intensity) 304 (M, 1), 171 (100), 143 (47), 134 (100), 119 (63). Anal. Calcd for $C_{14}H_{25}O_3PS$: C, 55.24; H, 8.28; P, 10.18. Found: C, 55.17; H, 8.41; P, 10.30.

***S-dl*-Patchenyl diethyl phosphorothiolate (entry 10, Table II)**: bp 175 °C (0.3 mmHg); IR (neat) 1670, 1255, 1015, 970, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (6 H, br s), 1.37 (6 H, t, J = 7.2 Hz), 1.07–2.01 (7 H, m), 3.03 (1 H, br), 3.53 (2 H, dd, J = 12.4, 8.0 Hz), 4.19 (4 H, dq, J = 8.6, 7.2 Hz), 5.11 (1 H, t, J = 8.0 Hz); mass spectrum, m/e (relative intensity) 318 (M, 12), 149 (100), 107 (31), 93 (67). Anal. Calcd for $C_{15}H_{27}O_3PS$: C, 56.58; H, 8.55; P, 9.73. Found: C, 56.76; H, 8.66; P, 9.46.

***S*-Geranyl diethyl phosphorothiolate (entry 11, Table II)**: bp 170 °C (0.3 mmHg); IR (neat) 1655, 1255, 1020, 970, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (6 H, t, J = 7.2 Hz), 1.63 (3 H, s), 1.71 (6 H, br s), 1.97–2.24 (4 H, m), 3.52 (2 H, dd, J = 13, 8.0 Hz), 4.21 (4 H, dq, J = 8.5, 7.2 Hz), 4.73–5.60 (2 H, br m); mass spectrum, m/e (relative intensity) 306 (M, <0.01), 237 (7), 171 (93), 170 (54), 136 (68), 93 (100), 80 (70). Anal. Calcd for $C_{14}H_{27}O_3PS$: C, 54.88; H, 8.88; P, 10.11. Found: C, 54.60; H, 8.93; P, 10.25.

***S-trans*-Crotyl ethyl phenylphosphonothiolate (eq 7 and footnote 7)**: bp 175 °C (2 mmHg); IR (neat) 1650, 1230, 1025, 950, 690 cm^{-1}; ^1H NMR (CCl_4) δ 1.36 (3 H, t, J = 7.2 Hz), 1.54 (3 H, d, J = 6.6 Hz), 3.31 (2 H, dd, J = 13, 6.2 Hz), 4.12 (2 H, dq, J = 9.0, 7.2 Hz), 5.18–5.72 (2 H, m), 7.24–8.00 (5 H, m); mass spectrum, m/e (relative intensity) 256 (M, 34), 202 (60), 142 (47), 141 (100). Anal. Calcd for $C_{12}H_{17}O_2PS$: C, 56.24; H, 6.69; P, 12.08. Found: C, 56.03; H, 6.77; P, 11.93.

Registry No. **3**, 74070-90-9; **6**, 74070-96-5; $(MeO)_2P(=O)SCH_2CH=CH_2$, 66498-87-1; $(EtO)_2P(=O)SCH_2CH=CH_2$, 10428-96-3; $Ph(Et_2N)P(=O)SCH_2CH=CH_2$, 74070-97-6; $Ph(EtNH)P(=O)SCH_2CH=CH_2$, 74070-98-7; $Ph(EtS)P(=O)SCH_2CH=CH_2$, 74070-99-8; $(EtO)_2P(=O)SCH_2CMe=CH_2$, 85082-99-1; *trans*-$(EtO)_2P(=O)SCH_2CH=CHMe$, 85083-00-7; $(EtO)_2P(=O)SCHMeCH=CH_2$, 32811-23-7; *trans*-$(EtO)_2P(=O)SCH_2CH=CHPh$, 85083-01-8; $(EtO)_2P(=O)SCH_2CH=CMe_2$, 10006-38-9; $(EtO)_2P(=O)SCH_2CH=CHCH=CHMe$, 85083-02-9; $(MeO)_2P(=S)OCH_2CH=CH_2$, 65715-80-2; $(EtO)_2P(=S)OCH_2CH=CH_2$, 74070-89-6; $Ph(Et_2N)P(=S)OCH_2CH=CH_2$, 74070-91-0; $Ph(EtNH)P(=S)OCH_2CH=CH_2$, 74070-92-1; $Ph(EtS)P(=S)OCH_2CH=CH_2$, 74070-93-2; $(EtO)_2P(=S)OCH_2CMe=CH_2$, 85083-07-4; $(EtO)_2P(=S)OCHMeCH=CH_2$, 74070-94-3; *trans*-$(EtO)_2P(=S)OCH_2CH=CHMe$, 85083-08-5; *cis*-$(EtO)_2P(=S)OCH_2CH=CHMe$, 85083-09-6; *trans*-$(EtO)_2P(=S)OCH_2CH=CHPh$, 85083-10-9; $(EtO)_2P(=S)OCH_2CH=Me_2$, 85083-11-0; $(EtO)_2P(=S)OCH_2CH=CHCH=CHMe$, 85083-12-1; $Pd(Ph_3P)_4$, 14221-01-3; *S*-(−)-myrtenyl diethyl phosphorothiolate, 85083-03-0; *S*-*l*-perillyl diethyl phosphorothiolate, 85083-04-1; *S*-*dl*-patchenyl diethyl phosphorothiolate, 85083-05-2; *S*-geranyl diethyl phosphorothiolate, 85083-06-3; *S*-*trans*-crotyl ethyl phenylphosphonothiolate, 85115-22-6; *O*-(−)-myrtenyl diethyl phosphorothiolate, 85083-13-2; *O*-*l*-perillyl diethyl phosphorothiolate, 85082-98-0; *O*-*dl*-patchenyl diethyl phosphorothiolate, 85083-14-3; *O*-geranyl diethyl phosphorothiolate, 85083-15-4; diglyme, 111-96-6.

