Tetrahedron Vol. 43, No. 9, pp. 2045 to 2057, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

AN APPROACH TO BUFADIENOLIDES FROM DEOXYCHOLIC ACID - 1.

STRATEGY AND SYNTHESIS OF A MODEL BUFADIENOLIDE

Hans Wolfgang Hoppe, Manfred Kaiser, Dietrich Müller, and Peter Welzel*

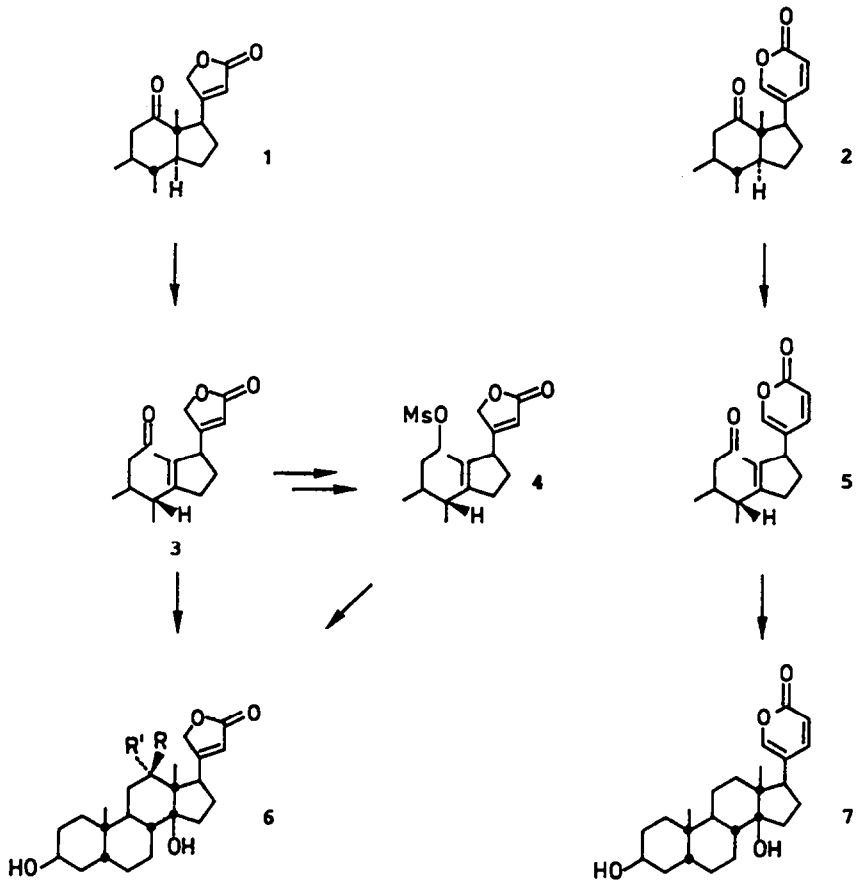
Fakultät für Chemie der Ruhr-Universität
Postfach 102148, D-4630 Bochum (FRG)

(*Received in Germany* 14 *January* 1987)

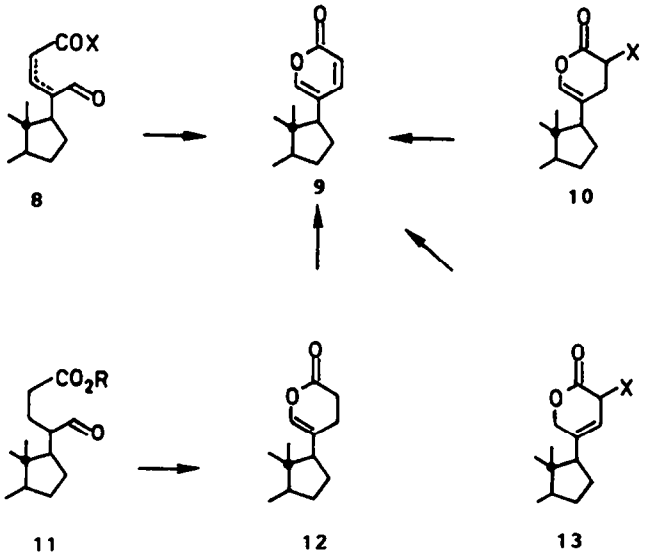
Abstract - A new procedure for the conversion of deoxycholic acid (14) to bufadienolide 27 is reported.

The cardiac glycosides which have been used in medicine for more than 200 years still belong to the most prescribed drugs. Because of their ability to slow the heart rate and, at the same time, to increase the contractibility of the heart muscle they are used in the treatment of heart deseases. A serious problem is, however, the dangerously high toxicity of these compounds. From structure-activity studies it is known that the cardioactive properties are exclusively associated with the steroid aglycone portions of the cardiac glycosides.[1] The heart-active steroids can be devided into the cardenolides (exemplified by digitoxigenine (6, R, R'=H)) and the bufadienolides (exemplified by bufalin (7)). Prominent in their structures are (i) cis-fusion of rings B and C, (ii) an oxygen functionality in the 14-position, and (iii) an unsaturated lactone grouping in the 17ß-position. The lactone consists of a butenolide ring in the case of cardenolides, and an α-pyrone ring in the case of bufadienolides. There has been a longstanding interest in developing efficient methodologies for the synthesis of cardiotonic steroids with the aim of making available structural analogues with an improved therapeutic index.[2] Behind such efforts a realistic background seems to exist. In the rat two different types of cardiac glycoside receptors mediating positive inotropy and toxicity have been identified. If two types of receptors could also be distinguished in human heart, there would be hope that more specific and saver drugs could be developed.[4] Recently, we have introduced a novel strategy for the synthesis of cardenolides, such as 6.[5] This approach is centered around a new method for the conversion of 14α-H into 14ß-OH steroids. For example, photochemical isomerization of the 12-oxo-14α-cardenolide 1 gave the unsaturated secoaldehyde 3 which under Prins conditions cyclized to the 12,14-diols 6 (R or R'=OH), whereas mesylate 4 obtained from 3 in two steps yielded 6 (R=R'=H) on solvolysis.

It occurred to us that one could make use of this procedure in a new bufadienolide synthesis. Different from the cardenolide case, however, introduction of the 14-OH group cannot be postponed to the last stage of the synthesis. It appears impossible to effect selectively the desired photochemical rearrangement of a 12-oxo bufadienolide such as 2 into 5 by irradiation into the $n\text{-}\pi^*$-band of the keto group since it is well-known that α-pyrones absorb at the same wavelength (300 nm) and react from the excited state(s) to give formyl ketenes.[6]

