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Hydrogen atom transfer methodology for the synthesis of C-22, C-23, and C-25 stereoisomers of cephalostatin north 1 side chain from spirostan sapogenins

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Abstract—A simple synthesis of all eight C-22, C-23, and C-25 diastereoisomers of the cephalostatin north 1 side chain has been accomplished from (25*R*)-5α-spirostan-3β-ol (tigogenin). The synthesis involves selective hydroxylations at C-23 and C-25 and reductive opening of the 1,6-dioxaspiro[4.5]decane spirostan system to give a conveniently protected 5α-furostan-3β,23,25,26-tetrol. The construction of the required 1,6-dioxaspiro[4.4]nonane system entailed an intramolecular hydrogen abstraction reaction promoted by the C-25 alkoxyl radical as the key step. Acid-catalyzed isomerization of the spiroketal unit suggested that 22*R* isomers are the thermodynamic products while the 22*S* isomers are the result of kinetic control. The acid-catalyzed equilibrium between 1,6-dioxaspiro[4.4]nonane and 1,6-dioxaspiro[4.5]decane systems was also studied. In the 1,6-dioxaspiro[4.4]nonane units, the observed $^{3}J_{23,24}$ coupling constants suggest that the five-membered puckered ring-F undergoes substantial conformational changes on going from 22*S* to 22*R* isomers.

1. Introduction

Cephalostatins[1] and the structurally related ritterazines[2] comprise a group of secondary metabolites isolated from marine invertebrates (*Cephalodiscus gilchristi* and *Ritterella tokioka*, respectively) which have attracted considerable attention from synthetic organic chemists and pharmacologists due to their complex structures and significant biological properties.[3] They are alkaloids constituted by two steroidal units linked through a pyrazine ring involving the C2-C3 position of each monomeric unit and are among the most potent cytotoxins ever isolated from a natural source. In most of these substances the steroidal eight-carbon side chain has been transformed into a 1,6-dioxaspiro [4.4]nonane system. In particular, a polyoxygenated (2*S*,4*R*,5*S*,9*S*)-2-hydroxymethyl-2,9-dimethyl-1,6-dioxaspiro [4.4]nonan-4-ol substructure is found in the side chain of the north unit in many cephalostatins (17 out of 19), and the majority of ritterazines have a 2,2,9-trimethyl-1,6-dioxaspiro[4.4]nonane system on one or other side of their skeletons (Fig. 1).

The syntheses of several of these natural products and analogues have been achieved[4] and during these studies very interesting methodologies have been brought to light.[5] Nevertheless, despite efforts by several research groups, the mechanism of biological action remains unknown.[6] The structure-activity relationship between cephalostatins and OSW-1 (Fig. 1), a related cholestane glycoside isolated from a terrestrial plant (*Ornithogalum saundersiae*),[7] supports the hypothesis that the bioactive intermediate might be an oxocarbenium ion located at rings E or F and originated by opening the dioxaspiro grouping.[6,7b,8] We can deduce from this that the stereochemistries at C-22, C-23, and C-25, which doubtless have a strong influence on the conformation and stability of the dioxaspiro[4.4]nonane system, may also influence the activity of cephalostatins.

With these ideas in mind, we decided to develop a simple methodology to permit the synthesis of all eight possible isomers of this system by modification of the steroidal side chain of a commercially available spirostan sapogenin,[9] the key step being the formation of the spiroketal system by an intramolecular hydrogen abstraction reaction (IHA) promoted by alkoxyl radicals.[10] In previous papers from this laboratory we have demonstrated the utility of IHA reactions in the synthesis of dioxaspiro[4.4]nonane ring systems in the carbohydrate field.[11] From this previous

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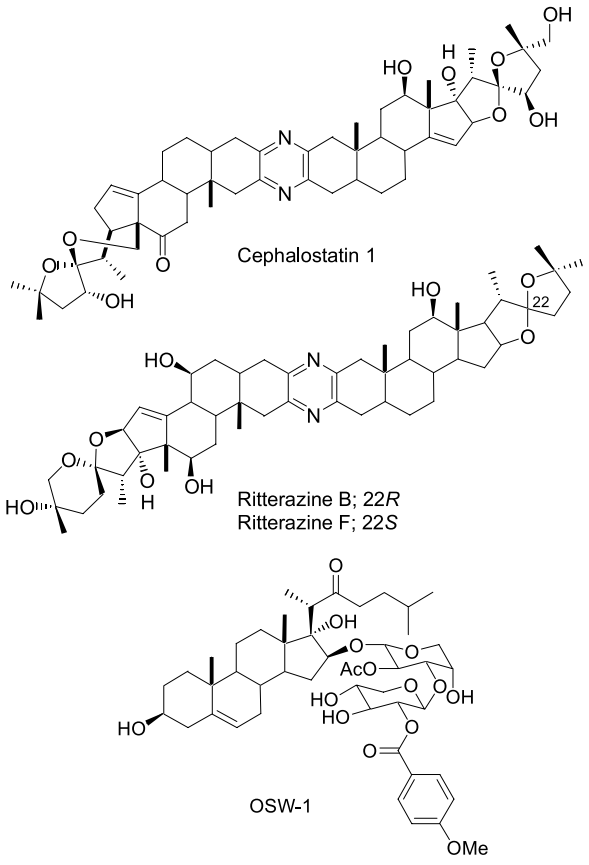
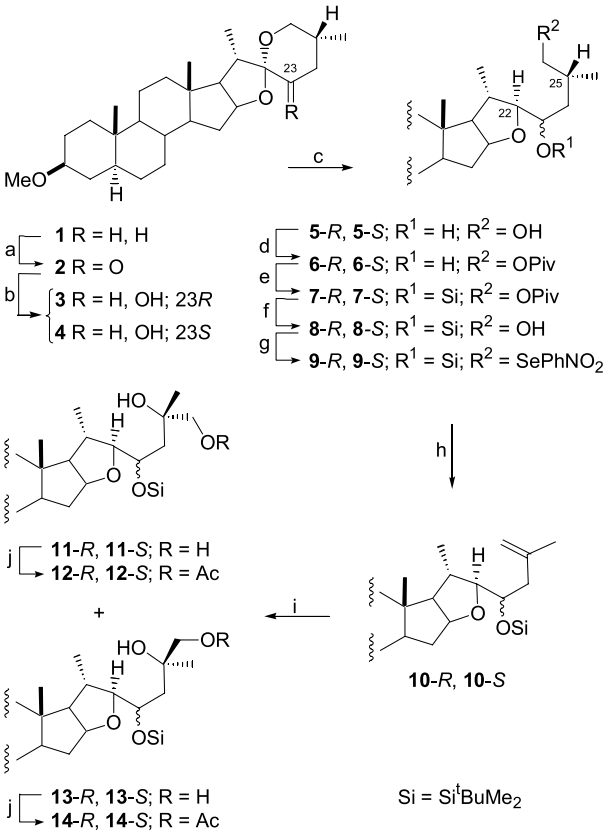


Figure 1. Examples of representative cephalostatins and reitterazines.



Scheme 1. Reagents and conditions: (a) $NaNO_2$, $BF_3{\cdot}Et_2O$, AcOH, rt, 1 h, 68%; (b) $NaBH_4$, EtOH, rt, 1 h, 91% (**3**/**4** ratio 5:95) or L-selectride, THF, −20 °C, 1.5 h, 72% (**3**/**4** ratio 63:37); (c) Ph_2SiH_2, $TiCl_4$, CH_2Cl_2, −20 °C; (d) pivaloyl chloride, Py, CH_2Cl_2, rt, **6**-*R* 95%, **6**-*S* 97%; (e) ^{t}BuMe$_2$SiOTf, CH_2Cl_2, Et_3N, rt, **7**-*R* 81%, **7**-*S* 98%; (f) KOH, MeOH, rt, **8**-*R* 92%, **8**-*S* 91%; (g) *o*-NO_2PhSeCN, *n*-Bu_3P, THF, rt, **9**-*R* 99%, **9**-*S* 97%; (h) H_2O_2, THF, rt, **10**-*R* 92%, **10**-*S* 82%; (i) OsO_4, Py, CH_2Cl_2, rt; (j) Ac_2O, Py, rt. [For yields of the (i) and (j) reactions, see supplementary data section]. The (*R*,*S*) designs the stereochemistry at C-23.

experience we were confident that both spiroketal isomers could be obtained using this methodology. This is synthetically important because in most of the ritterazines both stereoisomers at the spiroketal center were obtained from the natural source.[12]

