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MODEL STUDIES DIRECTED TOWARD FORSKOLIN: SYNTHESIS OF A TRICYCLIC MODEL COMPOUND FROM FARNESOL

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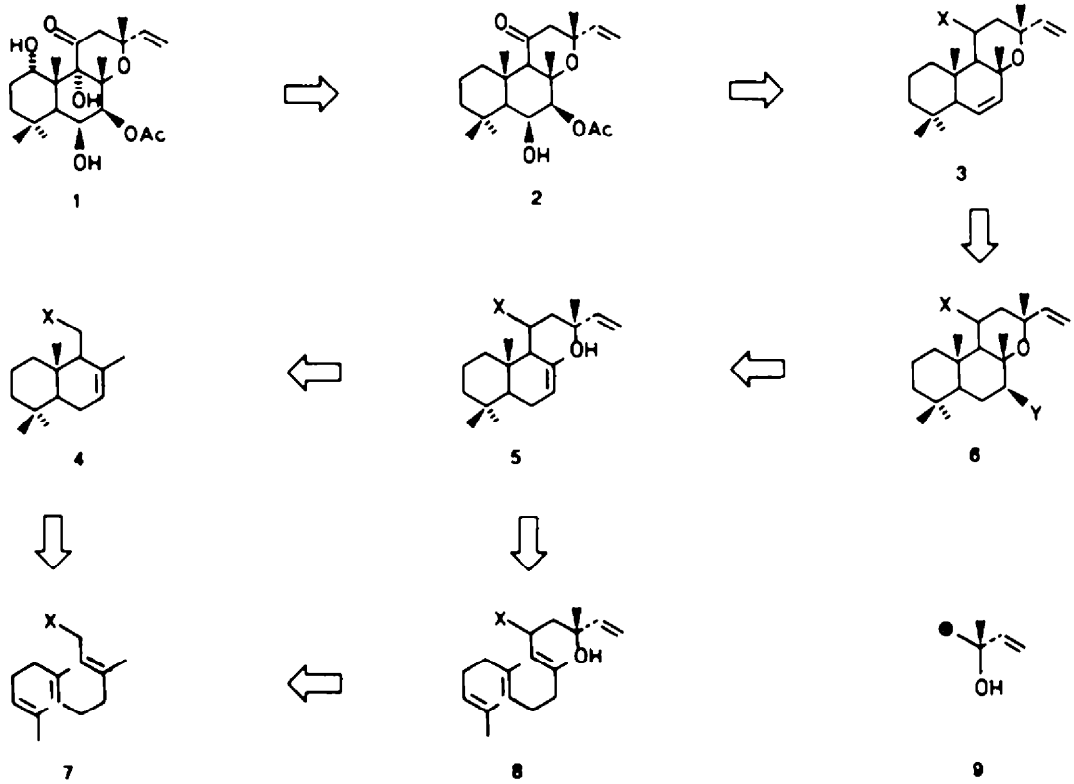
Abstract - From farnesol and (R)-methyloxirane the optically active bicyclic compounds **31** and **32** have been prepared. Cyclization of **31** led to the tricyclic compounds **29** and **30**, respectively, which differ configurationally from forskolin only at C-8.

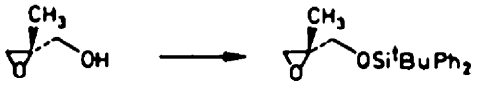
Some time ago we discussed a biogenetically patterned synthetic plan for forskolin (**1**)[1,2] via 1,9-dideoxyforskolin (**2**).[3] Part of this plan is depicted (in somewhat more elaborate form) in Scheme 1. In the present publication we report on results which were obtained, probing the chemistry which is connected with steps **4** → **5** → **6** and steps **7** → **8** → **5** → **6**.



Scheme 1.

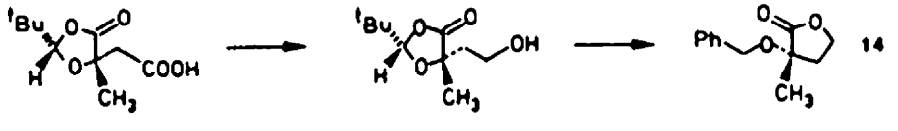
Synthesis of 11, 17, and 18

As synthetic equivalents of synthon 9, epoxide (R)-11[4] and the epoxide, derived from (S)-17 as well as aldehyde (S)-18 were selected. (R)-10 was obtained from 2-methyl-2-propen-1-ol using a) a modified version of the Sharpless epoxidation reaction [4,5,6] and b) the work-up procedure reported by Meister and Scharf.[4] The e.e. was shown by Mosher ester[7] analysis (see Experimental) to be 93%. For the conversion of 10 into 11 the Hernandez method[8] was employed. The synthesis of both 17 and 18 was based on Seebach's selfreproduction of chirality. 12, prepared from (S)-malic acid as described by Seebach[9] was reduced under carefully controlled conditions (otherwise the lactonic function was also reduced) with borane - dimethyl sulfide[10] to give 13. Attempted protection of the free OH group in 13 by benzylation led to the formation of 14, whereas silylation under the Hernandez conditions[8] cleanly provided 16. Reduction of the lactone grouping in 16 with borane - dimethyl sulfide yielded hemiacetal 15 (95% yield) rather than the desired diol 17. A 56% yield of 17 was obtained by reduction of 16 with lithium aluminium hydride. Swern oxidation[11] of 17 led to 18 in 65% yield.

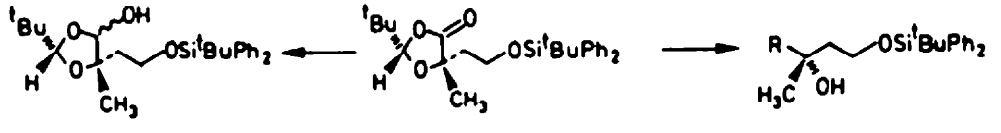


10 11

Scheme 2.



12 13



15 16

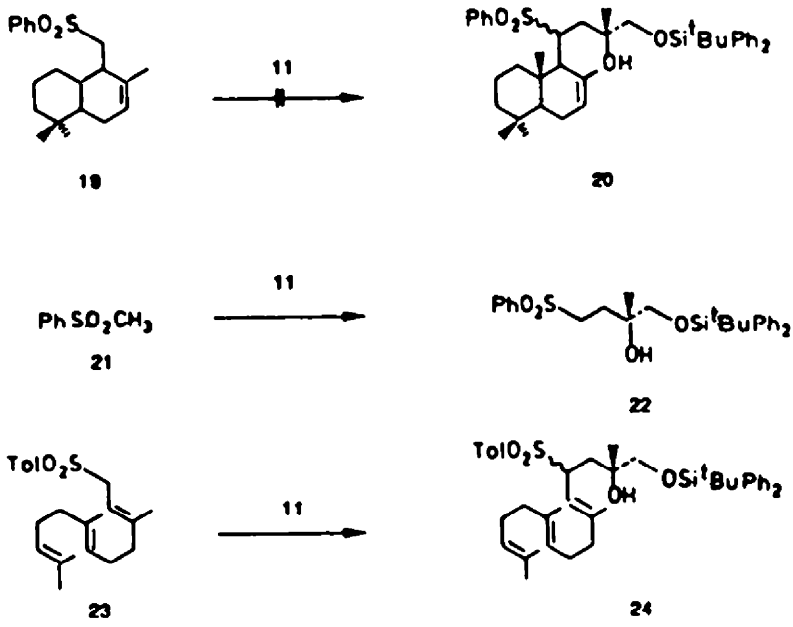
	R
17	CH_2OH
18	CHO

Scheme 3.