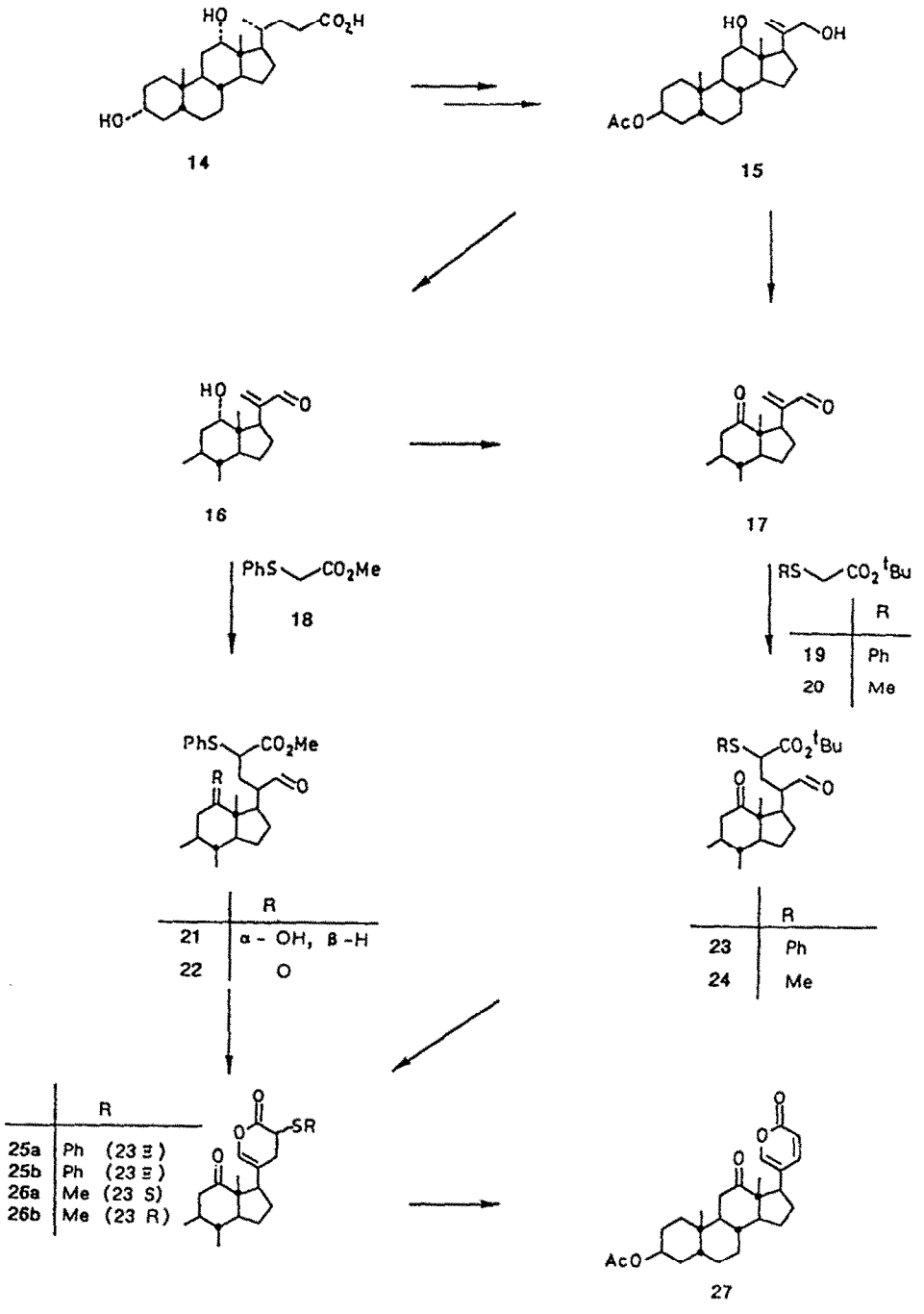


Scheme 1.



Scheme 2.

In earlier bufadienolide synthetic studies the α-pyrone ring has been elaborated either directly by cyclization of unsaturated esters of type **8**,[7] or from dihydro precursors of types **12**,[8] **10**, [9,10] and **13**.[11,12] Our conceptual approach was to introduce the 14β-OH group into a 20-bufenolide of type **10** (X=SR) and form the

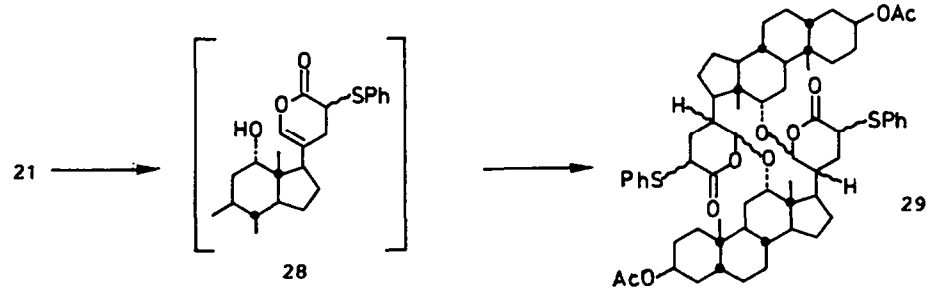


Scheme 3.

missing double bond in the final stage of the synthesis using the methodology developed by Trost.[13,14] As in our cardenolide synthesis,[5] deoxycholic acid (14) was selected as starting material since it has the correct configuration at C-5 and an oxygen functionality at C-12 which is necessary for the 14β-hydroxylation. 14 was transformed into 16 by (a) Iwasaki degradation, (b) Mitsunobu reaction, (c) photooxygenation-reduction, and (d) MnO_2 oxidation, as already described.[5] Swern oxidation [15] of 16 gave 17 in 90% yield. 17 was also obtained directly from 15 using the Swern procedure but the yield was lower (70%). What follows in this

article is (i) a description of experiments aimed at the synthesis of bufenolides **25** and **26** from **16** and **17** involving a Michael addition as a key feature, and (ii) the conversion of **25** and **26** into bufadienolide **27**.[16]

Reaction of **16** with the stabilized anion prepared from **18** with sodium methoxide proceeded cleanly in the 1,4-mode to give **21** as a 1.5 (**21a**) : 1.6 (**21b**) : 2.0 (**21c**) : 1 (**21d**) mixture of diastereoisomers isomeric at the newly created chiral centres at C-20 and C-23. Medium-pressure liquid chromatography (MPLC) provided pure **21a** and **21b** whereas **21c** and **21d** could not be separated. The rather complex CD spectra of these compounds (see Experimental) could not be assigned with certainty. Since **21a** and **21b** give CD-curves of enantiomorphic appearance they presumably differ in their configuration both at C-20 and C-23. PCC oxidation [18] of **21a** and **21b** furnished **22a** and **22b**, respectively, and from the mixture of **21c** and **21d** ketones **22c** and **22d** were obtained which could be separated at this stage. **22d** was rather unstable and rearranged into **22c**. Again, we were unable to deduce the configuration at C-20 and C-23 from the CD spectra.



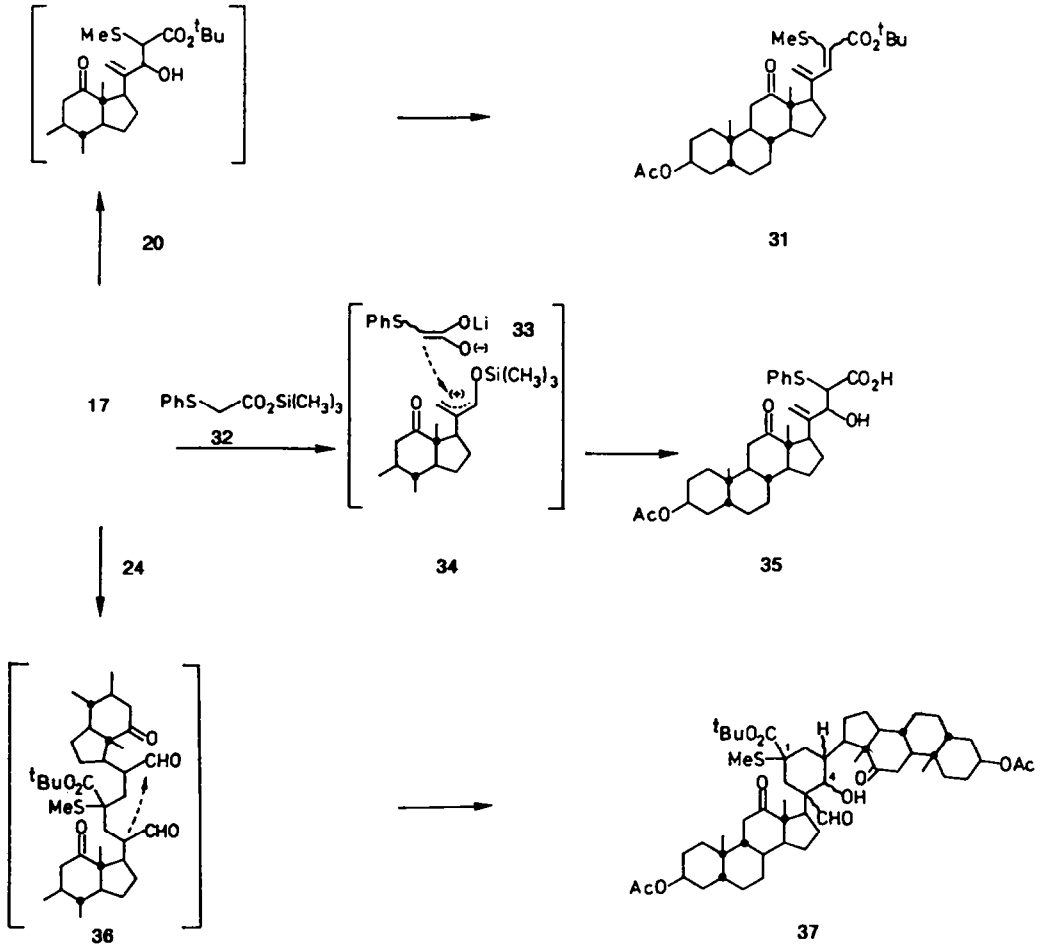
Scheme 4.