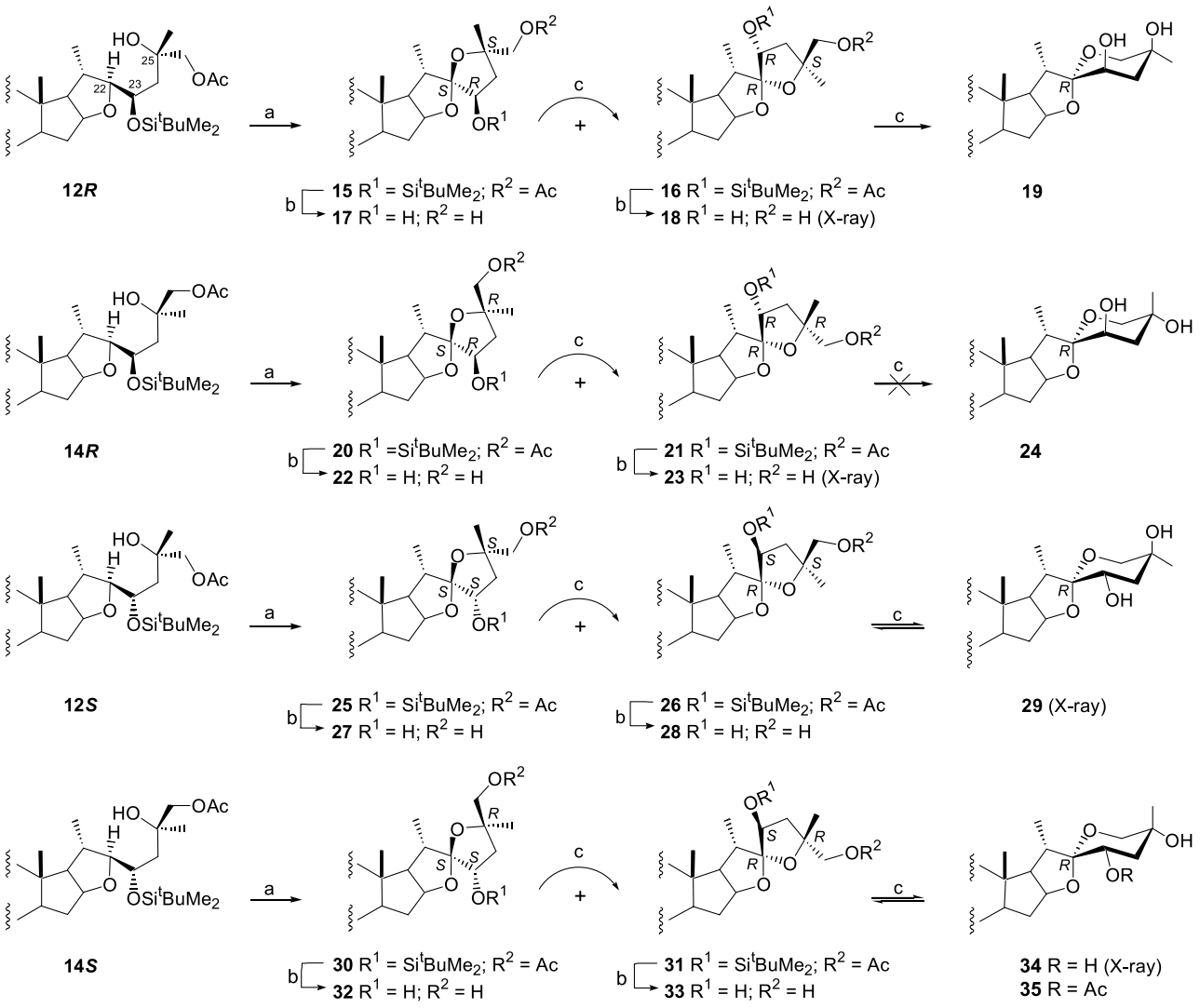
2. Results and discussion

The synthesis began with 3-methoxy-23-oxotigogenin (**2**) (Scheme 1) prepared by using a previously described procedure via oxidation of 3-methoxy-tigogenin (**1**) with $NaNO_2/BF_3{\cdot}Et_2O$.[13] The reduction of **2** with L-selectride furnished a mixture of alcohols **3** and **4** (72%, 1.7:1) from which the alcohol **3** with the correct natural orientation (23*R*) could be obtained in moderate yield. The reduction of **2** with $NaBH_4$ afforded preferentially the alcohol **4** (23*S*) with the non-natural stereochemistry (91%, 19:1).

The two C-23 diastereoisomers **3** and **4** were taken through the following steps of the synthesis separately (Scheme 1). The tigogenin dioxaespiro[4.5]decane system present in **3** was regio- and stereoselectively reduced with Ph_2SiH_2/$TiCl_4$ to give the diol **5**-*R*.[14] Conversion of **5**-*R* to the monoprotected secondary alcohol **8**-*R* was accomplished by a three-step protection-deprotection sequence involving formation of the primary pivalate **6**-*R*, silylation of the 23-alcohol with TBDMSOTf, and hydrolysis of pivalate **7**-*R* with KOH in methanol. Nitrophenylselenenylation of the primary alcohol in **8**-*R* followed by oxidative elimination furnished alkene **10**-*R*.[15] In a series of reactions identical to those described (Scheme 1), the 23*S* isomer **4** was converted into **10**-*S* via **5**-*S*, **6**-*S*, **7**-*S*, **8**-*S*, and **9**-*S*. Stoichiomeric osmylation of the **10**-*R* olefin afforded an inseparable mixture of diols **11**-*R* and **13**-*R* which could be separated after acetylation of the primary alcohol **12**-*R* and **14**-*R* in a 1:2 ratio (99%). In contrast, the osmylation of the **10**-*S* isomer afforded a separable mixture of diols **11**-*S* and **13**-*S* in a 2:1 ratio (98%), which were subsequently and separately acetylated to give **12**-*S* and **14**-*S*.

Initials attempts to asymmetrically dihydroxylate the 25-olefin were unsuccessful.[16] Using the Corey (1*S*,2*S*)-N^1,N^2-bis(mesitylmethyl)-1,2-diphenyl-1,2-ethanediamine reagent,[17] the **10**-*R* olefin gave the diols with similar yield and diastereomeric ratio (**11**-*R*/**13**-*R*, 1:2, 97%) compared with the uncatalyzed reaction. As both isomeric diols were required for this study the uncatalyzed osmylation reaction was preferred.

The IHA reaction was carried out by separately treating compounds **12**-*R*, **12**-*S*, **14**-*R*, and **14**-*S* with (diacetoxyiodo) benzene and iodine under irradiation with two 80 W tungsten-filament lamps at 50 °C (Scheme 2). The alcohols that possess the natural stereochemistry at C-23 (*R*) **12**-*R* and **14**-*R* gave 1,6-dioxaspiro[4.4]nonane compounds **15**



Scheme 2. Reagents and conditions: (a) $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 70 °C, **15** 23%, **16** 60%; **20** 28%, **21** 55%; **25** 23%, **26** 74%; **30** 28%, **31** 47%; (b) (i) TBAF, THF, rt, (ii) KOH, MeOH, rt (yields too steps: **17** 62%, **18** 73%, **22** 74%, **23** 70%, **27** 67%, **28** 87%, **32** 99%, **33** 91%); (c) H^+, CH_2Cl_2, rt.

and **16** (83%, 28:72) and **20** and **21** (83%, 33:67), respectively. On the other hand, the alcohols with the inverted stereochemistry at C-23 (*S*) **12**-*S* and **14**-*S* afforded after the IHA reaction dioxaspiro compounds **25**, and **26** (97%, 24:76) and **30** and **31** (75%, 37:63), respectively. The protecting groups of the alcohols at C-23 and C-25 were selected to favor the 1,5-hydrogen atom transfer reaction. A weak electron-withdrawing group (EWG) at C-23 (silyl ether) should favor the hydrogen abstraction and the subsequent oxidation of the C-22 radical to the oxocarbenium ion intermediate.[18] Also the stronger EWG at C-26 (acetyl ester) should prevent the competitive β-fragmentation of the alkoxyl radical. The choice of the protecting group could be critical and a hypothetical model where the two protecting groups have been interchanged (acetyl at C-23 and silyl at C-26) should give significant amounts of the methyl ketone from β-fragmentation.[19] The desired diols **17**, **18**, **22**, **23**, **27**, **28**, **32**, and **33** were obtained by hydrolysis of the silyl and acetyl protective groups. The structures of these eight stereoisomers of the cephalostatine north 1 side chain were determined by extensive ^1H and ^{13}C NMR 1D and 2D studies including DEPT, COSY, HMBC, and HSQC experiments. Using 2D NOESY and DNOE, the relative stereochemistry of the newly created stereogenic centers (C-22 and C-25) with respect to the known stereochemistry of the alcohol at C-23 may be assigned in each case.[20] As the flexibility of the 1,6-dioxaspiro system (vide infra) may introduce some uncertainty in the NOE results, the structure and stereochemistry were subsequently confirmed by X-ray crystallographic analysis of compounds **18** and **23**.[21] The (22*S*,23*R*,25*S*)-diol **17** possesses the stereochemistry of the natural cephalostatins. Compounds **17**, **22**, **27**, and **32** appear to be the products of kinetic control whereas **18**, **23**, **28**, and **33** are the thermodynamic products. The relative stability of these compounds was determined by following the evolution of the acid-catalyzed rearrangement through a C-22 oxocarbenium ion. Due to the presence of the 25,26-glycol, dioxaspiro compounds of the 1,6-dioxaspiro[4.5]decane type (e.g. **19**) may also be formed.[22]

In a preliminary experiment, diol **17** was transformed into the 22*R*-isomer **18** and both **17** and **18** finally led to the dioxaspiro[4.5]decane **19** under prolonged acid treatment

(Scheme 2). Subsequently, it was established that, in the 1,6-dioxaspiro[4.4]nonane system the 22*S* isomers **17**, **22**, **27**, and **32** are easily transformed, under mild acid conditions, into the 22*R* isomers **18**, **23**, **28**, and **33**, respectively, confirming that the 22*R* are the most stable compounds.

The transformation from the dioxaspiro [4.4]nonane to the [4.5]decane system deserves further comment.[23] Although compound **19** is obtained in moderate yield by acid-catalyzed isomerization of diol **18**, we observed that even under prolonged reaction times neither **22** nor **23** yielded the corresponding dioxaspiro[4.5]-compound **24** to any appreciable extent. Furthermore, the reactions of **28** and **33** under similar conditions reach an equilibrium (**28/29**, 60:40 and **33/35**, 66:34) after several hours at room temperature.

Aware that iodine is a Lewis acid, we also explored the iodine-catalyzed isomerization of 22*R*-isomers and similar results to those obtained with protic acids were achieved. For example, reaction of diol **27** in cyclohexane with iodine (10 mM) under the same conditions of the IHA reaction afforded after 1 h at 70 °C the equilibrium mixture of **28** and **29** in a ratio of 60:40. Analogously, **32** was isomerized to a mixture of **33** and **34** (60:40) under the same conditions. These findings suggest that a possible iodine-catalyzed partial isomerization between 22*S* and 22*R* isomers may well have occurred during the IHA reaction. Partial isomerization at the spirocenter may indeed be accomplished by treatment of fully protected compound **25** with iodine under conditions emulating the IHA reaction, to give a mixture of **25** and **26** (2:8) after 4 h at 70 °C.

These finding are in agreement with the results of a MM2 study (Table 1), compounds **17**, **24**, **27**, and **32** being the highest energy isomers in the respective series while **19**, **23**, **28**, and **33** are the most stable.[24] The isomeric pairs **28** and **29**, and **33** and **34** have similar energy ($\Delta E = 0.4$–0.6 Kcal/mol) and in consequence, an acid-catalyzed equilibrium (ca. 60:40) is reached after extended periods of time.

