Photochemical Approach to the Synthesis of the Pyrrolo[1,4]benzodiazepine Antibiotics

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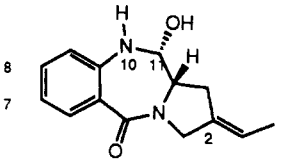
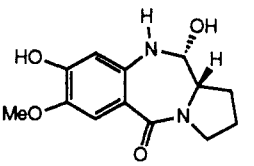
The total syntheses of the pyrrolo[1,4]benzodiazepine antitumor antibiotics prothracarcin and DC-81 were realized using, as a key step, the photochemical [$2\sigma + 2\pi$] ring expansion of the appropriately substituted *N*-pentenylphthalimide to afford the corresponding pyrrolobenzazepinedione. Conversion of the photoproduct into the antibiotic skeleton was effected by transformation of the benzylic ketone into a carbinolamine via a Curtius rearrangement sequence.

Anthramycin,[1] sibiromycin,[2] and tomaymycin,[3] all of which were isolated in the late 1960s to early 1970s, are the most thoroughly investigated members of the pyrrolo[1,4]benzodiazepine family of antitumor antibiotics. Other compounds of this family include neothramycins A and B,[4] and mazethramycin,[5] and prothracarcin[6] (1), along with the recently discovered DC-81[7] (2), SEN-215,[8] and chicamycins A and B.[9] Many of these natural products, which are isolated from various actinomycetes,[10] exhibit antiviral and antibacterial activity as well as antitumor activity against a variety of animal and human tumors.[10]

The mode of action of the pyrrolo[1,4]benzodiazepines is believed to involve the formation of a labile, covalent aminal linkage between the carbinolamine carbon (C-11) of the antibiotic and the 2-amino group of guanine residues in DNA.[10] The resulting DNA-antibiotic adduct inhibits DNA replication. Generally, polar substituents on the aromatic ring increase the activity of these compounds, presumably by providing secondary stabilizing forces in the DNA-antibiotic adduct.[10]



Prothracarcin (1)



DC-81 (2)

The classical approach to the synthesis of the antibiotic skeleton, exemplified by the synthesis of anthramycin by Leimgruber,[1b,10a] involves the reaction of a preformed pyrrolo ring with an aromatic electrophile (Figure 1). Selective reduction of the primary amide was difficult and forced a longer synthesis. Kaneko[3h,10b] has solved this problem by converting the primary amide to the imino thioether, which is subsequently transformed to the carbinolamine. By combining these two methodologies, the antibiotic can usually be synthesized in approximately 10 steps in good overall yields.

We report a synthetic route to the pyrrolo[1,4]benzodiazepines that utilizes a photochemical ring expansion as the key transformation and is illustrated by the syntheses of prothracarcin (1) and DC-81 (2).

Phthalimides have been shown to undergo several types of photochemical reactions with alkenes,[11] and it has been demonstrated that an intramolecular [$2\sigma + 2\pi$] photoaddition occurs with *N*-pentenylphthalimides **3** to give pyrrolobenzazepinediones **4**[12] (Scheme I). We felt that the photoproduct **4** could be converted to the antibiotic skeleton by transformation of the benzylic ketone (C-10) into a carbinolamine, elaboration of functionality into the C-2 ethylidene group required for prothracarcin (1), and establishment of the aromatic substitution pattern required for DC-81 (2). To test this strategy, the synthesis of the parent antibiotic[13] **5** was undertaken.

Two basic approaches were considered for the removal of the C-10 carbon. The first of these, a Beckmann ring expansion sequence, was applied to α-tetralone (**6**, serving as a model for **5**) to give lactam **8**, which would be deriv-

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(9) (a) Konishi, M.; Hatori, M.; Tomita, K.; Sugawara, M.; Ikeda, C.; Nishiyama, Y.; Imanishi, H.; Miyaki, T.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 191. (b) Konishi, M.; Ohkuma, H.; Naruse, N.; Kawaguchi, H. *J. Antibiot.* **1984**, *37*, 200.

(10) (a) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349, and references therein. (b) Kaneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C.; Bradner, W. T. *J. Med. Chem.* **1985**, *28*, 388. (c) Hurley, L. H.; Gairola, C.; Zmijewski, M. *Biochim. Biophys. Acta* **1977**, *475*, 521. (d) Hurley, L. H.; Gairola, C. *Antimicrob. Agents Chemother.* **1979**, *15*, 42. (e) Hurley, L. H.; Lasswell, W. L.; Ostrander, J. M.; Parry, R. *Biochemistry* **1979**, *18*, 4230. (f) Hurley, L. H.; Rokem, J. S.; Petrusek, R. L. *Biochem. Pharmac.* **1980**, *29*, 1307. (g) Petrusek, R. L.; Anderson, G. L.; Garner, F. T.; Fannin, Q. L.; Kaplan, D. J.; Zimmer, S. G.; Hurley, L. H. *Biochemistry* **1981**, *20*, 1111. (h) Thurston, D. E.; Langley, D. R. *J. Org. Chem.* **1986**, *51*, 705, and references therein.

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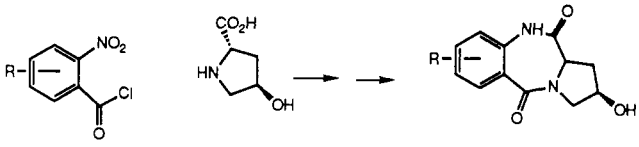
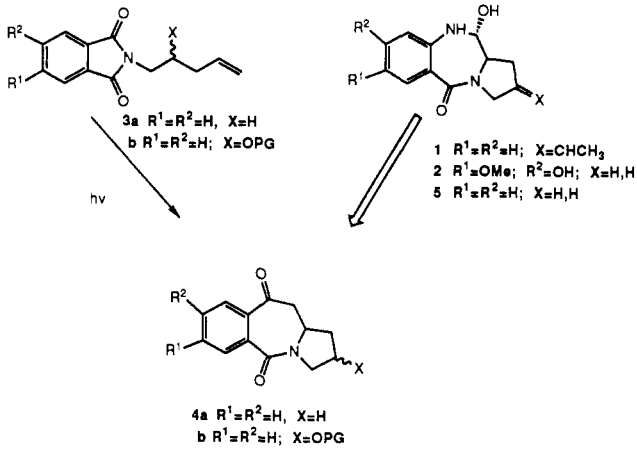
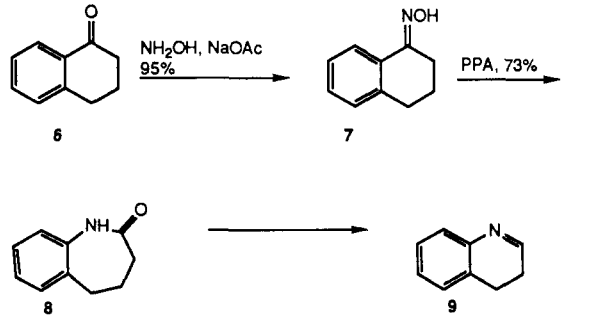


Figure 1.

Scheme I



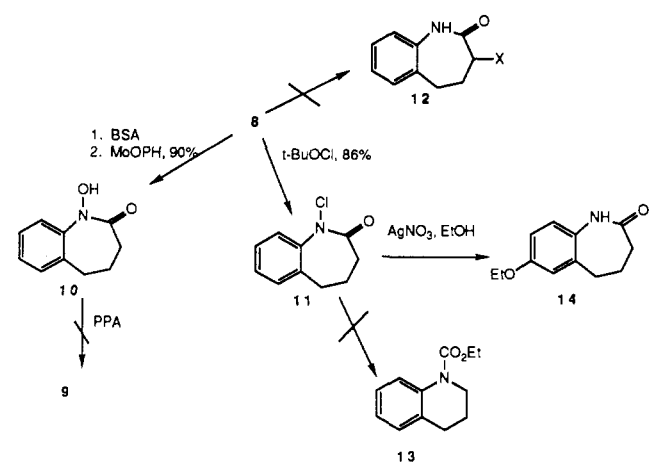
Scheme II



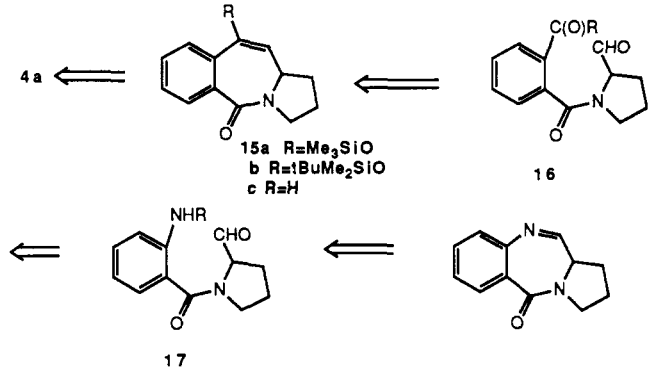
atized and subjected to rearrangement/ring contraction conditions to afford an imine **9** (Scheme II). The Beckmann sequence was carried out according to the literature[14] via oxime **7** to give the homocarbostyril **8**.

Several attempts were made to effect the ring contraction on derivatives of **8** as a model for the conversion of photoproduct **4** to the parent antibiotic **5**. The first involved the preparation of *N*-hydroxylactam **10** by oxidation of lactam **8** with bis(trimethylsilyl)acetamide/oxodiperoxomolybdenum (pyridine/HMPA,[15] Scheme III). Treatment of **10** with polyphosphoric acid (PPA, 190 °C) did not lead to imine **9** as expected[16] but resulted in a tarry residue from which traces of lactam **8** were isolated. In analogy with Baumgarten's[17] reported Favorskii-like rearrangements in acyclic systems, the *N*-chlorolactam **11**, prepared from **8** by treatment with *tert*-butyl hypochlorite,[18] was reacted with a variety of bases (*t*-BuOK/PhMe; $NaNH_2$/PhMe; *n*-BuLi/ether). Unfortunately, only dechlorination occurred to regenerate lactam **8**. The converse Favorskii-like rearrangement[19] of chlorolactam

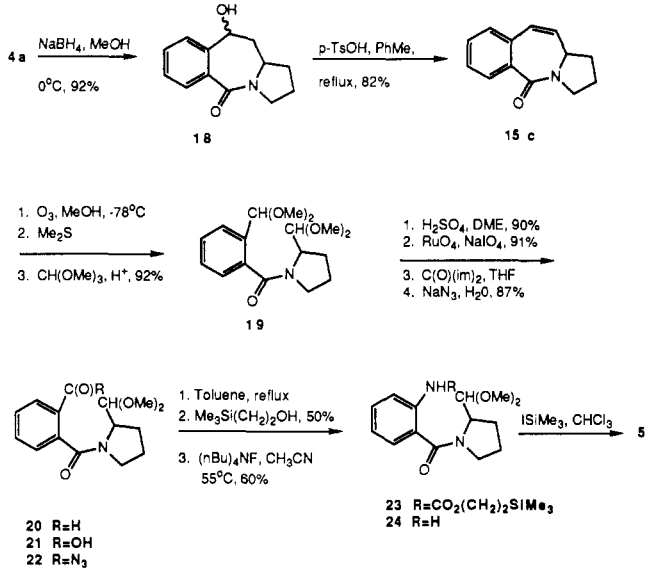
Scheme III



Scheme IV



Scheme V



12 could not be carried out due to the inability to halogenate only α to the carbonyl.

Finally, we attempted the silver ion assisted migration of *N*-chlorolactam **11** to give carbamate **13** on the basis of the work of Kovacic[20a] and Gassman.[20b] Unfortunately,

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(19) (a) Sarel, S.; Greenberger, A. *J. Org. Chem.* **1958**, *23*, 330. (b) Sarel, S.; Leader, H. *J. Am. Chem. Soc.* **1960**, *82*, 4752. (c) Sheehan, J. C.; Frankenfeld, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 4792. (d) Sheehan, J. C.; Lengyel, U. *J. Am. Chem. Soc.* **1964**, *86*, 1356.
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reaction of **11** with ethanolic silver nitrate produced the aromatic substitution[21] product **14** instead of carbamate **13**.

The failure of the rearrangement approach forced us to adopt a longer, stepwise sequence that involved conversion of photoproduct **4a** to an olefinic derivative **15** (Scheme IV). The undesired C-10 carbon would be removed by a sequence involving oxidative cleavage of the double bond to give **16** followed by a Curtius rearrangement to afford the protected amine **17**. Cyclization would lead to the parent **5** in the imine form.

Several olefinic derivatives **15** were examined. The trimethylsilyl enol ether **15a** was too unstable to be useful, but the *tert*-butyldimethylsilyl enol ether **15b** was more stable. Yet attempts to convert it to the cleavage product **16** by ozonolysis were unsuccessful.

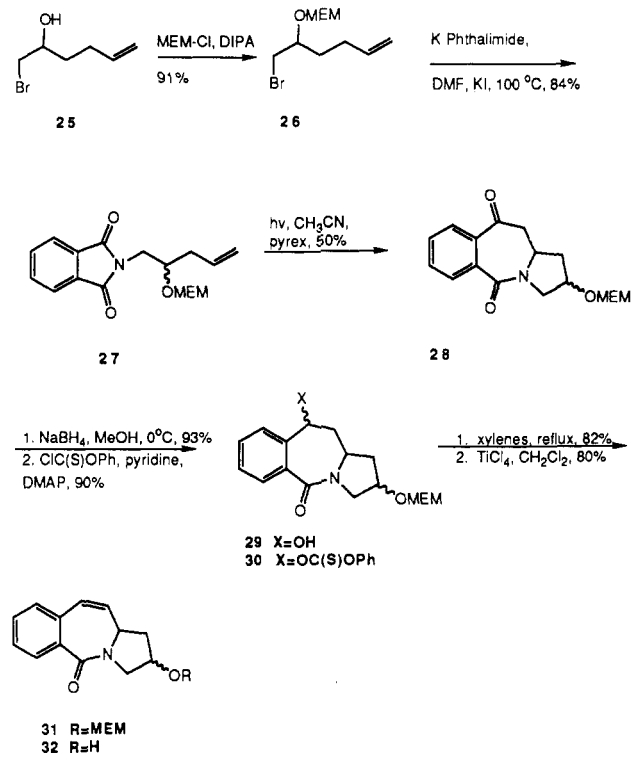
The simple olefinic derivative **15c** was a more fruitful intermediate (Scheme V). Photoproduct **4a**,[22] prepared by irradiation of *N*-pentenylphthalimide **3a**[23] in acetonitrile, was reduced to the diastereomeric alcohols **18** by using sodium borohydride. Acid-catalyzed dehydration of **18** produced olefin **15c**, which was ozonized according to the procedure of Frickel[24] to yield the bis(dimethyl)acetals **19**. Selective hydrolysis of the benzylic acetal[25] occurred to produce the benzaldehyde **20**, which gave carboxylic acid **21** upon oxidation[26] with ruthenium tetraoxide/$NaIO_4$.