Our intention was then to prepare the desired bufenolides from **21** and **22** using the two-step procedure of Pettit [19] which consists of selective saponification of the methyl ester and subsequent enollactonization with a catalytic amount of p-toluenesulfonic acid in refluxing benzene. When **21a**, **21b**, and the **21c/21d** mixture were individually subjected to these reaction conditions the same mixture of 4 compounds was formed (64% combined yield) from which two pure components could be isolated by MPLC. FAB-MS revealed immediately that instead of the desired enollactones **28** stereoisomeric dimers had been formed (m/z=1077,corresponding to $(M+H)^+$). Based on extensive spectroscopic studies the general structure **29** was assigned to these products. The ^{13}C NMR specta of both compounds displayed only one set of (30) signals indicating C_2 symmetry. The absence of a hydroxyl group was both apparent from the ^1H NMR (after addition of 1 equiv of trichloroacetyl isocyanate [20]) and the IR spectrum. In keeping with this an ether function in the 12-position was indicated by the large downfield shift of the C-12 signal (12 ppm) as compared to the 12-OH compounds **21a** and **21b** which is caused by the ß-effect of the O-substituent. The appearance of a ^1H NMR signal at δ= 5.6 and a ^{13}C NMR signal at δ =103 clearly points to the presence of an acetal unit.

In order to bypass the complications caused by the 12-OH group the 12-oxo compounds **22a**, **22b**, and the mixture of **22c** and **22d** were individually subjected to Pettit's hydrolysis-enollactonization procedure. In each case a 1:1 mixture of the epimeric enollactones **25a** and **25b** was obtained (60% combined yield) which was separated by MPLC. The configuration at C-23 of these compounds is at present unknown. An analysis of their 250 MHz ^1H NMR spectra (**25a**: $J_{22',23}$=4.0 Hz, $J_{22,23}$=6.0 Hz; **25b**: $J_{22',23}$=4.9 Hz, $J_{22,23}$=6.0 Hz) indicated that both in **25a** and **25b** the phenylsulfanyl substituent adopts an axial position.[21]

All attempts to cyclize methyl ester **22** directly [22] to enollactones **25a,b** met with no success. [23] We therefore examined the possibility of preparing the free acid

corresponding to 22 by reaction of 17 with the ester enolate derived from silyl ester 32. Unfortunately, only 1,2-adduct 35 was formed (after aqueous work-up) in 85% yield. We explain this rather unexpected result by a silyl group transfer from the anion of 32 to the aldehyde group of 17 giving the dianion 33 and the allyl cation 34 which react together to give an enol silyl ether from which 35 is formed under the work-up conditions. In a more practical route to enollactones such as 25a and 25b the unsaturated aldehyde 17 was then reacted with the anion derived from tert-butyl ester 19 to give 23 (mixture of diastereoisomers) in 75% yield. The analogous reaction of 17 with the ester enolate of the methylsulfanyl compound 20 provided 24 (mixture of stereoisomers) in moderate yield (38%) along with 31 (two stereoisomers, 8% combined yield) and 37 (5%). 37 is obviously formed by deprotonation of 24, followed by Michael addition to 24 (to give 36) and an intramolecular aldol reaction. 31 is derived from the 1,2-adduct 30. The structural assignments are consistent with the spectroscopic properties (see Experimental). The configuration at the newly created chiral centres of 37 and at C-23 of 31 has not been determined.



Scheme 5.

As hoped for and in contrast to a report by Kreiser et al.,[24] refluxing a benzene solution of 23 (mixture of diastereoisomers) in the presence of p-toluenesulfonic acid (1 equiv) provided 25a and 25b directly in 90% total yield. Similarly, the

direct cyclization of **24** (mixture of stereoisomers) furnished **26a** and **26b** (83%, 1:1 ratio) which were separated by MPLC. The assignment of the configuration at C-23 in **26a** and **26b** is based on their CD spectra which will be discussed in a later publication.

To complete the synthesis of **27** the bufenolides **25a** and **25b** were separately oxidized with sodium metaperiodate in methanol-water as described by Trost et al., [13] and the reaction mixtures were then heated in sealed tubes to 140° C for 1.5h to give **27** in 52% and 47% yield, respectively. Similarily, a mixture of **26a** and **26b** was oxidized at -78° C with m-chloroperbenzoic acid in CH_2Cl_2 solution.[13] Warming to room temperature caused already elimination to furnish **27** in 84% yield.

EXPERIMENTAL

General

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Sensitive liquids and solutions were transferred by syringe, and were introduced into the reaction flasks through rubber septa. Usual work-up means partitioning the reaction mixture between water and an organic solvent (given in parenthesis), drying the combined organic solutions over Na_2SO_4 and removal of the solvent by distillation in vacuo at 40°C using a rotatory evaporator. The instrumentation used was: ^1H NMR: T 60 (Varian); WP 80 (Bruker); WH-250 Bruker, AM-400 (Bruker); ^{13}C NMR: AM-400 (Bruker); IR: Perkin Elmer 257; MS: MAT-731 and MAT-CH-5 (Finnigan); MPLC: Medium-pressure chromatography using 31.0 cm x 2.5 cm glass tubes, silica gel Grace (50 m), Duramat pump (CfG); Thomachrom UV detector (Reichelt). The FAB mass spectra were obtained using a Finnigan MAT-731 instrument. Samples were dissolved in DMSO, and the matrix (triethyl citrate) was added. The solutions were placed on a stainless steel probe tip [25] and bombarded with 6 KeV Xenon from a modified Saddle Field Ion Source.

Methyl phenylsulfanylacetate (18).[26]

Starting with phenylsulfanylacetic acid, the Fischer esterification method [27] was used : yield 90%.

tert-Butyl methylsulfanylacetate (20).

Methylsulfanylacetic acid (7.0 ml, 0.08 mmol) and $SOCl_2$ (9.0 ml, 0.12 mmol) were heated to 60°C for 30 min. Excess $SOCl_2$ was removed by evaporation at 30°C/ 1.86 kPa. To a solution of the acid chloride in dry ether (19 ml) tert-butyl alcohol (8.0 ml, 0.08 mmol) and dimethylaniline (12.0 ml, 0.09 mmol) were added at 0°C, and the reaction mixture was stirred at 20°C for 12 h. After addition of ether (50 ml) the solution was washed with 2N HCl (3x) and with 5% $NaHCO_3$ (2x30 ml), dried over Na_2SO_4 and evaporated. Short-path distillation (30-32°C/ 13.3 Pa) gave **20** (6.4g, 50%).-IR (CCl_4): 1720 cm^{-1} (CO).- ^1H NMR (60 MHz, CCl_4): δ=1.42 (s,$OC(CH_3)_3$), 2.13 (s,SCH_3), 2.94 (s,CH_2).- (Found: C, 51.87; H, 8.73. $C_7H_{14}O_2S$ (162.2) requires C, 51.82; H, 8.70).

tert-Butyl phenylsulfanylacetate (19).

