Table I. NMR Data of 3a and 3b[a]

δ_H[b] (ppm) and HH coupling constants (Hz)		δ_{13C} (ppm)
3a	3b	3a
H_2 = 5.64, $^4J_{H_2H_6}$ = 1.8	H_2 = 5.96	C_1 = 187.1
H_5 = 7.90, $^2J_{H_5H_6}$ = 10.2	H_5 = 6.94, $^3J_{HH}$ = 10.3	C_2 = 99.7
H_6 = 6.42, $^2J_{H_6H_5}$ = 10.2, $^4J_{H_6H_2}$ = 1.8	H_6 = 6.08, J_{HH} = 10.3	C_3 = 151.9
OEt (on C_3)		C_4 = 133.6
CH_3 = 1.26, $^3J_{HH}$ = 7.3		C_5 = 128.7
CH_2 (AB pattern): H_A = 4.02, H_B = 3.96, $^2J_{H_AH_B}$ = 9.5		C_6 = 125.7
H_9 = 6.43, $^4J_{H_9H_{11}}$ = 2.4	H_9 = 6.55	C_7 = 140.6
H_{11} = 6.49, $^3J_{H_{11}H_{12}}$ = 8.7, $^4J_{H_{11}H_9}$ = 2.4	H_{11}[c]	C_8 = 157.6
H_{12} = 7.24, $^3J_{H_{12}H_{11}}$ = 8.7	H_{12} = 7.31, $^3J_{HH}$ = 8.4	C_9 = 103.5
OEt (on C_8)		C_{10} = 161.3
CH_3 = 0.84, $^3J_{HH}$ = 6.9		C_{11} = 104.8
CH_2 (AB pattern): H_A = 3.71, H_B = 3.66, $^2J_{H_AH_B}$ = 9.5		C_{12} = 129.1
OEt (on C_{10})		
CH_3 = 1.43, $^3J_{HH}$ = 7.0		
CH_2 (AB pattern): H_A = 4.09, H_B = 4.06, $^2J_{H_AH_B} \simeq$ 9.2		

[a] See the numbering of atoms in Scheme I. [b] Downfield from internal TMS reference. [c] Absorption not observed due to overlap with those of the abundant isomer.

Table II. X-ray Structure Data of 3a[a]

Bond Distances, Å			
O(1)–C(1)	1.238 (4)	C(5)–C(6)	1.342 (5)
C(1)–C(2)	1.452 (5)	C(6)–C(1)	1.455 (5)
C(2)–C(3)	1.347 (5)	N(1)–C(4)	1.345 (4)
C(3)–C(4)	1.456 (5)	N(1)–O(3)	1.284 (4)
C(4)–C(5)	1.434 (5)	N(1)–C(7)	1.447 (5)
Bond Angles, deg			
O(3)–N(1)–C(4)	120.7 (3)	N(1)–C(4)–C(5)	117.5 (3)
O(3)–N(1)–C(7)	113.6 (3)	N(1)–C(7)–C(8)	120.3 (3)
N(1)–C(4)–C(3)	124.0 (3)	N(1)–C(7)–C(12)	118.2 (3)
Dihedral Angles, deg			
C(8)–C(7)–N(1)–C(4)	60	O(3)–N(1)–C(4)–C(5)	9.8

[a] Esd's in units of the least significant figure are in parentheses.

with 1 is much faster than its nitration.

In the ^1H NMR spectrum of **3a**, the CH_2 and CH_3 assignments for each of the ethoxy groups were made on the basis of spin–spin decoupling experiments. Actually, the CH_2's of OEt groups appeared as an AB pattern due to the high asymmetry of the molecule. Their CH_3's gave triplets (1:2:1) because of overlapping of doubled doublets resulting from coupling with the nonequivalent CH_2 protons. The ^{13}C NMR spectrum showed a total of 12 resonances in the aromatic region. The six peaks in the range of 187.1–133.6 ppm were appreciably weaker than the other six peaks (128.7–99.5 ppm). Since carbon atoms not carrying hydrogen atoms are expected to have relatively long relaxation times and the spectrum was run under conditions of partial saturation, the weaker six peaks were assigned to carbon atoms not carrying hydrogen atoms and the other six peaks to carbons with directly bonded hydrogen atoms. The ^{13}C NMR spectrum also showed peaks due to the three OEt groups: CH_2's at 64.5, 64.0, and 64.0 ppm; CH_3's at 14.6, 14.4, and 13.3 ppm.

