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Steroid dimer formation: metal reduction of methyl androst-4-ene-3,17-dion-19-oate

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Abstract

Two isomeric dimeric steroids, 3,3′-bis(methyl 3-hydroxyandrost-4-en-17-on-19-oate-3-yl), with symmetrical (α,α') and unsymmetrical structures (α,β'), have been obtained by reduction of methyl androst-4-ene-3,17-dion-19-oate with zinc in aqueous acetic acid together with the major products, the isomeric methyl 5α- and 5β-androst-3-en-17-on-19-oates. The structures of the dimers and unsaturated products are supported by spectroscopic methods. The symmetrical dimer was also obtained from treatment of the 4-en-3-on-19-oate ester with lithium in ammonia.

Keywords: Bisteroid; Dimer; Reduction; Trimethylsilylation; Zinc

1. Introduction

Reduction of the steroid 4-en-3-one with zinc in acetic acid in both the estrane and androstane series is known to give mainly a mixture of the 5α- and 5β-3-ene and is the preferred method for their synthesis [1,2]. Templeton et al. have reported the isolation of a symmetrical 3,3′-dimer from zinc in acetic acid treatment of 17β-acetoxy-4-chloroandrost-4-en-3-one [2]. Such dimeric structures from photochemical, electrolytic, and metal reduction of the steroid 4-en-3-one have been reported [3–7]. Cholest-4-en-3-one yielded a dimer with Na amalgam in propanol-acetic acid that was shown later to have a pinacol structure [3–5]. Lund reported the formation of steroid dimers by electrolytic reduction of several steroid 4-en-3-ones [6]. From electrolytic reduction of 17β-hydroxyandrosta-1,4-dien-3-one at different pH (5 and 12.5), Lund obtained two dimeric products to which he assigned the α,α' and β,β' configurations, respectively. Bladon et al. [7] prepared 3,3′-bis(cholest-4-ene-3α-yl) by electrolytic reduction of the 4-en-3-one and established that the molecules were joined at C-3 in the α,α' positions but were critical of the basis of Lund's assignments [7]. House has discussed mechanistic aspects of these coupling reactions [8]. Here we report formation of both a symmetrical and an unsymmetrical 3,3′-dimer from methyl androst-4-ene-3,17-dion-19-oate together with examples of 4-en-3-ones where no dimer formation was detected. Structures have been established by spectroscopic methods.

2. Experimental procedures

2.1. General methods and equipment

Thin-layer chromatography (TLC) was performed on precoated silica gel plates (Analtech GFLF) in light petroleum (bp 35–60°C) (LP)/acetone (5:1). Compounds were visualized by dipping in EtOH/sulfuric acid (95:5 v/v) and heating on a hot-plate to ~120°C. Flash column chromatography (FCC) was carried out on silica gel (Merck type 60 H). Mps were determined on a Kofler type hot-stage apparatus and are uncorrected.

NMR spectra were recorded on Bruker AM300 instrument in $CDCl_3$ with Me_4Si as internal standard. For details of the experimental techniques and NMR methods employed see Ref. [9]. Assignments for compounds **2b** and **3a** were confirmed by 2D techniques carried out on a Bruker AMX500. Mass spectra (EIMS and FABMS) were obtained on a VG-7070E.

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*2.2. Androst-4-ene-3,17-dion-19-oic acid (**1a**)*

Treatment of 19-hydroxyandrost-4-ene-3,17-dione (10 g, 33 mmol) in acetone (250 ml), cooled in an ice-bath, with Jones reagent (30 ml, 80 mmol), added in portions over 40 min, gave the 19-acid (5.0 g, 48%), m.p. 146–148°C decomp. (from CH_2Cl_2-LP) (lit [10], m.p. 146°C), δ_H 0.91 (s, 13-Me), 5.95 (d, J = 1.2 Hz, 4-H); δ_C 33.68 (1), 34.78 (2), 198.73 (3), 127.19 (4), 161.55 (5), 32.57 (6), 31.37 (7), 35.56 (8), 53.68 (9), 50.52 (10), 21.64 (11), 29.97 (12), 47.58 (13), 50.93 (14), 21.98 (15), 35.70 (16), 220.00 (17), 13.90 (18), 175.54 (19).

