A Total Synthesis of Anthramycin: Application of Palladium-Catalyzed Coupling Reactions for the Attachment of the Acrylic Side Chain

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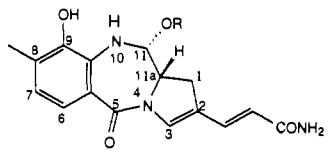
Abstract: Utilization of the palladium-catalyzed reactions of vinyl triflates **8** obtained from model N-substituted (11a*S*)-2,3,5,10,11,11a-hexahydro-2,5,11-trioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines (**5**, **6**) either with β-(tributylstannyl)acrylates or acrylic esters and amides yields coupled products (**9**–**13**) having the basic anthramycin framework. Generation of the enol triflates from the 2-keto precursors is regiospecific, introducing the double bond in the pyrrole ring into the 2,3-position. Oxidation of the benzaldehyde-protected (11a*S*)-2*R*-hydroxy-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (**17**) to the corresponding ketone (**18**) followed by conversion to the vinyl triflate **19** provided the appropriate coupling partner for the attachment of the acrylamide side chain via a palladium-catalyzed reaction with acrylamide. Reduction of the coupled product (**20**) with sodium borohydride and deprotection gave anthramycin methyl ether **1b**. This sequence for the attachment of the acrylamide side chain provides a relatively short pathway to anthramycin and allows the facile synthesis of anthramycin analogues.

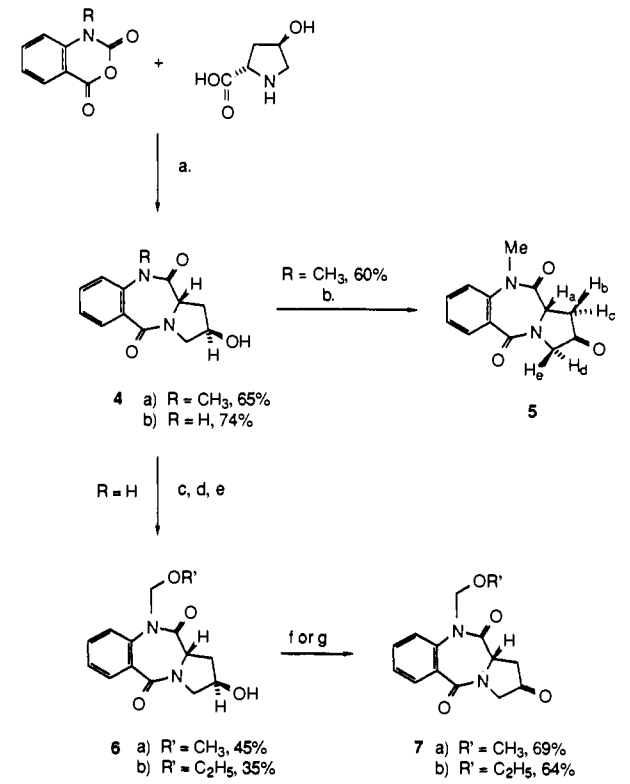
Anthramycin (**1**), a potent antitumor antibiotic produced by *Streptomyces refuineus*,[1] belongs to a group of structurally similar antibiotics,[2] all of which share the pyrrolo[1,4]benzodiazepine



1 a) R = H
b) R = CH_3

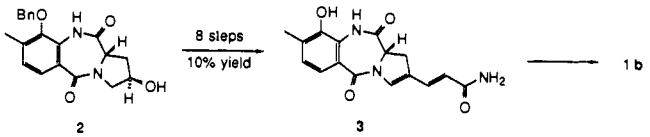
skeleton. The structure of anthramycin, isolated as a pure crystalline material, was first established through a combination of spectroscopic and chemical evidence[3] and was later confirmed by an X-ray structure.[4] It is active in vivo against Sarcome 180, Ehrlich solid and Ehrlich ascites carcinomas, Walker 256 carcinosarcoma, and human epithelioma No. 3.[5] Most importantly, no depression of the bone marrow was observed. The mechanism of action results from inhibition of nucleic acid synthesis through its covalent attachment to DNA[6] at N-2 of guanine to C-11 of anthramycin.[7] The right-handed twist of anthramycin[4] allows it to fit entirely within the minor groove of DNA.[8]

Scheme I[a]



[a] (a) DMSO, 115–120 °C, 2–5 h; (b) CrO_3, H_2O, H_2SO_4, CH_3CO-CH_3, 12 h; (c) TBDMSCl, imidazole, DMF (55%); (d) NaH, THF, CH_3OCH_2Cl (89%) or $C_2H_5OCH_2Cl$ (71%); (e) BF_3·OEt, THF, H_2O (R′ = Me, 95%; R′ = Et, 85%); (f) DMSO, $(COCl)_2$, CH_2Cl_2, TEA (R = CH_3, 69%). (g) PCC on alumina, CH_2Cl_2 (R = Et, 64%).

Anthramycin was first synthesized[3c] by building the acrylamide side chain onto the dilactam alcohol **2** followed by reduction of



the carbonyl at C-11. Construction of the acrylamide side chain required eight steps, dilactam **3** being obtained in about 10% overall yield.

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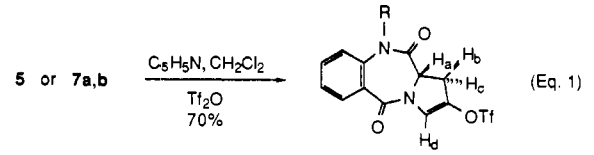
A much more efficient attachment of the acrylamide side chain was perceived as occurring via the palladium-catalyzed coupling reaction of an enol triflate[9]—generated from a carbonyl at C-2—with an acrylate unit, which could be derived either from an acrylic ester or amide in a Heck-type reaction[10] or from a β-stannylacrylate.[11] The palladium-catalyzed coupling reactions of enol triflates with a variety of vinylstannanes is known to take place under mild conditions and could be expected to proceed even in the presence of the functionality in **3**,[12,13] the reaction product. This paper describes such coupling reactions on intermediate anthramycin analogues and the use of the coupling reaction in the synthesis of anthramycin.

Results and Discussion

Generation of the enol triflate from the C-2 ketone required the desired regiochemistry with the double bond at C-2,3. In order to demonstrate regioselective triflate formation and to test the coupling chemistry, several intermediate anthramycin models were utilized. Enantiomerically pure ketone **5** (Scheme I) was obtained by the reaction of *N*-methylisatoic anhydride with hydroxyproline[14] followed by Jones oxidation of the dilactam alcohol **4** (R = CH_3). Both the methoxy methyl and ethoxy methyl protected ketones **7** were obtained starting from dilactam alcohol **4** (R = H). Selectively protecting the alcohol function, alkylating the amide nitrogen with either chloromethyl methyl ether or chloromethyl ethyl ether, and removal of the silyl protecting group gave the N-protected alcohols **6**, which were oxidized to the respective ketones (**7**) using either Swern conditions[15] or PCC on alumina.[16]

Model Coupling Reactions of Vinyl Triflates. Of the various bases and reaction conditions tried to convert ketones **5** and **7** to triflates, the best procedure used pyridine and triflic anhydride. The reaction of 1.2 equiv of pyridine with **5** or **7** in dichloromethane at ambient temperature to generate the enolate followed by the rapid addition of triflic anhydride in one portion consistently gave 70% yields of triflate **8** (eq 1).



(Eq. 1)

8 a) R = CH_3
b) R = CH_2OCH_3
c) R = $CH_2OC_2H_5$

The ^1H NMR spectrum of **8** showed that enolate formation and the subsequent trapping with triflic anhydride was regiospecific. For example, in the ^1H NMR spectrum of **5**, protons H_d and H_e appear as an AB pattern at δ 3.9 and 4.2 with a coupling constant of 20 Hz. This pattern is absent in the ^1H NMR spectrum of vinyl triflate **8a**, the vinyl proton H_d appearing at δ 7.16, while protons H_a, H_b, and H_c are slightly shifted, producing the same coupling pattern.

The palladium-catalyzed coupling reactions of the vinyl triflates (**8a–c**) were carried out utilizing both vinylstannanes in a direct coupling reaction and acrylates in a Heck-type coupling (Table I). Good yields of coupled product could be obtained in reactions of vinyl triflate **8a** with vinylstannanes; a lower yield was obtained in a Heck-type coupling reaction. Coupling reactions with **8b** did not give good yields either with a vinylstannane or with acrylamide under the usual reaction conditions. The low yields possibly can be attributed to the facile loss of the MOM protecting group under the reaction conditions since the coupling reaction of methyl β-(tributylstannyl)acrylate with **8c** containing the more robust ethoxy methyl ether protecting group gave a higher yield. Modification of the reaction conditions for the coupling of **8b** with acrylamide to include a stronger base to neutralize the triflic acid generated improved the yield of this reaction.

Thus, the coupling reaction with an organostannane or an acrylate with the benzodiazepine-derived triflate is an efficient procedure for attaching the acrylic side chain and should be adaptable for the synthesis of anthramycin. The specific rotations of the coupled products are unusually large as a result of the twist conferred on the molecule by the asymmetric center at C-11a. Models show that the plane of the acrylamide side chain, which is conjugated and coplanar with the dihydropyrrole ring, presents approximately a 135° dihedral angle with the plane of the benzene ring.

