Reduction of the Steroidal Sapogenin Spiro Ketal System[1]

ANTHONY H. ALBERT, GEORGE R. PETTIT,* AND PETER BROWN

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received November 21, 1972

Reduction of tigogenin (**1a**) and deoxytigogenin (**1b**) with lithium aluminum deuteride–aluminum chloride was shown to involve incorporation of hydride at the 22 position by an intermolecular mechanism. A possible alternative involving an intramolecular hydride shift from the 26 position was excluded. Position of the deuterium label was conclusively shown by pmr measurements and by chemical methods. An attempt to employ mass spectral evidence for assigning the deuterium position led to the observation of a rare seven-center transition state in an electron impact fragmentation sequence.

In our initial study of steroidal sapogenin reduction employing metal hydrides[2] it was suggested that reduction (**1** → **2**) of the spiro ketal system with lithium aluminum hydride–aluminum chloride might proceed *via* a hydride transfer mechanism. However, the possibility of either direct reduction of an oxonium ion intermediate or a completely different mechanism was also considered feasible. The oxonium ion possibility would be expected to proceed as outlined[3] for reduction of acetals and ketals by lithium aluminum hydride–aluminum chloride. Some evidence for the oxonium ion route was presented by Leggetter and Brown in 1964.[4] The most compelling evidence for this mechanistic pathway was provided by Eliel and colleagues from a deuterium labeling and mass spectral investigation of cyclohexanone ketal reduction with lithium aluminum deuteride–aluminum chloride.[5] By this means it was found that deuterium was only incorporated into the cyclohexane ring thereby demonstrating that no hydride shift had occurred. These results could not completely preclude the possibility of a hydride shift occurring with rather specialized spiro ketals of the steroidal sapogenin type. To either confirm or eliminate the latter mechanistic possibility we undertook the following examination of tigogenin (**1a**) and deoxytigogenin (**1b**) (Chart I) reduction by lithium aluminum deuteride–aluminum chloride.

As originally planned, this investigation simply required preparation of deuterium-labeled dihydrotigogenin (**2a**) using lithium aluminum deuteride–aluminum chloride and comparison of the mass and pmr spectra with those of the nondeuterated compound. If reduction yielded a monodeuterated product, spectral interpretation would help differentiate among (1) direct reduction of intermediate **3** to dihydrosapogenin **2**; (2) reduction of complex **4** to dihydro derivative **2** preceded by an intramolecular hydride transfer (**3** → **4**); (3) both mechanisms operative; or (4) an entirely different mechanism. With direct reduction (**3** → **2**) the deuterium label would be found at the 22 position. In the case of an intramolecular hydride shift (**3** → **4**), the label would appear at the 26 position.

To make use of pmr data it became necessary to determine the chemical shifts of dihydrosapogenin low field protons and this was accomplished using model systems. The pmr spectrum of 5α-furostan (**5**) demonstrated that the C-16 and C-22 protons have different chemical shifts (Table I). From the spirostan (no C-22 proton) spectra it was evident that the C-16 proton appears farthest down field. The dihydrosapogenins and their derivatives displayed a pair of broad peaks (δ ~3.30 and 4.26) corresponding to the α protons of the furan system in addition to the C-26 proton doublet. When dihydrosapogenins **2a** and **2c** were prepared using lithium aluminum deuteride–aluminum chloride, the C-22 proton signal at δ 3.30 was no longer present and the doublet corresponding to the C-26 protons remained unchanged. Similar results were also obtained with labeled acetate **2b** and ester **6b** (Table I). Thus, from the pmr data, it was apparent that the deuterium label resided at the 22 position.

Although the pmr data was considered unequivocal it was decided to add further support for the C-22 labeling using mass spectral data. In the mass spectrum of dihydrotigogenin (**2a**, Figure 1) the first major fragment observed (*m/e* 331) corresponded to anticipated[6] loss of the side chain. Located between this fragment and the molecular ion were several minor yet important fragments. Besides the M − 1, M − 2, M − CH_3 (*m/e* 403), M − H_2O (*m/e* 400), and M − CH_3 − H_2O (*m/e* 385) fragments, possible structures[7] for the four remaining important ions are pictured in Chart II.

