aromatic), 7.20 (s, 1 H, OH). IR (neat): ν 3410, 1650, 1620, 850 cm^{-1}. Mass: m/z 362 (100, M^+), 169 (40), 168 (55). HRMS: Calcd for $C_{22}H_{34}O_4$: 362.2457. Found: 362.2460.

Preparation of Irisquinone (1b). Irisquinone (23.3 mg) was obtained from **8b** (25 mg, 0.066 mmol) in 94% yield as yellow solid substance, mp 43 °C (lit.[4] mp 42.5–43.5 °C), adopting the same procedure as described for **1a**. ^1H NMR ($CDCl_3$): δ 0.9 (t, 3 H, J = 5.5 Hz, CH_2CH_2), 1.18–1.48 (m, 20 H, methylenes), 1.5 (m, 2 H, $ArCH_2CH_2$), 2.0 (m, 2 H, allylic), 2.42 (2 H, t, J_1 = 7 Hz, benzylic), 3.82 (s, 3 H, OCH_3), 5.34 (t, 2 H, J_1 = 2 Hz, CH=CH), 5.88 (d, 1 H, J = 3 Hz, aromatic), 6.46 (m, 1 H, aromatic). IR (neat): ν 1660, 1600, 845 cm^{-1}. Mass: m/z 374 (100, M^+), 167 (50), 153 (80), 55 (90). HRMS: Calcd for $C_{24}H_{38}O_3$: 374.2821. Found: 374.2828.

Registry No. **1a**, 82380-21-0; **1b**, 56495-82-0; **2**, 23030-48-0; **3a**, 139943-65-0; **3b**, 133099-84-0; **4a**, 139943-66-1; **4b**, 139943-67-2; **5a**, 139943-68-3; **5b**, 139943-69-4; **6a**, 139943-70-7; **6b**, 139943-71-8; **7a**, 139943-72-9; **7b**, 139943-73-0; **8a**, 139943-74-1; **8b**, 77285-25-7; 2,5-dihydroxy-3-methoxy-1-bromobenzene, 61654-67-9; 9-decen-1-ol, 13019-22-2; pentyltriphenylphosphonium bromide, 21406-61-1; *n*-heptyltriphenylphosphonium bromide, 13423-48-8.

Supplementary Material Available: ^1H NMR spectra of compounds **1a** and **1b** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Determination of Configurations of *N*-Methoxy Imidoyl Halides via Catalytic Hydrogenation. Synthesis of Pure (*E*)-Aldoximes

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The chemistry of *N*-alkoxy imidoyl halides has not been investigated as fully as that of *N*-alkyl and *N*-aryl imidoyl halides.[1] We have found that *N*-alkoxyalkanimidoyl halides are more stable chemically and thermally than the corresponding alkyl imidoyl halides and can be useful as synthetic intermediates.[2] *N*-Hydroxy imidoyl halides, which are precursors of nitrile oxides, are well-known. However, the corresponding *N*-alkoxy compounds, especially *N*-alkoxyalkanimidoyl halides, appear rarely in the literature. Johnson et al. determined the configurations of *N*-methoxyarenecarboximidoyl chlorides by X-ray crystallographic analysis[3b,4] and dipole moment measurement[3b] and carried out studies of the mechanisms and stereochemistry of their substitution reactions with alkoxides and amines.[3a-d] On the other hand, configurations of *N*-methoxyalkanimidoyl halides have not been determined completely, and their chemistry has been scarcely investigated.[2]

We have synthesized *N*-methoxy-2-(2-naphthyl)ethanimidoyl bromide (**6a**) by a conventional method and have found the compound to have the *Z* configuration by X-ray crystallography. Catalytic reduction of **6a** leads to the pure (*E*)-*O*-methylaldoxime, showing that dehalogenation proceeds with retention of configuration. Configurations of other *N*-methoxy imidoyl halides, synthesized by the same methods, were determined to be *Z* by catalytic reduction and ^1H NMR analyses[5] of the resulting aldoximes.