*2.3. Methyl androst-4-ene-3,17-dion-19-oate (**1b**)*

The 19-acid **1a** (2.26 g, 7.14 mmol) on treatment with diazomethane in Et_2O gave the methyl ester (2.1 g, 89%), m.p. 142–145°C (from EtOAc-LP) (lit [11], m.p. 142–142.5°C from Et_2O) δ_H 0.90 (s, 13-Me), 3.76 (s, 19-OMe), 5.90 (d, J = 1.5, 4-H): δ_C 33.82 (1), 34.91 (2), 198.57 (3), 126.76 (4), 161.96 (5), 32.56 (6), 31.35 (7), 35.59 (8), 53.75 (9), 50.85 (10), 21.64 (11), 30.06 (12), 47.52 (13), 50.88 (14), 21.92 (15), 35.69 (16), 219.97 (17), 13.77 (18), 171.63 (19), 50.85 (19-OMe).

*2.4. Methyl androst-4-ene-3,17-dion-19-oate (**1b**)*

To a solution of the dimer **3a** (13.4 mg, 0.04 mmol) in warm MeOH (3 ml) was added $NaIO_4$ (150 mg, 0.07 mmol) in hot water (1 ml) and the mixture refluxed for 4 h. On cooling the mixture was diluted with water and extracted with CH_2Cl_2 to give the methyl ester **1b** (13 mg) that showed TLC and ^1H and ^{13}C NMR in agreement with the ester **1b** obtained from the acid **1a** above.

*2.5. Methyl 5α- (**2a**) and 5β-androst-3-en-17-on-19-oate (**2b**) and bis(methyl 3-hydroxyandrost-4-en-17-on-19-oate-3α-yl) (**3a**)*

2.5.1. Method 1

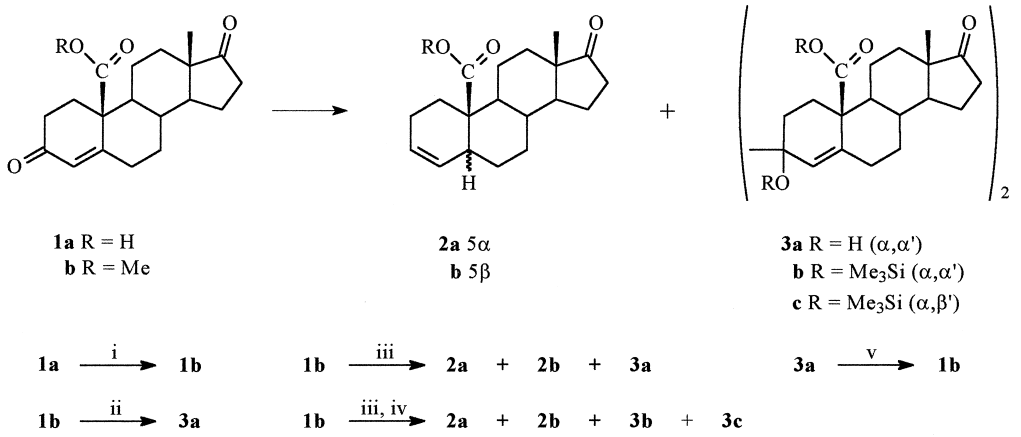
The methyl ester **1b** (526 mg, 1.6 mmol) was dissolved in acetic acid/water (1:1) (20 ml) and zinc powder (10 g) added in one portion. The mixture was stirred for 6 h at room temperature, filtered, and the filtrate extracted with CH_2Cl_2 to give a product that on FCC on silica gel on elution with 3–25% acetone-LP yielded 1) the 5β-isomer **2b** (75 mg, 15%), m.p. 143.5–145.5°C (from Et_2O-LP) (Found: C, 75.81; H, 9.15. $C_{20}H_{28}O_3$ requires C, 75.91; H, 9.15%); δ_H 0.96 (s, 13-Me), 2.44 (dd, J = 9.3, 19.1, 16β-H), 2.74 (br s, $W_{1/2}$ 11Hz, 5β-H), 3.67 (s, 19-OMe), 5.38 (ddd, J = 1.8, 3.6, 10.0, 4-H), 5.72 (m, 3-H); δ_C 28.52 (1), 21.45 (2), 126.80 (3), 130.99 (4), 39.18 (5), 28.77 (6), 25.97 (7), 35.86 (8), 40.27 (9), 47.30 (10), 21.62 (11), 32.03 (12), 48.08 (13), 51.56 (14), 21.68 (15), 35.99 (16), 221.51 (17), 14.01 (18), 176.81 (19), 51.42 (19-OMe) and a mixture of methyl 5α- and 5β-androst-3-en-17-on-19-oates **2a** and **2b** (5α:5β; 1:4) (150 mg, 30%) 2) the symmetrical dimer **3a**, (67 mg, 6.5%), m.p. 217–220°C (from CH_2Cl_2-EtOAc) (Found: C, 72.38; H, 8.62. $C_{40}H_{54}O_8$ requires C, 72.48; H, 8.22%); $\nu_{max}(CH_2Cl_2)$ cm^{-1} 3595, 3553 (3-OH), 1735 (17-C = O and 19-COOMe); δ_H 0.93 (s, 13-Me), 2.38 (m, 6β-H), 2.45 (dd, 9.3, 19.3, 16β-H), 3.69 (s, 19-OMe), 5.69 (s, 4-H); δ_C 29.71 (1), 28.62 (2), 73.60 (3), 124.63 (4), 143.06 (5), 33.94 (6), 31.56 (7), 36.19 (8), 52.74 (9), 50.22 (10), 21.71 (11), 31.70 (12), 47.83 (13), 51.54 (14), 21.71 (15), 35.72 (16), 221.00 (17), 13.84 (18), 174.32 (19), 51.42 (19-OMe); EIMS m/z 644 (1%, M^+-H_2O), 626 (25, M^+-$2H_2O$), 567 (12), 508 (7), 338 (100), 272 (64), 270 (76), 253 (43); FABMS *m/z* 685 [38%, $(M+Na)^+$], 663 [10%, $(M+H)^+$], 627 [78%, $(M\text{-}H\text{-}H_2O)^+$], 331 [100%, (M^{2+})].

