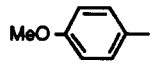
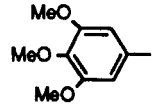
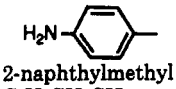
Table VI. Chemical Shifts of *O*-Methyloximes

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).

(11) Bogert, M. T.; Kohnstamm, L. *J. Am. Chem. Soc.* **1903**, *25*, 478.

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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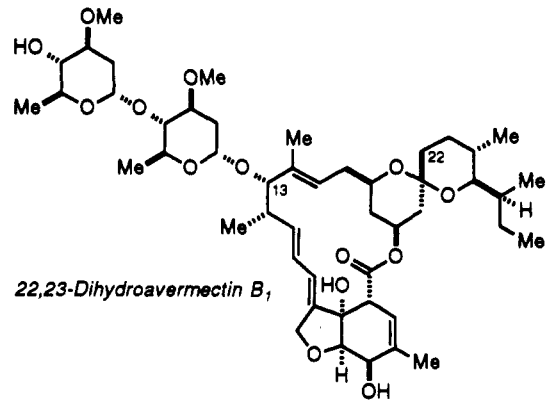


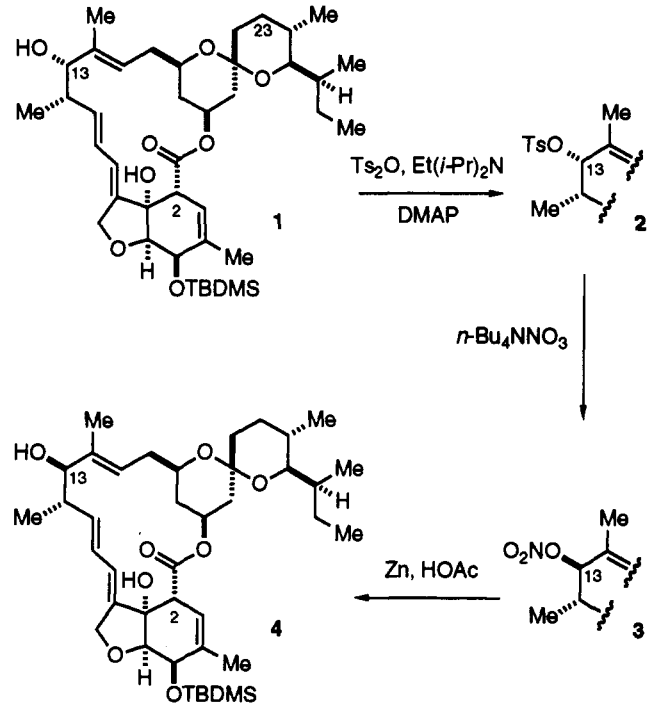
with good nucleophiles readily provides 13-β halogen or thio derivatives, oxygen nucleophiles are generally too basic to react without rearranging the base-sensitive C_2 stereochemistry. Several procedures for introducing the C_{13} hydroxy group into milbemycins provide exclusively 13-β products,[4] while reduction of the 13-ketone gives exclusively the 13-α alcohol. This paper describes a procedure for the inversion of stereochemistry at C_{13}.

Discussion

Previously, the inversion of stereochemistry at C_{13} was accomplished by tosylation, displacement with iodide, and silver-assisted solvolysis of the iodide in tetrahydrofuran/water.[2] This procedure suffered from a low overall yield and a difficult separation of the desired product from the major rearrangement byproduct, 13(14)-*en*-15-hydroxy-22,23-dihydroavermectin B_1 aglycon. Oxidation/reduction schemes to generate 13-*epi*-22,23-dihydroavermectin B_1 aglycon failed, as the predominant product of reduction was 22,23-dihydroavermectin B_1 aglycon. Attempted inversion of this hindered alcohol using a Mitsunobu reaction[5] resulted in no reaction.

It has been reported[6] that displacement with an oxygen nucleophile, nitrate, occurs without elimination in some sensitive systems. We therefore investigated displacement of the tosylate of 5-*O*-(*tert*-butyldimethylsilyl)-22,23-dihydroavermectin B_1 aglycon, **1**. The tosylate,[2] **2**, was prepared as shown in Scheme I from **1** with *p*-toluenesulfonic anhydride, *N*,*N*-diisopropylethylamine, and DMAP in CH_2Cl_2 at room temperature. The tosylate was not stable to chromatography and was extractively isolated and used crude in subsequent reactions. Dissolution of **2** in toluene followed by addition of 3 equiv of tetra-*n*-butylammonium nitrate, warming to 40 °C, and stirring for 96 h resulted