Anthramycin. The protected dilactam alcohol **2** required for oxidation to the ketone was synthesized from **14** by using the same procedure previously reported[3c] (Scheme II). Introduction of the asymmetric center was accomplished by the use of 4-hydroxy-L-proline to yield **16**, and formation of the diazepine ring was effected by reduction of the nitro group followed by closure. The specific rotation of dilactam alcohol **2** (+264°, *c* 0.0032, MeOH) matched that reported[3c] (+256°, *c* 0.15, MeOH).

Protection of both the phenol and the amide nitrogen was accomplished by hydrogenolysis of the benzyl group followed by reaction of the free phenol with benzaldehyde dimethyl acetal. The Swern oxidation of alcohol **17** to ketone **18** was accomplished in good yield; however, oxidations using pyridinium chlorochromate on alumina or pyridinium dichromate gave low yields of **18**. The ketone was converted to the vinyl triflate **19** by using 2 equiv of pyridine followed by the rapid addition of 2 equiv of triflic anhydride. Triflate **19** was sufficiently stable to be purified by column chromatography.

Of the two methods available for the attachment of the acrylamide side chain, the Heck-type coupling was chosen since it had been shown (Table I) to give the desired reaction product in moderate yield. The use of β-(tributylstannyl)acrylamide was expected to give a comparable yield, but it was necessary to prepare the tin reagent from methyl β-(tributylstannyl)acrylate using aluminum trimethyl and ammonium chloride.[17] The optimum reaction conditions for the Heck-type reaction—DABCO, MeOH, and $(CH_3CN)_2PdCl_2$—afforded a 50% yield of coupled product **20**. Coupling reactions of **19** with vinyl and acetylenic tin reagents took place readily to yield analogues **22** and **23**. Accordingly, this coupling reaction may be utilized to provide a number of anthramycin analogues.

Diene **20** was reduced selectively at C-11 with sodium borohydride in methanol to provide a quantitative yield of **21**. The ^1H NMR spectrum of **21** showed the OH proton atC-11 (δ 5.8) as a doublet, coupled (9.0 Hz) to the geminal proton on C-11 (δ 4.8). Treatment of the NMR sample with D_2O removed the doublet at δ 5.8, collapsing the doublet at δ 4.8 to a singlet. Because no coupling was observed between the proton at C-11 and C-11a, the stereochemistry at C-11 was assigned as shown, the dihedral angle between the two protons being ~90°.

Removal of the benzaldehyde protecting group using hydrochloric acid in methanol and isolation of anthramycin (**1b**) was carried out by the original procedure to give crude product, whose ^1H NMR spectrum was compared to an authentic sample.[18]

Experimental Section

All solvents were distilled from calcium hydride just prior to use except for tetrahydrofuran (THF), which was distilled from potassium. Absolute ethanol (Midwest Solvents) and methanol (EM Science) were anhydrous. All reagents were used as obtained from commercial suppliers

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(10) Scott, W. J.; Peña, M. R.; Sward, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302.
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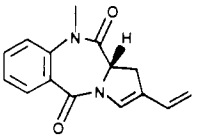
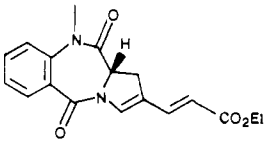
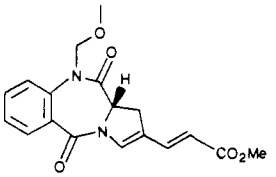
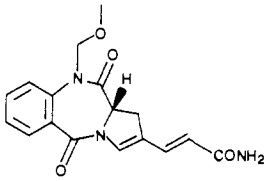
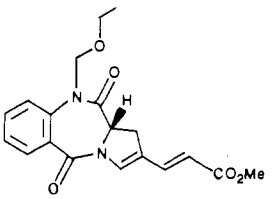
(18) The general procedure used for the hydrolysis (Experimental Section) was supplied by Drs. Andrew Batcho and Milan Uskokovic, Hoffmann-La Roche, Inc., who also generously provided an authentic sample of anthramycin methyl ether **1b**.

Table I. Coupling Reactions of Vinyl Triflate **8**

vinyl triflate	vinyl stannane[a]	acrylic[b]	product	% yield	$[\alpha]_D$, deg (°C, *c*, solvent)
8a	Bu_3Sn		 **9**	60	+744 (22, 0.0046, EtOAc)
	Bu_3Sn CO_2Et		 **1C**	78	+620 (22, 0.0074, $CHCl_3$)
		CO_2Et (DMSO, TEA)	**10**	40	
8b	Bu_3Sn CO_2Me		 **11**	22	
	Bu_3Sn $CONH_2$		 **12**	22	+537 (20, 0.0018, $CHCl_3$)
		$CONH_2$ (DMSO, TEA)	**12**	36	
		$CONH_2$ (MeOH, DABCO)		50	
8c	Bu_3Sn CO_2Me		 **13**	70	+594 (20, 0.0024, $CHCl_3$)

[a] Coupling reactions with vinylstannanes were carried out in THF with $(Ph_3P)_4Pd$ (4 mol %) as a catalyst and a 3-fold molar amount of LiCl. [b] All couplings were carried out at 50 °C with $(Ph_3P)_2PdCl_2$, except in the last example, which used $(CH_3CN)_2PdCl_2$.

unless otherwise noted. The following palladium catalysts were prepared according to published procedures:[19] bis(acetonitrile)palladium(*II*) chloride, bis(triphenylphosphine)palladium(II) chloride, and tetrakis-(triphenylphosphine)palladium(0). The following organotin reagents were prepared according to published procedures: (tributylvinyl) tin,[20] methyl and ethyl (*E*)-3-(tributylstannyl)propenoate,[21] and 3,3-dimethyl-1-(tributylstannyl)-1-butyne.[22] Isatoic anhydride, *N*-methylisatoic anhydride, and 4-methyl-3-hydroxy-2-nitrobenzoic acid[23] were obtained from the Aldrich Chemical Co.; *tert*-butyldimethylsilyl chloride was from Petrarch Inc.; 4-hydroxy-L-proline was from the Chemical Dynamics Corp. and triflic acid was from 3M. Thin-layer chromatography was performed with Baker glass-backed precoated plates (Si254F). Silica gel chromatography utilized Absorbenzien Woelm (Universal Scientific) 32-63 and 62-200.

^1H and ^{13}C NMR spectra were recorded on either an IBM WP-270-SY (270 MHz ^1H, 68 MHz ^{13}C) or Bruker AC300P. The following deuterated solvents were used: deuterochloroform ($CDCl_3$) with tetramethylsilane (TMS) (δ 0.00 ^1H) or chloroform (δ 77.00 ^{13}C); methanol-d_4 with methanol (δ 3.48 ^1H) (δ 39 ^{13}C) and dimethyl sulfoxide-d_6 with TMS (δ 0.00 ^1H) or dimethyl sulfoxide (δ 39.5 ^{13}C) were used as internal references. Infrared spectra were obtained with a Beckman 4240 spectrometer. Melting points were obtained on a Mel-Temp melting apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. High-resolution mass spectra were obtained from Midwest Center for Mass Spectrometry, Lincoln, NE.

(11a*S*)-2(*R*)-Hydroxy-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (4a). A suspension of 1.77 g (9.99 mmol) of *N*-methylisatoic anhydride [twice recrystallized from chloroform and hexane, mp 160 °C (lit.[21] mp 165 °C)] 1.40 g (10.6 mmol) of L-hydroxyproline and 5 mL of DMSO was heated for 2 h at 115 °C. Evolution of CO_2 was observed, which gradually decreased to no degassing 2 h later. The hot homogeneous solution was cooled and poured into 100 mL of cold water and extracted with several portions of chlo-

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(20) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515.
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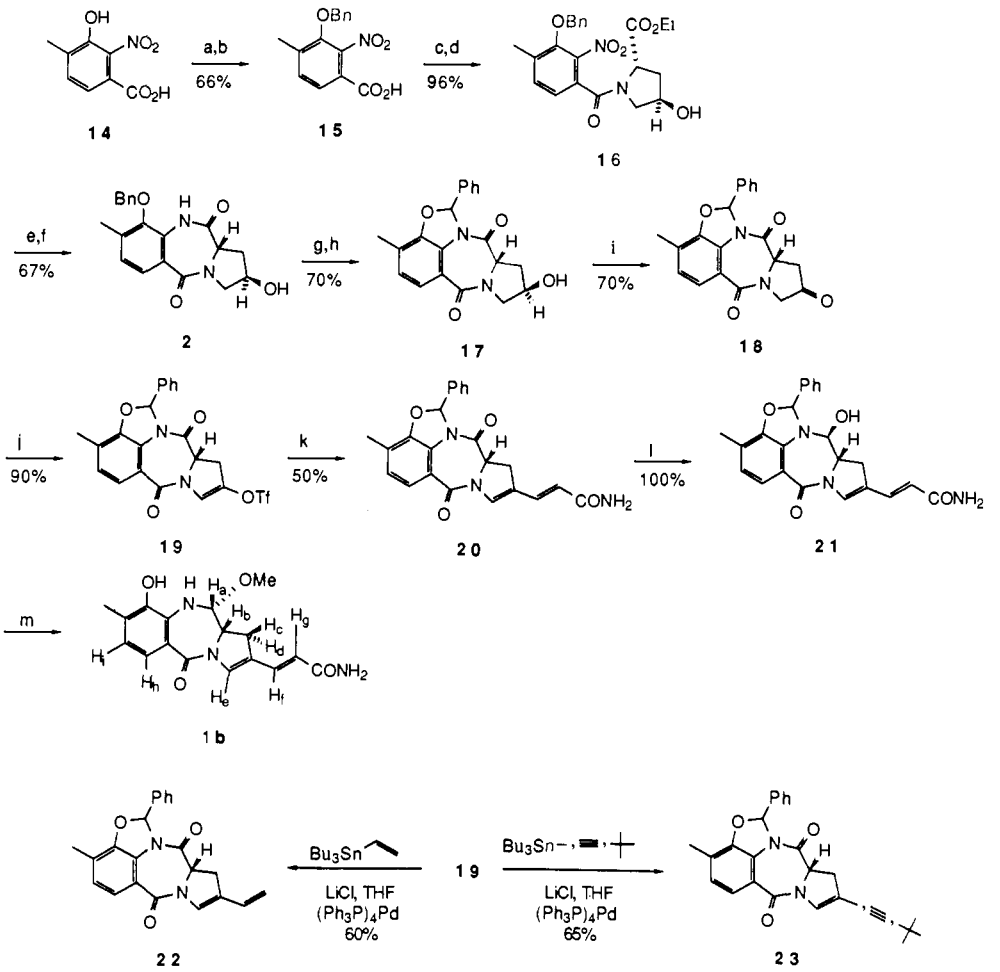
Scheme II[a]



