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AN APPROACH TO BUFADIENOLIDES FROM DEOXYCHOLIC ACID.[1] REACTIONS OF A STEROIDAL α,ß-UNSATURATED ALDEHYDE WITH SOME O-SILYLATED KETENE ACETALS

HANS-WOLFGANG HOPPE, BLANDA STAMMEN, ULRICH WERNER, HERMANN STEIN, and PETER WELZEL*

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

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Abstract - Reactions of the α,ß-unsaturated aldehyde **1** with the O-silyl ketene acetals **10** have been investigated. Both Michael addition and [4+2] cycloaddition products were formed, depending on the reaction conditions.

Introduction

The cardioactive steroids inhibit the membrane-bound Na^+K^+ -ATPase, an enzyme involved in the Na^+K^+ transport across the cell membrane. As a consequence, the Ca^{2+} content within the cell increases and this causes ultimately the well-known positive inotropic effect.[2] Structurally, the cardioactive steroids (e.g. bufalin (**8b**)) are characterized by cis-fused rings C and D, a hydroxy function at C-14, and a lactone ring attached to the 17ß-position. The remark "introduction of the required 17ß-lactone and of the 14ß-hydroxy group in the same molecule presents certain problems" by Sondheimer in his classical review on syntheses in the cardioactive steroid field, still seems to be valid inspite of the considerable progress that has been achieved in the past few years.[4]

We have recently developed a novel synthetic scheme for both 14α-H and 14ß-OH bufadienolides, such as **8a** and **8b**, via 12-oxo-bufenolides of type **7**.[5,6] The 23-thiosubstituted bufenolide ring was constructed from readily available unsaturated aldehyde **1** (obtained in 5 steps from deoxycholic acid) and the ester enolate of **3** (R=Me, Ph) by Michael addition (**1** -> **5**) and subsequent acid-catalyzed cyclization (**5** -> **7**).[6]

Ketene acetals of type **2** are synthetic equivalents of the enolate of **3**. They can, in principle, react with enal **1** either by 1,4-addition or by [4+2] cycloaddition (inverse-type hetero-Diels Alder reaction[7]) to give **4** and **6**, respectively. From both **4** and **6** the central intermediate **7** should be easily available. Investigations along these lines, using O-silylated ketene acetals[8] as equivalents for the general reagent **2**, are detailed below.

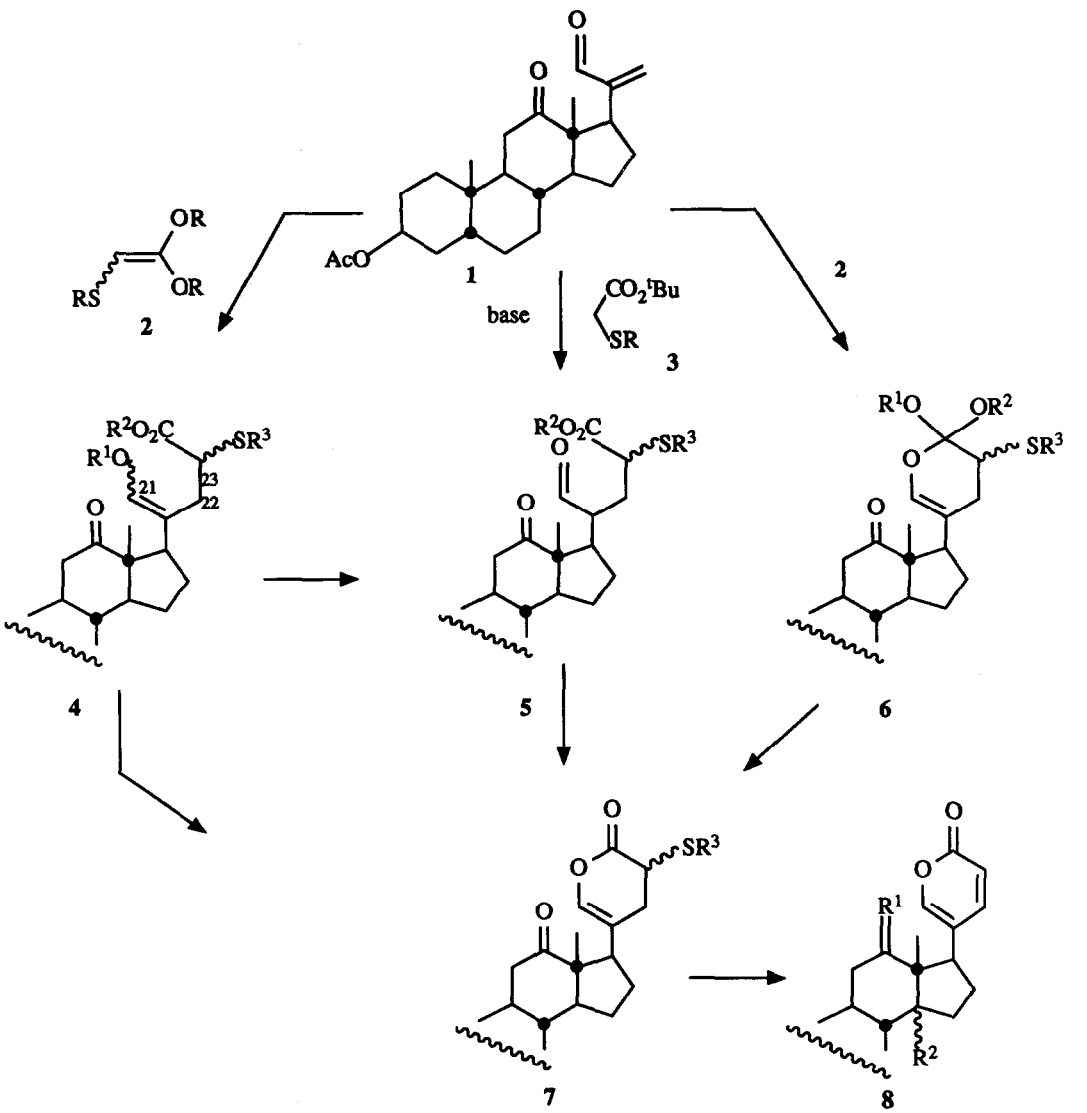
Preparation of the ketene acetals 10a - 10e

Two methods have been employed for the synthesis of the required ketene acetals:

a) Reaction of the acetates **9** with (i) LDA in THF and (ii) trapping of the ester enolates with a trialkylsilyl chloride (Ainsworth procedure[9]);

b) Reaction of the esters **9** with a trialkylsilyl triflate in the presence of triethylamine (Simchen procedure[10]).