Experimental Section

NMR Spectra. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Nicolet NT-300 spectrometer. The spectrometer was operated at 75.46 Hz for ^{13}C NMR with a time-shared deuterium lock on $CDCl_3$.

Nitration of 1,3-Diethoxybenzene (1). A mixture of 10.7 mL of 90% nitric acid and 50 mL of glacial acetic acid was added to a solution of 16.6 g (0.1 mol) of 1 in 50 mL of glacial acetic acid over 30 min during stirring at less than 10 °C. The solution was poured onto ice. After 10 min, an amber-red solid separated, which was collected by filtration, washed with water, and recrystallized from ethanol: 15 g (90.4%); mp 179–180 °C. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.3; H, 6.3; N, 4.2; O, 24.2. Found: C, 65.4; H, 6.3; N, 4.1; O, 24.2.

X-ray Structure Determination of 3a. A parallelogram with dimensions ~0.31 × 0.25 × 0.32 mm was mounted on a Syntex R3 diffractometer equipped with a monochromator and an LT-1 low-temperature refrigeration unit operating at −100 °C. The diffractometer routines indicated a monoclinic unit cell with dimensions a = 11.294 (1) Å, b = 14.140 (2) Å, c = 11.180 (2) Å, β = 90.54 (1)°. With Z = 4 the calculated density of $C_{18}H_{21}NO_5$ is 1.233 g/cm^3. A total of 1520 unique reflections with $I \leq 3.0\sigma(I)$ were obtained from $4.6° \leq 2\theta \leq 55.0°$ by using the ω-scan method with scan width = 1.30ω, scan speed = 2.00–9.80°/min. The structure was solved with direct methods (MULTAN) and refined by full-matrix least squares on F with weights proportional to $[\sigma^2(I) + 0.0009I^2]^{-1/2}$ (217 parameters, refined anisotropic: all nonhydrogen atoms, fixed H atoms). Scattering factors were taken from *International Tables for X-ray Crystallography*, Vol. IV. The final R values are R = 0.049, R_w = 0.045, error of fit = 1.37, max Δ/σ = 0.06, largest residual density = 0.31 e/Å^3, near C_{15}.

The X-ray powder diffraction data were collected on a large sample of the isomer mixture by using an automated Norelco diffractometer. The calculated pattern from the single-crystal data matched very well with the powder pattern, indicating that the single crystal used in the structure analysis was indeed representative of the abundant isomer **3a**.

Acknowledgment. We are thankful to Dr. Derick W. Overnall for running the ^{13}C NMR spectrum and to Dr. Gade S. Reddy for the proton decoupled spectrum. The X-ray work is by Drs. J. C. Calabrese and R. L. Harlow.

Supplementary Material Available: Tables containing fractional coordinates, anisotropic thermal parameters, interatomic distances, and intramolecular angles for **3a** (3 pages). Ordering information is given on any current masthead page.

Photoisomers of Avermectins

Helmut Mrozik,* Philip Eskola, Glenn F. Reynolds, Byron H. Arison, Graham M. Smith, and Michael H. Fisher

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Received October 16, 1987

Avermectins are 16-membered lactones containing a diene function at positions 8, 9, 10, and 11 of the macrocycle.[1] They are widely used as drugs for the prophylaxis and control of parasitic infections of animals[2] and are

(1) (a) Fisher, M. H.; Mrozik, H. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: 1984; pp 553–606. (b) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87–121.

(2) (a) Campbell, W. C. *Parasitol. Today* **1985**, *1*, 1. (b) Campbell, W. C.; Benz, G. W. *J. Vet. Pharamacol. Ther.* **1983**, *7*, 1.

