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An Assisted Solvolysis of 23-Spirostanyl Bromides and Tosylates. A New Rearrangement of Spirostanes to the Bisfuran Systems

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Steroidal sapogenins bearing a good leaving group at C23 undergo a completely stereospecific rearrangement under a variety of conditions via a mechanism involving neighboring-group participation by the acetal oxygen atom in the departure of the nucleofuge from C23. The reactions of equatorial (23*S*)-23-bromo- or (23*S*)-23-tosyloxyspirostanes with either the α (25*R*) or *β* (25*S*) oriented 25-methyl group lead to the bisfuran products with inversion of configuration at C23. The reactions of the starting compounds with axial substituents (23*R*) at C23 require drastic conditions and result in the formation of the corresponding olefin accompanied by the rearranged product (in the case of the *25S* isomer only).

Introduction

Steroidal saponins are widely distributed in plants.[1] The steroid aglycones (sapogenins) are cholestane, furostane, or spirostane derivatives. The latter compounds with the two additional spiro connected rings (E and F) are the most frequently found in plants. The naturally occurring compounds always have an *R* configuration at the spiro carbon atom. The 21-methyl group is usually α-oriented (20*S*). However, the spirostanes differ in configuration at C25. In compounds with an equatorial 27α-methyl group (e.g. hecogenin) it is *R*, while compounds with an axial 27*β*-methyl group, such as sarsasapogenin, have the 25*S* configuration. Of course, apart from the spiro system there are further structural differences between the saponins in the type of functionalization and stereochemistry at the ring junction (5α- and 5*β*-steroids).

The chemistry of spirostanes was intensively studied during the last century.[2] Plant sapogenins are relatively cheap raw materials for the synthesis of a number of medicinally important steroids.[3] One of the major challenges for steroid chemists was to elaborate an efficient route of spirostanol degradation to the C_{21} and C_{19} steroids.[4,5] Recently, spirostanes have been enjoying a renaissance, due to the intensive studies on cephalostatins and similar compounds by Fuchs and other chemists.[6]

Results and Discussion

Bromination and oxidation of spirostanes occur at C23 (Schemes 1 and 2).[7] In the case of the 25*R* spirostanes a mixture of 23-bromides (e.g. **1a** and **2a**) is formed with the equatorial one prevailing; a 23,23-dibromide can also be obtained with an excess of bromine. Contrary to this, the 25*S* spirostanes yield exclusively the equatorial bromide (such as **3a**) due to steric reasons (an axial approach of a bromine atom toward C23 would result in a strong 1,3-diaxial interaction with a 27*β*-methyl group). Spirostanes can be easily transformed into their 23-oxo derivatives by using the Barton's procedure recently improved by Cuban chemists.[8] 23-Oxo steroids obtained

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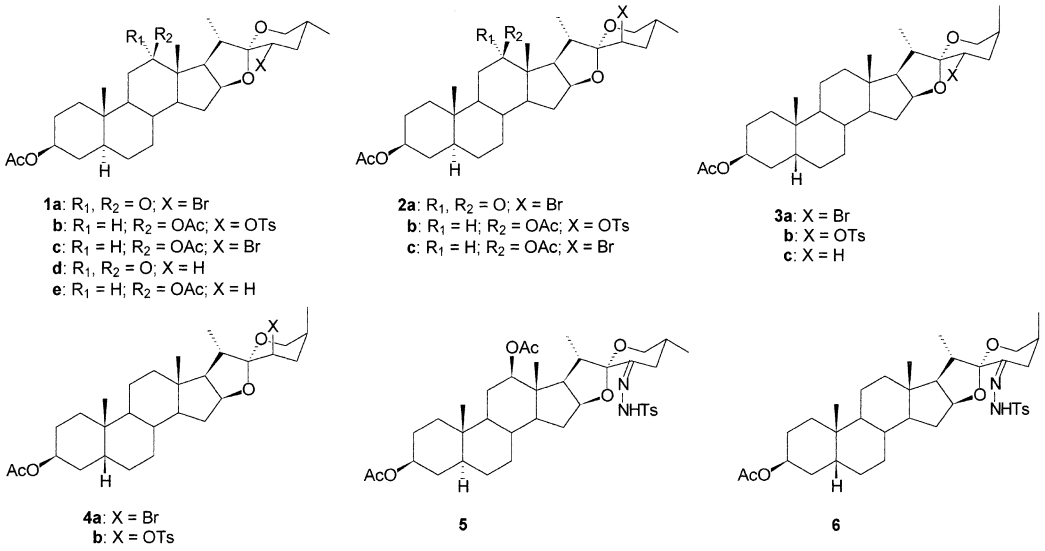
SCHEME 1



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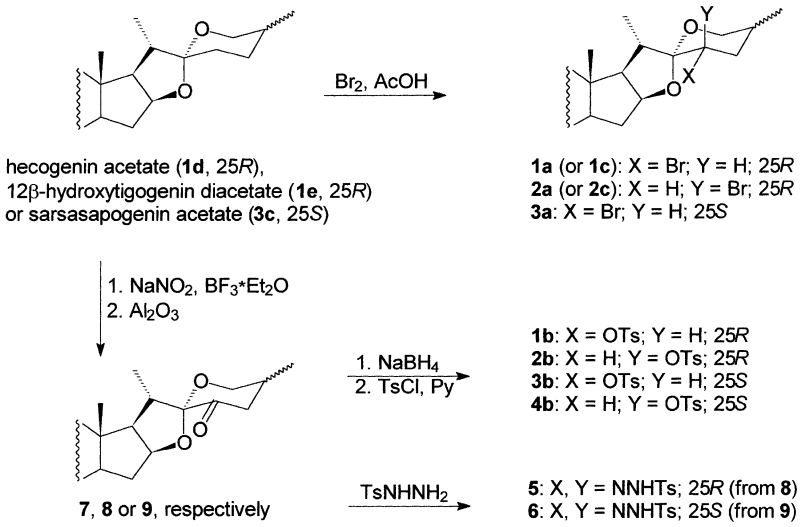

in this way were reduced with hydrides to the corresponding 23-alcohols (mixtures of C23 epimers). 25*R*-5α-Spirostane-3*β*,12*β*-diol-23-one 3-acetate (**8**) when reduced with sodium borohydride afforded a mixture of axial (23*R*) and equatorial (23*S*) 23-alcohols in the ratio 10:1. Analogous reduction of 23-oxosarsasapogenin acetate (**9**) yielded the 7:5 mixture of 23 alcohols in favor of the equatorial one. Relatively high amounts of axial alcohols were formed during reduction of 23-oxo steroids due to the easier approach of hydride from the α-side. 23*S*-Hydroxyspirostane saponins are compounds occurring in nature, e.g. they were found in the leaves of *Sansevieria trifasciata*.[9] Each of the four 23-alcohols obtained were converted to the corresponding tosylates **1b**, **2b**, **3b**, and **4b** in order to study their solvolytic reactions along with the bromide (**1a**, **1c**, **2a**, **2c**, and **3a**) transformations. Tosylhydrazones **5** and **6** were obtained in the usual way from the ketones **8** and **9**, respectively, and their decomposition reactions were also studied.

In a preliminary communication the rearrangement of equatorial 23-bromides to the bisfuran systems was reported.[10] Now, the results of a detailed study on solvolytic reactions of spirostanes with a good leaving group at C23 are presented (Table 1).

