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Synthesis of a 1α-amino-1-deoxy analogue of forskolin

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Abstract—1α-Amino-1,6,9-trideoxy forskolin was synthesized starting from drimenal and an isoprenoid C_5 unit. A tricyclic labdane with the entire forskolin skeleton was available in only four steps. Barton's nitrite photolysis was applied to functionalize C-1. © 2003 Elsevier Science Ltd. All rights reserved.

1. 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 investigations into the role of cyclic AMP in various physiological functions. Nine isoforms of adenylyl cyclase 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. They have been overexpressed in bacteria and have been shown to have forskolin-stimulated catalytic activity when they are mixed or tethered.[2,3] Two crystal structures have been reported some time ago by Zhang and co-workers[4] and by the Sprang group,[5] respectively. They revealed that forskolin has polar interactions to both C units, i.e. hydrogen bonds from 1α-OH and the 11-oxo group to one and hydrogen bonds of the other to the 7-acetyl group. It has been suggested that forskolin activates the adenylyl cyclases by promoting C_1/C_2 association resulting in formation of an active site. 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 the forskolin target and the essential ligand–protein interactions provides new incentives for 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 synthetically more readily accessible analogues, which nevertheless fulfill 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. On the basis of Zhang's X-ray analysis,[4] docking experiments were performed for forskolin **1a** and analogues to study the consequences of structural variations with respect to the binding behavior.[7] The docking experiments were carried out employing the Lamarckian genetic algorithm with local search (GA-LS) hybrid formalism of the latest version of the docking program AutoDock 3.0,[8] that predicts the bound conformations of flexible ligands to macromolecular targets. The docking results were in excellent agreement with the crystal structure (Fig. 1a).

The theoretically estimated K_D-value for forskolin was 14.8 nM agreeing fairly well with the experimental value of 18 nM.[9] For the 1α-amino-1-deoxy derivative **1b** a higher affinity than for forskolin was calculated (K_D-value of 5.2 nM). This was explained by an additional hydrogen bond to the protein (Fig. 1b). These results provoked synthetic studies aimed at making accessible an 1α-amino-1-deoxy-analogue of forskolin. As mentioned above, since the 6- and the 9-OH groups of forskolin are probably not involved in polar interactions with the enzyme we chose 1α-amino-1,6,9-trideoxy forskolin (**1c**) as our synthetic target.

Keywords: diterpenes; labdanes; Sharpless dihydroxylation; nitrite photolysis.

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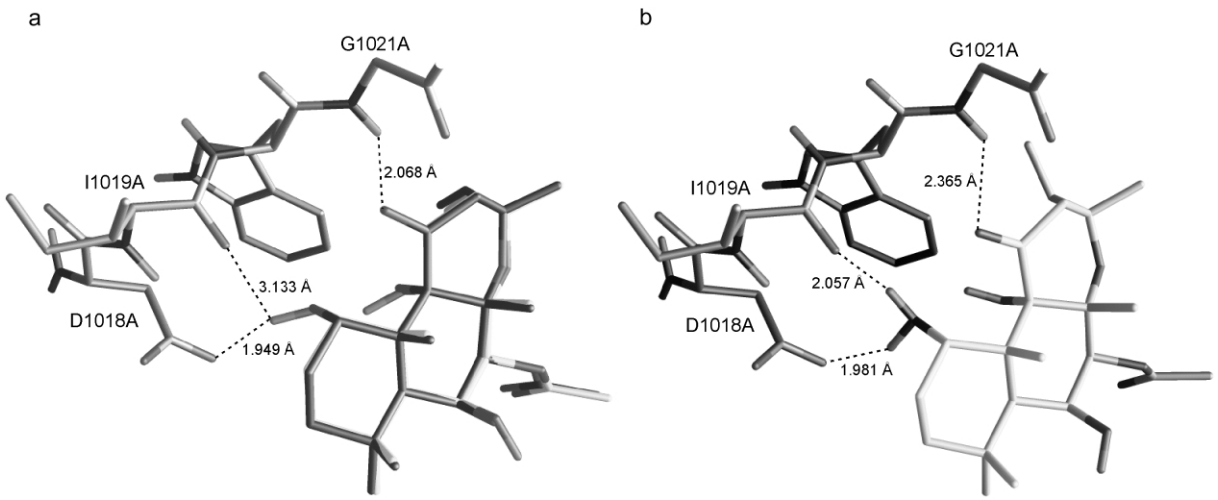


Figure 1. (a) Visualisation of forskolin (**1a**) rings A and C polar interactions with a catalytic adenylyl cylase domain. Superposition of the practically coincident crystal[4] (dark grey) and the most stable docking structures (grey); (b) Visualisation of rings A and C polar interactions of **1b**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

2. Results and discussion

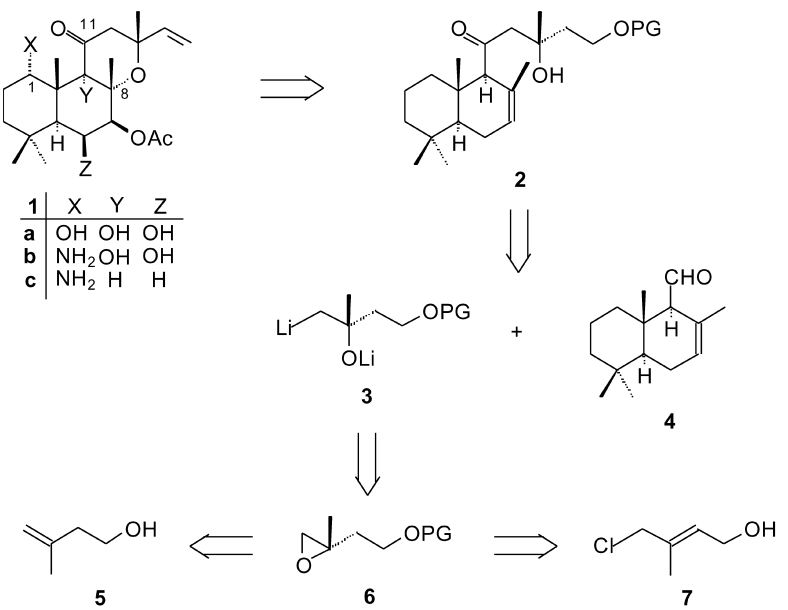
2.1. Synthetic design

Our previous work has demonstrated that racemic tricycle labdane derivatives can be obtained from a precursor of type **2** which is itself available from drimenal (**4**) and an isoprenoid C_5 unit.[7] Several nucleophilic C_5 building blocks have been employed the most efficient of which was epoxide **6** which was reductively opened with Freeman's radical anion (vide infra) to furnish dianion **3**. Reaction of the dianion with aldehyde **4** provided a C_{20} compound composing all carbon atoms of forskolin. Epoxide **6** was itself synthesized commencing from **7** with a Sharpless epoxidation as a key step.[7]

It was our intention (i) to simplify the synthesis of epoxide **6** starting from unsaturated alcohol **5**, (ii) to use our previously reported protocol for the stereoselective formation of the tetrahydropyran ring[10] and (iii) to introduce the 1-amino function by a suitable remote functionalization method (Scheme 1).

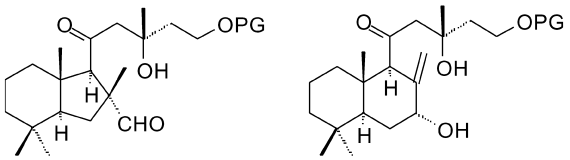
2.2. Synthesis of labdane 14a

rac-Drimenol was prepared making use of Vlad's fluorosulfonic acid-mediated cyclisation of (*E*,*E*)-farnesol.[11] Resolution of *rac*-drimenol was achieved via chromatographic separation of the diastereomeric (−)-camphanic acid esters and subsequent saponification as described previously.[12] Oxidation of (−)-drimenol with *o*-iodoxybenzoic acid (IBX: 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide)[13] gave optically pure (+)-drimenal (**4**). As described above, epoxide **6** was previously obtained from **7** in a rather lengthy sequence of steps. We now used results published by Corey and co-workers.[14,15] Thus, diol **8a** obtained via a Sharpless dihydroxylation was converted into tosylate **8b**. On treatment with base, **8b** cyclized to give the



Scheme 1.