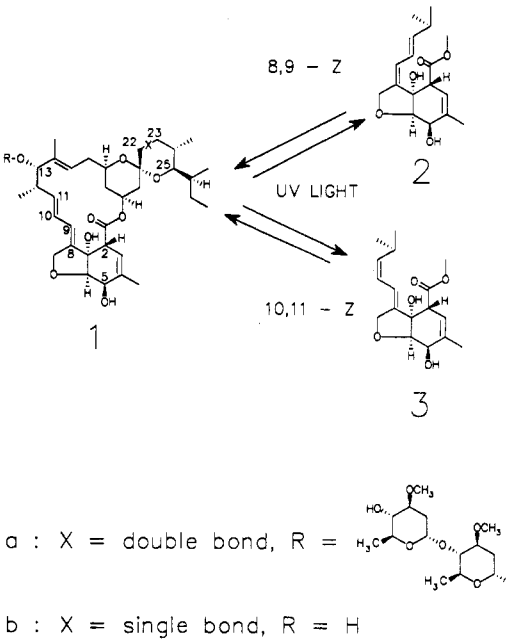
0022-3263/88/1953-1820$01.50/0

currently under investigation for the treatment of certain human filarial infections.[3] In addition they show a great potential as insecticides for agricultural crops.[4] It is in that application that the compounds are exposed to intense sunlight. For that reason it became important to know the reactivity of avermectins toward irradiation with light, particularly since the formation of an isomer under certain photochemical reaction conditions was observed previously.

When 22,23-dihydroavermectin B_1[5] was irradiated in cyclohexane or methanol solution in a Rayonet photoreactor using a light source with a maximum emission of 300 nm and a quartz vessel, a new compound was isolated from the reaction mixture. Mass spectra and ^1H NMR data suggested the formation of a double-bond isomer. HPLC analysis over the course of the photoreaction showed that in dilute solution, under these reaction conditions, equilibrium is reached after 30 to 60 min. A careful study of the photoisomerization was then carried out with a sample of avermectin B_1 consisting of 94% B_{1a} (**1a**) and 6% B_{1b}[6] in cyclohexane solution. The starting solution showed two peaks with retention times of 6.1 and 7.3 min in a ratio of 6 to 94 for avermectin B_{1b} and B_{1a}, respectively. After 20 min of irradiation three peaks were observed at 6.0, 7.3, and 8.6 min retention time (peaks A, B, C). Further irradiation for a total of 120 min changed the ratio only slightly to a final value of 17%, 45%, and 35%. Continued irradiation did not change this ratio; however, a slow decomposition to material devoid of UV absorption was observed over the next 24 h. Isolation of the three peaks by preparative HPLC, and ^1H NMR and mass spectral investigation confirmed peak B as avermectin B_{1a} (**1a**). Peak A was a mixture of a small amount of avermectin B_{1b} and a new isomer **3a**. Peak C (**2a**) was a different new isomer, apparently pure, and was the first to be subjected to structure determination. When pure isomers **2a** and **3a** were separately irradiated, the single peaks changed within 20 min to the identical three peak equilibrium mixtures as obtained from avermectin B_1.

Structure Determination

(8,9-*Z*)-Avermectin B_{1a} (**2a**). Mass, ^1H and ^{13}C NMR, and UV spectra suggested the structure of a double-bond isomer of **1a**. It was not possible, however, to identify the isomerized double bond. In order to simplify the task of interpreting NMR spectra of such a large molecule and to keep obscured signals to a minimum the photoisomers **2b** and **3b** of 22,23-dihydroavermectin B_1 aglycon **1b** were prepared and subjected to further NMR analysis. Although the coupling constants of the vinylic protons 9, 10, and 11 of isomer **2b** are similar to those of the parent compound **1b**, the diene was implied as the center for the proposed change because major shift differencies were confined only to that region, notably H-10, -12, -13, and -15. Of several possibilities the 8,9-*Z* isomer most readily provided an explanation for the striking 0.7 ppm downfield shift of H-10, assuming a close proximity of this proton to the lactone carbonyl group in this isomerized configuration. A computer-generated model of the 8,9-*Z* aglycon (starting from the X-ray structure conformation of avermectin B_{2a} aglycon) indeed places H-10 2.8 Å from the carbonyl where it is suitably positioned to be deshielded. The same model also indicated that the C-8a methylene protons and H-9 are separated by 2.8–2.9 Å, a distance close enough for an NOE to be observed. Irradiation of the C-8a methylene resulted in approximately a 13% increase in the area of H-9, thus establishing that these protons are in close proximity. No NOE enhancement was observed for H-9 when the analogous experiment was performed on the natural aglycon **1b**, where the 8a-CH_2 and H-9 are separated by 3.9 Å. A further confirmation of the 8,9-*Z* structure was obtained by comparison of the NOESY maps of avermectin B_{1a} (**1a**) and its 8,9-*Z* isomer (**2a**). Most significant are cross-peaks between H-9 and the 8a-methylene in **2a** establishing that the protons at these sites are in close proximity. An analogous observation in **1a** indicates that in this case H-10 and the 8a-methylene protons are close in space. There is no evidence for a cross-peak between H-10 and the 8a-CH_2 in the 8,9-*Z* isomer **2a** nor is a cross-peak detected between H-9 and the 8a-CH_2 in **1a**. Additional support for the 8,9-*Z* geometry is provided by the cross-peak between H-10 and H-3, indicating that these protons must be within 4–5 Å of each other.



