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Forskolin Studies

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Abstract—A new nucleophilic isoprenoid C_5 reagent is introduced which allowed synthesis of an advanced and optically active forskolin intermediate in a very efficient way. In addition, docking experiments that are based on X-ray results indicate that there might exist forskolin analogues with improved properties as far as binding to adenylyl cyclases and synthetic accessibility are concerned.

Introduction

Forskolin (**1a**) is a labdane diterpene that has been shown to interact with different membrane proteins including adenylyl cyclase, the glucose transporter, the voltage-gated potassium channel and ligand-gated ion channels.[1] The ability of forskolin to stimulate adenylyl cyclase in intact cells in the absence of hormonal agonists has been exploited by many laboratories for investigation of the role of cyclic AMP in various physiological functions. Nine isoforms of adenylylcyclase have been identified. With the exception of one, all of them are stimulated by forskolin. They all contain a short cytosolic amino terminus followed by two repeats of six transmembrane helices and a cytosolic domain. Each of the two cytoplasmic domains, designated as C_1 and C_2, respectively, are implicated in catalysis. The cytosolic domains can be overexpressed in bacteria. These proteins have been shown to have forskolin-stimulated catalytic activity when they are mixed ore tethered.[2,3] Two crystal structures have been reported some time ago by Zhang and coworkers[4] and by the Sprang group,[5] respectively. The Zhang group crystallized a C_2 construct of type II rat adenylyl cyclase with forskolin. The structure was shown to be a homo dimer containing two molecules of forskolin. The structure indicates that forskolin has polar interactions to both C_2 units, i.e. hydrogen bonds from 1 α-OH and the 11-oxo group to one (A) and hydrogen bonds of the other (B) to the 7-acetyl group (see Fig. 1). It has been suggested that forskolin activates adenylyl cyclase by promoting C_1/C_2 association resulting in formation of an active site.

The Sprang group on the other hand determined the crystal structure of a complex consisting of the C_1 and C_2 units of two different adenylyl cyclases, an activated $G_{s\alpha}$ protein ($G_{s\alpha}$·GTPγS), and a forskolin derivative. The binding of this forskolin analogue (one molecule only) to the two C units is analogous to that in the homo dimer as described above. It is interesting to note that according to the X-ray structures neither the 9- nor the 6-OH groups are involved in hydrogen bonds to the enzyme.

Knowledge of the X-ray structure of forskolin-binding partners and the essential ligand–protein interactions open new possibilities to stimulate the synthesis of analogues with comparable or even improved activity. This is of special importance in the case of forskolin, since the total syntheses performed so far, although they are of a high degree of sophistication, suffer from the fact that about 35 steps are needed to reach the target compound from a readily accessible starting material.[6] The search for more easily accessible analogues, which nevertheless fulfil the binding prerequisites of forskolin, may be supported by systematic docking studies, which provide the binding conformations of the potential ligands at their targets and the interaction energies as a measure for the stability of the complexes.

In the present paper, we wish to discuss some results of molecular modeling experiments and a new approach that allows preparation of an advanced forskolin synthetic intermediate in a very efficient way.

Keywords: nucleophilic isoprenoid C_5 reagent; forskolin intermediate; adenylyl cyclase.
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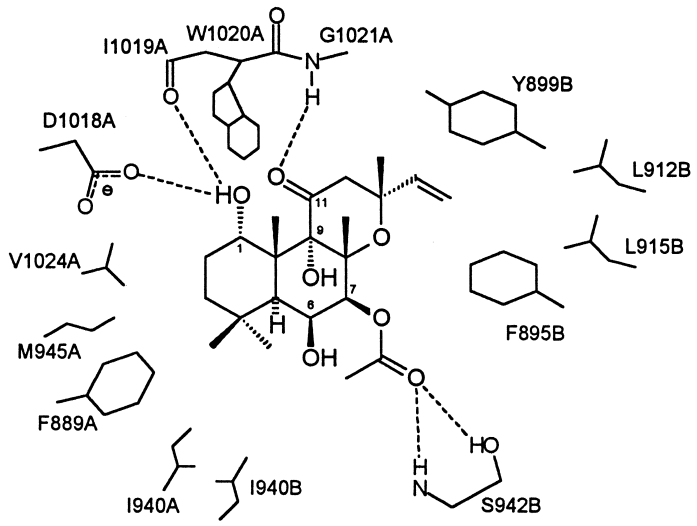


Figure 1. Schematic representation of polar interactions between forskolin and adenylyl cyclases according to Ref. 4.

Docking Experiments

On the basis of Zhang's X-ray analysis,[4] docking experiments were performed for forskolin **1a** and the analogues **1b**–**e** to study the consequences of structure variations for the binding behaviour and to find out possibilities of structure simplification for synthesis. The docking experiments were carried out employing the Lamarckian GA-LS (genetic algorithm with local search) hybrid formalism of the latest version of the docking program AutoDock 3.0,[7] that predicts the bound conformations of flexible ligands to macromolecular targets. This formalism represents a combination of a genetic search algorithm for global searching and a local search strategy to perform energy minimisation using a fast grid-based energy evaluation method for the protein–ligand interactions and an empirical binding free energy function to estimate affinity constants. The results of this procedure for numerous protein–ligand complexes demonstrate good agreement between the experimental and theoretical data.[8] The computational details of the docking procedure are given in the Experimental section. In order to test the reliability of the docking formalism for our purposes, forskolin (**1a**) was the first object of the docking studies. Fig. 2(a) shows the excellent agreement between the arrangements resulting from the X-ray for a protein obtained from rat brain and the most stable one provided by the docking studies.

The theoretically estimated K_D-value amounts to 14.8 nM (Table 1) and agrees fairly well with the experimental value of 18 nM.[9] Details of the docking results, which may be useful for an evaluation of the data that are given in Table 1. It is very interesting to see that the docking procedure reproduces both bindings sites of the dimer (denoted by A and B in Fig. 1) with nearly the same arrangement of the ligand in the various docking runs. This confirms the high efficiency of the method. The forskolin arrangement is also the distinctly preferred one for all analogues **1b**–**e**. The estimated K_D-values differ depending on structure modifications (Table 1). Three details should explicitly be

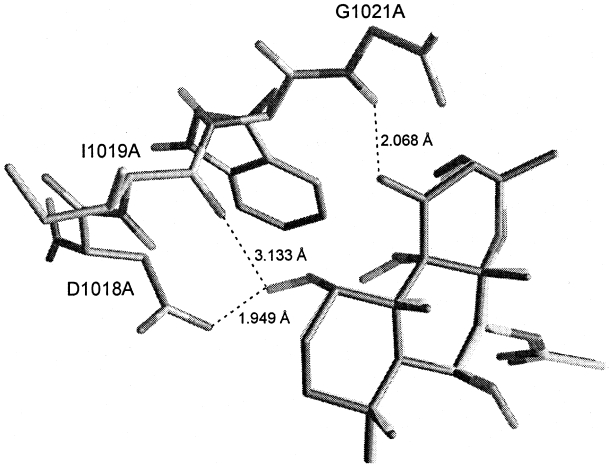


Figure 2a. Visualisation of forskolin (**1a**) rings A and C polar interactions with a catalytic adenylyl cylase domain. Superposition of the practically coincident crystal[4] (dark grey) and the most stable docking structures (grey).

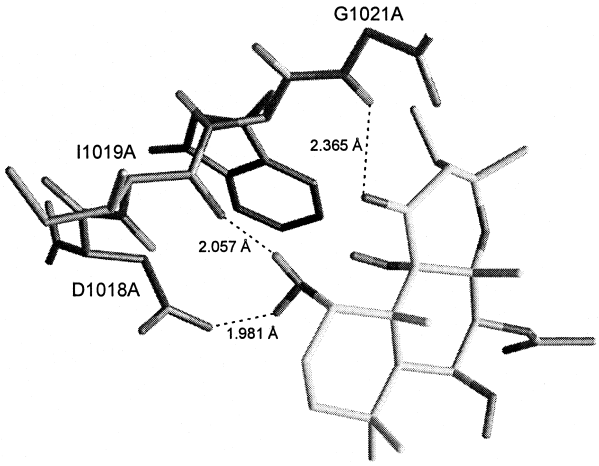


Figure 2b. Visualisation of rings A and C polar interactions of **1b** with the catalytic adenylyl cyclase domain as obtained from docking experiments. For details see text.

Table 1. Details of the docking studies

	1a	1b	1c	1d	1e
K_D (nM)	14.8	5.2	19.2	33.8	8.1
Number of torsions	6	6	6	5	5
Number of clusters[a]	6	5	4	5	5
Structures in cluser 1	6	5	4	5	5
A[b]	6	5	4	5	5
B[b]	11	13	5	4	8
E(A)[c]	−11.9	−12.4	−11.5	−11.4	−12.0
	(−11.6)	(−12.4)	(−11.3)	(−11.3)	(−11.9)
E(B)[c]	−11.6	−12.0	−11.4	−11.1	−11.6
	(−11.3)	(−11.7)	(−11.4)	(−11.0)	(−11.5)

[a] For computational details, see Experimental part.
[b] Number of structures found in the equivalent binding sites A and B of the dimer.
[c] Interaction energy in kcal mol^{-1}; first value: most stable structure in cluster 1, average value for all structures of cluster 1 in parentheses.

mentioned. The 1α-amino-1-deoxy derivative **1b** exhibits a higher affinity than forskolin with a K_D-value of 5.2 nM. This can well be explained by an additional hydrogen bond to the protein (Fig. 2b). Removal of the 1-OH group in **1d** decreases the affinity considerably. Contrary to this, removal of the 6-OH group in **1e** does not change the affinity. This hydroxyl group is obviously not essential for binding, thus confirming the corresponding conclusions from the X-ray data.

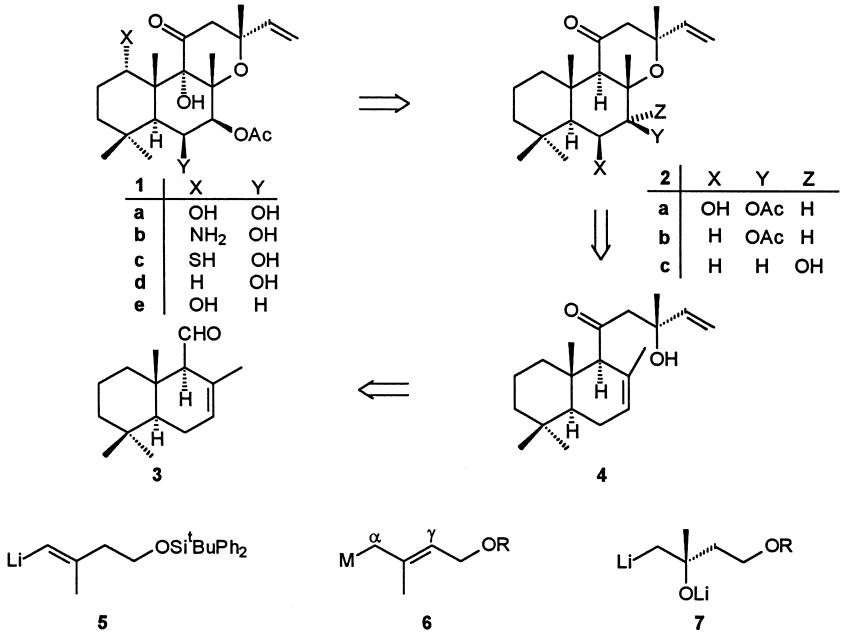
Synthetic Design

As mentioned above, the known total syntheses of forskolin suffer from the high number (≈35, vide supra) of synthetic steps.[6] It is our intention to develop a synthetic scheme for forskolin that is considerably shorter. Since 1,9-dideoxy forskolin (**2a**) can be converted into forskolin by a combination of chemical[10] and enzymatic steps[11] we selected **2a** as our immediate synthetic target. The X-ray results and docking experiments (vide supra) indicate that the 6-OH group of forskolin is most probably of minor importance for the biological activity. This means that **2c** as an intermediate to 6-deoxyforskolin (**1e**) might be an even simpler useful target.

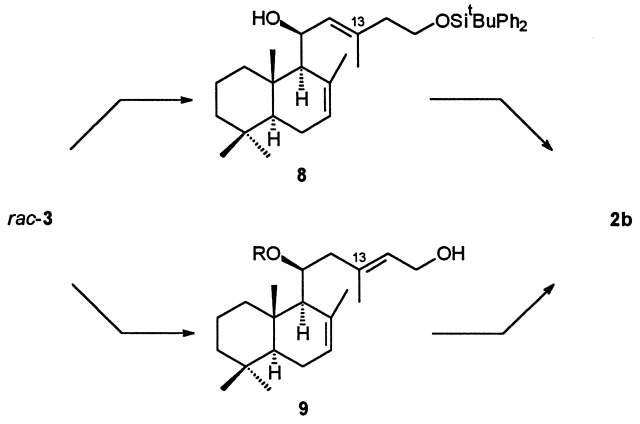
Our previous work has demonstrated that racemic tricyclic labdane derivatives of type *rac*-**2** can be obtained from a precursor of type *rac*-**4**, which is itself available from rac-drimenal (*rac*-**3**) and an isoprenoid C_5 unit (Scheme 1).