desired epoxide **9**. Reductive opening of **9** with the radical anion of 4,4′-di-*tert*-butylbiphenyl (Freeman's salt) furnished lithio alkoxide **3** which was trapped in situ with (+)-drimenal at −78°C to provide labdane **10** as a single diastereoisomer in 53% yield. The configuration at C-11 was assigned by analogy.[16] The 11-OH group of **10** was oxidized with IBX to give **11**. Epoxidation of the olefinic double bond of **11** with *m*-CPBA provided α-epoxide **12** in 80% yield.[16] One of the key steps in our synthesis is the acid-promoted formation of the tetrahydropyran ring by epoxide opening and attack of the 13-OH group at C-8 with formal retention of configuration which is accompanied by formation of an aldehyde of type **18** and an olefin such as **19**.[10] In the case of **12** we found the ratio of **13a** to the undesired side products to be strongly dependend on the reaction conditions. Camphorsulfonic acid, triflic acid, and trimethylsilyl triflate have been tried as promotors. Best results were obtained by treatment of **12** with triflic acid (1.1 equiv.) in toluene at 0°C. Under these conditions, **13a** was formed in 62% yield. The reaction with camphorsulfonic acid or TMSOTf furnished a complex mixture.[17] The use of $BF_3{\cdot}OEt_2$ was also unsuccessful.[17]



The vinyl group was established according to Grieco[18] via a selenide intermediate. First the *p*-methoxyphenyl protecting group in compound **13a** was removed in 89% yield by treatment with ceric ammonium nitrate. **13b** with the released primary OH-group on reaction with *o*-nitrophenyl selenocyanate in the presence of tri-*n*-butylphosphine furnished selenide **13c** in quantitative yield. Oxidation of the selenide with hydrogen peroxide led to the desired compound **14a**, again in quantitative yield. The structure of **14a** was confirmed by X-ray data (see Figure 2).

It is important to note that compound **14a** was also obtained commencing from *rac*-drimenal and (S)-**9**. Coupling furnished two diastereomers which were converted into selenide **13c** and its diastereoisomer with opposite configuration at all stereogenic centres except at C-13. At this stage, the mixture was easily separated by the means of medium pressure chromatography. This approach is very convenient and allows to omit the resolution of *rac*-drimenol (Scheme 2).

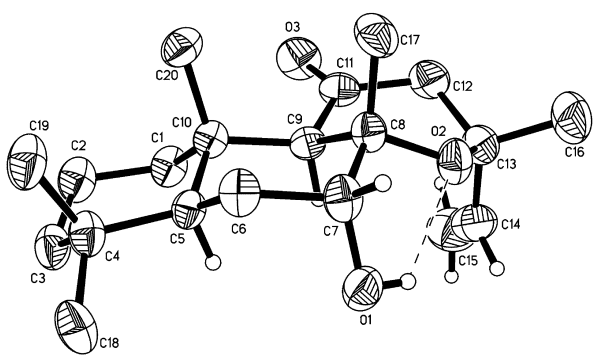
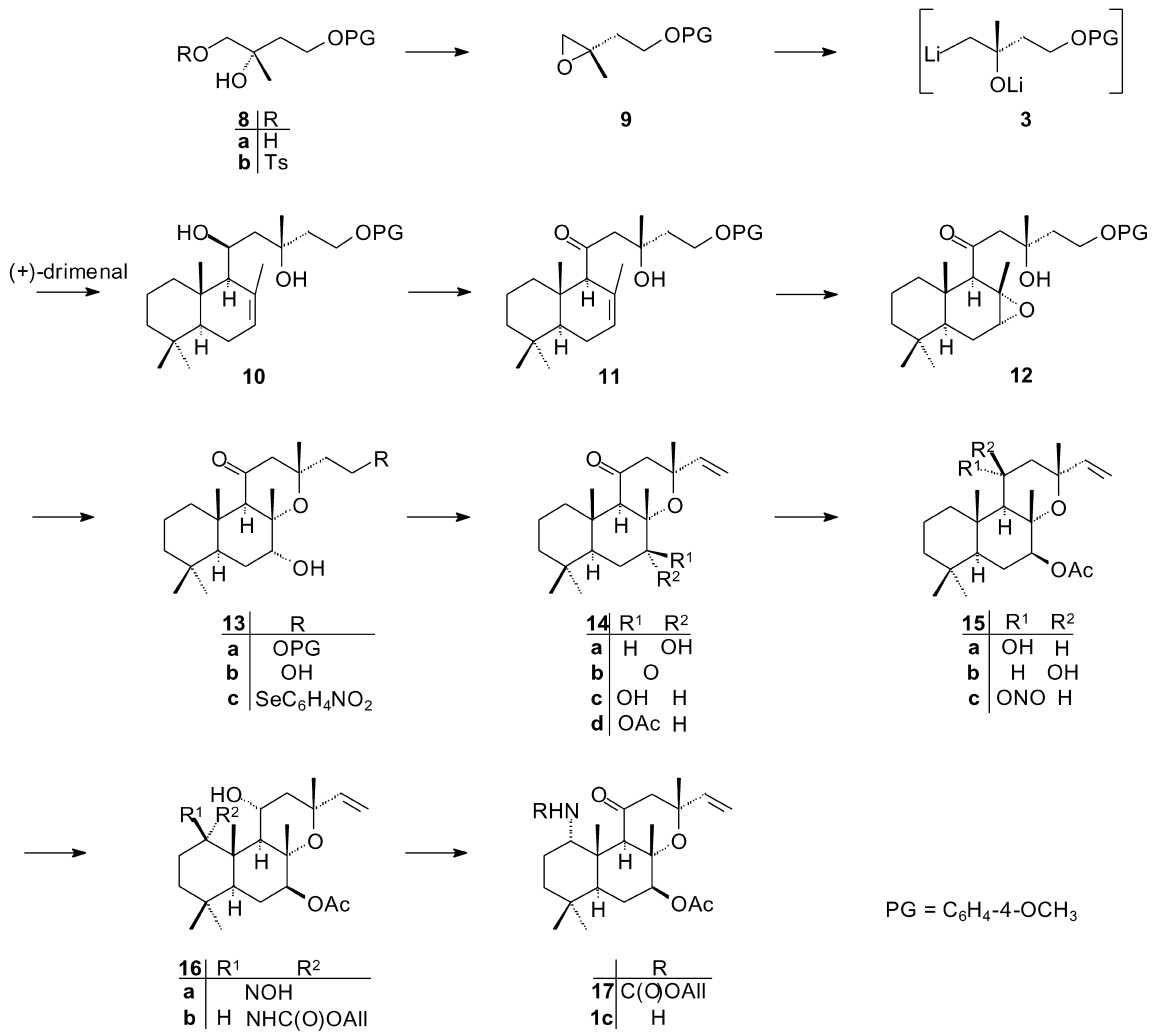


Figure 2. X-Ray structure of compound **14a**.

2.3. Establishing the functional groups of 1c

Since the 7-acetoxy group in forskolin has β-orientation, it was necessary to invert the configuration at C-7 of **14a**. Attempted Walden inversion was unsuccessful. We did not observe the formation of a mesylate because the hydroxyl group turned out to be very unreactive in agreement with previous observations.[19] A reason for the low reactivity may be a hydrogen bond between the 7-OH group and the tetrahydropyran oxygen that is seen in the X-ray structure. Therefore, an oxidation–reduction sequence was applied. Compound **14a** was quantitatively converted into diketo derivative **14b** by treatment with IBX. The subsequent reduction with sodium borohydride in ethanol at 0°C was highly regio- and stereoselective and gave the 7β-hydroxy derivative **14c** in 88% yield. The 7α-isomer **14a** was separated from the reaction mixture in 11% yield. Then **14c** was esterified with acetic anhydride in the presence of a catalytic amount of Steglich's base to provide the important intermediate 1,6,9-trideoxyforskolin **14d** in quantitative yield. The X-ray analysis confirmed the structure of **14d** (Fig. 3).

Our plan for the preparation of a 1α-amino-1-deoxy derivative **1c** of forskolin called for the following transformations: (i) stereoselective reduction of the 11-carbonyl group to give the equatorial alcohol, (ii) preparation of the 1-oximino derivative via a Barton nitrite photolysis and (iii) the steroselective reduction of the oxime. The stereoselective reduction of a 11-keto function to the equatorial 11α-alcohols is not a trivial matter. We tried a number of methods for this purpose. Metal borohydride reductions provided only the axial alcohol by backside attack. Catalytic Meerwein–Pondorf–Verley reduction of **14d** employing trimethylaluminium and 2-propanol[20] was unsuccessful and afforded the deacetylated derivative.[17] Therefore, we resorted to a reduction involving two one-electron reduction steps. The reagent used was samarium diiodide. From previous studies it was known that SmI_2 reduction of aldehydes and ketones demand a proton source, water or an alcohol, to obtain the corresponding alcohols in high yields. In some cases it was necessary to introduce additives such as HMPA[21] or inorganic salts.[22] We have studied the SmI_2-mediated reduction of **14d** in THF in the presence of various proton sources and additives. The most commonly used proton source is methanol. We found that in the presence of this alcohol the rate of reaction to be very slow. Only traces of the desired alcohol **15a** were detected even when the reaction was performed under reflux for 40 h.[17] Based on Corey's work[23] we performed the reduction in the presence of water (35 equiv.). After 8 h no starting compound was observed in the reaction mixture. Instead, two new compounds were detected by TLC which were isolated and identified as the 11β-hydroxy **15b** (42%) and 11α-hydroxy **15a** (56%) isomers. A threefold increase of the water content accelerated the rate of reaction (3 h) but the ratio of isomeric alcohols was found to be 1:1. A decrease in the amount of water (7 or 14 equiv.) slowed down the reaction rate. The addition of various additives such as



Scheme 2.

