Difunctionalized Brendanes via Thallium Triacetate Cleavage of the Cyclopropyl Ring of Triaxane

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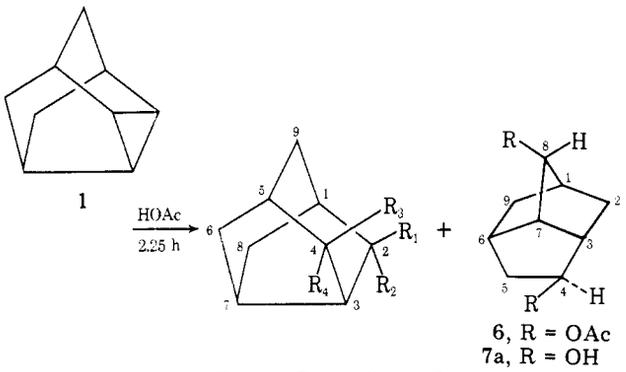
The reaction of triaxane with thallium triacetate in acetic acid gave a 90% yield of a diacetate mixture which contained 2-(a)-acetoxy-4-(e)-acetoxynoradamantane, 2,4-di-(e)-diacetoxynoradamantane, and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane in the ratio 3:15:82. The preponderant diacetate was isolated from the mixture in 43% yield. This reaction provides a simple synthetic route to previously unreported C-8 functionalized brendane derivatives. A structure proof for the brendyl diacetate is presented together with analytical and spectroscopic evidence for the two noradamantyl diacetates. The lead tetraacetate cleavage of triaxane was also investigated and found by GLC analysis to produce 2-acetoxytriaxane, an unidentified component, 2-acetoxynoradamantane, 2-(a)-acetoxy-4-(e)-acetoxynoradamantane, 2,4-di-(e)-diacetoxynoradamantane, and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane in the ratio of 72:1:8:<1:2:17.

The reaction of cyclopropanes with thallium triacetate has been reported to lead predominantly to ring-opened diacetates.[1] Our interest in bridged molecules for mechanistic studies led us to explore the applicability of this reaction for the preparation of difunctionalized systems, which are useful for selective multiple deuterium labeling. We wish to report that cleavage of the cyclopropyl ring of triaxane (1)[2] with thallium triacetate is largely accompanied by a rearrangement that provides a simple, stereospecific route to a C-4, C-8 difunctionalized brendane. Functionalization of the brendane system at C-8 has not been previously reported. Our treatment of 1 with thallium triacetate in refluxing acetic acid gave in



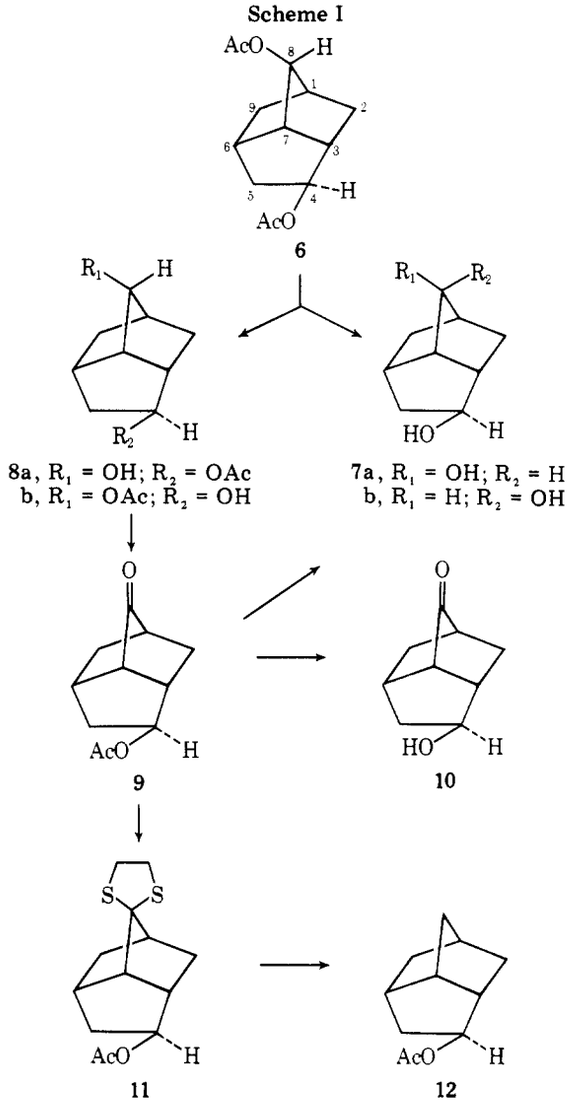
	R_1	R_2	R_3	R_4
2	OAc	H	H	OAc
3	H	OAc	H	OAc
4	OH	H	H	OH
5	H	OH	H	OH

90% yield a diacetate mixture that consisted of three components: 2-(a)-acetoxy-4-(e)-acetoxynoradamantane (**2**), 3%; 2,4-di-(e)-diacetoxynoradamantane (**3**), 15%; and 4-*exo*-acetoxy-8-*anti*-acetoxybrendane (**6**), 82%. Because **3** and **6** were unresolved on preparative GLC columns, we saponified the mixed diacetates to the diol mixture **4, 5,** and **7a.** Diol **7a** was isolated by preparative GLC and was acetylated to **6** with Ac_2O/Py. Diols **4** and **5** were unresolved on GLC but acetylation followed by preparative GLC gave the individual acetates **2** and **3.** Thus yields of separated **2, 3,** and **6** were ca. 0.5, 5, and 43%, respectively.

Structure Proof for Diacetate 6. Conversion of **6** to the known *exo*-4-acetoxybrendane (**12**)[3] by the route shown in Scheme I established the skeletal structure as well as the position and stereochemistry of the acetate group at C-4.

