2 H), 1.93–2.43 (m, 4 H), 2.27 (s, 4 H); IR (neat) 2950 (s), 2875 (s), 2310 (m), 2225 (w), 1620 (m), 1450 (m), 1350 (m), 1190 (m), 925 (w), 785 (m), 755 (m), 720 (s), 710 (m), 625 (s), 470 cm^{-1} (br s); MS (70 eV), *m/e* 126 (d_4 89%), 125 (d_3 11%).

Cyclohexane-1,4-dione-d_8 and Cycloheptane-1,4-dione-d_8. A solution of diketone (2.00 g, 0.02 mol) in 10 mL of D_2O containing 10 μL of 40% NaOD in D_2O was stirred at room temperature. Chloroform extracts of the reaction mixture were dried (Na_2SO_4) and concentrated. Deuterium incorporation was determined by NMR (using methylene chloride as the internal standard) and mass spectrometry.

After two such treatments of 1- and 2-h duration, cyclohexane-1,4-dione, in 20% overall yield, appeared to be 99% exchanged by NMR, whereas mass spectrometry revealed the distribution of label to be 86% d_8, 9% d_7, 2% d_6, and 3% d_5 (97% exchanged).

Cycloheptane-1,4-dione required three exchanges (1, 2, and 6 h) to produce 95% deuterium incorporation. The NMR spectrum was unaltered after a fourth exchange of 6 h. The isotopic composition of the dione, recovered in 50% overall yield, was shown by mass spectrometry to be 85% d_8, 10% d_7, 3% d_6, and 2% d_5 (97% exchanged).

Thermal Rearrangements. All thermal rearrangements were performed in 1.5 × 10 cm o.d. Corning 0120 lead potash ampules, which had been soaked in concentrated NH_4OH overnight, rinsed with distilled water until the washings were neutral, rinsed with acetone, and oven-dried.

The olefins (10-μL samples) were introduced with a microsyringe and degassed (two freeze–thaw cycles). Cumene (2 μL) was added to 1,4-bis(dideuteriomethylene)cyclohexane for thermolyses at temperatures > 400 °C. The ampules were sealed under vacuum (10^{-4} mm) and either suspended in the vapors of a boiling solvent bath by a copper wire fastened to a hook at the base of the ampule or loaded into a probe carrier and lowered into the Techne fluidized alumina bath.

The vapor bath consisted of a 5 × 50 cm Pyrex tube fused to either a 500-mL or 100-mL round-bottom flask. The apparatus was insulated with several layers of asbestos tape, glass wool, and an outer wrapping of Fiberglas. The uninsulated upper 10 cm was cooled on all sides with a rapid stream of air.

The temperature of the vapor was measured with an iron-constantan thermocouple and a Leeds and Northrup No. 8686 millivolt potentiometer. For high-temperature work, the thermocouple was calibrated against boiling sulfur (448 °C).

After being heated for a specified time, the ampules were removed from the bath and cooled. Quantitative recovery of the rearranged olefin was revealed by GLPC analysis (*n*-decane was the internal standard). The contents of the ampule were then transferred to an NMR tube for recording of the spectrum. The progress of the rearrangement was monitored by observing the appearance of vinylic signals at 4.70 ppm.

Ozonolyses of Dienes. The NMR sample in CCl_4 was transferred with methylene chloride to a 15-mL, three-necked, round-bottom flask fitted with a dry ice condenser and gas inlet. Ozone was bubbled through the solution until a blue color persisted. Excess ozone was blown off with a stream of nitrogen.

Hydrogenations of Ozonides. The solution of ozonide and 20 mg of PtO_2 was added to a 25-mL Erlenmeyer flask containing a magnetic stirring bar. The flask was secured with glass wool inside the stainless steel Parr bomb lined with a 150-mL glass beaker. After being purged with nitrogen, the bomb was pressurized with 250 psi hydrogen and vented. After a second cycle of pressurizing and venting, a final adjustment of hydrogen pressure was made and stirring was started.

1,4-Dimethylenecyclohexane diozonide was converted to 1,4-cyclohexanediol in 1 h at room temperature under 250 psi hydrogen. The 1,4-dimethylenecycloheptane diozonide was similarly treated; however, an additional 2 h of stirring at 65 °C and 500 psi hydrogen was required for complete conversion to 1,4-cycloheptanediol.

The bomb was cooled and vented. The catalyst was removed by filtration, and the filtrate was checked by TLC for completeness of reaction. After removal of solvent, the diol was stirred with 50 mg of phenyl isocyanate in a well-stoppered flask at room temperature overnight, for conversion to the diphenylurethane. Unreacted phenyl isocyanate was removed under reduced pressure. The solid residue was suitable for mass spectrometric analysis without further purification.

Acknowledgment. We note with gratitude that the Norman Fund in Organic Chemistry, in memory of Ruth Alice Norman Weil Halsband, supported the graduate studies of C. A. Troise, VII, 1973–VI, 1978, and that this material is based upon work supported by the National Science Foundation under Grant CHE 76-24300. Our best thanks to John C. Schmidhauser for the molecular mechanical calculations, to Prof. W. R. Roth for recalculations of the kinetic data and determination of the heat of hydrogenation of 1,4-dimethylenecyclohexane, to Prof. J. J. Gajewski for sharing with us his revised kinetic parameters and generously giving us permission to publish here, and to Prof. N. L. Allinger and K. B. Wiberg for their much-appreciated, helpful comments.

Registry No. 1d$_0$, 81389-52-8; **2d$_0$**, 97135-84-7; 1,4-bis(dimethylcarbamido)cyclohexane, 97135-81-4; 1,4-bis[(dimethylamino)dideuteriomethylene]cyclohexane, 97135-82-5; 1,4-bis[(dimethylamino)dideuteriomethylene]cyclohexane bis(oxide), 97135-83-6; 4-hydroxycycloheptanone, 67963-12-6; dideuteriomethylene iodide, 865-43-0; cycloheptane-1,4-dione-d_8, 97135-85-8; cyclohexane-1,4-dione-d_7, 97135-86-9; cyclohexane-1,4-dione-d_6, 97149-90-1; cyclohexane-1,4-dione-d_5, 97135-87-0; cycloheptane-1,4-dione-d_7, 97135-88-1; cycloheptane-1,4-dione-d_6, 97149-91-2; cycloheptane-1,4-dione-d_5, 97135-89-2; bicyclo[2.2.2]octa-1,4-diyl, 97135-90-5; bicyclo[3.2.2]nona-1,4-diyl, 97135-91-6; 1,4-cycloheptanedione, 14950-46-0; cycloheptane-1,4-dione-d_8, 1680-86-0; 1,4-cyclohexanedione, 637-88-7.

Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes: Formal Total Synthesis of Streptonigrin

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Abstract: A formal, total synthesis of streptonigrin is detailed and is based on the sequential implementation of two inverse electron demand Diels–Alder reactions: cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with *S*-methyl 6-methoxy-5-nitro-2-quinolinethioimidate for construction of the streptonigrin ABC ring system followed by [4 + 2] cycloaddition of the resulting dimethyl 5-(6-methoxy-5-nitro-2-quinolyl)-1,2,4-triazine-3,6-dicarboxylate with enamine derivatives of 2-(benzyloxy)-3,4-dimethoxypropiophenone for preparation of the streptonigrin CD biaryl ring system and completion of the assemblage of the streptonigrin carbon skeleton. A study of the factors effecting the regioselectivity of the [4 + 2] cycloaddition of 1,2,4-triazines with electron-rich olefins is detailed. Factors influencing the Diels–Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with nucleophilic dienophiles containing a C=N double bond are examined and detailed.

Streptonigrin[2] (**1**), an antitumor antibiotic isolated from *Streptomyces flocculus*, was identified and characterized in 1959,[3] its structure correctly determined in 1963[4] by a combination of chemical degradative and spectroscopic studies and confirmed in

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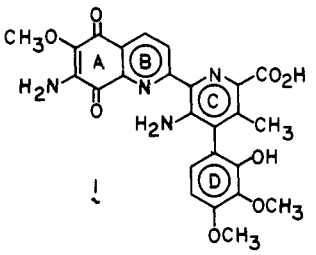
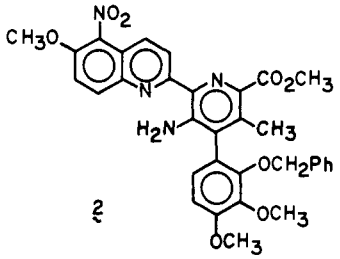
1975[5] with a single crystal X-ray analysis. Since the initial



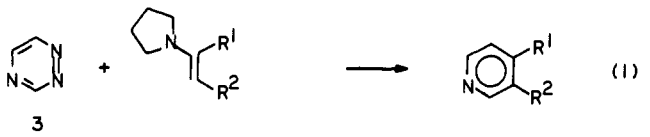
identification, streptonigrin (**1**) has been the subject of extensive synthetic,[2,6] biosynthetic,[2,7] biological,[2,8] and biochemical[2,9] studies. The complex structure of streptonigrin, a quinoline-5,8-quinone possessing a pentasubstituted pyridine, investigations on the chemical mechanism by which streptonigrin expresses its biological effects, efforts to define the essential structural features required for activity, and revealing biosynthetic investigations account for the continued interest in this structure.

A total synthesis of streptonigrin has been reported in full detail by Weinreb,[10] and a subsequent total synthesis by Kende[11] has been described in a preliminary communication. In addition, a number of approaches to the preparation of streptonigrin, as well as simplified and related systems, have been published.[2,6] Herein we describe full details[12] of a formal total synthesis of streptonigrin (**1**), which provides the advanced intermediate **2** in Kende's total synthesis of streptonigrin in six steps from readily available starting materials. Compound **2** has been converted to streptonigrin by a series of seven steps (ring A functionalization: five steps, followed by phenol and ester deprotection).[10,11] The approach, outlined in Scheme I, utilizes two sequential inverse electron demand Diels–Alder reactions of electron-deficient azadienes for the preparation of the pentasubstituted pyridine ring (ring C) *and* for assemblage of the complete carbon framework of streptonigrin.



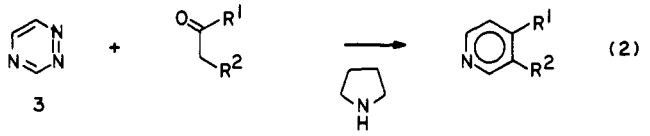
The ability[11] of the 6-methoxy-5-nitro-2-quinolyl system to serve as an appropriate precursor to the quinoline-5,8-quinone AB ring system of streptonigrin and the ability[11] of a carboxylate to serve as a potential functionality for introduction of the streptonigrin pyridyl amine (ring C, C-5 NH_2) simplified the implementation of this approach to streptonigrin.

Regioselectivity of the Inverse Electron Demand Diels–Alder Reactions of 1,2,4-Triazines: Studies on Streptonigrin CD Ring Construction. In preliminary studies, the potential utility of the inverse electron demand Diels–Alder reaction of 1,2,4-triazines with electron-rich olefins for construction of the streptonigrin CD biaryl ring system was investigated. Initial studies, which have been reported in detail,[13] revealed that the parent 1,2,4-triazine (**3**) undergoes a mild, regiospecific [4 + 2] cycloaddition with pyrrolidine enamines (eq 1). In each instance, the mode of



(1)

cycloaddition is across C-3 and C-6 of the 1,2,4-triazine nucleus, and the nucleophilic carbon of the electron-rich dienophile attaches to C-3 of 1,2,4-triazine. The reduction of this process to a catalytic Diels–Alder reaction with in situ generation of the pyrrolidine enamine, as expected, does not alter these observations,[13b] eq 2.