Starting with phenylsulfanylacetic acid, the above procedure was used: yield 50%.- B.p. 111°C/13.3 Pa.- IR (CCl_4): 1720 cm^{-1} (CO).- ^1H NMR (60 MHz,CCl_4): δ=1.33 (s, $OC(CH_3)_3$), 3.37 (s,CH_2), 6.93-7.33 (Ar-H).- (Found: C, 64.30; H, 7.21. $C_{12}H_{16}O_2S$ (224.3) requires C, 64.25; H, 7.19).

Trimethylsilyl phenylsulfanylacetate (32).

a) To a suspension of NaH (55% in oil, 0.67g, 15 mmol) in CH_2Cl_2 at 0°C was added

slowly a solution of phenylsulfanylacetic acid (2.0g, 12 mmol) in dry CH_2Cl_2 (30 ml). The reaction mixture was then refluxed for 55 min. At 0°C Me_3SiCl (6 ml, 47 mmol) was added and the mixture refluxed for 12h. Evaporation of the solvent and distillation at 82°C/5.3 Pa gave **32** (2.2 g, 76%).

b) To a solution of phenylsulfanylacetic acid (1.09 g, 6.48 mmol) in dry CH_2Cl_2 (1.5 ml) at ambient temp. was slowly (exothermic reaction) added the trimethylsilyl ketene acetal derived from methyl propionate [28] (1.5 ml, 8.87 mmol). The mixture was stirred at 20°C for 1h. Evaporation of the solvent, methyl propionate, and of excess ketene acetal under reduced pressure gave **32** (1.6g, 100%) which was used without further purification.- IR (CCl_4): 1710 cm^{-1} (CO).- ^1H NMR (CCl_4): δ=0.22 (s,$Si(CH_3)_3$), 3.47 (s,CH_2), 6.73-7.33 (Ar-H).-Found: 240.0640 (MS). Calc for $C_{11}H_{16}O_2SSi$: 240.0627.

3β-Acetoxy-12-oxo-23,24-dinor-5β-chol-20-en-22-al (17).

a) Swern oxidation of **16**: To a solution of oxalyl chloride (28.5 µl, 0.33 mmol) in anhydrous CH_2Cl_2 (0.75 ml) at -55°C was slowly added a solution of dry DMSO (50 µl, 0.70 mmol) in anhydrous CH_2Cl_2 (150 µl). After 5 min, to the stirred solution was slowly added at -55°C a solution of **16** (117.0 mg, 0.30 mmol) in CH_2Cl_2 (0.30 ml). After 30 min at -55°C triethylamine (0.25 ml) was added and the reaction mixture warmed to ambient temp. Usual work-up (ethyl acetate) and MPLC (hexanes - acetone 10:1) furnished **17** (105.5 mg, 90%).

b) Using the above procedure **15** (121.2 mg, 0.3 mmol) was oxidized with DMSO (98 µl, 1.4 mmol) and oxalyl chloride (58.7 µl, 0.7 mmol) to give **17** (84.0 mg, 70%).- M.p. 140-142°C (from CH_2Cl_2-hexanes).- IR (CCl_4): 1735 (ester), 1705 (ketone), 1615 cm^{-1} (C=C).- ^1H NMR (80 MHz, $CDCl_3$):δ=0.96 (s,CH_3-18), 1.09 (s,CH_3-19), 2.07 (s,3β-OAc), 3.09-3.45 (m,$W_{1/2}$= 6.0 Hz, 3α-H), 6.11 and 6.19 (CH_2-21), 9.57 (s, 22-H).- MS: m/z (%)= 386 (5, M^+), 358 (100), 314 (63), 255 (54).- (Found: C, 74.65; H, 8.89. $C_{24}H_{34}O_4$ (386.5) requires C, 74.58; H, 8.87).

Reaction of **16** with **18**.

Sodium methoxide was prepared from sodium (2.3 mg, 0.1 mmol) and dry methanol (1 ml). Excess methanol was removed by evaporation. A solution of **18** (980 mg, 5.3 mmol) in dry DMF (10 ml) was added to the sodium methoxide and the mixture stirred for 5 min at 20°C. A solution of **16** (590 mg, 1.5 mmol) in dry DMF (20 ml) was then rapidly added dropwise at 20°C. This mixture was stirred at 20°C for 20 min and then quenched with dilute HCl. Usual work-up (CH_2Cl_2) and MPLC (hexanes - ethyl acetate 7:2 → 7:4) afforded **21a** (151.3 mg), a mixture of **21a** and **21b** (79.1 mg), **21b** (202.2 mg), a mixture of **21b**, **21c**, **21d** (15.0 mg), a 2:1 mixture (^1H NMR) of **21c** and **21d** (390.0 mg). Total yield of **21a**, **21b**, **21c**, **21d**: 837.5 mg (90%).-

Methyl (23*E*)-3β-acetoxy-12α-hydroxy-21-oxo-23-phenylsulfanyl-5β,20*E*-cholan-24-oate (**21a**, **21b**, **21c**, **21d**).

21a: M.p. 150-152°C (from CH_2Cl_2-hexanes).- IR (CCl_4): 3600-3400 (OH), 1740 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$):δ= 0.70 (s,CH_3-18), 0.96 (s,CH_3-19), 2.05 (s,3β-OAc), 3.50-4.00 (m, 2H), 3.65 (s,OCH_3), 5.09 (m, $W_{1/2}$= 7.2 Hz, 3α-H), 7.20-7.55 (Ar-H), 9.55 (d, J= 3.6 Hz, 21-H).- ^{13}C NMR: see Table 1.- CD (CH_3CN): λ_{max} (Δε)= 329 (-0.18), 319 (-0.13), 274 (+2.74), 233 (-1.15), 219 (+2.12), 197 nm (+3.16).- MS: m/z (%) = 570 (4, M^+), 358 (53), 298 (28), 194 (100), 182 (31), 135 (46).- (Found: C, 69.38; H, 8.10. $C_{33}H_{46}O_6S$ (570.8) requires C, 69.44; H, 8.12).

21b: IR (CCl_4): 3600-3300 (OH), 1720 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ= 0.62 (s,CH_3-18), 0.92 (s,CH_3-19), 1.58 (OH), 2.06 (s,3β-OAc), 3.43-3.85 (m, 2 H), 3.67 (s,OCH_3), 5.08 (m, $W_{1/2}$= 7.2 Hz, 3α-H), 7.21-7.65 (Ar-H), 9.75 (d, J= 3.1 Hz, 21-H).- ^{13}C NMR: see Table 1.- CD (CH_3CN):λmax (Δε)= 312 (+0.47), 271 (-2.86), 233

(+0.43), 219 (-1.66), 194 nm (-4.64).- MS: m/z (%)= 570 (4, $M^{+\cdot}$), 538 (12), 376 (27), 358 (71), 298 (57), 194 (100), 182 (34), 135 (70).
21c,d (2:1 mixture): IR (CCl_4): 3600-3300 (OH), 1725 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$) δ= 0.68 (s,CH_3-18 of **21c**), 0.72 (s,CH_3-18 of **21d**), 0.97 (s,CH_3-19 of **21c**), 0.99 (s,CH_3-19 of **21d**), 2.05 (s,3ß-OAc of **21c**), 2.06 (s,3ß-OAc of **21d**), 3.41 -3.91 (m, 2H), 3.70 (s,OCH_3), 5.08 (m, $W_{1/2}$=7.2 Hz, 3α-H), 7.20 - 7.65 (Ar-H), 9.60 (d, J=3.6 Hz, 21-H of **21d**), 9.75 (d, J=3.6 Hz, 21-H of **21c**).- CD (CH_3CN): $_{max}$ ( )= 314 (+0.32), 271 (+0.95), 231 (-0.65), 207 (-0.26), 199 nm (+0.94).- Found: 570.3015 (MS). Calc for $C_{33}H_{46}O_6S$: 570.3015.