Partial saponification of **6** in aqueous methanol gave a mixture of five compounds in the following relative amounts and eluted on GLC in this order: diacetate **6,** 6%; 4-*exo*-hydroxy-8-*anti*-acetoxybrendane (**8b**), 9%; 4-*exo*-acetoxy-8-*anti*-hydroxybrendane (**8a**), 52%; an unidentified component, 2%; and diol **7a,** 31%. A combination of column chromatography and preparative GLC gave pure hydroxy acetates **8b** and **8a** in yields of 4 and 39%, respectively. Acetylation of **8a** and **8b** reverted each to diacetate **6.**

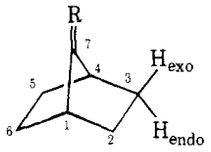
Scheme I



Hydroxy acetate **8a** was oxidized with Jones reagent[4] to 4-*exo*-acetoxybrendan-8-one (**9**). To ensure that no rearrangement occurred during the oxidation, **9** was reduced with

lithium aluminum hydride to a ca 1:1 mixture of 4-*exo*-hydroxy-8-*anti*- and -*syn*-hydroxybrendanes (**7a** and **7b**) as assayed by ^{1}H NMR. The mixture was not separated and analytical and spectroscopic data were not recorded for the pure diol **7b**. We also prepared 4-*exo*-hydroxybrendan-8-one (**10**) by saponification of keto acetate **9** with methanolic potassium hydroxide.

The ethylene dithioketal **11** was obtained by treatment of **9** with ethanedithiol in acetic acid and boron trifluoride etherate.[5] Spectroscopic data, but no elemental analyses, were recorded on a crystalline sample (mp 87.5–89 °C) of **11**. Desulfurization of **11** with Raney nickel[6] gave the known 4-*exo*-acetoxybrendane (**12**) in 67% yield based on starting keto acetate **9**. That no skeletal rearrangement occurred during the formation of ethylene dithioketal **11** was concluded from IR and NMR evidence. An unusually high frequency ketone vibration (1779 cm^{-1}) in keto acetate **9** is consistent with its location at C-8 in a brendane ring system. [cf. norbornan-7-one (**13**) absorbs at 1773 cm^{-1}].[7] Except for compounds that

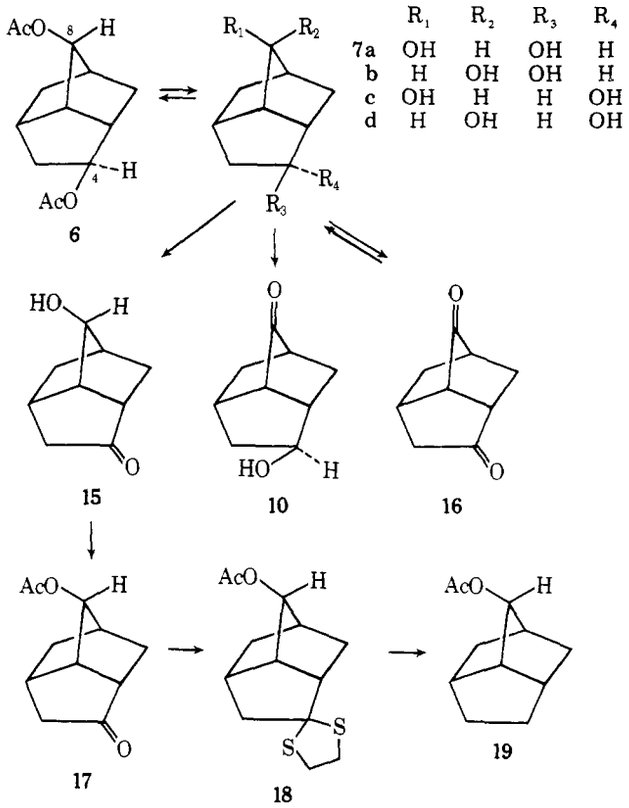


13, R = O
14, R = H, H

contain an endo hydroxyl group at C-4, the NMR spectra of all brendane derivatives in this study had two high-field protons which we have assigned as the C-2 and C-9 endo protons. Tori et al.[8] have reported that the endo and exo protons of norbornane (**14**) are at δ (CCl_4) 1.18 and 1.49, respectively. Pretsch et al.[9] report that the introduction of an endo methyl group at C-2 in **14** shifts the C-3 endo proton upfield to δ ($CDCl_3$) 0.55 and the C-3 exo proton downfield to δ 1.79. Foster and McIvor[10] have postulated that the upfield shifts of endo protons are caused by the diamagnetic anisotropy of the endo C–C bond of the neighboring substituent. Thus the C-4, C-5 bridge of the brendane system might be expected to shift the C-2 and C-9 endo protons upfield relative to the endo protons of norbornane. The reported[11] ^{1}H NMR (CCl_4) of brendane does indeed show a two-proton broad doublet at δ 0.79 (J_{gem} = 11 Hz) which we assign as the chemically equivalent C-2 and C-9 endo protons. The endo protons at C-2 and C-9 in ethylene dithioketal **11** appear as overlapped doublets at δ 1.18–0.84. Interestingly, the four protons of the ethylene dithioketal group appear as a sharp singlet at δ 3.17 ($W_{1/2} \sim 1$ Hz). That these protons do not split each other probably reflects their quasi-symmetrical local environment in **11**.

To establish the position of the second acetate group of diacetate **6** we proceeded as outlined in Scheme II. Diol **7a** was partially oxidized with Jones reagent at 0 °C. Gas chromatographic analysis of the crude product showed four components in the following relative amounts: brendane-4,8-dione (**16**), 8%; hydroxy ketone **10**, 7%; 8-*anti*-hydroxybrendan-4-one (**15**), 75%; and starting diol **7a**, 10%. Hydroxy ketone **15** was isolated in 56% yield by preparative GLC. Dione **16** could be obtained as the major product by oxidation at 25 °C. Acetylation of **15** gave 8-*anti*-acetoxybrendan-4-one (**17**), which produced 4-*endo*-hydroxy-8-*anti*-hydroxybrendane (**7c**) on reduction with lithium aluminum hydride. Although GLC of **7c** showed only one peak, the ^{1}H NMR revealed that ~2% of diol **7a** was present. The high stereoselectivity of this reduction was expected since similar reduction of brendan-4-one was reported to give 4-*endo*-hydroxybrendane with ca. 99.5% stereoselectivity.[12] Lithium aluminum hydride reduction of dione **16** led, as expected, to a mixture of the four stereoisomeric diols **7a–d**. The diol mixture was unresolved by GLC, but ^{1}H NMR showed that the stereoisomeric pair **7a** and **7b** (ca. 1:1) comprised ca. 15–20% of the mixture and the stereoisomeric pair **7c** and **7d** (ca. 1:1) comprised 80–85% of the mixture. Diol **7d** was never isolated pure and characterized.

