°C. After addition was complete, the mixture was allowed to warm to 0 °C and then poured into 500 mL of cold 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with 500 mL of saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The resulting oil (110 g) was homogeneous by silica gel TLC (R_f 0.55, EtOAc) and was used directly.

Bis(methanesulfonate) **3**[11] was dissolved in benzylamine (250 mL) and allowed to stand at ambient temperature for 96 h. The mixture (from which benzylammonium methanesulfonate had crystallized) was transferred to 1 L of cold 2 N NaOH, and the resulting solution was extracted with pentane (4 × 400 mL). The combined organic layers were concentrated and distilled to afford 64.9 g of **4** as a clear oil, bp 83–84 °C (2 mm).

A forerun containing benzylamine was filtered through alumina (activity I), eluting with 10% Et_2O/hexane. Concentration of the eluate afforded an additional 1.3 g of **4** for a total yield of 66.2 g (89%): $[\alpha]^{24}_D$ −109.7° (*c* 1.97, MeOH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (d, 6 H, *J* = 6.1 Hz), 1.25–1.45 (m, 2 H), 1.85–2.05 (m, 2 H), 2.90–3.04 (m, 2 H), 3.46 and 3.79 (AB q, 2 H, J_{AB} = 13.8 Hz), 7.12–7.37 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 16.9, 30.9, 51.6, 54.9, 126.3, 128.0, 128.3, 140.8; mass spectrum (70 eV) *m/z* (relative intensity) 190 (M + H, <1), 189 (M^+, 4), 174 (58), 91 (100).

(−)-(2*R*,5*R*)-2,5-Dimethylpyrrolidine (1). *N*-Benzylpyrrolidine **4** (39.3 g, 0.21 mol) was dissolved in glacial acetic acid (75 mL). The solution was transferred to a 500-mL Parr bottle, and 10% $Pd(OH)_2$ on carbon (2 g) was added. The mixture was shaken under H_2 (30–40 psig) for 36 h and filtered, and the catalyst was washed with methanol (2 × 10 mL). The filtrate was concentrated at 0 °C under vacuum (ca. 1 mm), and the resulting viscous oil was diluted with water (50 mL) and Et_2O (100 mL). At 0 °C, 50% NaOH (50 mL) was added dropwise over 30 min. The aqueous solution was extracted with ether (4 × 100 mL), and the combined organic layers were dried over KOH pellets. Ether was removed by careful fractional distillation, and the product was collected at 102–103 °C as a clear liquid (18.6 g). A small forerun was acidified with ethereal HCl, and 0.91 g of the amine was collected as the hydrochloride salt. The total yield was 19.5 g (94%) of **1**: ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (d, 6 H, *J* = 6.2 Hz), 1.20–1.40 (m, 3 H), 1.85–2.10 (m, 2 H), 3.20–3.40 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.2, 34.7, 53.2.

1·HCl: mp 200–203 °C; $[\alpha]^{24}_D$ + 5.57° (*c* 1.18, CH_2Cl_2) [lit.[7] mp 197–200 °C, $[\alpha]_D$ +5.47° (*c* 3.0, CH_2Cl_2)]; ^1H NMR (300 MHz, $CDCl_3$)[12] δ 1.52 (d, 6 H, *J* = 7.2 Hz), 1.55–1.80 (m, 2 H), 2.10–2.30 (m, 2 H), 3.75–3.90 (m, 2 H), 9.50–9.80 (br s, 2 H).

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Registry No. 1, 62617-70-3; 1·HCl, 70144-18-2; (*S*,*S*)-**2**, 34338-96-0; (*R*,*S*)-**2**, 38484-55-8; **3**, 119008-52-5; **4**, 119008-53-6; 2,5-hexanedione, 110-13-4; benzylamine, 100-46-9.

(11) Racemate: Jones, A. R. *J. Chem. Soc., Chem. Commun.* **1971**, 1042.

(12) The discrepancy between our ^1H NMR data for **1·HCl** and that previously reported is apparently due to typographical errors in ref 4b and 7.

An Improved Preparation of the Avermectin Disaccharide Unit

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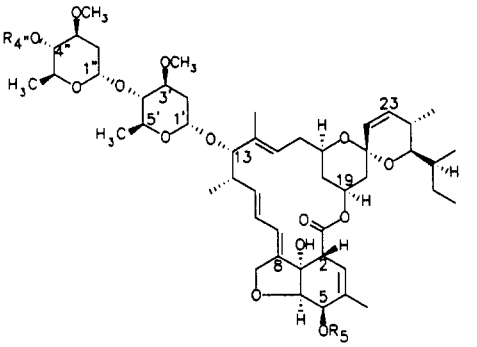
The avermectins and milbemycins are naturally occurring macrocyclic lactones with important anthelmintic and pesticidal activity.[1] The avermectins differ from the milbemycins primarily in the incorporation of a disaccharide (oleandrosyloleandrose) unit attached through an oxygen atom at position 13 of the macrocyclic ring. The extremely high antiparasitic activity of the avermectins has generated considerable interest in the synthesis of these compounds.[2] These synthetic efforts have been highlighted by the recent total synthesis of avermectin A_1 (**1a**) by Danishefsky et al.[2a,b] and the synthesis of avermectin B_1 (**1b**) by Hanessian et al.[2c,d] An important



