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MODEL STUDIES DIRECTED TOWARD FORSKOLIN: 1,9-DIDEOXYFORSKOLIN FROM A BICYCLIC PRECURSOR

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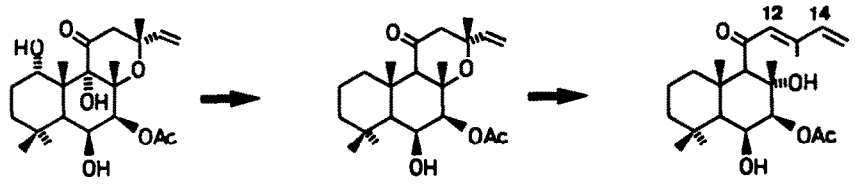
Abstract - From the bicyclic labdane derivative **4** the silyl ether of 1,9-dideoxyforskolin **22** was obtained by a) HCl addition (**4**→**16**), b) cyclization with N-phenylselenophthalimide-$SnCl_4$, and c) reductive elimination.

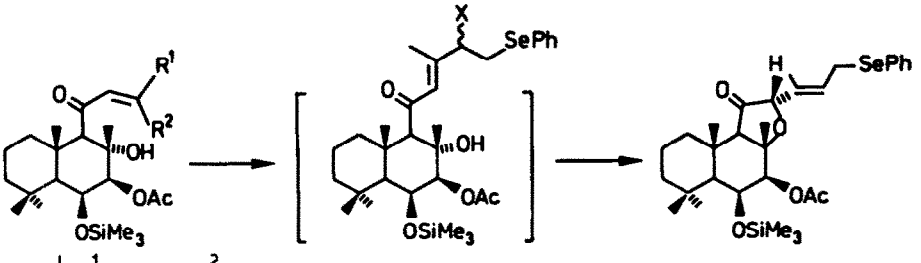
Introduction

Some time ago we discussed a novel synthetic plan for forskolin (**1**) via 1,9-dideoxyforskolin (**2**) which included as one of the disconnections the retro-1,4-addition **2** → **3**.[1,2] In attempting to test the feasibility of this synthetic scheme



1 **2** **3**

we tried to cyclize compounds of type **3**. We studied organoselenium-mediated cyclization reactions assuming that in **3** the phenylselenating reagent would attack the 12-position because of the conjugation of the two double bonds with the 11-keto group. Contrary to our expectations treatment of **4** with N-phenylselenophthalimide (NPSP) led exclusively to the formation of cyclization products such as **7**. Based on the mode of reaction of **4** with phenylselenyl chloride we proposed that the reaction



	R^1	R^2
4	$CH=CH_2$	CH_3
5	CH_3	$CH=CH_2$

6 **7**

of **4** with NPSP proceeds via an intermediate of type **6** from which **7** is formed by an S_N2' reaction.[1]

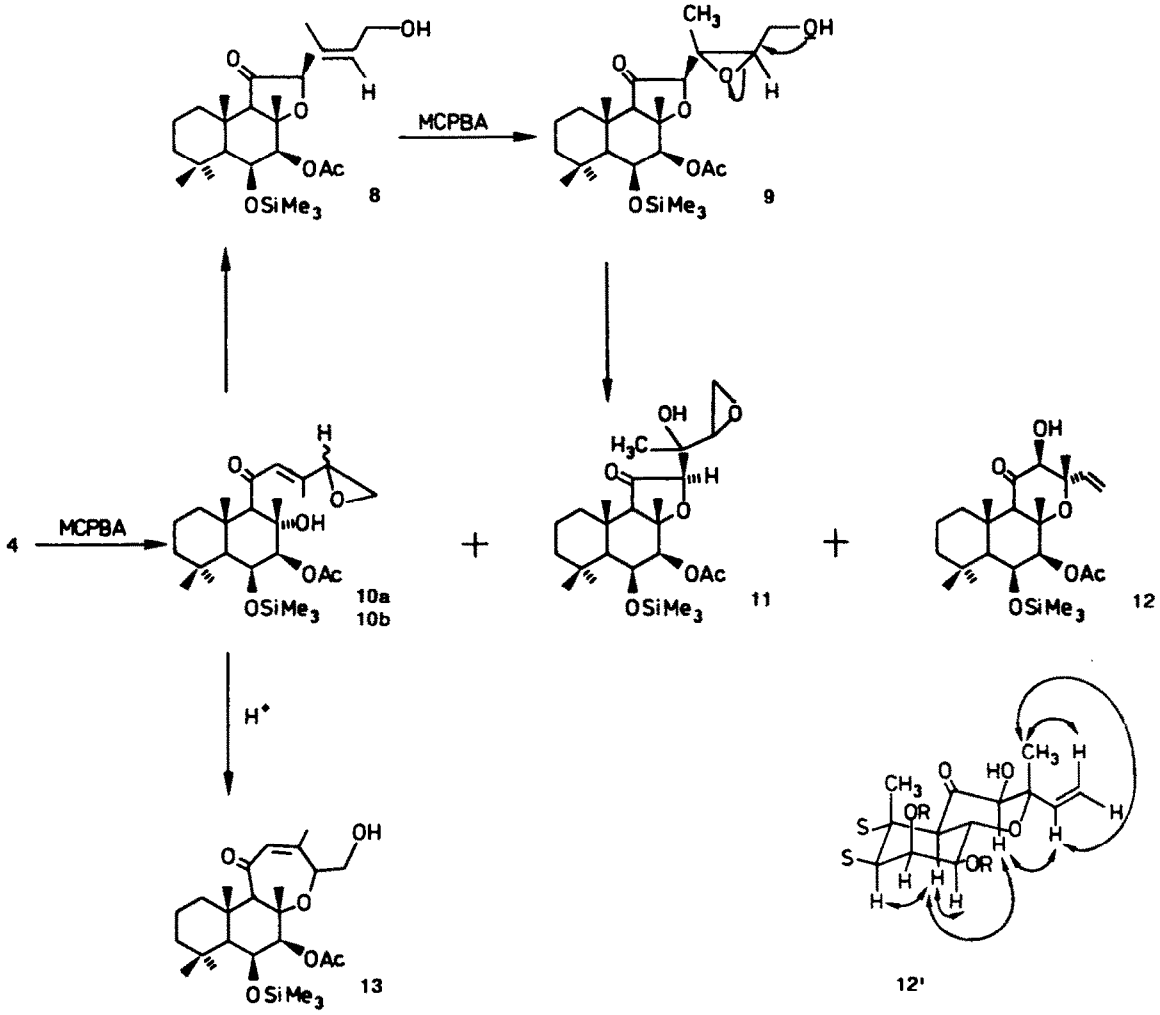
A logical consequence of this reasoning, which is supported by recent results of Hashimoto et al.,[3] is to repeat the cyclization reaction after protecting the 14-double bond in **4**. This is described in the present publication.