At this point, the removal of the benzylic carbon was performed. The carboxylic acid **21** was transformed into acyl azide **22** by treatment with carbonyl diimidazole and followed by aqueous sodium azide. A Curtius[27] rearrangement of acyl azide **22** proceeded quickly in refluxing toluene with the resulting isocyanate being trapped as the trimethylsilyl carbamate **23**.[27b,c] Deprotection[28] of silyl carbamate **23** with tetrabutylammonium fluoride in acetonitrile gave the aniline derivative **24**, which was cyclized to the imine form of **5** by treatment with iodotrimethylsilane[29] in chloroform. Product **5** was identical with that reported by Joshua and Lown.[13]

With the synthesis of the parent antibiotic **5** completed, the synthesis of prothracarcin (**1**) was undertaken using this methodology. Prothracarcin (**1**) has the added feature of a C-2 ethylidene group, which could be incorporated by manipulation of an alkoxy functionality on photoproduct **4**. This translates back to the 2-position of the *N*-pentenyl chain in phthalimide **3** (Scheme I). Potassium phthalimide was alkylated with bromide **26**, prepared from bromohydrin **25**[30] (Scheme VI).

Photoproducts **28**, formed by irradiation of phthalimide **27**, were reduced to the alcohols **29** with sodium borohydride in methanol. Dehydration of alcohols **29** using *p*-toluenesulfonic acid in refluxing toluene afforded the alkene **31** in low yield. Instead the alcohols **29** were converted to the thionocarbonates **30**,[31a] which underwent a pyrolytic syn elimination[31b] to produce alkene **31**. The MEM ether was deprotected[32] with titanium tetrachloride to afford alkene **32**. After ozonolysis[24] of alkene **32**, the C-2 alcohol was protected as the acetate **34** (Scheme VII), and the aldehyde **35**, formed by hydrolysis of the more labile benzylic acetal, was oxidized with ruthenium tetraoxide[26] to the carboxylic acid **36**. Activation of acid **36**, followed by thermal rearrangement and subsequent trapping of the isocyanate as in the model system resulted in the trimethylsilyl carbamate **37**.

Scheme VI



The next task was to elaborate the C-2 functionality into an ethylidene moiety. Reaction of acetate **37** with potassium carbonate in methanol[33] gave the alcohol **38**, which was oxidized[34] to ketone **39**. The Wittig olefination, according to the procedure of Takaya,[3f] gave an inseparable mixture of *E* and *Z* isomers **40**.

Treatment of silyl carbamates **40** with tetrabutylammonium fluoride[28] in acetonitrile produced the aniline–acetals **41**, which cyclized to *E* and *Z* prothracarcin (**1**) upon reaction with trimethylsilyl iodide.[29]

Examination of the proton and carbon NMR revealed that the minor component of the 1:3 mixture of isomers corresponded to natural prothracarcin (**1**).[6]

We turned our attention to the synthesis of DC-81 (**2**), which is unsubstituted at the C-2 position but has a C-7 methoxy, C-8 hydroxy substitution pattern. The retrosynthetic analysis is analogous to that described previously with the dioxygen-functionalized alkene **42** being the key intermediate, which can arise by three pathways (Scheme VIII).

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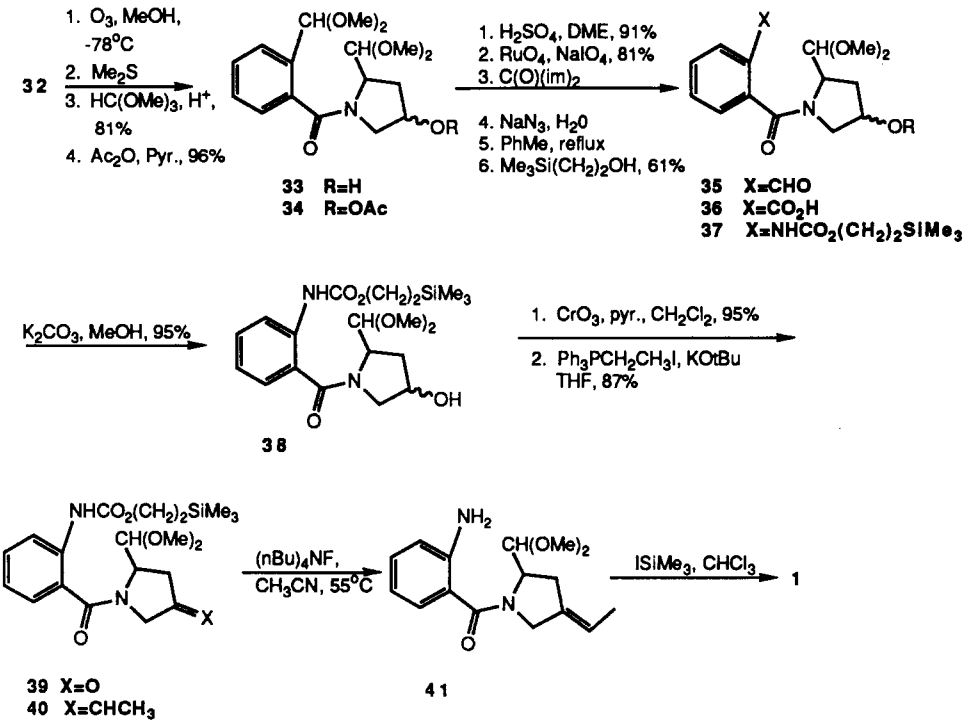
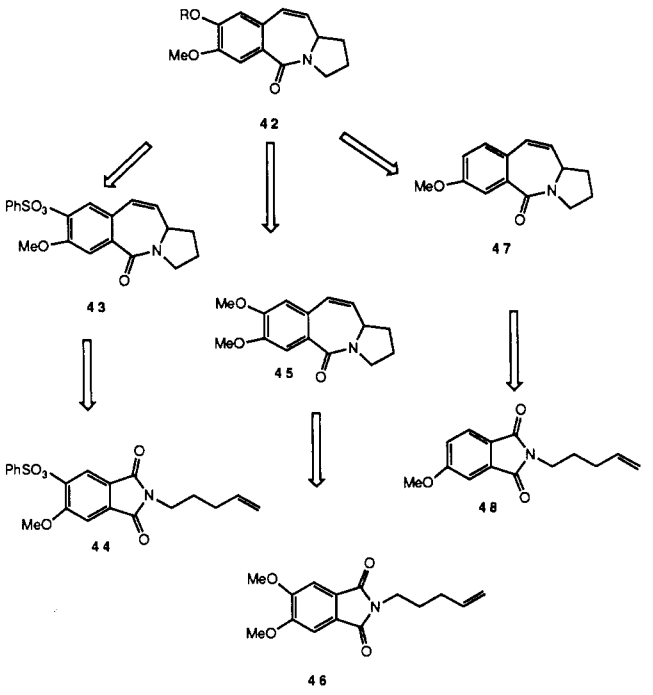
(34) Tam, T. F. Ph.D. Thesis, University of Waterloo, Ontario, Canada, 1978.

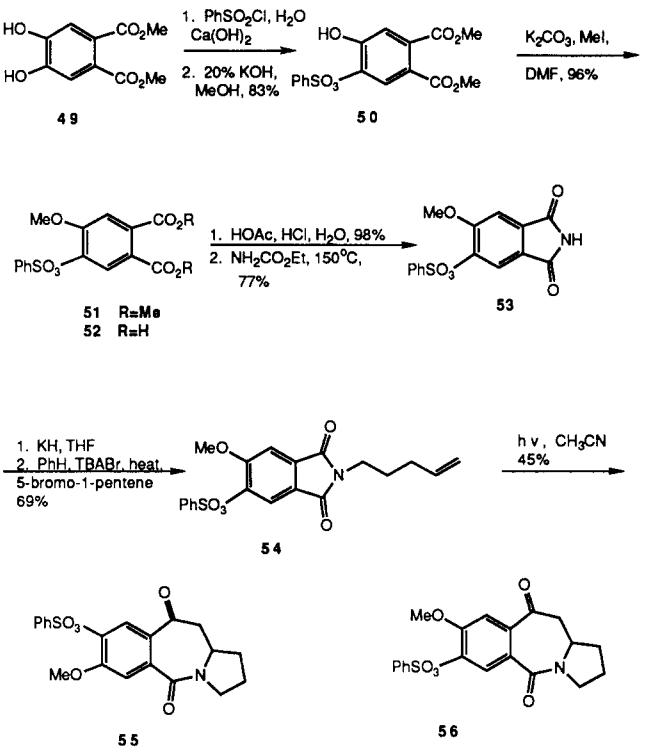
Scheme VII



Scheme VIII



Scheme IX



The most obvious method to establish the aromatic substitution pattern would be the photolysis of unsymmetrical phthalimide **44**, prepared as shown in Scheme IX from bis(phenol) **49**, since both substituents should be directing photoclosure[12c] along bond *b* of **44**. Bis(phenol) **49**[35] was converted to the monoprotected phenol **50** via the bis(benzenesulfonate).[36] Phenol **50** was methylated, and the esters were hydrolyzed to the phthalic acid **52**. Reaction of the diacid with ethyl carbamate[37] produced phthalimide **53**, which was alkylated to afford the *N*-pentenylphthalimide **54**.

Photolysis of phthalimide **54** resulted in the regioisomer ketones **55** and **56** in a 52:48 ratio and 45% combined yield (based on recovered starting material). The regiochemical identities of the photoproducts were deduced by conversion into the known phenolic alkenes **57** and **58** (vide infra) by reduction of the ketone, dehydration of the resulting al-

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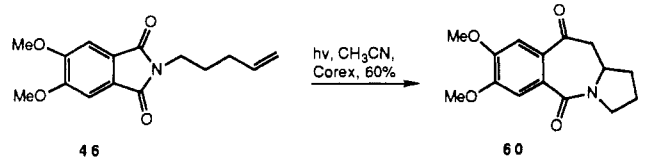
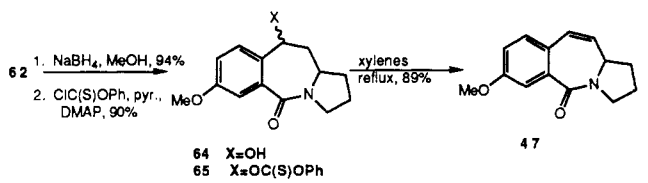
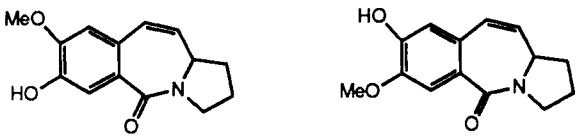
Scheme X



Scheme XI



cohol, and subsequent deprotection of the benzenesulfonate.



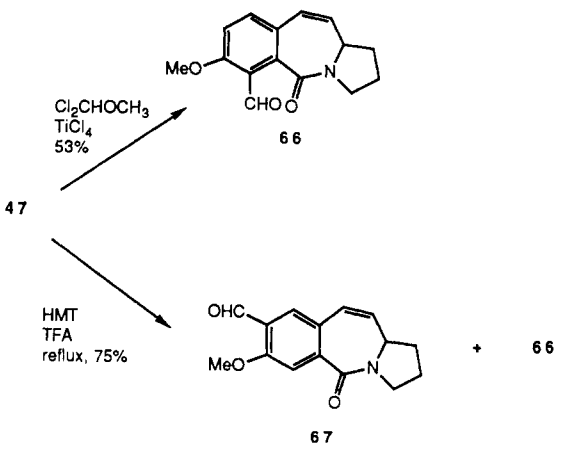
Due to the poor regioselectivity in the photochemical reaction, a second approach was undertaken that utilized the irradiation of symmetrical phthalimide **46**. The C-8 phenol would be introduced by a selective demethylation of the appropriate ether in alkene **45** (Scheme VIII).

The alkylated phthalimide **46**, which was prepared by reaction of 4,5-dimethoxyphthalimide[35] with sodium hydride and bromopentene, was irradiated to produce photoproduct **60** in a 60% yield (based on recovered starting material; Scheme X). Reduction of **60** and acid-catalyzed dehydration of the resulting alcohol **61** led to dimethoxyalkene **45**.

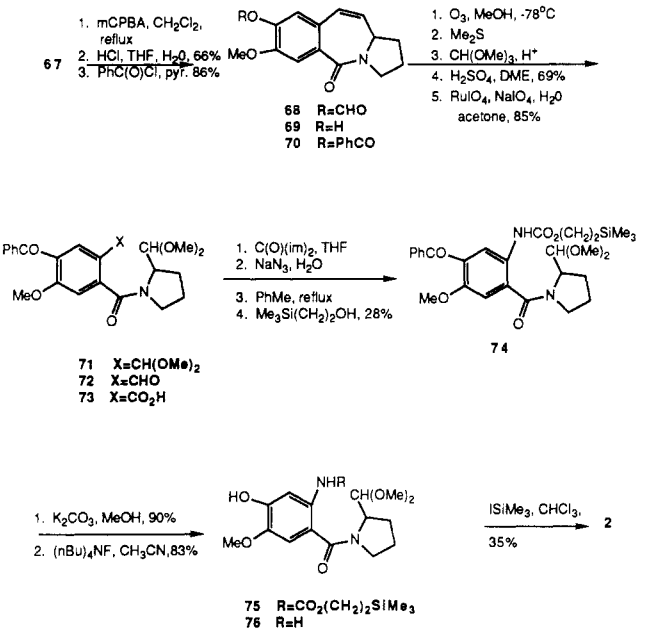
Hansson and Wickberg[38] observed that upon treatment with thiolates the ether ortho or para to the carbonyl of polymethoxylbenzaldehydes was preferentially cleaved. When dimethoxyalkene **45** was reacted with sodium thiopropoxide[39] in DMF at 100 °C, the C-7 ether was exclusively cleaved to form phenol **57** instead of phenol **58**. Attempts to change the selectivity of the reaction were unsuccessful.

Since the two previous approaches which incorporated both aromatic oxygen functionalities prior to the formation of the pyrrolobenzazepinedione skeleton were unsuccessful, the C-8 phenol was introduced after the photochemical

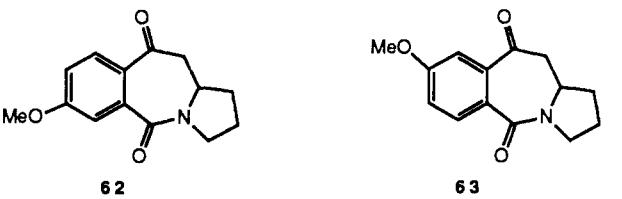
Scheme XII



Scheme XIII



step onto alkene **47** (Scheme VIII). This final route utilized the known regioselectivity of the photochemistry of 4-methoxy-*N*-pentenylphthalimide[12c] **48**, which produces the ketones **62** and **63** in a 4:1 ratio which can be separated by fractional recrystallization from diethyl ether.



The diastereomeric alcohols **64**, obtained by reduction of photoproduct **62**, were converted to the thionocarbonates[31a] **65**, which when heated in refluxing xylenes[31b] yielded alkene **47** (Scheme XI).

At this point in the synthesis, the C-8 phenol was introduced. Various Friedel–Craft acylation conditions led to starting material or decomposition. Formylation with dichloromethyl methyl ether and $TiCl_4$[40] produced benzaldehyde **66**, which arose by reaction at the C-6 position (Scheme XII).

(38) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191.
(39) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719.
(40) Reiche, A.; Gross, H.; Hoft, E. *Org. Synth.* *47*, 1.

Formylation using hexamethylenetetraamine in refluxing trifluoroacetic acid[41] led to two isomers **67** and **66** in a 3:2 ratio and 76% combined yield. Attempts to improve the selectivity met with no success.