HMPA, LiCl or NH_4Cl did neither change the ratio of the isomers nor the reaction time.[17] Himersson et al. have reported that various diols can accelerate the rate of reduction.[24] When we applied their observations the best results were obtained when **14d** was treated with SmI_2 in the presence of diethylene glycol (21 equiv.) to afford after separation the 11β- and 11α-hydroxy derivatives in a 1:2.4 ratio (overall yield: 82%). Some starting ketone **14d** was also isolated (17%).

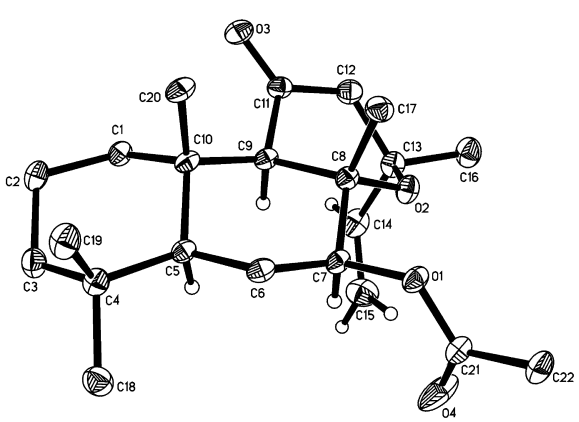


Figure 3. X-Ray structure of compound **14d**.

The next task of the synthesis of **1c** was the introduction of the 1α-amino group. We decided to prepare the 1-oximino derivative **16a** using Barton's nitrite photolysis.[25] The latter reaction has mainly been employed for the functionalization of axial methyl groups at rigid steroid or terpenoid backbones via a six-membered transition state starting from axial alcohols. In the case of an equatorial 11α-nitrite the intermediate oxygen radical can only reach the 1β-hydrogen via such a transition state.[26] Reaction of the thus formed carbon radical with NO gives an intermediate nitroso compound which on tautomerization furnishes the 1-oxime. In the event, the 11α-hydroxy compound **15a** was quantitatively converted into the corresponding nitrite **15c** by treatment with nitrosyl chloride in pyridine, and the unstable intermediate **15c** was irradiated immediately in dry benzene at 350 nm for 5 h to afford a mixture consisting of two main compounds, the desired oxime **16a** (50%) and the starting 11α-hydroxy material **15a** (ca. 10%). In the ^1H NMR spectrum of **16a** the signals of the protons at C-1 were missing and the signals of the C-2 protons were shifted to low field. The ^{13}C NMR signal of the C=N–OH group was clearly recognized at 167.19 ppm.

The reduction of oximes to primary amines can be achieved with a variety of reagents. However, the presence of an

acetyl and a vinyl group in **16a** strongly limited the choice of reagents. The reduction with borane, alkali metal in alcohols or hydrogenolysis could not be applied in our case. Both indium metal in acetic acid in THF under reflux[27] and sodium borohydride in the presence of transition metal ($TiCl_4$ or MoO_3) failed to reduce the oxime **16a** to the desired amino compound.[17] In all experiments, the reaction mixture still contained unreacted oxime. Reduction with L-Selectride® was also unsuccessful and removed the 7-acetyl group.[17] The two products formed on reduction with sodium cyanoborohydride in acetic acid[28] were identified by mass-spectrometry as the 1-hydroxylamino and the 1-amino derivatives in a ratio ca. 1:1.[17] We then submitted the oxime to the reduction with sodium cyanoborohydride in combination with $TiCl_3$.[29] Thus, a solution of **16a** in methanol was treated with sodium cyanoborohydride, and then a 30% solution of $TiCl_3$ in 2N HCl was added dropwise. After 15 h the product was isolated and treated with allyl chloroformate in dioxane–water (5:1) to furnish the *N*-protected 1-amino derivative **16b** in 77% yield for two steps. The allyloxy carbonyl group was chosen in favor of other protecting group because of its relatively small size and the ease with which it can be removed. In the ^1H NMR spectrum of **16b** new signals for 1-H (δ=4.40) and the NH-group (δ=5.21) were detected together with the signals of the allyl residue. The configurational assignment rests on an X-ray analysis (Fig. 4). The X-ray structure revealed an internal hydrogen bond between the urethane CO and the 11α-OH group. The unit cell contained two symmetry-independent molecules. They are held together in a head to tail fashion by two hydrogen bonds each between the 1-urethane NH and 7-acetyl CO group (see Figure 4b).

In the next step, the oxidation of the alcohol function of **16b** with IBX provided the carbonyl derivative **17** in a quantitative yield. The axial 1α-configuration of the allyloxycabonyl group was evident from the small coupling constants for the coupling between 1-H with the protons at C-2. The 1-H signal appeared as a multiplet at δ=4.41 from which $J_{1,NH}$=10.4 Hz and the two $J_{1,2}$ coupling constants of about 3.0 could be determined. The *N*-protecting group was efficiently removed by palladium(0)-mediated transfer to a soft nucleophile. Thus, when **17a** was briefly treated with palladium tetrakis(triphenylphosphine) (5 mol%) and an excess of morpholine as acceptor, the 1α-amino-1,6,9-deoxy forskolin (**1c**) was obtained in 93% yield after purification by reversed phase flash chromatography.

3. Conclusion

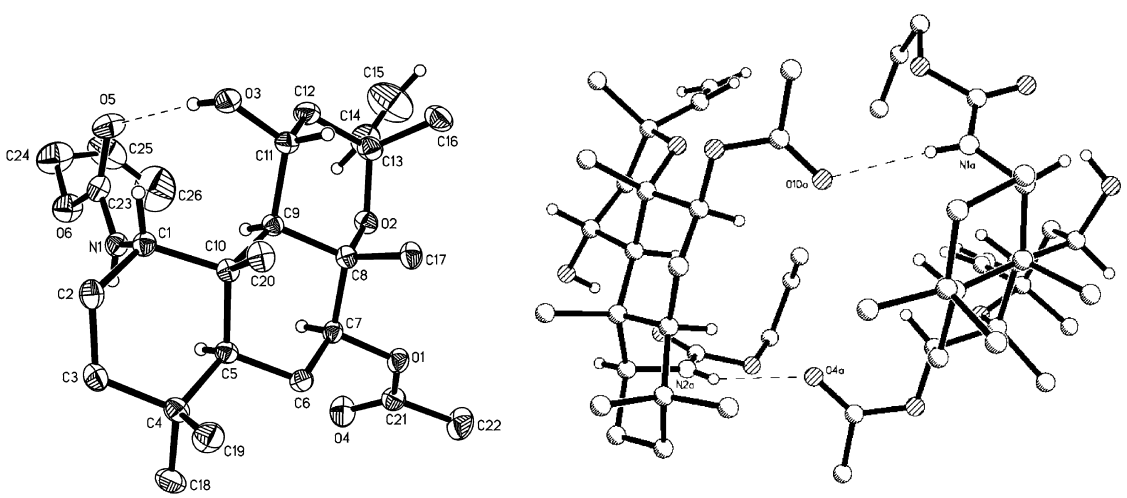
We have developed an efficient synthesis of the new forskolin analogue 1α-amino-1,6,9-trideoxyforskolin. The tricyclic forskolin derivative **13a** can readily be prepared from racemic or optically pure drimenal and C_5 unit **9** followed by stereoselective epoxidation and acid-mediated rearrangement. Installation of the side-chain double bond and oxidative–reductive inversion of the configuration at C-7 followed by acetylisation furnished 1,6,9-trideoxy forskolin **14d**.

Choice of the right proton source in the SmI_2 reduction of the 11-keto group in **14d** to give the equatorial 11α-alcohol **15a** was crucial for the success of the reaction. Finally, a Barton nitrite photolysis was successfully applied for the introduction of a nitrogen functionality at C-1. Reduction of oxime with sodium cyanoborohydride–$TiCl_3$ furnished a 1-amino compound with the desired α-configuration at C-1. The biological properties of **1c** are under investigation.