Reaction of 4 with m-chloroperbenzoic acid

In the reaction of **4** [1] with m-chloroperbenzoic acid (MCPBA) we wished to make use of the preferred reaction of the 14-double bond with electrophiles described above. In the event, reaction of **4** with MCPBA led to the formation of four products. **10a** and **10b**, which were obtained in 25% and 23% yield, respectively, correspond to the anticipated preferential attack on the terminal double bond. The formation of **11** (31%, unknown configuration at C-13 and C-14) can be understood assuming an acid-catalyzed rearrangement of **10a/10b** to give **8**, further oxidation (**8** → **9**) and a Payne-type rearrangement [4] (**9** → **11**).- The forskolin derivative **12** was isolated in 6% yield. It should be formed by electrophilic peracid attack in the 12-position.

With respect to the desired ring C forming cyclization epoxide **10a** proved unsuitable. All attempted cyclization reactions ($Hg(OCOCF_3)_2$, N-phenylselenophthalimide in the presence of tin tetrachloride (NPSP-$SnCl_4$), PhSeCl, and $SnCl_4$) led to complex product mixtures from which we could only isolate the 7-membered ring product **13**.

The configuration at C-12 in **12** was established by NOE difference spectroscopy. The most indicative enhancements are summarized in formula **12'**. The structure of 13



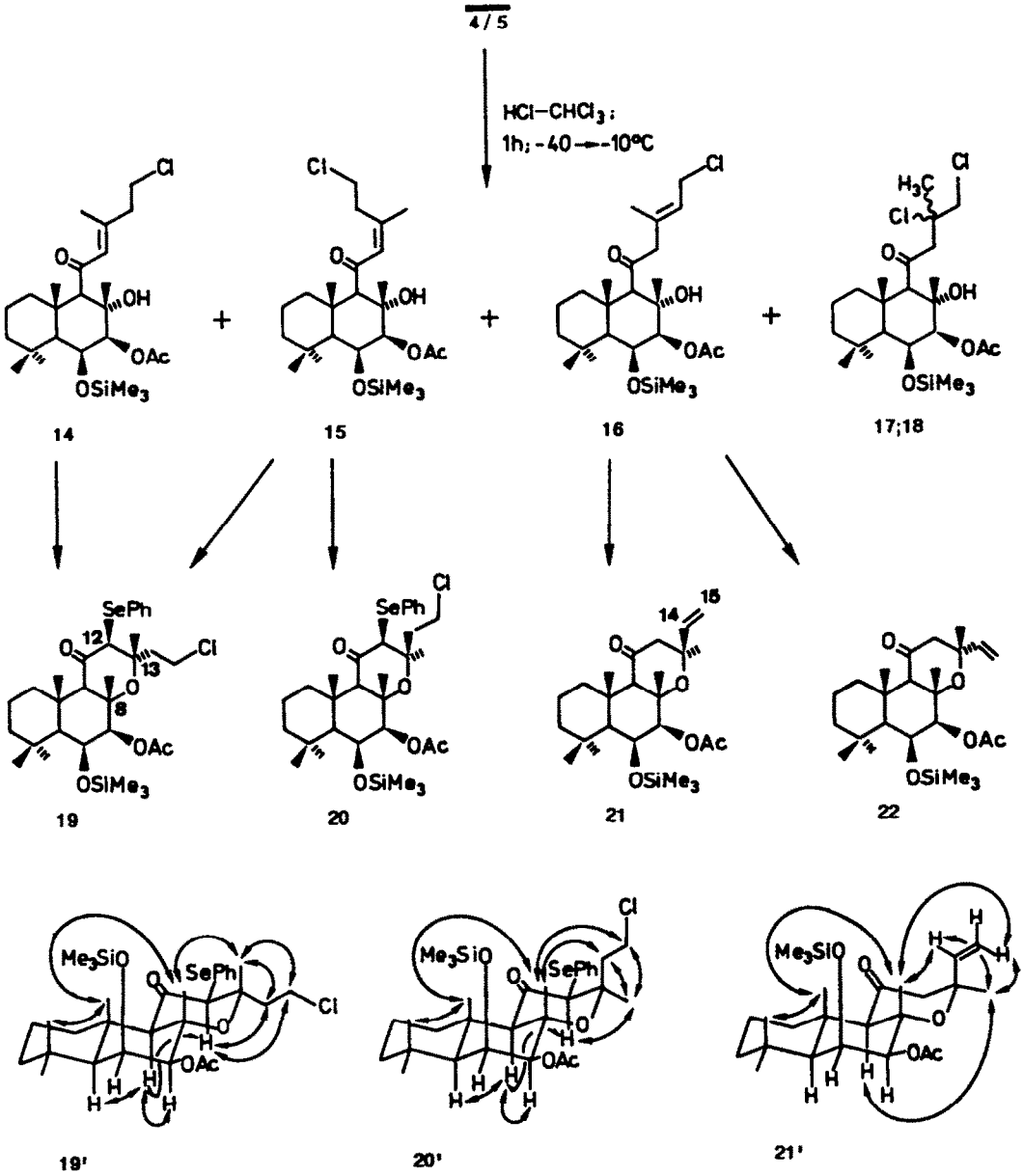
was suggested by ^{13}C NMR signals at δ=65.02 ($\underline{C}H_2$-15) and δ=67.20 ($\underline{C}H$-14). A full account of the spectral data which support the proposed structures is given in the Experimental.

It may be concluded from the results reported above that epoxides of type **10a/10b** are too acid-sensitive to be of use in electrophilic ring C forming reactions.