Baeyer–Villiger oxidation[42] of aldehyde **67** with mCPBA produced the formate **68**, which was hydrolyzed to phenol **69** (Scheme XIII). Ozonolysis[24] of benzoate ester **70** formed the bis(dimethylacetals) **71**, which yielded benzaldehyde acetal **72** upon treatment with dilute aqueous sulfuric acid.[25]

Carboxylic acid **73**, formed by RuO_4 oxidation[26] of aldehyde **72**, was subjected to the Curtius rearrangement/trapping sequence[27] to produce silyl carbamate **74**. The three remaining steps in the synthesis were deprotections. The benzoate was removed with potassium carbonate in methanol[33] to give phenol **75**, and reaction of silyl carbamate **75** with tetrabutylammonium fluoride in acetonitrile[28] produced amine **76**. Cyclization to the imine form of DC-81 (**2**)[7] occurred upon treatment of amine **76** with trimethylsilyl iodide.[29]

The total syntheses of the pyrrolo[1,4]benzodiazepine antibiotics prothracarcin (**1**) and DC-81 (**2**) have been accomplished using a photochemical ring expansion reaction of *N*-pentenylphthalimides to produce pyrrolobenzazepinediones. Due to the unfortunate failure of the shorter rearrangement routes, these syntheses are less efficient than previous approaches but still demonstrate the usefulness of photochemical reactions to organic synthesis.

Experimental Section

Melting points (uncorrected) were determined on a Mel-temp or a Fischer-Johns apparatus. Elemental analyses for C, H, N, and S were performed by Dr. Franz Kasler at the University of Maryland. Infrared spectra were recored on a Perkin-Elmer 281 spectrophotometer using polystyrene (1601.8 cm^{-1}) as a reference. Ultraviolet–visible spectra were recorded on a Hewlett-Packard Model 8450A spectrophotometer equipped with a Model 7470 plotter or a Perkin-Elmer Lambda 5 UV–vis spectrophotometer. Mass spectra were recorded on a Hitachi RMU-6E low-resolution mass spectrometer or a VG-7070E (EI) positive high-resolution mass spectrometer.

Proton NMR spectra were recorded on a Varian EM-360, IBM WP-200, IBM AF-200, or Bruker AM-400 instrument using either the δ 0.00 signal of tetramethylsilane of the δ 7.24 signal of chloroform as an internal standard. Reported proton data were obtained at 200 MHz unless otherwise noted. Carbon NMR spectra were recorded on an IBM WP-200, IBM AF-200, or Bruker AM-400 spectrometer at 50.32, 50.32, and 100.61 MHz, respectively. The δ 77.00 signal of deuteriochloroform was used as an internal standard.

Photochemical reactions were performed in either an immersion well with a Pyrex (λ = 280 nm) or a Corex (λ = 260 nm) filter or a Pyrex test tube using an Hanovia 450-W medium-pressure mercury lamp.

Flash chromatography refers to the method described by Still[43] using E. Merck silica gel 60 (230–400 mesh) or Florisil (100–200 mesh). Thin-layer chromatography was carried out on E. Merck glass-supported silica gel 60 (0.25 mm, F-254) or Analtech glass-supported silica gel GF (0.25 mm). High-pressure liquid chromatography (HPLC) was performed on a Varian Model 5000 equipped with an ultraviolet–visible detector (λ = 254 nm) and silica gel SI-10 column interfaced to a Hewlett-Packard Model 5350A integrator printer.

Solvent mixtures for chromatography were made up in volume/volume percentages. Ethyl acetate, hexanes, ether, and Skellysolve F were distilled prior to chromatographic use. Tetrahydrofuran (THF) was distilled from calcium hydride and then sodium/benzophenone. Trimethyl orthoformate was distilled from anhydrous potassium carbonate. Dichloromethane, benzene, acetonitrile, and toluene were dried by distillation from phosphorus pentoxide or calcium hydride. Pyridine, dimethylformamide (DMF), and triethylamine were dried by distillation from barium oxide.

4,5-Dihydro-3*H*-1-hydroxy-1-benzazepin-2-one (10). A solution of the lactam **8**[14] (6.0 g, 0.037 mol) and bis(trimethylsilyl)acetamide (BSA, 7.66 g, 0.038 mmol) in anhydrous acetonitrile (36 mL) was heated at reflux for 1 h under N_2. The volatiles were removed in vacuo, and the residue was taken up in anhydrous CH_2Cl_2 (40 mL).

Oxodiperoxymolybdenum/pyridine/hexamethylphosphoramide (MoOPH; 10.7 g, 0.025 mol) dissolved in anhydrous CH_2Cl_2 (120 mL) was added over 5 min to the silylated lactam via an addition funnel. The reaction mixture was stirred under N_2 at room temperature for 6 days and evaporated in vacuo, and the residue taken up in aqueous EDTA solution (50 mL, 0.1 N, buffered at pH 8.0). The aqueous solution was extracted continuously with CH_2Cl_2 (500 mL) for 24 h. The organic phase was evaporated in vacuo to give a brown residue which was stirred with ether (40 mL) to induce crystallization. The *N*-hydroxylactam **10** was isolated as an ochre-colored solid which gave a positive ferric chloride test (5.90 g, 90% yield); ^1H NMR ($CDCl_3$) δ 9.00 (br s, 1 H), 7.68 (dd, J = 7.6, 1.2 Hz, 1 H), 7.21–7.47 (m, 3 H), 2.81 (t, J = 7.0 Hz, 2 H), 2.20–2.61 (m, 4 H); IR (neat) 3600–3000, 2930, 1658, 1460, 1225 cm^{-1}.

1-Chloro-4,5-dihydro-3*H*-1-benzazepin-2-one (11). *tert*-Butyl hypochlorite (0.11 g, 0.12 mL; 1.00 mmol) was added to a solution of the lactam **8**[14] in absolute methanol (10 mL) at 0 °C. The reaction flask was protected from light (by wrapping it in aluminum foil) and kept at 0 °C for 17 h. The pale yellow solution was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were washed with water (20 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give the *N*-chlorolactam **11** as a cream-colored solid (0.169 g, 86% yield). Analytically pure white crystals (mp 45–46 °C) were obtained by recrystallization from ether/petroleum ether; ^1H NMR (60 MHz, $CDCl_3$) δ 7.12–7.71 (m, 4 H), 1.92–3.06 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 142.8, 135.0, 129.0, 128.0, 127.7, 124.6, 32.7, 29.7, 27.8; IR ($CHCl_3$) 2960, 1690, 1485, 759 cm^{-1}. Anal. Calcd for $C_{10}H_{10}NOCl$: C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.21; H, 5.06; N, 7.22; Cl, 18.25.

4,5-Dihydro-3*H*-7-ethoxy-1-benzazepin-2-one (14). A mixture of the *N*-chlorolactam **11** (0.169 g, 0.86 mmol), silver(I) nitrate (0.146 g, 0.86 mmol), and absolute ethanol (10 mL) was heated at reflux for 20 h. More silver(I) nitrate (0.300 g, 1.77 mmol) was added, and the mixture heated at reflux for 6 h, cooled to 0 °C, filtered through a pad of Celite, and evaporated to a brown solid which was purified by flash chromatography (80% ether/petroleum ether) to give product **14** as yellow needlelike crystals (0.049 g, 28% yield). Analytically pure cream-colored crystals (mp 128–129 °C) were obtained by recrystallization from ether/petroleum ether; ^1H NMR ($CDCl_3$) δ 8.46 (br s, 1 H), 6.91–6.96 (m, 1 H), 6.71–6.76 (m, 2 H), 4.02 (q, J = 6.9 Hz, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 2.17–2.38 (m, 4 H), 1.41 (t, J = 6.9 Hz, 3 H); IR ($CHCl_3$) 3400, 3190, 2950, 1660, 1500, 1245 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.11; N, 7.11.

10-(*tert*-Butyldimethylsiloxy)-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (15b). *N*-Butyllithium solution in hexanes (13.2 mL, 1.55 M, 2.05 mmol) was added over 2 min to a solution of anhydrous diisopropylamine (2.12 g, 2.10 mmol) in anhydrous THF (40 mL) at −77 °C under nitrogen. After 1 h, the ketone **4a**[22] (2.15 g, 10.00 mmol) in anhydrous THF (40 mL) was added to the LDA solution at −77 °C over 10 min. The reaction mixture was warmed to 0 °C, stirred for 40 min, and then cooled to −77 °C. A solution of *tert*-butyldimethylsilyl chloride (2.26 g, 15.00 mmol) in anhydrous THF (40 mL) was added over 5 min. The mixture was allowed to warm to room temperature and stir for 21 h. Water (150 mL) was added, and the mixture extracted with EtOAc (4 × 150 mL), dried (Na_2SO_4), filtered, and evaporated to give 4.03 g of crude product. Purification by florisil chromatography (ether/petroleum ether) gave the pure enol ether **15b** as a colorless liquid (1.59 g, 65% yield): ^1H NMR ($CDCl_3$)

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(42) Godrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.
(43) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

δ 7.93–7.98 (m, 1 H), 7.61–7.66 (m, 1 H), 7.24–7.48 (m, 2 H), 5.19 (d, J = 5.3 Hz, 1 H), 3.96 (ddd, J = 7.6, 5.3, 3.0 Hz, 1 H), 3.75–3.84 (m, 1 H), 3.48–3.61 (m, 1 H), 1.82–2.24 (m, 4 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 151.9, 135.0, 129.8, 129.7, 128.1, 126.0, 114.3, 52.5, 46.4, 32.8, 25.5, 24.1, 18.0; IR (neat) 2963, 2875, 1630, 1455, 840 cm^{-1}.

1,2,3,10,11,11a-Hexahydro-10-hydroxypyrrolo[1,2-*b*][2]benzazepin-5-one (18). Sodium borohydride (0.20 g, 5.3 mmol) was added in small portions over 5 min to a solution of the ketone **4a**[22] (0.22 g, 1.0 mmol) in absolute MeOH (6 mL) at 0 °C. After stirring for 20 min, the reaction was poured into aqueous HCl (15 mL, 1.0 N), extracted with CH_2Cl_2 (5 × 20 mL), dried (Na_2SO_4), filtered, and evaporated to give a mixture of the diastereomeric alcohols as a white solid (0.20 g, 92% yield). Recrystallization (EtOAc/petroleum ether) afforded analytically pure **18** (mp 139.5–141 °C, lit.[22b] mp 151–153 °C); ^{1}H NMR ($CDCl_3$) δ 7.28–7.70 (m, 4 H), 4.30–4.46 (m, 1 H), 3.38–3.69 (m, 3 H), 2.41–2.88 (br s, 1 H, exchanges with D_2O), 1.62–2.37 (m, 6 H); IR ($CHCl_3$) 3340 (br), 3010, 2890, 1618, 1425, 1070 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.99; H, 7.03; N, 6.46.

1,2,3,11a-Tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (15c). The alcohols **18** (0.996 g, 4.6 mmol) were heated at reflux in toluene (150 mL) with *p*-TsOH (0.60 g, 3.0 mmol) for 15 h by using a Dean–Stark apparatus. The brown solution was evaporated, and the residue taken up in CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with H_2O (50 mL), dried (Na_2SO_4), filtered, and evaporated to a light brown liquid (0.92 g). Purification by Kugelrohr distillation (166–185 °C/0.6 mmHg) afforded olefin **15c** as white crystals (mp 44–45 °C): ^{1}H NMR ($CDCl_3$) δ 8.07 (dd, J = 7.4, 2.0 Hz, 1 H), 7.32–7.50 (m, 2 H), 7.17–7.40 (m, 1 H), 6.70 (dd, J = 10.0, 2.0 Hz, 1 H), 5.98 (dd, J = 10.0, 4.8 Hz, 1 H), 3.74–4.06 (m, 2 H), 3.47–3.69 (m, 1 H), 1.90–2.37 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 135.7, 135.1, 134.7, 132.3, 130.4, 129.7, 128.5, 127.1, 52.9, 46.8, 32.2, 23.6; IR ($CHCl_3$) 3020, 1618, 1602, 1458, 1428 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.49; H, 6.57; N, 6.93.

1-(2′-(Dimethoxymethyl)benzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (19). A solution of the olefin **15c** (3.30 g, 16.5 mmol) in absolute MeOH (100 mL) at −77 °C was subjected to ozone through a fritted glass bubbler until a blue color persisted (15 min). Oxygen was then passed through the solution until the blue color disappeared (15 min). Dimethyl sulfide (2.0 mL, 1.7 g, 27.0 mmol) was added, followed by trimethyl orthoformate (19.7 mL, 19.1 g, 180.0 mmol) and saturated methanolic HCl (3.0 mL). The mixture was stirred under N_2, allowed to warm slowly to room temperature over 2.5 h, and then stirred at room temperature overnight. The reddish solution was poured into saturated $NaHCO_3$ (700 mL) and extracted with ether (3 × 300 mL). The combined ethereal layers were washed with H_2O (300 mL), dried (Na_2SO_4), filtered, and evaporated to give the bis(acetals) **19** as a reddish liquid (4.6 g, 86% yield) which was usually used directly in the next reaction; ^{1}H NMR ($CDCl_3$) δ 7.55–7.68 (m, 1 H), 7.13–7.45 (m, 3 H), 5.62 (s, 1 H), 4.92 (d, J = 2.6 Hz, 1 H), 4.42 (ddd, J = 8.5, 6.0, 2.6 Hz, 1 H), 3.57 (s, 3 H), 3.54 (s, 3 H), 3.14–3.48 (m, 8 H containing two 3 H singlets at δ 3.45 and 3.29), 1.53–2.28 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 137.0, 135.1, 128.4, 128.1, 126.5, 125.9, 104.8, 101.4, 58.3, 57.2, 55.9, 54.2, 53.2, 49.6, 24.6, 23.9; IR (neat) 2930, 1630, 1415, 1068 cm^{-1}.

1-(2′-Formylbenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (20). Aqueous sulfuric acid (420 mL, 0.044 N) was added over 5 min to a solution of the bis(acetal) **19** (4.19 g, 0.013 mol) in DME (420 mL) at 0 °C. The solution was allowed to warm to room temperature over 220 min. The solution was poured into saturated $NaHCO_3$ (700 mL) and extracted with CH_2Cl_2 (3 × 400 mL). The combined organic phases were washed with H_2O (500 mL), dried (Na_2SO_4), filtered, and evaporated to a light brown oil (3.42 g, 94% crude yield). Aldehyde **20** was usually used directly in the next reaction but could be purified to a pale yellow oil by florisil chromatography eluted with ether/petroleum ether; ^{1}H NMR ($CDCl_3$) δ 10.09 (s, 1 H), 7.93 (dd, J = 7.6, 1.3 Hz, 1 H), 7.45–7.70 (m, 2 H), 7.37 (dd, J = 6.7, 1.3 Hz, 1 H), 4.95 (d, J = 2.7 Hz, 1 H), 4.45 (ddd, J = 8.1, 5.1, 2.7 Hz, 1 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.00–3.21 (m, 2 H), 1.54–2.29 (m, 4 H); IR (neat) 3070, 2945, 1700, 1630, 1598, 1200, 1070 cm^{-1}; MS, m/z 277 (M^+), 202, 133 (base), 75.

