Notes

A New Route to Cross-Conjugated Bis(enamines) and an Unusual Reaction with DDQ

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In previous papers, we reported that thiazolidines derived from cysteine methyl ester and aldehydes react with silver carbonate and DBU; the reactions produce transient 1-substituted methyl 2-azadiene-3-carboxylates that act as dienes in the Diels−Alder reaction.[1] When we apply the same procedure to the thiazolidines **1a**−**d** we find that the products are isolable cross-conjugated bis(enamines) **3a**−**d**, the more stable tautomers of the azadienes **2a**−**d** (Scheme 1). This is a new versatile route to enamines of this type.

The diester **3a** is a known compound that has previously been prepared from methyl *β*-halo-α-aminopropionate hydrohalides by reaction with bases;[2] compounds **3b**−**d** are previously unknown. Other cross-conjugated bis(enamines) of this type have been produced by thermal rearrangement of vinylaziridines.[3] These compounds undergo an interesting photocyclization to 3,4-dihydropyrroles that can be intercepted, as 1,3-dipoles, in cycloaddition reactions with alkenes and alkynes.[2b,3,4] Compound **3a** is also reported to react as an electrophile with hydrazines[5] and with primary amines,[6] giving hydrazones and imines of methyl pyruvate as products.

In an attempt to cyclize the diester **3a** directly to dimethyl pyrrole-2,5-dicarboxylate by using DDQ as an oxidant, a single product was isolated in high yield. Instead of the pyrrole, it proved to be an interesting 1:1 adduct of the diester and DDQ whose structure **4** was established for the compound by X-ray crystallography (Figure 1).

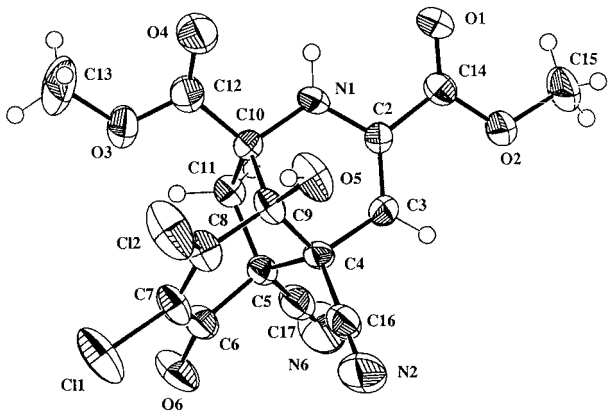
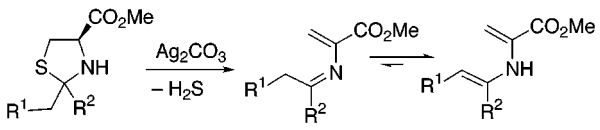


Figure 1. X-ray structure of compound **4**.

Scheme 1



1,2,3 **a**: R^1 = H, R^2 = CO_2Me
b: R^1 = H, R^2 = CO_2Et
c: R^1 = CO_2Et, R^2 = Me
d: R^1 = COMe, R^2 = Me

The X-ray analysis clearly shows that the C9−C10−N1−C2−C3−C4 and C4−C5−C6−C7−C8−C9 rings are fused cis around the common C4−C9 bond and are furthermore linked by the methylenic bridge C10−C11−C5. The conformation of the two above-mentioned rings is intermediate between E^1 envelope and $^1H_2$ half-chair, as shown by the ring puckering parameters[7] Q = 0.662(4) Å, θ = 53.8(3)°, ϕ = 13.9(4)° [C9−C10−N1−C2−C3−C4], Q = 0.630(4) Å, θ = 53.8(4)°, ϕ = 8.2(5)° [C4−C5−C6−C7−C8−C9]. The conformation of the bridging ring C4−C5−C11−C10−C9 is very close to $^5T_1$ (twisted around the C4−C9 bond), as shown by the puckering parameters $Q(2)$ = 0.566(4) Å, $\phi(2)$ = 163.3(4)°. The H1 atom is shared in a bifurcated intramolecular hydrogen bond [N1−H1···O1: 2.714(4) Å; N1−H1···O4: 2.677(5) Å, sum of the valence angles around H1 = 358.2°]. The methoxycarbonyl group attached to the sp^2 C2 atom is almost coplanar with the plane defined by the C10−N1−C2 atoms, whereas the other methoxycarbonyl group that is attached to the tetrahedric C10 atom is twisted by −16.9(5)° around the C10−C12 single bond. The H5 atom of the hydroxyl group is also involved in a bifurcated

