Aminodienylesters. II. A New Synthesis of 2,3-Dihydro-6*H*-1,3-oxazines by Heterocyclic Annelation Reactions of *sec*-Aminodienylesters with Acetaldehyde

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The reactions of *sec*-aminodienylesters 2, which were prepared by the reactions of methyl 5-(*N*,*N*-dimethylamino)-2,4-pentadienoate (*tert*-aminodienylester 1) with primary amines, with acetaldehyde afforded 2,3-dihydro-6*H*-1,3-oxazines 3, providing a new heterocyclic annelation reaction.

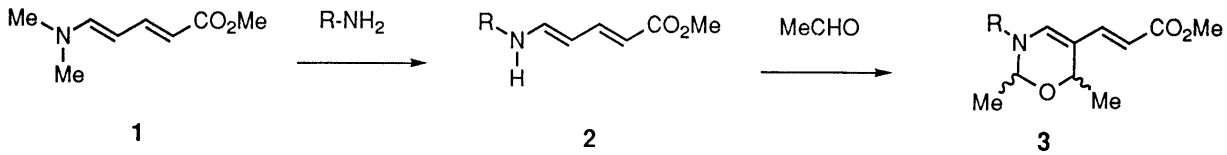
Key words aminodienylester; acetaldehyde; 2,3-dihydro-6*H*-1,3-oxazine; heterocyclic annelation reaction

In the preceding paper,[1] we reported the cycloaddition reactions of methyl 5-(*N*,*N*-dimethylamino)-2,4-pentadienoate (*tert*-aminodienylester **1**) with α,β-unsaturated carbonyl compounds. Since we are interested in nitrodienamines and aminodienylesters with enaminic and diene moieties and the electronic "push–pull" character which can lead to interesting cycloaddition reactions, we investigated the reactivities of the *sec*-aminodienylesters **2**,[2-4] prepared by the reaction of the *tert*-aminodienylester **1** with primary amines. The reaction of **2** with acetaldehyde afforded 2,3-dihydro-6*H*-1,3-oxazines **3**, providing a new heterocyclic annelation reaction. In this annelation reaction with acetaldehyde, we found several reaction sites, though one was predominant.

Synthesis of *sec*-Aminodienylesters 2 from *tert*-Aminodienylester 1 The following *sec*-aminodienylesters, namely, methyl 5-(benzylamino)-2,4-pentadienoate (**11**), methyl 5-(phenethylamino)-2,4-pentadienoate (**12**), methyl 5-[2-(3-indolyl)ethylamino]-2,4-pentadienoate (**13**), methyl 5-(4-pyridylmethylamino)-2,4-pentadienoate (**14**), methyl 5-(3-pyridylmethylamino)-2,4-pentadienoate (**15**), methyl 5-(2-pyridylmethylamino)-2,4-pentadienoate (**16**), and methyl 5-[2-(4-pyridyl)ethylamino]-2,4-pentadienoate (**17**) were selected for the present purpose (Chart 2). The *sec*-aminodienylesters **11**—**17** were prepared by the reaction of the *tert*-aminodienylester **1** with the corresponding primary amines, namely, benzylamine (**4**), phenethylamine (**5**), tryptamine (**6**), 4-picolylamine (**7**), 3-picolylamine (**8**), 2-picolylamine (**9**), and 4-(2-aminoethyl)pyridine (**10**) under reflux in tetrahydrofuran (THF), in yields of 73.8, 79.6, 75.3, 81.9, 86.1, 79.5, and 79.6%, respectively. However, the reaction of **1** with alkylamines, *sec*-alkylamines, and aniline by the above methods failed to give the corresponding products.

Synthesis of 2,3-Dihydro-6*H*-1,3-oxazines 3[5-7] **from *sec*-Aminodienylesters 2** First, we planned to prepare 1-benzyl-3-methoxycarbonyl-2-methyl-1,2-dihydropyridine by cycloaddition reaction of the *sec*-aminodienylester **11** with acetaldehyde. Unexpectedly, two heterocyclic annelation products, *cis*- and *trans*-3-benzyl-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazines (**18** and **19**), were obtained in 21.0 and 49.0% yields by heating of **11** with excess acetaldehyde in xylene in a sealed tube at 100 °C. The structures of the products **18** and **19** were proposed on the basis of the following physical evidence; **18** and **19** have the same molecular formula ($C_{17}H_{21}NO_3$) and their ^{1}H-NMR spectra show that they retain a benzyl group and an aminodienylester moiety. Further, **18** and **19** have two methyl groups and two methine protons. The nuclear Overhauser and exchange spectroscopy (NOESY) spectrum of **18** shows the presence of a cross-peak between the methine protons at δ 4.61 (q, J=5.8 Hz) and 4.71 (q, J=6.4 Hz) indicating that these two methine protons are in a *cis* relation. If the *cis*-dihydro-1,3-oxazine **18** existed in a configuration having two equatorial methyl groups on carbons 2 and 6, there would be no appreciable interaction between these methyl groups and between an equatorial methyl group and a methoxycarbonylethenyl group on carbon 5. Therefore, the *cis*-dihydro-1,3-oxazine **18** is considered to have two equatorial methyl groups on carbons 2 and 6. On the other hand, the NOESY spectrum of **19** showed the presence of the cross-peaks between a methine proton at δ 4.82 (q, J=5.8 Hz) and three protons of a methyl group at δ 1.39 (d, J=6.4 Hz). Therefore, **19** has an axial methyl group and an equatorial methyl group in *trans*-configuration. Formation of the *trans*-dihydro-1,3-oxazine **19** as the major product can be rationalized by assuming that the *trans*-configuration is sterically more stable than the *cis*-configuration.