1-(2′-Carboxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (21). Sodium periodate (5.6 g, 26.3 mmol) was added to a suspension of ruthenium(II) oxide hydrate (0.050 g, 0.37 mmol) in water (150 mL) and acetone (75 mL). After being stirred for 1 min, the black mixture changed to an olive-green solution. The aldehyde **20** (1.10 g, 3.97 mmol) in acetone was added all at once and stirred vigorously for 1 h. 2-Propanol (20 mL) was added to quench the excess oxidizing agent, and the resulting grey mixture stirred for 20 min before being filtered through a pad of Celite. The acetone was removed to give carboxylic acid **21** as a pale yellow liquid (1.06 g, 90% yield): ^{1}H NMR ($CDCl_3$) δ 7.85–8.25 (m, 2 H, 1 H exchanges with D_2O), 7.23–7.70 (m, 3 H), 4.93 (d, J = 2.7 Hz, 1 H), 4.36–4.49 (m, 1 H), 3.56 (s, 3 H), 3.54 (s, 3 H), 3.01–3.55 (m, 2 H), 1.60–2.44 (m, 4 H); IR (neat) 3440 (br), 3070, 2950, 1720 cm^{-1}. The acid was further characterized as the methyl ester prepared with diazomethane; ^{1}H NMR ($CDCl_3$) δ 7.95–8.05 (m, 1 H), 7.35–7.67 (m, 2 H), 7.22–7.35 (m, 1 H), 4.95 (d, J = 2.6 Hz, 1 H), 4.44 (ddd, J = 7.6, 4.7, 2.6 Hz, 1 H), 3.89 (s, 3 H), 3.58 (s, 3 H), 3.55 (s, 3 H), 3.14 (t, J = 7.3 Hz, 2 H), 1.16–2.36 (m, 4 H); IR (neat) 3080, 2960, 1725, 1635, 1420, 1280, 1080 cm^{-1}.

1-(2′-(Azidocarbonyl)benzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (22). A solution of the carboxylic acid **21** (0.235 g, 0.80 mmol), carbonyldiimidazole (0.141 g, 0.87 mmol) in anhydrous THF (4 mL) was stirred at room temperature for 1 h. Aqueous sodium azide (1.0 mL, 5 M) was added, and the mixture stirred vigorously for 2 h, poured into H_2O (30 mL), and extracted with ether (2 × 30 mL). The combined organic phases were washed with H_2O (30 mL), dried (Na_2SO_4), filtered, and evaporated to give the crude acyl azide **22** as a light brown liquid (0.22 g, 87% yield): ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.14–7.03 (m, 4 H), 4.92 (d, J = 3.0 Hz, 1 H), 4.14–4.64 (m, 1 H), 2.86–3.74 (m, 8 H), 1.52–2.48 (m, 4 H); IR (neat) 3080, 2960, 2182, 2147, 1700, 1637, 1242, 790 cm^{-1}.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)benzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (23). A solution of the acyl azide **22** in anhydrous toluene (20 mL) was heated at reflux for 20 min. The toluene solution was cooled to 60 °C, then 2-(trimethylsilyl)ethanol (0.19 g, 1.6 mmol) was added, and the mixture was stirred for 2 h. The volatiles were removed to give the crude carbamate which was purified by chromatography (50% ether/pet ether) to afford **23** as a colorless liquid (0.183 g, 50% yield from carboxylic acid **21**): ^{1}H NMR ($CDCl_3$) δ 8.64 (br s, 1 H), 8.14 (d, J = 8.1 Hz, 1 H), 7.18–7.43 (m, 2 H), 7.00 (td, J = 7.5, 1.0 Hz, 1 H), 4.81 (br s, 1 H), 4.33–4.54 (m, 1 H), 4.13–4.27 (m, 2 H), 2.70–3.90 (m, 8 H), 1.54–2.26 (m, 4 H), 0.93–1.08 (m, 2 H), 0.02 (s, 9 H); IR (neat) 3340 (br), 3080, 2960, 1727, 1625, 1593, 1523, 1412, 1217 cm^{-1}.

1-(2′-Aminobenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (24). A solution of the carbamate **23** (0.213 g, 0.54 mmol) in anhydrous acetonitrile (10 mL) and $(n\text{-}Bu)_4NF$ solution (1.0 mL, 1 M in THF) was stirred at 50–60 °C for 30 min. The volatiles were removed, and the crude amine was purified by flash chromatography (florisil, ether). The amine **24** was isolated as a colorless liquid (0.0856 g, 60% yield): ^{1}H NMR ($CDCl_3$) δ 7.09–7.25 (m, 2 H), 6.62–6.77 (m, 2 H), 4.15–5.10 (m, 4 H, 2 H exchanges with D_2O), 3.31–3.68 (m, 8 H), 1.81–2.30 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 145.8, 130.6, 127.9, 120.4, 116.7, 116.3, 104.4, 58.6, 57.5, 56.0, 50.1, 24.8, 23.8; IR (neat) 3470, 3370, 3072, 2952, 1620, 1495, 1075 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2O_3$ 264.1474, found 264.1467.

1,2,3,11a-Tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (5). A solution of amine acetal **24** (0.0310 g, 0.12 mmol) in $CHCl_3$ (2 mL) was added to a solution of iodotrimethylsilane (0.030 g, 0.021 mL, 0.14 mmol) in $CHCl_3$ (1 mL) at −60 °C. The mixture was allowed to warm to room temperature over 30 min and stir for 10 min. A saturated aqueous $NaHCO_3$ solution (2 mL) and aqueous $Na_2S_2O_5$ solution (1 mL, 10% w/v) were added, and the mixture was stirred vigorously until it decolorized. Water (10 mL) was added, and the mixture extracted with $CHCl_3$ (3 × 10 mL), dried (Na_2SO_4), filtered, and evaporated to a pale yellow liquid. The imine form of **5** exhibited physical properties identical with those reported by Joshua and Lown.[13] ^{1}H NMR ($CDCl_3$) δ 7.20–8.10 (m, 5 H), 3.40–4.00 (m, 3 H),

1.90–2.50 (m, 4 H); IR ($CHCl_3$) 3010, 1630 cm^{-1}.

5-Bromo-4-[(2-methoxyethoxy)methoxy]-1-pentene (26). A mixture of diisopropylamine (9.70 g, 0.075 mol) and (2-methoxyethoxy)methyl chloride (9.35 g, 0.075 mol) in anhydrous CH_2Cl_2 (50 mL) was stirred at 0 °C for 1 h under N_2. A solution of the bromohydrin **25**[30] in CH_2Cl_2 (50 mL) was added, and the mixture allowed to warm to room temperature and stir for 18 h. The amber-colored mixture was poured into H_2O (700 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were washed with H_2O (400 mL), dried (Na_2SO_4), and evaporated. The residue was vacuum distilled to afford the product **26** as a colorless liquid (bp 105–115 °C/2.25 mmHg; 11.5 g, 91% yield): ^1H NMR ($CDCl_3$) δ 5.60–5.95 (m, 1 H), 5.03–5.25 (m, 2 H), 4.81 (s, 2 H), 3.42–3.94 (m, 7 H), 3.40 (s, 3 H), 2.35–2.54 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 133.4, 118.2, 94.8, 76.1, 71.8, 67.3, 58.9, 37.6, 35.1; IR (neat) 3095, 2900, 1648, 1040 cm^{-1}; HRMS calcd for $C_9H_{17}O_3{}^{79}Br$ 252.0361, found 252.0373.

1-[2-[(2-Methoxyethoxy)methoxy]-4-pentenyl]phthalimide (27). A mixture of the bromide **26** (47.34 g, 0.187 mol), potassium phthalimide (36.31 g, 0.194 mol), potassium iodide (0.242 g, 1.45 mmol), and anhydrous DMF (120 mL) was heated at reflux for 1 h, cooled to room temperature, poured into water (800 mL), and extracted with $CHCl_3$ (3 × 400 mL). The combined organic phases were washed with KOH solution (1.0 N, 2 × 400 mL) and H_2O (800 mL) and evaporated to approximately 200 mL. The residue was taken up in ether (700 mL), washed with H_2O (4 × 500 mL), dried (Na_2SO_4), filtered, and evaporated to a light brown oil. Distillation (bp 180–190 °C/0.010 mmHg) afforded **27** as a light yellow oil (50.02 g, 84% yield): ^1H NMR ($CDCl_3$) δ 7.80–7.91 (m, 2 H), 7.67–7.78 (m, 2 H), 6.88 (ddt, J = 16.7, 10.0, 6.7 Hz, 1 H), 5.05–5.23 (m, 2 H), 4.74 (d, J = 6.7 Hz), 4.71 (d, J = 6.7 Hz), 3.98–4.14 (m, 1 H), 3.29–3.91 (m, 6 H), 3.28 (s, 3 H), 2.28–2.44 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.1, 133.8, 133.5, 132.0, 123.1, 117.7, 94.4, 74.2, 71.4, 67.0, 58.7, 41.1, 37.4; IR (neat) 3080, 2940, 2900, 1775, 1715, 1395, 1040 cm^{-1}; UV (CH_3CN) 228 ($\epsilon = 4.95 \times 10^4$), 241 ($\epsilon = 1.60 \times 10^4$), 256 ($\epsilon = 1.0 \times 10^4$), 292 nm ($\epsilon = 6.5 \times 10^3$). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.63; N, 4.39. Found: C, 63.70; H, 6.85; N, 4.60.

2,3,11,11a-Tetrahydro-2-[(2-methoxyethoxy)methoxy]-pyrrolo[1,2-*b*][2]benzazepine-5,10(1*H*)-dione (28). A solution of the phthalimide **27** (1.0 g, 3.1 mmol) in reagent grade acetonitrile (1600 mL) was irradiated for 385 min in an immersion well with a Pyrex filter. The acetonitrile was removed, and the yellow residue purified by chromatography (eluted with ether). Some starting material was obtained (0.31 g, 31% yield). The photoproducts **28** were obtained as a pale yellow liquid in a 1.3:1.0 ratio (0.50 g, 50% yield): ^1H NMR ($CDCl_3$) δ 7.91–8.05 (m, 1 H), 7.51–7.80 (m, 3 H), 4.80 and 4.76 (2 s, 2 H), 4.27–4.53 (m, 2 H), 3.94–4.17 (m, 1 H), 3.52–3.86 (m, 6 H), 3.40 and 3.39 (2 s, 3 H), 2.98 (d, J = 7.3 Hz), 2.86 (dd, J = 18.8, 2.1 Hz), 2.31–2.52 (m, 1 H), 1.85–2.18 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 201.2, 200.0, 166.7, 166.3, 136.2, 135.7, 133.9, 132.7, 132.4, 131.3, 130.6, 130.1, 128.4, 94.3, 74.3, 73.5, 71.6, 67.3, 67.2, 58.9, 52.9, 52.1, 51.9, 51.5, 51.3, 38.6, 37.3; IR (neat) 3075, 2940, 2900, 1685, 1640, 1425, 1041 cm^{-1}; MS, m/z 319 (M^+), 244, 230, 213, 146, 82, 59 (base).

1,2,3,10,11,11a-Hexahydro-10-hydroxy-2-[(2-methoxyethoxy)methoxy]pyrrolo[1,2-*b*][2]benzazepin-5-one (29). Ketone **28** was reduced in a manner analogous to that for **4a** to give the four diastereomeric alcohols **29** as a thick pale yellow oil (93% yield). White crystals of the diastereomeric mixture (mp 101–102 °C) were obtained by flash chromatography (5% MeOH/$CHCl_3$) of the crude product; ^1H NMR ($CDCl_3$) δ 7.25–7.73 (m, 4 H), 4.77 (s, 2 H), 4.24–4.57 (m, 2 H), 3.44–3.85 (m, 8 H), 3.41 (s, 3 H), 2.75 (dt, J = 7.70, 12.0 Hz, 1 H), 1.70–2.29 (m, 3 H); IR ($CHCl_3$) 3370 (br), 3020, 1622, 1607, 1420, 1045 cm^{-1}; MS, m/z 321 (M^+), 245, 232, 215, 82 (base).

1,2,3,10,11,11a-Hexahydro-2-[(2-methoxyethoxy)methoxy]-10-(((phenyloxy)thiocarbonyl)oxy)pyrrolo[1,2-*b*][2]-benzazepin-5-one (30). A solution of phenyl chlorothionocarbonate[31a] (0.60 g, 0.35 mmol) in anhydrous CH_2Cl_2 (3 mL) was added to a solution of the alcohols **29** (0.100 g, 0.324 mmol), anhydrous pyridine (0.055 g, 0.69 mmol), and DMAP (5.0 mg) in anhydrous CH_2Cl_2 (4 mL). The yellow solution was stirred for 16 h. More phenyl chlorothionocarbonate (0.060 g, 0.35 mmol) was added, and the reaction mixture stirred for an additional 24 h, poured into H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with HCl (30 mL, 0.1 N), H_2O (30 mL), dried (Na_2SO_4), filtered, and evaporated to a dark yellow liquid. The four diastereomeric thionocarbonates **30** were purified by flash chromatography (25% ether/petroleum ether) to give the two less polar diastereomers (0.051 g, 34% yield): ^1H NMR ($CDCl_3$) δ 7.74–7.84 (m, 1 H), 7.20–7.58 (m, 6 H), 6.98–7.15 (m, 2 H), 6.37–6.58 (m, 1 H), 4.76 (s, 2 H), 4.37–4.53 (m, 1 H), 3.50–4.07 (m, 8 H), 3.40 (s, 3 H), 1.92–2.84 (m, 4 H). The two more polar diastereomers were isolated as a pale yellow liquid (0.083 g, 56% yield): ^1H NMR ($CDCl_3$) δ 7.73–7.88 (m, 1 H), 6.95–7.60 (m, 8 H), 6.37–6.62 (m, 1 H), 4.73–4.91 (m, 2 H), 4.39–4.56 (m, 1 H), 3.48–4.07 (m, 8 H), 3.40 and 3.38 (2 s, 3 H), 2.94–3.33 (m, 1 H), 1.93–2.52 (m, 3 H); IR (neat) 3080, 2940, 2897, 1643, 1407, 1207, 770 cm^{-1}. HRMS calcd for $C_{24}H_{25}NO_6S$: 457.1361. Found: 457.1321.

1,2,3,11a-Tetrahydro-2-[(2-methoxyethoxy)methoxy]-pyrrolo[1,2-*b*][2]benzazepin-5-one (31). A solution of the thionocarbonates **30** (0.086 g, 0.19 mmol) in xylenes (25 mL) was heated at reflux for 1 h. The xylenes were removed, and the crude residue was purified by flash chromatography (EtOAc) to give the diastereomeric olefins **31** as a colorless liquid (0.047 g, 82% yield): ^1H NMR ($CDCl_3$) δ 8.06 (dd, J = 7.4, 1.5 Hz, 1 H), 7.31–7.53 (m, 2 H), 7.16–7.31 (m, 1 H), 6.59–6.78 (m, 1 H), 6.18 (dd, J = 10.0, 4.9 Hz), 5.96 (dd, J = 10.0, 4.6 Hz), 4.81 and 4.73 (2 s, 3 H), 4.36–4.56 (m, 1 H), 3.81–4.24 (m, 3 H), 3.49–3.81 (m, 4 H), 3.40 (s, 3 H), 2.14–2.53 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 166.2, 136.9, 134.9, 134.8, 134.5, 132.9, 131.3, 130.9, 130.6, 130.1, 128.8, 128.7, 127.5, 127.3, 94.1, 93.9, 74.2, 73.5, 71.5, 67.0, 53.3, 52.9, 52.3, 52.2, 51.6, 38.6, 37.6; IR (neat) 3070, 2930, 2880, 1620, 1605, 1458, 1420, 1042 cm^{-1}; MS, m/z 303 (M^+), 271, 228, 214, 197 (base).