Reaction of 4 and 5 with hydrochloric acid followed by organoselenium-mediated cyclizations

Reaction of both **4** and **5** with dry HCl in $CHCl_3$ at low temperature (-40°C→ -25°C) gave, irrespective of the configuration around the Δ^{12} double bond, after 20 min a mixture of the 1,2-addition products **14** (29%) and **15** (14%), as well as the bis-adduct **17** (18%). Increasing the reaction time to 1h furnished in addition to **14**, **15**, and **17** the 1,4-adduct **16** (17%) and a second bis-adduct **18**.

The double bond configuration in **14** and **15** was assigned on the basis of NOE difference spectra (irradation into the CH_3-16 and the olefinic proton signals, respectively). **15** slowly decomposed. In the ^1H NMR spectrum of a partly decomposed sample the signals of **4**, **5**, and the isomeric chloride **14** were identified.



14, **15**, and **16** were individually subjected to cyclization with NPSP-$SnCl_4$.[6] **14** furnished **19**, and from **15** both **19** and **20** were obtained. The formation of **19** and **20** in the cyclization reaction of **15** obviously reflects the ready rearrangement of **15** into the more stable isomer **14** (vide supra). The structures of **19** and **20** are based on their NMR spectra. Most specifically, the C-8 signal in **19** (δ=82.95) appeared at much lower field than in **14** (δ=75.47) indicative of the ether formation (β-Effekt). That the second ether carbon was C-13 could be deduced from a quaternary carbon signal at δ=83.73. A new tertiary carbon signal (as compared with **14**) at δ=67.55 with two satellites caused by ^{13}C-^{77}Se coupling (J=-65.7 Hz)[7] proved the 12-position of the PhSe substituent. The structural assignment of **20** rests on the same sort of arguments. The configuration at the newly formed chiral centers in **19** and **20** were deduced from the NOE difference spectra. The results are summarized in formulae **19'** and **20'**.

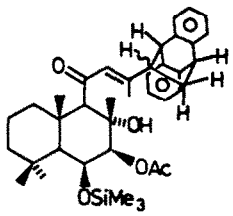
We speculated, that in the cyclization reaction of **16** a product with a phenylselanyl group at C-14 and the chloro substituent at C-15 should be formed, and we therefore subjected the cyclization mixture immediately to a reductive elimination reaction with Zn-Cu couple.

Indeed, compound **22** was formed in 41% overall yield along with the stereoisomer **21** (12%). **22** was identical in all respects with a sample obtained from 1,9-dideoxy-forskolin.[1] The β-position of the vinyl group in **21** was clearly visible from the NOE results summmarized in **21'**.

In concluding this paragraph, we wish to emphasize, that the cyclization reactions of compounds **14** - **16** took the desired course. From the synthetic point of view the cyclization of **16** followed by reductive elimination is particularly remarkable, since for the first time a forskolin derivative with the complete C_{20} carbon skeleton has been obtained from an AB precurser in a one-pot operation.

Diels-Alder reaction of **4b** with anthracene

A well-known method for the protecting of double bonds uses the Diels-Alder retro-Diels-Alder strategy.[8] In an attempt to apply this methodology in the present context we tried to form the Diels-Alder adduct of **4** with anthracene.[9] In the $TiCl_4$-catalyzed reaction the two isomeric adducts **23** and **24** were obtained but only in very moderate yields (11% and 5%, respectively). The main reaction products (38%) were the HCl addition products **14** and **15**. Experiments aimed at improving the yields of **23**/**24** using $Eu(fod)_3$ and high-pressure conditions,[10] respectively, were unrewarding.



23;**24**

E X P E R I M E N T A L

General

All reactions were performed in 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. If not otherwise stated, reactions were performed in Wheaton serum bottles sealed with aluminium caps with open top and Teflon-faced septum (Aldrich). The instrumentation used was: ^{1}H NMR: WP 80 (Bruker), AM 400 (Bruker); ^{13}C NMR: AM 400 (Bruker); IR: Perkin Elmer 257 and 681; MS: MAT-731 and MAT-CH-5 (Varian); LC: Medium pressure chromatography (MPLC) using 31.0 cm x 2.5 cm (column B, 60 g SiO_2) and 37.0 cm x 1.5 cm (column A, 17 g SiO_2) glass tubes, silica gel 50 µm, (Grace), Duramat pump (CfG); UV detector Chromatochord III (Serva).

Reaction of 4 with m-chloroperbenzoic acid.

To a solution of **4** [1] (400.0 mg, 0.889 mmol) in CH_2Cl_2 (2 ml) containing solid $NaHCO_3$ (224.0 mg, 2.667 mmol) at 0°C within 10 min a solution of MCPBA (80% MCPBA, 383.5 mg, 1.778 mmol) in CH_2Cl_2 (2 ml) was added. The mixture was then stirred at 0°C for 255 min. Filtration through SiO_2, elution with hexanes-acetone 3:1, solvent evaporation, and MPLC (column B, hexanes-acetone 8:1 → 7:1) furnished **10a** (93.4 mg, 23%), **10b** (101.5 mg, 25%), **12** (25.7 mg, 6%) and a mixture of stereoisomers (133.8 mg, 31%), from which the main component **11** was obtained by MPLC (column A, hexanes-ethyl acetate 2:1).

(14Ξ,12E)-7β-Acetoxy-14,15-epoxy-8-hydroxy-8β-trimethylsilanyloxy-labd-12-en-11-one (10a, unpolar isomer).

