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FORSKOLIN STUDIES

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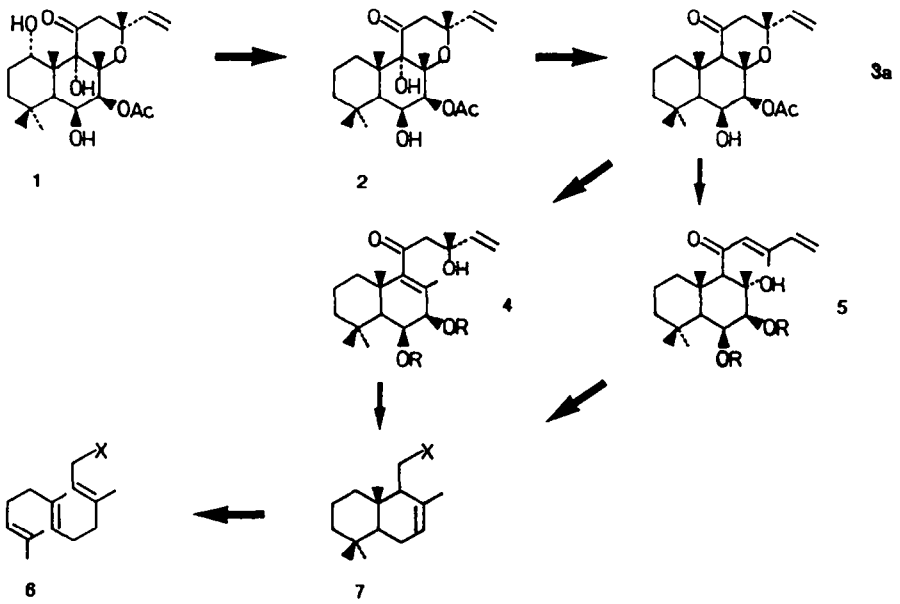
Abstract - a) The reactions of 1,9-dideoxyforskolin (**3a**) with various silylating agents were investigated. The 9(11)-silyl enol ether could not be obtained. Reaction of **3a** with $(Me_3Si)_2NH$ - Me_3SiI afforded cleavage products **9a** and **10a**.
b) Reaction of **9b** with phenylselenophthalimide - camphorsulfonic acid gave the 8,12-epoxy labdane derivatives **15** and **17**. Phenylselenyl chloride reacted with **9b** by addition across the double bond between C-14 and C-15.

Forskolin, a labdane diterpene isolated from the Indian herb Coleus forskohlii Briq. (Labiatae), was shown by Bhat et al. to have structure **1**. [1] It has been reported that **1** is a unique adenylate cyclase activator, lowers normal or elevated blood pressure in different animal species through a vasodilatory effect, has a positive inotropic action on the heart muscle, and causes marked inhibition of platelet activation. [2,3]
A reasonable synthetic plan for forskolin is summarized in Scheme 1. [4] It includes



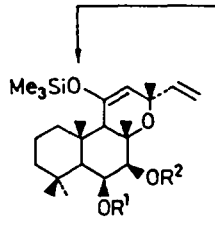
Scheme 1.

(a) cyclization of a farnesol derivative to give a drimenol derivative (**6** → **7**), [5] (b) conversion of **7** to the labdane derivatives **4** and **5**, respectively, (c) formation of ring C by intramolecular conjugate addition of an OH group to an α,β-unsaturated ketone (**4** → **3a** or **5** → **3a**, (d) introduction of the 9α-OH group by α-hydroxylation via the 9(11)-enolate of **3a** or the corresponding silyl enol ether [6] (**3a** → **2**), and, finally, (e) introduction of the 1α-OH group by microbial oxidation [7] (**2** → **1**).
We describe herein a number of reactions which were performed with the aim of judging the feasibility of this synthetic plan. Starting material in this study was 1,9-dideoxyforskolin (**3a**), another major diterpenoid constituent of *C. forskohlii*.[1]

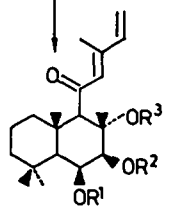
Reaction of **3a** with silylating agents

Reaction of **3a** with trimethylsilyl triflate - N-methylimidazol [8] (3 d at 20°C) resulted in clean silylation of the sterically hindered 7-OH group [1] to give **3c** in quantitative yield. Under the classic House conditions for the formation of equilibrium mixtures of silyl enol ethers from ketones (Me_3SiCl, Et_3N, DMF [9]) **3a** reacted very sluggishly. After 40 h at 130°C 5% of silyl enol ether **8a** were obtained along with 45% of **3c** and unreacted **3a**. **3d** (vide infra) yielded under similar conditions **8b** in 27% yield.
The structural assignments of these and the compounds to be described below rest mainly on NMR spectroscopy. Apart from an analysis of normal ^1H and ^{13}C NMR spectra (DEPT technique [10]), the following methods were employed (if necessary): standard two-dimensional (2D) $^1H/^1H$ chemical shift correlation spectroscopy (COSY [11]), heteronuclear $^{13}C/^1H$ 2D shift correlation using large ($^1J_{CH}$) C,H couplings [12], and $^1H/^1H$ nuclear Overhauser enhancement (NOE) difference spectroscopy.[13]
In the case of **8a** and **8b**, the presence of an olefinic 12-H signal (δ=4.62 and 4.60, respectively) and of the 9-H signal (δ=2.11 and 2.01, respectively) clearly proved the position of the enolic double bond.
Ethyl trimethylsilylacetate - tetra-N-butylammonium fluoride (ETSA-TBAF) has been recommended as a silylating reagent for alcohols and ketones under nearly neutral conditions. Unsymmetrical ketones were reported to give mainly the products of kinetic deprotonation at -78°C whereas at elevated temperatures equilibrium mixtures of the regioisomeric silyl enol ethers were obtained. [14] Refluxing a dioxane solution of **3a** with TBAF (0.4 equiv) and excess ETSA for 160 min led to a mixture of **3b** (25%), **3d** (13%), and the silyl enol ether **8b** (53%). It may be inferred from this result that the first process occurring under these conditions is the migration of the acetyl group from the 7- to the 6-oxygen. This type of rearrangement has precedent in the forskolin series. [1] The position of the acetyl group in **3b**, **3c**, and **8b** is evident from the rather low-field position of the 6-H signal (a doublet of doublets at 5.5-5.7, see Experimental). Even after longer reaction times we were unable to detect an isomeric 9(11)-silyl enol ether.
In 1979 Miller and McKean reported on the use of trimethylsilyl iodide in nonpolar solvents in conjunction with hexamethyldisilazane (HMDS) for the preparation of equilibrium mixtures of silyl enol ethers from unsymmetrical ketones under very mild conditions. [15] Treatment of a CH_2Cl_2 solution of **3a** with Me_3SiCl - HMDS at -10°C and allowing the reaction mixture to stand at ambient temperature for 2 h produced **8a** (9%), **8c** (51%) along with 24% of a 4:1 mixture (^1H NMR) of the stereoisomeric ring fission products **9a** and **10a**. Performing the reaction at 40°C (2.5 h) afforded the mixture of **9a** and **10a** in 66% yield accompanied by **8a** (5%). Since the **9a/10a** mixture could not be separated it was desilylated selectively in the 8-position in CH_3OH-$CHCl_3$ 3:1 solution in the presence of camphorsulfonic acid (0.1 equiv) to provide **9b** and **10b** which were readily separated by medium pressure liquid chromatography (MPLC). Selective cleavage of the silyl ether in the 8-position