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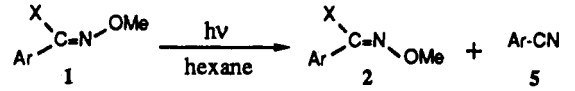
Table I. The *Z* → *E* Isomerization of *N*-Methoxy Imidoyl Halides by Irradiation



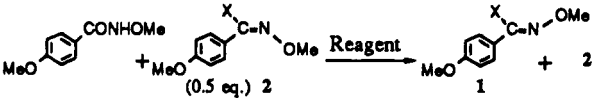
1 2 5

starting material	temp, °C	time, min	product (%)	recovery of 1 (%)
1a	0	10	**2a** (46), **5a** (18)	**1a** (28)
1b	0	18	**2b** (35), **5b** (21)	**1b** (32)
1d	25	120	**2d** (44), **5a** (8)	**1d** (15)

Table II. Chemical Shift Data for the *Z* and *E* Isomers of *N*-Methoxy Imidoyl Halides

compd	config	δ ($NOCH_3$)	$\Delta\delta$ ($Z - E$)
1a	*Z*	4.05	0.17
2a	*E*	3.88	
1b	*Z*	4.10	0.20
2b	*E*	3.90	
1d	*Z*	4.06	0.13
2d	*E*	3.93	

Table III. The *E* → *Z* Isomerization of *N*-Methoxy Imidoyl Halides 2 under Halogenation Conditions



run	reagent	temp, °C	time, h	X	yield 1 (%)	yield 2 (%)
1	PPh_3–CCl_4	reflux	2	Cl	**1d** (72)	**2d** (25)
2	PCl_5–$POCl_3$	100	0.5	Cl	**1d** (82)	**2d** (0)
3	$SOCl_2$	reflux	4	Cl	**1d** (38)	**2d** (0)
4	PPh_3–CBr_4	reflux	2	Br	**1a** (97)	**2a** (0)

Synthesis of (*E*)- and (*Z*)-*N*-Methoxy Imidoyl Halides. *N*-Methoxy imidoyl halides were synthesized from the corresponding *N*-methoxyamides with PCl_5, $POCl_3$, $SOCl_2$, PBr_3, or PPh_3–CX_4 (X = Cl, Br). In each case, the ^1H NMR spectrum and TLC of the crude product indicated that a single isomer had been formed. X-ray crystallographic studies of (*E*)- and (*Z*)-*N*-methoxy-4-nitrobenzenecarboximidoyl chlorides and subsequent dipole moment measurements proved that configurations of the single isomers obtained by above methods are *Z*.[3b,4] Johnson et al. synthesized nine pairs of *N*-alkoxybenzenecarboximidoyl chlorides by ultraviolet irradiation of hexane solutions of the corresponding *Z*-isomers and separation of the *E*/*Z* mixture by preparative gas chromatography; however, they could not obtain the corresponding *E*-bromides.[3e] By use of similar irradiation conditions and separation of the products by silica gel column chromatography, we have obtained the (*E*)-*N*-methoxybenzenecarboximidoyl bromides (**2b**), along with considerable amounts of the corresponding nitriles. The

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(2) Sakamoto, T.; Mori, H.; Takizawa, M.; Kikugawa, Y. *Synthesis* **1991**, 750.

(3) (a) Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, S. L.; Sitz, D. A. *J. Org. Chem.* **1985**, *50*, 3348. (b) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T.; Exner, O. *Ibid.* **1985**, *50*, 993. (c) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *Ibid*, **1981**, *46*, 3623. (d) Johnson, J. E.; Cornell, S. C. *Ibid.* **1980**, *45*, 4144. (e) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *Ibid.* **1976**, *41*, 252.

(4) Bertolasi, V.; Sacerdoti, M.; Tassi, D. *Cryst. Struct. Commun.* **1977**, *6*, 335.

(5) Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079; Buehler, E. *J. Org. Chem.* **1967**, *32*, 261.

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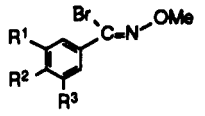
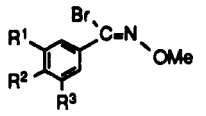
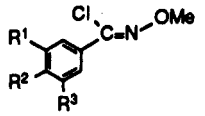


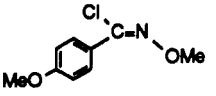
1a : $R^1 = R^3 = H$, $R^2 = OMe$
b : $R^1 = R^2 = R^3 = OMe$
c : $R^1 = R^3 = H$, $R^2 = NO_2$



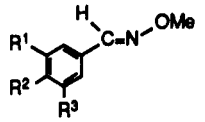
2a : $R^1 = R^3 = H$, $R^2 = OMe$
b : $R^1 = R^2 = R^3 = OMe$



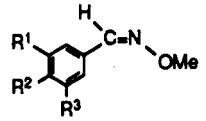
1d : $R^1 = R^3 = H$, $R^2 = OMe$
e : $R^1 = R^2 = R^3 = OMe$



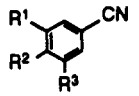
2d



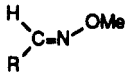
3a : $R^1 = R^3 = H$, $R^2 = OMe$
b : $R^1 = R^2 = R^3 = OMe$
c : $R^1 = R^3 = H$, $R^2 = NH_2$
d : $R^1 = R^3 = H$, $R^2 = NHAc$