For the two most likely reduction mechanisms, deuterium incorporation would be at positions 22 or 26. Location of the label at C-22 would be indicated by fragments **7** and **10** moving up 1 amu, while **8** and **9** would remain unchanged.[7] A C-26 deuteron would be detected by means of a change in the M − 1 and M − 2 peak heights compared with those of the unlabeled com-

(1) (a) This investigation was supported by U. S. Public Health Service Research Grants CA-10612-02 and CA-10612-05 from the National Cancer Institute, National Institutes of Health, and by National Science Foundation Grants GB-4939 and GP-6979 which provided financial assistance for purchase of the Atlas CH-4B and SM-1B mass spectrometers. The present contribution represents Steroids and Related Natural Products. 81. For part 80, see G. R. Pettit and Y. Kamano, *J. Chem. Soc., Perkin Trans. 1*, in press. (b) Abstracted in part from the Ph.D. dissertation submitted by A. A. to the graduate school, Arizona State University, Feb 1971. A preliminary communication based on part of the mass spectral study reported herein has been prepared by P. Brown, A. H. Albert, and G. R. Pettit, *J. Amer. Chem. Soc.*, **92**, 3212 (1970). After completing the present investigation an evaluation of reductive ring opening with the spiro ketal 9,9-dimethyl-1,6-dioxaspiro[4.5]decane was also completed; see G. R. Pettit, A. H. Albert, and P. Brown, *J. Amer. Chem. Soc.*, **94**, 8095 (1972).

(2) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960).

(3) E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958).

(4) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964).

(5) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

(6) The most abundant fragment in the spectra of α-alkylated tetrahydrofurans results from α cleavage of the alkyl group. This cleavage leaves the very stable cyclic oxonium ion. See H. Budzikiewiez, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 253; and K. Bieman, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 97.

(7) This fragmentation pattern is analogous to one proposed for the spirostans: C. Djerassi, personal communication, 1969; H. Budzikiewiez, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964; H. Budzikiewiez, K. Takada, and K. Schreiber, *Monatsh. Chem.*, **101**, 1003 (1970); W. H. Faul and C. Djerassi, *Org. Mass Spectrom.*, **3**, 1187 (1970).

TABLE I

ASSIGNMENT OF LOW FIELD SIGNALS IN THE PMR SPECTRA OF SPIROSTANS AND FUROSTANS[a,b]

Spirostan (1)

Registry no.	Substituent, R	Chemical shifts, ppm C-3	C-16	C-22	C-26 (J, Hz)[c]
5012-14-6	H		4.40		3.45 (d, 5)
77-60-1	OH	3.57	4.40		3.47 (d, 5)
2530-07-6	CH_3COO	4.62	4.35		3.36 (d, 5)
39636-32-3	p-$CH_3C_6H_4SO_3$	4.43	4.3[d]		3.42 (d, 5)

Furostan (2)

Registry no.	Substituents R	R_1	X	Chemical shifts, ppm C-3	C-16	C-22	C-26 (J, Hz)[c]
39636-33-4	H[e,f]	H	H		4.29	3.32	
39636-34-5	CH_3COO[e]	H	H	4.68	4.28	3.32	
39636-35-6	H	$(CH_3)_3C$	H		4.30	3.33	3.18 (d, 5)
39636-36-7	CH_3COO[g]	CH_3CO	H	4.52	4.14	3.13	3.81 (d, 6)
39636-37-8	$Cl_3CCONHCOO$	$Cl_3CCONHCO$	H	4.80	4.27	3.32	4.17 (d, 5)
39636-38-9	$(CH_3)_3CO$	$(CH_3)_3C$	H	3.2[d]	4.25	3.33	3.13 (d, 6)
39636-39-0	CH_3COO	26-Thio acetal	H	4.65	4.26	3.32	4.55 (d, 6)
39636-40-3	CH_3COO	26-Aldehyde	H	4.68	4.28	3.30	
39636-41-4	H	H	H		4.26	3.30	3.43 (d, 5)
39636-42-5	H	H	D		4.26		3.45 (d, 5)
39636-43-6	H	CH_3CO	H		4.28	3.28	3.92 (dd, 5, 1.5)
39636-44-7	H	CH_3CO	D		4.26		3.92 (dd, 5, 1.5)
39636-45-8	H	26-Methoxycarbonyl	H		4.26	3.30	
39636-46-9	H	26-Methoxycarbonyl	D		4.27		
39636-47-0	OH	OH	H	3.59	4.24	3.30	3.45 (d, 6)
39636-48-1	OH	OH	D	3.60	4.25		3.47 (d, 6)

