hydrogen atoms are more reactive at low NO_2 concentrations relative to simple alkenes. This may be of particular importance in biological systems, where polyunsaturated fatty acids are vital to the integrity of lipid membranes.

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Registry No. H_2, 1333-74-0; NO_2, 10102-44-0; N_2O_4, 10544-72-6; O_2, 7782-44-7; cyclohexene, 110-83-8; cyclopentene, 142-29-0; 1,4-hexadiene, 592-45-0; 2,3-dimethyl-2-butene, 563-79-1; 2,5-dimethyl-2,5-hexadiene, 927-97-9; allyl cyanide, 109-75-1; 3,3-dimethyl-3-phenylpropene, 18321-36-3; allyl chloride, 107-05-1; 3,3-dimethyl-1-butene, 558-37-2; allyl bromide, 106-95-6; 1-octene, 111-66-0; 1-hexene, 592-41-6; methyl oleate, 112-62-9; cyclooctene, 931-88-4; α-pinene, 80-56-8; β-pinene, 127-91-3; norbornene, 498-66-8; 2-methyl-2-pentene, 625-27-4; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3; allylbenzene, 300-57-2.

Studies on the Deconjugation–Epimerization Strategy en Route to Avermectin B_{1a}: Problems and Solutions

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Abstract: A method is presented whereby Δ^2-4(*R*)-avermectin B_{1a} is converted in a two-step process into avermectin B_{1a}, first by deconjugation to 2-epiavermectin B_{1a} and then by partial epimerization in the presence of imidazole.

Since their discovery,[1] the avermectins have been the subject of intensive investigations on several fronts.[2,3] Our studies[4] in this area have focused on the development of strategies and methodology for the synthesis of appropriate optically pure subunits. A culminating point in such synthetic studies was the first synthesis[5] of avermectin B_{1a} (**1**) (Scheme I) from a totally synthetic C_{11}–C_{28} extended spiroacetal subunit and an oxahydrindene derivative obtained from the degradation of the natural product.[6,7] Because of the tendency for aromatization of the oxahydrindene subunit, our original strategy was based on producing a Δ^2-avermectin derivative such as **7** or **8** and effecting a critical deconjugation to the desired target in a penultimate step based on known precedents.[8,9] We had reasoned[4,5] that upon treatment with acid a dienolate species or the ketene acetal intermediate

Scheme I

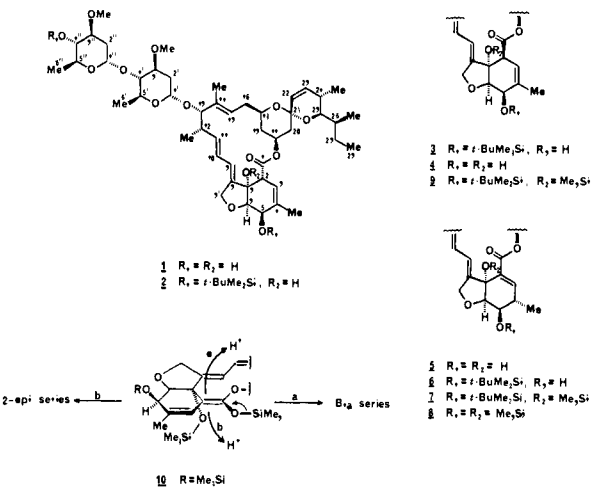

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Table I

entry	avermectin B_{1a} deriv or isomer	conditions	B_{1a}[l,m]	2-epi	Δ^2
1	**3**, 2-epi, di-OTBDMS	25% imidazole, benzene[a]	36 (33)	50 (44)	14 (13)
2	**3**, 2-epi, di-OTBDMS	25% imidazole, acetonitrile[b]	34	46	20
3	**4**, 2-epi, triol	25% imidazole, benzene[c]	47 (40)	42 (34)	11 (8)
4	**1**, B_{1a}, triol	25% imidazole, benzene[c]	49	42	9
5	**3**, 2-epi, di-OTBDMS	5 equiv of DBU, dichloroethane[d]	10	65	25
6	**3**, 2-epi, di-OTBDMS	5 equiv of DBU, methanol[e]	15	58	27
7	**3**, 2-epi, di-OTBDMS	0.032 M NaOMe, methanol[f]	22	56	22
8	**2**, B_{1a}, di-OTBDMS	0.032 M NaOMe, methanol[g]	27	56	17
9	**4**, 2-epi, triol	0.032 M NaOMe, methanol[h]	34	43	23
10	**1**, B_{1a}, triol	0.032 M NaOMe, methanol[h]	46	39	15
11	**9**, 2-epi, di-OTBDMS-7-OTMS	0.1 M NaOH, methanol, water[i]	8[j]	87	5
12	**9**, 2-epi, di-OTBDMS-7-OTMS	25% imidazole, benzene[k]	12	64	24

[a] 85 °C, 1 h. [b] 85 °C, 4 h. [c] 85 °C, 3 h. [d] 25 °C, 45 min; sample **3** was dried by azeotropic removal of moisture prior to DBU treatment. [e] 25 °C, 20 h. [f] 25 °C, 7.5 h. [g] 25 °C, 19 h. [h] 25 °C, 7.5 h. [i] 25 °C, 3 h. [j] Values correspond to deprotected 7-OH compounds (**2**, **3**, and **6**). After 4.5 h, the ratios were **2** (16%), **3** (75%), and **6** (7%). [k] 85 °C, 6 h. [l] Values in parentheses are for isolated pure product in percentage yield. [m] Product ratios as analyzed by HPLC (Waters Associates) on a μPorasil P/N 27477 column with UV detection at 254 nm (solvent, 6:4 ethyl acetate–hexanes; flow rate, 2.6 mL/min; retention times, **5**, 3.32 min; **1**, 3.76 min; **4**, 4.68 min. For the OTBDMS series: solvent, 92:8 hexanes–ethyl acetate; flow rate, 3.5 mL/min; retention times, 6, 5.03 min; **3**, 6.13 min; **2**, 7.3 min (base-line separation). HPLC chromatograms and graphs are available as supplementary material.

