

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*-aminodienyl-

ester **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 (C₁₇H₂₁NO₃) and their ¹H-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 methoxycarbonyl ethenyl 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-

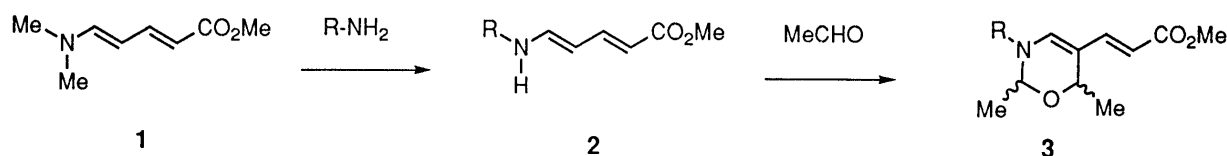


Chart 1

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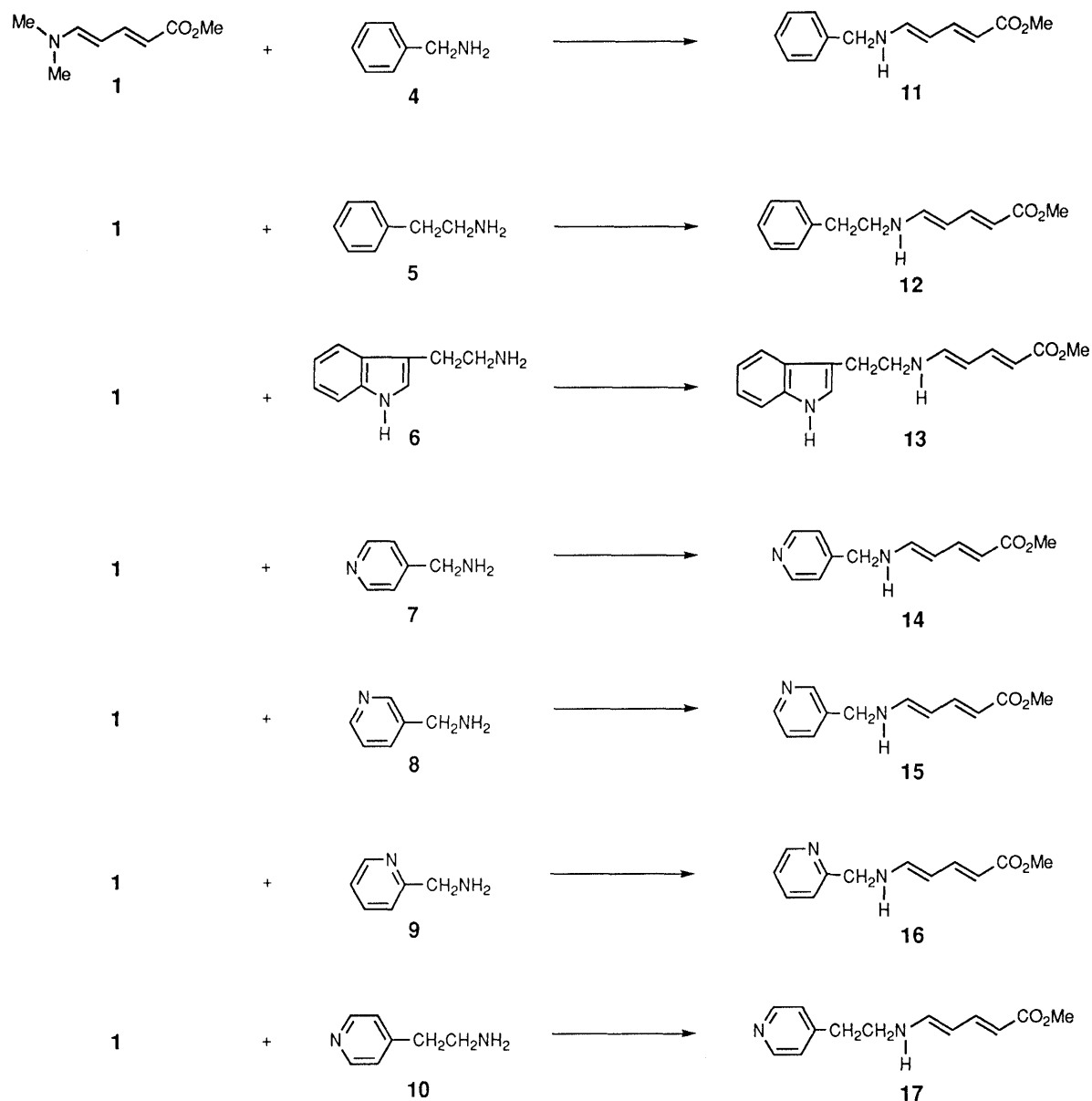