Bromide **1c** was subjected to mild hydrolysis with aqueous ammonia in *n*-butanol at reflux (Scheme 3). The reaction afforded slowly but steadily a more polar product **10c**. In a similar reaction of bromide **1a**, an analogous product **10a** was formed accompanied by a minor product **10b** with a free 3*β*-OH group. Compounds **10c** and **10a** showed the O−H absorption bands in their IR spectra and a characteristic pattern of fragmentation ($M^+ - C_5H_{10}O$) in MS. A similar fragmentation pathway was previously reported for 23-alcohols.[9] However, the 23-OH structure for the products was excluded since **10c** proved to be different from both epimeric alcohols obtained by reduction of the 23-ketone **8** (TLC, ^{1}H NMR). Moreover, attempts at acetylation of **10c** and **10a** failed, suggesting

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SCHEME 3

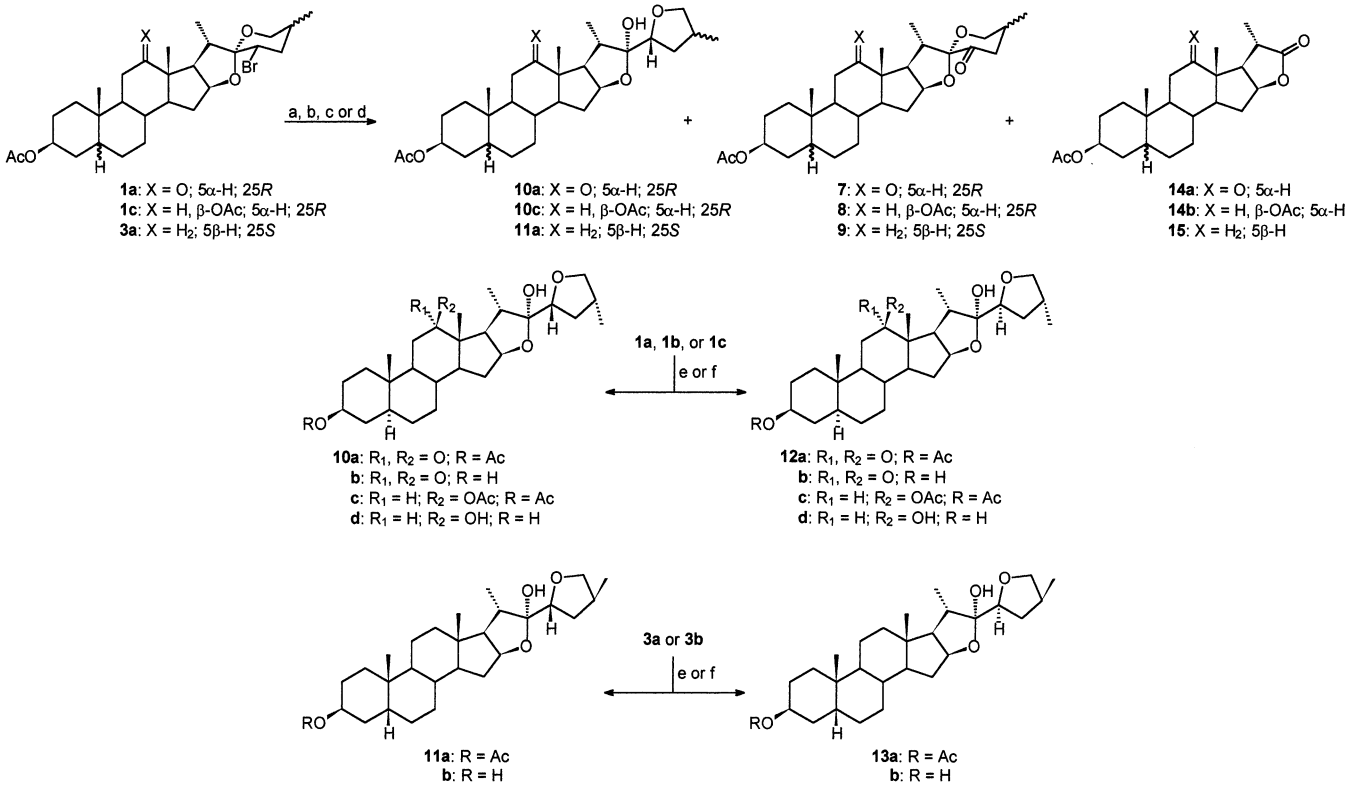


TABLE 1. Solvolytic Reactions of Compounds 1−6

entry	substrate	conditions[a]	products	yield, %
1	**1a**	a	**14a**	79
2	**1a**	b	**7**	72
3	**1a**	c	**10a**	63
4	**1c**	c (no water added)	**14b**	27[b]
5	**1a**	d	**10a**	18[b]
			10b	43
6	**1c**	d	**10c**	43[b]
7	**2a** or **2b**	a, b, c, or d	no reaction	
8	**2a**	e	hydrolysis of 3-acetate only	
9	**2a**	g	**16a**	34[b]
10	**3a**	a	**15**	32
11	**3a**	d	**11a**	75[b]
12	**3a**	e (K_2CO_3)	**11b**	23
			13b	12
13	**3b**	d	**11a**	44[b]
14	**3b**	f	**11b**	27
			13b	27
15	**4b**	g	**17**	9[b]
			18	5
16	**5**	f	**10d**	61
			12d	26
			16b	12
17	**6**	f	**17** + products not analyzed	

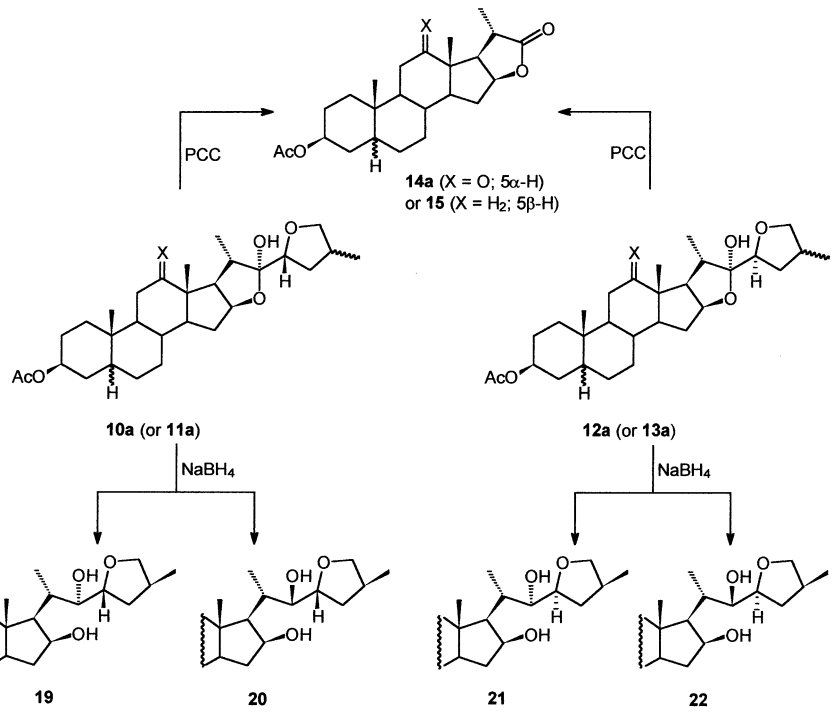
[a] Key: (a) $AgBF_4$, THF, reflux; (b) $AgBF_4$, glyme, H_2O, reflux; (c) $AgBF_4$, DMF, H_2O, reflux; (d) aq NH_3, *n*-BuOH, reflux; (e) Na_2CO_3, H_2O, *n*-BuOH, reflux; (f) KOH, H_2O, glycol, 120 °C; (g) KOH, H_2O, glycol, reflux. [b] The unreacted starting material was recovered (or product of its hydrolysis).