10 would undergo protonation from the β-face (concave side) by virtue of the bulk of the 7-OTMS group, leading to the desired B_{1a} isomer. Although this protocol appeared to be successful initially,[5] subsequent investigations in our laboratory and elsewhere[10] aimed at optimizing the deconjugation reaction based on our original conditions and variations thereof revealed an unpredictable variation in the nature of products, even with the slightest change in reaction conditions, scale of operation, or mode of workup.[10] In view of the importance of this step for the total synthesis or the semisynthesis of the avermectins, milbemycins,[2,3] and their analogues using such a deconjugation strategy, we deemed it necessary to investigate viable and reproducible alternatives. In this paper, we present the details of a two-step transformation of an O-protected Δ^2-avermectin into avermectin B_{1a} and additional relevant results. The desired Δ^2-avermectin derivative **6** was prepared from 4″,5-bis[*O*-(dimethyl-*tert*-butylsilyl)]avermectin B_{1a} (containing ~15% of the B_{1b} isomer) by treatment with DBU in dichloromethane.

Initially, deconjugation of **6** in the absence of trimethylsilyl chloride led to elimination and aromatization. Consequently, we hoped that addition of excess trimethylsilyl chloride would form the TMS ketene acetal[8] derivative **10** in situ and that subsequent acidification would lead to the desired target **1**. The deconjugation under such conditions (see Experimental Section) is a rapid process, requiring no more than 2–2.5 min at −78 °C for completion. The subsequent proton quench can be equally critical,[10] resulting in mixtures in which the B_{1a} isomer was either absent or detectable in trace amounts only. In fact, the 2-epi isomer[10,11] could be produced consistently, particularly under controlled acidic workup conditions. Variation in the nature of the acid is known to change the stereochemical course of protonation of lactone enolates.[12] However, no significant improvement was found when camphorsulfonic acid, pivalic acid, or saturated aqueous sodium sulfate was used as the proton source.[12] *On the basis of these results we must conclude that the material produced in our original deconjugation*[5] *was not the primary product of deconjugation, but possibly the result of a subsequent epimerization of an initially formed 2-epi isomer.*[10-13]

In view of these difficulties and the consistent formation of the kinetically favored 2-epi isomer, we sought conditions that would optimize its formation from the Δ^2-isomer **8**. Thus, addition of the Δ^2-isomer **8** to a preformed solution of LDA and excess trimethylsilyl chloride[8] in THF at −78 °C followed by rapid quenching with aqueous HCl in THF produced the 2-epi derivative

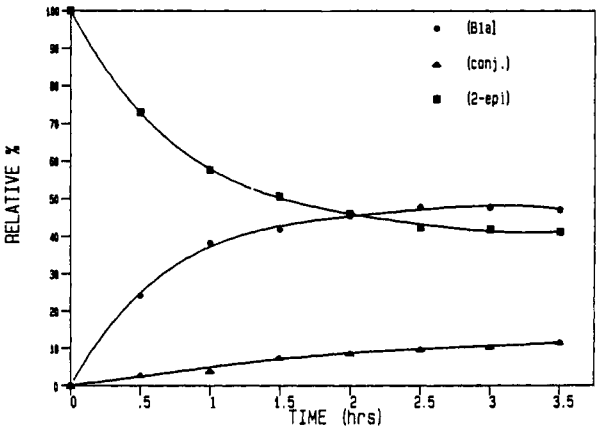


Figure 1. Epimerization of 2-epiavermectin B_{1a} in the presence of 25% imidazole in benzene at 80 °C (external temperature). HPLC analysis (see ref 16).

4 as a white foam in 82% yield after chromatographic purification. Similar results were obtained with **7**. In view of the different rates of hydrolysis of the 7-OTMS group upon addition of acetic acid,[5] we opted for a stronger acid in order to ensure rapid, but selective cleavage of the TMS ether group, thus simplifying chromatographic analysis. It is surprising that the presence of the smaller trimethylsilyl group at C_5, which would be expected to favor some β-face protonation as compared to the bulkier dimethyl-*tert*-butylsilyl group originally used,[5] also produces the 2-epi isomer as the major product. Our original rationale for using a 7-OTMS ether was in part to prevent internal proton transfer, which would produce the 2-epi isomer.[4,5] Evidently, the conformation in solution of such O-substituted derivatives of avermectin B_{1a} and dienolates derived therefrom favors almost exclusive α-face protonation during quenching with acids.[10,11]

Having thus a practical and reproducible method in hand for preparing the 2-epi isomer from the readily available Δ^2-avermectin, we turned our attention to the important problem of epimerization of the 2-epi isomer to avermectin B_{1a}.

Pivnichny and co-workers[11] have shown that treatment of avermectin B_{1a} with methanolic potassium hydroxide affords a mixture of **1**, the 2-epi isomer **4**, and the Δ^2-isomer **5** (HPLC analysis). A subsequent study[10] showed the formation of **1** (25%) and **5** (70%) from **4** with methanolic aqueous sodium hydroxide, based on an NMR analysis of the mixture.[14] It was also con-

(10) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.

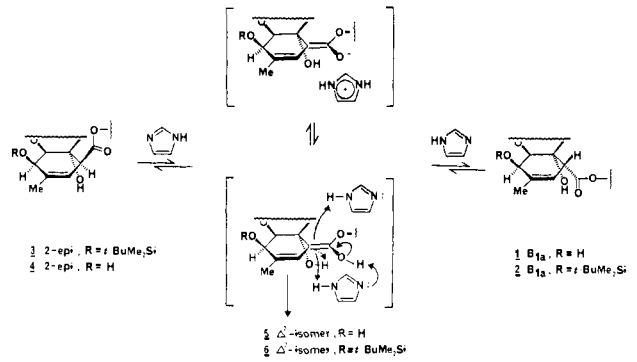
(11) Pivnichny, J. V.; Shim, J.-S. K.; Simmerman, L. A. *J. Pharm. Sci.* **1983**, *72*, 1447.

(12) Takano, S.; Uchid, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.

(13) A product isolated in 14% yield after chromatographic separation in our original work[5] was later identified as being the 2-epi isomer **3**.

(14) The reported deconjugation experiments conducted on **7**[10] produce **3**, but no reaction time for the critical deconjugation was given. Moreover, the ratios of products, which changed with the slightest variation in reaction conditions and/or acidic workup (also experienced by us), were determined by NMR analysis at 300 MHz, which is not as sensitive as HPLC (compare this study, Table I; see also ref 11).

Scheme II



cluded[10] that partial epimerization of **4** to **1** was possible "only in a protic medium and only if the polarity of the molecule is appropriate".