Several other interesting features in the structure of these compounds are shown in Table 1. For instance, compounds with the same stereochemistry at C-23 display significantly different coupling constants between the protons H_{23} and H_{24} on changing from the 22*R* to the 22*S* series of compounds (compare the coupling constant of **17** with **18** or **22** with **23** in which the stereochemistry at C-23 is always *R*, or **27** with **28** and **32** with **33** where the stereochemistry is 23*S*). The small couplings (0, 5 Hz) suggest a pseudoaxial orientation of the C-23 alcohol (e.g. **18**) while the larger couplings (8, 10 Hz) are more consistent with a pseudo-equatorially disposed alcohol (e.g. **17**).[25] Nevertheless, a reasonable explanation for this phenomenon is necessarily associated with a change of the conformation of the tetrahydrofuran F-ring on going from the 22*S* to 22*R* series of compounds (Fig. 2). The study of the conformation of this 1,6-dioxaspiro ring system may not be an easy task due to the significant flexibility of the puckered five-membered rings, although, in this case, some conformational constraint, exerted by the substituents and the fused D-ring, may be expected.[26] In this approach we have determined the conformations of the E- and F-rings of the eight different

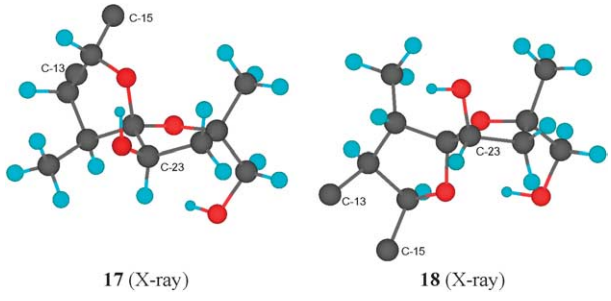


Figure 2. Ring F conformations of **17** and **18**, taken from the X-ray crystal structures. For the sake of clarity only E and F rings are shown.

Table 1. Structural characteristics of dioxaspiro compounds

Compound	ΔE[a] (kcal/mol)	P[b] (conformation)[c]		$^3J_{23,24}$[d] (Hz)
		E-ring	F-ring	
17	6.8	134 (E_{16})	146 ($^{23}T_{22}$)	8.1, 8.4
17 (X-ray)[e]	—	127 (E_{16})	145 ($^{23}T_{22}$)	—
18	3.4	102 ($^{o}T_{16}$)	339 (E_{23})	0.0, 5.7
18 (X-ray)	—	93 (^{o}E)	332 ($^{22}T_{23}$)	—
19	0.0	96 (^{o}E)	— ($^{22}C_{25}$)	2.8, 2.8
22	2.9	141 ($^{17}T_{16}$)	155 (^{23}E)	8.1, 9.8
23	0.0	85 (^{o}E)	320 ($^{22}T_{23}$)	0.0, 5.6
23 (X-ray)	—	90 (^{o}E)	324 ($^{22}T_{23}$)	—
24	4.3	99 (^{o}E)	— ($^{22}C_{25}$)	—
27	4.4	148 ($^{17}T_{16}$)	144 ($^{23}T_{22}$)	0.0, 4.9
28	0.0	89 (^{o}E)	346 (E_{23})	8.3, 10.5
29	0.4	89 (^{o}E)	— ($^{22}C_{25}$)	5.3, 11.6
29 (X-ray)	—	80 ($^{o}T_{22}$)	— ($^{22}C_{25}$)	—
32	4.6	145 ($^{17}T_{16}$)	153 ($^{23}T_{22}$)	0.0, 4.6
33	0.0	85 (^{o}E)	320 ($^{22}T_{23}$)	8.5, 9.8
34	0.6	91 (^{o}E)	— ($^{22}C_{25}$)	5.3, 11.7
34 (X-ray)	—	72 ($^{o}T_{22}$)	— ($^{22}C_{25}$)	—

[a] Changes of the relative MM2 energy (in kcal/mol) with respect to the lowest energy isomer in the respective series.
[b] Altone-Sundaralingam phase angle (in degrees) as defined in Ref. 29c.
[c] An adaptation of the IUPAC nomenclature of carbohydrates is used (Ref. 30).
[d] Experimental $^3J_{HH}$ coupling from 500 MHz spectra.
[e] Data were taken from the X-ray analysis of (22*S*,23*R*,25*S*)-3β,12β-diacetoxy-22,25-epoxy-5α-furostan-23,26-diol (Ref. 27).

isomers over minimized structures (MM2) using the X-ray structures **17**,[27] **18**, and **23** (X-ray) as starting geometry.[28] With this study we are not attempting to make a complete conformational analysis of the 1,6-dioxaspiro system, but simply to explain the apparently anomalous coupling constants observed for the proton at C-23.

The structures of lowest energy calculated by this methodology have E- and F-ring conformations that were very similar to those found in the crystallographic structures. A comparison of the conformations from the crystal structure with those established by molecular mechanics calculations is presented in Table 1 [compare **17** with **17** (X-ray), **18** with **18** (X-ray), and **23** with **23** (X-ray)]. The ring conformations have been described by the Altone-Sundaralingam phase angle[29] and the IUPAC conformational nomenclature for the furanose form of monosaccharides has been adapted to these rings.[30] The E-ring of the 22*S*-isomers (**17**, **22**, **27**, and **32**) adopts a preferred conformation E_{16} or $^{17}T_{16}$ ($P=134$–$148°$) in the southern hemisphere of the pseudorotational itinerary of the ring (Table 1).[29] The E-ring conformation in the 22*R* series of isomers (**18**, **23**, **28**, and **33**) is located in the east ^{o}E ($P=102$–$85°$) of the pseudorotational wheel. On the other hand, the F-ring of the 22*S*-isomers adopts a preferred conformation $^{23}T_{22}$ or ^{23}E ($P=144$–$155°$) in the southern hemisphere, while, conformations $^{22}T_{23}$ or E_{23} ($P=320$–$346°$) in the northern hemisphere are found for the F-ring of the 22*R*-isomers.

The experimental $^{3}J_{23,24}$ H-H coupling constants were measured in 500 MHz spectra (Table 1), and are in agreement with those calculated over minimized structures using the HLA equation,[31] the largest individual discrepancy between experimental and calculated constants being 1.4 Hz.

In the 1,6-dioxa[4.5]decane compounds **19**, **29** and **34**, firm evidence in favor of a $^{22}C_{25}$ conformation for the F-ring was obtained by the $^{3}J_{23,24}$ coupling constants. The alternative $^{25}C_{22}$ chair conformation can be ruled out on the basis of the same measurements (Table 1).[32] X-ray diffraction analysis confirmed the $^{22}C_{25}$ conformation in the solid state for **29** and **34**.[21]

3. Conclusion

In summary, we have demonstrated the usefulness of the IHA reaction in the construction of the steroidal 1,6-dioxaspiro[4.4]nonane ring system.[33] Since thermodynamically less stable isomers at the spirocenter can be obtained, this methodology should be especially useful in the synthesis of the natural products when both isomers are isolated from nature, as described for several ritterazines.[12]

The preparation of all eight possible isomers has led to the discovery that the spirocenter stereochemistry can profoundly influence the conformation of the F-ring. Taking such an effect into account, the apparently anomalous coupling constant for the proton at C-23, observed in the NMR spectra of these compounds, can be readily explained. From these findings the question that now arises is whether the conformation of the F-ring might influence the biological activity, as occurs in other types of tetrahydrofuran derivatives.[29c,34] In any case, this should be taken into consideration in the development of new biologically active cephalostatin and ritterazin analogs.

Although we are aware that our conclusions regarding the stability and conformation of the spiroketal side chain in the different series of these simple monomers may not be fully extrapolatable to the bioactive products, we believe that they could help in designing such compounds.

4. Experimental

4.1. General methods

Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured at the sodium line at ambient temperature in $CHCl_3$ solutions. IR spectra were recorded in $CHCl_3$ solutions unless otherwise stated. NMR spectra were determined at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ unless otherwise stated, in the presence of TMS as internal standard. Mass spectra were determined at 70 eV. Merck silica gel 60 PF (0.063–0.2 mm) was used for column chromatography. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used on a Chromatotron for centrifugally assisted chromatography. Commercially available reagents and solvents were analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagents for TLC analysis were conducted with 0.5% vanillin in H_2SO_4–EtOH (4:1) and further heating until development of color.

4.1.1. (22*S*,23*R*,25*S*)-3β-Methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (15) and (22*R*,23*R*,25*S*)-3β-methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (16). A solution of the alcohol **12**-*R* (60 mg, 0.096 mmol) in cyclohexane (10 mL) containing (diacetoxyiodo)benzene (40 mg, 0.124 mmol) and iodine (25 mg, 0.098 mmol) was irradiated with two 80 W tungsten-filament lamps at 50 °C for 3.5 h. The reaction mixture was then poured into aqueous solution of sodium thiosulfate (10%) and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 95:5) of the residue afforded compound compound **15** (14 mg, 0.022 mmol, 23.4%) and **16** (36 mg, 0.058 mmol, 60%). Compound **15**: amorphous; $[\alpha]_D$ −18 (*c* 0.23); IR 1746 cm^{-1}; ^{1}H NMR 0.07 (3H, s), 0.09 (3H, s), 0.64 (1H, m), 0.81 (3H, s), 0.87 (3H, s), 0.90 (9H, s), 1.06 (3H, d, $J=7.2$ Hz), 1.32 (3H, s), 1.91 (1H, dd, $J=11.0$, 11.4 Hz), 2.03 (1H, dd, $J=7.6$, 11.6 Hz), 2.08 (3H, s), 2.30 (1H, dddd, $J=7.0$, 7.0, 7.0, 7.0 Hz), 3.12 (1H, dddd, $J=4.6$, 4.6, 10.9, 10.9 Hz), 3.35 (3H, s), 3.88 (2H, s), 4.30 (1H, dd, $J=7.8$, 10.4 Hz), 4.62 (1H, ddd, $J=7.1$, 7.1, 7.1 Hz); ^{13}C NMR −5.4 (CH_3), −4.0 (CH_3), 12.3 (CH_3), 16.1 (CH_3), 16.6 (CH_3), 17.8 (C), 20.9 (CH_2), 21.1 (CH_3), 25.8 (4×CH_3), 27.9 (CH_2), 28.8 (CH_2), 32.3 (CH_2), 32.4 (CH_2), 34.3 (CH_2), 35.0 (CH), 35.9 (C), 36.9 (CH_2), 37.5 (CH), 40.2 (CH_2), 40.3 (CH_2), 41.1 (C), 44.8 (CH), 54.5 (CH), 55.5 (CH_3), 55.6 (CH), 61.6 (CH),