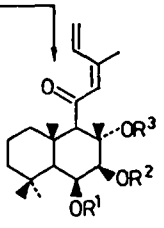
3	R^1	R^2
a	H	Ac
b	Ac	H
c	$SiMe_3$	Ac
d	Ac	$SiMe_3$



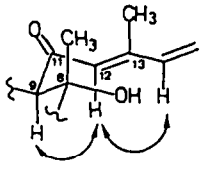
8	R^1	R^2
a	$SiMe_3$	Ac
b	Ac	$SiMe_3$
c	H	Ac



9	R^1	R^2	R^3
a	$SiMe_3$	Ac	$SiMe_3$
b	$SiMe_3$	Ac	H



10	R^1	R^2	R^3
a	$SiMe_3$	Ac	$SiMe_3$
b	$SiMe_3$	Ac	H



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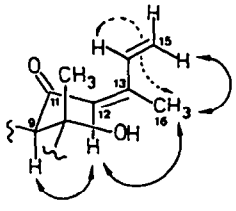

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under these conditions was evident from the reactions that will be described below. The 6-position of the retained trimethylsilyl ether grouping in **9b** and **10b** was also indicated by spectroscopic results. For **3a** in acetone-d_6 solution the rate of proton exchange is sufficiently reduced to permit observation of the 6-H, 6-OH coupling in the ^1H NMR spectrum. No such coupling was observable in the spectra of both **9b** and **10b** (acetone-d_6 solution).

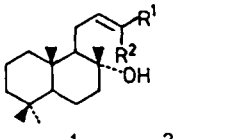
An NOE difference experiment revealed the existence of nuclear Overhauser enhancements between 12-H and 14-H as well as between 12-H and 9-H (see formula **11**). On this basis we assign to **9b** the E-configuration around the 12-double bond and the preferred conformation shown in **11**. The planar arrangement of the chromophoric system in **9b** is also indicated by the very strong intensity (ε=22000) of the $\pi \rightarrow \pi^*$ transition (λ_{max} (CH_3CN) = 270 nm). When 12-H of **10b** was similarly examined by NOE, strong through-space interactions with CH_3-16 and 9-H were detected. This result indicates the Z-configuration around the 12-double bond and the S-cis (O=)C-C(=C) conformation. From a nuclear Overhauser enhancement between CH_3-16 and one of the protons of C-15 it can be concluded that the preferred conformation of the diene unit is S-trans. Clear evidence for this conformation comes also from the very low-field position of the 14-H signal (δ =7.59), which is strongly deshielded by the anisotropic carbonyl group. For comparison, the chemical shift of 14-H in **9b** is δ=6.32. Again the UV spectrum (λ_{max} (CH_3CN) = 272 nm, ε =13000) supports the planar arrangement of the chromophoric system and the S-cis conformation of the enone unit. [16] A very small NOE effect between CH_3-16 and 14-H may be indicative of the existence of the S-cis conformation as well.

In conclusion, using the methods described above we have been unable to obtain a 9(11)-enolate or the corresponding silyl enol ether, starting from **3a**. This seems to indicate that the formation of this type of intermediate which is essential for steps **4** → **3a** and **3a** → **2** in Scheme 1, is not a favoured process.

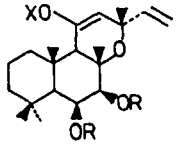
Organoselenium-mediated cyclization reactions of **9b**

Oxidative cyclization reactions (with singlet oxygen, m-chloroperbenzoic acid, and lead tetraacetate) of (12E)- and (12Z)-abienols (**13a** and **13b**) respectively, to give both 8,12-epoxy-labdane and 8,13-epoxy-labdane derivatives, have been investigated extensively by Enzell and coworkers. [17,18]

Attempts to effect cyclization of **9a/10a** under acidic conditions (under these conditions the 8-OH group is liberated) and of **9b** under basic conditions to give **3a** and **3c**, respectively, by conjugate addition of the 8-OH group to the enone unit failed. The reason for this failure may well be, that the intermediate enols or enolates of type **14** reverse to the ring-opened starting materials. We tried, therefore, to trap these intermediates with an electrophilic phenylselenating agent. It is well-known that enols and enolates react with reagents delivering "$PhSe^+$" to furnish α-selenoketones. [19] Our objective to cyclize **9b** with a phenylselenating



13	R^1	R^2
a	$CH{=}CH_2$	CH_3
b	CH_3	$CH{=}CH_2$



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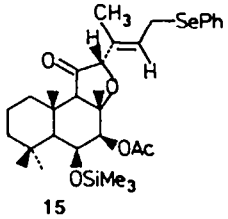

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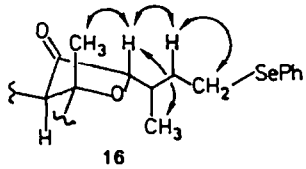