It is therefore clear that finding conditions that epimerize the 2-epi isomer to the desired natural isomer without concomitant conjugation and/or aromatization presents a major challenge. After investigating a number of reagents and conditions (Table I), we found that *imidazole in benzene* is an effective reagent for the partial conversion of the 2-epi isomers **4** or **3** into **1** and **2** in 40% and 33% isolated yields, respectively (Figure 1). The other products were unreacted 2-epi isomers and a small quantity (~ 10%) of the Δ^2-isomer. These could be recycled through the same deconjugation–epimerization process, thus enhancing the overall yield.

The epimerization caused by imidazole is of mechanistic interest, particularly that it is most effective when the C_7 hydroxy group is unsubstituted (compare entries 1 and 12). A pseudoequilibrium mixture appears to be formed within 3 h with a slight preponderance of the B_{1a} isomer over the 2-epi isomer (entries 3 and 4). While the precise role of imidazole has not been determined at this stage, one can envisage a stepwise (or relay) deprotonation–protonation process leading to the mixture of C_2 epimers via the intermediacy of an enol (or alternatively an imidazolium enolate) as illustrated in Scheme II. The formation of the 2-epi isomer **3** or **4** may be favored by virtue of the better accessibility of the reagent to the α-face of the oxahydrindene ketene hemiacetal or, possibly, via internal proton transfer from the 7-hydroxyl group. In an "ideal" equilibrium situation, without concurrent formation of the Δ^2-isomer, the natural B_{1a} isomer should prevail under quasi-neutral conditions due to its inherent stability. It is in this regard that imidazole offers an advantage over other bases studied to date, since the Δ^2-isomer is held to a minimum while epimerization is in progress.

Examination of the data in Table I reveals a number of interesting observations, with regard to conjugation, deconjugation, and epimerization of avermectin B_{1a} and its isomeric derivatives. It is clear that *regardless of the polarity of the molecule*, the 2-epi isomers can be epimerized to the B_{1a} series to varying extents under a number of conditions (entries 1, 3, 7, and 9), *including* methoxide in methanol. In the latter instance, the undesired Δ^2-isomer increases with time to the detriment of the B_{1a} and the 2-epi isomer,[11] and conjugation is more facile with the C_2 epimer (entries 9 and 10). Although of qualitative interest, epimerization is also possible under *aprotic conditions* (entry 5) and even in aqueous medium (entry 11), in contrast to the reported results[10] based on an NMR and TLC analysis of products.

In conclusion, we have demonstrated that the critical deconjugation–epimerization sequence can be achieved by a two-step process from Δ^2-avermectin B_{1a}. The assembly of avermectin B_{1a} and related products by the initially proposed strategy[4,5] based on the intermediacy of a Δ^2-isomer remains a viable preparative route.

Experimental Section

General. ^{1}H NMR and 2D ^{1}H NMR spectra were recorded on a Bruker WH-400 instrument using deuteriochloroform as solvent ($CHCl_3$ standard, δ = 7.265) (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent; obsc, obscured). Infrared spectra were recorded with a Perkin-Elmer 781 infrared spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter as solutions in chloroform at 25 °C. Combustion analysis was performed by Guelph Laboratories Ltd., Guelph, Ontario, Canada. Chromatography was done by the flash method. HPLC analysis was performed on a Waters Associates model chromatograph using a μPorasil P/N 27477 column and UV detection at 254 nm. All reactions were carried out under an argon atmosphere. The numbering system for spectral assignments is that depicted in Scheme I.

4″,5-Bis[*O*-(dimethyl-*tert*-butylsilyl)]avermectin B_{1a} (2). To a stirred solution of avermectin B_{1a} (872 mg, 1.0 mmol) in anhydrous DMF (8 mL) were added imidazole (490 mg, 7.2 mmol), 4-DMAP (25 mg, 0.2 mmol), and *tert*-butyldimethylsilyl chloride (452 mg, 3.0 mmol). The mixture was stirred at room temperature for 24 h and then cooled to 0 °C. Water (10 mL) was added and the mixture was poured into ether (80 mL) and water (50 mL). The aqueous layer was extracted with ether (4 × 20 mL), the combined organic extracts were washed with water (3 × 20 mL) and brine (2 × 20 mL) and then dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (elution with 10% ethyl acetate–hexanes) to give **2** as a white foam (1.011 g, 92%): $[\alpha]_D$ +31.5° (*c* 0.40); IR ν (cm^{-1}) 3480, 2970, 2940, 2900, 1715, 1415, 1390, 1340, 1255, 1130, 1100, 990, 840; ^{1}H NMR δ 5.86–5.71 (4 H, m, 3-H, 10-H, 11-H, 22-H), 5.56 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.43–5.31 (3 H, m, 9-H, 19-H, 1″-H), 5.04–4.96 (1 H, m, 15-H), 4.80–4.76 (1 H, m, 1′-H), 4.69 (1 H, dd, $J_{8'A,8'B}$ = 14 Hz, $J_{8'B,9}$ = 2.4 Hz, 8′-H_B), 4.60 (1 H, dd, $J_{8'A,8'B}$ = 14 Hz, $J_{8'A,9}$ = 2.4 Hz, 8′-H_A), 4.47–4.42 (1 H, m, 5-H), 4.12 (1 H, s, OH), 3.96–3.92 (1 H, br, 13-H), 3.92–3.80 (3 H, m, 5′-H *or* 5″-H, 6-H, 17-H), 3.75–3.57 (3 H, m, 5″-H *or* 5′-H,3′-H, 3″-H), 3.49 (1 H, dd, $J_{24,25}$ = 10 Hz, $J_{25,26}$ = 1.6 Hz, 25-H), 3.45 (3 H, s, OCH_3), 3.42–3.38 (1 H, m, 2-H), 3.35 (3 H, s, OCH_3), 3.22 (1 H, app t, $J_{4',5'}$ = 8.4 Hz, $J_{3',4'}$ = 8.4 Hz, 4′-H), 3.14 (1 H, app t, $J_{4'',5''}$ = 8.4 Hz, 4″-H), 2.58–2.47 (1 H, m, 12-H), 2.39–2.17 (5 H, m, 16-H, 24-H, 2′-H_{eq}, 2″-H_{eq}), 2.09–2.00 (1 H, m, 18-H_{eq}), 1.79 (3 H, s, C_4-CH_3), 1.79–1.74 (1 H, m, 2″-H_{eq}, 2′-H_{ax} *or* 2″-H_{ax}), 1.66–1.45 (5 H, m, 20-H, 26-H, 27-H), 1.50 (3 H, s, C_{14}-CH_3), 1.27 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.2 Hz, 6′-H *or* 6″-H), 1.22 (3 H, d, $J_{5',6'}$ *or* $J_{5'6'}$ = 6.2 Hz, 6′-H *or* 6″-H), 1.17 (3 H, d, J_{12,CH_3} = 7.2 Hz, C_{12}-CH_3), 1.03–0.84 (11 H, m, 18-H_{ax}, 2″-H_{ax} *or* 2′-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.94 and 0.90 (9 H each, 2 s, 2 × SiC_4H_9), 0.14 (6 H, s, 2 × $SiCH_3$), 0.10 and 0.08 (3 H each, 2 s, 2 × $SiCH_3$). Anal. Calcd for $C_{60}H_{100}O_{14}Si_2 \cdot 4H_2O$: C, 61.40; H, 9.28. Found: C, 61.43; H, 9.09.

