found to be low at ≥170 °C. Molten $(1H)_2$ at ≥175 °C or in solution (e.g., in mesitylene) at ≈165 °C reacts slowly but irreversibly by way of various C–C hydroboration and other reactions. During the heating (≈20 h) the >BH borane bonds of $(1H)_2$ disappear completely.[4] Gas is not evolved. The ^{11}B NMR spectrum of the dark yellow viscous product shows new narrow signals at 90, 87, and 84 ppm and broad resonance signals in the region of +15 to −17 ppm. The obtained mixture consists of a volatile fraction (≈50%), containing (gas chromatography/mass spectra) the 9-alkyl-9-BBN derivatives [C_1–C_8; **3a–3h**; C_9–C_{11}; **3j–3l**) with homologous unbranched alkyl groups, the 9-cyclooctyl-9-BBN (**3i**), as well as the three compounds **4–6** with the presumed structures depicted in Scheme II. [**4**; *m/e* 242 (B_2); **5**; *m/e* 256 (B_2); **6**; *m/e* 270 (B_2); $\delta_{^{11}B}$ 90, 87, and 84 pm, respectively]. The resinous residue of the high-vacuum distillation ($\delta_{^{11}B}$ +15 to −17 ppm) probably consists of organoboron derivatives with carborane structures.

Similar results were obtained when dimeric 1- and 2-methyl-9-H-9-BBN derivatives (Me-$1H)_2$[5] were heated to >170 °C. Me-**3a–l** are formed as the main products (gas chromatography/mass spectra).

The thermal transformation of the diorganohydroboranes $(1H)_2$ or (Me-$1H)_2$ to the triorganoboranes **3a–l** or Me-**3a–l** are probably the result of a series of irreversible hydroborations of various C–C single bonds, as well as carboborations of C=C double bonds. In the formation of **4–6**, hydroborations of intermediates having B_3C groupings may also be assumed.[6]

Experimental Section

Gas chromatograms were obtained with a Siemens Sinchromat 1 instrument with a 30m OV 101 capillary column, injection port at 120 °C, oven at 60–330 °C, programmed at 6 deg/min; mass spectra were obtained on a Varian Mat CH 7A; ^{11}B NMR spectra were obtained on a Brucker WH 400 and ^{13}C NMR on a Brucker WM 300 spectrometer. All operations were performed under an argon atmosphere.

Thermal Isomerization of $(1D)_2$. (a) Formation of $(1H\text{-}d_x)_2/(1D\text{-}d_x)_2$; $x \leq 3$. $(1D)_2$ (1 g) was kept in molten state at ≈160 °C for ≈5 min, then cooled to ≈20 °C; mass spectrum (70 eV; *m/e*, relative intensity): **1H** (M^+, 122, 33), **1D** or **1H**-d_1 (M^+, 123, 39), **1D**-d_1 or **1H**-d_2 (M^+, 124, 22), **1D**-d_2 or **1H**-d_3 (M^+, 125, 6). The products were analyzed after conversion to 9-ethyl-9-BBN mixtures by the reaction of a THF solution of $(1H\text{-}d_x)_2/(1D\text{-}d_{x-1})_2$ at 60–70 °C with ethylene; ^{13}C NMR (75.5 MHz, [D_8]toluene) δ 33.23 (s) [C2(2 H) attached to C3(2 H)], 33.14 (s) [C2(2 H) attached to C3(HD)], 32.85 (t) [C2(HD) attached to C3(2 H)], 32.75 (t) [C2(HD) attached to C3(HD)], 30.9 (br) [C1], 23.40 (s), [C3(2 H) attached to C2(2 H) and C4(2 H)], 23.31 (s) [C3(2 H) attached to C2(HD) and C4(2 H)], 23.21 (s) [C3(2 H) attached to C2(HD) and C4(HD)], 22.97 (t) [C3(HD) attached to C2(2 H) and C4(2 H)], 22.88 (t) [C3(HD) attached to C2(HD) and C4(HD)], 22.79 (t) [C3(HD) attached to C2(HD) and C4(HD)], 19.9 (br) [C9], 8.06 (s) [C9′(3 H)], and 7.77 (t) [C9″(2 H, D)].