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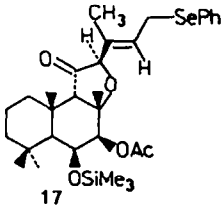

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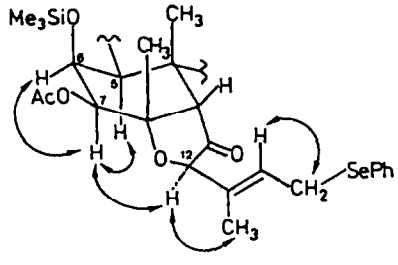

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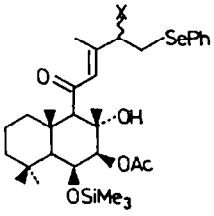

19	X
a	OH
b	Cl

reagent was based on the assumption that the two electron-deficient double bonds in **9b** are too unreactive to be attacked directly by an electrophile. In the event, reaction of **9b** in CH_2Cl_2 solution with N-phenylselenophthalimide (NPSP) [23] in the presence of camphorsulfonic acid (0.1 equiv) led to the formation of two main reaction products (TLC: hexanes-ethyl acetate 8:1, 2x developed) which proved to be rather unstable, decomposing under the separation conditions (partly back to **9b**). The yield of these compounds for which structures **15** and **17** was inferred from their spectral data was, therefore, rather low (21% and 7%). In a second experiment, only **15** could be isolated (37%). Again TLC indicated that at the end of the reaction **9b** was completely consumed, but after chromatographic separation a substantial amount of **9b** (25%) was recovered.

The position of the phenylselenyl group in **15** follows straightforwardly from the fact that the ^{13}C NMR signal of C-15 (δ=24.9) is accompanied by two satellites which originate from $^{13}C,^{77}Se$ coupling (J=-57.8Hz, ^{77}Se: 7.58%, I=1/2).[24] The NMR spectra of **15** displayed the C-12 signal at δ=81.9 (CH in the DEPT spectrum) and the 12-H signal as a singlet at δ=4.06 (assigned on the basis of the $^{13}C/^{1}H$ shift correlation). These experimental results are only consistent with the presence of a five-membered ring. The rather low-field position of the C-8 ^{13}C NMR signal (δ=79.4) also points to the presence of a tetrahydrofuran unit. In related compounds with a six-membered ring C the C-8 signal appears in the δ=74 region (see Experimental and ref [18]). The configurations at C-12 and around the 13-double bond were deduced from the NOE results which are summarized in formula **16**.

The ^{13}C NMR spectrum of **17** displayed the C-8 signal (identified from the DEPT spectrum) at δ=81.5. This chemical shift indicates that the oxygen at C-8 is involved in an ether grouping (tetrahydrofuran derivative). The NMR signal of 12-H appeared as a singlet at δ=4.14. Hence **17** contains an 8,12-epoxy group and is a stereoisomer of **15**. Major differences in the ^{13}C NMR spectra of **15** and **17** were found for the C-9 (δ=66.9 in **15**, 63.9 in **17**) and C-12 signals (δ=81.9 in **15**, 75.0 in **17**). The NOE results summarized in **18**, especially the through-space interactions between 12-H and 7-H, seem only consistent with cis-fused rings B and C (9β-H) and β-orientation of the side chain at C-12.

Treatment of **9b** with phenylselenyl bromide in CH_2Cl_2 solution gave a complex mixture of reaction products from which by careful separation two pure compounds could be isolated (in 8% and 4% yield) having according to their spectral data structures very similar to **15** and **17**, respectively, but containing a bromine at C-15 instead of the phenylselenyl substituent. [25]

Finally, **9b** was allowed to react with phenylselenyl chloride - pyridine in CH_2Cl_2 solution essentially as described by Liotta and coworkers. [21] The reaction was complete within 2 h at 20°C. TLC of the reaction mixture indicated the formation of two reaction products (less polar than **9b**). In a separate experiment **9b** was treated with phenylselenyl chloride - pyridine-d_5 in $CDCl_3$ solution. After 2 h at 20°C an ^{1}H NMR spectrum (80 MHz) displayed the 12-H signal of the reaction products as a broad singlet at δ=6.20 hence the 12-double bond was still present. In addition, the spectrum contained a two-proton signal complex at δ=4.38 attributed to an allylic -CHCl- proton, whereas C-14 and C-15 olefinic proton signals (which form a characteristic signal pattern in **9b**) were absent. Unfortunately, we were unable to isolate the two reaction products formed from **9b** with phenylselenyl chloride-pyridine. On attempted chromatographic separation they mainly reversed to **9b** (re-isolated in 65% yield). In addition, a new product (1:1 mixture of stereoisomers) formed under the separation conditions was isolated in 14% yield to which structure **19a** was assigned on the basis of spectral evidence. Two CH signals (DEPT) at δ=73.98 and 74.13 are attributed to C-14 of both isomers. The corresponding ^{1}H NMR signals appeared at δ=4.04.

From these results it may be concluded that **9b** reacts with phenylselenyl chloride - pyridine to give the unstable addition products **19b** from which **9b** and **19a** are formed on the silica gel column by elimination and reaction with water, respectively. It seems reasonable to assume that **15** and **17** are also formed from intermediates of type **19** or a related selenonium ion intermediate by an S_N2'-type substitution process [28] involving nucleophilic attack of the 8-OH group at C-12.

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: ^1H 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); UV: Duospac 203 (Jobin-Yvon); CD: Jobin-Yvon-ISA dichrograph Mark III connected online to a PDP-8/e; 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).

1,9-Dideoxyforskolin (3a).

3a was isolated from a partly purified extract of *C. forskohlii* as described by Bhat et al. [1]

7β-Acetoxy-8,13-epoxy-6β-trimethylsilanyloxy-labd-14-en-11-one (3c).