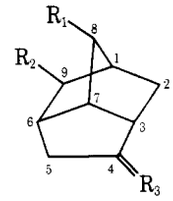
Scheme II



Keto acetate **17** was converted to its crystalline ethylene dithioketal **18** and directly desulfurized to give the previously unreported 8-acetoxybrendane (**19**) in 61% yield. The brendane skeleton in **19** was established as described earlier in Scheme I. The ^{1}H NMR of **19** had the expected high-field C-2 and C-9 endo protons at δ 0.83, the acetate methyl at δ 1.93, and the C-8 proton at δ 4.78. In the brendyl skeleton secondary acetates are possible only at C-2 (or equivalent C-9), C-4 (or equivalent C-5), and C-8. The endo and exo acetates at C-2[12] and C-4[3,13] are all known compounds. Our acetate **19** was spectroscopically (IR and NMR) different from all of these known brendyl secondary acetates; thus it must be the C-8 acetate.

The anti configuration of the C-8 acetate group relative to the C-4 functional group in **6** was assigned on the basis of the long-range "W" coupling $J_{9\text{-endo},8\text{-syn}}$ in the ^{1}H NMR spectrum of keto acetate **17**. Similar "W" couplings of 1.3–2.6 Hz have been reported in heterocyclic brendane derivatives[14] and couplings of ~3–4 Hz have been reported for norbornane derivatives.[15] To eliminate as a possible structure the C-8 epimer, 8-*syn*-acetoxybrendan-4-one, whose NMR would be expected to show a $J_{2\text{-endo},8\text{-anti}}$ long-range "W" coupling, we first established unambiguously our individual assignments for the C-2 and C-9 endo protons of **17**. Comparison of **19** with **20** (Table I) shows that the acetate group at C-8 has little effect on the position of either endo proton. Likewise an acetate group at C-9 has little effect on the C-2 endo proton (cf. **21** with **20**). In contrast a carbonyl group at C-4 causes a pronounced downfield shift for the C-2 endo proton (cf. **22** and **21**). Thus in keto acetate **17** the resonances at δ 1.34 and 1.01 can be assigned to the C-2 and C-9 endo protons, respectively. Spin–spin decoupling by irradiation of the C-8 proton of **17** caused a change in the splitting pattern of the C-9 endo proton

Table I. Chemical Shifts (CCl_4) for the C-2 and C-9 Endo Protons of Brendane and Its Derivatives



				2-Endo		9-Endo		
Compd	R_1	R_2	R_3	δ	$\Delta\delta^a$	δ	$\Delta\delta^a$	Ref
20	H	H	H, H	0.79		0.79		11
19	OAc	H	H, H	0.83	−0.04	0.83	−0.04	This work
21	H	OAc	H, H	0.70	+0.09	4.06	−3.27	13
22	H	OAc	O	1.25	−0.46	4.13	−3.34	18
23	H	H	O	1.58	−0.79	0.91	−0.12	11
17	OAc	H	O	1.34	−0.55	1.01	−0.22	This work

[a] δ_{brendane} (**20**) minus δ_{compd}.

but the pattern for the C-2 endo proton was unchanged. This decoupling result establishes the stereochemistry of the OAc group in **17** and, thereby, the anti configuration at C-8 in diacetate **6**.

Spectroscopic Evidence for Diacetate Structures 2 and 3. As expected for symmetrical diacetate **3** its ^{1}H NMR showed equivalent acetate methyl groups at δ 1.93 (6 H) and equivalent α-acetoxy protons at δ 4.79 (2 H, $W_{1/2} \sim 3$ Hz), broadened as expected for axial protons in noradamantyl systems.[16] That the equivalence of the acetate methyls was not accidental was supported by use of the shift reagent, Eu(fod)$_3$.[17] Additions of as much as 1.65 molar equiv of shift reagent failed to alter the equivalence of the acetate groups. The shift reagent also revealed the existence of four nonequivalent protons (H_3, H_7, H_{9syn}, and H_{9anti}) and three additional pairs of equivalent protons (H_1 and H_5, H_{6e} and H_{8e}, and H_{6a} and H_{8a}) as expected for structure **3**. At molar ratios of shift reagent larger than 0.44 one proton was shifted farther downfield than the α-acetoxy protons (δ 11.37 vs. 10.85 at mole ratio 0.44). This large shift would be expected for the C-3 proton of diacetate **3** because of its unique, proximate position between the C-2 and C-4 acetate groups. At a molar ratio of shift reagent of 0.12 the assigned C-3 bridgehead proton appeared as a multiplet at δ 4.74 which was coupled to an apparent quartet ($J \sim 6$ Hz) at δ 2.84. Irradiation at δ 4.74 collapsed the apparent quartet to a triplet ($J \sim 6$ Hz). The C-7 bridgehead proton of diacetate **3** would be expected to appear as a doublet of overlapping triplets or as an apparent quartet, if $J_{7,6e(8e)} \simeq J_{7,3}$, which may be broadened or slightly split by long-range "W" couplings. Irradiation of the C-3 proton would collapse the C-7 proton to a triplet and thus this decoupling experiment can be explained by a diacetate of structure **3**. We feel that this preponderance of NMR evidence strongly supports our assigned structure for diacetate **3**.