^{1}H NMR (400 MHz, COSY, C_6D_6)[11]: δ = 0.15 (s, 9H, $Si(CH_3)_3$), 0.76 (d, 1H, 5-H), 0.89 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-18), 1.73, 1.77 and 1.80 (3xs, 3x3H, CH_3-20, $OCOCH_3$ and CH_3-17), 1.98 (d, 3H, CH_3-16), 2.17 and 2.34 (AB part of an ABX system, 2H, CH_2-15), 2.57 (s, 1H, 9-H), 2.98 (X-part of the ABX system, 1H, 14-H), 4.45 (dd, 1H, 6-H), 4.88 (d, 1H, 7-H), 6.47 (broad s, $W_{1/2}$=3.5 Hz, 1H, 12-H)); $^4J_{16,12}$=1.5 Hz, $|J_{15,15'}|$=6.0 Hz, $J_{15,14}$ =2.5 Hz, $J_{15',14}$=4.0 Hz, $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.47 ($Si(CH_3)_3$), 13.08 (C-16), 16.05 (C-20), 18.29 (C-2), 20.66 and 20.70 (C-17 and $OCO\underline{C}H_3$), 23.13 (C-19), 32.88 (C-18), 33.66 (C-4), 40.40 (C-10), 42.06 (C-1), 43.53 (C-3), 47.02 (C-15), 54.24 and 55.22 (C-14 and C-5), 70.07 and 71.56 (C-9 and C-6), 75.56 (C-8), 82.35 (C-7), 129.61 (C-12), 149.37 (C-13), 170.38 ($O\underline{C}OCH_3$), 201.13 (C-11).- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1685 (C=O, enone), 1620 cm^{-1} (C=C).- $C_{25}H_{42}O_6Si$ (466.7), MS: m/z (%) = 466 (0.5, M$^+$), 448.2633 (14, Calc for $C_{25}H_{40}O_5Si$: 448.2645), 383 (13), 323 (17), 263 (30), 233 (58), 225 (75), 73 (75), 43 (100).

(14Ξ,12E)-7β-Acetoxy-14,15-epoxy-8-hydroxy-8β-trimethylsilanyloxy-labd-12-en-11-one (10b, polar isomer).

^{1}H NMR (80 MHz, C_6D_6): δ = 0.17 (s, 9H, $Si(CH_3)_3$), 0.76 (d, 1H, 5-H), 0.90 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-18), 1.75 and 1.79 (2s, 3H and 6H, CH_3-20, CH_3-17 and $OCOCH_3$), 2.03 (d, 3H, CH_3-16), 2.06-2.47 (AB part of an ABX system, 2H, CH_2-15), 2.60 (s, 1H, 9-H), 2.92 (X part of the ABX system, 1H, 14-H), 4.45 (dd, 1H, 6-H), 4.88 (d, 1H, 7-H), 6.49 (broad s, $W_{1/2}$=1.7 Hz, 12-H); $^4J_{16,12}$=0.8 Hz, $|J_{15,15'}|$=6.2 Hz, $J_{14,15}$=2.5 Hz, $J_{14,15'}$=4.1 Hz, $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1685 (C=O, enone), 1620 cm^{-1} (C=C).- $C_{25}H_{42}O_6Si$ (466.7), MS: m/z (%) = 466 (0.4, M$^+$), 448.2645 (4.4, Calc for $C_{25}H_{40}O_5Si$: 448.2645), 391 (4.3), 389 (4.2), 383 (5.0), 323 (9), 296 (8), 263 (16), 233 (23), 225 (24), 73 (47), 43 (100).

(12R,13E,14E)-7β-Acetoxy-8,12;14,15-diepoxy-13-hydroxy-6β-trimethylsilanyloxy-labdan-11-one (11).

^{1}H NMR (400 MHz, COSY, C_6D_6)[12]: δ = 0.11 (s, 9H, $Si(CH_3)_3$), 0.83 (s, 3H, CH_3-18), 1.07 (s, 3H, CH_3-19), 1.36 (s, 3H, CH_3-16), 1.54 (s, 3H, CH_3-17), 1.62 (s, 3H, CH_3-20), 1.77 (s, 3H, $OCOCH_3$), 2.32 and 2.51 (AB system of an ABX system, 2H, CH_2-15), 2.61 (s, 1H, 9-H), 2.87 (X part of the ABX system, 1H, 14-H), 3.80 (s, 1H, 12-H), 4.35 (dd, 1H, 6-H), 4.70 (d, 1H, 7-H); $|J_{15,15'}|$=6.0 Hz, $J_{14,15}$=3.0 Hz, $J_{14,15'}$=4.0 Hz, $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.43 ($Si(CH_3)_3$), 13.06 (C-20), 15.75 (C-17), 18.10 (C-2), 20.87 and 20.89 (C-19 and $OCOCH_3$), 23.10 (C-16), 32.77 (C-4), 33.57 (C-18), 40.50 (C-10), 41.87 (C-1), 43.26 (C-3), 44.37 (C-15), 52.80 and 54.75 (C-14 and C-5), 62.93 (C-9), 64.30 (C-13), 67.51 (C-12), 71,27 (C-6), 75.20 (C-8), 82.64 (C-7), 170.54 ($OCOCH_3$), 204.86 (C-11).- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).- MS: m/z (%) = 482.2697 (1.2, M^+, Calc for $C_{25}H_{42}O_7Si$: 482.2700), 439 (3.2), 405 (50), 383 (11), 323 (11), 305 (9), 251 (10), 225 (32), 73 (50), 43 (100); impurity at 503 (1.3).

(13S)-7β-Acetoxy-8,13-epoxy-12β-hydroxy-6β-trimethylsilanyloxy-labd-14-en-11-one (12).

^{1}H NMR (400 MHz, C_6D_6)[12]: δ = 0.14 (s, 9H, $Si(CH_3)_3$), 0.64 (d, 1H, 5-H), 0.86 (s, 3H, CH_3-18), 1.11 (s, 3H, CH_3-19), 1.43 (s, 3H, CH_3-16), 1.65 (s, 3H, CH_3-17), 1.70 (s, 3H, CH_3-20), 1.78 (s, 3H, $OCOCH_3$), 2.79 (s, 1H, 9-H), 3.88 (s, 1H, 12-H), 4.42 (dd, 1H, 6-H), 4.87 (d, 1H, 7-H), 5.02 and 5.24 (AB part of an ABX system, 2H, CH_2-15), 5.63 (X part of the ABX system, 1H, 14-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $J_{14,15}$=10.5 Hz, $J_{14,15'}$=17.5 Hz, $|J_{15,15'}|$=2.0 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.43 ($Si(CH_3)_3$), 14.17 (C-20), 16.70 (C-17), 18.19 (C-2), 20.66 and 20.70 (C-16 and C-19), 23.07 ($OCOCH_3$), 32.75 (C-18), 33.55 (C-4), 40.51 (C-10), 41.61 (C-1), 43.15 (C-3), 54.69 (C-5), 62.55 (C-13), 67.71 and 68.63 (C-6 and C-12), 71.33 (C-9), 75.17 (C-8), 81.99 (C-7), 116.85 (C-15), 139.85 (C-14), 170.24 ($OCOCH_3$), 205.53 (C-11).- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1720 cm^{-1} (C=O, ketone).- MS: m/z (%) = 466.2748 (1.3, M^+, Calc for $C_{25}H_{42}O_6Si$: 466.2751), 420 (6.4), 383 (5.2), 323 (11), 233 (82), 225 (100), 73 (83), 43 (78).