Δ^2-4(*R*)-Avermectin B_{1a} (5). To a solution of avermectin B_{1a} (500 mg, 0.573 mmol) in dichloromethane (4 mL) was added DBU (2 mL). The mixture was stirred at room temperature for 18 h, diluted with ether (100 mL), washed with 10% HCl (2 × 20 mL), water (20 mL), and brine (50 mL), and dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (elution with 60–70% ethyl acetate–hexanes) to give **5** as a white foam (464 mg, 93%): $[\alpha]_D$ +214° (*c* 1.10); IR ν (cm^{-1}) 3480, 2970, 2940, 2880, 1740, 1700, 1660, 1640, 1450, 1380, 1290, 1240, 1120, 1050, 970, 935; ^{1}H NMR δ 6.20–6.13 (2 H, m, $J_{3,4}$ = 2 Hz, 3-H, 11-H), 5.85–5.64 (3 H, m, 9-H, 10-H, 22-H), 5.58 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.42 (1 H, br d, $J_{1'',2''ax}$ ~ 3.5 Hz, 1″-H), 5.43–5.33 (1 H, m, obsc, 19-H), 5.00–4.90 (1 H, br, 15-H), 4.78–4.73 (2 H, m, 1′-H, C_7-OH), 4.58 (1 H, dd, $J_{8'A,8'B}$ = 14 Hz, $J_{8'B,9}$ = 2.4 Hz, 8′-H_B), 4.52 (1 H, dd, $J_{8'A,8'B}$ = 14 Hz, $J_{8'A,9}$ = 2.4 Hz, 8′-H_A), 4.06 (1 H, d, $J_{5,6}$ = 2 Hz, 6-H), 3.96–3.73 (4 H, m, 13-H, 17-H, 5′-H, 5″-H), 3.70–3.56 (2 H, m, 3′-H, 3″-H), 3.52–3.42 (2 H, obsc, 5-H, 25-H), 3.49 (3 H, s, OCH_3), 3.44 (3 H, s, OCH_3), 3.25 (1 H, app t, $J_{4',5'}$ = 8.8 Hz, $J_{3',4'}$ = 8.8 Hz, 4′-H), 3.18 (1 H, app t, $J_{4'',5''}$ = 8.8 Hz, 4″-H), 2.58–2.43 (3 H, m, 4-H, 12-H, 2″-H_{eq}), 2.40–2.20 (4 H, m, 16-H, 24-H, 2′-H_{eq}), 2.04–1.95 (1 H, m, 18-H_{eq}), 1.92–1.80 (2 H, m, 2′-H_{ax} *or* 2″-H_{ax}, C_5-OH), 1.70–1.40 (6 H, m, 20-H, 26-H, 27-H, $C_{4''}$-OH), 1.47 (3 H, s, C_{14}-CH_3), 1.29 (3 H, d, $J_{5'',6''}$ *or* $J_{5',6'}$ = 6.4 Hz, 6″-H *or* 6′-H), 1.26 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.7 Hz, 6′-H *or* 6″-H), 1.24 (3 H, d, J_{12,CH_3} = 7.7 Hz, C_{12}-CH_3), 1.17 (3 H, d, J_{4,CH_3} = 7.2 Hz, C_4-CH_3), 0.99–0.86 (10 H, m, 2″-H_{ax} *or* 2′-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.77 (1 H, app q, $J_{18ax,18eq}$ ~ $J_{17,18ax}$ ~ $J_{18ax,19}$ = 11.8 Hz, 18-H_{ax}).

4″,5-Bis[*O*-(dimethyl-*tert*-butylsilyl)]-Δ^2-4(*R*)-avermectin B_{1a} (6). To a stirred solution of **2** (90 mg, 0.082 mmol) in dichloromethane (2 mL) was added DBU (0.2 mL). The mixture was stirred at room temperature for 16 h, poured into ether (40 mL), washed with 10% HCl (2 × 10 mL), water (10 mL), saturated aqueous sodium hydrogen carbonate (2 × 10 mL), and brine (10 mL), and dried ($MgSO_4$). The solvent was removed with a rotary evaporator, and the crude product was purified by chromatography on silica gel (elution with 11% ethyl acetate–hexanes) to give 6 as a white foam (83.4 mg, 93%): $[\alpha]_D$ +144° (*c* 0.4); IR ν (cm^{-1}) 3510, 2960, 2940, 2860, 1700, 1650, 1465, 1390, 1300, 1255, 1105, 1070, 970,