[a] Protons not below δ 3 or absent are left blank. [b] Solvent was $CDCl_3$ in all cases except where noted. [c] d, doublet; dd, doublet of doublets. [d] Approximate. [e] Supplied by Dr. J. C. Knight. [f] 5β hydrogen. [g] Carbon tetrachloride as solvent.

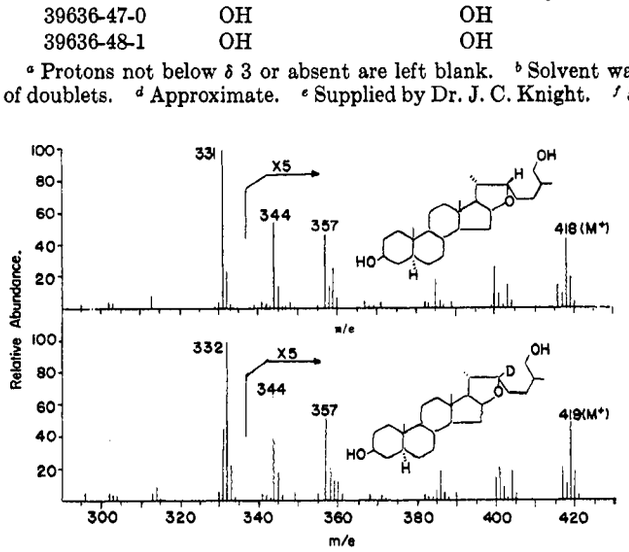


Figure 1.—Mass spectra of labeled and unlabeled dihydrotigogenin (2a).

pound plus the appearance of an M − 3 peak and no change in the mass of all other fragments. In practice, the product (**2d**) of lithium aluminum deuteride–aluminum chloride reduction of tigogenin displayed a high degree of monodeuteration, but the fragmentation pattern (Figure 1) presented a challenge. From the mass spectral data it was possible to rule out a C-26 deuterium label, but it was not possible to confirm a C-22 deuteron owing to the presence of both M − 87 (*m/e* 332) and M − 88 (*m/e* 331) peaks (Chart II, fragment **10**).

To determine whether an oxygen-containing fragment, other than loss of the side chain, was responsible for the M − 88 (*m/e* 331) peak in the mass spectrum of dihydrotigogenin-d_1 (**2d**), a study of 3-deoxytigogenin was made. The appropriate dihydro derivatives (**2c** and **2e**) were prepared by reduction with either lithium aluminum hydride or deuteride with aluminum chloride. The respective mass spectral fragments, between the molecular ion and loss of the side chain, are listed in Table II. Again, both the M − 87 (*m/e* 316) and

TABLE II

MASS SPECTRA OF UNLABELED (2c) AND DEUTERIUM-LABELED (2e) DIHYDRO-3-DEOXYTIGOGENIN

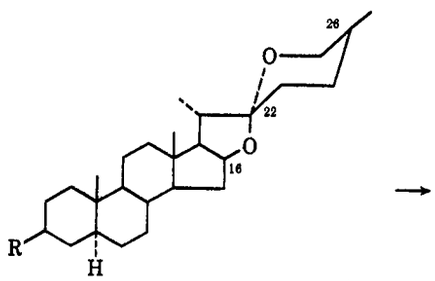
Unlabeled (2c) *m/e* (rel intensity)	Labeled (2e) Fragment	*m/e* (rel intensity)
402 (10)	M^+	403 (11)
401 (1)	M − 1	402 (2)
400 (4)	M − 2	401 (5)
387 (3)	M − 15	388 (3)
384 (5)	M − H_2O	385 (3)
	M − HDO	384 (2)
369 (3)	M − 15 − H_2O	370 (2)
	M − 15 − HDO	369 (1)
343 (4)	7	344 (2)
	7	343 (2)
341 (8)	8	341 (11)
328 (11)	9	328 (14)
315 (100)	10	316 (100)
	10	315 (37)