In order to prevent extensive formation of C-silylated products, the tert-butyldimethylsilyl ketene acetals have been prepared in all cases.[11,12] Reaction of phenylsulfanylacetate **9b** with LDA in THF at -78°C followed by addition of $^{t}BuMe_2SiCl$ provided (after distillation) a 4:1 mixture of (E)-**10b** and (Z)-**10b** (see Scheme 2), whereas the Simchen method (reaction of **9b** with $^{t}BuMe_2SiOTf$ and NEt_3 at 0°C) gave an approximately 1:5 mixture of (E)-**10b** and (Z)-**10b**.[13] The configuration around the double bond in both compounds was assigned on the basis of the NOE results depicted in formulae (E)-**10b'** and (Z)-**10b'**.[14] The reactant-like transition states leading to (E)-**10b** and (Z)-**10b** under the Ainsworth conditions may be schematically depicted as shown in **11** and **12**, respectively.[15] Obviously, the steric interaction of the phenylsulfanyl group with the C=O oxygen complexed with the lithium base and solvent is more severe than with the OCH_3 group, favoring transition state **11**. Our result is in agreement with the stereochemistry of the ester enolate formation of propionates: Reaction with LDA in THF followed by trapping with a silyl chloride was reported to give a 85:15 mixture of the respective (E)- and (Z)-ketene acetals, whereas in THF-HMPA 77:23 (solvation of the counter ion) exclusively the (Z)-isomer was formed.[16,17,18] For the Simchen reaction a late transition state has been suggested,[10] and factors affecting the relative stabilities of the stereoisomeric products (E)-**10b** and (Z)-**10b** should be reflected in the corresponding transition states. This view is supported by the observation, that (E)-**10b** (the minor product under Simchen's conditions) rearranged in solution into (Z)-**10b**. The conditions under which the rearrangement has been observed are summarized in Table 1. The exact nature of the rearrangement process is still unknown. Since the samples of the ketene acetals (E)-**10b**/(Z)-**10b** used for these studies contained some of the starting ester **9b** it may well be that **9b** takes part in the equilibration reaction.[19]

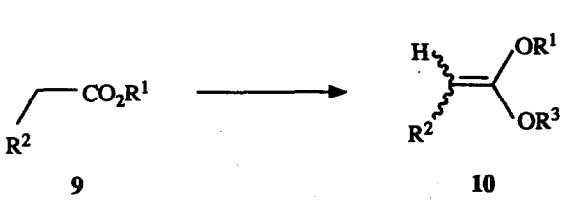


4,5,6	R^1	R^2	R^3
a	Si^tBuMe_2	Me	Ph
b	Si^tBuMe_2	^{t}Bu	Me
c	Si^tBuMe_2	Me	Me

7	R
a	(23R) - SPh
b	(23S) - SPh
c	(23R) - SMe
d	(23S) - SMe

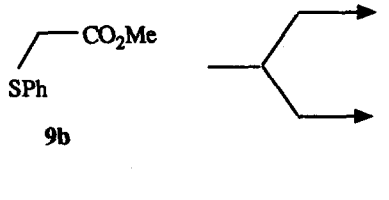
8	R^1	R^2
a	O	α -H
b	H,H	β -OH

Scheme 1

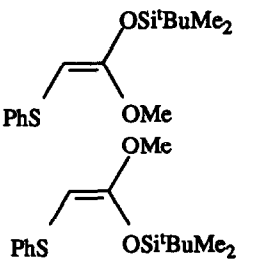


9 10

9,10	R^1	R^2	R^3
a	Me	H	Si^tBuMe_2
b	Me	SPh	Si^tBuMe_2
c	^{t}Bu	SMe	Si^tBuMe_2
d	$SiMe_3$	SPh	$SiMe_3$
e	Me	SMe	Si^tBuMe_2

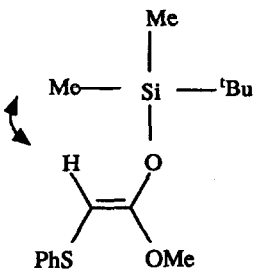


9b

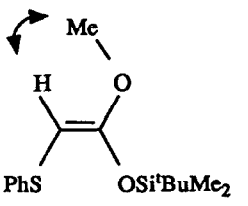


(E)-10b

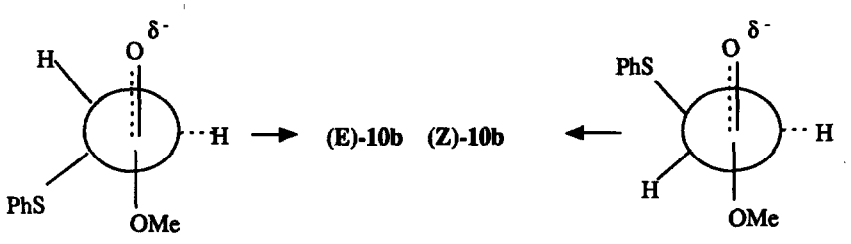
(Z)-10b



(E)-10b'



(Z)-10b'



11 12

Scheme 2

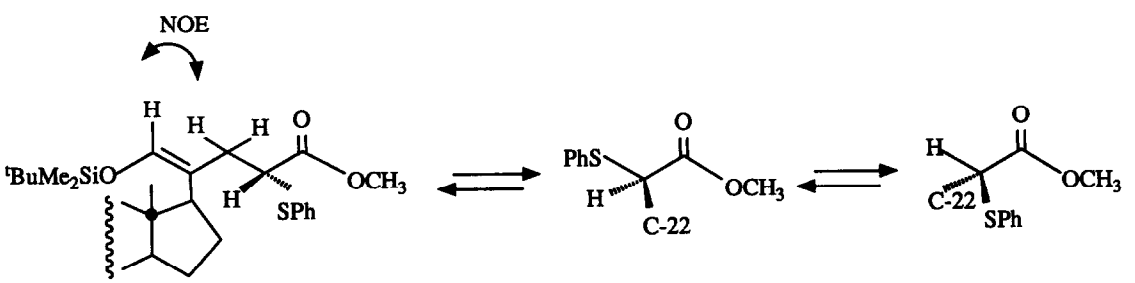
Table 1. Isomerization (E)-10b⇌(Z)-10b

Solvent	Temp.(°C)	Reaction time	Ratio (E)-10b / (Z)-10b[a] t_0	t_{end}
hexanes	20	5 d	2.6:1.0	1.0:13.0
acetonitrile	100	0.5 h	2.3:1.0	1.1: 1.0

[a] From ^{1}H NMR spectra, calibrated against ester **9b** present as impurity.

Reaction of the unsaturated aldehyde 1 with O-silyl ketene acetal 10b

In a number of recent publications the reactions of O-silyl ketene acetals with α,ß-unsaturated ketones in polar solvents (acetonitrile,[20] nitromethane[21]), under high-pressure conditions,[22,23] and catalyzed by either Lewis acids,[24,25,26] clay montmorillonite,[27] or fluoride[21,25,28] have been discussed.[29] In all but one cases, even when the enone unit was not fixed in a transoid conformation, conjugate addition (c.f. **1->4**) was observed, in most cases accompanied (or driven) by a silyl group transfer. The only example of a [4+2] cycloaddition between an O-silyl ketene acetal and an α,ß-unsaturated carbonyl compound (c.f. **1->6**) we are aware of was recently reported by Maier and Schmidt.[30]



13 (**4a-a**) **13'** **13''**

Scheme 3

The phenylsulfanyl substituted silyl ketene acetal **10b** (4:1 mixture of (E)-**10b** and (Z)-**10b**) was so reactive as to add to enal **1** even in CH_2Cl_2 solution

(19 h at 60°C in a sealed flask). A 3.6:1:1:2 mixture of four stereoisomeric Michael adducts **4a** (isomeric at C-21 and C-23) was obtained in 55% combined yield. The same products (3:1:1.3:2.6 ratio) were isolated when the reaction was performed in acetonitrile solution at 100°C. Three of the stereoisomers (**4a-a**, **4a-b**, and **4a-d**) were obtained in pure state by chromatographic separation. The main isomer **4a-a** has the Z-configuration around the 20,21-double bond as shown by the NOE result depicted in formula **13**. The positive Cotton effect of **4a-a** at 263 nm may indicate the (R)-configuration at C-23 (see formula **13'**). This conclusion rests on two assumptions: (i) conformation **13'** with the C-22 - C-23 bond syn-periplanar with the carboxyl C=O is the most preferred in solution (solvent: acetonitrile)[31] and (ii) the axial haloketone rule[32] is valid in the case of α-sulfanyl-substituted esters as for ketones axially substituted with an α-sulfanyl group.[33] Presumably, **4a-b** has the same configuration at C-23 (positive CD at 263 nm), whereas **4a-d** displayed a negative CD band at 263 nm.