(2)

Similar results have been reported for a number of electron-rich dienophiles. Variations in the mode of cycloaddition and the regioselectivity from that observed here seem to occur only when more reactive electron-rich dienophiles are employed.[14] Table I details a study which was conducted to determine the feasibility of this approach for the preparation of the streptonigrin CD biaryl ring system and which illustrates the effects of substitution of the electron-deficient 1,2,4-triazine nucleus with electron-withdrawing groups. In the two cases studied, the position and number of such groups control the reactivity as well as the observed regioselectivity without altering the mode of cycloaddition. The mode of [4 + 2] cycloaddition of enamines with 3-carboethoxy-1,2,4-triazine (**4**)[15] is across C-3 and C-6 of the 1,2,4-triazine nucleus *but* the

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(5) Chiu, Y.-Y.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1975**, *97*, 2525.

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(11) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271.

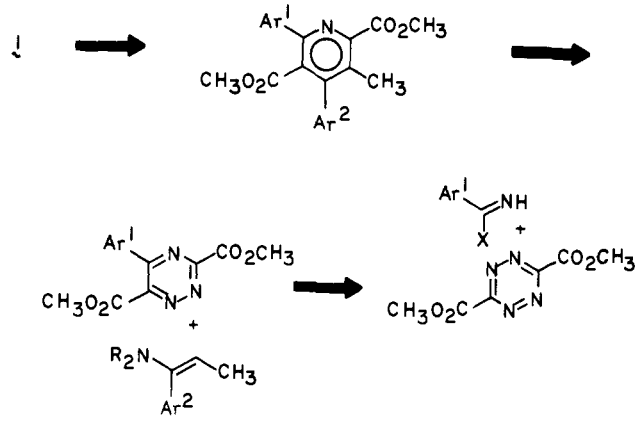
(12) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. (b) Boger, D. L.; Panek, J. S. *Ibid.* **1982**, *47*, 3763. (c) Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1983**, *24*, 4511. (d) Boger, D. L.; Panek, J. S.; Duff, S. R.; Yasuda, M., unpublished observations.

(13) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179. (b) Boger, D. L.; Panek, J. S.; Meier, M. M. *Ibid.* **1982**, *47*, 895.

(14) (a) For a recent review, see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) In nearly all reported instances, the mode of cycloaddition of electron-rich olefins with 1,2,4-triazines is across C-3/C-6. Alternative modes of cycloaddition of electron-rich dienophiles with **4** have been reported, addition across C-5/N-2, and these observations appear to be restricted to instances employing ynamines as dienophiles. The site of nucleophilic attack on 1,2,4-triazine **4**: e.g., CN^- and H_2O (cf. Krass, D. K.; Paudler, W. W. *J. Heterocycl. Chem.* **1974**, *11*, 43. Paudler, W. W.; Chen, T.-K. *Ibid.* **1970**, *7*, 767) has been demonstrated to occur selectively at C-5. This suggests that cycloadditions across C-5/N-2 of 1,2,4-triazine (**4**) may, in fact, represent a two-step nucleophilic addition–cyclization involving a discrete dipolar intermediate and that cycloadditions across C-3/C-6 of the 1,2,4-triazine nucleus may not proceed via a discrete dipolar intermediate resulting from initial, nucleophilic attack at C-3.

(15) Paudler, W. W.; Barton, J. M. *J. Org. Chem.* **1966**, *31*, 1720; Paudler, W. W.; Krass, D. *Synthesis* **1974**, 351.

Scheme I

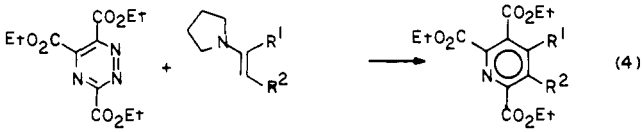


nucleophilic carbon of the electron-rich dienophile attaches to C-6, eq 3 and entries 1–6 (Table I). Thus, the mode of addition is

(3)

4

identical with that of the parent system but occurs with the opposite regiospecificity. In addition, the overall reactivity is qualitatively diminished despite the additional electron-withdrawing character of the ethoxycarbonyl group. This is evident from the example detailed in entry 3 of Table I where enamine isomerization to the less stable, and less hindered, isomer is faster than the initial [4 + 2] cycloaddition. By contrast, 3,5,6-tricarboethoxy-1,2,4-triazine (**5**)[16] undergoes rapid reaction with enamines with addition occurring across C-3 and C-6 of the 1,2,4-triazine nucleus and the nucleophilic carbon of the dienophile attaches to C-3, eq 4 and entries 7–9 (Table I). This is quali-



(4)

5

tatively the same behavior observed with the parent system, 1,2,4-triazine (**3**), with the exception that the overall reactivity appears to be enhanced. For instance, 1-phenyl-1-[(trimethylsilyl)oxy]ethylene is sufficiently reactive to participate in a [4 + 2] cycloaddition with **5** (entry 10, Table I) but fails to react with 1,2,4-triazine (**3**). Entry 9 detailed in Table I confirmed the potential of this approach for the preparation of the streptonigrin biaryl CD ring system.[12b]

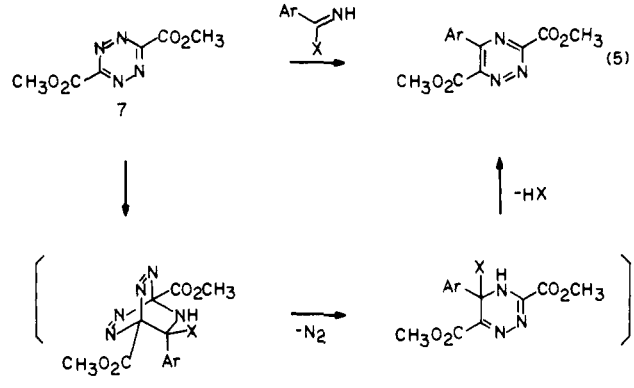
The structures of the Diels–Alder products in Table I were proven by hydrolysis and exhaustive decarboxylation of **6a–c,h–i** and subsequent comparison of the resultant aryl pyridines with samples of a known structure.[17]

Attempts to utilize the catalytic Diels–Alder conditions with in situ generation of the pyrrolidine enamines were modestly successful with **4**, entries 4–6 (Table I), and unsuccessful with **5** due to competing 1,2,4-triazine carboxamide formation.

Additional examples of the cycloadditions of 3,5,6-tricarboethoxy-1,2,4-triazine (**5**) in studies to construct the lavendamycin β-carboline CDE ring system, an antitumor antibiotic structurally related to streptonigrin, are to be detailed in a later report.[12d] These studies further implicate an important steric component (dienophile) in determining the rate of cycloaddition, a result which is evident from entries 3 and 10 in Table I.

In many instances the initial reaction of the enamines with substituted 1,2,4-triazines, particularly 3,5,6-tricarboethoxy-1,2,4-triazine (**5**), occurs at a satisfactory rate at 25 °C with the evolution of nitrogen, and the rate-limiting step in the formation of the pyridine products is the final aromatization step involving loss of the secondary amine (entries 7–9, Table I). All efforts to promote a low-temperature [4 + 2] cycloaddition of enamines with the substituted 1,2,4-triazines by the addition of conventional Lewis acids have been unsuccessful to date. However, in instances when the [4 + 2] cycloaddition does not proceed at a satisfactory rate at reasonable temperatures, the pressure-promoted Diels–Alder reaction has proved useful in increasing the rate of cycloaddition at mild reaction temperatures (25 °C), entry 10, Table I. Thus, many of the sensitive electron-rich olefins can be induced to undergo the [4 + 2] cycloaddition at temperatures which ensure their stability and, as detailed in the formal total synthesis of streptonigrin, with increased regioselectivity by conducting the reaction under modest pressures (6.2 kbar).

1,2,4-Triazine Preparation by Thermal Cycloaddition of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate with C=N Dienophiles: Studies on the Streptonigrin ABC Ring System. Assured that the [4 + 2] cycloaddition of an appropriately substituted 1,2,4-triazine with an enamine derived from 2-(benzyloxy)-3,4-dimethoxypropiophenone[18] could serve as a potential approach to the preparation of the streptonigrin CD ring system, the utility of a second inverse electron demand Diels–Alder reaction for the preparation of the required 1,2,4-triazine was investigated, eq 5. Investigations on the thermal cycloaddition of substituted 1,2,4,5-tetrazines with heterodienophiles[14] have been reported, and short accounts of their reaction with imidates[19a] and amidines[19b] suggested the likely potential of this approach for the preparation of 1,2,4-triazines. Table II details the results of a study of this reaction which illustrate the importance of the nucleophilic character of the dienophile and the leaving group ability of the X, eq 5.



(5)

7

Initial efforts employing aryl nitriles and amidines were unsuccessful. 2-Cyanopyridine failed to react with dimethyl

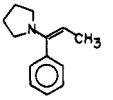
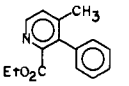
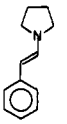
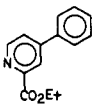
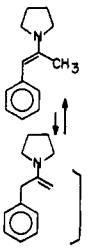
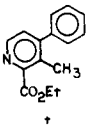
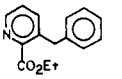
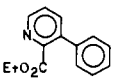
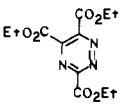
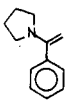
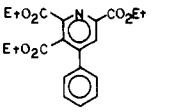
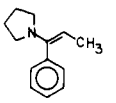
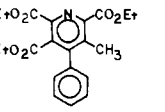
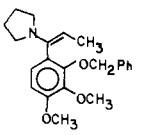
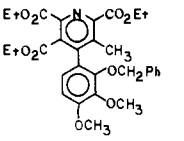
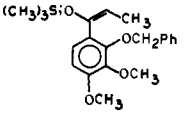
(16) (a) Ratz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931. (b) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth.*, submitted.

(17) Structures **6a–c, e, f, h**, and **i** were verified by exhaustive decarboxylation (LiCl, wet Me_2SO, 170 °C) as follows: **6a** afforded 4-methyl-3-phenylpyridine (Pridgen, L. N. *J. Heterocycl. Chem.* **1975**, *12*, 443). **6b** and **6h** afforded 4-phenylpyridine (Aldrich Chemical Co.). **6c** and **6i** afforded 3-methyl-4-phenylpyridine (Abramovitch, R. A.; Saha, M. *Can. J. Chem.* **1966**, *44*, 1765). **6e** afforded 3-phenylpyridine (Aldrich Chemical Co.). **6a** and **6c** are isomeric of one another. **6b** is isomeric with **6e**. **6f** afforded 3-ethyl-4-methylpyridine (ICN K and K Laboratories).

(18) 2-(Benzyloxy)-3,4-dimethoxypropiophenone was prepared as described: Liao, T. K.; Wittek, P. J.; Cheng, C. C. *J. Heterocycl. Chem.* **1976**, *13*, 1283.

(19) (a) Roffey, P.; Verge, J. P. *J. Heterocycl. Chem.* **1969**, *6*, 497. (b) Figeys, H. P.; Mathy, A. *Tetrahedron Lett.* **1981**, *22*, 1393. See also: Figeys, H. P.; Mathy, A. Dralants, A. *Synth. Commun.* **1981**, *11*, 655. (c) For experimental procedures followed for the conversion of nitriles to the substrates employed, see the following. Amidines: Partridge, M. W.; Short, W. F. *J. Chem. Soc.* **1947**, *390*. *N,N*-Diethylamidines: Lorz, E.; Baltzly, R. *J. Am. Chem. Soc.* **1948**, *70*, 1904. Imidates: Libman, D. D.; Slack, R. *J. Chem. Soc.* **1956**, 2253. *S*-Methyl thioimidates: Boon, W. P. *J. Chem. Soc.* **1945**, *601*; Reynaud, P.; Moreau, R. C.; Thu, N. H.; Delepine, M. M. *Comp. Rend.* **1961**, *253*, 1968.