4. Experimental

4.1. General

Thin layer chromatography was carried out using pre-coated aluminum plates (Kieselgel 60 F_{254}, Merck) which were visualized with the phosphor molybdate–ceric sulfate reagent.[30] Flash column chromatography (FC) was performed on silica gel (Kieselgel 60, Merck 40–63 μm). IBX was prepared as described.[13] Melting points were



a) b)

Figure 4. (a) X-Ray structure of compound **16b**, (b) arrangement of **16b** in the unit cell.

determined in capillary tubes with a Büchi (B-540) apparatus. Optical rotations were measured at the sodium D-line with a Perkin–Elmer Model 141 polarimeter. IR spectra were determined on a FT-IR spectrometer (ATI Mattson, Genesis series). ^{1}H and ^{13}C NMR spectra were obtained on Varian Gemini 200, Gemini 2000, Gemini 300 and Bruker DRX-400, DRX-600 spectrometers in $CDCl_3$ as a solvent unless otherwise stated. The signals of $CHCl_3$ (δ=7.26) and of $CDCl_3$ (δ=77.16) were used as internal references. *J* values are given in Hz. Signals were assigned by means of 2D proton–proton (COSY) and proton–carbon (HMQC, HMBC) shift-correlation spectra. Mass spectra were recorded on a VG ZAB-HSQ (VG Analytics) using 3-nitrobenzyl alcohol as a matrix (FAB MS), Finnigan MAT 212 (EI) and by FT ICR (MS 7 T APEX II, Bruker-Daltonics) in the positive or negative mode (ESI MS). Photolysis at 350 nm was performed in a Rayonet Photochemical Chamber Reactor RPR-100 supplied with RPR-3500 Å lamps.

4.1.1. (*S*)-2-Hydroxy-4-(4-methoxyphenoxy)-2-methylbutyl tosylate (8b). A solution of 4-(4-methoxyphenoxy)-2-methylbutane-1,2-diol[14] (**8a**, 4.65 g, 20.5 mmol), *p*-toluenesulfonyl chloride (3.91 g, 20.5 mmol) and pyridine (3.32 mL, 41.0 mmol) in anhydrous $CHCl_3$ (50 mL) was boiled for 3 h, cooled to rt and washed with water. The organic phase was dried over Na_2SO_4, the solvent was evaporated and the residue was purified by FC (petroleum ether–EtOAc 2:1) to give **8b** (7.41 g, 95%). Mp 49–50°C (from petroleum ether); $[\alpha]_D^{20}$=+11 (*c* 2.0, $CHCl_3$); IR (KBr): 3552, 1509, 1349, 1232, 1174, 1031, 971, 852, 819, 671 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.26 (s, 3H, 2-CH_3), 1.92–2.05 (m, 2H, CH_2-3), 2.44 (s, 3H, CH_3-Ts), 2.51 (br s, 1H, OH), 3.77 (s, 3H, OCH_3), 3.90 and 3.94 (AB system, 2H, *J*=9.9 Hz, CH_2-1), 3.97–4.09 (m, 2H, CH_2-4), 6.73–6.85 (m, 4H, O–C_6H_4–O), 7.30–7.36, 7.76–7.82 (m, 4H, C_6H_4–Ts); ^{13}C NMR (75 MHz, APT) δ 21.90 (CH_3–Ts, −), 24.80 (2-CH_3, −), 37.25 (C-3, +), 55.99 (OCH_3, −), 65.30 (C-4, +), 71.35 (C-2, +), 75.79 (C-1, +), 114.96, 115.79 (CH–PG, −), 128.27, 130.18 (CH–Ts, −), 132.87, 145.27 (C_q–Ts, +), 152.51, 154.52 (C_q–PG, +); $C_{19}H_{24}O_6S$ (380.46, 380.1294), ESI MS: *m/z* 403.1 $[M+Na]^+$, 419.2 $[M+K]^+$.

4.1.2. (*S*)-1,2-Epoxy-4-(4-methoxyphenoxy)-2-methylbutane (9). To a suspension of sodium hydride (75% dispersion in oil, 1.4 g, 58.5 mmol) in dry THF (20 mL) a solution of tosylate **8b** (7.4 g, 19.5 mmol) in THF (20 mL) was added dropwise at 0°C, and the suspension was stirred overnight at rt. Quenching with water (1 mL), solvent evaporation and FC (CH_2Cl_2) afforded **9** (3.44 g, 84%). Mp 49–50°C (from petroleum ether); $[\alpha]_D^{21}$=+9 (*c* 2.0, $CHCl_3$); IR (KBr): 1508, 1234, 1037 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.34 (s, 3H, 2-CH_3), 1.98 (m, 2H, CH_2-3), 2.57 and 2.68 (AB system, 2H, *J*=4.8 Hz, CH_2-1), 3.71 (s, 3H, OCH_3), 3.95 (m, 2H, CH_2-4), 6.77 (m, 4H, Ar–Hs); ^{13}C NMR (50.3 MHz) δ 21.76 (2-CH_3, −), 36.30 (C-3, +), 54.14 (C-1, +), 55.48 (C-2, +), 55.89 (OCH_3, −), 65.04 (C-4, +), 114.85, 115.61 (*C*H–Ar, −), 152.99, 154.09 (C_q–Ar, +); $C_{12}H_{16}O_3$ (208.26, 208.1099), EI MS: *m/z* 208.0 $[M]^{+\cdot}$, 124.0 $[CH_3C_6H_4OH]^{+\cdot}$.

4.1.3. (11*S*,13*S*)-15-(4-Methoxyphenoxy)-labd-7-ene-11,13-diol (10). To a solution of 4,4′-di-*tert*-butylbiphenyl (2.17 g, 8.16 mmol) in anhydrous THF (20 mL) under argon lithium (3 mm granulate, 85 mg, 12.2 mmol) was added. The mixture was sonicated until a blue colour appeared and was then vigorously stirred overnight at 0°C. At −78°C solutions of epoxide **9** (849 mg, 4.08 mmol) in THF (5 mL) and (15 min later) of (+)-drimenal (0.90 g, 4.08 mmol) in THF (5 mL) were successively added. The reaction mixture was stirred for 2 h at −78°C. Water (5 mL) was added and the mixture was allowed to warm to rt. After extraction with CH_2Cl_2 and FC (petroleum ether–EtOAc 5:1) the yield of **10** (oil) was 0.93 g (53%). $[\alpha]_D^{20}$=−2 (*c* 2.0, $CHCl_3$,); IR (film): 3600–3200, 1506, 1465, 1230, 1039, 829, 754 cm^{-1}; ^{1}H NMR (600 MHz, H,H COSY, HMQC, HMBC) δ 0.87 (s, 3H, CH_3-18), 0.90 (s, 3H, CH_3-19), 0.88–0.95 (m, overlapping with s at 0.90, 1-H_a), 1.01 (s, 3H, CH_3-20), 1.09–1.20 (m, 2H, 5-H, 3-H_a), 1.39 (s, 3H, CH_3-16), 1.34–1.48 (m, overlapping with s at 1.39, 2-H_a, 3-H_b, 12-H_a), 1.53–1.62 (m, 1H, 2-H_b), 1.76 (br s, 1H, 9-H), 1.87 (s, 3H, CH_3-17), 1.88–2.03 (m, 5H, 1-H_b, CH_2-6, CH_2-14), 2.37 (dd, 1H, $J_{12b,11}$=11.6 Hz, $J_{12b,12a}$=14.3 Hz, H_b-12), 3.76 (s, 3H, OCH_3), 4.10–4.20 (m, 2H, CH_2-15), 4.49 (dd, 1H, $J_{11,12a}$=2.1 Hz, $J_{11,12b}$=11.6 Hz, 11-H), 5.59 (m, 1H, $W_{1/2}$=12, 7-H), 6.80–6.88 (m, 4H, Ar–Hs); ^{13}C NMR (50.3 MHz) δ 14.75 (C-20, −), 19.08 (C-2, +), 22.58 (C-19, −), 23.72 (C-6, +), 25.23 (C-17, −), 26.16 (C-16, −), 33.19 (C-4, +), 33.71 (C-18, −), 37.63 (C-10, +), 40.49 (C-1, +), 42.47 (C-14, +), 42.66 (C-3, +), 48.89 (C-12, +), 50.32 (C-5, −), 56.04 (OCH_3, −), 61.04 (C-9, −), 65.71 (C-15, +), 67.15 (C-11, −), 73.57 (C-13, +), 114.99, 115.88 (CH–Ar, −), 126.76 (C-7, −), 132.76 (C-8, +), 152.99, 154.34 (C_q–Ar); $C_{27}H_{42}H_4$ (430.63, 430.3083), EI MS: *m/z* 430.0 $[M]^{+\cdot}$.

