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A RADICAL APPROACH TO THE SYNTHESIS OF 9(10→19)ABEO-STEROIDS

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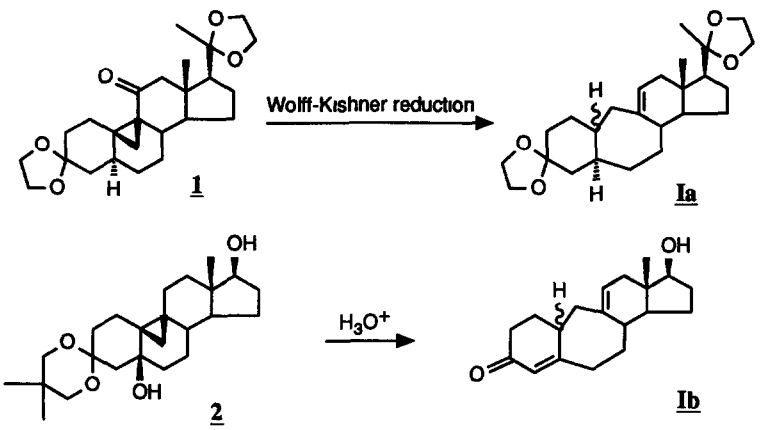
Summary: Tributyltin hydride reduction of a 19-iodo-9(11)-androstene derivative stereoselectively produces B-homosteroids of the 9(10→19)*abeo*-type.

B-Homosteroids of type I have been obtained by Wolff-Kishner reduction of 11-oxo-9ß,10ß-cyclosteroid **1**[1] and, more recently, by acid cleavage of cyclopropane derivative **2**[2]. Both approaches originally aimed at the synthesis of progesterone and testosterone 9ß,10ß-cyclo analogues failed to produce the desired result, instead steroids of the 9(10→19)*abeo* type were isolated as C-10 epimeric mixtures, difficult to separate by either chromatography or crystallization



1 **Ia** **2** **Ib**

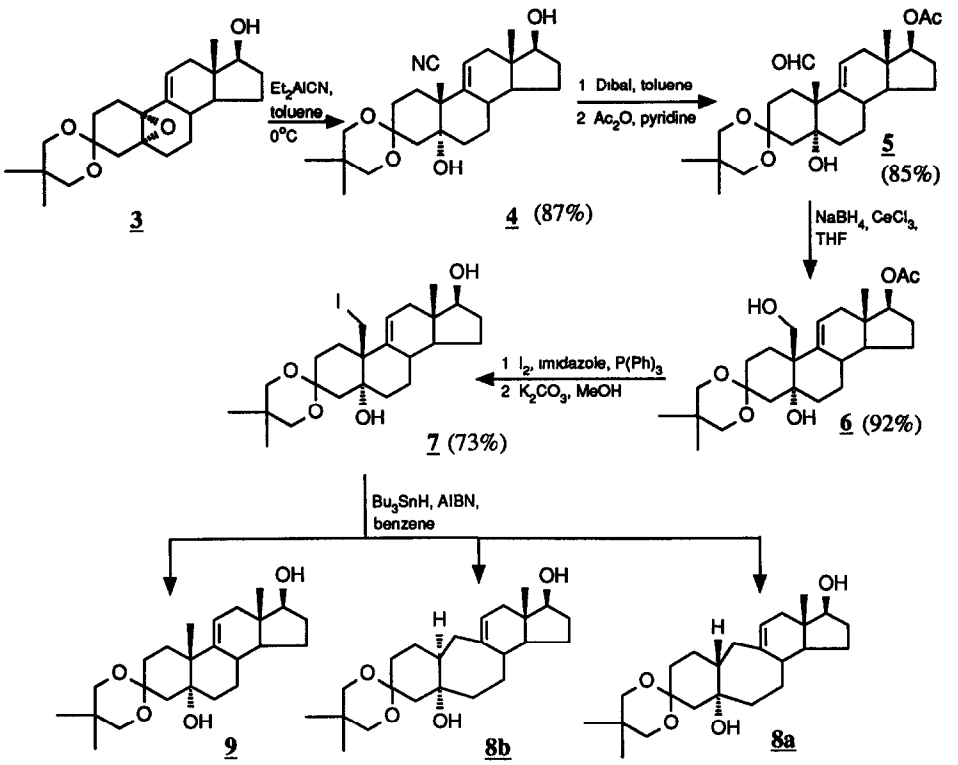
Considering the rather tedious preparation of precursors **1**[3] and **2**[2] we began to search for a new concept that, hopefully, would provide 9(10→19)*abeo* steroids more conveniently and stereoselectively Furthermore, our previous work[2] in the field contained an element of uncertainty since configurational assignment at C-10 for epimers **Ib** had been based solely on CD-spectroscopic data