From the composition of the mixture of stereoisomeric Michael adducts probably no information on the stereoselectivity with regard to the two enantiotopic faces of (E)-**10b** and (Z)-**10b** can be gained, since we observed that at least in acetonitrile solution at 100°C ketene acetals (E)-**10b** /(Z)-**10b** are not configurationally stable. The formation of the four stereoisomers **4a-a** - **4a-d** implies, however, that both from the cisoid and the transoid conformations of enal **1** Michael adducts were formed.

Remarkably, when **1** and **10b** were allowed to react in $CHCl_3$ solution in the presence of the mild Lewis acid Eu(fod)$_3$ (15 d at 20°C), not the Michael products were formed but rather a [4+2] cycloaddition[34,35] occurred to give **6a**, according to the ^{1}H NMR spectrum as a 1:1 mixture of two stereoisomers (72% yield, after correction for recovered **1**). The ortho esters **6a** were very unstable und the structure was mainly inferred from their 400 MHz ^{1}H NMR spectra. Fully in accord with the proposed structure, **6a** reacted with anhydrous HCl in $CHCl_3$ to give **7a/7b** (1:1 mixture) in 85% yield.[36] The diastereoisomeric dihydropyrans **7a/7b** have previously been obtained via the ester enolate route (**1**->**5**->**6**) and have been converted into bufadienolide **8a** in two steps.[6]

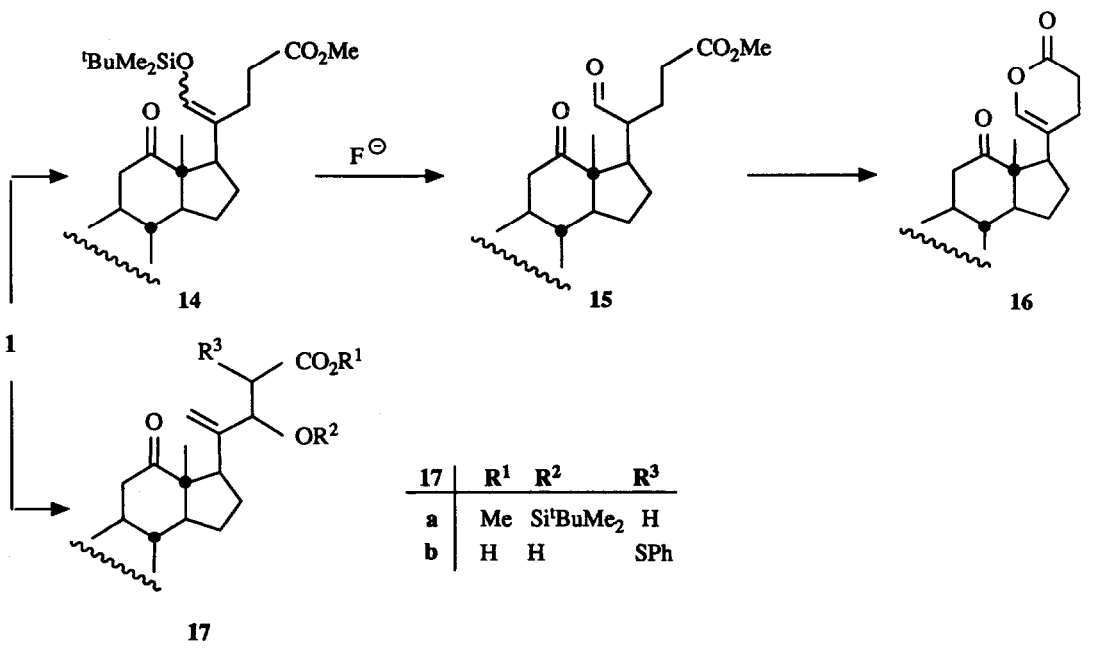
Reaction of **1** with ketene acetals **10c** and **10e**

The methylsulfanylketene acetal **10c** was much less reactive than **10b**. Even in acetonitrile or nitromethane solution (at 60-70°C) it did not react with **1**. However, $ZnCl_2$-catalysis promoted the formation of the 1,4-adduct **4b** (mixture of stereoisomers) in 58% yield. Treatment of **4b** with potassium fluoride in THF-methanol led to aldehyde **5b** (96%, mixture of stereoisomers), the

cyclization of which to give **7c/7d** (90% yield) and conversion to **8a** and to bufalin (**8b**), respectively, have already been reported.[5,6]
$Eu(fod)_3$-catalyzed reaction of **1** with the methylsulfanylketene acetal **10e** proceeded in the [4+2] cycloaddition mode to give **6c** (according to ^1H NMR as a 1.2:1 mixture of two stereoisomers) in 79% yield (after correction for recovered **1**) . Treatment of **6c** with dry HCl in $CHCl_3$ led to the formation of the 23-epimeric bufenolides **7c/7d** in 82% yield. At present this seems to be the most efficient way to prepare **7c/7d** which can be converted to bufalin (**8b**) in few further steps.[5]

Reaction of 1 with ketene acetals 10a and 10d

In the $ZnCl_2$-catalyzed reaction of **1** with the unsubstituted ketene acetal **10a** a pronounced solvent effect was observed. Reaction in acetonitrile at 20°C led (after selective silyl enol ether cleavage with fluoride) to the 1,4- and 1,2-addition products **15** and **17a**, respectively, in a 1:2 ratio, whereas in dimethoxyethane solution the reaction was very fast even at -78°C and provided **15** as the main product (58%) alongside with **17a** (24%). From **15**, making use of Pettit's two-step procedure[3,7] ((i) ester hydrolysis, (ii) acid-catalyzed enol lactone formation) bufenolide **16** was obtained in 55% yield.