Reaction of sulfones 19, 21, and 23 with oxirane 11

As synthetic equivalents of synthons 4 and 7 the sulfones 19[12] and 23[13], respectively,[14,15] were chosen. It is well-known that lithiated sulfones react rather sluggishly with (especially sterically hindered) oxiranes[16,17] and that the reaction rate can be enhanced considerably by addition of a Lewis acid such as boron trifluoride etherate or titanium(IV) isopropoxide.[16-20] But even in the presence of (a) $Ti(O^iPr)_4$, (b) $BF_3{\times}Et_2O$, (c) $(^tBu)_2AlOSO_2CF_3$, [21,22] or (d) $Me_3SiOSO_2CF_3$, the lithiated sulfone 19 failed to react with 11,[23,24] and also the anion derived from

19 with EtMgBr resisted the desired reaction.[23] In a model experiment epoxide 10 was treated with the lithio derivative of methyl phenyl sulfone in the presence of $Ti(O^iPr)_4$. Even in this case the reaction was very slow, and after 4d at 20°C a 10% yield of 22 was obtained. One may wonder wether this low reactivity is steric in origin or the result of an unfavourable HOMO-LUMO interaction, since the anion derived from the allylic sulfone 23 reacted smoothly (in the absence of a Lewis acid!) with 11 to provide 24, the "C_{19}-precursor" of 2, in 72% yield (1:1 mixture of two stereoisomers).



Scheme 4.

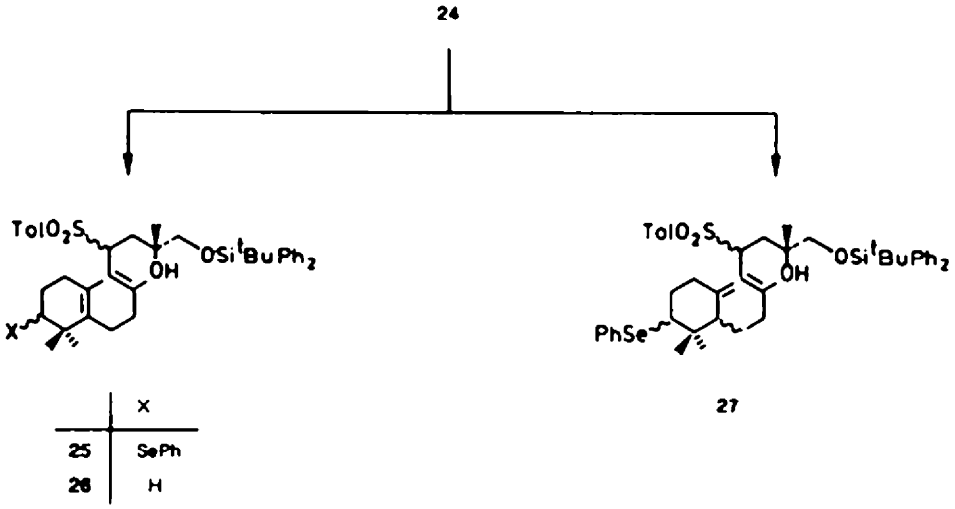
Selenium-mediated cyclization of 24

By cyclization of optically active 24, in principle,[12,25-29] access might be gained to very elaborate precursors of 2. Unfortunately, until now we have been unable to find proper conditions to effect the cyclization in the desired manner. On organoselenium-induced cyclization[31] of 24 with N-phenylselenophthalimide (NPSP)[32] in the presence of $SnCl_4$ (24h at 20°C) exclusively the monocyclic products 25 and 27 as mixtures of stereoisomers were obtained (37% combined yield). The structure of 27 followed straightforwardly from the ^1H and ^{13}C NMR spectra (see Experimental). The structural assignment of 25 was confirmed by spectral analysis after reduction with tri-n-butyltin hydride to give 26.

Tricyclic compounds 30 and 34 from rac. 19 and methyloxirane

$Ti(O^iPr)_4$-assisted reaction[19] of the lithio derivative of rac. 19 with both (R)-[33] and rac.-methyloxirane (28) provided[24] the two substitution products 31 and 32 in optically active and racemic form, respectively, as 11-epimers.[34]
The gross structures of 31 and 32 followed from spectral data, whereas the (relative) configuration at the newly formed chiral centres was assigned on the basis of the results outlined below. Selenium-induced cyclization of both 31 and 32 led to the formation of the respective tricyclic compounds 29 and 33 (87% and 78% yield, respectively). From an extensive NMR spectroscopic analysis[35] the configuration

shown in 29 and the preferred conformation depicted in 29' were deduced.
Most specifically, the 7-position of the phenylselenyl residue was indicated by the fact that the ^{13}C NMR signal of C-7 (δ=57.80) is accompanied by two satellites which originate from ^{13}C, ^{77}Se coupling (J=-68.2 Hz).[40] 7-H gives rise to the X-part of an "ABX" system with $J_{7,6}+J_{7,6'}$=7.0 Hz which would correspond to an equatorial position in a chair-like ring B. The through-space interactions between CH_3-14 and 7-H, 9-H, and 13-H (summarized in 29') seem only consistent with the -configuration of this methyl group. The NOE enhancements between 11-H and CH_3-20 are best accommodated assuming a boat or twist conformation of ring C. This view is supported by the multiplicity of the 11-H ^1H NMR signal which appears as a doublet