3,5-Disubstituted Isoxazoles as Synthons for (±)-Pyrenophorin and (±)-Vermiculine Synthesis

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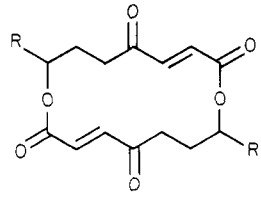
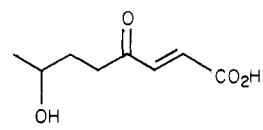
A new approach to suitably protected forms **21**, **29**, and **30** of the monomeric units **3** and **4**, which correspond to the dimeric macrolide antibiotics (±)-pyrenophorin (**1**) and (±)-vermiculine (**2**), involved ethyl 3-(3-butenyl)-5-isoxazolecarboxylate (**6**) as common starting material. The partial structure composed of an α,β-unsaturated acid with an oxygen function at the γ-position, featured in both the natural compounds, was efficiently created by reductive fission of the N–O bond of the isoxazole nucleus bearing a 5-carboxylate, which contains it in a latent form, followed by suitable operations. The terminal double bond of **6** allowed us to introduce the missing functions, namely, a hydroxyl group for **3** and a β-hydroxy ketone moiety for **4**. A Markovnikov hydration to give **8** and regiospecific cycloaddition of acetonitrile oxide followed by reductive opening of the formed isoxazoline **22** secured the appropriate functional groups for **3** and **4**, respectively.

A great deal of effort has been devoted toward the synthesis of pyrenophorin (**1**), a macrocyclic bis lactone

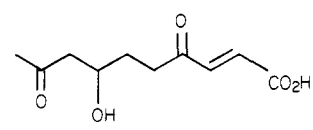


1, R = Me
2, R = CH_2COMe

antibiotic produced by the plant pathogenic fungus *Pyrenophora avenae*, and vermiculine (**2**), a structurally related antibiotic isolated from *Penicillum vermiculatum* Dangeard.[1] Both compounds are characterized by a 16-membered ring derived by head to tail lactonization of two identical C-8 and C-10 hydroxy acid subunits, **3** and **4**,



3



4

respectively. The preparation of these progenitors in a suitable protected form was the initial goal of most of the synthetic approaches to the targets **1** and **2**, which were

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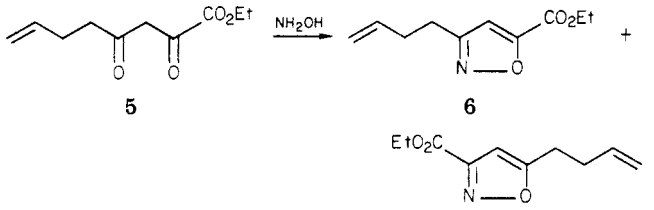
(1) For a comprehensive review of previous synthetic studies, see: Mali, S. R.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Justus Liebigs Ann. Chem.* **1981**, 2272–2284.

0022-3263/83/1948-1297$01.50/0

Scheme I



then obtained by using known dimerization procedures.[2] Our analysis of the synthetic problem posed by the functionalities presented here by **3** and **4** was strongly influenced by knowledge we have been accumulating about the chemistry of 3,5-disubstituted isoxazoles.[3] Earlier work has firmly established that 3,5-disubstituted isoxazoles can be regarded as synthetic equivalents of both α,β-unsaturated ketones[4,5] as well as β-hydroxy ketones.[6,7] This suggested to us that a new entry to **3** and **4** from these intermediates could be evolved, which would also be sufficiently flexible to permit the elaboration of both compounds from a common starting material.

Synthetic Strategy

With this in mind we selected ethyl 3-(3-butenyl)isoxazole-5-carboxylate (**6**) as the starting material since it incorporated in its eight carbon atom frame the features essential to the problem. The carboxylate group placed in position 5 of a 3,5-disubstituted isoxazole might serve well as a synthetic equivalent of the γ-oxy-α,β-unsaturated ester moiety present either in 3 or in **4**. The terminal double bond is properly located for easy introduction of the missing functions, a hydroxyl group for the pyrenophorin subunit (**3**) and a β-hydroxy ketone for the vermiculine subunit (**4**). The first problem could be readily solved by utilizing a Markovnikov hydration process.[8] On the other hand, the necessary two-carbon extension to complete the skeleton of **4** at the proper oxidation level could be created by applying the well-known cycloaddition–reduction sequence.[9]

Starting Material. The preparation of **6** (Scheme I) was readily accomplished by action of free hydroxylamine[10] on the oxalyl derivative (**5**)[11] of the commercially available 1-hexen-5-one, followed by treatment with concentrated sulfuric acid in EtOH in order to promote cyclization. Spinning-band distillation allowed the separation of **6** from a 7:3 mixture with the unwanted isomer **6a**, which was the sole reaction product when free hydroxylamine was substituted for its hydrochloride. This separation proved to be necessary only in the case of the synthesis of the progenitor of **3**, while it may be omitted in the case of the synthesis of **4**, where the purification proved easier at a later stage of the synthesis. The structure of **6** was assigned on the basis of the chemical shift of the C(4) proton (see Experimental Section).

Synthesis of the (±)-Seco Hydroxy Acid 3. The Markovnikov hydration of **6** was performed by following the original procedure of Brown and Geoghegan,[8] giving rise to the hydroxy acid **7** in 76% yield, owing to concomitant saponification. Reesterification with ethereal diazomethane gave quantitatively the hydroxy ester **8** which was further converted to the acetyl derivative **9** by a standard procedure. The same compound can also obtained by an independent synthesis, which entailed on the cycloaddition of the nitrile oxide generated in situ[12] from the nitro compound **10** on the tetrahydropyranyl derivative of the propargyl alcohol **11** to produce a 58.9% yield of the isoxazole **12**. Removal of the protective group[13] led to the primary alcohol **13**, which was oxidized by Jones reagent to the corresponding acid **14**, easily transformed to **9** (Scheme II).