Well-known 5α,10α-epoxide **3** conveniently accessible by various routes[4] served as starting material for our new approach S_N2 opening with diethylaluminum cyanide cleanly proceeded with formation of ß-hydroxy nitrile **4**[5]. Reduction of **4** with diisobutylaluminum hydride followed by a tartaric acid work-up resulted in the formation of aldehyde **5** which after protection at C-17 (acetate) was further reduced with sodium borohydride to give C-19 alcohol **6**.

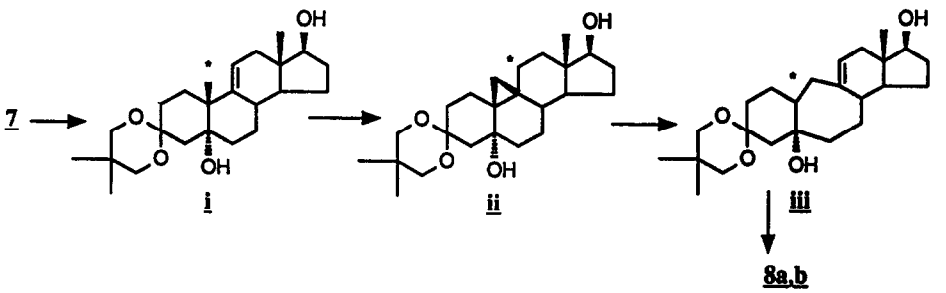
Conversion to iodide 7 was effected by the procedure recently described by Lange[6]. After saponification, iodo-diol 7 was subjected to radical formation[7]. Tributyltin hydride concentration turned out to be the critical parameter of selectivity[8]

Performing reduction of 7 with a high stationary concentration of tin hydride, we obtained three products which were separated by chromatography and, in the order of elution, identified as **8a** (1.3%, m p 226-228°C, $[\alpha]_D$ -32 5°, $CHCl_3$, c = 0 51), **9** (57 9%, m p 210-212°C, $[\alpha]_D$ -22 0°, $CHCl_3$, c = 0.525) and **8b** (28 8%, m p 183-185°C, $[\alpha]_D$ -69.1°, $CHCl_3$, c = 0.505)

Product ratio was almost reversed when stationary hydride concentration was kept low. Upon slow addition of tributyltin hydride to a gently boiling solution of iodide 7 and azobisisobutyronitrile in benzene formation of 9 became drastically suppressed to give a product distribution of **8a** (12 3%), **9** (8%) and **8b** (78.5%)



As expected primary radical **i** is perfectly located to interact with a 9(11)-double bond[9] to form cylopropylcarbinyl radical **ii** which immediately rearranges to give tertiary radical **iii** Hydrogen transfer occurs stereoselectively to favor 10α-epimer **8b** This result is in marked contrast to the ratio of C-10-epimers observed by Kupchan and coworkers[1] upon Wolff-Kishner reduction of precursor 1 (ß/α = 6 4) Therefore, it appears highly unlikely that deoxygenation of cylopropyl ketone 1 runs through a radical intermediate Our findings are in agreement with a recent study by Taber[10] aimed at proving the intermediacy of a carbanion during Wolff-Kishner reduction



After acetate formation at C-17, major isomer **8b** delivered suitable crystals for X-ray analysis. Thus unambiguous assignment of configuration was settled.