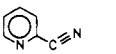
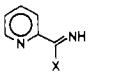
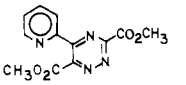
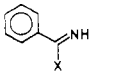
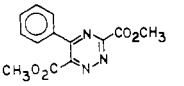
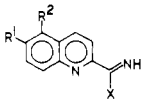
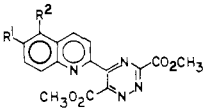
Table I. [4 +2] Cycloadditions of 1,2,4-Triazines 4 and 5

entry	1,2,4-triazine	dienophile	conditions[a] solv, temp, °C (time, h)	prod[b]	% yield[c]
1[d]	 4		$CHCl_3$, 45 (24) $PhCH_3$, 80 (18) neat, 80 (5)		6a 10% 37% 0%
2[e]	4		$CHCl_3$, 45 (6) $CHCl_3$, 60 (24)		6b 38% 49%
3[f]	4		$CHCl_3$, 45 (13) neat, 50 (28)	 + 	6c <10% 10% 6d 20% 36%
4	4		$CHCl_3$, 45 (48)[g]		6e 47%
5	4		$CHCl_3$, 45 (20)[g]		6f 24%
6	4		$CHCl_3$, 45 (36)[g]		6g 19%[h]
7[f]	 5		$CHCl_3$, 45 (24) $CHCl_3$, 60 (18)		6h 45% (>95%)[i] 79% (26:1)[i]
8[d]	5		$CHCl_3$, 45 (8)		6i 73% (>9:1)[i]
9[d]	5		$CHCl_3$, 45 (3)		6j 59% (9:1)[i]
10	5				
		X = $OSiMe_3$, R = H[j]		$CHCl_3$, 60 (22) CH_2Cl_2, 6.2 kbar, 25 (24)	6h 72% (7.2:1)[i] 54% (>95%)[i]
		X = $OSiMe_3$, R = CH_3[j]		$CHCl_3$, 60(16)[l] CH_2Cl_2, 6.2 kbar, 25 (24)	6i 0% 0%
		X = SEt, R = CH_3[m]		$CHCl_3$, 80–160 (10–20)[l]	6i 0%
11[l]	5			$CHCl_3$, 65 (24) CH_2Cl_2, 6.2 kbar, 25 (24)	6j 0% 0%

Footnote to Table I

[a] The [4 + 2] cycloadditions were run under an atmosphere of nitrogen (0.1–0.2 M substrate) as described in the Experimental Section. [b] All products exhibited the expected or previously reported ^{1}H NMR, IR, and MS characteristics consistent with the assigned structure. All new compounds gave satisfactory CHN analysis or HRMS information. [c] All yields are based on pure material isolated by chromatography (SiO_2). [d] The pyrrolidine enamine was prepared with the aid of titanium tetrachloride: White, W. A.; Weingarten, H. *J. Org. Chem.* 1967, *32*, 213. [e] The pyrrolidine enamine was prepared with the aid of anhydrous magnesium sulfate: Zoretic, P. A.; Barcelos, F.; Branchaud, B. *Org. Prep. Proced. Int.* 1976, *8*, 211. [f] The pyrrolidine enamine was prepared with the aid of 4-Å molecular sieves: Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* 1971, *36*, 1570. [g] The reaction was run in the presence of 4-Å molecular sieves (50 mg/mmol of substrate) in chloroform containing 1.0 equiv (entry 6) or 2.0 equiv (entries 4–5) of pyrrolidine; see ref 13b. [h] The major product isolated (38%) was an unaromatized dihydropyridine. [i] For **6h** derived from the pyrrolidine enamine (entry 7) or trimethylsilyl enol ether (entry 10) of acetophenone, the regioselectivity of the cycloaddition was accurately determined [26:1 **6h** (79%)/regioisomer (3%) for entry 7 and 7.3:1 **6h** (72%)/regioisomer (9%) for entry 10] by isolation and characterization of the isomeric products. For **6i** and **6j** (entries 8 and 9), the regioselectivity of the cycloaddition was estimated by ^{1}H NMR by inspection (integration and peak height measurements) of the aryl methyl signals in the crude reaction products. Purification by recrystallization provided pure **6i**. Less than 6% of the regioisomer of **6j** could be detected in the crude reaction product; **6j**/regioisomer, 9:1. [j] 1-phenyl-1-[(trimethylsilyl)oxy]ethylene was purchased from Fluka AG. 1-Phenyl-1-[(trimethylsilyl)oxy]-1-propene, and 1-[2-(benzyloxy)-3,4-dimethoxyphenyl]-1-[(trimethylsilyl)oxy]-1-propene were prepared from the corresponding propiophenone (lithium diisopropylamide/trimethylsilylchloride): House, H.; Czuba, L.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* 1968, *34*, 2324. [k] A detailed procedure for this conversion is available; see ref 16b. [l] Additional similar reactions in toluene, dioxane, acetonitrile, or neat were unsuccessful. [m] The vinyl sulfide was prepared with the aid of titanium tetrachloride: Mukaiyama, T.; Saigo, K. *Chem. Lett.* 1973, 479.

Table II. Diels–Alder Reaction of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate (**7**) with C=N Heterodienophiles

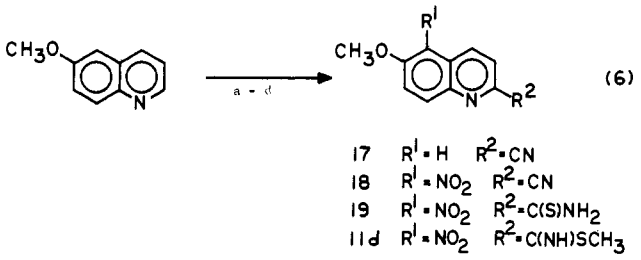
		conditions		
	dienophile	temp, °C (time, h)[a]	prod[b]	% yield[c]
8		80–100 (15–42) 150 (10)[d]		*e*
				12
9a	X = SCH_3	80 (20)		68%
9b	= OEt	80 (8–12)		37%
9c	= NH_2	25 (5)		*f*
9d	= NEt_2	25–50 (25)		*f*
				13
10a	X = SCH_3	80 (24)		64%
10b	= OEt	60 (10)		27%[g]
10c	= NH_2	25 (1)		*h*
				14
11a	$R^1 = R^2 = H$; X = SCH_3	80 (4)		70%
11b	= OEt	80 (20)		33%
	$R^1 = OCH_3$ $R^2 = H$			15
11c	X = SCH_3	80 (4)		78%
	$R^1 = OCH_3$ $R^2 = NO_2$			16
11d	X = SCH_3	80 (20–24)[i]		82%

[a] All reactions were run in dry dioxane under an atmosphere of nitrogen (0.1–0.3 M in substrate) in the presence of 2.0 equiv of **7** unless otherwise noted. [b] All products exhibited the expected or reported ^{1}H NMR, IR, and MS characteristics consistent with the assigned structure. All new compounds gave satisfactory CHN analysis or HRMS information. [c] Yield of purified product isolated by chromatography (SiO_2). [d] *o*-Dichlorobenzene was employed as solvent. [e] No detectable reaction. [f] Rapid, exothermic reaction accompanied by the evolution of nitrogen; no detectable 1,2,4-triazine product. [g] See ref 19a. [h] See ref 19b. [i] **7** (1.3 equiv) was employed.

1,2,4,5-tetrazine-3,6-dicarboxylate[20] (**7**), and no identifiable products could be isolated from the reaction of **7** with arylamidines **9c,d** and **10c**[19c] under a range of conditions despite an initial exothermic reaction which was accompanied by the evolution of nitrogen. Aryl imidates **9–11b**[19c] were found to provide the desired 1,2,4-triazine products **12–14** albiet in modest yields. In sharp contrast, the *S*-methyl thioimidates **9–11a** and **11c–d**[19c] provided the [4 + 2] cycloaddition products **12–16** in dependable yields under mild, controllable reaction conditions (45–90 °C, dioxane). In no instance was there evidence of the product 1,2,4-triazine participating or competing with **7** in a subsequent Diels–Alder reaction with unreacted *S*-methyl thioimidate. The success of the [4 + 2] cycloaddition reaction of *S*-methyl thioimidates with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) can be attributed to the optimal combination of the nucleophilic character of the C=N dienophile (amidine, *N,N*-dialkylamidine > *S*-methyl thioimidate ≃ ethyl imidate) and the leaving group ability of X ($-SCH_3$ > $-OEt$ > $-NH_2$, $-N(R)_2$), eq 5.

Formal Total Synthesis of Streptonigrin. The starting material for the synthesis of **2** was the *S*-methyl thioimidate **11d** which was prepared in four steps from commercially available 6-methoxyquinoline, eq 6. Treatment of 6-methoxyquinoline with *p*-toluenesulfonyl chloride/potassium cyanide in a methylene chloride–water two-phase reaction system for a prolonged reaction period afforded 2-cyano-6-methoxyquinoline (**17**) directly without isolation of the intermediate Reissert compound. The generality of this method for the direct preparation of 2-cyanoquinolines has been demonstrated and further extended to allow the direct preparation of 1-cyanoisoquinolines.[21] Nitration of **17** provided

(20) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435; Spencer, G. H.; Cross, P. C.; Wiberg, K. B. *J. Chem. Phys.* **1961**, *35*, 1939; Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer J. *J. Org. Chem.*, in press.



17 R^1 = H R^2 = CN
18 R^1 = NO_2 R^2 = CN
19 R^1 = NO_2 R^2 = C(S)NH_2
11d R^1 = NO_2 R^2 = C(NH)SCH_3

(6)

[a] (a) 1.6 equiv of *p*-TsCl, 3.0 equiv of KCN, CH_2Cl_2–H_2O, 25 °C, 120 h, 81%. (b) 1.5 equiv of 70% HNO_3, H_2SO_4, 25 °C, 82%. (c) H_2S, catalytic Et_2NH, dioxane, 0–25 °C, 24 h, 75–88%. (d) 2–4 equiv of CH_3I, CH_3CN, 80 °C, 2 h; saturated aqueous $NaHCO_3$–$CHCl_3$, 25 °C, 15 min, 56%.

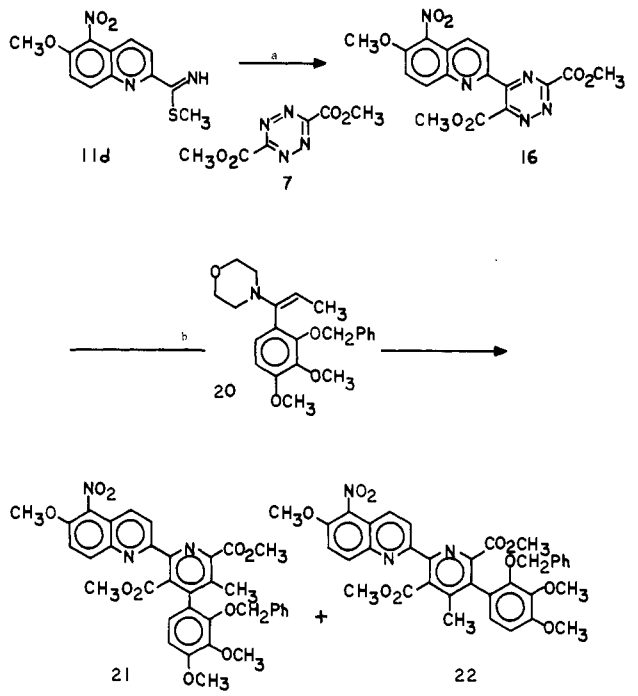
18 cleanly.[22] Conversion of the nitrile to the *S*-methyl thioimidate **11d** via the thioamide **19** completed the preparation of the starting material.

