Synthesis of N-Substituted 4-(2-Oxoalkyl)-1,4-dihydronicotinates and Their Inverse Electron Demand Diels-Alder Reaction with 3,4-Dichlorothiophene 1,1-Dioxide

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Received July 2, 1986

N-Substituted 4-(2-oxoalkyl)-1,4-dihydronicotinates 4 were prepared in high yields by the reaction of quaternized nicotinium salts with silyl enol ethers. These 1,4-dihydronicotinates acted as dienophiles in Diels-Alder reactions with the electron-deficient 3,4-dichlorothiophene 1,1-dioxide. The cycloaddition proceeded regio- and stereoselectively in good yield to give 1,4,4a,8a-tetrahydroquinolines 8.

Dihydropyridines have been extensively studied,[1] and current interest in these compounds includes NADH, synthesis of NADH model compounds, and the mechanism of reduction by these compounds.[2] 1,2-Dihydropyridines have been utilized as dienes in intra- or intermolecular Diels-Alder reactions to afford isoquinuclidines.[3,4] In contrast, 1,4-dihydropyridines have not been utilized as dienophiles, although a Diels-Alder reaction is very useful for the construction of heterocycles with high stereoselectivity. The absence of such reactions may be due to the electron-rich nature of the reagent and the thermal instability of some dihydropyridines. However, 1,4-dihydronicotinates bearing an electron-withdrawing substituent should be stable. In this paper we describe the synthesis of 1,4-dihydronicotinates **4a-m**, their inverse electron demand Diels-Alder reactions with 3,4-dichlorothiophene 1,1-dioxide (**7**), and some stereochemical features of the addition.

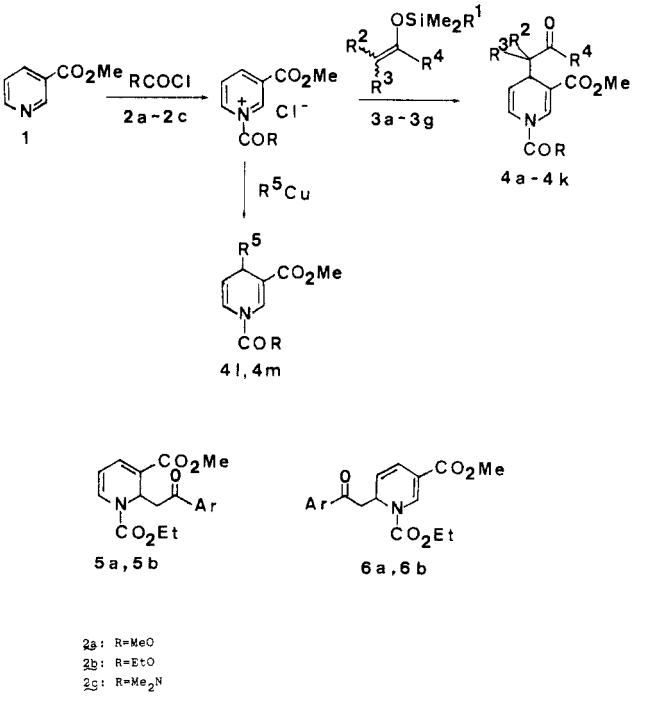
Synthesis of Methyl 4-(2-Oxoalkyl)-1,4-dihydronicotinates. We have reported the regioselective synthesis of 1-acyl-4-(2-oxoalkyl)-1,4-dihydropyridines[5] and other 4-substituted 1,4-dihydropyridines[6] by reaction of quaternized pyridines with silyl enol ethers. We have now used this reaction to obtain methyl 4-(2-oxoalkyl)-1,4-dihydronicotinates **4a-k** in yields of 58-97% (Table I). When we used the trimethylsilyl enol ethers of acetophenones (**3a,b**, R^1 = Me), 1,2- (**5**) and 1,6-dihydronicotinates (**6**) were obtained as byproducts (**4**/**5**/**6** = 5:1:1) (Scheme I). Use of *tert*-butyldimethylsilyl enol ethers **3a** and **3b** (R^1 = *t*-Bu) improved this ratio to 10:1:1.[5] More severe reaction conditions were required for preparation of **4i-k** since the formation of the quaternized nicotinium salts was sluggish because of the lower reactivity of dimethylcarbamoyl chloride.[7] 4-Alkyl-1,4-dihydronicotinates **4l,m** were synthesized by reaction of the nicotinium salt with methylcopper or *p*-tolylcopper prepared from methyllithium or *p*-tolyllithium and 1 equiv of copper(I) iodide.[8]

Table I. Synthesis of 1,4-Dihydronicotinate 4

4	R	R^2	R^3	R^4	R^5	total yield, %
4a	OEt	H	H	Ph		63[a,b]
4b	OEt	H	H	*p*-$MeOC_6H_4$		58[a,c]
4c	OEt	H	Ph	OMe		85
4d	OEt	Me	Me	OMe		61
4e	OMe	H	Me	Et		69
4f	OMe	H	Me	Ph		96
4g	OMe	Me	Me	Me		93
4h	Me	Me	Me	Me		76
4i	NMe_2	Me	Me	OMe		63
4j	NMe_2	H	Ph	OMe		97
4k	NMe_2	Me	Me	OMe		60
4l	OMe				Me	76
4m	OMe				*p*-Tolyl	71

[a] *tert*-Butyldimethylsilyl enol ether was used. [b] Product ratio 1,4/1,2/1,6 = 10:1:1. [c] 1,4, 47%; 1,2 + 1,6, 11%.