Racemic drimenal is accessible from (*E*,*E*)-farnesol in two steps.[12] A number of nucleophilic isoprenoid C_5 synthons can be envisaged. In a first series of experiments the vinyllithium reagent **5** was coupled to *rac*-**3** to furnish the labdane derivative *rac*-**8** (Scheme 2). The oxygen functionality at C-13 was then introduced by a diastereoselective Sharpless I epoxidation.[13] This route allowed preparation of the advanced forskolin intermediate *rac*-**2c** in eight steps.[14]

We reasoned that an allylic alcohol intermediate of type *rac*-**9** might be even more rewarding because we expected to have then the option of introducing the 13-oxygen functional group via a Katsuki–Sharpless epoxidation[15] and thus perform a kinetic resolution at this step.[16] It appeared to us



Scheme 1.



Scheme 2.

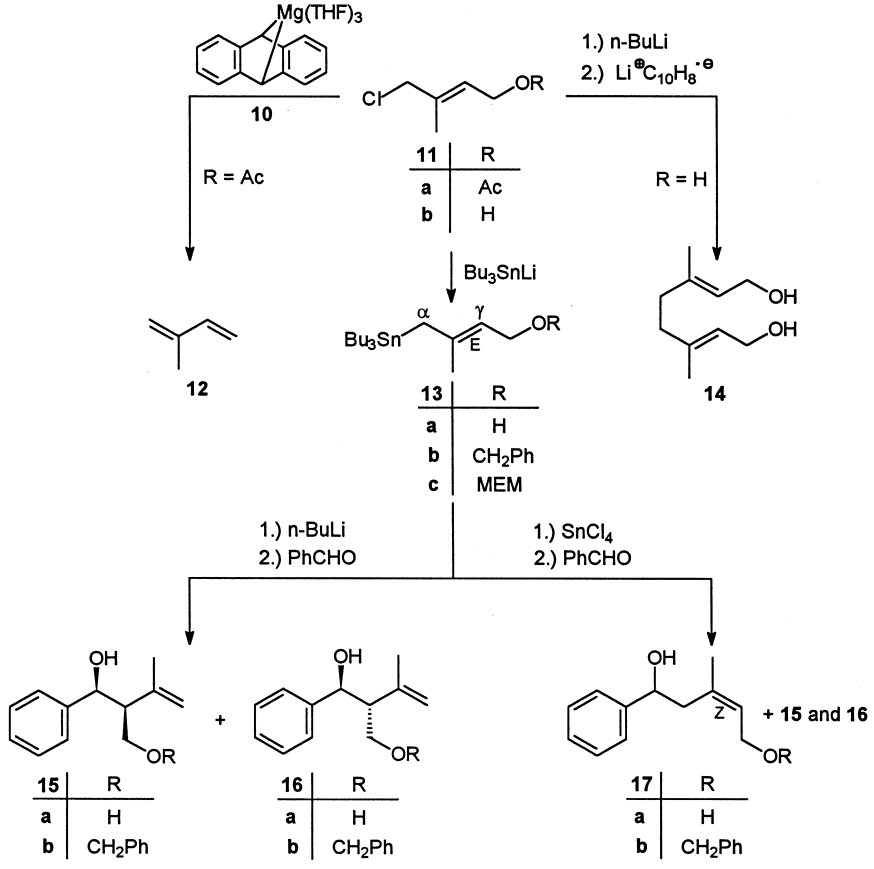
that reagent control was more likely for *rac*-**9** than for *rac*-**8**. *rac*-**9** should be attainable from racemic drimenal using an *allylic* nucleophilic reagent of type **6**.[17]

It turned out to be impossible to couple **11a** with drimenal via a Grignard reagent even when the reaction was performed at −78°C using the highly active magnesium powder obtained from magnesium anthracene (**10**). The only product obtained from **11a** was isoprene (**12**).[16] Guided by work of Seebach,[18] Barluenga[19] and Kessler,[20] **11b** was converted into its alkoxide on reaction with *n*-BuLi and subsequently into the dianion with lithium naphthalenide at −100°C. No reaction with benzaldehyde was observed (Scheme 3). The sole product formed from **11b** was the Wurtz coupling product **14** (66%). In order to avoid this unwanted reaction, **11b** was converted into the allyl stannane **13a** and this in turn into the dianion with *n*-butyllithium (2 equiv.). After subsequent trapping with benzaldehyde the desired C–C bond formation was observed, however, with allylic inversion. A mixture of the racemic diastereoisomers **15a** and **16a** was obtained in 55% yield. It is known that the problem of allylic inversion can be overcome by a sequence of two S_E' reactions.[21,22] When, for example an allyl stannane is treated with a Lewis acid such as $SnCl_4$, it is assumed that a reactive trichlorostannane intermediate is formed with the $SnCl_3$ substituent in the γ position which then reacts with the aldehyde with a second allylic inversion. Under these conditions *rac*-**17a** was obtained in 25% yield from **13a** and benzaldehyde. The configuration at the double bond was determined by NMR spectroscopy and found to be (*Z*) as expected from the mechanistic rationale of Thomas.[22] Besides *rac*-**17a** the γ-products *rac*-**15a** and *rac*-**16a** were isolated (40%).

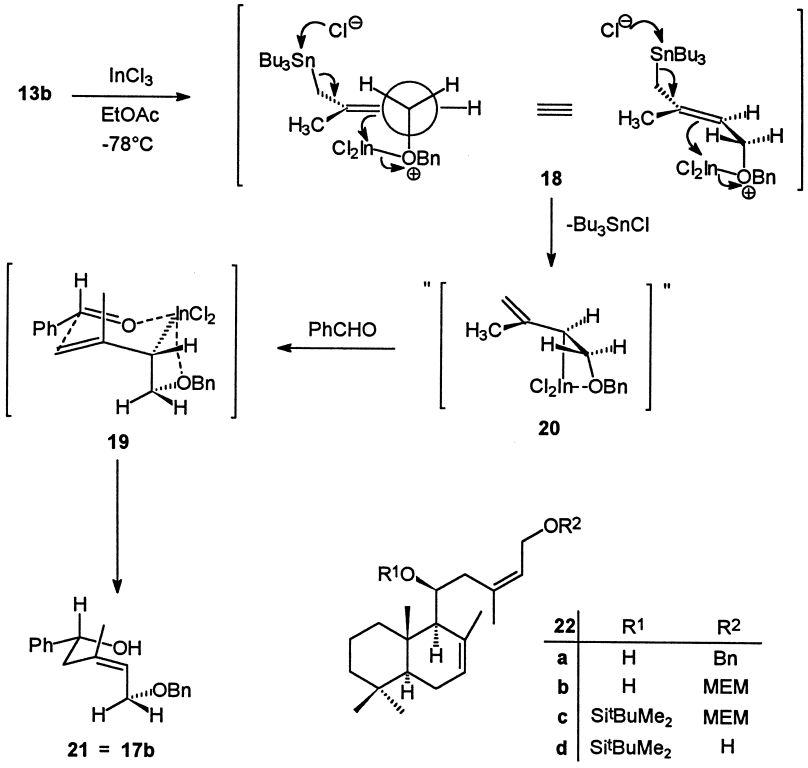
When the same sequence of reactions was performed starting from **13b** the overall yield was higher (82%), but again the γ-products (*rac*-**15b** and *rac*-**16b**) were formed in excess.[23]

It is the purpose of the present paper

- to describe experiments that allowed eventually to perform the reaction *rac*-**3**+**6**, as desired
- to discuss the Katsuki–Sharpless epoxidation of *rac*-**22d**



Scheme 3.



Scheme 4.

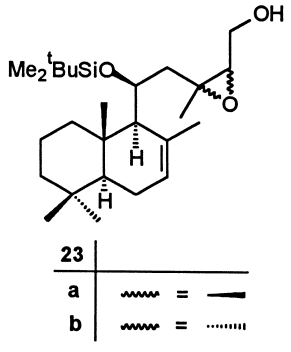
- to introduce a new nucleophilic C_5 reagent of type **7** that simplifies the synthesis of **2c** considerably.

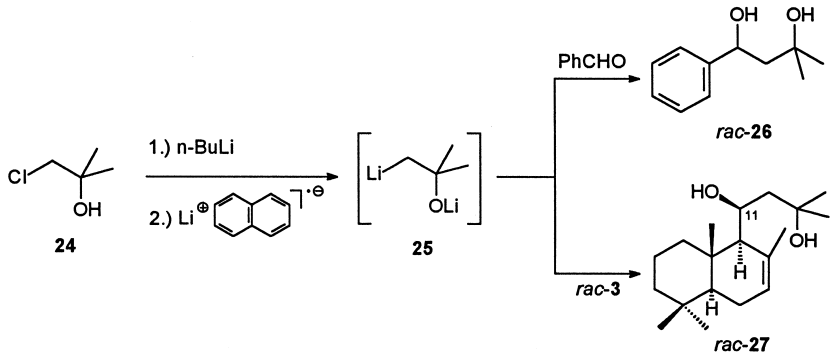
Synthesis of *rac*-22d[24]

Some time ago, Marshall demonstrated that in the case of α-oxygenated allylic stannanes the α-selective reaction with aldehydes profits from the use of $InCl_3$ as Lewis acid.[25] We were interested whether similar improvements could be established with δ-alkoxy allylic stannanes such as **13b**. Thus, $InCl_3$ was sonicated in ethyl acetate and to this solution benzaldehyde was added. Then at −78°C the allylic stannane **13b** was added and the mixture was allowed to warm to ambient temperature. After work-up *rac*-**21** was isolated in 98% yield probably via **20** and the cyclic transition state **19**.[22,26] Under the same conditions from **13b** and racemic drimenal (*rac*-**3**) labdane *rac*-**22a** was obtained in 66% yield, and the MEM-protected allylic stannane **13c** was coupled to *rac*-**3** to furnish *rac*-**22b** in 66% yield (Scheme 4). In neither case was a γ-product found. The configuration around the side chain double bond was (*Z*) as shown by ^{13}C NMR ($\delta(CH_3) > 20$).

Katsuki–Sharpless epoxidation of *rac*-22d

For the next phase of the synthesis some protecting group manipulations were necessary. Thus, the 11-OH group of *rac*-**22b** was silylated (*t*$BuMe_2SiOTf$) to give *rac*-**22c** in a rather sluggish reaction (65% yield, 30% of *rac*-**22b** were recovered) and the MEM group was removed under carefully optimized reactions. With $ZnBr_2$ under various conditions only decomposition was observed. Finally, use of $FeCl_3/Ac_2O$ and subsequent base hydrolysis as described by Holton[27] provided *rac*-**22d** in 72% yield. The epoxidation of *rac*-**22d** (stochiometric amounts of (L)-(+)-DIPT, complete consumption of *rac*-**22d**) gave an epoxide fraction in 65% yield displaying a single spot on TLC and a single set of ^1H NMR signals, i.e. contrary to our expectations, it was not a mixture of diastereoisomers. The reaction product was then treated with the acid chloride of Mosher's acid [(*R*)-(−) enantiomer]. According to TLC a mixture of two new compounds was formed. The ^1H NMR spectrum clearly showed the compounds to be the desired Mosher esters. The resolution was not sufficient to determine the ratio of the stereoisomers. However, from the ^{19}F NMR spectrum it was obvious that the two Mosher esters were present in a 1:1 ratio. The results are only compatible with the assumption that the Katsuki–Sharpless epoxidation in the case of *rac*-**22d** was completely substrate-controlled and that a racemic mixture of **23a** or **23b** was obtained. The configuration around the oxirane ring was not determined.





Scheme 5.

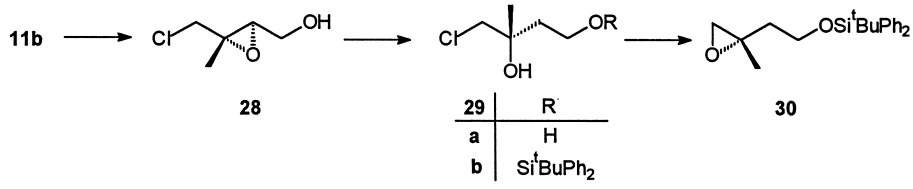
Development of a new nucleophilic isoprenoid reagent

In view of the above results we decided to perform the Katsuki–Sharpless epoxidation already at the C_5 stage. In a series of model experiments, which were based on results of the Seebach group,[18] chlorohydrin **24** was converted into the dianion **25** ((1) alkoxide formation with *n*-BuLi, (2) reductive replacement of Cl by Li with lithium naphthalenide). Subsequent trapping at low temperatures with benzaldehyde and *rac*-drimenal, respectively, gave the corresponding additon products *rac*-**26** and *rac*-**27** in good yields (75% and 69%, respectively) (Scheme 5). With *rac*-**3** a single (racemic) diastereoisomer was formed which probably has (11*SR*) configuration, according to previous results.[12]

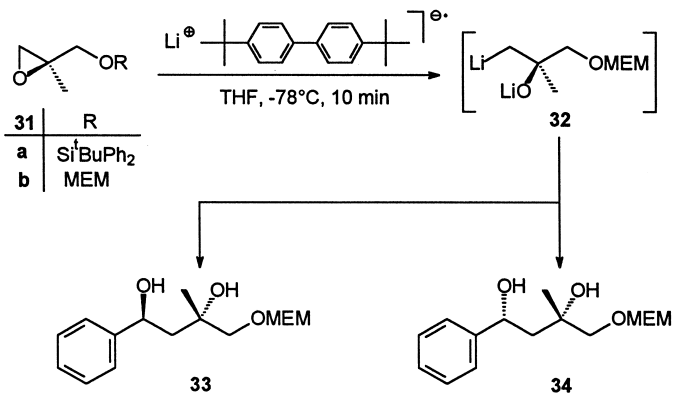
Encouraged by these results, we prepared compound **29a** by Katsuki–Sharpless epoxidation ((D)-(−)-DET, **11b→28**), followed by REDAL reductive opening of the oxirane ring (**28→29a**). The yield in the epoxidation reaction was 69%, and the e.e. was determined by GC (chiral β-cyclodextrin stationary phase) to be 93%. When the reaction was performed with (D)-(−)-DIPT the yield was higher (93%) but the e.e. was somewhat lower (90%). The primary OH group of **29a** was then selectively protected to give **29b**. When **29b** was submitted to the experimental conditions successful in the model series no dianionic species was formed, i.e. no trapping product could be isolated after addition of *rac*-drimenal. Instead, epoxide **30** was obtained in 78% yield. The reason, why in this case the nucleophilic substitution reaction is favoured is not clear (Scheme 6).