840; ^{1}H NMR δ 6.19–6.11 (2 H, m, $J_{3,4}$ = 2.1 Hz, 3-H, 11-H), 5.82–5.73 (2 H, m, 9-H, 22-H), 5.69 (1 H, dd, $J_{10,11}$ = 14.8 Hz, $J_{9,10}$ = 10.8 Hz, 10-H), 5.58 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.43–5.33 (1 H, m, 19-H), 5.33 (1 H, br d, $J_{1''2''ax} \sim$ 3.5 Hz, 1''-H), 4.98–4.91 (1 H, m, 15-H), 4.78–4.73 (2 H, m, 1'-H, OH), 4.58 (1 H, dd, $J_{8'A,8'B}$ = 14.2 Hz, $J_{8'B,9}$ = 2.1 Hz, 8'-H_B), 4.50 (1 H, dd, $J_{8'A,8'B}$ = 14.2 Hz, $J_{8'A,9}$ = 2.1 Hz, 8'-H_A), 3.96 (1 H, d, $J_{5,6}$ = 1.9 Hz, 6-H), 3.94–3.80 (3 H, m, 13-H, 17-H, 5'-H *or* 5''-H), 3.75–3.59 (4 H, m, 5-H, 3'-H, 3''-H, 5''-H *or* 5-H), 3.49 (3 H, s, OCH_3), 3.52–3.47 (1 H, obsc, 25-H), 3.36 (3 H, s, OCH_3), 3.22 (1 H, app t, $J_{4',5'}$ = 8.8 Hz, $J_{3',4'}$ = 8.8 Hz, 4'-H), 3.14 (1 H, app t, $J_{4'',5''}$ = 8.8 Hz, $J_{3'',4''}$ = 8.8 Hz, 4''-H), 2.70–2.60 (1 H, m, 4-H), 2.53–2.43 (1 H, m, 12-H), 2.41–2.17 (5 H, m, 16-H, 24-H, 2'-H_{eq}, 2''-H_{eq}), 2.02–1.95 (1 H, m, 18-H_{eq}), 1.94–1.84 (1 H, m, 2'-H_{ax} *or* 2''-H_{ax}), 1.70–1.42 (5 H, m, 20-H, 26-H, 27-H), 1.46 (3 H, br, s, C_{14}-CH_3), 1.26 (3 H, d, $J_{5'',6''}$ *or* $J_{5',6'}$ = 6.2 Hz, 6''-H *or* 6'-H), 1.22 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.4 Hz, 6'-H *or* 6''-H), 1.16 (6 H, app t, $J_{4,CH_3} \sim J_{12,CH_3}$ = 7 Hz, C_4-CH_3, C_{12}-CH_3), 1.02–0.73 (11 H, m, 18-H_{ax}, 2''-H_{ax} *or* 2'-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.93 and 0.90 (9 H each, 2 s, 2 × SiC_4H_9), 0.13, 0.12, 0.10, and 0.08 (3 H each, 4 s, 4 × $SiCH_3$). Anal. Calcd for $C_{60}H_{100}O_{14}Si_2 \cdot 4H_2O$: C, 61.40; H, 9.28. Found: C, 61.37; H, 8.95.

4'',5-Bis[*O*-(dimethyl-*tert*-butylsilyl)]-7-*O*-(trimethylsilyl)-Δ^2-4(*R*)-avermectin B_{1a} (7). To a stirred solution of **6** (97 mg, 0.088 mmol) in dichloromethane (3 mL) and triethylamine (0.25 mL) at 0 °C were added 4-DMAP (2.2 mg, 0.018 mmol) and then dropwise trimethylsilyl chloride (0.112 mL, 0.886 mmol). The mixture was stirred at 0 °C for 1 h and then room temperature for 24 h. Water (3 mL) was added, the mixture was poured into ether (20 mL), washed with 10% HCl (2 × 5 mL), water (5 mL), saturated aqueous sodium hydrogen carbonate (5 mL), and brine (10 mL) and dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (elution with 8–10% ethyl acetate–hexanes) to give **7** as a white foam (99.5 mg, 96%): $[\alpha]_D$ +161° (*c* 0.94); IR ν (cm^{-1}) 2970, 2940, 2900, 2860, 1730, 1665, 1470, 1390, 1255, 1200, 1125, 1105, 1075, 990, 840; ^{1}H NMR δ 6.23 (1 H, br, d, $J_{10,11} \sim$ 10.4 Hz, 11-H), 6.12 (1 H, d, $J_{3,4}$ = 2.1 Hz, 3-H), 5.76 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{22,24}$ = 1.6 Hz, 22-H), 5.72–5.60 (2 H, m, 10-H, 9-H), 5.55 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.2 Hz, 23-H), 5.33 (1 H, br d, $J_{1'',2''ax} \sim$ 3.5 Hz, 1''-H), 5.32–5.20 (1 H, m, 19-H), 4.99–4.92 (1 H, m, 15-H), 4.76 (1 H, br d, $J_{1',2'ax} \sim$ 3.5 Hz, 1'-H), 4.53 (1 H, dd, $J_{8'A,8'B}$ = 14.2 Hz, $J_{8'B,9}$ = 2.1 Hz, 8'-H_B), 4.46 (1 H, dd, $J_{8'A,8'B}$ = 14.2 Hz, $J_{8'A,9}$ = 2.1 Hz, 8'-H_A), 3.97–3.92 (4 H, m, $J_{5,6}$ = 2.2 Hz, 6-H, 17-H, 13-H, 5'-H *or* 5''-H), 3.77–3.61 (4 H, m, 5-H, 3'-H, 3''-H, 5''-H *or* 5'-H), 3.52 (3 H, s, OCH_3), 3.48 (1 H, br d, $J_{24,25} \sim$ 10.2 Hz, 25-H), 3.35 (3 H, s, OCH_3), 3.22 (1 H, app t, $J_{4',5'}$ = 8.8 Hz, $J_{3',4'}$ = 8.8 Hz, 4'-H), 3.14 (1 H, app t, $J_{4'',5''}$ = 8.8 Hz, $J_{3'',4''}$ = 8.8 Hz, 4''-H), 2.60–2.43 (2 H, m, 4-H, 12-H), 2.39–2.18 (5 H, m, 16-H, 24-H, 2'-H_{eq}, 2''-H_{eq}), 2.01–1.87 (2 H, m, 18-H_{eq}, 2'-H_{ax} *or* 2''-H_{ax}), 1.69–1.43 (5 H, m, 20-H, 26-H, 27-H), 1.47 (3 H, br, s, C_{14}-CH_3), 1.26 (3 H, d, $J_{5'',6''}$ *or* $J_{5',6'}$ = 6.2 Hz, 6''-H *or* 6'-H), 1.22 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.4 Hz, 6'-H *or* 6''-H), 1.17 (3 H, d, J_{12,CH_3} = 7 Hz, C_{12}-CH_3), 1.15 (3 H, d, J_{4,CH_3} = 7.2 Hz, C_4-CH_3), 1.01–0.83 (10 H, 2'-H_{ax} *or* 2''-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.94 and 0.90 (9 H each, 2 s, 2 × SiC_4H_9), 0.72–0.60 (1 H, m, 18-H_{ax}), 0.24 (9 H, s, C_7-$OSi(CH_3)_3$), 0.14, 0.13, 0.10, and 0.09 (3 H each, 4 s, 4 × $SiCH_3$). Anal. Calcd for $C_{63}H_{108}O_{14}Si_3$: C, 64.67; H, 9.28. Found: C, 64.68; H, 9.23.