Further, *cis*- and *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-phenethyl-6*H*-1,3-oxazines (**20** and **21** in 14.4 and 57.4% yields), *cis*- and *trans*-2,3-dihydro-3-[2-(3-indolyl)ethyl]-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazines (**22** and **23** in 15.3 and 61.4% yields), *cis*- and *trans*-2,3-dihydro-



1 2 3

Chart 1

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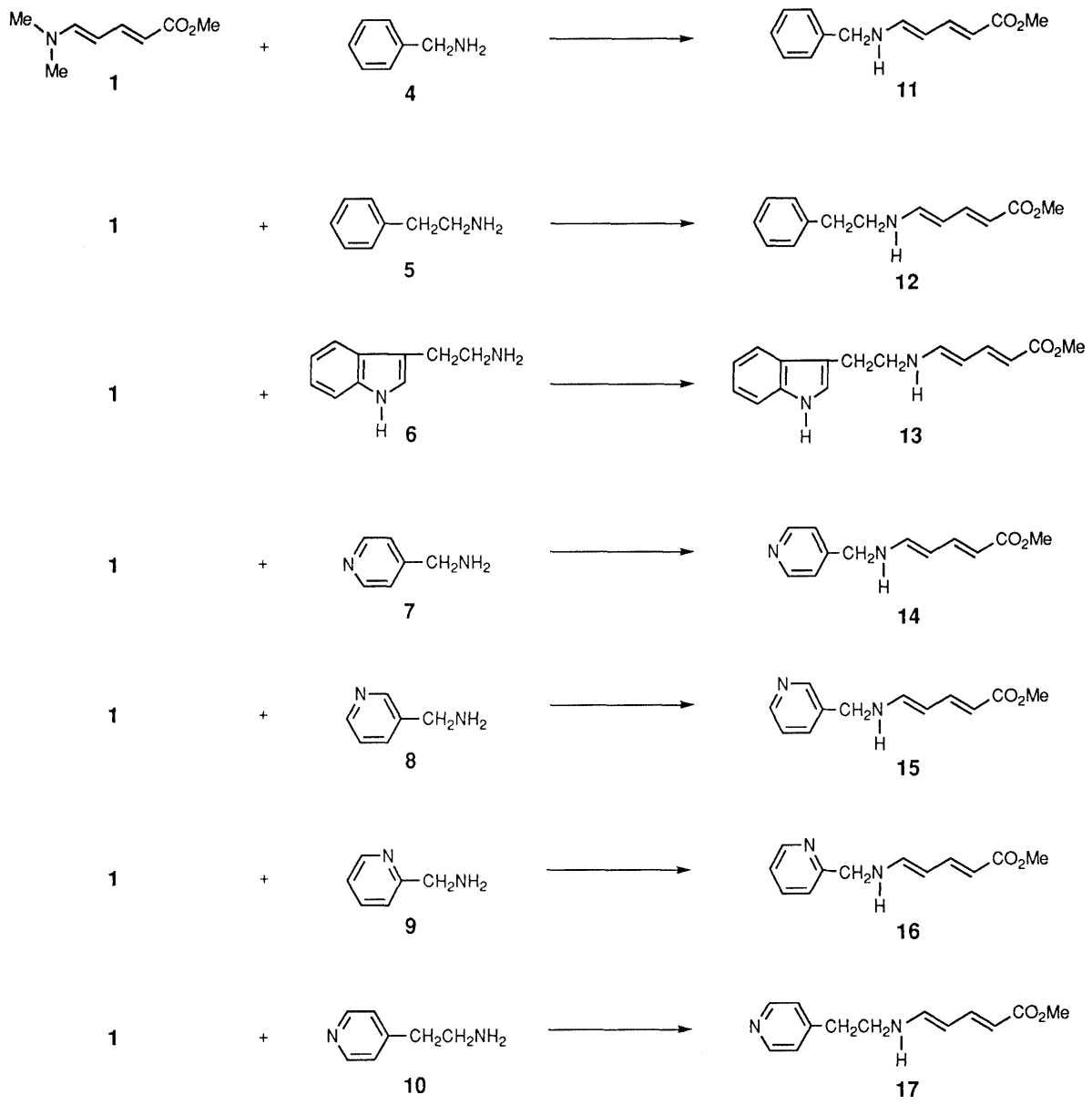

Chart 2

5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(4-pyridylmethyl)-6*H*-1,3-oxazines (**24** and **25** in 34.0 and 51.0% yields), *cis*- and *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(3-pyridylmethyl)-6*H*-1,3-oxazines (**26** and **27** in 34.7 and 52.0% yields), *cis*- and *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(2-pyridylmethyl)-6*H*-1,3-oxazines (**28** and **29** in 31.6 and 47.4% yields), and *cis*- and *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-[2-(4-pyridyl)ethyl]-6*H*-1,3-oxazines (**30** and **31** in 29.4 and 44.0% yields) were similarly obtained (Chart 3).