2-Hydroxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (32). A solution of titanium tetrachloride (3.20 mL, 29.0 mmol) in anhydrous CH_2Cl_2 and petroleum ether (30 mL) was added over a period of 10 min to a solution of the MEM-protected alcohols **31** (2.94 g, 9.7 mmol) in anhydrous CH_2Cl_2 (100 mL) and petroleum ether (50 mL) at 0 °C under N_2. After this stirred for 1 h at 0 °C, more titanium tetrachloride (3.20 mL, 29.0 mmol) was added. After 1.5 h at 0 °C, the reaction was quenched by the careful addition of concentrated ammonium hydroxide (60 mL). After stirring for 15 min, the mixture was filtered through Celite. The filtrate was poured into H_2O (1 L) and extracted with CH_2Cl_2 (3 × 400 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to a brown residue. Flash chromatography (5% MeOH/$CHCl_3$) afforded a mixture of diastereomeric alcohols **32** as white needles (mp 169.5–170.5 °C; 1.67 g, 80% yield): ^1H NMR ($CDCl_3$) δ 7.90–8.06 (m, 1 H), 7.27–7.48 (m, 2 H), 7.12–7.24 (m, 1 H), 6.68 (dd, J = 10.0, 2.0 Hz), 6.61 (dd, J = 9.9, 2.0 Hz), 6.25 (dd, J = 9.9, 4.9 Hz), 5.95 (dd, J = 10.0, 4.6 Hz), 4.44–4.64 (m, 1 H), 4.21 (tdd, J = 7.6, 4.6, 2.0 Hz), 4.05 (tdd, J = 6.9, 4.9, 2.0 Hz), 3.61–4.01 (m, 2 H), 3.53 (br s, 1 H, exchanges with D_2O), 2.04–2.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.0, 166.6, 137.6, 135.2, 135.1, 134.9, 134.4, 133.0, 131.2, 131.0, 130.7, 130.4, 129.0, 128.9, 127.6, 127.4, 69.8, 68.8, 56.2, 55.1, 52.7, 51.8, 40.8, 39.8; IR ($CHCl_3$) 3380 (br) 3015, 2960, 1618, 1595, 1458, 1428 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.50. Found: C, 72.39; H, 6.02; N, 6.39.

1-(2′-(Dimethoxymethyl)benzoyl)-4-hydroxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (33). Olefins **32** were ozonized in a manner analogous to that for **15c** to give the diastereomeric bis(acetals) **33** as a pale yellow liquid (81% yield): ^1H NMR ($CDCl_3$) δ 7.14–7.69 (m, 4 H), 5.59–5.67 (2 s, 1 H), 5.05 and 4.95 (2 d, J = 2.3 and 2.7 Hz, respectively, 1 H), 4.45–4.70 (m, 1 H), 4.10–4.45 (m, 1 H), 2.85–4.00 (m, 15 H), 1.92–2.48 (m, 2 H); IR (neat) 3430 (br), 3065, 2940, 1625, 1430 cm^{-1}.

1-(2′-(Dimethoxymethyl)benzoyl)-4-acetoxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (34). A solution of the alcohols **33** (0.250 g, 0.74 mmol) in acetic anhydride (3 mL) and anhydrous pyridine (3 mL) were stirred at room temperature under nitrogen for 14 h. The volatiles were removed in vacuo, and the light brown residue was purified by flash chromatography (florisil, 50% EtOAc/hexanes) to give the acetate **34** as a colorless oil (0.261 g, 96% yield): ^1H NMR ($CDCl_3$) δ 7.57–7.68 (m, 1 H), 7.25–7.50 (m, 2 H), 7.13–7.24 (m, 1 H), 5.64 (s, 1 H), 4.90–5.24 (m, 1 H), 4.95 and 4.86 (2 d, J = 2.7 and 3.6 Hz, respectively, 1 H), 4.46–4.65 (m, 1 H), 3.11–3.64 (m, 14 H), 1.96–2.59 (m, 2 H), 2.01 and 2.00 (2 s, 3 H); IR (neat) 2950, 1743, 1640, 1420, 1245,

1070 cm^{-1}; MS, m/z 350 (M − 31), 306, 231, 179.

1-(2′-Formylbenzoyl)-4-acetoxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (35). Bis(dimethyl)acetals **34** were hydrolyzed in a manner analogous to that for **19** to give the monoaldehydes **35** as a pale yellow liquid (91% yield): ^1H NMR ($CDCl_3$) δ 10.10 and 10.09 (2 s, 1 H), 7.88–7.99 (m, 1 H), 7.50–7.73 (m, 2 H), 7.32–7.43 (m, 1 H), 5.36–5.50 and 5.12–5.23 (2 m, 1 H), 4.98–4.93 (2 d, J = 2.0 and 3.6 Hz, respectively, 1 H), 3.52–3.62 (m, 6 H), 3.02–3.25 (m, 2 H), 2.05–2.60 (m, 2 H), 2.01 and 2.00 (2 s, 3 H); IR (neat) 2950, 1742, 1701, 1638, 1425, 1248, 1070 cm^{-1}.

1-(2′-Carboxybenzoyl)-4-acetoxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (36). Aldehyde **35** was oxidized in a manner analogous to that for **20** to give the carboxylic acid **36** as a tan liquid (81% yield): ^1H NMR (60 MHz, $CDCl_3$) δ 7.76–8.11 (m, 1 H), 6.81–7.76 (m, 4 H, 1 H exchanges with D_2O), 4.11–5.41 (m, 3 H), 2.74–4.00 (m, 8 H), 1.81–2.60 (m, 5 H); IR (neat) 3470 (br), 2940, 1740, 1620, 1250, 790 cm^{-1}. The acid **36** was further characterized as the methyl ester: ^1H NMR ($CDCl_3$) δ 7.92–8.08 (m, 1 H), 7.20–7.68 (m, 3 H), 4.87–5.52 (m, 3 H), 4.49–4.69 (m, 1 H), 3.89 and 3.88 (2 s, 3 H), 2.99–3.70 (m, 8 H, containing singlets at δ 3.60, 3.55, and 3.53), 1.95–2.63 (m 5 H, containing singlets at v 2.02 and 2.00); IR (neat) 3020, 1730, 1630, 1432, 1250 cm^{-1}; HRMS (CI) calcd. for $C_{18}H_{23}NO_7$ 366.1552 $(M + 1)^+$, found 366.1521.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-benzoyl)-4-acetoxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (37). A solution of carboxylic acids **36** (1.55 g, 4.4 mmol) and carbonyl diimidazole (0.79 g, 4.8 mmol) in anhydrous THF was stirred under N_2 for 105 min at room temperature. Aqueous sodium azide (7.2 mL, 5 M) was added, and the mixture stirred vigorously for 2 h, poured into water (150 mL), and extracted with $CHCl_3$ (3 × 150 mL). The combined organic phases were washed with water (2 × 140 mL), dried (Na_2SO_4), filtered, and evaporated to give the acyl azide which was used directly in the next reaction; crude ^1H NMR (60 MHz, $CDCl_3$) δ 6.73–8.23 (m, 4 H), 2.69–5.48 (m, 11 H, containing two 3 H singlets at δ 3.48 and 3.45), 1.61–2.69 (m, 5 H, containing 3 H singlet at δ 1.95); IR (neat) 3080, 2945, 2140, 1745, 1700, 1645, 1245 cm^{-1}. The acyl azide (1.45 g, 3.9 mmol) was heated at reflux in anhydrous toluene (250 mL) for 2 h. The temperature was then lowered to 60 °C, and (trimethylsilyl)ethanol (1.82 g, 15.3 mmol) was added. This was allowed to stir for 12 h. The volatiles were removed in vacuo, and the residue purified by flash chromatography (50% ether/petroleum ether). The pure carbamate **37** was isolated as a colorless liquid (1.10 g, 61% yield from acid **36**): ^1H NMR ($CDCl_3$) δ 8.61 (br s, 1 H), 8.17 (d, J = 8.6 Hz, 1 H), 7.29–7.46 (m, 1 H), 7.13–7.29 (m, 1 H), 6.91–7.08 (m, 1 H), 4.42–5.30 (m, 3 H), 4.10–4.28 (m, 2 H), 3.17–4.01 (m, 8 H), 2.00–2.51 (m, 2 H), 2.00 and 1.95 (2 s, 3 H), 0.92–1.10 (m, 2 H), 0.03 (s, 9 H); IR (neat) 3340, 3080, 2960, 1740, 1627, 1590, 1523, 1220 cm^{-1}; HRMS calcd for $C_{22}H_{34}N_2O_7Si$ 466.2135, found 466.2197.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-benzoyl)-4-hydroxypyrrolidine-2-carboxaldehyde Dimethyl Acetal (38). A mixture of the acetates **37** (0.992 g, 2.13 mmol) and potassium carbonate (0.922 g, 10.0 mmol) in methanol (103 mL) was stirred at room temperature for 15 min, poured into water (100 mL), and extracted with CH_2Cl_2 (8 × 50 mL). The combined organic phases were washed with water (100 mL), dried (Na_2SO_4), filtered, and evaporated to give the alcohols **38** as a colorless oil (0.862 g, 95% yield): ^1H NMR ($CDCl_3$) δ 8.39 (br s, 1 H), 7.96–8.17 (m, 1 H), 7.17–7.45 (m, 2 H), 6.95–7.11 (m, 1 H), 4.10–5.03 (m, 5 H), 2.77–4.00 (m, 8 H), 1.79–2.42 (m, 3 H), 0.91–1.09 (m, 2 H), 0.03 (s, 9 H); IR (neat) 3390, 2970, 1735, 1620, 1595, 1523, 1065 cm^{-1}; HRMS calcd for $C_{20}H_{32}N_2O_6Si$ 424.2029, found 424.2017.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-benzoyl)-4-oxopyrrolidine-2-carboxaldehyde Dimethyl Acetal (39). Chromium trioxide (1.77 g, 19.0 mmol) was added in four portions over a period of 7 min to a solution of anhydrous pyridine (2.77 g, 35.0 mmol) and anhydrous CH_2Cl_2 (29 mL) at approximately 15 °C under N_2. The cooling bath was removed, and the reddish mixture stirred for an additional 20 min. The alcohols **38** (0.756 g, 1.78 mmol) in anhydrous CH_2Cl_2 (57 mL) was added all at once, and the resulting brown mixture stirred for 3.75 h at room temperature. Celite was added, and the mixture poured into ether (200 mL) and passed through a short (3 cm) column of florisil (topped with 2 cm of Celite). The column was washed with ether (1 L). The solvent was evaporated to leave a pale yellow liquid. Purification by florisil chromatography (50% ether/petroleum ether) afforded ketone **39** as a colorless liquid (0.714 g, 95% yield): ^1H NMR ($CDCl_3$) δ 8.36 (br s, 1 H), 8.15 (d, J = 8.3 Hz, 1 H), 7.33–7.48 (m, 1 H), 7.18–7.31 (m, 1 H), 7.05 (t, J = 7.3 Hz, 1 H), 5.10 (br s, 1 H), 4.55 (br s, 1 H), 4.13–4.29 (m, 2 H), 4.03–2.88 (m, 8 H), 2.36–2.84 (m, 2 H), 0.94–1.09 (m, 2 H), 0.03 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 208.5, 169.1, 153.5, 136.7, 131.0, 127.0, 123.5, 122.1, 120.9, 105.4, 63.2, 56.9, 56.2, 55.3, 54.8, 36.0, 17.5, −1.7; IR (neat) 3320, 3080, 2965, 1765, 1725, 1630, 1590, 1512, 1410, 1220 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{30}N_2O_6Si$ 423.1951 $(M + 1)^+$, found 423.1976. Anal. Calcd for $C_{20}H_{30}N_2O_6Si$: C, 56.85; H, 7.16; N, 6.63. Found: C, 56.58; H, 7.19; N, 6.52.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-benzoyl)-4-ethylidenepyrrolidine-2-carboxaldehyde Dimethyl Acetal (40). Ethyltriphenylphosphonium iodide (0.618 g, 1.48 mmol; dried for 24 h at 90 °C in vacuo) was added to a solution of potassium *tert*-butoxide (0.165 g, 1.48 mmol) in anhydrous THF (3.2 mL) at 0 °C under N_2. The orange mixture was stirred at 0–25 °C for 1.5 h. The ketone **39** (0.133 g, 0.014 mmol) in anhydrous THF (6.8 mL) was added, and the mixture heated at reflux for 30 min. The mixture was allowed to cool to room temperature and stir for 15 h. The mixture was evaporated to dryness and taken up in CH_2Cl_2 (25 mL) and water (13 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were evaporated to give the crude isomeric products, which were isolated by prepative TLC (two 1000-μm plates, silica gel GF, Analtech, developed with 50% ether/petroleum ether) to give the olefins **40** as a colorless liquid (0.119 g, 87% yield): ^1H NMR ($CDCl_3$) δ 8.46 (br s, 1 H), 8.13 (d, J = 8.1 Hz, 1 H), 7.13–7.50 (m, 2 H), 6.88–7.13 (t, J = 6.9 Hz, 1 H), 5.32 (br s, 1 H), 3.70–5.00 (m, 6 H), 2.85–3.70 (m, 6 H), 2.35–2.85 (m, 2 H), 1.30–1.70 (m, 3 H), 0.99–1.08 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.1, 153.8, 137.1, 135.3, 130.8, 127.3, 124.0, 122.1, 120.6, 116.7, 104.7, 63.3, 56.6, 55.7, 55.4, 51.0, 31.2, 17.7, 14.6, 14.3, −1.5; IR (neat) 3340, 3070, 2965, 1735, 1628, 1590, 1523, 1410, 1220 cm^{-1}; HRMS calcd for $C_{22}H_{34}N_2O_5Si$ 435.2315 $(M + 1)^+$, found 435.2333.

1-(2′-Aminobenzoyl)-4-ethylidene-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (41). Carbamates **40** were deprotected in a manner analogous to that for **23**. The residue was purified by flash chromatography (50% ether/petroleum ether) to give the amine **41** (75% yield): ^1H NMR ($CDCl_3$) δ 7.10–7.33 (m, 2 H), 6.71–6.92 (m, 2 H), 3.70–5.65 (m, 6 H, 2 H exchange with D_2O), 2.80–3.68 (m, 6 H), 2.45–2.83 (m, 2 H), 1.38–1.75 (m, 3 H); IR (neat) 3450, 3345, 3050, 2930, 1623, 1592, 1418, 1080 cm^{-1}.