Treatment of *S*-methyl thioimidate **11d** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) provided 1,2,4-triazine **16** (Table II, 82%), and subsequent treatment of **16** with the morpholino enamine of 2-(benzyloxy)-3,4-dimethoxypropiophenone **20a** afforded a mixture of Diels–Alder adducts **21** and **22** of which the preferred adduct **21** proved to contain the carbon framework of streptonigrin,[23] Scheme II.

Table III summarizes representative details of our initial investigation of the pyridyl CD ring construction of streptonigrin. In agreement with the results of our preliminary studies detailed in Table I, the morpholino enamine **20a** cycloadds exclusively across C-3/C-6 of the 1,2,4-triazine nucleus of **16**. However, the decreased reactivity of **16** toward cycloaddition relative to 3,5,6-tricarboethoxy-1,2,4-triazine (**5**) and the thermal instability of the morpholino enamine **20a** required a select set of reaction conditions for cycloaddition. The results detailed in Table III indicate a clear trend; the nucleophilic carbon of the electron-rich dienophile prefers attachment at C-3 of the 1,2,4-triazine **16**, results consistent with the studies with 3,5,6-tricarboethoxy-1,2,4-triazine (**5**, Table I), but the vigorous reaction conditions required for complete reaction eliminate the observed regioselectivity. Thus, the choice of reaction conditions can determine the relative amount of **22**. It is not unlikely that the 5-(6-methoxy-5-nitro-2-quinolyl) group on the 1,2,4-triazine **16** is a stronger electron-withdrawing substituent than an ethoxycarbonyl group (e.g., in 5) and thus responsible for the diminished rate of cycloaddition (**16** vs. **5**) *and* the observed regiospecificity (compare **16**, **5**, and **4**).

All efforts to promote the [4 + 2] cycloaddition of the morpholino enamine of 2-(benzyloxy)-3,4-dimethoxypropiophenone **20a** or the corresponding pyrrolidine enamine **20b** with **16** by the use of conventional Lewis acids have been unsuccessful and promoted only the decomposition of the electron-rich olefin with no evidence of Diels–Alder catalysis.[23c] In addition, efforts to effect

Scheme II[a]



[a] (a) Dioxane, 80 °C, 22 h, 82%, Table II. (b) $CHCl_3$, 120 °C, 42 h, 68% (21/22, 1:1) or CH_2Cl_2, 6.2 kbar, 25 °C, 96 h, 58% (21/22, 1.4:1), Table III.

Table III. Cycloaddition Reaction of 1,2,4-Triazine **16** with Morpholino Enamine **20a**

conditions: equiv **20a**, solv, temp, °C (time, h)	% yield (**21**/**22**)[a]
4.0, CH_3CN, 80 (12–24)	15–26 (4:1)[b]
2.0, CH_3CN, 120 (16)[c]	30 (1:1)
2.0–6.0, $CHCl_3$, 45–80 (12–48)	*d*
2.0, $CHCl_3$, 120 (16)[c]	30 (1:1)
4.0, $CHCl_3$, 120 (42)[c]	68 (1:1)
4.0, CH_2Cl_2, 6.2 kbar, 25 (120)	58 (1.4:1)
4.0, CH_3CN, 6.2 kbar, 25 (96)	0

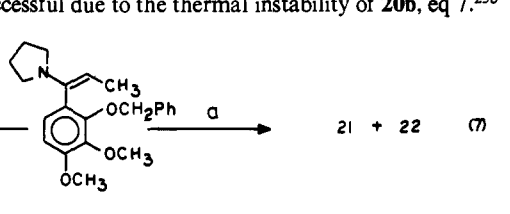
[a] Yield of purified product isolated by column chromatography (SiO_2). [b] 35–45% 1,2,4-triazine **16** recovered. [c] Reaction run in a sealed reaction vessel. [d] Trace of **21** detected chromatographically.

Table IV. Cycloaddition Reaction of 1,2,4-Triazine **16** with Pyrrolidine Enamine **20b**

conditions: equiv **20b**, solv, temp, °C (time, h)	% yield (**21**/**22**)[a]
2.0–4.0, $CHCl_3$, 60–120 (12–48)	0
2.0–4.0, CH_3CN, 60–120 (12–48)	0
2.0, CH_2Cl_2, 6.2 kbar, 25 (120)	37 (2.8:1)
4.0, CH_2Cl_2, 6.2 kbar, 25 (120)	65 (2.8:1)

[a] Yield of purified product isolated by chromatography (SiO_2).

the reaction of the pyrrolidine enamine **20b** with **16** thermally were likewise unsuccessful due to the thermal instability of **20b**, eq 7.[23b]



(7)

20b

(a) Table IV, 6.2 kbar, CH_2Cl_2, 25 °C, 120 h, 65% (21/22 2.8:1)

Convinced that the expected regioselectivity would be observed provided mild, thermal conditions could be devised for effecting the [4 + 2] cycloaddition of **20a** or **20b** with **16**, pressure-promoted

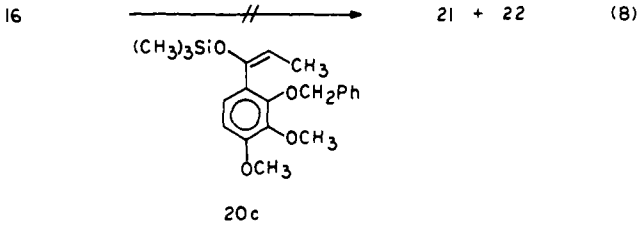
(21) Boger, D. L.; Brotherton, C. E.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4056. Boger, D. L.; Brotherton, C. E. *Ibid.* **1984**, *49*, 4050.

(22) Clean nitration of **17** requires slow addition of HNO_3 and maintenance of the reaction temperature at 0 °C. Nitration of 6-methoxyquinoline afforded 6-methoxy-5-nitroquinoline which failed to provide **17** upon treatment with *p*-toluenesulfonyl chloride/potassium cyanide in methylene chloride–water.

(23) (a) The ^1H NMR ($CDCl_3$) of **21** was identical with the spectrum of authentic **21** provided by Prof. A. S. Kende. (b) The morpholino enamine **20a** was prepared from 2-(benzyloxy)-3,4-dimethoxypropiophenone with the aid of titanium tetrachloride; see: White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. Details are provided in the supplementary material. The instability of the pyrrolidine enamine of 2-(benzyloxy)-3,4-dimethoxypropiophenone **20b** precluded its use in a successful thermal cycloaddition with 1,2,4-triazine **16**. (c) Attempts to catalyze the cycloaddition reaction of **16** with **20a** by the addition of conventional Lewis acid catalysts [$AlCl_3$, BF_3·OEt_2, $FeCl_3$, $Cu(BF_4)_2$, $Cu(AcAc)_2$, $Co(AcAc)_2$, and $Ni(AcAc)_2$] or with the use of tris-(*p*-bromophenyl)hexachloroantimonate [see: Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem Soc. C* **1969**, 2719] were unsuccessful and promoted decomposition of enamine **20a**. (d) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664. Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282.

Diels–Alder reaction conditions were examined.[23d] In addition, as a result of observations made in related studies, it was expected that the pyrrolidine enamine of 2-(benzyloxy)-3,4-dimethoxypropiophenone **20b** would show a significant increase in the regioselectivity of cycloaddition with **16** compared to the corresponding morpholino enamine provided that mild, thermal conditions could be maintained.[12d] Consistent with these expectations, the pressure-promoted (6.2 kbar, 25 °C) cycloaddition of **20a**, Scheme II and Table III, and **20b**, eq 7 and Table IV, provided the desired adducts **21**/**22** with a preference for the predicted and desired regioisomer **21** (1.4:1 and 2.8:1 **21**/**22**, respectively) in acceptable yields. Under the best conditions examined, the desired product **21** was isolated in nearly 50% yield from the reaction of **20b** with **16** (6.2 kbar, 25 °C), Table IV.

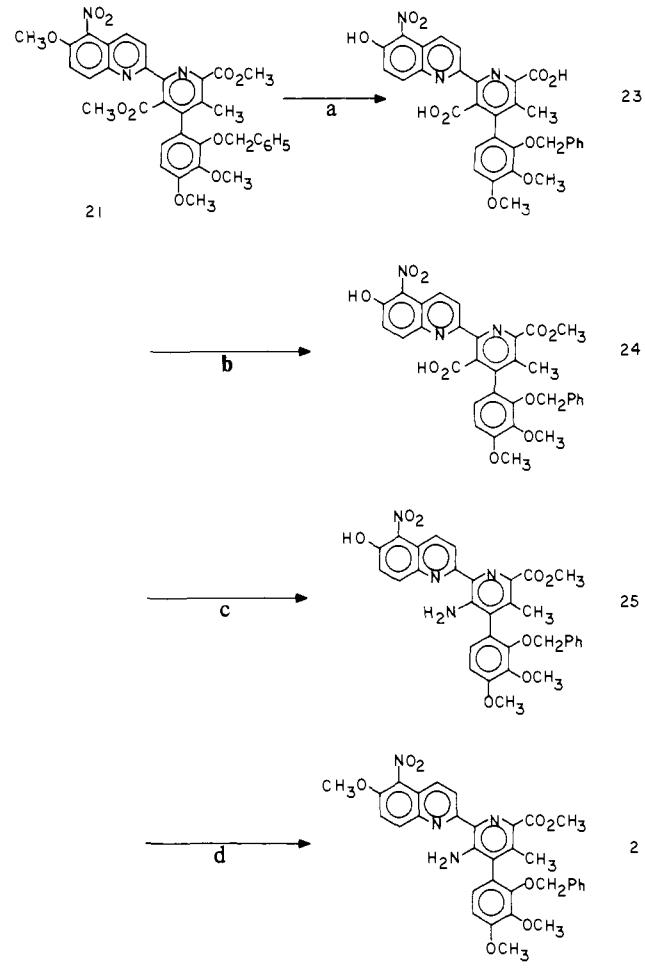
In contrast, and in agreement with the observations detailed in Table I (entry 11), the trimethylsilyl enol ether of 2-(benzyloxy)-3,4-dimethoxypropiophenone **20c** failed to undergo a [4 + 2] cycloaddition with **16** under thermal or pressure-promoted Diels–Alder conditions, eq 8.



20c

The final conversions of **21** to the streptonigrin advanced intermediate **2** are detailed in Scheme III. This formally required conversion of the pyridyl-5-carboxylate to an amino group and the utilization of a modified Curtius rearrangement on the free 5-carboxylic acid has been reported to effectively provide this conversion.[11] The initial plan to simply hydrolyze both methyl esters (pyridyl C-2 and C-5) and selectively reesterify the unhindered carboxylic acid (pyridyl C-2) proved more difficult than anticipated. All direct hydrolytic methods of deesterification failed to effect hydrolysis of the hindered 5-carbomethoxy group.[24] Methods involving dealkylative deesterification were found to be satisfactory for conversion of the hindered ester to the carboxylic acid, but in all instances the aryl methoxy group ortho to the electron-withdrawing nitro group underwent dealkylative demethylation prior to hydrolysis of the hindered ester. Thus, treatment of **21** with the sodium salt of phenylselenol under the conditions described by Liotta[25] afforded **23**. Simple, and selective, Fischer esterification of the unhindered carboxylic acid provided **24**. Conversion of the 5-carboxylate to an amine using a modified Curtius rearrangement and Shioiri–Yamada's reagent,[26] diphenylphosphoroazidate, followed by methylation[27] of the free phenol provided **2**. The tetracyclic amine **2** was identical in all respects with the material previously described in the work of Kende and co-workers.[11,28,29]

Scheme III[a]



[a] (a) 5.0 equiv of NaSePh, THF–HMPA, 70 °C, 21 h. (b) 10% HCl, CH_3OH, 25 °C, 18 h. (c) 10 equiv of $(PhO)_2P(O)N_3$, C_6H_6, 80 °C, 2.5 h; H_2O–C_6H_6, 80 °C, 1 h, 40% from **21**. (d) CH_3I, K_2CO_3, THF, 65 °C, 21 h, 94%.