Oxidation of 21a, 21b, and the 21c/21d mixture.

To a suspension of pyridinium chlorochromate (77.8 mg, 0.36 mmol) and sodium acetate trihydrate (9.8 mg, 0.07 mmol) in CH_2Cl_2 (0.4 ml) was rapidly added dropwise a solution of **21c/21d** (2:1 mixture, 137.1 mg, 0.24 mmol) in dry CH_2Cl_2 (0.5 ml). The mixture was stirred for 90 min at 20°C. Dry diethyl ether (3 ml) was added. The supernatant liquid was separated by decantation, and the residue was washed thoroughly with ether. The combined ether solutions were filterd through a pad of silica gel. Following solvent evaporation the residue was separated by MPLC (hexanes - ethyl acetate 7:3) to furnish **22d** (21 mg), a mixture of **22d** and **22c** (64 mg), and **22c** (21 mg). Total yield of **22c** and **22d**: 106.0 mg (80%).
Using the above procedure **22a** was obtained from **21a** (65%) and **22b** from **21b** (78%).

Methyl (23Ξ)-3ß-acetoxy-12,21-dioxo-23-phenylsulfanyl-5ß,21Ξ-cholan-24-oate (22a, 22b, 22c, 22d).

22a: IR (CCl_4): 1740 and 1715 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$):δ= 1.04 (s,CH_3-18), 1.08 (s,CH_3-19), 2.08 (s,3ß-OAc), 3.41-3.72 (m, 1H), 3.68 (s,OCH_3), 5.08 (m, $W_{1/2}$= 7.0 Hz, 3-αH), 7.18-7.66 (Ar-H), 9.70 (d, J= 3.5 Hz, 21-H).- CD (CH_3CN):$^{\lambda}$ max (Δε)=319 (-0.16), 309 (+0.8), 276 (+1.82), 243 (-0.41), 221 nm (+1.08).- MS: m/z (%) = 568 (4, $M^{+\cdot}$), 508 (35), 387 (50), 374 (100), 341 (93).
22b: M.p. 138-140°C (from CH_2Cl_2-hexanes).- IR (CCl_4): 1730 and 1700 cm^{-1} (CO).- ^1H NMR (80 MHZ, $CDCl_3$): δ= 0.99 (s,CH_3-18), 1.03 (s,CH_3-19), 2.04 (s,3ß-OAc), 3.39-3.75 (m, 1H), 3.66 (s,OCH_3), 5.07 (m, $W_{1/2}$= 6.5 Hz, 3α-H), 7.08-7.62 (Ar-H), 9.50 (d, J=4.1 Hz, 21-H).- CD(CH_3CN): λ_{max} (Δε)= 324 (+0.18), 307 (+0.69), 271 (-3.04), 233 (+0.95), 220 (-1.71), 195 nm (-6.61).- MS: m/z (%) = 568 (1,$M^{+\cdot}$), 508 (76), 374 (79), 341 (100).- (Found: C, 69.88; H, 7.88. $C_{33}H_{44}O_6S$ (568.8) requires C, 69.69; H, 7.80).
22c: M.p.: 153-155°C (from CH_2Cl_2-hexanes).- IR (CCl_4): 1745 and 1715 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ= 0.90 (s,CH_3-18), 0.93 (s,CH_3-19), 1.93 (s,3ß-OAc), 3.14-3.60 (m, 1H), 3.47 (s,OCH_3), 4.85 (m, $W_{1/2}$= 5.5 Hz, 3α-H), 7.03-7.48 (Ar-H), 9.34 (d,J= 5.1Hz, 21-H).- CD (CH_3CN): λ_{max} (Δε) = 308 (+0.90), 276 (+3.91), 230 (-2.58), 205 nm (-3.64).- MS: m/z (%) = 568 (4, $M^{+\cdot}$), 508 (40), 387 (53), 374 (91), 341 (100).- (Found: C, 69.64; H, 7.87. $C_{33}H_{44}O_6S$ (568.8) requires C, 69.69; H, 7.80).
22d: IR (CCl_4): 1740 and 1715 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.02 (s,CH_3-18), 1.07 (s,CH_3-19), 2.04 (s,3ß-OAc), 3.44-3.69 (m, 1H), 3.62 (s,OCH_3), 5.07 (m, $W_{1/2}$=6.6 Hz, 3α-H), 7.01-7.48 (Ar-H), 9.34 (d, J=5.1 Hz, 21-H).- MS: m/z (%) = 568 (1, $M^{+\cdot}$), 508 (100), 387 (16), 374 (64), 341 (88).

Dimers 29.

To a stirred solution of **21c/21d** (2:1 mixture, 81.7 mg (0.14 mmol)) in THF (6 ml) and methanol (3 ml) at 20°C was slowly added 5% aqueous $NaHCO_3$ solution (5 ml). The mixture was left at 20°C for 30 min and then neutralized with dilute HCl. After usual work-up (CH_2Cl_2) the residue (65 mg) was dissolved in dry benzene (20 ml), and the mixture was refluxed after addition of p-toluenesulfonic acid (1.8 mg, 0.01

mmol) for 20h using a Soxhlet apparatus charged with 4 A molecular sieves (2g) to remove water. After cooling to 20°C the mixture was washed with 5% $NaHCO_3$ solution. Solvent evaporation followed by MPLC (hexanes -ethyl acetate 9:2) furnished **29a** (11.0 mg), a 1:1 mixture (^{1}H NMR) of **29b** and **29c** (16.7 mg), a mixture of **29b**, **29c**, and **29d** (9.0 mg), and **29d** (10.8 mg). Total yield of **29a**, **29b**, **29c**, **29d**: 47.4 mg (64% ,based on **21c/21d**). Using the above procedure **21a** and **21b** were individually converted into the same mixture of **29a**, **29b**, **29c**, and **29d**.

29a: M.p.: 264-267°C (from CH_2Cl_2-hexanes).- IR (CCl_4): 1740 and 1770 cm^{-1} (CO).- ^{1}H NMR (250 MHz, $CDCl_3$): δ= 0.76 (s,CH_3-18), 0.98 (s,CH_3-19), 2.09 (s,3ß-OAc), 3.72 (m, $W_{1/2}$= 7.9Hz, 12ß-H), 4.18 (X-part of an ABX system $J_{23,22+J23,22'}$ =18.7 Hz, 23-H), 4.81 (m,$W_{1/2}$= 7.9Hz, 3α-H), 5.45 (broad s, 21-H), 7.22-7.73 (Ar-H).- ^{13}C NMR: see Table 1.- FAB-MS: m/z = 1077 ($(M+H)^+$).

29b/29c: IR (CCl_4): 1740 and 1770 cm^{-1} (CO).- ^{1}H NMR (250 MHz, $CDCl_3$):δ= 0.77 and 0.78 (2s, CH_3-18 of **29b** and **29c**), 0.98 and 1.02 (2s, CH_3-19 of **29b** and **29c**), 2.06 and 2.07 (2s,3ß-OAc of **29b** and **29c**) 3.76 (m, $W_{1/2}$=8.3 Hz, 12ß-H), 3.95 and 4.19 (X-parts of ABX-systems, $J_{23,22+J23,22'}$ =18.7 Hz, 23-H of **29b** and **29c**), 4.81 (m, $W_{1/2}$= 8.7Hz, 3α-H), 5.47 and 5.51 (2 broad s's, 21-H of **29b** and **29c**), 7.21-7.68 (Ar-H).