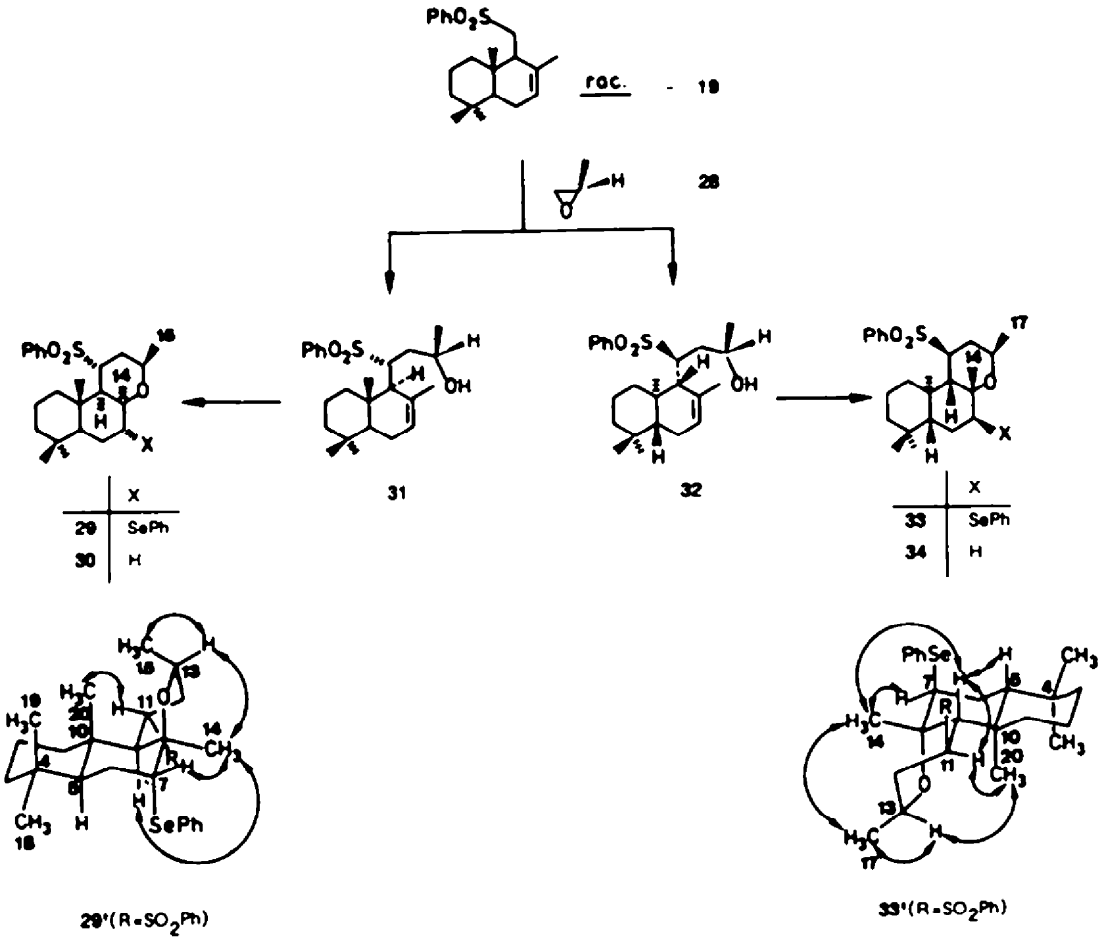
Scheme 5.

with J=9.5 Hz which means that the torsional angle 11-H(C-11 - C-12)12α-H is almost 180° whereas the corresponding angles for 11-H/9-H and 11-H/12β-H are around 90°. The NOE effect between CH_3-20 and 7-H indicates that the ring B conformation may also differ from the ideal chair.
For the cyclization product of 32 configuration and conformation as depicted in 33 and 33' were deduced from the Overhauser effects summarized in formula 33'. The more complicated 11-H signal (as compared with 29) which consists of 6 lines ($J_{9,11}$=1.5 Hz, $J_{11,12\alpha}+J_{11,12\beta}$=9.5 Hz) indicates ring C to be in a somewhat different conformation than in 29.
In a second set of experiments rac-31 and rac-32 were cyclized with mercuric trifluoroacetate. Subsequent reduction with sodium borohydride[40] gave 33 and 34 in 62% and 42% yield, respectively. 33 and 34 were again submitted to careful NMR spectroscopic analysis fully in accord with the proposed structures (see Experimental). Finally, 29 and 33 were reductively converted with tri-n-butyltin hydride into 30 and 34, respectively.

Conclusion

From farnesol and (R)-methyloxirane (28) the optically active bicyclic compounds 31 and 32 have been prepared. Cyclization of 31 led to 29 and 30, respectively, which differ configurationally from forskolin only at C-8. If the reluctance of 19 to react with 10 or an electrophilic reagent derived from 17 can be overcome and if the cyclization would then lead to a tricyclic compound of type 29 with the correct configuration at C-8, a highly advanced intermediate for 1,9-dideoxyforskolin would

result with the proper functionality in ring B to introduce the 6,7-diol group by elimination and cis-hydroxylation. Further work along these lines is in progress.



Scheme 6.

EXPERIMENTAL

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). Usual work-up means partioning the reaction mixture between water and an organic solvent (given in parenthesis), drying the combined organic solution over Na_2SO_4, and removal of the solvent by distillation in vacuo at 40°C, using a rotatory evaporator. The instrumentation used was: ^1H NMR: 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).

(S)-2-Methyl-2-epoxy-1-propanol (10).

10 was prepared from 2-methyl allyl alcohol (26.1 ml, 331 mmol) as described by Meister and Scharf.[4] The work-up procedure of Meister and Scharf was followed until a product (25.3 g) was obtained containing mainly (S)-10 alongside with small amounts of the starting material, tert-butyl alcohol, and CH_2Cl_2. The Mosher ester of (S)-10 was compared with the Mosher ester of rac.-10 and was found (HPLC: Lichrosorb Si 100, 5 µm; isooctane - tert-butyl methyl ether 15:1; flow: 1 ml/min; UV detection at 219 nm) to have an e.e. of 93%.

(R)-2-(tert-Butyl-diphenyl-silanyloxymethyl)-2-methyl-oxirane (11).

To a solution of a slightly impure specimen of 10 prepared as described above (2.00 g, 22.72 mmol) in CH_2Cl_2 (50 ml) at 0°C triethylamine (6.33 ml, 45.45 mmol), 4-dimethylaminopyridine (277.3 mg, 2.27 mmol), and tert-butylchlorodiphenylsilane (10.0 ml, 38.59 mmol) were added. The mixture was stirred at 20°C for 22 h. Filtration through SiO_2 (40 g, covered with Florisil (5 g), elution with hexanes - ethyl acetate 10:1) followed by solvent evaporation and MPLC (column C, hexanes - ethyl acetate 10:1) provided (R)-11 (5.80 g, 78%).- $(\alpha)_D^{20}$ = +7.3 (c 3.37 in $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ = 1.10 (s, 9H, $C(CH_3)_3$), 1.40 (s, 3H, CH_3), 2.52-2.81 (AB-system, 2H, CH_2-3), 3.69 (s, 2H, CH_2-1), 7.30-7.80 (10H, Ar-H); $|J_{3,3'}|$=5.0 Hz.- $C_{20}H_{26}O_2Si$ (326.5), MS: m/z (%) = 269.0998 (32, Calc for $C_{16}H_{17}O_2Si$: 269.0998), 239 (76), 191 (100), 183 (96).

(2S,5S)-2-tert-Butyl-5-(2-hydroxy-ethyl)-5-methyl-[1,3]dioxolan-4-one (13).