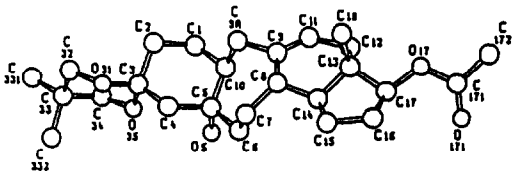
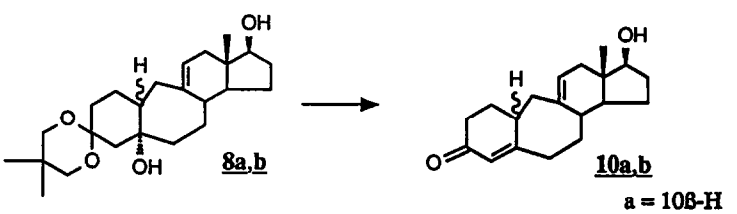


Figure 1: Molecular structure of **8b** (17β-acetate) on the basis of X-ray coordinates.

Acid treatment (2n-H_2SO_4, acetone, 50°C) of epimers **8a** and **8b** yielded unsaturated ketones **10a** (m.p. 146-148°C, $[\alpha]_D$-46.3°, $CHCl_3$, c = 0.505) and **10b** (m.p. 162-163°C, $[\alpha]_D$-46.8°, $CHCl_3$, c = 0.525), which could be compared with their counterparts obtained by our previous route.

The assignments made in our 1987 report[2] for C-10 configuration turned out to be wrong; our false interpretation of the CD spectroscopic data had suffered from an incorrect prediction of the conformation that a seven-membered ring would preferentially adopt in the case of compounds **10a,b**.



Experimental

General

^{1}H- and ^{13}C-NMR spectra were taken on Bruker AMX-500 and Bruker AC-300 spectrometers using standard software Chemical shifts are reported in δ values relative to the appropriate reference signals (tetramethylsilane· δ = 0 00 ppm, $CDCl_3$: δ = 77.0 ppm) Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The optical rotations were measured in chloroform with Perkin-Elmer Polarimeter 241 IR-spectra were recorded on an Bruker IFS 25 spectrometer. Mass spectra were taken on a VG 70-70 E (Fisons Instruments) Elemental analyses were performed by the Department of Analytical Chemistry of Schering AG.

10β-Cyano-3,3-(2,2-dimethyl-trimethylenedioxy)-9(11)-estrene-5α,17-diol (**4**). A 0.66 M solution of diethyaluminum cyanide in toluene (294 ml, 194 mmol) was added dropwise with ice-water cooling to a solution of epoxide **3** (28 g, 74.7 mmol) in methylene chloride (84 ml). After addition stirring was continued for 25 min at ambient temperature whereupon the reaction solution was slowly dripped into ice-cold 2N NaOH (200 ml). The methylene chloride phase was separated and washed with water and brine. After drying (Na_2SO_4) and evaporation in vacuo , the crude product was recrystallized from methylene chloride /diisopropyl ether to yield 10ß-cyano-3,3-(2,2-dimethyl-trimethylenedioxy)-9(11)-estren-5α,17- diol **4**
(25 3 g, 84 3%), m p 218-220°C. ^{1}H NMR (90 MHz,$CDCl_3$) δ=0, 0 78 ppm (s,3H,H-18), 0.92 (s,3H,ketal-CH_3, 1.02 (s,3H,ketal-CH_3), 3 38-3.70 (m,4H,ketal-CH_2), 3.74 (m,1H,H-17), 4 41 (s,1H,5α-OH), 5.60 (m,1H,H-11). IR (KBr) 3520 and 3480 cm^{-1} (OH), 2230 (CN)