There exist a number of other methods[28–34] that allow to prepare β-lithio alkoxides of type **7**. We choose the reductive opening of epoxides with Freeman's[35,36] radical anion of 4,4′-di-*tert*-butylbiphenyl.[37] In model experiments the commercially available (*R*)-methylglycidol was converted into the silyl- and MEM-protected derivatives **31a** and **31b**, respectively (Scheme 7). When the Freeman radical anion was treated with silyl ether **31a** and subsequently benzaldehyde was added, TLC indicated the formation of many products and no addition products could be isolated. On the other hand, submitting the MEM-protected (*R*)-methylglycidol **31b** to the same reaction conditions nicely led to the formation of the desired addition products in 82% yield as a 1:1 mixture of two stereoisomers (**33** and **34**). Thus, in agreement with previous results[18] no reagent control was observed. The stereoisomers were separated after removal of the protecting group.

Encouraged by these results chlorohydrin **29a** was converted into the corresponding epoxide (with *n*-BuLi) and the free OH group was protected to give MEM ether **35** (80% over two steps). **35** was submitted to the reaction conditions of the model series and the intermediate β-lithio alkoxide was treated with *rac*-drimenal to provide the desired addition products in a combined yield of 69%. Of the four possible stereoisomers only two were formed as indicated by ^{13}C NMR. In this case, in agreement with the above results, only substrate control was operating. We assume that the steric course is the same as was observed previously for the addition of other organolithium compounds to drimenal.[12] Thus, the configuration at C-11 in the stereoisomers should be as indicated in formulae **37a** and **38a**. We were not able to separate the stereoisomers at this stage. In order to achieve this goal and to determine the configuration by chemical correlation an exchange of the protecting group was performed (**37a→37b→37c** and **38a→38b→38c**) and the 11-OH group was oxidised to give a mixture of **39** and **40**. The ^{13}C NMR spectrum displayed two sets of signals in a 1:1 ratio and both in the ^{1}H and ^{13}C NMR spectra the signals of the known compound *rac*-**39** could be identified. But still, the mixture could not be separated. Therefore, we went one step further in the synthesis and converted **39** and **40** into their respective epoxides. Happily, at this stage the separation could be performed and the more polar compound (TLC: petrol–ethyl acetate 5:1) was identical with an authentic sample



Scheme 6.



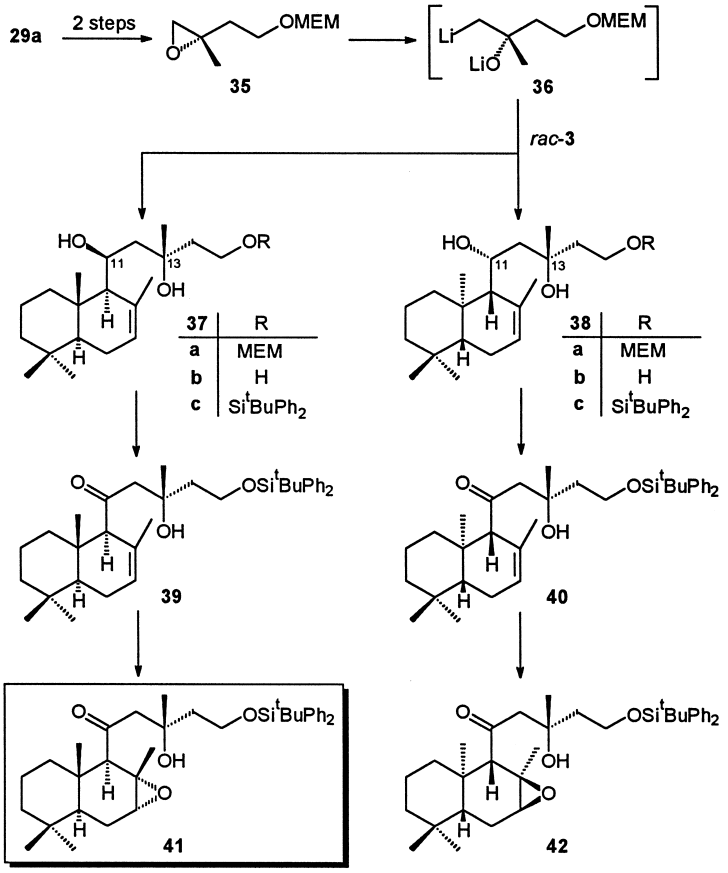
Scheme 7.

of *rac*-**41** as far as TLC behaviour and ^{1}H NMR spectra are concerned. To correlate the configuration with chiroptical properties the CD spectrum of **41** was measured. It displayed a positive Cotton effect at 307 nm ($\Delta\epsilon$=+5.8) (Scheme 8).

Conclusions

We have been able to develop a new isoprenoid C_5 reagent that could be coupled to *rac*-drimenal to furnish a mixture of **37a** and **38a**. The advanced optically active forskolin intermediate **41** has been obtained from (*E*,*E*)-farnesol in seven steps. The conversion of *rac*-**41** into *rac*-**2c** has already been achieved. If the protecting group exchange at the end of the synthesis (which here was performed with the aim of determining the configuration) is omitted, the MEM analogue of **41** may be available from (*E*,*E*)-farnesol in five steps. The optically active C_5 compound **35** can be prepared from isoprene in five steps. The synthesis is devoid of all problems connected with double stereoselection.

In addition, docking experiments that are based on X-ray results indicate that there might exist forskolin analogues with improved properties as far as binding to adenylyl cyclases and synthetic accessibility are concerned.



Scheme 8.

Experimental

All O_2- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminum caps with open top and Teflon-faced septum (Aldrich). Usual work-up means partitioning the reaction mixture between an aqueous phase and CH_2Cl_2, drying the combined organic solutions over Na_2SO_4, and removing the solvent by distillation using a rotatory evaporator (bath temperature 45°C). Solvents were purified by standard techniques. The following materials and methods were used for chromatographic separations: preparative gravitational liquid chromatography (LC): silica gel 63–100 μm (ICN Biomedicals); flash chromatography (FC):[38] silica gel 32–63 μm (ICN Biomedicals); medium-pressure liquid chromatography (MPLC): silica gel 40–60 μm (Grace), Duramat pump (CfG); preparative HPLC: Jasco PU-987 pump and Jasco Lichrosorb column (Si 60, 10 μm, 250×25 mm), flow rate: 4.5 mL min^{-1}, detection with the multi wavelength UV detector Jasco 875-UV; analytical TLC: Merck precoated silica gel 60 F_{254} plates (0.2 mm), spots were identified under a UV lamp (Camag 29 200) and with a 2.22 mol L^{-1} H_2SO_4 solution which contained $Ce(SO_4)_2 4H_2O$ (10 g L^{-1}) and $H_3[PO_4(Mo_3O_9)_4]H_2O$ (25 g L^{-1})[39] and heating at 140°C; GC: HP 5890 Series II (Hewlett–Packard), 25 m×0.25 mm CP-Chirasil-Dex CB, Chrompack, carrier gas: H_2 (4.24 kPA), 90°C, FID. NMR and MS equipment: NMR: UNITY 400 (Varian), DRX 400 (Bruker), DRX 600 (Bruker), GEMINI 200 (Varian), GEMINI 2000 (Varian); MS: VG-Autospec (Fisons). IR: Carl Zeiss Specord M80, Genesis FTIR (ATI Mattson), solvent was in all cases $CHCl_3$, concentration 5 mg/0.2 mL. UV: Beckman DU 650. CD: Jasco J-715 (10 mm cuvette).

(*E*)-4-(Tributylstannyl)-3-methyl-2-buten-1-ol (13a). To a stirred solution of hexabutylditin (6.10 g, 5.32 mL, 10.52 mmol) in THF (25 mL) *n*-BuLi (10.52 mmol, 7.01 mL of a 1.50 M solution in hexane) was added at 0°C. After 15 min the resulting solution of tributylstannyllithium (10.52 mmol) was treated at −78°C with a solution of **11b** (1.2691 g, 10.52 mmol) in THF (15 mL). The reaction mixture was stirred for 1 h at this temperature. After addition of H_2O (10 mL) the mixture was allowed to warm to ambient temperature. Usual work-up and FC (petrol–ethyl acetate 6:1) yielded **13a** (2.0524 g, 52%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, HETCOR): δ=0.82–0.96 (m, 15H, 3 CH_3, 3 CH_2Sn, butyl), 1.24–1.36 (m, 6H, 3 CH_2, butyl), 1.41–1.60 (m, 6H, 3 CH_2, butyl), 1.68 (s, with an indication of a long range coupling, $J_{5/2}\approx$1 Hz, 3H, CH_3-5), 1.78 (s, 2H, CH_2-4), 4.11 (dd, $J_{1/2}\approx J_{1,OH}$, after exchange with D_2O: d, $J_{1/2}$=7.0 Hz, 2H, CH_2-1), 5.29 (t, with an indication of a long range coupling, $J_{2/1}$=7.0 Hz and $J_{5/2}\approx$1 Hz, 1H, H-2). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT, HETCOR): δ=10.03 (3 CH_2Sn, butyl), 14.16 (3 CH_3, butyl), 18.97 (CH_3-5), 22.98 (CH_2-4), 27.83 (3 CH_2, butyl), 29.57 (3 CH_2, butyl), 60.10 (CH_2-1), 119.23 (CH-2), 141.97 (C_q-3). IR (film): 3325 (OH), 1463 (C=C), 999 (C–O) cm^{-1}. $C_{17}H_{36}OSn$ (375.16), EI MS (*m*/*z*) (%): 319 $[M-57]^+$ (6), 291 (23), 251 (100).

(*E*)-4-Benzyloxy-1-(tributylstannyl)-2-methyl-2-butene (13b). To a stirred solution of **13a** (410.4 mg, 1.09 mmol) in THF (2 mL) NaH (28.8 mg, 1.20 mmol) was added. After 10 min benzyl bromide (93.5 mg, 65 μL, 0.54 mmol) and tetrabutylammonium iodide (40.3 mg, 0.11 mmol) were added to the reaction mixture. When all benzyl bromide was consumed (18 h, TLC), the mixture was hydrolysed with H_2O (1 mL). Usual work-up and FC (petrol–ethyl acetate 5:1) yielded **13b** (196.9 mg, 79%, based on benzyl bromide). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.83–0.93 (m, 15H, 3 CH_3, 3 CH_2Sn, butyl), 1.21–1.38 (m, 6H, 3 CH_2, butyl), 1.39–1.63 (m, 6H, 3 CH_2, butyl), 1.65 (s with an indication of a long range coupling, $J_{5/3}\approx$1 Hz, 3H, CH_3-5), 1.81 (s, 2H, CH_2-1), 4.01 (d, 2H, $J_{4/3}$=7.0 Hz, CH_2-4), 4.49 (s, 2H, OCH_2Ph), 5.26 (t, with an indication of a long range coupling, $J_{3/4}$=7.0 Hz, $J_{3/5}\approx$1 Hz, 1H, 3-H), 7.28–7.36 (m, 5H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=10.04 (3 CH_2Sn, butyl), 14.17 (3 CH_2, butyl), 19.25 (CH_3-5), 23.05 (CH_2-1), 27.85 (3 CH_2, butyl), 29.60 (3 CH_2, butyl), 67.28 (CH_2-4), 71.95 (OCH_2Ph), 116.75 (CH-3), 127.85 (Ar–C-*p*), 128.19 (Ar–C-*o*), 128.76 (Ar–C-*m*), 139.39 (C_q-2), 142.33 (Ar–C-*ipso*). IR (film): 1455 (C=C), 1081 (C–O), 735 cm^{-1}. $C_{24}H_{42}OSn$ (465.28), EI MS *m*/*z* (%): 341 (37), 269 (19), 235 (37), 177 (54), 91 (100).

Reaction of 13b with benzaldehyde in the presence of $SnCl_4$

To a stirred solution of **13b** (73.0 mg, 0.157 mmol) in CH_2Cl_2 (1 mL) a $SnCl_4$-solution (173 μL of 1 M solution in CH_2Cl_2, 0.173 mmol) was added at −78°C. After 5 min a precooled solution of benzaldehyde (18.4 mg, 0.173 mmol, 17.6 μL) in CH_2Cl_2 (0.5 mL) was added. The brown solution was stirred for 1 h and then quenched with H_2O (1 mL). Warming to ambient temperature, treatment with NEt_3 to remove tin byproducts followed by usual work up and FC (petrol–ethyl acetate 8:1+0.1 vol% NEt_3) yielded a mixture of *rac*-**15b** and *rac*-**16b** (29.7 mg, 67%) alongside with *rac*-**17b** (6.8 mg, 15%, identical with the sample described below).