To a solution of 12 (271.3 mg, 1.26 mmol) in THF (2.5 ml) at -20°C dropwise borane-dimethyl sulfide (2M solution in THF, 0.69 ml, 1.38 mmol) was added. When the H_2 evolution had ceased the reaction mixture was stirred at 20°C for 18 h. Excess borane-dimethyl sulfide was destroyed by addition of methanol (80 µl). Solvent evaporation and SC (20 g SiO_2, hexanes-acetone 6:1) provided 13 (254.6 mg, 100%).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.98 (s, 9H, $C(CH_3)_3$), 1.43 (s, 3H, CH_3), 2.08 (t, 2H, CH_2-1'), 3.79 (t, 2H, CH_2-2'), 4.17 (s, 1H, 2-H); $J_{1',2'}$=6.9 Hz.- IR ($CHCl_3$): 3700-3200 (OH), 1790 cm^{-1} (C=O).- MS: m/z (%) = 145 (11, $(M-C(CH_3)_3)^+$), 99 (51), 71 (41), 43 (100).- (Found C, 59.28; H, 9.00. $C_{10}H_{18}O_4$ (202.3) requires C, 59.39; H, 8.97).

(2S,5S)-2-tert-Butyl-5-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-5-methyl-[1,3] dioxolan-4-one (16).

To a solution of 13 (1.45 g, 7.18 mmol) in CH_2Cl_2 (12 ml) at 0°C dimethylaminopyridine (263 mg, 2.15 mmol, dissolved in 3 ml of CH_2Cl_2), triethylamine (2.40 ml, 17.23 mmol), and tert-butylchlorodiphenylsilane (4.10 ml, 15.80 mmol) were added. The mixture was stirred at 20°C for 6.5 h. Most of the solvent was removed by distillation, and the concentrated solution was filtered through SiO_2 (15 g, covered with Florisil (3 g), elution with hexanes-ethyl acetate 5:1). MPLC of the crude product (column C, hexanes-ethyl acetate 30:1 10:1) gave 16 (2.86 g, 91%).- $(\alpha)_D^{20}$ = +3.5 (c 1.39 in $CHCl_3$).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.92 (s, 9H, $C(CH_3)_3$), 1.08 (s, 9H, $C(CH_3)_3$), 1.43 (s, 3H, CH_3), 2.10 (t, 2H, CH_2-1'), 3.84 (t, 2H, CH_2-2'), 5.15 (s, 1H, 2-H), 7.29-7.53 (6H, Ar-H), 7.57-7.81 (4H, Ar-H); $J_{1',2'}$=7.0 Hz.- IR (CCl_4): 1805 cm^{-1} (C=O).- MS: m/z (%) = 383 (52, $(M-C_4H_9)^+$), 297 (36), 267 (100).- Found C, 70.79; H, 8.26. $C_{26}H_{36}O_4Si$ (440.6) requires C, 70.87; H, 8.23).

(2S,4=,5S)-2-tert-Butyl-5-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-5-methyl-[1,3]dioxolan-4-ol (15).

To a solution of 16 (207.0 mg, 0.47 mmol) in THF (0.35 ml) at 0°C borane-dimethyl sulfide (2M solution in THF, 0.52 ml, 1.04 mmol) was added. At 50°C dimethyl sulfide was removed by distillation (1 h) at ordinary pressure under careful exclusion of water. The sealed reaction flask was then heated to 50°C for 3 h. Excess borane-dimethyl sulfide was hydrolyzed at 20°C by addition of

methanol (70 µl). Solvent evaporation and SC (SiO_2 (20 g), hexanes-ethyl acetate 10:1) provided **15** (197.1 mg, 95%) as a 2:1 mixture (^{1}H NMR) of the C-4 epimers.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.86 and 0.93 (2s, 18H, 2x$C(CH_3)_3$), 1.05 (s, 18H, 2x $C(CH_3)_3$), 1.20 and 1.23 (2s, 6H, 2xCH_3), 1.70-2.19 (4H, 2xCH_2-1'), 2.58 and 4.47 (2d, 2H, exchangeable with D_2O, 2xOH), 3.49-4.12 (4H, 2xCH_2-2'), 4.67 and 4.84 (2s, 2H, 2x2-H), 5.04 and 5.28 (2d, 2H, 2x4-H), 7.27-7.49 (6H, Ar-H) 7.55-7.80 (4H, Ar-H); $J_{4,OH}$=5.0 Hz and 9.0 Hz.- IR (CCl_4): 3650-3200 cm^{-1} (OH).- MS: m/z (%) = 385 (8), 269 (10), 221 (100), 199 (59), 177 (29).- (Found C, 70.60; H, 8.67. $C_{26}H_{38}O_4Si$ (442.7) requires C, 70.55; H, 8.65).

Reduction of 16.

To a suspension of $LiAlH_4$ (46.1 mg, 1.21 mmol) in diethyl ether (1 ml) at -78°C slowly a solution of **16** (531.4 mg, 1.21 mmol) in diethyl ether (3 ml) was added. Within 2 h the mixture was allowed to warm to -30°C and was stirred 2 more h at this temperature. The reaction was quenched at -30°C with saturated aq. NH_4Cl (10 ml). At 20°C the mixture was transferred into a seperatory funnel and partitioned between saturated aq. NH_4Cl (10 ml) and diethyl ether (10 ml). The aqueous layer was extracted with diethyl ether (5x20 ml). The combined organic solutions were dried over Na_2SO_4 and filtered. Solvent evaporation and SC (SiO_2 (50 g), hexanes-ethyl acetate 5:1→ 2:1) gave **15** (68.4 mg, 13%) and **17** (239.5 mg, 56%).

(S)-4-(tert-Butyl-diphenyl-silanyloxy)-2-methyl-butane-1,2-diol (17).

$(\alpha)_D^{20}$ = +6.8 (c 1.76 in $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$-D_2O): δ = 1.05 (s, 9H, $C(CH_3)_3$), 1.20 (s, 3H, CH_3), 1.38-2.15 (2H, CH_2-3), 3.46 (s, 2H, CH_2-1), 3.74-4.14 (2H, CH_2-4), 7.28-7.80 (10H, Ar-H).- IR (CCl_4): 3700-3200 cm^{-1} (OH).- MS: m/z (%) = 283 (20), 249 (12), 223 (13), 205 (21), 199 (100), 85 (94), 61 (72), 43 (96).- (Found C, 70.38; H, 8.49. $C_{21}H_{30}O_3Si$ (358.5) requires C, 70.35; H, 8.43).

(S)-4-(tert-Butyl-diphenylsilanyloxy)-2-hydroxy-2-methyl-1-butanal (18).

