Figure 2. Side-on view of the N-$CH_3HTPPBr_4$ molecule indicating the relative orientations of the pyrrole rings. The position of the hydrogen atom on nitrogen is strongly indicated to be across from the methylated pyrrole.

core in the final electron density map. At this point, $R = 0.082$ and $R_w = 0.098$.[17] The crystallographic numbering scheme used for this N-methylporphyrin is displayed in Figure 1, and the side-on view of the structure shown in Figure 2 emphasizes the distortions of the porphyrin core from planarity (see below).

Three types of N-alkylporphyrin structures may now be compared—that of the free base N-$CH_3HTPPBr_4$, that of the protonated species 21-(ethoxycarbonylmethyl)octaethylporphyrin hydrogen iodide,[15] and that of a typical transition-metal complex. The structures of the transition-metal complexes are quite similar, and that of ClFeN-CH_3TPP[14] will be used for purposes of comparison since its coordination geometry presumably very closely resembles that of the intermediate in cytochrome P-450 decomposition.[18] In each of these cases, the bulk of the N-alkyl group forces the substituted ring to be the most highly canted from the reference N1-N2-N3 plane (27.7, 19.1, and 36.6°, respectively), and the two adjacent pyrrole rings are tilted in the direction opposite to that of the N-alkylated ring (by 10.2 and 11.9°, 4.8 and 2.2°, and 9.8 and 11.3°, respectively). The N-alkylated ring and the pyrrole ring opposite to it are tilted in the same direction in the free base (27.7 and 8.1°) while the corresponding nonalkylated ring in the protonated N-ethoxycarbonylmethyl species and the iron complex is canted in the same direction as the adjacent rings (11.7 and 6.4°, respectively).

It is evident from van der Waals radii and the size of the cavity of a planar porphyrin[19] that a hydrogen atom and a methyl group with a N(sp^2)-C bond cannot simultaneously reside in the cavity. The structure of N-$CH_3HTPPBr_4$ shows that the steric requirements of the N-methyl group are accommodated in several ways. First, the angle betwewen the N1-C5 bond and the plane of the N1 pyrrole ring is considerably less than 180° (120.2°). In addition, the N-alkylated pyrrole ring is tilted (by 27.7°), and the adjacent pyrrole rings are rotated away from the alkyl group (10.2° and 11.9°). For the N-$CH_3HTPPBr_4$ and N-(ethoxycarbonylmethyl)octaethylporphyrin hydrogen iodide, the unprotonated pyrrole rings (N2 and N3 for the neutral species and N4 for the hydrogen iodide salt) are tilted away from the alkyl group to a similar extent (10.2 and 11.9° for the present structure and 11.7° for the hydrogen iodide case). The protonated pyrrole rings, however, are oriented very differently in these two nonmetalated species, however (-8.1° for the present case, compared with 4.6 and 2.2° for the protonated hydrogen case).

These tilting distortions of the pyrrole rings result in exposure of the nonbonding electrons on N2 and N3 of the free-base N-methylporphyrin, and thus a metal ion should be able to bind readily. In this regard, the similarity of the orientation of the N2 and N3 pyrrole rings in N-$CH_3HTPPBr_4$ and ClFe(N-CH_3TPP) is striking. The distortion from planarity and, presumably, the resulting loss of resonance stabilization are greater for the free-base N-alkylporphyrin studied, N-$CH_3HTPPBr_4$, than for the protonated N-substituted porphyrin (N-(ethoxycarbonylmethyl)-octaethylporphyrin hydrogen iodide) previously studied.[15] Since the opposite effect is expected when a nonalkylated porphyrin becomes distorted on protonation,[20] the greater basicity of N-alkylporphyrins appears to be consistent with structural properties. As noted above, only part of the steric requirement of the alkyl group is met by rotation of the alkylated pyrrole ring, and the free base retains a large degree of aromaticity. The observed position of the N-methyl group is consistent with the large upfield shifts observed in proton NMR spectra (4.1 ppm for N-$CH_3HTPPBr_4$) for the protons of the N-methyl moiety.

