J = 12.2, 4.9, 1 H), 4.15-4.12 (dd, J = 12.2, 2.4, 1 H), 3.90-3.86 (ddd, J = 9.5, 5.0, 2.5, H-5), 2.35 (s, $SCOCH_3$), 2.06 (s, OAc), 2.05 (s, OAc); ^{13}C NMR (75 MHz) δ 193.13 (C=O), 170.15 (C=O), 170.02 (C=O), 127.99, 127.75 (C-2, C-3), 78.21 (C-1), 69.95 (C-5), 64.58 (C-4), 62.67 (C-6), 30.93 ($SCOCH_3$), 20.95, 20.75 (OAc); $J_{C\text{-}1,H}$ = 171; IR (film) 3056, 2985, 2903, 2870, 1793, 1704, 1700, 1242, and 1097; MS (CI-C_4H_{10}), m/z (relative intensity) 289 (5, MH^+); (HREI) calcd for $M^+ - SCOCH_3$ $C_{10}H_{13}O_6$, 213.0765 found 213.0958.

S-Acetyl 2,3,6-Trideoxy-4-O-acetyl-1-thio-α,β-L-erythro-hex-2-enopyranosides (21, 22). From 3,4-di-O-acetyl-L-rhamnal (**8**) (100 mg, 0.46 mmol) and (thionoacetoxy)trimethylsilane (136 mg, 0.92 mmol) after 1 h of stirring, nonaqueous workup, chromatography, and semipreparative HPLC were obtained **21** and **22** (81 mg, 86% **21**:**22** = 1:1.7). Data for **21**: R_f 0.72 (30% EtOAc/hexane); t_R 11.2 min (20% EtOAc/hexane, 2.0 mL/min); ^1H NMR (500 MHz) δ 6.18-6.17 (d, J = 2.2, H-1), 5.89-4.97 (m, H-2, H-3), 5.07-5.04 (ddd, J = 6.3, 1.7, 1.3, H-4), 3.95-3.90 (dq, J = 6.4, 6.4, H-5), 2.39 (s, $SCOCH_3$), 2.11 (s, OAc), 1.31-1.30 (d, J = 6.4, C-6); ^{13}C NMR (75 MHz) δ 1.93.37 (C=O), 170.36 (C=O), 129.66, 126.73 (C-2, C-3), 76.41 (C-1), 73.24 (C-5), 68.97 (C-4), 30.65 ($SCOCH_3$), 20.98 ($OCOCH_3$), 18.18 (CH_3); $J_{C\text{-}1,H}$ = 177; IR (film) 3149, 3051, 2985, 1733, 1701, 1375, 1264, 1244, 1045.

Data for **22**: R_f 0.72 (30% EtOAc/hexane); t_R 11.6 min (20% EtOAc/hexane, 2.0 mL/min); ^1H NMR (500 MHz) δ 6.20 (br s, H-1), 5.82-5.80 (d, J = 9.9, H-2), 5.90-5.85 (ddd, J = 10.0, 3.0, 1.7, H-3), 5.30-5.26 (ddd, J = 9.0, 3.6, 1.7, H-4), 3.96-3.90 (dq, J = 9.0, 6.13, H-5), 2.36 (s, $SCOCH_3$), 2.07 (s, OAc), 1.22-1.21 (d, J = 6.18, C-6); ^{13}C NMR (75 MHz) δ 193.90 (C=O), 179.32 (C=O), 128.16, 128.04 (C-2, C-3), 78.17 (C-1), 70.16 (C-5), 68.26 (C-4), 30.95 ($SCOCH_3$), 21.04 ($OCOCH_3$), 18.01 (CH_3); $J_{C\text{-}1,H}$ = 172; IR (film) 3149, 3051, 2985, 1733, 1701, 1375, 1264, 1244, and 1045; MS (CI-C_4H_{10}), m/z (relative intensity) 289 (5, MH^+); (HREI) calcd for $C_{13}H_{11}O_3$ ($M^+ - SCOCH_3$) 155.0708, found 155.0709.

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Registry No. **3**, 2873-29-2; **4** (diastereomer 1), 112247-47-9; **4** (diastereomer 2), 112247-48-0; **5** (diastereomer 1), 112247-49-1; **5** (diastereomer 2), 112247-50-4; **6**, 112247-51-5; **8**, 34819-86-8; **9**, 112247-52-6; **10**, 16740-98-0; **11** (diastereomer 1), 112247-53-7; **11** (diastereomer 2), 112344-70-4; **12**, 112247-54-8; **13**, 112247-56-0; **14**, 53657-41-3; **15**, 112247-57-1; **16**, 112247-58-2; **17**, 112247-59-3; **18**, 112247-60-6; **19**, 4631-35-0; **20**, 23025-38-9; **21**, 112247-61-7; **22**, 112247-62-8; PhSH, 108-98-5; Me_3SiSPh, 4551-15-9; $Me_3SiOC(S)CH_3$, 13247-83-1; D-glucal, 13265-84-4; 2-thiopyridine, 2637-34-5; 2-[(trimethylsilyl)thio]pyridine, 112247-55-9.

Supplementary Material Available: X-ray data of **6** including X-ray diffractometer set up, methods, tables of fractional coordinates, thermoparameters, interatomic distances and angles, intramolecular distances, torsional angles and least-squares planes for **6** and list of CD data of compounds in Figures 2 and 3 (9 pages). Ordering information is given on any current masthead page.