4'',5,7-Tris[*O*-(trimethylsilyl)]-Δ^2-4(*R*)-avermectin B_{1a} (8). To a solution of **5** (1.58 g, 1.812 mmol) in dichloromethane (30 mL) and triethylamine (15.2 mL) at 0 °C were added 4-DMAP (44 mg, 0.362 mmol) and then dropwise trimethylsilyl chloride (6.9 mL, 54.4 mmol). The mixture was stirred at 0 °C for 1 h and then room temperature for 24 h. The mixture was processed as usual, and the crude product was purified by chromatography on silica gel (elution with 10% ethyl acetate–hexanes) to give **8** (1.95 g, 99%) as a white foam: $[\alpha]_D$ +124° (*c* 1.41); IR ν (cm^{-1}) 2960, 2940, 2900, 1725, 1665, 1455, 1390, 1350, 1250, 1120, 1105, 1070, 990, 905; ^{1}H NMR δ 6.23 (1 H, br d, $J_{10',11} \sim$ 15 Hz, 11-H), 6.12 (1 H, d, $J_{3,4}$ = 2 Hz, 3-H), 5.76 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{22,24}$ = 1.6 Hz, 22-H), 5.73–5.60 (2 H, m, 10-H, 9-H), 5.55 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.6 Hz, 23-H), 5.33 (1 H, br d, $J_{1'',23''ax} \sim$ 3.5 Hz, 1''-H), 5.32–5.21 (1 H, m, 19-H), 4.98–4.90 (1 H, br, 15-H), 4.75 (1 H, br d, $J_{1',2'ax}$ = 3.5 Hz, 1'-H), 4.55 (1 H, dd, $J_{8'A,8'B}$ = 14.1 Hz, $J_{8'B,9}$ = 2.1 Hz, 8'-H_B), 4.47 (1 H, dd, $J_{8'A,8'B}$ = 14.1 Hz, $J_{8'A,9}$ = 2.1 Hz, 8'-H_A), 3.92–3.80 (4 H, m, $J_{5,6}$ = 2.1 Hz, 6-H, 13-H, 17-H, 5'-H *or* 5''-H), 3.71–3.60 (4 H, m, 5-H, 3'-H, 3''-H, 5''-H *or* 5'-H), 3.52 (3 H, s, OCH_3), 3.47 (1 H, br d, $J_{24,25}$ = 10 Hz, 25-H), 3.38 (3 H, s, OCH_3), 3.21 (1 H, app t, $J_{4',5'} \sim J_{3',4'} \sim$ 8.8 Hz, 4'-H), 3.13 (1 H, app t, $J_{4'',5''} \sim J_{3'',4''} \sim$ 8.8 Hz, 4''-H), 2.60–2.43 (2 H, m, 4-H, 12-H), 2.38–2.17 (5 H, m, 16-H, 24-H, 2'-H_{eq}, 2''-H_{eq}), 1.99–1.85 (2 H, m, 18-H_{eq}, 2'-H_{ax} *or* 2''-H_{ax}), 1.68–1.48 (5 H, m, 20-H, 26-H, 27-H), 1.46 (3 H, br s, C_{14}-CH_3), 1.25 (3 H, d, $J_{5'',6''}$ *or* $J_{5',6'}$ = 7 Hz, 6''-H *or* 6'-H), 1.19 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.6 Hz, 6'-H *or* 6''-H), 1.15 (3 H, d, J_{12,CH_3} = 7 Hz, C_{12}-CH_3), 1.13 (3 H, d, J_{4,CH_3} = 7.4 Hz, C_4-CH_3), 0.99–0.85 (10 H, 2'-H_{ax} *or* 2''-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.73–0.61 (1 H, m, 18-H_{ax}), 0.24, 0.19, 0.14 (9 H each, 3 s, 3 × $Si(CH_3)_3$).

4'',5-Bis[*O*-(dimethyl-*tert*-butylsilyl]-2-epiavermectin B_{1a} (3) from 7. To a stirred solution of LDA (0.5 M in THF, 1.75 mL, 0.875 mmol) at −78 °C was added trimethylsilyl chloride (0.555 mL, 4.37 mmol). The mixture was stirred at −78 °C for 5 min, and a precooled (−78 °C) solution of **7** (205 mg, 0.175 mmol) in THF (1.8 mL) was added via a double-tip syringe. The resulting pale yellow solution was stirred at −78 °C for 2 min and then quenched with a mixture of 2 N HCl (2.0 mL) and THF (2.0 mL) (precooled briefly prior to addition). The cooling bath was removed, and the mixture was stirred at room temperature for 3 h. The mixture was then diluted with ethyl acetate (20 mL), washed with saturated aqueous sodium hydrogen carbonate (2 × 15 mL), water (10 mL), and brine (10 mL), and dried ($MgSO_4$), and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on silica gel (elution with 5–8% ethyl acetate–hexanes) to give **3** as a white foam (162.7 mg, 85%): $[\alpha]_D$ +140° (*c* 0.81); IR ν (cm^{-1}) 3510, 2960, 2940, 2860, 1705, 1460, 1390, 1260, 1125, 1105, 990, 880, 840; ^{1}H NMR δ 5.96–5.89 (1 H, br, m, 11-H), 5.78 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{22,24}$ = 1.6 Hz, 22-H), 5.74–5.63 (3 H, m, 3-H, 9-H, 10-H), 5.58 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.54–5.43 (1 H, m, 19-H), 5.34 (1 H, br d, $J_{1'',2''ax} \sim$ 3.5 Hz, 1''-H), 4.96–4.88 (1 H, br, 15-H), 4.76 (1 H, br d, $J_{1',2ax} \sim$ 3.5 Hz, 1'-H), 4.61 (1 H, br d, $J_{8'A,8'B} \sim$ 14 Hz, 8'-H_B), 4.39–4.33 (1 H, br, 5-H), 4.16 (1 H, dd, $J_{8'A,8'B} \sim$ 14 Hz, $J_{8'A,9}$ = 2.4 Hz, 8'-H_A), 4.15 (1 H, d, $J_{5,6}$ = 2.4 Hz, 6-H), 3.95 (1 H, s, OH), 3.95–3.80 (3 H, m, 13-H, 5'-H *or* 5''-H, 17-H), 3.77–3.59 (3 H, m, 3'-H, 3''-H, 5''-H *or* 5'-H), 3.51–3.48 (1 H, br, 25-H, 3.50 (3 H, s, OCH_3), 3.36 (3 H, s, OCH_3), 3.22 (1 H, app t, $J_{4',5'}$ = 9 Hz, $J_{3',4'}$ = 9 Hz, 4'-H), 3.20–3.16 (1 H, m, 2-H), 3.15 (1 H, app t, $J_{4'',5''}$ = 8.7 Hz, $J_{3'',4''}$ = 8.7 Hz, 4''-H), 2.55–2.18 (6 H, m, 12-H, 16-H, 24-H, 2'-H_{eq}, 2''-H_{eq}), 1.98–1.91 (1 H, m, 18-H_{eq}), 1.86 (3 H, br s, C_4-CH_3), 1.84–1.80 (1 H, m, 2'-H_{ax} *or* 2''-H_{ax}), 1.73–1.48 (5 H, m, 20-H, 26-H, 27-H), 1.47 (3 H, br s, C_{14}-CH_3), 1.27 (3 H, d, $J_{5',6''}$ *or* $J_{5',6'}$ = 6 Hz, 6''-H *or* 6'-H), 1.23 (3 H, d, $J_{5',6'}$ *or* $J_{5'',6''}$ = 6.4 Hz, 6'-H *or* 6''-H), 1.17 (3 H, d, J_{12,CH_3} = 6.8 Hz, C_{12}-CH_3), 0.98–0.70 (11 H, m, 18-H_{ax}, 2'-H_{ax} *or* 2''-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3), 0.95 and 0.90 (9 H each, 2 s, 2 × SiC_4H_9), 0.15, 0.14, 0.11, and 0.08 (3 H each, 4 s, 4 × $SiCH_3$). Anal. Calcd for $C_{60}H_{100}O_{14}Si_2 \cdot 4H_2O$: C, 61.40; H, 9.28. Found: C, 61.00; H, 8.87.