Mixture of (1*S,2*S**)- and (1*S**,2*R**)-2-benzyloxymethyl-3-methyl-1-phenyl-3-buten-1-ol (*rac*-15b and *rac*-16b).** Diastereomer ratio 1.7 (A):1(B) (based on the CH_3-5 ^{1}H NMR signals). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.52 (s, indication of a long range coupling with $J\approx$1 Hz, 3H, CH_3-5, A), 1.78 (s, with an indication of a long range coupling, $J\approx$1 Hz, 3H, CH_3-5, B), 2.62–2.77 (m, 2H, 2-H of A and 2-H of B), 3.33/3.40 (AB of ABX, 2H, $J_{6a/6b}$=9.5 Hz, $J_{6a/2}$=7.0 Hz, $J_{6b/2}$=5.7 Hz, 6-H_a and 6-H_b B), 3.72/3.82 (AB of ABX, 2H, $J_{6a/6b}$=9.5 Hz, $J_{6a/2}$=7.5 Hz, $J_{6b/2}$=4.6 Hz, 6-H_a and 6-H_b of A), 4.04 (broad s, 2H, OH of A and B), 4.36/4.46 (AB, 2H, $J_{H'/H(benzyl)}$=12.1 Hz, OCH_2Ph of B), 4.54/4.58 (AB, 2H, $J_{H'/H(benzyl)}$=11.9 Hz, OCH_2Ph of A), 4.73–4.88 (mk, 5H, 1-H of A, 4-H_a and 4-H_b of A and B), 5.04 (m, 1H, 1-H of B), 7.26–7.38 (mk, 20H, Ar–H of A and B). ^{13}C NMR (50.3 MHz, $CDCl_3$, trace impurity of Bu_3SnCl): δ=21.43 (CH_3-5, B), 23.03 (CH_3-5, A), 53.60 (CH-2, A), 55.21 (CH-2, B), 70.43/73.18/73.39/73.63/74.09/78.02 (CH-1, CH_2-6, OCH_2Ph of A and B), 114.04 (CH_2-4, A), 115.61 (CH_2-4, B), 127.15 (Ar–C), 127.30 (Ar–C), 127.86 (Ar–C), 128.12 (Ar–C), 128.34

(Ar–C), 128.43 (Ar–C), 128.52 (Ar–C), 128.72 (Ar–C), 128.87 (Ar–C), 129.05 (Ar–C), 138.02/138.61/142.72/143.53/143.80/144.33 (Ar–C-*ipso*, C_q-3 of A and B). IR (film): 3447 (O–H), 1450 (C=C), 1100 (C–O), 739, 699 cm^{-1}. $C_{19}H_{22}O_2$ (282.38), FAB MS *m/z*: 305.2 $[M+Na]^+$, 281.2 $[M+H-H_2]^+$, 265.2 $[M+H-H_2O]^+$. HRMS: calcd for $C_{19}H_{22}O_2Na$ $[M+Na]^+$: 305.1517, found 305.1516.

***rac*-(*Z*)-5-Benzyloxy-3-methyl-1-phenyl-3-penten-1-ol (*rac*-17b).** A suspension of anhydrous $InCl_3$ (33.2 mg, 0.15 mmol) in ethyl acetate (3.7 mL) was sonicated for 15 min at 20°C. Then benzaldehyde (15.9 mg, 0.15 mmol, 15.3 μL) was added. The stirred solution was cooled to −78°C and a solution of **13b** (102.1 mg, 0.22 mmol) in ethyl acetate (0.5 mL) was added. The reaction mixture was allowed to warm to ambient temperature. The progress of the reaction was monitoring by TLC. When benzaldehyde was consumed the mixture was quenched with cold 1 M HCl (3 mL). The reaction mixture was then treated with NEt_3 to remove tin byproducts. Usual work-up (Et_2O) and FC (petrol–ethyl acetate 6:1+0.2 vol.% NEt_3) furnished *rac*-**17b** (42.4 mg, 98%). ^{1}H NMR (200 MHz, $CDCl_3$, Homo decoupling): δ=1.85 (s, 3H, CH_3-6), 2.31/2.66 (AB of ABX, $J_{2a/2b}$=13.4 Hz, $J_{2a/1}$=3.9 Hz, $J_{2b/1}$=9.2 Hz, 2H, 2-H_a and 2-H_b), 3.24 (d, $J_{OH/1}$=3.4 Hz, 1H, OH), 3.85/4.02 (AB of ABX, $J_{5a/5b}$=10.9 Hz, $J_{5a/4}$=7.0 Hz, $J_{5b/4}$=7.6 Hz, 2H, 5-H_a and 5-H_b), 4.55 (s, 2H, OC*H*$_2$Ph), 4.78 (td, not completely resolved, $J_{1/2b}$=9.2 Hz, $J_{1/2a}$=3.9 Hz, 1H, 1-H), 5.70 (t-type dd, $J_{4/5a,5b}\approx$7 Hz, 1H, 4-H), 7.25–7.40 (m, 10 H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, DEPT): δ=24.30 (CH_3-6), 43.58 (CH_2-2), 66.14 (CH_2-5), 71.82 (CH-1), 73.20 (O*C*H$_2$Ph), 124.87 (CH-4), 126.08 (Ar–C), 127.75 (Ar–C-*p*), 128.29 (Ar–C-*p*), 128.60 (Ar–C), 128.82 (Ar–C), 128.95 (Ar–C), 138.35 (Ar–C-*ipso*), 139.68 (Ar–C-*ipso*), 145.36 (C_q-3). IR (film): 3428 (O–H), 1449 (C=C), 1060 (C–O), 745, 699 cm^{-1}. $C_{19}H_{22}O_2$ (282.38), FAB MS *m/z*: 283.2 $[M+H]^+$. HRMS: calcd for $C_{19}H_{23}O_2$ $[M+H]^+$: 283.1698, found 283.1696.

***rac*-(11*S*, 13*Z*)-15-Benzyloxy-labd-7,13-dien-11-ol (*rac*-22a).** The $InCl_3$-mediated coupling of **13b** to *rac*-drimenal (*rac*-**3**) was performed as described above. Work-up (vide supra) and FC (petrol–ethyl acetate 12:1+0.3 vol.% NEt_3) provided *rac*-**22a** (66%). ^{1}H NMR (200 MHz, $CDCl_3$, H,H-COSY, HETCOR (400 MHz)): δ=0.87/0.90/0.96 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 1.07–1.22 (mk, 3H), 1.39–1.63 (mk, 4H), 1.80–1.98 (mk, 10H) with 1.84 and 1.88 (2s, CH_3-16, CH_3-17), 2.03/2.81 (AB of ABX, 2H, $J_{12a/12b}$= 13.4 Hz, $J_{12a/11}$=4.0 Hz, $J_{12b/11}$=10.1 Hz, 12-H_a and 12-H_b), 3.96–4.09 (m, 1H, 11-H), 3.98 (d, 2H, $J_{15/14}$= 7.0 Hz, CH_2-15), 4.49/4.54 (AB, $J_{H'(benzyl),H(benzyl)}$=11.7 Hz, 2H, OC*H*$_2$Ph), 5.58–5.67 (mk, 2H, 7-H, 14-H), 7.30-7.36 (m, 5H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=14.79 (−) (C-20), 19.28 (+) (C-2), 22.71 (−) (C-19), 23.93 (+) (C-6), 24.51 and 25.15 (−) (C-16 and C-17), 33.37 and 37.58 (+) (C-4 and C-10), 33.86 (−) (C-18), 40.52 and 42.63 (+) (C-1 and C-3), 42.98 (+) (C-12), 50.53 (−) (C-5), 60.32 (−) (C-9), 66.52 (+) (C-15), 67.61 (−) (C-11), 72.88 (+) (O*C*H$_2$Ph), 124.56 and 126.57 (−) (C-7 and C-14), 128.11 (−) (Ar–C-*p*), 128.39 (−) (Ar–C-*m*), 128.86 (−) (Ar–C-*o*), 132.92/138.63/139.80 (+) (C-8, C-13, Ar–C-*ipso*). IR (film): 3472 (O–H), 1450, 1383 (C=C), 1066 (C–O), 736 cm^{-}. $C_{27}H_{40}O_2$ (396.61), FAB MS *m/z*: 419.3 $[M+Na]^+$, 397.3 $[M+H]^+$.

(*E*)-1-(Tributylstannyl)-4-(methoxyethoxymethoxy)-2-methyl-2-butene (13c). To a stirred solution of **13a** (84.2 mg, 0.224 mmol) in CH_2Cl_2 (1.5 mL) diisopropylethylamine (43.4 mg, 57.1 μL, 0.336 mmol) was added at 20°C. After 10 min the solution was treated with MEMCl (39.1 mg, 35.5 μL, 0.314 mmol). After stirring for 2 h H_2O (1.5 mL) was added. Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 7:1) yielded **13c** (77.3 mg, 75%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.80–0.92 (mk, 15H, 3 CH_3, 3 CH_2Sn, butyl), 1.20–1.38 (m, 6H, 3 CH_2, butyl), 1.39–1.56 (m, 6H, 3 CH_2, butyl), 1.66 (s, indication of a longe coupling, $J_{5/3}$=1.1 Hz, 3H, CH_3-5), 1.79 (s, 2H, CH_2-1), 3.40 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.54–3.60 and 3.65–3.73 (2m, 4H, $OCH_2OCH_2CH_2OCH_3$), 4.06 (d, $J_{4/3}$=7.0 Hz, 2H, CH_2-4), 4.71 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 5.19 (t, $J_{3/4}$= 7.0 Hz and $J_{3/5}$=1.1 Hz, 1H, 3-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=10.02 (3 CH_2Sn, butyl) (+), 14.15 (3 CH_3, butyl) (−), 19.15 (CH_3-5) (−), 23.05 (CH_2-1) (+), 27.82 (3 CH_2, butyl) (+), 29.57 (3 CH_2, butyl) (+), 59.46 ($OCH_2OCH_2CH_2OCH_3$) (−), 64.43 (CH_2-4) (+), 67.09 and 72.35 ($OCH_2OCH_2CH_2OCH_3$) (+), 94.72 ($OCH_2OCH_2CH_2OCH_3$) (+), 115.95 (CH-3) (−), 142.81 (C_q-2) (+). IR (film): 1460 (C=C), 1106, 1043 (C–O) cm^{-1}. $C_{21}H_{44}O_3Sn$ (463.29), EI MS (*m/z*) (%): 464 $[M]^{+\cdot}$ von $C_{21}H_{44}O_3{}^{120}Sn$.

***rac*-(11*S*,13*Z*)-15-(Methoxyethoxymethoxy)-labd-7,13-dien-11-ol (*rac*-22b).** The $InCl_3$-mediated coupling of **13c** to *rac*-drimenal (*rac*-**3**) was performed as described above. Quenching was performed with aq. sat. NH_4Cl. Work-up (vide supra) and FC (petrol–ethyl acetate 4:1+0.3 vol.% NEt_3) provided *rac*-**22b** (66%). ^{1}H NMR (200 MHz, $CDCl_3$, HETCOR): δ=0.86/0.89 (2s, 6H, CH_3-18, CH_3-19), 0.96 (s, 3H, CH_3-20), 1.05–1.28 (mk, 3H), 1.36–1.68 (mk, 4H), 1.78–1.98 (mk, 10H) with 1.84 and 1.92 (2s, CH_3-16, CH_3-17), 2.02/2.86 (AB of ABX, 2H, $J_{12a/12b}$=13.4 Hz, $J_{12a/11}$=4.0 Hz, $J_{12b/11}$=10.0 Hz, 12-H_a and 12-H_b), 3.39 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.52–3.60/3.63–3.72 (2m, 4H, $OCH_2OCH_2CH_2OCH_3$), 3.98–4.16 (mk, 3H, 11-H, CH_2-15), 4.73 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 5.52–5.64 (mk, 2H, 7-H, 14-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, HETCOR, APT): δ=14.77 (C-20) (−), 19.28 (C-2) (+), 22.70 (C-19) (−), 23.92 (C-6) (+), 24.48 and 25.17 (C-16 and C-17) (−), 33.37 and 37.59 (C-4 and C-10) (+), 33.86 (C-18) (−), 40.55 and 42.63 (C-1 and C-3) (+), 42.93 (C-12) (+), 50.53 (C-5) (−), 59.48 ($OCH_2OCH_2CH_2OCH_3$) (−), 60.37 (C-9) (−), 64.04 (C-15) (+), 67.30 and 72.23 ($OCH_2OCH_2CH_2OCH_3$) (+), 67.56 (C-11) (−), 95.22 ($OCH_2OCH_2CH_2OCH_3$) (+), 124.12 and 126.56 (C-7 and C-14) (−), 132.87 and 139.90 (C-13 and C-8) (+). IR (film): 3499 (O–H), 1455, 1442 (C=C), 1110 (C–O–C), 838 cm^{-1}. $C_{24}H_{42}O_4$ (394.59), FAB MS *m/z*: 417.2 $[M+Na]^+$, 395.3 $[M+H]^+$, 377.2 $[M+H-H_2O]^+$, 319.2, 297.2, 221.2. HRMS: calcd for $C_{24}H_{43}O_4$ $[M+H]^+$: 395.3161, found 395.3151.