Intramolecular Cycloaddition Reactions of *N*-Acyl Imines. A Stereoselective Approach to the N-Terminal Amino Acid Component of Nikkomycin B

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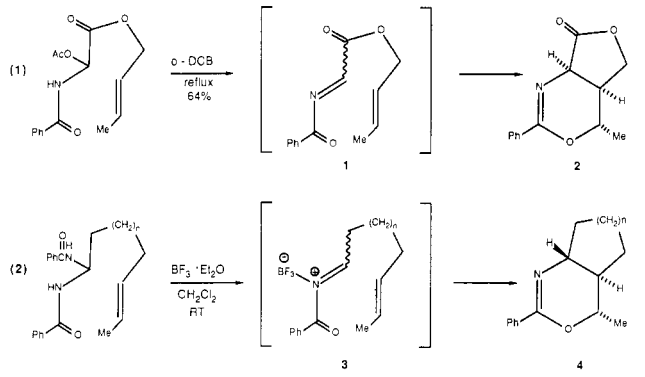
Diels-Alder cyclizations of *N*-acyl imines derived from glyoxylates **5** and **8** stereoselectively produced cis-fused bicyclo-1,3-dihydrooxazine γ-lactones **7** and **10**, respectively. The cycloaddition failed to yield the corresponding δ-lactone **12** derived from precursor **11**. Selective ring cleavages of cycloadduct **2** afforded hydroxy amide **13** and α-amino lactone **14**. Efficient application of this methodology to the stereoselective synthesis of the N-terminal amino acid portion **15** of nikkomycin B (**16**) is described. Diels-Alder precursor **21**, readily available in three steps from known allylic chloride **17**, was cyclized to the bicyclodihydrooxazine **22**. This compound was readily converted to lactone **26**.

In 1984 we described the first example of an intramolecular [4 + 2]-cycloaddition involving an *N*-acyl imine and an alkene[1a,2] (eq 1). The reaction proved to be totally stereoselective and afforded the cis-fused bicyclic dihydro-1,3-oxazine γ-lactone shown in structure **2**. This result prompted us to investigate the type of cycloaddition shown in eq 2.[1b] In these cases trans-fused bicyclic dihydrooxazines such as **4** were formed exclusively. Interestingly, the systems in eq 2 cyclized under Lewis acid catalysis, but *not* thermally. We have postulated that in the thermal cyclization (eq 1) an acyl imine **1** is involved, whereas in the BF_3·Et_2O-promoted reactions (eq 2) an acyl iminium complex **3** is an intermediate. Moreover, we have previously attempted to rationalize these stereochemical results,[1] although we are still not certain if **2** is in fact a kinetic reaction product. Since we initially investigated only a single example of a cyclization of a glyoxylate-derived acyl imine **1**,[1a] we decided to look at a few additional cases of this type and to explore the application of this

(1) (a) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (b) Scola, P. M.; Weinreb, S. M. *Ibid.* **1986**, *51*, 3248.

(2) For reviews of intermolecular cycloadditions of this type see: Schmidt, R. R. *Synthesis* **1972**, 333. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212. See also: Boger, D. R.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: Orlando, 1987.

0022-3263/88/1953-0850$01.50/0



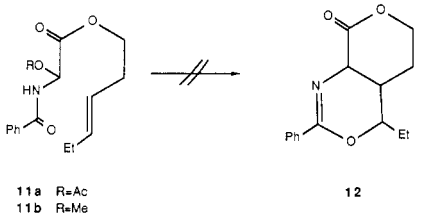
methodology to synthesis of an unusual α-amino acid component of the nikkomycins.[3] This recent work is described below.

Results and Discussion

Aldehyde **5** was prepared from the bromoacetate ester of (*Z*)-crotyl alcohol by using the Emmons–Kornblum procedure.[1,4] This compound was converted to acetate **6** by methodology that we have previously used.[1] As anticipated, thermolysis of **6** in refluxing *o*-dichlorobenzene produced a single cycloaddition product **7** (75%), which has a cis-fused ring system but is epimeric to **2** at the methyl-bearing carbon (Scheme I).

Similarly, glyoxylate ester **8** was synthesized and converted to Diels–Alder precursor **9** by analogous chemistry. Thermal cyclization of **9** produced *cis*-fused dihydrooxazine **10** in good yield. Several attempts were also made to catalyze the reaction in eq 1 with boron trifluoride etherate. Although dihydrooxazine **2** was still the only [4 + 2]-cycloaddition product that could be isolated, yields were markedly inferior to the thermal reaction.

In an effort to extend the scope of this methodology, Diels–Alder precursors **11a** and **11b** were synthesized and several attempts were made to cyclize these compounds to the [6,6]-fused dihydrooxazine **12**. However, a variety of thermal and Lewis acid catalyzed conditions failed to produce any adduct **12**. This failure was somewhat surprising in light of our observation that the precursors in eq 2 having $n = 2$ smoothly cyclized to [6,6]-systems.



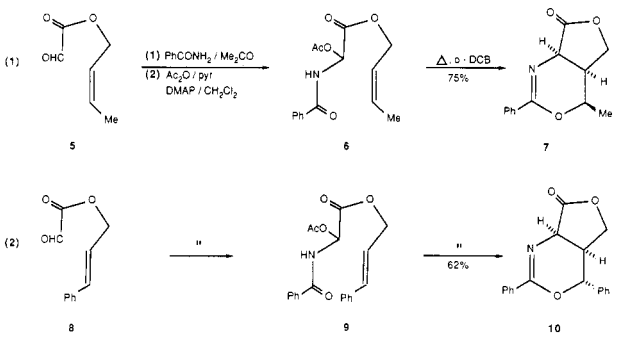
11a R=Ac
11b R=Me

12

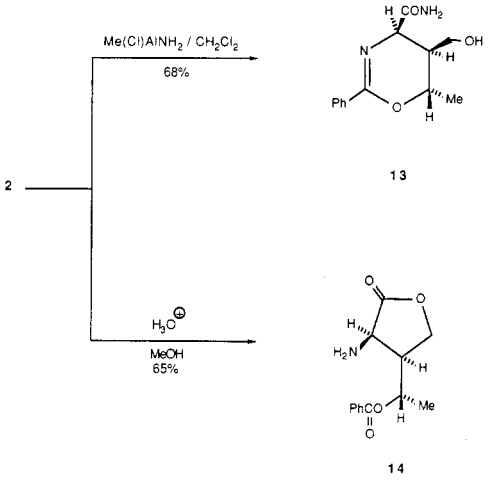
We have also looked at some transformations of bicyclic dihydrooxazine **2** in order to ascertain whether the two rings can be selectively opened. Treatment of **2** with the aluminum amide reagent[5] derived from trimethylaluminum and ammonium chloride cleanly gave hydroxy amide **13** (Scheme II). The dihydrooxazine ring of **2** could be opened selectively via an acidic hydrolysis to afford amino benzoate **14**.[6]