Acknowledgment. We are grateful for the support of the NIH (CA 25457) and the BSC-PHE grants program of the City University of New York. The Nicolet R3/E X-ray diffractometer and computing system at Colorado State University was purchased with funds provided by the National Science Foundation (Grant No. CHE 8103011).

Registry No. N-$CH_3HTPPBr{\cdot}CH_2Cl_2$, 82414-87-7.

Supplementary Material Available: Table I listing atomic coordinates for non-hydrogen atoms of N-$CH_3HTPPBr_4{\cdot}CH_2Cl_2$ and Table II listing anisotropic thermal parameters (4 pages). Ordering information is given in any current masthead page.

(17) A larger data set will be collected with Mo Kα radiation, and the complete structural analysis using these data will be reported subsequently. Crystal data for $C_{45}H_{28}H_4Br_4{\cdot}CH_2Cl_2$ are currently as follows: monoclinic, space group $P2_1/c$ ($Z = 4$), $a = 15.440$ (2) Å, $b = 16.261$ (2) Å, $c = 17.534$ (2) Å, $\beta = 108.16$ (1)°, $V = 4183.0$ Å^3, formula weight = 1029.31, ρ calcd. = 1.64 g cm^{-3}. The relatively high R and R_w reported are primarily due to thermal motion of the CH_2Cl_2 found to occur as lattice solvent. No absorption corrections were made.

(18) Lavallee, D. K. *J. Inorg. Biochem.* **1982**, 16, 135-143.

(19) Hoard, J. L. In "Porphyrins and Metalloporphyrins"; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975; pp 317-380.

(20) Hrung, C. P.; Tsutsui, M.; Cullin, D. C., Meyer, E. F., Jr.; Moritomo, C. N. *J. Am. Chem. Soc.* **1978**, *100*, 6068-6075.

Total Synthesis of Milbemycin β_3

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In 1975, research laboratories of Sankyo Co., Ltd., Japan, reported isolation of a new family of antibiotics from a cultured *Stretptomyces* strain (B-41-146), demonstrating highly potent pesticidal activity against a variety of species of mites, beetles, and tent caterpillers without phytotoxicity.[1] Milbemycins α_1-α_{10} and β_1-β_3 have been identified, and these closely related structures have been primarily assigned following NMR studies and X-ray crystallographic analysis.[2] Subsequently a family of eight disaccharides, known as the avermectins, were discovered at Merck, Sharp and Dohme, and these compounds were found to be structurally related to the milbemycins.[3] The avermectins are highly efficacious agents for elimination of essentially all gastrointestinal and systemic nematodes and demonstrate extraordinary toxicity to mites, ticks, and larvae of biting flies.[4]

Our chemical investigations have led to the successful preparation of milbemycin β_3 (**1**), the simplest member of the milbemycin-avermectin family, along a highly convergent route. By

(1) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kywano, H.; Saito, A. *Tetrahedron Lett.* **1975**, 711, and papers of the 18th Symposium on the Chemistry of Natural Products, Kyoto, Japan, 1974, page 309.

(2) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120.

(3) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(4) For references concerning the biological activity, see: *Ann. Rep. Med. Chem.* **1981**, *16*, 130, 163, 165, 269.

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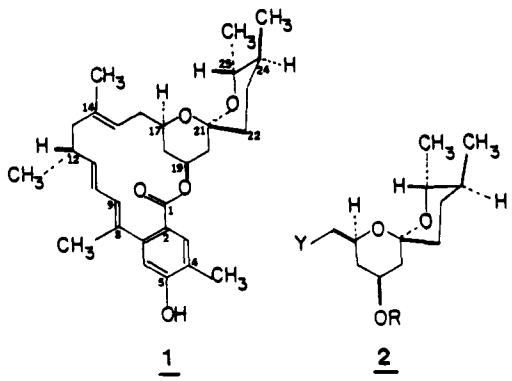
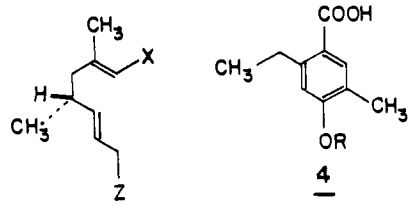