4-Ethylidene-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (1). Propene gas was bubbled into $CHCl_3$ (1 mL) at −60 °C for 5 min. Iodotrimethylsilane (0.013 g, 0.064 mmol) was added, and the mixture stirred for 1 min. The amine–acetal **41** (0.0152 g, 0.053 mmol) in $CHCl_3$ (2 mL) was added, and the mixture slowly allowed to warm to room temperature under N_2 over a period of 30 min. An aqueous $NaHCO_3$ solution (0.5 mL, 5% w/v) and an aqueous $Na_2S_2O_5$ solution (0.4 mL, 10% w/v) were added, and the mixture was stirred vigorously until it decolorized. Water (5 mL) was added, and the mixture extracted with $CHCl_3$ (4 × 5 mL), dried (Na_2SO_4), filtered and evaporated to a yellow liquid. The residue was purified by prepative TLC (1000 μm, silica gel GF, Analtech; development with 50% acetone/benzene) to give the products **1** as an approximately 1:3 mixture of the *E* and *Z* olefins, respectively, as cream-colored crystals (mp 128–130 °C (dec); lit.[6] mp for the natural product 85–87 °C): ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 7.0 Hz, 1 H), 7.77 (d, J = 4.4 Hz, 1 H), 7.54 (t, J = 7.0 Hz, 1 H), 7.34 (t, J = 7.0 Hz, 2 H), 5.4–5.68 (m, 1 H), 4.13–4.45 (m, 2 H), 3.82–3.95 (m, 1 H), 2.85–3.15 (m, 2 H), 1.75 and 1.70 (2 d, each J = 6.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 145.7, 132.8, 131.5, 130.1, 126.6, 126.5, 119.5, 53.7, 53.2, 51.6, 48.3, 35.3, 31.1, 14.9; UV (MeOH) 228 (ϵ = 1.70 × 10^4), 313 nm (ϵ = 3.32 × 10^3); IR ($CHCl_3$) 3020, 1620, 1478, 1200 cm^{-1}; MS, m/z 226 (M^+), 211, 197, 103, 96, 76.

Dimethyl 4-((Phenylsulfonyl)oxy)-5-hydroxyphthalate (50). Powdered calcium hydroxide was added in small portions to a stirring solution of dimethyl 4,5-dihydroxyphthalate[35] (**49**, 27.71 g, 0.118 mol) and benzenesulfonyl chloride (36.6 mL, 0.287 mol) in water (500 mL) until the solution was permanently alkaline. After this stirred at room temperature for 45 h, the

brownish solid was filtered, crushed in a mortar, suspended in water (750 mL), and acidified with concentrated HCl (pH = 1). The resulting beige solid was filtered, washed with water, and dried. Purification by flash chromatography (50% EtOAc/Skelly F) afforded bis(benzenesulfonate) as a white powder (52.26 g, 87% yield; mp 144.5–145.5 °C): ^{1}H NMR ($CDCl_3$) δ 7.47–7.77 (m, 12 H with 2 H singlet at δ 7.63), 3.91 (s, 6 H); IR ($CHCl_3$) 3030, 2960, 1730, 1585, 1390, 1190 cm^{-1}. Bis(benzenesulfonate) (52.26 g, 0.1035 mol) was suspended in methanol (480 mL). A 20% methanolic potassium hydroxide solution (60 mL) was added over 5 min, and the resulting solution heated at 40–45 °C for 30 min. After dilution with water (1000 mL) and the addition of one crystal of sodium thiosulfate, the solution was acidified with concentrated HCl (pH = 1) and stored in the freezer overnight. The white precipitate was filtered, dried, and triturated with petroleum ether to afford the monobenzenesulfonate **50** (36.05 g, 93% yield; mp 123–124 °C): ^{1}H NMR ($CDCl_3$) δ 7.52–7.96 (m, 5 H), 7.36 (s, 1 H), 7.19 (s, 1 H), 6.56 (br s, 1 H, exchanges with D_2O), 3.89 (s, 3 H), 3.82 (s, 3 H); IR ($CHCl_3$) 3580, 3150, 2980, 1740, 1390, 1200 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_8S$: C, 52.46; H, 3.85; S, 8.75. Found: C, 52.29; H, 3.82; S, 9.00.

Dimethyl 4-((Phenylsulfonyl)oxy)-5-methoxyphthalate (51). Potassium carbonate (1.00 g, 7.24 mmol), methyl iodide (0.50 mL, 8.03 mmol), and phenol **50** (0.260 g, 0.710 mmol) in anhydrous DMF (5 mL) were stirred at room temperature for 20 h. Water (30 mL) was added to the reaction flask. This was extracted with ether (3 × 20 mL). The combined ethereal layers were dried ($MgSO_4$), filtered, and evaporated in vacuo. The resulting solid was triturated with petroleum ether to afford pure **51** (0.260 g, 96% yield; mp 106–108 °C): ^{1}H NMR ($CDCl_3$) δ 7.54–7.90 (m, 6 H with 1 H singlet at δ 7.67), 7.01 (s, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.60 (s, 3 H); IR ($CHCl_3$) 3020, 2950, 1735, 1390, 1200 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_8S$: C, 53.68; H, 4.24; S, 8.43. Found: C, 53.66; H, 4.22; S, 8.52.

4-((Phenylsulfonyl)oxy)-5-methoxyphthalic Acid (52). Phthalic ester **51** (12.20 g, 32.1 mmol), glacial acetic acid (155 mL), water (50 mL), and concentrated HCl (5 mL) were heated at reflux for 4. h. After this cooled, the solvents were evaporated in vacuo to afford crude diacid **52** (11.40 g). Recrystallization from water provided pure **52** as white crystals (11.13 g, 98% yield; mp 173–175 °C): ^{1}H (d_6-acetone) δ 7.66–7.94 (m, 6 H with 1 H singlet at δ 7.69), 7.25 (s, 1 H), 3.67 (s, 3 H); IR (KBr) 3350, 3200–2500 (br), 1775, 1695, 1380, 1200 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_8S$: C, 51.14; H, 3.43; S, 9.10. Found: C, 50.89; H, 3.35; S, 9.22.

4-((Phenylsulfonyl)oxy)-5-methoxyphthalimide (53). 4-((Phenylsulfonyl)oxy)-5-methoxyphthalic acid (**52**, 3.65 g, 10.4 mmol) and ethyl carbamate (2.77 g, 31.3 mmol) in a flask equipped with a distillation head, condenser, and receiving flask were heated in an oil bath at 150–160 °C for 65 h. The brown solid was crushed in a mortar, washed with saturated $NaHCO_3$ (200 mL), and collected by filtration. Recrystallization of the crude phthalimide **53** from ethanol afforded off-white crystals (2.66 g, 77% yield; mp 210–212 °C): ^{1}H NMR (60 MHz, d_6-acetone) δ 7.63–7.90 (m, 5 H), 7.53 (s, 1 H), 7.34 (s, 1 H), 3.70 (s, 3 H); IR (KBr) 3440, 1775, 1760, 1725, 1715, 1620, 1390, 1200 cm^{-1}.

4-((Phenylsulfonyl)oxy)-5-methoxy-*N*-(4-pentenyl)phthalimide (54). A solution of phthalimide **53** (0.427 g, 1.28 mmol) in anhydrous THF (20 mL) was added dropwise over 40 min to a vigorously stirring suspension of KH (0.230 g of 24.6%, 1.41 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere. After this stirred for 2 h, the flask was cooled to 0 °C, and the thick, yellow precipitate collected by filtration. This was dried in an Abderhalden apparatus overnight. A mixture of the potassium salt of phthalimide **53**, 5-bromo-1-pentene (0.17 mL, 0.144 mmol), and tetrabutylammonium bromide (TBABr, 0.018 g, 0.056 mmol) in anhydrous benzene (15 mL) was heated at reflux under a nitrogen atmosphere for 22 h. After the addition of ether (5 mL) and filtration through a pad of Celite, the solvents were removed in vacuo to give a yellow, waxy solid. Purification by flash chromatography (15% EtOAc/Skelly F) afforded pure **54** as white crystals (0.355 g, 69% yield; mp 97–98.5 °C): ^{1}H NMR ($CDCl_3$) δ 7.81–7.89 (m, 2 H), 7.60–7.68 (m, 1 H), 7.45–7.56 (m, 3 H with H singlet at δ 7.55), 7.31 (s, 1 H), 5.90 (ddt, J = 17.0, 10.1, 6.6 Hz, 1 H), 4.95–5.10 (m, 2 H), 3.71 (s, 3 H), 3.66 (t, J = 7.3 Hz, 2 H), 2.08–2.18 (m, 2 H), 1.80 (quintet, J = 7.3 Hz, 2 H); IR ($CHCl_3$) 1780, 1720, 1400, 1300 cm^{-1}; UV (CH_3CN) 238 (ϵ = 4.53 × 10^4), 252 (ϵ = 1.75 × 10^4), 273 (ϵ = 2.82 × 10^3), 289 (ϵ = 1.91 × 10^3), 310 (ϵ = 1956 × 10^3), 315 nm (ϵ = 1.39 × 10^3). Anal. calcd for $C_{20}H_{19}NO_6S$: C, 59.84; H, 4.78; N, 3.49. Found: C, 59.64; H, 4.68; N, 3.47.

8-((Phenylsulfonyl)oxy)-7-methoxy-2,3,11,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepine-5,10(1*H*)-dione (55). A solution of phthalimide **54** (157.5 mg) in photrex grade acetonitrile (40 mL) was irradiated in a large Pyrex test tube for 30 min. The solvent was evaporated in vacuo to produce a gold solid. Flash chromatography (florisil; gradient solvent system starting with 20% EtOAc/Skelly F) afforded starting material (39.4 mg) and two regioisomeric pyrrolobenzazepinediones **55** and **56** (53.8 mg total; 45% yield, based on recovered starting material) as white solids in a 52:48 ratio as determined by analytical HPLC. The less polar isomer **55** (mp 158.5–161 °C) gave the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.95 (m, 2 H), 7.76 (s, 1 H), 7.67–7.71 (m, 1 H), 7.54–7.58 (m, 2 H), 7.21 (s, 1 H), 4.21–4.27 (m, 1 H), 3.67–3.76 (m, 5 H with 3 H singlet at δ 3.72), 3.02 (dd, J = 18.9, 12.1 Hz, 1 H), 2.87 (dd, J = 18.9, 2.3 Hz, 1 H), 1.80–2.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 199.3, 164.6, 154.1, 141.6, 136.7, 135.6, 134.2, 129.1, 128.4, 127.8, 126.5, 112.2, 56.1, 52.9, 51.1, 47.1, 32.1, 23.2; IR ($CHCl_3$) 3010, 2980, 1670, 1630, 1600, 1440, 1380 cm^{-1}. The more polar isomer **56** (mp 135.5–138.0 °C) gave the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.95 (m, 2 H), 7.49–7.76 (m, 5 H with 1 H singlets at δ 7.60 and 7.49), 4.21–4.28 (m, 1 H), 3.67–3.81 (m, 5 H with 3 H singlet at δ 3.70), 2.98 (dd, J = 18.9, 11.8 Hz, 1 H), 2.84 (dd, J = 18.9, 2.2 Hz, 1 H), 1.81–2.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 197.6, 164.9, 155.3, 140.2, 136.3, 134.8, 134.2, 129.0, 128.5, 126.4, 124.8, 114.5, 56.2, 53.0, 50.8, 47.3, 32.2, 23.1; IR ($CHCl_3$) 3010, 1675, 1640 (sh), 1630, 1595, 1430, 1385 cm^{-1}; M/S, m/z 401 (M$^+$), 260 (M$^+$ – $PhSO_2$); HRMS calcd for $C_{20}H_{19}NO_6S$ 401.0932, found 401.0946.

4,5-Dimethoxy-*N*-(4-pentenyl)phthalimide (46). 4,5-Dimethoxyphthalimide[35] (0.424 g, 2.04 mmol) in anhydrous DMF (45 mL) was added over 20 min to a stirring suspension of NaH (0.170 g of 50%, 3.56 mmol) in anhydrous DMF (9 mL) at room temperature under a nitrogen atmosphere. The resulting yellow solution was heated in an oil bath at 70–80 °C for 2 h. 5-Bromo-1-pentene (0.756 g, 5.07 mmol) was added, and heating continued for 21.5 h. The clear yellow solution was poured into CH_2Cl_2 (35 mL), washed with 2 N NaOH (25 mL) and water (2 × 25 mL), dried ($MgSO_4$), filtered, and evaporated. Pure alkylated phthalimide **46** was isolated as white needles (0.336 g, 60% yield; mp 167–168 °C) upon flash chromatography (15% EtOAc/Skelly F). Recrystallization from ether afforded an analytically pure sample: ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 2 H), 5.82 (ddt, J = 16.7, 10.2, 6.5 Hz, 1 H), 4.95–5.11 (m, 2 H), 4.00 (s, 6 H), 3.65 (t, J = 7.2 Hz, 2 H), 2.06–2.16 (m, 2 H), 1.76 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 168.5, 153.9, 137.4, 125.6, 115.1, 105.4, 56.5, 37.5, 30.9, 27.8; IR ($CHCl_3$) 3020, 2980, 1705, 1680 (sh), 1402, 1315 cm^{-1}; UV (CH_3CN) 247 (ϵ = 4.00 × 10^4), 296 (ϵ = 1.50 × 10^3), 340 nm (ϵ = 1.40 × 10^3). Anal. Calcd for $C_{15}H_{17}O_4N$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.29; H, 6.19; N, 5.00.

7,8-Dimethoxy-2,3,11,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepine-5,10(1*H*)-dione (60). A solution of phthalimide **46** (183.3 mg, 0.665 mmol) in photrex acetonitrile (200 mL) was irradiated for 21 h in an immersion well through a Corex filter. The solvent was removed in vacuo, and the yellow solid purified by flash chromatography (eluted with EtOAc). Some starting material (95.6 mg, 52% yield) was obtained. Photoproduct **60** was isolated as a white powder (71.8 mg, 39% yield; 82% based on recovered starting material; mp 191–192 °C): ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1 H), 7.30 (s, 1 H), 4.10–4.30 (m, 1 H), 4.00 (s, 3 H), 3.97 (s, 3 H), 3.79 (t, J = 6.8 Hz, 2 H), 3.03 (dd, J = 18.8, 11.5 Hz, 1 H), 2.85 (dd, J = 18.8, 2.7 Hz, 1 H), 1.76–2.34 (m, 4 H); IR ($CHCl_3$) 3010, 1680, 1630, 1600, 1440, 1290 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.22; N, 5.09. Found: C, 64.97; H, 6.19; N, 5.17.

7,8-Dimethoxy-1,2,3,10,11,11a-hexahydro-10-hydroxypyrrolo[1,2-*b*][2]benzazepin-5-one (61). Ketone **60** was reduced in a manner analogous to that for **4a** to give the diastereomeric alcohols **61** as a white foam (98% yield). Careful column chromatography (50% EtOAc/Skelly F) separated the two isomers. The less polar alcohol (upper spot) was isolated as a white solid (66.0 mg; mp 157–158.5 °C): ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 2 H), 3.90–4.07 (m, 7 H and 2 3 H singlets at δ 3.91 and 3.96), 3.40–3.52

(m, 3 H), 1.72–2.23 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 151.0, 147.6, 135.9, 124.8, 111.0, 106.7, 68.0, 56.1, 55.9, 55.4, 46.1, 31.0, 23.2; IR ($CHCl_3$) 3160–3620 (br), 3020, 2980, 1620, 1602, 1430, 1280 cm^{-1}. The more polar diastereomer was also obtained as a white solid (32.8 mg; mp 175–178 °C): ^{1}H NMR δ ($CDCl_3$) 7.34 (s, 1 H), 6.69 (s, 1 H), 4.84 (d, J = 4.6 Hz, 1 H), 3.92 (s, 6 H), 3.50–3.80 (m, 3 H), 1.95–2.32 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.0, 149.9, 148.6, 134.5, 127.7, 113.0, 111.0, 72.9, 55.9, 55.1, 46.1, 45.2, 31.0, 22.7; IR ($CHCl_3$) 3100–3600 (br), 3010, 2980, 1625, 1605, 1440, 1275 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.78; H, 7.07; N, 4.78.