29d: IR (CCl_4): 1740 cm^{-1} (CO).- ^{1}H NMR (250 MHz, $CDCl_3$): δ= 0.74 (s,CH_3-18), 0.96 (s,CH_3-19), 1.98 (s,3ß-OAc), 3.66 (m, $W_{1/2}$= 7.9 Hz, 12ß-H), 3.84 (X-part of an ABX system, $J_{23,22+J23,22'}$=18.5 Hz, 23-H), 4.72 (m, $W_{1/2}$= 8.3 Hz, 3α-H), 5.44 (broad s, 21-H), 7.15-7.75 (Ar-H).- FAB-MS: m/z = 1077 ($(M+H)^+$), 1017 ($(M+H-HOAc)^+$).- ^{13}C NMR: see Table 1.

(22Ξ,23Ξ)-3ß-Acetoxy-22-hydroxy-12-oxo-23-phenylsulfanyl-5ß-chol-20-en-24-oic acid (35).

To a freshly prepared solution of LDA [28] (0.12 mmol) in THF (0.17 ml) containing a small amount of 2,2-dipyridine [29] at -78°C was added over 10 min a solution of **32** (0.12 mmol) in dry THF (0.1 ml). The mixture was stirred at -78°C for 30 min (change of colour from red to yellow). A solution of **17** (30 mg, 0.07 mmol) in dry THF (0.1 ml) was added. After 1h the reaction mixture was warmed to 20°C and the reaction was quenched with 5% NH_4Cl (0.1 ml). Usual work-up (ethyl acetate) gave **35** (33.5 mg, 85%).- IR (CCl_4): 3700-2400 (OH), 1730, 1700 (CO), 1640 cm^{-1} (C=C).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.97 (s,CH_3-18), 1.07 (s,CH_3-19), 2.05 (s,3ß-OAc), 4.15 (d,23-H), 4.72-5.53 (m,5H), 4.85 (d,22-H), 5.06 (m, 3α-H), 5.14 (broad s,21-H), 5.47 (broad s, 21-H), 7.15-7.68 (Ar-H), $J_{22,23}$=5.0 Hz (decoupling experiment).- FAB-MS: m/z = 555 ($(C_{32}H_{42}O_6S+H)^+$), 577 ($(M+Na)^+$).

tert-Butyl (23Ξ)-3ß-acetoxy-12,21-dioxo-23-phenylsulfanyl-5ß,20Ξ-cholan-24-oate (23, mixture of stereoisomers).

To a stirred slurry of NaH (55% in oil, 46.0mg, 1.0 mmol) in dry 1,2-dimethoxyethane (DME) at 0°C was added dropwise tert-butylalkohol (98.7 µl, 1.0 mmol). Once the addition was complete the mixture was stirred at 20°C for 1h. To a solution of **17** (233.1 mg, 0.6 mmol) and **19** (270 µl, 1.2 mmol) in DME (3 ml) were added at 20°C 0.23 ml (0.14 mmol) of the freshly prepared suspension of sodium tert-butoxide in DME. The reaction mixture was stirred at 20°C for 1h and then quenched with 0.1 N HCl (0.3 ml). Usual work-up (ethyl acetate) and MPLC (hexanes - ethyl acetate 10:1 --► 4:1) gave **23** as a mixture of stereoisomers (273.3 mg, 75%).- IR (CCl_4): 1740-1700 cm^{-1} (CO).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 1.00, 1.03, 1.05, and 1.07 (4 s's, CH_3-18 and CH_3-19 signals), 1.32 and 1.34 (2 s's, $OC(CH_3)_3$ signals), 2.03 (3ß-OAc), 3.26-3.58 (m, 23-H), 5.02 (m, $W_{1/2}$= 8.0 Hz, 3α-H), 7.15-7.56 (Ar-H), 9.51 (d, $J_{20,21}$= 4.2 Hz, 21-H).- MS: m/z (%)= 554 (4, $(M-tert\ Bu)^+$), 509 (16), 508 (36), 482 (11), 427 (17), 374 (90), 341 (54), 57 (100).

Reaction of 20 with 17.

20 and **17** were reacted using the procedure described for the preparation of **23**. KH was used instead of NaH. MPLC (hexanes - ethyl acetate 3:1) gave **31** (32.6 mg, 5%), **24** (244.0 mg, 38%), **37a** (74.8 mg, 7%), and **37b** (15.3 mg, 1%).

tert-Butyl (23E)-3ß-acetoxy-23-methylsulfanyl-12,21-dioxo-5ß,20E-cholan-24-oate (24, mixture of stereoisomers).

IR (CCl_4): 1730-1700 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$):δ= 1.00, 1.01 (6H), and 1.04 (s's, CH_3-18 and CH_3-19 signals), 1.46 and 1.48 (2 s's, $OC(CH_3)_3$ signals), 2.00 (3ß-OAc), 2.10 and 2.12 (2 s's, SCH_3 signals), 2.75-3.05 (m, 17α-H), 5.05 (m, $W_{1/2}$= 7.0 Hz, 3α-H), 9.45-9.62 (m, 21-H).- MS: m/z (%) = 533 (4, $(C_{31}H_{48}O_6S\text{-}CH_3)^+$), 477 (17), 446 (12), 402 (12), 387 (36), 374 (52), 341 (43), 57 (100).

tert-Butyl (23E)-3ß-acetoxy-23-methylsulfanyl-12-oxo-5ß-chola-20,22-dien-24-oate (31).

IR (CCl_4): 1730 and 1705 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.93 (s,CH_3-18), 1.05 (s,CH_3-19), 1.52 (s,$OC(CH_3)_3$), 2.05 (s,3ß-OAc), 2.12 (s,SCH_3), 2.85-3.20 (m, 17 -H), 5.05 (m,$_{W1/2}$= 7.0 Hz, 3α-H), 5.31 and 5.45 (m, $W_{1/2}$=3.6 Hz,CH_2-21), 7.46 (broad s, 22-H).- MS: m/z (%)= 530 (8, M^+), 399 (32), 381 (100).- Found: 530.3054 (MS). Calc for $C_{31}H_{46}O_5S$: 530.3066.

tert-Butyl (1E,3E,4E,5E)-3,5-bis(3ß-acetoxy-12-oxo-5ß-androstan-17ß-yl)-3-formyl-4-hydroxy-1-methylsulfanyl-1-cyclohexanecarboxylate (37a and 37b).

37a: IR (CCl_4): 3400 (OH), 1730, 1710 and 1690 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$) δ=1.01, 1.05 (6H) and 1.11 (3 s's CH_3-18 and CH_3-19 signals), 1.40 (s,$OC(CH_3)_3$), 2.03 (s,3ß-OAc), 2.10 (s,SCH_3), 2,50 (broad s), 2.86-3.19 (m,17α-H), 3.61 (4'-H), 4.68 (d, OH), 5.01 (m, $W_{1/2}$= 6.0 Hz, 3α-H), 9.66 (s, -CHO), $J_{4',OH}$=5.0 Hz.- FAB-MS: m/z = 935.6 ($(C_{55}H_{82}O_{10}S+H)^+$).

37b: IR (CCl_4): 3410 (OH), 1730, 1710 and 1690 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$): δ=1.00 (overlapping CH_3-18 and CH_3-19 signals), 1.45 (s,$OC(CH_3)_3$), 1.95 (s,SCH_3), 2.00 (s,3ß-OAc), 3.55-3.78 (m, 4'-H), 4.75 (d, OH), 5.02 (m,$W_{1/2}$= 7.0 Hz, 3α-H), 9.75 (CHO), $J_{4',OH}$=5.0 Hz.- FAB-MS: m/z = 935.6 ($(C_{55}H_{82}O_{10}S+H)^+$).