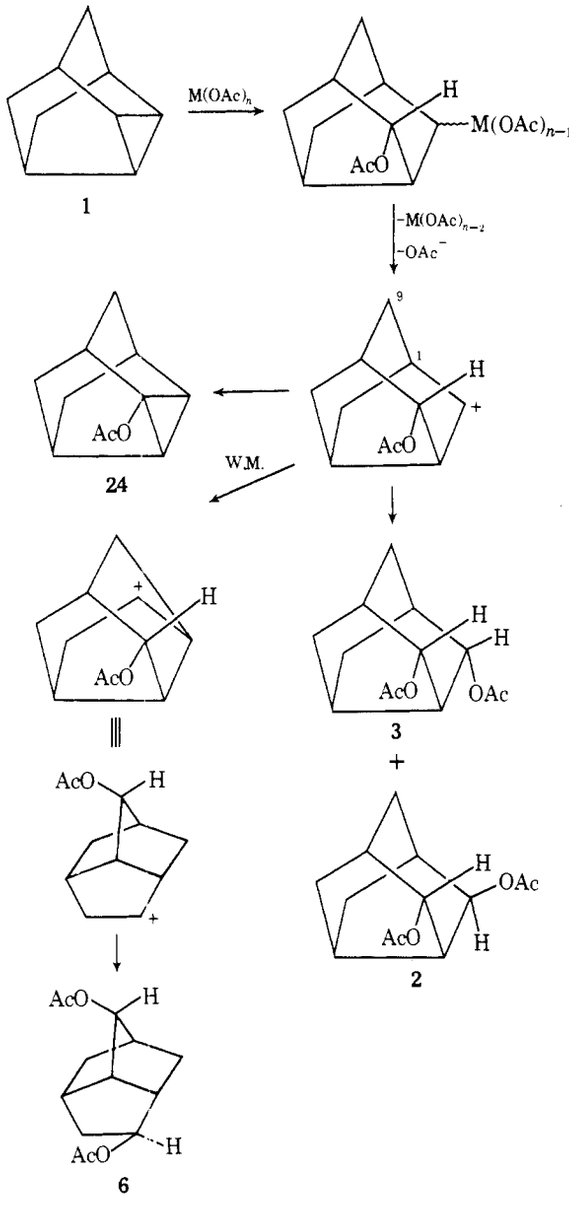
The assignment of structure for diacetate **2** is considered to be tentative and is based solely on a partial analysis of the ^{1}H NMR. The methyl protons of the two acetate groups appear at δ 2.11 and 1.97. One α-acetoxy proton appeared as a singlet at δ 5.30 ($W_{1/2} \sim 3$ Hz) and the other appeared as a multiplet (J = 1.5, 3.5, 7 Hz) at δ 4.95 as expected for an axial and equatorial proton, respectively, in a noradamantyl system.

Comparison of Thallium Triacetate and Lead Tetraacetate Cleavage of Triaxane. A lead tetraacetate oxidation of triaxane was carried out under essentially the same conditions as those used for the thallium triacetate oxidation, and the products were examined by GLC. This analysis revealed six components: 2-acetoxytriaxane (**24**),[19] 72%; 2-acetoxynoradamantane[16] (configurational homogeneity unknown) and an unidentified peak, 9%; diacetate **2**, <1%; diacetate **3**, 2%; and diacetate **6**, 17%. These results are not unexpected since different product distributions from the oxidation of the same cyclopropanes by these reagents have been reported.[1,20] The formation of cyclopropyl acetates by lead tetraacetate oxidation of cyclopropanes has also been reported.[21] Scheme III [$M(OAc)_n$ = thallium triacetate or lead tetraacetate] shows one simple mechanistic pathway to rationalize the products of oxidations by both reagents. The formation of 2-acetoxynoradamantane is not shown in this scheme because we presume that it arises trivially from opening of triaxane with acetic acid; and our use of simple cationic intermediates does not imply any preference for stepwise over concerted bonding processes.

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Proton magnetic resonance spectra were recorded on a Varian Associates Model HA-100 spectrometer equipped with a Hewlett-Packard Model 522 B electronic counter and Model 200 ABR audio oscillator for spin–spin decoupling. Chemical shifts are given in δ units (ppm) downfield from tetramethylsilane internal standard. The multiplicity is identified by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or b (broad); and coupling constants (J) are reported in hertz. Subscripts n and x indicate endo and exo, respectively. Infrared spectra were recorded on a Perkin-Elmer Model 457 A double-beam spectrometer equipped with a grating. Characteristic bands are listed in units of reciprocal centimeters. The letters sh, w, m, s, and br represent shoulder, weak, medium, strong, and broad bands, respectively. Full NMR and IR spectra are reproduced in the Ph.D. Dissertation of D. F. Covey, the Johns Hopkins University, 1973. Analytical gas–liquid phase chromatography (GLC) was performed on a Perkin-Elmer Model 900 analytical gas chromatograph with a flame ionization detector and a Honeywell Model 16 recorder equipped with a disk integrator. The carrier gas was helium. All integrations reported are approximate since detector response variation was not calibrated for each compound. Components are listed in order of increasing retention time. Analytical columns and conditions used were Golay R 150 ft, 0.01 in. i.d. with polypropylene glycol liquid phase (UCON oil LB-550-X), 140 °C, 50 psi (conditions 1); and 9 ft, 0.125 in. o.d., 10% Carbowax 20M on Chromosorb W 80/100, 200 °C, 50 psi (conditions 2). Preparative GLC was done on a Varian Aerograph Autoprep Model A-700 chromatograph (carrier gas, helium) equipped with a thermal conductivity detector and a Honeywell recorder. Columns used were 4 ft, 0.25 in. o.d., 20% Carbowax 20M on Anakrom ABS 80/90 (column 1); 12 ft, 0.25 in. o.d., 5% Carbowax 20M on Chromosorb W 60/80 (column 2); and 6 ft, 0.25 in. o.d., 20% Carbowax 20M on Anakrom ABS 80/90 (column 3). A saturated solution of sodium chloride or sodium bicarbonate is referred to as "brine" or "bicarbonate". Solvents were removed on a rotary evaporator under aspirator vacuum unless otherwise stated. Sublimations and bulb to bulb distillations were done at 136 °C, ca. 0.2 mm, in a Kugelrohr apparatus. Solvents and other chemicals were reagent grade. Pyridine was distilled from

Scheme III



calcium hydride. Acetone was distilled from potassium permanganate. Magnesium sulfate was used as a drying agent. Elemental analyses were performed by either Mr. Joseph Walter of this department or by M-H-W Laboratories, Garden City, Mich. The europium shift reagent Eu(fod)$_3$ and thallium oxide were purchased from Ventron Corp., Alfa Products Division. Silica gel for column chromatography was 0.05–0.2 mm manufactured by EM Reagents Division, Brinkmann Instruments, Inc. Raney nickel catalyst powder no. 2813 was purchased from W. R. Grace and Co.