3,3-(2,2-Dimethyl-trimethylenedioxy-10β-formyl-9(11)-estrene-5α17β-diol (**5a**). A 20% solution of diisobutylaluminum hydride in toluene (260 ml) was slowly added to nitrile **4** (22.3 g, 55.5 mmol) dissolved in toluene (370 ml). Temperature was kept at -20°C and maintained for 60 min after hydride addition A solution of tartaric acid (5% in water, 500 ml) was freshly prepared and added dropwise to the reaction mixture. Stirring was continued for 1 5 h with a gradual temperature rise to 25°C. The suspension, thus formed, was filtered through Celite, the filter residue being washed with ethyl acetate The organic phase was separated from the filtrate, dried over Na_2SO_4 and evaporated to give crude aldehyde **5a** Recrystallization from hexane/diisopropylether yielded 19 0 g (84 5%), m p 148-150°C, $[\alpha]_D$ -209.2° (CH_2Cl_2, c = 0 565). ^{1}H NMR (90 MHz, $CDCl_3$) δ = 0 64 ppm (s,3H,H-18), 0.92 (s,3H,ketal-CH_3), 0 97 (s,3H,ketal-CH_3), 3.51 (m,4H,ketal-CH_2), 3 72 (m,1H,H-17), 4 47 (s,1H,5α-OH), 5 63 (m,1H,H-11); 9.09 (s,1H,CHO) IR (KBr) 3495 cm^{-1} (OH), 1725 (C=O)

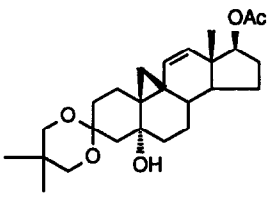
17β-Acetoxy-3,3-(2,2-dimethyl-trimethylenedioxy)-10β-formyl-9(11)-estren-5α-ol (**5b**) A solution of aldehyde **5a** (5.0 g, 12 4 mmol) in acetic anhydride (20 ml) and pyridine (10 ml) was stirred at room temperature for 12 h Excess anhydride was destroyed by slowly pouring the reaction mixture into saturated, aqueous $NaHCO_3$ solution Extraction with ethylacetate and recrystallization of the crude product from diisopropyl ether gave acetate **5b**

(5 2 g, 94.2%), m.p. 151-153 °C, $[\alpha]_D$ -217.4° (CH_2Cl_2, c = 0.505). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 ppm (s,3H,H-18), 0 94 (s,3H,ketal-CH_3), 0.98 (s,3H,ketal-CH_3); 2.05 (s,3H,OAc); 3.49-3 60 (m,4H,ketal-CH_2); 4.48 (s,1H,5α-OH); 4.69 (m,1H,H-17); 5.62 (m,1H,H-11); 9.10 (s,1H,CHO). IR (KBr): 3500 cm^{-1} (OH); 1740 and 1725 (C=O) Anal.calc. for $C_{26}H_{38}O_6$ (446.58): C, 69.93%; H, 8.58%; O, 21.50%; found: C, 69.89%, H, 8.53%; O, 21.25%

17-Acetoxy-3,3-(2,2-dimethyl-trimethylenedioxy)-10β- hydroxymethyl-9(11)-estren-5α-ol (6). Aldehyde **5b** (5.6 g, 12 5 mmol) dissolved in THF (68 ml) and methanol (68 ml) was combined with a solution of $CeCl_3$ (heptahydrate) in methanol (68 ml) After cooling the mixture to 5°C, sodium borohydride (533 mg) was added in one portion and stirring continued for 60 min. Dilution with water and extraction with methylene chloride was followed by chromatography on neutral alumina. Elution with hexane/ethyl acetate gave alcohol **6** (4 68 g, 83.2%), m.p. 193-195°C (CH_2Cl_2, diisopropyl ether), $[\alpha]_D$ -21.2° ($CHCl_3$, c = 0.5) ^1H NMR (500 MHz, $CDCl_3$): δ = 0 76 ppm (s,3H,H-18), 0 92 (s,3H,ketal-CH_3), 1.00 (s,3H,ketal-CH_3); 2.06 (s,3H,OAc), 3 40-3 71 (m,6H,ketal-CH_2 and H-19), 4 69 (m,1H,H-17); 5 42 (m,1H,H-11) IR (KBr): 3500 cm^{-1} (OH), 1735 (C=O) Anal calc. for $C_{26}H_{40}O_6$ (448 49). C, 69.61%, H, 8.99%, O, 21.40%, found: C, 69 48%, H, 8.83%, O, 21.45%