that the hydroxy group in these compounds is tertiary.[11] The reaction of 23α-bromosarsasapogenin acetate (**3a**) with aqueous ammonia in refluxing *n*-butanol was slightly faster than that in the 25*R* series and cleanly afforded the rearranged product **11a**. A similar reaction of the corresponding tosylate **3b** yielded the same product. Its structure was unequivocally confirmed by an X-ray study (see Supporting Information). In particular, the study proved the configurations at the chiral centers C22 (*S*) and C23 (*R*). The crystal structure showed no intramolecular hydrogen bonds. The ring E of **11a** exists in a slightly distorted 22α,O*β*-half-chair conformation, whereas the ring F conformation is an intermediate between a 25*β*-envelope and a 24α,25*β*-half-chair. The oxygen atoms in the "furanose" rings are approximately trans located (the torsion angle O(16)−C22−C23−O(26) amounts to 75.0°). The conformation of the five-membered ring D is a nearly pure 14α-envelope. The X-ray study proved inversion of configuration at C23 during rearrangement. This can be explained assuming participation of electrons of the C22−O(26) bond in the bromide departure. It should be added that an anti coplanar relationship of the atoms O(26)−C22−C23−Br in the substrate is ideal for such participation.

Bromide **1a** was also subjected to solvolysis under different conditions. When **1a** was treated with silver tetrafluoroborate in aqueous DMF, once again the rearranged compound **10a** was formed as the main product. However, when DMF was replaced by glyme, the oxidation to the ketone **7** took place instead. Compound **7** was identified by comparison with the product of hecogenin acetate **1d** oxidation with sodium nitrite. The reaction of **1a** with $AgBF_4$ performed in THF under anhydrous

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wileley & Sons: New York, 1991; Chapter 2.

SCHEME 4



conditions resulted in the formation of the fragmentation product, lactone **14a**.[12]

The solvolytic reactions of the equatorial bromides and tosylates were also performed in the more alkaline medium (sodium carbonate or potassium hydroxide was used as a base). It was found that the reaction rates do not depend on the basicity of the medium. However, when a stronger base was used, a new product (**12** or **13**) was formed in addition to the described earlier rearranged products **10** or **11**. In a separate experiment it was proved that this slightly more polar product is formed by base-catalyzed isomerization of the primary rearranged product. Most likely the base forms the alkoxide of the hemiacetal moiety of compounds **10** and **11**, which opens up (reversibly) to the corresponding 16-hydroxy-22-oxo derivative allowing for epimerization at C22. Enolization of the 22-ketone could then result in epimerization at C21 and/or C23. In the base-promoted equilibrium the most stable product should prevail. A molecular modeling performed for the compound **11b** equilibration revealed that of the eight isomeric structures taken into consideration, the most stable are the 20*S*,22*R*,23*R* isomer **13b** and the starting compound **11b** (Table 2). Similar results were obtained for the 25*R* series with the hecogenin skeleton. A conclusion could be drawn from these results that the base-catalyzed epimerization took place at C23 during the reaction. To confirm this conclusion compounds **11a** and **13a** were subjected to sodium borohydride reduction (Scheme 4). In both cases mixtures of epimers at C22 were obtained. However, the two pairs of epimeric diols (**19** + **20** and **21** + **22**) were not identical, proving that structures **11a** and **13a** differ in their configurations at C20 or C23, not at C22. To distinguish between these two possibilities both compounds were

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TABLE 2. Calculated Steric Energies (kcal/M) for Eight Stereomers of Bisfurans in the Hecogenin (25*R*) and Sarsasapogenin (25*S*) Series[a]

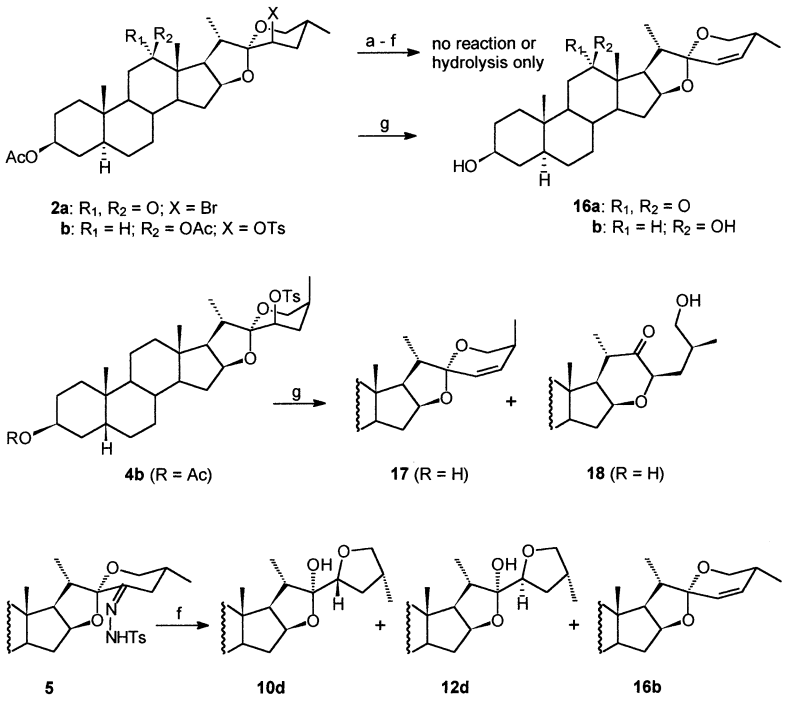
stereomer	25*R* series	25*S* series
20*R*,22*R*,23*R*	66.58	65.58
20*R*,22*R*,23*S*	67.80	65.43
20*R*,22*S*,23*R*	68.88	66.12
20*S*,22*R*,23*R*	66.03	64.17
20*R*,22*S*,23*S*	67.64	65.37
20*S*,22*R*,23*S*	66.99	64.15
20*S*,22*S*,23*R*	63.19 (**10b**)	61.35 (**11b**)
20*S*,22*S*,23*S*	63.28 (**12b**)	60.31 (**13b**)

[a] HyperChem, Release 5.01 for Windows from Hypercube, Inc.; minimizations employed the MM+ force field and the Polak−Ribiere algorithm with RMS gradient 0.001 kcal/Å·M.

then oxidized with PCC. The reactions were highly efficient (about 90% yield) and led to the same lactone **15**. This proves that **11a** and **13a** have the same configuration (*S*) at C20 and differ, by elimination, in configuration at C23.