Scheme I



in a 57% yield of chromatographically homogeneous inverted nitrate ester. At elevated temperatures, the yields were lower (50 °C, 10 h, 54%; 90 °C, 2 h, 40%). The identity of the nitrate ester was secured by EIMS (M^+ = 745) and NMR data (nitrate ester: H_{13} = d, J = 10.6 Hz, at 4.95 ppm, C_{13} = 93.1 ppm; aglycon: H_{13} = br s, 3.97 ppm, C_{13} = 77.2 ppm). The crude nitrate ester was contaminated with ~5% of a mixture of unknown products.[7] The purified nitrate ester was reduced at room temperature to the inverted alcohol with activated zinc[6] in tetrahydrofuran/acetic acid (6:1) in 88% yield. The temperature of the reduction must be monitored since this reaction is exothermic. The 13-*epi*-22,23-dihydroavermectin B_1 aglycon isolated after chromatography (50% overall) was free from elimination and rearrangement products.

In summary, this activation/displacement/reduction provides a means of generating 13-*epi*-22,23-dihydroavermectin B_1 aglycon, free from isomeric impurities, from the very sensitive 22,23-dihydroavermectin B_1 aglycon in reasonable overall yield. This procedure has also been successfully applied to suitably protected avermectin B_1 and B_2 derivatives.[8]

Experimental Section

General. Analytical thin-layer chromatography (TLC) was performed on EM Reagents 0.25-mm silica gel 60-F plates. Visualization was accomplished with UV light and by dipping in an aqueous ceric ammonium molybdate solution followed by heating. Column chromatography was performed with EM Science silica gel (40–63 μm). Solvents used for extraction were reagent grade. Solvents used for reactions were dried with 3- or 4-Å molecular sieves. All reactions were performed under an inert atmosphere of dry nitrogen in dry glassware. ^1H NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 (299.94-MHz) spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 (75.4-MHz) spectrometer. Chemical shifts are

(1) (a) Blizzard, T.; Fisher, M. H.; Mrozik, H.; Shih, T. L. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin-Heidelberg, 1990; pp 65–102. (b) Fisher, M. H.; Mrozik, H. In *Macrolide Antibiotics*; Omura, S. Ed.; Academic Press: New York, 1984; Chapter 14, pp 553–606. (c) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87–121.

(2) Mrozik, H.; Linn, B. O.; Eskola, P.; Lusi, A.; Matzuk, A.; Preiser, F. A.; Ostlind, D. A.; Schaeffer, J. M.; Fisher, M. H. *J. Med. Chem.* **1989**, *32*, 375–381.

(3) Blizzard, T. A.; Margiatto, G. M.; Mrozik, H.; Shoop, W. L.; Frankshun, R. A.; Fisher, M. H. *J. Med. Chem.*, in press.

(4) (a) Frei, B.; Huxley, P.; Maienfisch, P.; Mereyala, H. B.; Rist, G.; O'Sullivan, A. C. *Helv. Chim. Acta* **1990**, *73*, 1905–17. (b) Ramos, G. M.; Ghisalba, O.; Shär, H.-P.; Frei, B.; Maienfisch, P.; O'Sullivan, A. C. *Agric. Biol. Chem.* **1989**, *53*, 1531–5. (c) Sato, K.; Yanai, T.; Kinoto, T.; Mio, S. EP 184,308 A1; *Chem. Abstr.* **1987**, *106*, 67005.

(5) Mitsunobu, O. *Synthesis* **1981**, 1–28. See also: Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.

(6) (a) Cainelli, G.; Manescalchi, F.; Martelli, G.; Panunzio, M.; Plessi, L. *Tetrahedron Lett.* **1985**, *26*, 3369–3372. (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron* **1985**, *41*, 1385–1392.

(7) ^1H and ^{13}C NMR spectra indicate that the impurities (<5% isolated) are inverted at C_{13}; mass spectra predominantly show only elimination of the group attached to C_{13}. A trace (<1%) of elimination product has been observed and identified.

(8) Frankshun, R. F.; Waksmunski, F.; Mrozik, H. Unpublished results.

reported in ppm from the central peak of $CDCl_3$ (77.0 ppm) (J values are given in Hz). Assignments were made with the aid of APT data. Combustion analyses were obtained from Microlit Laboratories, Inc., Caldwell, NJ.