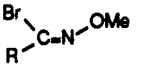
4a : $R^1 = R^3 = H$, $R^2 = OMe$
b : $R^1 = R^2 = R^3 = OMe$



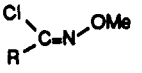
5a : $R^1 = R^3 = H$, $R^2 = OMe$
b : $R^1 = R^2 = R^3 = OMe$
c : $R^1 = R^3 = H$, $R^2 = NH_2$



7a : R = 2-naphthylmethyl
b : $R = C_6H_5CH_2CH_2$
c : $R = 4\text{-}AcC_6H_4CH_2CH_2$
d : $R = 4\text{-}MeOC_6H_4CH_2$
e : $R = MeO_2C(CH_2)_7$
f : $R = Et_2NOC(CH_2)_7$
g : $R = NC(CH_2)_{10}$



6a : R = 2-naphthylmethyl
b : $R = C_6H_5CH_2CH_2$
c : $R = 4\text{-}AcC_6H_4CH_2CH_2$
d : $R = 4\text{-}MeOC_6H_4CH_2$
e : $R = MeO_2C(CH_2)_7$
f : $R = Et_2NOC(CH_2)_7$
g : $R = NC(CH_2)_{10}$



6h : $R = C_6H_5CH_2CH_2$

results are presented in Table I. In all of the compounds synthesized by Johnson and by us, the chemical shift of the *O*-methyl singlet was found to be further downfield in the case of the *Z*-isomer than in the corresponding *E*-isomer. The results are presented in Table II. This correlation enabled us to make configurational assignment for those compounds for which both isomers are obtainable. In order to clarify why only (*Z*)-*N*-methoxy imidoyl halides are produced by halogenation of *N*-methoxyamides, *N*,4-dimethoxybenzamide was halogenated in the presence of the corresponding *E*-halides. The results are presented in Table III. The *E*-isomers were completely isomerized to the *Z*-isomers during halogenation. As is shown in run 1, however, the system PPh_3–CCl_4 had little effect on the *E*/*Z* product distribution, and no substantial isomerization to the *Z*-halides occurred, indicating that not only acidic conditions, but also the conformation of the reaction intermediate, plays an important role in the exclusive formation of *Z*-isomers.

X-ray Crystallographic Study of *N*-Methoxy-2-(2-naphthyl)ethanimidoyl Bromide. In the case of *N*-methoxyarenecarboximidoyl halides, X-ray crystallographic analyses of (*Z*)- and (*E*)-*N*-methoxy-4-nitrobenzenecarboximidoyl chlorides were carried out by two groups,[3b,4] and configurations of both isomers were unequivocally determined.

In contrast, syntheses of *N*-alkoxyalkanimidoyl halides rarely appear in the literature, and configurations of only two compounds were assumed to be *Z* by dipole moment measurements, which are not entirely reliable.[3b,4] Furthermore, as (*E*)-*N*-alkanimidoyl halides have never been isolated, the determination of configurations of these compounds is more difficult since there is no possibility for comparison. Thus, we required the determination of configurations of *N*-methoxyalkanimidoyl halides for our research.

We have undertaken an X-ray crystallographic study of *N*-methoxy-2-(2-naphthyl)ethanimidoyl bromide (**6a**) which is a single isomer synthesized by conventional methods and confirmed the configuration to be *Z*.

Catalytic Hydrogenation of *N*-Methoxy Imidoyl Halides. Initially, we investigated catalytic hydrogenation of *N*-methoxy imidoyl halides, the configurations of which had been previously determined. The results are presented in Table IV. A single isomer of oxime was obtained from the corresponding (*E*)- or (*Z*)-*N*-methoxy imidoyl bromides with retention of configuration, although considerable amounts of the corresponding nitriles were obtained by hydrogenation of *E*-isomers. ^1H NMR measurements have shown that either isomer, on storage in polar solvents or during distillation, undergoes isomerization to give a mixture of *E*- and *Z*-isomers [**7b** isomerizes in deuteriochloroform to a mixture of *E* (84%) and *Z* (16%) isomers after 4 days]. Generally, *N*-methoxyarenecarboximidoyl halides resist reduction and large amounts of catalyst, which cause increased nitrile formation, are required. On the other hand, *N*-methoxyalkanimidoyl halides are readily hydrogenated to give single isomers. Use of the combination of the bromide, *tert*-butyl alcohol as solvent and 2–3% by weight of palladium on carbon brought about suppression of nitrile formation and an increase in yield of oxime. The results are presented in Table V.

^1H NMR measurements of the products show that all the oximes are *E*, which indicates that configurations of the starting *N*-methoxy imidoyl halides are *Z*.