M − 88 (*m/e* 315) fragments were present in the labeled derivative (**2e**) spectrum. Thus, it appeared that a C-3 oxygen containing fragment was not responsible for the M − 88 peak. High resolution mass studies further demonstrated that the peak at *m/e* 315 of dihydro-3-deoxytigogenin (**2c**) was due to a fragment with composition $C_{22}H_{33}O$ (**10**). We next excluded multiple pathways leading to M − 87 (*m/e* 316) and M − 88 (*m/e* 315) ions by observing the electron energy independence of the peak ratio [315]/[316] from 70 eV to threshold.[1b]

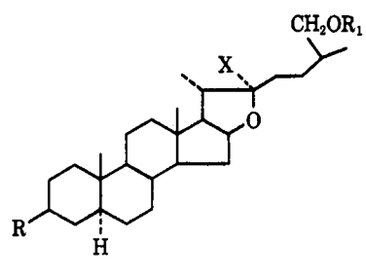
When labeled dihydro-3-deoxytigogenin was con-

verted to acetate **2f** and subjected to electron impact, a marked effect upon composition of the oxonium ion fragment **10** was apparent. As shown in Table III, a peak corresponding to the M − 88 (*m/e* 315) ion was no longer present. Similarly, when dihydro-3-deoxytigogenins **2c** and **2e** were oxidized and methylated to yield methyl-(22*R*,25ε)-5α-furostan-26-oates (**6a** and **6b**) only the M − 87 (*m/e* 316) peak was found in the labeled derivative (**6b**) mass spectrum (Table IV). These results indicated that the 26-hydroxyl group was responsible for the ambiguous mass spectral results obtained with the dihydrotigogenins.

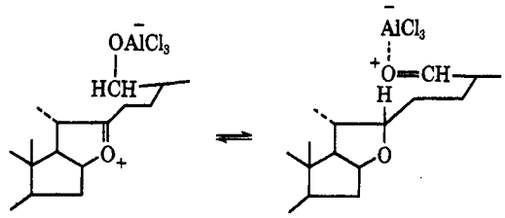
CHART I



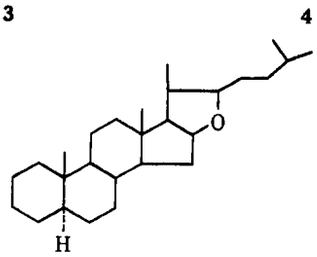
1a, R = OH
b, R = H



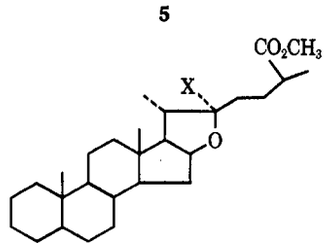
2a, R = OH; R_1 = X = H; M^+ 418
b, R = OH; R_1 = $COCH_3$
c, R = R_1 = X = H; M^+ 402
d, R = OH; R_1 = H; X = D; M^+ 419
e, R = R_1 = H; X = D; M^+ 403
f, R = H; R_1 = $COCH_3$; X = D
g, R = H; R_1 = $COCH_3$; X = H
h, R = H; R_1 = D



3 **4**

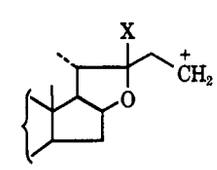


5



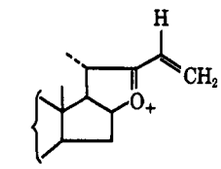
6a, X = H
b, X = D

CHART II



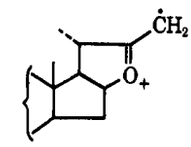
7

m/e 359; R = OH; X = H
m/e 360; R = OH; X = D
m/e 343; R = H; X = H
m/e 344; R = H; X = D