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(1) (a) Gilchrist, T. L.; Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D. *Tetrahedron* **1994**, *50*, 13709−13724. (b) Pinho e Melo, T. M. V. D.; Fausto, R.; Rocha Gonsalves, A. M. d'A.; Gilchrist, T. L. *J. Org. Chem.* **1998**, *63*, 5350−5355.

(2) (a) Mitsuhashi, K. *Asahi Garasu Kogyo Gijutsu Shoreikai Kenkyu Hokoku* **1973**, *23*, 355−362; *Chem. Abstr.* **1975**, *82*, 86591. (b) Zaima, T.; Matsunaga, Y.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1983**, *20*, 1−4.

(3) Gelas-Mialhe, Y.; Mabiala, G.; Vessière, R. *J. Org. Chem.* **1987**, *52*, 5395−5400.

(4) (a) Zaima, T.; Matsuno, C.; Matsunaga, Y.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1984**, *21*, 445−448. (b) Zaima, T.; Matsuno, C.; Matsunaga, Y.; Mitsuhashi, K. *Nippon Kagaku Kaishi* **1984**, 1293−1298; *Chem. Abstr.* **1984**, *101*, 230340.

(5) Zaima, T.; Mitsuhashi, K. *Nippon Kagaku Kaishi* **1979**, 901−905; *Chem. Abstr.* **1979**, *91*, 140303.

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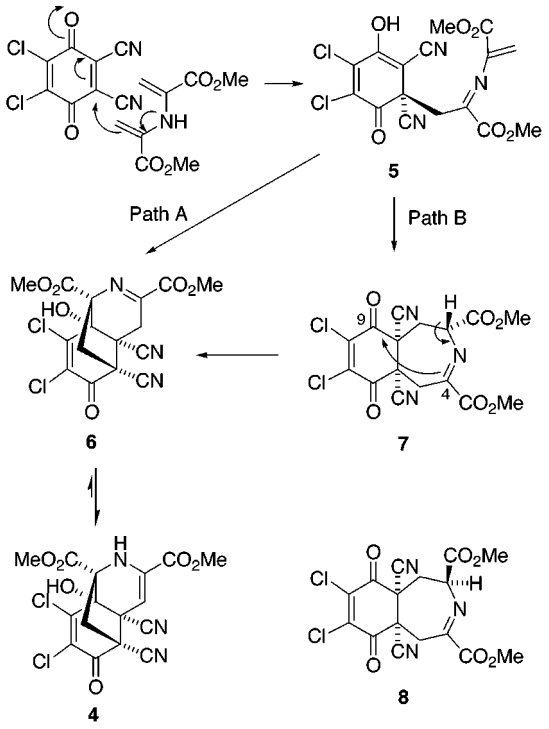
Scheme 2



hydrogen bond, being donated to both the Cl2 atom [O5−H5···Cl2: 2.922(3) Å] and to the carbonyl O1 atom of a neighboring molecule [O5−H5···O1^{i} 2.815(4) Å, $i = {}^{1}/_{2} - x$, ${}^{1}/_{2} + y$, $1 - z$].