(b) Preparation of $(1D\text{-}d_6)_2$. To a sample of 0.2 g of $(1D)_2$, which had been melted at ≈160 °C and then cooled, was added 0.4 ml of deuteroalkyldiborane(6). After the mixture was heated (≈5 min) to 80–100 °C, the volatiles were removed in vacuo. This procedure was repeated ten times. A $(1H\text{-}d_x)_2/(1D\text{-}d_{x-1})_2$ mixture with 75% $(1D\text{-}d_6)_2$ [refluxing $(1H)_2$ or $(1D)_2$ with an excess of the deuterium donor led to perdeuteration of the C_8 ring, i.e., $(1D\text{-}d_{6+x})$, $x < 8$] was obtained.

Thermolysis of $(1H)_2$. Formation of 9-Alkyl-9-BBN Derivatives 3a–l and 4–6. $(1H)_2$ (8.5 g, 35 mmol) was heated at 170 °C for 72 h. From the dark yellow product that was viscous at room temperature 4.1 g of colorless liquid was obtained by distillation at 0.001 torr and up to 180 °C. The distillate was analyzed by gas chromatography; t_r (min, %): **3a** (5.0, 3.8), **3b** (7.2, 4.8), **3c** (9.2, 1.9), **3d** (11.4, 2.5), **3e** (3.7, 2.3), **3f** (16.0, 7.8), **3g** (18.1, 12.4), **3h** (20.3, 27.5), **4i** (22.6, 7.2), **3j** (22.2, 1.9), **3k** (24.0, 4.0), **3l** (25.8, 2.6), **4** (22.5, 7.2), **5** (24.5, 6.9), **6** (26.0, 4.6). MS (relative intensity): **4** *m/z* 242 (M^+, B_2, 90), 132 (B_2, 60), 120 (B_1, 95), 41 (100); **5** *m/z* 256 (M^+, B_2, 100), 145 (B_2, 80), 41 (75); **6** *m/z* 270 (M^+, B_2, 35), 148 (B_1, 100), 41 (53).

Acknowledgment. We are grateful to Dr. R. Benn and Dr. R. Mynott for ^{11}B and ^{13}C NMR spectra and to F. Sageb and W. Schmöller for the gas chromatographic and mass spectroscopic analyses.

Registry No. $(1D)_2$, 88644-67-1; $(1H)_2$, 21205-91-4.

(4) From DSC analysis a half-life time of 0.7 h for $(1H)_2$ at 200 °C can be estimated.

(5) The mixture of (1-Me-$1H)_2$ and (2-Me-$1H)_2$ was prepared from 1-methylcycloocta-1,5-diene and ethyldiboranes(6) according to ref 1.

(6) Cf. ref 1, 4th ed., 1984, Vol. XIII/3c, p 162.

A Simple Method for Distinguishing Optical Isomers of Chiral Amines, Hydroxylamines, Amino Acids, and Peptides

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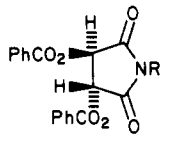
Received January 13, 1986

Distinguishing the optical isomers of amino acids, amines, and other functional chiral compounds is of considerable importance.[1] The demonstrated utility of dibenzoyltartarimide (DBT) derivatives **1** for the resolution of D,L-*O*-(tetrahydropyranyl)hydroxylamine (**2**)[2] and *O*-α-phenethylhydroxylamine (**3**)[4] suggested that related derivatives might be useful for the determination of the optical purity of other amines and amino acids. Herein we report on the general utility of DBT derivatives for differentiating the optical isomers of amino acids and other amines.