70.3 (CH_2), 73.2 (CH), 79.0 (C), 79.8 (CH), 81.7 (CH), 117.9 (C), 170.6 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 561 (6), 475 (30), 287 (23); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4255. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.01; H, 10.17. Compound **16**: amorphous; $[\alpha]_D$ −45 (*c* 0.24); IR 1745 cm^{-1}; ^1H NMR 0.07 (3H, s), 0.08 (3H, s), 0.62 (1H, m), 0.76 (3H, s), 0.80 (3H, s), 0.90 (9H, s), 1.06 (3H, d, *J*=6.9 Hz), 1.33 (3H, s), 1.59 (1H, dd, *J*=0.0, 13.3 Hz), 1.93 (1H, ddd, *J*=5.7, 7.5, 12.4 Hz), 2.05 (3H, s), 2.22 (1H, dd, *J*=5.4, 13.3 Hz), 2.32 (1H, dddd, *J*=6.1, 6.1, 6.1, 6.1 Hz), 3.11 (1H, dddd, *J*=4.5, 4.5, 10.8, 10.8 Hz), 3.33 (3H, s), 3.88 (1H, d, *J*=10.9 Hz), 4.10 (1H, d, *J*=10.9 Hz), 4.14 (1H, d, *J*=4.6 Hz), 4.44 (1H, ddd, *J*=5.6, 7.8, 7.8 Hz); ^{13}C NMR −5.1 (CH_3), −5.0 (CH_3), 12.3 (CH_3), 16.3 (CH_3), 16.8 (CH_3), 17.9 (C), 20.9 (CH_2), 21.0 (CH_3), 25.0 (CH_3), 25.7 (3×CH_3), 27.9 (CH_2), 28.7 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.3 (CH), 35.9 (C), 36.2 (CH), 36.9 (CH_2), 39.8 (CH_2), 41.0 (C), 42.3 (CH_2), 44.7 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 63.1 (CH), 70.8 (CH_2), 78.5 (CH), 79.8 (CH), 81.3 (CH), 82.0 (C), 120.9 (C), 171.0 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 561 (2), 545 (7), 475 (32), 287 (43); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4238. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.93; H, 10.22.

4.1.2. (22*S*,23*R*,25*S*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (17). To a solution of compound **15** (13 mg, 0.021 mmol) in THF (3 mL) was added TBAF (0.1 mL, 0.1 mmol, 1.0 M in THF) and stirred at room temperature for 2 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (benzene–EtOAc, 90:10) of the residue afforded (22*S*,23*R*,25*S*)-3β-methoxy-26-acetoxy-22,25-epoxy-5α-furostan-23-ol (8.6 mg, 0.017 mmol, 81%): mp 151–154 °C (from EtOAc); IR 3447, 1744 cm^{-1}; ^1H NMR 0.64 (1H, m), 0.81 (3H, s), 0.91 (3H, s), 1.13 (3H, d, *J*=7.5 Hz), 1.29 (3H, s), 2.01 (1H, ddd, *J*=5.7, 7.2, 12.3 Hz), 2.07 (3H, s), 2.27 (1H, dd, *J*=7.8, 12.6 Hz), 2.34 (1H, dddd, *J*=3.5, 7.4, 7.4, 7.4 Hz), 3.11 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.33 (3H, s), 3.86 (2H, s), 4.25 (1H, ddd, *J*=8.8, 8.8, 8.8 Hz), 4.54 (1H, ddd, *J*=7.0, 7.0, 7.0 Hz); ^{13}C NMR 12.3 (CH_3), 16.1 (CH_3), 17.5 (CH_3), 20.9 (CH_3), 20.9 (CH_2), 25.8 (CH_3), 27.9 (CH_2), 28.8 (CH_2), 32.4 (CH_2), 34.0 (CH_2), 34.3 (CH_2), 34.8 (CH), 35.9 (C), 36.9 (CH_2), 39.1 (CH), 40.1 (CH_2), 41.5 (C), 41.9 (CH_2), 44.8 (CH), 54.5 (CH), 55.48 (CH), 55.52 (CH_3), 63.3 (CH), 70.2 (CH_2), 73.0 (CH), 78.9 (C), 79.8 (CH), 83.7 (CH), 118.5 (C), 170.7 (C); MS *m/z* (rel intensity) 486 ($M^+ - H_2O$, 3), 471 (<1), 426 (4), 413 (4), 361 (39), 287 (100); HRMS calcd for $C_{30}H_{46}O_5$ 486.3345; found 486.3363. Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.71. A solution of this acetate (8 mg, 0.0158 mmol) in MeOH (5 mL) containing KOH (0.15 g) was stirred at room temperature for 4 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) of the residue afforded compound **17** (5.6 mg, 0.012 mmol, 76%): mp 187.5–190 °C (from EtOAc-*n*-hexane); $[\alpha]_D$ +11 (*c* 0.19); IR 3417 cm^{-1}; ^1H NMR 0.64 (1H, m), 0.81 (3H, s), 0.92 (3H, s), 1.13 (3H, d, *J*=7.4 Hz), 1.27 (3H, s), 1.69 (1H, dd, *J*=8.4, 12.6 Hz), 2.02 (1H, ddd, *J*=5.6, 7.3, 12.4 Hz), 2.20 (1H, br d, *J*=10.0 Hz), 2.29 (1H, dd, *J*=8.1, 12.6 Hz), 2.34 (1H, dddd, *J*=4.0, 7.5, 7.5, 7.5 Hz), 3.12 (1H, dddd, *J*=4.7, 4.7, 11.0, 11.0 Hz), 3.29 (1H, d, *J*=11.3 Hz), 3.34 (3H, s), 3.38 (1H, d, *J*=11.3 Hz), 4.22 (1H, ddd, *J*=8.4, 8.4, 8.4 Hz), 4.56 (1H, ddd, *J*=7.0, 7.0, 8.7 Hz); ^{13}C NMR 12.3 (CH_3), 16.2 (CH_3), 17.5 (CH_3), 20.9 (CH_2), 25.3 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 32.3 (CH_2), 33.9 (CH_2), 34.3 (CH_2), 34.8 (CH), 35.9 (C), 36.9 (CH_2), 39.4 (CH), 40.1 (CH_2), 41.5 (C), 41.7 (CH_2), 44.8 (CH), 54.5 (CH), 55.4 (CH_3), 55.5 (CH), 63.4 (CH), 69.7 (CH_2), 73.3 (CH), 79.8 (CH), 81.3 (C), 83.7 (CH), 118.6 (C); MS *m/z* (rel intensity) 461 (M^+ −H, <1), 431 (4), 287 (100); HRMS calcd for $C_{28}H_{45}O_5$ 461.3267; found 461.3225. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.81; H, 10.19.

4.1.3. (22*R*,23*R*,25*S*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (18). To a solution of compound **16** (35 mg, 0.056 mmol) in THF (5 mL) was added TBAF (0.3 mL, 0.3 mmol, 1.0 M in THF) and stirred at room temperature for 3 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 80:20) of the residue afforded (22*R*,23*R*,25*S*)-3β-methoxy-26-acetoxy-22,25-epoxy-5α-furostan-23-ol (23 mg, 0.045 mmol, 81%): mp 208.5–209 °C (from EtOAc-*n*-hexane); $[\alpha]_D$ −57 (*c* 1.03); IR 3516, 1723 cm^{-1}; ^1H NMR 0.62 (1H, m), 0.77 (3H, s), 0.80 (3H, s), 1.09 (3H, d, *J*=6.9 Hz), 1.34 (3H, s), 1.93 (1H, ddd, *J*=5.8, 7.4, 12.6 Hz), 2.07 (3H, s), 2.28 (1H, dd, *J*=5.6, 13.7 Hz), 2.39 (1H, dddd, *J*=6.4, 6.4, 6.4, 6.4 Hz), 3.11 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.33 (3H, s), 3.93 (1H, d, *J*=10.9 Hz), 4.09 (1H, d, *J*=10.9 Hz), 4.18 (1H, br d, *J*=4.9 Hz), 4.44 (1H, ddd, *J*=5.7, 7.8, 7.8 Hz); ^{13}C NMR 12.3 (CH_3), 16.1 (CH_3), 16.8 (CH_3), 20.9 (CH_3), 21.0 (CH_2), 25.5 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.2 (CH), 35.9 (C), 36.1 (CH), 36.9 (CH_2), 39.7 (CH_2), 41.0 (C), 42.0 (CH_2), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 63.3 (CH), 70.9 (CH_2), 78.1 (CH), 79.8 (CH), 81.2 (CH), 81.6 (C), 120.2 (C), 171.0 (C); MS *m/z* (rel intensity) 504 (M^+ <1), 486 (11), 431 (6), 287 (100); HRMS calcd for $C_{30}H_{48}O_6$ 504.3451; found 504.3455. Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.06; H, 9.86. A solution of this acetate (20 mg, 0.0397 mmol) in MeOH (10 mL) containing KOH (0.35 g) was stirred at room temperature for 4 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) of the residue afforded compound **18** (16.5 mg, 0.036 mmol, 90%): mp 211.5–213.5 °C (from EtOAc-*n*-hexane); $[\alpha]_D$ −55 (*c* 0.108); IR 3426, 1453 cm^{-1}; ^1H NMR 0.63 (1H, m), 0.78 (3H, s), 0.81 (3H, s), 1.10 (3H, d, *J*=7.2 Hz), 1.30 (3H, s), 1.58 (1H, dd, *J*=0.0, 13.8 Hz), 1.96 (1H, m), 2.46 (1H, dddd, *J*=7.0, 7.0, 7.0, 7.0 Hz), 2.56 (1H, dd, *J*=5.7, 13.8 Hz), 3.11 (1H, dddd, *J*=4.5, 4.5, 10.7, 10.7 Hz), 3.31 (1H, d, *J*=9.0 Hz), 3.33 (3H, s), 3.49 (1H, d, *J*=9.0 Hz), 4.21 (1H, d, *J*=5.7 Hz), 4.53 (1H, ddd, *J*=5.6, 7.5, 7.5 Hz); ^{13}C NMR 12.3 (CH_3), 16.0 (CH_3), 17.0 (CH_3), 20.9 (CH_2), 25.2 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.2 (CH), 35.5 (CH), 35.9 (C), 36.9 (CH_2), 39.5 (2×CH_2), 41.1 (C), 44.7 (CH), 54.4 (CH),

55.5 (CH_3), 56.2 (CH), 63.5 (CH), 68.5 (CH_2), 78.9 (CH), 79.8 (CH), 81.8 (CH), 85.3 (C), 120.3 (C); MS *m/z* (rel intensity) 462 (M^+, <1), 444 (1), 431 (28), 287 (100); HRMS calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3338. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.83; H, 9.78.