(14E)-7β-Acetoxy-8,14-epoxy-15-hydroxy-6β-trimethylsilanyloxy-labd-12-en-11-one (13).

To a solution of **10a** (30 mg, 0.064 mmol) in CH_2Cl_2 (0.5 ml) at -78°C a solution of $SnCl_4$ (2.26 µl, 0.019 mmol) in CH_2Cl_2 (0.1 ml) was added. The mixture was stirred at -78°C for 5h and at -40°C for 100 min. At -40°C saturated aq. $NaHCO_3$ (0.5 ml) was added. Usual work-up (ether) and MPLC (column A, hexanes-ethylacetate 13:10) gave **10a** (3.6 mg, 12%), **13** (7.7 mg, 26%), as well as more polar compounds which were not characterized.- ^{1}H NMR (400 MHz, $CDCl_3$)[11]: δ = 0.17 (s, 9H, $Si(CH_3)_3$), 0.92 and 1.10 (2s, 2x3H, CH_3-18 and CH_3-19), 1.48 and 1.53 (2s, 2x3H, CH_3-17 and CH_3-20), 2.10 (d, 1H, CH_3-16), 2.17 (s, 3H, $OCOCH_3$), 2.81 (s, 1H, 9-H), 3.80 (AB part of an ABX system, 2H, CH_2-15), 4.35 (X part of the ABX system, 1H, 14-H), 4.40 (dd, 1H, 6-H), 4.79 (d, 1H, 7-H), 6.40 (broad s, $W_{1/2}$=3.0 Hz, 1H, 12-H); $^4J_{16,12}$=1.2 Hz, $J_{14,15}+J_{14,15'}$=5.0 Hz, $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$)[11]: δ = 0.78 ($Si(CH_3)_3$), 15.99 (C-20), 18.29 (C-2), 20.46 and 21.44 (C-17 and C-19), 23.12 ($OCOCH_3$), 33.17 (C-18), 33.90 (C-4), 40.66 (C-10), 42.41 (C-1), 43.81 (C-3), 55.65 (C-5), 65.02 (C-15), 67.20 (C-14), 70.55 (C-9), 71.45 (C-6), 75.89 (C-8), 81.96 (C-7), 131.61 (C-12), 147.43 (C-13), 171.01 ($OCOCH_3$), 33.17 (C-18), 33.90 (C-4), 40.66 (C-10), 42.41 (C-1), 43.81 (C-3), 55.65 (C-5), 65.02 (C-15), 67.20 (C-14), 70.55 (C-9), 71.45 (C-6), 75.89 (C-8), 81.96 (C-7), 131.61 (C-12), 147.43 (C-13), 171.01 ($OCOCH_3$), 202.58 (C-11).- IR (CCl_4): 3650- 3300 (OH), 1740 (C=O, ester), 1685 (C=O, enone), 1585 cm^{-1} (C=C).- $C_{25}H_{42}O_6Si$ (466.7), MS: m/z (%) = 450.2796 (0.2, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 417 (1.8), 323 (1.3), 225 (11), 217 (100), 199 (66), 77 (55).

Addition of HCl to 5

To a $CHCl_3$ solution saturated at 0°C with anhydrous HCl gas at -40°C (3.5 ml) a solution of **5** (200 mg, 0.444 mmol) in $CHCl_3$ (2 ml) was added. The mixture was stirred at -40°C → -25°C for 20 min, and

the reaction was then quenched by addition of saturated aq. $NaHCO_3$ (3 ml) at -25°C. Usual work-up (CH_2Cl_2) and MPLC (column B, hexanes-ethyl acetate 5:1) furnished **14** (61.8 mg, 29%), **15** (30.9 mg, 14%), **17** (38.9 mg, 18%) along with **5** (12.0 mg, 6%).

Addition of HCl to **4**

4 (500 mg, 1.111 mmol) was treated with a solution of HCl in $CHCl_3$ for 1h at -40°C → -10°C. Reaction conditions and working-up procedure as described above. MPLC (column B, hexanes-ethyl acetate 5:1) provided **14** (127.4 mg, 24%), **15** (91.2 mg, 17%), **16** (92.2 mg, 17%) along with **18** (35.0 mg, 6%) and **17** (68.7 mg, 12%).

(12E)-7β-Acetoxy-15-chloro-8-hydroxy-6β-trimethylsilanyloxy-labd-12-en-11-one (**14**).

M.p. 124-126°C (from hexane).- ^{1}H NMR (400 MHz, COSY, C_6D_6): δ = 0.14 (s, 9H, $Si(CH_3)_3$), 0.82 (d, 1H, 5-H), 0.89 (s, 3H, CH_3-18), 1.15 (s, 3H, CH_3-19), 1.73 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.97 (d, 3H, CH_3-16), 2.08 (t, 2H, CH_2-14), 2.61 (s, 1H, 9-H), 3.13 (t, 2H, CH_2-15), 4.46 (dd, 1H, 6-H), 4.91 (d, 1H, 7-H), 6.11 (broad s, $W_{1/2}$=4.0 Hz, 1H, 12-H); $^4J_{16,12}$=1.5 Hz, $J_{14,15}$=7.0 Hz, $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.45 $Si(CH_3)_3$), 16.07 (C-20), 17.99 (C-16), 18.35 (C-2), 20.72 ($OCO\underline{C}H_3$ and C-17), 23.12 (C-19), 32.90 (C-18), 33.67 (C-4), 40.44 (C-10), 41.57 and 43.11 (C-14 and C-15), 42.22 (C-1), 43.61 (C-3), 55.38 (C-5), 70.06 and 71.59 (C-6 and C-9), 75.47 (C-8), 82.32 (C-7), 131.40 (C-12), 149.22 (C-13), 170.36 ($O\underline{C}OCH_3$), 201.25 (C-11).- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1685 (C=O, enone), 1615 cm^{-1} (C=C).- MS: m/z (%) = 450.2796 (35, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 225 (98), 95 (100), 43 (91).- (Found C, 61.72; H, 8.91; Cl, 7.20. $C_{25}H_{43}ClO_5Si$ (487.2) requires C, 61.64; H 8.90; Cl 7.28).