At -55°C to a solution of oxalyl chloride (30.4 µl, 0.349 mmol) in CH_2Cl_2 (1 ml) anhydrous DMSO (53.4 µl, 0.699 mmol) was added. After 3 min within 5 min a solution of **17** (113.7 mg, 0.318 mmol) in CH_2Cl_2 (0.3 ml) was added dropwise. After being stirred at -55°C for 15 min the mixture was treated with triethylamine (221 µl, 1.588 mmol), and after further 5 min it was warmed to 20°C. Usual work-up (CH_2Cl_2) and SC (SiO_2 (10 g), hexanes- ethyl acetate 8:1→ 4:1) gave **17** (22.8 mg, 20%) and **18** (76.1 mg, 67%).- $(\alpha)_D^{20}$ = -7.95 (c 1.58 in $CHCl_3$).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.06 (s, 9H, $C(CH_3)_3$), 1.32 (s, 3H, CH_3), 1.65-2.35 (2H, CH_2-3), 3.40-3.92 (2H, CH_2-4), 3.98 (s, 1H, OH), 7.30-7.80 (10H, Ar-H), 9.70 (s, 1H, 1-H).- IR (CCl_4): 3600-3400 (OH), 1735 cm^{-1} (C=O).- MS: m/z (%) = 269 (2), 249 (6), 221 (100), 199 (59), 177 (44).- (Found C, 70.76; H, 8.00. $C_{21}H_{28}O_3Si$ (356.5) requires C, 70.74; H 7.92).

(RS)-4-(tert-Butyl-diphenyl-silanyloxy)-3-methyl-1-benzenesulfonyl-butan-3-ol (22).

Methyl phenyl sulfone (**21**) (50.0 mg, 0.320 mmol) and (RS)-**11** (156.5 mg, 0.480 mmol) were converted into **22** as described for **31** and **32** (vide infra). SC (SiO_2 (28 g), hexanes acetone 5:1) gave **22** (15.5 mg, 10%). 111.0 mg (71%) of **21** were recovered.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.03 (s, 9H, $C(CH_3)_3$), 1.10 (s, 3H, CH_3), 1.65-2.40 (m, 2H, CH_2-2), 3.00-3.38 (m, 2H, CH_2-1), 3.42 (s, 2H, CH_2-4), 7.30-8.10 (15H, Ar-H).- IR (CCl_4): 3650-3400 (OH), 1315, 1305 and 1150 cm^{-1} (SO_2).- $C_{27}H_{34}O_4SSi$ (482.7), MS: m/z (%) = 426 (3.6, $(M-C_4H_9)^+$), 408 (2.7), 348 (49), 200 (100).

Alkylation of 23 with (R)-11.

To a stirred solution of **23**[13] (846 mg, 2.35 mmol) in 3:1 THF-HMPT (17.4 ml) at -20°C n-butyllithium

(1.63 M solution in hexane, 1.73 ml, 2.82 mmol) was added. Stirring was continued for 20 min, and the deeply red solution was then cooled to -78°C. After 30 min a solution of (R)-**11** (1.146 g, 3.53 mmol) in THF (4.6 ml) was added. The mixture was stirred at 40-45°C for 6 h and then treated with saturated aq. NH_4Cl (25 ml). Usual work-up (diethyl ether) and MPLC (column B, hexanes-ethyl acetate 8:1) gave an 1:1 mixture (^1H NMR) of **24** (1102 mg, 72%). Part of this mixture was separated by MPLC (column B, hexanes-ethyl acetate-ethanol 30:2.7:0.3).

(2R,4Ξ,5E,9E)-1-(tert-Butyl-diphenyl-silanyloxy)-2,6,10,14-tetramethyl-4-toluenesulfonyl-pentadeca-5,9,13-trien-2-ol (**24**, unpolar isomer).

$(\alpha)_D^{20}$ = +19.6 (c 1.59 in $CHCl_3$).- ^1H NMR (400 MHz, COSY, $COCl_3$): δ = 1.03 (s, 3H, CH_3), 1.08 (s, 9H, $C(CH_3)_3$), 1.21 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.85-2.10 (m, 8H, including 3-H), 2.41 (s, 3H, CH_3-Ar), 2.54 (s, 1H), 2.71 (dd, 1H, 3'-H), 3.42 (s, 2H, CH_2-1), 4.09 (m, 1H, 4-H), 4.98-5.11 (3H, olefin. H), 7.22-7.29 (2H, Ar-H), 7.33-7.48 (6H, Ar-H), 7.59-7.72 (6H, Ar-H); $J_{3',4}$=2.5 Hz, $|J_{3,3'}|$=15.0 Hz.- ^{13}C NMR (100.6 MHz, DEPT, $COCl_3$)[42]: δ = 15.9 (6-CH_3), 16.4 (10-CH_3), 17.6 (14-CH_3), 19.2 ($\underline{C}(CH_3)_3$), 21.6 (CH_3-Ar), 23.2 (2-CH_3), 25.7 (C-15), 26.0 (C-8), 26.6 (C-12), 26.8 (-$C(\underline{C}H_3)_3$), 35.9 (C-3), 39.6 (C-7 und C-11), 60.9 (C-4), 71.4 (C-1), 71.9 (C-2), 119.1 (C-5), 123.4 (C-9), 124.2 (C-13), 127.8 (aromat. C), 129.2 (aromat. C), 129.3 (aromat. C), 129.8 (aromat. C), 131.3 (C-14), 135.6 (C-10); 132.79, 132.81, 134.8, 144.1, 144.6 (C-6 und aromat. C).- IR ($CHCl_3$): 3600-3400 (OH), 1665, 1605 (C=C), 1305, 1150 cm^{-1} (SO_2).- MS: m/z (%) = 686.3814 (0.2, Calc for $C_{42}H_{58}O_4SSi$: 686.3825), 629 (0.2, $(M-C_4H_9)^+$), 513 (3.5), 337 (3.1), 255 (54), 235 (100).- (Found C, 73.27; H, 8.47. $C_{42}H_{58}O_4SSi$ requires C, 73.42; H, 8.51).

(2R,4Ξ,5E,9E)-1-(tert-Butyl-diphenyl-silanyloxy)-2,6,10,14-tetramethyl-4-toluenesulfonyl-pentadeca-5,9,13-trien-2-ol (**24**, polar isomer).

$(\alpha)_D^{20}$ = -12.3 (c 1.80 in $CHCl_3$).- ^1H NMR (80 MHz, $COCl_3$): δ = 1.06 (s, $(C(CH_3)_3$), 1.12 (d, J=1.2 Hz, CH_3), 1.20 (s, 3H, CH_3), 2.41 (s, 3H, CH_3-Ar), 3.41 (s, 2H, CH_2-1), 3.80-4.17 (m, $W_{1/2}$=22.7 Hz, 1H, 4-H), 4.80-5.28 (3H, olefin. H), 7.15-7.79 (14H, Ar-H).- IR (CCl_4): 3600-3400 (OH), 1600 (C=C), 1315, 1150 cm^{-1} (SO_2).- MS: m/z (%) = 686.3819 (0.6, Calc for $C_{42}H_{58}O_4SSi$: 686.3825), 629.3116 (0.5, Calc for $C_{38}H_{49}O_4SSi$: 629.3121), 513 (6.8), 255 (66), 235 (100), 199 (91).- (Found C, 73.35; H, 8.60. $C_{42}H_{58}O_4SSi$ requires C, 73.42; H, 8.51).

Cyclization of **24** (polar stereoisomer).