***rac*-(11*S*,13*Z*)-11-(*tert*-Butyldimethylsilyloxy)-15-(methoxyethoxymethoxy)-labd-7,13-diene (*rac*-22c).** To a stirred solution of *rac*-**22b** (336.2 mg, 0.85 mmol) in CH_2Cl_2 (3 mL) pyridine (1010.9 mg, 1.1 mL, 12.78 mmol) and

tert-butyldimethylsilyl triflate (2252.2 mg, 1.96 mL, 8.52 mmol) were added at 20°C. Sequentially the reaction mixture was kept at 45°C for 30 h and then treated with aq. 5% $NaHCO_3$ (5 mL). Usual work-up and FC (petrol–ethyl acetate 4:1+0.1 vol%. NEt_3) furnished *rac*-**22c** (281.1 mg, 65%). 100.6 mg of *rac*-**22b** were recovered. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.07/0.10 (2s, 6H, Si(CH_3)$_2$), 0.82/0.86/0.87 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.98–1.24 (mk, 3H), 1.28–1.52 (mk, 4H), 1.78–2.00 (mk, 10H) with 1.81 and 1.93 (2s, CH_3-16, CH_3-17), 2.11/2.86 (AB of ABX, poorly resolved, $J_{12a/12b}\approx$ 12 Hz, $J_{12a/11}\approx$12 Hz, 2H, 12-H_a and 12-H_b), 3.38 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.51–3.57/3.62–3.72 (mk, 4H, $OCH_2OCH_2CH_2OCH_3$), 4.05–4.22 (mk, 3H, 11-H, CH_2-15), 4.72 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 5.42–5.52 (mk, 2H, 7-H, 14-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=−4.07 and −2.12 (Si(CH_3)$_2$) (−), 15.79 (C-20) (−), 18.61 (SiC(CH_3)$_3$) (+), 19.34 (C-2) (+), 22.67 (C-19) (−), 23.98 (C-6) (+), 24.85 and 24.91 (C-16 and C-17) (−), 26.50 (SiC(CH_3)$_3$) (−), 33.40 and 36.73 (C-4 and C-10) (+), 33.81 (C-18) (−), 40.50/42.55/42.70 (C-1/C-3/C-12) (+), 50.59 (C-5) (−), 56.82 (C-9) (−), 59.48 ($OCH_2OCH_2CH_2OCH_3$) (−), 64.61 (C-15) (+), 67.30 and 72.25 ($OCH_2OCH_2CH_2OCH_3$) (+), 69.07 (C-11) (−), 95.33 ($OCH_2OCH_2CH_2OCH_3$) (+), 124.46 and 124.65 (C-7 and C-14) (−), 134.22 and 137.52 (C-13 and C-8) (+). IR (film): 1466 (C=C), 1254, 1047, 1105 (C–O–C), 834, 773 cm^{-1}. $C_{30}H_{56}O_4Si$ (508.85), FAB MS *m/z*: 531.4 $[M+Na]^+$, 507.4 $[M+H-H_2]^+$, 491.4, 449.3.

***rac*-(11*S*, 13*Z*)-11-(*tert*-Butyldimethylsilyloxy)-labd-7,13-dien-15-ol (*rac*-22d).** Anhydrous $FeCl_3$ (12.0 mg, 74 μmol) was dissolved in acetic anhydride (264.4 mg, 270 μL, 2.59 mmol) at −60°C with stirring. After 10 min at −60°C a solution of *rac*-**22c** (94.4 mg, 0.185 mmol) in CH_2Cl_2 (2 mL) was added. After 30 min NEt_3 (2 mL) was added and the mixture was stirred for further 15 min at −60°C. The cooling bath was removed, the stirred reaction mixture was treated with H_2O (1 mL) and then the organic layer was separated. Usual work-up (CH_2Cl_2, washing of the organic layer with 5 mL aq. sat. $NaHCO_3$) gave a mixture of acetates as a pale yellow oil. To the crude product a saturated solution of $NaOCH_3$ in methanol (1 mL) was added. After stirring for 1 h at 20°C hexane (2 mL) was added to furnish two layers. Usual work-up and FC (petrol–ethyl acetate 6:1) yielded *rac*-**22d** (56.1 mg, 72%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.07/0.11 (2s, 6H, Si(CH_3)$_2$), 0.83/0.86/0.88 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.98–1.75 (mk, 10H), 1.78–1.92 (mk, 7H) with 1.80/1.92 (2s, CH_3-16, CH_3-17), 2.13/2.82 (AB of ABX, poorly resolved, 2H, $J_{12a/12b}\approx$12 Hz, $J_{12a/11}\approx$12 Hz, CH_2-12), 4.10 (X of ABX, $J_{11/12a}$=11.4 Hz, $J_{11/12b}$=4.0 Hz, 1H, 11-H), 4.08–4.22 (m, 2H, CH_2-15), 5.36–5.53 (mk, 2H, 7-H, 14-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=−4.07 and −2.11 (Si(CH_3)$_2$) (−), 15.81 (C-20) (−), 18.63 (SiC(CH_3)$_3$) (+), 19.34 (C-2) (+), 22.67 (C-19) (−), 23.98 (C-6) (+), 24.84 and 24.92 (C-16 and C-17) (−), 26.51 (SiC(CH_3)$_3$) (−), 33.42 and 36.77 (C-4 and C-10) (+), 33.78 (C-18) (−), 40.65/42.55/42.68 (C-1/C-3/C-12) (+), 50.64 (C-5) (−), 56.90 (C-9) (−), 60.10 (C-15) (+), 69.11 (C-11) (−), 124.59 and 127.66 (C-7 and C-14) (−), 134.13 and 136.42 (C-8 and C-13) (+). IR (film): 3433 (O–H), 1633, 1466 (C=C), 1254 (C–O), 834, 773 cm^{-1}. $C_{26}H_{48}O_2Si$ (420.75), FAB MS *m/z*: 443.3 $[M+Na]^+$, 421.3 $[M+H]^+$, 401.3, 335.2, 203.2, 73.0. HRMS: calcd for $C_{26}H_{49}O_2Si$ $[M+H]^+$: 421.3501, found 421.3486.

Katsuki–Sharpless epoxidation of *rac*-22d

To a stirred suspension of freshly activated molecular sieves (4 Å powder, 6 mg) in CH_2Cl_2 (0.4 mL) Ti(O^{i}Pr)$_4$ (5.2 mg, 5.4 μL, 18.5 μmol) and L-(+)-DIPT (4.3 mg, 18.5 μmol) were added at −40°C. After 10 min the mixture was treated with a solution of *rac*-**22d** (7.8 mg, 18.5 μmol) in CH_2Cl_2 (0.2 mL) and of anhydrous ^{t}BuOOH (5.5 M solution in nonane, 3.3 μL, 18.5 μmol). After complete consumption (18 h) the reaction mixture was treated with water (0.6 mL) at −40°C and allowed to warm to ambient temperature. Usual work-up and FC (petrol–*tert*-butyl methyl ether 4:1) furnished *rac*-**23a** or *rac*-**23b** (5.2 mg, 65%) and traces of a more polar compound.

***rac*-(11*S*,13*R*,14*S*) or *rac*-(11*S*,13*S*,14*R*)-(*tert*-Butyldimethylsilyloxy)-13,14-epoxy-labd-7-en-15-ol (*rac*-23a or *rac*-23b).** ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.07/0.11 (2s, 6H, Si(CH_3)$_2$), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.85/0.88/0.91 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 0.98–1.30 (mk, 3H), 1.34–1.52 (mk, 6H) with 1.43 (s, CH_3-16), 1.53–1.78 (mk, 3H), 1.79–1.98 (mk, 5H) with 1.85 (s, indication of a longe coupling, CH_3-17), 1.99–2.20 (m, 2H, 12-H_a, 12-H_b), 2.98 (dd, 1H, $J_{14/15a}$=7.0 Hz, $J_{14/15b}$=4.2 Hz, 14-H), 3.62–3.74/3.82–3.98 (2m, 2H, 15-H_a, 15-H_b), 4.20 (dd, 1H, $J_{11/12a}$=10.0 Hz, $J_{11/12b}$=3.8 Hz, 11-H), 5.42–5.54 (m, 1H, 7-H). IR (CCl_4): 3432 (O–H), 1667 (C=C), 1451, 1385, 1068 (C–O) cm^{-1}. $C_{26}H_{48}O_3Si$ (436.75), FAB MS *m/z*: 459.4 $[M+Na]^+$, 437.3 $[M+H]^+$.

Preparation of the Mosher esters

To a stirred and cooled (0°C) solution of *rac*-**23a** or *rac*-**23b** (2.8 mg, 6.41 μmol) in pyridine (0.7 mL) R-(−)-Mosher acid chloride (2.4 mg, 9.61 μmol) were added. After 3 h the reaction mixture was filtered through a Florisil pad and the filtrate was concentrated under reduced pressure. FC (petrol–ethyl acetate 20:1) yielded a mixture of two diastereomeric mosher esters (4.1 mg, 98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.57 (s, OCH_3, diastereomer A), 3.58 (s, OCH_3, diastereomer B). ^{19}F NMR (188.2 MHz, $CDCl_3$): δ=5.94 (s, CF_3, diastereomer A), 6.00 (s, CF_3, diastereomer B), 1:1 ratio. $C_{36}H_{55}O_5SiF_3$ (652.91), FAB MS *m/z*: 675.4 $[M+Na]^+$, 653.4 $[M+H]^+$, 651.4 $[M+H-H_2]^+$. HRMS: calcd for $C_{36}H_{55}O_5SiF_3Na$ $[M+Na]^+$: 675.3668, found 675.3667.

(2*R*, 3*S*)-4-Chloro-2,3-epoxy-3-methylbutan-1-ol (28). *D-(−)-DET:* To a stirred and cooled (−25°C) suspension of freshly activated molecular sieves (4 Å powder, 2 g) in CH_2Cl_2 (60 mL) Ti(O_iPr)$_4$ (1677 mg, 1.73 mL, 5.9 mmol) and D-(−)-DET (1216 mg, 1.0 mL, 5.9 mmol) were added. After 10 min a solution of **11b** (711.5 mg, 5.9 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) and of anhydrous ^{t}BuOOH (5.5 M solution in nonane, 2.1 mL, 11.8 mmol) were added. This mixture was stored in a refrigerator overnight at −23°C. Water (10 mL) was added and the mixture was allowed to warm to ambient temperature. Usual work-up ($CHCl_3$) and FC ($CHCl_3$–EtOH 20:0.5) furnished **28**

(552.3 mg, 69%). The e.e was determined by GLC (for conditions, vide supra). Retention times for *ent*-**28** and **28**: 15.58 and 15.97 min, respectively, ratio: 3.5:96.5. $[\alpha]_D^{24}=+3.7$ (*c* 9.83 $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, homo decoupling, OH⟶OD exchange): $\delta=1.44$ (s, 3H, CH_3-5), 2.33 (broad s, 1H, OH), 3.14 (X of ABX, 1H, $J_{2/1a}=6.5$ Hz, $J_{2/1b}=4.4$ Hz, 2-H), 3.45/3.53 (AB, 2H, $J_{4a/4b}=11.4$ Hz, 4-H_a, 4-H_b), 3.71/3.86 (AB of ABX, 2H, $J_{1a/1b}=12.4$ Hz, $J_{1a/2}=6.5$ Hz, $J_{1b/2}=4.4$ Hz, 1-H_a, 1-H_b). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): $\delta=15.24$ (CH_3-5) (−), 50.80 (CH_2-4) (+), 60.52 (C_q-3) (+), 61.41 (CH_2-1) (+), 63.39 (CH-2) (−). IR (film): 3397 (O–H), 1428, 1387 (C–O), 1029 (C–O), 736 (C–Cl) cm^{-1}. $C_5H_9ClO_2$ (136.57), EI MS *m*/*z* (%): 105 $[M-CH_2OH]^+$.

D-(−)-DIPT: The reaction was performed under the same conditions as described above. **28** was isolated in a yield of 83%, the e.e. was 90%.

(2*RS*, 3*SR*)-4-Chloro-2,3-epoxy-3-methylbutan-1-ol (*rac*-28). To a solution of **11b** (62.7 mg, 0.52 mmol) in CH_2Cl_2 (3 m) mCPBA (107.7 mg, 0.62 mmol) was added in portions. The mixture was stirred at 20°C for 3 h. Addition of sat. $NaHCO_3$, usual work-up, and FC (petrol–ethyl acetate 3:2) provided *rac*-**28** (61.8 mg, 87%) whose ^1H NMR spectrum was identical with that of **28**.