We next turned our attention to application of this hetero Diels–Alder methodology to synthesis of an unusual

Scheme I



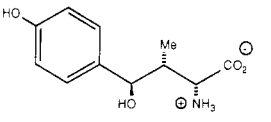
Scheme II



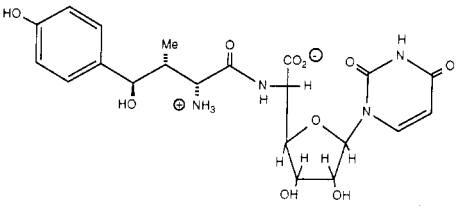
13

14

γ-hydroxy-β-methyl-α-amino acid **15**, which is found in the nucleoside antibiotic nikkomycin B (**16**).[3] Compound **15** has previously been synthesized by a nonstereoselective route during the structure elucidation of **16**.[3,7] More recently, Barrett et al.[8] have developed an elegant stereoselective synthesis of this amino acid.



15

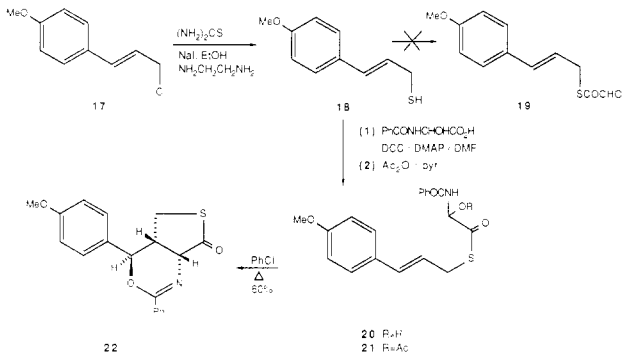


16

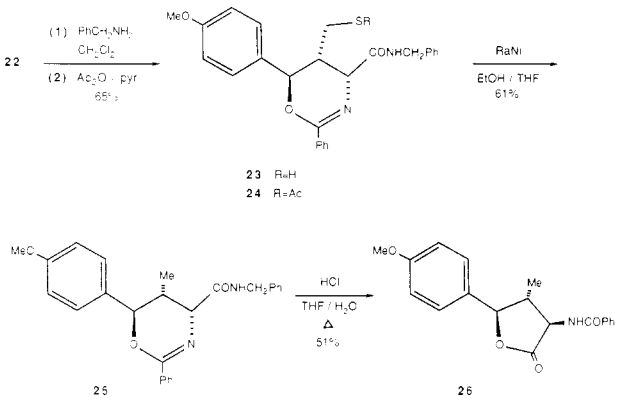
Our approach to **15** begins with (*E*)-*p*-methoxycinnamyl chloride (**17**),[9] which was converted to thiol **18** by a standard procedure (Scheme III).[10] A number of attempts

(3) Konig, W. A.; Hess, W.; Dehler, W.; Fiedler, H.-P.; Zahner, H. *Justus Liebigs Ann. Chem.* **1980**, *1980*, 622.
(4) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865. Emmons, W. D.; Freeman, J. P. *Ibid.* **1955**, *77*, 4415.
(5) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(6) Cf.: Schollkopf, U.; Jentsch, R.; Madawinata, K.; Harms, R. *Justus Liebigs Ann. Chem.* **1976**, *1976*, 2105.
(7) See also: Hass, W.; Konig, W. A. *Justus Liebigs Ann. Chem.* **1982**, *1982*, 1615. Konig, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Bormann, C.; Dehler, W.; Kurth, R.; Zahner, H. *Ibid.* **1986**, *1986*, 407.
(8) Banks, B. J.; Barrett, A. G. M.; Russell, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 873.
(9) White, W. N.; Fife, W. K. *J. Am. Chem. Soc.* **1961**, *83*, 3846. Wigfield, D. C.; Feiner, S.; Malbacho, G.; Taymaz, K. *Tetrahedron* **1974**, *30*, 2949.
(10) Cossar, B. C.; Fournier, J. O.; Fields, D. L.; Reynolds, D. D. *J. Org. Chem.* **1962**, *27*, 93.

Scheme III



Scheme IV



were made to transform **18** to the thioglyoxylate **19** via the Emmons–Kornblum procedure used to prepare **5** and **8**. However, these experiments were uniformly disappointing. In addition, variations of other known glyoxylate ester syntheses applied to thiol **18** were attempted unsuccessfully.[11] In the end, a very simple route from **18** to the necessary Diels–Alder precursor was developed. Condensation of allylic thiol **18** with commercially available α-hydroxyhippuric acid could be effected with DCC to produce hydroxy thioester **20** in 48% yield. Acetylation of **20** subsequently gave the requisite ester **21** (94%). After some experimentation, it was found that **21** could be cyclized to the desired dihydrooxazine **22** in chlorobenzene solution at 145–150 °C in a sealed tube, which has been *thoroughly deoxygenated*. As expected from our model studies, only the isomer shown in **22**, which has the relative stereochemistry necessary for nikkomycin B, was produced. Thus, the relative stereochemistry of three chiral centers of **15** was selectively generated in a single step from an achiral precursor.