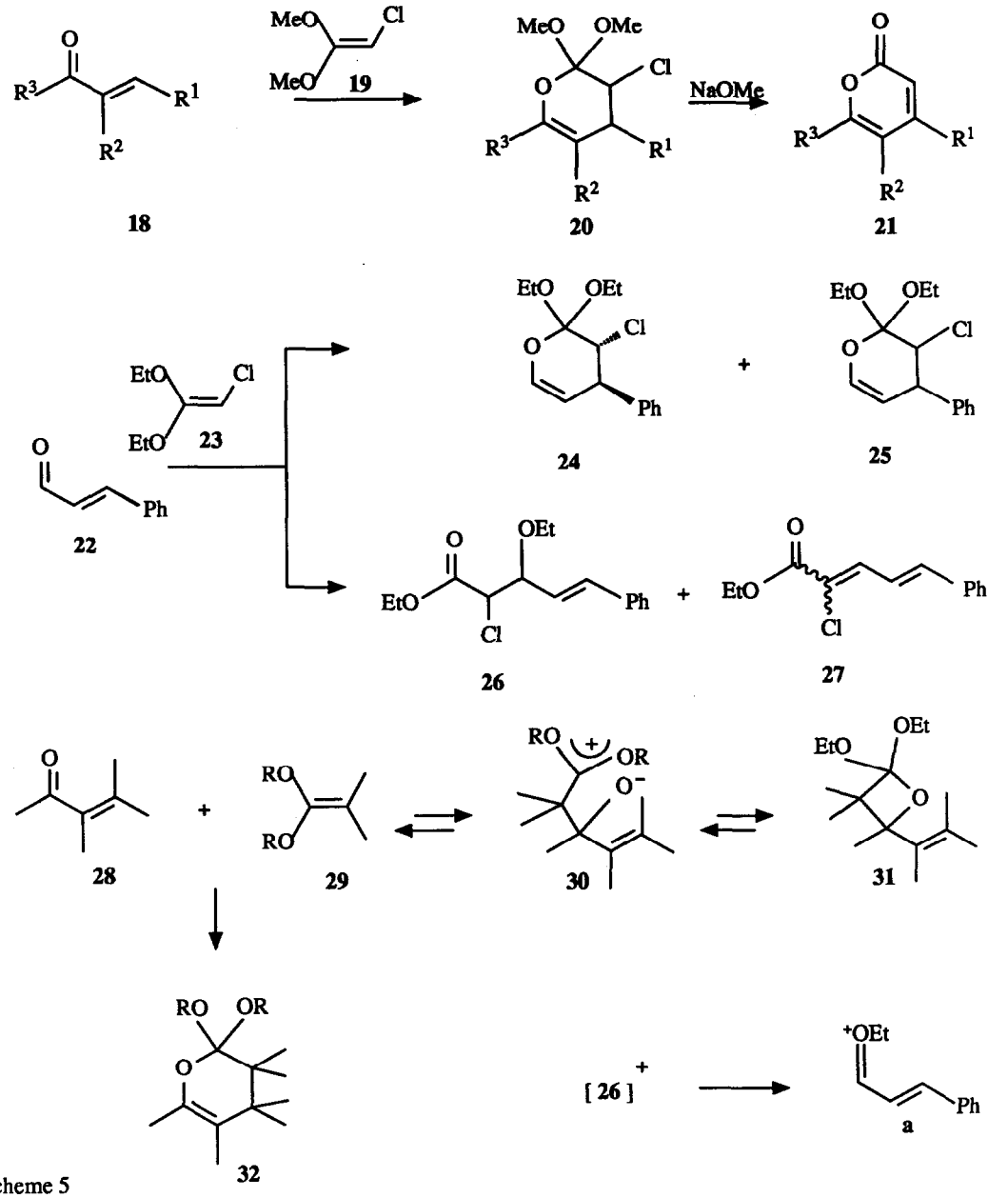
17	R^1	R^2	R^3
a	Me	Si^tBuMe_2	H
b	H	H	SPh

Scheme 4

From the reaction of **1** with the bis-silylated ketene acetal **10d** only the 1,2-addition product was obtained. After silyl ether cleavage **17b** was isolated in 67% yield.

Some Comments on the Bélanger-Brassard α-Pyrone Synthesis

It seems appropriate to mention here the α-pyrone synthesis that was published some 17 years ago by Bélanger and Brassard.[38] They found that α,ß-unsaturated carbonyl compounds such as **18** on heating with chloroketene dimethyl acetal (**19**) gave the cycloadducts **20** which on treatment with sodium methoxide in DMSO or DMF furnished α-pyrones **21**. This method has been employed in the synthesis of a bufadienolide of the 14α-H series.[39] For our approach towards biologically active 14ß-OH-bufadienolides (e.g.**8b**), which requires stable intermediates of type **6**, the Brassard method seems less well suited since the cycloaddition products **20** were reported to be very unstable and had to be converted immediately into the α-pyrones **21**. We can confirm this observation: All attempts to make use of this method for our aims proved fruitless.[40] One set of experiments is described below indicating competing reactions not reported previously. Bélanger and Brassard obtained from cinnamaldehyde and **19** (heating to 150°C for 72 h) trans-**20** (R^1 = Ph, R^2, R^3 = H) in 42% yield. We performed the reaction in toluene at 180°C (16 h) and used the diethyl acetal **23** instead of **19**. Besides the trans-product **24** (37%) the very unstable cis-cycloadduct **25** (22%) could be isolated alongside with a third compound that on the basis of its spectral properties is assigned structure **27** (21%). When the reaction was performed in acetonitrile at 100°C no cycloadduct formation was detected by TLC, and only **27** was obtained (50% yield). From a reaction performed in toluene solution at 150°C (6 h) after chromatographic separation besides cycloadduct **24** the ethoxy compound **26** could be isolated, the structural assignment of which is based on NMR and mass spectra (c.f. ion **a** in Scheme 5). **26** is the obvious precursor of **27**. The formation of **26** can nicely be explained on the basis of results published by Scheeren and coworkers.[41] They have reported that the Lewis acid-catalyzed reaction of α,ß-unsaturated carbonyl compounds with dialkyl ketene acetals leads kinetically controlled to oxetanes **31** via dipolar intermediates of type **30**. At higher temperatures the oxetanes reverse to the starting materials and the thermodynamically more stable dihydropyrans **32** are formed. In the absence of a catalyst under high-temperature conditions generally the dihydropyrans are the main products. **26** may thus be formed from an intermediate of type **30** by a nucleophilic substitution process.



18 20 21

22 24 25

26 27

28 29 30 31

32

a

Scheme 5

EXPERIMENTAL

General

All O_2- or moisture-sensitive reactions were performed on oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe, and were introduced into reaction flasks through rubber septa. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminium caps with open top and Teflon-faced septum (Aldrich). 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. Intrumentation and materials: ^1H NMR: T 60 (Varian), WP 80 (Bruker), AM 400 (Bruker); ^{13}C NMR: AM 400 (Bruker); IR: Perkin Elmer 257; MS: MAT-731 and MAT-CH-5 (Finnigan); medium-pressure liquid chromatography (MPLC): 20.0 cm x 1.5 cm glass tubes (column A, 9 g SiO_2), 31.0 cm x 2.5 cm glass tubes (column B, 60 g SiO_2), silica gel Si 35-70 µm (Amicon), Duramat pump (CfG), UV detector Thomachrom III (Reichelt); classic column chromatography (LC): ICN Silica 63-100 µm (ICN Biomedicals).