In the Nenitzescu indole synthesis, *p*-benzoquinones react with primary enamides to produce 5-hydroxyindoles. The first step is a conjugate addition of the enamide, through the β-carbon atom, to benzoquinone. We suggest that, in a similar way, **3a** first reacts with DDQ by conjugate addition to give the intermediate **5** (Scheme 2). Two possible ways in which this intermediate could be converted into the final product **4** are shown in Scheme 2. The most direct route (path A) is an intramolecular Diels−Alder reaction in which the enol of the six-membered ring acts as the dienophile, giving compound **6** that would be expected to tautomerize to the final product **4**. An alternative (path B) is a second conjugate addition reaction to give the tetrahydroazepine **7**. The lowest energy conformation of compound **7**, as determined by molecular mechanics calculations,[8−10] is illustrated in Figure 2a. The estimated distance between the reacting centers (C4 and C9) is 4.13 Å, and they are suitably aligned to promote a second cyclization to compound **6**. In contrast, the more stable conformation of the isomer **8**, shown in Figure 2b, does not favor the cyclization step. Path B therefore requires the intermediacy of compound **7**, either formed stereoselectively in the conjugate addition step or by epimerization of **8**.

The formation of an adduct of this type with benzoquinones has not previously been reported, so we carried out a limited investigation of the scope of the reaction. As expected, compound **3b** also reacted with DDQ to give

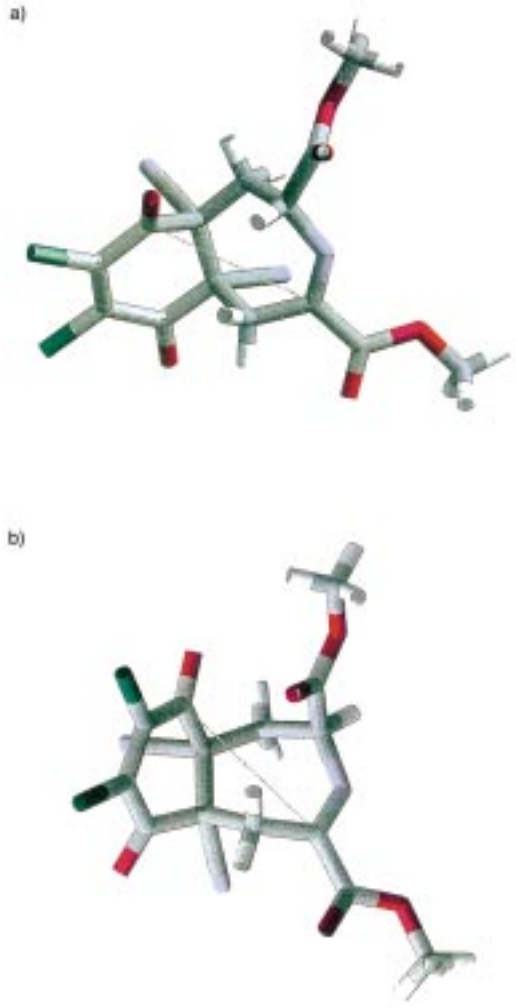
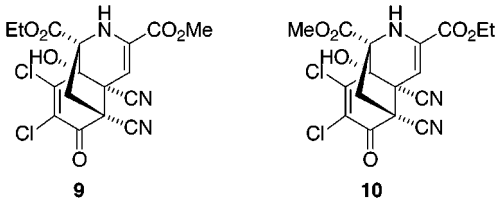


Figure 2. Lowest energy conformation of **7** (a) and **8** (b) determined by molecular mechanics calculations.[8−10]

in this case the adducts **9** and **10** as an inseparable mixture in a 1:1 ratio. The mechanism would lead the bis(enamines) **3c** and **3d** to give complex mixtures under the same conditions as we experimentally observed.



Reactions of the diester **3a** with electrophilic alkenes were briefly investigated. With methyl vinyl ketone it gave the tetrahydropyridine **11** in moderate yield. The formation of this product can also be rationalized as a conjugate addition−cyclization sequence, somewhat analogous to the Hantzsch dihydropyridine synthesis[11] (Scheme 3).