The solvolytic reactions of the axial 23-spirostanyl bromides and tosylates were also studied (Scheme 5). These compounds were found to be much less reactive when compared with the equatorial 23-epimers, proving that there is no assistance from electrons of the C22−O(16) bond. Bromide **2a** and tosylate **2b** were recovered unchanged from the reaction mixtures. Only when drastic conditions were used (KOH, glycol, reflux) slow elimination to the olefin **16a** was observed. In the case of the axial tosylate **4b** with a 25*S* configuration the reaction also required forced conditions and the olefin **17** was accompanied by a minor product, which was identified as **18**, an expected product of rearrangement. It was formed by migration of the C22−O(16) bond to C23 followed by water addition. In this case the hemiketal form is less stable than the open-chain hydroxy-ketone **18**. However, this product was formed in 5% yield only

SCHEME 5



a: $AgBF_4$, THF, reflux; b: $AgBF_4$, glyme, H_2O, reflux; c: $AgBF_4$, DMF, H_2O, reflux; d: NH_3aq, *n*-BuOH, reflux; e: Na_2CO_3, H_2O, *n*-BuOH, reflux; f: KOH, H_2O, glycol, 120°C; g: KOH, H_2O, glycol, reflux

and the reaction was much slower than that of the equatorial tosylate **3b**. The most likely explanation is that the electrons of the C22−O(16) bond do not participate in the reaction and products are formed through a carbocation at C23 (S_N1 mechanism). The configuration (*S*) of compound **18** at C20 was unequivocally established by analysis of its ^{1}H NMR spectra, particularly selective 1D NOE. Upon irradiation of 20-H, a 2.2% enhancement of the 18-H singlet at δ 1.00 and a 0.9% enhancement of the 21-H doublet at δ 0.96 were observed. This proved that the 18-methyl protons are close to the proton at C20. The proton occupies a *pseudo*axial position as can be concluded from its coupling constant $J_{17\alpha,20} = 9.8$ Hz. The molecular modeling of compound **18** shows that the six-membered ring E exists in the boat form with the oxygen and C20 atoms located above the plane. The four-carbon atom side chain at C23 is presumably *pseudo*equatorial (23*R* configuration) since it is more stable by about 2 kcal/mol than the 23*S* epimer. The side chain rotates rapidly around the $C_{23}-C_{24}$ bond and for this reason 23-H comes out as a triplet at δ 3.79 with an averaged coupling constant $J_{23,24} = 6.2$ Hz.

The reactions of tosylhydrazones **5** and **6** were also briefly examined. Decomposition of **5** under basic conditions afforded olefin **16b** and both rearranged products of different configuration at C23: **10d** and **12d**. The olefin that is probably formed via a carbene intermediate becomes the main product under aprotic conditions (diglyme), the yield falling as the solvent becomes more hydroxylic in character. In hydroxylic solvents tosylhydrazone decomposes to afford the C23 carbocation that undergoes rearrangement to the more stable C22 carbocation. The primary product **10d** partially isomerizes to **12d** under the basic reaction conditions. The analogous reaction of tosylhydrazone **6** afforded a complex mixture consisting of olefin **17** and several other products that were not analyzed.

The ^{1}H NMR spectra of compounds described in this paper were briefly studied (Table 3). It is clear from the spectra that the starting bromides and tosylates preferably exist in the usual "prone" conformation **A** (Scheme 6). The alternative "upright" conformation **B** suffers from the strong interaction of the 20-methyl group and the hydrogen atoms on C24 and C26.[7a] Molecular modeling indicates that such a conformation is rather unlikely (steric energy is at least 5 kcal/mol higher) and even in the case of compound **4b** there is no spectral evidence of its occurrence. Both the 23-tosylate and the 27-methyl group of **4b** occupy axial (probably slightly disturbed) positions despite the 1,3-diaxial interaction. Compounds with rearranged structure (**10**−**13**) are relatively easy to distinguish by the significant downfield shift of their 16α-H signals (they appear in the range of δ 4.59−4.67 ppm compared to δ 4.34−4.45 ppm for the starting compounds). Geminal coupling constants of the 26-protons for compounds with five-membered rings are smaller ($J_{gem} = 7.4-8.0$ Hz) than those in the starting bromides or tosylates ($J_{gem} = 11.1-11.4$ Hz). The signals are well separated ($\Delta\delta = 0.55-0.70$ ppm) and resemble triplets. The signals of 23-H appear in the narrow range of δ 3.93−4.02 ppm as triplets or doublets of doublets.

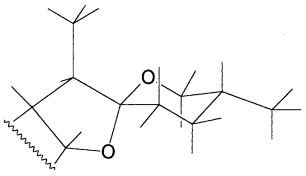
Conclusions

Equatorial 23-bromides and 23-tosylates are much more reactive than their axial epimers and readily undergo the highly stereoselective rearrangement to the bisfuran products. A concerted mechanism is suggested

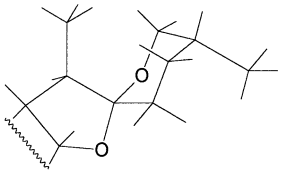
TABLE 3. Proton Chemical Shifts δ (ppm) and Coupling Constants J (Hz) Measured in $CDCl_3$ at 25 °C Carrying Structurally Relevant Information

	proton							
compd	16-H	18-H	19-H	21-H	23-H	26-H (ax)	26-H (eq)	27-H
1a	4.34 (m)	1.17 (s)	0.93 (s)	1.03 (d) J = 6.9	4.10 (dd) J_{aa} = 12.3; J_{ae} = 4.5	3.41 (t) $J_{gem} = J_{aa}$ = 11.2	3.49 (dd) J_{gem} = 11.2; J_{ea} = 5.0	0.83 (d) J = 6.6
2a	4.44 (m)	1.10 (s)	0.93 (s)	1.31 (d) J = 7.0	4.09 (t) $J_{ea} = J_{ee}$ = 3.1	3.45 (t) $J_{gem} = J_{aa}$ = 11.4	3.58 (dd) J_{gem} = 11.4; J_{ea} = 5.0	0.82 (d) J = 6.7
3a	4.41 (m)	0.88 (s)	0.99 (s)	0.97 (d) J = 7.0	4.31 (dd) J_{aa} = 12.8; J_{ae} = 4.7	3.99 (dd) J_{gem} = 11.1; J_{ae} = 2.6	3.29 (dd) J_{gem} = 11.1; J_{ee} = ~1.2	1.13 (d) J = 7.2
3b	4.38 (m)	0.75 (s)	0.98 (s)	0.83 (d) J = 7.0	4.60 (dd) J_{aa} = 12.3; J_{ae} = 5.2	3.85 (dd) J_{gem} = 11.2; J_{ae} = 2.8	3.18 (br d) J_{gem} = 11.2	1.06 (d) J = 7.3
4b	4.43 (m)	0.54 (s)	0.97 (s)	1.01 (d) J = 7.0	4.36 (t) $J_{ea} = J_{ee}$ = 3.0	3.95 (dd) J_{gem} = 11.2; J_{ae} = 3.2	3.34 (br d) J_{gem} = 11.2	1.15 (d) J = 7.2
10b	4.60 (m)	1.06 (s)	0.90 (s)	1.13 (d) J = 6.9	3.99 (dd) J_{trans} = 9.0; J_{cis} = 6.7	3.35 (dd) J_{trans} = 9.5; J_{gem} = 7.8	3.91 (t) $J_{gem} = J_{cis}$ = 7.8	1.05 (d) J = 6.5
10d	4.67 (m)	0.78 (s)	0.84 (s)	1.11 (d) J = 6.7	4.01 (dd) J_{trans} = 8.9; J_{cis} = 6.7	3.37 (dd) J_{trans} = 9.3; J_{gem} = 7.8	3.92 (t) $J_{gem} = J_{cis}$ = 7.8	1.06 (d) J = 6.7
11a	4.63 (m)	0.78 (s)	0.98 (s)	1.03 (d) J = 6.9	4.02 (t) $J_{trans} = J_{cis}$ = 8.7	4.01 (dd) J_{trans} = 10.4; J_{gem} = 8.0	3.31 (dd) J_{gem} = 8.0; J_{cis} = 7.1	1.02 J = 6.8
12b	4.59 (m)	1.09 (s)	0.91 (s)	1.19 (d) J = 6.9	3.96 (t) $J_{trans} = J_{cis}$ = 7.7	4.02 (t) $J_{gem} = J_{trans}$ = 7.4	3.42 (dd) J_{gem} = 7.4; J_{cis} = 5.9	1.04 (d) J = 6.9
13b	4.65 (m)	0.78 (s)	0.98 (s)	1.06 (d) J = 7.0	3.93 (dd) J_{trans}=10.7; J_{cis} = 5.2	3.36 (dd) J_{trans} = 9.0; J_{gem} = 8.0	4.02 (t) $J_{gem} = J_{cis}$ = 8.0	1.07 (d) J = 6.7