Cleavage of Triaxane (1) with Thallium Triacetate. Thallium triacetate (9.616 g, 25.2 mmol) prepared from thallium oxide[22a] was refluxed with triaxane (**1**, 1.445 g, 12.0 mmol) in acetic acid (50 ml) for 2.25 h. The solution was cooled, added to water (500 ml), and extracted with ether (5 × 100 ml). The extracts were washed with water (3 × 100 ml) and bicarbonate (1 × 100 ml) and dried. GLC (condition 1) indicated no starting material and three products in the relative ratio of 3 (**2**):15 (**3**):82 (**6**). Bulb to bulb distillation gave a colorless liquid (2.58 g, 90%). Although diacetate **2** could be purified by preparative GLC, diacetates **3** and **6** were unresolved by all our preparative GLC columns. Pure samples of **3** and **6** were obtained by esterification of the corresponding diols as obtained by sensitive preparative GLC.

4-*exo*-Hydroxy-8-*anti*-hydroxybrendane (7a). The diacetate mixture (1.003 g, 4.21 mmol) was saponified with methanolic potassium hydroxide (0.347 g, 6.20 mmol, in 20 ml) at 25 °C for 2.5 h. After removal of methanol, ether (50 ml) and water (2 ml) were added and the two-phase mixture was dried. GLC (condition 2) showed predominantly (>98%) two components in the ratio of 82 (**7a**):18 (unresolved **4** and **5**). Solvent removal (ca. 55 °C, ca. 0.2 mm) left a white solid (0.61 g, 94%). Typically diol **7a** was isolated in 50% yield by preparative GLC (column 1, 180 °C, 30 psi): white solid, mp 110–112 °C; 99% pure (condition 2); IR (KBr) 3322 cm^{-1} (b, bonded OH); NMR (pyridine-d_5) δ 5.91 (s, 2, $W_{1/2} \sim 23$ Hz, CHO**H**, C-4, C-8), 4.45 (s, 1, $W_{1/2} \sim 4$ Hz, syn C**H**OH, C-8), 4.34 (d of d, 1, $J_{4n,5x} = 3$, $J_{4n,5n} = 6$ Hz, endo C**H**OH, C-4), 3.00–1.64 (m, 8), 0.90 (superimposed d of m, 2, J_{gem} of each d ~ 12 Hz, endo HC**H**, C-2 and C-9).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.09; H, 9.26.

4-*exo*-Acetoxy-8-*anti*-acetoxybrendane (6). Diol **7a** (43 mg, 0.39 mmol) was stirred in pyridine (1 ml) and acetic anhydride (2 ml) at 25 °C for ca. 21 h. Water (10 ml) was added and the solution was made basic with solid sodium bicarbonate, extracted with ether (4 × 10 ml), and dried. The pale yellow liquid (65 mg) was distilled bulb to bulb (130 °C, ca. 0.2 mm) to give the diacetate as a colorless liquid (60 mg, 91%): ca. >99% pure (condition 1); IR (neat) 1746 (s, ester C=O), 1245 cm^{-1} (s); NMR ($CDCl_3$) δ 5.02–4.86 (d of d, 1, endo C**H**OAc, C-4; overlapped by s, 1, syn C**H**OAc, C-8), 2.68–1.65 (m, 8), 2.01 (s, 3, $OCOCH_3$), 1.97 (s, 3, $OCOCH_3$), 1.12–0.78 (d of d, 1, endo HC**H**, C-2; overlapped by d of m, 1, endo HC**H**, C-9).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.63; H, 7.61. Found: C, 65.51; H, 7.53

2,4-Di-(e)-diacetoxynoradamantane (3). Unresolved diols **4** and **5** were typically isolated in 8% yield by preparative GLC (column 1, 180 °C, 30 psi) of the saponified diacetate mixture. A sublimed (138 °C, ca. 0.2 mm) mixture of diols **4** and **5** (56 mg) was acetylated by the procedure used to prepare diacetate **7a** to give a colorless liquid (81 mg), which GLC (condition 2) showed to be a 11:89 mixture of diacetates **2** and **3**. The diacetates were separated by preparative GLC (column 2, 162 °C, 40 psi). Diacetate **3** was initially obtained as a colorless liquid (60 mg) which crystallized when shaken with pentane. Recrystallization from pentane gave white crystals (53 mg): mp 71.5–72.5 °C, >99% pure (condition 1); IR (CCl_4) 1758 (s, ester C=O), 1250 cm^{-1} (s); NMR (CCl_4) δ 4.79 (s, 2, $W_{1/2} \sim 3$ Hz, axial C**H**OAc, C-2, C-4), 2.42 (m, 2), 2.28–1.86 (m, 4), 1.93 (s, 6, $OCOCH_3$, C-2, C-4), 1.59 (t, 2, $J = 3$ Hz, $CHCH_2CH$, C-9), 1.47 (d, 2, $J_{gem} = 11$ Hz, axial HC**H**, C-6, C-8).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.60.

2-(a)-Acetoxy-4-(e)-acetoxynoradamantane (2). Diacetate **2** was obtained by preparative GLC along with diacetate **3** by the procedure described for the isolation of **3**. Bulb to bulb distillation (136 °C, ca. 0.2 mm) gave **2** as a colorless liquid (7 mg): ca. 99% pure (condition 1); IR (CCl_4) 1751 (s, ester C=O), 1248 cm^{-1} (s); NMR (CCl_4) δ 5.30 (s, 1, axial C**H**OAc, C-2), 4.95 (m, 1, J = 1.5, 3.5, 7 Hz, equatorial C**H**OAc, C-4), 2.66–1.38 (m, 10), 2.11 (s, 3, $OCOCH_3$), 1.97 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.63; H, 7.39.

2,4-Di-(e)-dihydroxynoradamantane (5). Diacetate **3** (48 mg, 0.02 mmol, mp 71.5–72.5 °C) was saponified with methanolic potassium hydroxide (38 mg, 0.68 mmol, in 10 ml) at 25 °C for 1 h. Workup as previously reported for the preparation of diol **7a** afforded white crystals (30 mg). Sublimation (136 °C, ca. 0.2 mm) gave diol **5** (26 mg, 84%): mp 256–257.5 °C (sealed capillary); IR (KBr) 3310 cm^{-1} (b, bonded OH); NMR (pyridine-d_5) δ 5.95 (s, 2, $W_{1/2} \sim 6$ Hz, CHO**H**, C-2, C-4), 4.25 (s, 2, $W_{1/2} \sim 4$ Hz, axial C**H**OH, C-2, C-4), 2.92–2.42 (m, 4), 2.30–2.06 (br s, 2, $W_{1/2} \sim 8$ Hz, CH, C-1, C-5), 1.76–1.24 (m, 4).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.39; H, 8.89.