(10,11-*Z*)-Avermectin B_{1a} (**3a**). The minor photoreaction product was suspected to be the 10,11-*Z* isomer on the basis of its mass, ^1H NMR, and UV spectra. It was also converted rapidly by further UV irradiation to the identical three-component equilibrium mixture obtained from **1a**. The key diagnostic feature for this geometric isomer is the observation of a 12.0-Hz coupling constant between H-10 and H-11, which is in the range for a cis double bond but well outside the 15–17 Hz values for a trans stereochemical relationship, as observed in the natural avermectins **1a** and **1b**. Another consequence of the stereochemical change is the approximate 0.65-ppm downfield shift of H-9 to 6.50 ppm, which probably results from its close proximity to the carbonyl group. Interestingly while aglycon **3b** has at room temperature a normal ^1H NMR spectrum, the large 13-bis(oleandrosyl) substituent of isomer **3a** apparently puts severe restriction on the conformational movement, so that only after heating to 55 °C protons 9, 10, 11, and 12 did change from very broad signals to sharp recognizable peaks.

Energy Calculations for (8,9-*Z*)-Avermectins. Severe steric interactions in particular between carbons 1 and

(3) Dadzie, K. Y.; Bird, A. C.; Awadzi, K.; Schulz-Key, H.; Gilles, H. M.; Aziz, M. A. *Brit. J. Ophthalmol.* **1987**, *71*, 78.
(4) Putter, I.; MacConnell, J. G.; Preiser, F. A.; Haidri, A. A.; Ristich, S. S.; Dybas, R. A. *Experientia* **1981**, *37*, 963.
(5) Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H.; Campbell, W. C.; Egerton, J. R.; Ostlind, D. A. *J. Med. Chem.* **1980**, *23*, 1134.
(6) Avermectin B_{1b} is the lower homologue of 1a containing at position 25 an isopropyl instead of the *sec*-butyl substituent.

Table I

structure	calcd energy, kcal	rel energy, kcal	C1-C10 dist, Å	C1-H10 dist, Å	C1-H9 dist, Å
1 = 8,9-*E*	33.5	0.0	4.7	5.3	3.2
2 = 8,9-*Z*	36.2	2.7	3.6	2.9	4.8
3 = 10,11-*Z*	39.4	5.9	4.8	5.4	3.2

10 could be expected for the 8,9-*Z* configuration (**2**), particularly when looking at the flat two-dimensional structure projection. Therefore empirical force field calculations were performed on the three isomers to determine their relative strain energies and geometries. From the final geometries the proximities of hydrogen atoms suitable for NOE NMR experiments could be determined. The natural isomer **1** was derived directly from the original X-ray structure of avermectin B_{2a} aglycon.[7] The structure energy was minimized by using our in-house version of MM2 (Optimol). The two isomers **2** and **3** were generated by using the program FRODO. The C-15 to C-16 bond was opened and the dihedral angle for the 8,9 or 10,11 double bond set to form the cis bond. Then the dihedral angles of the single bonds in the macrocyclic ring were adjusted to close the 15,16 bond, giving the correct configuration for the 14,15 double bond. During this process the adjustments to the dihedral angles were kept as small as possible while closing the ring with reasonable bond lengths, bond angles, and dihedral angles at the closure, therefore giving a conformation as similar to the original as possible. These structures were then submitted to the same energy minimization procedure. The resulting energies indicate that the 8,9-*Z* (**2**) and 10,11-*Z* (**3**) isomers are 3 and 6 kcal/mol more strained, respectively, than the natural isomer **1** (Table I). The smaller increase in calculated strain for the 8,9-*Z* isomer (**2**) relative to the 10,11-*Z* isomer (**3**) could be explained by examining the three-dimensional models. They show the lactone carbonyl oxygen in close contact with carbon 10 in the 10,11-*Z* (**3**) model, but not in the 8,9-*Z* (**2**) model because of the nonplanar cis-fused oxahydrindene ring. The higher strain of **3** versus **2** is also reflected in the ^1H NMR spectrum of **3a** (vide supra) which suggests steric restriction to free conformational changes at room temperature.

