred 12 h more at 25 °C. The reaction mixture is diluted with 100 mL of $H_2O$/100 mL of $CH_2Cl_2$ and the organic phase separated. The aqueous phase is extracted 2× with 50 mL of $CH_2Cl_2$. The combined organic extracts are washed 2× with 100 mL of 5% HCl, 1× with 100 mL of 10% $Na_2CO_3$, and 1′ with 100 mL of saturated NaCl and dried ($Na_2SO_4$). Removal of the solvent in vacuo leaves crude enone **13b** as a heavy, brown oil. Column chromatography ($SiO_2$, 60–200 mesh, 50:1, 3% EtOAc/$CH_2Cl_2$) affords pure azo enone **13b** [4.2 g, 13.6 mmol (68% from alcohol **12b**)] as a slightly yellow-tinted oil: TLC ($SiO_2$, 5% EtOAc/$CH_2Cl_2$) $R_f$ 0.50; IR (NaCl) 3.4 (CH), 4.7 ($N_3$), 5.8 (C=O) 6.1 (C=C) μm; $^1$H NMR ($CDCl_3$) δ 7.15 (s, 1, arom), 6.5 (s, 1, arom), 6.38 (dd, $J$ = 17 Hz, 10 Hz, styrene), 6.0 (s, 2, methylenedioxy), 5.65 (dd, $J$ = 17 Hz, 2 Hz, 1, styrene), 5.1 (dd, $J$ = 10 Hz, 2 Hz, 1, styrene), 3.25 (t, 2, $CH_2N_3$), 2.65 ($A_2B_2$, 4, 2 $CH_2$), 2.4 (brt, $J$ = 7 Hz, 2, $CH_2$), 1.8 (m, $J$ = 7 Hz, $CH_2$); exact mass for $C_{17}H_{17}CH_2N_3O_3$, calcd 311.126, found 311.124.

***trans*-4-Chloro-5-(phenylsulfony )-2-cyclopentene (14).** To a vigorously stirring suspension of *N*-chlorosuccinimide (34.74 g, 255 mmol) in 250 mL of $CH_2Cl_2$ at 25 °C in a flask equipped with a pressure-equalizing addition funnel and water-cooled condenser is added 10% of a total 27.55 g (250 mmol) of thiophenol. After initiation of sulfenyl chloride formation[18] (indicated by an intense orange color), the reaction flask is immersed in an ice–water bath and the remaining thiophenol added at a rate that maintains a gentle reflux. The cold bath is removed and the solution stirred at 25 °C for 30 min. The orange sulfenyl chloride solution is then cooled to −78 °C and added via cannula to a −78 °C solution of cyclopentadiene (66 g, 1 mol) in 500 mL of $CH_2Cl_2$, care being taken to maintain the reaction temperature at <−50 °C. The cold bath is removed and the reaction allowed to warm to room temperature. The reaction mixture is then filtered, and the solvent and excess cyclopentadiene are removed on a rotary evaporator *with no heat applied to the bath*. The residue is dissolved in 600 mL of $CH_2Cl_2$, washed 1× with 250 mL of $H_2O$, and dried ($Na_2SO_4$) and the solution concentrated to a total volume of 200–250 mL.

The sulfide solution is added dropwise to a rapidly stirring suspension of 85% MCPBA (110 g, 510 mmol) in 1 L of $CH_2Cl_2$ immersed in an ice–water bath. The reaction mixture is allowed to warm to 25 °C and stirred for 16 h. The excess oxidant is quenched with saturated $Na_2S_2O_3$ and the reaction mixture filtered to remove *m*-chlorobenzoic acid. The solution is washed 1× with saturated $Na_2S_2O_3$ and 2× with $Na_2CO_3$, dried ($Na_2SO_4$), and decolorized (Darco) for 18 h at 25 °C. The solution is filtered and the solvent removed to give a tan solid. Recrystallization from 100% EtOH affords pure chloro sulfone **14** [47.5 g, 196 mmol (78%)] as an off-white solid: mp 72 °C; TLC ($SiO_2$, 10% $Et_2O/CH_2Cl_2$) $R_f$ 0.67; IR ($CHCl_3$) 3.33 (CH), 6.17, 6.33 (C=C), 6.94 ($C_6H_5$), 7.58, 8.62 ($SO_2$) μm; $^1$H NMR ($CDCl_3$) δ 7.5–8.0 (m, 5, aryl sulfone), 5.75, 5.65 (m, 2, H-2, H-3), 5.25 (m, 1, H-4), 4.0 (m, 1, H-5), 2.9 (m, 2, H-1, β); $^{13}$C NMR ($CDCl_3$) δ 137.45 (s, ipso arom, C-$SO_2$), 134.00 (d, arom, p), 132.86 (d, C=C, C-3), 130.76 (d, C=C, C-2), 129.25, 128.35 (d, arom, ortho, meta), 70.85 (d, C-4), 62.41 (d, C-5), 32.61 (t, C-1); exact mass for $C_{11}H_{11}ClO_2S$, calcd 242.0168; found 242.0132.