To a solution of **3a** (10 mg, 26.4 µmol) in dry CH_2Cl_2 (200 µl) were added N-methylimidazol (25.2 µl, 0.32 mmol) and $Me_3SiOSO_2CF_3$ (28.6 µl, 0.15 mmol). After being stirred for 3 d at 20°C the solution was filtered through Florisil and evaporated to dryness to give pure 3c (11.6 mg, 100%).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.15 (s, 9H, 6-O-Si(CH_3)$_3$), 0.90 (s, 3H, CH_3-19), 1.10 (s, 3H, CH_3-18), 1.20 (s, 3H, CH_3-16), 1.40 (s, 3H, CH_3-20), 1.48 (s, 3H, CH_3-17), 2.15 (s, 3H, -OCOCH_3), 2.58 (broadened s, 2H, 12-H), 2.79 (broadened s, 1H, 9-H), 4.35 (dd, 1H, 6-H), 5.02 and 5.23 (AB part of an ABX system, 2H, CH_2-15), 5.06 (d, 1H, 7-H), 5.97 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $|J_{15,15'}|$=1.5 Hz, $J_{cis\ 14,15}$=11.0 Hz, $J_{trans\ 14,15}$=17.0 Hz.- IR ($CHCl_3$): 1720 cm^{-1} (ester).- MS: m/z (%) = 391.2666 (100, $(M-OAc)^+$), Calc for $C_{23}H_{39}O_3Si^+$: 391.2668), 375 (20), 225 (26).

7β-Acetoxy-8,13-epoxy-6β,11-bis(trimethylsilanyloxy)-labd-11,14-diene (8a).

To a solution of **3a** (30 mg, 0.08 mmol) in dry DMF (30 µl) were added NEt_3 (53.7 µl, 0.38 mmol) and Me_3SiCl (24.4 µl, 0.19 mmol). The mixture was stirred for 40 h at 130°C. Conversion of **3a** was then about 60% as judged from TLC (hexanes-ethyl acetate 4:1). The reaction mixture was diluted with $CHCl_3$ and filtered through Florisil (1 g). Concentration of the solution followed by MPLC (column A, hexanes-ethyl acetate 30:1 → 5:1) gave **8a** (2.1 mg, 5%), **3c** (16.1 mg, 45%) and recovered **3a** (10.8 mg, 35%).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.18 (s, 9H, 6-O-Si(CH_3)$_3$), 0.26 (s, 9H, 11-O-Si(CH_3)$_3$), 0.93 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-18), 1.19 (s, 3H, CH_3-16), 1.36 (s, 3H, CH_3-20), 1.50 (s, 3H, CH_3-17), 2.11 (d, 1H, 9-H), 2.18 (s, 3H, -OCOCH_3), 4.40 (dd, 1H, 6-H), 4.62 (d, 1H, 12-H), 4.78 and 5.10 (AB part of an ABX system, 2H, CH_2-15), 4.89 (d, 1H, 7-H), 5.72 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.5 Hz, $J_{6,7}$=3.5 Hz, $^4J_{9,12}$=2.0 Hz, $|J_{15,15'}|$=2.4 Hz, $J_{cis\ 14,15}$=10.0 Hz, $J_{trans\ 14,15}$=18.0 Hz.- IR ($CHCl_3$): 1725 (ester), 1645 cm^{-1} (C=C).- MS: m/z (%) = 522 (6, M^+), 507.2960 (29, $(M-CH_3)^+$), Calc for $C_{27}H_{47}O_5Si_2$: 507.2962), 225 (76), 73 (100).

6β-Acetoxy-8,13-epoxy-7,11-bis(trimethylsilanyloxy)-labd-11,14-diene (8b).

To a solution of **3d** (80 mg, 0.18 mmol) in dry DMF (300 µl) were added Me_3SiCl (30 µl, 0.21 mmol) and NEt_3 (60 µl, 0.43 mmol). After being stirred at 100°C for 11 d (29% conversion of **3d**) the reaction mixture was directly transferred onto the top of a chromatographic column (8 g SiO_2, covered by 2 g Florisil). Elution with hexanes-ethyl acetate-NEt_3 35:1:0.036 furnished **8b** (30.2 mg, 27%) along with **3d** (56.5 mg, 71%).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.10 (s, 9H, 7-O-Si($\underline{CH_3}$)$_3$), 0.27 (s, 9H, 11-O-Si($\underline{CH_3}$)$_3$), 0.92 (s, 3H, $\underline{CH_3}$-19), 1.00 (s, 3H, $\underline{CH_3}$-18), 1.22 (s, 3H, $\underline{CH_3}$-16), 1.31 (s, 3H, $\underline{CH_3}$-20), 1.40 (s, 3H, $\underline{CH_3}$-17), 2.01 (s, 4H, OCO$\underline{CH_3}$ and 9-H), 3.57 (d, 1H, 7-H), 4.60 (d, 1H, 12-H), 4.78 and 5.03 (AB part of an ABX system, 1H, CH_2-15), 5.57 (dd, 1H, 6-H), 5.78 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.5 Hz, $J_{6,7}$=4.3 Hz, $^4J_{9,12}$=2.1 Hz, $|J_{15,15'}|$=2.0 Hz, $J_{cis\ 14,15}$=10.7 Hz, $J_{trans\ 14,15}$=17.0 Hz.- IR ($CHCl_3$): 1745 (ester), 1650 cm^{-1} (C=C).- MS: m/z (%) = 522.3197 (5, M^+, Calc for $C_{28}H_{50}O_5Si_2$: 522.3198), 507 (40), 417 (34), 73 (100).

Reaction of **3a** with Ethyl trimethylsilylacetate - tetra-N-butylammonium fluoride (ETSA-TBAF).

To a solution of **3a** (200 mg, 0.53 mmol) and TBAF (21.2 µl of a 1 molar THF solution, 21.2 µmol) was added at 100°C ETSA (387.2 µl, 1.06 mmol). The reaction mixture was maintained for 135 min at 100°C and then again TBAF (21.2 µl, of the 1 molar THF solution) was added. After another 25 min at 100°C the solvent was evaporated. MPLC (column B, hexanes-ethyl acetate 10:1) gave **8b** (146 mg, 53%), **3d** (30.7 mg, 13%) and **3b** (49.3 mg, 25%).

6β-Acetoxy-8,13-epoxy-7β-hydroxy-labd-14-en-11-one (3b).