Experimental Section

Pure avermectin B_{1a} (**1a**) was obtained from commercial abamectin (mixture of 94% and 6% avermectin B_{1a} and B_{1b}, and a moisture/solvent content of 19%) through preparative reverse-phase HPLC on a Whatman Partisil M20 10/50 ODS-3 column. A batch of 700 mg of abamectin dissolved in 4.5 mL of 80% aqueous MeOH was injected and eluted with 88% aqueous MeOH at a rate of 11.25 mL/min. The appropriate fractions were combined and concentrated in vacuo to a white foam consisting of 480 and 21 mg of avermectin B_{1a} (**1a**) and B_{1b},[7] respectively. They showed a single peak on analytical HPLC and were identified by their ^1H NMR spectra. The new compounds were obtained as amorphous lyophilizates, purified by chromatography on silica gel GF Uniplates, Analtech, 0.25–1.0 mm thickness, and/or by reverse-phase high-performance liquid chromatography on a Whatman Partisil M20 10/50 ODS-3 column. Purity of products and progress of reactions were determined by analytical TLC on silica gel plates, visualized by UV fluorescence and staining with phosphomolybdic acid, and analytical HPLC on a Whatman Partisil PXS 10/25 ODS-3 column using UV absorption at 254 nm for detection. ^1H and ^{13}C NMR spectra were recorded on Varian XL-200 and XL-400 instruments in $CDCl_3$ solution with Me_4Si as internal reference. Mass spectra were obtained on an LKB Model 9000 or Varian MAT 212 mass spectrometer.

(8,9-*Z*)-Avermectin B_{1a} (2a). Pure avermectin B_{1a} (**1a**, 650 mg) was dissolved in 1000 mL of cyclohexane with gentle warming. The solution was transferred into a quartz tube, stirred under N_2, and irradiated in a Rayonet photoreactor with eight tubes emitting UV light with a 300-nm maximum. The progress of the reaction was followed by probes, which were analyzed by HPLC. After 2.25 h three peaks were present in the ratio of 8%, 51%, and 41% for **3a**, **1a**, and **2a**, respectively. The reaction mixture was transferred into a round-bottom flask with a little MeOH and concentrated in vacuo to 600 mg of white foam. This was dissolved in 5 mL of MeOH–CH_2Cl_2 (8:2 mixture) and subjected to preparative HPLC in two portions. The fractions were checked by analytical HPLC and the appropriate ones combined and concentrated in vacuo to give 40 mg of **3a** (see below), 335 mg of **1a**, and 202 mg of **2a**: HPLC (85:15 MeOH–H_2O, 1.0 mL/min) t_R 12.3, 14.5 min (3, 97%); UV λ_{max} (MeOH) 243 nm (ϵ 28 700); MS, *m/e* 872 (M^+); 400-MHz ^1H NMR ($CDCl_3$) δ 6.43 (1 H, ddd, J = 15, 11, 2 Hz, $C_{10}H$), 5.84 (1 H, d, J = 11 Hz, C_9H), 5.78 (1 H, dd, J = 10, 2 Hz, $C_{22}H$), 5.73 (1 H, dd, J = 15, 4 Hz, $C_{11}H$), 5.70 (1 H, s, C_7OH), 5.57 (1 H, dd, J = 10, 2 Hz, $C_{23}H$), 5.40 (1 H, d, J = 3 Hz, $C_{1''}H$), 5.25 (2 H, m, $C_{15}H$, $C_{19}H$), 4.78 (1 H, d, J = 3 Hz, $C_{1'}H$), 4.59 and 4.52 (2 × 1 H, 2 brd, J = 14 Hz, $C_{8a}H_2$), 4.31 (1 H, m, C_5H), 4.20 (1 H, d, J = 4 Hz, $C_{13}H$), 4.03 (1 H, d, J = 6 Hz, C_6H), 3.40 and 3.37 (2 × 3 H, 2 s, $C_{3''}OCH_3$ and $C_{3'}OCH_3$), 3.26 (1 H, m, C_2H), 2.74 (1 H, br s, $C_{12}H$), 1.86 (3 H, s, C_4CH_3). Anal. Calcd for $C_{48}H_{72}O_{14}$ (873.088): C, 66.03; H, 8.31. Found: C, 65.75; H, 8.46.