Cyclization of 24.

A solution of **24** (mixture of stereoisomers, 104.0 mg, 0.19 mmol) and p-toluenesulfonic acid (42.5 mg, 0.18 mmol) in benzene (40 ml) was refluxed for 7 h. The reaction flask was connected to a Soxhlet apparatus charged with 4 A molecular sieves for removal of the water formed in the reaction. After cooling usual work-up (benzene) and MPLC (hexanes - ethyl acetate 6:1) gave **26a** (26.4 mg), a mixture of **26a** and **26b** (14.6 mg), and **26b** (30.0 mg). Total yield: 71.0 mg (83%).

(23S)-3ß-Acetoxy-12-oxo-23-methylsulfanyl-5ß-buf-20-enolide (26a).

M.p.: 108-112°C (from acetone).- IR (CCl_4): 1750, 1730 and 1700 cm^{-1} (CO).- ^1H NMR (400 MHz, C_6D_6): δ= 0.55 (s,CH_3-18), 0.78 (s,CH_3-19), 1.75 (s,3ß-OAc); 1.98 (s,SCH_3); 2.51 (22-H), 2.72 (22'-H), 2.73 (broad s, 17α-H), 3.13 (23-H), 5.07 (m, $W_{1/2}$=4.5 Hz, 3α-H), 6.30 (m, $W_{1/2}$=5.0 Hz,21-H); 21-H, 22-H, 22'-H, and 23-H form a 4-spin system; from a decoupling experiment: $|J_{22,22'}|$=18.1 Hz, $J_{22,23}$= 6.2 Hz, $J_{22',23}$= 2.7 Hz.- CD (CH_3CN): λ_{max} (Δε)= 264 (+9.3), 235 nm (-5.3).- MS: m/z (%) = 474 (< 1, M^+), 426 (100), 366 (26), 349 (36).- (Found: C, 68.38, H, 8.11. $C_{27}H_{38}O_5S$ (474.6) requires C, 68.32, H, 8.11).-

(23R)-3ß-Acetoxy-12-oxo-23-methylsulfanyl-5ß-buf-20-enolide (26b).

IR (CCl_4): 1750, 1730 and 1700 cm^{-1} (CO).- ^1H NMR (80 MHz, $CDCl_3$: δ = 1.02 (s,CH_3-

18), 1.06 (s,CH_3-19), 2.03 (s,3ß-OAc), 2.19 (s,SCH_3), 2.20-3.00 (m, which includes: 2.82 ("d", J= 5.0 Hz, CH_2-22), 3.45 (dd, $J_{22,23}=J_{22',23}$=5.0 Hz, 23-H), 5.06 (m, $W_{1/2}$ = 6.0 Hz, 3α-H), 6.38 (m, 21 -H).- CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 297 (+0.96), 263 (-7.66), 235 nm (+4.07).- MS: m/z (%)= 474 (1,M^+), 426 (100), 366 (27), 349 (23).

(23 S)-3ß-Acetoxy-12-oxo-23-phenylsulfanyl-5ß-buf-20-enolide (25a and 25b).

a) Using the procedure described for the conversion of **21** into **29**, a 1:1 mixture (^{1}H NMR) of **25a** and **25b** was prepared from **22c/22d**. The mixture was separated by MPLC (hexanes -ethyl acetate 5:1). Total yield of **25a** and **25b**: 45% (based on **22c/22d**). Using the same procedure, **25a/25b** (1:1 mixture) were obtained from **22a** in a total yield of 60% and from **22b** in 75% yield.

b) Starting from **23**, the procedure described for the conversion of **24** (mixture of stereoisomers) to **26a** and **26b** was used. Yield of **25a** and **25b** (1:1 mixture, ^{1}H NMR): 90%.

25a: M.p. 189-191°C (from CH_2Cl_2-hexanes).- IR ($CHCl_3$): 1768, 1740 and 1715 cm^{-1} (CO).- ^{1}H NMR (250 MHz, C_6D_6): δ= 0.63 (s,CH_3-18), 0.88 (s,CH_3-19), 1.83 (s,3ß-OAc), 2.65 (22-H), 2.75-2.89 (m,17α-H), 2.99 (22'-H), 3.80 (23-H), 5.19 (m, $W_{1/2}$= 5.3 Hz, 3α-H), 6.38 (21-H), 6.99-7.81 (m,Ar-H); 21-H,22-H,22'-H,and 23-H form a 4-spin system; from a decoupling experiment: $|J_{22,22'}|$=17.9 Hz, $J_{22,23}$=6.0 Hz, $J_{22',23}$=4.0 Hz.- MS: m/z (%) = 536 (2, M^+), 427 (100), 367 (11), 349 (25).- CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 310 (+0.23), 284 (-1.58), 252 (-1.69), 240 (+1.77), 227 (-1.57), 211 nm (-2.40).- (Found: C, 71.56; H, 7.57. $C_{32}H_{40}O_5S$ (536.7) requires C, 71.61; H 7.51).

25b: M.p. 203-206°C (from CH_2Cl_2-hexanes).-IR ($CHCl_3$): 1768, 1735 and 1710 cm^{-1} (CO).- ^{1}H NMR (250 MHz, C_6D_6): δ= 0.84 (CH_3-18), 0.88 (CH_3-19), 1.85 (3ß-OAc), 2.61 (22-H), 2.73-2.88 (m,17α-H), 2.99 (22'-H), 3.78 (23-H), 5.18 (m, $W_{1/2}$= 5.6 Hz, 3 -H), 6.38 (21-H), 6.93-7.83 (Ar-H); 21-H,22-H,22'-H, and 23-H form a 4-spin system; from a decoupling experiment: $|J_{22,22'}|$=17.9 Hz, $J_{22,23}$=6.0 Hz, $J_{22',23}$=4.9 Hz).- MS: m/z (%) = 536 (3,M^+), 427 (100), 367 (9), 349 (20).- CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 310 (+0.2), 286 (+3.04), 252 (+1.70), 240 (-2.28), 228 (+0.79), 220 (-0.37), 211 nm (+1.35).- (Found C, 71.68; H, 7.54. $C_{32}H_{40}O_5S$ (536.7) requires C, 71.61; H, 7.51).

3ß-Acetoxy-12-oxo-5ß-bufa-20,22-dienolide (27).

a) To a stirred solution of **25a** (29.0 mg, 0.05 mmol) in CH_3CN (2 ml) was added dropwise a solution of $NaIO_4$ (120.6 mg, 0.5 mmol) in methanol-water 1.7:1 (1.8ml). The reaction vessel was then sealed with a rubber septum and the mixture was heated to 140°C for 90 min. After cooling the mixture was filtered through silica gel (7g, elution with hexanes - ethyl acetate 5:1). Evaporation of the solvents and MPLC (hexanes - ethyl acetate 3.6 : 1) gave **27** (11.0 mg, 52%).- Using the same procedure, **25b** was converted to **27** in 47% yield.

b) To a solution of **26a** and **26b** (1:1 mixture, 40.6 mg, 0.1 mmol) in dry CH_2Cl_2 (1 ml) at -78° C was added within 3 min a solution of 85% m-chloroperbenzoic acid (19 mg, 0.1 mmol) in dry CH_2Cl_2 (0.5 ml). The mixture was stirred at -78°C for 35 min and then added to 10% Na_2SO_3. After addition of CH_2Cl_2 the organic layer was separated, washed with H_2O, dried over Na_2SO_4 and then left at 20°C for 36 h. Evaporation of the solvent and MPLC (hexanes - ethyl acetate 2:1) gave **27** (30.8 mg, 84%).- M.p. 183-186°C (from CH_2Cl_2/hexanes).- IR (CCl_4): 1740 and 1715 (CO), 1645 cm^{-1} (C=C).- ^{1}H NMR (80 MHz, $CDCl_3$): δ= 0.90 (s,CH_3-18), 1.08 (s,CH_3-19), 2.03 (s,3ß-OAc), 3.02-3.38 (m, 17α-H), 5.09 (m, $W_{1/2}$= 9.0 Hz, 3α-H), 6.26 (dd,23-H), 7.43 (m, 21-H), 7.68 (dd, 22-H), $J_{21,22}$=3.0 Hz, $J_{22,23}$=10.0 Hz, $J_{21,23}$=1.6 Hz).- CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 321 (-0.60); 280 (+1.12); 257 (+0.99), 237 (+0.92), 216 (-2.08), 191 (+6.38).- MS: m/z (%) = 426 (100, M^+), 411 (19), 366 (40), 323 (15).- (Found C, 73.16; H, 8.00. $C_{26}H_{34}O_5$ (426.5) requires C, 73.21; H, 8.03).