The heterocyclic annelation reactions of *sec*-aminodienylesters **2** with acetaldehyde may proceed as follows. Initially, the condensation reaction of the reactive enamine moiety of **2** with acetaldehyde may generate the intermediate **32**, followed by condensation of another acetaldehyde to afford the intermediate **33**. Then, intramolecular ring closure by dehydration of **33** may form the 2,3-dihydro-6*H*-1,3-oxazines **34** and **35** as shown in Chart 4.

These results provide a new heterocyclic annelation method with potential utility for the synthesis of 2,3-dihydro-6*H*-1,3-oxazines.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-200 or JASCO FT/IR-8000 spectrometer, and ^{1}H-NMR spectra with a JEOL EX-90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. ^{1}H–^{1}H, and ^{1}H–^{1}H long-range correlation spectroscopy (COSY) and NOESY spectra were obtained with the usual pulse sequences and data processing was performed with the standard JEOL software. MS were recorded with a JEOL JMS-D 300 spectrometer. Wakogel C-200 (silica gel) and Merck Kieselgel G nach Stahl (silica gel) and NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysya Chemical Ltd.) were used for column chromatography and thin layer chromatography (TLC), respectively. All runs were carried out under argon.

General Procedure for Reactions of *tert*-Aminodienylester 1 with Primary Amines 4—9 A solution of the *tert*-aminodienylester **1** (3 mmol) and an amine (1 mmol) in THF (4 ml) was refluxed for an appropriate period until the disappearance of **1** (checked by TLC). The reaction mixture was concentrated under a vacuum, and the residue was subjected