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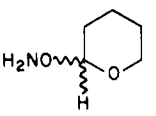

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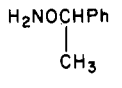
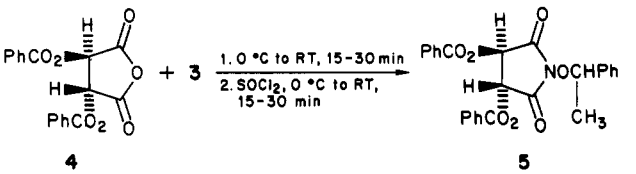


3

The simple reaction of dibenzoyl-L-(natural)tartaric anhydride (DBTA, **4**)[3] with DL-*O*-α-phenethylhydroxylamine (**3**) provided the diastereomeric dibenzoyl-DL-*N*-α-phenethoxytartarimides **5** (eq 1). Especially notable about



4 5

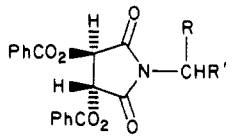
(1)

the NMR spectrum of **5** were the two sharp singlets at 5.65 and 5.74 ppm corresponding to the two methine protons of the DBT residue (Table I, entry 31). Similarly, the ^1H NMR spectrum of dibenzoyl-*N*-DL-α-phenethyl-L-tartarimide (Table I, entry 1) displayed two singlets at 5.83 and 5.91 ppm. However, the NMR spectrum of the *N*-D-phenethyl derivative (Table I, entry 2) displayed only *a single sharp singlet at 5.83 ppm.*

†Fellow of the Alfred P. Sloan Foundation (1981–1985). Recipient of an NIH Research Career Development Award (1983–1988).

0022-3263/86/1951-3055$01.50/0

Table I. DBT Derivatives



entry	R	R′	method	% yield[a]	mp, °C	m/e	$[\alpha]^D$	methine proton positions in the NMR spectra of the DBT derivatives[b] DL	L	D
1.	CH_3	C_6H_5	A[c]	98	107–108	443	+173.0	5.91; 5.83		
2.	CH_3	C_6H_5	A	~100	85–86	443	+217.4			5.83
3.	CH_3	CH_2CH_3	A[c]	~100	178–180	395[d]	+212.7	5.86; 5.85		
4.	H	CO_2CH_3	B	85	125–127	411	+158.7	6.03		
5.	CH_3	CO_2CH_3	B	91	144–145	425[e]	+217.5			5.95
6.	CH_3	CO_2CH_3	B	74	111–112	425	+189.0	5.98; 5.96		
7.	CH_3	CO_2CH_3	B	95	131–132	425	+153.5		5.97	
8.	C_2H_5	CO_2CH_3	A	90	66–68	439	+182.5	5.97; 5.96		
9.	i-C_3H_7	CO_2CH_3	B	45	66–68	453	+150.2	5.96; 5.95		
10.	i-C_3H_7	CO_2CH_3	B	55	78–80	453	+104.5			5.96
11.	i-C_3H_7	CO_2CH_3	B	60	oil	453	+173.8		5.98	
12.	i-C_4H_9	CO_2CH_3	B	74	oil	467	+132.6	6.00; 5.99		
13.	i-C_4H_9	CO_2CH_3	A	93	70–72	467	+108.0		5.99	
14.	CH_2Ph	CO_2CH_3	A	84	oil	501	+159.4	5.85; 5.78		
15.	CH_2Ph	CO_2CH_3	B	87	oil	501	+20.0		5.83	
16.	Ph	CO_2CH_3	A	88	oil	487	+142.8	6.03; 5.98		
17.	Ph	CO_2CH_3	B	97	59–61	487	+136.8			6.07
18.	CH_2OH	CO_2CH_3	C	68	71–73	423[f]	+111.4		6.11	
19.	CH_2OH	CO_2CH_3	C	80	80–82	423[f]	+175.8	6.11; 6.09		
20.	H	$NHCO_2CH_2CCl_3$ | $(CH_2)_2CHCO_2CH_3$	B	82	oil	644	+87.0	5.83; 5.81		
21.	H	$CHCO_2CH_3$ | $(CH_2)_2NHCO_2CH_2CCl_3$	B	67	oil	644	+130.8		5.80	
22.	CO_2CH_3	$(CH_2)_3NH$-Cbz	B	83	oil	494[g]	+114.3	5.99; 5.97		
23.	CO_2CH_3	$(CH_2)_3NH$-Cbz	B	73	81–83	602	+107.9		5.99	
24.	CO_2CH_3	$(CH_2)_2CO_2CH_3$	B	93	62–65	497	+89.9		6.02	
25.	CO_2CH_3	$(CH_2)_2CO_2CH_3$	B	68	oil	497	+133.0	5.98; 5.96		
26.	H	$CONHCHCH(OH)CO_2CH_3$ | CO_2CH_3	C	48	oil	556	+95.8			5.99
27.	H	$CONHCHCH(OH)CO_2CH_3$ | CO_2CH_3	C	38	113–115	556	+142.16		6.02	
28.	H	$CONHCHCH(OH)CO_2CH_3$ | CO_2CH_3	C	47	oil	556	+105.7	6.03; 6.00		
29.	$CH_2C_6H_5$	$CONHCHCH(OH)CO_2CH_3$ | CO_2CH_3	C	46	oil	660	+2.1			5.67
30.	$CH_2C_6H_5$	$CONHCHCH(OH)CO_2CH_3$ | CO_2CH_3	C	45	oil	660	+11.6		5.64	
31.	DBT = $NOCHPh$ | CH_3		A[a]	83	49–50	459	+110.4	5.74; 5.65		
32.	DBT = $NOCHCO_2CH_3$ | CH_3		B	83	88–89	441	+155.4	5.83; 5.82		