Chart 2

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 ¹H-NMR spectra with a JEOL EX-90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. ¹H–¹H, and ¹H–¹H 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

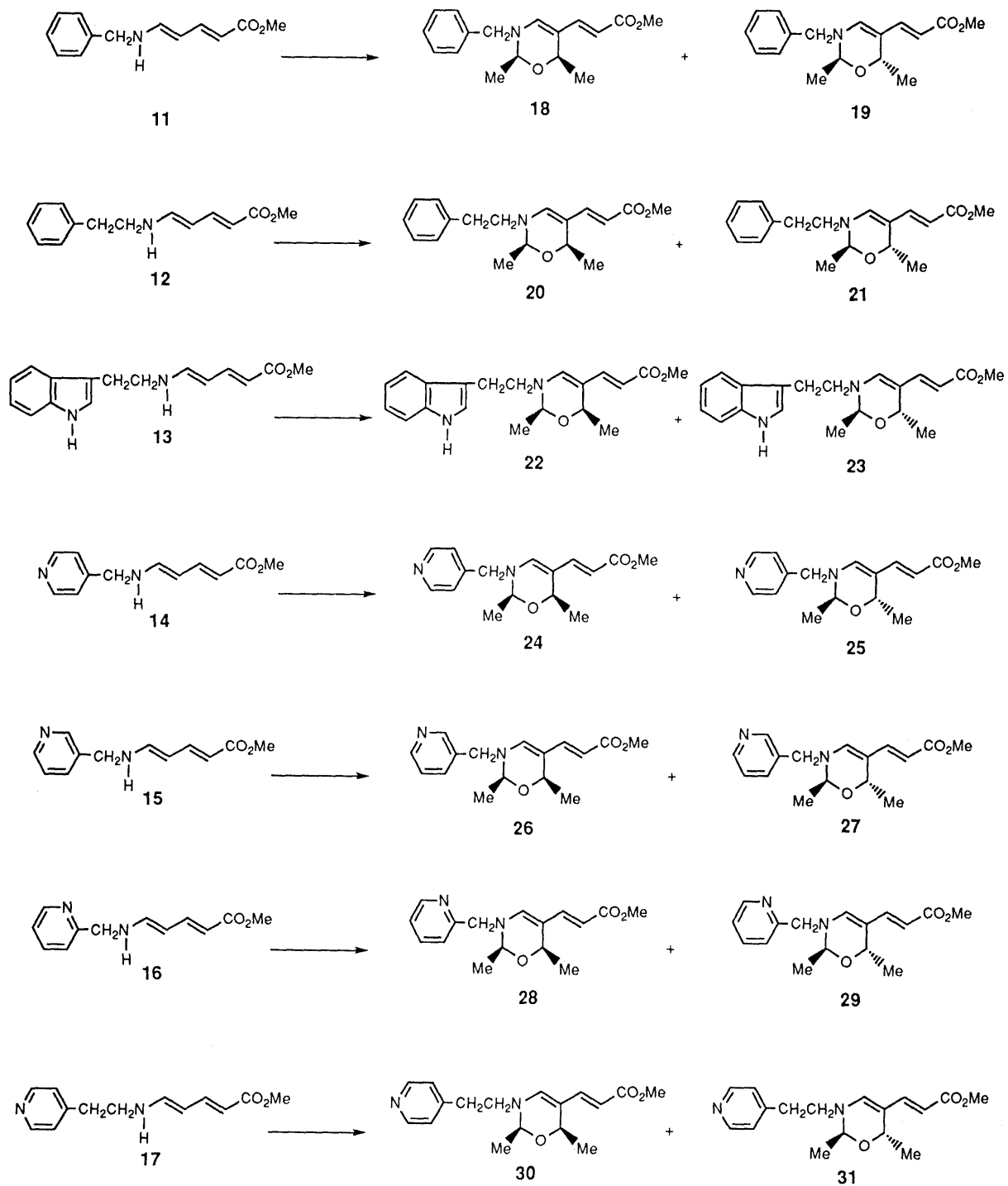


Chart 3

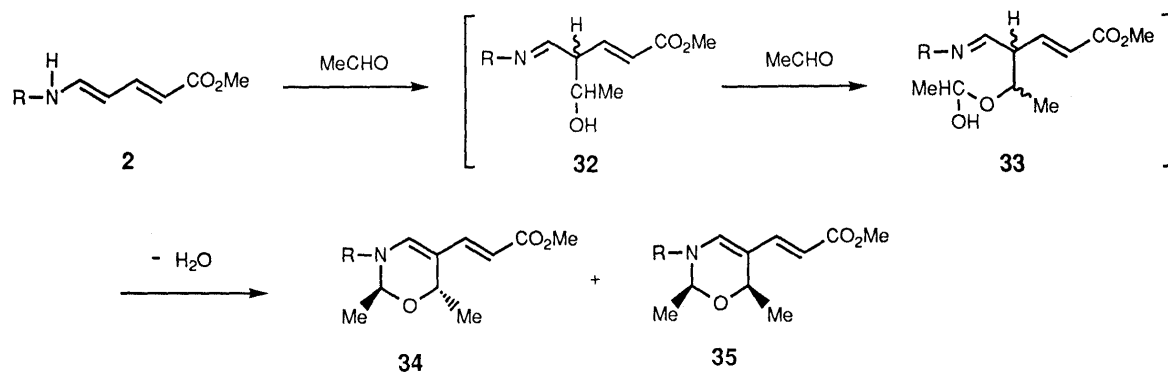


Chart 4

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. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.68 (3H, s, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{13}\text{H}_{15}\text{NO}_2$: 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. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{14}\text{H}_{17}\text{NO}_2$: 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. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.03 (2H, t, $J=6.8$ Hz, methylene H), 3.40 (2H, q, $J=6.8$ Hz, methylene H), 3.69 (3H, s, $-\text{CO}_2\text{Me}$), 4.25 (1H, br, NH), 5.31 (2H, 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 $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$: 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. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.67 (3H, s, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$: 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. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.67 (3H, s, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$: 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. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 3.68 (3H, s, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$: 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.

$^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$: 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-6H-1,3-oxazine (**18**), a light yellow oil. IR (neat) cm^{-1} : 1720, 1701, 1597. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{17}\text{H}_{21}\text{NO}_3$: 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-6H-1,3-oxazine (**19**), a light yellow oil. IR (neat) cm^{-1} : 1720, 1701, 1597. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{17}\text{H}_{21}\text{NO}_3$: 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-6H-1,3-oxazine (**20**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1701, 1591. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{18}\text{H}_{23}\text{NO}_3$: 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-6H-1,3-oxazine (**21**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1583. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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 $\text{C}_{18}\text{H}_{23}\text{NO}_3$: 301.1678. Found: 301.1706.

Reaction with Methyl 5-[2-(3-Indolyl)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-6H-1,3-oxazine (**22**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1684, 1583. $^1\text{H-NMR}$ (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, $-\text{CO}_2\text{Me}$), 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-6H-1,3-oxazine (**23**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1684, 1583. 1H -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)-6H-1,3-oxazine (**24**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1591. 1H -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)-6H-1,3-oxazine (**25**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1591. 1H -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)-6H-1,3-oxazine (**26**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1589. 1H -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)-6H-1,3-oxazine (**27**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1591. 1H -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)-6H-1,3-oxazine (**28**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1591. 1H -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)-6H-1,3-oxazine (**29**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1699, 1591. 1H -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]-6H-1,3-oxazine (**30**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1695, 1589. 1H -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]-6H-1,3-oxazine (**31**), a light yellow oil. IR (neat) cm^{-1} : 1730, 1695, 1589. 1H -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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