4.1.4. (13*S*)-13-Hydroxy-15-(4-methoxyphenoxy)-labd-7-en-11-one (11). IBX (1.21 g, 4.32 mmol) was dissolved in DMSO (20 mL) under stirring at rt. A solution of **10** (0.93 g, 2.16 mmol) in DMSO (20 mL) was added and the mixture was stirred for 2 h at rt. Extraction with petroleum ether (4×100 mL), solvent evaporation and FC (petroleum ether–EtOAc 20:1) gave **11** (amorphous solid, 0.845 g, 91%). $[\alpha]_D^{20}$=+70 (*c* 3.0, $CHCl_3$); IR (KBr): 3600–3200, 1695, 1506, 1228, 756 cm^{-1}; ^{1}H NMR (600 MHz, H,H COSY, HMQC, HMBC) δ 0.87 (s, 3H, CH_3-18), 0.90 (s, 3H, CH_3-19), 0.93 (s, 3H, CH_3-20), 1.20–1.30 (m, 2H, H-5, 3-H_a), 1.32 (s, 3H, CH_3-16), 1.35–1.45 (m, 3H, 1-H_a, 2-H_a, 3-H_b), 1.51 (s, 3H, CH_3-17), 1.55–1.65 (m, 2H, 1-H_b, 2-H_b), 1.80–2.10 (m, 4H, CH_2-6, CH_2-14), 2.60–2.90 (m, 2H, CH_2-12), 3.17 (br s, 1H, 9-H), 3.76 (s, 3H, OCH_3), 4.00–4.20 (m, CH_2-15), 4.26 (s, 1H, probably OH), 5.52 (br s, 1H, 7-H), 6.80–6.85 (m, 4H, Ar–Hs); ^{13}C NMR (50.3 MHz, APT) δ 14.81 (C-20, −), 18.78 (C-2, +), 21.55 (C-17, −), 21.99 (C-19, −), 23.82 (C-6, +), 27.22 (C-16, −), 33.17 (C-4, +), 33.49 (C-18, −), 37.61 (C-10, +), 40.81 (C-14, +), 41.52 (C-1, +), 42.05 (C-3, +), 49.56 (C-5, −), 55.84 (OCH_3, −), 57.48 (C-12, +), 65.04 (C-15, +), 68.27 (C-9, −), 71.30 (C-13, +), 114.79, 115.55 (CH–Ar, −), 125.05 (C-7, −), 130.03 (C-8, +), 152.98; 154.00 (C_q–Ar, +), 215.74 (C-11); $C_{27}H_{40}O_4$ (428.61, 428.2927), EI MS: *m/z* 428.1 $[M]^{+\cdot}$.

4.1.5. (7*R*,8*S*,13*S*)-7,8-Epoxy-13-hydroxy-15-(4-methoxyphenoxy)-labdan-11-one (12). To a solution of *m*-chloroperbenzoic acid (57%, 0.80 g, 2.80 mmol) in $CHCl_3$ (50 mL) a solution of **11** (0.80 g, 1.87 mmol) in $CHCl_3$

(50 mL) was added and the mixture stirred for 2 h at rt. Addition of sat. aq. $NaHCO_3$ solution (20 mL), usual work-up (extraction with CH_2Cl_2, 3×100 mL), and FC ($CHCl_3$–EtOAc 20:1) furnished **12** (oil, 0.63 g, 80%). $[\alpha]_D^{20}=+16$ (*c* 2.0, $CHCl_3$); IR (film): 3600–3300, 1702, 1508, 1463, 1380, 1230, 1039, 827 cm^{-1}; ^1H NMR (400 MHz, H,H COSY) δ 0.79 (s, 3H, CH_3-18), 0.82 (s, 3H, CH_3-19), 0.95 (m, 1H, 5-H), 0.97 (s, 3H, CH_3-20), 1.02–1.06 (m, 2H, 1-H_a, 3-H_a), 1.18 (s, 3H, probably OH), 3.96–4.10 (m, 2H, CH_2-15), 6.73–6.81 (m, 4H, Ar–Hs); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 14.92 (CH_3-20, −), 18.51 (C-2, +), 22.32 (C-19, −), 23.08 (C-6, +), 23.24 (C-17, −), 27.22 (C-16, −), 33.11 (C-18, −), 33.16 (C-4, +), 37.58 (C-10, +), 39.92 (C-1, +), 40.58 (C-14, +), 42.04 (C-3, +), 45.32 (C-5, −), 55.99 (OCH_3, −), 57.69 (C-8, +), 58.61 (C-12, +), 60.62 (C-7, −), 65.14 (C-15, +), 67.32 (C-9, −), 71.39 (C-13, +), 114.94, 115.67 (CH–Ar, −), 153.05, 154.13 (Cq–Ar, +), 214.66 (C-11, +); $C_{27}H_{40}O_5$ (444.61, 444.2876), ESI MS: *m/z* 445.3 $[M+H]^+$, 467.2 $[M+Na]^+$.

4.1.6. (7*R*,8*S*,13*S*)-8,13-Epoxy-7-hydroxy-15-(4-methoxy-phenoxy)-labdan-11-one (13a). To a solution of epoxide **12** (0.76 g, 1.70 mmol) in dry toluene (20 mL) triflic acid (150 μL, 1.70 mmol) was added at 0°C under argon (the mixture turned brown). After stirring at 0°C for 1 h, Et_3N (460 μL, 3.40 mmol) was added. The mixture was stirred for 10 min then evaporated. FC (petroleum ether–$CHCl_3$–EtOAc, 5:5:1) furnished **13a** (amorphous solid, 0.47 g, 62%). $[\alpha]_D^{20}=-64°$ (*c* 2.0, $CHCl_3$); IR (KBr): 3600–3300, 1712, 1506, 1226, 1035 cm^{-1}; ^1H NMR (400 MHz, H,H COSY, HMQC, HMBC) δ 0.72 (s, 3H, CH_3-18), 0.79 (s, 3H, CH_3-19), 0.75–0.83 (m overlapping with s at 0.79, 1H, 1-H_a), 1.00 (s, 3H, CH_3-20), 1.05–1.15 (m, 1H, 3-H_a), 1.25 (s, 3H, CH_3-17), 1.30 (s, 3H, CH_3-16), 1.30–1.35 (m, 2H, 2-H_a, 3-H_b), 1.35–1.45 (m, 2H, 5-H, 6-H_a), 1.50–1.65 (m, 1H, 2-H_b), 1.75–1.80 (m, 1H, 6-H_b), 1.85–2.05 (m, 2H, CH_2-14), 2.15–2.20 (m, 1H, 1-H_b), 2.30 and 2.60 (AB system, 2H, *J*=15.0 Hz, CH_2-12), 2.68 (s, 1H, 9-H), 3.62 (br s, 1H, 7-H), 3.69 (s, 3H, OCH_3), 3.95–4.10 (m, 2H, CH_2-15), 6.75–6.80 (m, 4H, Ar–Hs); ^{13}C NMR (50.3 MHz, APT, HMQC, HMBC) δ 15.36 (C-20, −), 18.43 (C-2, +), 21.65 (C-19, −), 24.84 (C-6, +), 25.74 (C-17, −), 29.70 (C-16, −), 32.78 (C-4, +), 33.29 (C-18, −) 36.75 (C-10, +), 38.73 (C-1, +), 42.03 (C-3, +), 44.06 (C-14, +), 46.36 (C-5, −), 52.78 (C-12, +); 55.85 (OCH_3, −), 62.93 (C-9, −), 64.74 (C-15, +), 72.96 (C-7, −), 77.45 (C-13, +), 80.62 (C-8, +), 114.81, 115.62 (CH–Ar, −), 152.66, 154.15 (C_q–Ar, +), 208.40 (C-11, +); $C_{27}H_{40}O_5$ (444.61, 444.2876), ESI HRMS: found 445.2950, calcd for $[M+H]^+$ 445,2954, found 467.2772, calcd for $[M+Na]^+$ 467,2773.