2.5.2. Method 2

To a stirred solution of liquid NH_3 (150 ml) and tetrahydrofuran (10 ml) containing dissolved Li metal (700 mg, 0.1 mol) was added a solution of the methyl ester **1b** (709 mg, 2.15 mmol) in THF (20 ml) over 20 min. After stirring for a further hour solid NH_4Cl (6 g, 11 mmol) was added followed by CH_2Cl_2 (150 ml). After evaporation of the NH_3 the organic layer gave a residue that on FCC on elution with LP/EtOAc (4:1) yielded the dimer **3a** (170 mg, 12%), m.p. 217–220°C (from CH_2Cl_2-EtOAc-LP). ^1H and ^{13}C NMR were in agreement with the product above.

*2.6. Methyl 5α- (**2a**) and 5β-androst-3-en-17-on-19-oate (**2b**) and 3α,3α′-bis(methyl 3-trimethylsilyloxyandrost-4-en-17-on-19-oate-3-yl) (**3b**), and 3α,3β-bis(methyl 3-trimethylsilyloxyandrost-4-en-17-on-19-oate-3-yl) (**3c**)*

The methyl ester **1b** (2.22 g, 6.72 mmol) in acetic acid/water (1:1) (40 ml) was stirred with zinc powder (40 g) for 2.5 h and the residue after work-up was treated with trimethylsilyl-imidazole reagent (2.24 ml, 15.3 mmol) in CH_2Cl_2 (5 ml) for 1 h. FCC of the product gave fractions of 1) the methyl 5β-androst-3-en-17-on-19-oate **2b** (133 mg, 6.3%), m.p. 143–145.5°C (from Et_2O-LP), 2) a mixture of methyl 5α- and 5β-androst-3-en-17-on-19-oate **2a** and **2b** (1.07 g, 52%), 3) the non-crystalline methyl 5α-androst-3-en-17-on-19-oate **2a** (70 mg, 3.3%) δ_H 0.90 (13-Me), 2.45 (dd, J = 9.5, 18.8, 16β-H), 2.50 (d, J = 12.7, 5α-H overlapping with the 16β-H), 3.66 (s, 19-OMe), 5.46 (dd, J = 1.8, 9.8, 4-H), 5.55 (ddd, J = 2.1, 6.5, 9.8, 3-H); δ_C 27.51 (1) 24.41 (2), 126.00 (3), 134.39 (4), 44.55 (5), 30.41 (6), 31.54 (7), 35.69 (8), 51.31 (9), 50.04 (10), 21.74 (11), 32.02 (12), 47.73 (13), 51.54 (14), 21.81 (15), 35.81 (16), 220.91 (17), 13.86 (18), 174.65 (19), 51.84 (19-OMe) and 4) the silylated symmetrical dimer **3b** (270 mg, 6%), m.p. 258–260°C (from CH_2Cl_2-EtOAc) (R_f 0.17, 30% Et_2O-LP) (Found: C, 68.24; H, 9.00. $C_{46}H_{70}O_8Si_2$ requires C, 68.44; H, 8.74%); $\nu_{max}(CH_2Cl_2)$ cm^{-1} 1735 (17-C = O and 19-COOMe); δ_H 0.04 (s, $SiMe_3$), 0.90 (s, 13-Me), 2.46 (dd, J = 8.8, 19.2, 16β-H), 2.62, (td, J = 3.3, 13.7, 6β-H), 3.67 (s, 19-OMe), 5.63 (s, 4-H); δ_C 31.07 (1), 30.50 (2), 77.90 (3),