[a] Representative elemental analyses include the following. Entry 2: calcd for $C_{26}H_{21}NO_6$; C (70.43), H (4.74), N (3.16). Found: C, (70.26), H (4.66), N (3.08). Entry 7: calcd for $C_{22}H_{19}NO_8$; C (62.12), H (4.47), N (3.29). Found: C (62.19), H (4.41), N (3.24). Entry 27: calcd for $C_{26}H_{24}N_2O_{12}$; C (56.12), H (4.32), N (5.04). Found: C, 56.16), H (4.32), N (5.04). Entry 31: calcd for $C_{26}H_{21}NO_7$; C (67.97), H (4.57), N (3.05). Found: C, (68.08), H (4.41), N (2.99). [b] All of the NMR spectra were 300 MHz except for entries 15, 17, and 31 which were 90 MHz. [c] The starting amines used in these cases were liquid free amines, so the addition of diethylamine during their preparation was not necessary. [d] High resolution mass spectrum for $C_{22}H_{21}NO_8$: calcd 395.1369; found 395.137. [e] High resolution mass spectrum for $C_{24}H_{19}NO_8$: calcd 425.1111; found 425.109. [f] m/e 423 corresponds to M − 18 (− H_2O). [g] m/e 494 corresponds to M − 108 (− $HOCH_2Ph$).

The NMR spectra of many DBT derivatives of other amines, amino acids, peptides, and hydroxylamines subsequently prepared revealed consistent trends (Table I). In all cases, the NMR spectra of DBT derivatives of racemic substrates displayed two distinct peaks for the tartarimide methine protons, whereas the spectra of DBT derivatives of optically pure substrates contained only a singlet. The chemical shift differences of the two singlets

(1) References to recently developed methods for distinguishing optical isomers of amines and amino acids include: (a) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5018. (b) Terunuma, D.; Kato, M.; Kamei, M.; Uchida, H.; Nohira, H. *Chem. Lett.* **1985**, 13. (c) Pirkle, W. H.; Tsipouras, A. *Tetrahedron Lett.* **1985**, *26*, 2989. (d) Nago, Y.; Yogi, M.; Ikeda, T.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 205 and references therein. For earlier work, see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(2) Kolasa, T.; Chimiak, A. *Rocz. Chem.* **1976**, *50*, 367.
(3) Butler, C. L.; Cretcher, L. H. *J. Am. Chem. Soc.* **1933**, *55*, 2605.
(4) Kolasa, T.; Miller, M. J., unpublished results.