4.1.7. (7*R*,8*S*,13*S*)-8,13-Epoxy-7α,15-dihydroxy-labdan-11-one (13b). To a solution of **13a** (0.149 g, 0.335 mmol) in acetonitrile (4 mL) a solution of CAN (0.367 g, 0.670 mmol) in water (4 mL) was added over a period of 5 min. After 10 min the mixture was extracted with $CHCl_3$ (2×10 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by FC (petroleum ether–EtOAc 1:1) to give pure **13b** (oil, 0.101 g, 89%). $[\alpha]_D^{20}=-59$ (*c* 2.0, $CHCl_3$); IR (film): 3600–3300, 1704, 1184, 1072, 784, 759 cm^{-1}; ^1H NMR (300 MHz) δ 0.78, 0.84 (2s, CH_3-18, CH_3-19), 0.85–0.95 (m, 1H, 1-H_a), 1.07 (s, CH_3-20), 1.31, 1.33 (2 s, CH_3-16, CH_3-17), 1.10–1.95 (complex of overlapping multiplets), 2.23 and 2.64 (AB system, *J*=14.5 Hz, CH_2-12), 2.16–2.29 (m, 1-H_b), 2.80 (br s, 1H, 9-H), 3.30 (br s, probably 2×OH), 3.71 (m, $W_{1/2}$=6.9 Hz, 1H, 7-H), 3.82–3.95 (m, 2H, CH_2-15); ^{13}C NMR (75.4 MHz, ATP) δ 15.44 (C-20, −), 18.41 (C-2, +), 21.66 (C-19, −), 25.49 (C-6, +), 25.72 (C-17, −), 39.85 (C-16, −), 32.76 (C-4, +), 33.20 (C-18, −), 36.74 (C-10, +), 38.68 (C-1, +), 42.03 (C-3, +), 45.89 (C-14, +), 46.43 (C-5, −), 52.48 (C-12, +), 58.97 (C-15, +), 62.77 (C-9, −), 72.80 (C-7, −), 78.90 (C-13, +), 81.09 (C-8, +), 208.92 (C-11, +); $C_{20}H_{34}O_4$ (338.49, 338.2457), ESI MS: *m/z* 338.9 $[M+H]^+$, 361.0 $[M+Na]^+$.

4.1.8. (7*R*,8*S*,13*R*)-8,13-Epoxy-7-hydroxy-15-(*o*-nitrophenyl-selanyl)-labdan-11-one (13c). A solution of **13b** (12 mg, 0.0366 mmol) and *o*-nitrophenyl selenocyanate (10 mg, 0.0436 mmol) in THF (3 mL) was treated at rt under argon with tri-*n*-butylphosphine (10.7 μL, 0.0436 mmol). Progress of the reaction was monitored by TLC (EtOAc). After 15 min approximately one half of **13b** was consumed, during the next 3 h no changes were observed. Another 1.2 equiv. of *o*-nitrophenyl selenocyanate and 1.2 equiv. of tri-*n*-butylphosphine were added. After 30 min the reaction was complete (TLC). Quenching with ethanol (2 mL), solvent evaporation, and FC (petroleum ether–EtOAc 5:1)[31] provided **13c** (yellow solid, 18 mg, 94%). $[\alpha]_D^{20}=-6$ (*c* 1.4, $CHCl_3$); IR (film): 3600–3300, 1708, 1511, 1332, 1297, 1064, 730 cm^{-1}; ^1H NMR (600 MHz, H,H COSY, HMQC, HMQC) δ 0.73, 0.80 (2 s, 6H, CH_3-18, CH_3-19), 0.78–0.85 (m, 1H, 1-H_a), 1.03 (s, 3H, CH_3-20), 1.09–1.16 (m, 1H, 3-H_a), 1.28 (s, 3H, CH_3-17), 1.32 (s, 3H, CH_3-16), 1.31–1.41 (m, overlapping with s at 1.32, 2-H_a, 3-H_b), 1.38 (dd, 1H, $J_{5,6a}$=13.2 Hz, $J_{5,6b}$=2.6 Hz, 5-H), 1.47 (dt, 1H, $J_{6a,5}$=13.2 Hz, $J_{6a,6b}$=13.2 Hz, $J_{6a,7}$=2.3 Hz, 6-H_a), 1.58 (qt, 1H, *J*=13.6, 3.4 Hz, 2-H_b), 1.80 (dt, 1H, $J_{6b,6a}$=13.2 Hz, $J_{6b,5}$=2.6 Hz, $J_{6b,7}$=2.6 Hz, 6-H_b), 1.91–2.01 (m, 2H, CH_2-14), 2.10–2.15 (m, 1H, 1-H_b), 2.26, 2.51 (AB system, 2H, *J*=13.9 Hz, CH_2-12), 2.70 (s, 1H, 9-H), 2.87–2.97 (2 m, 2H, CH_2-15), 3,17 (br s, 1H, OH), 3.68 (t, 1H, *J*=2.6 Hz, 7-H), 7.27 (ddd, 1H, *J*=8.3, 7.0, 1.3 Hz, Ar-H), 7.44 (dd, 1H, *J*=8.3, 1.3 Hz, Ar-H), 7.50 (ddd, 1H, *J*=8.3, 7.0, 1.3 Hz, Ar-H), 8.22 (dd, 1H, *J*=8.3 Hz, *J*=1.3 Hz, Ar-H); ^{13}C NMR (150.9 MHz, APT) δ 15.39 (C-20, −), 18.42 (C-2, +), 20.20 (C-15, +), 21.63 (C-19, −), 24.95 (C-6, +), 25.63 (C-17, −), 28.11 (C-16, −), 32.80 (C-4, +), 33.30 (C-18, −), 36.73 (C-10, +), 38.67 (C-1, +), 42.07 (C-3, +), 44.39 (C-14, +), 46.59 (C-5, −) 53.58 (C-12, +), 63.19 (C-9, −), 73.04 (C-7, −), 78.93 (C-13, +), 81.57 (C-8, +), 125.72 (−), 126.65 (−), 128.81 (−), 133.21 (+), 133.90 (−), 147.03 (+) (C–Ar), 207.96 (C-11, +); $C_{26}H_{37}NO_5^{80}Se$ (522.54, 523.1837), FAB MS: *m/z*=524.2 $[M+H]^+$, 546.2 $[M+Na]^+$.

4.1.9. (7*R*,8*S*,13*R*)-8,13-Epoxy-7-hydroxy-14-labden-11-one (14a). To a solution of selenide **13c** (1.95 g, 3.73 mmol) in THF (70 mL) was slowly added 50% aqueous hydrogen peroxide (2.04 mL) at 0°C. Stirring was maintained for 20 h at 20°C. Water (60 mL) was added. Standard work-up (extraction with petroleum ether) followed by FC (petroleum ether–EtOAc 5:1) afforded olefin **14a** (1.15 g, 97%). Mp 140–142°C (from petroleum ether); $[\alpha]_D^{20}=-113$ (*c* 3.0, $CHCl_3$); IR (KBr): 3531, 1708, 1457, 1388, 1213, 1174, 1068, 507 cm^{-1}; ^1H NMR (600 MHz, H,H COSY,

HMQC, HMBC) δ 0.79 (s, 3H, CH_3-19), 0.86 (s, 3H, CH_3-18), 0.89 (m, 1H, 1-H_a), 1.01 (s, 3H, CH_3-20), 1.18 (m, 1H, 3-H_a), 1.30 (s, 3H, CH_3-17), 1.33 (s, 3H, CH_3-16), 1.34–1.40 (m, 2H, 2-H_a, 3-H_b), 1.43–1.53 (m, 2H, 5-H, 6-H_b), 1.56–1.68 (m, 1H, 2-H_b), 1.82–1.91 (m, 1H, 6-H_a), 2.42 (ddd, 1H, $J_{1b,2a}$=1.7 Hz, $J_{1b,2b}$=4.8 Hz, $J_{1b,1a}$=13.1 Hz, 1-H_b), 2.55 and 2.71 (AB system, 1H, J=17.6 Hz, CH_2-12), 2.86 (s, 1H, 9-H), 3.67 (dd, 1H, $J_{7,6a}$=2.4 Hz, $J_{7,6b}$=3.5 Hz, 7-H), 5.04 (d, 1H, $J_{15b,14}$=17.5 Hz, 15-H_b), 5.05 (d, 1H, $J_{15a,14}$=10.8 Hz, 15-H_a) 5.88 (ddd, 1H, $J_{\text{long range}}$=0.7 Hz, $J_{14,15a}$=10.8 Hz, $J_{14,15b}$=17.5 Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 15.27 (C-20, −), 18.47 (C-2, +), 21.73 (C-19, −), 24.71 (C-6, +), 27.06 (C-17, −), 30.76 (C-16, −), 32.79 (C-4, +), 33.34 (C-18, −), 37.07 (C-10, +), 39.07 (C-1, +), 41.96 (C-3, +), 46.00 (C-5, −), 49.72 (C-12, +), 61.71 (C-9, −), 72.67 (C-7, −), 75.67 (C-13, +), 79.65 (C-8, +), 112.32 (C-15, +), 145.82 (C-14, −), 207.99 (C-11, +); $C_{20}H_{32}O_3$ (320.47, 320.2351), FAB MS: m/z=342.8 $[M+Na]^+$. Crystal data for $C_{20}H_{32}O_3$: space group $P2_1$, a=7.2382(11) Å, b=11.6093(17) Å, c=11.0671(16) Å, β=96.558(3)°. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 196904). Copies may be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@c.ck.cam.ac.uk).