[a](a) K_2CO_3, DMF, $PhCH_2Br$; (b) KOH, H_2O, THF; (c) $(COCl)_2$, CH_2Cl_2; (d) ethyl-L-hydroxyproline hydrochloride, THF, TEA; (e) $Na_2S_2O_4$, THF, H_2O; (f) H_2O, THF, H^+; (g) Pd/C, H_2, MeOH; (h) $PhCH(OMe)_2$, H^+, H_2O/THF; (i) DMSO, $(COCl)_2$, TEA; (j) C_5H_5N, Tf_2O. (k) CH_2=$CHCONH_2$, $(CH_3CN)_2PdCl_2$, DABCO, MeOH; (l) $NaBH_4$, MeOH; (m) 0.1 M HCl, MeOH.

roform. The organic layers were combined, washed with water and brine, and then dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo left a yellow, viscous oil. The oil was purified by column chromatography (EtOAc) to afford 1.68 g (62%) of the product as a tan powder. The tan solid was recrystallized from EtOAc/hexanes as fat, colorless prisms: R_f = 0.22 (EtOAc); mp 149–150 °C; $[\alpha]^{22}_D$ +450° (*c* 0.0074, $CHCl_3$); IR ($CHCl_3$) 3400, 2860, 1675, 1630, 1600, 1420, 900, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (m, 1 H), 2.9 (m, 1 H), 3.2 (br hump, 1 H), 3.4 (s, 3 H), 3.6 (dd, 1 H, *J* = 4.9, 12.6 Hz), 3.9 (br d, 1 H, *J* = 12.6 Hz), 4.2 (dd, 1 H), 4.6 (quin, 1 H), 7.2 (m, 2 H), 7.5 (m, 1 H), 7.8 (dd, 1 H, *J* = 1.1, 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 165.7, 140.5, 131.9, 130.2, 129.0, 125.5, 121.7, 68.9, 56.0, 53.9, 35.9, 35.1. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.72; N, 11.37. Found: C, 63.47; H, 5.77; N, 11.33.

(11a*S*)-2,3,5,10,11,11a-Hexahydro-10-methyl-2,5,11-trioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (5). To a solution of 3.89 g (15.8 mmol) of alcohol (**4a**) in 40 mL of acetone was added slowly a solution made up of 2.11 g (21.1 mmol) of CrO_3, 5 mL of water, and 0.5 mL of H_2SO_4. The resulting orange-green solution was stirred overnight and then poured into water and chloroform. The product was extracted with several portions of chloroform. The chloroform extracts were combined, washed with water, and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a viscous oil. The ketone was further purified by column chromatography (EtOAc) and recrystallized (EtOAc) to give 2.25 g (60%) of fat, colorless crystals: R_f = 0.53 (EtOAc); mp 225 °C (dec.); $[\alpha]^{22}_D$ +565° (*c* 0.0048, $CHCl_3$); IR (Nujol) 1765, 1680, 1670, 1645, 1600, 1380, 1150, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7–2.8 (ddd, 1 H, *J* = 1.4, 9.9, 19.3 Hz), 3.4 (s, 3 H), 3.5–3.6 (dd, 1 H, *J* = 3.2, 19.3 Hz), 3.9 (d, 1 H, *J* = 20.1 Hz), 4.2 (d, 1 H, *J* = 20.1 Hz), 4.5 (dd, 1 H, *J* = 3.1, 9.9 Hz), 7.3 (d, 1 H), 7.4 (dt, 1 H), 7.6 (dt, 1 H), 7.9 (dt, 1 H); ^{13}C NMR ($CDCl_3$) δ 206.25, 168.12, 165.58, 140.42, 132.34, 130.01, 128.16, 125.79, 121.87, 54.22, 51.89, 37.14, 35.87. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.82; H, 4.99; N, 11.44.

(11a*S*)-5,10,11,11a-Tetrahydro-10-methyl-2-[[(trifluoromethyl)sulfonyl]oxy]-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (8a). To a stirred solution of 0.977 g (4.00 mmol) of ketone **5** in 0.978 mL (4.80 mmol, 1.20 equiv) of pyridine and 50 mL of dichloromethane was added quickly 0.74 mL (4.4 mmol, 1.1 equiv) of freshly distilled triflic anhydride. The initially bright yellow solution, which gradually darkened to a light brown homogenous solution, was allowed to stir overnight. The reaction was worked up by pouring the solution into EtOAc and cold aqueous sodium bicarbonate. The product was extracted with several portions of EtOAc. The organic layers were combined, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo left a brown oil. The residue was further purified by column chromatography (50% EtOAc/hexane) to give 1.04 g (70.0%) of vinyl triflate as a pale yellow, viscous oil. The product was not fully characterized but carried on to the next step: R_f = 0.78 (EtOAc); ^1H NMR ($CDCl_3$) δ 3.1–3.2 (ddd, 1 H, *J* = 2.3, 11.06, 16.3 Hz), 3.5 (s, 3 H), 3.9 (ddd, 1 H, *J* = 1.7, 3.5, 16.4 Hz), 4.6 (dd, 1 H, *J* = 3.6, 11.03 Hz), 7.1 (br s, 1 H), 7.3 (m, 2 H), 7.6 (t, 1 H), 7.9 (d, 1 H).

(11a*S*)-2(*R*)-Hydroxy-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (4b). A mixture of 42.9 g (0.262 mol, 1.00 equiv) of recrystallized isatoic anhydride, 33.8 g (0.257 mol, 0.980 equiv) of hydroxyproline, and 350 mL of DMSO was stirred and heated to 120 °C until no more CO_2 evolution was observed (about 5 h). The dark brown solution was cooled and then poured into 2 L of cold water. The product slowly crystallized out of solution. The solution was chilled in an ice bath and the product was filtered as a light brown solid. The brown solid was recrystallized from water to give 44.5 g (74.3%) of white needles: R_f = 0.32; mp 198–200 °C; $[\alpha]^{22}_D$ +415° (*c* 0.02, MeOH); IR (Nujol) 3540, 3425, 1675, 1635, 1600, 1570, 1375, 750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.9 (m, 1 H), 2.6 (m, 1 H), 3.49 (m, 1 H), 3.6 (dd, 1 H, *J* = 3.24, 12.0 Hz), 4.21 (dd, 1 H, *J* = 6.01, 7.92 Hz), 4.3 (m, 1 H), 5.2 (d, 1 H, *J* = 4.0 Hz), 7.15 (d, 1 H, *J* = 7.98 Hz), 7.2 (t, 1 H, *J* = 7.25 Hz), 7.5 (m, 1 H), 7.8 (dd, 1 H, *J* = 1.38, 7.84 Hz), 10.5 (s, 1 H); ^{13}C NMR (DMSO-d_6) 170.41, 165.22, 136.30, 132.20, 130.46, 125.99,

124.01, 121.34, 67.44, 55.27, 54.03, 34.42. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.20; N, 12.06. Found: C, 61.98; H, 5.21; N, 12.02.

(11a*S*)-2(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine. A mixture of 2.32 g (10.0 mmol) of alcohol **4b**, 3.31 g (22.0 mmol, 2.20 equiv) of *tert*-butyldimethylsilyl chloride, 3.4 g (50 mmol, 5.0 equiv) of imidazole, and 30 mL DMF was stirred overnight at room temperature. The reaction was worked-up by extraction with CH_2Cl_2 and water. The CH_2Cl_2 layers were combined, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of solvent in vacuo left a white solid. The product was further purified by column chromatography (50% EtOAc/hexane) to give 1.91 g (55%). The product was recrystallized from EtOAc/hexane as white needles: R_f = 0.5 (50% EtOAc/hexane); mp 197–198 °C; $[\alpha]^{22}_D$ +300.9° (*c* 0.001, CH_2Cl_2); IR (Nujol) 3600, 1690, 1620, 1250, 1130, 900, 830, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.1 (s, 6 H), 0.85 (s, 9 H), 2.0–2.1 (dt, 1 H, *J* = 8.15, 10.3 Hz), 2.8–2.9 (dt, 1 H, *J* = 8.15, 10.3 Hz), 3.6–3.7 (ddd, 2 H, *J* = 12.0 Hz), 4.2 (dd, 1 H, *J* = 4.6, 8.1 Hz), 4.5 (quin, 1 H), 7.0 (d, 1 H), 7.3 (m, 1 H), 7.5 (m, 1 H), 8.0 (d, 1 H), 8.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.92, 165.80, 135.30, 132.34, 131.49, 126.79, 125.15, 120.90, 69.39, 55.64, 54.36, 35.45, 25.72, 17.95, −4.82; HRMS calcd for $C_{18}H_{26}N_2O_3Si$ M − CH_3 331.1478 and M − C_4H_9 289.1009, found M − CH_3 331.1479, M − C_4H_9 289.1011.