17β-Acetoxy-3,3-(2,2-dimethyl-trimethylenedioxy)-10β-iodomethyl-9(11)-estren-5α-ol (7a) Iodine (3 34 g) was added portionwise to a precooled (0°C)solution of alcohol **6** (6.0 g, 13 4 mmol), triphenylphosphine (6 9 g) and imidazole (1 79 g) in THF (75 ml). Iodine addition was followed by vigorous stirring for another two hours at room temperature, whereupon the reaction mixture was poured into $Na_2S_2O_3$ solution (5% in water) and extracted with ethyl acetate Column chromatography on neutral alumina with hexane/ethyl acetate yielded iodide **7a*** (7.15 g, 95 7%), m.p. 99-102°C (hexane/diisopropyl ether), $[\alpha]_D$ -24 9° ($CHCl_3$, c = 0 505) ^1H NMR (300 MHz, $CDCl_3$). δ = 0 88 ppm (s,3H,H-18), 0 92 (s,3H,ketal-CH_3), 1 02 (s,3H,ketal-CH_3), 2.06 (s,3H,OAc); 3.40-3.73 (m,6H,ketal-CH_2 and CH_2-I); 4.55 (s,1H,5α-OH), 4.68 (m,1H,H-17), 5 30 (m,1H,H-11) IR (KBr) 3500 cm^{-1} (OH); 1738 (C=O)

* Even after recrystallization the product contained an impurity (≤ 5%) identified as compound I



I

I, ^1H NMR (300 MHz, $CDCl_3$). δ = 4 49 ppm (d,J=4 6 Hz,1H,H-19), 0.68 (dd,J=4 6 and 1 6 Hz,1H,H-19); 0 90 (s,3H,H-18), 0 96 (s,3H,ketal-CH_3), 0 99 (s,3H,ketal-CH_3), 2 06 (s,3H,OAc), 3 48-3.63 (m,4H,ketal-CH_2), 4 48 (d,J=1 4 Hz,1H,5α-OH), 4 77 (q,J=7 5 and 1 3 Hz,1H,H-17), 5 19 (d,J=10 Hz,1H,H-11), 5.98 (d,J=10 Hz,1H,H-12)

3,3-(2,2-Dimethyl-trimethylenedioxy)-10β-iodomethyl-9(11)-estrene-5α,17β- diol (7b). A suspension of iodo-acetate 7a (2.26 g, 4.0 mmol) and potassium carbonate (10 g) in methanol (10 ml) and water (3.5 ml) was stirred at room temperature for 4.5 h. After dilution with water and extraction with ethyl acetate the crude product was filtered through neutral alumina (200 g). Elution with hexane/ethyl acetate and crystallization from ethyl acetate/diisopropyl ether yielded iodo-diol 7b (1.55 g, 74.2%), m.p. 140-142°C, $[\alpha]_D$ -8 4° ($CHCl_3$, c = 0.520) ^1H NMR (300 Mhz, $CDCl_3$): δ = 0.84 ppm (s,3H,H-18); 0.92 (s,3H,ketal-CH_3), 1.01 (s,3H,ketal-CH_3); 3.42-3.79 (m,7H.ketal-CH_2,H-17,CH_2-I); 4.55 (d,J = 1.2 Hz,1H,OH); 5.32 (m,1H,H-11)

*3,3-(2,2-Dimethyl-trimethylenedioxy)-9(10→19)*abeo-*10β-androst-9(11)-ene-5α,17β-diol (8a).*
3,3-(2,2-Dimethyl-trimethylenedioxy)-9(10→19)*abeo*-10α-androst-9(11)-ene-5α,17ß-diol *(8b).*
3,3-(2,2-Dimethyl-trimethylenedioxy)-androst-9(11)-ene-5α,17ß-diol (9).