To a solution of NPSP (299.2 mg, 0.990 mmol) in CH_2Cl_2 (20 ml) at 20°C a solution of **24** (456.5 mg, 0.665 mmol) in CH_2Cl_2 (5 ml) and $SnCl_4$ (10 percent solution in CH_2Cl_2, 388.1 µl, 0.332 mmol) were added. The mixture was stirred at 20°C for 24 h, then solid $NaHCO_3$ was added. Solvent evaporation, followed by a crude chromatographic separation (SiO_2 (25 g), hexanes-acetone 12:1) gave a mixture of products (309.7 mg) which was separated by repeated MPLC (a: column B, hexanes-acetone 12:1, b: column B, hexanes-ethyl acetate 8:1) to give **25** (173.0 mg, 31%) and **27** (33.4 mg, 6%).

(11Ξ,13R,8E)-14-(tert-Butyl-diphenyl-silanyloxy)-3ξ-phenylselanyl-11-toluenesulfonyl-9,10-seco-15-nor-labda-5(10),8-dien-13-ol (**25**, mixture of 2 stereoisomers).

The analytical sample was further purified by prep. HPLC (column: LiChrosorb Si 100 (5 µm); solvent: isooctane - $CHCl_3$ - 2-propanol 25:1:0.1; flow 8 ml/min; detection: UV, 254 nm). ^1H NMR (400 MHz, COSY, $COCl_3$): δ = 0.95 (d, 1H), 1.11 ($C(CH_3)_3$), 1.18-1.46 (CH_3-signals), 1.88s and 1.89s (3H, CH_3-Ar), 2.05 (12-H and 2-H), 2.43 (m, 1H, 2-H'), 2.80 (m, 1H, 12-H'), 3.29 (m, 1H, 3-H), 3.40 and 3.52 (AB-system, 2H, CH_2-14), 4.30 (m, 1H, 11-H), 5.19 (m, 1H, 9-H), 6.80 (2H, Ar-H), 7.02 (3H, -Ar-H), 7.21 (6H, Ar-H), 7.60 (2H, Ar-H), 7.70 (4H, Ar-H), 7.81 (2H, Ar-H); $|J_{14,14'}|$=10.0 Hz (for both isomers).- IR (CCl_4): 3650-3400 (OH), 1660, 1600 and 1580 (C=C), 1310, 1300 and 1150 cm^{-1} (SO_2).- MS: m/z (%) = 842.3337 (Calc for $C_{48}H_{62}O_4S^{80}SeSi$: 842.3303), 686 (100), 869 (66), 626 (41),

557 (23), 512 (31), 255 (32), 235 (100).

(5Ξ,11Ξ,13R,8E)-14-(tert-Butyl-diphenyl-silanyloxy)-3ξ-phenylselanyl-11-toluenesulfonyl-9,10-seco-15-nor-labda-8,10(20)-dien-13-ol (27, mixture of 2 stereoisomers).

The analytical sample was further purified by prep. HPLC (conditions as reported for 25). ^{1}H NMR (400 MHz, COSY, C_6D_6): δ = 0.88 and 0.90 (s, 3H, CH_3), 1.10 and 1.11 (s, 9H, $C(\underline{C}H_3)_3$), 1.15, 1.17, 1.21, 1.24, 1.30 (CH_3-signals), 1.88 and 1.89 (s, 3H, CH_3-Ar), 1.91-2.25 (5H, including 12-H and CH_2-2), 2.68dd and 2.72dd (1H, 12-H'), 3.13dd and 3.23 (1H, 3-H), 3.42 and 3.50 (2 AB systems, 2H, CH_2-14), 4.20-4.34 (m, 1H, 11-H), 4.53d and 4.82d (J=7.5 Hz, and 5.0 Hz, 2H, $=CH_2$-10), 5.20 (m, 1H, 9-H), 6.75-6.85 (2H, Ar-H), 6.97-7.06 (3H, Ar-H), 7.19-7.26 (6H, Ar-H), 7.57-7.63 (2H, Ar-H), 7.65-7.74 (4H, Ar-H), 7.78-7.85 (2H, Ar-H); $|J_{12,12'}|$=14.0 Hz, $|J_{14,14'}|$=12.0 Hz (for both stereoisomers).- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[43]: δ = 16.47 (CH_3-17), 19.46 ($\underline{C}(CH_3)_3$), 21.18 (CH_3-Ar), 24.44 and 24.49 (C-2), 25.06 (CH_3-19), 25.45 and 25.51 (CH_3-16), 27.05 ($C(\underline{C}H_3)_3$), 29.05 and 29.09 (CH_3-18), 34.31, 36.69 and 36.86 (C-7, C-6 and C-12), 38.99 and 39.07 (C-1), 41.55 (C-4), 53.16 and 53.52 (C-5), 58.93 and 59.04 (C-3, $J_{Se,C}$=-57.7 Hz), 61.38 and 61.55 (C-11), 70.53 and 70.88 (C-14), 72.39 and 72.46 (C-13), 108.13 and 108.27 (C-10), 120.28 and 120.45 (C-9), 127.37-147.32 (olefin. and aromat. C).- IR (CCl_4): 3650-3400 (OH), 1310, 1300 and 1145 cm^{-1} (SO_2).- $C_{48}H_{62}O_4SSeSi$ (842.1), MS: m/z (%) = 685.3749 (Calc for $C_{42}H_{57}O_4SSi$: 685.3746), 511 (3.6), 337 (3.0), 255 (47), 235 (100), 199 (66), 135 (63).

(13R,8E)-14-(tert-Butyl-diphenyl-silanyloxy)-11ξ-toluenesulfonyl-9,10-seco-15-nor-labda-5(10),8-dien-13-ol (26).

To a solution of 25 (10.1 mg, 11.8 µmol) in toluene (0.3 ml) tri-n-butyltin hydride (4.8 µl, 17.7 µmol) and a catalytical amount of AIBN were added. The mixture was stirred at 110°C for 2 h. SC (SiO_2 (1 g), hexanes-acetone 12:1) gave 26 (4.9 mg, 68%).- ^{1}H NMR (400 MHz, COSY, C_6D_6): δ = 0.98 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.12 (s, 9H, $C(CH_3)_3$), 1.19 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.84 (s, 3H, CH_3-Ar), 2.05 (dd, 1H, 12-H), 2.43 (s, 1H), 2.82 (dd, 1H, 12-H'), 3.42 and 3.53 (AB system, 2H, CH_2-14), 4.30 (8 lines, 1H, 11-H), 5.22 (d, 1H, 9-H), 6.78 (d, J=8.5 Hz, 2H, Ar-H), 7.17-7.26 (6H, Ar-H), 7.64-7.73 (4H, Ar-H), 7.76-7.84 (2H, Ar-H); $|J_{12,12'}|$=14.2 Hz, $J_{12,11}$=9.5 Hz, $J_{12',11}$=2.5 Hz, $|J_{14,14'}|$=10.0 Hz, $J_{9,11}$=10.5 Hz.- ^{13}C NMR (100.6 MHz, DEPT, C_6D_6)[43]: δ = 16.47 (C-17), 19.46 ($\underline{C}(CH_3)_3$), 19.87 (C-2), 19.91 (C-19), 21.15 (CH_3-Ar), 25.57 (C-16), 27.05 ($C(\underline{C}H_3)_3$ and C-10), 27.38 (C-6), 28.74 (C-18), 32.97 (C-7), 35.13 (C-4), 36.66 (C-12), 40.05 and 40.66 (C-1 and C-3), 61.44 (C-11), 70.49 (C-14), 72.45 (C-13), 120.04 (C-9), 127.47-144.11 (olefin. and aromat. C).- IR (CCl_4): 3650-3400 (OH), 1660, 1600 (C=C), 1310, 1300 and 1145 cm^{-1} (SO_2).- $C_{42}H_{58}O_4SSi$ (687.1), MS: m/z (%) = 513.3547 (4, $C_{35}H_{49}OSi$: 513.3553), 473 (1.1), 377 (1.2), 337 (2.9), 255 (38), 235 (100).