Table 1. ^{13}C spectral data (α-values) of compounds **21a**, **21b**, **29a**, and **29c** (in $CDCl_3$)

Assignment	21a	21b	29a	29c
CH_3-18	13.16	13.49	12.82	12.86
$\underline{C}H_3$-CO	21.53	21.47	21.56	21.56
CH_3-19	23.56	23.50	23.71	23.53
	23.77	23.19	24.32	24.53
	24.86	24.83	24.38	24.59
	25.53	25.71	25.59	26.14
	25.80	25.86	26.92	26.50
CH_2 signals	26.35	26.29	27.02	27.32
	29.50	28.71	27.96	26.68
	29.96	31.35	30.23	29.38
	30.50	30.47	30.78	30.81
	30.59	30.53	31.02	31.20
C-10	34.41	34.38	35.57	35.66
C-13	47.09	46.24	46.33	46.51
	33.23	33.20	33.96	33.05
	35.81	35.72	35.99	36.42
	37.27	37.23	36.95	37.30
CH signals	41.90	42.12	43.00	41.66
	47.36	47.70	47.51	44.79
	47.61	47.97	47.70	46.67
	52.43	52.67	43.06	44.65
O-CH_3	52.29	52.28		
C-3	70.68	70.68	70.96	71.26
C-12	72.20	71.02	83.17	84.21
	128.39	128.39	129.64	127.57
ArC signals	128.96	129.02	130.28	129.21
	132.40	132.42	134.68	130.60
	133.45	133.21	135.04	135.09
$CH_3\underline{C}O$	170.75	170.66	170.54	170.45
C-24	172.30	171.96	171.12	170.02
C-21	203.85	205.50	103.06	102.85

Acknowledgements - We wish to thank Prof.G.Snatzke for the CD spectra and Dr.O.-Weißbach (Beilstein-Institut) for his advice in naming the compounds. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

1) Reviews: R.Thomas, J.Boutagy, and A.Gelbart, J.Pharm.Sci. **63**, 1649 (1974); Th.W.Güntert and H.H.A.Linde, Experientia **33**, 697 (1977); J.Engel, Chem.-Ztg. **108**, 195 (1984).
2) For a recent discussion of this point, see ref. [3]
3) K.Wiesner and Th.Y.R.Tsai, Proceedings of the 3rd International Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Publishing House of the Bulgarian Academy of Sciences, Sofia 1985, Vol.3,p.215
4) E.Erdmann, K.Werdan, and L.Brown, Trends Pharmacol.Sci. **6**, 293 (1985), and references cited therein.
5) P.Welzel, H.Stein, and T.Milkova, Liebigs Ann.Chem. **1982**, 2119.
6) J.P.Guthrie, C.L.McIntosh, and P.De Mayo, Canad.J.Chem. **48**, 237 (1970); Y.Kamano and M.Komatsu, Chem.Pharm.Bull. **17**, 1698 (1969); Y.Kamano, Y.Tanaka, and M.Komatsu, ibid. **17**, 1706 (1969).
7) Ch.R.Engel and G.Dionne, Canad.J.Chem. **56**, 424 (1978); Ph.Bauer, K.S.Kyler, and D.S. Watt, J.Org.Chem. **48**, 34 (1983); M.M.Kabat, A.Kurek, and J.Wicha, J.Org.Chem. **48**, 4248 (1983), and references cited therein.
8) W.Haede, W.Fritsch, K.Radscheit, U.Stache, and H.Ruschig, Liebigs.Ann.Chem. **741**, 92 (1970); G.R.Pettit and J.R.Dias, J.Org.Chem. **36**, 3207 (1971); Ch.R.Engel, R.Bouchard, A.F. de Krassny, L.Ruest, and J.Lessard, Steroids **14**, 637 (1969); and references cited therein.
9) Y.Takeuchi, Y.Makinov, K.Maruyama, and E.Yoshii, Heterocycles **14**, 163 (1980).
10) see also A.Belanger, P.Brassard, G.Dionne, and Ch.R.Engel, Steroids **24**, 377 (1974).
11) S.Sarel, Y.Shalon, Y.Yanuka, Chem.Commun. **1970**, 81; E.Yoshii, T.Oribe, T.Koizumi, I.Hayashi, and K.Tumura, Chem.Pharm.Bull. **25**, 2249 (1977).
12) K.Wiesner, T.Y.R.Tsai, A.Sen, R.Kumar, and M.Tsubuki, Helv.Chim.Acta **66** 2632 (1983), and previous papers in this series.
13) B.M.Trost, Chem.Rev. **78**, 363 (1978).
14) c.f. ref. [9]
15) A.J.Mancuso and D.Swern, Synthesis **1981**, 165.
16) Part of the present material has appeared in a preliminary communication. [17]
17) H.-W.Hoppe and P.Welzel, Tetrahedron Lett. **27**, 2459 (1986).
18) Review: G.Piancatelli, A.Scettri and M.D.Auria, Synthesis **1982**, 245.
19) G.R.Pettit, D.C.Fessler, K.D.Paull, P.Hofer, and J.C.Knight, J.Org.Chem. **35**, 1398 (1970).
20) V.W.Goodlet, Anal.Chem. **37**, 431 (1965); I.R.Trehan, C.Monder, and A.K.Bose, Tetrahedron Lett. **1968**, 67.
21) B.M.Trost, T.N.Salzmann, and K.Hiroi, J.Am.Chem.Soc. **98**, 4887 (1976).
22) R.K.Dieter and J.R.Fishpaugh, J.Org.Chem. **48**, 4439 (1983).
23) H.-W.Hoppe, Dissertation, Univ.Bochum **1985**.
24) W.Kreiser and H.A.F.Heinemann, Liebigs.Ann.Chem. **1976**, 1222.
25) S.A.Martin, C.E.Costello, and K.Biemann, Anal.Chem. **54**, 2362 (1982).
26) G.Barbieri, M.Cinquini, S.Colona, and F.Montaniri, J.Chem.Soc. (C) **1968**, 656.
27) R.Pummerer, Chem.Ber. **43**, 1401 (1910).
28) Y.Kita, J.Haruta, J.Segawa, and Y.Tamura, Tetrahedron Lett. **1979**, 4311.
29) Y.Kita, J.Segawa, J.Haruta, H.Yasada, and Y.Tamura, J.Chem.Soc. Perkin Trans. 1 **1982**, 1099.
30) M.Gall and H.O.House, Org.Synth. **52**, 39 (1972).
31) Naming these compounds applying the existing IUPAC rules was very complicated. The simplest systematic name could be derived using the phane nomenclature. Compounds **29** are then: 1^{3}ß,3^{3}ß-diacetoxy-1^{21},3^{21}-dihydroxy-1^{23E},3^{23E}-bis-phenysulfanyl-2,4-dioxa-1,3-di(12, 21E) (5ß,20E-cholana)-cyclobutaphane-1^{24}, 3^{24}-dioic-dilactone.