Recently, Scheuer and Carroll[6] determined the structures of four sponge metabolites showing significant cytotoxicity against KB cells, two of which bore (*E*)-*O*-

Table IV. Catalytic Hydrogenation of *N*-Methoxy Imidoyl Halides Having Established Configurations

		product (%)	
starting material	time, h	oxime	nitrile
1a	1	3a (63)	5a (8)
1c	0.3	3c (50)	5c (25)
2a	1	4a (11)	5a (69)
6a	2	7a (76)	

Table V. Catalytic Hydrogenation of *N*-Methoxy Imidoyl Halides

		product (%)	
starting material	time, h	oxime	nitrile
1b	5.5	3b (70)	
2b	1		5b (88)
6b	2	7b (78)	
6c	2	7c (84)	
6d	1.5	7d (85)	
6e	1.8	7e (77)	
6f	1.5	7f (77)	
6g	2	7g (69)	
6h	1.5	7b (64)	

(6) Carroll, A. R.; Scheuer, P. J. *Tetrahedron* **1990**, *46*, 6637.

methylaldoximes. Generally, condensation of aldehydes and hydroxylamines gives a mixture of *E*- and *Z*-oximes and their separation is troublesome. Therefore, this catalytic method is useful not only for determination of configuration of *N*-methoxy imidoyl halides, but also for preparation of pure *E*-aldoximes.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were measured at 60 or 270 MHz with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. Low- and high-resolution mass (MS) spectra were obtained with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Material. All *N*-alkoxyamides were prepared in high yield by the Schotten–Baumann reaction, using the corresponding acid chlorides and methoxyamines and gave satisfactory spectral data and elemental analyses. The following amides are known compounds: *N*,4-dimethoxybenzamide,[3e] *N*-methoxy-4-nitrobenzamide,[3e] *N*-methoxy-3-phenylpropanamide,[7] *N*-methoxy-2-(4-methoxyphenyl)acetamide,[7] *N*-methoxy-2-(2-naphthyl)acetamide,[7] *N*-methoxy-8-(methoxycarbonyl)octanamide,[2] *N*-methoxy-11-cyanoundecanamide.[2]

N,3,4,5-Tetramethoxybenzamide: mp 144–145 °C (AcOEt–hexane). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.71; H, 6.13; N, 5.86.

N-Methoxy-8-((diethylamino)carbonyl)octanamide: colorless oil; MS calcd for $C_{15}H_{18}N_2O_3$ 272.2099, found 272.2102.

(*Z*)-*N*-Methoxy imidoyl halides **1a–e** and **6a–h** were prepared according to the published procedure.[2] Compounds **1a,c,d** and **6b,d,e,g,h** were reported previously.[2,3a]

(*Z*)-*N*,3,4,5-Tetramethoxybenzenecarboximidoyl bromide (1b): colorless crystals; yield 97%; mp 85–87 °C (hexane); IR (KBr) 1595, 1560, 1510, 1140 cm^{-1}; NMR δ 3.85 (3 H, s, OCH_3), 3.86 (6 H, s, $OCH_3 \times 2$), 4.10 (3 H, s, $NOCH_3$), 7.03 (2 H, s, Ar H); MS *m/z* (relative intensity) 303 (M^+, 30), 305 ($M^+ + 2$, 30), 193 (100). Anal. Calcd for $C_{11}H_{14}NO_4Br$: C, 43.44; H, 4.64; N, 4.61. Found: C, 43.31; H, 4.49; N, 4.32.

(*Z*)-*N*,3,4,5-Tetramethoxybenzenecarboximidoyl chloride (1e): colorless crystals; yield 99%; mp 71–72 °C (hexane); IR (KBr) 1590, 1560, 1510, 1130 cm^{-1}; NMR δ 3.83 (3 H, s, OCH_3), 3.86 (6 H, s, $OCH_3 \times 2$), 4.10 (3 H, s, $NOCH_3$), 7.08 (2 H, s, Ar H); MS *m/z* (relative intensity) 259 (M^+, 100), 261 ($M^+ + 2$, 34), 244 (41), 193 (55). Anal. Calcd for $C_{11}H_{14}NO_4Cl$: C, 50.88; H, 5.43; N, 5.39. Found: C, 50.82; H, 5.41; N, 5.23.

(*Z*)-*N*-Methoxy-2-(2-naphthyl)ethanimidoyl bromide (6a): colorless crystals; yield 91%; mp 72–73 °C (hexane); IR (KBr) 1600, 1120, 1020 cm^{-1}; NMR δ 4.20 (5 H, s, CH_2 and $NOCH_3$), 7.12–7.67 (3 H, m, Ar H), 7.63–8.05 (4 H, m, Ar H); MS *m/z* (relative intensity) 277 (M^+, 19), 279 ($M^+ + 2$, 19), 193 (40), 141 (100). Anal. Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04. Found: C, 55.90; H, 4.43; N, 4.84.