4-*exo*-Acetoxy-8-*anti*-hydroxybrendane (8a). Diacetate **6** (463 mg, 1.95 mmol, >99% pure, condition 1) was dissolved in stirred 50% aqueous methanol (10 ml). Potassium hydroxide (66 mg, 1.18 mmol) in 50% aqueous methanol (4 × 1 ml) was added with a 10-min interval after addition of each 1 ml. The solvent was removed (25 °C, ca. 0.2 mm), ether (50 ml) was added, and the solution was dried. GLC (condition 2) showed five components in the following relative ratios: diacetate **6** (6%), hydroxy acetate **8b** (9%), hydroxy acetate **8a** (52%), an unidentified component (2%), and diol **7a** (31%). The components were partially separated by column chromatography on silica gel (10 g, column o.d. 14 mm) with 3:7 ether/pentane (12 × 40 ml) followed by methanol (1 × 200 ml). Fractions 1–3 contained diacetate **6** (27 mg). Hydroxy acetate **8a** and the unidentified component (161 mg) were eluted together in fractions 4–8. Fractions 9–12 contained **8a** and **8b** and the unknown component (42 mg). The methanol fraction contained diol **7a** (149 mg). Pure **8a** was obtained by preparative GLC (column 3, 175 °C, 29 psi) of fractions 4–8 as a colorless liquid (149 mg, 39%): ca. >99% pure (condition 2); IR (neat, 3430 (b, bonded OH),

1745 (s, ester C=O), 1725 (sh), 1253 cm^{-1} (s); NMR ($CDCl_3$) δ 4.91 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 7 Hz, endo CHOAc, C-4), 4.17 (s, 1, $W_{1/2}$ ~ 4 Hz, syn CHOH, C-8), 2.69–1.64 (m, 8), 2.51 (s, 1, CHOH, C-8), 1.97 (s, 3, $OCOCH_3$), C-4), 0.97 (overlapped d of m, l, J_{gem} = 12 Hz, endo HCH, C-2 or C-9), 0.88 (overlapped br d, 1, J_{gem} ~ 12 Hz, endo HCH, C-2 or C-9).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.58.

4-*exo*-Hydroxy-8-*anti*-acetoxybrendane (8b). Hydroxy acetate **8b** was isolated as a colorless liquid in 4% yield by the identical procedure reported for the preparation of hydroxy acetate **8a**: ca. >99% pure (condition 2); IR (neat) 3420 (b, bonded OH), 1746 (s, ester C=O), 1252 cm^{-1} (s); NMR ($CDCl_3$) 4.93 (m, 1, $W_{1/2}$ ~ 5 Hz, syn CHOAc, C-8), 4.15 (d of d, 1, $J_{4n,5x}$ = 2, $J_{4n,5n}$ = 7 Hz, endo CHOH, C-4), 2.76–1.52 (m, 8), 2.01 (s, 3, $OCOCH_3$, C-8), 1.83 (s, 1, CHOH, C-4), 1.02–0.74 (overlapped d of m, 2, endo HCH, C-2 and C-9).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.31.

Brendane-4,8-dione (16). The diol mixture (340 mg, 1.97 mmol) obtained by saponification of the unseparated diacetates from the thallium triacetate reaction was oxidized with Jones reagent[4] (5 ml added dropwise over 4 min) in acetone (20 ml) at 25 °C for 3 h. Methanol (6 ml) was added to destroy the excess of oxidant. Solid potassium carbonate was added to neutralize any acid present, and the solution was dried. GLC (condition 2) showed three components: dione **16** (94%), an unidentified product, and some unoxidized diol (6% total for both components). The crude product (273 mg) was purified by column chromatography on silica gel (10 g, column o.d. 14 mm). The column was eluted successively with 1:9 ether/pentane (5 × 40 ml), 2:8 ether/pentane (6 × 40 ml), and 3:7 ether/pentane (8 × 40 ml). The dione was eluted in fractions 13–18. Sublimation (136 °C, ca. 0.2 mm) gave the diketone as a white solid (109 mg, 37%): mp 159–161 °C; >99% pure (condition 2); IR (CCl_4) 1794 (s, C=O), 1763 cm^{-1} (s, C=O); NMR (CCl_4) δ 3.03–1.92 (m, 8), 1.51 (d of d, 1, $J_{2n,3}$ = 2, J_{gem} = 13 Hz, endo HCH, C-2), 1.23 (d of d, 1, $J_{9n,6}$ = 2, J_{gem} = 13 Hz, endo HCH, C-9).

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.71; H, 6.52.

8-*anti*-Hydroxybrendan-4-one (15). Diol **7a** (158 mg, 1.03 mmol, ca. 98% pure, condition 2) was dissolved in acetone (20 ml) and cooled to 0 °C. Jones reagent[4] was added dropwise until a yellowish-green color, characteristic of unreduced oxidant, persisted for ca. 5 min. Methanol (5 drops) was added and the solution was filtered through a sintered glass funnel. GLC (condition 2) showed four components in the following ratios: dione **16** (8%), hydroxy ketone **10** (7%), hydroxy ketone **15** (75%), and diol **7a** (10%). Hydroxy ketone **15** was isolated by preparative GLC (column 1, 180 °C, 30 psi) from the crude product (155 mg) as a white solid (88 mg, 56%): mp 166.5–167.5 °C; ca. 98.5% pure (condition 2); IR ($CHCl_3$) 3622 (w, OH), 3452 (b, bonded OH), 1739 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.25 (s, 1, $W_{1/2}$ ~ 5 Hz, syn CHOH, C-8), 3.17 (s, 1, $W_{1/2}$ ~ 10 Hz, CHOH, C-8), 2.83–1.76 (m, 8), 1.32 (d of m, 1, J_{gem} = 12 Hz, endo HCH, C-2 or C-9), 1.00 (d of d, 1, J_{gem} = 12 Hz, endo HCH, C-9 or C-2).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.71; H, 8.00.