Scheme I



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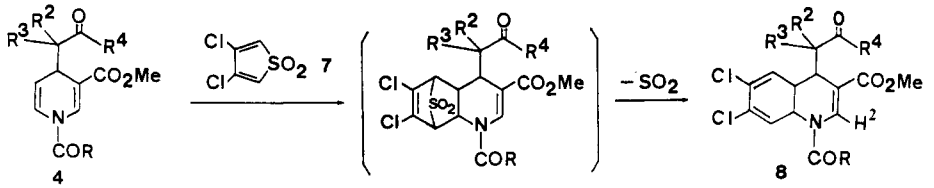
(7) Sluggish formation of a similar pyridinium salt was noticed. Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1983**, *24*, 3683.

0022-3263/86/1951-5328$01.50/0

Scheme II

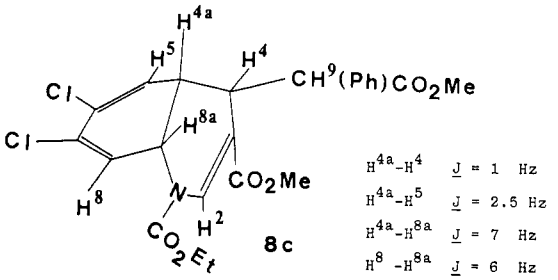


Reaction of 4 with Dienes. The reactions of **4g** with three dienes were carried out to explore its reactivity as a dienophile. When 2,3-dimethyl-1,3-butadiene was heated with **4g** in benzene-d_6 to 60 °C for 33 h, **4g** was recovered in 90% yield. No reaction occurred on heating **4g** with a large excess of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (Danishefsky's diene[9]) at 100 °C for 7 h in toluene. However, when **4g** was heated with 2 equiv of 3,4-dichlorothiophene 1,1-dioxide (**7**)[10] in refluxng toluene for 12 h, a rather complex mixture was obtained from which the expected adduct **8g** was isolated in 15% yield. Other products included recovered **4g** (4%), the dimer of **7**, and methyl nicotinate (**1**, 36%), probably formed by the decomposition of **4g**. The fact that **8g** was obtained encouraged us to explore reactions of **7** with other 1,4-dihydronicotinates with different substituents at the C-4 position. Although **4a** gave the same results as **4g** (**8a**/**1**/**4a** = 21:38:20), no **1** was obtained in the reactions of **4c** and **4d**, showing the different effects of the β-(alkoxycarbonyl)alkyl group and the 2-oxoalkyl group at the C-4 position of **4**.

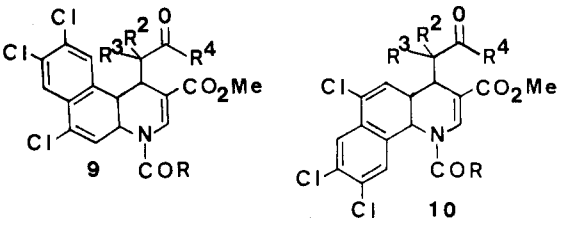
The structures **8** were determined by ^{1}H NMR, MS, and elemental analyses to be the 1:1 adducts of **4** and **7** with the elimination of SO_2. When we carried out the reaction with **4a,d,g**, the diastereomerically pure **4c**, only one isomer of the corresponding **8** was obtained. Thus the reaction proceeded regio- and stereoselectively (syn and anti). One notable feature of the ^{1}H NMR of **10** is a singlet at low field (δ 8.1–8.3 for R = OMe, OEt; δ 7.2–7.7 for R = NMe_2). Such a signal is characteristic of a β-proton in an α,β-unsaturated ester, that is, H2 in the adduct **8**. Consequently, cycloaddition must have taken place at the 5,6-double bond in **4** to give **8** as shown in Scheme II. Since the ^{1}H NMR patterns of **8** were quite similar, the structure of a diastereomerically pure sample of **8c** was determined precisely in order to elucidate the stereochemistry of the cycloaddition. In order to determine the relative stereochemistry at C4a–C8a and C4–C4a, the relationships between protons were determined by decoupling experiments, assuming that the lowest field proton peak (δ 3.87) of the four sp^3 ones belonged to H8a adjacent to the nitrogen atom. The results are shown in Scheme III.