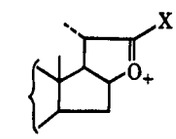
8

m/e 357, R = OH
m/e 341, R = H



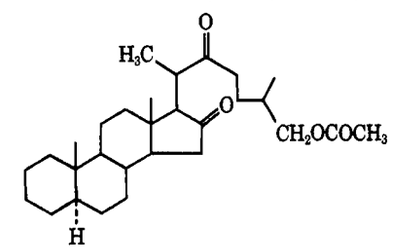
9

m/e 344, R = OH
m/e 328, R = H

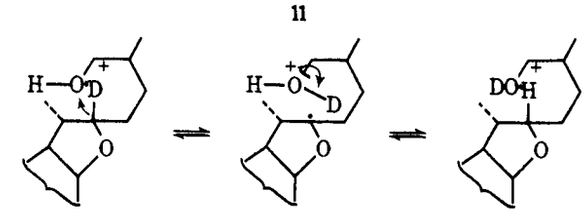


10

m/e 331, R = OH; X = H
m/e 332, R = OH; X = D
m/e 315, R = H; X = H
m/e 316, R = H; X = D



11



12 **13** **14**

TABLE III
MASS SPECTRA OF UNLABELED (**2g**) AND DEUTERIUM-LABELED (**2h**) DIHYDRO-3-DEOXYTIGOGENIN ACETATE

Unlabeled (**2g**)	Labeled (**2h**)	
m/e (rel intensity)	Fragment	*m/e* (rel intensity)
444 (12)	M^+	445 (13)
429 (19)	M − 15	430 (18)
427 (5)	M − 17	428 (2)
426 (6)	M − H_2O	427 (4)
	M − HDO	426 (4)
411 (3)	M − H_2O − CH_3	412 (2)
400 (2)	M − 44	401 (17)
384 (19)	M − HOAC	385 (11)
	M − DOAC	384 (8)
369 (9)	M − HOAC − CH_3	370 (6)
355 (15)	*m/e* 384 − 29	355 (12)
341 (32)	*m/e* 384 − 43	341 (27)
328 (15)	9	328 (11)
315 (100)	10	316 (100)

TABLE IV

MASS SPECTRA OF UNLABELED (6a) AND DEUTERIUM-LABELED (6b) METHYL-5α-(22*R*,25ε)-FUROSTAN-26-OATE

Unlabeled (6a) *m/e* (rel intensity)	Fragment	Labeled (6b) *m/e* (rel intensity)
431 (17)	M^+	430 (28)
416 (9)	M − 15	415 (11)
413 (10)	M − H_2O	412 (21)
412 (14)	M − HDO	
400 (7)	M − OCH_3	399 (8)
	M − CH_3OH	398 (8)
398 (9)	M − CH_3OD M − CH_3 − H_2O	397 (7)
384 (10)	M − CH_3OH − CH_3	383 (12)
371 (6)	M − CH_3OH − CO	370 (9)
370 (4)	M − CH_3OD − CO	
361 (5)		360 (5)
344 (16)		343 (17)
328 (27)	M − $CH_3CHCOOCH_3$	328 (45)
316 (100)		315 (100)

The best evidence that deuterium had been incorporated only into the 22 position was obtained by oxidizing deuterium-labeled dihydro-3-deoxytigogenin acetate (**2f**) to 26-acetoxy-16,22-dioxo-(25*R*)-5α-cholestane (**11**) and comparing its mass spectrum with that of a sample prepared from the nondeuterated analog **2c**. In this manner it was shown that deuterium had indeed been incorporated into the 22 position since all label was lost.

To account for the presence of both M − 87 and M − 88 peaks (see **10**) in the spectra of the labeled dihydrotigogenins, a reciprocal H/D exchange between C-22 and the alcohol O atom was proposed (**12** ⇄ **13**).[1b] This novel exchange not only accounts for the presence of both the labeled and unlabeled oxonium ion fragments (**10**) but also the anomalous HDO loss and M − 60 fragment (*cf.* **7**). In such an exchange mechanism, dihydrosapogenins containing an O-*d* label should also display both M − 87 (**7**, X = D) and M − 88 (**7**, X = H) peaks, but the ratio of the two peaks would be exactly opposite to that found in the C-22 labeled analogs. This situation was in fact found to be the case for dihydro-3-deoxytigogenin-*O*-*d* (**2h**, Table V). Thus, the hydrogen (deuterium) atom of position 22 can exchange with the hydroxyl proton (deuteron) *via* a novel[8] seven-centered transition state.[1b] Undoubtedly, the relative position of the tetrahydrofuran ring (which gives rise to a very stable radical) to the hydroxyl group is responsible for this unusual reaction.