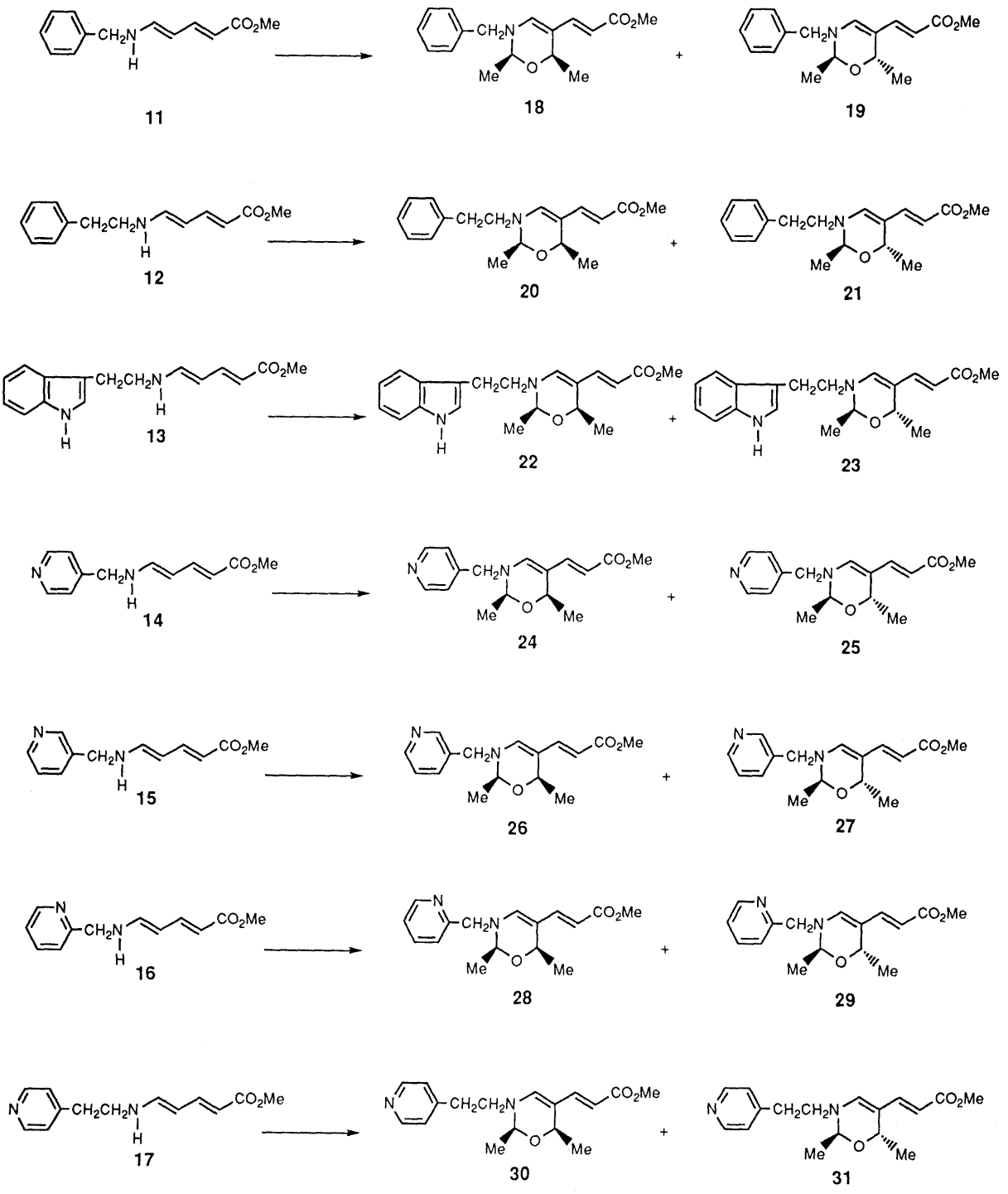

Chart 3

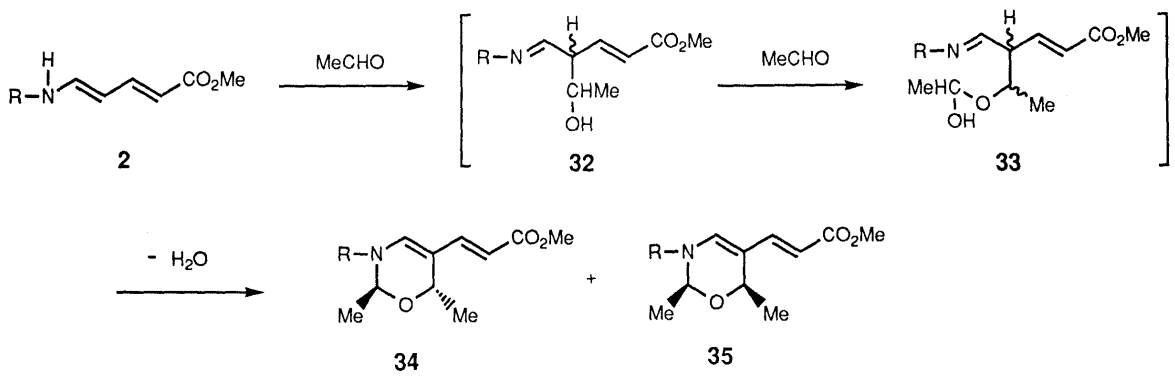

Chart 4

to N–H silica gel column chromatography with appropriate solvents.

Reaction with Benzylamine (4) Reaction period, 72 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: 160.1 mg (73.8%) of methyl 5-(benzylamino)-2,4-pentadienoate (**11**), a light yellow oil. IR (neat) cm^{-1}: 1732, 1687, 1597, 1514. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.68 (3H, s, -CO_2Me), 4.23 (2H, d, J=5.6 Hz, methylene H), 4.51 (1H, br, NH), 5.35 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.47 (1H, d, J=14.9 Hz, olefinic H), 6.79 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.28 (2H, td, J=6.1, 1.2 Hz, aromatic H), 7.30 (1H, tt, J=6.1, 1.2 Hz, aromatic H), 7.33 (1H, dd, J=14.9, 11.6 Hz, olefinic H), 7.34 (2H, dd, J=6.1, 1.2 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{13}H_{15}NO_2$: 217.1101. Found: 217.1085.

Reaction with Phenethylamine (5) Reaction period, 96 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: 184.7 mg (79.6%) of methyl 5-(phenethylamino)-2,4-pentadienoate (**12**), a light yellow oil. IR (neat) cm^{-1}: 1734, 1687, 1620, 1597, 1520. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.86 (2H, t, J=6.8 Hz, methylene H), 3.33 (2H, q, J=6.8 Hz, methylene H), 3.69 (3H, s, -CO_2Me), 4.18 (1H, br, NH), 5.31 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.48 (1H, d, J=14.7 Hz, olefinic H), 6.67 (1H, dd, J=13.1, 7.9 Hz, olefinic H), 7.17—7.37 (6H, m, aromatic and olefinic H). High-resolution EI-MS m/z: Calcd for $C_{14}H_{17}NO_2$: 231.1256. Found: 231.1253.

Reaction with Tryptamine (6) Reaction period, 84 h. Solvent for chromatography, 50% ethyl acetate in hexane. Product: 203.3 mg (75.3%) of methyl 5-[2-(3-indolyl)ethylamino]-2,4-pentadienoate (**13**), a light brown oil. IR (neat) cm^{-1}: 1730, 1680, 1591, 1504. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.03 (2H, t, J=6.8 Hz, methylene H), 3.40 (2 H, q, J=6.8 Hz, methylene H), 3.69 (3H, s, -CO_2Me), 4.25 (1H, br, NH), 5.31 (2 H, dd, J=13.1, 11.6 Hz, olefinic H), 5.47 (1H, d, J=14.8 Hz, olefinic H), 6.66 (1H, dd, J=13.1, 7.9 Hz, olefinic H), 7.03 (1H, d, J=2.5 Hz, aromatic H), 7.13 (1H, td, J=8.2, 0.9 Hz, aromatic H), 7.22 (1H, td, J=8.2, 0.9 Hz, aromatic H), 7.31 (1H, dd, J=14.8, 11.6 Hz, olefinic H), 7.38 (1H, dt, J=8.2, 0.9 Hz, aromatic H), 7.58 (1H, dt, J=8.2, 0.9 Hz, aromatic H), 8.15 (1H, br, NH). High-resolution EI-MS m/z: Calcd for $C_{16}H_{18}N_2O_2$: 270.1369. Found: 270.1372.