1a $R_{4''}$ = H , R_5 = CH_3
1b $R_{4''}$ = R_5 = H
1c $R_{4''}$ = R_5 = TBDMS

consideration in the planning of an avermectin synthesis is the source of the requisite disaccharide unit (**2**). Danishefsky and co-workers solved this problem by devising a total synthesis of **2** (10 steps from acetaldehyde to the glycal analogue of 2-4″-acetate).[2b] Other total syntheses of derivatives of **2** have been developed by Nicolaou,[3a] by Wuts,[3b] and by Barrett.[3c] An alternative method is to prepare **2** by chemical degradation of a naturally occurring avermectin. This was the approach used by Hanessian and co-workers to prepare **2** (five steps from avermectin B_1)[3d] required for their synthesis of avermectin B_1.[2c,d] This method appears to be more convenient when large amounts of material are required for synthesis of avermectin analogues from aglycone derivatives, provided one has access to a large supply of natural avermectin B_1. We therefore focused on this approach when we required material for a program of avermectin analogue synthesis.

The method used by Hanessian et al.[3d] to prepare **2** involved five steps and was apparently designed primarily

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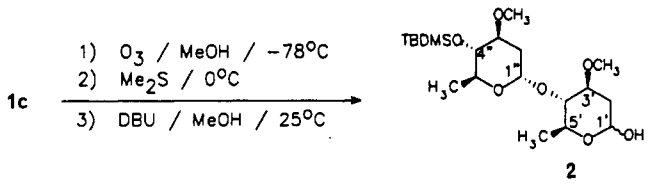
0022-3263/89/1954-1756$01.50/0

Scheme I



to provide a source of aglycon fragments to be used in a relay synthesis. Their route started with base-catalyzed saponification of avermectin B_1 followed by diazomethane esterification. The resulting seco-acid ester was then silylated and treated with one equivalent of ozone ($NaBH_4$ workup) to cleave the 10,11 double bond.[3e] The northern half fragment was isolated and oxidized (PCC) to an aldehyde. The aldehyde was isolated and treated with a strong base ($KN(TMS)_2$) to effect β-elimination of the disaccharide **2**. Although **2** can be obtained by this approach a more direct route involving fewer isolation and chromatography steps would require less time and would be much more convenient. Examination of the Hanessian route revealed that the saponification–esterification step could be eliminated from the sequence. Furthermore, a methyl sulfide workup (rather than $NaBH_4$ workup) of the ozonolysis reaction would afford a suitable aldehyde directly, thus eliminating the need for the PCC oxidation. Finally, isolation of the aldehyde fragment should not be necessary since it should be possible to effect β-elimination in situ by adding a strong base to the reaction mixture. We therefore concluded that the five-step sequence could be reduced to only two steps (silylation followed by a one-pot ozonolysis–elimination sequence). This modified procedure would afford the disaccharide more directly (albeit at the cost of total destruction of the aglycone portion) and would thus require less time than the previous method. We are pleased to report that the shorter route does in fact work quite well and describe the details herein.

A methanol solution of 4″,5-bis-*O*-(TBDMS)avermectin B_1 (**1c**, prepared in one step from avermectin B_1 using the published procedures)[4] was treated sequentially (one pot) with ozone, methyl sulfide, and DBU (Scheme I, see Experimental Section for details). After workup and chromatography the desired disaccharide derivative **2** was obtained in 57% yield from **1c**. The ozonolysis–elimination sequence (starting from **1c**) can be carried out in a single day and is amenable to preparation of reasonably large amounts of **2**. Thus our improved procedure is considerably more convenient than the previous procedures.[5] Future publications from this laboratory will describe the use of **2** in the synthesis of several interesting avermectin analogues.

Experimental Section

Proton (^1H) NMR spectra were measured in $CDCl_3$ solution at 300 MHz on a Varian XL-300 instrument. Chemical shifts are reported in δ units with the 7.24 ppm resonance of residual chloroform as an internal standard. Signal assignments were made with the assistance of ^1H–^1H correlation spectroscopy (COSY). Mass spectra were measured on a Varian MAT 731 instrument.