Scheme 1. Reagents: i, CH_2N_2; ii, Li-NH_3; iii, Zn-50% HOAc-H_2O; iv, Me_3Si-imidazole; v, $NaIO_4$.

127.27 (4), 140.85 (5), 33.95 (6), 31.57 (7), 36.03 (8), 53.09 (9), 50.02 (10), 21.64 (11), 31.35 (12), 47.83 (13), 51.26 (14), 21.74 (15), 35.80 (16), 220.88 (17), 13.88 (18), 174.21 (19), 2.55 (Me_3Si), 51.41 (19-OMe); FABMS: *m/z* 829 [3%, $(M+Na)^+$], 807 [1, $(M+H)^+$], 717 [0.5, $(M+H\text{-}Me_3SiOH)^+$], 627 [6, $(M+H\text{-}2Me_3SiOH)^+$] and 403 [100, $(M)^{2+}$] and 5) the silylated unsymmetrical dimer **3c** (130 mg, 2.5%) m.p. 181–182°C (from MeOH-EtOAc) (R_f 0.06, LP/Et_2O (70:30 v/v)) (Found: C, 68.21; H, 9.01 $C_{46}H_{70}O_8Si_2$ requires C, 68.44; H, 8.74%); δ_H 0.02, 0.06 (s, 3-$SiMe_3$), 0.84, 0.86 (s, 18-Me), 2.42 (dd, J = 8,8, 18.8, 16β-H), 2.52, 2.62 (two overlapping td, J = 3.3, 13.7, 6β-H), 3.62, 3.65 (s, 19-OMe), 5.35, 5.69 (s, 4-H); δ_C 29.72, 30.34 (1), 28.95, 29.72 (2), 77.89, 78.06 (3), 127.30, 127.55 (4), 140.09, 140.82 (5), 33.80, 33.96 (6), 31.42, 31.52 (7), 35.89, 35.96 (8), 52.27, 52.87 (9), 49.86, 49.98 (10), 21.63, 21.79 (11), 30.73, 30.89 (12), 47.58, 47.71 (13), 51.10, 51.14 (14), 22.13, 22.55 (15), 35.71, 35.71 (16), 220.54, 220.59 (17), 13.76, 13.81 (18), 173.53, 173.83 (19), 2.73, 3.19 ($SiMe_3$), 51.22, 51.26 (19-OMe); FABMS: *m/z* 829 [6%, $(M+Na)^+$], 807 [1, $(M+H)^+$], 717 [0.5, $(M+H\text{-}Me_3SiOH)^+$], 627 [8, $(M+H\text{-}2Me_3SiOH)^+$], 403 [100, $(M)^{2+}$].

3. Results and discussion

3.1. Chemistry

Jones oxidation of 19-hydroxyandrost-4-ene-3,17-dione gave the 19-acid **1a** that was treated with diazomethane to give the methyl ester **1b** (Scheme 1) [10,11]. Treatment of the methyl ester **1b** with Zn in aqueous acetic acid gave a mixture of the isomeric 5α- and 5β-3-enes **2a** and **2b** (5α:5β, 1:4, estimated by comparison of the overlapping 3-H and 4-H NMR signals) (45%) together with a dimeric steroid **3a** (6.5%). Further chromatography of the least polar fractions gave the non-crystalline 5α-3-ene **2a** and the crystalline 5β-3-ene **2b**. Alternatively, treatment of the crude reaction product with trimethylsilyl-imidazole reagent gave, on chromatographic separation, fractions of the 5α- and 5β-3-enes (52%) and two dimeric products as the bis-trimethylsilyl ethers **3b** and **3c** derived from the tertiary C-3 alcohols that were isolated in 6% and 2.5% yields, respectively. The symmetrical dimer **3a** was obtained in a higher yield (12%) from Li-NH_3 reduction.