4.1.4. (22*S*,23*R*,25*S*)-3β-Methoxy-5α-spirostan-23,25-diol (19). A solution of compound **18** (10 mg, 0.02 mmol) in $CHCl_3$ (10 mL) was treated with an undetermined catalytic amount of HCl (some gas taken with a Pasteur pipet from of a concd HCl bottle) and stirred at room temperature for 24 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ and extracted with $CHCl_3$. Chromatotron chromatography (hexanes–EtOAc, 85:15) of the residue afforded compound **19** (5 mg, 0.01 mmol, 50%): mp 250.5–252.5 °C (from EtOAc-*n*-hexane); $[\alpha]_D$ −80 (*c* 0.45); IR 3601, 3492 cm^{-1}; ^1H NMR 0.63 (1H, m), 0.77 (3H, s), 0.80 (3H, s), 1.12 (3H, s), 1.15 (3H, d, *J*=6.9 Hz), 1.82 (1H, ddd, *J*=2.8, 2.8, 14.3 Hz), 1.96 (1H, dd, *J*=3.2, 14.3 Hz), 2.30 (1H, dddd, *J*=6.9, 6.9, 6.9, 6.9 Hz), 3.11 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.33 (3H, s), 3.39 (1H, dd, *J*=2.8, 11.8 Hz), 3.63 (1H, dd, *J*=2.8, 2.8 Hz), 3.77 (1H, d, *J*=11.8 Hz), 4.47 (1H, ddd, *J*=5.7, 7.8, 7.8 Hz); ^{13}C NMR 12.3 (CH_3), 16.2 (CH_3), 16.7 (CH_3), 20.9 (CH_2), 26.2 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.2 (CH), 35.9 (C), 36.9 (CH_2), 38.3 (CH_2), 39.6 (CH_2), 40.4 (CH), 41.0 (C), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.4 (CH), 64.1 (CH), 68.8 (C), 69.2 (CH_2), 70.9 (CH), 79.8 (CH), 81.8 (CH), 108.7 (C); MS *m/z* (rel intensity) 462 (M^+, 2), 444 (2), 426 (2), 411 (2), 361 (46), 287 (100); HRMS calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3401. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.71; H, 10.13.

4.1.5. (22*S*,23*R*,25*R*)-3β-Methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (20) and (22*R*,23*R*,25*R*)-3β-methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (21). A solution of the alcohol **14**-*R* (137 mg, 0.22 mmol) in cyclohexane (25 mL) containing (diacetoxyiodo)benzene (84 mg, 0.264 mmol) and iodine (56 mg, 0.22 mmol) was irradiated with two 80 W tungsten-filament lamps at 55 °C for 7 h. The reaction mixture was then poured into aqueous solution of sodium thiosulfate (10%) and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 95:5) of the residue afforded compound **20** (38 mg, 0.061 mmol, 27.8%) and compound **21** (76 mg, 0.122 mmol, 55.3%). Compound **20**: amorphous; $[\alpha]_D$ −27 (*c* 0.064); IR 1746 cm^{-1}; ^1H NMR 0.07 (3H, s), 0.10 (3H, s), 0.63 (1H, m), 0.80 (3H, s), 0.85 (3H, s), 0.90 (9H, s), 1.06 (3H, d, *J*=7.3 Hz), 1.20 (3H, s), 1.85 (1H, dd, *J*=7.5, 11.1 Hz), 1.90 (1H, ddd, *J*=6.0, 6.8, 12.3 Hz), 1.98 (1H, dd, *J*=11.2, 10.4 Hz), 2.05 (3H, s), 2.31 (1H, dddd, *J*=6.9, 6.9, 6.9, 6.9 Hz), 3.10 (1H, dddd, *J*=4.6, 4.6, 10.7, 10.7 Hz), 3.35 (3H, s), 4.01 (1H, d, *J*=10.9 Hz), 4.10 (1H, d, *J*=10.9 Hz), 4.22 (1H, dd, *J*=7.5, 10.4 Hz), 4.59 (1H, ddd, *J*=6.8, 6.8, 6.8 Hz); ^{13}C NMR −5.3 (CH_3), −4.0 (CH_3), 12.3 (CH_3), 16.0 (CH_3), 16.5 (CH_3), 17.8 (C), 21.0 (CH_2), 21.0 (CH_3), 25.0 (CH_3), 25.8 (3×CH_3), 27.9 (CH_2), 28.8 (CH_2), 32.3 (CH_2), 33.4 (CH_2), 34.3 (CH_2), 35.0 (CH), 35.9 (C), 36.9 (CH_2), 37.4 (CH), 40.1 (CH_2), 40.2 (CH_2), 41.2 (C), 44.8 (CH), 54.5 (CH), 55.5 (CH_3), 55.6 (CH), 61.9 (CH), 71.0 (CH_2), 72.7 (CH), 78.5 (C), 79.8 (CH), 81.8 (CH), 118.0 (C), 170.9 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 617 (<1), 561 (6), 475 (31), 287 (20); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4335. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.98; H, 10.22. Compound **21**: amorphous; $[\alpha]_D$ −58.2 (*c* 0.5); IR 1745 cm^{-1}; ^1H NMR 0.06 (3H, s), 0.07 (3H, s), 0.63 (1H, m), 0.76 (3H, s), 0.80 (3H, s), 0.89 (9H, s), 1.02 (3H, d, *J*=7.0 Hz), 1.29 (3H, s), 1.84 (1H, dd, *J*=0.0, 13.5 Hz), 1.96 (1H, ddd, *J*=5.7, 7.3, 12.7 Hz), 2.04 (1H, dd, *J*=5.1, 13.5 Hz), 2.06 (3H, s), 2.33 (1H, dddd, *J*=6.9, 6.9, 6.9, 6.9 Hz), 3.11 (1H, dddd, *J*=4.5, 4.5, 10.9, 10.9 Hz), 3.33 (3H, s), 4.04 (1H, d, *J*=10.6 Hz), 4.08 (1H, d, *J*=10.6 Hz), 4.17 (1H, d, *J*=4.4 Hz), 4.52 (1H, ddd, *J*=5.7, 7.9, 7.9 Hz); ^{13}C NMR −5.1 (CH_3), −5.0 (CH_3), 12.3 (CH_3), 16.4 (CH_3), 16.8 (CH_3), 17.9 (C), 20.91 (CH_2), 20.96 (CH_3), 25.7 (3×CH_3), 26.1 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.3 (CH), 35.9 (C), 36.4 (CH), 36.9 (CH_2), 39.8 (CH_2), 41.1 (C), 42.7 (CH_2), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 63.2 (CH), 70.4 (CH_2), 78.7 (CH), 79.8 (CH), 81.4 (CH), 81.8 (C), 122.0 (C), 170.9 (C); MS *m/z* (rel intensity) 618 (M^+, 1), 603 (<1), 561 (43), 545 (23), 287 (68); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4324. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.71; H, 9.98.

4.1.6. (22*S*,23*R*,25*R*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (22). To a solution of compound **20** (38 mg, 0.061 mmol) in THF (8 mL) was added TBAF (0.4 mL, 0.4 mmol, 1.0 M in THF) and stirred at room temperature for 1.5 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (benzene–EtOAc, 90:10) of the residue afforded (22*S*,23*R*,25*R*)-3β-methoxy-26-acetoxy-22,25-epoxy-5α-furostan-23-ol (28 mg, 0.055 mmol, 90%): amorphous; $[\alpha]_D$ +10 (*c* 0.39); IR 3443, 1745 cm^{-1}; ^1H NMR 0.62 (1H, m), 0.80 (3H, s), 0.89 (3H, s), 1.12 (3H, d, *J*=7.5 Hz), 1.19 (3H, s), 1.82 (1H, dd, *J*=9.1, 12.4 Hz), 1.87 (1H, ddd, *J*=5.7, 7.3, 12.2 Hz), 2.06 (3H, s), 2.36 (1H, dddd, *J*=3.5, 7.4, 7.4, 7.4 Hz), 3.11 (1H, dddd, *J*=4.5, 4.5, 10.6, 10.6, Hz), 3.33 (3H, s), 3.96 (1H, d, *J*=10.8 Hz), 4.06 (1H, d, *J*=10.8 Hz), 4.25 (1H, ddd, *J*=8.8, 8.8, 8.8 Hz), 4.54 (1H, ddd, *J*=7.0, 7.0, 7.0 Hz); ^{13}C NMR 12.2 (CH_3), 15.9 (CH_3), 17.3 (CH_3), 20.9 (CH_3), 20.9 (CH_2), 25.2 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 32.3 (CH_2), 32.8 (CH_2), 34.2 (CH_2), 34.7 (CH), 35.9 (C), 36.8 (CH_2), 39.1 (CH), 40.0 (CH_2), 41.4 (C), 41.7 (CH_2), 44.7 (CH), 54.5 (CH), 55.5 (CH), 55.5 (CH_3), 63.3 (CH), 70.4 (CH_2), 72.4 (CH), 78.5 (C), 79.7 (CH), 83.7 (CH), 128.3 (C), 170.8 (C); MS *m/z* (rel intensity) 505 (M^+ + H, < 1), 486 (< 1), 471 (<1), 413 <1), 361 (83), 287 (100); HRMS calcd for $C_{30}H_{46}O_5$ 486.3345; found 486.3335. Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.52; H, 9.71. A solution of this acetate (24 mg, 0.047 mmol) in MeOH (15 mL) containing KOH (0.3 g) was stirred at room temperature for 8 h. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) of the residue afforded compound **22** (18 mg, 0.039 mmol, 82%): mp 166.5–168 °C (from EtOAc-*n*-hexane); $[\alpha]_D$ −4