(11a*S*)-2(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5,10,11,11a-hexahydro-10-(methoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine. A mixture of 0.057 g (1.2 mmol, 1.2 equiv) of NaH (50% oil dispersion) and 5 mL of THF was cooled to −40 °C. A solution of (11a*S*)-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (0.346 g, 1 mmol) in 5 mL of THF was slowly added via a syringe to the cooled slurry of NaH. The resulting solution was then stirred at −40 °C for 30 min. The reaction mixture was quenched with 0.08 mL (1.10 mmol) of chloromethyl methyl ether (MOMCl; **caution**: potent carcinogen!). The reaction mixture was then allowed to warm to room temperature overnight. The reaction was worked up by extraction with chloroform and water. The organic layers were combined, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of solvent in vacuo left the product as a viscous oil. The product was further purified by column chromatography (50% EtOAc/hexane) to give 0.35 g (89%) of a viscous oil: R_f = 0.57 (50% EtOAc/hexane); IR (Neat) 2960, 1675, 1650, 1600, 1570, 1460, 1410, 1380, 1250, 1110, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.1 (s, 6 H), 0.85 (s, 9 H), 2.0 (m, 1 H), 2.8–2.9 (m, 1 H), 3.4 (s, 3 H), 3.5 (dd, 1 H, *J* = 5.3, 11.9 Hz), 3.7 (dd, 1 H, *J* = 5.7, 11.9 Hz), 4.2 (dd, 1 H, *J* = 3.98, 8.1 Hz), 4.58 (quin, 1 H), 4.69 (d, 1 H, *J* = 9.7 Hz), 5.4 (d, 1 H, *J* = 9.7 Hz), 7.3 (t, 1 H), 7.5 (t, 1 H), 7.6 (d, 1 H), 7.9 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.97, 165.37, 139.52, 131.97, 130.12, 129.43, 126.15, 122.40, 79.64, 69.60, 56.75, 56.33, 53.58, 35.61, 25.56, 17.70, −4.97. Anal. Calcd for $C_{20}H_{30}N_2O_4Si$: C, 61.50; H, 7.74; N, 7.17. Found: C, 61.34; H, 7.77; N, 7.13.

(11a*S*)-2(*R*)-Hydroxy-2,3,5,10,11,11a-hexahydro-10-(methoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (6a). A solution of 0.253 g (0.647 mmol) of the silyl ether (above), 0.079 mL (0.647 mmol) of boron trifluoride etherate (BF_3·OEt_2), and 10 mL of wet THF was stirred at room temperature until TLC analysis showed complete consumption of starting material (about 20 h). The solvent was removed in vacuo and the residue was purified by column chromatography (EtOAc) to give 0.166 g (92%) of a waxy solid. Recrystallization from EtOAc/hexane gave the product as white prisms: R_f = 0.24 (EtOAc); mp 149–150 °C; $[\alpha]^{23}_D$ +373° (*c* 0.003, $CHCl_3$); IR (Nujol) 3350, 2900, 1700, 1620, 1460, 1380, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (m, 1 H), 2.6 (br s, 1 H), 2.9 (m, 1 H), 3.4 (s, 3 H), 3.6 (d, 1 H, *J* = 4.6, 12.6 Hz), 3.9 (br dd, 1 H, *J* = 1.53, 12.7 Hz), 4.3 (dd, 1 H, *J* = 4.0, 7.8 Hz), 4.6 (quin, 1 H), 4.7 (d, 1 H, *J* = 9.7 Hz), 5.4 (d, 1 H, *J* = 9.7 Hz), 7.3 (m, 1 H), 7.5 (m, 1 H), 7.6 (dd, 1 H), 7.8 (dd, 1 H, *J* = 1.3, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 169.95, 165.90, 139.63, 132.34, 130.30, 129.27, 126.42, 122.61, 79.95, 69.22, 57.01, 56.43, 54.06, 35.13. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.14. Found: C, 60.68; H, 5.89; N, 10.11.

(11a*S*)-2,3,5,10,11,11a-Hexahydro-10-(methoxymethyl)-2,5,11-trioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (7a). To a solution of 1.26 g (4.57 mmol) of alcohol **6a**, in 90 mL of dichloromethane was added 9 g of PCC on alumina (1 mmol of PCC for every 1.5 g of alumina). The reaction mixture was stirred until TLC analysis showed complete consumption of starting material (about 2 days). The reaction mixture was worked up by filtering the alumina and subsequent evaporation of the solvent in vacuo. The brown residue was purified by column chromatography (EtOAc) to afford 0.884 g (70.5%) of the product as a white powder. The product was recrystallized from EtOAc/hexane as white prisms: R_f = 0.61 (EtOAc); mp 182–184 °C; $[\alpha]^{23}_D$ +459° (*c* 0.007, $CHCl_3$); IR ($CHCl_3$) 3020, 1770, 1690, 1640, 1600, 1460, 1410, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7–2.8 (dd, 1 H, *J* = 9.8, 19.2 Hz), 3.4 (s, 3 H), 3.6 (m, 1 H), 3.8 (d, 1 H, *J* = 20.05 Hz), 4.2 (d, 1 H, *J* = 20.07 Hz), 4.6 (dd, 1 H, *J* = 2.74, 9.78 Hz), 4.7 (d, 1 H, *J* = 9.8 Hz), 5.4 (d, 1 H, *J* = 9.78 Hz), 7.4 (t, 1 H), 7.6 (t, 1 H), 7.7 (d, 1 H), 7.9 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.9, 168.8, 165.7, 139.4, 132.6, 130.0, 128.4, 126.6, 122.6, 79.74, 56.86, 54.58, 51.89, 37.14. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.34; H, 5.17; N, 10.20.

(11a*S*)-5,10,11,11a-Tetrahydro-10-(methoxymethyl)-2-[[(trifluoromethyl)sulfonyl]oxy]-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (8b). To a vigorously stirred solution of 0.855 g (3.11 mmol) of ketone **7a**, 0.264 mL (3.27 mmol, 1.05 equiv) of pyridine, and 50 mL of dichloromethane was quickly added 0.524 mL (3.11 mmol) of freshly distilled triflic anhydride. The initially bright yellow solution gradually darkened to a light brown homogeneous solution. The solution was left to stir overnight. The reaction was worked up by pouring the mixture into dichloromethane and cold aqueous sodium bicarbonate. The product was extracted with several portions of CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo left a brown oil. The residue was further purified by column chromatography (50% EtOAc/hexane) to afford 0.942 g (74%) of the product as a pale yellow viscous oil. This product was not fully characterized but was carried on to the next step: R_f = 0.61 (50% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 3.1–3.2 (ddd, 1 H, *J* = 2.38, 10.93, 16.38 Hz), 3.46 (s, 3 H), 3.9 (m, 1 H), 4.6 (dd, 1 H, *J* = 3.57, 10.96 Hz), 4.7 (d, 1 H, *J* = 9.8 Hz), 5.49 (d, 1 H, *J* = 9.8 Hz), 7.1 (t, 1 H, *J* = 1.9 Hz), 7.4 (t, 1 H), 7.55 (t, 1 H), 7.7 (d, 1 H), 7.9 (d, 1 H).

(11a*S*)-2(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5,10,11,11a-hexahydro-10-(ethoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine. The silyl ether (11a*S*)-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine was alkylated with sodium hydride in THF and chloromethyl ethyl ether (−78 °C) to give the fully protected intermediate as thin, white needles in 74% yield: R_f = 0.65 (50% EtOAc/hexane); mp 81–82 °C; $[\alpha]^{22}_D$ +277.4° (*c* 0.0292, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.87 (s, 9 H), 1.2 (t, 2 H, *J* = 7.0 Hz), 2.0 (m, 1 H), 2.8 (m, 1 H), 3.5–3.8 (m, 4 H), 4.2 (d, 1 H, *J* = 3.78, 8.15 Hz), 4.6 (quin, 1 H), 4.7 (d, 1 H, *J* = 9.9 Hz), 5.5 (d, 1 H, *J* = 9.9 Hz), 7.35 (t, 1 H), 7.55 (t, 1 H), 7.7 (d, 1 H), 7.9 (t, 1 H). Anal. Calcd for $C_{21}H_{32}N_2O_4Si$: C, 62.34; H, 7.97; N, 6.92. Found: C, 62.41; H, 8.01; N, 6.89.

(11a*S*)-2(*R*)-Hydroxy-2,3,5,10,11,11a-hexahydro-10-(ethoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (6b). The silyl protecting group was efficiently removed with BF_3·OEt_2 in wet THF to give the alcohol **6b** in 85% yield as a viscous oil: R_f = 0.38 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H), 2.1 (m, 1 H), 2.9 (m, 1 H), 3.6–3.7 (m, 3 H), 3.9 (br d, 1 H, *J* = 12.4 Hz), 4.3 (m, 1 H), 4.6 (quin, 1 H), 4.7 (d, 1 H, *J* = 10.0 Hz), 5.5 (d, 1 H, *J* = 9.97 Hz), 7.3 (t, 1 H), 7.52 (t, 1 H), 7.7 (d, 1 H), 7.83 (d, 1 H).