Titanium(IV) isopropoxide-catalyzed alkylation of rac. 19 with 28.

a) with (RS)-28

To a stirred solution of rac-19[12] (481 mg, 1.39 mmol) in 4:1 THF-HMPT (5 ml) at -78°C n-butyllithium (1.48 M solution in hexane, 1.23 ml, 1.80 mmol) was added. The solution was permitted to warm to 0°C, and after 30 min at 0°C it was recooled to -78°C. After addition of titanium(IV) isopropoxide (619 µl, 2.08 mmol) the mixture was warmed to 0°C, maintained at this temperature for 30 min, and then recooled to -78°C. (RS)-28 (154 µl, 2.77 mmol) was added and the reaction mixture was then stirred at 20°C for 48 h. Saturated aq. NH_4Cl (10 ml) and 5 percent aq. tartaric acid (10 ml) were then added. Usual work-up (diethyl ether) followed by MPLC (column B, hexanes-ethyl acetate 5:1) furnished rac. 31 (176.1 mg, 31%) and rac. 32 (236.0 mg, 42%); 110.7 mg (23%) of rac. 19 were recovered.

b) with (R)-28

The analogous reaction of rac. **19** (202.4 mg, 0.58 mmol) with (R)-28 (81.2 µl, 1.16 mmol) provided (-)-**31** (57.8 mg, 24%) and (-)-**32** (85.0 mg, 36%); 53.2 mg (26%) of rac. **19** were recovered.

(13R)-11α-Benzenesulfonyl-14,15-dinor-labd-7-en-13-ol (31).

$(\alpha)_D^{20}$ = -6.5 (c 1.34 in $CHCl_3$).- The following analytical data were obtained from (±)-**31**. M.p. 142-143°C (from acetone/CCl_4).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.72 (s, 3H, CH_3), 0.81 (s, 6H, 2xCH_3), 1.25 (d, 3H, CH_3-16), 1.76 (d, 3H, CH_3-17), 2.13-2.72 (2H), 3.41-4.11 (3H, 1H exchangeable with D_2O, 13-H, 11-H and 13-OH), 5.63 (m, $W_{1/2}$=10.9 Hz, 1H, 7-H), 7.33-7.70 (3H, Ar-H), 7.79-8.08 (2H, Ar-H); $J_{13,16}$=6.0 Hz, $^4J_{17,7}$=2.0 Hz.- IR (CCl_4): 3495 (OH), 1295 and 1140 cm^{-1} (SO_2).- MS: m/z (%) = 262 (100, $(M-PhSO_2H)^+$), 218 (87), 109 (58), 94 (86).- (Found C, 71.18; H, 8.93. $C_{24}H_{36}O_3S$ (404.6) requires C, 71.24; H, 8.97).

ent-(13S)-11α-Benzenesulfonyl-13,14-seco-15,16-dinor-pimar-7-en-13-ol (32).

$(\alpha)_D^{20}$ = -18.1 (c 1.33 in $CHCl_3$).- The following analytical data were obtained from (±)-**32**. M.p. 140-142°C (from acetone/CCl_4).- ^1H NMR (80 MHz, $CDCl_3$): δ = 0.83 (s, 6H, 2xCH_3), 0.87 (s, 3H, CH_3), 1.12 (d, 3H, CH_3-17), 1.81 (broad s, $W_{1/2}$=4.0 Hz, 3H, CH_3-14), 2.15-2.90 (2H), 3.48-4.10 (2H, 11-H

Hz.- IR (CCl_4): 3650-3350 (OH), 1300 and 1140 cm^{-1} (SO_2).- MS: m/z (%) = 262 (100, $(M-PhSO_2H)^+$), 218 (69), 121 (45), 109 (51), 95 (55), 94 (55).- (Found C, 71.30; H, 8.90. $C_{24}H_{36}O_3S$ (404.6) requires C, 71.24; H, 8.97).

rac-(13R)-7α-Phenylselanyl-11α-benzenesulfonyl-8,13-epoxy-13,14-seco-16,17-dinor-pimarane (29, ent-29).

To a solution of rac. **31** (40.0 mg, 0.099 mmol) in CH_2Cl_2 (1 ml) at -78°C a solution of NPSP (44.7 mg, 0.148 mmol) in CH_2Cl_2 (0.5 ml) and then $SnCl_4$ (57.8 µl of a 10 percent solution in CH_2Cl_2, 0.049 mmol) were added. Within 2 h the mixture was permitted to warm to 20°C and was then stirred at this temperature for 90 min. Solvent removal (by passing argon over the surface) followed by SC (SiO_2 (5 g), hexanes-ethyl acetate 10:1) furnished rac-**29** (48 mg, 87%).- M.p. 107-110°C (from acetone/hexane).- ^1H NMR (400 MHz, COSY, NOE, C_6D_6): δ = 0.73 (s, 3H, CH_3-19), 0.82 (s, 3H, CH_3-20), 0.90 (s, 3H, CH_3-18), 1.02 (d, 3H, CH_3-15), 1.07-1.61 (9H, including 12'-H and 5-H), 1.92 (m, 1H, 6'-H), 2.00 (dd, 1H, 12-H), 2.10 (s, 1H, CH_3-14), 2.31 (m, 1H, 6-H), 2.56 (s, 1H, 9-H), 3.33 (d, 1H, 11-H), 3.95 (dd, 1H, 7-H), 4.31 (m, $W_{1/2}$=22.0 Hz,1H, 13-H), 6.97 (6H, Ar-H), 7.50 (2H, Ar-H), 7.89 (2H, Ar-H); $J_{15,13}$=6.4 Hz, $J_{11,12}$ =9.5 Hz, $J_{7,6}+J_{7,6'}$= 7.0 Hz.- ^{13}C NMR (100.6 MHz, DEPT, $^1H/^{13}C$ correlation, C_6D_6): δ = 18.33 (C-20), 18.84 (C-2), 22.35 (C-19), 23.06 (C-15), 26.36 (C-6), 27.36 (C-14), 28.88 (C-12), 33.33 (C-4), 33.64 (C-18), 39.52 (C-10), 40.24 and 41.42 (C-1 and C-3), 46.08 (C-9), 50.39 (C-5), 57.80 (C-7, $J_{C,Se}$=-68.2Hz), 59.51 (C-11), 62.77 (C-13), 76.57 (C-8), 127.11, 128.48, 129.23 (aromat. C's), 132.27 (aromat. C-Se), 133.07, 134.22 (aromat. C's), 141.90 (aromat. C-SO_2).- IR (CCl_4): 1580 (C=C), 1315, 1305 und 1145 cm^{-1} (SO_2).- MS: m/z (%) = 560 (8, M^+), 403 (14), 261 (100), 205 (26).- (Found C, 64.43; H, 7.22. $C_{30}H_{40}O_3SSe$ (559.7) requires C, 64.38; H, 7.20).