***trans*-4-Chloro-*cis*-2,3-dihydroxy-5-(phenylsulfonyl)-cyclopentane (15).** To a vigorously stirring suspension of tetraethylammonium acetate (1.70 g, 6.50 mmol), sodium acetate (8.20 g, 100 mmol), and 90% *tert*-butyl hydroperoxide[9] (10.0 g, 100 mmol) in 20% $H_2O$/acetone (100 mL) at 0 °C is added a solution of olefin **14** (12.10 g, 50 mmol) in 30 mL of acetone followed by osmium tetroxide (0.64 g, 2.50 mmol) in 10% $H_2O$/acetone (0.010 g/mL). The reaction is stirred at 0 °C for 1 h; the cold bath is then removed and the reaction flask covered with aluminum foil to exclude light. The reaction is stirred at 25 °C until all olefin is reacted as determined by TLC (3–4 days). The reaction is diluted with 125 mL of $Et_2O$ and cooled to 0 °C and the osmium tetroxide reduced by slow addition of 20–25 mL of freshly prepared saturated $NaHSO_3$ followed by stirring for 1 h at 25 °C. The aqueous layer is saturated with NaCl; the organic layer is separated and washed 1× with saturated NaCl. The aqueous layers are combined and reextracted 2× with 50 mL of $Et_2O$ and 1× with 50 mL of $CH_2Cl_2$. The combined organics are dried ($Na_2SO_4$) and the solvents removed to give a viscous oil containing the diol and *tert*-butyl alcohol. Addition of EtOAc and hexane with vigorous stirring affords solid diol **15** as a mixture of diastereomers: 11.30 g, 40.9 mmol (81.7%); TLC ($SiO_2$, 20% $Et_2O/CH_2Cl_2$) $R_f$ 0.16; $^1$H NMR (acetone-$d_6$) δ 7.6–8.0 (m, 5, aryl sulfone), 3.8–4.5 (cm, 4, H-2, H-3, H-4, H-5), 2.9 (brs, 2, OH), 2.3 (m, 2, H-1, β); $^{13}$C NMR ($Me_2SO$-$d_6$, major diastereomer) δ 138.03 (ipso arom, $CSO_2$), 134.42 (arom, para), 129.70, 128.69 (arom, ortho, meta), 74.56 (C-3), 70.25 (C-4), 68.05 (C-2), 58.48 (C-5), 30.92 (C-1); exact mass for $C_{11}H_{13}ClO_4S$, calcd 276.0223, found 276.0222.