7,8-Dimethoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (45). Diastereomeric alcohols **61** (41.8 mg, 0.151 mmol) and *p*-TsOH (40.8 mg, 0.214 mmol) were heated at reflux in toluene (20 mL) under a nitrogen atmosphere for 1 h. The toluene was evaporated, and the residue dissolved in CH_2Cl_2 (10 mL). This was extracted with saturated aqueous $NaHCO_3$ (4 × 5 mL). The combined organic layers were washed with water (100 mL), dried ($MgSO_4$), filtered, and evaporated. Purification by chromatography (25% EtOAc/Skelly F) afforded alkene **45** as a pale yellow oil (29.7 mg, 76% yield): ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1 H), 6.65 (s, 1 H), 6.60 (dd, J = 10.1, 2.1 Hz, 1 H), 5.88 (dd, J = 10.1, 5.0 Hz, 1 H), 3.90–4.00 (m, 7 H with 2 3 H singlets at δ 3.96 and 3.92), 3.58–3.86 (m, 2 H), 1.91–2.30 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 165.7, 150.3, 148.2, 134.0, 132.2, 129.2, 128.4, 112.8, 110.8, 55.9, 55.8, 53.4, 47.1, 32.4, 23.9; IR ($CDCl_3$) 3020, 2980, 1620, 1602, 1441, 1265 cm^{-1}; MS, m/z 259 (M^+, base); HRMS calcd for $C_{15}H_{17}NO_3$ 259.1207, found 259.1217.

7-Hydroxy-8-methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (57). Propanethiol (9 μL, 0.0993 mmol) was added to NaH (50% in oil, 5.2 mg, 0.108 mmol) in anhydrous DMF (1 mL) under nitrogen. After stirring for 10 min, dimethoxyalkene **45** (9.0 mg, 0.035 mmol) in DMF (3 mL) was added to the solution via an addition funnel. This was heated in an oil bath at 100 °C under a nitrogen atmosphere for 4 h, during which the clear gold solution turned a cloudy dark rust. After acidification with 10% HCl, the solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 10% NaOH (2 × 5 mL). The basic layer was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water (5 mL), dried (Na_2SO_4), filtered, and evaporated to afford phenol **57**. Purification by chromatography (pipet column; silica gel; 30% EtOAc/Skelly F) gave product **57** (3.0 mg, 30% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1 H), 6.73 (s, 1 H), 6.53 (dd, J = 10.1, 1.9 Hz, 1 H), 5.93 (br s, 1 H), 5.85 (dd, J = 10.1, 5.0 Hz, 1 H), 3.90–3.95 (m, j H with 3 H singlet at δ 3.94), 3.75–3.81 (m, 1 H), 3.52–3.59 (m, 1 H), 1.93–2.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 147.7, 146.3, 134.0, 132.4, 130.0, 127.7, 114.5, 112.7, 56.1, 53.6, 47.3, 32.5, 24.1; IR ($CDCl_3$) 3540, 3100–3440 (br), 3020, 2980, 1600, 1275 cm^{-1}. MS, m/z 245 (M^+, base); HRMS calcd for $C_{14}H_{15}NO_3$ 245.1051, found 245.1068.

1,2,3,10,11,11a-Hexahydro-10-hydroxy-7-methoxypyrrolo[1,2-*b*][2]benzazepin-5-one (64). Photoproduct **62**[12c] was reduced in a manner analogous to that for **4a** to give the diastereomeric alcohols **64** as a white foam (94% yield; mp 140–150 °C) which becomes a fluffy powder upon trituration with Skelly F; ^{1}H NMR ($CDCl_3$) δ 7.53 and 7.70 (2 d, J = 8.6 Hz, 1 H), 6.71 and 7.14 (2 d, J = 2.5 Hz, 1 H), 6.78 and 6.85 (2 dd, J = 8.6, 2.5 Hz, 1 H), 3.93–4.03 (m, 1 H), 3.83 and 3.87 (2 s, 3 H), 3.35–3.65 (m, 3 H), 1.65–2.25 (m, 6 H); IR ($CHCl_3$) 3150–3500 (br), 3010, 1630, 1605, 1445 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.08; H, 7.00; N, 5.40.

1,2,3,10,11,11a-Hexahydro-7-methoxy-10-(((phenyloxy)thionocarbonyl)oxy)pyrrolo[1,2-*b*][2]benzazepin-5-one (65). Alcohols **64** were converted to **65** in a manner analogous to that for **30**. The crude diastereomeric thionocarbonates **65** were isolated as a dark green oil. Purification by flash chromatography (50% ether/hexanes) afforded the product as a beige solid (90% yield; mp 113–118 °C): ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8. Hz, 1 H), 7.10–7.48 (m, 5 H), 7.01 (d, J = 2.4 Hz, 1 H), 6.91 (dd, J = 8.5, 2.4 Hz, 1 H), 6.45 (dd, J = 10.5, 7.9 Hz, 1 H), 3.61–3.89 (m, 6 H with 3 H singlet at δ 3.86), 2.72 (dt, J = 7.7, 12.2 Hz, 1 H), 1.79–2.22 (m, 5 H); IR ($CHCl_3$) 3010, 2980, 1630, 1605, 1405, 1290, 1270, 1200, 770 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NSO_4$: C, 65.78; H, 5.52; N, 3.65; S, 8.36. Found: C, 65.57; H, 5.44; N, 3.71; S, 8.00.

7-Methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (47). A solution of the thionocarbonats **65** (2.53 g, 6.59 mmol) in reagent grade xylenes (200 mL) was heated at reflux under nitrogen for 8 h. After cooling, the xylenes were removed in vacuo. The crude alkene was chromatographed (45% EtOAc/Skelly F) to afford pure **47** as a pale yellow viscous oil (1.35 g, 89% yield) which crystallized upon storage in the freezer (mp 59–61.5 °C): ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 1 H), 6.92 (dd, J = 8.8, 2.5 Hz, 1 H), 6.69 (d, J = 2.5 Hz, 1 H), 6.65 (dd, J = 10.4, 1.6 Hz, 1 H), 5.97 (dd, J = 10.4, 4.9 Hz, 1 H), 3.98–4.01 (m, 1 H), 3.85 (s, 3 H), 3.76–3.82 (m, 1 H), 3.56–3.66 (m, 1 H), 1.94–2.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 160.6, 136.7, 136.0, 132.6, 132.4, 128.0, 113.7, 112.7, 55.1, 53.1, 46.8, 32.3, 23.8; IR ($CHCl_3$) 3020, 1620, 1601, 1450, 1418 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.27; H, 6.68; N, 5.88.

6-Formyl-7-methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (66). Alkene **47** (144.3 mg, 0.629 mmol) and dichloromethyl methyl ether (0.18 mL, 1.99 mmol) in anhydrous methylene chloride (2.0 mL) were cooled to 0 °C under nitrogen. Titanium tetrachloride ($TiCl_4$, 0.25 mL, 2.274 mmol) in CH_2Cl_2 (3.0 mL) was added to the flask via an addition funnel over a 10-min period. The rust-colored solution was stirred at room temperature for 6.25 h and then poured into ice water (30 mL). This was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), water (20 mL), and saturated NaCl (20 mL), dried ($MgSO_4$), filtered, and evaporated to afford a yellow foam (150.6 mg). Pure aldehyde **66** was obtained upon flash chromatography (35% ether/Skelly F) as a white powder (85.0 mg, 53% yield; mp 198–200.5 °C): ^{1}H NMR ($CDCl_3$) δ 10.65 (s, 1 H), 8.27 (d, J = 8.9 Hz, 1 H), 7.20 (dd, J = 10.5, 1.7 Hz, 1 H), 7.07 (d, J = 8. Hz, 1 H), 6.05 (dd, J = 10.5, 5.8 Hz, 1 H), 3.79–4.01 (m, 5 H with 3 H singlet at δ 3.99), 3.47–3.54 (m, 1 H), 1.96–2.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 191.7, 165.2, 164.0, 137.8, 136.5, 129.8, 120.8, 110.9, 56.0, 52.8, 46.7, 31.9, 23.9; IR ($CHCl_3$) 3010, 2890, 1685, 1615, 1590, 1270 cm^{-1}; MS, m/z 257 (M^+), 228 (M^+ – CHO).

8-Formyl-7-methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (67). A solution of alkene **47** (253.8 mg, 1.107 mmol) and hexamethylenetetraamine (HMT, 414.0 mg, 2.953 mmol) in trifluoroacetic acid (TFA, 5.5 mL) was heated at reflux for 48 h under a nitrogen atmosphere. After this cooled, 50% H_2SO_4 (4 mL) and water (4 mL) were added, and this was stirred at room temperature for 30 min. The solution was carefully neutralized with solid sodium bicarbonate, and the resulting brown–red solution extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with water (30 mL), dried ($MgSO_4$), filtered, and evaporated. Purification by florisil flash chromatography (gradient solvent system starting with 10% EtOAc/Skelly F to 100% EtOAc) afforded the desired aldehyde **67** (upper spot) as white crystals (97.9 mg, 43% yield; mp 196–200 °C (dec)) and the undesired aldehyde **66** (lower spot) as a white powder (74.4 mg, 33% yield; mp 198–200.5 °C) as well as alkene **47** (50.7 mg); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1 H), 8.50 (s, 1 H), 6.72 (s, 1 H), 6.65 (dd, J = 10.2, 1.9 Hz, 1 H), 6.08 (dd, J = 10.2, 5.0 Hz, 1 H), 3.96–4.04 (m, 4 H with 3 H singlet at δ 3.97), 3.75–3.87 (m, 1 H), 3.52–3.66 (m, 1 H), 1.94–2.33 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 188.6, 161.7, 141.9, 138.7, 138.0, 133.5, 132.1, 128.5, 124.2, 111.0, 55.9, 53.2, 47.2, 32.5, 24.0; IR ($CHCl_3$) 3020, 2980, 2880, 1692, 1625, 1605 cm^{-1}; HRMS calcd for $C_{15}H_{15}NO_3$ 257.1051 (M^+), found 257.1050.

8-(Formyloxy)-7-methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (68). Aldehyde **67** (97.9 mg, 0.381 mmol) and *m*-chloroperbenzoic acid (mCPBA, 108.7 mg, 0.630 mmol) in anhydrous CH_2Cl_2 (12 mL) were heated at reflux under nitrogen for 72 h. The solvent was evaporated, and the residue dissolved in ethyl acetate (15 mL) and extracted with saturated $NaHCO_3$ (2 × 5 mL) and water (5 mL), dried (Na_2SO_4), filtered, and evaporated to afford crude formate **68**. Usually the crude formate **68** was used directly in the next step but could be purified using flash chromatography on florisil (20% EtOAc/Skelly F): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1 H), 7.81 (s, 1 H), 6.74 (s, 1 H), 6.61 (dd, J = 10.1, 2.0 Hz, 1 H), 5.97 (dd, J = 10.1, 5.0 Hz, 1 H), 3.96–4.02 (m, 1 H), 3.86 (s, 3 H), 3.73–3.82 (m, 1 H), 3.55 (dt, J = 12.0, 7.6 Hz, 1 H), 1.92–2.28 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 158.5, 152.2, 138.1, 136.4, 135.0, 131.9, 128.7, 125.2, 111.9,

56.0, 53.3, 47.2, 32.5, 23.9; IR ($CDCl_3$) 3000, 2980, 1745, 1620 (sh), 1610, 1455, 1275 cm^{-1}.

8-Hydroxy-7-methoxy-1,2,3,11a-tetrahydropyrrolo[1,2-*b*][2]benzazepin-5-one (69). Crude formate **68** and 1.0 N HCl (8 mL) in THF (25 mL) were heated at reflux for 2 h. The volatile solvents were evaporated, and the remaining aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with 1.0 N NaOH (2 × 10 mL). The basic phases were acidified (pH = 1) with concentrated HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), filtered, and evaporated to a white solid (61.5 mg, 66% yield from aldehyde **67**; mp 205–206.5 °C (dec)): ^1H NMR ($CDCl_3$) δ 8.04 (br s, exchanges with D_2O, 1 H), 7.91 (s, 1 H), 6.57 (s, 1 H), 6.52 (dd, J = 10.1, 2.1 Hz, 1 H), 5.76 (dd, J = 10.1, 5.0 Hz, 1 H), 3.69–3.93 (m, 5 H with 3 H singlet at δ 3.84), 3.45–3.59 (m, 1 H), 1.85–2.21 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 149.2, 145.9, 133.2, 132.5, 128.6, 128.5, 117.6, 110.9, 55.9, 53.6, 47.3, 32.5, 24.0; IR ($CDCl_3$) 3540, 3000–3500 (br), 2980, 1605, 1570, 1455, 1275 cm^{-1}; MS, m/z 245 (M^+, base); HRMS calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1054.

8-(Benzoyloxy)-7-methoxy-1,2,3,11a-tetrahydropyrrolo-[1,2-*b*][2]benzazepin-5-one (70). Phenol **69** (240.0 mg, 0.978 mmol), pyridine (1.30 mL, 16.07 mmol), and benzoyl chloride (2.50 mL, 21.53 mmol) in CH_2Cl_2 (50 mL) were stirred under nitrogen at room temperature for 3.25 h. The solution was poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (35 mL) and water (35 mL), dried ($MgSO_4$), filtered, and evaporated. The crude ester **70** was purified by flash chromatography (30% EtOAc/Skelly F) to afford pure **70** (293.6 mg, 86% yield; mp 164.5–166 °C) as a white powder: ^1H NMR ($CDCl_3$) δ 8.16–8.22 (m, 2 H), 7.88 (s, 1 H), 7.40–7.67 (m, 3 H), 6.76 (s, 1 H), 6.65 (dd, J = 10.2, 2.0 Hz, 1 H), 5.97 (dd, J = 10.2, 5.0 Hz, 1 H), 4.00–4.12 (m, 1 H), 3.83 (s, 3 H), 3.73–3.79 (m, 1 H), 3.56 (dt, J = 12.0, 7.6 Hz, 1 H), 1.91–2.30 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 165.1, 164.4, 152.7, 139.4, 135.9, 134.5, 133.4, 132.1, 130.2, 129.3, 128.6, 128.4, 125.5, 111.9, 55.9, 53.3, 47.1, 32.5, 23.9; IR ($CDCl_3$) 2980, 1740, 1615, 1605, 1450, 1270 cm^{-1}; MS, m/z 348 $(M - 1)^+$, 244 (M – PhCO), 105 (PhCO, base); HRMS calcd for $C_{21}H_{19}NO_4$ 349.1314, found 349.1313.