This work provided a novel route to cross conjugated bis(enamines), useful building blocks for the synthesis of nitrogen containing heterocycles.[2−4] We are currently exploring the asymmetric reduction of these compounds as a source of new amino acids. An unusual reaction of

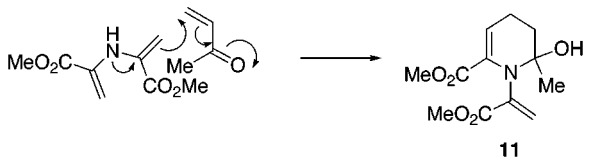
(8) (a) Molecular mechanics PCFF300 (101) force field[9] calculations were undertaken using the Cerius[2] (version 3.5) molecular modeling program.[10]

(9) (a) Sun, H. *J. Comput. Chem.* **1994**, *15*, 752. (b) Sun, H.; Mumby, S. J.; Maple, J. R.; Hagler, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2978.

(10) Cerius[2] (version 3.5), Molecular Simulation, San Diego, CA 92111-3712, 1997.

(11) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron* **1987**, *43*, 5171−5186.

Scheme 3



11

2-iminobis(propenoic) diester with DDQ is described, and this led to the novel structures **4**, **9**, and **10**.

Experimental Section

General Methods. General methods of characterization have been described previously.[1a] Light petroleum refers to the fraction bp 40−60 °C. Thiazolidines **1a**−**d** were prepared by the general procedure described earlier, starting from L-cysteine methyl ester hydrochloride.[1a] A preparation of the thiazolidine **1c** has been described in the literature,[12] and the thiazolidine **1a** has been described as a component of a reaction mixture.[13]

Dimethyl 2-Methylthiazolidine-2,4-dicarboxylate (1a). Compound **1a** (diastereoisomeric mixture 82:18) was obtained as an oil (90%): IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.94 and 2.11 (3 H, 2 × s), 3.11 (1 H, t, J = 10.44 Hz), 3.62 (1 H, dd, J = 5.5, 10.2 Hz), 4.03, 4.04 and 4.05 (6 H, 3 × s), and 4.26 (1 H, dd, J = 5.5, 10.4 Hz); MS (EI) 220 (M^+, 0.5), 160 (100), 119 (49), 100 (92), and 59 (85). Anal. Calcd for $C_8H_{13}NO_4S$: C, 43.83; H, 5.93; N, 6.39. Found: C, 43.39; H, 5.90; N, 6.25.

2-Ethyl 4-Methyl 2-Methylthiazolidine-2,4-dicarboxylate (1b). Compound **1b** (diastereoisomeric mixture 80:20) was obtained as an oil (87%): IR (film) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (3 H, t), 1.70 and 1.87 (3 H, 2 × s), 2.88 (1 H, t, J = 10.45 Hz), 3.38 (1 H, dd, J = 5.77, 10.45 Hz), 3.80 and 3.81 (3 H, 2 × s), 4.03 (1 H, dd, J = 5.77, 10.45 Hz),and 4.27 (2 H, q); MS (EI) 234 (M^+, 10), 160 (100), 119 (89), 100 (100), and 59 (93). Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.35; H, 6.43; N, 6.00. Found: C, 46.38; H, 6.60; N, 6.11.

Methyl 2-Methyl-2-(ethoxycarbonylmethyl)thiazolidine-4-carboxylate (1c). Compound **1c** (diastereoisomeric mixture 72:28) was obtained as an oil (90%): IR (film) 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22−1.32 (3 H, m), 1.57 and 1.84 (3 H, 2 × s), 2.76 and 2.88 (2 H, 2 × s), 2.91−3.20 (1 H, m) 3.35−3.45 (1 H, m), 3.79 and 3.80 (3 H, 2 × s), 4.04−4.13 (1 H, m), and 4.07−4.24 (2 H, m); MS (EI) 247 (M^+, 16), 214 (20), 188 (57), 160 (100), 100 (96), and 59 (58).