5-*O*-(*tert*-Butyldimethylsilyl)-13-*O*-(*p*-toluenesulfonyl)-22,23-dihydroavermectin B_1 Aglycon (2). A 25-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 1 (1.28 g, 1.82 mmol), *p*-toluenesulfonic anhydride (1.19 g, 3.65 mmol), *N,N*-diisopropylethylamine (0.95 mL, 0.70 g, 5.5 mmol), DMAP (445 mg, 3.65 mmol), and CH_2Cl_2 (5.1 mL). The resulting solution was stirred at 20 °C for 24 h. (The tosylation can be monitored by removing a 20-μL aliquot, dissolving it in 0.6 mL of $CDCl_3$, obtaining a ^1H NMR, and integrating the signal for H_{13}. H_{13} of 1: 3.98 (br s). H_{13} of 2: 4.82 (br s)). The resulting mixture was cooled to 0 °C, and hexane (10.2 mL) was added followed by aqueous $NaHSO_4$ (10 mL, 1 N) at a rate to maintain the internal temperature at or below 5 °C (~10 min). The resulting pH was ~2. The layers were separated, and the aqueous layer was extracted with 2:1 hexane/CH_2Cl_2 (15 mL). The organic layers were individually washed with 15 mL of saturated aqueous $NaHCO_3$ and 15 mL of water. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to provide 2 (~2 g, impure) as an orange solid. This material was used as is in subsequent reactions after concentrating it from dry toluene (2 × 10 mL).

5-*O*-(*tert*-Butyldimethylsilyl)-13β-nitrooxy-22,23-dihydroavermectin B_1 Aglycon (3). A 25-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 2 (~2 g, see above, ~1.82 mmol, crude mixture from previous experimental procedure), tetra-*n*-butylammonium nitrate (1.66 g, 5.45 mmol), and toluene (8 mL). The resulting solution was stirred at 40 °C for 96 h. (The displacement can be monitored by TLC: R_f (starting material) = 0.40; R_f (nitrate ester) = 0.57 in 4:1 hexane/ethyl acetate). The resulting mixture was cooled to 20 °C, concentrated to ~3 mL, and chromatographed twice (5 × 30 cm column; 92:8 hexane/ethyl acetate) to provide 3 (774 mg, 57%). The impurities have slightly higher R_f's than the desired nitrate ester (ΔR_f ~0.07 in 92:8 hexane/ethyl acetate). NMR analysis of the isolated three-component impurity mixture (~5%) was complicated since the individual componenents of this mixture were not readily separable from each other. Data for 3: ^1H NMR δ 5.85 (dd, J = 14.3, 11.4, H_{10}), 5.60 (dt, J = 11.3, 1.9, H_9), 5.42 (m, H_{15}), 5.30 (m, H_3, H_{11}), 5.20 (m, H_{19}),4.95 (d, J = 10.6, H_{13}), 4.65 (dd, J = 14.4, 1.9, H_{8a}), 4.54 (dd, J = 14.4, 1.9, H_{8a}), 4.40 (m, H_5), 4.00 (s, OH), 3.79 (d, J = 5.5, H_6), 3.60 (m, H_{17}), 3.32 (m, H_2), 3.14 (m, H_{25}), 2.55 (m, H_{12}), 2.30 (m, 2 × H_{16}), 1.99 (dd, J = 11.8, 3.6, H_{20eq}), 1.77 (br s, 3 × H_{4a}), 1.55 (s, 3 × H_{14a}), 1.10 (d, J = 6.5, H_{12a}), 0.94 (t, J = 7.3, 3 × H_{28}), 0.90 (s, $SiC(CH_3)_3$), 0.82 (d, J = 6.6, H_{26a}), 0.10 (s, $Si(CH_3)_2$); ^{13}C NMR δ_C 173.6 (C_1), 142.5, 137.5, 133.3 (C_4, C_8, C_{14}), 135.4 (C_{11}), 129.0, 125.5, 118.7, 117.3 (C_3, C_9, C_{10}, C_{15}), 97.5 (C_{21}), 93.1 (C_{13}), 80.2 (C_6), 80.1 (C_7), 77.4 (C_{25}), 69.3, 68.6, 66.6 (C_5, C_{17}, C_{19}), 67.7 (C_{8a}), 45.6 (C_2), 42.3 (C_{20}), 38.3 (C_{12}), 36.6, 35.7, 34.7 (C_{18}, C_{22}, C_{26}), 35.7 (C_{16}), 31.2 (C_{24}), 28.0, 27.5 (C_{23}, C_{27}), 25.6 ($SiC(CH_3)_3$), 20.1, 18.8, 17.5 (C_{4a}, C_{12a}, C_{24a}), 12.6, 11.7, 11.0 (C_{14a}, C_{26a}, C_{28}); MS (EI, 70 eV) 745 (M^+, 5), 503 (18), 307 (30), 225 (30), 223 (32), 195 (70), 151 (72) 137 (72), 95 (100), 75 (70), 73 (80), 69 (66). Anal. Calcd for $C_{40}H_{63}NO_{10}Si$: C, 64.40; H, 8.51; N, 1.88. Found: C, 64.14; H, 8.58; N, 1.79.