**4-Chloro-2,3-(isopropylidenedioxy)-5-(phenylsulfonyl)-cyclopentane (16).** To a suspension of diol **15** (12.59 g, 45.5 mmol) in 25 mL of $CH_2Cl_2$ at 25 °C is added 2,2-dimethoxypropane (21.0 g, 200 mmol) and a large crystal of *p*-toluenesulfonic acid monohydrate. The heterogeneous reaction mixture is stirred for 2 h at 25 °C, by which time the solution is homogeneous. The solvent and excess 2,2-dimethoxypropane are removed, and the residue is dissolved in 200 mL of $CH_2Cl_2$, washed 1× with saturated $NaHCO_3$, and dried ($Na_2SO_4$). The solvent is removed to afford crude acetonide **16** [14.25 g, 45 mmol (99%)], which is used without further purification: TLC ($SiO_2$, 20% $Et_2O/CH_2Cl_2$) $R_f$ 0.67; $^1$H NMR ($CDCl_3$) δ 7.5–8.0 (m, 5, aryl sulfone), 4.65 (cm, 2, H-2, H-3), 4.15 (m, 1, H-4), 3.75 (m, 1, H-5), 2.17 (cm, 2, H-1, β), 1.45 (s, 3, $CH_3$), 1.3 (s, 3, $CH_3$); $^{13}$C NMR ($CDCl_3$, major diastereomer) δ 138.28 (ipso arom, $CSO_2$), 134.09 (arom, para), 129.11, 128.74 (arom, ortho, meta), 110.89 (quat, acetonide), 80.34 (C-3), 76.51 (C-4), 66.77 (C-2), 56.98 (C-5), 31.88 (C-1), 25.78 ($CH_3$ exo), 23.93 ($CH_3$ endo).

**(3*S*,3*R*)-*rac*-2,3-(Isopropylidenedioxy)-5-(phenylsulfonyl)-4-cyclopentene (17).** Crude acetonide **16** (14.25 g, 45.0 mmol) in 200 mL of $CH_2Cl_2$ at 0 °C is treated with triethylamine (9.1 g, 90 mmol) and DBU (13.7 g, 90 mmol) and the reaction warmed to 25 °C. The reaction is stirred for 16 h and diluted with 100 mL of $CH_2Cl_2$. The reaction mixture is washed 2× with 5% HCl, 1× with saturated $NaHCO_3$, and 1× with saturated NaCl, dried ($Na_2SO_4$), and decolorized (Darco) at room temperature for 24 h, and the solvent is removed to give a pale yellow oil. The oil is dissolved in $Et_2O$ and hexane added to cloud point; the recrystallization affords vinyl sulfone **17** [11.76 g, 42 mmol (93%)] as a white solid: mp 66 °C; TLC ($SiO_2$, 10% $Et_2O/CH_2Cl_2$) $R_f$ 0.50; IR ($CHCl_3$) 3.39 (CH), 6.19, 6.33 (C=C), 6.94 ($C_6H_5$), 7.58, 8.62 ($SO_2$) μm; $^1$H NMR ($CDCl_3$) δ 7.55–8.0 (m, 5, aryl sulfone), 6.65 (m, 1, H-4), 5.2 (dd, $J$ = 5 Hz, 2 Hz, 1, H-3), 4.8 (dd, $J$ = 5 Hz, 2 Hz, 1, H-2), 2.71 (m, 2, H-1, β), 1.30 (merging s, 6, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$) δ 145.35 (s, C-5), 138.91 (d, C-4), 138.91 (s, arom, $CSO_2$), 133.72 (d, arom, para), 129.18, 127.92 (d, arom, ortho, meta), 110.59 (s, quat, acetonide), 83.97 (d, C-3), 78.17 (d, C-2), 36.82 (t, C-1), 27.26 (q, $CH_3$ exo), 25.58 (q, $CH_3$ endo); exact mass for $C_{14}H_{16}O_4S$, calcd 280.0768, found 280.0746.

**3-Azido-1-propanol and 1-Azido-3-iodopropane (18).** To a rapidly stirring suspension of $NaN_3$ (9.43 g, 145 mmol) in 60 mL of DMF is added 3-chloro-1-propanol (11.31 g, 119.6 mmol) and the reaction mixture heated at 100 °C for 48 h. The reaction mixture is cooled and diluted with 200 mL of $Et_2O$. The solution is washed 5× with saturated NaCl and dried ($Na_2SO_4$), and the solvent is removed to afford 3-azidopropanol [10.4 g, 103 mmol (86%)] as a colorless liquid used without further purification: IR (neat) 2.98 (OH), 3.42 (CH), 4.76 ($N_3$) μm; $^1$H NMR ($CDCl_3$) δ 3.7 (brq, 2, $J$ = 8 Hz, $CH_2OH$), 3.41 (t, $J$ = 8 Hz, 2, $CH_2N_3$), 3.29 (brs, 1, OH), 1.81 (m, $J$ = 8 Hz, 2, $CH_2$).