M.p. 140-143°C (from hexanes-ethyl acetate).- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 3H, $\underline{CH_3}$-19), 0.97 (s, 3H, $\underline{CH_3}$-18), 1.27 (s, 3H, $\underline{CH_3}$-16), 1.36 (s, 3H, $\underline{CH_3}$-20), 1.43 (s, 3H, $\underline{CH_3}$-17), 2.05 (s, 3H, OCO$\underline{CH_3}$), 2.62 (s, 3H, 12-H and 9-H), 3.85 (dd, 1H, 7-H), 4.98 and 5.14 (AB part of an ABX system, 2H, CH_2-15), 5.74 (dd, 1H, 6-H), 5.95 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.0 Hz, $J_{6,7}$=4.3 Hz, $J_{7,OH}$=2.0 Hz, $|J_{15,15'}|$=1.0 Hz, $J_{cis\ 14,15}$=11.0 Hz, $J_{trans\ 14,15}$=17.5 Hz.- ^{13}C-NMR [26] (100.6 MHz, DEPT, $CDCl_3$): δ = 16.5 (C-20), 18.2 (C-2), 21.5 (C-17), 22.7 (C-19), 23.0 (OCO$\underline{CH_3}$), 31.4 (C-16), 33.0 (C-18), 33.9 (C-4), 38.00 (C-10), 41.2 (C-1), 43.8 (C-3), 49.6 (C-12), 53.9 (C-5), 65.0 (C-7), 70.6 (C-9), 75.0 (C-8), 79.2 (C-13), 79.8 (C-16), 112.3 (C-15), 146.4 (C-14), 170.9 ($\underline{OCOCH_3}$), 205.9 (C-11).- IR ($CHCl_3$): 3600-3300 (OH), 1740-1720 cm^{-1} (ester, ketone).- MS: m/z (%) = 378.2404 (4, M^+, Calc for $C_{22}H_{34}O_5$: 378.2406), 363 (12), 345 (15), 293 (22), 233 (19), 207 (26), 43 (100).

6β-Acetoxy-8,13-epoxy-7β-trimethylsilanyloxy-labd-14-en-11-one (3d).

M.p. 88-91°C (from CH_3CN).- ^1H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 9H, 7-O-Si($\underline{CH_3}$)$_3$), 0.89 (s, 3H, $\underline{CH_3}$-19), 0.97 (s, 3H, $\underline{CH_3}$-18), 1.23 (s, 3H, $\underline{CH_3}$-16), 1.32 (s, 3H, $\underline{CH_3}$-20), 1.36 (s, 3H, $\underline{CH_3}$-17), 2.08 (s, 3H, OCO$\underline{CH_3}$), 2.59 (narrow m, $W_{1/2}$=3Hz, 2H, CH_2-12), 2.61 (s, 1H, 9-H), 3.72 (d, 1H, 7-H), 5.01 and 5.12 (AB part of an ABX system, 2H, CH_2-15), 5.53 (dd, 1H, 6-H), 5.94 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.0 Hz, $J_{6,7}$=4.5 Hz, $|J_{15,15'}|$=1.0 Hz, $J_{cis\ 14,15}$=11.0 Hz, $J_{trans\ 14,15}$=17.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.2 (7-O-Si(CH_3)$_3$), 16.3 (C-20), 18.2 (C-2), 21.3 (C-17), 22.9 (OCO$\underline{CH_3}$ and C-19), 31.2 (C-16), 33.0 (C-18), 33.8 (C-4), 37.5 (C-10), 41.2 (C-1), 43.9 (C-3), 49.6 (C-12), 53.9 (C-5), 65.6 (C-7), 71.8 (C-9), 74.6 (C-8), 79.3 (C-13), 79.8 (C-6), 111.8 (C-15), 146.9 (C-14), 169.9 ($\underline{OCOCH_3}$), 206.5 (C-11).- IR ($CHCl_3$): 1740 (ester), 1720 cm^{-1} (ketone) .- MS: m/z (%) = 435.2567 (12, $(M-CH_3)^+$), Calc for $C_{24}H_{39}O_5Si^+$: 435.2567), 367 (15), 307 (50), 279 (42), 233 (32), 117 (67), 73 (100).

Reaction of **3a** with Me_3SiI - $(Me_3Si)_2NH$.

1.) To a solution of carefully dried **3a** (100 mg, 0.26 mmol) and $(Me_3Si)_2NH$ (132 µl, 0.63 mmol) in

dry CH_2Cl_2 (4.0 ml) was added at -10°C Me_3SiI (80 µl, 0.59 mmol). The solution was allowed to warm to ambient temperature (20 min) and then stirred at 20°C for 205 min. Filtration through Florisil, evaporation of the solvent and MPLC (column B, hexanes-ethyl acetate 30:1 → 10:1) gave **8a** (12.4 mg, 9%), **8c** (60.3 mg, 51%), and a 4:1 mixture (^{1}H NMR) of **9a** and **10a** (33.1 mg, 24%).

2.) To a solution of carefully dried **3a** (500 mg, 1.32 mmol) and $(Me_3)_2SiNH$ (825 µl, 3.94 mmol) in dry CH_2Cl_2 (8 ml) was added at 0°C Me_3SiI (531 µl, 3.92 mmol). The mixture was stirred at 40°C for 150 min. After solvent evaporation and crude separation on SiO_2 (45 g, the top of the column was covered with 5 g of Florisil, hexanes-ethyl acetate-NEt_3 25:1:0.026) followed by MPLC (column B, hexanes-ethyl acetate-NEt_3 35:1:0.036) gave a 4:1 mixture of **9a** and **10a** (458 mg, 66%) along with **8a** (32.5 mg, 5%).

7β-Acetoxy-8,13-epoxy-6β-hydroxy-11-trimethylsilanyloxy-labd-11,14-diene (**8c**).