SCHEME 6



"prone" conformation **A**



"upright" conformation **B**

for bisfuran formation consisting of simultaneous departure of a leaving group and shift of an oxygen atom from C20 to C22, followed by addition of water to the stabilized carbocation. Most likely the migration of the neighboring C22−O(26) bond commences when the leaving group is still weakly bonded. This mechanism implies inversion of configuration at C23. In the case of axial tosylate **4b** involvement of the neighboring electrons begins only when the positive charge at C23 reaches a value greater than in the transition state, so that although no anchimeric assistance is observed, the product **18** is formed by migration of the C22−O(16) bond placed trans to the leaving group. The described rearrangement is fully stereoselective but the primary products may undergo equilibration under the basic reaction conditions. The rearrangement also takes place when a highly reactive carbocation is generated at C23 by the tosylhydrazone decomposition.

Experimental Section

General Methods. Melting points are uncorrected. Routine NMR spectra were taken at 200 MHz in $CDCl_3$. Spectra available as Supporting Information were measured at 25 °C at 500 MHz. Infrared spectra were recorded in chloroform. Mass spectra were obtained at 70 eV. The reaction products were isolated by column chromatography performed on 70−230 mesh silica gel. Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use.

Determination of the crystal structure of **11a** was performed on a diffractometer applying graphite-monochromated Mo Kα radiation. The details of X-ray measurements, structural computations, and crystal data are given in the Supporting Information.

Bromination Procedure (Synthesis of 1a, 2a, and 3a). To a stirred solution of hecogenin acetate **1d** (about 5 g; 12 mmol) in glacial acetic acid (150 mL) was added dropwise a 1 M solution of bromine in glacial acetic acid (12 mL) at room temperature. After completion of bromination (disappearance of a bromine color) the reaction mixture was poured into water, neutralized with $NaHCO_3$, and extracted with chloroform. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. The reaction resulted in the formation of a mixture of bromides **1a** and **2a** in the ratio 3:1 (81%), respectively. Bromides **1a** and **2a** were separated by fractional crystallization of the mixture from hexane/dichloromethane. The products were identical with respective bromides described in the literature.[7] A full characterization of these compounds is given therein, including melting points, IR and ^1H NMR; also X-ray crystallographic data of their close relatives are available.[7a]

Similar bromination of sarsasapogenin acetate **3c** was performed at slightly higher temperature (35 °C). A single bromide **3a** was obtained in 78% yield, identical in all respects with the compound described in the literature.[7a]

Synthesis of Tosylates (1b, 2b, 3b, and 4b). 23-Oxosarsasapogenin acetate (**9**; 1.04 g, 2.2 mmol) was reduced with 0.4 g of sodium borohydride in methanol (8 mL) and dioxane (6 mL). The crude reaction product was dissolved in anhydrous pyridine (20 mL) and *p*-tosyl chloride (0.5 g, 2.6 mmol) was added. The reaction mixture was stirred overnight at room temperature, poured into an aqueous solution of cupric sulfate, and extracted with chloroform. The extract was dried over

magnesium sulfate and solvent was evaporated in vacuo. Silica gel column chromatography with hexane−ethyl acetate (93:7) elution afforded 23*R*,25*S*-5*β*-spirostane-3*β*,23-diol 3-acetate 23-tosylate (**4b**; 0.44 g, 32%) and 23*S*,25*S*-5*β*-spirostane-3*β*,23-diol 3-acetate 23-tosylate (**3b**; 0.65 g, 47%).

Compound **4b**: mp 177−178 °C; IR, ν_{max} 1724, 1450, 1178, 1027 cm^{-1}; ^{1}H NMR, δ 7.80 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.3 Hz), 5.06 (1H, m), 4.43 (1H, m), 4.36 (1H, t, J = 3.0 Hz), 3.95 (1H, dd, J = 11.2, 3.2 Hz), 3.34 (1H, d, J = 11.2 Hz), 2.44 (3H, s), 2.03 (3H, s), 1.15 (3H, d, J = 7.2 Hz), 1.01 (3H, d, J = 7.0 Hz), 0.97 (3H, s), 0.54 (3H, s); ^{13}C NMR, δ 213.3 (C), 170.6 (C), 129.9 (CH × 2), 128.1 (CH × 2), 81.8 (CH), 73.5 (CH), 70.9 (CH), 70.8 (C), 64.1 (CH_2), 61.6 (CH), 56.6 (CH), 40.4 (CH_2), 40.2 (CH), 37.5 (CH), 36.2 (CH), 35.5 (CH), 32.6 (CH_2), 31.8 (CH_2), 30.99 (CH_2), 30.8 (CH_2), 30.6 (C), 30.1 (CH), 29.9 (C), 26.6 (CH_2 × 2), 25.2 (CH_2), 24.1 (CH_3), 21.9 (CH_3), 21.8 (C), 21.7 (CH_3), 21.1 (CH_2), 17.2 (CH_3), 16.6 (CH_3), 13.7 (CH_3); EI-MS, *m*/*z* (%) 456 (M^+ − TsOH, 100), 396 (4), 389 (16), 255 (34), 141 (54).

Compound **3b**: mp 154−156 °C; IR, ν_{max} 1724, 1451, 1176, 969 cm^{-1}; ^{1}H NMR, δ 7.80 (2H, d, J = 8.3 Hz), 7.34 (2H, d, J = 8.3 Hz), 5.06 (1H, m), 4.60 (1H, dd, J = 12.3, 5.2 Hz), 4.38 (1H, m), 3.85 (1H, dd, J = 11.2, 2.8 Hz), 3.18 (1H, d, J = 11.2 Hz), 2.45 (3H, s), 2.04 (3H, s), 1.06 (3H, d, J = 7.3 Hz), 0.98 (3H, s), 0.83 (3H, d, J = 7.0 Hz), 0.75 (3H, s); ^{13}C NMR, δ 213.3 (C), 170.6 (C), 129.9 (CH × 2), 128.2 (CH × 2), 82.3 (CH), 79.5 (CH), 70.9 (CH), 70.8 (C), 64.8 (CH_2), 64.1 (CH), 56.7 (CH), 40.7 (CH), 40.2 (CH), 39.8 (CH_2), 39.7 (C), 37.5 (CH), 35.6 (CH), 32.0 (CH_2), 31.2 (CH_2), 30.9 (CH_2), 30.85 (C), 30.8 (CH_2), 26.6 (CH_2 × 2), 25.9 (CH), 25.2 (CH_2), 24.1 (CH_3), 21.8 (CH_3), 21.75 (C), 21.7 (CH_3), 20.9 (CH2), 19.4 (CH_3), 16.1 (CH_3 × 2); EI-MS, *m*/*z* (%) 456 (M^+ − TsOH, 100), 396 (9), 390 (7), 255 (36), 141 (90).