4.1.10. (8*S*,13*R*)-8,13-Epoxy-14-labdene-7,11-dione (14b). A solution of olefin **14a** (0.75 mg, 2.34 mmol) in DMSO (30 mL) was added at 20°C to a stirred solution of IBX (1.31 mg, 4.68 mmol) in DMSO (20 mL). After 2 h water (50 mL) was added and the white precipitated was removed by filtration and washed carefully with water (2×10 mL), and CH_2Cl_2 (5×40 mL). Extraction of the water phase with CH_2Cl_2 (3×20 mL), combining of the CH_2Cl_2 solutions, solvent removal and FC (petroleum ether–$CHCl_3$–EtOAc 5:5:1) gave diketone **14b** (0.73 g, 99%). Mp 173–174°C (from petroleum ether); $[\alpha]_D^{20}$=−129 (c 2.0, $CHCl_3$); IR (KBr): 1722 cm^{-1}; ^{1}H NMR (400 MHz, H,H COSY, HMQC, HMBC) δ 0.72–0.76 (m, 1H, 1-H_a), 0.77 (s, 3H, CH_3-19), 0.79 (s, 3H, CH_3-18), 1.08 (dd, 1H, $J_{5,6a}$=3.2 Hz, $J_{5,6b}$=13.8 Hz, 5-H), 1.10–1.13 (m, 1H, 3-H_a), 1.18 (s, 3H, CH_3-20), 1.30 (s, 3H, CH_3-16), 1.34–1.41 (m, 2H, 2-H_a, 3-H_b), 1.38 (s, 3H, CH_3-17), 1.55–1.62 (m, 1H, 2-H_b), 2.40 (dd, 1H, $J_{6a,5}$=3.2 Hz, $J_{6a,6b}$=14.1 Hz, 6-H_a), 2.44–2.48 (m, 1H, 1-H_b), 2.47 (dd, 1H, $J_{6b,5}$=13.8 Hz, $J_{6b,6a}$=14.1 Hz, 6-H_b), 2.53 and 2.60 (AB system, 2H, J=18.7 Hz, CH_2-12), 2.99 (s, 1H, 9-H), 5.04 (dd, 1H, $J_{15a,15b}$=1.1 Hz, $J_{15a,14}$=10.9 Hz, 15-H_a), 5.21 (dd, 1H, $J_{15b,15a}$=1.1 Hz, $J_{15b,14}$=17.3 Hz, 15-H_b), 5.88 (dd, 1H, $J_{14,15a}$=10.9 Hz, $J_{14,15b}$=17.3 Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 15.08 (C-20, −), 18.07 (C-2, +), 21.09 (C-19, −), 26.88 (C-17, −), 31.70 (C-16, −), 32.90 (C-18, −), 33.75 (C-4, +), 36.19 (C-6, +), 37.19 (C-10, +), 39.20 (C-1, +), 41.40 (C-3, +), 49.70 (C-12, +), 54.89 (C-5, −), 66.14 (C-9, −), 75.24 (C-13, +), 81.40 (C-8, +), 113.96 (C-15, +), 145.65 (C-14, −), 205.28 (C-11, +), 207.85 (C-7, +); $C_{20}H_{30}O_3$ (318.46, 318.2195), FAB MS: m/z 319.2 $[M+H]^+$.

4.1.11. (7*S*,8*S*,13*R*)-8,13-Epoxy-7-hydroxy-14-labden-11-one (14c). A solution of $NaBH_4$ (6.3 mg, 0.167 mmol) in ethanol (0.8 mL) was added to a cooled (0°C) solution of diketone **14b** (106.0 mg, 0.333 mmol) in ethanol (10 mL). The mixture was stirred for 15 min and after addition of water (0.2 mL) for another 30 min. Solvent evaporation and FC (petroleum ether–$CHCl_3$–EtOAc 5:5:2) furnished **14a** (12.1 mg, 11%) and **14c** (93.6 mg, 88%). Mp 86–88°C (from petroleum ether); $[\alpha]_D^{20}$=−106 (c 2.0, $CHCl_3$); IR (KBr): 3469, 1714, 1388, 1178, 1072 cm^{-1}; ^{1}H NMR (600 MHz, H,H COSY, HMQC, HMBC) δ 0.75–0.79 (m, 1H, 1-H_a), 0.81 (s, 3H, CH_3-19), 0.87 (s, 3H, CH_3-18), 0.91 (dd, 1H, $J_{5,6a}$=2.1 Hz, $J_{5,6b}$=12.5 Hz, 5-H), 1.01 (s, 3H, CH_3-20), 1.06–1.16 (m, 1H, 3-H_a), 1.28/1.29 (2s, 6H, CH_3-16, CH_3-17), 1.29 (m mostly hidden by the 1.28/1.29 singlets, 1H, 6-H_b), 1.36–1.40 (m, 2H, 2-H_a, 3-H_b), 1.59–1.67 (m, 1H, 2-H_b), 1.84 (ddd, 1H, $J_{6a,5}$=2.1 Hz, $J_{6a,7}$=4.2 Hz, $J_{6a,6b}$=13.1 Hz, 6-H_a), 2.22 (br s, 1H, OH), 2.41–2.45 (m, 1H, 1-H_b), 2.51 (s, 1H, 9-H), 2.56 and 2.62 (AB system, 2H, J=17.8 Hz, CH_2-12), 3.83 (dd, 1H, $J_{7,6a}$=4.2 Hz, $J_{7,6b}$=11.5 Hz, 7-H), 5.04 (dd, 1H, $J_{15a,15b}$=1.1 Hz, $J_{15a,14}$=10.5 Hz, 15-H_a) and 5.19 (dd, 1H, $J_{15b,15a}$=1.1 Hz, $J_{15b,14}$=17.3 Hz, 15-H_b), 5.93 (dd, 1H, $J_{14,15a}$=10.5 Hz, $J_{14,15b}$=17.3 Hz, 14-H); ^{13}C NMR (150.9 MHz, APT, HMQC, HMBC) δ 15.75 (C-20, −), 18.41 (C-2, +), 21.79 (C-19, −), 22.24 (C-17, −), 26.80 (C-6, +), 31.31 (C-16, −), 33.33 (C-4, +), 33.67 (C-18, −), 37.68 (C-10, +), 39.28 (C-1, +), 41.82 (C-3, +), 50.22 (C-12, +), 53.28 (C-5, −), 65.44 (C-9, −), 75.43 (C-13, +), 80.52 (C-8, +), 80.79 (C-7, −), 112.35 (C-15, +), 146.58 (C-14, −), 206.71 (C-11, +); $C_{20}H_{32}O_3$ (320.47, 320.2351), FAB MS: m/z 343.1 $[M+Na]^+$.

4.1.12. (7*S*,8*S*,13*R*)-7-Acetoxy-8,13-epoxy-14-labden-11-one (14d). Acetic anhydride (54.0 μL) was added to a solution of 7β-hydroxy compound **14c** (61.0 mg, 0.190 mmol), anhydrous pyridine (0.5 mL) and a catalytic amount of DMAP in CH_2Cl_2 (6 mL) and the reaction mixture was stirred for 2 h. Stirring was maintained for 30 min after addition of water (2 mL). Standard work-up (10% aqueous HCl, water, dichloromethane) and purification by FC (petroleum ether–$CHCl_3$–EtOAc 5:5:1) gave 7β-acetoxy derivative **14d** (67.8 mg, 98%). Mp 127–128°C (from petroleum ether); $[\alpha]_D^{20}$=−122 (c 2.0, $CHCl_3$); IR (KBr): 1732, 1392, 1243, 1034 cm^{-1}; ^{1}H NMR (600 MHz, HMQC, HMBC) δ 0.75–0.78 (m, 1H, 1-H_a), 0.79 (s, 3H, CH_3-19), 0.86 (s, 3H, CH_3-18), 0.97 (dd, 1H, $J_{5,6a}$=2.1 Hz, $J_{5,6b}$=13.1 Hz, 5-H), 1.04 (s, 3H, CH_3-20), 1.11–1.16 (m, 1H, 3-H_a), 1.21 (s, 3H, CH_3-16), 1.30 (s, 3H, CH_3-17), 1.32–1.40 (m, 3H, 2-H_a, 3-H_b, 6-H_b), 1.57–1.66 (m, 1H, 2-H_b), 1.82 (ddd, 1H, $J_{6a,5}$=2.1 Hz, $J_{6a,7}$=4.7 Hz, $J_{6a,6b}$=13.1 Hz, 6-H_a), 2.09 (s, 3H, CH_3CO), 2.39–2.43 (m, 1H, 1-H_b), 2.50 and 2.61 (AB system, 2H, J=18.3 Hz, CH_2-12), 2.67 (s, 1H, 9-H), 5.05 (dd, 1H, $J_{15a,15b}$=1.0 Hz, $J_{15a,14}$=10.6 Hz, 15-H_a), 5.08 (dd, 1H, $J_{7,6a}$=4.7 Hz, $J_{7,6b}$=12.0 Hz, 7-H), 5.27 (d, 1H $J_{15a,15b}$=1.0 Hz, $J_{15b,14}$=17.2 Hz, 15-H_b), 5.93 (dd, 1H, $J_{14,15a}$=10.6 Hz, $J_{14,15b}$=17.2 Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 15.70 (C-20, −), 18.36 (C-2, +), 21.52 (CH_3CO, −), 21.72 (C-19, −), 23.11 (C-17, −), 25.71 (C-6, +), 31.52 (C-16, −), 33.33 (C-4, +), 33.48 (C-18, −), 37.23 (C-10, +), 39.14 (C-1, +), 41.73 (C-3, +), 50.37 (C-12, +), 53.02 (C-5, −), 65.60 (C-9, −), 75.23 (C-13, +), 78.77 (C-8, +), 81.08 (C-7, −), 112.77 (C-15, +), 146.39 (C-14, −), 170.55 (CH_3CO, +), 206.68 (C-11, +); $C_{22}H_{34}O_4$ (362.51, 362.2457), FAB MS: m/z 363.2 $[M+H]^+$. Crystal data for