(11a*S*)-2,3,5,10,11,11a-Hexahydro-10-(ethoxymethyl)-2,5,11-trioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (7b). Alcohol **6b** was oxidized to ketone **7b** in 64% yield as a viscous oil with PCC on alumina: R_f = 0.65 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.28 (t, 1 H), 2.8 (dd, 1 H, *J* = 9.73, 19.28 Hz), 3.5–3.8 (m, 3 H), 3.9 (d, 1 H, *J* = 20.09 Hz), 4.1 (d, 1 H, *J* = 20.10 Hz), 4.6 (dd, 1 H, *J* = 2.97, 9.78 Hz), 4.8 (d, 1 H, *J* = 9.81 Hz), 5.5 (d, 1 H, *J* = 9.93 Hz), 7.4 (t, 1 H), 7.6 (t, 1 H), 7.75 (d, 1 H), 7.92 (d, 1 H).

(11a*S*)-5,10,11,11a-Tetrahydro-10-(ethoxyethyl)-2-[[(trifluoromethyl)sulfonyl]oxy]-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (8c). Vinyl triflate **8c** was obtained from ketone **7b** in 69% yield with 1.2 equiv of pyridine and 1.1 equiv of triflic anhydride: R_f = 0.75 (50% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 1.2 (t, 1 H), 3.1–3.3 (ddd, 1 H, *J* = 2.1, 10.97, 16.35 Hz), 3.6–3.8 (m, 2 H), 3.9 (br d, 1 H), 4.6 (dd, 1 H, *J* = 3.52, 10.94 Hz), 4.7 (d, 1 H, *J* = 9.96 Hz), 5.6 (d, 1 H, *J* = 9.88 Hz), 7.16 (s, 1 H), 7.4 (t, 1 H), 7.6 (t, 1 H), 7.75 (d, 1 H), 7.9 (d, 1 H).

(11a*S*)-2-Vinyl-5,10,11,11a-tetrahydro-10-methyl-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (9). A mixture of 1.09 g (2.91 mmol) of vinyl triflate **8a**, 1.01 g (3.2 mmol, 1.1 equiv) of (tributylvinyl)tin, 1.23 g (29.0 mmol, 10 equiv) of lithium chloride, 0.168 g (5 mol%) of tetrakis(triphenylphosphine)palladium(0), and 40 mL of THF was heated to reflux until TLC analysis showed complete consumption of the starting material (about 24 h). The reaction was worked up by extraction with chloroform and 10% aqueous ammonium hydroxide. The organic layers were combined, washed with water and brine, and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a viscous oil. The residue was further purified by column chromatography (50% EtOAc/hexanes) to give 0.444 g (60%) of the product as pale green crystals: R_f = 0.42 (50% EtOAc/hexane); mp >230 °C; $[\alpha]^{22}_D$ +744° (*c* 0.0046, EtOAc); IR (Nujol) 3120, 1670, 1640, 1400, 1235, 880, 840, 745, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85–2.95 (br ddd, 1 H, *J* = 1.6, 10.6, 16.0

Hz), 3.4 (s, 3 H), 3.7 (br d, 1 H), 4.5 (dd, 1 H, J = 3.46, 10.71 Hz), 5.2 (m, 3 H), 6.5 (dd, 1 H, J = 10.7, 17.2 Hz), 7.0 (s, 1 H), 7.2 (m, 2 H), 7.58 (dt, 1 H), 7.9 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.85, 161.68, 140.42, 132.18, 130.48, 129.75, 125.94, 125.68, 124.89, 122.08, 114.84, 57.07, 36.30, 29.74. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.54; N, 11.01. Found: C, 70.87; H, 5.56; N, 10.98.

(11a*S*)-Ethyl 3-(5,10,11,11a-Tetrahydro-10-methyl-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-2-yl)propenoate (10). A reaction mixture of 0.823 g (2.18 mmol) of vinyl triflate **8a**, 0.885 g (2.27 mmol, 1.04 equiv) of (*E*)-(tributylstannyl)ethyl propenoate, 0.927 g (21.8 mmol, 10.0 equiv) of lithium chloride, 75.8 mg (3 mol%) of tetrakis(triphenylphosphine)palladium(0), and 25 mL of THF was heated to reflux under Ar overnight. The reaction mixture was worked up by extraction with chloroform and washing with water. The organic layers were combined and washed with water and brine, and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a yellow viscous oil. The residue was dissolved in acetonitrile and washed with several portions of hexane (to remove tributyltin chloride). The acetonitrile solvent was removed in vacuo leaving a viscous oil. The residue was further purified by column chromatography (50% EtOAc/hexane) to give 0.595 g (78%) of pale yellow solid: R_f = 0.42 (50% EtOAc/hexane); mp 158–160 °C; $[\alpha]^{22}_D$ +620° (c 0.0074, $CHCl_3$); IR ($CHCl_3$) 1700, 1680, 1650, 1610, 1450, 1405, 1165, 1140, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 7.1 Hz), 2.9 (br dd, 1 H), 3.45 (s, 3 H), 3.8 (br d, 1 H), 4.2 (q, 2 H, J = 7.1 Hz), 4.6 (dd, 1 H, J = 3.47, 10.8 Hz), 5.8 (d, 1 H, J = 15.57 Hz), 7.3 (m, 3 H), 7.5 (d, 1 H, J = 15.59 Hz), 7.6 (t, 1 H), 7.9 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.38, 166.60, 162.12, 140.30, 137.03, 132.69, 130.94, 130.60, 128.27, 125.94, 123.47, 122.25, 118.66, 60.25, 57.41, 36.53, 29.57, 14.17. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.15; H, 5.61; N, 8.50.

This compound was also prepared by the Heck-type coupling of vinyl triflate **8a** and ethyl acrylate with bis(triphenylphosphine)palladium(II) chloride as catalyst, dimethylformamide (DMF) as solvent, and triethylamine (TEA) as base. This reaction resulted in a 40% yield of the diene **10**, which was identical with that obtained using the organostannane approach.

(*E*)-3-(*Tributylstannyl*)propenamide. A solution of 0.481 g (9.00 mmol, 3.00 equiv) of ammonium chloride (NH_4Cl) in 50 mL of benzene was cooled in an ice bath and 4.5 mL (9.00 mmol, 3.00 eq) of trimethylaluminum (2 M in hexanes) was added slowly. The cloudy solution was stirred in the ice bath for 30 min and then at room temperature for 2 h. The solution was then transferred via a syringe to a second 100-mL round-bottom flask containing 1.12 g (3.00 mmol) of the tin ester, methyl (*E*)-3-(tributylstannyl)propenoate.[21] The resulting solution was heated in an oil bath at 60 °C overnight. The reaction mixture was diluted with chloroform and the organic layer was washed with water. The organic layer was dried over $MgSO_4$. Filtration and evaporation in vacuo left a brown residue which was further purified by column chromatography (50% EtOAc/hexane) to give 0.931 g (64%) of a pale yellow oil: R_f = 0.62 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.9–1.6 (m, 27 H), 5.7 (br s, 1 H), 5.95 (br s, 1 H), 6.2 (d, 1 H, J = 19.19 Hz), 7.5 (d, 1 H, J = 19.15 Hz). Anal. Calcd for $C_{15}H_{31}NOSn$: C, 50.03; H, 8.67; N, 3.88. Found: C, 50.11; H, 8.69; N, 3.83.

(11a*S*)-Methyl 3-(5,10,11,11a-Tetrahydro-10-(methoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazopin-2-yl)propenoate (11). A mixture of 0.701 g (1.72 mmol) of vinyl triflate **2b**, 0.679 g (1.8 mmol) of methyl (*E*)-3-(tributylstannyl)propenoate, 0.73 g (17.2 mmol, 10.0 equiv) of lithium chloride, 99 mg (5 mol%) of tetrakis(triphenylphosphine)palladium(0), and 20 mL of THF was heated to reflux under Ar overnight. The reaction mixture was poured into chloroform and extracted with water. The organic layer was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent left a viscous oil which was dissolved in acetonitrile and extracted with hexane to remove the tributyltin chloride. The acetonitrile was removed in vacuo and the residue was recrystallized from EtOAc/hexane to give 0.28 g (47%) of a pale yellow solid: mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 2.94 (dd, 1 H, J = 10.7, 16.3 Hz), 3.49 (s, 1 H), ~3.75 (dd, 1 H, J = 3.2, ~16 Hz), 3.77 (s, 1 H), 4.67 (dd, 1 H, J = 10.7, 16.3 Hz), 4.76 (d, 1 H, J = 9.8 Hz), 5.49 (d, 1 H, J = 9.8 Hz), 5.89 (d, 1 H, J = 15.58 Hz), 7.32 (s, 1 H), 7.51 (d, 1 H, J = 15.58 Hz), 7.36–7.95 (m, 4 H).