(*Z*)-*N*-Methoxy-3-(4-acetylphenyl)propanimidoyl bromide (6c): colorless crystals; yield 86%; mp 36–37 °C (Et_2O–hexane); IR (KBr) 1690, 1680, 1650, 1040 cm^{-1}; NMR δ 2.56 (3 H, s, $COCH_3$), 2.80–3.13 (4 H, m, $CH_2 \times 2$), 3.90 (3 H, s, $NOCH_3$), 7.30 (2 H, d, J = 8.0 Hz, Ar H), 7.90 (2 H, d, J = 8.0 Hz, Ar H); MS *m/z* (relative intensity) 283 (M^+, 25), 285 ($M^+ + 2$, 24), 204 (44), 172 (89), 115 (100). Anal. Calcd for $C_{13}H_{12}NOBr$: C, 56.14; H, 4.35; N, 5.04. Found: C, 55.90; H, 4.43; N, 4.84.

(*Z*)-*N*-Methoxy-8-((diethylamino)carbonyl)octanimidoyl bromide (6f): colorless oil; yield 79%; bp 157–158 °C (1 mmHg); IR (neat) 1640, 1460, 1430, 1040 cm^{-1}; NMR δ 0.81–1.17 (16 H, m, $CH_2 \times 5$ and $CH_2CH_3 \times 2$), 2.00–2.87 (4 H, m, $CH_2 \times 2$), 3.00–3.62 (4 H, m, $CH_2CH_3 \times 2$), 3.92 (3 H, s, $NOCH_3$); MS *m/z* (relative intensity) 334 (M^+, 0.6), 336 ($M^+ + 2$, 0.6), 255 (3), 115 (100). Anal. Calcd for $C_{14}H_{27}N_2O_2Br$: C, 50.15; H, 8.12; N, 8.36. Found: C, 50.13; H, 7.89; N, 8.20.

General Procedure for Preparation of (*E*)-*N*-Methoxyarenecarboximidoyl Halides. A solution of (*Z*)-*N*,4-dimethoxybenzenecarboximidoyl bromide (**1a**) (250 mg, 1.02 mmol) in hexane (100 mL) was irradiated with a 400-W high-pressure mercury lamp through a Pyrex filter, with ice cooling for 10–20 min. The hexane solution was washed with 5% Na_2CO_3 (2 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was fractionated by column chromatography on silica gel. Elution with benzene–hexane (1:4) first afforded starting material **1a** (71 mg, 28%) followed by (*E*)-*N*,4-dimethoxybenzenecarboximidoyl bromide (**2a**) (116 mg, 46%): colorless crystals; mp 33–34 °C (hexane); IR (KBr) 1610, 1510, 1060, 840 cm^{-1}; NMR δ 3.73 (3 H, s, OCH_3), 3.88 (3 H, s, $NOCH_3$), 6.85 (2 H, d, J = 9.0 Hz, Ar H), 7.67 (2 H, d, J = 9.0 Hz, Ar H); MS *m/z* (relative intensity) 243 (M^+, 18), 245 ($M^+ + 2$, 17), 164 (48), 133 (100). Anal. Calcd for $C_9H_{10}NO_2Br$: C, 44.29; H, 4.13; N, 5.74. Found: C, 44.28; H, 4.04; N, 5.51. Further elution afforded 4-methoxybenzonitrile (**5a**) (25 mg, 18%): mp 58–59 °C (lit.[8] 59.5–60.5 °C). The yields of other (*E*)-*N*-methoxy imidoyl halides and nitriles are reported in Table I.

(*E*)-*N*,3,4,5-Tetramethoxybenzenecarboximidoyl bromide (2b): colorless crystals; mp 69–70 °C (hexane); IR (KBr) 1595, 1510, 1130, 810 cm^{-1}; NMR δ 3.83 (9 H, s, $OCH_3 \times 3$), 3.96 (3 H, s, $NOCH_3$), 6.92 (2 H, s, Ar H); MS *m/z* (relative intensity) 303 (M^+, 17), 305 ($M^+ + 2$, 17), 193 (100). Anal. Calcd for $C_{11}H_{14}NO_4Br$: C, 43.44; H, 4.64; N, 4.61. Found: C, 43.33; H, 4.52; N, 4.32.

(*E*)-*N*,4-Dimethoxybenzenecarboximidoyl chloride (2d): mp 39–40 °C (lit.[3e] mp 40–41 °C).