Table II. HPLC of Representative DBT Derivatives[a]

entry[b]	solvent system	t_R, min D isomer	t_R, min L isomer
5–7	hexanes–0.5% IPA[c]/CH_2Cl_2 (70:30)	19	21
9–11	hexanes–0.3% IPA/CH_2Cl_2 (75:25)	39	42
20, 21	0.075% THF/CH_2Cl_2	48	50 (sh)
26–28	0.6% IPA/CH_2Cl_2	33	38
29–30	0.4% IPA/CH_2Cl_2	22	24

[a] Normal phase (5-μm silica gel), 250 × 4.6 mm column, flow rate = 3 mL/min. [b] Corresponds to the entries given in Table I. [c] IPA = isopropyl alcohol.

generally ranged from 0.01 to 0.09 ppm. These differences were easily distinguishable with 300-MHz NMR and frequently with 90-MHz NMR. *In all cases, the chemical shift of the DBT derivative of substrate's S enantiomer was downfield relative to that of the R enantiomer.* These observations indicate that, within NMR detection limits, easily prepared DBT derivatives might be used for the determination of the optical purity of chiral amines, the determination of the degree of racemization during reactions of chiral amines, and even the assignment of the absolute configuration of unknown compounds by comparing the NMR spectra of both optical isomers or one optically enriched isomer to that of the racemate. These observations remain consistent even when the chiral center under question is quite distant from the tartarimide group (see Table I, entries 20–21). The same trends were also noted in peptides (entries 26–30). Thus, the method might also be useful as a racemization test during peptide syntheses.

Overall this method for distinguishing optical isomers is quite attractive because (a) the DBT derivatives are easily prepared, (b) the NMR signals corresponding to the methine protons of the DBT derivative appear in a generally unobscured area of the spectrum (5.6–6.2 ppm), and (c) the chiral amines can usually be recovered by hydrazinolysis[2] of the DBT derivatives. Preliminary studies with representative samples (entries 5–7, 9–11, 20–21, 26–30) indicate that diastereomeric DBT derivatives can also be separated by HPLC (normal phase, eluting with combinations of hexanes, methylene chloride, and 2-propanol) with the DBT derivative of the D-amino acid generally eluting first.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained as neat films (oils) or in $CHCl_3$. NMR spectra were obtained in chloroform-*d* with tetramethylsilane as a reference on a Varian EM 390, Magnachem A200, or Nicolet NB300 spectrometer. Field desorption and fast atom bombardment mass spectra were recorded by John Occolowitz at Eli Lilly and Co. Electron impact mass spectra were recorded on an AEI Scientific Apparatus MS 902. High pressure liquid chromatography was carried out on a Beckman/Altex Model 332 chromatograph. Optical rotations were obtained on a Rudolf Autopol III polarimeter of solutions in CH_2Cl_2. TLC was carried out on aluminum backed silica gel 60 F-254, 0.2 mm plates, purchased from MCB Reagents, NJ. Solvents used were dried and purified by standard methods. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Procedures for the Preparation of Dibenzoyltartarimides. (*Note*: Reaction times may need to be increased in some new cases to avoid selective reaction of one optical isomer with the optically active tartaric anhydride.) **A.** Finely powdered amino acid ester hydrochloride (1 mmol) was suspended in dry THF (10 mL) and 1 mmol of diethylamine was added by syringe. The mixture was vigorously stirred for a few minutes and then filtered to remove the diethylamine hydrochloride. Dibenzoyl-L-(natural,*d*)-tartaric anhydride[3] (DBTA, 1 mmol) was added to the filtrate. The resulting solution was stirred at room temperature for 15–30 min and then cooled to 0 °C. $SOCl_2$ (2 mmol) was added and the solution was then allowed to warm to room temperature over 15–30 min while stirring. The THF was then evaporated. The residue was dissolved in ethyl acetate and washed with 1 N HCl, H_2O, 5% $NaHCO_3$, H_2O, and brine. Evaporation of the organic layer gave the products which usually required no further purification. However, the samples could also be recrystallized from ethyl acetate–hexanes to obtain analytically pure samples. Of course such purification can affect diastereomeric ratios.