Reaction with 4-Picolylamine (7) Reaction period, 48 h. Solvent for chromatography, 50% ethyl acetate in hexane. Product: 178.5 mg (81.9%) of methyl 5-(4-pyridylmethylamino)-2,4-pentadienoate (**14**), light yellow plates (ether), mp 91—92°C. IR (KBr) cm^{-1}: 1720, 1687, 1624, 1583, 1527. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.67 (3H, s, -CO_2Me), 4.29 (2H, d, J=5.5 Hz, methylene H), 4.82 (1H, br, NH), 5.25 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.46 (1H, d, J=14.9 Hz, olefinic H), 6.80 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.21 (2H, dt, J=4.5, 1.2 Hz, aromatic H), 7.29 (1H, dd, J=14.9, 11.6 Hz, olefinic H), 8.56 (2H, dd, J=4.5, 1.2 Hz, aromatic H). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H,6.47; N, 12.84. Found: C, 65.86; H, 6.32; N, 12.74.

Reaction with 3-Picolylamine (8) Reaction period, 54 h. Solvent for chromatography, 50% ethyl acetate in hexane. Product: 188.9 mg (86.1%) of methyl 5-(3-pyridylmethylamino)-2,4-pentadienoate (**15**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1691, 1599. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.67 (3H, s, -CO_2Me), 4.27 (2H, d, J=5.4 Hz, methylene H), 4.88 (1H, br, NH), 5.32 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.47 (1H, d, J=14.9 Hz, olefinic H), 6.80 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.29 (1H, t, J=7.9 Hz, aromatic H), 7.30 (1H, dd, J=14.9, 11.6 Hz, olefinic H), 7.63 (1H, dt, J=7.9, 1.8 Hz, aromatic H), 8.53 (1H, dt, J=7.9, 1.8 Hz, aromatic H), 8.54 (1H, t, J=1.8 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{12}H_{14}N_2O_2$: 218.1055. Found: 218.1063.

Reaction with 2-Picolylamine (9) Reaction period, 62 h. Solvent for chromatography, 50% ethyl acetate in hexane. Product: 174.3 mg (79.5%) of methyl 5-(2-pyridylmethylamino)-2,4-pentadienoate (**16**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1691, 1599. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.68 (3H, s, -CO_2Me), 4.35 (2H, d, J=5.2 Hz, methylene H), 5.32 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.49 (1H, t, J=14.9 Hz, olefinic H), 5.67 (1H, br, NH), 6.91 (1H, dd, J=13.1, 7.3 Hz, olefinic H), 7.21 (1H, dd, J=7.5, 5.1 Hz, aromatic H), 7.25 (1H, d, J=7.5 Hz, aromatic H), 7.36 (1H, dd, J=14.9, 11.6 Hz, olefinic H), 7.68 (1H, t, J=7.5 Hz, aromatic H), 8.55 (1H, d, J=5.1 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{12}H_{14}N_2O_2$: 218.1055. Found: 218.1063.

Reaction with 4-(2-Aminoethyl)pyridine (10) Reaction period, 68 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: 184.7 mg (79.6%) of methyl 5-[2-(4-pyridyl)ethylamino]-2,4-pentadienoate (**17**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1685, 1620, 1599. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.87 (2H, t, J=6.8 Hz, methylene H), 3.37 (2H, q, J=6.8 Hz, methylene H), 3.69 (3H, s, -CO_2Me), 4.23 (1H, br, NH), 5.33 (1H, dd, J=13.1, 11.6 Hz, olefinic H), 5.51 (1H, d, J=14.9 Hz, olefinic H), 6.67 (1H, dd, J=13.1, 7.6 Hz, olefinic H), 7.12 (2H, dd, J=4.4, 1.6 Hz, aromatic H), 7.31 (1H, dd, J=14.9, 11.6 Hz, olefinic H), 8.53 (2H, dd, J=4.4, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{13}H_{16}N_2O_2$: 232.1212. Found: 232.1237.

General Procedure for Reactions of *sec*-Aminodienylesters 11—17 with Acetaldehyde A solution of a *sec*-aminodienylester (1 mmol) and excess acetaldehyde in xylene (4 ml) in a sealed tube was heated at 100 °C for an appropriate period until the aminodienylester was no longer detectable by TLC. The reaction mixture was concentrated under a vacuum, and then the residue was subjected to N–H silica gel column chromatography with appropriate solvents.