Diels–Alder adduct **22** was further elaborated as outlined in Scheme IV. The thiolactone ring of **22** could be opened under mild conditions with benzylamine to afford a sensitive thiol amide **23**, which was immediately acetylated to the more stable thioester **24**. Attempted direct Raney nickel reduction of thiol **23** gave a complex mixture of products. However, thiolacetate **24** could be dihydrooxazine reduced to yield amide **25** (61%). Hydrolysis of the dihydrooxazine ring of **25** could then be effected with aqueous hydrochloric acid to give racemic γ-lactone **26**. Although we have not carried **26** any farther, it should be noted that closely related compounds have been transformed to amino acid **15**.[3,7,8]

Conclusion

The work described in this paper shows that intramolecular thermal [4 + 2]-cycloadditions of glyoxylate-derived *N*-acyl imines are stereoselective processes which provide cis-fused bicyclic dihydrooxazine γ-lactones. The geometry of the olefinic dienophile is maintained in these reactions, as is the case in related intermolecular processes.[2,12,13] We have applied this methodology to synthesis of a derivative **26** of the nikkomycin B amino acid component **15**. The synthesis of **26** is relatively short, totally stereoselective, and utilizes simple starting materials. We are currently investigating other applications and extentions of this methodology.

Experimental Section

All melting points and boiling points are uncorrected. Melting points were measured on a Fisher Johns apparatus. Infrared spectra were recorded on either a Perkin-Elmer Model 197 or 1310 spectrophotometer. ^{1}H NMR spectra (60 mHz) were recorded on a Varian EM 360A NMR spectrometer. NMR spectra (200 MHz) were measured on a Bruker WP-200 instrument, and 360-MHz spectra were recorded on a Bruker WM-360 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on the Bruker WP-200 instrument at 50 MHz. Mass spectra were recorded at an ionizing voltage of 50–70 eV by electron impact on an Associated Electrical Industries, Ltd. MS-9/50 double-focusing mass spectrometer. Chemical-ionization mass spectra (CIMS) were obtained on a Finnigan 3200 quadrupole mass spectrometer with isobutane as a carrier gas. Combustion analyses were performed by Microtech Laboratories (Skokie, IL).

Synthesis of Glyoxylate 8. A solution of (*E*)-cinnamyl alcohol (2.8 g, 21 mmol) and pyridine (2.49 g, 32 mmol) in 20 mL of methylene chloride was cooled to 0 °C. A solution of bromoacetyl bromide (5.01 g, 23 mmol) in 10 mL of methylene chloride was added dropwise with stirring over a period of 10 min. The mixture was stirred for 20 min, poured onto ice, and extracted three times with 50 mL of methylene chloride. The organic phase was washed with 50 mL of 5% HCl solution and 50 mL of water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residual oil was vacuum distilled (bp 117–120 °C, 0.08 Torr) to yield 3.91 g (73%) of light yellow bromoacetate ester: IR (film) 3040, 2960, 1740, 1280, 1160, 1150, 965, 780, 695 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (5 H, s), 6.65 (1 H, d, J = 16.5 Hz), 6.15 (1 H, dt, J = 5.5, 16.5 Hz), 4.75 (2 H, d, J = 5.5 Hz), 3.80 (2 H, s); MS, m/z (relative intensity) 257 (23), 255 (23), 176 (100), 134 (46), 118 (74), 116 (89), 92 (25), 51 (15).

Silver nitrate (5.21 g, 31 mmol) was added to a stirred solution of the bromo ester (3.91 g, 15 mmol) in 25 mL of freshly distilled acetonitrile. The mixture was stirred in the dark for 24 h and was evaporated in vacuo. The residue was taken up in 50 mL of ethyl ether and was filtered. The filter cake was washed with 50 mL of ethyl ether. The combined filtrate was washed once with 100 mL of water and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo yielded 3.42 g (94%) of nitrate ester as pale yellow crystals, which was judged by TLC and ^{1}H NMR to be sufficiently pure for use in the next step. A sample recrystallized from pentane had mp 49–50 °C: IR (film) 3040, 2960, 1760, 1655, 1410, 1360, 1290, 1205, 1055, 965, 845, 690 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (5 H, s), 6.68 (1 H, d, J = 16.5 Hz), 6.15 (1 H, dt, J = 6.0, 16.5 Hz), 4.85 (2 H, s), 4.75 (2 H, m); MS, m/z (relative intensity) 237 (24), 175 (9), 133 (59), 117 (100), 105 (22), 91 (27), 39 (11).

Sodium acetate (189 mg, 2.31 mmol) was added slowly to a solution of the above nitrate ester (500 mg, 2.11 mmol) in 5 mL of dimethyl sulfoxide. The mixture was stirred for 25 min, poured

(11) For example see: Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Leuand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. Johnson, A. P.; Pelter, A. *J. Am. Chem. Soc.* **1964**, *86*, 520. Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544. Hook, J. M. *Synth. Commun.* **1984**, *14*, 83. Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952.

(12) Giordano, C.; Abis, L. *Gazz. Chim. Ital.* **1974**, *104*, 1181.

(13) For mechanistic studies of the intermolecular cycloaddition see: Schmidt, R. R.; Machat, R. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 311. Schmidt, R. R.; Hoffman, A. R. *Chem. Ber.* **1974**, *107*, 78.

into 25 mL of ice–brine, and extracted five times with 20 mL of ethyl acetate. The organic layer was washed with 20 mL of saturated sodium bicarbonate solution and 20 mL of water, and the aqueous washings were back extracted two times with 20 mL of ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residual yellow oil was vacuum distilled to give the glyoxylate **8** (370 mg, 92%) as a colorless liquid, which readily hydrated upon exposure to the atmosphere making NMR analysis difficult: bp 150–155 °C (0.080 Torr); IR (film) 3425 (br), 3025, 1745, 1445, 1270 (br), 1210, 1000, 965, 745, 690 cm^{-1}.