To 3-azidopropanol (10.4 g, 103 mmol) in 300 mL of $CH_2Cl_2$ at 0 °C is added DMAP (1.22 g, 10 mmol), triethylamine (20.85 g, 206 mmol), and methanesulfonyl chloride (15.46 g, 135 mmol). The reaction mixture is stirred at 0 °C for 30 min, diluted with 100 mL of $CH_2Cl_2$, and poured into iced $H_2O$. The organic layer is separated, washed 2× with iced 5% HCl, 1× with saturated NaCl, and dried ($Na_2SO_4$) and the solvent removed to afford crude mesylate as a yellow, odorous liquid. The mesylate is dissolved in 50 mL of acetone and added to a solution of NaI (18.0 g, 120 mmol) in 150 mL of acetone. The solution is stirred at 25 °C for 48 h and then filtered. The filtrate is washed 2× with 50 mL of acetone and discarded. The acetone is evaporated in vacuo, the residue dissolved in $Et_2O$, washed 1× with saturated $Na_2S_2O_3$,

1× with iced 5% HCl, and 1× with saturated $NaHCO_3$, and dried ($K_2CO_3$), and the solvent evaporated. The crude iodide is distilled under reduced pressure to afford pure **18** [15.51 g, 73.5 mmol (71%)] as a colorless liquid: bp 64–67 °C (2.5 torr); IR (neat) 3.39 (CH), 4.57 ($N_3$) μm; $^1H$ NMR ($CDCl_3$) δ 3.4 (t, $J$ = 8 Hz, 2, $CH_2N_3$), 3.21 (t, $J$ = 8 Hz, 2, $CH_2I$), 2.01 (m, $J$ = 8 Hz, 2, $CH_2$); mass for $C_3H_6IN_3$, calcd 211, found 211 (EI).

**(2*S*,3*R*,4*R*,5*S*)-*rac*-5-(3-Azidopropyl)-2,3-dihydroxy-5-(phenylsulfonyl)-4-[6-vinyl-3,4-(methylenedioxy)phenyl]-cyclopentane (20).** To a −78 °C solution of aryl anion **8b** [prepared by the dropwise addition of *tert*-butyllithium (1.8 M pentane, 11.25 mmol) at −78 °C to bromostyrene **7b** (1.157 g, 5.62 mmol) in 23 mL of $Et_2O$ and stirring for 25 min] is added dropwise a solution of vinyl sulfone **17** (1.416 g, 5.06 mmol) in 15 mL of $Et_2O$. The reaction mixture is stirred at −78 °C for 20 min. To the homogeneous solution of the resultant sulfonyl anion is added dropwise at −78 °C a solution of **18** (1.78 g, 8.43 mmol), HMPA (10% of the total reaction volume), THF (10% of the total reaction volume), and LiH (to ensure anhydrous conditions) followed by immediate warming to 25 °C. The reaction mixture is quenched with saturated $NH_4Cl$ and extracted 3× with 100 mL of $CH_2Cl_2$. The combined organics are evaporated to a brown residue of acetonide **19** which is dissolved in 50 mL of MeOH and 5 mL of $H_2O$. Approximately 200 mg of *p*-toluenesulfonic acid monohydrate is added and the reaction mixture stirred at 25 °C for 48 h. The solvent is evaporated and the residue dissolved in 100 mL of $CH_2Cl_2$, washed 1× with saturated $NaHCO_3$, and dried ($Na_2SO_4$). The solvent is evaporated and the brown oil subjected to plug filtration ($SiO_2$, 60–200 mesh, 40:1, 1× void volume hexane, 3× void volume 1:1 EtOAc/hexane, and then EtOAc until all the compound is eluted) to afford pure diol **20** [1.624 g, 3.45 mmol (68%)] as a white solid: mp 160–162 °C, TLC ($SiO_2$, $CH_2Cl_2$) $R_f$ 0.13; IR ($CHCl_3$) 2.94 (OH), 3.48 (CH), 4.76 ($N_3$), 6.76 ($C_6H_5$), 7.72, 8.77 ($SO_2$) μm; $^1H$ NMR ($CDCl_3$) δ 7.4–7.6 (m, 5, aryl sulfone), 7.4 (s, 1, arom), 6.85 (dd, 1, styrene), 6.71 (s, 1, arom), 5.98 (d, 2, methylenedioxy), 5.18 (dd, 1, styrene), 5.09 (dd, 1, styrene), 4.8 (m, 1, H-2), 4.31 (merging dd, 1, H-3), 3.75 (d, $J$ = 10 Hz, 1, H-4), 3.25 (brm, 2, $CH_2N_3$), 2.72 (br, 2, 2 OH), 2.5 (C, 1, H-1β), 2.7–2.0 (cm, 5, 2 $CH_2$, H-1); $^{13}C$ NMR ($Me_2SO$-$d_6$) δ 146.78, 146.57 (ipso arom, C-15, C-16), 137.15 (ipso arom, C-$SO_2$), 135.64 (arom, para), 133.31, 133.12 (arom, C-12, C-13), 129.82, 128.61 (arom, ortho, meta), 127.92 (styrene, C-11), 114.74 (styrene, C-10), 111.08, 105.77 (arom, C-14, C-17), 101.13 (methylenedioxy), 75.92 (C-3), 74.61 (C-5), 69.17 (C-2), 54.91 (C-4), 51.20 (C-8), 47.63 (C-7), 32.23 (C-1), 24.07 (C-6); exact mass for $C_{23}H_{25}N_3O_6S$, calcd 471.1464; found 471.1465.