1 2



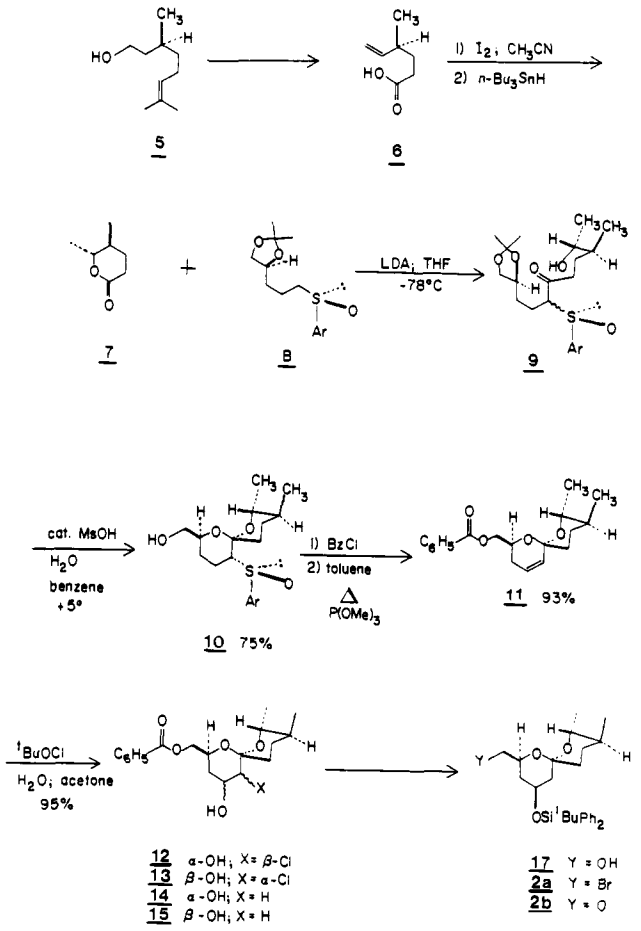
3 4

retrosynthetic considerations, the approach has subdivided milbemycin β_3 (**1**) into three components: (a) the spiroketal moiety **2**; (b) a carbon chain **3** bearing a remote chiral center at C-12; (c) the substituted benzoic acid **4**.

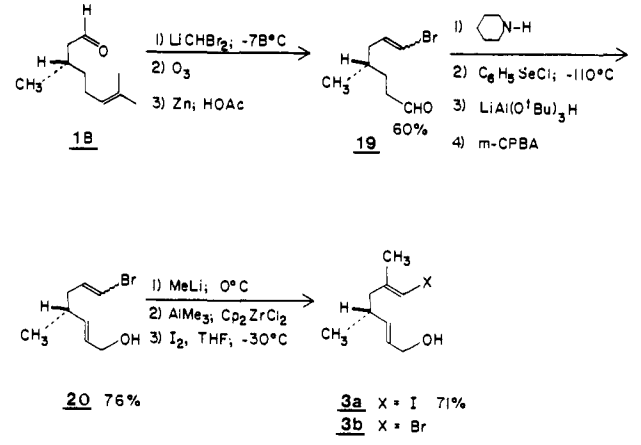
Our planning recognized three basic aspects of stereocontrol in the milbemycin problem. First, the efficient control of relative stereochemistry was required in preparation of the 1,7-dioxaspiro[5.5]undecanol **2**. Secondly, avoiding the producting of diastereoisomers, we obtained the asymmetric components **2** and **3** with their correct absolute configurations, beginning, in each case, with the same readily available chiral starting material, (−)-(3*S*)-citronellol.[5] Additionally, our route chose to avoid intermediates that might allow facile epimerization of established stereochemical features. Finally, selective methods were considered for construction of olefin geometries, as molecular models seemed to indicate that both *E* and *Z* configurations of carbon double bonds could afford diastereomeric 16-membered macrocycles.