Similar reduction of 25*R*-5α-spirostane-3*β*,12*β*-diol-23-one diacetate (**8**) with sodium borohydride followed by tosylation yielded compounds **2b** and **1b** in the ratio of 10:1.

Synthesis of Tosylhydrazones (5 and 6). To a solution of 25*R*-5α-spirostane-3*β*,12*β*-diol-23-one diacetate (**8**; 1.25 g; 2.3 mmol) in anhydrous ethanol (36 mL) was added tosylhydrazine (0.55 g; 2.9 mmol). The reaction mixture was refluxed for 1.5 h, poured into water, and extracted with benzene. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. Pure tosylhydrazone (**5**; 1.26 g, 77%), mp 105−107 °C, was obtained by silica gel column chromatography with hexane−ethyl acetate (82.5:17.5) elution.

Tosylhydrazone **6** was obtained from 23-oxo-sarsasapogenin acetate (**9**) in a similar way.

Solvolytic Reactions of 23*S*,25*R*-23-Bromides 1a and 1c. Entry 1: To a solution of 23*S*,25*R*-23-bromo-5α-spirostan-3*β*-ol-12-one acetate (**1a**; 250 mg, 0.45 mmol) in dry THF (15 mL) was added silver tetrafluoroborate (174 mg, 0.9 mmol). The mixture was refluxed for 24 h, poured into water, and extracted with chloroform. The extract was dried over magnesium sulfate and solvent was evaporated in vacuo. Pure lactone **14a** (144 mg, 79%) was obtained by silica gel column chromatography with hexane−ethyl acetate (75:25) elution, mp 220−223 °C; IR, ν_{max} 1765, 1720 (shoulder), 1708, 1255, 1182, 1031 cm^{-1}; ^{1}H NMR, δ 4.89 (1H, m), 4.67 (1H, m), 2.59 (2H, m), 2.02 (3H, s), 1.39 (3H, d, J = 7.5 Hz,), 1.06 (3H, s), 0.92 (3H, s); ^{13}C NMR, δ 212.3 (C), 180.7 (C), 170.6 (C), 80.8 (CH), 73.0 (CH), 55.7 (C), 55.5(CH), 53.9 (CH), 50.8 (CH), 44.4 (CH), 37.2 (CH_2), 36.6 (CH), 36.2 (CH_2), 36.1 (C), 34.1 (CH), 33.7 (CH_2), 32.4 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 27.1 (CH_2), 21.3 (CH_3), 17.2 (CH_3), 13.8 (CH_3), 11.8 (CH_3); EI-MS *m*/*z* (%) 402 (M^+, 6), 342 (100), 288 (16). HR-MS calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2390. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.45; H, 8.40.

Entry 2: To a solution of **1a** (250 mg, 0.45 mmol) in glyme (15 mL) and water (3 mL) was added silver tetrafluoroborate (174 mg, 0.9 mmol). The mixture was refluxed for 4 days, poured into water, and extracted with chloroform. Pure ketone **7** (160 mg, 72%) was eluted from silica gel column with hexane−ethyl acetate (93:7), mp 279−283 °C; IR, ν_{max} 1728, 1708, 1255, 1026, 965 cm^{-1}; ^{1}H NMR, δ 4.62 (1H, m), 4.53 (1H, m), 3.77 (1H, def. t, J = 10.9 Hz), 3.63 (1H, m), 2.78 (1H, m), 2.03 (3H, s), 1.06 (3H, s), 1.03 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 6.7 Hz), 0.92 (3H, s); ^{13}C NMR, δ 212.9 (C), 201.6 (C), 170.6 (C), 109.8 (C), 81.7 (CH), 73.1 (CH), 65.7 (CH_2), 55.8 (CH), 55.5 (C), 55.4 (CH), 53.1 (CH), 45.2 (CH_2), 44.5 (CH), 37.6 (CH_2), 36.3 (CH_2), 36.1 (C), 35.5 (CH), 35.4 (CH), 34.3 (CH), 33.8 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 21.4 (CH_3), 17.1 (CH_3), 15.8 (CH_3), 13.0 (CH_3), 11.9 (CH_3); EI-MS, *m*/*z* (%) 458 (M^+ − H_2O, 49), 404 (95), 386 (100), 357 (17); HR ES-MS calcd for $C_{29}H_{42}O_6Na$ 509.2879, found 509.2853.

Entry 3: To a solution of **1a** (250 mg, 0.45 mmol) in DMF (15 mL) and water (3 mL) was added silver tetrafluoroborate (174 mg, 0.9 mmol). The mixture was refluxed for 4 days, poured into water, and extracted with chloroform. Pure bisfuran **10a** (140 mg, 63%) was obtained by silica gel column chromatography with hexane−ethyl acetate (65:35) elution, mp 151−154 °C; IR, ν_{max} 3392, 1723, 1706, 1254, 1033 cm^{-1}; ^{1}H NMR, δ 4.63 (2H, m), 3.98 (1H, dd, J = 8.8, 6.6 Hz), 3.91 (1H, t, J = 7.4 Hz), 3.34 (1H, dd, J = 9.3, 8.0 Hz), 3.20 (1H, bs), 2.54 (1H, dd, J = 8.8, 6.5 Hz), 2.02 (3H, s), 1.13 (3H, d, J = 6.9 Hz), 1.06 (3H, s), 1.04 (3H, d, J = 6.4 Hz), 0.91 (3H, s); ^{13}C NMR, δ 213.2 (C), 170.6 (C), 109.6 (C), 81.8 (CH), 80.1 (CH), 74.9 (CH_2), 73.1 (CH), 55.5 (C), 55.4 (CH), 55.3 (CH), 53.4 (CH), 44.4 (CH), 38.9 (CH), 37.6 (CH_2), 36.2 (CH_2), 36.1 (C), 34.9 (CH), 34.6 (CH_2), 34.3 (CH), 33.8 (CH_2), 31.4 (CH_2), 31.1 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 21.4 (CH_3), 16.4 (CH_3), 16.0 (CH_3), 14.2 (CH_3), 11.8 (CH_3); EI-MS, *m*/*z* (%) 470 (M^+ − H_2O, 100), 455 (6), 403 (14), 385 (10). Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 70.98; H, 9.10.

Entry 4: To a solution of 23*S*,25*R*-23-bromo-5α-spirostane-3*β*,12*β*-diol diacetate (**1c**; 40 mg, 0.067 mmol) in DMF (10 mL) was added silver tetrafluoroborate (25 mg, 0.13 mmol). The mixture was refluxed for 3 days, poured into water, and extracted with chloroform. Pure product **14b** (8 mg, 27%) was eluted from a silica gel column with hexane−ethyl acetate (82:18).