3,4,5-Trimethoxybenzonitrile (5b): mp 92–93 °C (lit.[9] mp 95 °C).

Catalytic Reduction of (*Z*)- or (*E*)-*N*-Methoxyarenecarboximidoyl Halides. General Procedure. (*Z*)-*N*,4-Dimethoxybenzenecarboximidoyl bromide (**1a**) (292 mg, 1.20 mmol) and Et_3N (0.2 mL, 1.44 mmol) in *t*-BuOH (6 mL) containing 58 mg of 10% Pd–C were hydrogenated at atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with AcOEt (50 mL) and H_2O (25 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude products were separated by column chromatography on silica gel. Elution with AcOEt–hexane (1:8) afforded (*E*)-4-methoxybenzaldehyde *O*-methyloxime (**3a**) (124 mg, 63%) as a colorless oil: bp 155–156 °C (53 mmHg) [lit.[10] bp 137–139 °C (22 mmHg)]. Further elution with the same solvents afforded 4-methoxybenzonitrile (**5a**) (13 mg, 8%): mp 58–59 °C (lit.[8] mp 59.5–60.5 °C). The yields of other *O*-methyloximes and nitriles are reported in Table IV.

(*Z*)-4-Methoxybenzaldehyde *O*-methyloxime (4a): colorless crystals; mp 30–31 °C; IR (KBr) 1610, 1510, 1060, 910 cm^{-1}; NMR δ 3.80 (3 H, s, OCH_3), 3.96 (3 H, s, $NOCH_3$), 6.90 (2 H, d, J = 9.0 Hz, Ar H), 7.36 (1 H, s, CH=N), 7.85 (2 H, d, J = 9.0 Hz, ArH); MS *m/z* (relative intensity) 165 (M^+, 100), 134 (51), 107 (35), 77 (44).

(*E*)-3,4,5-Trimethoxybenzaldehyde *O*-methyloxime (3b): colorless crystals; mp 78–79 °C (hexane); IR (KBr) 1570, 1235, 1130 cm^{-1}; NMR δ 3.77 (9 H, s, $OCH_3 \times 3$), 3.87 (3 H, s, $NOCH_3$), 6.70 (2 H, s, Ar H), 7.87 (1 H, s, CH=N); MS *m/z* (relative intensity) 255 (M^+, 100), 210 (58). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.80; H, 6.57; N, 5.94.

(*E*)-4-Aminobenzaldehyde *O*-methyloxime (3c): colorless oil; bp 117 °C (2 mmHg); IR (neat) 3570, 3357, 3225, 1630, 1610, 1525, 1060 cm^{-1}; NMR δ 3.73 (2 H, br s, NH_2), 3.86 (3 H, s, $NOCH_3$), 6.55 (2 H, d, J = 9.0 Hz, Ar H), 7.36 (2 H, d, J = 9.0 Hz, Ar H), 7.96 (1 H, s, CH=N); MS *m/z* (relative intensity) 150 (M^+, 100), 119 (61), 92 (71), 65 (49). To confirm the structure, **3c** was acetylated (Ac_2O–pyridine) to give (*E*)-4-acetamidobenzaldehyde *O*-methyloxime (**3d**): colorless crystals; yield 88%; mp 162–164 °C; IR (KBr) 3300, 1670, 1655, 1620, 1600, 1071 cm^{-1}; NMR δ 2.05 (3 H, s, $COCH_3$), 3.83 (3 H, s, $NOCH_3$), 7.54 (4 H, s, Ar H), 8.08 (1 H, s, CH=N), 10.00 (1 H, br s, NH); MS *m/z* (relative intensity) 192 (M^+, 96), 150 (100), 119 (74), 92 (45). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.45; H, 6.20; N, 14.51.

4-Aminobenzonitrile (5c): colorless crystals; mp 81–83 °C (lit.[11] mp 85.5–86 °C).

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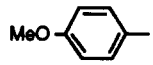
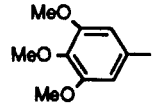
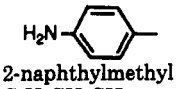
Table VI. Chemical Shifts of *O*-Methyloximes

RCH=NOMe R	CH=N (δ) *E*	CH=N (δ) *Z*	NOMe (δ) *E*	NOMe (δ) *Z*
	7.95	7.56	3.90	3.96
	7.87	7.12	3.93	4.00
	7.96	7.37	3.86	4.05
2-naphthylmethyl	7.54	6.87	3.89	3.97
$C_6H_5CH_2CH_2$	7.40	6.67	3.82	3.86
$4\text{-}AcC_6H_4CH_2CH_2$	7.33	6.63	3.80	3.83
$MeO_2C(CH_2)_7$	7.32	6.56	3.78	3.83
$Et_2NOC(CH_2)_7$	7.25	6.56	3.75	3.83
$NC(CH_2)_{10}$	7.32	6.57	3.80	3.85