Reductive fission of the labile N–O bond of **9** afforded quantitatively the enamino ketone **15**, which was subsequently treated with benzoyl chloride in pyridine to give the vinylogous imide **16**. Selective reduction of the carbonyl group of **16** cannot be achieved with sodium borohydride as usual, since reduction of the ester function also took place. It can, however, be effected in good yields by treatment with 1 equiv of $LiAlH(OBu\text{-}t)_3$ in cold THF. The crude reduction product (**17**) was then exposed to aqueous acetic acid to give the hydroxy ketone **18** as an inseparable mixture of diastereoisomers.[14a] The latter was smoothly dehydrated[14b] to **19** by treatment with 1 mol of methansulfonyl chloride in triethylamine, which was subsequently ketalized by a standard procedure to produce a 90% yield of **20**. Upon treatment with potassium carbonate in aqueous methanol, **20** underwent facile saponification of the two ester functions to give the known hydroxy acid **21**, which has already been[15] taken to **1** (Scheme III).

Synthesis of the (±)-Seco Hydroxy Acid 4. The carbon backbone required for the synthesis of **4** calls for a method for the introduction of a two carbon atom unit in form of an acetyl group at one end of the terminal double bond of **6**, while the other end needs a formal "oxidation". It is well-known[16] that nitrile oxides add regiospecifically on terminal alkenes, producing Δ^2-isoxazolines. A carbon–carbon bond takes place between the terminal atom of the cycloaddend and the carbon atom of

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(3) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Gandolfi, C. *J. Org. Chem.* **1981**, *46*, 4518–4524 and references quoted therein.
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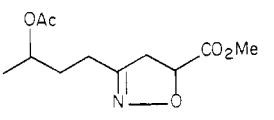
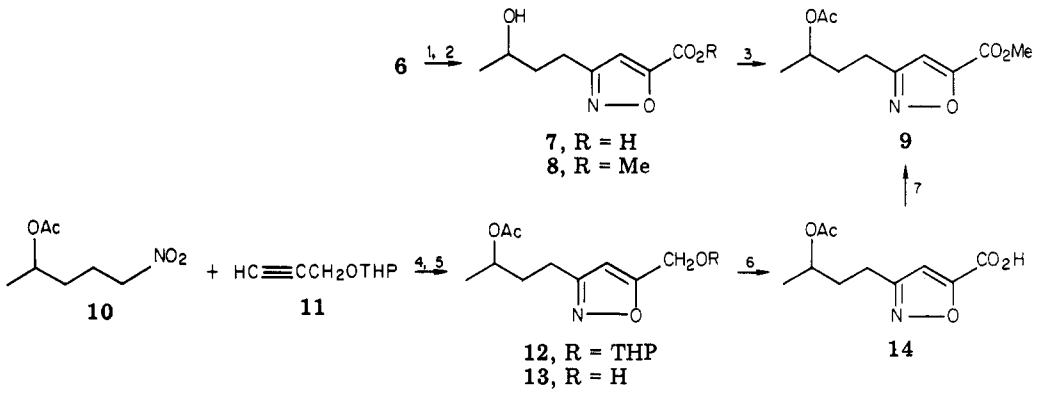
(14) (a) Compound **18** was also obtained in 89% yield by reductive ring opening in methanol/acetic acid (15:1) solution in the presence of Raney Ni followed by an aqueous workup of the Δ^2-isoxazoline (i). The



i

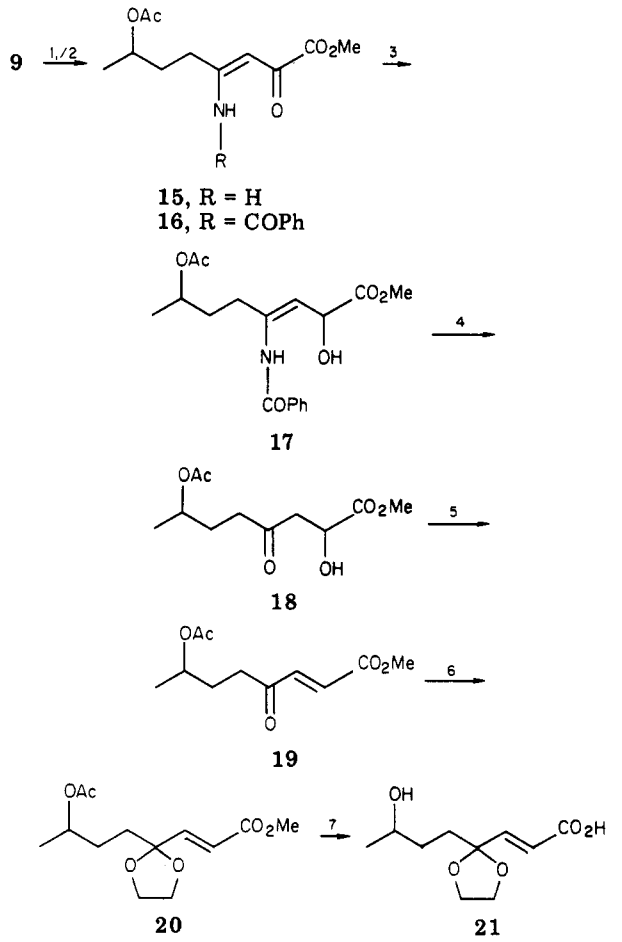
latter was in turn prepared in 87.2% yield by cycloaddition of **10** with methyl acrylate and showed the following spectroscopic properties: IR (film) 1740, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.7–2.1 (m, 2 H), 2.00 (s, 3 H), 2.4 (m, 2 H), 3.25 (m, 2 H), 3.8 (s, 3 H), 4.8–5.1 (m, 2 H). (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11–14.
(15) Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137–3139.
(16) Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971.

Scheme II[a]



[a] Reagents: (1) $Hg(OAc)_2$, $NaBH_4$; (2) CH_2N_2; (3) Ac_2O, Et_3N; (4) $POCl_3$, Et_3N; (5) H^+; (6) Jones reagent; (7) CH_2N_2.

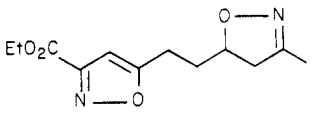
Scheme III[a]



[a] Reagents: (1) H_2, Raney Ni; (2) PhCOCl, Py; (3) $LiAlH(OBu\text{-}t)_3$; (4) AcOH, H_2O; (5) $MeSO_2Cl$, Et_3N; (6) $(CH_2OH)_2$, $HC(OEt)_3$, BF_3Et_2O; (7) KOH.

the dipole. The oxygen–carbon bond involves the other end of the dipolarophile. It was also known[9] that hydrogenolytic scission of the nitrogen–oxygen bond in acetic acid produces β-hydroxy ketones through transfer of the oxygen atom from the dipole to the dipolarophile, thus setting up the hydroxyl group at the proper site. Cycloaddition of the nitrile oxide generated "in situ" from nitroethane[17] on **6** produced **22** as a crystalline compound in 88% yield. When the latter was submitted to reductive fission in the presence of 10% C/Pd, 1 mol of hydrogen was rapidly adsorbed, giving rise to the expected **23** derived by the exclusive ring opening of the isoxazole nucleus.