Methyl 2-Methyl-2-(acetylmethyl)thiazolidine-4-carboxylate (1d). The reaction of cysteine methyl ester with acetylacetone led to the formation of two products: the expected thiazolidine **1d** (diastereoisomeric mixture 57:43) was formed in 62% yield and *N*-(4-oxobut-2-ene)cysteine methyl ester disulfide in 8% yield. The products were isolated by flash chromatography light petroleum−ethyl acetate (2:1), light petroleum−ethyl acetate (1:1) then ethyl acetate]. Compound **1d** was obtained as an oil: IR (film) 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.97 and 2.04 (3 H, 2 × s), 2.18 and 2.25 (3 H, 2 × s), 2.80−3.06 and 3.28−3.39 (2 H, m), 3.78 and 3.80 (3 H 2 × s), and 4.02−4.04, and 4.37−4.44 (1 H, m); MS (EI) 217 (M^+, 68), 202 (11), 158 (87), 128 (52), and 110 (100). Anal. Calcd for $C_9H_{15}NO_3S$: C, 49.75; H, 6.96; N, 6.45. Found: C, 49.67; H, 7.02; N, 6.62.

***N*-[2-(4-oxo-pent-2-ene)]cysteine methyl ester disulfide:** mp 106−107 °C (from dichloromethane−diethyl ether); IR (KBr) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.95 (6 H, s), 2.03 (6 H, s), 2.98 (2 H, dd, J = 8.2, 14.0 Hz), 3.20 (2 H, dd, J = 5.2, 14.0 Hz), 3.78 (6 H, s). 4.45−4.52 (2 H, m), and 5.07 (2 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.0, 28.9, 40.8, 52.7, 54.8, 97.2, 161.0, 170.3, and 196.2; MS (EI) 433 (M^+, 8), 249 (16), 216 (87), 174 (51), 142 (17), and 114 (26). Anal. Calcd for $C_{18}H_{28}N_2O_6S_2$: C, 49.98; H, 6.52; N, 6.48. Found: C, 49.85; H, 6.52; N, 6.21.

Preparation of Bis(enamines). General Procedure. The thiazolidine **1** (1.0 mmol) was dissolved in dry acetonitrile (10 mL). The solution was cooled to −20 °C, and silver carbonate (277 mg, 1 mmol) was added, followed by a solution of DBU (30 mg, 0.2 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred for 2 h at 0 °C and then for 8 h at room temperature. Diethyl ether was added, the reaction mixture was filtered, and the solvent was evaporated from the filtrate. The products were isolated by flash chromatography.

2-Iminobis(propenoic acid) Dimethyl Ester (3a). Dimethyl 2-methylthiazolidine-2,4-dicarboxylate **1a** gave, by the general procedure, followed by flash chromatography [light petroleum−ethyl acetate (4:1) then light petroleum−ethyl acetate (3:1)] 2-iminobis(propenoic acid) dimethyl ester **3a** as a yellow solid (139 mg, 75%): mp 44−45 °C (lit.[2b] mp 51−51.5 °C); IR (film) 1724 and 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 6 H), 5.06 (m, 2 H), and 5.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 52.9, 97.3, 134.1, and 165.1; MS (EI) 185 (M^+, 66), 153 (100), 94 (86), and 66 (64). Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.94; N, 7.56. Found: C, 51.99; H, 6.06; N, 7.35.