Catalytic Reduction of (*Z*)-*N*-Methoxyalkanimidoyl Bromides. General Procedure. (*Z*)-*N*-Methoxy-2-(2-naphthyl)ethanimidoyl bromide (**6a**) (208 mg, 0.748 mmol) and Et_3N (0.12 mL, 0.900 mmol) in *t*-BuOH (7.5 mL) containing 6.5 mg of 10% Pd–C was hydrogenated at atmospheric pressure for 2 h. The catalyst was filtered off, the filtrate was concentrated under reduced pressure, and the residue was diluted with AcOEt (50 mL) and H_2O (25 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was chromatographed on a column of silica gel with benzene–hexane (2:1) as the eluent to give (*E*)-2-(2-naphthyl)acetaldehyde *O*-methyloxime (**7a**) (118 mg, 76%): colorless crystals; mp 30–32 °C (hexane); IR (KBr) 1600, 1510, 1100, 1045 cm^{-1}; NMR (270 MHz) δ 3.68 (2 H, d, *J* = 6.39 Hz, CH_2 × 2), 3.89 (3 H, s, $NOCH_3$), 7.34 (1 H, d, *J* = 8.41 Hz, Ar H), 7.41–7.51 (2 H, m, Ar H), 7.54 (1 H, t, *J* = 6.39 Hz, CH=N), 7.66 (1 H, s, Ar H), 7.75–7.89 (3 H, m, Ar H); MS *m/z* (relative intensity) 199 (M^+, 59), 167 (100), 141 (57). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.64; H, 6.73; N, 7.04. The yields of other (*E*)-*O*-methyloximes are reported in Tables IV and V.

(*E*)-3-Phenylpropanal *O*-methyloxime (7b): colorless oil; IR (neat) 1600, 1495, 1450, 1040 cm^{-1} NMR (270 MHz) δ 2.45–2.67 (2 H, m, CH_2), 2.82 (2 H, t, *J* = 7.9 Hz, CH_2), 3.82 (3 H, s, $NOCH_3$), 7.60–7.44 (5 H, m, Ar H), 7.40 (1 H, t, *J* = 6.2 Hz, CH=N); MS *m/z* (relative intensity) 163 (M^+, 26), 132 (11), 91 (100).

(*E*)-3-(4-Acetylphenyl)propanal *O*-methyloxime (7c): colorless oil; IR (neat) 1685, 1610, 1275, 1045 cm^{-1}; NMR δ 2.26–3.16 (4 H, m, CH_2 × 2), 2.56 (3 H, s, $COCH_3$), 3.80 (3 H, s, $NOCH_3$), 7.26 (2 H, d, *J* = 8.0 Hz, Ar H), 7.33 (1 H, t, *J* = 6.0 Hz, CH=N), 7.90 (2 H, d, *J* = 8.0 Hz, Ar H); MS *m/z* (relative intensity) 205 (M^+, 80), 190 (18), 174 (21), 146 (46), 133 (100).

(*E*)-4-Methoxyphenylacetaldehyde *O*-methyloxime (7d): colorless oil; IR (neat) 1615, 1515, 1250, 1040 cm^{-1}; NMR δ 3.45 (2 H, d, *J* = 6.8 Hz, CH_2), 3.79 (3 H, s, OCH_3), 3.85 (3 H, s, $NOCH_3$), 6.85 (2 H, d, *J* = 8.6 Hz, Ar H), 7.12 (2 H, d, *J* = 8.6 Hz, Ar H), 7.43 (1 H, t, *J* = 6.8 Hz, CH=N); MS *m/z* (relative intensity) 179 (M^+, 47) 147 (71), 132 (100).

(*E*)-8-(Methoxycarbonyl)octanal *O*-methyloxime (7e): colorless oil; IR (neat) 1740, 1440, 1200, 1170, 1060 cm^{-1}; NMR δ 1.06–1.93 (10 H, m, CH_2 × 5), 2.00–2.63 (4 H, m, CH_2 × 2), 3.63 (3 H, s, $COOCH_3$), 3.78 (3 H, s, $NOCH_3$), 7.32 (1 H, t, *J* = 6.0 Hz, CH=N); MS *m/z* (relative intensity) 215 (M^+, 1), 184 (5), 73 (100).