We first examined Dreiding models of the ring junction and found that in cis-fused **8** there are two conformations in which the dihedral angle between H4a–H8a is ca. 60°. However, in trans-fused **8** there is only one rigid conformation, with a dihedral angle of ca. 180°. The coupling constant J_{4a-8a} of **8c** was 7 Hz, indicating that the ring junction is cis. In one of the two conformations of cis-fused **8**, the dihedral angles between H4a–H5 and H8–H8a are ca. 30° and ca. 90°, respectively; in the other conformer

Scheme III



H^{4a}–H^4 J = 1 Hz
H^{4a}–H^5 J = 2.5 Hz
H^{4a}–H^{8a} J = 7 Hz
H^8–H^{8a} J = 6 Hz
H^5–H^{8a} J = 1 Hz



the magnitudes of the angles are reversed. In **8c**, J_{4a-5} is 2.5 Hz and J_{8-8a} is 6 Hz, thus the conformation shown in Scheme III is preferred. We observed 18% NOE at H5 (δ 5.57) when H4 and H9 (δ 3.53–3.63) were irradiated, with less NOE at H4a (5–9%; δ 2.92). Hence it can be concluded that the diene moiety is anti to the C4 substituent. The exclusive formation of the cis–anti adduct shows that the reaction proceeded not in a stepwise but in a concerted manner from the less hindered side; a similar stereoselectivity has been reported in the 1,3-dipolar cycloaddition with 1,2-dihydropyridines.[11]

Two problems were examined in efforts to improve the yield of **8**. One was the secondary Diels–Alder reaction of **8** with **7** to give **9** and/or **10**. In a reaction of **4d** with **7**, **9d** was obtained in 8% yield. The structures of **9** and **10** were assigned by ^{1}H NMR. The use of a large excess and stepwise addition of **7** could be the cause for the secondary reaction, and better yields of **8c** and **8d** were obtained when 5 equiv of **7** was added to a concentrated toluene solution of **4c** or **4d** all at once and the mixture heated to reflux. The desired end point of the reaction was determined by monitoring with TLC.

A second problem was the decomposition of **4** to **1**, which is probably caused by HCl generated in the dimerization of **7**. Actually this decomposition took place only with β-keto substituents (**4a,g**) and not with β-alkoxycarbonyl substituents (**4c,d**). Because of the sensitivity of **4** to HCl, we employed acetyl and dimethylcarbamoyl chlorides instead of ethoxycarbonyl chloride as acylating reagents. However, in the reaction of the *N*-acetyl compound **4h** with 2 equiv of **7**, only 3% yield of **8b** was obtained and 57% of methyl nicotinate (**1**) was recovered. Likewise, the *N*-carbamoyl compound **4k** reacted with 3 equiv of **7** to

(8) From pyridinium salt with alkyl- or arylcopper or alkyl- or arylcopper–BF_3 complex. Akiba, K-y.; Iseki, Y.; Wada. M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994. From pyridinium salt with alkyl or aryl Grignard reagent–5% cuprous iodide, see: Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151.

(9) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(10) For synthesis of **7**: Bluestone, H.; Bimber, R.; Berkey, R.; Mandel, Z. *J. Org. Chem.* **1961**, *26*, 346. For applications with **7**: Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 867.

(11) Dubey, S. K.; Knaus, E. E. *J. Org. Chem.* **1984**, *49*, 123.

Table II. Synthesis of 1,4,4a,8a-Tetrahydroquinoline[a]

entry	8	R	R^2	R^3	R^4	R^5	base	yield recov, % 8	4	1
1	**8a**	OEt	H	H	Ph			21	20	38
2	**8a**	OEt	H	H	Ph		*b*	61	13	
3	**8b**	OEt	H	H	*p*-$MeOC_6H_4$		*b*	60	0	
4	**8c**	OEt	H	Ph	OMe			52	11	
5	**8d**	OEt	Me	Me	OMe			36	60	
6	**8e**	OMe	H	Me	Et		*b*	55	38	
7	**8f**	OMe	H	Me	Ph		*b*	31	38	
8	**8g**	OMe	Me	Me	Me		*b*	22	65	
9	**8i**	NMe_2	Me	Me	Me		*b*	26	40	
10	**8j**	NMe_2	H	Ph	OMe			54	29	
11	**8k**	NMe_2	Me	Me	OMe			36	39	
12	**8l**	OMe				Me		70	0	
13	**8m**	OMe				*p*-Tolyl		65	0	

[a] Entries 1, 4, 5, and 10–13, 4/7 = 1:5; entries 2, 3, and 6–9, 4/7/base = 1:10:15. [b] 2,6-Lutidine was used as the base.

give only 5% yield of **8k** with 60% recovery of **1**. Therefore we tried to avoid this decomposition by the addition of a base. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), 1,8-bis(dimethylamino)naphthalene (proton sponge), or pyridine reacted with **7** immediately at room temperature to form black tars. In contrast, 2,2,6,6-tetramethylpiperidine, 1,2,2,6,6-pentamethylpiperidine, 2,6-lutidine, and 4-methyl-2,6-di*tert*-butylpyridine did not react as rapidly with **7**. And we carried out the reaction of **4g** with 5 equiv of **7** in the presence of these sterically hindered bases. The best yield of **8g** (22%) was obtained by use of 2,6-lutidine; 2,2,6,6-tetramethylpiperidine and 1,2,2,6,6-pentamethylpiperidine gave only half as much. A complex reaction occurred with 4-methyl-2,6-di-*tert*-butylpyridine, and no **8g** was obtained. Therefore we carried out the reaction of other **4** with 10 equiv of **7** in the presence of 15 equiv of 2,6-lutidine and obtained still better yields of **8** (Table II). The effect of the base is shown by entries 1 and 2.