(12Z)-7β-Acetoxy-15-chloro-8-hydroxy-6β-trimethylsilanyloxy-labd-12-en-11-one (**15**).

M.p. 100-101°C (from hexane).- ^{1}H NMR (80 MHz, C_6D_6): δ = 0.13 (s, 9H, $Si(CH_3)_3$), 0.78 (d, 1H, 5-H), 0.88 (s, 1H, 3H, CH_3-18), 1.13 (s, 3H, CH_3-19), 1.59 (d, 3H, CH_3-16), 1.68 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.51 (s, 1H, 9-H), 2.89 ("t", 2H, CH_2-14), 3.50 (m, 2H, CH_2-15), 4.45 (dd, 1H, 6-H), 4.87 (d, 1H, 7-H), 6.13 (broad s, $W_{1/2}$=4.0 Hz, 1H, 12-H); $J_{5,6}$=2.0 Hz, $^4J_{12,16}$=1.5 Hz, $J_{6,7}$=3.5 Hz, $J_{14,15}$= 7.0 Hz (taken from the "t" of CH_2-14).- IR (CCl_4): 3650-3300 (OH), 1740 (C=O, ester), 1685 (C=O, enone), 1615 cm^{-1} (C=C).- MS: m/z (%) = 450.2805 (12, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 263 (12), 225 (34), 131 (34), 95 (69), 73 (64), 43 (100).- (Found C, 61.73; H, 8.90. $C_{25}H_{43}ClO_5Si$ (487.2) requires C, 61.64; H, 8.90).

(13E)-7β-Acetoxy-15-chloro-8-hydroxy-6β-trimethylsilanyloxy-labd-13-en-11-one (**16**).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.12 (s, 9H, $Si(CH_3)_3$), 0.67 (d, 1H, 5-H), 0.85 (s, 3H, CH_3-18), 1.10 (s, 3H, CH_3-19), 1.62 and 1.63 (2s, 2x3H, CH_3-20 and CH_3-17), 1.68 (d, 3H, 16-CH_3), 1.75 (s, 3H, $OCOCH_3$), 2.43 (s, 1H, 9-H), 3.04 and 3.32 (AB system, 2H, CH_2-12), 3.82 (d, 2H, CH_2-15), 4.40 (dd, 1H, 6-H), 4.78 (d, 1H, 7-H), 5.42 (t, 1H, 14-H); $J_{5,6}$= 2.0 Hz, $J_{6,7}$=3.5 Hz, $J_{14,15}$=8.0 Hz, $J_{14,16}$=1.5 Hz, $|J_{12,12'}|$=17.5 Hz.- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1720 cm^{-1} (CO, ketone).- $C_{25}H_{43}ClO_5Si$ (487.2), MS: m/z (%) = 450.2801 (3, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 391 (20), 383 (30), 323 (14), 251 (13), 233 (22), 225 (16), 205 (19), 187 (22), 137 (65), 73 (90), 43 (100).

(13E)-7β-Acetoxy-13,15-dichloro-8-hydroxy-6β-trimethylsilanyloxy-labdan-11-one (**17**, unpolar isomer).

M.p. 99-100°C (from ethanol).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.18 (s, 9H, $Si(CH_3)_3$), 0.95 (s, 3H, CH_3-18), 1.12 (s, 3H, CH_3-19), 1.48 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.19 (s, 3H, $OCOCH_3$), 2.26-2.77 (mk, 2H, CH_2-14), 2.60 (s, 1H, 9-H), 2.96 and 3.41 (AB system, 2H, CH_2-12), 3.66 (t, 2H, CH_2-15), 4.41 (dd, 1H, 6-H), 4.72 (d, 1H, 6-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $J_{14,15}$=8.0

Hz, $|J_{12,12'}|$=19.0 Hz.- IR (CCl_4): 3650-3300 (OH), 1740 (C=O, ester), 1720 cm^{-1} (C=O, ketone).- MS: m/z (%) = 445.2076 (40, Calc for $C_{23}H_{39}{}^{35}Cl_2O_2Si$: 445.2097), 427 (5), 383 (9), 323 (8), 263 (8), 251 (7), 233 (13), 225 (25), 73 (77), 43 (100).- (Found C, 57.37; H, 8.50; Cl, 13.58. $C_{25}H_{44}Cl_2O_5Si$ (523.6) requires C, 57.35; H, 8.47; Cl, 13.54).

(13E)-7β-Acetoxy-13,15-dichloro-8-hydroxy-6β-trimethylsilanyloxy-labdan-11-one (18, polar isomer).

M.p. 154-156°C (from ethanol).- ^1H NMR (400 MHz, C_6D_6): δ = 0.10 (s, 9H, $Si(CH_3)_3$), 0.61 (d, 1H, 5-H), 0.86 (s, 3H, CH_3-18), 1.09 (s, 3H, CH_3-19), 1.54 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.97 (s, 1H), 2.16 (s, 1H, 9-H), 2.60 (m, $W_{1/2}$=42 Hz, 2H, CH_2-14), 2.91 and 3.35 (AB system, 2H, CH_2-12), 3.59 (m, $W_{1/2}$=37 Hz, 2H, CH_2-15), 4.37 (dd, 1H, 6-H), 4.70 (d, 1H, 7-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $|J_{12,12'}|$=19.0 Hz.- IR (CCl_4): 3650-3300 (OH), 1740 (C=O, ester), 1715 cm^{-1} (C=O, keton).- MS: m/z (%) = 445 (35), 383 (15), 323 (7), 263 (8), 251 (7), 233 (9), 225 (20), 205 (11), 187 (11), 157 (17), 137 (25), 73 (74), 43 (100).- (Found C, 57.40; H, 8.48; Cl, 13.61. $C_{25}H_{44}Cl_2O_5Si$ (523.6) requires C, 57.35; H, 8.47; Cl, 13.54).