Formation of spiroketal **2** was completed as illustrated in Scheme I.[6] Dehydration of citronellol **5** followed by oxidative cleavage of the trisubstituted olefin[7] and Jones' oxidation gave carboxylic acid **6**. Iodolactonization as described by Bartlett[8] and reduction with tri-*n*-butyltin hydride afforded *trans*-4,5-dimethylvalerolactone (**7**, bp 80–82 °C (1.0 mmHg), $[\alpha]^{24}_D$ +13.1° (*c* 4.86, $CHCl_3$) in approximately 40% overall yield (15:1 trans/cis). Condensation of **7** with the α-lithiosulfinyl carbanion **8**[9] (Ar = *p*-tolyl) yielded crude adduct **9** as a mixture of two diastereoisomers, and internal ketalization occurred in wet benzene (6–8 drops of H_2O) with a catalytic amount of acid affording spiroether **10**. Stereochemistry of the resulting asymmetric center

Scheme I



Scheme II



is thermodynamically controlled with each of the ether oxygens in pseudoaxial dispositions owing to the anomeric effect as commonly seen in carbohydrates. Additionally, equilibration occurs at C-20 to provide the equatorial sulfoxide; however, 10% of the corresponding axial (β) sulfoxide is also obtained but utilized in the synthetic scheme. Protection of **10** as its benzoate ($[\alpha]^{23}_D$ +98.9° (*c* 0.855, MeOH) and subsequent pyrolysis in refluxing toluene (22 h) gave the expected olefin **11** (mp 45–46 °C, $[\alpha]^{26}_D$ −11.6° (*c* 3.65, MeOH)). In earlier studies we noted a substantial rate difference for syn elimination of (*R*)- and (*S*)-phenyl sulfoxides as the corresponding (*S*)-sulfoxide configuration for **10** gave olefin only under more forcing conditions (xylene, reflux, 49 h, 72% conversion). The alkene was quite unreactive owing to the inductive effect of the allylic oxygen substituents; however, chlorohydrin formation occurred readily, providing two separable products, **12** and **13**, in a 5:1 ratio. Although the reaction offered

(5) We thank Dr. Günther Ohloff, Firmenich SA, Geneva, Switzerland, for providing a very generous sample of (−)-citronellol (levocitrol) ($[\alpha]^{21}_D$ −4.1°).

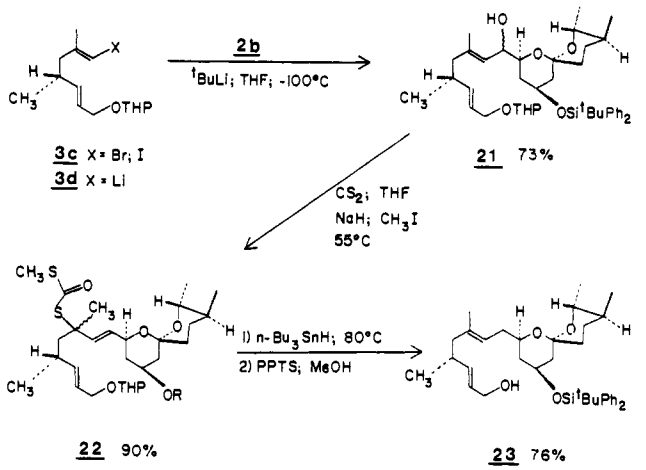
(6) All yields are reported for purified samples, characterized by infrared, nuclear magnetic resonance, and mass spectral data and combustion analysis. The ^1H and ^{13}C NMR spectra were recorded on a 360-MHz instrument in $CDCl_3$ (0.1% Me_4Si) solutions. Complete details will be provided in the full paper.

(7) Cernigliaro, G. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, *42*, 3622. Jones' oxidation of the aldehyde afforded carboxylic acid **6** (bp 75–77 °C (1.0 mmHg), $[\alpha]^{23}_D$ +12.1° (*c* 2.39, $CHCl_3$)).

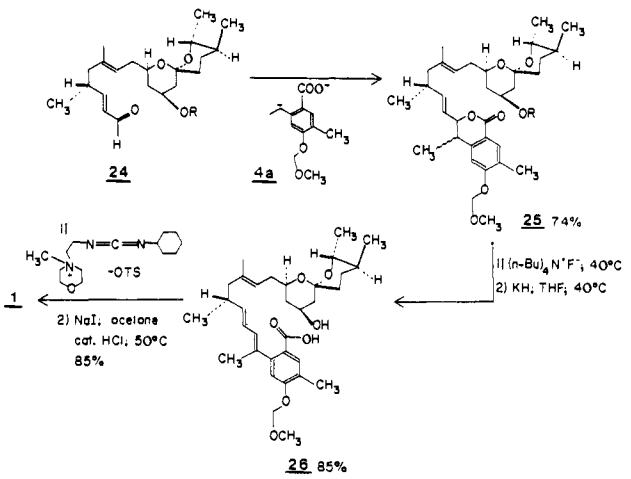
(8) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625. After reduction, tin residues were removed as reported: Leibner, J. E.; Jacobus, J. *Ibid.* **1979**, *44*, 449.