In summary, Diels–Alder adducts **8** were obtained in good yields by using excess 2,6-lutidine to trap hydrogen chloride generated in situ. Table II shows that the yield of **8** decreased as the steric hindrance of **4** increased (entries 5,8,9,11), as might be expected because the Diels–Alder reaction is quite susceptible to steric hindrance.

Experimental Section

Melting points were taken on a micro melting point apparatus and are uncorrected. IR spectra were obtained on a Hitachi 215 spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Hitachi R-90H spectrometer. Mass spectra were recorded on a Hitachi RMU-6L spectrometer. Flash column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed with Merck silica gel GF-254 plates. 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene[9] and 3,4-dichlorothiophene 1,1-dioxide[10] were prepared by the reported method.

Synthesis of 1-[Alkoxycarbonyl(or acetyl)]-3-(methoxycarbonyl)-4-(2-oxoalkyl)-1,4-dihydropyridines (4a–h) with Trimethylsilyl Enol Ethers 3. General Procedure. Ethyl (or methyl) chloroformate (or acetyl chloride) (7 mmol) was added to a solution of methyl nicotinate (7 mmol) in 10 mL of dichloromethane at 0 °C. Trimethylsilyl enol ether **3** (8 mmol) was added, and the reaction mixture was stirred under nitrogen at room temperature for 10–12 h. The resulting reaction mixture was treated with 5% $NaHCO_3$ (20 mL), and the product was extracted with ether (25 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography with hexane and ethyl acetate (4:1–2:1) or dichloromethane as eluent to afford **4**.

1-(Ethoxycarbonyl)-3-(methoxycarbonyl)-4-(2-oxo-2-phenylethyl)-1,4-dihydropyridine (4a): oil; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 3.02 (dd, 1 H, *J* = 15, 9 Hz, CH_2COPh), 3.41 (dd, 1 H, *J* = 15, 3 Hz, CH_2COPh), 3.75 (s, 3 H, CO_2Me), 3.95 (ddd, 1 H, *J* = 9, 5, 3 Hz, H4), 4.30 (q, 2 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 5.25 (dd, 1 H, *J* = 9, 5 Hz, H5), 6.76 (d, 1 H, *J* = 9 Hz, H6), 7.3–7.6 (m, 3 H, Ph), 7.8–8.2 (m, 3 H, Ph + H2).

1-(Ethoxycarbonyl)-3-(methoxycarbonyl)-4-[2-(*p*-methoxyphenyl)-2-oxoethyl]-1,4-dihydropyridine (4b): mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H, *J* = 7 Hz), 2.95 (dd, 1 H, *J* = 15, 6 Hz), 3.42 (dd, 1 H, *J* = 15, 4 Hz), 3.75 (s, 3 H), 3.84 (s, 3 H), 3.90–4.15 (m, 1 H), 4.28 (q, 2 H, *J* = 7 Hz), 5.24 (dd, 1 H, *J* = 4, 8 Hz), 6.75 (dd, 1 H, *J* = 8, 1 Hz), 6.90 (d, 2 H, *J* = 9 Hz), 7.95 (d, 2 H, *J* = 9 Hz), 7.97 (d, 1 H, *J* = 1 Hz). Anal. Calcd for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.35; H, 5.89; N, 4.10.

1-(Ethoxycarbonyl)-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)benzyl]-1,4-dihydropyridine (4c). The initially eluted diastereomer of **4c** from flash column chromatography (dichloromethane): oil; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, *J* = 8 Hz), 3.67 (s, 3 H), 3.79 (s, 3 H), 3.9–4.2 (m, 2 H), 4.17 (q, 2 H, *J* = 8 Hz), 5.30 (dd, 1 H, *J* = 5, 8 Hz), 6.67 (dd, 1 H, *J* = 8, 1 Hz), 6.95–7.4 (m, 5 H), 7.73 (d, 1 H, *J* = 1 Hz). Anal. Calcd for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.37; H, 6.03; N, 4.17. Another diastereomer: oil; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, *J* = 8 Hz), 3.45 (s, 3 H), 3.62 (s, 3 H), 3.5–4.1 (m, 2 H), 4.31 (q, 2 H, *J* = 8 Hz), 5.15 (dd, 1 H, *J* = 5, 7 Hz), 6.85 (dd, 1 H, *J* = 7, 1 Hz), 6.9–7.4 (m, 5 H), 7.93 (d, 1 H, *J* = 1 Hz).

1-(Ethoxycarbonyl)-3-(methoxycarbonyl)-[1-(methoxycarbonyl)-1-methylethyl]-1,4-dihydropyridine (4d): oil; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.09 (s, 3 H), 1.36 (t, 3 H, *J* = 7 Hz), 3.65 (s, 3 H), 3.74 (s, 3 H), 3.80 (d, 1 H, *J* = 6 Hz), 4.33 (q, 2 H, *J* = 7 Hz), 5.07 (dd, 1 H, *J* = 8, 6 Hz), 6.95 (dd, 1 H, *J* = 8, 1 Hz), 8.03 (d, 1 H, *J* = 1 Hz). Anal. Calcd for $C_{15}H_{21}O_6N$: C, 57.87; H, 6.80; N, 4.50. Found: C, 58.00; H, 6.61; N, 4.43.