(13S)-7β-Acetoxy-15-chloro-8,13-epoxy-12β-phenylselanyl-6β-trimethyl-silanyloxy-labdan-11-one (19).

To a suspension of NPSP (44.0 mg, 0.146 mmol) in CH_2Cl_2 (0.4 ml) at -78°C a solution of $SnCl_4$ (5.66 µl, 0.049 mmol) in CH_2Cl_2 (0.1 ml) was added then a solution of **14** (47.2 mg, 0.097 mmol) in CH_2Cl_2 (1.0 ml). Within 2h the mixture was allowed to warm to 0°C and was then kept at this temperature for 2h. Filtration through SiO_2 (4g, elution with hexanes ethyl acetate 15:1) followed by solvent evaporation and MPLC (hexanes-ethyl acetate 40:1 → 30:1) gave **19** (43.3 mg, 71%) and **20** (1.4 mg, 2%).- ^1H NMR (400 MHz, C_6D_6)[12]: δ = 0.13 (s, 9H, $Si(CH_3)_3$), 0.62 (d, 1H, 5-H), 0.83 (s, 3H, CH_3-18), 1.11 (s, 3H, CH_3-19), 1.15 (s, 3H, CH_3-16), 1.51 (s, 3H, CH_3-17), 1.69 (s, 3H, CH_3-20), 1.80 (s, 3H, $OCOCH_3$), 2.02 (m, 1H), 2.13-2.31 (2H, CH_2-14), 2.18 (s, 1H, 9-H), 3.59 ($W_{1/2}$=23 Hz, CH_2-15), 4.00 (s, 1H, 12-H), 4.38 (dd, 1H, 6-H), 5.04 (d, 1H, 7-H), 6.97 (complex of signals, 3H, Ar-H), 7.56 (complex of signals, 2H, Ar-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.76 ($Si(CH_3)_3$), 16.87 (C-20), 18.43 (C-2), 20.87 (C-17), 22.05 and 23.27 ($OCO\underline{C}H_3$ and C-19), 25.32 (C-16), 32.85 (C-18), 33.93 (C-4), 38.22 (C-10), 39.91 and 40.28 (C-1 and C-14), 44.00 (C-3), 47.55 (C-15), 55.80 (C-5), 67.55 (C-12, $^1J_{13C,77Se}$=-65.7 Hz), 70.07 (C-6), 72.08 (C-9), 80.74 (C-7), 82.95 (C-8), 83.73 (C-13), 127.88 (aromat. C), 129.39 (aromat. C), 130.32 (aromat. C-1), 135.24 (aromat. C), 169.33 ($O\underline{C}OCH_3$), 201.36 (C-11).- IR (CCl_4): 1750 cm^{-1} (C=O).- MS: m/s (%) = 643.2127 (2.3, M^+, Calc for $C_{31}H_{48}{}^{35}ClO_5Si^{80}Se$: 643.2125), 537 (6.2), 449 (2.2), 307 (2.9), 225 (100), 73 (44), 43 (58).

(13R)-7β-Acetoxy-15-chloro-8,13-epoxy-12β-phenylselanyl-6β-trimethylsilanyloxy-labdan-11-one (20).

15 (19.7 mg, 0.041 mmol) was treated with NPSP (18.4 mg, 0.061 mmol) and 0.1 ml (0.020 mmol) of a $SnCl_4$ solution (23.7 µl, 0.203 mmol $SnCl_4$ in CH_2Cl_2 (1 ml)) as described for **19** (reaction time: 3 h). Work-up as described above and MPLC (column A, hexanes-ethyl acetate 40:1) furnished **19** (2.9 mg, 11%) and **20** (10.8 mg, 42%).- ^1H NMR (400 MHz, C_6D_6)[12]: δ = 0.12 (s, 9H, $Si(CH_3)_3$), 0.53 (d, 1H, 5-H), 0.84 (s, 3H, CH_3-18), 1.11 (s, 3H, CH_3-19), 1.29 (s, 3H, CH_3-16), 1.59 (s, 3H, CH_3-17), 1.66 (s, 3H, CH_3-20), 1.80 (s, 3H, $OCOCH_3$), 2.00 (m, 1H), 2.16 (s, 1H, 9-H), 2.24 ("t", 2H, CH_2-14), 3.40-3.63 (complex of signals, 2H, CH_2-15), 3.95 (s, 1H, 12-H), 4.41 (dd, 1H, 6-H), 5.03 (d, 1H, 7-H), 6.95 (complex of signals, 3H, Ar-H), 7.53 (complex of signals, 2H, Ar-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $J_{14,15}$=7.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[11]: δ = 0.75 ($Si(CH_3)_3$), 16.94 (C-20), 18.43 (C-2), 20.68 and 20.88 (C-17 and C-19), 23.28 ($OCO\underline{C}H_3$), 29.89 (C-16), 32.84 (C-18), 33.91 (C-4), 38.21 (C-10), 40.19, 40.46 and 41.26 (C-1, C-14 and C-15), 43.94 (C-3), 55.42 (C-5), 69.03 (C-12), 70.01 (C-6), 71.84 (C-9), 81.35 (C-7), 82.87 and 84.20 (C-8 and C-13), 128.24 (aromat. C), 129.34 (aromat. C), 130.59 (aromat. C-1), 135.10 (aromat. C), 169.43 ($O\underline{C}OCH_3$), 201.28 (C-11).- IR (CCl_4): 1750 und 1740 cm^{-1} (C=O).- $C_{31}H_{48}ClO_5SiSe$ (643.2), MS: m/z (%) = 536.1861 (6.7, Calc for

$C_{27}H_{40}O_4Si^{80}Se$: 536.1861), 225 (100), 73 (29), 43 (36).

Cyclization of **16**.