5-*O*-(*tert*-Butyldimethylsilyl)-13-*epi*-22,23-dihydroavermectin B_1 Aglycon (4). Zinc (~1 g) was stirred for 5 min in 1 N HCl, filtered, and washed with water (3 × 10 mL; final pH of wash >6), MeOH (2 × 10 mL), and toluene (2 × 5 mL). The resulting material was air dried, and a portion of it was used in the following reduction. A 15-mL flask fitted with a nitrogen inlet tube and Teflon-coated stirring bar was charged with 3 (513 mg, 0.688 mmol), tetrahydrofuran (4.3 mL), and acetic acid (0.7 mL). The solution was stirred in a water bath at 20 °C, and Zn (450 mg, 6.88 mmol, see above) was added in one portion. The resulting suspension was stirred for 10 min as the temperature rose to 25 °C. (The reduction can be monitored by TLC: R_f (nitrate ester) = 0.57; R_f (β-alcohol) = 0.29; R_f (α-alcohol) = 0.19 in 4:1 hexane/ethyl acetate). The resulting mixture was filtered through a coarse glass frit, and the solids were washed with 3 × 7 mL of EtOAc. The washings were combined and cautiously washed with saturated aqueous $NaHCO_3$ (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated, and chromatographed (3 × 30-cm column; 80:20 hexane/ethyl acetate) to provide 4 (425 mg, 88%). The sample of 4 prepared in this manner was identical (TLC, ^1H, ^{13}C NMR) to that previously reported:[2a] ^1H NMR δ 5.75 (m, H_9, H_{10}), 5.30 (m, H_3, H_{11}), 5.20 (m, H_{15}, H_{19}), 4.65 (dd, J = 14.4, 1.9, H_{8a}), 4.54 (dd, J = 14.4, 1.9, H_{8a}), 4.42 (m, H_5), 3.98 (OH), 3.78 (d, J = 5.5, H_6), 3.70 (d, J = 10.0, H_{13}), 3.55 (m, H_{17}), 3.35 (m, H_2), 3.15 (m, H_{25}), 2.35 (m, H_{12}), 1.78 (s, 3 × H_{4a}), 1.55 (s, 3 × H_{14a}), 1.12 (d, J = 6.5, 3 × H_{12a}), 0.94 (t, J = 7.3, 3 × H_{28}), 0.90 (s, $SiC(CH_3)_3$), 0.82 (d, J = 6.6, H_{26a}), 0.10 (s, $Si(CH_3)_2$); ^{13}C NMR δ_C 173.8 (C_1), 140.9, 140.2, 137.4 (C_4, C_8, C_{14}), 138.6 (C_{11}), 123.9, 123.3 (C_9, C_{10}), 119.3, 117.4 (C_3, C_{15}), 97.5 (C_{21}), 83.4 (C_{13}), 80.3 (C_6), 80.1 (C_7), 77.1 (C_{25}), 69.4, 68.7, 67.1 (C_5, C_{17}, C_{19}), 68.0 (C_{8a}), 45.7 (C_2), 41.6 (C_{12}), 41.4 (C_{20}), 36.5, 35.7, 34.5 (C_{16}, C_{18}, C_{22}), 35.5 (C_{26}), 28.1, 27.4 (C_{23}, C_{27}), 25.9 ($SiC(CH_3)_3$)), 20.1, 19.0, 17.5 (C_{4a}, C_{12a}, C_{24a}), 18.4 ($SiC(CH_3)_3$)), 12.5, 11.9, 10.6 (C_{14a}, C_{26a}, C_{28}). Anal. Calcd for $C_{40}H_{64}O_8Si$: C, 68.53; H, 9.20. Found: C, 68.15; H, 9.28.

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Vinylformylation Utilizing Propeniminium Salts

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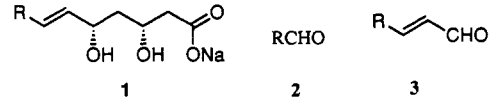
In our efforts to find a practical and efficient method toward a commercial synthesis of dihydroxyheptenoates 1,[1] which are HMG-CoA reductase inhibitors, we investigated two alternative routes. One, a linear strategy,[1] involved the use of dianions derived from acetoacetates and the other, a convergent method,[2] utilized a six-carbon synthon. Trans-α,β-unsaturated aldehydes of the type 3 are used as key intermediates in the linear strategy at Sandoz[1] and by other groups.[3] The need to produce these aldehydes in kilogram quantities led us to a detailed investigation of the Vilsmeier–Haack conditions for vinylformylation, utilizing propeniminium salts as three-carbon synthons.[4]



1 2 3

Earlier reports[5] elaborate on the preparation of α,β-unsaturated aldehydes 3 from aldehydes 2. Concurrent with these studies was a report involving the 2-formylation of substituted indoles.[6] When subjected to $POCl_3$/DMF (Vilsmeier–Haack reagent), 4 gave **4b**, in moderate yield,

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