1,3-Bis(methoxycarbonyl)-(1-methyl-2-oxobutyl)-1,4-dihydropyridine (4e). The initially eluted diastereomer of **4e** from flash column chromatography (4:1 hexane/AcOEt): oil; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 7 Hz), 1.06 (t, 3 H, *J* = 7 Hz), 2.33–3.20 (m, 3 H), 3.77 (s, 3 H), 3.90 (s, 3 H), 3.90–4.10 (m, 1 H), 4.92 (dd, 1 H, *J* = 8, 4 Hz), 6.88 (dd, 1 H, *J* = 8, 1 Hz), 7.97 (d, 1 H, *J* = 1 Hz). Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.74; H, 7.03; N, 4.78. Another diastereomer: oil; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 7 Hz), 1.00 (t, 3 H, *J* = 7 Hz), 2.18–3.00 (m, 3 H), 3.73 (s, 3 H), 3.90 (s, 3 H), 3.70–4.10 (m, 1 H), 5.10 (dd, 1 H, *J* = 8, 4 Hz), 6.87 (dd, 1 H, *J* = 8, 1 Hz), 7.90 (d, 1 H, *J* = 1 Hz).

1,3-Bis(methoxycarbonyl)-4-(1-methyl-2-oxo-2-phenylethyl)-1,4-dihydropyridine (4f). The initially eluted diastereomer of **4f** from flash column chromatography (4:1 hexane/AcOEt): mp 104–106 °C; ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, *J* = 7 Hz), 3.84 (s, 3 H), 3.88 (s, 3 H), 3.8–4.1 (m, 2 H), 4.78 (dd, 1 H, *J* = 4, 8 Hz), 6.90 (d, 1 H, *J* = 8 Hz), 7.4–7.6 (m, 3 H), 8.0–8.3 (m, 3 H). Another diastereomer: oil; ^1H NMR ($CDCl_3$) δ 1.18 (d, 3 H, *J* = 7 Hz), 3.66 (s, 3 H), 3.84 (s, 3 H), 3.7–4.0 (m, 2 H), 5.22 (dd, 1 H, *J* = 5, 8 Hz), 6.84 (dd, 1 H, *J* = 8, 1 Hz), 7.3–7.6 (m, 3 H), 7.7–7.9 (m, 3 H).

1,3-Bis(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4-dihydropyridine (4g): mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.08 (s, 3 H), 2.18 (s, 3 H), 3.73 (s, 3 H), 3.82 (d, 1

H, J = 5 Hz), 3.90 (s, 3 H), 5.05 (dd, 1 H, J = 5, 8 Hz), 6.95 (dd, 1 H, J = 8, 1 Hz), 8.02 (d, 1 H, J = 1 Hz). Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.94; H, 7.04; N, 4.99.

1-Acetyl-3-(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4-dihydropyridine (4h): oil; ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 0.87 (s, 3 H), 1.01 (s, 3 H), 2.12 (s, 3 H), 2.30 (s, 3 H), 3.67 (s, 3 H), 3.73 (dd, 1 H, J = 6, 1 Hz), 5.12 (dd, 1 H, J = 6, 8 Hz), 7.06 (dd, 1 H, J = 8, 2 Hz), 7.97 (dd, 1 H, J = 2, 1 Hz).

Synthesis of 1-[(Dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-(2-oxoalkyl)-1,4-dihydropyridines (4i–k). General Procedure. A mixture of methyl nicotinate (7 mmol) and dimethylcarbamoyl chloride (9 mmol) was heated to 100 °C for 1 h. To this solution was added trimethylsilyl enol ether **3** (9 mmol) through a syringe, and the reaction mixture was stirred under nitrogen at 100 °C for 8 h. The resulting reaction mixture was treated with 5% $NaHCO_3$ (20 mL), and the product was extracted with ether (25 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evoporated in vacuo. The crude product was purified by flash column chromatography with dichloromethane as an eluent to afford **4**.

1-[(Dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4-dihydropyridine (4i): oil; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.95 (s, 3 H), 2.05 (s, 3 H), 2.83 (s, 6 H), 3.55 (s, 3 H), 3.69 (d, 1 H, J = 6 Hz), 4.82 (dd, 1 H, J = 6, 7 Hz), 6.55 (d, 1 H, J = 7 Hz), 7.60 (s, 1 H). Anal. Calcd for $C_{15}H_{22}O_4N_2$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.06; H, 7.69; N, 9.24.

1-[(Dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)benzyl]-1,4-dihydropyridine (4j). The initially eluted diastereomer of **4j** from column chromatography (CH_2Cl_2): oil; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 4.01 (d, 1 H, J = 4 Hz), 4.25 (t, 1 H, J = 4 Hz), 5.27 (dd, 1 H, J = 4, 8 Hz), 6.37 (dd, 1 H, J = 8, 1.5 Hz), 7.0–7.25 (m, 5 H), 7.41 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{19}H_{22}O_5N_2$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.80; H, 6.13; N, 8.00. Another diastereomer: oil; ^{1}H NMR ($CDCl_3$) δ 2.92 (s, 6 H), 3.54 (s, 3 H), 3.63 (s, 3 H), 3.61–3.80 (m, 1 H), 3.98 (t, 1 H, J = 6 Hz), 4.99 (dd, 1 H, J = 6, 8 Hz), 6.53 (dd, 1 H, J = 8, 1.5 Hz), 6.92–7.5 (m, 5 H), 7.69 (d, 1 H, J = 1.5 Hz).