(*c* 0.55); IR 3408 cm^{-1}; ^1H NMR 0.62 (1H, m), 0.80 (3H, s), 0.89 (3H, s), 1.13 (3H, s), 1.16 (3H, d, $J=7.5$ Hz), 1.96 (1H, dd, $J=8.1$, 12.3 Hz), 2.04 (1H, ddd, $J=7.3$, 7.3, 7.3 Hz), 2.15 (1H, dd, $J=9.8$, 12.4 Hz), 2.39 (1H, dddd, $J=3.3$, 7.3, 7.3, 7.3 Hz), 3.11 (1H, dddd, $J=4.5$, 4.5, 10.7, 10.7 Hz), 3.25 (1H, d, $J=11.4$ Hz), 3.33 (3H, s), 3.45 (1H, d, $J=11.5$ Hz), 4.26 (1H, dd, $J=9.0$, 9.0 Hz), 4.58 (1H, ddd, $J=7.3$, 7.3, 7.3 Hz); ^{13}C NMR 12.2 (CH_3), 16.1 (CH_3), 17.2 (CH_3), 20.8 (CH_2), 24.9 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 32.2 (CH_2), 34.0 (CH_2), 34.2 (CH_2), 34.8 (CH), 35.9 (C), 36.9 (CH_2), 38.5 (CH), 38.5 (CH_2), 39.7 (CH_2), 41.5 (C), 44.7 (CH), 54.4 (CH), 55.4 (CH_3), 55.6 (CH), 63.8 (CH), 68.1 (CH_2), 73.4 (CH), 79.7 (CH), 81.7 (C), 83.8 (CH), 118.2 (C); MS *m/z* (rel intensity) 444 (M^+-H_2O, 2), 431 (6), 426 (9), 411 (4), 287 (100); HRMS calcd for $C_{28}H_{44}O_4$ 444.3240; found 444.3221. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.71; H, 10.14.

4.1.7. (22*R*,23*R*,25*R*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (23). To a solution of compound **21** (23 mg, 0.037 mmol) in THF (5 mL) was added TBAF (0.2 mL, 0.2 mmol, 1.0 M in THF) and stirred at room temperature for 3 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was saponified with methanolic KOH (10 mL, 3%) for 4 h at room temperature. Chromatotron chromatography (benzene–EtOAc, 75:25) of the residue afforded compound **23** (12 mg, 0.026 mmol, 70%): mp 269.5–270 °C (from MeOH); $[\alpha]_D$ −72 (*c* 0.122); IR 3317 cm^{-1}; ^1H NMR 0.63 (1H, m), 0.79 (3H, s), 0.80 (3H, s), 1.11 (3H, d, $J=6.7$ Hz), 1.27 (3H, s), 1.93 (1H, dd, $J=0.0$, 14.0 Hz), 1.96 (1H, ddd, $J=5.8$, 7.4, 12.4 Hz), 2.28 (1H, dd, $J=5.5$, 14.0 Hz), 2.53 (1H, dddd, $J=7.0$, 7.0, 7.0, 7.0 Hz), 3.11 (1H, dddd, $J=4.5$, 4.5, 10.7, 10.7 Hz), 3.33 (3H, s), 3.39 (1H, d, $J=11.2$ Hz), 3.65 (1H, d, $J=11.2$ Hz), 4.02 (1H, d, $J=5.5$ Hz), 4.51 (1H, ddd, $J=5.7$, 7.9, 7.9 Hz); ^{13}C NMR 12.3 (CH_3), 16.1 (CH_3), 17.1 (CH_3), 20.9 (CH_2), 26.2 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 35.1 (CH), 35.9 (C), 36.3 (CH), 36.9 (CH_2), 39.8 (CH_2), 41.1 (C), 42.4 (CH_2), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 63.6 (CH), 68.9 (CH_2), 77.0 (CH), 79.8 (CH), 81.0 (CH), 83.2 (C), 120.6 (C); MS *m/z* (rel intensity) 444 (M^+-H_2O, <1), 413 (2), 287 (45); HRMS calcd for $C_{28}H_{44}O_4$ 444.3240; found 444.3268. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.69; H, 9.90.

4.1.8. (22*S*,23*S*,25*S*)-3β-Methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (25) and (22*R*,23*S*,25*S*)-3β-methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (26). A solution of the alcohol **12**-*S* (420 mg, 0.68 mmol) in cyclohexane (70 mL) containing (diacetoxyiodo)benzene (437 mg, 1.36 mmol) and iodine (172 mg, 0.68 mmol) was irradiated with a 80 W tungsten-filament lamp at 70 °C for 1 h. The reaction mixture was then poured into aqueous solution of sodium thiosulfate (10%) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Flash-chromatography (hexanes–EtOAc, 93:7) of the residue afforded compound **25** (96 mg, 0.15 mmol, 23%) and compound **26** (310 mg, 0.50 mmol, 74%). Compound **25**: mp 62.4–63.7 °C (from EtOAc); $[\alpha]_D$ +21.2 (*c* 0.08); IR 1745 cm^{-1}; ^1H NMR 0.07 (3H, s), 0.08 (3H, s), 0.64 (1H, m), 0.81 (3H, s), 0.86 (3H, s), 0.90 (9H, s), 1.13 (3H, d, $J=7.2$ Hz), 1.33 (3H, s), 1.89 (1H, dd, $J=3.3$, 13.1 Hz), 2.01 (1H, dd, $J=5.2$, 13.1 Hz), 2.07 (3H, s), 3.11 (1H, dddd, $J=4.7$, 4.7, 11.0, 11.0 Hz), 3.33 (3H, s), 4.02 (1H, d, $J=10.7$ Hz), 4.11 (1H, d, $J=10.4$ Hz), 4.26 (1H, dd, $J=3.4$, 5.1 Hz), 4.38 (1H, ddd, $J=7.5$, 7.5, 9.4 Hz); NOE correlation from 23-H to 21-Me and to 27-Me; ^{13}C NMR (100.6 MHz) −5.2 (CH_3), −3.8 (CH_3), 12.3 (CH_3), 16.2 (CH_3), 17.0 (CH_3), 17.8 (C), 20.9 (CH_3), 21.2 (CH_2), 25.6 (CH_3), 25.9 (3×CH_3), 27.9 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 33.1 (CH_2), 34.3 (CH_2), 34.4 (CH), 36.0 (C), 36.9 (CH_2), 39.4 (CH), 41.0 (CH_2), 41.1 (C), 42.6 (CH_2), 44.9 (CH), 54.6 (CH), 54.9 (CH), 55.5 (CH_3), 62.1 (CH), 70.5 (CH_2), 77.7 (CH), 79.8 (CH), 80.5 (C), 81.7 (CH), 120.6 (C), 170.8 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 561 (3), 545 (2), 198 (100); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4317. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.92; H, 10.04. Compound **26**: mp 135.0–136.0 °C (from EtOAc); $[\alpha]_D$ −34 (*c* 0.10); IR 1745 cm^{-1}; ^1H NMR 0.06 (3H, s), 0.07 (3H, s), 0.60 (1H, m), 0.77 (3H, s), 0.78 (3H, s), 0.88 (9H, s), 0.92 (3H, d, $J=6.9$ Hz), 1.17 (3H, s), 1.89 (1H, dd, $J=7.9$, 11.8 Hz), 2.05 (3H, s), 2.14 (1H, m), 3.10 (1H, dddd, $J=4.6$, 4.6, 10.9, 10.9 Hz), 3.32 (3H, s), 3.97 (1H, d, $J=10.8$ Hz), 4.01 (1H, dd, $J=7.8$, 10.6 Hz), 4.04 (1H, d, $J=10.8$ Hz), 4.43 (1H, ddd, $J=7.4$, 7.4, 7.4 Hz); NOE correlation from 23-H to 21-Me and to 27-Me; ^{13}C NMR (100.6 MHz) −4.8 (CH_3), −4.7 (CH_3), 12.3 (CH_3), 14.0 (CH_3), 16.6 (CH_3), 18.2 (C), 20.9 (CH_2), 20.9 (CH_3), 25.1 (CH_3), 25.8 (3× CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 34.9 (CH), 35.0 (CH), 35.8 (C), 36.9 (CH_2), 40.1 (CH_2), 40.5 (CH_2), 40.9 (C), 44.7 (CH), 54.4 (CH), 55.5 (CH_3), 56.2 (CH), 61.4 (CH), 70.6 (CH), 71.1 (CH_2), 78.0 (C), 79.8 (CH), 80.8 (CH), 116.7 (C), 170.8 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 562 (3), 545 (2), 287 (100); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4317. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.84; H, 10.26.

4.1.9. (22*S*,23*S*,25*S*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (27). To a solution of compound **25** (96 mg, 0.15 mmol) in THF (22 mL) was added TBAF (0.75 mL, 0.75 mmol, 1.0 M in THF) and stirred at room temperature for 2 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. A solution of the residue in MeOH (46 mL) containing KOH (1.5 g) was stirred at room temperature for 0.5 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) afforded compound **27** (48 mg, 0.10 mmol, 67%): mp 172.5–173.2 °C (from *n*-hexane-EtOAc); $[\alpha]_D$ +30.8 (*c* 0.12); IR 3352 cm^{-1}; ^1H NMR 0.62 (1H, m), 0.79 (3H, s), 0.94 (3H, s), 1.19 (3H, d, $J=7.3$ Hz), 1.25 (3H, s), 1.89 (1H, dd, $J=0.0$, 13.6 Hz), 2.19 (1H, dd, $J=4.9$, 13.7 Hz), 2.36 (1H, dddd, $J=2.0$, 7.2, 7.2, 7.2 Hz), 3.11 (1H, dddd, $J=4.6$, 4.6, 11.0, 11.0 Hz), 3.32 (3H, s), 3.33 (1H, d, $J=11.2$ Hz), 3.53 (1H, d, $J=11.2$ Hz), 3.93 (1H, dd, $J=0.0$, 4.8 Hz), 4.54 (1H, ddd, $J=7.8$, 7.8, 7.8 Hz); NOE correlation from 23-H to 21-Me; ^{13}C NMR (100.6 MHz) 12.2 (CH_3), 16.1

(CH_3), 19.3 (CH_3), 21.1 (CH_2), 26.1 (CH_3), 27.8 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 33.7 (2×CH_2), 34.3 (CH), 35.9 (C), 36.8 (CH_2), 38.6 (CH), 41.0 (CH_2), 41.4 (C), 42.2 (CH_2), 44.8 (CH), 54.6 (2×CH), 55.5 (CH_3), 64.2 (CH), 68.3 (CH_2), 74.8 (CH), 79.8 (CH), 82.4 (C), 83.8 (CH), 121.7 (C); MS *m/z* (rel intensity) 462 (M^+, <1), 444 (7), 426 (16), 287 (100); HRMS calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3326. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.77; H, 10.03.