Experimental Section[30]

General Experimental Procedure for the Inverse Electron Demand Diels–Alder Reactions of 1,2,4-Triazines 4 and 5 (Table I, Entries 1–3, 7–10): 5-Methyl-4-[2-(benzyloxy)-3,4-dimethoxyphenyl]-2,3,6-tricarboethoxypyridine (6j). A solution of 3,5,6-tricarboethoxy-1,2,4-triazine[16] (126 mg, 0.5 mmol) in $CHCl_3$ (0.5 mL) was treated with 1-pyrrolidinyl-1-(2-benzyloxy-3,4-dimethoxyphenyl)-1-propene[18,23b] (353 mg, 1.0 mmol, 2.0 equiv) in $CHCl_3$ (0.5 mL) under nitrogen (25 °C), and the resulting dark-orange solution was warmed at 45 °C for 3 h. Chromatography of the crude product (SiO_2, 30% ether–pentane eluant) afforded 167 mg (274 mg theoretical, 59%) or pure **6j** as a viscous yellow oil: ^1H NMR ($CDCl_3$) δ 7.45–6.76 (7 H, m, aromatic), 5.07 (1 H, d, J = 13 Hz, OCH_2Ph), 4.73 (1 H, d, J = 13 Hz, OCH_2Ph), 4.47 (2 H, q, J = 8 Hz, CH_2), 4.45 (2 H, q, J = 8 Hz, CH_2), 4.15 (2 H, q, J = 8 Hz, CH_2), 3.91 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 2.22 (3 H, s, $ArCH_3$), 1.45 (3 H, t, J = 8 Hz, CH_3), 1.42 (3 H, t, J = 8 Hz, CH_3), 1.05 (3 H, t, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.5 (C=O), 165.9 (C=O), 164.4 (C=O), 154.8 (C-4′), 150.3 (C-2), 149.9 (C-6), 147.5 and 142.8 (C-2′/C-4), 137.4 (C-3), 136.5 (C-5), 133.4 (C-8′), 128.4 (C-3′), 128.3 (C-10′), 127.7 (C-11′), 124.6 (C-9′), 124.1 (C-6′), 122.5 (C-1′), 107.5 (C-5′), 75.2 (C-7′), 62.4 (CH_2), 62.0 (CH_2), 61.6 (CH_2), 61.0 (OCH_3), 56.1 (OCH_3), 16.4 ($ArCH_3$), 14.16 (CH_3), 13.99 (CH_3),

(24) Unsuccessful attempts include: (a) LiOH, MeOH–THF–H_2O, see: Corey, E. J.; Szekely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, 3529. (b) KO_2, see: Filippo, J. S.; Ramano, L. J.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* **1976**, *41*, 586. (c) *t*-BuOK–H_2O (anhydrous hydroxidee, see: Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918. (d) 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU), xylene, see: Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1973**, *38*, 1223. (e) EtSH–$AlCl_3$, see: Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.* **1978**, 5211.

(25) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365; **1977**, 4369. Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605. See also: McMurray, J. *Org. React.* **1976**, *24*, 187.

(26) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

(27) Attempts to methylate the free phenol with excess diazomethane resulted in phenol and *N*-methylation.

(28) We are grateful to Professor A. S. Kende, University of Rochester, for providing ^1H NMR and IR spectra of **2** and a sample of **2** for direct comparison. Synthetic **2** described herein and the sample of **2** provided by Prof. Kende were identical in all comparisons (^1H NMR, IR, MS, HRMS, TLC EtOAc, 50% EtOAc–hexane, 30% EtOAc–hexane, 1% MeOH–$CHCl_3$ solvent systems).

(29) The initial route to streptonigrin detailed by the Weinreb group[10] which provides for the final stages of all subsequent work requires 32 steps, 0.034% overall, from readily available materials (34 steps, 0.011% overall, from commercially available materials), the Rochester route[11] requires 22 steps, 0.5% overall, from readily available materials (27 steps, 0.069% overall, from commercially available materials), and the route detailed herein requires 13 steps, 1.8% overall, from readily available materials (17 steps, 0.5% overall, from commercially available materials).

13.82 (CH_3); IR (film) ν_{max} 3050, 3000, 2950, 2900, 1725 (C=O), 1595, 1480, 1450, 1370, 1340, 1080, 895, 843, 782, 718 cm^{-1}; EIMS, *m/e* (rel intensity) 551 (M^+, 5), 506 (2), 479 (3), 478 (10), 370 (3), 342 (2), 314 (5), 297 (4), 243 (1), 242 (3), 91 (base), 65 (4).

Anal. Calcd for $C_{30}H_{33}NO_9$: C, 65.32; H, 6.03; N, 2.54. Found: C, 64.99; H, 6.28; N, 2.40.

General Procedure for the Inverse Electron Demand Diels–Alder Reaction of 3-Carboethoxy-1,2,4-triazine (4) with in Situ Generated Pyrrolidine Enamines (Table I, Entries 4–6): Ethyl 3-Phenylpyridine-2-carboxylate (6e). A solution of 3-carboethoxy-1,2,4-triazine[15] (4, 77.0 mg, 0.5 mmol) in $CHCl_3$ (2.0 mL) under N_2 was treated sequentially with acetophenone (60.1 mg, 0.5 mmol) and pyrrolidine (71.0 mg, 1.0 mmol, 2.0 equiv) in $CHCl_3$ (0.5 mL) at 25 °C. Activated 4-Å molecular sieves (ca. 0.4 g) were added, and the mixture warmed at 45 °C (48 h). Chromatography (SiO_2, 50% Et_2O–pentane eluant) afforded 53.0 mg (113.5 mg theoretical, 47% yield) of pure **6e** as a light-yellow oil: ^1H NMR ($CDCl_3$) 8.85 (1 H, dd, J = 8, 2 Hz, aromatic), 7.75 (1 H, dd, J = 8, 2 Hz, aromatic), 7.45–7.20 (6 H, m, aromatic), 4.18 (2 H, q, J = 8 Hz, CH_2), 1.10 (3 H, t, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.9 (C=O), 149.5 (C-2), 148.1 (C-6), 138.4 (C-3), 138.3 (C-4), 137.3 (C-1′), 128.5 (C-3′ and C-5′), 128.4 (C-2′ and C-6′), 128.1 (C-4′), 125.0 (C-5), 61.6 (CH_2), 13.8 (CH_3); IR (film) ν_{max} 3057, 2984, 1734, 1446, 1304, 1292, 1197, 1136, 1109, 762, 702 cm^{-1}; EIMS, *m/e* (rel intensity) 227 (M^+, 20), 183 (37), 155 (base), 154 (86), 153 (12), 128 (10), 127 (51), 126 (18), 76 (20); HRMS, *m/e* for $C_{14}H_{13}NO_2$ 227.0946, found 227.0950.

Ethyl 4-Methyl-3-phenylpyridine-2-carboxylate (6a): ^1H NMR ($CDCl_3$) δ 8.45 (1 H, d, J = 7 Hz, aromatic), 7.45–7.20 (6 H, m, aromatic), 4.05 (2 H, q, J = 8 Hz, CH_2), 2.16 (3 H, s, $ArCH_3$), 1.01 (3 H, t, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.83 (C=O), 149.81 (C-2), 148.0 (C-6), 147.09 (C-4), 136.98 (C-3), 136.89 (C-1′), 128.92 (C-2′), 128.30 (C-3′), 127.79 (C-4′), 126.65 (C-5), 61.30 (CH_2), 20.11 ($ArCH_3$), 13.73 (CH_3); IR (film) ν_{max} 3055, 2982, 1734, 1584, 1460, 1445, 1304, 1177, 1156, 1024, 1007, 771, 758, 704 cm^{-1}; EIMS, *m/e* (rel intensity) 241 (M^+, 2), 197 (29), 169 (29), 168 (base), 167 (27), 166 (7), 153 (2), 141 (5), 140 (5), 139 (8), 116 (2), 115 (15), 114 (2), 63 (5), 52 (3), 51 (10); HRMS, *m/e* for $C_{14}H_{13}NO_2$ 241.1101, found 241.1112.

Ethyl 4-Phenylpyridine-2-carboxylate (6b): mp 53–56 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 8.78 (1 H, d, J = 6 Hz, aromatic), 8.36 (1 H, d, J = 2 Hz, aromatic), 7.75–7.40 (6 H, m, aromatic), 4.51 (2 H, q, J = 8 Hz, CH_2), 1.46 (3 H, t, J = 8 Hz, CH_3); IR (KBr) ν_{max} 2984, 1730, 1593, 1472, 1308, 1250, 1233, 1152, 1105, 758, 683, 615 cm^{-1}; EIMS, *m/e* (rel intensity) 227 (M^+, 1), 183 (13), 156 (15), 155 (base), 154 (23), 128 (23), 127 (19), 126 (5), 102 (2), 101 (2), 77 (15); HRMS, *m/e* for $C_{14}H_{13}NO_2$ 227.0946, found 227.0957.

Ethyl 4-Phenyl-3-methylpyridine-2-carboxylate (6c): mp 109–112 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 8.53 (1 H, d, J = 6 Hz, aromatic), 7.50–7.22 (6 H, m, aromatic), 4.47 (2 H, q, J = 8 Hz, CH_2), 2.38 (3 H, s, $ArCH_3$), 1.44 (3 H, t, J = 8 Hz, CH_3); IR (KBr) ν_{max} 2984, 1711, 1460, 1310, 1285, 1228, 1204 cm^{-1}; EIMS, *m/e* (rel intensity) 241 (M^+, 26), 240 (66), 196 (21), 195 (23), 170 (12), 169 (89), 168 (base), 167 (66), 166 (72), 141 (13), 140 (19), 139 (19), 127 (11), 116 (7), 115 (40), 114 (4), 102 (5), 101 (3), 100 (2), 62 (5); HRMS, *m/e* for $C_{15}H_{15}NO_2$ 241.1101, found 241.1109.

Ethyl 3-Benzylpyridine-2-carboxylate (6d): ^1H NMR ($CDCl_3$) δ 8.51 (1 H, dd, J = 6, 2 Hz, aromatic), 7.55–7.25 (7 H, m, aromatic), 4.38 (2 H, q, J = 8 Hz, CH_2), 4.33 (2 H, s, $ArCH_2Ph$), 1.35 (3 H, t, J = 8 Hz, CH_3); IR (film) ν_{max} 3061, 3028, 2982, 1725, 1453, 1441, 1300, 1240, 1175, 1090, 747, 700 cm^{-1}; EIMS, *m/e* (rel intensity) 241 (M^+, 53), 196 (29), 195 (base) 168 (21), 167 (52), 166 (24), 140 (11), 139 (12), 115 (9), 84 (5), 65 (7), 63 (7); HRMS, *m/e* for $C_{15}H_{15}NO_2$ 241.1101, found 241.1113.