1-[(Dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)-1-methylethyl]-1,4-dihydropyridine (4k): mp 79–80.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.11 (s, 3 H), 2.97 (s, 6 H), 3.66 (s, 3 H), 3.72 (s, 3 H), 3.84 (d, 1 H, J = 6 Hz), 4.99 (dd, 1 H, J = 6, 8 Hz), 6.71 (d, 1 H, J = 8 Hz), 7.76 (s, 1 H). Anal. Calcd for $C_{15}H_{22}O_5N_2$: C, 58.05; H, 7.14; N, 9.03. Found: C, 58.09; H, 7.05; N, 9.18.

Synthesis of 1,3-Bis(methoxycarbonyl)-4-methyl-1,4-dihydropyridine or -4-*p*-tolyl-1,4-dihydropyridine (4l or 4m) with Methyl- or *p*-Tolylcopper. General Procedure. Methyl- or *p*-tolyllithium (13.5 mmol) was added to a suspension of CuI (2.57 g, 13.5 mmol) in 30 mL of THF at −78 °C. The mixture was stirred for 10 min and warmed to −30 °C and stirred for 20 min at that temperature. The mixture was transferred through a double-ended needle to a suspension of nicotinium salt in 15 mL of THF at −30 °C, which was preparard from methyl nicotinate (1.00 g, 7.3 mmol) and methyl chloroformate (0.64 mL, 8 mmol). The resulting mixture was stirred for 5–6 h at room temperature, then treated with 5% $NaHCO_3$ (20 mL). The product was extracted with ether (25 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography with hexane and ethyl acetate (5:1) as eluent to afford **4l** or **4m**.

1,3-Bis(methoxycarbonyl)-4-methyl-1,4-dihydropyridine (4l): ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3 H, J = 6.6 Hz), 3.31 (dq, 1 H, J = 6.6, 4.6 Hz), 3.75 (s, 3 H), 3.87 (s, 3 H), 5.08 (dd, 1 H, J = 4.6, 8 Hz), 6.72 (dd, 1 H, J = 8, 1.5 Hz), 7.87 (d, 1 H, J = 1.5 Hz).

1,3-Bis(methoxycarbonyl)-4-*p*-tolyl-1,4-dihydropyridine (4m): mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.63 (s, 3 H), 3.91 (s, 3 H), 4.41 (d, 1 H, J = 4.3 Hz), 5.13 (dd, 1 H, J = 4.3, 8 Hz), 6.85 (br d, 1 H, J = 8 Hz), 8.03 (br s, 1 H). Anal. Calcd for $C_{16}H_{17}O_4N$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.57; H, 5.91; N, 5.18.

Reaction of 3,4-Dichlorothiophene 1,1-Dioxide with 4-[2-(Alkoxycarbonyl)alkyl]-Substituted 1,4-Dihydropyridines (4c,d,j,k) or 4-Alkyl- or 4-Aryl-Substituted 1,4-Dihydropyridines (4l,m). General Procedure. A mixture of a 1,4-dihydropyridine **4** (1 mmol) and 5 equiv of **7** was dissolved in 1 mL of toluene and heated to reflux. The reaction was monitored by TLC and stopped when a small amount of the secondary product appeared on TLC. The mixture was separated by flash column chromatography (dichloromethane or ethyl acetate–hexane) to afford **8** (**8c,d,j–m**).

6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)benzyl]-1,4,4a,8a-tetrahydroquinoline (8c). Diastereomerically pure **4c** (initially eluted isomer) gave a single product with **7**: mp 109–112 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 6 Hz, $CO_2CH_2CH_3$), 2.92 (ddd, 1 H, J = 1.1, 2.5, 7 Hz, H4a), 3.53–3.63 (m, 2 H, H4 and H9), 3.61 (s, 3 H, CO_2Me), 3.78 (s, 3 H, CO_2Me), 3.87 (ddd, 1 H, J = 1, 6, 7 Hz, H8a), 4.25 (q, 2 H, J = 6 Hz, CO_2CH_2Me), 5.57 (dd, 1 H, J = 1, 2.5 Hz, H5), 6.35 (d, 1 H, J = 6 Hz, H8), 7.33 (s, 5 H, Ph), 8.20 (s, 1 H, H2). Anal. Calcd for $C_{23}H_{23}NO_6Cl_2$: C, 57.51; H, 4.83; N, 2.92. Found: C, 57.25; H, 5.10; N, 2.82.

6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)-1-methylethyl]-1,4,4a,8a-tetrahydroquinoline (8d): oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.22 (s, 3 H), 1.37 (t, 3 H, J = 7 Hz), 3.10–3.38 (m, 2 H), 3.65 (s, 3 H), 3.75 (s, 3 H), 4.10–4.40 (m, 3 H), 5.50 (br s, 1 H), 6.46 (d, 1 H, J = 6 Hz), 8.25 (s, 1 H).