Reaction with Methyl 5-(Benzylamino)-2,4-pentadienoate (11) Reaction period, 2 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: first eluate, 60.3 mg (21.0%) of *cis*-3-benzyl-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazine (**18**), a light yellow oil. IR (neat) cm^{-1}: 1720, 1701, 1597. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.36 (3H, d, J=5.8 Hz, -Me), 1.42 (3H, d, J=6.4 Hz, -Me), 3.71 (3H, s, -CO_2Me), 4.35 (1H, d, J=16.7 Hz, methylene H), 4.55 (1H, d, J=16.7 Hz, methylene H), 4.61 (1H, q, J=5.8 Hz, methine H), 4.71 (1H, q, J=6.4 Hz, methine H), 5.28 (1H, d, J=15.6 Hz, olefinic H), 6.73 (1H, s, olefinic H), 7.19 (1H, d, J=15.6 Hz, olefinic H), 7.20 (2H, td, J=7.3, 2.1 Hz, aromatic H), 7.29 (1H, tt, J=7.3, 2.1 Hz, aromatic H), 7.35 (2H, dd, J=7.3, 2.1 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{21}NO_3$: 287.1519. Found: 287.1506. Second eluate, 140.6 mg (49.0%) of *trans*-3-benzyl-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazine (**19**), a light yellow oil. IR (neat) cm^{-1}: 1720, 1701, 1597. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=5.8 Hz, -Me), 1.39 (3H, d, J=6.4 Hz, -Me), 3.70 (3H, s, -CO_2Me), 4.34 (2H, s, methylene H), 4.66 (1H, q, J=6.4 Hz, methine H), 4.82 (1H, q, J=5.8 Hz, methine H), 5.30 (1H, d, J=15.6 Hz, olefinic H), 6.65 (1H, s, olefinic H), 7.18 (1H, d, J=15.6 Hz, olefinic H), 7.21 (2H, dd, J=7.3, 2.1 Hz, aromatic H), 7.29 (1H, tt, J=7.3, 2.1 Hz, aromatic H), 7.36 (2H, dd, J=7.3, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{21}NO_3$: 287.1519. Found: 287.1506.

Reaction with Methyl 5-(Phenethylamino)-2,4-pentadienoate (12) Reaction period, 1.5 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: first eluate, 43.3 mg (14.4%) of *cis*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-phenethyl-6*H*-1,3-oxazine (**20**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1701, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.38 (3H, d, J=6.4 Hz, -Me), 1.43 (3H, d, J=5.8 Hz, -Me), 2.73—2.83 (2H, m, methylene H), 3.29—3.41 (2H, m, methylene H), 3.71 (3H, s, -CO_2Me), 4.56 (1H, q, J=5.8 Hz, methine H), 4.71 (1H, q, J=6.4 Hz, methine H), 5.23 (1H, d, J=15.6 Hz, olefinic H), 6.50 (1H, s, olefinic H), 7.10 (1H, d, J=15.6 Hz, olefinic H), 7.15 (2H, td, J=7.3, 2.1 Hz, aromatic H), 7.29 (1H, tt, J=7.3, 2.1 Hz, aromatic H), 7.35 (2H, dd, J=7.3, 2.1 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{18}H_{23}NO_3$: 301.1679. Found: 301.1705. Second eluate, 172.8 mg (57.4%) of *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-phenethyl-6*H*-1,3-oxazine (**21**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, d, J=6.4 Hz, -Me), 1.39 (3H, d, J=5.8 Hz, -Me), 2.79 (1H, ddd, J=14.0, 8.1, 6.7 Hz, methylene H), 2.84 (1H, ddd, J=14.0, 7.9, 6.4 Hz, methylene H), 3.31 (1H, ddd, J=14.6, 7.9, 6.7 Hz, methylene H), 3.46 (1H, ddd, J=14.6, 8.1, 6.4 Hz, methylene H), 3.69 (3H, s, -CO_2Me), 4.60 (1H, q, J=6.4 Hz, methine H), 4.82 (1H, q, J=5.8 Hz, methine H), 5.23 (1H, d, J=15.6 Hz, olefinic H), 6.39 (1H, s, olefinic H), 7.07 (1H, d, J=15.6 Hz, olefinic H), 7.15 (2H, dd, J=7.3, 2.1 Hz, aromatic H), 7.24 (1H, tt, J=7.3, 2.1 Hz, aromatic H), 7.30 (2H, dd, J=7.3, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1706.

Reaction with Methyl 5-[2-(3-Indoyl)ethylamino]-2,4-pentadienoate (13) Reaction period, 2 h. Solvent for chromatography, 30% ethyl acetate in hexane. Product: first eluate, 52.0 mg (15.3%) of *cis*-2,3-dihydro-3-[2-(3-indolyl)ethyl]-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazine (**22**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1684, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.39 (3H, d, J=6.4 Hz, -Me), 1.46 (3H, d, J=5.8 Hz, -Me), 2.96 (1H, ddd, J=14.0, 8.0, 6.4 Hz, methylene H), 2.98 (1H, ddd, J=14.0, 7.8, 6.8 Hz, methylene H), 3.44 (1H, ddd, J=14.5, 7.8, 6.4 Hz, methylene H), 3.49 (1H, ddd, J=14.5, 8.0, 6.8 Hz, methylene H), 3.71 (3H, s, -CO_2Me), 4.61 (1H, q, J=5.8 Hz, methine H), 4.71 (1H, q, J=6.4 Hz, methine H), 5.21 (1H, d, J=15.6 Hz,