When **6** was utilized in the cycloaddition step as a mixture with its isomer **6a**, the corresponding cycloadduct **22a** is formed together with **22**. Reductive treatment of



22a

the mixture in the presence of Pd/C revealed that the 5-carbethoxy substituent greatly facilitates the N–O fission, the isoxazole ring of **22** being opened selectively, to give **23**, which can be advantageously separated at this stage by flash chromatography. Benzoylation of **23** took place readily as described above for **15** to give the corresponding enamido derivative **23a**. At this stage we tried to unmask the β-hydroxy ketone function latent in the isoxazoline part of the molecule through hydrogenolytic treatment in acetic acid. However, this attempt led instead to a complex mixture of reduction products, owing to the concomitant reduction at other sites of **23a**. To avoid this, we directly reduced **23** in methanol containing acetic acid in the presence of Raney Ni to give a good yield of **24**, which was transformed to **25** by (dimethylamino)pyridine[18] -catalyzed acetylation. The latter was then benzoylated as usual to give **26** as a crystalline compound, which was subsequently transformed to **27** by selective reduction of the α-keto ester function with $LiAlH(OBu\text{-}t)_3$ in THF at 0 °C followed by treatment with 90% aqueous acetic acid to hydrolyze the enamide moiety. The latter compound was smoothly dehydrated by action of methansulfonyl chloride in Et_3N,[14] affording the α,β-unsaturated compound **28**. Bis ketalization of **28** as well as bis thioketalization proceeded cleanly under standard conditions to give the known[19] **29** and **30**, respectively, which were previously converted to (±)-**2**, thus completing a new formal synthesis. The entire sequence is outlined in Scheme IV.

The preparation of the precursors of both targets **1** and **2** in a suitable protected form from a single readily available material represents an advantage compared to most previous syntheses, although some of them proceed in higher overall yield.[1] However, our synthetic strategy provided a further demonstration of the versatility of 3,5-disubstituted isoxazoles and isoxazolines through the selectivity of the reductive cleavage.

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(18) Höfle, G.; Steglish, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583.

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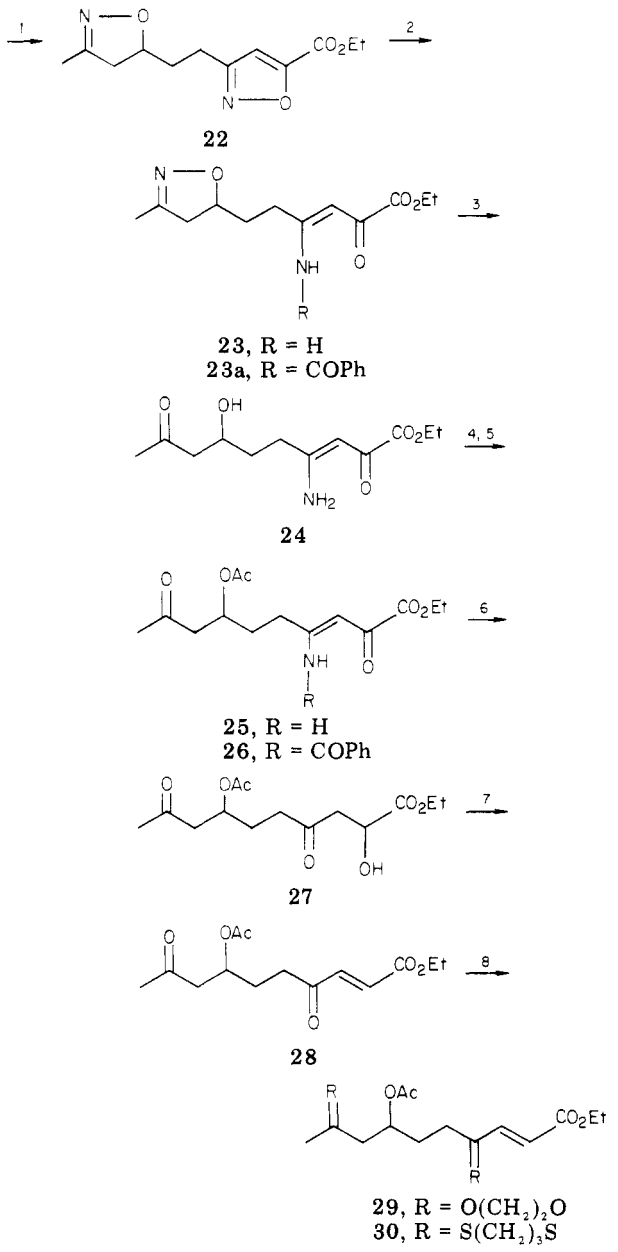
Scheme IV[a]



22

23, R = H
23a, R = COPh

24

25, R = H
26, R = COPh

27

28

29, R = $O(CH_2)_2O$
30, R = $S(CH_2)_3S$

[a] Reagents: (1) $EtNO_2$, PhNCO, Et_3N; (2) H_2, 10% C/Pd; (3) H_2, Raney Ni, AcOH; (4) Ac_2O, Et_3N; (5) PhCOCl, Py, (6) $LiAlH(OBu\text{-}t)_3$; (7) $MeSO_2Cl$, Et_3N; (8) $(CH_2OH)_2$, $HC(OEt)_3$, $BF_3 \cdot Et_2O$ or $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$.