6,7-Dichloro-1-[(dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)benzyl]-1,4,4a,8a-tetrahydroquinoline (8j). Diastereomerically pure **4j** (initially eluted isomer) gave a single product with **7**: mp 172.5–175 °C; ^{1}H NMR ($CDCl_3$) δ 2.89 (s, 6 H), 3.35–3.90 (m, 4 H), 3.67 (s, 3 H), 3.78 (s, 3 H), 5.70–5.78 (m, 1 H), 6.16 (d, 1 H, J = 7.5 Hz), 7.32 (s, 5 H), 7.66 (s, 1 H). Anal. Calcd for $C_{23}H_{24}O_5N_2Cl_2$: C, 57.63; H, 5.05; N, 5.84. Found: C, 57.83; H, 5.33; N, 5.63.

6,7-Dichloro-1-[(dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-[1-(methoxycarbonyl)-1-methylethyl]-1,4,4a,8a-tetrahydroquinoline (8k): mp 137.5–139 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 6 H), 2.90 (s, 6 H), 2.90–3.20 (m, 2 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 4.22 (dd, 1 H, J = 7, 7 Hz), 5.65 (br s, 1 H), 6.28 (d, 1 H, J = 7 Hz), 7.71 (s, 1 H). Anal. Calcd for $C_{19}H_{24}N_2O_5Cl_2$: C, 52.99; H, 5.57; N, 6.34. Found: C, 52.91; H, 5.61; N, 6.50.

2,3,5-Trichloro-7-[(dimethylamino)carbonyl]-9-(methoxycarbonyl)-10-[1-(methoxycarbonyl)-1-methylethyl]-6a,7,10,10a-tetrahydrobenzo[*f*]quinoline (9k): ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 6 H), 2.61 (s, 6 H), 2.85–2.90 (m, 2 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 4.39 (dd, 1 H, J = 6, 5 Hz), 6.44 (d, 1 H, J = 6 Hz), 7.27–7.35 (m, 2 H), 7.61 (s, 1 H).

2,3,5-Trichloro-10-[(dimethylamino)carbonyl]-8-(methoxycarbonyl)-7-[1-(methoxycarbonyl)-1-methylethyl]-6a,7,10,10a-tetrahydrobenzo[*h*]quinoline (10k): ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6 H), 2.67 (s, 6 H), 2.93–3.20 (m, 2 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 4.59 (d, 1 H, J = 4 Hz), 5.65 (br s, 1 H), 7.45 (s, 1 H), 7.53 (br s, 2 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-methyl-1,4,4a,8a-tetrahydroquinoline (8l): oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 7 Hz), 2.26–2.90 (m, 2 H), 3.73 (s, 3 H), 3.84 (s, 3 H), 4.79 (dd, 1 H, J = 4, 6.5 Hz), 6.10 (d, 1 H, J = 4 Hz), 6.17 (d, 1 H, J = 5 Hz), 8.61 (s, 1 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(*p*-methylphenyl)-1,4,4a,8a-tetrahydroquinoline (8m): ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 2.63 (m, 1 H), 3.52 (s, 3 H), 3.70 (d, 1 H, J = 8 Hz), 3.87 (s, 3 H), 4.82 (dd, 1 H, J = 3.7, 6.8 Hz), 5.94 (d, 1 H, J = 5.5 Hz), 6.02 (d, 1 H, J = 3.7 Hz), 6.83–7.15 (m, 4 H), 8.20 (s, 1 H).

Reaction of 3,4-Dichlorothiophene 1,1-Dioxide with 3-(Methoxycarbonyl)-4-(2-oxoalkyl)-Substituted 1,4-Dihydropyridines 4a,b,e–g,i in the Presence of 2,6-Lutidine. General Procedure. To a solutioin of the 1,4-dihydropyridine (1 mmol) and 10 equiv of **7** in 2 mL of toluene was added 15 equiv of 2,6-lutidine. The mixture was heated to reflux. The reaction was monitored by TLC and stopped when a small amount of secondary product (**9**, **10**) appeared on TLC. The resulting mixture was treated with 5% $NaHCO_3$ (20 mL), and the product was extracted with dichloromethane (25 mL × 3). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The product was separated with flash column chromatography (1:2 or 1:4 ethyl acetate/hexane or dichloromethane).

6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-(2-oxo-2-phenylethyl)-1,4,4a,8a-tetrahydroquinoline (8a): mp 164.4–165.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 2.9–3.56 (m, 4 H), 3.71 (s, 3 H), 4.31 (q, 2 H, J = 7 Hz), 4.56 (dd, 1 H, J = 6, 6 Hz), 5.87 (d, 1 H, J = 4 Hz), 6.25 (d, 1 H, J = 6 Hz), 7.3–7.6 (m, 3 H), 7.9–8.03 (m, 2 H), 8.15 (s, 1 H). Anal. Calcd for $C_{22}H_{21}O_5NCl_2$: C, 58.67; H, 4.70; N, 3.11. Found: C, 58.69; H, 4.41; N, 2.85.