1-(tert-Butyl-dimethyl-silanyloxy)-1-methoxy-2-phenylsulfanylethylene (10b).

a) Ainsworth procedure: To a solution of LDA[42] (24.3 mmol) in anhydrous THF (60 ml) at -78°C were added: a) 2,2'-bipyridine[43] (0.5 mg, red colour) and b) (within 30 min) a solution of methyl phenylsulfanylacetate (**9b**)[5] (4.60 g, 25.0 mmol) in THF (25 ml). After 30 min at -78°C the mixture was colourless. A solution of $^tBuMe_2SiCl$ (4.86 g) in THF (5 ml) was added and the reaction mixture was stirred at -78°C for 2 h and was then allowed to warm to 20°C (1 h). Solvent evaporation and Kugelrohr distillation (160°C/13 Pa) gave a 4:1 mixture (^1H NMR, vide infra) of (E)-**10b** and (Z)-**10b** (5.80 g, 85%, colourless oil).

b) Simchen procedure: To a suspension of **9b** (0.77 g, 3.85 mmol) in Et_3N (3 ml) at 0°C $^tBuMe_2SiOSO_2CF_3$ (1.24 ml, 5.40 mmol) was added. The reaction mixture was stirred at 0°C for 15 min and at 25°C for 14 h. Dilution with ether, filtration through Florisil, solvent evaporation, and Kugelrohr distillation (160 °C, 13 Pa) provided a 1:4 mixture (4:1 ratio of the 2-H signals at δ = 4.19 ((Z)-**10b**) and δ = 4.47 ((E)-**10b**) of (E)-**10b** and (Z)-**10b** (0.63 g, 42%). In a second experiment a 1:7 mixture of (E)-**10b** and (Z)-**10b** was obtained.-

Analytical data of the 4:1 mixture of (E)-**10b** and (Z)-**10b**: ^1H NMR (80 MHz, C_6D_6): δ = 0.05 and 0.13 (2s's, ratio 4:1, $Si(CH_3)_2$), 0.81 and 0.89 (2 s's, ratio 4:1, $SiC(CH_3)_3$), 3.05 and 3.30 (2s's, ratio 1:4, OCH_3), 4.19 and 4.47 (2 s's, ratio 1:4, 2-H), 6.82-7.49 (Ar-H).- IR (CCl_4): 1605 cm^{-1} (C=C).- MS: m/z (%) = 296 (37, M^+), 239 (8), 225 (19), 183 (7), 150 (42), 73 (100).- (Found C, 60.79; H, 8.20. $C_{15}H_{24}O_2SSi$ (296.5) requires C, 60.76; H, 8.16).

1-(tert-Butyl-dimethyl-silanyloxy)-1-tert-butoxy-2-methylsulfanylethylene (10c).

10c was prepared from tert-butyl methylsulfanylacetate (**9c**)[5] as described for **10b** (Ainsworth procedure). After Kugelrohr distillation (130°C/13 Pa) a 64% yield of stereochemically homogeneous **10c** was obtained.- ^1H NMR (60 MHz, CCl_4, TMS): δ = 0.13 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.28 (s, 9H, $OC(CH_3)_3$), 2.03 (s, 3H, SCH_3), 4.33 (s, 1H, 2-H).- IR (CCl_4): 1605 cm^{-1} (C=C).- MS: m/z (%) = 220 (40, $[M-57]^+$), 204 (17), 163 (70), 88 (76), 75 (100), 73 (96).- (Found C, 56.52; H, 10.27. $C_{13}H_{28}O_2SSi$ (276.5) requires C, 56.47; H, 10.21).

1-(tert-Butyl-dimethyl-silanyloxy)-1-methoxy-2-methylsulfanylethylene (10e).

10e was prepared from methyl methylsulfanylacetate (**9e**) [44] as described for **10b** (Simchen procedure). Yield after Kugelrohr distillation (120-130°C/13 Pa): 84%.- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.20 (s, $Si(CH_3)_2$), 0.98 (s, $SiC(CH_3)_3$), 2.13 (s, SCH_3), 3.57 (s, OCH_3), 4.12 (s, 2-H).- IR ($CHCl_3$):

2860, 1740 (trace of **9e**), 1615 cm^{-1} (C=C).- $C_{10}H_{22}O_2SSi$ (234.4), MS: m/z (%) = 234 (20, M^+), 193 (9), 89 (60), 88 (78), 73 (100).

Michael reaction between 1 and ketene acetal 10b.

a) In CH_2Cl_2 solution: A solution of **1** (65.9 mg, 0.17 mmol) and **10b** ((E)/(Z) 4:1, 150 mg, 0.5 mmol) in CH_2Cl_2 was heated to 60°C for 20 h. Solvent evaporation and MPLC (column B, hexanes - ethyl acetate 15:1) furnished **4a-a** (30.1 mg, 26%), **4a-b** (8.8 mg, 8%), and a 1:2 mixture (¹H NMR) of **4a-c** and **4a-d** (24.6 mg, 21%) from which a sample of pure **4a-d** was obtained by MPLC under the same conditions.

b) In CH_3CN solution: A solution of **1** (44.0 mg, 0.11 mmol) and **10b** ((E)/(Z) 1:13.5, 96.8 mg, 0.33 mmol) in CH_3CN (0.4 ml) was heated to 100°C for 43 h. Solvent evaporation and MPLC (column A, hexanes - ethyl acetate 15:1 --> 10:1) provided **4a-a** (11.6 mg, 15%), **4a-b** (4.1 mg, 5%), and a 1:2 mixture of **4a-c** and **4a-d** (15.3 mg), 12.6 mg of **1** were reisolated.

Methyl (21E,23E)-3β-acetoxy-21-(tert-butyl-dimethyl-silanyloxy)-12-oxo-23-phenylsulfanyl-5β-chol-20-en-24-oate (4a).

Isomer **4a-a** (probably (21Z,23R) configuration): ¹H NMR (400 MHz, ¹H-¹H COSY, $CDCl_3$): δ = 0.07 (s, $Si(CH_3)_2$), 0.85 (s, $SiC(CH_3)_3$), 1.04 (2 s's, CH_3-18 and CH_3-19), 2.02 (s, 3β-OAc), 2.20 (dd, 22-H), 2.40-2.53 (dd, CH_2-11), 2.60 (dd, J = 9 and 10 Hz, 17α-H), 2.99 (ddd, 22-H'), 3.57 (s, OCH_3), 3.96 (dd, 23-H), 5.01 (m, $W_{1/2}$ = 6.0 Hz, 3α-H), 6.16 (d, 21-H), 7.19 - 7.61 (Ar-H); $J_{22/23}$ = 12 Hz, $J_{22'/23}$ = 4.5 Hz, $J_{22,22'}$ = 13 Hz, $J_{22',23}$ = 1.2 Hz.- IR (CCl_4): 1730 (ester), 1700 (ketone), 1650 cm^{-1} (C=C).- CD (CH_3CN): λ_{max} (Δε) = 328 (-0.10), 282 (+2.64), 263 (+1.50), 235 nm (-1.31).- $C_{35}H_{49}O_6SSi$ (683.0), MS: m/z (%) = 682 (0.6, M^+), 625.3018 (6.6, Calc for $C_{35}H_{49}O_6SSi$: 625.3018), 573 (5.9), 501 (100), 73 (94).

Isomer **4a-b**: ¹H NMR (80 MHz, $CDCl_3$): δ = 0.11 (s, $Si(CH_3)_2$), 0.91 (s, $SiC(CH_3)_3$ and CH_3-18), 1.05 (s, CH_3-19), 2.04 (s, 3β-OAc), 2.05-3.06 (m, 6H), 3.60 (s, OCH_3), 4.34 (dd, 23-H), 5.05 (m, $W_{1/2}$ = 6.0 Hz, 3α-H), 6.33 (broad s, 21-H), 7.14 - 7.60 (Ar-H); $J_{23/22}$ = 7.0 Hz, $J_{23/22'}$ = 10.0 Hz.- IR (CCl_4): 1725 (ester), 1700 (ketone), 1645 cm^{-1} (C=C).- CD (CH_3CN): λ_{max} (Δε) = 282 (+2.73), 263 (+1.70), 232 nm (-0.80).- $C_{39}H_{58}O_6SSi$ (683.0), MS: m/z (%) = 682 (0.6, M^+), 625.3021 (7, Calc for $C_{35}H_{49}O_6SSi$: 625.3018), 573 (5), 501 (100), 73 (100).