(11a*S*)-3-(5,10,11,11a-Tetrahydro-10-(methoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-2-yl)acrylamide (12). A mixture of 1.14 g of vinyl triflate **8b**, 0.506 g (7.12 mmol, 3.00 equiv) of acrylamide, 0.798 g (7.12 mmol, 3.00 equiv) of 1,4-diazabicyclo[2.2.2]octane (DABCO), 30.0 mg (4 mol%) of bis(acetonitrile)palladium(II) chloride, and 30 mL of anhydrous methanol was heated to 50 °C in an oil bath until TLC analysis showed complete consumption of the starting material (about 8 h). The reaction mixture was then poured into aqueous sodium bicarbonate and chloroform. The aqueous phase was extracted with several portions of chloroform. The chloroform layers were combined, washed once with water, and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a brown residue. The residue was further purified by column chromatography (EtOAc + 5% MeOH) to afford 0.400 g (50% yield) after recrystallization (MeOH): R_f = 0.19 (EtOAc); mp 222–223 °C; $[\alpha]^{23}_D$ +537° (c 0.0018, $CHCl_3$); IR (Nujol) 3400, 3200, 1700, 1680, 1640, 1625, 1250, 1150, 1120, 1070, 990, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.9 (br dd, 1 H), 3.48 (s, 3 H), 3.7 (br d, 1 H), 4.6 (dd, 1 H, J = 2.9, 10.6 Hz), 4.7 (d, 1 H, J = 9.86 Hz), 5.4 (m, 3 H), 5.8 (d, 1 H, J = 15.21 Hz), 7.29 (s, 1 H), 7.39 (t, 1 H), 7.45 (d, 1 H, J = 15.3 Hz), 7.55 (t, 1 H), 7.7 (d, 1 H), 7.9 (d, 1 H); ^{13}C NMR (DMSO-d_6) δ 168.25, 166.57, 161.31, 138.63, 132.83, 132.76, 129.90, 129.73, 128.81, 126.39, 123.90, 123.41, 122.28, 78.76, 57.43, 55.95, 29.37. Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.34; H, 5.24; N, 12.82. This compound was also prepared by the coupling of vinyl triflate **8b** and (*E*)-3-(tributylstannyl)-propenamide with tetrakis(triphenylphosphine)palladium(0) as catalyst, lithium chloride, and tetrahydrofuran (THF) as solvent. This reaction resulted in a 22% yield of the desired diene **12**, which was identical with that obtained using the Heck coupling with acrylamide.

(11a*S*)-Methyl 3-(5,10,11,11a-Tetrahydro-10-(ethoxymethyl)-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-2-yl)propenoate (13). Vinyl triflate **8c** was coupled with the tin reagent to give the diene **13** in 70% yield with tetrakis(triphenylphosphine)palladium(0) (4 mol%), lithium chloride (3 equiv), and THF as solvent. Diene **13** was obtained as pale green needles: R_f = 0.34 (50% EtOAc/hexane); mp 173–174 °C; $[\alpha]^{23}_D$ +594° (c 0.0024, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.9–3.0 (br dd, 1 H), 3.5–3.7 (m, 6 H), 4.6 (dd, 1 H, J = 3.49, 10.7 Hz), 4.7 (d, 1 H, J = 9.98 Hz), 5.5 (d, 1 H, J = 9.91 Hz), 5.8 (d, 1 H, J = 15.57 Hz), 7.31 (s, 1 H), 7.39 (t, 1 H), 7.48 (d, 1 H, J = 15.81 Hz), 7.5 (t, 1 H), 7.7 (d, 1 H), 7.9 (d, 1 H). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.65; N, 7.87. Found: C, 64.09; H, 5.69; N, 7.82.

4-Methyl-3-(benzyloxy)-2-nitrobenzoic Acid (15). To a solution of 5.91 g (30.0 mmol) of 4-methyl-3-hydroxy-2-nitrobenzoic acid (**14**)[23] (Aldrich) in 70 mL of dry DMF was added 7.31 mL (61 mmol) of benzyl bromide and finely powdered K_2CO_3 (9.1 g, 62 mmol). This mixture was stirred at 65 °C under Ar for 36 h. The reaction was worked up by pouring the solution into water and EtOAc. The product was extracted with several portions of EtOAc. The ethyl acetate layers were combined, washed with water and brine, and dried over $MgSO_4$. Filtration and evaporation in vacuo gave a viscous red oil which slowly crystallized. The solid was recrystallized from EtOAc/hexane to give 9.2 g (81%) of the product as pale yellow crystals: R_f = 0.9 (50% EtOAc/hexane); mp 87–88 °C; IR (Nujol) 2900, 1720, 1540, 1370, 1270, 1010, 980, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 4.96 (s, 2 H), 5.3 (s, 2 H), 7.4 (m, 11 H), 7.7 (d, 1 H, J = 8.1 Hz). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.87; H, 5.13; N, 3.68.

Hydrolysis of 1.13 g (3.00 mmol) of ester **15** was carried out with 0.84 g (15 mmol) of KOH, 10 mL of THF, 10 mL of water, and 15 mL of methanol. The reaction was stirred until TLC analysis showed complete consumption of the starting material (about 12 h). The reaction was acidified and extracted with several portions of chloroform. The chloroform layers were combined and washed with water and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo left a pale yellow powder. The product was recrystallized from EtOAc/hexane to give 0.688 g (80%) of white crystals: mp 173–174 °C; IR (Nujol) 1670, 1600, 1210, 1175, 900, 830, 740, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 4.9 (s, 2 H), 7.4 (m, 6 H), 7.8 (d, 1 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) 167.64, 148.71, 146.43, 141.04, 135.60, 132.38, 128.65, 128.22, 126.98, 119.99, 77.26, 16.90. Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.87. Found: C, 62.60; H, 4.58; N, 4.82.

***N*-[4-Methyl-3-(benzyloxy)-2-nitrobenzoyl]hydroxyproline Ethyl Ester (16).** A mixture of 2.87 g (10.0 mmol) of the acid (**15**), 1.13 mL (1.3 equiv) of oxalyl chloride, 80 mL of dichloromethane, and 2 drops of DMF was heated to reflux for 40 min. The dichloromethane and excess oxalyl chloride was distilled until a viscous, yellow oil was obtained. The residue was dissolved in THF and quickly transferred to a 250-mL round-bottom flask containing 2.34 g (12.0 mmol, 1.2 equiv) of 4-hydroxy-L-proline ethyl ester hydrochloride, 3.48 mL (2.5 equiv, 25 mmol) of triethylamine, and 100 mL of THF all cooled to 0 °C in an ice bath. After addition of the acid chloride, the solution was stirred at 0 °C for 30 min. The reaction was worked up by pouring the solution into a flask containing EtOAc and aqueous $NaHCO_3$. The product was extracted with several portions of ethyl acetate. The ethyl acetate extracts were combined and washed with water and brine and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo afforded the product as a pale yellow solid. The product was recrystallized from EtOAc/hexane to give 4.12 g (96%) of a pale yellow powder: R_f = 0.57 (EtOAc); mp 120–122 °C; $[\alpha]^{23}_D$ −166° (c 0.0038, $CHCl_3$); IR ($CHCl_3$) 3500, 3020, 1735, 1630, 1530, 1430, 1355, 1260, 1080, 1030, 655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7.09 Hz), 2.15 (m, 1 H), 2.3 (s,

3 H, $ArCH_3$), 3.4 (d, 1 H, J = 11.39 Hz), 3.6 (dd, 1 H, J = 3.9, 11.3 Hz), 4.2 (q, 2 H, J = 7.09 Hz), 4.49 (br s, 1 H), 4.75 (t, 1 H, J = 8.39 Hz), 4.9 (d, 1 H, J = 10.5 Hz), 5.1 (d, 1 H, J = 10.5 Hz), 7.19 (d, 1 H, J = 7.78 Hz), 7.3 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.6, 165.5, 149.3, 143.5, 135.9, 135.8, 133.7, 129.9, 128.5, 128.2, 122.6, 76.78, 70.02, 61.35, 57.70, 57.17, 38.03, 16.32, 13.99 (missing 1 carbon atom). Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.64; N, 6.53. Found: C, 61.54; H, 5.71; N, 6.48.

(11a*S*)-2(*R*)-Hydroxy-8-methyl-9-(benzyloxy)-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (2). A mixture of 49.6 g (0.115 mol) of the nitro ester **16**, 100 g (0.574 mol, 5 equiv) of $Na_2S_2O_4$, 3 L of THF, and 2 L of water was stirred at room temperature until TLC analysis showed complete consumption of the starting material (about 1.5 days). The reaction was worked up by pouring the mixture into water and chloroform. The product was extracted with several portions of chloroform. The chloroform extracts were combined, washed with water and brine, and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left the product as a yellow, viscous oil. To the oil was added 100 mL of THF and 700 mL of water (containing 2 mL of concentrated HCl). The solution was stirred for 2 days at room temperature. The product crystallized out of the solution as a pink solid. The solution was filtered and the solid was recrystallized from MeOH. The product was isolated (27.5 g, 67.4% yield for both steps) as white needles: R_f = 0.45 (EtOAc); mp 245–246 °C; $[\alpha]^{22}_D$ +264° (c 0.0032, MeOH) [lit.[3] $[\alpha]^{22}_D$ +256° (c 0.5, MeOH)]; IR (Nujol) 3400, 3360, 2900, 1680, 1630, 1610, 1230, 1070, 870, 745, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (m, 1 H), 2.4 (s, 3 H), 2.8 (m, 1 H), 3.6 (m, 1 H), 3.9 (m, 2 H), 4.5 (m, 1 H), 4.8–5.0 (dd, 2 H, J = 11.16 Hz), 7.0 (d, 1 H, J = 8.1 Hz), 7.35 (m, 6 H), 7.6 (d, 1 H, J = 8.1 Hz), 7.7 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) 166.17, 161.27, 143.76, 133.24, 131.44, 126.50, 125.27, 124.84, 124.70, 123.33, 122.90, 121.78, 70.89, 64.10, 51.82, 50.56, 31.09, 12.73. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.94. Found: C, 68.10; H, 5.74; N, 7.92.