(9) The chiral (*R*)-sulfoxide **8** was readily available from the acetonide of (+)-glyceraldehyde derived from D-mannitol and advantageously eliminates the production of diastereoisomers. Details of preparation for **8** will be presented in the full account of this work.

Scheme III



Scheme IV



excellent regiocontrol, the major product **12** resulting from diaxial addition to the carbon double bond was of the undesired configuration. Thus, direct reduction (n-Bu_3SnH, toluene, reflux) of each of the crystalline chlorohydrins clearly gave **14** (mp 79–80.5 °C, $[\alpha]^{26}_D$ +29.8° (c 3.18, MeOH) 87% yield), and the equatorial alcohol **15** (mp 83–84 °C, $[\alpha]^{26}_D$ +31.6° (c 1.12, MeOH), 90% yield). Inversion of the axial alcohol **14** was best accomplished by oxidation (PCC, CH_2Cl_2, 25 °C) to ketone **16** (mp 54–55 °C), and subsequent reduction ($NaBH_4$, DME, 0 °C) affording the desired alcohol in 70% yield for the two steps. Protection of **15** as a silyl ether (CH_2Cl_2, Ph_2-t-BuSiCl, DMAP, 22 °C) and saponification of the benzoate (LiOH, THF, 22 °C) gave primary alcohol **17** in 96% yield, which was subsequently transformed into two key intermediates for attachment of the carbon chain **3** by preparation of the bromide **2a** and by Swern oxidation (Me_2SO, oxalyl chloride, Et_3N, −50 °C), providing aldehyde **2b** in 92% yield.[10]

Construction of chiral carbon chain **3** was completed from (−)-(3S)-citronellal, **18**, as demonstrated in Scheme II.[6] Addition of lithiodibromomethane, ozonolysis, and treatment with zinc–acetic acid gave vinyl bromide **19** (60% overall) (55/45 E/Z).[11] Phenylselenenylation of the enamine of aldehyde **19** with subsequent reduction and oxidative elimination provided allylic alcohol **20** with stereoselective introduction of the trans-disubstituted olefin while avoiding possible epimerization of the chiral methyl substituent.[12] Elimination to the terminal acetylene (92% yield) and utilization of the methodology and conditions as described by Negishi[13] were found to be superior to other techniques for stereospecific formation of the trisubstituted alkene **3** affording either vinyl iodide **3a** or vinyl bromide **3b** (NBS, −40 °C, $[\alpha]^{24}_D$ +1.6° (c 1.08, $CHCl_3$)).

The union of components **2** and **3** proceeded as shown in Scheme III by transmetalation[14] of tetrahydropyranyl ether **3c** affording the vinyllithium reagent **3d** (X = Li), which failed to undergo alkylation reactions. Preparation of mixed Gilman reagents from **3** also failed to react with **2a** or its corresponding iodide. However, the vinyllithium intermediate provided rapid addition to aldehyde **2b** and efficient formation of the allylic alcohols **21**.

Removal of the hydroxyl group proved difficult. Xanthate formation occurred with [3,3] sigmatropic rearrangement to yield the dithiocarbonates **22** bearing exclusively the *trans*-(E)-olefin geometry, and subsequent reduction with tri-n-butyltin hydride[15] afforded the desired alcohol **23** after removal of the tetrahydropyranyl ether.[16,17]