^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 0.23 (s, 9H, 11-O-Si(CH_3)$_3$), 0.93 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-18), 1.20 (s, 3H, CH_3-16), 1.44 (s, 3H, CH_3-20), 1.61 (s, 3H, CH_3-17), 2.07 (d, 1H, 9-H), 2.14 (s, 3H, -OCOCH_3), 4.34 (dd, 1H, 6-H), 4.58 (d, 1H, 12-H), 4.78 and 5.12 (AB part of an ABX system, 2H, CH_2-15), 4.89 (d, 1H, 7-H), 5.70 (X part of an ABX system, 1H, 14-H). $J_{6,5}$=2.0 Hz, $J_{6,7}$=3.6 Hz, $^4J_{9,12}$=2.5 Hz, $|J_{15,15'}|$=2.0 Hz, $J_{cis\ 14,15}$=10.5 Hz, $J_{trans\ 14,15}$=17.0 Hz.- IR ($CHCl_3$): 3600 (OH), 1735 (ester), 1650 cm^{-1} (C=C).- MS: m/z (%) = 450 (3, M$^+$), 435.2567 (23, (M-CH_3)$^+$), Calc for $C_{24}H_{39}O_5Si^+$: 435.2567), 183 (24), 83 (100).

Mixture of (12E)-7β-Acetoxy-6β,8-bis(trimethylsilanyloxy)-labda-12,14-dien-11-one (**9a**) and (12Z)-7β-Acetoxy-6β,8-bis(trimethylsilanyloxy)-labda-12,14-dien-11-one (**10a**).

^{1}H NMR (400 MHz, COSY, ^{13}C/^{1}H correlation, $CDCl_3$): δ = -0.06 (s, 9H, 8-O-Si(CH_3)$_3$), 0.13 (s, 9H, 6-O-Si(CH_3)$_3$), 0.89 (s, 3H, CH_3-19), 1.05 (d, 1H, 5-H), 1.08 (s, 3H, CH_3-18), 1.32 (m, 3H), 1.46 (s, 3H, CH_3-20), 1.65 (s, 3H, CH_3-17), 2.14 and 2.19 (2s, 2x3H, OCOCH_3 and CH_3-16), 2.81 and 2.83 (2s, 2x1H, 9-H of **9a** and **10a**) 4.36 (dd, 1H, 6-H), 4.75 (d, 1H, 7-H), 5.42 and 5.61 (AB part of an ABX system, CH_2-15 of **9a**), 5.42 and 5.56 (AB part of an ABX system, CH_2-15 of **10a**), 6.10 and 6.15 (2s, 12-H of **9a** and **10a**), 6.31 (X part of an ABX system 14-H of **9a**), 7.70 (X part of an ABX system 14-H of **10a**). $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $|J_{15,15'}|$ not observable, $J_{cis\ 14,15}$ of **9a** = 13.2 Hz, $J_{trans\ 14,15}$ of **9a** = 17.7 Hz, $J_{cis\ 14,15}$ of **10a** = 8.8 Hz, $J_{trans\ 14,15}$ of **10a** = 17.6 Hz. From the integrals of separated signals of both isomers a 4:1 ratio of **9a** and **10a** was estimated. ^{13}C NMR (100.61 MHz, ^{13}C/^{1}H-correlation, $CDCl_3$): δ = 1.1 (6-O-Si(CH_3)$_3$), 2.7 (8-O-Si(CH_3)$_3$), 13.5 (C-16), 16.1 (C-20), 18.5 (C-2), 20.5 (C-17), 22.2 (OCOCH_3), 23.3 (C-19), 33.3 (C-18), 33.9 (C-4), 40.8 (C-10), 42.7 (C-1), 44.3 (C-3), 56.1 (C-5), 71.6 (C-6), 72.6 (C-9), 79.9 (C-8), 83.2 (C-7), 120.3 (C-15 of **9a**), 121.2 (C-15 of **10a**), 131.4 (C-12 of **10a**), 133.0 (C-12 of **9a**), 135.0 (C-14 of **10a**), 141.1 (C-14 of **9a**), 146.7 (C-13 of **10a**) 148.0 (C-13 of **9a**), 170.5 (OCOCH$_3$), 202.8 (C-11 of **10a**), 203.8 (C-11 of **9a**).- IR ($CHCl_3$): 1730 (ester), 1675 (CO, enone), 1580 cm^{-1}(C=C).- MS: m/z (%) = 522.3198 (12, M$^+$, Calc for $C_{28}H_{50}O_5Si_2$: 522.3197), 289 (22), 225 (54), 95 (100).- UV (CH_3CN):λ_{max} = 270nm, ε = 11900.

9b and **10b** from **3a**.

A 25 ml two-necked flask equipped with a reflux condenser and a gas inlet was charged with **3a** (1500 mg, 3.97 mmol), dry CH_2Cl_2 (15 ml), $(Me_3Si)_2NH$ (2.28 ml, 10.81 mmol), and Me_3SiI (1.47 ml, 10.33 mmol). The mixture was refluxed for 6 h. It was then cooled to 20°C and immediately filtered through SiO_2 (100 g, the top of the column was covered with 15 g Florisil, elution with hexanes-ethyl acetate-NEt_3 40:1:0.041) to give after solvent evaporation a crude product (**9a** and **10a**, 1.964 g) which was dissolved in CH_3OH-$CHCl_3$ 3:1. After 4 h at 20°C camphorsulfonic acid was added (87.4 mg, 0.37 mmol) and the mixture stirred at 20°C for 30 min. Neutralization with solid $NaHCO_3$, solvent evaporation and MPLC (column B, hexanes-ethyl acetate 8:1 → 4:1) gave **9b** (809 mg, 45% based

on **3a**) and **10b** (327 mg, 18% based on **3a**).

(12E)-7β-Acetoxy-8-hydroxy-6β-trimethylsilanyloxy-labda-12,14-dien-11-one (**9b**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 9H, 6-O-Si(CH_3)), 0.92 (s, 3H, CH_3-19), 1.05 (d, 1H, 5-H), 1.11 (s, 3H, CH_3-18), 1.47 (s, 3H, CH_3-20), 1.59 (s, 3H, CH_3-17), 2.18 (s, 6H, -OCOCH_3 and CH_3-16), 2.79 (s, 1H, 9-H), 4.39 (dd, 1H, 6-H), 4.75 (d, 1H, 7-H), 5.41 and 5.62 (AB part of an ABX system, 2H, CH_2-15), 6.20 (s, 1H, 12-H), 6.32 (X part of an ABX system, 1H, 14-H). $J_{5,6}$=1.5 Hz, $J_{6,7}$=3.5 Hz, $|J_{15,15'}|$ not observable, $J_{cis\ 14,15}$=11.0 Hz, $J_{trans\ 14,15}$=17.5 Hz.- IR ($CHCl_3$): 3600-3300 (OH), 1735 (ester), 1675 (CO, enone), 1620, 1580 cm^{-1} (C=C).- MS: m/z (%) = 450.2802 (17, M^+, Calc for $C_{25}H_{42}O_5Si$: 450.2801), 225 (44), 95 (100).- UV (CH_3CN): λ_{max} = 270nm, ε = 22000.- CD (CH_3CN), λ_{max} (Δε) = 271 nm (+2.81).