From the above pmr and mass spectral results, it was concluded that the mechanism of metal hydride reduction of the steroidal sapogenin spiro ketal system is best represented by an intermolecular hydride insertion (**3** → **2**). Stereochemical aspects were next considered. An X-ray crystallographic study of the sapogenins[9] has substantiated[10a] that the configuration about C-22 is "*R*."[10b] However, the configuration at C-22 in the dihydrosapogenins has not been established. Since metal hydride reduction of the spiro ketal gives a nearly quantitative yield of sharp melting solid, it would appear that the dihydrotigogenins must consist of one isomer rather than a mixture of epimers.[11] By examining a model, it can be seen that the 18-methyl group poses a greater amount of steric hinderance to a group approaching at C-22 than the 21-methyl group. For these steric reasons it should be easier for the incoming group to approach from the remote α side of the steroid resulting in an *R* configuration at C-22. Also, as the alcohol resulting from steric approach control accounts for 90% of the camphor–lithium aluminum hydride reduction product,[12] it seems quite plausible that the larger[5,13] $AlHCl_2$ might attack the slightly less hindered oxonium ion **3** with selectivity.[14]

Instead of steric approach control, the reduction product might result from product development control. Inspection of models suggests that the most stable final product (**2**) should have the bulky side chain in the α position and thereby removed from the 18-methyl group. In this configuration the side chain would remain cis and in close proximity to the 21α-methyl group. If, on the other hand, the side chain were to assume the β or *R* configuration, a change in conformation of the E ring would allow a positioning remote to both methyl groups. Thus, it appears that by approaching the stereochemical problem from either steric approach or product development control the same configuration (*R*) is indicated for the dihydrosapogenin 22 position.

An alternative to the stepwise reduction mechanism discussed above is a concerted one. For example, certain stereoselective reductions of epoxides have been postulated[14] to proceed by simultaneous ring opening and hydride insertion. With epoxides it has been suggested[14] that only the weaker Lewis acid AlH_3 (stronger hydride donor) is involved in a concerted attack. With spiro ketals, it is possible that the electron density around the incipient carbonium ion is sufficiently altered by the adjacent oxygen atom to allow the weaker hydride donor $AlHCl_2$ to also react in a concerted manner. If, indeed, reduction is concerted, the C-22 stereochemistry should be maintained and lead to the (22*R*)-dihydrosapogenin. Regardless of whether the mechanism is stepwise or concerted the configuration at C-22 should be *R*. Similar arguments for the stereo-

(8) See, for example, J. H. Beynon, B. E. Job, and A. E. Williams, *Zeit. Fur Naturforsch.*, **20a**, 883 (1965); S. Meyerson and J. L. Corbin, *J. Amer. Chem. Soc.*, **87**, 3045 (1965); A. N. H. Yeo and D. H. Williams, *ibid.*, **91**, 3582 (1969); and G. A. Smith, and D. H. Williams, *ibid.*, **91**, 5254 (1969).

(9) R. Callow, *J. Chem. Soc. C*, 288 (1966).

(10) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 822; (b) G. R. Pettit, *Experientia*, **19**, 124 (1963).

(11) Although the yield was quantitative, this does not preclude the possibility that a small amount of an epimeric mixture was removed during recrystallization.

(12) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 31.

(13) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966); U. E. Diner, H. A. Davis, and R. K. Brown, *Can. J. Chem.*, **45**, 207 (1967); E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **6**, 333 (1951); E. Wiberg and M. Schmidt, *ibid.*, **6**, 460 (1951). The actual reducing species in mixed hydride reductions are AlH_3, AlH_2Cl, $AlHCl_2$, and $AlHCl_2 \cdot AlCl_3$ when the ratio of aluminum chloride to lithium aluminum hydride is 1:3, 1:1, 3:1, and 4:1, respectively. See E. C. Ashby and B. Cooke, *J. Amer. Chem. Soc.*, **90**, 1625 (1968). The excess aluminum chloride in the 4:1 ratio ($AlCl_3$:$LiAlH_4$) was found not to take part in the reduction of epoxides.