8-*anti*-Acetoxybrendane-4-one (17). Hydroxy ketone **15** (89 mg, 0.59 mmol, ca. 98.5% pure, condition 2) was stirred with acetic anhydride (2 ml) and pyridine (1 ml) at 25 °C for 22 h. Brine (10 ml) was added and the solution was extracted with ether (3 × 10 ml). The extracts were washed with aqueous 5% HCl (2 × 10 ml), water (2 × 10 ml), and bicarbonate (10 ml) and dried. Recrystallization of the crude product (92 mg) from pentane gave white crystals (81 mg, 71%): mp 59–60 °C; >99% pure (condition 2); IR (CCl_4) 1754 (s, C=O and ester C=O), 1245 cm^{-1} (s); NMR (CCl_4) δ 4.87 (m, 1, $W_{1/2}$ ~ 4 Hz, syn CHOAc, C-8), 2.89–2.57 (m, 2), 2.47–1.85 (m, 6), 1.99 (s, 3, anti $OCOCH_3$, C-8), 1.34 (d of d, 1, $J_{2n,3}$ = 2, J_{gem} = 12 Hz, endo HCH, C-2), 1.01 (d of m, 1, J_{gem} = 12 Hz, endo HCH, C-9).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.90; H, 7.47.

8-*anti*-Acetoxybrendan-4-one Ethylene Dithioketal (18). Boron trifluoride etherate (1.5 ml) was added to a solution of keto acetate **17** (30 mg, 0.15 mmol, >99% pure, condition 2) and ethanedithiol (2 ml), and stirred at 25 °C for 16 h. The solution was poured over ice (40 g), water (50 ml) was added, and the mixture was extracted with ether (4 × 30 ml). The extracts were washed with aqueous 10% sodium hydroxide (3 × 20 ml) and brine (1 × 30 ml) and dried. Removal of solvent left a pale yellow oil. Recrystallization from pentane (twice) gave white crystals (16 mg, 38%): mp 86.5–87.5 °C; IR (CCl_4) 1751 (s, ester C=O), 1249 cm^{-1} (s); NMR (CCl_4) δ 4.86 (s, 1, $W_{1/2}$ ~ 4 Hz, syn CHOAc, C-8), 3.40–2.94 (m, 4, SCH_2CH_2S, C-4), 2.86–1.70 (m, 8), 1.92 (s, 3, $OCOCH_3$, C-8), 1.40 (d of d, 1, $J_{2n,3}$ = 3, J_{gem} = 13 Hz, endo HCH, C-2), 1.05 (bd, 1, J_{gem} = 11 Hz, endo HCH, C-9).

8-Acetoxybrendane (19). Ethylene dithioketal **18** (34 mg, combined crystals and mother liquor residue) and activated Raney nickel[22b] were refluxed in ethanol (13 ml) for 1.5 h. The mixture was filtered through Celite, and water (65 ml) was added. The solution was extracted with ether (3 × 30 ml), washed with brine (30 ml), and dried. GLC (condition 2) showed three components: two unidentified products (3% total) and acetate **19** (97%). Preparative GLC (column 2, 110 °C, 30 psi) gave **19** as a colorless liquid (17 mg, 61% based on starting keto acetate **18**: >99% pure, condition 2 (temperature lowered to 140 °C); IR (CCl_4) 1748 (s, ester C=O), 1255 cm^{-1} (s); NMR (CCl_4) δ 4.78 (s, 1, $W_{1/2}$ ~ 4 Hz, CHOAc, C-8), 2.52–1.37 (m, 10), 1.93 (s, 3, $OCOCH_3$, C-8), 0.83 (superimposed d of m, 2, J_{gem} each d ~ 12 Hz, endo HCH, C-2 and C-9).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 9.07.

4-*exo*-Acetoxybrendan-8-one (9). Hydroxy acetate **8a** (149 mg, 0.76 mmol, 99% pure, condition 2) was oxidized with Jones reagent[4] (0.5 ml) in acetone (10 ml) at 25 °C for 2 h. Methanol (10 drops) was added to destroy the excess of oxidant. The solution was filtered and solvent was removed. Ether (30 ml) and bicarbonate (1 ml) were added, and the two-phase mixture was dried. GLC (condition 2) showed a single component. Bulb to bulb distillation (136 °C, ca. 0.2 mm) gave the keto acetate **9** as a colorless liquid (140 ml, 95%): IR (neat) 1779 (s, C=O), 1749 (s, ester C=O), 1251 cm^{-1} (s); NMR ($CDCl_3$) δ 5.12 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 6 Hz, endo CHOAc, C-4), 2.80–1.84 (m, 8), 1.99 (s, 3, $OCOCH_3$, C-4), 1.26 (overlapped d of d, 1, J = 2, J_{gem} = 13 Hz, endo HCH, C-2 or C-9), 1.11 (overlapped d of d, 1, J = 2, J_{gem} = 13 Hz, endo HCH, C-2 or C-9).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.06; H, 7.21.

4-*exo*-Acetoxybrendan-8-one Ethylene Dithioketal (11). Keto acetate **9** (32 mg, 0.16 mmol, >99% pure, condition 2) was converted to its ethylenedithioketal **11** by the identical procedure used to convert keto acetate **17** to ethylene dithioketal **18**. Recrystallization from pentane (twice) gave white crystals (17 mg, 38%): mp 87.5–89 °C; IR (CCl_4) 1745 (s, ester C=O), 1250 cm^{-1} (s); NMR (CCl_4) δ 4.94 (d of d, 1, $J_{4n,5x}$ = 3, $J_{4n,5n}$ = 7 Hz, endo CHOAc, C-4), 3.17 (s, 4, $W_{1/2}$ ~ 1 Hz, SCH_2CH_2S, C-8), 2.63–1.62 (m, 8), 1.90 (s, 3, $OCOCH_3$, C-4), 1.18–0.84 (overlapping d of d, 2, endo HCH, C-2, and C-9).