(10,11-*Z*)-Avermectin B_{1a} (3a) was obtained as a byproduct of **2a** (see above) as 40 mg of white foam **3a**: HPLC (85:15 MeOH–H_2O, 1.5 mL/min; t_R 5.6, 6.3 min, 92%, 8%); UV λ_{max} (MeOH) 247 nm (ϵ 23 370); HRMS calcd for $C_{48}H_{70}O_{13}$ (M^+–H_2O) 854.4816, found 854.4788; 400-MHz ^1H NMR ($CDCl_3$, 55 °C) δ 6.48 (1 H, d, J = 12 Hz, C_9H), 5.80 (1 H, t, J = 12 Hz, $C_{10}H$), 5.76 (1 H, dd, J = 10, 2 Hz, $C_{22}H$), 5.59 (1 H, dd, J = 10, 2 Hz, $C_{23}H$), 5.56 (1 H, brm, $C_{11}H$), 5.47 (1 H, m, $C_{15}H$), 5.37 (1 H, d, J = 3, $C_{1''}H$), 5.34 (1 H, m, $C_{19}H$), 4.24 (1 H, t, J = 6 Hz, C_5H), 4.14 (1 H, d, J = 2 Hz, $C_{13}H$), 3.95 (1 H, d, J = 6 Hz, C_6H), 2.82 (1 H, brt, J = 8, $C_{12}H$).

(8,9-*Z*)-22,23-Dihydroavermectin B_{1a} Aglycon (2b). A solution of 200 mg of 22,23-dihydroavermectin B_{1a} aglycon (**1b**) in 600 mL of cyclohexane was irradiated for 4 h as above and concentrated in vacuo to 200 mg of light foam. This was separated into two fractions on three preparative silica gel layer (1.5 mm) plates by developing twice with 3:7 hexane–ether solvent. The faster band (67 mg, HPLC 8:2 MeOH–H_2O, 1.0 mL/min, t_R 11.1, 12.5, 13.3 min, 10%, 14%, 74%) contained mainly starting material according to ^1H NMR. The slower band (88 mg, HPLC t_R 12.3, 13.7 min, 19%, 75%) contained impure 8,9-*Z* isomer. This band was further chromatographed on two 1.0 mm thick 20 × 20 cm silica gel plates developed 4 times with 8:2 cyclohexane–acetone solvent yielding 11 mg of slower band, identified as 10,11-*Z* isomer (see below) and 70 mg of faster band, 8,9-*Z* isomer, HPLC t_R 11.9, 12.6, 14.0 min, 7%, 7%, 84%. A 12-mg aliquot of the latter was purified a third time on a 0.5 mm thick 20 × 20 cm silica gel plate developed 3 times with 8:2 cyclohexane–acetone giving 10 mg of 8,9-*Z* isomer **2b**: HPLC (8:2 MeOH–H_2O, 1.0 mL/min) t_R 12.4, 14.6 min (9%, 89%); UV λ_{max} (MeOH) 243 nm (ϵ 21 100); HRMS, *m/e* (M^+) calcd for $C_{34}H_{50}O_8$ 586.3506, found 586.3507; 200-MHz ^1H NMR ($CDCl_3$) δ 6.45 (1 H, ddd, J = 15, 11, 2 Hz, $C_{10}H$), 5.90 (1 H, s, C_7OH), 5.85 (1 H, d, J = 11 Hz, C_9H), 5.75 (1 H, dd, J = 15, 6 Hz, $C_{11}H$), 5.45 (1 H, m, $C_{15}H$), 5.28 (2 H, m, C_3H, $C_{19}H$), 3.24 (1 H, m, C_2H), 2.85 (1 H, brs, $C_{12}H$), 1.86 (3 H, s, C_4CH_3), 1.07 (3 H, d, J = 6, $C_{12}CH_3$).