(14) Generally, it is assumed that the reduction of a ketone with lithium aluminum hydride proceeds *via* a four-centered transition state. The metal atom is coordinated with the oxygen and a hydride with the electron-deficient carbon atom. This mode of action has been considered for other hydride-donating species (see ref 13).

TABLE V

HYDROGEN–DEUTERIUM EXCHANGE[a]

—Dihydro-3-deoxytigogenin—			——Dihydro-3-deoxytigogenin-22-d[b]——				——————Dihydro-3-deoxytigogenin-O-d——————				
400	401	402	400	401	402	403	400	401	402	403	404
28	3	70	1	29	3	67	33	5	32	29	2
314	315	316	314	315	316	317	313	314	315	316	317
4	96	0	3	25	72	0	2	7	80	11	0
				26	74				76	24[c]	

[a] Corrected for ^{13}C isotopic contributions; all values are in per cent; each peak normalized to 100%; reproducibility ±1%. [b] <97% d_1. [c] Corrected to 100% O-d_1.

chemical course of the hydrogenation[15] route to dihydrosapogenins also points to an R configuration at C-22 and our[2] earlier comparison of dehydrosapogenins prepared by catalytic hydrogenation and lithium aluminum hydride–aluminum chloride methods provides compelling support for the stereochemical assignments.

Experimental Section

Boiling points and melting points (Kofler hot stage apparatus) are uncorrected. Each analytical sample was colorless and displayed a single spot on thin layer chromatography. The (Beckman IR-12), pmr (Varian A-60, tetramethylsilane internal standard), and ORD (Jasco ORD/UV-5) spectra were recorded by Miss K. Reimer. An Atlas CH4B instrument equipped with a molecular beam direct inlet system was employed for low resolution mass spectra. The experimental conditions employed were electron energy of 70 eV, trap current of 19 μA, source temperature of 200°, probe temperature of 70–75°, and accelerating voltage of 3 kV. Accurate mass measurements were determined using an Atlas SM1B double focussing instrument with electron energy of 70 eV, trap current of 290 μA, source temperature of 180°, probe temperature of 70–75°, accelerating voltage of 8 kV, and ~10,000 resolutions.

Dihydrotigogenin-*22-d* (**2d**).—Lithium aluminum deuteride–aluminum chloride reduction of tigogenin was accomplished using our previously described[2] method employing lithium aluminum hydride. The deuterated specimen of dihydrotigogenin was isolated in essentially quantitative yield: mp 168–169.5°; ir ($CHCl_3$) 3630 (m), 3450 (m, br), 2100 (w, br), 1040 cm^{-1} (s).

Dihydro-3-deoxytigogenin-*22-d* (**2e**).—The procedure used above for the preparation of deuterium-labeled dihydrotigogenin (**2d**) was applied to 3-deoxytigogenin (**1b**) and dihydro-3-deoxytigogenin-*22-d* was obtained in quantitative yield: mp 92.5–95°; ir ($CHCl_3$) 3370 (m, br), 2090 (w, br), 1055 cm^{-1} (s).

Dihydro-3-deoxytigogenin Acetate [26-Acetoxy-(22*R*,25*R*)-5α-furostan] (**2g**).—A solution of alcohol **2c** (1 g) in 60 ml of an acetic anhydride–perchloric acid acetylating reagent[16] was allowed to remain at room temperature for 10 min. After dilution with saturated sodium bicarbonate solution the corresponding acetate (**2g**) was isolated in 91% yield: bp 165° (bath, 0.008 mm) (the pure product slowly solidified, but melted over the range of 50–60°); ir (CCl_4) 1745 (s), 1175 (m), 1100 (m), 1005 cm^{-1} (w, sh); ORD ($CHCl_3$) $[\alpha]^{25}$, λ (mμ), −9.0 (400), −13.3 (350), −25.5 (312, min), −24.0 (307, infl), −12.2° (290).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.08; H, 10.80.