4.1.10. (22*R*,23*S*,25*S*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (28). To a solution of compound **26** (83 mg, 0.13 mmol) in THF (19 mL) was added TBAF (0.65 mL, 0.65 mmol, 1.0 M in THF) and stirred at room temperature for 1 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. A solution of the residue in MeOH (40 mL) containing KOH (1.3 g) was stirred at room temperature for 0.5 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 6:4) afforded compound **28** (54 mg, 0.12 mmol, 87%): mp 183.8–184.2 °C (from *n*-hexane-EtOAc); $[\alpha]_D$ −46.7 (*c* 0.06); IR 3571, 3466 cm^{-1}; ^1H NMR 0.63 (1H, m), 0.77 (3H, s), 0.78 (3H, s), 0.94 (3H, d, *J*=7.0 Hz), 1.14 (3H, s), 1.97 (1H, dd, *J*=8.3, 12.3 Hz), 2.12 (1H, dd, *J*=10.5, 12.4 Hz), 2.31 (1H, dddd, *J*=6.9, 6.9, 6.9, 6.9 Hz), 3.10 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.29 (1H, d, *J*=10.3 Hz), 3.32 (3H, s), 3.44 (1H, d, *J*=11.3 Hz), 4.04 (1H, m), 4.55 (1H, ddd, *J*=7.1, 7.1, 8.7 Hz); NOE correlation from 23-H to 21-Me, to 20-H and to 27-Me; ^{13}C NMR (100.6 MHz) 12.2 (CH_3), 14.3 (CH_3), 16.4 (CH_3), 20.9 (CH_2), 24.6 (CH_3), 27.8 (CH_2), 28.6 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 34.2 (CH_2), 34.9 (CH), 35.0 (CH), 35.8 (C), 36.8 (CH_2), 38.1 (CH_2), 39.9 (CH_2), 41.1 (C), 44.7 (CH), 54.3 (CH), 55.5 (CH_3), 56.0 (CH), 61.7 (CH), 68.3 (CH_2), 72.2 (CH), 79.7 (CH, C-3), 82.0 (C), 82.3 (CH), 116.8 (C); MS *m/z* (rel intensity) 431 ($M^+ - CH_2OH$, 26), 413 (11), 287 (100); HRMS calcd for $C_{27}H_{43}O_4$ 431.3161; found 431.3106. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.75; H, 9.92.

4.1.11. (22*S*,23*S*,25*S*)-3β-Methoxy-5α-spirostan-23,25-diol (29). A solution of compound **28** (47 mg, 0.1 mmol) in $CHCl_3$ (2.4 mL) was treated with *p*-TsOH (5 mg dissolved in 0.5 mL $CHCl_3$) and stirred at room temperature for 1 h. The reaction mixture was neutralized with Amberjet 4400 OH, filtered and concentrated. Chromatotron chromatography (toluene-EtOAc, 60:40) of the residue afforded starting material **28** (30 mg, 0.06 mmol, 60%) and compound **29** (15 mg, 0.03 mmol, 30%). Compound **29**: mp 214–216 °C (from acetone); $[\alpha]_D$ −92.2 (*c* 0.09); IR 3579 cm^{-1}; ^1H NMR 0.64 (1H, m), 0.80 (6H, s), 1.00 (3H, d, *J*=7.0 Hz), 1.13 (3H, s), 1.56 (1H, dd, *J*=12.3, 12.3 Hz), 2.05 (1H, ddd, *J*=2.7, 5.3, 12.7 Hz), 2.56 (1H, dddd, *J*=6.9, 6.9, 6.9, 6.9 Hz), 3.11 (1H, dddd, *J*=4.7, 4.7, 10.9, 10.9 Hz), 3.23 (1H, dd, *J*=2.7, 11.6 Hz), 3.33 (3H, s), 3.62 (1H, d, *J*=11.5 Hz), 3.75 (1H, dd, *J*=5.3, 11.6 Hz), 4.45 (1H, ddd, *J*=7.1, 7.1, 7.1 Hz); NOE correlation from 23-H to 20-H, to 21-H_3 and from 26-H_b to 24-H_a; ^{13}C NMR (100.6 MHz) 12.3 (CH_3), 14.0 (CH_3), 16.6 (CH_3), 21.0 (CH_2), 24.8 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 31.7 (CH_2), 32.3 (CH_2), 34.3 (CH_2), 34.9 (CH), 35.7 (CH), 35.9 (C), 36.9 (CH_2), 40.1 (CH_2), 41.1 (C), 42.6 (CH_2), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 61.5 (CH), 64.3 (CH), 68.4 (CH_2), 70.3 (C), 79.8 (CH), 82.1 (CH), 110.5 (C); MS *m/z* (rel intensity) 462 (M^+, 6), 444 (3), 426 (3), 287 (100); HRMS calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3324. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.67; H, 10.17.

4.1.12. (22*S*,23*S*,25*R*)-3β-Methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (30) and (22*R*,23*S*,25*R*)-3β-methoxy-23-*tert*-butyldimethylsilyloxy-26-acetoxy-22,25-epoxy-5α-furostan (31). A solution of the alcohol **14**-*S* (49 mg, 0.08 mmol) in cyclohexane (8.6 mL) containing (diacetoxyiodo)benzene (52 mg, 0.16 mmol) and iodine (21 mg, 0.08 mmol) was irradiated with a 80 W tungsten-filament lamp at 70 °C for 1 h. The reaction mixture was then poured into aqueous solution of sodium thiosulfate (10%) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 93:7) of the residue afforded compound **30** (14 mg, 0.02 mmol, 28%) and compound **31** (23 mg, 0.04 mmol, 47%). Compound **30**: mp 144.0–144.7 °C (from EtOAc); $[\alpha]_D$ +24 (*c* 0.10); IR 1745 cm^{-1}; ^1H NMR 0.07 (3H, s), 0.08 (3H, s), 0.62 (1H, m), 0.80 (3H, s), 0.89 (3H, s), 0.91 (9H, s), 1.13 (3H, d, *J*=7.3 Hz), 1.34 (3H, s), 1.67 (1H, dd, *J*=2.3, 13.1 Hz), 2.06 (3H, s), 2.12 (1H, dd, *J*=5.12, 13.0 Hz), 2.33 (1H, m), 3.10 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.33 (3H, s), 3.98 (1H, d, *J*=10.7 Hz), 4.03 (1H, d, *J*=10.7 Hz), 4.18 (1H, dd, *J*=2.3, 5.0 Hz), 4.37 (1H, ddd, *J*=7.4, 7.4, 7.4 Hz); NOE correlation from 23-H to 21-Me and to 26-H_2; ^{13}C NMR (100.6 MHz) −5.2 (CH_3), −3.7 (CH_3), 12.3 (CH_3), 16.1 (CH_3), 17.7 (CH_3), 17.8 (C), 20.9 (CH_3), 21.1 (CH_2), 25.2 (CH_3), 25.9 (3× CH_3), 27.9 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 33.1 (CH_2), 34.3 (CH_2), 34.5 (CH), 35.1 (C), 36.9 (CH_2), 39.2 (CH), 40.9 (CH_2), 41.2 (C), 42.7 (CH_2), 44.8 (CH), 54.6 (CH), 54.9 (CH), 55.5 (CH_3), 62.8 (CH), 71.4 (CH_2), 76.9 (CH), 79.8 (CH), 80.5 (C), 81.9 (CH), 121.1 (C), 171.0 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 561 (5), 198 (100); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4321. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.80; H, 10.07. Compound **31**: mp 157.0–157.8 °C (from EtOAc); $[\alpha]_D$ −37.5 (*c* 0.12); IR 1746 cm^{-1}; ^1H NMR 0.04 (6H, s), 0.60 (1H, m), 0.76 (3H, s), 0.77 (3H, s), 0.85 (3H, d, *J*=5.3 Hz), 0.87 (9H, s), 1.28 (3H, s), 1.91 (1H, dd, *J*=10.6, 11.9 Hz), 2.02 (3H, s), 2.11 (1H, m), 3.07 (1H, dddd, *J*=4.5, 4.5, 10.8, 10.8 Hz), 3.29 (3H, s), 3.77 (1H, d, *J*=11.2 Hz), 3.93 (1H, d, *J*=11.2 Hz), 4.04 (1H, dd, *J*=8.1, 10.4 Hz), 4.48 (1H, ddd, *J*=7.3, 7.3, 7.3 Hz); NOE correlation from 23-H to 21-Me and to 20-H; ^{13}C NMR (100.6 MHz) −4.9 (CH_3), −4.8 (CH_3), 12.2 (CH_3), 13.9 (CH_3), 16.6 (CH_3), 18.2 (C), 20.8 (CH_3), 20.9 (CH_2), 25.8 (3×CH_3), 26.0 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 34.2 (CH_2), 35.0 (2×CH), 35.8 (C), 36.9 (CH_2), 40.1 (CH_2), 40.4 (CH_2), 40.9 (C), 44.7 (CH), 54.3 (CH), 55.4 (CH_3), 56.2 (CH), 61.6 (CH), 70.3 (CH_2), 71.2 (CH), 78.3 (C), 79.7 (CH), 80.8 (CH), 116.5 (C), 170.5 (C); MS *m/z* (rel intensity) 618 (M^+, <1), 561 (6), 545 (1), 75 (100); HRMS calcd for $C_{36}H_{62}O_6Si$ 618.4316; found 618.4303. Anal. Calcd for $C_{36}H_{62}O_6Si$: C, 69.86; H, 10.10. Found: C, 69.95; H, 10.13.