(10,11-*Z*)-22,23-Dihydroavermectin B_{1a} Aglycon (3b). During the purification of **2b** there was obtained as byproduct 11 mg of **3b**: HPLC (8:2 MeOH–H_2O, 1.0 mL/min) t_R 10.4, 12.6 min (16%, 84%); UV λ_{max} (MeOH) 245 nm (ϵ 20 100); HRMS, *m/e* (M^+) calcd for $C_{34}H_{50}O_8$ 586.3506, found 586.3507; 400-MHz ^1H NMR ($CDCl_3$) δ 6.50 (1 H, d, J = 12 Hz, C_9H), 5.76 (1 H, td, J = 12, 1.5 Hz, $C_{10}H$), 5.57 (1 H, dd, J = 12, 6 Hz, $C_{11}H$), 5.46 (1 H, m, $C_{15}H$), 5.44 (1 H, brs, C_3H), 5.28 (1 H, m, $C_{19}H$), 4.68

(7) Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(2 H, s, $C_{8a}H_2$), 4.29 (2 H, brm, $C_{13}H$, C_5H), 3.94 (1 H, d, J = 6 Hz, C_6H), 3.74 (1 H, brm, $C_{17}H$), 3.39 (1 H, m, C_2H), 3.19 (1 H, d, J = 8 Hz, $C_{25}H$), 2.90 (1 H, brs, $C_{12}H$), 1.88 (3 H, s, C_4CH_3), 1.27 (3 H, d, J = 7 Hz, $C_{12}CH_3$).

Acknowledgment. We thank H. Flynn, D. L. Zink, and V. Mayo for NMR, mass, and UV spectral data.

An Efficient Synthesis of Both Enantiomers of *trans*-1,2-Cyclopentanediol and Their Conversion to Two Novel Bidentate Phosphite and Fluorophosphinite Ligands

Allan F. Cunningham, Jr., and E. Peter Kündig*

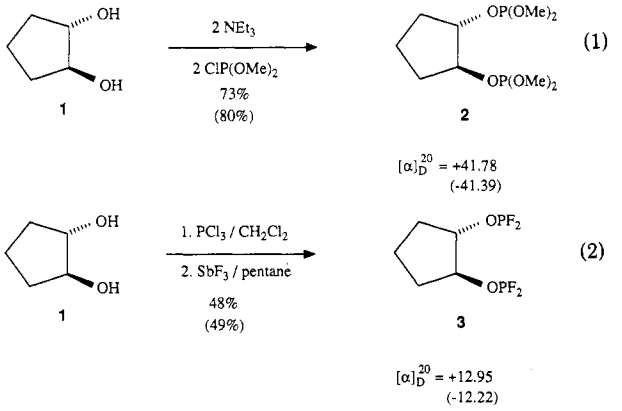
Department of Organic Chemistry, University of Geneva, CH-1211 Geneva 4, Switzerland

Received October 26, 1987

Ancillary ligands occupy a central role in organometallic chemistry as they are used to fine tune the electron density and to modify the steric environment at the metal center. In this capacity trivalent phosphorous ligands have been used extensively because this class of compounds exhibits a wide range of steric and electronic properties.[1] Chiral bidentate ligands in particular have been found to be very useful in asymmetric synthesis via organometallics—primarily in asymmetric catalysis.[2] However, all of the chiral phosphorous ligands known are the relatively electron-rich bis-phosphines and bis-phosphinites.[3] In conjunction with a study of asymmetric induction in the sequential addition of nucleophiles and electrophiles to arene chromium complexes,[4] we required better π-acceptor bidentate ligands. We here describe the synthesis of enantiomerically pure (+)- and (−)-*trans*-1,2-bis(dimethoxyphosphinoxy)cyclopentane (**2**) and *trans*-1,2-bis(difluorophosphinoxy)cyclopentane (**3**), the first examples of chiral chelating phosphite and fluorophosphinite ligands.

Reaction of common diols such as ethylene glycol and 2(*R*),3(*R*)-butanediol with dimethyl phosphorochlorodite[5] led to complex mixtures of products. Material balances were never greater than 45%. This suggested that in addition to the desired intermolecular reaction, polymerization and intramolecular processes were also occurring because of the lability of the P–OMe bond to nucleophilic displacement.