Isomer **4a-c**: ¹H NMR taken from the spectrum of the mixture of **4a-c**/**4a-d** by comparison with the spectrum of **4a-d** (80 MHz, $CDCl_3$): δ = 0.94 (s, $SiC(CH_3)_3$), 1.06 (s, CH_3-19), 2.05 (s, 3β-OAc), 3.65 (s, OCH_3), 4.25 (dd, 23-H), 5.05 (m, $W_{1/2}$ = 6 Hz, 3α-H), 6.37 (broad s, 21-H), $J_{23,22}$ = 7 Hz, $J_{23,22'}$ = 9 Hz.

Isomer **4a-d**: ¹H NMR (80 MHz, $CDCl_3$): δ = 0.12 and 0.15 (2 s's, $Si(CH_3)_2$), 0.96 (s, $SiC(CH_3)_3$), 1.04 and 1.06 (2 s's, CH_3-18 and CH_3-19), 2.05 (s, 3β-OAc), 2.10-3.13 (17α-H, CH_2-11, CH_2-22), 3.65 (s, OCH_3), 4.01 (dd, 23-H), 5.05 (m, $W_{1/2}$ = 6.0 Hz, 3α-H), 6.21 (broad s, 21-H), 7.10 - 7.55 (Ar-H); $J_{23/22}$ = 5.0 Hz, $J_{23/22'}$ = 9 Hz.- IR (CCl_4): 1730 (ester), 1700 (ketone), 1650 cm^{-1} (C=C).- CD (CH_3CN): λ_{max} (Δε) = 308 (+0.29), 278 (-1.71), 270 (-1.50), 234 nm (+1.94).- $C_{39}H_{58}O_6SSi$ (683.0), MS: m/z (%) = 682 (< 0.5, M^+), 625 (1), 541 (17), 501 (100), 73 (100).

(23E,24E)-3β-Acetoxy-24-(tert-butyl-dimethyl-silanyloxy)-21,24-epoxy-24-methoxy-23-phenylsulfanyl-5β-chol-20-en-12-one (6a).

A solution of **1** (100.0 mg, 0.26 mmol), **10b** (140.0 mg, 0.47 mmol) and $[D_{27}]Eu(fod)_3$ (80.0 mg, 0.08 mmol) in dry $CHCl_3$ (1 ml) was stirred at 20°C for 15 d. MPLC (column B, hexanes - ethyl acetate 10:1) gave **6a** (1:1 mixture of two stereoisomers (¹H NMR), 92.7 mg, 53%),

26.8 mg of **1** were recovered.- ^{1}H NMR (400 MHz, C_6D_6): δ = 0.30 and 0.37 (2 s's, $Si(CH_3)_2$), 0.68-0.90 (CH_3 singlets), 1.08 and 1.09 (2 s's, $SiC(CH_3)_3$), 1.73 (s, OAc), 2.78-3.03 (CH_2-22), 3.32 and 3.36 (2 s's, OCH_3), 3.54-3.65 (23-H), 5.08 (m, 3α-H), 6.37 and 6.50 (2 s's, 21-H), 6.92-7.65 (Ar-H).- IR ($CHCl_3$): 1730 (ester), 1710 (ketone), 1660 cm^{-1} (C=C).- $C_{39}H_{58}O_6SSi$ (683.0), MS: m/z (%) = 668 (1), 550 (5), 534 (6), 508 (20), 427 (54), 374 (30), 341 (26), 147 (30), 135 (31), 110 (78), 109 (46), 107 (40), 43 (100).

(23R)- and (23S)-3β-Acetoxy-12-oxo-23-phenylsulfanyl-5β-buf-20-enolide (**7a** and **7b**).
To a solution of dry HCl in $CHCl_3$ (saturated at 0°C, 35 ml) was added at -40°C a solution of **6a** (60.0 mg, 82.6 μmol) in $CHCl_3$ (10 ml). The mixture was left at -40°C for 1h, then $NaHCO_3$ (saturated solution in H_2O, 30 ml) was added at -25°C. Usual work-up (CH_2Cl_2), followed by MPLC (column B, hexanes - ethyl acetate 5:1) furnished **7a** (12.1 mg, 27%), **7b** (11.4 mg, 26%), and a fraction containing both **7a** and **7b** (14.2 mg, 32%). **7a** and **7b** were identical with authentic samples.[5]

tert-Butyl (21 E ,23 E)-3β-acetoxy-21-(tert-butyl-dimethyl-silanyloxy)-23-methylsulfanyl-12-oxo-5β-chol-20-en-24-oate (**4b**), mixture of stereoisomers.
To a solution of **1** (879.4 mg, 2.2 mmol) in dry CH_3CN (16 ml) were added (i) anhydrous $ZnCl_2$ (41.0 mg, 0.3 mmol) and (ii) **10c** (1.2 ml, 4.3 mmol). The mixture was stirred at 20°C for 105 min, then NEt_3 (0.2 ml) was added. Solvent evaporation and SC (40g SiO_2, hexanes - ethyl acetate 10:1 --> 4:1) gave **4b** (477.1 mg, 35%); 391.0 mg of **1** were recovered.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.05-0.10 (4s, $Si(CH_3)_2$), 0.90, 0.93 ($SiC(CH_3)_3$ and CH_3-18 signals), 1.04 (CH_3-19), 1.42 and 1.47 (2s's, $OC(CH_3)_3$), 2.03, 2.09 and 2.19 (3β-OAc and SCH_3 signals), 5.04 (complex of multiplets, $W_{1/2}$ = 6.2 Hz, 3α-H), 6.16 and possibly small signals at 6.25 and 6.30 (21-H signals).- IR (CCl_4): 1730 (ester), 1710 (ketone), 1640 cm^{-1} (C=C).- $C_{37}H_{62}O_6SSi$ (663.0), MS: m/z (%) = 662.4036 (0.4, M$^+$, Calc for $C_{37}H_{62}O_6SSi$: 662.4036), 605 (6), 558 (6), 501 (100), 73 (76).

tert-Butyl (20 E ,23 E)-3β-acetoxy-23-methylsulfanyl-12,21-dioxo-5β-cholan-24-oate (**5b**), mixture of stereoisomers.
To a solution of **4b** (477.1 mg, 0.72 mmol) in wet THF (5 ml) was added KF (1 mol/l solution in methanol, 2.8 ml), and the mixture was stirred at 20°C for 10 h. Usual work-up (ethyl acetate) gave pure **5b** as a mixture of stereoisomers (381.8 mg, 96%), identical with a specimen prepared by a different route.[5]