olefinic H), 6.51 (1H, s, olefinic H), 6.97 (1H, d, J=2.5 Hz, aromatic H), 7.08 (1H, d, J=15.6 Hz, olefinic H), 7.14 (1H, ddd, J=8.0, 7.0, 0.9 Hz, aromatic H), 7.21 (1H, ddd, J=8.2, 7.0, 0.9 Hz, aromatic H), 7.37 (1H, dd, J=8.2, 0.9 Hz, aromatic H), 7.54 (1H, dd, J=8.0, 0.9 Hz, aromatic H), 8.15 (1H, br, -NH). High-resolution EI-MS m/z: Calcd for $C_{20}H_{24}N_2O_3$: 340.1787. Found: 340.1807. Second eluate, 208.8 mg (61.4%) of *trans*-2,3-dihydro-3-[2-(3-indolyl)ethyl]-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-6*H*-1,3-oxazine (**23**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1684, 1583. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, d, J=6.4 Hz, -Me), 1.40 (3H, d, J=5.8 Hz, -Me), 2.95 (1H, ddd, J=14.0, 8.0, 6.8 Hz, methylene H), 3.00 (1H, ddd, J=14.0, 7.8, 6.4 Hz, methylene H), 3.38 (1H, ddd, J=14.5, 7.8, 6.8 Hz, methylene H), 3.52 (1H, ddd, J=14.5, 8.0, 6.4 Hz, methylene H), 3.69 (3H, s, -CO_2Me), 4.61 (1H, q, J=6.4 Hz, methine H), 4.87 (1H, q, J=5.8 Hz, methine H), 5.22 (1H, d, J=15.6 Hz, olefinic H), 6.41 (1H, s, olefinic H), 6.98 (1H, d, J=2.5 Hz, aromatic H), 7.06 (1H, d, J=15.6 Hz, olefinic H), 7.14 (1H, ddd, J=8.0, 7.0, 0.9 Hz, aromatic H), 7.21 (1H, ddd, J=8.2, 7.0, 0.9 Hz, aromatic H), 7.37 (1H, dd, J=8.2, 0.9 Hz, aromatic H), 7.54 (1H, dd, J=8.0, 0.9 Hz, aromatic H), 8.15 (1H, br, NH). High-resolution EI-MS m/z: Calcd for $C_{20}H_{24}N_2O_3$: 340.1787. Found: 340.1807.

Reaction with Methyl 5-(4-Pyridylmethylamino)-2,4-pentadienoate (14) Reaction period, 2 h. Solvent for chromatography, 30% hexane in ethyl acetate. Product: first eluate, 97.9 mg (34.0%) of *cis*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(4-pyridylmethyl)-6*H*-1,3-oxazine (**24**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.35 (3H, d, J=5.8 Hz, -Me), 1.44 (3H, d, J=6.4 Hz, -Me), 3.72 (3H, s, -CO_2Me), 4.32 (1H, d, J=17.1 Hz, methylene H), 4.38 (1H, d, J=17.1 Hz, methylene H), 4.64 (1H, q, J=5.8 Hz, methine H), 4.78 (1H, q, J=6.4 Hz, methine H), 5.34 (1H, d, J=15.6 Hz, olefinic H), 6.67 (1H, s, olefinic H), 7.17 (2H, td, J=4.5, 1.6 Hz, aromatic H), 7.18 (1H, d, J=15.6 Hz, olefinic H), 7.35 (2H, dd, J=4.5, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1472. Found: 188.1472. Second eluate, 146.9 mg (51.0%) of *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(4-pyridylmethyl)-6*H*-1,3-oxazine (**25**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.33 (3H, t, J=5.8 Hz, -Me), 1.42 (3H, d, J=6.4 Hz, -Me), 3.71 (3H, s, -CO_2Me), 4.32 (2H, s, methylene H), 4.69 (1H, q, J=6.4 Hz, methine H), 4.86 (1H, q, J=5.8 Hz, methine H), 5.46 (1H, d, J=15.6 Hz, olefinic H), 6.59 (1H, s, olefinic H), 7.16 (2H, dd, J=4.5, 1.6 Hz, aromatic H), 7.17 (1H, d, J=15.6 Hz, olefinic H), 8.59 (2H, dd, J=4.5, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1472. Found: 188.1472.

Reaction with Methyl 5-(3-Pyridylmethylamino)-2,4-pentadienoate (15) Reaction period, 3 h. Solvent for chromatography, 30% hexane in ethyl acetate. Product: first eluate, 79.1 mg (34.7%) of *cis*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(3-pyridylmethyl)-6*H*-1,3-oxazine (**26**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1589. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.39 (3H, d, J=5.8 Hz, -Me), 1.42 (3H, d, J=6.4 Hz, -Me), 3.71 (3H, s, -CO_2Me), 4.33 (1H, d, J=16.5 Hz, methylene H), 4.39 (1H, d, J=16.5 Hz, methylene H), 4.60 (1H, q, J=5.8 Hz, methine H), 4.75 (1H, q, J=6.4 Hz, methine H), 5.32 (1H, d, J=15.6 Hz, olefinic H), 6.69 (1H, s, olefinic H), 7.17 (1H, d, J=15.6 Hz, olefinic H), 7.29 (1H, t, J=7.9 Hz, aromatic H), 7.58 (1H, dt, J=7.9, 1.8 Hz, aromatic H), 8.51 (1H, t, J=1.8 Hz, aromatic H), 8.55 (1H, dt, J=7.9, 1.8 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1471. Found: 288.1449. Second eluate, 149.8 mg (52.0%) of *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(3-pyridylmethyl)-6*H*-1,3-oxazine (**27**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=5.8 Hz, -Me), 1.39 (3H, d, J=6.4 Hz, -Me), 3.70 (3H, s, -CO_2Me), 4.36 (2H, s, methylene H), 4.66 (1H, q, J=6.4 Hz, methine H), 4.82 (1H, q, J=5.8 Hz, methine H), 5.34 (1H, d, J=15.6 Hz, olefinic H), 6.62 (1H, s, olefinic H), 7.16 (1H, d, J=15.6 Hz, olefinic H), 7.31 (1H, t, J=7.9 Hz, aromatic H), 7.60 (1H, dt, J=7.9, 1.8 Hz, aromatic H), 8.51 (1H, t, J=1.8 Hz, aromatic H), 8.56 (1H, dt, J=7.9, 1.8 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1471. Found: 288.1449.