Ethyl 4-Methyl-3-ethylpyridine-2-carboxylate (6f): ^1H NMR ($CDCl_3$) δ 8.33 (1 H, d, J = 6 Hz, aromatic), 7.13 (1 H, d, J = 6 Hz, aromatic), 4.42 (2 H, q, J = 8 Hz, $CO_2CH_2CH_3$), 2.67 (2 H, q, J = 8 Hz, $ArCH_2$), 2.42 (3 H, s, $ArCH_3$), 1.41 (3 H, t, J = 8 Hz, $CO_2CH_2CH_3$), 1.21 (3 H, t, J = 8 Hz, $ArCH_2CH_3$); IR (film) ν_{max} 2995, 2972, 1725, 1590, 1460, 1293, 1172, 1062, 905, 720 cm^{-1}; EIMS, *m/e* (rel intensity) 193 (M^+, 30), 165 (4), 164 (31), 149 (7), 148 (19), 147 (12), 122 (12), 121 (base), 120 (98), 119 (60), 118 (32), 104 (10), 93 (20), 92 (11), 91 (18), 78 (11), 77 (33), 65 (21); HRMS, *m/e* for $C_{11}H_{15}NO_2$ 193.1101, found 193.1102.

Ethyl 5,6,7,8-Tetrahydroisoquinoline-1-carboxylate (6g): ^1H NMR ($CDCl_3$) δ 8.35 (1 H, d, J = 6 Hz, aromatic), 7.09 (1 H, d, J = 6 Hz, aromatic), 4.43 (2 H, q, J = 8 Hz, CH_2), 3.10–2.60 (4 H, m, two $ArCH_2$), 1.80–1.60 (4 H, m, CH_2CH_2), 1.42 (3 H, t, J = 8 Hz, CH_3); IR (film) ν_{max} 2983, 2863, 1725, 1585, 1291, 1183, 1153, 1026, 731 cm^{-1}; EIMS, *m/e* (rel intensity) 205 (M^+, 31), 176 (4), 160 (12), 159 (28), 133 (55), 132 (46), 131 (base), 130 (76), 118 (7), 117 (2), 116 (7), 105 (7), 104 (12), 103 (16), 79 (11), 78 (13), 77 (34), 65 (11), 51 (17); HRMS, *m/e* for $C_{12}H_{15}NO_2$ 205.1101, found 205.1092.

4-Phenyl-2,3,6-tricarboethoxypyridine (6h): mp 99–100.5 °C (trituration 3 times, ether); ^1H NMR ($CDCl_3$) δ 8.25 (1 H, s, aromatic), 7.44 (5 H, br s, Ph), 4.47 (2 H, q, J = 8 Hz, CH_2), 4.45 (2 H, q, J = 8 Hz, CH_2), 4.18 (2 H, q, J = 8 Hz, CH_2), 1.45 (3 H, t, J = 8 Hz, CH_3), 1.42 (3 H, t, J = 8 Hz, CH_3), 1.05 (3 H, t, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.4 (C=O), 164.5 (C=O), 164.0 (C=O), 150.5 (C-2), 148.4 (C-6), 147.1 (C-4), 136.5 (C-3), 132.7 (C-1′), 129.4 (C-4′), 128.8 (C-3′), 128.2 (C-2′), 127.9 (C-5), 62.7 (CH_2), 62.5 (CH_2), 62.0 (CH_2), 14.3 (CH_3), 14.1 (CH_3), 13.6 (CH_3); IR (KBr) ν_{max} 2984, 1744 and 1727 (C=O), 1586, 1474, 1449, 1397, 1377, 1345, 1285, 1250, 1146, 1067, 1022, 916, 870, 774 cm^{-1}; EIMS, *m/e* (rel intensity) 371 (M^+, 1), 328 (6), 327 (29), 299 (93), 298 (51), 253 (83), 227 (base), 225 (81), 224 (20), 181 (24), 180 (29), 155 (33), 153 (16), 152 (13), 128 (14), 53 (5).

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.56; H, 5.80; N, 3.50.

For the regioisomer 5-phenyl-2,3,6-tricarboethoxypyridine: ^1H NMR ($CDCl_3$) δ 8.20 (1 H, s, aromatic), 7.40 (5 H, br s, Ph), 4.44 (2 H, q, J = 8 Hz, CH_2), 4.38 (2 H, q, J = 8 Hz, CH_2), 4.15 (2 H, q, J = 8 Hz, CH_2), 1.41 (3 H, t, J = 8 Hz, CH_3), 1.37 (3 H, t, J = 8 Hz, CH_3), 1.06 (3 H, t, J = 8 Hz, CH_3); IR (KBr) ν_{max} 2980, 1730, 1715, 1470, 1445, 1412, 1372, 1325, 1292, 1225, 1176, 1151, 1075, 1022, 857, 754 cm^{-1}.

5-Methyl-4-phenyl-2,3,6-tricarboethoxypyridine (6i): mp 95–96 °C (trituration 3 times, ether); ^1H NMR ($CDCl_3$) δ 7.47–7.19 (5 H, m, Ph), 4.47 (2 H, q, J = 8 Hz, CH_2), 4.45 (2 H, q, J = 8 Hz, CH_2), 4.02 (2 H, q, J = 8 Hz, CH_2), 2.25 (3 H, s, $ArCH_3$), 1.43 (3 H, t, J = 8 Hz, CH_3), 1.40 (3 H, t, J = 8 Hz, CH_3), 0.94 (3 H, t, J = 8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.2 (C=O), 165.9 (C=O), 164.3 (C=O), 150.5 (C-2), 150.4 (C-6), 147.0 (C-4), 135.2 (C-3), 134.6 (C-5), 133.0 (C-1′), 128.7 (C-4′), 128.6 (C-3′), 128.4 (C-2′), 62.4 (CH_2) 62.2 (CH_2), 61.6 (CH_2) 16.6 ($ArCH_3$), 14.1 (CH_3), 13.6 (CH_3), 13.3 (CH_3); IR ($CHCl_3$) ν_{max} 3010, 2995, 1720 (C=O), 1548, 1428, 1358, 1322, 1270, 1232, 1200, 1155, 1132, 1080, 995, 835, 673, cm^{-1}; EIMS, *m/e* (rel intensity) 385 (M^+, 13), 384 (22), 341 (33), 340 (30), 314 (19), 313 (94), 312 (57), 269 (13), 268 (71), 241 (base), 240 (47), 239 (71), 238 (43), 195 (32), 194 (44), 193 (15), 167 (31), 166 (42), 165 (17), 164 (13), 140 (23), 139 (25), 115 (23), 77 (11).

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.18; H, 5.92; N, 3.63.

General Procedure for the Inverse Electron Demand Diels–Alder Reaction of Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate (7) with C=N Heterodienophiles (Table II): Dimethyl 5-(6-Methoxy-5-nitro-2-quinolyl)-1,2,4-triazine-3,6-dicarboxylate (16). A stirred solution of *S*-methyl thioimidate **11d** (680 mg, 2.45 mmol) in dry dioxane (70 mL) was treated with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[20] (**7**, 630 mg, 3.18 mmol, 1.3 equiv) at 25 °C under N_2. The heterogeneous mixture was warmed at 80 °C (22 h). The reaction mixture was cooled to 25 °C and the solvent removed in vacuo. The crude product was triturated with Et_2O (3 × 20 mL), affording 800 mg (978 mg theoretical, 82% yield) of pure **16**: mp 230–235 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.77 (1 H, d, J = 9 Hz, aromatic), 8.28 (1 H, d, J = 9 Hz, aromatic), 8.21 (1 H, d, J = 9 Hz, aromatic), 7.67 (1 H, d, J = 9 Hz, aromatic), 4.17 (3 H, s, CO_2CH_3), 4.13 (3 H, s, CO_2CH_3), 4.10 (3 H, s, $ArOCH_3$); IR ($CHCl_3$) ν_{max} 3038, 2980, 1749, 1634, 1530, 1442, 1346, 1270, 1164, 1150, 1066, 970, 866, 810 cm^{-1}; EIMS, *m/e* (rel intensity) 399 (M^+, 15), 341 (base), 255 (22), 228 (59), 179 (24), 178 (26), 167 (27), 153 (78), 152 (20), 129 (36), 127 (26), 101 (22), 81 (23), 69 (53); HRMS, *m/e* for $C_{17}H_{13}N_5O_7$ 399.0814, found 399.0787.

Dimethyl 5-(2-Pyridyl)-1,2,4-triazine-3,6-dicarboxylate (12): mp 123–125 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.70–8.45 (2 H, m, aromatic), 7.94 (1 H, dt, J = 8, 1 Hz, aromatic), 7.44 (1 H, ddd, J = 8, 8, 1 Hz, aromatic), 4.15 (3 H, s, CO_2CH_3), 4.06 (3 H, s, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3028, 2978, 1728, 1518, 1441, 1400, 1384, 1301, 1202, 1035, 810 cm^{-1}; EIMS, *m/e* (rel intensity) 274 (M^+, 9), 244 (2), 243 (9), 217 (9), 216 (34), 203 (11), 202 (6), 188 (31), 187 (5), 131 (14), 130 (base), 105 (11), 104 (12), 103 (51), 78 (51), 77 (11); HRMS, *m/e* for $C_{12}H_{10}N_4O_4$ 274.0701, found 274.0710.

Dimethyl 5-Phenyl-1,2,4-triazine-3,6-dicarboxylate (13): mp 109–113 °C (triturated with Et_2O) [lit.[19a] mp 110–113 °C]; ^1H NMR ($CDCl_3$) δ 7.90–7.74 (2 H, m, aromatic), 7.62–7.41 (3 H, m, aromatic), 4.14 (3 H, s, CO_2CH_3), 3.97 (3 H, s, CO_2CH_3); IR (KBr) ν_{max} 2961, 1747, 1701, 1518, 1495, 1443, 1397, 1293, 1223, 1179, 1071, 824, 777, 706 cm^{-1}.

Dimethyl 5-(2-Quinolyl)-1,2,4-triazine-3,6-dicarboxylate (14): mp 181–183 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.68 (1 H, d, J = 9 Hz, aromatic), 8.39 (1 H, d, J = 9 Hz, aromatic), 8.12–7.51 (4 H, m, aromatic), 4.17 (3 H, s, CO_2CH_3), 4.14 (3 H, s, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3022, 2984, 1734, 1526, 1455, 1303, 1205, 1180, 1078, 978, 822 cm^{-1}; EIMS, *m/e* (rel intensity) 324 (M^+, 43), 293 (11), 267 (11), 266 (67), 253 (23), 252 (11), 238 (23), 207 (11), 181 (14), 180 (80), 179 (11), 154 (21), 153 (base), 152 (19), 140 (10), 128 (41), 101 (13); HRMS, *m/e* for $C_{16}H_{12}N_4O_4$ 324.0857, found 324.0863.

Dimethyl 5-(6-Methoxy-2-quinolyl)-1,2,4-triazine-3,6-dicarboxylate (15): mp 188–191 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.63 (1 H, d, J = 9 Hz, aromatic), 8.24 (1 H, d, J = 9 Hz, aromatic), 7.95 (1 H, d, J = 9 Hz, aromatic), 7.43 (1 H, dd, J = 9, 3 Hz, aromatic), 7.13 (1 H, d, J = 3 Hz, aromatic), 4.16 (3 H, s, CO_2CH_3), 4.13 (3 H, s, CO_2CH_3), 3.97 (3 H, s, $ArOCH_3$); IR ($CHCl_3$) ν_{max} 3038, 2990, 1742, 1636, 1521, 1490, 1427, 1395, 1213, 1178, 1122, 1078, 1030, 982, 893, 860, 835 cm^{-1}; EIMS, m/e (rel intensity) 354 (M^+, 29), 323 (4), 296 (20), 211 (10), 210 (29), 184 (22), 183 (base), 159 (7), 158 (14), 140 (10); HRMS, m/e for $C_{17}H_{14}N_4O_5$ 354.0963, found 354.0972.