Experimental Section

Melting and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by TLC on precoated silica gel 60 F_{254} plates (Merck). Infrared spectra were measured on a Perkin-Elmer 237 spectrometer. Nuclear magnetic resonance (^1H NMR) spectra were obtained with a Perkin-Elmer R 32, and peak positions are given in parts per millions downfield from tetramethylsilane as an internal standard. All drying operations were performed over anhydrous magnesium sulfate. Column chromatography (medium pressure) was carried out by using the "flash" technique.[20] Petroleum ether refers to the fraction of boiling range 40–60 °C.

Ethyl 3-(3-Butenyl)-5-isoxazolecarboxylate (6). A mixture of 1-hexen-5-one (4.5 g, 46 mmol) and diethyl oxalate (6.7 g, 46 mmol) was added dropwise to an ice-cooled solution of EtONa (1.1 g, 0.048 mol, of metallic Na) in absolute EtOH (50 mL). After being allowed to stand overnight at room temperature, the mixture was diluted with water (100 mL), acidified with 10% HCl, and extracted with Et_2O (5 × 25 mL). The combined extracts were washed with brine (2 × 20 mL), dried, and concentrated in vacuo to leave a brown oil, which was distilled at 0.05 mmHg to give **5**: 6.5 g (71.5%); bp 80–85 °C; IR (film) 1740, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H, J = 6 Hz), 2.2–3 (m, 4 H), 4.3 (q, 2 H, J = 6 Hz), 4.95–5.3 (m, 2 H), 5.65–6.10 (m, 1 H), 6.4 (s, 1 H). To a solution of $NH_2OH \cdot HCl$ (16 g, 230 mmol) in H_2O (30 mL) neutralized with NaOH (9.2 g, 230 mmol) in water (30 mL) was added the oxalyl derivative **5** (40 g, 202 mmol), and the mixture was stirred at room temperature for 1 h. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 75 mL), dried, and concentrated in vacuo. The oily residue was dissolved in EtOH (200 mL) containing concentrated H_2SO_4 (23 g) and refluxed for 5 h. Most of EtOH was removed in vacuo, the residue was poured in water (25 mL), and the separated oil was taken up with Et_2O. The dried organic extracts were concentrated in vacuo and the residue purified by spinning-band distillation to give two fractions, the low-boiling being **6**: bp 62 °C (0.01 mmHg); 19.6 g (50%); IR (film) 1740, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 2.35–3.1 (m, 4 H), 4.35 (q, 2 H, J = 6 Hz), 4.95–5.3 (m, 2 H), 5.65–6.1 (m, 1 H), 6.82 (s, 1 H). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.37; H, 6.65; N, 7.03.

The higher boiling fraction (bp 64 °C) gave **6a**: 7 g (17.8%); IR (film) 1740, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 2.25–3.1 (m, 4 H), 4.35 (q, 2 H, J = 6 Hz), 4.95–5.3 (m, 2 H), 5.6–6.1 (m, 1 H), 6.45 (s, 1 H). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.46; H, 6.79; N, 7.12.

3-(3-Hydroxybutyl)-5-isoxazolecarboxylic Acid (7). A solution of **6** (1 g, 5.12 mmol) in THF (10 mL) was rapidly added to a stirred solution of $Hg(OAc)_2$ (1.7 g, 5.3 mmol) in 1:1 H_2O/THF (20 mL). After 30 min, the clear solution was first treated with 3 N NaOH (20 mL), stirred further 30 min, and then treated with $NaBH_4$ (0.4 g, 10 mmol) portionwise. After 1 h the mixture was acidified with 6 N HCl and most of the solvent evaporated in vacuo. The residue was extracted with EtOAc (5 × 15 mL), dried, and concentrated. The acid **7** was obtained as a crystalline solid: 0.72 g (76%); mp 102–103 °C (THF/n-hexane, 1:5); IR ($CHCl_3$) 3400–2700, 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (d, 3 H, J = 6 Hz), 1.9 (m, 2 H), 2.9 (m, 2 H), 4.1 (m, 1 H), 6.9 (s, 1 H), 7.3 (br s, 1 H). Anal. Calcd for $C_8H_{11}NO_4$: C, 51.08; H, 5.99; N, 7.56. Found: C, 50.91; H, 6.08; N, 7.41.

Methyl 3-(3-Hydroxybutyl)-5-isoxazolecarboxylate (8). A solution of **7** (1 g, 5.4 mmol) in methanol (6 mL) was treated at 0 °C with excess of ethereal diazomethane. Removal of the solvent in vacuo followed by rapid chromatography (eluent Et_2O/petroleum ether, 7:3) gave **8** as an oil in essentially quantitative yield: 1.07 g; IR (film) 3350, 1740, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz) 1.85 (m, 2 H), 2.35 (br s, 1 H), 2.9 (t, 2 H), 3.9 (s, 3 H), 3.9–4.2 (m, 1 H), 6.85 (s, 1 H). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.44; H, 6.37; N, 6.88.

Methyl 3-[3-(Acetyloxy)butyl]-5-isoxazolecarboxylate (9). To an ice-cooled solution of **8** (1.6 g, 8 mmol) in $CHCl_3$ (20 mL) containing triethylamine (10 mmol) was added acetyl chloride (0.7 mL, 9.6 mmol) in $CHCl_3$ (5 mL) dropwise, and the mixture was allowed to stand overnight. Water (20 mL) was added, and the organic extracts were washed with 5% HCl (5 mL), brine (10 mL), and 5% $NaHCO_3$ solution. The dried organic phase was concentrated in vacuo and flash chromatographed (eluent Et_2O/petroleum ether, 1:1) to give **9** as a solid: 1.74 g (90%); mp 49–50 °C (from Et_2O/petroleum ether, 1:1); IR ($CHCl_3$) 1740, 1720, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.8–2.1 (m, 2 H), 2.00 (s, 3 H), 2.85 (m, 2 H), 3.9 (s, 3 H), 4.95 (m, 1 H), 6.8 (s, 1 H). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.73; H, 6.26; N, 5.77.