Entry 5: To a solution of **1a** (200 mg, 0.36 mmol) in *n*-butanol (50 mL) was added aqueous ammonia (7 mL). The mixture was refluxed for 7 days. A 5-mL portion of aqueous ammonia was added every day. The solvents were evaporated in vacuo. Pure products **10a** (310 mg, 18%) and **10b** (70 mg, 43%), mp 169−172 °C, were eluted from a silica gel column with hexane−ethyl acetate 65:35 and 20:80, respectively.

Entry 6: Compound **1c** yielded **10c** (43%), mp 152−154 °C, under similar conditions.

Solvolytic Reactions of 23*R*,25*R*-23-Bromide 2a and Tosylate 2b. Entry 7: There was no reaction of **2a** or **2b** with silver tetrafluoroborate or aqueous ammonia (conditions a−d).

Entry 8: Reaction of **2a** with a solution of sodium carbonate in *n*-butanol−water at reflux resulted in hydrolysis of the 3-acetate group only.

Entry 9: Compound **2a** (126 mg) was dissolved in ethylene glycol (20 mL) and a solution of KOH (20 mg) in 3 mL of water was added. The reaction mixture was heated for 3 days at reflux. Then it was poured into water and extracted with dichloromethane. The extract was washed with water several times, dried (anhydrous $MgSO_4$), and evaporated in vacuo. Chromatography of the crude product afforded olefin **16a** eluted with hexane−ethyl acetate 60:40, in addition to the hydrolyzed starting bromide. Compound **16a**: mp 245−247 °C; IR, ν_{max} 3605, 3455, 1703, 1077, 1043, 979 cm^{-1}; ^{1}H NMR, δ 5.88 (1H, d, J = 10.0 Hz), 5.54 (1H, dd, J = 10.0, 2.5 Hz), 4.45 (1H, m), 3.69 (1H, m), 3.60 (1H, m), 3.45 (1H, t, J = 10.9 Hz), 2.61 (1H, dd, J = 8.7, 7.0 Hz), 1.09 (3H, s), 1.02 (d, J = 7.0 Hz), 0.91 (3H, s), 0.89 (d, J = 7.2 Hz); ^{13}C NMR, δ 213.2 (C), 137.2 (CH), 126.1 (CH), 107.1 (C), 80.1 (CH), 70.9 (CH), 65.4 (CH_2), 55.7 (CH), 55.5 (CH), 55.2 (C), 53.6 (CH), 44.6 (CH), 42.4 (CH), 37.82 (CH_2), 37.78 (CH_2), 36.5 (CH_2), 36.1 (C), 34.3 (CH), 31.5 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 29.0 (CH), 28.2 (CH_2),

16.0 (CH_3), 15.7 (CH_3), 13.2 (CH_3), 11.9 (CH_3). Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.55; H, 9.40.

Solvolytic Reactions of 23*S*,25*S*-23-Bromide 3a and Tosylate 3b. Entry 10: The reaction of **3a** with silver tetrafluoroborate in THF at reflux was performed in the same way as described for **1a** (entry 1). Lactone **15**, mp 163−165 °C, was obtained in 32% yield in addition to the unreacted starting material. Compound **15**: IR, ν_{max} 1759, 1724, 1263, 1027 cm^{-1}; ^1H NMR, δ 5.07 (1H, m), 4.94 (1H, dt, J = 7.7, 4.6 Hz), 2.58 (1H, q, J = 7.6 Hz), 2.27 (1H, m).

Entry 11: To a solution of **3a** (160 mg, 0.29 mmol) in *n*-butanol (50 mL) was added aqueous ammonia (7 mL). The mixture was refluxed for 7 days. An additional portion of aqueous ammonia (5 mL) was added every second day. The solvents were evaporated in vacuo. The silica gel column chromatography afforded pure **11a** (105 mg, 75%) eluted with hexane−ethyl acetate (80:20), mp 138−140 °C. IR, ν_{max} 3538, 1724, 1264, 1239, 1025, 980 cm^{-1}; ^1H NMR, δ 5.04 (1H, m), 4.60 (1H, m), 4.01 (2H, m), 3.30 (2H, bs and t, J = 7.6 Hz), 2.38 (1H, m), 2.00 (3H, s), 1.00 (6H, d, J = 6.8 Hz), 0.96 (3H, s), 0.75 (3H, s); ^{13}C NMR, δ 170.6 (C), 109.6 (C), 81.6 (CH), 80.6 (CH), 75.3 (CH_2), 70.6 (CH), 62.0 (CH), 56.2 (CH), 41.0 (C), 40.1 (CH_2), 39.9 (CH), 38.2 (CH), 37.2 (CH), 35.2 (CH), 34.9 (CH_2), 34.4 (CH), 33.8 (C), 31.7 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 26.3 (CH_2 × 2), 24.9 (CH_2), 23.8 (CH_3), 21.4 (CH_3), 20.8 (CH_2), 17.7 (CH_3), 16.4 (CH_3), 15.4 (CH_3); EI-MS, *m*/*z* (%) 456 ($M^+ - H_2O$, 9), 389 (35), 329 (100), 255 (87). Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.15; H, 9.59.

Entry 12: A solution of bromide **3a** (178 mg) in 2 mL of dichloromethane and 15 mL of *n*-butanol was treated with a 10% aqueous solution (5 mL) of potassium carbonate. The reaction mixture was heated at reflux for 4 days. Then solvents were evaporated in vacuo and the residue was chromatographed on a silica gel column. Pure compounds **11b** (36 mg, 23%), mp 145−147 °C, and **13b** (19 mg, 12%), mp 75−77 °C, were eluted with hexane−ethyl acetate (2:1). Compound **13b**: IR, ν_{max} 3614, 3539, 1036, 1002 cm^{-1}; ^1H NMR, δ 4.64 (1H, m), 4.08 (1H, m), 4.01 (1H, t, J = 7.6 Hz), 3.91 (1H, dd, J = 10.7, 5.3 Hz), 3.34 (1H, m), 2.96 (1H, bs), 2.35 (1H, m), 1.05 (6H, d, J = 6.6), 0.96 (3H, s), 0.79 (3H, s); ^{13}C NMR, δ 108.6 (C), 83.8 (CH), 81.5 (CH), 75.3 (CH_2), 66.9 (CH), 63.9 (CH), 56.4 (CH), 41.1 (C), 39.9 (CH_2), 39.8 (CH), 37.7 (CH), 36.4 (CH), 35.8 (CH_2), 35.3 (C), 35.1 (CH), 34.5 (CH_2), 33.4 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 27.7 (CH_2), 26.44 (CH_2), 26.37 (CH_2), 23.8 (CH_3), 20.7 (CH_2), 16.5 (CH_3), 16.1 (CH_3), 15.6 (CH_3); EI-MS, *m*/*z* (%) 414 ($M^+ - H_2O$, 99), 329 (20), 255 (51).

Entry 13: The reaction of **3b** with ammonia was performed under conditions analogous to these described in entry 11. Compound **11b** was obtained in 44% yield in addition to the unreacted starting material.

Entry 14: To a solution of tosylate **3b** (80 mg, 0.13 mmol) in ethylene glycol (20 mL) was added a 10% solution of potassium hydroxide in water. The reaction mixture was stirred 1 h at 120 °C. Then it was poured into water and extracted with dichloromethane. The reaction products were separated by silica gel column chromatography to afford **11b** (19 mg, 27%) and **13b** (19 mg, 27%).