(3*S*)-4-Chloro-3-methylbutane-1,3-diol (29a). A stirred solution of **28** (1335.2 mg, 9.78 mmol) in THF (70 mL) was cooled to −25°C. Then a 3.5 M solution of Red-Al® in toluene (3.65 mL, 12.72 mmol) was added. After 30 min the excess of the reagent was destroyed with 1.5 N HCl (10 mL) at −25°C and the mixture was allowed to warm to ambient temperature. Usual work-up (CH_2Cl_2) and FC (chloroform–ethanol 20:1) yielded **29a** (1067.9 mg, 79%). 129.8 mg of **28** were recovered. $[\alpha]_D^{24}=+0.81$ (*c* 17.24 $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.33$ (s, 3H, CH_3-5), 1.69-1.99 (dddd, 2H, 2-H_a, 2-H_b), 3.24 (s, 2H, 2OH), 3.53 (s, 2H, CH_2-4), 3.84–3.92 (ddd, 2H, CH_2-1). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=25.45$ (CH_3-5), 39.64 (CH_2-2), 53.58 (CH_2-4), 59.85 (CH_2-1), 73.65 (C_q-3). IR (film): 3366 (O–H), 1426, 1378, 1121, 1056 (C–O), 739 (C–Cl) cm^{-1}. $C_5H_{11}ClO_2$ (138.59), FAB MS *m*/*z*: 139 $[M+H]^+$, 121 $[M+H-H_2O]^+$, 93, 75, 57. HRMS: calcd for $C_5H_{12}O_2{}^{37}Cl$ $[M+H]^+$: 141.0496, found 141.0501.

(3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-4-chloro-3-methylbutan-3-ol (29b). To a stirred solution of **29a** (42.1 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) DMAP (9.16 mg, 0.075 mmol), triethylamine (37.9 mg, 52 μL, 0.375 mmol) and *tert*-butyldiphenylchlorosilane (103.1 mg, 96 μL, 0.375 mmol) were added at 20°C. After stirring for 2.5 h the reaction mixture was hydrolyzed with water (1 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 10:1) furnished **29b** (113.0 mg, quant.). $[\alpha]_D^{24}=-2.9$ (*c* 5.61 $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, homo decoupling): $\delta=1.07$ (s, 9H, $C(CH_3)_3$), 1.34 (s, 3H, CH_3-5), 1.76–2.04 (m, 12 lines, 2H, 2-H_a, 2-H_b), 3.53/3.58 (AB, 2H, $J_{4a/4b}=10.9$ Hz, 4-H_a, 4-H_b), 3.88–3.94 (t-type m, 2H, 1-H_a, 1-H_b), 4.08 (s, 1H, OH), 7.38–7.48 (m, 6H, Ar–H), 7.67–7.76 (m, 4H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=19.49$ ($C(CH_3)_3$), 25.71 (C-5), 27.29 ($C(CH_3)_3$), 39.38 (C-2), 52.79 (C-4), 61.89 (C-1), 73.35 (C-3), 128.37 (Ar–C-*m*), 130.48 (Ar–C-*p*), 133.10 (Ar–C-*ipso*), 136.02 (Ar–C-*o*). IR (film): 3476 (O–H), 1427, 1110 (C–O), 703 cm^{-1}. $C_{21}H_{29}ClO_2Si$ (376.99), FAB MS *m*/*z*: 399.1 $[M+Na]^+$, 377.2 $[M+H]^+$, 199.1 $[Ph_2SiOH]^+$. HRMS: calcd for $C_{21}H_{30}ClO_2Si$ $[M+H]^+$: 377.1704, found 377.1704.

***rac*-3-Methyl-1-phenylbutane-1,3-diol (*rac*-26).** A stirred solution of 3-Chloro-2-methylpropan-2-ol (**24**) (217.2 mg, 0.2 mL, 2.0 mmol) in THF (15 mL) was cooled to −78°C. Then *n*-BuLi (1.5 M solution in hexane, 1.33 mL, 2 mmol) was added. After 15 min the temperature was decreased to −100°C and the mixture was then treated with lithium-naphthalenide (1 M solution in THF, 4 mL, 4 mmol). After stirring for 5 h at −78°C benzaldehyde (318.4 mg, 0.3 mL, 3.0 mmol) was added to the resulting dianion solution. The reaction mixture was allowed to warm to ambient temperature and hydrolyzed with water (5 mL). Usual work-up (CH_2Cl_2) and FC (first petrol–ethyl acetate 3:2 and then toluol–*iso*-propanol 20:1) furnished *rac*-**26** (270.4 mg, 75%). ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.27$ and 1.43 (2s, 6H, CH_3-4 and CH_3-5), 1.68/1.96 (AB of ABX, 2H, $J_{2a/2b}=14.6$ Hz, $J_{2a/1}=2.4$ Hz, $J_{2b/1}=11.0$ Hz, 2-H_a and 2-H_b), 3.14 (s, 2H, 2OH), 5.06 (X of ABX, 1H, $J_{1/2b}=11.0$ Hz, $J_{1/2a}=2.4$ Hz, 1-H), 7.24–7.39 (m, 5H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): $\delta=28.05$ and 32.31 (CH_3-4 and CH_3-5) (−), 50.85 (CH_2-2) (+), 72.18 (C_q-3) (+), 72.80 (CH-1) (−), 126.18 (Ar–C-*o*) (−), 127.99 (Ar–C-*p*) (−), 128.99 (Ar–C-*m*) (−), 145.28 (Ar–C-*ipso*) (+). IR (film): 3336 (O–H), 699 cm^{-1}. $C_{11}H_{16}O_2$ (180.24), EI MS *m*/*z* (%): 180 $[M]^{+*}$ (2), 162 $[M-H_2O]^+$ (30), 147 (22), 107 (100). HRMS: calcd for $C_{11}H_{16}O_2$ $[M]^{+*}$: 180.1150, found 180.1149.

***rac*-(11*S*)-15-Norlabd-7-ene-11,13-diol (*rac*-27).** The coupling reaction of **25** to *rac*-drimenal (*rac*-**3**) was performed as described above. Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 5:1) furnished *rac*-**27** (69%). ^1H NMR (200 MHz, $CDCl_3$; HETCOR (400 MHz); H,H-COSY, NOESY (600 MHz)): $\delta=0.87$ (s, 3H, CH_3-18), 0.90 (s, 3H, CH_3-19), 1.00 (s, 3H, CH_3-20), 0.90/1.90 (2m, 2H, 1-H_a, 1-H_b), 1.10 (m, 1H, 5-H), 1.13/1.39 (2m, 2H, 3-H_a, 3-H_b), 1.25 and 1.34 (2s, 6H, CH_3-14 and CH_3-16), 1.46/1.55 (2m, 2H, 2-H_a, 2-H_b), 1.76 (m, 1H, 9-H), 1.90 (s, 3H, CH_3-17), 1.90/1.94 (2m, 2H, 6-H_a, 6-H_b), 1.35/2.27 (unresolved and dd, 2H, $J_{12a/12b}=14.5$ Hz, $J_{12a/11}=12.1$ Hz, 12-H_a, 12-H_b), 2.38 (broad s, 2H, 2 OH), 4.43 (dd, 1H, $J_{11/12a}=12.1$ Hz, $J_{11/12b}=2.6$ Hz, 11-H), 5.60–5.62 (m, 1H, 7-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): $\delta=14.94$ (C-20) (−), 19.22 (C-2) (+), 22.76 (C-19) (−), 23.86 (C-6) (+), 25.37 (C-17) (−), 28.13 and 32.26 (C-14 and C-16) (−), 33.34 and 37.74 (C-4 and C-10) (+), 33.87 (C-18) (−), 40.59 (C-1) (+), 42.61 (C-3) (+), 50.33 (C-12) (+), 50.44 (C-5) (−), 61.09 (C-9) (−), 67.98 (C-11) (−), 72.11 (C-13) (+), 127.24 (C-7) (−), 132.74 (C-8) (+). IR (KBr): 3432 (O–H), 1461 (C=C), 1152 (C–O), 839 cm^{-1}. $C_{19}H_{34}O_2$ (294.48), FAB MS *m*/*z*: 317.3 $[M+Na]^+$, 295.2 $[M+H]^+$, 281.1 $[M+Na-2H_2O]^+$, 259.2 $[M+H-2H_2O]^+$. HRMS: calcd for $C_{19}H_{34}O_2Na$ $[M+Na]^+$: 317.2456, found 317.2458.

(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl-1-methyloxirane (31a). A stirred solution of **29b** (75.4 mg, 0.2 mmol) in THF

(1.5 mL) was cooled to −78°C. Then *n*-BuLi (1.5 M solution in hexane, 133 μL, 0.2 mmol) was added. After 15 min the temperature was decreased to −100°C and the mixture was treated with lithiumnaphthalenide (1 M solution in THF, 0.4 mL, 0.4 mmol). After stirring for 5 h at −78°C *rac*-drimenal (*rac*-**3**) (66.1 mg, 0.3 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and hydrolyzed with water (0.5 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 10:1) furnished **30** (53.1 mg, 78%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.05 (s, 9H, C(CH_3)$_3$), 1.31 (s, 3H, CH_3-3), 1.58–1.77/1.85–2.00 (2m, 2H, 1′-H_a and 1′-H_b), 2.59 (dd, 1H, $J_{2a/2b}$=4.9 Hz, $J_{2a/1'a}$=1.0 Hz, 2-H_a), 2.70 (d, 1H, $J_{2b/2a}$=4.9 Hz, 2-H_b), 3.77 (dd, 2H, J=6.9 Hz, J=5.6 Hz, CH_2-2′), 7.31–7.42 (m, 6H, Ar–H), 7.59–7.69 (m, 4H, Ar–H). $C_{21}H_{28}O_2Si$ (340.53).

(*S*)-1-(*tert*-Butyldiphenylsilyloxy)methyl-1-methyloxirane (31a). To a stirred solution of (*R*)-methylglycidol (1057.2 mg, 960 μL, 12.0 mmol) in CH_2Cl_2 (80 mL) DMAP (366.5 mg, 3.0 mmol), triethylamine (1517.8 mg, 2.1 mL, 15 mmol) and *tert*-butyldiphenylchlorosilane (4122.9 mg, 3.8 mL, 15 mmol) were added at 20°C. After stirring for 2.5 h the reaction mixture was hydrolysed with water (20 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 10:1) yielded **31a** (3839.7 mg, 98%). $[\alpha]_D^{24}$=−4.9 (*c* 13.38 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.07 (s, 9H, C(CH_3)$_3$), 1.39 (s, 3H, CH_3-3), 2.59/2.71 (AB, 2H, $J_{2a/2b}$=5.0 Hz, CH_2-2), 3.67 (s, 2H, CH_2-1), 7.38–7.45 (m, 6H, Ar–H), 7.66–7.72 (m, 4H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=18,67 (CH_3-3), 19.69 (*C*(CH_3)$_3$), 27.19 (C(*C*H_3)$_3$), 52.08 (CH_2-2), 57.56 (C_q-1), 67.53 (CH_2-1′), 128.22 (Ar–C-*m*), 130.25 (Ar–C-*p*), 133.86 (Ar–C-*ipso*), 136.12 (Ar–C-*o*), 136.19 (Ar–C-*o*). IR (film): 1111 (C–O), 704 cm^{-1}. $C_{20}H_{26}O_2Si$ (326.51), FAB MS *m*/*z*: 349.2 $[M+Na]^+$, 327.2 $[M+H]^+$, 309.2 $[M+H-H_2O]^+$. HRMS: calcd for $C_{20}H_{27}O_2Si$ $[M+H]^+$: 327.1780, found 327.1781.

(*R*)-1-(Methoxyethoxymethoxy)methyl-1-methyloxirane (31b). To a stirred solution of (*R*)-methylglycidol (1057.2 mg, 960 μL, 12.0 mmol) in CH_2Cl_2 (40 mL) diisopropylethylamine (3102.0 mg, 4.1 mL, 24.0 mmol) and MEMCl (2242.2 mg, 2.0 mL, 18.0 mmol) were added at 20°C. After stirring for 4 h the reaction mixture was hydrolysed with water (10 mL). Usual work-up (CH_2Cl_2) and FC (hexane–ethyl acetate 1:1) furnished **31b** (1903.1 mg, 92%). $[\alpha]_D^{24}$=−7.5 (*c* 7.5 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.37 (s, 3H, CH_3-3), 2.62/2.76 (AB, 2H, $J_{2a/2b}$=4.8 Hz, CH_2-2), 3.38 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.49–3.72 (mk, 6H, $OCH_2OCH_2CH_2OCH_3$, CH_2-1), 4.73 (s, 2H, $OCH_2OCH_2CH_2OCH_3$). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=19.03 (CH_3-3) (−), 52.13 (CH_2-2) (+), 56.22 (C_q-1) (+), 59.49 ($OCH_2OCH_2CH_2OCH_3$) (−), 67.42/71.14/72.20 ($OCH_2OCH_2CH_2OCH_3$, CH_2-1′) (+), 96.06 ($OCH_2OCH_2CH_2OCH_3$) (+). IR (film): 1116 (C–O), 1050 (C–O) cm^{-1}. $C_8H_{16}O_4$ (176.21), EI MS (*m*/*z*) (%): 101 $[M-OCH_2CH_2OCH_3]^+$ (7), 89 $[CH_2=OCH_2CH_2OCH_3]^+$ (24), 59 (100).