4-*exo*-Acetoxybrendane (12). Desulfurization of 11 (61 mg) was by the procedure used on ethylene dithioketal **18**. The product was isolated by preparative GLC (column 2, 115 °C, 30 psi) as a colorless liquid (20 mg, 67% based on starting keto acetate **9**): >99.5% pure, condition 2 (temperature lowered to 140 °C). The IR and NMR of this product were identical with those of an authentic sample of **12**.[3]

4-*exo*-Hydroxybrendan-8-one (10). Keto acetate **9** (237 mg, 1.22 mmol, 88% pure by NMR, containing 12% of 4-(e)-acetoxynoradamantan-2-one) prepared by Jones oxidation of a 88:12 mixture (determined by NMR) of unresolved hydroxy acetates **8a** and 2-(e)-hydroxy-4-(e)-acetoxynoradamantane (identified in a similar mixture by hydrolysis to diol **5** and esterification to diacetate **3**) was stirred with potassium hydroxide (35 mg, 0.62 mmol) in methanol (12 ml) for 15 min at 25 °C. The methanol was removed under aspirator vacuum at 40 °C. Ether (50 ml) and water (20 drops) were added to the residue and the solution was dried. GLC (condition 2) showed three components: the unresolved hydroxy ketones (97.5%) and two other unidentified components (2.5% total). The unresolved hydroxy ketones were isolated by preparative GLC (column 1, 180 °C, 30 psi) as a white solid (129 mg, 69%). This solid was extremely hygroscopic and liquefied during an attempt to transfer it from the GLC collector to a vial. The solid was recovered by sublimation (136 °C, ca. 0.2 mm) and analyzed by GLC (condition 2) and NMR. GLC indicated the purity of the unresolved hydroxy acetates as 98%. NMR integration of the CHOH protons indicated <5% of noradamantyl hydroxy ketone in hydroxy ketone **10**: mp unrecorded owing to extreme hygroscopic properties; IR ($CHCl_3$) 3638 (m, free OH), 3472 (b, bonded OH), 1774 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.31 (d of d, 1, $J_{4n,5x}$ = 2, $J_{4n,5n}$ = 6 Hz, endo CHOH, C-4), 3.01 (s, 1, $W_{1/2}$ ~ 4 Hz, CHOH, C-4), 2.80–1.52 (m, 8), 1.08 (superimposed doublets, 2, J_{gem} ~ 12 Hz, endo HCH, C-2 and C-9).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.86; H, 8.04.

4-*endo*-Hydroxy-8-*anti*-hydroxybrendane (7c). Keto acetate **17** (41 mg, 0.21 mmol, >99% pure, condition 2) was added dropwise in ether (5 ml) to a stirred slurry of lithium aluminum hydride (43 mg, 1.13 mmol) in ether (10 ml) at 25 °C. After 11 h the reaction mixture was worked up by the method of Micovic and Mihailovic[23] to give a white solid (31 mg). Preparative GLC (column 3, 185 °C, 30 psi) gave

>98% stereoisomerically pure (determined by NMR) diol **7c** (25 mg, 76%): mp 212.5–213.5 °C; IR (KBr) 3346 cm^{-1} (b, bonded OH); NMR (pyridine-d_5) δ 5.95 (s, 2, $W_{1/2} \sim 26$ Hz, CHOH, C-4 and C-8), 4.60 (m, 1, $J_{4x,3} = 5$, $J_{4x,5n} = 5$, $J_{4x,5x} = 9$ Hz, exo CHOH, C-4), 4.47 (s, 1, $W_{1/2} \sim 5$ Hz, syn CHOH, C-8), 2.96–2.24 (m, 5), 2.24–1.94 (m, 2), 1.90–1.42 (m, 2), 1.25 (d, 1, $J_{gem} = 10$ Hz, endo HCH, C-9).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.25.

Lithium Aluminum Hydride Reduction of Keto Acetate 9. Keto acetate **9** (41 mg, 0.21 mmol, >99% pure, condition 2) was reduced with lithium aluminum hydride (45 mg, 1.21 mmol) by the procedure used for keto acetate **17**. The crude, oily product (37 mg) was purified by preparative GLC (column 3, 185 °C, 30 psi) to give a white solid (24 mg, 73%) shown by NMR to be a ca. 1:1 mixture of diols **7a** and **7b**. Some assigned signals from **7b** that were superimposed on, and therefore masked by, the previously described signals of diol **7a** follow: NMR (pyridine-d_5) 4.52 (overlapping d of d, $J_{4n,5x} \sim 4$, $J_{4n,5n} \sim 4$ Hz, endo CHOH, C-4), 4.40 (s, anti CHOH, C-8), ca. 1.01 (d of d, $J_{2n,3} = 2$, $J_{gem} \sim 10$ Hz, endo HCH, C-2), ca. 0.77 (d of d, $J_{9n,6} = 1$, $J_{gem} \sim 10$ Hz, endo HCH, C-9).

Lithium Aluminum Hydride Reduction of Dione 16. Dione **16** (109 mg, 0.73 mmol, >99% condition 2) was reduced with lithium aluminum hydride (70 mg, 1.84 mmol) by the procedure used for keto acetate **17**. Part (61 mg) of the crude solid product (89 mg) was purified by preparative GLC (column 3, 185 °C, 30 psi) to give a white solid (43 mg) whose NMR showed the presence of all four stereoisomeric diols **7a–d**. The stereoisomeric pair **7a** and **7b** (ca. 1:1) comprised ca. 15–20% of the mixture and the stereoisomeric pair **7c** and **7d** (ca. 1:1) comprised 80–85% of the mixture. Some assigned signals from diol **7d** that were superimposed on the previously described signals of the other stereoisomers follow: NMR (pyridine-d_5) 4.66 (m, $J_{4x,3} \sim 6$, $J_{4x,5n} \sim 6$, $J_{4x,5x} \sim 10$ Hz, exo CHOH, C-4), 4.50 (s, anti CHOH, C-8), 1.09 (d, $J_{gem} = 10$ Hz, endo HCH, C-9).

Cleavage of Triaxane with Lead Tetraacetate. Triaxane (50 mg, 0.42 mmol, ca. 98% pure) and lead tetraacetate (390 mg) were refluxed in acetic acid for 2 h. Water (20 ml) was added to the cooled solution, and it was extracted with ether (3 × 20 ml). The extracts were washed with water (2 × 10 ml) and bicarbonate (10 ml) and dried. GLC (condition 1) of the liquid (71 mg) showed six peaks: 2-acetoxytriaxane (**24**, 72%), 2-acetoxynoradamantane and an unidentified peak (9%), diacetate **2** (<1%), diacetate **3** (2%), and diacetate **6** (17%). Our GLC conditions are known[12] not to resolve the epimers of 2-acetoxynoradamantane.

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