Preparation of Glyoxylate Ester 5. This compound was synthesized from (*Z*)-crotyl alcohol by a route identical with that described above.

Bromoacetate ester: (67%) colorless oil; bp 46 °C (0.070 Torr); IR (film) 3040, 2960, 1735, 1280, 960 cm^{-1}; MS, *m/z* (relative intensity) 194 (0.3), 192 (0.3), 113 (100), 71 (99), 55 (80), 39 (49).

Nitrate ester: (86%) yellow liquid; bp 62–67 °C (0.30 Torr); IR (film) 3025, 2950, 1755, 1650, 1415, 1285, 1205, 1055, 840 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.00–5.30 (2 H, m), 4.90 (2 H, s), 4.75 (2 H, d, J = 6.5 Hz), 1.80 (3 H, d, J = 6.5 Hz); MS, *m/z* (relative intensity) 101 (66), 71 (75), 55 (100), 46 (50), 29 (36).

Glyoxylate ester: (66%) colorless liquid; bp 48–52 °C (0.050 Torr); IR (film) 3425 (br), 3030, 2950, 1745, 1440, 1205, 1090 (br), 945 cm^{-1}.

Synthesis of Diels–Alder Precursor 9. A solution of glyoxylate **9** (650 mg, 3.42 mmol) and benzamide (455 mg, 3.76 mmol) in 25 mL of acetone was stirred for 72 h at room temperature. The solvent was removed in vacuo, and the residual yellow solid was purified by flash chromatography (ethyl acetate–hexanes, 1:1) to afford 700 mg (60%) of a white crystalline adduct. A sample recrystallized from ethyl acetate–hexanes had mp 129–130 °C: IR (film) 3360 (br), 3060, 1745, 1660, 1575, 1530, 1445, 1210, 1000, 965, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77–7.73 (2 H, m), 7.48–7.19 (9 H, m), 6.64 (1 H, d, J = 15.9 Hz), 6.23 (1 H, dt, J = 6.5, 15.9 Hz), 5.78 (1 H, d, J = 6.9 Hz), 4.85 (2 H, dd, J = 1.2, 6.6 Hz), 4.58 (1 H, br s, OH); MS, *m/z* (relative intensity) 311 (0.1), 190 (13), 121 (52), 117 (100), 105 (82), 77 (76), 51 (39). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51. Found: C, 68.84; H, 5.62.

The above product (200 mg, 0.64 mmol) was dissolved in 10 mL of methylene chloride, and pyridine (0.52 mL, 6.40 mmol) and acetic anhydride (0.61 mL, 6.40 mmol) were added dropwise with stirring. A catalytic amount of 4-(dimethylamino)pyridine was added, and the mixture was stirred for 5 min, poured into 20 mL of water, and extracted four times with 20 mL of methylene chloride. The organic phase was washed with 50 mL of 5% HCl solution, 50 mL of saturated $NaHCO_3$ solution, and 50 mL of water and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residual oil was purified by flash chromatography (ethyl acetate–hexanes, 1:3) to yield 205 mg (90%) of the acetate **9** as a colorless oil: IR (film) 3335 (br), 3020, 1745, 1665, 1520, 1370, 1230, 1200, 1030, 965, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.79–7.74 (2 H, m), 7.53–7.19 (9 H, m), 6.62 (1 H, d, J = 15.9 Hz), 6.35 (1 H, d, J = 8.9 Hz), 6.20 (1 H, dt, J = 6.5, 15.8 Hz), 4.82 (2 H, dd, J = 1.2, 6.5 Hz), 2.07 (3 H, s); CIMS 354 ($M^+ + 1$).

Synthesis of Acetate 6. This compound was prepared by the route described above for **9**.

Glyoxylate **5**–benzamide adduct: (50%); a sample recrystallized from ethyl acetate–hexanes had mp 97–98 °C: IR (film) 3300 (br), 1745, 1640, 1535, 1345, 1205, 1090, 950, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85–7.79 (2 H, m), 7.71 (1 H, d, J = 7.4 Hz, NH), 7.57–7.37 (3 H, m), 5.89–5.69 (2 H, m), 5.63–5.50 (1 H, m), 5.51 (1 H, d, J = 6.3 Hz, OH), 4.80 (2 H, d, J = 6.8 Hz), 1.70 (3 H, dd, J = 1.4, 6.9 Hz); MS, *m/z* (relative intensity) 150 (16), 121 (44), 105 (100), 77 (74), 55 (86), 28 (58). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.07. Found: C, 62.65; H, 6.10.

Acetate **6**: (89%) colorless oil; purified by flash chromatography (ethyl acetate–hexanes, 1:3); IR (film) 3350 (br), 1745, 1660, 1530, 1230, 1205 (sh), 1165, 1035, 715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.86–7.81 (2 H, m), 7.64–7.41 (4 H, m), 6.58 (1 H, d, J = 8.9 Hz), 5.82–5.72 (1 H, m), 5.61–5.51 (1 H, m), 4.79 (2 H, d, J = 6.8 Hz), 2.12 (3 H, s), 1.71 (3 H, dd, J = 1.4, 6.9 Hz); MS, *m/z* (relative intensity) 231 (2), 192 (7), 150 (17), 105 (100), 77 (44), 43 (25).