2-Epiavermectin B_{1a} (4) from 8. To a stirred solution of diisopropylamine (0.841 mL, 6 mmol) in THF (5.83 mL) at 0 °C was added *n*-butyllithium (1.46 M in hexanes; 3.43 mL, 5 mmol) dropwise over 5 min. After stirring at 0 °C for 20 min, the solution was cooled to −78 °C and trimethylsilyl chloride (3.17 mL, 25 mmol) was added dropwise over 2 min. The mixture was stirred at −78 °C for 5 min and then a precooled solution of **8** (1.088 g, 1 mmol) in THF (15 mL) at −78 °C was introduced by double-tip syringe over 20 s. The resultant pale yellow solution was stirred at −78 °C for 2.5 min and then quenched with a mixture of 2 N HCl (15 mL) and THF (15 mL) in one portion (precooled briefly prior to addition). The cooling bath was removed and the mixture was stirred at room temperature for 5 h. The mixture was processed as usual and the crude product was purified by chromatography on silica gel (elution with 50–70% ethyl acetate–hexanes) to give **4** (713 mg, 82%) as a white foam: $[\alpha]_D$ +188° (*c* 1.10); IR ν (cm^{-1}) 3470, 2970, 2930, 2880, 1705, 1660, 1450, 1380, 1260, 1160, 1115, 1050, 970, 935. ^{1}H NMR δ 5.96 (1 H, br d, $J_{10,11} \sim$ 15 Hz, 11-H), 5.82–5.62 (4 H, m, 3-H, 9-H, 10-H, 22-H), 5.58 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.57–5.45 (1 H, m, 19-H), 5.42 (1 H, br d, $J_{1'',2''ax} \sim$ 3.5 Hz, 1''-H), 4.98–4.90 (1 H, br, 15-H), 4.77 (1 H, br d, $J_{1',2'ax} \sim$ 3.5 Hz, 1'-H), 4.62 (1 H, br d, $J_{8'A,8'B} \sim$ 14 Hz, 8'-H_B), 4.35–4.29 (2 H, m, 6-H, C_7-OH), 4.29–4.22 (1 H, br, 5-H), 4.14 (1 H, dd, $J_{8'A,8'B}$ = 14 Hz, $J_{8'B,9}$ = 2 Hz, 8'-H_A), 3.97–3.73 (4 H, m, 13-H, 17-H, 5'-H, 5''-H), 3.70–3.61 (2 H, m, 3'-H, 3''-H), 3.53–3.48 (1 H, obsc, 25-H), 3.49 (3 H, s, OCH_3), 3.43 (3 H, s, OCH_3), 3.25 (1 H, app t, $J_{4',5'} \sim J_{3',4'}$ = 8.8 Hz, 4'-H), 3.24–3.19 (1 H, m, 2-H), 3.17 (1 H, app t, $J_{4'',5''} \sim J_{3'',4''}$ = 8.8 Hz, 4''-H), 2.58–2.18 (6 H, m, C_5-OH, 12-H, 16-H, 24-H, 2'-H_{eq}), 1.99–1.93 (1 H, m, 18-H_{eq}), 1.91 (3 H, s, C_4-CH_3), 1.89–1.80 (1 H, m, 2'-H_{ax} *or* 2''-H_{ax}), 1.73–1.42 (6 H, m, $C_{4''}$-OH, 20-H, 26-H, 27-H), 1.48 (3 H, br s, C_{14}-CH_3), 1.28 (3 H, d, $J_{5',6'}$ *or* $J_{5''6''}$ = 6 Hz, 6'-H *or* 6''-H), 1.25 (3 H, d, $J_{5'',6''}$ *or* $J_{5',6'}$ = 6.4 Hz, 6''-H *or* 6'-H), 1.17 (3 H, d, J_{12,CH_3} = 7 Hz, C_{12}-CH_3), 0.99–0.74 (11 H, m, 2''-H_{ax} *or* 2'-H_{ax}, 18-H_{ax}, 28-H, C_{24}-CH_3, C_{26}-CH_3).

Conversion of 2-Epiavermectin B_{1a} into Avermectin B_{1a}. A solution of **4** (80 mg, 0.092 mmol) and imidazole (1.25 g) in benzene (5.0 mL) was heated at 80–85 °C and monitored by HPLC for 3 h. The pale yellow reaction mixture was allowed to cool to room temperature, diluted with ether (30 mL), washed with water (3 × 10 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The mixture **5** + **1** + **4** (11:47:42 by HPLC) was separated on 2-mm Kieselgel F-254 (20 × 20

cm) (four plates) using ether–hexanes–MeOH (80:18:2) as eluant (six elutions), which gave 6.6 mg of **5** (8% yield), 31.9 mg of **1** (40% yield), and 27.4 mg of **4** (34% yield). Avermectin B_{1a} isolated from such experiments was identical with authentic material (400-MHz NMR, $[\alpha]_D$, HPLC).[16]

Conversion of 3 into 4″,5-Bis[*O*-(dimethyl-*tert*-butylsilyl)]avermectin B_{1a}. A solution of **3** (40 mg, 0.036 mmol) and imidazole (1.0 g) in benzene 4 mL) was heated at 80–85 °C and monitored by HPLC for 60 min. The pale yellow reaction mixture was allowed to cool to room temperature, diluted with ether (30 mL), washed with water (3 × 10 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The mixture **6** + **2** + **3** (14:36:50 by HPLC) was separated on 0.5-mm Kieselgel F-254 (20 × 20 cm) (four plates) using hexanes–ethyl acetate–MeOH (92.5:5.5:2.0) as eluant (six elutions), which gave 17.6 mg of **3** (44% yield), 13.3 mg of **2** (33% yield), and 5.1 mg of **6** (13% yield). The product **2** was identical in all respects with authentic material (400-MHz NMR, $[\alpha]_D$, HPLC, TLC).