**5-(1-Azidopropan-3-ylidene)-3-hydroxy-4-[6-vinyl-3,4-(methylenedioxy)phenyl]-3-cyclopenten-2-one (21).** To a solution of sulfur trioxide–pyridine[21] (1.592 g, 10 mmol) and triethylamine (1.11 g, 11 mmol) in 4 mL of $Me_2SO$/0.5 mL of THF at 10 °C is added in one portion solid diol **20** (0.471 g, 1.0 mmol). The reaction mixture is stirred at 25 °C for 2–3 h. The reaction is quenched with 20 mL of $H_2O$ and the aqueous phase extracted 2× with 25 mL of $Et_2O$ and 1× with 15 mL of $CH_2Cl_2$. The combined organic layers are washed 1× with 5% HCl and 2× with saturated NaCl and dried ($Na_2SO_4$), and the solvent removed to leave a brown residue. Flash chromatography ($SiO_2$, 230–400 mesh, 10% $Et_2O/CH_2Cl_2$) affords compound **21** [0.248 g, 0.76 mmol (76%)] as a pale orange foam: TLC ($SiO_2$, 25% $Et_2O/CH_2Cl_2$) $R_f$ 0.52; IR ($CHCl_3$) 3.0 (OH), 3.51 (CH), 4.81 ($N_3$), 5.90 (C=O), 6.78 ($C_6H_5$) μm; $^1H$ NMR ($CDCl_3$) δ 7.15 (s, 1, arom), 6.65 (s, 1, arom), 6.51 (dd, $J$ = 17 Hz, 10 Hz, 1, styrene), 5.98 (s, 2, methylenedioxy), 5.56 (dd, $J$ = 17 Hz, 1, styrene), 5.31 (t, $J$ = 7 Hz, 1, vinyl H, H-6), 5.12 (dd, $J$ = 10 Hz, 2 Hz, 1, styrene), 3.27 (t, $J$ = 7 Hz, 2, $CH_2N_3$), 3.09 (s, 2, H-1, β), 2.41 (q, $J$ = 7 Hz, 2, H-7's); $^{13}C$ NMR ($CDCl_3$) δ 196.23 (C=O, C-2), 150.72 (=COH, C-3), 147.59, 146.35 (ipso arom, C-15, C-16), 140.10 (C-4), 134.36, 129.52 (ipso arom, C-12, C-13), 132.93 (styrene, C-11), 122.14 (C-5), 120.31 (C-6), 112.49 (styrene, C-10), 107.80, 103.95 (arom, C-14, C-17), 100.38 (methylenedioxy), 49.50 (C-8), 34.26 (C-1), 28.37 (C-7).

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