To a suspension of NPSP (37.3 mg, 0.123 mmol) in CH_2Cl_2 (1 ml) at -78°C a) a solution of $SnCl_4$ (48.2 µl, 0.412 mmol) in CH_2Cl_2 (1 ml), and b) a solution of **16** (40.0 mg, 0.083 mmol) in CH_2Cl_2 (0.5 ml) were added. The mixture was allowed to warm to -40°C with 1 h and was kept at that temperature for 5 h. Then Zn-Cu couple (168.1 mg, 1.30 mmol) was added, and the mixture was stirred at -40°C for 90 min. Filtration through SiO_2 (3 g, covered with Florisil (1 g), elution with hexanes-ethyl acetate 3:1), solvent evaporation, and MPLC (column A, hexanes-ethyl acetate 50:1) gave **22** (15.3 mg, 41%), **21** (4.5 mg, 12%), and a mixture of **22** and **21** (3.4 mg, 9%).

7β-Acetoxy-8,13-epoxy-6β-trimethylsilanyloxy-labd-14-en-11-one (**22**).

M.p. 120-122°C (from ethanol).
22 was identical (tlc (hexanes-ethyl acetate 6:1) and ^1H NMR) with a sample of **22** obtained from **2**[1]; m.p. of the authentic sample 122-123°C (from ethanol).

(13S)-7β-Acetoxy-8,13-epoxy-6β-trimethylsilanyloxy-labd-14-en-11-one (**21**).

^1H NMR (400 MHz, C_6D_6)[12]: δ = 0.16 (s, 9H, $Si(CH_3)_3$), 0.63 (d, 1H, 5-H), 0.86 (s, 3H, CH_3-18), 1.14 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-16), 1.65 (s, 3H, CH_3-17), 1.69 (s, 3H, CH_3-20), 1.89 (s, 3H, $OCOCH_3$), 2.19 (s, 1H, 9-H), 2.21 and 2.70 (2d, 2H, CH_2-12), 2.43 (m, 1H), 4.48 (dd, 1H, 6-H), 4.80 and 5.06 (AB part of an ABX system, 2H, CH_2-15), 5.15 (d, 1H, 7-H), 5.85 (dd, 1H, 14-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $|J_{12,12'}|$=14.0 Hz, $J_{14,15}$=11.0 Hz, $J_{14,15'}$=17.5 Hz, $|J_{15,15'}|$=0.5 Hz.- IR (CCl_4): 1740 (C=O, ester), 1720 cm^{-1} (C=O, ketone).- $C_{25}H_{42}O_5Si$ (450.7), MS: m/z (%) = 391.2666 (93, Calc for $C_{23}H_{39}O_3Si$: 391.2668), 375 (20), 367 (6), 345 (8), 307 (11), 279 (11), 225 (25), 73 (71), 43 (100).

Diels-Alder reaction of **4** with anthracene.

A solution of **4** (207.0 mg, 0.460 mmol), anthracene (164.0 mg, 0.920 mmol), and $TiCl_4$ (37.9 µl, 0.345 mmol) in CH_2Cl_2 (5 ml) was stirred at 20°C for 5 h. Then saturated aq. $NaHCO_3$ (5 ml) was added. Usual work-up (CH_2Cl_2) and MPLC (column B, hexanes - ethyl acetate 4:1 and then column B, hexanes - ethyl acetate - 2-propanol 15:1:0.2) provided **23** (32.8 mg, 11%), **24** (14.5 mg, 5%), **14** (51.4 mg, 25%) and **15** (27.0 mg, 13%).

(14E,12E)-7β-Acetoxy-14,15-(9,10-dihydro-anthracen-9,10-diyl)-8-hydroxy-6β-trimethylsilanyloxy-labd-12-en-11-one (**23**, unpolar isomer).

^1H NMR (80 MHz, C_6D_6): δ = 0.17 (s, 9H, $Si(CH_3)_3$), 0.89 (s, 3H, CH_3-18), 1.14 (s, 3H, CH_3-19), 1.70 (s, 3H, CH_3), 1.81 (s, 3H, $OCOCH_3$), 1.83 (s, 3H, CH_3), 1.98 (d, 3H, CH_3-16), 2.46 (s, 1H, 9-H), 4.00 (t, 1H, 10'-H), 4.17 (d, 1H, 9'-H), 4.49 (dd, 1H, 6-H), 4.92 (d, 1H, 7-H), 5.77 (broad s, $w_{1/2}$=4.0 Hz, 1H, 12-H), 6.70-7.50 (Ar-H); $J_{6,7}$=3.5 Hz, $^4J_{16,12}$=0.9 Hz, $J_{14,9'}$= 2.0 Hz, $J_{15,10'}$=3.0 Hz.- IR (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1680 (C=O, enone), 1605 cm^{-1} (C=C).- $C_{39}H_{52}O_5Si$ (628.9), MS: m/z (%) = 450.2796 (2, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 383 (10), 323 (4), 251 (4), 233 (7), 225 (7), 205 (6), 187 (7), 178.0782 (100, Calc for $C_{14}H_{10}$: 178.0782).

(14E,12E)-7β-Acetoxy-14,15-(9,10-dihydro-anthracen-9,10-diyl)-8-hydroxy-6β-trimethylsilanyloxy-labd-12-en-11-one (**24**, polar isomer).

^1H NMR (80 MHz, C_6D_6): δ = 0.13 (s, 9H, $Si(CH_3)_3$), 0.89 (s, 3H, CH_3-18), 1.16 (s, 3H, CH_3-19), 1.76 (s, 9H, 3xCH_3), 2.04 (d, 3H, CH_3-16), 2.48 (s, 1H, 9-H), 4.01 (t, 1H, 10'-H), 4.13 (d, 1H, 9'-H),

4.47 (dd, 1H, 6-H), 4.82 (d, 1H, 7-H), 5.71 (broad s, $W_{1/2}$=4.0 Hz, 1H, 12-H), 6.80-7.50 (Ar-H); $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $^4J_{16,12}$=1.0 Hz, $J_{14,9'}$=2.0 Hz, $J_{15,10'}$=2.5 Hz.- IR: (CCl_4): 3650-3300 (OH), 1735 (C=O, ester), 1680 (C=O, enone), 1605 cm^{-1} (C=C).- $C_{39}H_{52}O_5Si$ (628.9), MS: m/z (%) = 450.0782 (1.9, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 263 (1.2), 225 (5.1), 178.0782 (100, Calc for $C_{14}H_{10}$: 178.0782), 95 (23), 43 (26).

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