3-[3-(Acetyloxy)butyl]-5-[(tetrahydropyranyloxy)methyl]isoxazole (12). To an ice-cooled solution of the nitro compound **10**[21] (3 g, 17 mmol) and propargyl tetrahydropyranyl

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(21) Prepared in 80% yield by treatment of the corresponding nitro alcohol[22] (1 mmol) with Ac_2O (1.1 mmol) and triethylamine (1 mmol) in the presence of (dimethylamino)pyridine (catalytic) in CH_2Cl_2: bp 73 °C (0.01 mmHg); IR (film) 1735, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H), 2.00 (s, 3 H), 4.4 (t, 2 H), 5.00 (m, 1 H).

ether (11; 3.57 g, 25.5 mmol) in dry $CHCl_3$ (19 mL) and triethylamine (6.8 mL, 48 mmol) was added dropwise $POCl_3$ (2.8 g, 18 mmol) in $CHCl_3$ (4 mL), and the mixture was stirred at room temperature overnight. The mixture was poured into water (50 mL), the organic phase was separated and dried, and the solvents were removed in vacuo. The residue was purified by a rapid chromatography technique on silica gel (eluent Et_2O/petroleum ether, 1:1) to give **12** as a colorless oil: 3 g (58.9%); IR (film) 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.5–2.15 (m, 8 H), 2.01 (s, 3 H), 2.7 (m, 2 H), 3.4–4 (m, 2 H), 4.6–5.1 (m, 4 H), 6.15 (s, 1 H). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.74; H, 7.66; N, 4.62.

3-[3-(Acetyloxy)butyl]-5-(hydroxymethyl)isoxazole (13). A solution of **12** (2.97 g, 10 mmol) in MeOH (40 mL) and water (3 mL) was stirred in the presence of Amberlite H-15 (0.2 g) at 50 °C for 3 h.[13] Filtration and removal of the solvents in vacuo left **13** (2.13 g) as a practically pure oil, which was used in the next step without further purification: IR (film) 3400, 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.7–2.1 (m, 2 H), 2.0 (s, 3 H), 2.7 (m, 2 H), 3.5 (br s, 1 H), 4.7 (s, 2 H), 4.95 (m, 1 H), 6.12 (s, 1 H). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.09; H, 7.24; N, 6.66.

3-[3-(Acetyloxy)butyl]-5-isoxazolecarboxylic Acid (14). To an ice-cooled solution of **13** (1 g, 4.7 mmol) in acetone (50 mL) was added 2 N Jones reagent (~11 mL) dropwise until a persistent reddish color was obtained. The excess oxidant was destroyed by addition of some EtOH, the inorganic salts were filtered through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (20 mL) and washed with brine (1 mL). After the usual operations, **14** was obtained as a crystalline compound: 0.85 g (80%); mp 75 °C (Et_2O/petroleum ether, 1:2); IR ($CHCl_3$), 3400–2700, 1720, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.7–2.1 (m, 2 H), 2.02 (s, 3 H), 2.85 (m, 2 H), 4.95 (m, 1 H), 6.9 (s, 1 H), 8.45 (br s, 1 H). Esterification of **14** with ethereal diazomethane gave quantitatively **9** as above reported. Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.83; H, 5.76; N, 6.14.

Methyl 7-(Acetyloxy)-4-amino-2-oxo-3-octenoate (15). A solution of the isoxazole **9** (2.41 g, 10 mmol) in MeOH (10 mL) was added to a prehydrogenated mixture of PtO_2 (0.1 g) prereduced by adding a small amount of Raney nichel in MeOH (5 mL). After the hydrogenation was complete, the mixture was filtered through Celite and concentrated in vacuo to give **15** (2.4 g), which was used without further purification in the next step: IR (film) 3300, 3150, 1740–1710, 1600, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.8–2.1 (m, 2 H), 2.00 (s, 3 H), 2.5 (m, 2 H), 3.9 (s, 3 H), 4.95 (m, 1 H), 5.9 (s, 1 H), 7.9 (br s, 1 H), 10.5 (br s, 1 H). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.12; H, 6.87; N, 5.89.

Methyl 7-(Acetyloxy)-4-benzamido-2-oxo-3-octenoate (16). To an ice-cooled solution of crude **15** (1 g, 4.1 mmol) in anhydrous pyridine (10 mL) was added benzoyl chloride (0.56 mL, 4.9 mmol) dropwise. The mixture was left at room temperature overnight, diluted with water (10 mL), and extracted with Et_2O (3 × 25 mL). The extracts were washed with brine (15 mL), dried, and concentrated. The residue was flash chromatographed on silica gel (Et_2O/petroleum ether, 6:4) to give **16**: 1 g (70%); as an oil; IR (film) 1740, 1700, 1640, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz) 1.8–2.1 (m, 2 H), 2.00 (s, 3 H), 3.1 (m, 2 H), 3.9 (s, 3 H), 5.1 (m, 1 H), 6.4 (s, 1 H), 7.55–8.15 (m, 5 H), 13.25 (br s, 1 H). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.09; H, 5.99; N, 3.91.

Methyl 7-(Acetyloxy)-2-hydroxy-4-oxooctanoate (18). To an ice-cooled solution of **16** (0.7 g, 2.0 mmol) in dry THF (10 mL) was added solid $LiAlH(OBu\text{-}t)_3$ (0.6 g, 2.3 mmol) portionwise. After a further 10 min at 0 °C, 5% hydrochloric acid (7 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The dried organic extracts were concentrated in vacuo, and the crude **17** was dissolved in 90% aqueous acetic acid (20 mL) and left overnight at room temperature. Most of the acetic acid was removed in vacuo (0.5 mmHg), and the residue was treated with water (10 mL) and extracted with Et_2O (3 × 25 mL). After the usual workup, the residue was flash chromatographed on silica gel (eluent Et_2O) to give **18**[14a] as a colorless oil: 0.44 g, (90% yield); IR (film) 3450, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.7–2.1 (m, 2 H), 2.00 (s, 3 H), 2.55 (t, 2 H, J = 7 Hz), 2.95 (m, 2 H), 3.55 (br s, 1 H), 3.9 (s, 3 H), 4.5 (m, 1 H), 4.95 (m, 1 H). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.48; H, 7.52.