4.1.13. (22*S*,23*S*,25*R*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (32). To a solution of compound **30** (55 mg, 0.09 mmol) in THF (12.6 mL) was added TBAF (0.42 mL, 0.42 mmol, 1.0 M in THF) and stirred at room temperature for 3 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. A solution of the residue in MeOH (26 mL) containing KOH (0.9 g) was stirred at room temperature for 1.5 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) afforded compound **32** (41 mg, 0.09 mmol, 99%): mp 145.1–146.7 °C (from AcOEt); $[\alpha]_D$ +7.8 (*c* 0.09); IR 3629, 3448 cm^{-1}; ^1H NMR 0.62 (1H, m), 0.79 (3H, s), 0.93 (3H, s), 1.25 (3H, d, *J*=7.3 Hz), 1.31 (3H, s), 1.55 (1H, dd, *J*=0.0, 13.5 Hz), 2.46 (1H, dddd, *J*=3.1, 7.3, 7.3, 7.3 Hz), 2.56 (1H, dd, *J*=4.6, 13.6 Hz), 3.11 (1H, dddd, *J*=4.6, 4.6, 11.0, 11.0 Hz), 3.31 (1H, d, *J*=10.3 Hz), 3.32 (3H, s), 3.54 (1H, d, *J*=11.3 Hz), 4.15 (1H, dd, *J*=0.0, 4.5 Hz), 4.53 (1H, ddd, *J*=7.1, 7.1, 9.3 Hz); NOE correlation from 23-H to 21-H_3; ^{13}C NMR 12.2 (CH_3), 15.9 (CH_3), 18.7 (CH_3), 20.9 (CH_2), 25.8 (CH_3), 27.8 (CH_2), 28.6 (CH_2), 32.3 (CH_2), 33.5 (CH_2), 34.2 (CH_2), 34.4 (CH), 35.8 (C), 36.8 (CH_2), 38.4 (CH), 39.1 (CH_2), 40.5 (CH_2), 41.4 (C), 44.7 (CH), 54.5 (CH), 55.0 (CH), 55.4 (CH_3), 64.6 (CH), 68.3 (CH_2), 76.7 (CH), 79.8 (CH), 83.1 (CH), 84.4 (C), 120.6 (C); MS *m*/*z* (rel intensity) 444 (M^+-H_2O, 5), 426 (34), 287 (100); HRMS calcd for $C_{28}H_{44}O_4$ 444.3240; found 444.3239. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.85; H, 9.74.

4.1.14. (22*R*,23*S*,25*R*)-3β-Methoxy-22,25-epoxy-5α-furostan-23,26-diol (33). To a solution of compound **31** (108 mg, 0.17 mmol) in THF (25 mL) was added TBAF (0.84 mL, 0.84 mmol, 1.0 M in THF) and stirred at room temperature for 1 h. The mixture was then poured into aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. A solution of the residue in MeOH (50 mL) containing KOH (1.7 g) was stirred at room temperature for 5 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatotron chromatography (hexanes–EtOAc, 7:3) afforded compound **33** (74 mg, 0.16 mmol, 91%): mp 198.5–199.7 °C (from *n*-hexane-EtOAc); $[\alpha]_D$ −47.7 (*c* 0.13); IR 3567 mmolcm^{-1}; ^1H NMR 0.64 (1H, m), 0.77 (3H, s), 0.79 (3H, s), 0.95 (3H, d, *J*=7.0 Hz), 1.26 (3H, s), 1.69 (1H, dd, *J*=9.8, 12.4 Hz), 2.32 (1H, dd, *J*=8.5, 12.4 Hz), 3.10 (1H, dddd, *J*=4.6, 4.6, 11.0, 11.0 Hz), 3.30 (1H, d, *J*=11.0 Hz), 3.32 (3H, s), 3.39 (1H, d, *J*=11.3 Hz), 4.03 (1H, ddd, *J*=9.0, 9.0, 9.0 Hz), 4.55 (1H, ddd, *J*=6.6, 6.6, 8.7 Hz); NOE correlation from 23 to 21-Me, to 20-H and to 26-H_2; ^{13}C NMR (100.6 MHz) 12.2 (CH_3), 14.3 (CH_3), 16.4 (CH_3), 20.9 (CH_2), 25.6 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 34.3 (CH_2), 34.9 (CH), 35.5 (CH), 35.8 (C), 36.8 (CH_2), 40.0 (CH_2), 41.0 (C), 41.3 (CH_2), 44.7 (CH), 54.3 (CH), 55.5 (CH_3), 56.1 (CH), 61.8 (CH), 69.8 (CH_2), 72.2 (CH), 79.7 (CH), 81.3 (CH), 81.3 (C), 116.7 (C); MS *m*/*z* (rel intensity) 444 (M^+-H_2O, 5), 426 (27), 287 (100); HRMS calcd for $C_{28}H_{44}O_4$ 444.3240; found 444.3252. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.72; H, 9.98.

4.1.15. (22*S*,23*S*,25*R*)-3β-Methoxy-22,26-epoxy-5α-spirostan-23,25-diol (34). A solution of compound **33** (46 mg, 0.1 mmol) in $CHCl_3$ (2.5 mL) was treated with *p*-TsOH (5 mg dissolved in 0.5 mL $CHCl_3$) and stirred at room temperature for 24 h. The reaction mixture was neutralized with Amberjet 4400 OH, filtered and concentrated. Chromatotron chromatography (toluene-EtOAc, 65:35) of the residue afforded starting material **33** (31 mg, 0.06 mmol, 60%) and compound **34** (13 mg, 0.03 mmol, 30%). Compound **34**: mp 263–263.5 °C (from acetone); $[\alpha]_D$ −132.8 (*c* 0.07); IR 3576 cm^{-1}; ^1H NMR 0.64 (1H, m), 0.79 (3H, s), 0.80 (3H, s), 0.95 (3H, d, *J*=7.0 Hz), 1.30 (3H, s), 1.99 (1H, ddd, *J*=5.5, 7.6, 12.3 Hz), 2.07 (1H, ddd, *J*=2.5, 5.2, 11.6 Hz), 2.50 (1H, dddd, *J*=7.0, 7.0, 7.0, 7.0 Hz), 3.11 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.19 (1H, dd, *J*=2.5, 10.4 Hz), 3.33 (3H, s), 3.49 (1H, dd, *J*=5.3, 11.7 Hz), 3.50 (1H, d, *J*=10.2 Hz), 4.46 (1H, ddd, *J*=7.1, 7.1, 8.7 Hz); NOE correlation from 23-H to 20-H, to 21-H_3; ^{13}C NMR (100.6 MHz) 12.3 (CH_3), 13.9 (CH_3), 16.6 (CH_3), 21.0 (CH_2), 25.0 (CH_3), 27.8 (CH_2), 28.7 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 34.3 (CH_2), 34.9 (CH), 35.6 (CH), 35.9 (C), 36.9 (CH_2), 40.1 (CH_2), 41.0 (C), 44.6 (CH_2), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.2 (CH), 61.5 (CH), 65.8 (CH), 68.2 (CH_2), 68.9 (C), 79.8 (CH), 82.0 (CH), 110.0 (C); MS *m*/*z* (rel intensity) 462 (M^+, 1), 444 (2), 426 (5), 287 (100); HRMS calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3336. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.89; H, 10.13.

4.1.16. (22*S*,23*S*,25*R*)-3β-Methoxy-23-acetoxy-5α-spirostan-23,25-diol (35). The compound **34** (4 mg, 8.6×10^{-3} mmol) was acetylated with Ac_2O and pyridine to give after chromatography (hexanes–EtOAc, 85:15) compound **35** (3 mg, 5.9×10^{-3} mmol, 68%): amorphous; $[\alpha]_D$ −72.0 (*c* 0.05); IR 3434, 1745 cm^{-1}; ^1H NMR 0.64 (1H, m), 0.78 (3H, s), 0.80 (3H, s), 0.96 (3H, d, *J*=7.0 Hz), 1.37 (3H, s), 2.04 (3H, s), 2.07 (1H, m), 3.12 (1H, dddd, *J*=4.6, 4.6, 10.9, 10.9 Hz), 3.22 (1H, dd, *J*=2.0, 10.5 Hz), 3.33 (3H, s), 3.60 (1H, d, *J*=10.6 Hz), 4.45 (1H, ddd, *J*=7.7, 7.7, 7.7 Hz), 4.84 (1H, dd, *J*=5.3, 11.9 Hz); NOE correlation from 23-H to 20-H, to 21-H_3 and to 27-H_3; ^{13}C NMR (100.6 MHz) 12.3 (CH_3), 13.9 (CH_3), 16.1 (CH_3), 20.9 (CH_2), 21.0 (CH_3), 25.3 (CH_3), 27.9 (CH_2), 28.7 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 34.3 (CH_2), 35.2 (CH), 35.9 (C), 36.0 (CH), 36.9 (CH_2), 39.9 (CH_2), 40.3 (CH_2), 41.1 (C), 44.8 (CH), 54.4 (CH), 55.5 (CH_3), 56.3 (CH), 61.5 (CH), 66.7 (CH), 68.1 (CH_2), 69.0 (C), 79.8 (CH), 81.6 (CH), 108.2 (C), 170.4 (C); MS *m*/*z* (rel intensity) 504 (M^+, 3), 486 (6), 444 (31), 287 (100); HRMS calcd for $C_{30}H_{48}O_6$ 504.3451; found 504.3418. Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.27; H, 9.84.

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Supplementary data

Detailed experimental procedures, and spectral and analytical data for compounds **6**-*R*, **6**-*S*, **7**-*R*, **7**-*S*, **8**-*R*, **8**-*S*, **9**-*R*, **9**-*S*, **10**-*R*, **10**-*S*, **11**-*S*, **12**-*R*, **12**-*S*, **13**-*S*, **14**-*R*, and **14**-*S* (15 pages) are provided. A figure with the pseudorotational wheels for E and F-rings is also included.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.077

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