B. Et_3N (1 mmol) was added to a stirred solution of amino acid ester hydrochloride (1 mmol) in $CHCl_3$ at 0 °C. The cooling bath was removed and 1 mmol of L-DBTA was added. The solution was stirred for 30 min and cooled to 0 °C, and 2 mmol of $SOCl_2$ was added. Again the cooling bath was removed and the solution was allowed to stir for 30 min while it warmed to room temperature. The reaction mixture was worked up by the same procedure used in method A.

C (For N-Cbz Protected Peptides). A mixture of 1 mmol of α-*N*-carbobenzoxy peptide and 1 mmol of L-DBTA in 10 mL of dry THF was hydrogenated with H_2/Pd–C (10%) at atmospheric pressure until infrared analysis of an aliquot indicated complete disappearance of the anhydride band (1825 cm^{-1}) of the L-DBTA (by reaction with the α-amino group released by the hydrogenation). The catalyst was removed by filtration and washed with a small portion of THF. After cooling the combined filtrate to 0 °C (ice bath), 2 mmol of $SOCl_2$ was added and the mixture was allowed to stir for 30 min while warming to room temperature. The reaction mixture was worked up by the procedure described in method A.

Yields (not optimized), mp, mass spectra, optical rotation, and selected NMR data are given in Table I. All compounds also had consistent IR spectra. HPLC data for representative compounds are provided in Table II.

Acknowledgment. We are grateful for support of this research by the NIH. The 300-MHz NMR spectrometer used was made available by grants from the NIH and the University of Notre Dame. Technical assistance was provided by Kathleen Peterson.

Registry No. 1 (R = (*S*)-CH(Me)Ph), 102921-32-4; 1 (R = (*R*)-CH(Me)Ph), 102921-33-5; 1 (R = (*R*)-CH(Me)Et), 102921-34-6; 1 (R = (*S*)-CH(Me)Et), 102921-35-7; 1 (R = CH_2COOMe), 102921-36-8; 1 (R = (*R*)-CH(Me)COOMe), 102921-37-9; 1 (R = (*S*)-CH(Me)COOMe), 102940-21-6; 1 (R = (*R*)-CH(Et)COOMe), 102921-38-0; 1 (R = (*S*)-CH(Et)COOMe), 102921-39-1; 1 (R = (*R*)-CH(*i*-Pr)COOMe), 102921-40-4; 1 (R = (*S*)-CH(*i*-Pr)COOMe), 102921-41-5; 1 (R = (*R*)-CH(*i*-Bu)COOMe), 102921-42-6; 1 (R = (*S*)-CH(*i*-Bu)COOMe), 102921-43-7; 1 (R = (*R*)-CH($PhCH_2$)-COOMe), 102921-44-8; 1 (R = (*S*)-CH($PhCH_2$)COOMe), 102921-45-9; 1 (R = (*R*)-CH(Ph)COOMe), 102921-46-0; 1 (R = (*S*)-CH(Ph)COOMe), 102921-47-1; 1 (R = (*R*)-CH(CH_2OH)-COOMe), 102921-48-2; 1 (R = (*S*)-CH(CH_2OH)COOMe), 102921-49-3; 1 (R = (*R*)-$(CH_2)_3$CH(NHCOOCH$_2$CCl$_3$)COOMe), 102921-50-6; 1 (R = (*S*)-$(CH_2)_3$CH(NHCOOCH$_2$CCl$_3$)COOMe), 102921-51-7; 1 (R = (*S*)-$(CH_2)_3$CH(NHCOOMe)COOCH$_2$CCl$_3$, 102921-52-8; 1 (R = (*R*)-CH($(CH_2)_3$NHCbz)COOMe), 102921-53-9; 1 (R = (*S*)-CH($(CH_2)_3$NHCbz)COOMe), 102921-54-0; 1 (R = (*R*)-CH(CH_2CH_2COOMe)COOMe), 102921-55-1; 1 (R = (*S*)-CH-(CH_2CH_2COOMe)COOMe), 102921-56-2; 1 (R = CH_2CONH-D-CH(COOMe)CH(OH)COOMe), 102921-57-3; 1 (R = CH_2CONH-L-CH(COOMe)CH(OH)COOMe), 103001-61-2; 1 (R = CH-($PhCH_2$)CONHCH(COOMe)CH(OH)COOMe), 102921-58-4; 1 (R = (*R*)-OCH(Me)Ph), 102921-59-5; 1 (R = (*S*)-OCH(Me)Ph), 102921-60-8; 1 (R = (*R*)-OCH(Me)COOMe), 102921-61-9; 1 (R = (*S*)-OCH(Me)COOMe), 102921-62-0; L-4, 64339-95-3; (±)-NH_2CH(Me)Ph, 618-36-0; (*S*)-NH_2CH(Me)Ph, 2627-86-3; (±)-NH_2CH(Me)Et, 33966-50-6; H-Gly-Ome·HCl, 5680-79-5; H-D-Ala-OMe·HCl, 14316-06-4; H-DL-Ala-OMe·HCl, 13515-97-4; H-L-Ala-OMe·HCl, 2491-20-5; (±)-NH_2CH(Et)COOMe·HCl, 7682-18-0; H-DL-Val-OMe·HCl, 5619-05-6; H-D-Val-OMe·HCl, 7146-15-8; H-L-Val-OMe·HCl, 6306-52-1; H-DL-Leu-OMe·HCl, 6322-53-8; H-L-Leu-OMe·HCl, 7517-19-3; H-DL-Phe-OMe·HCl, 5619-07-8; H-L-Phe-OMe·HCl, 7524-50-7; (±)-NH_2CH(Ph)COOMe·HCl, 15028-40-7; (*R*)-NH_2CH(Ph)COOMe·HCl, 19883-41-1; H-L-Ser-