Reaction with Methyl 5-(2-Pyridylmethylamino)-2,4-pentadienoate (16) Reaction period, 3 h. Solvent for chromatography, 30% hexane in ethyl acetate. Product: first eluate, 91.0 mg (31.6%) of *cis*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(2-pyridylmethyl)-6*H*-1,3-oxazine (**28**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.38 (3H, d, J=5.8 Hz, -Me), 1.43 (3H, d, J=6.4 Hz, -Me), 3.71 (3H, s, -CO_2Me), 4.44 (1H, d, J=16.7 Hz, methylene H), 4.48 (1H, d, J=16.7 Hz, methylene H), 4.67 (1H, q, J=5.8 Hz, methine H), 4.78 (1H, q, J=6.4 Hz, methine H), 5.30 (1H, d, J=15.6 Hz, olefinic H), 6.75 (1H, s, olefinic H), 7.20 (1H, d, J=15.6 Hz, olefinic H), 7.21 (1H, dd, J=7.6, 5.8 Hz, aromatic H), 7.27 (1H, d, J=7.6 Hz, aromatic H), 7.68 (1H, td, J=7.6, 1.8 Hz, aromatic H), 8.55 (1H, dd, J=5.8, 1.8 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1471. Found: 288.1461. Second eluate, 136.5 mg (47.4%) of *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-(2-pyridylmethyl)-6*H*-1,3-oxazine (**29**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1699, 1591. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=5.8 Hz, -Me), 1.41 (3H, d, J=6.4 Hz, -Me), 3.71 (3H, s, -CO_2Me), 4.42 (1H, d, J=16.5 Hz, methylene H), 4.49 (1H, d, J=16.5 Hz, methylene H), 4.68 (1H, q, J=5.8 Hz, methine H), 4.92 (1H, q, J=6.4 Hz, methine H), 5.32 (1H, d, J=15.6 Hz, olefinic H), 6.66 (1H, s, olefinic H), 7.19 (1H, d, J=15.6 Hz, olefinic H), 7.20 (1H, dd, J=7.6, 5.8 Hz, aromatic H), 7.27 (1H, d, J=7.6 Hz, aromatic H), 7.69 (1H, td, J=7.6, 1.8 Hz, aromatic H), 8.56 (1H, dd, J=5.8, 1.8 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{16}H_{20}N_2O_3$: 288.1471. Found: 288.1461.

Reaction with Methyl 5-[2-(4-Pyridyl)ethylamino]-2,4-pentadienoate (17) Reaction period, 3 h. Solvent for chromatography, 30% hexane in ethyl acetate. Product: first eluate, 88.8 mg (29.4%) of *cis*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-[2-(4-pyridyl)ethyl]-6*H*-1,3-oxazine (**30**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1695, 1589. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.38 (3H, t, J=6.4 Hz, -Me), 1.44 (3H, d, J=5.8 Hz, -Me), 2.27—2.87 (2H, m, methylene H), 3.31—3.37 (2H, m, methylene H), 3.71 (3H, s, -CO_2Me), 4.56 (1H, q, J=5.8 Hz, methine H), 4.71 (1H, q, J=6.4 Hz, methine H), 5.27 (1H, d, J=15.6 Hz, olefinic H), 6.51 (1H, s, olefinic H), 7.11 (1H, d, J=15.6 Hz, olefinic H), 7.12 (2H, td, J=4.5, 1.6 Hz, aromatic H), 8.53 (2H, dd, J=4.5, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{22}N_2O_3$: 302.1631. Found: 302.1661. Second eluate, 132.9 mg (44.0%) of *trans*-2,3-dihydro-5-[2-(methoxycarbonyl)ethenyl]-2,6-dimethyl-3-[2-(4-pyridyl)ethyl]-6*H*-1,3-oxazine (**31**), a light yellow oil. IR (neat) cm^{-1}: 1730, 1695, 1589. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=6.4 Hz, -Me), 1.40 (3H, d, J=5.8 Hz, -Me), 2.27—2.28 (2H, m, methylene H), 3.34 (1H, ddd, J=14.7, 7.9, 6.7 Hz, methylene H), 3.45 (1H, ddd, J=14.7, 8.2, 6.4 Hz, methylene H), 3.70 (3H, s, -CO_2Me), 4.61 (1H, q, J=6.4 Hz, methine H), 4.84 (1H, q, J=5.8 Hz, methine H), 5.27 (1H, d, J=15.6 Hz, olefinic H), 6.40 (1H, s, olefinic H), 7.08 (1H, d, J=15.6 Hz, olefinic H), 7.11 (2H, dd, J=4.5, 1.6 Hz, aromatic H), 8.54 (2H, dd, J=4.5, 1.6 Hz, aromatic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{22}N_2O_3$: 302.1631. Found: 302.1661.

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