Benzaldehyde Protected (11a*S*)-2(*R*),9-Dihydroxy-8-methyl-2,3,5,10,11,11a-hexahydro-5,11-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (17). Into a Fischer–Porter tube was placed 1.05 g (3.00 mmol) of the benzyl ether **2**, 30 mL of MeOH, and 10 mg of palladium on carbon. The tube was attached to the pressure regulator and pressurized to 40 psi of H_2. The assembly was placed in a 60 °C oil bath and stirred for 5 h. The reaction was cooled and the solution was filtered to remove the palladium on carbon. The methanol was reduced in volume and cooled to crystallize the phenol. Filtration of the cold methanol afforded 0.696 g (89%) of the phenol as white needles: mp 265 °C dec; $[\alpha]^{23}_D$ +431° (c 0.0056, MeOH); IR (Nujol) 3440, 3370, 3340, 2900, 1690, 1605, 1510, 1260, 1090, 825, 755 cm^{-1}; ^1H NMR (CH_3OH-d_4) δ 2.1 (m, 1 H), 2.3 (s, 3 H), 2.85 (m, 1 H), 3.3 (m, 1 H, OH), 3.6 (dd, 1 H, J = 4.9, 12.3 Hz), 3.78 (dd, 1 H, J = 3.7, 12.3 Hz), 4.3 (dd, 1 H, J = 5.86, 7.9 Hz), 4.5 (quin, 1 H), 7.05 (d, 1 H, J = 8.10 Hz), 7.35 (d, 1 H, J = 8.09 Hz); ^{13}C NMR (CH_3OH-d_4) δ 171.8, 168.2, 146.19, 130.6, 127.8, 126.4, 126.0, 122.1, 69.34, 57.07, 54.91, 35.30, 16.43. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.45; H, 5.40; N, 10.62. The phenol and amide nitrogen were protected by heating 0.262 g (1.00 mmol) of the phenol and 3 mL of benzaldehyde dimethyl acetal to reflux (~175 °C) under argon for 24 h. The reaction was cooled and then transferred to a 50-mL round-bottom flask containing 20 mL of THF, 20 mL of water and a few drops of concentrated HCl. The solution was stirred overnight. The reaction mixture was worked up by extraction with chloroform and water. The chloroform layers were combined, washed with brine, and dried over $MgSO_4$. Filtration and evaporation of the solvent left a viscous oil. The product was further purified by column chromatography (EtOAc) to first give excess benzaldehyde and then 0.278 g (79.4%) of a viscous oil, which slowly crystallized upon standing: R_f = 0.48 (EtOAc); mp 161–162 °C; $[\alpha]^{22}_D$ +393° (c 0.0039, $CHCl_3$); IR ($CHCl_3$) 3520, 2920, 1680, 1640, 1590, 1260, 1240, 1120, 975, 840, 815, 710, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.3 (s, 4 H), 2.7 (m, 1 H), 3.4 (dd, 1 H, J = 3.8, 12.7 Hz), 3.6 (br s, 1 H), 4.22–4.28 (dt, 1 H, J = 2.0, 12.7 Hz), 4.3 (t, 1 H, J = 7.8 Hz), 4.5 (br s, 1 H), 6.97 (d, 1 H, J = 8.2 Hz), 7.28 (s, 1 H), 7.31–7.4 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.34, 166.18, 148.45, 136.61, 129.70, 128.66, 127.30, 126.15, 125.64, 123.42, 121.82, 118.04, 94.06, 68.41, 57.65, 54.68, 35.63, 14.75; HRMS calcd for $C_{20}H_{18}N_2O_4$ 350.1267, found 350.1263. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.17; N, 7.99. Found: C, 68.52; H, 5.21; N, 7.96.

Ketone 18. A solution of 30 mL of CH_2Cl_2 and 0.143 mL (1.1 equiv, 1.65 mmol) of freshly distilled oxalyl chloride was cooled to −78 °C and a solution of 0.234 mL (3.30 mmol, 2.20 equiv) of DMSO and 5 mL of CH_2Cl_2 was added to the oxalyl chloride solution over 2 min. A solution of alcohol **17** (0.525 g, 1.50 mmol in 5 mL of CH_2Cl_2) was added. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of triethylamine (1.00 mL, 7.5 mol) in 5 mL of CH_2Cl_2. The dichloromethane solution was warmed to room temperature and the organic layer was washed with several portions of water and then dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a viscous, yellow oil. The residue was further purified by column chromatography (50% EtOAc/hexane) to give 0.36 g (70%) of a pale yellow oil, which slowly crystallized upon standing: R_f = 0.45 (50% EtOAc/hexane); mp 195–197 °C dec; $[\alpha]^{22}_D$ +490° (c 0.0083, $CHCl_3$); IR (Nujol) 2920, 1760, 1680, 1630, 1500, 1250, 1180, 1020, 820, 755, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 2.86–2.97 (ddd, 1 H, J = 1.4, 10.68, 19.86 Hz), 3.6 (dd, 1 H, J = 4.35, 19.87 Hz), 3.8 (d, 1 H, J = 20.17 Hz), 4.5 (d, 1 H, J = 20.32 Hz), 4.6 (dd, 1 H, J = 4.36, 10.69 Hz), 7.05 (d, 1 H, J = 8.22 Hz), 7.32 (s, 1 H), 7.34–7.44 (m, 5 H), 7.5 (d, 1 H, J = 8.21 Hz); ^{13}C NMR ($CDCl_3$) δ 206.72, 168.11, 165.81, 148.64, 136.36, 129.91, 128.77, 127.82, 126.14, 125.65, 124.11, 121.91, 117.43, 94.40, 56.11, 53.12, 37.01, 14.87. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.95; H, 4.62; N, 8.04. Found: C, 68.86; H, 4.66; N, 8.01.

Triflate 19. To a rapidly stirred solution of 1.79 g (5.14 mmol) of ketone (**18**), 0.914 mL (11.3 mmol, 2.20 equiv) of pyridine and 70 mL of CH_2Cl_2 was added quickly 1.81 mL (10.8 mol, 2.10 equiv) of freshly distilled triflic anhydride. The black solution was stirred for 3 h at room temperature. The reaction mixture was poured into CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was washed with several portions of aqueous $NaHCO_3$ and water, and then dried over Na_2SO_4. Filtration and evaporation of solvent in vacuo left a red oil. The residue was further purified by column chromatography (25% EtOAc/hexane) to give 2.2 g (90%) of the product as a pale yellow, viscous oil. This intermediate was not fully characterized but instead carried on to the next step: R_f = 0.31 (25% EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.23–3.34 (ddd, 1 H, J = 2.28, 11.91, 16.74 Hz), 3.90–3.99 (ddd, 1 H, J = 1.85, 5.16, 16.75 Hz), 4.7 (dd, 1 H, J = 5.15, 11.92 Hz), 7.04 (d, 1 H, J = 8.34 Hz), 7.15 (t, 1 H, J = 2.00 Hz), 7.34 (s, 1 H), 7.35–7.44 (m, 5 H), 7.50 (d, 1 H, J = 8.19 Hz); LRMS calcd for $C_{21}H_{15}N_2O_6SF_3$ M^+ 480.42, found 480.6.

Acrylamide 20. A mixture of 0.873 g (1.40 mmol) of the vinyl triflate **19**, 0.213 g (3.00 mmol, 2.00 equiv) of acrylamide, 0.336 g (3.00 mmol, 2.00 equiv) of 1,4-diazobicyclo[2.2.2]octane (DABCO), 30.0 mg (5 mol%) of bis(acetonitrile)palladium(II) chloride, and 25 mL of anhydrous methanol was stirred at 45 °C overnight. The reaction was worked up by pouring the mixture into chloroform and aqueous $NaHCO_3$. The aqueous layer was extracted with several portions of chloroform. The chloroform extracts were combined, washed with water, and then dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a red-brown solid. The residue was further purified by flash chromatography (EtOAc + 1% MeOH) to give 0.73 g (50%) of the product as a dull yellow powder: R_f = 0.16 (EtOAc); mp 200 °C dec; $[\alpha]^{22}_D$ +842° (c 0.005, DMSO); IR (Nujol) 3338.9, 2953, 2926, 2854, 1684, 1649, 1458, 1376, 1250 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.9 (br dd, 1 H, J = 12.2, 15.7 Hz), 3.3 (s, 3 H), 3.4 (br dd, 1 H, J = 3.68, 16.0 Hz), 5.0 (dd, 1 H, J = 4.22, 11.4 Hz), 5.9 (d, 1 H, J = 15.4 Hz), 6.97 (br s, 2 H), 7.1 (d, 1 H, J = 8.24 Hz), 7.3 (d, 1 H, J = 15.4 Hz), 7.37 (m, 8 H); ^{13}C NMR (DMSO-d_6) δ 14.49, 29.97, 58.38, 94.20, 117.20, 121.42, 122.07, 122.70, 123.14, 125.67, 126.40, 127.08, 128.89, 129.73, 131.87, 132.66, 136.95, 148.25, 161.68, 166.61, 168.38; HRMS calcd M + 1 402.1455, found: 402.1454. Anal. Calcd for $C_{23}H_{19}N_3O_4$: C, 68.81; H, 4.77; N, 10.46. Found: C, 68.68; H, 4.81; N, 10.35.