(*E*)-8-((Diethylamino)carbonyl)octanal *O*-methyloxime (7f): colorless oil; IR (neat) 1645, 1565, 1430, 1070 cm^{-1}; NMR δ 0.85–1.88 (16 H, m, CH_2 × 5 and CH_2CH_3 × 2), 1.92–2.55 (4 H, m, CH_2 × 2), 2.97–3.62 (4 H, m, CH_2CH_3 × 2), 3.75 (3 H, s, OCH_3), 7.25 (1 H, t, *J* = 6.0 Hz, CH=N); MS *m/z* (relative intensity) 256 (M^+, 1), 225 (37), 58 (100).

(*E*)-11-Cyanoundecanal *O*-methyloxime (7g): colorless oil; IR (neat) 2490, 2860, 1470, 1430, 1055 cm^{-1}; NMR δ 0.93–1.93 (16 H, m, CH_2 × 8), 1.96–2.56 (4 H, m, CH_2 × 2), 3.80 (3 H, s, $NOCH_3$), 7.32 (1 H, t, *J* = 6.0 Hz, CH=N); MS *m/z* (relative intensity) 224 (M^+, 0.6), 193 (2), 73 (100).

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The chemical shifts of CH=N and OCH_3 are summarized in Table VI.

3-Phenylpropanal *O*-methyloxime: bp 95 °C (4 mmHg). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03, N, 8.58. Found: C, 73.68; H, 8.13; N, 8.64.

3-(4-Acetylphenyl)propanal *O*-methyloxime: bp 130–132 °C (2 mmHg). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.37; N, 6.64.

(4-Methoxyphenyl)acetaldehyde *O*-methyloxime: bp 84–86 °C (4 mmHg). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.13; H, 7.17; N, 7.67.

8-(Methoxycarbonyl)octanal *O*-methyloxime: bp 113–114 °C (3 mmHg). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.38; H, 9.61; N, 6.24.

8-((Diethylamino)carbonyl)octanal *O*-methyloxime: bp 137–138 °C (2 mmHg). Anal. Calcd for $C_{14}H_{28}N_2O_2$: C, 65.59; H, 11.01; N, 10.93. Found: C, 65.68; H, 10.73; N, 10.67.

11-Cyanoundecanal *O*-methyloxime: bp 126 °C (3 mmHg). Anal. Calcd for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.41; H, 10.59; N, 12.30.

Registry No. **1a**, 140462-99-3; **1b**, 140463-00-9; **1c**, 97315-84-9; **1d**, 57139-36-3; **1e**, 140463-01-0; **2a**, 140463-02-1; **2b**, 140463-03-2; **2c**, 57139-29-4; **3a**, 70286-37-2; **3b**, 140463-12-3; **3c**, 140463-13-4; **3d**, 140463-14-5; **4a**, 87861-04-9; **5a**, 874-90-8; **5b**, 1885-35-4; **5c**, 873-74-5; **6a**, 140463-04-3; **6b**, 140463-05-4; **6c**, 140463-06-5; **6d**, 140463-07-6; **6e**, 140463-08-7; **6f**, 140463-09-8; **6g**, 140463-10-1; **6h**, 140463-11-2; **7a**, 140463-15-6; **7b**, 140463-16-7; **7c**, 140463-17-8; **7d**, 140463-18-9; **7e**, 140463-19-0; **7f**, 140463-20-3; **7g**, 140463-21-4; *N*,3,4,5-tetramethoxybenzamide, 25563-19-3; *N*-methoxy-2-naphthaleneacetamide, 113519-26-9; 3-(4-acetoxyphenyl)-*N*-methoxypropanamide, 140463-22-5; 8-[(diethylamino)-carbonyl]-*N*-methoxyoctanamide, 140463-23-6.

Supplementary Material Available: Listings of crystal structure data, positional and thermal parameters, and bond distances and angles for **6a** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of 13-*epi*-22,23-Dihydroavermectin B_1 Aglycon

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Introduction

The avermectins are naturally occurring macrocyclic lactones with important anthelmintic and pesticidal activity.[1] The structural novelty of avermectins and the closely related milbemycins has attracted the attention of a number of synthetic organic chemistry groups. The avermectin aglycones contain an interesting sterically constrained C_{13} α-allylic and homoallylic hydroxy group. In an effort to improve the biological profile of avermectins, several analogues of 22,23-dihydroavermectin B_1 aglycon have been prepared by modification at C_{13},[2] including analogues with the stereochemistry at C_{13} inverted from the configuration found in avermectin.[3] Inversion of stereochemistry at C_{13} provides analogues with an improved safety profile while maintaining good activity.[3] Therefore, 13-β analogues have been prepared, but by an indirect process of solvolysis of 13-β iodo analogues.[2,3] Whereas replacement of suitably modified α-leaving groups

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