Methyl 7-(Acetyloxy)-4-oxo-2-octenoate (19). A solution of **18** (0.7 g, 2.84 mmol) in CH_2Cl_2 (30 mL) was treated at 0 °C with methansulfonyl chloride (0.45 mL, 5.8 mmol) and triethylamine (0.84 mL, 6 mmol) and left at the same temperature for a further 20 min. Then the same amount of triethylamine was added and the mixture allowed to warm at room temperature for 30 min. The mixture was washed with 10% aqueous citric acid solution (10 mL), and the organic phase was separated, washed with brine, and worked up as usual to leave an oil which was flash chromatographed (eluent Et_2O/petroleum ether, 1:1) to give **19**: 0.6 g (92.5%); IR (film) 1740–1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.8–2.1 (m, 2 H), 2.00 (s, 3 H), 2.8 (m, 2 H), 3.9 (s, 3 H), 4.95 (m, 1 H), 6.65 (d, 1 H, J = 16 Hz), 7.1 (d, 1 H, J = 16 Hz). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.99; H, 7.00.

Methyl 3-[2-[-3-(Acetyloxy)butyl]-1,3-dioxolan-2-yl]-2-propenoate (20). A solution of **19** (0.6 g, 2.6 mmol) in dry benzene (15 mL) containing ethylene glycol (0.24 mL, 4.0 mmol), triethyl orthoformate (0.45 mL, 2.7 mmol), and 2 drops of BF_3·Et_2O was refluxed for 24 h. The cooled mixture was washed with saturated $NaHCO_3$, dried, and concentrated. The residue was chromatographed (eluent Et_2O/petroleum ether, 1:1) to afford **20** as an oil: 0.67 g (93.7%); IR (film) 1730, 1665 cm^{-1}; ^1H NMR δ 1.25 (d, 3 H, J = 6 Hz), 1.7 (m, 4 H), 2.00 (s, 3 H), 3.75 (s, 3 H), 3.9 (m, 4 H), 4.95 (m, 1 H), 6.05 (d, 1 H, J = 16 Hz), 6.75 (d, 1 H, J = 16 Hz). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.29; H, 7.46.

3-[2-(3-Hydroxybutyl)-1,3-dioxolan-2-yl]-2-propenoic Acid (21). A solution of **20** (0.4 g, 1.47 mmol) in MeOH (10 mL) was allowed to stand at room temperature for 5 h with 2 N aqueous KOH solution (5 mL). The mixture was cooled to −5 °C, acidified to pH 3.5 with 2 N H_2SO_4, and rapidly extracted with $CHCl_3$ (3 × 15 mL). The organic extracts were washed with brine, dried, and concentrated to leave **21** as an oil, which showed the same spectroscopic characteristics described in the literature; 0.3 g (94%).[15] Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.59; H, 7.40.

Ethyl 3-[2-(3-Methyl-4,5-dihydroisoxazol-5-yl)ethyl]-5-isoxazolecarboxylate (22). To a solution of **6** (1.5 g, 7.6 mmol) and nitroethane (0.7 mL, 9.7 mmol) in dry benzene 3 mL) containing triethylamine (0.5 mL) was added phenylisocyanate (1.8 mL, 16 mmol) in benzene (5 mL) dropwise at room temperature, and the mixture was allowed to stand overnight. The cooled mixture (5 °C) was filtered, the filtrate was concentrated in vacuo, and the solid residue was crystallized from Et_2O to give **22**: 1.7 g (88%); mp 67–69 °C; IR ($CHCl_3$) 1740, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 1.98 (s, 3 H), 1.98–2.2 (m, 2 H), 2.5–3.2 (m, 4 H), 4.25–4.8 (m, 3 H), 6.8 (s, 1 H). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.09; H, 6.40; N, 11.15.

When the cycloaddition step was performed on a 7:3 mixture of **6** and **6a**, a mixture of **22** and **22a** was obtained from which **22** could be separated by repeated crystallization from Et_2O. However, this purification proved to be unnecessary.

3-Methyl-5-(3-amino-5-carbethoxy-5-oxo-3-penten-1-yl)-4,5-dihydroisoxazole (23). A stream of hydrogen was passed into a solution of **22** (1.5 g, 5.9 mmol) in absolute EtOH for 1 h in the presence of 10% Pd/C (0.2 g). After filtration of the catalyst through Celite and removal of the solvent in vacuo, the solid residue was crystallized form Et_2O to give **23** in essentially quantitative yield: 1.51 g; mp 64–65 °C; IR ($CHCl_3$) 3480, 1740, 1600, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 1.98 (s, 3 H), 1.9–2.2 (m, 3 H), 2.3–3.3 (m, 4 H), 4.25 (q, 2 H), 4.6 (m, 1 H), 5.8 (s, 1 H), 7.5 (br s, 1 H), 10.2 (br s, 1 H). Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.72; H, 7.11; N, 10.93.

The same operation performed on a mixture of **22** and **22a** (1.5 g) gave a residual oil, which was chromatographed on silica gel (eluent EtOAc). Unreacted **22a**, the fast moving component, was removed from **23** and characterized as the pure compound: mp

(22) Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735–738.

65 °C (from Et_2O); IR ($CHCl_3$) 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 1.98 (s, 3 H), 1.9–2.2 (m, 2 H), 2.4–3.3 (m, 4 H), 4.35–4.8 (m, 3 H), 6.45 (s, 1 H). The second eluted fraction afforded **23** (0.8 g) which was identical with that described above.

Ethyl 4-Amino-2,9-dioxo-7-hydroxy-3-decenoate (24). A solution of **23** (0.75 g, 2.9 mmol) in absolute MeOH (5 mL) containing acetic acid (1 mL) was hydrogenated in the presence of Raney nickel (0.1 g) for 5 h at room temperature. After filtration through Celite, the solvent was eliminated in vacuo and the residue chromatographed (eluent EtOAc/MeOH, 9.5:0.5) to give **24**: 0.6 g (79%); IR (film) 3350, 1710, 1600, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 6 Hz) 1.6–2.00 (m, 2 H), 2.2 (s, 3 H), 2.3–2.6 (m, 4 H), 3.65 (br s, 1 H), 4–4.4 (m, 3 H), 5.85 (s, 1 H), 7.1 (br s, 1 H), 10.35 (br s, 1 H). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.82; H, 7.58; N, 5.36.