(23 E ,24 E)-3β-Acetoxy-24-(tert-butyl-dimethyl-silanyloxy)-21,24-epoxy-24-methoxy-23-methylsulfanyl-5β-chol-20-ene-12-one (**6c**), mixture of two stereoisomers.
6c was prepared from **1** (150.0 mg, 0.39), **10e** (150.0 mg, 0.51 mmol), and [D_{27}]Eu(fod)$_3$ (120 mg, 0.11 mmol) as described for **6a**. Reaction time: 19 d. MPLC (column B, hexanes - ethyl acetate 10:1) provided **6c** (1.2:1 mixture (^{1}H NMR) of two stereoisomers, 114.2 mg, 47%); 61.0 mg of **1** were recovered.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.04, 0.05, 0.08 and 0.09 (4 s's, $Si(CH_3)_2$), 0.88 (s, $SiC(CH_3)_3$), 0.93 and 1.03 (2s's, CH_3-18 and CH_3-19), 2.02 (s, 3β-OAc), 2.13, 2.14 (2s's, SCH_3), 3.29, 3.33 (2 s's, ratio 1:1.2, OCH_3), 5.03 (m, $W_{1/2}$ = 6 Hz, 3α-H), 6.02 (m, $W_{1/2}$ = 4 Hz, 21-H).- IR ($CHCl_3$): 1725 (ester), 1705 (ketone), 1655 cm^{-1} (C=C).- $C_{34}H_{56}O_6SSi$ (621.0), MS: m/z (%) = 620 (0.1, M$^+$), 588 (1), 563 (1), 429 (6), 89 (100), 75 (86).

(23R)- and (23S)-3β-Acetoxy-12-oxo-23-methylsulfanyl-5β-buf-20-enolide (**7c** and **7d**).
The mixture of the **6c** stereoisomers (80.0 mg, 0.19 mmol) was converted into **7c** and **7d** as described for the reaction **6a** --> **7a/7b**. MPLC (column B, hexanes - ethyl acetate 5:1) gave **7d** (13.7 mg, 22%), **7c** (14.2 mg, 23%), and a

fraction containing both **7c** and **7d** (22.8 mg, 37%). **7c** and **7d** were identical with authentic samples.[5]

Reaction of **1** with 1-methoxy-1-trimethylsilanyloxy-propene (**10a**).
a) In acetonitrile at 20°C: To a solution of **1** (50.2 mg, 0.13 mmol) and anhydrous $ZnCl_2$ (2.6 mg, 0.02 mmol) in dry acetonitrile (0.5 ml) **10a**[20] (50 µl, 0.26 mmol) was added. The mixture was stirred at 20°C for 1 h. After addition of Et_3N (50 µl), solvent evaporation and SC (5g SiO_2, hexanes - ethyl acetate) 49.8 mg (68%) of a 1.5:1 mixture (^1H NMR) of the 1,2- and 1,4-adducts was obtained which could not be separated. The mixture was dissolved in THF (1 ml) and treated with tetrabutylammonium fluoride (TBAF, 1 mol/l solution in THF, 0.1 ml) for 5 min at 20°C. Work-up (ethyl acetate) and LC (5g SiO_2, hexanes - ethyl acetate 5:1) gave **17a** (23.8 mg, 32%) and **15** (11.3 mg, 18%).
b) In dimethoxyethane (DME) at -78°C: To a solution of **1** (665.4 mg, 1.73 mmol) and anhydrous $ZnCl_2$ (53.2 mg, 0.39 mmol) in dry DME (40 ml) was added at -78°C **10a** (0.65 ml, 3.45 mmol). The mixture was stirred at -78°C for 100 min. After addition of Et_3N (0.2 ml) the mixture was allowed to warm to 20°C, then treated with TBAF (1 mol/l in THF, 6 ml) for 5 min at 20°C. Work-up (ethyl acetate) and LC (30 g SiO_2, hexanes - ethyl acetate 4:1) gave **17a** (241.0 mg, 24%) and **15** (465.4 mg, 58%).

Methyl (22*E*)-3β-acetoxy-22-(tert-butyl-dimethyl-silanyloxy)-12-oxo-5β-chol-20-en-24-oate (**17a**).
^1H NMR (80 MHz, $CDCl_3$): δ = -0.08 and 0.05 (2 s's, $Si(CH_3)_2$), 0.88 (s, $SiC(CH_3)_3$), 0.97 and 1.05 (2 s's, CH_3-18 and CH_3-19), 2.01 (s, 3β-OAc), 3.67 (s, OCH_3), 4.83-5.17 (3α-H, 21-H, 22-H), 5.47 (m, $W_{1/2}$=3.0 Hz, 21-H).- IR (CCl_4): 1740 (ester), 1710 (ketone), 1650 cm^{-1} (C=C).- $C_{33}H_{54}O_6Si$ (574.9), MS: m/z (%) = 574.3695 (0.23, M^+, Calc for $C_{33}H_{54}O_6Si$: 574.3690), 559 (1), 543 (1), 517 (92), 475 (29), 351 (79), 89 (100).

Methyl (20*E*)-3β-acetoxy-12,21-dioxo-5β-chol-24-oate (**15**), mixture of two stereoisomers.
^1H NMR (80 MHz, $CDCl_3$): δ = 1.03, 1.05 and 1.08 (CH_3-18 and CH_3-19 signals), 2.04 (s, 3β-OAc), 3.63 (s, OCH_3), 5.05 (m, $W_{1/2}$ = 6.7 Hz, 3α-H), 9.41-9.58 (21-H signals).- IR (CCl_4): 1730 (ester), 1710 cm^{-1} (aldehyde).- $C_{27}H_{40}O_6$ (460.0), MS: m/z (%) = 432 (26, $[M^+-28]^+$), 414 (12), 372 (8), 359 (6), 291 (49), 231 (85), 121 (100).

3β-Acetoxy-12-oxo-5β-buf-20-enolide (**16**).
A mixture of **15** (465.4 mg, 1.01 mmol), THF (43 ml), methanol (21 ml) and Na_2CO_3 (5% solution in water, 21 ml) was stirred at 20°C for 3 h. The pH value was then adjusted to 5 by addition of 2N HCl. Usual work-up (ethyl acetate) provided a crude acid (416.2 mg) which was dissolved in benzene (150 ml). After addition of p-toluenesulfonic acid, monohydrate (150 mg, 0.79 mmol) the solution was refluxed for 15 h. The reaction flask was connected to a Soxhlet apparature charged with 4 Å molecular sieves to remove water formed in the reaction. After cooling, addition of Et_3N (0.2 ml), solvent evaporation and LC (20 g SiO_2, hexanes - ethyl acetate 4:1) amorphous **16** (250.3 mg, 55%) was obtained.- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.90 (s, CH_3-18), 1.05 (s, CH_3-19), 2.03 (s, 3β-OAc), 2.03 - 3.00 (m, 8H), 5.03 (m, $W_{1/2}$ = 8.0 Hz, 3α-H), 6.40 (m, $W_{1/2}$ = 3.6 Hz, 21-H).- ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 13.0 (CH_3-18), 21.4 ($\underline{C}H_3CO$), 23.1, (CH_3-19), 23.4, 23.5, 24.1 (C-2, C-16, C-23), 24.7 (C-15), 25.7 (C-6), 26.3 (C-7), 28.5 (C-22), 30.4, 30.6 (C-1, C-4), 35.5 (C-10), 35.6 (C-8), 36.8 (C-5), 38.2 (C-11), 43.0, 44.2 (C-9, C-17), 57.1 (C-14), 58.1 (C-13), 70.0 (C-3), 119.2 (C-20), 139.1 (C-21), 169.1 (C-24), 170.5 ($CH_3\underline{C}O$), 214.3 (C-12).- IR (CCl_4): 1775 (enol lactone), 1740 (ester), 1710 cm^{-1} (ketone).- CD (CH_3CN): λ_{max} ($\Delta\varepsilon$) = 329 (-0.07), 297 (+1.25), 238 nm (+0.88).- $C_{26}H_{36}O_5$ (428.6), MS: m/z (%) = 428.2576 (28, M^+, Calc for $C_{26}H_{36}O_5$: 428.2563), 367 (6), 359 (4), 349 (6), 314 (4), 218 (38), 43 (100).