6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-[2-oxo-2-(*p*-methoxyphenyl)ethyl]-1,4,4a,8a-tetrahydroquinoline (8b): oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 2.83–3.50 (m, 4 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 4.55 (dd, 1 H, J = 5, 5 Hz), 5.86 (d, 1 H, J = 4 Hz), 6.28 (d, 1 H, J = 5 Hz), 6.95 (d, 2 H, J = 9 Hz), 7.96 (d, 2 H, J = 9 Hz), 8.27 (s, 1 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1-methyl-2-oxobutyl)-1,4,4a,8a-tetrahydroquinoline (8e). Diastereomerically pure **4e** (initially eluted isomer) gave a single product with **7**: oil; ^{1}H NMR $CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 1.06 (t, 3 H, J = 7 Hz), 2.35–3.30 (m, 5 H), 3.77 (s, 3 H), 3.88 (s, 3 H), 4.75 (dd, 1 H, J = 7, 4 Hz), 5.82 (d, 1 H, J = 5 Hz), 6.10 (d, 1 H, J = 4 Hz), 8.14 (s, 1 H). Anal. Calcd for $C_{18}H_{21}O_5NCl_2$: C, 53.78; H, 2.98; N, 5.29. Found: C, 53.74; H, 3.48; N, 5.26.

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1-methyl-2-oxo-2-phenylethyl)-1,4,4a,8a-tetrahydroquinoline (8f). Diastereomerically pure **4f** (initially eluted isomer) gave a single product with **7**: oil; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3 H, J = 7 Hz), 2.76 (dd, 1 H, J = 7, 7 Hz), 3.20 (dd, 1 H, J = 7, 4 Hz), 3.83 (s, 3 H), 3.88 (s, 3 H), 4.4–4.7 (m, 1 H), 4.85 (dd, 1 H, J = 7, 3 Hz), 5.80 (d, 1 H, J = 6 Hz), 5.86 (d, 1 H, J = 3 Hz), 7.3–7.7 (m, 3 H), 8.0–8.3 (m, 3 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4,4a,8a-tetrahydroquinoline (8g): oil; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6 H), 2.22 (s, 3 H), 3.10–3.31 (m, 2 H), 3.75 (s, 3 H), 3.84 (s, 3 H), 4.40 (dd, 1 H, J = 6, 6 Hz), 5.55 (br s, 1 H), 6.46 (d, 1 H, J = 6 Hz), 8.27 (s, 1 H).

6,7-Dichloro-1-[(dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4,4a,8a-tetrahydroquinoline (8i): oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.15 (s, 3 H), 2.22 (s, 3 H), 2.92 (s, 6 H), 2.90–3.25 (m, 2 H), 3.71 (s, 3 H), 4.25 (ddd, 1 H, J = 6, 6, 1.5 Hz), 5.70 (dd, 1 H, J = 2, 1.5 Hz), 6.28 (d, 1 H, J = 6 Hz), 7.27 (s, 1 H).

Acknowledgment. We are grateful to Chisso, Ltd. for the gift of silyl chlorides and to the Grant-in-Aid for Special Project Research (59104002) administered by the Japanese Ministry of Education, Science, and Culture.

Supplementary Material Available: IR spectral data for **4a–k,m** and **8a–c,e,i–l** and mass spectral data for **4b–k,m** and **8a–c,e,j–l** (3 pages). Ordering information is given on any current masthead page.

Electrophilic Sulfur Transfer Reactions in Organic Synthesis. Preparation of a Diastereomer of the Key Macrocyclic Component of Griseoviridin

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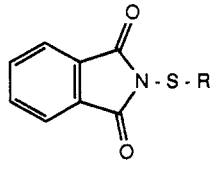
Received July 10, 1986

The utility of electrophilic sulfur transfer reactions was demonstrated by the synthesis of a diastereomer of the key macrocyclic cysteine containing component of griseoviridin. The key step involved direct reaction at the sulfur of *N*-(carbobenzyloxy)-*S*-phthalimido-L-cysteine *tert*-butyl ester with the anion derived from methyl 3-oxa-5(*S*)-[(*tert*-butyldimethylsilyl)oxy]hexanoate.

N-(Alkylthio)- or *N*-(arylthio)phthalimides **1** serves as sulfenyl transfer reagents upon reaction with a variety of heteroatoms[1] and active methylene compounds.[2] We have found this type of electrophilic reaction at sulfur to be especially useful for the preparation of several sulfur-containing molecules of biological interest, including the novel N–S containing β-lactams **2** and **3**.[3] Although related attempts to sulfenylate active methylene compounds often gave mixtures of mono- and bissulfenylated products, we have recently found that anions derived from active methylene compounds **4** react with *S*-phthalimidocysteine derivatives **5** to give the corresponding monosulfenylated products **6** in good yield (eq 1). Since these reactions provide an effective way of transfering an entire cysteine unit to another carbon framework by reaction at sulfur, no racemization of the α-chiral center is expected. This has encouraged us to study the utility of cysteine-based sulfur transfer reactions for the synthesis of other biologically interesting molecules. Herein we report on the successful use of a cysteine-based electrophilic sulfur transfer reaction as the key step in the synthesis of a diastereomer of a primary component (**7**) of griseoviridin (**8**).



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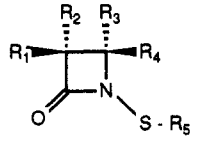

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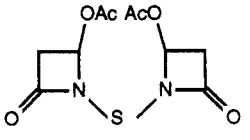

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