rac-(13S)-7α-Phenylselanyl-11α-benzenesulfonyl-8,13-epoxy-13,14-seco-15,16-dinor-pimarane (33, ent-33).

rac-**32** (40.0 mg, 0.099 mmol) on reaction with NPSP (44.7 mg, 0.148 mmol) and $SnCl_4$ (10 percent solution in CH_2Cl_2, 57.8 µl, 0.049 mmol), exactly as described for rac-**31**, gave rac-**33** (43.1 mg, 78%).- M.p. 192-193°C (from benzene).- ^1H NMR (400 MHz, COSY, NOE, C_6D_6): δ = 0.74 (s, 3H, CH_3-19), 0.78 (s, 3H, CH_3-20), 0.86 (s, 3H, CH_3-18), 0.98 (d, 1H, CH_3-17), 1.04-1.61 (9H, including 5-H and 12'-H), 1.86 (s, 3H, CH_3-14), 1.93 (m, 1H, 6'-H), 2.21 (2H, 6-H and 12-H), 2.57 (d, 1H, 9-H), 3.24

(dt, 1H, 11-H), 3.56 (m, $W_{1/2}$=23.5 Hz, 1H, 13-H), 3.91 (t, 1H, 7H), 6.94 (6H, Ar-H), 7.49 (2H, Ar-H), 7.82 (2H, Ar-H); $J_{17,13}$=6.0 Hz, $J_{9,11}$=1.5 Hz, $J_{11,12\alpha}$=10.0 Hz, $J_{7,6}+J_{7,6'}$=4.5 Hz.- IR ($CHCl_3$): 1580 (C=C), 1315, 1305 und 1150 cm^{-1} (SO_2).- $C_{30}H_{40}O_3SSe$ (559.7), MS: m/z (%) = 560 (5, M^+), 403 (28), 261 (63), 205 (37), 43 (100).- (Found C, 66.08; H, 7.19. $C_{30}H_{40}O_3SSe$ × 0.5 C_6H_6 requires C, 66.20; H, 7.24).

rac-(13R)-11α-Benzenesulfonyl-8,13-epoxy-13,14-seco-16,17-dinor-pimarane (30, ent-30).

A solution of rac-31 (37.5 mg, 0.093 mmol) in THF (0.5 ml) was added at 0°C to anhydrous mercury-(II) trifluoroacetate (79.2 mg, 0.186 mmol). The mixture was stirred at 20°C for 9 h. The reaction mixture was poured into an ice-cold solution which was prepared from 3M NaOH (2 ml) and 0.5M $NaBH_4$ in 3M NaOH (0.5 ml). The mixture was then allowed to warm to 20°C. Usual work-up (diethyl ether) followed by SC (SiO_2 (5 g), hexanes-ethyl acetate 15:1) gave rac-30 (23.2 mg, 62%); 7.7 mg (20%) of rac. 31 were recovered.- m.p. 190-192°C (from acetone/hexane).- ^1H NMR (400 MHz, C_6D_6): δ = 0.80 (s, 3H, CH_3) 0.82 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 1.08 (d, 1H, CH_3-15), 1.77 (s, 3H, CH_3-14), 1.96 (dd, 1H), 2.10 (m, 1H), 2.30 (s, 1H, 9-H), 3.32 (d, 1H, 11-H), 4.48 (m, $W_{1/2}$=22.5 Hz, 1H, 13-H), 6.98 (mk, 3H, Ar-H), 7.91 (2H, Ar-H); $J_{15,13}$=6.0 Hz, $J_{11,12\alpha}$=9.0 Hz.- IR (CCl_4): 1315, 1305 and 1145 cm^{-1} (SO_2).- MS: m/z (%) = 389 (6.3, $(M-CH_3)^+$), 263 (11), 247 (100).- (Found C, 71.20; H, 8.98. $C_{24}H_{36}O_3S$ (404.6) requires C, 71.24; H, 8.97).

rac-(13S)-11α-Benzenesulfonyl-8,13-epoxy-8,14-seco-15,16-dinor-pimarane (34, ent-34).

rac-32 (42.6 mg, 0.105 mmol) on reaction with mercury(II) trifluoroacetate (90.0 mg, 0.211 mmol) exactly as described for 30, gave rac-34 (18.0 mg, 42%); 24.4 mg (57%) of rac-32 were recovered.- m.p. 186-189°C (from acetone/ hexane).- ^1H NMR (400 MHz, COSY, C_6D_6): δ = 0.78 (dd, 1H, 5-H), 0.83 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 1.01 (d, 3H, CH_3-17), 1.10-1.43 (7H, including 12-H), 1.56 (s, 3H, CH_3-14), 2.02 (m, 1H), 2.20 (d, 1H, 9-H), 2.26 (m, 1H, 12'-H), 3.20 (ddd, 1H, 11-H), 3.48 (m, $W_{1/2}$=25.0 Hz, 1H, 13-H), 6.95 (3H, Ar-H), 7.33 (2H, Ar-H); $J_{5,6}$=2.0 Hz, $J_{5,6'}$=12.5 Hz, $J_{17,13}$=6.0 Hz, $J_{11,9}$=2.0 Hz, $J_{11,12}+J_{11,12'}$=20.0 Hz.- IR (CCl_4): 1320, 1305 and 1150 cm^{-1} (SO_2).- MS: m/z (%) = 389 (11, $(M-CH_3)^+$), 247 (100).- (Found C, 71.22; H, 9.00. $C_{24}H_{36}O_3S$ (404.6) requires C, 71.24; H, 8.97).

30 from 29 and 34 from 33.

Solutions of small samples (5 mg, 8.9 μmol) of rac-29 and rac-33 in toluene (0.2 ml), individually treated with tri-n-butyltin hydride (3.6 μl, 13.4 μmol) and catalytic amounts of AIBN, were heated to 110°C for 90 min. TLC analysis (hexanes-ethyl acetate 5:1, 2x developed) indicated the formation of 30 and 34, respectively.

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