(22 E ,23 E)-3ß-Acetoxy-22-hydroxy-12-oxo-23-phenylsulfanyl-5ß-chol-20-en-24-oic acid (17b).
From trimethylsilyl phenylsulfanylacetate[5] (9d, 22.2 ml, 11.1 mmol) 1,1-bis(trimethylsilylanyloxy)-2-phenylsulfanyl-ethylene (10d) was prepared as described for 10b (Ainsworth procedure). After Kugelrohr distillation (130°C/67 Pa) 2.8g (75%) of a specimen of 10d was obtained that was according to its ^{1}H NMR spectrum (characteristic signals: δ = 0.20 and 0.34 (2 s's, Si(CH$_3$)$_3$), 4.36 (s, =CH)) not completely pure.
A solution of 1 (31.3 mg, 0.08 mmol) and 10d (75 µl, 0.28 mmol) in dry CH_2Cl_2 (0.1 ml) was heated to 60°C for 13 h. Then a further portion of 10d (70 µl, 0.26 mmol) was added, and heating to 60°C was continued for 3 h. Work-up (ethyl acetate) followed by LC (1 g of SiO_2, hexanes - ethyl acetate 2:1) provided 17b (30.5 mg, 67%) the spectral data of which were identical with those of a sample of 17b previously prepared by another method.[5]

Reaction of cinnamaldehyde (22) with 2-chloro-1,1-diethoxy-ethylene (23).
a) In toluene at 180°C: A solution of 22 (freshly distilled, 396.3 mg, 3 mmol), 23 (freshly prepared,[45] 1252 mg, 7.5 mmol), and hydroquinone in toluene (2 ml) was heated to 180°C (sealed vessel) for 16 h. Solvent removal and MPLC (column B, hexanes - ethyl acetate 50:1, followed by a second separation of impure fractions with hexanes - ethyl acetate 100:1) gave 24 (185.0 mg, 37%), 25 (111.3 mg, 22%), and 27 (89.3 mg, 21%), 162 mg of 22 were recovered.
b) In toluene at 150°C: Heating 22 (463.2 mg, 3.5 mmmol), 23 (1465 mg, 8.8 mmol), and hydroquinone (20.1 mg) in toluene (2 ml) solution to 150°C for 6 h gave after separation as described above provided 24 (81.0 mg, 19%) and 26 (136.0 mg, 33%), 268.1 mg of 22 were recovered.
c) In acetonitrile at 100°C: A solution of 22 (325 mg, 2.45 mmol), 23 (1027 mg, 6.2 mmol), and hydroquinone (13.0 mg) in acetonitrile (2.5 ml) was heated to 100°C for 46 h. Separation as described above gave 27 (107.5 mg, 50%), 224.1 mg of 22 were recovered. The formation of 24 and 25 could not be detected.

(±)-trans-3-Chloro-2,2-diethoxy-3-phenyl-3,4-dihydro-2H-pyran (24).
M.p. 92-95°C (from acetone-H_2O).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.25 and 1.29 (2 t's, J = 7 Hz, C$\underline{H}_3$CH$_2$O), 3.69 (q, CH$_3$C$\underline{H}_2$O), 3.85 (dd, 4-H), 4.10 (d, 5-H), 4.82 (dd, 3-H), 6.35 (dd, 2-H), 7.35 (s, Ar-H); $J_{4,5}$=9 Hz, $J_{4,2}$=2 Hz, $J_{3,2}$=6 Hz, $J_{3,4}$=2 Hz.- ^{13}C NMR ($CDCl_3$): δ = 15.23 (C$\underline{H}_3$CH$_2$O), 47.23 (C-4), 57.77 and 59.62 (CH$_3$C$\underline{H}_2$O), 61.34 (C-5), 105.75 (C-3), 111.73 (C-6), 127.45 and 128.58 (C-2 and aromat. C_2-C_6), 141.07 (aromat. C_1).- IR (CCl_4): 1650 (C=C), 1600 and 1490 (C=C,arom.) 1225 cm^{-1} (C-O).- $C_{15}H_{19}ClO_3$ (282.8), MS: m/z (%) = 282 (4, M$^+$), , 247 (3), 237 (14), 209 (7), 173 (4), 150 (100), 132 (18), 122 (31), 115 (33), 94 (53), 77 (15).

(±)-cis-3-Chloro-2,2-diethoxy-3-phenyl-3,4-dihydro-2H-pyran (25).
^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.25 and 1.29 (2 t's, J = 7 Hz, C$\underline{H}_3$CH$_2$O), 3.65 and 3.75 (2 q's, CH$_3$C$\underline{H}_2$O), 4.20-4.35 (d, 5-H and m, $W_{1/2}$=4 Hz, 4-H), 4.93 (m, 3-H), 6.41 (2-H), 7.35 (s, Ar-H); $J_{3,4}$ = 1 Hz, $J_{2,3}$ = 6 Hz, $J_{4,5}$ = 6 Hz.

Ethyl (2E, 3E,4E)-2-chloro-3-ethoxy-5-phenyl-pent-4-enoate (26).
^{1}H NMR (60 MHz, CCl_4): δ = 1.05-1.40 (C$\underline{H}_3$CH$_2$O triplets), 3.30-3.90 (m, CH$_3$C$\underline{H}_2$O), 4.00-4.35 (CH$_3$C$\underline{H}_2$OCO, 2-H, 3-H), 5.97 (m, 4-H), 6.58 (dd, 5-H), 7.00-7.40 (m, Ar-H); $J_{4,5}$ = 16 Hz, $J_{3,5}$ = 2 Hz.- IR (CCl_4): 1740 (C=O), 1645 (C=C), 1595 and 1490 cm^{-1} (C=C, arom.).- $C_{15}H_{19}ClO_3$ (282.8), MS: m/z (%) = 237 (1, [M-C_2H_5O]$^+$), 201 (1), 178 (2), 161 (100, ion a, see Scheme 5).

Ethyl (2Z,4E)-2-chloro-5-phenyl-penta-2,4-dienoate (27).
^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.33 (t, J = 7 Hz, CH_3CH_2O), 4.20 (q, CH_3CH_2O), 6.40-6.80 (4-H), 7.00-7.50 (3-H, 5-H and Ar-H).- IR ($CHCl_3$): 1710 (C=O), 1615 (C=C), 1585 (C=C, aromat.) 1270 cm^{-1} (C-O).- $C_{13}H_{13}ClO_2$ (236.7), MS: m/z (%) = 236 (22, M^+), 207 (8), 201 (1), 191 (21), 176 (30), 163 (34), 162 (38), 106 (98), 105 (100).

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