OMe·HCl, 5680-80-8; H-DL-Ser-OMe·HCl, 5619-04-5; Cl_3CCH_2OCO-DL-Orn-OMe·HCl, 102921-63-1; MeOCO-L-Orn-OCH_2CCl_3·HCl, 102921-64-2; H-DL-Orn(Cbz)-OMe·HCl, 97371-32-9; H-L-Orn(Cbz)-OMe·HCl, 5874-75-9; H-L-Glu(OMe)-OMe·HCl, 23150-65-4; H-DL-Glu(OMe)-OMe·HCl, 13515-99-6; H-Gly-NH-D-CH(COOMe)CH(OH)COOMe·HCl, 103001-62-3; H-Gly-NH-L-CH(COOMe)CH(OH)COOMe·HCl, 103001-63-4; H-Gly-NH-DL-CH(COOMe)CH(OH)COOMe·HCl, 103001-64-5; H-D-Phe-NHCH(COOMe)CH(OH)COOMe·HCl, 102921-65-3; H-L-Phe-NHCH(COOMe)CH(OH)COOMe·HCl, 103001-65-6; (±)-$NH_2OCH(Me)Ph$, 102921-66-4; (±)-$NH_2OCH(Me)COOMe$, 102921-67-5.

Mercuric Acetate Oxidation of Avermectin A_{2a} as a Route to the Selective Cleavage of the Allylic C-5-Methoxy Group

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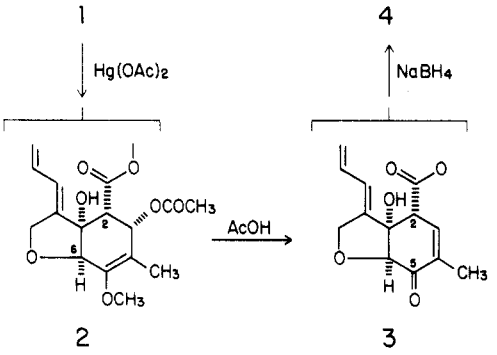
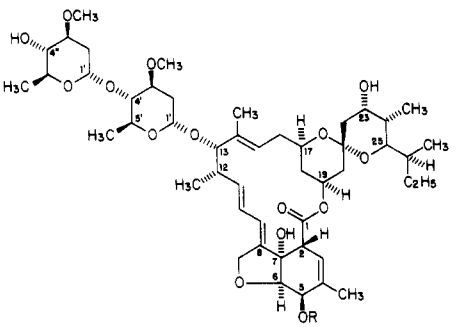
Received January 16, 1986