(12Z)-7β-Acetoxy-8-hydroxy-6β-trimethylsilanyloxy-labda-12,14-dien-11-one (**10b**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 9H, 6-O-Si(CH_3)$_3$), 0.93 (s, 3H, CH_3-19), 1.03 (d, 1H, 5-H), 1.11 (s, 3H, CH_3-18), 1.47 (s, 3H, CH_3-20), 1.57 (s, 3H, CH_3-17), 1.94 (s, 3H, CH_3-16), 2.17 (s, 3H, OCOCH_3), 2.78 (s, 1H, 9-H), 4.41 (dd, 1H, 6-H), 4.74 (d, 1H, 7-H), 5.42 and 5.59 (AB part of an ABX system, 2H, CH_2-15), 6.13 (s, 1H, 12-H), 7.59 (X part of an ABX system, 1H, 14-H). $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $|J_{15,15'}|$ not observable, $J_{cis\ 14,15}$=11.0 Hz, $J_{trans\ 14,15}$=17.5 Hz.- IR ($CHCl_3$): 3600-3300 (OH), 1735 (ester), 1670 (CO, enone), 1615, 1575 cm^{-1} (C=C).- MS: m/z (%) = 450.2801 (17, M^+, Calc for $C_{25}H_{42}O_5Si$: 450.2802), 435 (2), 375 (4), 225 (43), 95 (84), 43 (100).- UV (CH_3CN): λ_{max} = 272nm, ε = 13000.- CD (CH_3CN), λ_{max} (Δε) = 267 nm (+5.02).

Reaction of **9b** with N-phenylselenophthalimide (NPSP).

1.) To a solution of **9b** (150 mg, 0.33 mmol) in dry CH_2Cl_2 (3 ml) (10 ml two-necked flask) was added camphorsulfonic acid (7 mg, 0.03 mmol). The mixture was cooled to 0°C and after addition of NPSP (151 mg, 0.50 mmol) it was stirred at 0°C for 1 h. After being allowed to warm to 20°C it was stirred at 20°C for 24 h. Solvent evaporation, filtration through Florisil (15 g, elution with hexanes-ethyl acetate 20:1), solvent evaporation and MPLC (hexanes-ethyl acetate 25:1 → 5:1) gave **15** (24.7 mg, 21%) **17** (12.9 mg, 7%), and **9b** (13.8 mg, 9%).

2.) In a second experiment **9b** (100 mg, 0.22 mmol) was treated with camphorsulfonic acid (4.7 mg, 0.02 mmol) and NPSP (100.7 mg, 0.33 mmol) as described above. Conditions: 12 h at 20°C. TLC analysis (hexanes-ethyl acetate 8:1, 2 x developed) indicated complete conversion of **9b**. MPLC as described gave **15** (48 mg, 37%) and **9b** (25 mg, 25%).

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

^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 0.18 (s, 9H, 6-O-Si(CH_3)$_3$), 0.95 (s, 3H, CH_3-19), 1.10 (s, 3H, CH_3-18), 1.29 (s, 3H, CH_3-20), 1.40 (d, 3H, CH_3-16), 1.48 (s, 3H, CH_3-17), 2.11 (s, 1H, 9-H), 2.19 (s, 3H, OCOCH_3), 3.43-3.57 (m, 2H, CH_2-15), 4.06 (s, 1H, 12-H), 4.57 (dd, 1H, 6-H), 5.06 (d, 1H, 7-H), 5.84 (m, 1H, 14-H), 7.22 (m, 3H, Ar-H), 7.48 (m, 2H, Ar-H). $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz, $^4J_{16,14}$=1.0 Hz.- ^{13}C NMR (100.6 MHz, DEPT, ^{13}C/^{1}H correlation, $CDCl_3$): δ = 0.8 (6-O-Si(CH_3)$_3$), 12.6 (C-16), 17.0 (C-20), 17.9 (C-2), 19.1 (C-17), 21.6 (OCOCH_3), 22.7 (C-19), 24.9 (C-15, two satellites: $^1J_{13C,77Se}$=-57.8 Hz), 32.8 (C-18), 33.8 (C-4), 36.2 (C-10), 40.0 (C-1), 44.2 (C-3), 57.6 (C-5), 66.9 (C-9), 72.0 (C-6), 79.4 (C-8), 80.4 (C-7), 81.9 (C-12), 123.2 (C-14), 127.4 (aromatic C), 128.9 (aromatic C), 129.4 (C-13), 133.5 (aromatic C-1), 134.3 (aromatic C), 170.1 (O$COCH_3$), 208.8 (C-11).- IR ($CHCl_3$): 1760 (ester), 1740 cm^{-1} (ketone).- MS: m/z (%) = 449.2724 (4.4, (M-PhSe)$^+$), Calc for $C_{25}H_{41}O_5Si^+$: 449.2723), 396 (5), 314 (17), 225 (100), 156.9538 (28, Calc for $C_6H_5{}^{80}Se^+$: 156.9556).

(12R,13E)-7β-Acetoxy-8,12-epoxy-15-phenylselanyl-6β-trimethylsilanyloxy-9βH-labd-13-en-11-one (17).