1-(2′-(Dimethoxymethyl)-4′-(benzoyloxy)-5′-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetals (71). Olefin **70** was ozonized in a manner analogous to that for olefin **15c** to afford the crude bis(dimethyl)acetals **71** as a pale yellow oil (85–90% crude). Usually this was not purified but used directly in the next reaction; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17–8.20 (m, 2 H), 7.40–7.65 (m, 3 H), 7.28 (s, 1 H), 7.02 (s, 1 H), 5.64 (s, 1 H), 4.84 (d, J = 2.8 Hz, 1 H), 4.38 (ddd, J = 8.8, 6.0, 2.8 Hz, 1 H), 3.84 (s, 3 H), 3.24–3.57 (m, 14 H with 3 H singlets at δ 3.28, 3.46, 3.49, and 3.50), 1.61–2.15 (m, 4 H); IR ($CDCl_3$) 3000, 2970, 1695, 1610, 1270 cm^{-1}.

1-(2′-Formyl-4′-(benzoyloxy)-5′-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (72). Bis(dimethyl)acetals **71** were hydrolyzed in a manner analogous to that for **19** to afford **72** as a clear viscous oil (71% from alkene **70**): ^1H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1 H), 8.17–8.19 (m, 2 H), 7.45–7.66 (m, 5 H with 1 H singlets at δ 7.51 and 7.57), 4.91 (d, J = 2.9 Hz, 1 H), 4.43 (ddd, J = 8.1, 5.2, 2.9 Hz, 1 H), 3.89 (s, 3 H), 3.53 (s, 3 H), 3.51 (s, 3 H), 3.13–3.28 (m, 2 H), 1.66–2.20 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 189.8, 166.4, 163.9, 152.4, 144.1, 134.0, 133.9, 131.7, 130.4, 128.7, 128.5, 122.2, 111.1, 104.6, 59.0, 57.4, 56.7, 56.3, 50.5, 24.9, 24.1; IR ($CHCl_3$) 3000, 2920, 1735, 1685, 1610, 1600, 1255 cm^{-1}; MS, m/z 322 (M^+ – PhCO), 105 (base).

1-(2′-Carboxy-4′-(benzoyloxy)-5-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (73). The oxidation of **72** was performed in a manner analogous to that for **20** to afford crude acid **73** as a pale gold oil (84% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.16–8.19 (m, 2 H), 7.89 and 7.72 (2 s, 1 H), 7.62–7.67 (m, 1 H), 7.48–7.55 (m, 2 H), 7.08 and 6.84 (2 s, 1 H), 4.91 and 4.85 (2 d, J = 2.6 and 2.7 Hz, respectively, with br s 4.50–5.10, 2 H), 4.36–4.55 (m, 1 H), 3.87 and 3.86 (2 s, 3 H), 3.12–3.53 (m, 8 H), 1.71–2.20 (m, 4 H); IR ($CDCl_3$) 3700–2500 (br), 2980, 1745, 1710, 1700 (sh), 1620 (sh), 1610, 1455, 1265 cm^{-1}. The acid was further characterized as the methyl ester (isolated as a colorless oil), which exhibited the following properties: ^1H NMR ($CDCl_3$) δ 8.16–8.23 (m, 2 H), 7.45–7.85 (m, 4 H with 1 H singlet at δ 7.63), 7.10 (s, 1 H), 4.96 and 7.91 (2 d, J = 2.5 Hz, 1 H), 4.34–4.47 (m, 1 H), 3.90, 3.89, 3.87, and 3.85 (4 s, 6 H), 3.15–3.58 (m, 8 H with o H singlets at δ 3.54 and 3.53), 1.67–2.21 (m, 4 H); IR ($CHCl_3$) 3010, 1740, 1730, 1628, 1440, 1275, 1250, 1055 cm^{-1}; MS, m/z 426 (M^+ – MeOH), 312 ($M^+ - C_7H_{14}O_2N$, base); HRMS calcd for $C_{17}H_{13}O_6$ (base peak, C(O)–N amide cleavage) 313.0712, found 313.0718.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-4′-(benzoyloxy)-5′-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (74). The Curtius sequence on acid **73** was performed in a manner analogous to that for acid **36** to afford a brown oil. Purification by florisil chromtography (10% EtOAc/Skelly F) gave carbamate **74** as a clear oil (28% yield from acid **73**): ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (br s, 1 H), 8.16–8.19 (m, 2 H), 8.06 (br s, 1 H), 7.59–7.63 (m, 1 H), 7.46–7.50 (m, 2 H), 6.91 (s, 1 H), 4.84 (br s, 1 H), 4.45 (br s, 1 H), 4.16–4.24 (m, 2 H), 3.76 (s, 3 H), 3.36–3.57 (m, 8 H), 1.87–2.16 (m, 4 H), 0.98–1.24 (m, 2 H), 0.02 (s, 9 H); IR ($CDCl_3$) 2980, 1740, 1725 (sh), 1625, 1600, 1420 cm^{-1}; MS, m/z 380 (M^+ – (PhCO and $SiMe_3$)), 105 (base); HRMS calcd for $C_{28}H_{38}O_8SiN_2$ 558.2397, found 558.2392.

1-(2′-(((2-(Trimethylsilyl)ethoxy)carbonyl)amino)-4′-hydroxy-5′-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetals (75). Carbamate–ester **74** (25.0 mg, 0.0448 mmol) and potassium carbonate (31.3 mg, 0.226 mmol) in absolute MeOH (10 mL) were stirred under nitrogen at room temperature for 3.5 h. This was poured into saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (5 mL), dried (Na_2SO_4), filtered, and evaporated to afford **75** as a pale yellow oil (18.1 mg, 90% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (br s, 1 H), 7.75 (br s, 1 H), 6.77 (s, 1 H), 5.96 (br s, 1 H), 4.77 (br s, 1 H), 4.42 (br s, 1 H), 4.16–4.24 (m, 2 H), 3.82 (s, 3 H), 3.34–3.64 (m, 8 H), 1.88–21.5 (m, 4 H), 0.85–1.04 (m, 2 H), 0.02 (s, 9 H); IR ($CDCl_3$) 3800, 3640, 3620–3100 (br), 2980, 1720, 1630 (sh), 1600, 1520 cm^{-1}.

1-(2′-Amino-4′-hydroxy-5′-methoxybenzoyl)-2-pyrrolidinecarboxaldehyde Dimethyl Acetal (76). Phenol–carbamate **75** was deprotected in a manner analogous to that for **23**. The resulting green residue was chromatographed on a pipet column (florisil; 50% EtOAc/Skelly F) to afford pure amine **76** as a yellow oil which darkened to greenish yellow upon standing (83% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1 H), 6.28 (s, 1 H), 5.73 (br s, 1 H), 4.71 (br s, 1 H), 4.42 (br s, 3 H), 3.78 (s, 3 H), 3.30–3.53 (m, 8 H), 1.89–2.15 (m, 4 H); IR ($CDCl_3$) 3520, 3600–3100 (br), 2980, 1630 (sh), 1610 (sh), 1600, 1500 cm^{-1}.

DC-81 (2). Cyclization of **76** was performed in a manner analogous to that for **5** to afford crude DC-81 (**2**, 35% yield). The spectral data were identical with that reported in the Japanese patent.[7] ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 4.8, 1 H), 7.48 (s, 1 H), 6.89 (s, 1 H), 6.0 (br s, u H), 3.87 (s, 3 H), 3.30–3.81 (m, 3 H), 1.82–2.35 (m, 4 H); IR ($CDCl_3$) 3200–3500 (br), 3000, 1600 cm^{-1}.

Registry No. (±)-**1** (imine), 105498-29-1; (±)-(*Z*)-**1** (imine), 105498-28-0; (±)-**2** (imine), 123355-42-0; (±)-**4a**, 123266-87-5; (±)-**5** (imine), 123355-35-1; **8**, 4424-80-0; **10**, 113961-86-7; **11**, 123266-85-3; **14**, 123266-86-4; (±)-**15b**, 123266-88-6; (±)-**15c**, 123266-91-1; (±)-*cis*-**18**, 123266-90-0; (±)-*trans*-**18**, 123266-89-7; (±)-**19**, 123266-92-2; (±)-**20**, 123266-93-3; (±)-**21**, 123266-94-4; (±)-**22**, 123266-95-5; (±)-**23**, 123266-96-6; (±)-**24**, 123266-97-7; (±)-**25**, 123266-98-8; (±)-**26**, 123266-99-9; (±)-**27**, 123267-00-5; (±)-*cis*-**28**, 123267-01-6; (±)-*trans*-**28**, 123267-02-7; (±)-**29** (isomer 1), 123267-03-8; (±)-**29** (isomer 2), 123355-36-2; (±)-**29** (isomer 3), 123355-37-3; (±)-**29** (isomer 4), 123355-38-4; (±)-**30** (isomer 1), 123267-04-9; (±)-**30** (isomer 2), 123355-39-5; (±)-**30** (isomer 3), 123355-40-8; (±)-**30** (isomer 4), 123355-41-9; (±)-*cis*-**31**, 123267-05-0; (±)-*trans*-**31**, 123267-06-1; (±)-*cis*-**32**, 123267-07-2; (±)-*trans*-**32**, 123267-08-3; (±)-*cis*-**33**, 123267-09-4; (±)-*trans*-**33**, 123267-10-7; (±)-*cis*-**34**, 123267-11-8; (±)-*trans*-**34**, 123267-12-9; (±)-*cis*-**35**, 123267-13-0; (±)-*trans*-**35**, 123267-14-1; (±)-*cis*-**36**, 123267-15-2; (±)-*trans*-**36**, 123267-16-3; (±)-*cis*-**36** (methyl ester), 123267-17-4; (±)-*trans*-**36** (methyl ester), 123267-18-5; (±)-*cis*-**37**, 123267-21-0; (±)-*trans*-**37**, 123267-22-1; (±)-*cis*-37 (azide), 123267-19-6; (±)-*trans*-**37** (azide), 123267-20-9; (±)-*cis*-**38**, 123267-23-2; (±)-*trans*-**38**, 123267-24-3; (±)-**39**, 123267-25-4; (±)-(*E*)-**40**, 123267-26-5; (±)-(*Z*)-**40**, 123267-27-6; (±)-(*E*)-**41**, 123267-28-7; (±)-(*Z*)-**41**, 123267-29-8; (±)-**45**, 123267-42-5; **46**,

123267-38-9; (±)-47, 123267-48-1; 49, 66323-03-3; 50, 123267-31-2; 50 bis(benzenesulfonate), 123267-30-1; 51, 123267-32-3; 52, 123267-33-4; 53, 123267-34-5; 54, 123267-35-6; (±)-55, 123267-36-7; (±)-56, 123267-37-8; (±)-57, 123289-28-1; (±)-60, 123267-39-0; (±)-*cis*-61, 123267-41-4; (±)-*trans*-61, 123267-40-3; (±)-62, 123267-43-6; (±)-*cis*-64, 123267-44-7; (±)-*trans*-64, 123267-45-8; (±)-*cis*-65, 123267-46-9; (±)-*trans*-65, 123267-47-0; (±)-66, 123267-49-2; (±)-67, 123267-50-5; (±)-68, 123267-51-6; (±)-69, 123267-52-7; (±)-70, 123267-53-8; (±)-71, 123267-54-9; (±)-72, 123267-56-1; (±)-73, 123267-56-1; (±)-73 methyl ester, 123267-57-2; (±)-74, 123267-58-3; (±)-75, 123267-59-4; (±)-76, 123267-60-7; ClC(S)OPh, 1005-56-7; $Ph_3PCH_2CH_3I$, 4736-60-1; H_2NCO_2Et, 51-79-6; $Br(CH_2)_3CH{=}CH_2$, 1119-51-3; potassium phthalimide, 1074-82-4; 4,5-dimethoxyphthalimide, 4764-20-9.

Synthesis of Azetidine-2,3-diones (α-Keto β-Lactams) via 3-(Phenylthio)-2-azetidinones[1]

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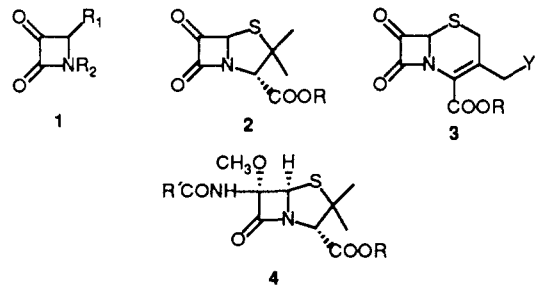
Stereospecific syntheses of tras and cis 3-(phenylthio)-2-azetidinones have been devised. Treatment of these β-lactams with sulfuryl chloride leads in high yield to single isomers of 3-chloro-3-(phenylthio)-2-azetidinones via a Pummerer type reaction. The structure of one of these compounds was confirmed by single-crystal X-ray diffraction analysis. The chloro group in these β-lactams is very active chemically; stereospecific replacement in high yield was used for preparing 3-methoxy-3-(phenylthio)-2-azetidinones. Hydrolysis of 3-chloro-3-(phenylthio)-2-azetidinones with moist silica gel and catalytic amounts of zinc chloride led to azetidine-2,3-diones in excellent yield.

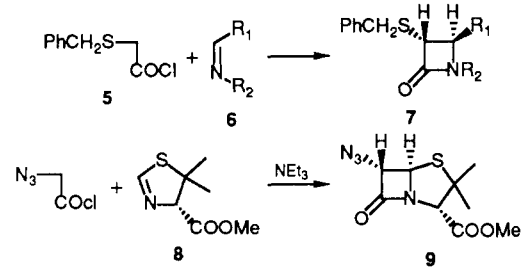
Azetidine-2,3-diones or α-keto β-lactams (**1**) are potentially very useful intermediates by virtue of the high concentration of functional groups in a small ring. In 1972 Lo and Sheehan[2] described the preparation of 6-oxopenicillanic acid (**2**) derivatives froim penicilin G and showed that the keto group adjacent to the β-lactam carbonyl was chemically very active. The same compound was also reported by Jen et al.[3] Later 7-oxocepham (**3**) derivatives were described by Applegate and co-workers[4] and also by Rapoport et al.[5] Sheehan and Lo[6] developed a Wittig type reaction involving 6-oxopenicillanic esters that led to **4**, a penicillin nucleus with the cephamycin type of side chain. Recently, Tufariello et al.[7] have reported a synthesis of azetidine-2,3-diones from α-ethylidene β-lactams.



1 **2** **3** **4**

We have prepared monocyclic α-keto β-lactams by several different methods.[8a] In a brief communication[8b] we have described the synthesis of this family of β-lactam derivatives via a Pummerer type reaction of α-phenylthio β-lactams. We describe now some highly functionalized β-lactams prepared by this general approach as well as details of our earlier work.[8b]

Steric Course of α-Phenylthio β-Lactam Formation. Previously[9] we have reported that the reaction between *S*-benzylthioglycolyl chloride (**5**), a Schiff base (**6**), and triethylamine produced a single isomer of β-lactam (**7**). On the basis of ^1H NMR spectral evidence, the trans configuration was assigned to this compound. The reaction of azidoacetyl chloride and triethylamine with a thioimidate (**8**) leads to a trans β-lactam (**9**).[10] Phenoxyacetyl chloride, triethylamine, and a Schiff base, however, generate mostly a cis β-lactam if the acid chloride is added slowly to the rest of the reactants.[11] The reason for this stereospecific formation of trans β-lactams with a thio group at C-3 or C-4 is not understood.



5 **6** **7** **8** **9**

For the preparation of 3-(phenylthio)-2-azetidinones (**13**)

† Deceased.

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