Mixture of (*1S,3S*)- and (*1R,3S*)-4-(methoxyethoxymethoxy)-3-methyl-1-phenylbutane-1,3-diol (33 and 34). To a stirred solution (glass coated stirrer) of 4,4′-di-*tert*-butylbiphenyl (1678.4 mg, 6.3 mmol) in THF (15 mL) lithium metal (43.7 mg, 6.3 mmol, 0.3 cm-granulate) was added and the mixture was sonicated until a blue colour appeared. The solution was vigorously stirred for 6 h at 0°C. The deep blue solution of the radical anion was cooled to −78°C and epoxide **31b** (528.6 mg, 3.0 mmol) was added dropwise. The colour of the reaction mixture changed from blue to red. 5 min after the addition was complete benzaldehyde (477.5 mg, 460 μL, 4.5 mmol) was added at −78°C (the red colour of the reaction mixture disappeared). At the end of the addition the mixture was stirred for 1 h, water (3 mL) was added and the mixture was allowed to warm to 20°C. After usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 1:2) a non-separable 1:1 mixture (^{1}H NMR integrals of the CH_3-5 signals) of **33** and **34** (699.5 mg, 82%) was obtained. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.25 and 1.39 (2s, 6H, 2 CH_3-5), 1.55–2.10 (mk, 4H, 2×CH_2-2), 3.37 and 3.39 (2s, 6H, 2 $OCH_2OCH_2CH_2OCH_3$), 3.44–3.89 (mk, 12H, 2 $OCH_2OCH_2CH_2OCH_3$, 2×CH_2-4), 4.73 and 4.79 (2s, 4H, 2 $OCH_2OCH_2CH_2OCH_3$), 4.95–5.14 (2 dd, 2H, 2×1-H), 7.24–7.48 (mk, 10H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=23.65 and 27.30 (CH_3-5) (−), 46.87 and 47.52 (CH_2-2) (+), 59.47 and 59.51 ($OCH_2OCH_2CH_2OCH_3$) (−), 71.69 and 72.23 (C-1) (−), 67.74/72.13/72.17/73.07/73.42/75.12/77.80 ($OCH_2OCH_2CH_2OCH_3$, C-3, C-4) (+), 96.63 and 96.71 ($OCH_2OCH_2CH_2OCH_3$) (+), 126.07 and 126.18 (Ar–C-*o*) (−), 127.76 and 127.86 (Ar–C-*p*) (−), 128.85 and 128.90 (Ar–C-*m*) (−), 145.28 and 145.32 (Ar–C-*ipso*) (+). IR (film): 3400 (O–H), 1115 (C–O), 1048 (C–O), 701 cm^{-1}. $C_{15}H_{24}O_5$ (284.35), FAB MS *m*/*z*: 307 $[M+Na]^+$, 285 $[M+H]^+$, 267 $[M+H-H_2O]^+$. HRMS: calcd for $C_{15}H_{24}O_5Na$ $[M+Na]^+$: 307.1521, found 307.1540.

Deprotection of 33 and 34

A solution of the **33**/**34** mixture (410.0 mg, 1.44 mmol) in 3 mol L^{-1} HCl in methanol (4 mL) was stirred at 20°C for 4 h. Water (2 mL) and CH_2Cl_2 were added until a two-phase system resulted. Usual work-up and FC (chloroform–ethanol 20:1) provided the free triols (87.6 mg, 31% of one diasteroisomer; 42.4 mg, 15% of the other and 90.4 mg, 32% of a mixture of both).

(1*S*, 3*S*)-3-Methyl-1-phenyl-1,3,4-butanetriol and (1*R*, 3*S*)-3-methyl-1-phenyl-1,3,4-butanetriol (formulae not shown). *Diastereomer A:* $[\alpha]_D^{24}$=−22.6 (*c* 2.83 MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.45 (s, 3H, CH_3-5), 1.97 (broad s, 3H, 3OH), 2.07 (ddd, 1H, $J_{2a/2b}$=13.2 Hz, $J_{2a/1}$=7.0 Hz, $J_{2a/4a}$=1.4 Hz, 2-H_a), 2.42 (dd, 1H, $J_{2b/2a}$=13.2 Hz, $J_{2b/1}$=8.2 Hz, 2-H_b), 3.68 (d, 1H, $J_{4b/4a}$=9.2 Hz, 4-H_b), 3.97 (dd, 1H, $J_{4a/4b}$=9.2 Hz, $J_{4a/2a}$=1.4 Hz, 4-H_a), 4.99 (t-type dd, 1H, $J_{1/2a}$=7.0 Hz, $J_{1/2b}$=8.2 Hz, 1-H), 7.26–7.42 (m, 5H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=24.86 (CH_3-5) (−), 49.83 (CH_2-2) (+), 79.22 (C_q-3) (+), 80.71 (CH_2-4) (+), 81.11 (CH-1) (−), 126.25 (Ar–C-*o*) (−), 128.01 (Ar–C-*p*) (−), 129.03 (Ar–C-*m*) (−), 143.09 (Ar–C-*ipso*) (+). IR (film): 3400 (O–H), 1052 (C–O), 755, 699 cm^{-1}. $C_{11}H_{16}O_3$ (196.24), EI MS *m*/*z*: 160 $[M-2H_2O]^+$.

Diastereomer B: $[\alpha]_D^{24}$=+59.5 (*c* 0.97 MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.46 (s, 3H, CH_3-5), 1.92 (broad s,

3H, 3OH), 1.87 (dd, 1H, $J_{2a/2b}$=13.0 Hz, $J_{2a/1}$=10.2 Hz, 2-H_a), 2.38 (ddd, 1H, $J_{2b/2a}$=13.0 Hz, $J_{2b/1}$=6.1 Hz, $J_{2b/4a}$=1.0 Hz, 2-H_b), 3.90 (dd, 1H, $J_{4a/4b}$=9.4 Hz, $J_{4a/2b}$=1.0 Hz, 4-H_a), 3.94 (d, 1H, $J_{4b/4a}$=9.4 Hz, 4-H_b), 5.25 (dd, 1H, $J_{1/2a}$=10.2 Hz, $J_{1/2b}$=6.1 Hz, 1-H), 7.25–7.36 (m, 5H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=24.92 (CH_3-5) (−), 50.38 (CH_2-2) (+), 79.77 (C_q-3) (+), 80.75 (CH_2-4) (+), 80.98 (CH-1) (−), 126.04 (Ar–C-*o*) (−), 127.93 (Ar–C-*p*) (−), 128.95 (Ar–C-*m*) (−), 143.12 (Ar–C-*ipso*) (+). IR (film): 3398 (O–H), 1050 (C–O), 755, 699 cm^{-1}. $C_{11}H_{16}O_3$ (196.24), EI MS *m/z*: 160 $[M-2H_2O]^+$.

(1*S*)-1-(Methoxyethoxymethoxy)ethyl-1-methyloxirane (35). To a stirred solution of **29a** (671.0 mg, 4.85 mmol) in THF (40 mL) *n*-BuLi (1.5 M solution in hexane, 6.5 mL, 9.7 mmol) was added at −78°C. Then the reaction mixture was slowly allowed to warm to ambient temperature within 2 h. The mixture was filtered through a florisil pad to separate LiCl and the solvent was evaporated under reduced pressure (not below 350 mbar!). The crude epoxy alcohol was obtained as volatile oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.37 (s, 3H, CH_3-5), 1.76–2.03 (m, 14 lines, 2H, CH_2-2), 2.27 (broad, 1H, OH), 2.63/2.80 (AB, 2H, $J_{4a/4b}$=4.4 Hz, CH_2-4), 3.62–3.83 (m, 14 lines, 2H, CH_2-1). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=22.38 (CH_3-5), 38.17 (CH_2-2), 53.53 (CH_2-4), 56.97 (C_q-3), 59.70 (CH_2-1). IR (film): 3400 (O–H), 1050 (C–O) cm^{-1}. $C_5H_{10}O_2$ (102.13), EI MS *m/z* (%): 101 (15), 87 $[M-CH_3]^+$ (61), 71 (22), 57 $[C_4H_9]^+$ (60), 43 (88), 41 (100). The crude product was dissolved in CH_2Cl_2 (20 mL) and the stirred solution was treated with diisopropylethylamine (1253.7 mg, 1.66 mL, 9.7 mmol) and MEMCl (906.8 mg, 830 μL, 7.28 mmol) at 20°C. After stirring for 4.5 h the reaction mixture was hydrolysed with H_2O (10 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 1:1) furnished the optically active epoxide **35** (738.0 mg, 80% based on **29a**). $[\alpha]_D^{24}$=+5.92 (*c* 19.92 $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.32 (s, 3H, CH_3-3), 1.71–1.97 (m with 11 lines, 2H, CH_2-1′), 2.56/2.65 (AB, 2H, $J_{2a/2b}$=5.0 Hz, 2-H_a, 2-H_b), 3.37 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.51–3.69 (mk, 6H, OCH_2OCH_2-CH_2OCH_3, CH_2-2′), 4.68 (s, 2H, $OCH_2OCH_2CH_2OCH_3$). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ =21.74 (CH_3-3), 36.93 (CH_2-1′), 54.27 (CH_2-2), 55.70 (C_q-1), 59.43 (OCH_2-$OCH_2CH_2OCH_3$), 64.63 (CH_2-2′), 67.28 and 72.20 ($OCH_2OCH_2CH_2OCH_3$), 95.95 ($OCH_2OCH_2CH_2OCH_3$). IR (film): 1392, 1116 (C–O) cm^{-1}. $C_9H_{18}O_4$ (190.23), FAB MS *m/z*: 213 $[M+Na]^+$, 191 $[M+H]^+$. HRMS: calcd for $C_9H_{18}O_4Na$ $[M+Na]^+$: 213.1102, found 213.1091.

Mixture of (5*S*,9*R*,10*S*,11*S*,13*S*)- and (5*R*,9*S*,10*R*,11*R*,13*S*)-15-(methoxyethoxymethoxy)-labd-7-ene-11,13-diol (37a and 38a). To a stirred solution (glass coated stirrer) of 4,4′-di-tert-butylbiphenyl (159.8 mg, 0.6 mmol) in THF (4 mL) lithium metal (4.2 mg, 0.6 mmol, 0.3 cm pieces) was added and then the mixture was sonicated (3 min) until the colour of the solution turned to blue. For complete dissolution of lithium metal, the solution was stirred for 6 h at 0°C. The resulting deeply blue radical anion solution was cooled to −78°C and then **35** (114.1 mg, 0.6 mmol) was added until the colour of the reaction mixture turned to deeply red. After 5 min the dianion was trapped at −78°C with *rac*-drimenal (*rac*-**3**) (88.1 mg, 0.4 mmol). The reaction mixture was stirred for 90 min at −78°C and then was hydrolysed with H_2O (2 mL) at −65°C. The mixture was allowed to warm to ambient temperature. Usual work-up (CH_2Cl_2) and FC (chloroform–ethyl acetate 5:1) furnished a mixture of two diastereomers (probably **37a** and **38a**) (85.4 mg, 69%). 39.5 mg of **35** was recovered. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.85 and 0.88 (2s, 12H) 0.98 and 1.00 (2s, 6H) (2 CH_3-18, 2 CH_3-19, 2 CH_3-20), 0.90–2.00 (mk, 46H) with 1.24 and 1.33 (2s, 2 CH_3, CH_3-16), 1.89 (s, 2 CH_3, CH_3-17), 2.10–2.37 (mk, 2H, 2×12-H_a), 2.92 (d, 1H, *J*=1.8 Hz), 3.13 (s, 1H), 3.382 and 3.385 (2s, 6H, $OCH_2OCH_2CH_2OCH_3$), 3.52–3.85 (mk, 12H, $OCH_2OCH_2CH_2OCH_3$, CH_2-15), 4.38–4.48 (t-type m, 2H, 2×11-H), 4.70 and 4.71 (2s, 4H, $OCH_2OCH_2CH_2OCH_3$), 5.53–5.59 (m, 2H, 2×7-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=14.84 (CH_3-20) (−), 19.27 (CH_2-2) (+), 22.72 (−), 23.88 (+), 25.39 (−), 26.20 (−), 28.86 (−), 31.03 (−), 33.35 (+), 33.86 (−), 37.78 (+), 37.83 (+), 38.97 (+), 40.69 (+), 42.65 (+), 49.24 (+), 50.28 (+), 50.52 (−), 50.58 (−), 59.52 ($OCH_2OCH_2CH_2OCH_3$) (−), 61.27 (−), 65.09 (+), 65.51 (+), 66.95 (−), 67.59 (+), 72.22 (+), 73.90 (+), 74.13 (+), 96.07 and 96.13 (OCH_2OCH_2-CH_2OCH_3) (+), 126.28 and 126.51 (CH-7) (−), 133.20 and 133.31 (C_q-8) (+). IR (CCl_4): 3476 (O–H), 1729, 1456, 1387, 1117, 1044 (C–O) cm^{-1}. $C_{24}H_{44}O_5$ (412.61), FAB MS *m/z*: 435 $[M+Na]^+$, 413 $[M+H]^+$. HRMS: calcd for $C_{24}H_{45}O_5$ $[M+H]^+$: 413.3267, found 413.3270.