Tributyltin hydride reduction of iodide (7b)

Procedure A (low stationary hydride concentration): A solution of iodide 7b (1.4 g. 2.7 mmol) and azobisisobutyronitrile (20 mg) in benzene (35 ml) was heated to gentle reflux. Tributyltin hydride (1.64 ml) was slowly added dropwise (1 drop/min) After complete addition heating under reflux was continued for 60 min, before the reaction mixture was cooled to room temperature and poured into NaF-solution (5% in water). Dilution with ethyl acetate and phase separation resulted in an oily crude product which was chromatographied on neutral alumina (hexane/ethyl acetate) to give in the order of elution:
8a (130 mg, 12.3%), m.p. 226-228°C, $[\alpha]_D$ -32.5° ($CHCl_3$, c = 0.51). ^1H NMR (300 MHz, $CDCl_3$): δ = 0 78 ppm (s,3H,H-18); 0.92 (s,3H,ketal-CH_3); 1 01 (s,3H,ketal-CH_3); 3.45-3.59 (m,4H,ketal-CH_2); 3.69 (d,J = 1 4 Hz,1H,OH); 3.73 (m,1H,H-17); 5.28 (m,1H,H-11). Anal calc. for $C_{24}H_{38}O_4$: C, 73.81%; H, 9.81%; O, 16.39%, found· C, 73.83%, H, 9 71%; O, 16.36%
9 (148 mg, 14%), m.p 210-212°C, $[\alpha]_D$ -22.0° ($CHCl_3$, c = 0.525). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.70 ppm (s,3H,H-18), 0 95 (s,3H,ketal-CH_3), 0.98 (s,3H,ketal-CH_3); 1.12 (s,3H,H-19); 3.46-3.59 (m,4H,ketal-CH_2), 3 74 (m,1H,H-17), 4 29 (d,J = 1 4 Hz,1H,OH); 5 33 (m,1H,H-11).
8b (770 mg, 72.8%), m.p 183-185°C, $[\alpha]_D$ -69 1° ($CHCl_3$, c = 0 505). ^1H NMR (300 MHz, $CDCl_3$)· δ = 0 73 ppm (s,3H,H-18), 0 92 (s,3H,ketal-CH_3), 1 02 (s,3H,ketal-CH_3), 3.46-3.52 (m,4H,ketal-CH_2); 3.74 (m,1H,H-17), 4 09 (broad s,1H,OH), 5 37 (m,1H,H-11)

Procedure B (high stationary hydride concentration). A solution of iodide 7b (16 g, 30.9 mmol), azobisisobutyronitrile (35 mg) and Bu_3SnH (18 7 ml) in benzene (350 ml) was heated under reflux for 2 h Workup and chromatography as described above gave· 8a (160 mg, 1.3%), 9 (7.0 g, 57.9%), and 8b (3.49 g, 28 8%)

*17β-Hydroxy-9(10→19)*abeo-*10β-androsta-4,9(11)-dien-3-one (10a).* A solution of 8a (336 mg, 0.86 mmol) in acetone (8 ml) and 2N H_2SO_4 (1 ml) was stirred at 50°C for 1,5 h. After cooling the mixture is diluted with water and extracted with ethyl acetate

Chromatography on silica gel with ethyl acetate/hexane and crystallization from ethyl acetate/diisopropyl ether provides **10a** (218 mg, 88 5%), m p 146-148°C, $[\alpha]_D$ -46.3° ($CHCl_3$, c = 0.505). ^1H NMR (300 MHz, $CDCl_3$): δ = 0 74 ppm (s,3H,H-18), 3 73 (t,J = 7 5 Hz,1H, H-17); 5 38 (m,1H,H-11); 5.82 (s,1H,H-4)