Dihydro-3-deoxytigogenin-*22-d* Acetate (**2f**).—The acetate derivative of dihydro-3-deoxytigogenin-*22-d* (**2f**) was obtained as an oil: bp 180° (bath, 0.012 mm); ir (CCl_4) 2080 (w, br), 1740 (s), 1240 cm^{-1} (s); ORD ($CHCl_3$) $[\alpha]^{25}$, λ (mμ), −5.2 (500), −8.4 (400), −13.8 (338, infl), −18.5 (310, max).

26-Acetoxy-16,22-dioxo-(25*R*)-5α-cholestane (**11**).—Dihydro-3-deoxytigogenin acetate (**2g**) was converted to diketone **11** in 81% yield using the general chromium trioxide procedure of Iwasaki.[17] Recrystallization of the product from methanol afforded an analytical sample (colorless needles): mp 95.5–97°; ir (KBr) 1745 (s), 1715 (s), 1253 cm^{-1} (s); pmr ($CDCl_3$) δ 2.08 (s), 2.61 (d, broad, J = 3 Hz), 3.95 ppm (d, J = 5.5 Hz); mass spectrum (70 eV) m/e (rel intensity) 458 (0.5, M^+), 398 (20), 383 (8), 329 (51), 302 (90), 301 (100), 287 (44); ORD ($CHCl_3$) $[\alpha]^{25}$, λ (mμ), −1090 (350), −3880 (315, min), −3250 (308, infl), 0.0 (294), +3100 (271, max).

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.20; H, 9.90.

A sample of dihydro-3-deoxytigogenin-*22-d* acetate (**2f**) was oxidized to diketocholestane **11** using the procedure described above (*cf.* **11**). Both ir and mass spectral analysis demonstrated that no deuterium was present in the product (**11**), mp 92–95°.

Methyl (22*R*,25ε)-5α-Furostan-26-oate (**6a**).—Dihydro-3-deoxytigogenin (**2a**) was oxidized and methylated in the same manner as described below for labeled derivative **2e**: mp 85.5–95°; ir (KBr) 1740 (s), 1170 cm^{-1} (m).

Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 77.85; H, 10.88.

Methyl (22*R*,25ε)-5α-Furostan-26-oate-*22-d* (**6b**).—Dihydro-3-deoxytigogenin-*22-d* (**2e**, 0.60 g) in 30 ml of acetone was slowly treated with 1 ml of Jones reagent[18] while the temperature was kept below 10° (ice bath). The mixture was then allowed to remain at room temperature for 25 min. Excess oxidant was destroyed with methanol and the mixture poured into 100 ml of water and continuously extracted with ether for 22 hr. Removal of the solvent *in vacuo* yielded 0.62 g of colorless solid, mp 123–140°. Recrystallization from acetone (twice) at −7° and from hexane (once) gave a product melting at 138–153°. The acid was treated with freshly distilled diazomethane (in ether) to yield an oil. Recrystallization from methanol at Dry Ice–isopropyl alcohol temperature and twice from methanol at −7° gave a colorless solid: mp 76–83°; ir (KBr) 2100 (w, br), 1745 (s), 1170 cm^{-1} (m).

Registry No.—**2c**, 39636-41-4; **2d**, 39636-50-5; **2h**, 39636-51-6; **11**, 39636-52-7.

(15) The catalytic reduction of acetals and ketals has been proposed to proceed *via* an enol ether: M. Acke and M. Anteunis, *Bull. Soc. Chim. Belges*, **74**, 41 (1965), and W. L. Howard and J. H. Brown, *J. Org. Chem.*, **26**, 1026 (1961). If this proposal is extended to the sapogenins, hydrogenation of the unsaturated intermediate (pseudosapogenin) from the least hindered α side would produce the (20*R*,22*R*)-furostan derivative. The product would have the incorrect configuration at C-20. However, it has been demonstrated by R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 2645 (1958), that this isomer can readily be converted by acidic hydrogenation media to the more stable 20*S* configuration.

(16) E. D. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(17) M. Iwasaki, *Tetrahedron*, **23**, 2145 (1967).

(18) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).