Synthesis of Dihydrooxazine 10. A solution of acetate **9** (80 mg, 0.23 mmol) in 8 mL of dry 1,2-dichlorobenzene was saturated with dry nitrogen gas for 10 min. The solution was heated at reflux for 20 h, and the solvent was removed by vacuum distillation. The residual oil was purified by preparative TLC (methanol–methylene chloride, 2:98) to yield 41 mg (62%) of white crystalline dihydrooxazine **10**. A sample of **10** recrystallized from ethyl acetate–hexanes had mp 202–205 °C: IR (film) 3040, 1785, 1645, 1445, 1325, 1250, 1165, 1120, 1000, 760, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.08–8.02 (2 H, m), 7.53–7.27 (8 H, m), 4.74 (1 H, d, J = 11.0 Hz), 4.66 (1 H, d, J = 7.4 Hz), 4.37 (1 H, dd, J = 5.8, 10.2 Hz), 4.16 (1 H, dd, J = 1.2, 10.2 Hz), 2.88 (1 H, dddd, J = 1.1, 5.8, 7.1, 11.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.86, 158.34, 136.72, 132.08, 131.44, 129.49, 129.11, 128.08, 127.80, 127.43, 75.35, 65.97, 55.54, 37.84; MS, *m/z* (relative intensity) 293 (6), 249 (4), 188 (9), 105 (100), 77 (24); exact mass calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1061.

Dihydrooxazine **7** was prepared in identical fashion in 75% yield from acetate **6** as white crystals purified by flash chromatography (ethyl acetate–hexanes, 1:1). A sample of **7** recrystallized from chloroform–hexanes had mp 144–146 °C: IR (film) 2980, 1785, 1640, 1325, 1175, 1145, 1115, 1030, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.97–7.80 (2 H, m), 7.48–7.36 (3 H, m), 4.49 (1 H, dq, J = 3.1, 6.6 Hz), 4.44 (1 H, dd, J = 8.7, 9.0 Hz), 4.39 (1 H, d, J = 7.6 Hz), 4.25 (1 H, t, J = 9.5 Hz), 3.01 (1 H, dddd, J = 3.0, 7.7, 8.3, 9.5 Hz), 1.38 (3 H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.68, 157.75, 132.31, 131.37, 128.08, 127.51, 67.34, 65.80, 55.67, 37.70, 17.73; MS, *m/z* (relative intensity) 231 (12), 105 (100), 77 (29), 51 (9); exact mass calcd for $C_{13}H_{13}NO_3$ 231.0895, found 231.0905. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.14; H, 5.73.

Preparation of Hydroxy Amide 13. An aluminum amide reagent was generated by the dropwise addition of 0.295 mL (0.589 mmol) of trimethylaluminum (2.0 M solution in hexanes) to a stirred slurry of anhydrous ammonium chloride (31.5 mg, 0.589 mmol) in 4 mL of dry methylene chloride.[5] The mixture became homogeneous over 20 min. The lactone **2**[1a] (68 mg, 0.294 mmol) in 1 mL of methylene chloride was added dropwise with stirring over 5 min, and the mixture was stirred at room temperature for 1 h and was refluxed for 18 h. The reaction was quenched by careful addition of 1 mL of saturated NH_4Cl solution, and the aqueous phase was extracted three times with 15 mL of ethyl acetate. The combined organics were washed with 10 mL of water and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residual solid was purified by preparative TLC eluting with methanol–methylene chloride (1:9) to give 50 mg (68%) of amide **13** as a light yellow solid: IR (film) 3440, 3350 (br), 2980, 1670, 1645 (sh), 1580, 1295, 1155, 1125, 1045, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.98–7.91 (2 H, m), 7.49–7.32 (5 H, m) 6.55 (1 H, d, J = 3.4 Hz), 4.81 (1 H, dq, J = 2.6, 6.5 Hz), 4.24 (1 H, d, J = 5.0 Hz), 3.64 (1 H, dd, J = 5.6, 11.3 Hz), 3.47 (1 H, dd, J = 8.4, 11.2 Hz), 2.44 (1 H, ddd, J = 2.7, 5.3, 8.2 Hz), 1.44 (3 H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 175.60, 155.86, 132.93, 130.96, 128.14, 128.04, 127.61, 127.12, 71.60, 59.38, 53.72, 39.96, 20.49; MS, *m/z* (relative intensity) 248 (0.2), 204 (36), 160 (13), 105 (100), 77 (35).

Synthesis of α-Amino Lactone 14. To a solution of dihydrooxazine **2**[1a] (50 mg, 0.22 mmol) in 2 mL of methanol–water (9:1) was added three drops of concentrated sulfuric acid. The solution was stirred until the reaction was complete as indicated by TLC (approximately 45 min). The solvent was removed in vacuo, and the residue was diluted with 10 mL of saturated sodium bicarbonate solution and extracted with three 10-mL portions of ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residual oil was purified by flash chromatography eluting with ethyl acetate–hexanes (3:1) to give 36 mg (65%) of α-amino lactone **14** as a colorless oil: IR (film) 3390, 2950, 1780, 1715, 1275, 1115, 1000, 715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.05–8.02 (2 H, m), 8.00–7.42 (3 H, m), 5.54 (1 H, dq, J = 4.9, 6.6 Hz), 4.46 (1 H, dd, J = 3.3, 9.7 Hz), 4.34 (1 H, dd, J = 6.2, 9.7 Hz), 3.96 (1 H, d, J = 8.0 Hz), 2.97 (1 H, dddd, J = 3.3, 4.7, 6.2, 8.0 Hz), 1.41 (3 H, d, J = 6.6 Hz); MS, *m/z* (relative intensity) 249 (5), 144 (10), 127 (37), 105 (100), 83 (62), 77 (87), 56 (52).