The avermectins[1] and the milbemycins[2] are two groups of closely related 16-membered macrocyclic lactones. Avermectins containing an unsubstituted allylic hydroxy group at their 5-position are of particular interest because of their potent antiparasitic[3] and insecticidal[4] effects. The fermentation of the actinomycete *Streptomyces avermitilis*, however, produces avermectins in mixtures containing both 5-hydroxy and the less potent 5-methoxy derivatives,[5] and it is therefore desirable to cleave selectively the 5-methyl ether bond to obtain the corresponding alcohols. A 5-methoxy group can also serve as a convenient protecting group in the total syntheses of avermectins and milbemycins containing the sensitive oxahydrindene part structure,[6] provided a suitable deprotection method exists. The avermectins have additional methoxy groups at the 3′- and 3″-positions and also contain glycoside bonds of 2-deoxy sugars which are highly susceptible to acid hydrolysis, so that conventional acidic ether cleavage reactions do not appear promising.[7] They are unstable under certain basic conditions due to epimerization at C-2 and double bond migration from the 3,4- to the 2,3-position into conjugation with the lactone carbonyl.[8] Therefore basic nucleophiles must be avoided. During related oxidation experiments we found that mercuric acetate reacts selectively with the 3,4-double bond resulting in substitution at C-3 and shift of the double bond into the 4,5-position, thus transforming an allylic methoxy group into a hydrolytically labile vinyl ether. Accordingly, avermectin A_{2a} (1) gives upon heating with $Hg(OAc)_2$ in toluene at 100 °C for 30–60 min the 3α-acetoxy 4,5-enol methyl ether **2** as the major product in good yield (Scheme I). The structure determination of **2** is based on the comparison of the proton NMR spectra of **1**[1a] and **2**. Compound **2** shows a new methyl singlet at δ 2.15 for the acetyl group, two sharp doublets at δ 5.73 and 2.92 with a coupling constant of 4.3 Hz for the C-3 and the C-2 protons, a singlet at δ 4.22 for C-6-H, and minor shifts of three singlets at δ 4.68, 3.77, and 1.73 for C-7-OH, C-5-OCH_3, and C-4-CH_3 groups. ^{13}C NMR and mass spectra are in agreement with the proposed structure. Epimerization of the C-2 proton during this reaction is not likely since subsequent reaction products (see below) contain the natural 2β-H configuration. The acetoxy enol ether **2** is not fully stable under the reaction conditions and is slowly transformed into a new compound which was identified as the known avermectin B_{2a} 5-ketone **3**, previously obtained from avermectin B_{2a} by MnO_2 oxidation.[9] Proton NMR, mass, and UV spectra as well as HPLC and TLC of the avermectin A_{2a} derived reaction product **3** and of authentic **3**[9] are identical in all respects. The ketone **3** can be obtained readily from acetoxy enol ether **2** or its crude reaction mixture by hydrolysis of the enol ether in glacial acetic acid at room temperature, which occurs with simultaneous elimination of the 3α-acetoxy group. The stereospecific reduction of ketone **3** with $NaBH_4$ to the naturally occurring avermectin B_{2a} (**4**) is described,[9] and when carried out with the avermectin A_{2a} derived ketone **3** afforded a product indistinguishable from natural avermectin B_{2a} by TLC, HPLC, and 400-MHz ^1H and ^{13}C NMR. Since the

Scheme I





1. R=CH_3 Avermectin A_{2a}
4. R=H Avermectin B_{2a}

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