Mixture of (5*S*,9*R*,10*S*,11*S*,13*S*)- and (5*R*,9*S*,10*R*,11*R*,13*S*)-labd-7-ene-11,13,15-triol (37b and 38b). **37a** and **38a** (63.5 mg, 0.154 mmol) were treated with 3 N HCl in methanol (2 mL) and the reaction mixture was stirred for 4 h at 20°C. Water (2 mL) was added and the mixture was diluted with CH_2Cl_2 until two layers appeared. Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 1:1) yielded a mixture of **37b** and **38b** (43.0 mg, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.86/0.90/0.99 (3s, 18H, 6 CH_3, CH_3-18, CH_3-19 and CH_3-20), 1.07–2.00 (mk, 38H) with 1.29 and 1.37 (2s, 2 CH_3, CH_3-16), 1.90 (s, 2 CH_3-17), 2.17–2.50 (m, 2H, 2×12-H_a), 3.28 (broad, 6H, 6 OH), 3.78–4.11 (m, 4H, 2 CH_2-15), 4.44–4.54 (m, 2H, 2×11-H), 5.61 (broad s, 2H, 2×7-H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=14.96 (CH_3-20) (−), 19.20 (CH_2-2) (+), 22.74 (CH_3-19) (−), 23.84 (CH_2-6) (+), 25.37 (CH_3-17) (−), 26.43 (CH_3-16) (−), 28.52 (−), 31.02 (−), 33.33 (C_q-4 or C_q-10) (+), 33.86 (CH_3-18) (−), 37.75 (C_q-4 or C_q-10) (+), 40.16 (+), 40.62 (+), 42.57 (+), 44.25 (+), 48.33 (CH_2-12) (+), 50.26 (+), 50.42 (CH-5) (−), 60.06 and 60.36 (CH_2-15) (+), 60.99 and 61.04 (CH-9) (−), 67.24 and 67.71 (CH-11) (−), 75.01 and 75.20 (C_q-13) (+), 127.25 and 127.58 (CH-7) (−), 132.45 and 132.65 (C_q-8) (+). The signals of **37b** were clearly identified both in the ^{1}H NMR and in the ^{13}C NMR spectra on comparison with the known spectra of *rac*-**37b**.10 IR (film): 3365 (O–H), 1717, 1405, 1107 (C–O) cm^{-1}. $C_{20}H_{36}O_3$ (324.50), FAB MS *m/z*: 347.3 $[M+Na]^+$, 325.3 $[M+H]^+$, 307.1 $[M+H-H_2O]^+$, 289.2 $[M+H-2H_2O]^+$. HRMS: calcd for $C_{20}H_{37}O_3$ $[M+H]^+$: 325.2743, found 325.2744.

Mixture of (5*S*,9*R*,10*S*,11*S*,13*S*)- and (5*R*,9*S*,10*R*,11*R*,13*S*)-15-(*tert*-butyldiphenylsilyloxy)-labd-7-ene-11,13-diol (37c and 38c). To a stirred solution of **37b** and **38b** (28.2 mg, 87 μmol) in CH_2Cl_2 (3 mL) DMAP (2.6 mg,

22 μmol), triethylamine (11.4 mg, 16 μL, 113 μmol) and *tert*-butyldiphenylchlorosilane (29.8 mg, 28 μL, 109 μmol) was added at 20°C. The reaction was complete after 5 h and the mixture was hydrolysed with water (1 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 10:1) furnished a mixture of **37c** and **38c** (47.1 mg, 96%). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.85–2.00 (mk, 78H) with 0.87/0.91 (2s, 4 CH_3, CH_3-18 and CH_3-19), 1.03 (2s, 2 CH_3, CH_3-20), 1.04/1.05 (2s, 2 C(CH_3)$_3$), 1.30/1.37 (2s, 2 CH_3, CH_3-16), 1.92/1.97 (2s, 2 CH_3, CH_3-17), 2.17–2.49 (m, 2H, 2×12-H_a), 3.84–4.06 (m, 4H, 2 CH_2, CH_2-15), 4.37–4.53 (m, 2H, 2×11-H), 5.85 (broad s, 2H, 2×7-H), 7.38–7.47 (m, 12H, Ar–H), 7.65–7.72 (m, 8H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=14.69 and 14.75 (CH_3-20) (−), 19.22 (+), 19.33 (+), 19.38 (+), 22.65 (−), 23.82 (+), 25.33 (−), 25.48 (−), 26.45 (−), 27.15 and 27.20 (C(*C*H_3)$_3$) (−), 28.90 (−), 33.30 (+), 33.81 (−), 37.75 (+), 37.84 (+), 40.16 (+), 40.65 (+), 40.71 (+), 42.64 (+), 43.93 (+), 48.76 (+), 50.45 (+), 50.55 and 50.64 (CH-5) (−), 61.29 and 61.35 (CH-9) (−), 61.91 and 62.16 (CH_2-15) (+), 66.63 and 66.77 (CH-11) (−), 74.72 and 74.93 (C_q-13) (+), 125.97 and 126.09 (CH-7) (−), 128.37 (Ar–C-*m*) (−), 130.47 (Ar–C-*p*) (−), 133.07/133.16/133.27 (Ar–C-*ipso*) (+), 133.63 and 133.73 (C_q-8) (+), 136.04/136.07/136.10 (Ar–C-*o*) (−). IR (film): 3367 (O–H), 1720, 1528, 1349, 1100 (C–O) cm^{-1}. $C_{36}H_{54}O_3Si$ (562.90), FAB MS *m*/*z*: 585.4 $[M+Na]^+$, 563.4 $[M+H]^+$, 199.1 $[Ph_2SiOH]^+$. HRMS: calcd for $C_{36}H_{55}O_3Si$ $[M+H]^+$: 563.3920, found 563.3904.

Mixture of (*5S,9R,10S,13S*)- and (*5R,9S,10R,13S*)-15-(*tert*-butyldiphenylsilyloxy)-13-hydroxy-labd-7-en-11-one (39 and 40). To a stirred solution of *o*-iodoxybenzoic acid (86.2 mg, 308 μmol) in DMSO (0.8 mL) **37c** and **38c** (28.9 mg, 51.3 μmol, as solution in 0.5 mL of DMSO) were added. After stirring for 17 h the reaction mixture was filtered through a Florisil pad and the resulting filtrate solution was concentrated. FC (petrol–ethyl acetate 10:1) yielded a mixture of **39** and **40** (26.8 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.798/0.803 (2s, 6H) and 0.820/0.825 (2s, 12H) (2×CH_3-18, 2×CH_3-19, 2×CH_3-20), 0.982 and 0.986 (2s, 18H, 2×C(CH_3)$_3$), 1.203 and 1.208 (2s, 6H, 2×CH_3-16), 1.392 and 1.419 (2s, 6H, 2×CH_3-17), 2.68/2.76 and 2.73 (AB and s, 4H, $J_{2a/12b}$=18.7 Hz, 2×CH_2-12), 3.07 (broad s, 2H, $W_{1/2}\approx$6 Hz, 2×9-H), 3.70–3.76 (m, 2H, CH_2-15 of diastereomer A), 3.78–3.84 (m with 7 lines, 2H, CH_2-15 of diastereomer B), 5.43 (broad s, 2H, $W_{1/2}\approx$ 6 Hz, 2×7-H), 7.30–7.37 (m, 12H, Ar–H), 7.58–7.60 (m, 8H, Ar–H). ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ=14.96 (CH_3-20) (−), 15.01 (−), 19.04 (CH_2-2) (+), 19.45 (Si*C*$(CH_3)_3$) (+), 19.49 (+), 21.82 (−), 22.27 (−), 21.87 (−), 24.13 (CH_2-6) (+), 27.26 (SiC(*C*H_3)$_3$) (−), 27.47 (CH_3-16) (−), 27.57 (−), 30.10 (+), 33.45 (C_q-4 or C_q-10) (+), 33.79 (CH_3-18) (−), 37.75 (C_q-4 or C_q-10) (+), 37.81 (+), 41.78 and 42.40 (CH_2-1 and CH_2-3) (+), 42.87 (+), 43.48 (CH_2-14) (+), 49.89 (CH-5) (−), 58.23 (CH_2-12) (+), 58.43 (+), 61.43 (CH_2-15) (+), 61.51 (+), 68.52 (CH-9) (−), 72.14 (C_q-13) (+), 72.20 (+), 125.27 (CH-7) (−), 125.33 (−), 128.27 (Ar–C-*m*) (−), 130.29 (Ar–C-*p*) (−), 130.60 (+), 130.67 (C_q-8) (+), 133.77 and 133.88 (Ar–C-*ipso*) (+), 136.06 (Ar–C-*o*) (−), 214.95 and 215.33 (C=O, C-11) (+). The ^{1}H NMR and ^{13}C NMR spectra displayed all signals of the known compound *rac*-**39**. IR (CCl_4): 3494 (O–H), 1709 (C=O), 1389, 1106 (C–O), 702 cm^{-1}. $C_{36}H_{52}O_3Si$ (560.89), FAB MS *m*/*z*: 583.5 $[M+Na]^+$, 561.5 $[M+H]^+$, 543.5 $[M+H-H_2O]+$, 503.5. HRMS: calcd for $C_{36}H_{53}O_3Si$ $[M+H]^+$: 561.3763, found 561.3746.

Epoxidation of 39 and 40

To a stirred solution of mCPBA (57%, 20.6 mg, 67.9 μmol) in chloroform (3 mL) **39** and **40** (25.4 mg, 45.3 μmol, as a solution in 1 mL of chloroform) were added. After 2 h the reaction was completed and the reaction mixture was treated with aq. sat. $NaHCO_3$ (1 mL). Usual work-up (CH_2Cl_2) and FC (petrol–ethyl acetate 5:1) furnished a mixture of optically active epoxides **41** and **42** (22.5 mg, 86%). At this stage TLC (petrol–ethyl acetate 10:1) showed two spots. The more polar compound had the same R_f value as an authentic sample of *rac*-**41**. The preparative separation was not optimised. From one run (22.5 mg) the desired epoxide **41** (4.0 mg, 15%) was obtained alongside with a fraction containing both **41** and **42** (17.1 mg, 65%).

(5*S*,7*R*,8*S*,9*R*,10*S*,13*S*)- and (5*R*,7*S*,8*R*,9*S*,10*R*,13*S*)-15-(*tert*-Butyldiphenylsilyloxy)-7,8-epoxy-13-hydroxy-labdan-11-one (41 and 42). ^{1}H NMR of **41** and **42** (200 MHz, $CDCl_3$): δ=0.86/0.89/1.02 (3s, 18H, 2 CH_3-18, 2 CH_3-19, 2 CH_3-20), 1.06 (s, 18H, 2 C(CH_3)$_3$), 1.20 and 1.22 (2s, 6H, 2 CH_3-16), 1.29 (s, 6H, 2 CH_3-17), 1.65–1.98 (mk, 6H), 2.10 (2 overlapped dd, 2H, 2×1α-H), 2.66–2.87 (mk, 6H, 2 CH_2-12 and 2×9-H), 2.99 (m, 2H, 2×7-H), 3.73–3.96 (mk, 4H, 2 CH_2-15), 4.20 (s, 1H, OH ?), 7.39–7.43 (m, 12H, Ar–H), 7.65–7.70 (m, 8H, Ar–H). $C_{36}H_{52}O_4Si$ (576.89), FAB MS *m*/*z*: 599.5 $[M+Na]^+$, 577.5 $[M+H]^+$, 559.5 $[M+H-H_2O]^+$. HRMS: calcd for $C_{36}H_{52}O_4SiNa$ $[M+Na]^+$: 599.3532, found 599.3547.

(5*S*,7*R*,8*S*,9*R*,10*S*,13*S*)-15-(*tert*-Butyldiphenylsilyloxy)-7,8-epoxy-13-hydroxy-labdan-11-one (41). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.86/0.88/1.01 (3s, 9H, CH_3-18, CH_3-19, CH_3-20), 1.05 (s, 9H, C(CH_3)$_3$), 1.21, 1.28 (2s, 6H, CH_3-16, CH_3-17), 1.62–1.98 (mk, 3H, CH_2-14, 6β-H), 2.09 (dd, 1H, $J_{1\alpha/1\beta}$ =15.3 Hz, $J_{1\alpha/2}$=4.2 Hz, 1α-H), 2.68 (s, 1H, 9-H), 2.77/2.91 (AB, 2H, $J_{12a/12b}$= 18.3 Hz, CH_2-12), 2.99 (m, 1H, $W_{1/2}$=5 Hz, 7-H), 3.73–3.94 (m, 2H, CH_2-15), 4.19 (s, 1H, OH), 7.39–7.43 (m, 6H, Ar–H), 7.65–7.70 (m, 4H, Ar–H).[40] CD (c=0.21·10^{-3} mol L^{-1}, CH_3CN): λ_{max} ($\Delta\epsilon$)=306.6 nm (5.8).

Docking procedure

The structure data for the rat type II adenylyl cyclase C2 domain/forskolin complex were taken from the Brookhaven Protein Data Bank (1ab8). Polar hydrogens and CHARMM22 united-atom charges were added to the protein. Prior to docking, electrostatic potential (ESP) charges for the ligands were calculated on the basis of AM1-optimized geometries using the MOPAC 6.0 program. The grid with 88×64×64 grid points in *x*, *y*, *z* and a grid spacing of 0.375 Å was centred in such a way that it was possible to consider the two equivalent binding sites for forskolin. In each case, 24 independent docking runs were performed and the resulting structures were clustered by

geometry allowing RMSD deviations of ≤ 1 Å^2. The GA-LS procedure was applied with 100.000 energy evaluations per run, a mutation rate of 0.10, a crossover rate of 0.80, and a local search frequency of 0.06 subjected to a population of 50 randomly initiated individuals for each ligand. Free rotation around all single bonds was allowed using the AutoTors module. Free Enthalpy costs of 0.3113 kcal mol^{-1} per torsional degree of freedom with exception of those with NH and OH groups were applied.

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