Three isomeric dimers linked at C-3 are possible, namely, two symmetrical dimers connected at C-3 in the α,α′ or β,β′ positions and the unsymmetrical dimer linked α,β′ (Fig. 1). Of the two possible structures for the symmetrical dimer, the sterically favored product from α,α′-face coupling, proposed previously for the 10-methyl analogues [2–7], has been assigned to dimer **3a**. The product from α,β′ face coupling has been assigned to the unsymmetrical dimer **3c** [6,7].

Treatment of the dimer **3a** with $NaIO_4$ gave the starting monomer **1b** consistent with the symmetrical pinacol structure of the dimer.

Earlier we reported that treatment of androst-4-ene-3,17-dion-19-al with Zn in aqueous acetic acid or lithium in ammonia gave the 19-(R)- and 19-(S)-hydroxy-5β,19-cyclosteroid derivatives [12]. In that reaction no C-3 unsaturated isomers or dimeric products were observed on TLC or ^{1}H NMR [12] consistent with a faster rate of intramolecular cyclization. Similarly, dimer formation was not observed on Zn–HOAc treatment of 17β-acetoxyandrost-4-en-3-one and estr-4-ene-3,17-dione that yielded the 5α- and 5β-3-ene isomers as the major products possibly because of conformational differences between the A rings and metal surface requirements resulting in reaction rate differences.

3.2. Spectroscopic analysis

The structures of the unsaturated 5α- and 5β-isomers **2a** and **2b** were established by NMR analysis. The ^{1}H spectrum shows two vinylic protons with chemical shift values in

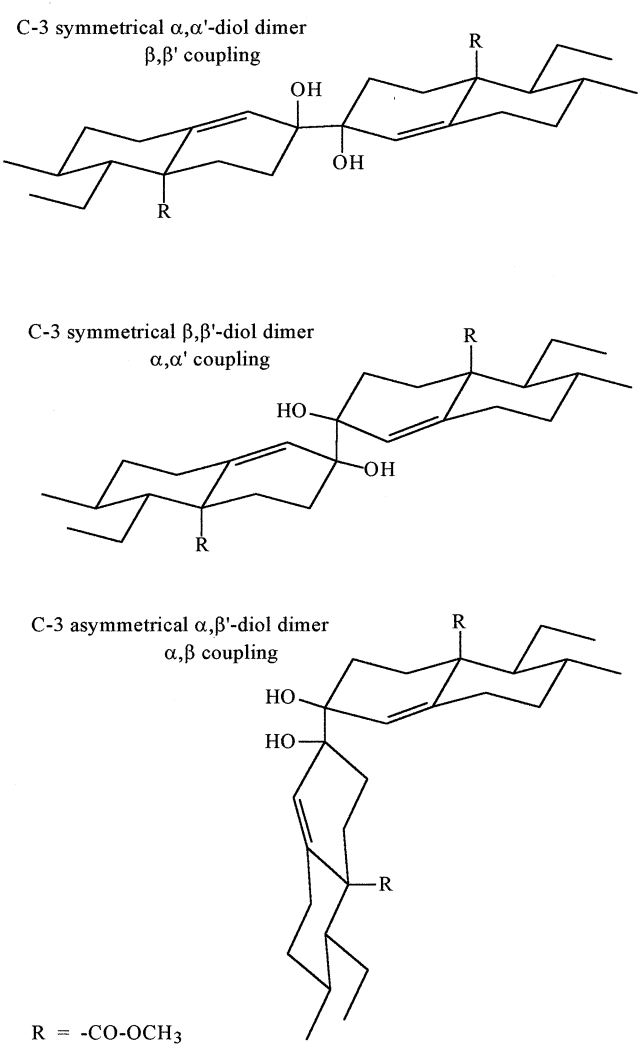


Fig. 1. Three isomeric C-3 dimers (α, α', β, β', α, β); the α, α and β, β isomers are symmetrical whereas the α, β is asymmetrical.