Solvolysis of 23R,25*S*-23-Tosylate 4b. Entry 15: To a solution of tosylate **4b** (96 mg, 0.15 mmol) in ethylene glycol (20 mL) was added a solution of potassium hydroxide (10%) in water. The mixture was stirred 24 h at reflux. Compounds **17** (6 mg, 9%) and **18** (3.5 mg, 5%) were obtained by silica gel column chromatography with hexane−ethyl acetate elution (75:25 and 60:40, respectively). Compound **17**: mp 144−146 °C; ^1H NMR, δ 6.03 (1H, ddd, J = 9.9, 4.2, 1.1 Hz), 5.53 (1H, dd, J = 9.9, 1.1 Hz), 4.53 (1H, m), 4.12 (1H, m), 4.05 (1H, dd, J = 11.1, 3.5 Hz), 3.48 (1H, d, J = 11.1 Hz), 1.09 (3H, d, J = 7.0 Hz), 0.99 (3H, s), 0.94 (3H, d, J = 4.3 Hz), 0.81 (3H, s); ^{13}C NMR, δ 135.6 (CH), 126.5 (CH), 107.3 (C), 81.9 (CH), 67.1 (CH), 64.3 (CH_2), 62.3 (CH), 56.5 (CH), 41.8 (CH), 40.9 (C), 40.3 (CH_2), 39.8 (CH), 36.5 (CH), 35.3 (C), 35.2 (CH), 33.6 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 28.9 (CH), 27.8 (CH_2), 26.5 (CH_2 × 2), 23.9 (CH_3), 20.9 (CH_2), 18.0 (CH_3), 16.5 (CH_3), 14.3 (CH_3). Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.95; H, 10.20. Compound **18**: mp 136−139 °C;^1H NMR, δ 4.12 (2H, m), 3.92 (1H, dd, J = 14.6, 8.1 Hz), 3.78 (1H, t, J = 6.2 Hz), 3.53 (1H, dd, J = 11.1, 5.0 Hz), 3.45 (1H, dd, J = 11.1, 6.5 Hz), 2.81 (1H, dq, J = 10.3, 6.4 Hz), 2.22 (1H, m), 1.07 (3H, d, J = 6.4 Hz), 1.00 (3H, s), 0.99 (3H, s), 0.96 (3H, d, J = 6.9 Hz,); ^{13}C NMR, δ 217.6 (C), 81.6 (CH), 78.8 (CH), 67.5 (CH_2), 67.0 (CH), 57.4 (CH), 53.1 (CH), 43.0 (C), 40.4 (CH_2), 39.8 (CH), 39.3 (CH), 36.5 (CH_2), 36.4 (CH), 35.2 (CH), 33.5 (CH_2), 32.9 (CH_2), 32.7 (CH and C), 29.9 (CH_2), 27.8 (CH_2), 26.52 (CH_2), 26.48 (CH_2), 23.9 (CH_3), 20.9 (CH_2), 16.9 (CH_3), 14.8 (CH_3), 12.5 (CH_3). Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.09; H, 10.20.

Solvolysis of 25*R*-23-Tosylhydrazone 5. Entry 16: (25*R*)-3β,12β-Diacetoxy-5α-spirostan-23-one tosylhydrazone (**5**; 322 mg) was dissolved in ethylene glycol and a 10% aqueous solution of KOH (6 mL) was added. The reaction mixture was heated 1 h under reflux at 120 °C, poured into water, and extracted with benzene. The extract was washed with water, dried with anhydrous $MgSO_4$, and evaporated in vacuo and the residue was chromatographed on a silica gel column with hexane−ethyl acetate (from 50% to 70%) elution. Olefin **16b** (mp 78−79 °C, yield 12%) and rearranged products of different configuration at C23, **10d** (mp 149−151 °C, yield 61%) and **12d** (mp 69−70 °C, yield 26%), were consecutively eluted.

Oxidation of Bisfurans to the Lactones. To a solution of **10a** (24.7 mg, 0.05 mmol) in dry CH_2Cl_2 was added pyridinium chlorochromate (105 mg, 0.5 mmol). The reaction mixture was stirred 3 days at room temperature and filtered through a silica gel column with hexane−ethyl acetate (75:25) elution. Lactone **14a** obtained in 95% yield was proved identical with compound **14a** described in entry 1.

Oxidation of **12a** with PCC afforded the same product.

Similar oxidation of compounds **11a** and **13a** to the corresponding lactone **15** was also performed.

Sodium Borohydride Reduction of Bisfurans. Compound **11a** (67 mg, 0.14 mmol) was dissolved in dry THF and $NaBH_4$ (26 mg, 0.68 mmol) was added. The reaction mixture was refluxed 3 h, poured into water, and extracted with chloroform. Solvent was removed in vacuo from the dried (anhydrous $MgSO_4$) extract and the residue (a mixture of products **19** and **20**) was subjected to the chromatographic separation on a silica gel column. Elution with ethyl acetate−hexane (38:62) mixture afforded 20.6 mg (30.6%) of a less polar product and 37.3 mg (55.4%) of a more polar product. Less polar product: mp 197−200 °C; IR, ν_{max} 3469, 1724, 1265, 1023 cm^{-1}; ^1H NMR, δ 5.07 (1H, narrow m), 4.43 (1H, m), 4.16 (1H, dt, J = 7.5, 3.1 Hz), 4.03 (1H, dd, J = 8.3, 6.6 Hz), 3.70 (1H, dd, J = 8.7, 3.1 Hz), 3.31 (1H, dd, J = 8.3, 7.4 Hz), 2.05 (3H, s), 1.05 (3H, d, J = 6.7 Hz), 0.97 (3H, s), 0.95 (3H, d, J = 7.4 Hz), 0.90 (3H, s). More polar product: mp 170−171 °C; IR, ν_{max} 3435, 1724, 1265, 1023 cm^{-1}; ^1H NMR, δ 5.06 (1H, narrow m), 4.37 (1H, m), 4.03 (1H, m), 3.95 (1H, dd, J = 8.3, 3.1 Hz), 3.59 (1H, dd, J = 7.3, 1.8 Hz), 3.33 (1H, dd, J = 8.3, 6.1 Hz), 2.04 (3H, s), 1.04 (6H, d, J = 6.9 Hz), 0.97 (3H, s), 0.89 (3H, s).

Similar reduction of **13a** with $NaBH_4$ led to the mixture of **21** and **22**.

Isomerization of Bisfurans. To a solution of **11b** (60.8 mg; 0.14 mmol) in *n*-butanol (5 mL) was added a 10% aqueous solution (5 mL) of potassium carbonate. The reaction mixture was heated 6 days at reflux. After removal of the solvent in vacuo, a residue was subjected to chromatographic separation on a silica gel column. Compounds **11b** (42.6 mg, 70%) and **13b** (18.1 mg, 30%) were eluted with a hexane−ethyl acetate (2:1) mixture.

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Supporting Information Available: ^{1}H NMR spectra recorded at 500 MHz, 1D TOCSY[13] and 1D NOE[14] measured with selective excitation pulse, 2D TOCSY[15] spectra of compounds **1a**, **2a**, **3a**, **3b**, **4b**, **10b**, **10d**, **11a**, **12b**, and **13b**, crystal data and structure refinement parameters for **11a**, and an ORTEP view of molecule **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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