(*E*)-3-(*p*-Methoxyphenyl)-2-propene-1-thiol (18). A solution of (*E*)-*p*-methoxycinnamyl chloride (**17**; 3.33 g, 0.018 mol), sodium iodide (4.11 g, 0.027 mol), and thiourea (1.53 g, 0.020 mol) in 66 mL of absolute ethanol was refluxed for 2 h, and the solution was

cooled to ambient temperature.[10] Ethylenediamine (1.22 mL, 0.018 mol) was added dropwise, and the mixture was refluxed for an additional 30 min. The solution was cooled, diluted with 150 mL of water and extracted with three 75-mL portions of benzene. The organic layer was washed with 70 mL of 5% citric acid solution and 70 mL of water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residual solid was purified by flash chromatography (ethyl ether–hexanes, 1:9) to give 1.97 g (60%) of the allyic thiol **18** as a white crystalline solid. A sample of **18** recrystallized from benzene–hexanes had mp 46–48 °C: IR (film) 2950, 2830, 2550 (w), 1605, 1510, 1285, 1175, 1030, 970, 805 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.20 (2 H, d, J = 9 Hz), 6.80 (2 H, d, J = 9 Hz), 6.45 (1 H, d, J = 16 Hz), 6.20–5.70 (1 H, m), 3.80 (3 H, s), 3.30 (2 H, dd, J = 6, 7 Hz), 1.55 (1 H, t, J = 7 Hz, SH); MS, m/z (relative intensity) 180 (19), 147 (100), 91 (20), 28 (20). Anal. Calcd for $C_{10}H_{12}OS$: C, 66.57; H, 6.71; S, 17.78. Found: C, 66.51; H, 6.73; S, 17.51.

Formation of Hydroxy Thiol Ester 20. Dicyclohexylcarbodiimide (857 mg, 4.16 mmol) was added in one portion to a solution of thiol **18** (500 mg, 2.77 mmol), α-hydroxyhippuric acid (Aldrich, 542 mg, 2.77 mmol), and 4-(dimethylamino)pyridine (68 mg, 0.55 mmol) in 10 mL of dry dimethylformamide cooled to 0 °C. The reaction was allowed to warm to room temperature after 10 min and was stirred for an additional 4 h. The heterogeneous mixture was filtered, and the filter cake was washed with 150 mL of ethyl acetate. The organic phase was washed with 100 mL of 5% citric acid solution, 100 mL of 5% HCl solution, and 100 mL of saturated sodium bicarbonate solution and was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residual solid was purified by flash chromatography (ethyl acetate–hexanes, 2:3) to afford 480 mg (48%) of white crystalline thiol ester **20**. A sample of **20** recrystallized from chloroform–hexanes had mp 114–115.5 °C; IR (film) 3400 (sh), 3290 (br), 1690, 1645, 1525 (sh), 1510, 1250, 1175, 1080, 1030, 965, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.75–7.71 (2 H, m), 7.49–7.30 (4 H, m), 7.19 (2 H, d, J = 8.7 Hz), 6.76 (2 H, d, J = 8.8 Hz), 6.47 (1 H, d, J = 15.6 Hz), 6.01–5.86 (1 H, m), 5.82 (1 H, d, J = 7.3 Hz), 5.31 (1 H, br s, OH), 3.72 (3 H, s), 3.67 (2 H, dd, J = 1.1, 7.5 Hz); MS, m/z (relative intensity) 236 (M^+ – $PhCONH_2$, 10), 147 (100), 105 (53), 77 (48). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.84; H, 5.36; S, 8.97. Found: C, 63.54; H, 5.56; S, 8.75.

Formation of Acetate 21. Acetic anhydride (0.30 mL, 3.08 mmol) and pyridine (0.050 mL, 0.62 mmol) were added dropwise to a stirred solution of hydroxy thiol ester **20** (110 mg, 0.31 mmol) in 3 mL of dry methylene chloride. The mixture was stirred for 20 min, poured into 20 mL of water, and extracted three times with 20 mL of methylene chloride. The combined organic extracts were washed with 20 mL of 5% HCl solution, 20 mL of saturated sodium bicarbonate solution, and 20 mL of water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residual oil was purified by flash chromatography (ethyl ether–hexanes, 1:1) to yield 116 mg (94%) of acetate **21** as a pale yellow viscous oil: IR (film) 3340 (br), 2950, 2830, 1755, 1680, 1605, 1510, 1250, 1225, 1175, 1030, 965, 715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78–7.73 (2 H, m), 7.55 (1 H, d, J = 9.3 Hz, NH), 7.51–7.32 (3 H, m), 7.19 (2 H, d, J = 8.8 Hz), 6.74 (2 H, d, J = 8.8 Hz), 6.62 (1 H, d, J = 9.3 Hz), 6.45 (1 H, d, J = 15.6 Hz), 5.99–5.84 (1 H, m), 3.70 (3 H, s), 3.70–3.68 (2 H, m), 2.06 (3 H, s).

Preparation of Diels–Alder Adduct 22. The acetate **21** (155 mg, 0.39 mmol) dissolved in 30 mL of dry chlorobenzene in a thick-walled glass tube was degassed via four freeze–pump–thaw cycles and sealed under vacuum. The tube was heated at 145–150 °C for 17 h and cooled, and the chlorobenzene was removed by vacuum distillation. The residual oil was purified by preparative TLC, eluting with ethyl ether–benzene–hexanes (1:2:2) to yield 80 mg (60%) of dihydrooxazine **22** as a pale yellow solid. A sample of **22** recrystallized from chloroform–hexanes had mp 175–177 °C: IR (film) 3000, 2830, 1705, 1640, 1610, 1510, 1445, 1250, 1175, 1135, 1060, 1025, 950, 830, 755, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.06–8.00 (2 H, m), 7.56–7.31 (5 H, m), 7.00 (2 H, d, J = 8.7 Hz), 4.98 (1 H, d, J = 10.4 Hz), 4.58 (1 H, d, J = 6.4 Hz), 3.86 (3 H, s), 3.49 (1 H, dd, J = 6.3, 12.2 Hz), 3.04) (1 H, dd, J = 1.48, 12.2 Hz), 2.83 (1 H, ddd, J = 1.48, 6.33, 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 203.95, 160.28, 157.38, 132.33, 131.20, 129.10, 128.54, 128.00, 127.74, 114.34, 74.89, 65.33, 55.34, 38.73, 28.48; MS, m/z (relative intensity) 399 (6), 311 (11), 234 (42), 191 (36), 152 (47), 105 (100), 77 (51); exact mass calcd for $C_{19}H_{17}NO_3S$ 339.0929, found 339.0946.