agreement with the 3-enes [1]. The C-5 stereochemistry can be distinguished by the proton patterns in their NMR spectra. In the 5α-3-ene **2a**, the proton signal at 2.45 ppm (J = 8.2, 12.7 Hz) has been assigned to the 5α-H based on the larger coupling (J = 12.5 Hz) that is compatible with both the 5α-H and 6β-H being axial. In compound **2b**, a broad singlet at 2.74 ppm has been assigned to the 5β-H based on the absence of an axial coupling to the 6β-H. The broad unresolved singlet at 2.74 ppm is indicative of the conformational flexibility of ring A. Furthermore, the ^{13}C NMR spectrum showed an upfield shift between **2a** (5α) and **2b** (5β) in the γ carbons 1, 7, 9, and 19 confirming the assigned stereochemistry at C-5 [2].

The structures of the symmetrical dimer **3a** and the bis-trimethylsilyl ether **3b** are based on the following evidence. The ^{1}H and ^{13}C data are consistent with unsaturation at C-4,5 showing a one proton vinylic singlet compatible with a tertiary alcohol center at C-3, and vinylic methine and quaternary carbons, respectively. Loss of the C-3 carbonyl and formation of a new quaternary carbon (73.60 ppm) is indicative of a hydroxyl group at C-3. In agreement, this carbon (77.90 ppm) was shifted downfield on silylation. A ^{13}C T_1 measurement for the symmetrical dimer **3a** in $CDCl_3$ gave an average T_1 value of 231 ms for the CH_2 carbon atoms compared with the more usual value of 600 ms for steroid monomers under the same conditions (Marat K, unpublished results). For a given class of molecules in the same solvent and temperature, the ^{13}C T_1 is inversely proportional to the correlation time for rotation [13]. The T_1 value is therefore consistent with the dimeric structure.

The EIMS of the dimer **3a** does not show a molecular ion peak, however, signals corresponding to loss of one and two molecules of water are present together with the most abundant ion $(M\text{-}2H)^{2+}$ corresponding to cleavage of the dimer 3,3′-bond. The FABMS of the symmetrical dimer **3a** shows signals indicative of the intact molecular ion $(M+H)^+$ and $(M+Na)^+$ together with $(M+H\text{-}H_2O)^+$ and M^{2+} ions. Similarly, the trimethylsilylated dimer **3b** indicates the intact molecular ion by the presence of $(M+H)^+$ and $(M+Na)^+$ ions that show consecutive loss of one and two Me_3SiOH molecules in agreement with the dimeric structure.

The unsymmetrical trimethylsilylated dimer **3c** shows two parallel sets of signals in both the ^{1}H and ^{13}C NMR spectra consistent with the presence of two identical, but not equivalent, steroid ring structures. The proton and carbon assignments are analogous with the dimer **3b**. Whereas one vinyl hydrogen in dimer **3c** (5.69 ppm) has a chemical shift similar to the dimer **3b** (5.63 ppm), the second vinyl hydrogen is shifted upfield (5.35 ppm). The chemical shift difference are consistent with α and β coupling at C-3 on comparison with the H-4 coupling observed in the analogous 3α- and 3β-hydroxyandrost-4-en-17-one of 5.49 and 5.31 ppm, respectively [14]. As with the symmetrical dimer **3b** the ^{1}H and ^{13}C data are in agreement with C-4,5 unsaturation showing a one proton vinyl singlet compatible with a tertiary alcohol center at C-3, and a vinylic methine and quaternary carbons, respectively. Loss of the C-3 carbonyl and formation of new quaternary carbons (77.89, 78.06 ppm) in the ^{13}C NMR spectrum of **3c** is again consistent with a derivatized hydroxy group at C-3.

As observed with the symmetrical dimer **3a** the EIMS of the trimethylsilylated dimer **3c** does not show a molecular ion peak, however, signals corresponding to loss of one and two molecules of water are present together with loss of other small fragments. The FABMS spectrum of the dimer **3c** does show a signal $(M+Na)^+$ indicative of the molecular ion. Consecutive loss of one and two Me_3SiOH groups is also consistent with the dimeric structure.

The symmetry of the two symmetrical isomers does not allow NMR techniques to distinguish between them. Similarly the availability of only one symmetrical isomer does not allow a relative assignment to be made by NMR. Suitable crystals of the symmetrical dimers **3a** and **3b** for X-ray crystallographic analysis were not obtained.

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