Alcohol 21. A solution of 200 mg (0.498 mmol) of diene **20** in 50 mL of anhydrous methanol was cooled in an ice bath and then 490 mg (1.50 mmol, 3.00 equiv) of sodium borohydride ($NaBH_4$) was added. The reaction was stirred until the complete consumption of starting material and the appearance of a blue fluorescent spot at a lower R_f were observed (about 4.5 h). The reaction was worked up by pouring the solution into water and ethyl acetate (EtOAc). The aqueous layer was extracted with several portions of ethyl acetate. The ethyl acetate layers were combined, washed with brine, and then dried over Na_2SO_4. Filtration and evaporation of solvent in vacuo afforded 0.500 g (99%) of a bright yellow powder: ^1H NMR (DMSO-d_6) δ 2.09 (s, 3 H), 2.6 (dd, 1 H, J = 4.34, 15.87 Hz), 3.0 (dd, 1 H, J = 11.01, 15.55 Hz), 4.25 (dd, 1 H, J = 4.52, 11.04 Hz), 4.8 (d, 1 H, J = 9.0 Hz), 5.7 (d, 1 H, J = 15.37 Hz), 5.8 (d, 1 H, J = 9.1 Hz), 6.55 (d, 1 H, J = 8.2 Hz), 6.76 (s, 1 H), 7.1 (d, 1 H, J = 8.2 Hz), 7.27 (d, 1 H, J = 15.39 Hz), 7.4–7.5 (m, 6 H); HRMS calcd for $C_{23}H_{21}N_3O_4$ M + 1 404.1611, found M + 1 404.1605.

Diene 22. A mixture of 0.624 g (1.29 mmol) of vinyl triflate **19**, 0.535 g (1.68 mmol, 1.3 equiv) of (tributylvinyl)tin, 0.220 g (3.89 mmol, 3.00 equiv) of lithium chloride, and 60.0 mg (4 mol%) of tetrakis(triphenylphosphine)palladium(0) in 30 mL of THF was heated to reflux overnight. The solution was cooled and then poured into $CHCl_3$. The organic layer was washed with several portions of water and then with 10% aqueous ammonium hydroxide. The organic layer was dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo left a yellow powder which was further purified by column chromatography (25% EtOAc/hexanes)

to give 0.279 g (60%) of a pale yellow solid: mp 180 °C dec; $[\alpha]^{23}_D$ +745° (c 0.0042, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.0-3.1 (ddd, 1 H, J = 1.33, 11.56, 16.46 Hz), 3.7 (dd, 1 H, J = 3.90, 16.48 Hz), 4.6 (dd, 1 H, J = 4.62, 11.50 Hz), 5.1 (m, 2 H), 6.5 (m, 1 H), 6.9 (m, 2 H), 7.3-7.4 (m, 7 H), 7.5 (d, 1 H, J = 8.21 Hz); ^{13}C NMR ($CDCl_3$) 168.30, 162.40, 148.81, 136.60, 129,85, 129.62, 128.80, 127.65, 126.73, 125.73, 125.05, 124.05, 122.09, 117.88, 115.04, 94.42, 58.69, 30.58, 14.95 (1 carbon atom missing); HRMS calcd for $C_{22}H_{18}N_2O_3$ M + 1 358.1318, M - C_6H_6N 266.0817, found M + 1 358.1327, M - C_6H_6N 266.0819.

Enyne 23. A mixture of 0.375 g (0.780 mmol) of vinyl triflate **19**, 0.347 g (0.936 mmol, 1.2 equiv) of 3,3-dimethyl-1-(tributylstannyl)-1-butyne, 99.2 mg (2.34 mmol, 3.00 equiv) of lithium chloride, and 36.0 mg (4 mol%) of tetrakis(triphenylphosphine)palladium(0) in 30 mL of THF was heated to reflux overnight. The reaction was cooled and then poured into $CHCl_3$. The organic layer was washed with several portions of water and then with 10% aqueous ammonium hydroxide. The organic layer was dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo left a black residue, which was further purified by column chromatography (25% EtOAc/hexanes) and recrystallized from EtOAc/hexanes to give 209 mg (65%) of thin, golden needles: mp 205-206 °C; $[\alpha]^{23}_D$ +682° (c 0.0038, EtOAc); ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 2.3 (s, 3 H), 3.0 (ddd, 1 H, J = 2.28, 11.56, 16.67 Hz), 3.7 (ddd, 1 H, J = 1.81, 4.51, 16.67 Hz), 4.5 (dd, 1 H, J = 4.52, 11.53 Hz), 7.00 (d, 1 H, J = 8.24 Hz), 7.04 (t, 1 H, J = 2.03 Hz), 7.3-7.4 (m, 6 H), 7.48 (d, 1 H, J = 8.19 Hz); ^{13}C NMR ($CDCl_3$) δ 168.04, 161.98, 148.76, 136.55, 131.22, 129.82, 128.77, 127.65, 125.80, 125.68, 124.10, 122.11, 117.81, 107.41, 103.64, 94.31, 72.48, 58.22, 35.02, 30.88, 28.18, 14.95; HRMS calcd for $C_{26}H_{24}N_2O_3$ M^+ 412.1788, M - CH_3 397.1553, M - $C_{11}H_{12}NO$ 238.0868, found: M^+ 412.1806, M - CH_3 397.1562, M - $C_{11}H_{12}NO$ 238.0864. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.70; H, 5.86; N, 6.79. Found: C, 75.62; H, 5.89; N, 6.73.

Anthramycin Methyl Ether 1b.[18] A solution of 200 mg (0.500 mmol) of alcohol **22** and 50 mL of methanol and 30 mL of a 0.02 M aqueous hydrochloric acid was stirred for 2 days at ambient temperature. The solution was neutralized with $NaHCO_3$ and then all of the solvent was removed in vacuo at ambient temperature to leave a yellow residue. The residue was dissolved in 50 mL of methanol, filtered through a plug of glass wool and then stirred at 45 °C for 2 h. The solvent was removed in vacuo to obtain the crude anthramycin: ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 2.69 (q H_c, J = 5.85, 15.89 Hz), 3.10 (q H_d, J = 11.23, 15.4 Hz), 3.24 (s, 3 H), 4.2 (q, H_b, J = 5.48, 11.30 Hz), 4.7 (d, H_a, J = 6.54 Hz), 5.7 (d, H_g, J = 15.37 Hz), 6.49 (d, H_i, J = 8.55 Hz), 7.2 (d, H_f, J = 15.6 Hz), 7.29 (s, H_e). See **1b** of Scheme II for proton designation. This spectrum contained the same peaks as that of an authentic sample.

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Comparison of the Structure and Charge Delocalization in an Unsaturated Imine and Its Corresponding Iminium Salt[1]

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Abstract: The crystal structures of *N*-phenyl-3-(*p*-chlorophenyl)-2-propenimine, **1**, and *N*-methyl-*N*-phenyl-3-(*p*-chlorophenyl)-2-propeniminium perchlorate, **2**, have been determined by single-crystal X-ray techniques. Both compounds exist as monoclinic crystals, space group $P2_1/c$, with four molecules per unit cell. The imine **1** has cell dimensions of a = 14.438 (4) Å, b = 14.348 (4) Å, c = 6.240 (2) Å, and β = 101.57 (3)°. The corresponding iminium salt **2** has cell dimensions of a = 7.811 (2) Å, b = 16.811 (5) Å, c = 13.876 (3) Å, and β = 113.26 (2)°. The three-dimensional structures of **1** and **2** are remarkably similar in terms of geometry and bond lengths. However, the C_1,N bond in **2** is significantly longer than in **1**. It was concluded that the C_1,N bond lengthening and close anion contact to C_1 in **2** are a result of positive charge delocalization to C_1. The conclusions reached from the crystallographic data have been compared with ^{13}C NMR spectroscopic data as well as theoretical studies.

The visual pigment rhodopsin and the light harvesting protein bacteriorhodopsin each contain a retinal chromophore linked to a lysine residue of a protein backbone via a protonated Schiff base.[2] Despite the existence a great number of studies on the properties and chemistry of the in vivo chromophore and in vitro studies on the corresponding iminium salts of retinal lacking the protein backbone, there remain many fundamental questions about these systems. These include detailed information on their structure, conformation and charge delocalization, the way such properties change between an imine and its corresponding iminium salt, and the importance of the nature and placement of the corresponding

Table I. ^{13}C NMR Data

	1[a]	2[b]	2(s)
C(1)	161.5	169.6	170.8
C(2)	126.5	116.4	118.5
C(3)	142.6	164.8	163.0
C(4)	134.8	131.9	131.5
C(5), C(9)	129.5	132.0	131.5
C(6), C(8)	129.5	130.1	131.5
C(7)	142.6	142.6	138.8
C(10)	152.2	144.5	143.7
C(11), C(15)	121.2	122.1	123.8
C(12), C(14)	129.1	130.6	131.5
C(13)	126.5	131.5	131.5
C(16)		41.8	41.4

[a] CD_2Cl_2. [b] Trifluoracetic acid.

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