Cleavage of Thiolactone 22. To a solution of thiolactone **22** (50 mg, 0.148 mmol) in 5 mL of dry methylene chloride was added benzylamine (32 mg, 0.295 mmol) dropwise, and the solution was stirred for 24 h at room temperature. The solvent was removed in vacuo at aspirator pressure, and the remaining benzylamine was removed on the vacuum pump. The resulting yellow oil was used directly in the next step due to extensive decomposition upon attempted purification: IR (film) 3370, 2830, 2550 (w), 1655, 1520, 1270, 1250, 1170, 1050, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.07–8.02 (2 H, m), 7.97–7.92 (1 H, m, NH), 7.52–7.28 (8 H, m), 7.17 (2 H, d, J = 8.9 Hz), 6.90 (2 H, d, J = 8.8 Hz), 6.05 (1 H, s), 4.55 (2 H, t, J = 6.0 Hz), 4.01 (1 H, d, J = 4.2 Hz), 3.80 (3 H, s), 2.88–2.65 (2 H, m), 2.42–2.24 (1 H, m); MS, m/z (relative intensity) 446 (2.4), 339 (4), 268 (13), 105 (100), 77 (49).

Preparation of Thiolacetate 24. Acetic anhydride (140 μL, 1.48 mmol) and pyridine (120 μL, 1.48 mmol) were added dropwise to a solution of crude thiol **23** (66 mg, 0.148 mmol) in 5 mL of dry methylene chloride. The mixture was stirred for 12 h at room temperature, and the solvent, the excess acetic anhydride, and pyridine were removed under vacuum. The remaining yellow oil was purified by flash chromatography (ethyl acetate–ethyl ether–hexanes, 1:4:5) to give 47 mg (65% from **22**) of thiolacetate **24** as a yellow oil; IR (film) 3360, 2920, 1685 (sh), 1655, 1520, 1285, 1245, 1135, 830, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.09–8.04 (2 H, m), 7.96–7.91 (1 H, m, NH), 7.52–7.30 (8 H, m), 7.13 (2 H, d, J = 8.9 Hz), 6.88 (2 H, d, J = 8.8 Hz), 5.62 (1 H, s), 4.57 (2 H, dd, J = 6.3, 9.9 Hz), 4.00 (1 H, d, J = 4.3 Hz), 3.80 (3 H, s), 3.07–2.90 (2 H, m), 2.88–2.79 (1 H, m), 2.40 (3 H, s); MS, m/z (relative intensity) 488 (10), 445 (4), 399 (7), 278 (10), 105 (100), 91 (32), 77 (41); exact mass calcd for $C_{28}H_{28}N_2O_4S$ 488.1770, found 488.1794.

Reduction of Thiolacetate 24. To a stirred suspension of W-2 Raney nickel (780 mg) in 4 mL of absolute ethanol was added dropwise the thiolacetate **24** (52 mg, 0.107 mmol) in 4 mL of tetrahydrofuran. The mixture was stirred vigorously at room temperature for 8 h and filtered through a pad of Celite, and the pad was washed with 20 mL of methanol. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash chromatography (ethyl acetate–hexanes, 3:7) to yield 27 mg (61%) of the dihydrooxazine **25** as a colorless oil: IR (film) 3370 (br), 2920, 2830, 1650, 1520, 1285, 1245, 1145, 1025, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.04–7.99 (2 H, m), 7.89 (1 H, d, J = 6.7 Hz, NH), 7.50–7.20 (8 H, m), 7.10 (2 H, d, J = 8.8 Hz), 6.83 (2 H, d, J = 8.7 Hz), 5.35 (1 H, s), 4.51 (2 H, d, J = 6.1 Hz), 3.84 (1 H, d, J = 4.3 Hz), 3.74 (3 H, s), 2.79–2.73 (1 H, m), 1.05 (3 H, d, J = 7.0 Hz); MS, m/z (relative intensity) 414 (7.5), 293 (9), 280 (11), 268 (22), 105 (100), 91 (39), 77 (39); exact mass calcd for $C_{26}H_{26}N_2O_3$ 414.1943, found 414.1949.

Preparation of γ-Lactone 26. Six drops of concentrated HCl was added to a solution of dihydrooxazine **25** (4.7 mg, 0.011 mmol) in 1 mL of THF–water (1:1), and the mixture was heated at 70 °C for 3.5 h. The reaction mixture was cooled, diluted with 3 mL of saturated sodium bicarbonate solution, and extracted three times with 5-mL portions of ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residual oil was purified by prepartive TLC (ethyl acetate–hexanes, 1:1) to give 1.9 mg (51%) of lactone **26** as a colorless oil: IR (film) 3330 (br), 2830, 1770, 1640, 1525 (sh), 1510, 1320, 1245, 1165, 975, 830, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.85–7.80 (2 H, m), 7.52–7.31 (5 H, m), 6.89 (3 H, d, J = 8.8 Hz, overlap with NH), 4.96 (1 H, d, J = 10.1 Hz), 4.85 (1 H, dd, J = 7.8, 11.8 Hz), 3.82 (3 H, s), 2.57 (1 H, ddq, J = 6.6, 10.4, 11.9 Hz), 1.24 (3 H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 175.25, 167.58, 160.29, 132.80, 131.94, 128.49, 127.94, 127.15, 114.09, 85.58, 56.80, 55.27, 46.51, 29.67, 13.62; MS, m/z (relative intensity) 325 (5), 268 (8), 176 (14), 160 (63), 105 100), 77 (49); exact mass calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1317.

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