2-Iminobis(propenoic acid) Ethyl Methyl Ester (3b). *2*-Ethyl 4-methyl 2-methylthiazolidine-2,4-dicarboxylate 9**1b**) gave, by the general procedure, followed by flash chromatography [light petroleum−ethyl acetate (4:1) then light petroleum−ethyl acetate (3:1)] 2-iminobis(propenoic acid) ethyl methyl ester (**3b**) (101 mg, 51%) (as an oil at room temperature, solid with low mp): IR (film) 1724 and 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (t, 3 H), 3.85 (s, 3 H), 4.30 (q, 2 H), 5.03−5.05 (m, 2 H), 5.53−5.54 (m, 2 H),and 7.35 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.1, 52.8, 62.0, 96.9, 97.1, 134.1, 134.3, 164.5, and 165.0; MS (EI) 199 (M^+, 80), 167 (55), 153 (96), 94 (73), and 66 (88). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.03. Found: C, 54.15; H, 6.56; N, 7.06.

3-(1-Methoxycarbonylvinylamino)but-2-enoic Acid Ethyl Ester (3c). Methyl 2-(ethoxycarbonylmethyl)-2-methylthiazolidine-4-carboxylate (**1c**) gave, by the general procedure, followed by flash chromatography [light petroleum−ethyl acetate (4:1) then light petroleum−ethyl acetate (3:1)] 3-(1-methoxycarbonylvinylamino)but-2-enoic acid ethyl ester (**3c**) (107 mg, 50%) (as an oil at room temperature, solid with low mp): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3 H), 2.10 (s, 3 H), 3.85 (s, 3 H), 4.11 (q, 2 H), 4.72 (s, 1 H), 5.17 (s, 1 H), and 5.71 (s, 1 H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.04; N, 6.57. Found: C, 56.41; H, 7.09; N, 6.49.

Methyl 2-(1-Methyl-3-oxo-but-1-enylamino)acrylate (3d). Methyl 2-(acetylmethyl)-2-methylthiazolidine-4-carboxylate (**1d**) gave, by the general procedure, followed by flash chromatography [light petroleum−ethyl acetate (4:1) then light petroleum−ethyl acetate (3:1)] methyl 2-(1-methyl-3-oxo-but-1-enylamino)-acrylate (**3d**) (130 mg, 71%): mp 52−53 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 6H), 3.85 (s, 3H), 5.21 (s, 1H), 5.32 (s, 1H), and 5.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.0, 29.0, 52.6, 99.9, 110.1, 133.9, 157.4, 163.9, and 196.4; MS (EI) 183 (M^+, 22), 168 (4), 140 (40), 124 (14), and 108 (41). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.06; H, 6.90; N, 7.39.

Preparation of 4-Oxo-11-azatricyclo[5.4.0.0^{3,8}]undeca-5,9-dienes. General Procedure. A solution of the divinylamine (6.23 mmol) in toluene (40 mL) was stirred under nitrogen, and DDQ (1.47 g, 6.5 mmol) was added. The resulting mixture was heated under reflux for 2.5 h. The product precipitated on cooling and was isolated by filtration.

5,6-Dichloro-3,8-dicyano-7-hydroxy-4-oxo-11-azatricyclo-[5.4.0.0^{3,8}]undeca-5,9-diene-1,10-dicarboxylic Acid Dimethyl Ester (4). Product **4** was isolated as a yellow solid (2.46 g, 96%): mp 209−211 °C (from diethyl ether−light petroleum bp 40−60 °C); IR (KBr) 2256, 1719, 1635, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.85 (d, 1 H, J = 15.0 Hz), 2.97 (d, 1 H, J = 15.0 Hz), 3.87 (s, 3 H), 3.91 (s, 3 H), 5.59 (s, 1 H), and 5.89 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 41.8, 53.4, 56.0, 63.4, 67.9, 77.8, 102.5, 113.2, 113.9, 130.1, 135.5, 154.7, 161.5, 166.1, and 178.3; MS (FAB) 411 [M^+ (^{35}Cl), 34]. Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_6$: C, 46.62; H, 2.69; N, 10.19. Found: C, 46.61; H, 2.70; N, 10.19.