*17β-Hydroxy-9(10→19)*abeo-*10α-androsta-4,9(11)-dien-3-one* (***10b***) Compound **8b** (395 mg, 1 01 mmol) in acetone (8 ml) and 2N H_2SO_4 was stirred at 50°C for 3 h Usual workup and chromatography as above yield enone **10b** (248 mg, 85.6%), m p 162-163°C (ethyl acetate/diisopropyl ether), $[\alpha]_D$-46,8° ($CHCl_3$, c = 0 525) ^1H NMR (300 MHz, $CDCl_3$) δ = 0 76 ppm (s,3H,H-18), 3 76 (t,J = 7.5 Hz,1H, H-17), 5.50 (m,1H,H-11), 5.82 (s,1H,H-4). Anal calc for $C_{19}H_{26}O_2$ (286 41). C, 79 68%; H, 9 15%, O, 11 17%, found: C, 80.05%, H, 8.85%, O, 11.54%

X-ray crystallographic structure determination

17ß-Acetate of **8b**: A solution of **8b** (600 mg) in acetic anhydride (5 ml) and pyridine (2.5 ml) was stirred at room temperature for 16 h Usual workup and crystallization from ethyl acetate/diisopropyl ether gave the acetate (520 mg), m.p. 203-204°C, $[\alpha]_D$-71.0° ($CHCl_3$, c = 0.505). ^1H NMR (300 MHz, $CDCl_3$) δ = 0 78 ppm (s,3H,H-18), 0 92 (s,3H,ketal-CH_3), 1 02 (s,3H,ketal-CH_3), 2 05 (s,3H,OAc), 3.47-3.62 (m,4H,ketal-CH_2), 4 03 (s,1H,OH), 4.70 (t,J = 7.5 Hz,1H,H-17); 5.34 (m,1H,H-11) Anal calc for $C_{26}H_{40}O_5$ C, 72 19%, H, 9 32%, O, 18,49%, found C, 72.43%, H, 9.15%, O, 18.35%

Crystal data[11)]

$C_{26}H_{40}O_5$, M = 423,6 g/mol, colourless, needle-shaped crystals from ethyl acetate / diisopropyl ether, monoclinic, space-group $P2_1$, a=9.530(2) A,b=12 406(1) A,c=21.093(3) A,ß=102.42(1)°, V=2436(8) A^3, Z=4, F(000)=944, D_c=1.108 g/cm^3, u=0.60 mm^{-1}, Ni-filtred CuK_{alpha} radiation (lambda=1.5418 A). 5108 unique reflections (2 $theta_{max}$=120°, omega/2 theta scan) of which 4463 were observed (F>3 sigma (F) were measured on a ENRAF Nonius CAD4 four-circle diffractometer. The data were corrected for Lorentz- and polarization effects

The structure was solved by direct methods using SHELXS (G.M Sheldrick in Crystallographic Computing 3 (G M Sheldrick, c. Kruger and P Goddard, eds), pp 175-189, Oxford University Press, Oxford (1985) Hydrogen atoms were located from difference Fourier maps or included in calculated positions Refinement by the full-matrix least-squares method (G M Sheldrick, SHELX76, Program for Crystal Structure Determination, University of Cambridge, 1976) with anisotropic thermal parameters for all non-hydrogen atoms converged at R=0 057, R_w=0 059

The asymmetric unit contains two crystallographically independent molecules which adopt nearly identical conformations with an RMS deviation of 0 23 A for the superposition of all atoms belonging to rings A, C and D. The main difference between molecules I and II (see Fig. 1) is a disorder of atoms C6 and C7 in molecule I. Occupancy factors for the two alternative positions of the two atoms were refined to 0.7 and 0.3 , respectively.

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11 Comprehensive crystal data were deposited at Cambridge Data Centre