^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 0.17 (s, 9H, 6-O-Si(CH_3)$_3$), 0.90 (s, 3H, CH_3-19), 1.09 (s, 3H, CH_3-18), 1.14 (d, 1H, 5-H), 1.40 (broadened s, 3H, CH_3-16), 1.42 (s, 3H, CH_3-20), 1.69 (s, 3H, CH_3-17), 1.97 (s, 1H, 9-H), 2.15 (s, 3H, OCOCH_3), 3.42-3.59 (m, 2H, CH_2-15), 4.14 (s, 1H, 12-H), 4.33 (dd, 1H, 6-H), 4.68 (d, 1H, 7-H), 5.78 (m, 1H, 14-H), 7.21 (m, 3H, Ar-H), 7.47 (m, 2H, Ar-H). $J_{5,6}$=2.0 Hz, $J_{6,7}$=3.5 Hz.- ^{13}C-NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.8 (6-O-Si(CH_3)$_3$), 12.5 (C-16), 18.0 (C-2), 21.2 (OCOCH_3), 23.5 (C-20), 23.7 (C-17), 24.9 (C-15), 25.0 (C-19), 32.8 (C-18), 33.8 (C-4), 34.4 (C-1), 38.3 (C-10), 43.7 (C-3), 50.6 (C-5), 63.9 (C-9), 71.5 (C-6), 75.0 (C-12), 81.9 (C-8), 82.1 (C-7), 123.8 (C-14), 127.4 (aromatic C), 128.8 (aromatic C), 129.4 (C-13), 134.0 (aromatic C-1), 134.4 (aromatic C), 170.0 (OCOCH$_3$), 212.4 (C-11).- IR (in $CHCl_3$): 1745 cm^{-1} (ester, ketone).- MS: m/z (%) = 449.2724 (4, (M-PhSe)$^+$), Calc for $C_{25}H_{41}O_5Si^+$: 449.2723), 314 (34), 225 (100), 156.9556 (60, Calc for $C_6H_5{}^{80}Se^+$: 156.9556).

Reaction of **9b** with phenylselenyl chloride - pyridine.

1.) To a solution of PhSeCl (14.0 mg, 73 µmol) in dry $CDCl_3$ (200 µl) was added pyridine-d_5 (6.5 µl, 81 µmol) at 20°C. The mixture was allowed to stand at 20°C for 10 min. The orange solution was then added to a solution of **9b** (30 mg, 66 µmol) in $CDCl_3$ (100 µl). After 2 h at 20°C a ^{1}H NMR spectrum (80MHz) indicated complete conversion of **9b**: δ = 0.12 (s, Si(CH_3)$_3$-6), 0.89 (s, CH_3-19), 1.08 (s, CH_3-18), 1.43 (s, CH_3-20), 1.57 (s, CH_3-17), 2.10 (s, OCOCH_3 and CH_3-16), 2.74 (s, 9-H), 3.13-3.34 (m, 15-H), 4.28-4.49 (m, 6-H + 14-H), 4.62-4.80 (m, 7-H), 6.18 (s, 12-H).

2.) The reagent was prepared from PhSeCl (70.2 mg, 0.37 mmol) and pyridine (32.4 µl, 0.40 mmol) in CH_2Cl_2 (0.7 ml) as described above. To this mixture was added a solution of **9b** (150 mg, 0.33 mmol) at 20°C. After being stirred at 20°C for 170 min the reaction mixture was treated with another portion of PhSeCl - pyridine, prepared from PhSeCl (35.1 mg, 0.19 mmol) and pyridine (16.2 µl, 0.20 mmol) in CH_2Cl_2. The mixture was stirred at 20°C for further 115 min. TLC (hexanes-ethyl acetate 2:1) indicated complete conversion of **9b** and the formation of mainly two reaction products (less polar than **9b**). Solvent evaporation and rapid chromatographic separation on 15 g SiO_2 (hexanes-ethyl acetate 8:1) caused decomposition of the primary reaction products and furnished **9b** (97.7 mg, 65%) and **19a** (29.2 mg, 14%).

(14S, 12E)-7β-Acetoxy-8,14-dihydroxy-15-phenylselanyl-6β-trimethylsilanyloxy-labd-12-en-11-one (19a).

^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 0.16 (s, 6-O-Si(CH_3)$_3$), 0.92 (s, CH_3-19), 1.10 (s, CH_3-18), 1.47 (s, CH_3-20), 1.510 and 1.515 (2s, CH_3-17 of both 14-epimers), 1.930 and 1.935 (CH_3-16), 2.140 and 2.143 (OCOCH_3), 2.78 (s, 9-H), 2.82-3.01 (m, 15-H), 3.11-3.23 (m, 15-H), 4.04 (X part of an ABX system, 14-H), 4.39 (m, $W_{1/2}$=7 Hz, 6-H), 4.75 (m, $W_{1/2}$=4 Hz, 7-H), 6.37 (m, $W_{1/2}$=4 Hz, 12-H), 7.28 (m, Ar-H), 7.53 (m, Ar-H).- ^{13}C NMR (100.6 MHz, DEPT, $CDCl_3$): δ = 0.7 (6-O-Si(CH_3)$_3$); 15.3, 15.6, 15.9 (C-16 and C-20 of both isomers); 18.2 (C-2); 20.3 (C-17); 21.4 (OCOCH_3); 23.1 (C-19); 33.1 (C-18); 33.8 (C-4); 34.9 and 35.1 (C-15); 40.5 (C-10); 42.4 (C-1); 43.8 (C-3); 55.7 and 55.8 (C-5); 70.5 (C-9); 71.4 (C-6); 74.0 and 74.1 (C-14); 75.8 (C-8); 82.0 (C-7); 127.6, 127.9, 128.7 (C-12 and aromatic C's)); 129.0 (aromatic C); 133.4 (aromatic C); 153.0 and 153.2 (C-13); 171.0 (OCOCH$_3$); 202.8 (C-11).- IR ($CHCl_3$): 3600-3200 (OH), 1735 (CO, ester), 1680 (CO, enone), 1620, 1580 cm^{-1} (C=C).- MS: m/z (%) = 624 (0.4, M$^+$), 466.2748 (3, (M-PhSeH)$^+$), Calc for $C_{25}H_{42}O_6Si^+$: 466.2751), 449 (18), 389 (6), 314 (13), 312 (13), 225 (66), 156.9556 (24, Calc for $C_6H_5{}^{80}Se^+$: 156.9556), 43 (100).

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