Ethyl 7-(Acetyloxy)-4-amino-2,9-dioxo-3-decenoate (25). A solution of **24** (0.75 g, 3 mmol) in dry CH_2Cl_2 (10 mL) was cooled at 0 °C and treated with Ac_2O (0.35 mL, 3.4 mmol), triethylamine (0.47 mL, 3.4 mmol), and (dimethylamino)pyridine[18] (50 mg). After 5 min at 0 °C, the mixture was washed with brine (5 mL) and the organic phase worked up as usual to leave an oil which was chromatographed on silica gel (eluent EtOAc/Et_2O, 7:3) to give **25** as a colorless oil in essentially quantitative yield: 0.85 g; IR (film) 3300, 1730–1690, 1610, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz), 1.6–1.95 (m, 2 H), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.2–2.8 (m, 4 H), 4.3 (q, 2 H, J = 6 Hz), 5.3 (m, 1 H), 5.9 (s, 1 H), 7.2 (br s, 1 H), 10.35 (br s, 1 H). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.30; H, 7.01; N, 4.49.

Ethyl 7-(Acetyloxy)-4-benzamido-2,9-dioxo-3-decenoate (26). A solution of **25** (0.5 g, 1.7 mmol) in dry pyridine (5 mL) was cooled at 0 °C and treated with freshly distilled benzoyl chloride (0.4 mL, 3.4 mmol). After 5 min at 0 °C, water (20 mL) was added and the mixture extracted with Et_2O (3 × 20 mL). After the usual workup, the residue was chromatographed on silica gel (eluent Et_2O/petroleum ether, 7:3) to give **26** as a solid: 0.6 g (89.5%); mp 74–75 °C (from Et_2O/petroleum ether, 1:1); IR ($CHCl_3$) 1740–1700, 1630, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, J = 7 Hz), 2.02 (s, 3 H), 2.12 (s, 3 H), 2.0–2.15 (m, 2 H), 2.75–3.3 (m, 4 H), 4.3 (q, 2 H, J = 7 Hz), 5.3 (m, 1 H), 6.3 (s, 1 H), 7.55–8.15 (m, 5 H), 13.2 (br s, 1 H). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.53; H, 6.27; N, 3.43.

Ethyl 7-(Acetyloxy)-4,9-dioxo-2-hydroxydecanoate (27). A solution of **26** (0.3 g, 0.75 mmol) in dry THF (5 mL) was cooled at 0 °C while solid LiAlH (OBu-t)$_3$ (0.190 g, 0.75 mmol) was added portionwise. After 10 min at 0 °C, 5% hydrochloric acid (1.5 mL) was added and the mixture extracted with Et_2O (3 × 15 mL). The dried organic extracts were evaporated to give an oil, which was dissolved in 90% acetic acid (5 mL) and left at room temperature for 5 h. Most of the acetic acid was removed in vacuo (0.5 mmHg), and the residue was extracted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$. The dried organic phase was concentrated in vacuo to give a residue oil which was chromatographed on silica gel (eluent Et_2O/EtOAc, 8:2) to afford **27** as an unseparable mixture of diastereoisomers: 0.165 g (73%); IR (film) 3350, 1740, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 6 Hz), 1.99 (s, 3 H), 2.11 (s, 3 H), 1.9–2.2 (m, 2 H), 2.45–3.05 (m, 6 H), 4.2 (q, 2 H, J = 6 Hz), 4.5 (m, 1 H), 5.2 (m, 1 H). Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34. Found: C, 55.49; H, 7.22.

Ethyl 7-(Acetyloxy)-4,9-dioxo-*trans*-2-decenoate (28). An ice-cooled solution of **27** (0.150 g, 0.50 mmol) in CH_2Cl_2 was treated with methansulfonyl chloride (0.055 mL, 0.72 mmol) and triethylamine (0.1 mL, 0.72 mmol). After 10 min at 0 °C, the same amount of triethylamine in CH_2Cl_2 (10 mL) was added dropwise during 5 h at the same temperature. The mixture was washed with 10% aqueous citric acid solution, and the separated organic phase was dried and concentrated in vacuo. The residue was chromatographed (eluent Et_2O/petroleum ether, 3:7) to give **28** as a pure oil: 0.12 g (85%); IR (film) 1740, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H, J = 6 Hz), 2.00 (s, 3 H), 2.12 (s, 3 H), 2.00–2.9 (m, 6 H), 4.25 (q, 2 H, J = 6 Hz), 5.25 (m, 1 H), 6.75 (d, 1 H, J = 16 Hz), 7.15 (d, 1 H, J = 16 Hz). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.01; H, 6.98.

Ethyl 3-[2-[3-(Acetyloxy)-4-(2-methyl-1,3-dioxolan-2-yl)-butyl]-1,3-dioxolan-2-yl]-2-propenoate (29). A solution of **28** (1 g, 3.5 mmol) in dry benzene (10 mL) containing ethylene glycol (0.744 mL, 12 mmol), triethyl orthoformate (1.33 mL, 8 mmol), and 2 drops of BF_3·Et_2O was refluxed for 24 h. The cooled mixture was washed with saturated aqueous $NaHCO_3$, and the separated organic extracts were dried and evaporated. The residue was chromatographed (eluent Et_2O/petroleum ether, 3:7) to give **29** (1 g, 78%), as an oil whose spectroscopic properties are identical with those previously reported by Seebach et al.[19] Anal. Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.10; H, 7.52.

Ethyl 3-[2-[3-(Acetyloxy)-4-(2-methyl-1,3-dithian-2-yl)butyl]-1,3-dithian-2-yl]-2-propenoate (30). To a solution of **28** (0.5 g, 1.76 mmol) in CH_2Cl_2 (10 mL) containing propanedithiol (0.35 mL, 3.5 mmol), were added 2 drops of BF_3·Et_2O, and the mixture was left at room temperature 48 h. After treatment with 5% $NaHCO_3$ solution (2 × 10 mL), the dried organic phase was concentrated and flash chromatographed on silica gel (eluent ether/petroleum ether, 7:3) to give **30** as an oil (0.49 g, 60%), whose spectroscopic properties agree with the reported ones.[19] Anal. Calcd for $C_{20}H_{32}O_4S_4$: C, 51.72; H, 6.94. Found: C, 51.65; H, 6.98.

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