To avoid these side reactions, we employed a diol in which the hydroxyl functionalities were sterically constrained from intramolecular interaction. The reaction of racemic *trans*-1,2-cyclopentanediol (**1**)[6] with dimethyl phosphorochlorodite afforded a 72% yield of the desired bis(dimethylphosphite) **2** (eq 1). A more electron-withdrawing bidentate ligand, bis(difluorophosphite) **3**, was also prepared via a simple two-step procedure (eq 2). First, the



diol **1**, as a solution in CH_2Cl_2/ether (10:1), was slowly added to 10 equiv of PCl_3 in CH_2Cl. After removal of the solvent and excess PCl_3 at room temperature, the residue was treated with SbF_3 in refluxing pentane. Trap-to-trap distillation afforded a 48% yield of the tetrafluoride **3**. Purification of the intermediate tetrachloride by distillation (130 °C, 0.1 mmHg) led to lower yields as this material is prone to polymerization. The direct approach to **3**, involving the condensation of **1** with PF_3 in the presence of pyridine,[7] was unsuccessful.

Having developed facile syntheses of the racemic bidentate ligands **2** and **3**, their preparation in optically pure form was undertaken. When we began our work, neither (1*R*,2*R*)-(−)- nor (1*S*,2*S*)-(+)-cyclopentanediol ((−)-**1** or (+)-**1**) was available in optically pure form. In a preparation of *trans*-1,2-bis(diphenylphosphinoxy)cyclopentane[8] (which shows some promise as a ligand in asymmetric homogeneous hydrogenation), (+)-**1** was obtained with an enantiomeric excess of 67% from repeated crystallizations of the strychnine salt of its bis-hydrogensulfate.[9] Schneider and co-workers have reported an enzymatic hydrolysis of racemic *trans*-1,2-diacetoxycyclopentane which furnished the monoacetate of (−)-**1** with 63% ee and the diacetate of (+)-**1** with 50% ee.[10] A very recent report by Sakai and co-workers[11] described an enzymatic hydrolysis that afforded the same compounds with >99% ee and 95% ee, respectively. We have accomplished the synthesis of enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-cyclopentanediol ((−)-**1** and (+)-**1**) from the corresponding diethyl tartrates (Scheme I). This creates easy access to both pure enantiomers of ligands **2** and **3**.

The dibenzyl ether of L-(+)-diethyl tartrate (**4**) was prepared via the procedure described by Seebach et al.[12,13] Reduction of **4** with LAH in refluxing ether for 4 h afforded the diol **5** in a yield of 87%. Longer reaction periods resulted in lower yields due to reduction of the benzyl ether functionalities. Ditosylation of **5** under standard conditions led to **6** (86%) which was treated with 3 equiv of LiBr in DMSO to give the dibromide **7** (91%). It should be noted that **7** contains four of the five carbons of (1*S*,2*S*)-(+)-cyclopentanediol ((+)-**1**) and the proper stereochemistry of the vicinal hydroxyl functionalities. The addition of the fifth carbon and ring closure by cy-

(1) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organometallic Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 3.3.
(2) *Asymmetric Synthesis*; Morrison, J., Ed.; Academic Press: New York, 1985, Vol. 5 (Chiral Catalysis).
(3) For a recent review, see: Kagan, H. B. "Chiral Ligands for Asymmetric Catalysis", in ref 2, p 1.
(4) (a) Kündig, E. P.; Simmons, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1320. (b) Kündig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855. (c) Cunningham, A. F., Jr.; Dupré, C.; Kündig, E. P., manuscript in preparation.
(5) Ramirez, F.; Chaw, Y. F.; Maracek, J. F.; Ugi, I. *J. Am. Chem. Soc.* **1974**, *96*, 2429.
(6) Owen, L. N.; Smith, P. N. *J. Chem. Soc.* **1952**, 4026.
(7) (a) Centofanti, L. F.; Lines, L. *Inorg. Synth.* **1976**, *16*, 166. (b) Lines, L.; Centofanti, L. F. *Inorg. Chem.* **1973**, *12*, 2111.
(8) Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1977**, 295.
(9) Derx, H. G. *Recl. Trav. Chim. Pays-Bas* **1922**, *41*, 312.
(10) Crout, D. H. G.; Gaudet, V. S. B.; Laumen, K.; Schneider, M. F. *J. Chem. Soc., Chem. Commun.* **1986**, 808.
(11) Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838.
(12) Kalinowski, H.-O.; Crass, G.; Seebach, D. *Chem. Ber.* **1981**, *114*, 477.
(13) Yields and optical rotations for the (−) enantiomers prepared from D-(−)-diethyl tartrate are reported in parentheses in Scheme I.

0022-3263/88/1953-1823$01.50/0