General Procedure for Deprotection of 4″,5-Bis[*O*-(dimethyl-*tert*-butylsilyl)] Derivatives of Avermectins Using Aqueous HF and Pyridine in Acetonitrile. Avermectin B_{1a} from 3. The deprotection procedure is a standard method similar to that described by Johnson.[18] To a premixed solution of 48% aqueous HF (2 drops/mmol of substrate) and pyridine[19] (0.2 mL/mmol of substrate) in acetonitrile (8 mL/mmol of substrate) is added the substrate in acetonitrile (1 mL/mmol of substrate). A cloudiness in the reaction mixture which persists is observed. The mixture is stirred at room temperature until reaction is complete (36–72 h) (TLC monitor with both 12% ethyl acetate–hexanes and 75% ethyl acetate–hexanes). Additional aliquots of pyridine and 48% HF may be added during the reaction.[19] The reactions were worked up by cautiously adding saturated aqueous sodium hydrogen carbonate, extracting (3–4 times) with ethyl acetate, and washing the combined organic extracts with water and brine. The crude products were purified by chromatography on silica gel (elution with 75% ethyl acetate–hexanes) to give the desilylated products in 80–90% yield.[20]

Avermectin B_{1a} (**1**): $[\alpha]_D$ +53.5° (*c* 1.00); IR ν (cm^{-1}) 3470, 2980, 2940, 1715, 1455, 1380, 1340, 1160, 1120, 1055, 990, 760; ^1H NMR δ 5.90–5.84 (1 H, m, 3-H), 5.80–5.72 (3 H, m, 22-H, 10-H, 11-H), 5.56 (1 H, dd, $J_{22,23}$ = 10 Hz, $J_{23,24}$ = 2.4 Hz, 23-H), 5.46–5.34 (3 H, m, 9-H, 19-H, 1″-H), 5.03–4.96 (1 H, m, 15-H), 4.77 (1 H, br, d, $J_{1',2'ax} \sim$ 3.5 Hz, 1′-H), 4.74–4.62 (2 H, m, 8′-H_B, 8′-H_A), 4.32–4.25 (1 H, br, 5-H), 4.08 (1 H, s, C_7-OH), 3.95 (1 H, d, $J_{5,6}$ = 6.4 Hz, 6-H), 3.97–3.93 (1 H, br, obsc, 13-H), 3.93–3.72 (3 H, m, 17-H, 5′-H, 5″-H), 3.63–3.58 (2 H, m, 3′-H, 3″-H), 3.49 (1 H, br d, $J_{24,25} \sim$ 10 Hz, 25-H), 3.44 (3 H, s, OCH_3), 3.42 (3 H, s, OCH_3), 3.32–3.27 (1 H, m, 2-H), 3.24 (1 H, app t, $J_{4',5'}$ = 8 Hz, $J_{3',4'}$ = 8 Hz, 4′-H), 3.15 (1 H, app t, $J_{4'',5''}$ = 8 Hz, $J_{3'',4''}$ = 8 Hz, 4″-H), 2.89–2.84 (1 H, br s, $C_{4''}$-OH), 2.59 (1 H, d, $J_{5,OH}$ = 8 Hz, C_5-OH), 2.57–2.50 (1 H, m, 12-H), 2.39–2.18 (5 H, 16-H, 24-H, 2′-H_{eq}, 2″-H_{eq}), 2.07–1.99 (1 H, m, 18-H_{eq}), 1.89 (3 H, s, C_4-CH_3), 1.84–1.76 (1 H, m, 2′-H_{ax} *or* 2″-H_{ax}), 1.66–1.44 (5 H, m, 20-H, 26-H, 27-H), 1.51 (3 H, s, C_{14}-CH_3), 1.27 (6 H, app t, (2d), $J_{5'',6''} \sim J_{5',6'} \sim$ 7 Hz, 6′-H, 6″-H), 1.17 (3 H, d, J_{12,CH_3} = 7 Hz, C_{12}-CH_3), 0.98–0.82 (11 H, m, C_{24}-CH_3, C_{26}-CH_3, 28-H, 2″-H_{ax} *or* 2′-H_{ax}, 18-H_{ax}).

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Registry No. 1, 65195-55-3; **2**, 81924-42-7; **3**, 106621-62-9; **4**, 110352-54-0; **5**, 110415-68-4; **6**, 103024-46-0; **7**, 103002-45-5; **8**, 110319-01-2; **9**, 106544-70-1.

Supplementary Material Available: ^1H NMR spectra and HPLC data (14 pages). Ordering information is given on any current masthead page.

(15) HPLC (Waters Associates), μPorasil P/N 27477 column, UV detector, 6:4 ethyl acetate–hexanes, flow rate 2.6 mL/min. Retention times: **5**, 3.32 min; **1**, 3.76 min; **4**, 4.68 min.

(16) Although **4** may be separated from **1** and **5** by flash column chromatography, **1** and **5** are best separated by preparative thick-layer chromatography.

(17) HPLC (Waters Associates), μPorasil P/N 27477 column, UV detector, 92:8 hexanes–ethyl acetate, flow rate 3.5 mL/min. Retention times: **6**, 5.03 min; **2**, 7.30 min; **3**, 6.13 min.

(18) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

(19) In the absence of pyridine, rapid destruction of the substrate was observed. Consequently, additional aliquot additions of pyridine and aqueous HF sequentially may be necessary.

(20) Desilylation with *n*-Bu_4NF as described by Nicolaou et al. (*J. Am. Chem. Soc.* **1984**, *106*, 4189) and used by us[5] is not suitable on scaling up due to incomplete desilylation and formation of side products; see also: Lukacs, G., et al. *J. Chem. Soc., Chem. Commun.* **1987**, 368.