4′-*O*-[4″-*O*-(*tert*-Butyldimethylsilyl)oleandrosyl]oleandrose (2). Ozone (in a stream of oxygen from a Wellsbach ozone generator) was bubbled through a cold (−78 °C) solution of 2.75 g (2.5 mmol) of 4″,5-bis-*O*-(TBDMS)avermectin B_1 (**1c**)[4] in 40 mL of methanol until the blue ozone color persisted (ca. 13 min). Nitrogen gas was then bubbled through the solution for 2 min (blue color disappeared). Methyl sulfide (1.28 mL, 17.5 mmol) was added, and the solution was warmed to 0 °C. The solution was stirred at 0 °C for 50 min, and then 1.87 mL (12.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The solution was warmed to room temperature and stirred for 2 h. The dark (almost black) solution was then partitioned between ether (100 mL) and 0.5 N HCl (40 mL). The aqueous layer was extracted with ether (50 mL), and the combined organic layers were washed sequentially with 2% $NaHCO_3$ (25 mL) and saturated NaCl (25 mL), dried ($MgSO_4$), filtered, and evaporated to an amber oil (2.30 g). Analytical TLC (silica gel, eluted with 3.5% methanol in methylene chloride, stained with 4% ethanolic phosphomolybdic acid and charred) of this crude product showed only one major product spot (R_f 0.26) plus a few minor spots in addition to baseline material. The crude product was purified by flash chromatography[6] (50 mm column, 8 in. of 230–400 mesh silica gel, eluted with 3.5% methanol in methylene chloride). The fractions containing the desired product (R_f 0.26) were combined and evaporated to a light yellow oil (0.815 g). This material was further purified by flash chromatography (50-mm column, 7 in. of 230–400 mesh silica gel, eluted with 3:2 hexane–ether). The fractions containing the desired product (R_f 0.16) were combined and evaporated to a colorless oil (0.603 g, analytically pure, 57% yield from **1c**), which is a 2:1 mixture of the 1′-α and -β anomers of 4′-*O*-[4″-*O*-(*tert*-butyldimethylsilyl)oleandrosyl]oleandrose (**2**): ^1N NMR (300 MHz, $CDCl_3$) δ 5.32 (0.66 H, br s, $H_{1'}$ (1′-α-anomer)), 5.29 (1 H, d, J = 3 Hz, $H_{1''}$), 4.77 (0.34 H, ddd, J = 9, 7, 2 Hz, $H_{1'}$ (1′-β-anomer)), 3.90 (0.66 H, dq, J = 9, 6 Hz, $H_{5'}$ (1′-α-anomer)), 3.73–3.58 (1.66 H, m, $H_{3'}$ (1′-α-anomer) + $H_{5''}$), 3.38–3.25 (1.68 H, m, $H_{5'}$ (1′-β-anomer) + $H_{3'}$ (1′-β-anomer) + $H_{3''}$), 3.35 (3 H, s, 3″-OCH_3), 3.30 (1.98 H, s, 3′-OCH_3 (1′-α-anomer)), 3.29 (1.02 H, s, 3′-OCH_3 (1′-β-anomer)), 3.20 (0.34 H, dd, J = 9, 9 Hz, $H_{4'}$ (1′-β-anomer)), 3.19 (0.66 H, dd, J = 9, 9 Hz, $H_{4'}$ (1′-α-anomer)), 3.11 (1 H, dd, J = 9, 9 Hz, $H_{4''}$), 3.05 (0.34 H, d, J = 7 Hz, OH (1′-β-anomer)), 2.52 (0.66 H, dd, J = 2, 2 Hz, OH (1′-α-anomer)), 2.39 (0.34 H, ddd, J = 12, 5, 2 Hz, $H_{2'eq}$ (1′-β-anomer)), 2.31–2.21 (1.66 H, m, $H_{2'eq}$ (1′-α-anomer) + $H_{2''eq}$), 1.56–1.37 (2 H, m, $H_{2'ax}$ + $H_{2''ax}$), 1.32 (1.02 H, d, J = 6 Hz, $H_{6'}$ (1′-β-anomer)), 1.26 (1.98 H, d, J = 6 Hz, $H_{6'}$ (1′-α-anomer)), 1.19 (3H, d, J = 6 Hz, $H_{6''}$), 0.87 (s, 9 H, ^{t}BuSi), 0.07 and 0.05 (6 H, 2 s, $Si(Me)_2$); FAB mass spectrum, m/e 427 (M + Li); Anal. Calcd for $C_{20}H_{40}O_7Si$: C, 57.11; H, 9.56. Found: C, 57.47; H, 9.70.

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Registry No. **1c**, 81924-42-7; α-**2**, 119245-51-1; β-**2**, 119245-52-2.

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(5) Note that this procedure should work equally well with the minor components (such as avermectin B_2 and the avermectin A series) isolated from fermentation of *S. avermitilis*. In principle, the procedure could also be used to prepare 4-*O*-TBDMS-oleandrose by using 4″,5-bis-*O*-(TBDMS)avermectin B_1 monosaccharide as the starting material.

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1,1-Bis(methylthio)-2-(phenylsulfonyl)ethene: A Useful Ketene Anion Enolate Synthon

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Sulfur-stabilized acyl anion equivalents and their Michael-accepting homologues are very useful reagents in organic synthesis.[1] For example, 2-lithio-1,3-dithiane,[2] the

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