2-Cyano-6-methoxyquinoline (17). A mixture of 6-methoxyquinoline (11.1 g, 70.0 mmol) in CH_2Cl_2 (140 mL) and H_2O (40 mL) containing KCN (13.70 g, 210 mmol, 3.0 equiv) was treated dropwise (30 min) with a solution of *p*-toluenesulfonyl chloride (22.0 g, 115.0 mmol, 1.6 equiv) in CH_2Cl_2 (150 mL) at 25 °C. After stirring for 120 h at 25 °C, the mixture was filtered through Celite (washed with CH_2Cl_2, 4 × 30 mL) and the filtrate was concentrated in vacuo. The crude product was dissolved in $CHCl_3$ and passed through a plug of SiO_2 ($CHCl_3$ eluant). The combined $CHCl_3$ fractions were concentrated in vacuo, and the product was recrystallized from ethanol–water, affording 10.40 g (12.81 g theoretical, 81%) of pure **17**: mp 175–176 °C (ethanol–water) [lit.[31] mp 177–178 °C]; ^1H NMR ($CDCl_3$) δ 8.15 (1 H, d, J = 9 Hz, aromatic), 8.04 (1 H, d, J = 9 Hz, aromatic), 7.62 (1 H, d, J = 9 Hz, aromatic), 7.42 (1 H, dd, J = 9, 2 Hz, aromatic), 7.09 (1 H, d, J = 2 Hz, aromatic), 3.96 (3 H, s, $ArOCH_3$); ^{13}C NMR ($CDCl_3$) δ 160.0 (C-6), 144.6 (C-8a), 135.6 (C-4), 131.5 (C-8), 130.8 (C-4a/C-2), 130.3 (C-2/C-4a), 124.6 (C-5), 123.8 (C-3), 117.9 (C≡N), 104.7 (C-7); IR (KBr) ν_{max} 2949, 2228 (C≡N), 1622, 1499, 1472, 1412, 1387, 1246, 1201, 1167, 1115, 1019, 860, 835 cm^{-1}; EIMS, m/e (rel intensity) 184 (M^+, base), 169 (8), 155 (12), 154 (37), 142 (4), 141 (63), 115 (4), 114 (28), 89 (4), 88 (5), 87 (4), 63 (5), 62 (6), 61 (2).

Anal. Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.45; H, 4.21; N, 15.00.

2-Cyano-6-methoxy-5-nitroquinoline (18). A solution of 2-cyano-6-methoxyquinoline (10.0 g, 54.3 mmol) in concentrated H_2SO_4 (60 mL) cooled to 0 °C was treated dropwise (10 min) with 70% nitric acid (HNO_3, 10.5 mL). The reaction mixture was stirred for 10 min (0 °C) before being poured onto crushed ice. The mixture was neutralized with 20% KOH with ice cooling. The product was collected by filtration and washed with H_2O (2 × 50 mL). Crystallization (EtOH–H_2O) gave 6.7 g of pure **18**. The mother liquor was concentrated to dryness and the residue recrystallized (EtOH–H_2O) to give an additional 3.0 g of **18**: 9.70 g total (12.43 g theoretical, 81%); mp 158–160 °C (EtOH–H_2O); ^1H NMR ($CDCl_3$) δ 8.35 (1 H, d, J = 9 Hz, aromatic), 8.23 (1 H, d, J = 9 Hz, aromatic), 7.75 (1 H, d, J = 9 Hz, aromatic), 7.67 (1 H, d, J = 9 Hz, aromatic), 4.14 (3 H, s, $ArOCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 151.2 (C-6), 141.2 (C-8a), 134.4 (C-4), 133.2 (C-5), 131.9 (C-2), 130.8 (C-8), 126.3 (C-3), 121.2 (C-4a), 119.7 (C-7), 114 (C≡N), 57.8 (ArO-CH_3); IR ($CHCl_3$) ν_{max} 3010, 2938, 2800, 2226, 1618, 1522, 1120, 1057, 802 cm^{-1}; EIMS, m/e (rel intensity) 229 (M^+, base), 199 (30), 182 (31), 174 (11), 172 (67), 168 (46), 156 (18), 154 (22), 153 (87), 141 (17), 140 (70), 128 (27), 127 (19), 126 (30), 114 (10), 113 (46), 102 (15), 101 (21), 100 (17), 88 (17), 87 (24), 86 (16), 77 (16), 76 (18), 75 (25), 64 (16), 63 (20), 62 (41).

Anal. Calcd for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.28; H, 3.00; N, 18.45.

6-Methoxy-5-nitro-2-(thioamido)quinoline (19). A solution of **18** (2.0 g, 9.0 mmol) in dry dioxane (100 mL) was saturated with hydrogen sulfide (H_2S) and treated with Et_2NH (219 mg, 3.0 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C (30 h). The solvent was removed in vacuo and the crude product triturated with EtOH (2 × 20 mL), affording 2.08 g (2.36 g theoretical, 88%) of pure **19**: mp 236–246 °C dec (EtOH); ^1H NMR (Me_2SO-d_6) δ 10.20 (2 H, br s, NH_2), 8.73 (1 H, d, J = 9 Hz, aromatic), 8.53 (1 H, d, J = 9 Hz, aromatic), 8.16 (1 H, d, J = 9 Hz, aromatic), 8.03 (1 H, d, J = 9 Hz, aromatic), 4.12 (3 H, s, $ArOCH_3$); ^{13}C NMR (Me_2SO-d_6) δ 194.0 (ArC=S), 150.4 (C-6), 150.1 (C-2), 139.2 (C-8a), 134.5 (C-4), 133.6 (C-5), 129.5 (C-8), 123.7 (C-3), 120.9 (C-4a), 118.6 (C-7), 57.7 (ArO-CH_3); IR (KBr) ν_{max} 3352, 3252, 3168, 1662, 1526, 1501, 1354, 1269, 1075, 824, 808 cm^{-1}; EIMS, m/e (rel intensity) 263 (M^+, base), 236 (41), 233 (14), 231 (12), 230 (75), 204 (48), 183 (14), 157 (24), 156 (18), 155 (15), 154 (15), 130 (11), 129 (16), 128 (34), 127 (26), 103 (12), 102 (14), 101 (21), 100 (14), 89 (11), 88 (14), 87 (15), 77 (20), 76 (24), 75 (18), 74 (11).

Anal. Calcd for $C_{12}H_{11}N_3SO_2$: C, 51.98; H, 3.98; N, 15.16. Found: C, 51.58; H, 4.04; N, 14.89.

***S*-Methyl 6-Methoxy-5-nitro-2-quinolinethioimidate (11d)**. A suspension of **19** (2.0 g, 7.60 mmol) in dry CH_3CN (150 mL) was treated with MeI (2.15 g, 15.20 mmol, 2 equiv, 0.94 mL) at 25 °C under N_2. The reaction was warmed at 80 °C for 2.0 h before being slowly cooled to 0 °C. The precipitated hydroiodide salt was collected by fiiltration, washed with Et_2O (2 × 10 mL), and suspended in $CHCl_3$ (60 mL). The suspension was treated with saturated $NaHCO_3$ (20 mL) for 15 min at 25 °C. The two phases were separated, and the $CHCl_3$ layer was washed with saturated NaCl (1 × 20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo affording 1.18 g (2.11 g, theoretical, 56%) of pure **11d** as a light-yellow solid: mp 190–192 °C (EtOH); ^1H NMR ($CDCl_3$) δ 8.28 (1 H, d, J = 9 Hz, aromatic), 8.25 (1 H, d, J = 9 Hz, aromatic), 8.18 (1 H, br s, NH), 8.07 (1 H, d, J = 9 Hz, aromatic), 7.60 (1 H, d, J = 9 Hz, aromatic), 4.09 (3 H, s, $ArOCH_3$), 2.45 (3 H, s, SCH_3); ^{13}C NMR (Me_2SO-d_6) δ 169.4 (C=NH), 153.3 (C-6), 149.8 (C-2), 140.2 (C-8a), 134.2 (C-4), 133.5 (C-5), 130.0 (C-8), 121.1 (C-4a), 120.9 (C-3), 118.2 (C-7), 57.5 ($ArOCH_3$), 11.4 (SCH_3); IR ($CHCl_3$) ν_{max} 3010, 2945, 2835, 1624, 1574, 1528, 1495, 1425, 1312, 1262, 1160, 1068, 835 cm^{-1}; EIMS, m/e (rel intensity) 277 (M^+, 24), 263 (15), 231 (16), 230 (base), 229 (62), 204 (15), 203 (12), 199 (21), 184 (14), 183 (18), 182 (17), 171 (24), 157 (11), 156 (25), 155 (22), 154 (23), 153 (43), 141 (11), 140 (81), 129 (10), 128 (29), 114 (14), 113 (19), 102 (17), 101 (19), 100 (17), 88 (14), 87 (16), 77 (16), 76 (22), 45 (21), 44 (13), 64 (12), 63 (18), 62 (23).

Anal. Calcd for $C_{12}H_{11}N_3SO_2$: C, 51.98; H, 3.98; N, 15.16. Found: C, 51.58; H, 4.04; N, 14.89.

Dimethyl 4-[2-(Benzyloxy)-3,4-dimethoxyphenyl]-6-(6-methoxy-5-nitro-2-quinolyl)-3-methylpyridine-2,5-dicarboxylate (21) and Dimethyl 3-[2-(Benzyloxy)-3,4-dimethoxyphenyl]-6-(6-methoxy-5-nitro-2-quinolyl)-4-methylpyridine-2,5-dicarboxylate (22). Thermal Reaction of 16 with 20a. A suspension of **16** (20.0 mg, 0.05 mmol) in $CHCl_3$ (1.5 mL) was treated with the morpholine enamine **20a**[23b] (74.0 mg, 0.20 mmol, 4.0 equiv) in $CHCl_3$ (0.5 mL) at 23 °C in a resealable Kontes vial. The reaction vessel was flushed with N_2, sealed, and warmed to 120 °C (24 h). Chromatography (SiO_2, 40% EtOAc–hexane eluant) afforded 22.0 mg (32.65 mg theoretical, 68% yield) of pure **21** and **22** (1:1). MPLC (SiO_2, 9 × 250 cm, 30–35% EtOAc–hexane eluant) afforded 8.6 mg of pure **22** (R_f 0.46, 50% EtOAc-hexane) and 8.2 mg of pure **21** (R_f 0.38, 50% EtOAc–hexane) plus 4.4 mg of a mixture of **21** and **22**.

For **21**[23a]: ^1H NMR ($CDCl_3$) δ 8.64 (1 H, d, J = 9 Hz, aromatic), 8.10 (1 H, d, J = 9 Hz, aromatic), 8.04 (1 H, d, J = 9 Hz, aromatic), 7.48 (1 H, d, J = 9 Hz, aromatic), 7.20–6.95 (5 H, m, Ph), 6.86 (1 H, d, J = 10 Hz, aromatic), 6.72 (1 H, d, J = 10 Hz, aromatic), 5.06 (1 H, d, J = 13 Hz, OCH_2Ph), 4.81 (1 H, d, J = 13 Hz, OCH_2Ph), 4.06 (3 H, s, $CO_2CH_3/ArOCH_3$), 4.02 (3 H, s, $CO_2CH_3/ArOCH_3$), 3.93 (3 H, s, $ArOCH_3$), 3.90 (3 H, s, $ArOCH_3$), 3.62 (3 H, s, CO_2CH_3), 2.26 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 2950, 2932, 1734 (C=O), 1628, 1594, 1531, 1497, 1456, 1358, 1294, 1271, 1094, 1078 cm^{-1}; EIMS, m/e (rel intensity) 653 (M^+, 1), 595 (1), 594 (4), 393 (2), 382 (1), 381 (1), 380 (1), 340 (1), 293 (1), 283 (2), 255 (1), 228 (1), 178 (1), 167 (1), 127 (1), 100 (1), 93 (1), 92 (8), 91 (base), 65 (4); HRMS, m/e for $C_{35}H_{31}N_3O_{10}$ 653.2007, found 653.2019.