Attachment of the aromatic moiety **4** and completion of the total synthesis is summarized in Scheme IV.[6] Swern oxidation of **23** gave the α,β-unsaturated aldehyde **24** (95% yield). Benzylic deprotonation of the substituted benzoic acid **4**[18] gave a burgundy-colored solution of dianion **4a** (NaH, THF, then *tert*-butyllithium, −78 °C, 1 h), and addition of aldehyde **24** at −78 °C afforded the desired 6-membered lactone **25** (74% yield) as two diastereomers after mild acid treatment. Desilylation of each purified diastereoisomer and elimination provoked by potassium hydride yielded a single dienecarboxylic acid, **26** ($[\alpha]^{22}_D$ +25.2° (c 0.42, EtOH), UV_{max} (abs EtOH) 243 nm (ϵ 19 760), 270 (sh) (ϵ 13 260)). Finally total synthesis of synthetic milbemycin β_3 (**1**) (mp 185–187 °C, $[\alpha]^{22}_D$ +26.5° (c 0.20, MeOH), UV_{max} (abs EtOH) 247 nm (ϵ 27 200)) was most efficiently achieved by macrocyclic lactonization using 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate with subsequent deprotection of the methoxymethyl ether.[19] Further developments, stemming from these investigations, will be forthcoming.

Acknowledgment. We thank the National Institutes of Health (Grant AI 17668) and the Research Corp. for generous support of our work. We thank P. D. Magnus for helpful discussions and encouragement and A. B. Smith for providing us with spectra of natural and synthetic milbemycin β_3.

Registry No. **1**, 56198-39-1; **2a**, 82431-65-0; **2b**, 82415-05-2; **3a**, 82415-06-3; **3b**, 82467-24-1; **3c** (X = Br), 82415-07-4; **3c** (X = I), 82415-08-5; **3d**, 82415-09-6; **4**, 82415-10-9; **5**, 7540-51-4; **6**, 69274-86-8; **7**, 82467-25-2; **8**, 82430-64-6; 9, isomer 1, 82415-11-0; **9**, isomer 2, 82467-26-3; **10**, 82415-12-1; **10** benzoate, 82415-13-2; **11**, 82415-14-3; **12**, 82415-15-4; **13**, 82467-27-4; **14**, 82415-16-5; **15**, 82467-28-5; **16**, 82415-17-6; **17**, 82415-18-7; **18**, 5949-05-3; (*E*)-**19**, 82415-19-8; (*Z*)-**19**, 82415-20-1; **20**, 82415-21-2; **21**, 82415-22-3; **22**, 82415-23-4; **23**, 82431-66-1; **24**, 82415-24-5; **25**, 82415-25-6; **26**, 82415-26-7.

Supplementary Material Available: Spectral information and analyses for key substances (2 pages). Ordering information is given on any current masthead page.

(10) The isomeric aldehyde (epimer at C-17) with the carbonyl substituent in an axial disposition is readily isomerized to **2b** (DBU, THF, 22 °C).

(11) Williams, D. R.; Nishitani, K.; Bennett, W.; Sit, S. Y. *Tetrahedron Lett.* **1981**, 3745. The vinylbromide **3b** was also prepared in accord with Scheme II beginning with the corresponding methyl ketone of **18**. However, zinc–acetic acid reduction gave a mixture of E and Z olefins from which the desired E isomer was clearly separated.

(12) Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, 4417.

(13) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4096.

(14) Neumann, H.; Seeback, D. *Chem. Ber.* **1978**, *111*, 2785.

(15) The related deoxygenation–stannylation of primary allylic alcohols has been described: Ueno, Y.; Sano, H.; Okawara, M. *Tetrahedron Lett.* **1980**, *21*, 1767.

(16) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(17) The reduction was stereoselective as chromatography affording pure **23** also gave a forerun fraction (~25% from **21**) containing three olefinic isomers which have not been separated or fully characterized.

(18) The necessary benzoic acid **4** was obtained via methylation of 4-(methoxymethyleneoxy)-2,5-dimethylbenzoic acid (NaH, THF, then *tert*-butyllithium, −78 °C, 1 h, dimethylsulfate, −78 → −50 °C) in 85% yield.

(19) Our synthetic material was identical with ^{13}C and ^1H NMR, ultraviolet, infrared, and mass spectral data of authentic milbemycin β_3. We extend our congratulations to Professor A. B. Smith and co-workers on their recent completion of a total synthesis of (±)-milbemycin β_3.