5,6-Dichloro-3,8-dicyano-7-hydroxy-4-oxo-11-azatricyclo-[5.4.0.0^{3,8}]undeca-5,9-diene-1,10-dicarboxylic acid 1-Ethyl 10-Methyl Ester (9) and 5,6-Dichloro-3,8-dicyano-7-hydroxy-4-oxo-11-azatricyclo[5.4.0.0^{3,8}]undeca-5,9-diene-1,10-dicarboxylic Acid 10-Ethyl 1-Methyl Ester (10). The 1:1

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mixture of **9** and **10** was isolated by filtration as a yellow solid (2.3 g, 87%): mp 194−196 °C (from diethyl ether−light petroleum bp 40−60 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, 3 H), 1.39 (t, 3 H), 2.84 (d, 1 H, J = 15.6 Hz), 2.85 (d, 1 H, J = 15.3 Hz), 2.96 (d, 1 H, J = 15.6 Hz), 2.97 (d, 1 H, J = 15.3 Hz), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.35 (q, 2 H), 4.36 (q, 2 H), 5.56 (bs, 2 H), and 5.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.7, 14.0, 41.8, 41.9, 53.4, 54.7, 56.0, 56.1, 63.0, 63.3, 64.6, 67.8, 67.9, 77.8, 77.9, 102.2, 102.5, 113.2, 135.5, 135.6, 154.5, 161.0, 161.5, 165.7, 165.7, and 178.3; MS (FAB) 426 [M^+ (^{35}Cl), 85]. Anal. Calcd for $C_{17}H_{13}Cl_2N_3O_6$: C, 47.91; H, 3.07; N, 9.86. Found: C, 47.72; H, 3.05; N, 9.91.

6-Hydroxy-1-(1-methoxycarbonylvinyl)-6-methyl-1,4,5,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (11). A solution of the divinylamine **3a** (185 mg, 1.0 mmol) in methyl vinyl ketone (5 mL) was maintained at room temperature for 48 h. The excess methyl vinyl ketone was distilled off, and the residue was subjected to flash chromatography. This gave [with light petroleum ether (4:1), light petroleum−ethyl acetate (3:1) then ethyl acetate] the tetrahydropyridine **11** (102 mg, 40%) as an oil: IR (film) 3404, 1751, 1717, and 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.71−1.72 (m, 4 H), 1.90−2.10 (m, 3 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 4.50 (br t, 1 H), 4.81 (d, 1 H, J = 1.1 Hz), 5.01 (s, 1 H), and 5.05−5.06 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.6 (t), 19.7 (q), 29.8 (t), 52.7 (q), 52.8 (q), 85.4 (s), 95.0 (d), 95.6 (t), 175.7 (s), 148.3 (s), 165.3 (s), and 170.6 (s); MS (EI) 255 (M^+, 1), 194 (53), 151 (50), 134 (43), and 91 (44). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.47; H, 6.66; N, 5.49. Found: C, 56.20; H, 6.86; N, 5.06.

Crystallographic Data for 5,6-Dichloro-3,8-dicyano-7-hydroxy-4-oxo-11-azatricyclo[5.4.0.0^{3,8}]undeca-5,9-diene-1,10-dicarboxylic Acid Dimethyl Ester (4). X-ray diffraction analysis on compound **4** was carried out on a Enraf Nonius CAD-4 diffractometer at room temperature. The structure of this compound (C_{16} H_{11} Cl_2 N_3 O_6, M_w 412.18 amu) was determined from a prismatic crystal of dimensions 0.07 × 0.10 × 0.15 mm (space group $P2_1/a$) with unit cell a = 10.522(5) Å, b = 13.014-(6) Å, c = 13.386(6) Å, β = 97.57(4)°, V = 1817.0(15) Å^3. It was four molecules per cell, D_x = 1.507 gcm^{-3}, μ = 0.396 mm^{-1}. Mo Kα (λ = 0.71073 Å). 2204 reflections with $I > 2\sigma(I)$, R_w = 0.035.

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Supporting Information Available: Crystallographic data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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