For **22**: ^1H NMR ($CDCl_3$) δ 8.69 (1 H, d, J = 9 Hz, aromatic), 8.21 (1 H, d, J = 9 Hz, aromatic), 8.20 (1 H, d, J = 9 Hz, aromatic), 7.54 (1 H, d, J = 9 Hz, aromatic), 7.18–6.85 (5 H, m, Ph), 6.78 (2 H, br s,

(30) (a) Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian FT-80A spectrometer and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). Infrared spectra (IR) were recorded on an IBM FTIR 32 or a Beckman IR-32 spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (EIMS), chemical ionization mass spectra (CIMS), and high-resolution mass spectra (HRMS) were recorded on a Varian CH-5 or Ribermag R10-10 spectrometer by Dr. Charles Judson and Robert Drake. Microanalyses were performed by Tho I. Nguyen on a Hewlett-Packard Model 185 CHN analyzer at the University of Kansas. Medium-pressure liquid chromatography (MPLC) was performed on Merck silica gel 60 (230–400 mesh).[30b] All extraction and chromatographic solvents, ethyl acetate (EtOAc), ether (Et_2O), hexane, methylene chloride (CH_2Cl_2), and chloroform ($CHCl_3$) were distilled prior to use. Dioxane, triethylamine, and acetonitrile (CH_3CN) were distilled from CaH_2. Benzene, tetrahydrofuran (THF), and ether (Et_2O) were distilled from benzophenone ketyl before use. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under reduced pressure. All reactions requiring anhydrous conditions were run under a nitrogen atmosphere in oven-dried glassware. All other solvents and reagents were used as received from commercial sources. Pressure reactions, 6.2 kbar, were conducted in a pressure generator available from Leco Corp.[30c] in glass-plug-sealed, heat-shrinkable Teflon tubing. (b) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247. (c) DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proced. Int.* **1982**, *14*, 369. The pressure-promoted reactions were carried out in a AGP-10002 pressure generator manufactured by Leco Corp. Tem-Pres Division, Bellefonte, PA 16823.

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aromatic D-ring protons), 5.04 (1 H, d, J = 11 Hz, OCH_2Ph), 4.80 (1 H, d, J = 11 Hz, OCH_2Ph), 4.09 (3 H, s, $ArOCH_3$), 3.92 (6 H, s, two $ArOCH_3$), 3.90 (3 H, s, CO_2CH_3), 3.72 (3 H, s, CO_2CH_3), 2.14 (3 H, s, CO_2CH_3); IR (KBr) ν_{max} 2950, 1736, 1628, 1599, 1532, 1497, 1456, 1360, 1294, 1271, 1092, 1053, 1012 cm^{-1}; EIMS, m/e (rel intensity) 553 (M^+, 1), 596 (1), 595 (1), 594 (2), 487 (1), 486 (1), 472 (1), 471 (1), 425 (1), 339 (1), 204 (1), 91 (base); HRMS, m/e for $C_{35}H_{31}N_3O_{10}$ 653.2007, found 653.2021.

Pressure-Promoted Reaction of 16 with 20b. A mixture of triazine **16** (30 mg, 0.075 mmol) and the pyrrolidine enamine **20b** (106 mg, 0.30 mmol) in 0.30 mL of methylene chloride was sealed in a Teflon tube and pressurized at 6.2 kbar at 25 °C for 5 days.[30b] After depressurization, the solvent was removed in vacuo and the resulting crude product was chromatographed (SiO_2, 50% EtOAc–hexane eluant) to yield 32 mg (65%) of **21** and **22** (2.8:1).[33]

Similarly, a mixture of triazine **16** (20 mg, 0.05 mmol) and the morpholine enamine **20a** (74 mg, 0.20 mmol) in 0.30 mL of methylene chloride afforded 19 mg (58%) of **21** and **22** (1.4:1).[33]

Methyl 5-Amino-4-[2-(benzyloxy)-3,4-dimethoxyphenyl]-6-(6-hydroxy-5-nitro-2-quinolyl)-3-methylpyridine-2-carboxylate (25). The following procedure is representative of numerous conversions. A solution of **21** (6.0 mg, 0.0092 mmol) in dry THF (0.25 mL) was treated with a 0.25 M solution of $NaSePh$[25] (0.061 mmol, 5.0 equiv, 0.245 mL) in THF containing 1.0 equiv of HMPA. The resulting mixture was warmed at 70 °C in a resealable Kontes vial under N_2. After 21 h, the reaction was cooled to 25 °C and diluted with H_2O (5 mL). The aqueous solution was basified with 5% K_2CO_3. The basic solution was washed with EtOAc (3 × 5 mL, to remove excess PhSeSePh), acidified with 10% HCl, and extracted with EtOAc (3 × 5 mL). The EtOAc layer was dried (Na_2SO_4) and filtered and the solvent removed in vacuo to give crude diacid phenol **23**. The diacid was dissolved in absolute MeOH (0.5 mL) and added to a solution of 10% HCl–MeOH (5.0 mL) at 25 °C. The reaction mixture was stirred for 18 h (25 °C) before being poured onto H_2O (10 mL), extracted with EtOAc (2 × 15 mL), and dried (Na_2SO_4). The solvent was removed in vacuo to afford 8.0 mg of crude monoacid ester **24**. For purified **24**: ^1H NMR ($CDCl_3$) δ 9.35 (1 H, d, J = 9 Hz, aromatic), 8.68 (1 H, d, J = 9 Hz, aromatic), 8.21 (1 H, d, J = 9 Hz, aromatic), 7.50–6.92 (6 H, m, aromatic), 6.85 (1 H, d, J = 9 Hz, aromatic D-ring), 6.72 (1 H, d, J = 9 Hz, aromatic D-ring), 5.06 (1 H, d, J = 11 Hz, O*CH*Ph), 4.81 (1 H, d, J = 11 Hz, O*CH*Ph), 4.04 (3 H, s, CO_2CH_3), 3.92 (3 H, s, $ArOCH_3$), 3.91 (3 H, s, $ArOCH_3$), 2.25 (3 H, s, $ArCH_3$); EIMS, m/e (rel intensity) 625 (M^+, 1), 534 (1), 502 (2), 491 (2), 490 (6), 459 (1), 458 (2), 432 (1), 431 (1), 430 (4), 91 (base); HRMS, m/e for $C_{33}H_{27}N_3O_{10}$ 625.1695, found 625.1675.

The crude monoacid ester **24** (8.0 mg, 0.0128 mmol) in dry benzene (1.5 mL) was treated sequentially with diphenylphosphoroazidate[26] (35.2 mg, 0.128 mmol, 10 equiv) and Et_3N (13.0 mg, 0.128 mmol, 10 equiv) at 25 °C under N_2. The reaction mixture was warmed at reflux for 2.5 h and cooled, and H_2O (1 drop) was added and the reaction mixture was warmed at reflux for an additional 1.0 h. The reaction mixture was cooled to 25 °C and the solvent removed in vacuo to afford crude **25**. Chromatography (SiO_2, 35% EtOAc–hexane eluant) afforded 2.30 mg (5.48 mg, theoretical, 41% from dimethyl ester **21**) of pure **25**: ^1H NMR ($CDCl_3$) δ 9.05 (1 H, d, J = 9 Hz, aromatic), 8.15 (1 H, d, J = 9 Hz, aromatic), 7.91 (1 H, d, J = 9 Hz, aromatic), 7.30–6.31 (8 H, m, aromatic), 4.93 (2 H, s, CH_2Ph), 3.98 (3 H, s), 3.95 (3 H, s), 3.92 (3 H, s), 2.24 (3 H, s, $ArCH_3$); IR (KBr) ν_{max} 3463, 3240, 2928, 1718, 1601, 1538, 1492, 1456, 1294, 1202, 1094, 1041, 1023, 974, 950 cm^{-1}; CIMS (NH_3), m/e (rel intensity) 597 (M + 1, 1), 449 (1), 365 (2), 351 (2), 350 (1), 349 (2), 337 (20), 320 (2), 310 (1), 309 (2), 295 (3), 281 (3), 268 (1), 267 (3), 253 (4), 239 (40), 225 (5), 211 (5), 209 (50), 194 (6), 183 (8), 169 (8), 168 (5), 156 (2), 155 (13), 154 (4), 153 (4), 141 (15), 139 (13), 127 (29), 126 (14), 125 (27), 113 (26), 112 (13), 111 (42), 99 (47), 98 (24), 97 (70), 96 (13), 95 (44), 85 (98), 71 (base), 70 (50), 69 (83), 68 (10), 67 (16).

Methyl 5-Amino-4-[2-(benzyloxy)-3,4-dimethoxyphenyl]-6-(6-methoxy-5-nitro-2-quinolyl)-3-methylpyridine-2-carboxylate (2). The aminophenol **25** (1.0 mg, 0.0016 mmol) in dry THF (0.1 mL) was treated sequentially with excess anhydrous K_2CO_3 and MeI (3 drops). The resulting reaction mixture was warmed at 65 °C (22 h) in a resealable Kontes vial. After cooling to 25 °C, the reaction mixture was diluted with THF (0.5 mL), filtered through a plug of glass wool, and concentrated. Chromatography (SiO_2, 50% EtOAc–hexane eluant) afforded 0.94 mg (1.02 mg, theoretical, 94% yield) of pure **2**:[28] ^1H NMR ($CDCl_3$) δ 8.98 (1 H, d, J = 9 Hz, aromatic), 8.18 (1 H, d, J = 9 Hz, aromatic), 8.08 (1 H, d, J = 9 Hz, aromatic), 7.46 (1 H, d, J = 9 Hz, aromatic), 7.25–6.50 (7 H, m, aromatic), 4.81 (2 H, s, OCH_2Ph), 4.06 (3 H, s, CO_2CH_3), 3.98 (3 H, s, $ArOCH_3$), 3.95 (6 H, s, two $ArOCH_3$), 2.26 (3 H, s, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3460, 3242, 2932, 1725, 1600, 1558, 1483, 1455, 1358, 1318, 1270, 1205, 1072, 1038, 1000 cm^{-1}; EIMS, m/e (rel intensity) 610 (M^+, 4), 593 (1), 550 (2), 533 (2), 516 (20), 504 (2), 503 (5), 487 (2), 471 (3), 459 (3), 448 (4), 443 (7), 412 (1), 411 (1), 383 (1), 368 (1), 354 (21), 326 (2), 325 (2), 298 (1), 268 (1), 170 (3), 142 (2), 141 (2), 128 (2), 127 (2), 91 (base); HRMS, m/e for $C_{33}H_{30}N_4O_8$ 610.2061, found 610.2080.

Acknowledgment. This work was assisted financially by the National Institutes of Health (CA 33668/42056), the Searle Scholars Program, and a University of Kansas General Research Allocation (3244-XO-0038). We thank Prof. Kende for spectra of authentic **21**, for a comparison sample of **2**, and for discussions. Dr. Masami Yasuda, to whom we are grateful, is responsible for all studies on the pressure-promoted [4 + 2] cycloadditions detailed in Table I. Dr. Steven R. Duff is responsible for the pressure-promoted [4 + 2] cycloadditions detailed in Tables II and III. We would also like to thank Prof. H. Neunhoeffer for discussions.

Supplementary Material Available: Complete experimental procedures and spectral information on **7**, **9a–d**, **10a–c**, **11a–c**, and **20a,b** (8 pages). Ordering information is given on any current masthead page.

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(33) The ratio of **21**/**22** was accurately determined by comparison (integration and peak height measurements) of the ^1H NMR aryl methyl signals at δ 2.26 and 2.14, respectively.