$C_{22}H_{34}O_4$: space group $P2_12_12_1$, a=10.4750(3) Å, b=10.6194(2) Å, c=18.0635(5) Å. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 196906). Copies may be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@c.ck.cam.ac.uk).

4.2. Reduction with samarium diiodide

The reactions were performed under careful exclusion of oxygen (evacuation of the reaction flask and flushing with argon several times, sonication of solutions under argon).

Water as proton source. To a stirred solution of acetoxyketone **14d** (460.0 mg, 1.27 mmol) in THF (10 mL) and water (0.4 mL, 22.2 mmol) a freshly prepared 0.1 mol L^{-1} solution of SmI_2 in THF (38 mL, 3.81 mmol) was added and the reaction was stirred for 4 h. Then again water (0.4 mL) and SmI_2 solution (64 mL, 6.35 mmol) were added and stirring was maintained for another 4 h. The flask was exposed to air to quench the reaction. Standard work-up (5% HCl (20 mL), CH_2Cl_2 (100 mL), washing with $Na_2S_2O_3$ solution (20 mL)) and purification by FC (toluene–acetone 30:1) gave 11α-hydroxy compound **15a** (258.4 mg, 56%) and the 11β-isomer **15b** (202.1 mg, 42%).

Diethylene glycol as proton source. The reaction was performed as described above replacing water by diethylene glycol. Yields: 11α-hydroxy compound **15a** (oil, 90.9 mg, 58%) and the 11β-isomer **15b** (oil, 37.0 mg, 24%).

4.2.1. (7*S*,8*S*,11*R*,13*R*)-7-Acetoxy-8,13-epoxy-14-labden-11-ol (15a). $[\alpha]_D^{20}$=+9 (*c* 2.0, $CHCl_3$); IR (film): 3467, 1728, 1243, 1035 cm^{-1}; ^1H NMR (300 MHz, H,H COSY, HMQC, HMBC) δ 0.79 (s, 3H, CH_3-19), 0.87 (s, 6H, CH_3-18, CH_3-20), 1.04–1.12 (m, 2H, 1-H_a, 5-H), 1.14 (s, 3H, CH_3-16), 1.15–1.19 (m, 1H, 3-H_a), 1.29 (s, 3H, CH_3-17), 1.31–1.42 (m, 3H, 2-H_a, 3-H_b, 6-H_b), 1.45 (d, 1H, $J_{9,11}$=7.7 Hz, 9-H), 1.47–1.61 (m, 1H, 2-H_b), 1.68–1.74 (m, 1H, 1-H_b), 1.82 (ddd, 1H, $J_{6a,5}$=2.5 Hz, $J_{6a,7}$=4.9 Hz, $J_{6a,6b}$=12.9 Hz, 6-H_a), 1.92 (dd, 1H, $J_{12a,11}$=1.4 Hz, $J_{12a,12b}$=15.4 Hz, 12-H_a), 2.07 (s, 3H, CH_3CO), 2.29 (dd, 1H, $J_{12b,11}$=6.1 Hz, $J_{12b,12a}$=15.4 Hz, 12-H_b), 3.95 (ddd, 1H, $J_{11,12a}$=1.4 Hz, $J_{11,12b}$=6.1 Hz, $J_{11,9}$=7.7 Hz, 11-H), 4.95 (dd, 1H, $J_{7,6a}$=4.9 Hz, $J_{7,6b}$=11.8 Hz, H-7), 5.08 (dd, 1H, $J_{15a,15b}$=1.9 Hz, $J_{15a,14}$=10.4 Hz, 15-H_a), 5.46 (dd, 1H, $J_{15a,15b}$=1.9 Hz, $J_{15b,14}$=17.0 Hz, 15-H_b), 5.97 (dd, 1H, $J_{14,15a}$=10.4 Hz, $J_{14,15b}$=17.0 Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 16.28 (C-20, −), 18.42 (C-2, +), 21.52 (*C*H_3CO, −), 21.57 (C-19, −), 23.27 (C-17, −), 25.86 (C-6, +), 31.83 (C-16, −), 33.32 (C-4, +), 33.40 (C-18, −), 37.93 (C-10, +), 39.61 (C-1, +), 41.69 (C-3, +), 43.07 (C-12, +), 53.72 (C-5, −), 61.35 (C-9, −), 64.83 (C-11, −), 72.98 (C-13, +), 76.01 (C-8, +), 81.58 (C-7, −), 112.97 (C-15, +), 147.84 (C-14, −), 170.70 (CH_3*C*O, +); $C_{22}H_{33}O_4$ (364.53, 364.2614), ESI MS: *m*/*z* 365.2 $[M+H]^+$, 387.2 $[M+Na]^+$.

4.2.2. (7*S*,8*S*,11*S*,13*R*)-7-Acetoxy-8,13-epoxy-14-labden-11-ol (15b). $[\alpha]_D^{20}$=+33 (*c* 2.0, $CHCl_3$); IR (film): 3467, 2956, 1728, 1243, 1035 cm^{-1}; ^1H NMR (300 MHz, H,H COSY, HMQC, HMBC) δ 0.81 (s, 3H, CH_3-19), 0.84 (s, 3H, CH_3-18), 0.91–0.95 (m, 1H, 1-H_a), 1.00 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{5,6b}$=12.6 Hz, 5-H), 1.07–1.13 (m, 1H, 3-H_a), 1.18 (s, 3H, CH_3-20), 1.25 (d, 1H, $J_{9,11}$=3.6 Hz, 9-H), 1.36 (s, 3H, CH_3-16), 1.37–1.50 (m, 3H, 2-H_a, 3-H_b, 6-H_b), 1.62 (s, 3H, CH_3-17), 1.64–1.72 (m, 1H, 2-H_b), 1.75–1.84 (m, 2H, 1-H_b, 6-H_a), 1.85 (dd, 1H, $J_{12a,11}$= 5.0 Hz, $J_{12a,12b}$=14.3 Hz, 12-H_a), 1.97 (d, 1H, $J_{12b,11}$= 5.5 Hz, $J_{12b,12a}$=14.3 Hz, 12-H_b), 2.08 (s, 3H, CH_3CO), 4.48 (ddd, 1H, $J_{11,9}$=3.6 Hz, $J_{11,12a}$=5.0 Hz, $J_{11,12b}$= 5.5 Hz, 11-H), 4.88 (dd, 1H, *J*=6.1, 15.3 Hz, 7-H), 4.90 (dd, 1H, $J_{15a,15b}$=1.6 Hz, $J_{15a,14}$=10.7 Hz, 15-H_a), 5.17 (d, 1H, $J_{15a,15b}$=1.6 Hz, $J_{15b,14}$=17.3 Hz, 15-H_b), 5.84 (dd, 1H, $J_{14,15a}$=10.7 Hz, $J_{14,15b}$=17.3 Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 17.22 (C-20, −), 18.50 (C-2, +), 21.51 (*C*H_3CO, −), 21.60 (C-19, −), 22.40 (C-17, −), 26.08 (C-6, +), 30.09 (C-16, −), 33.32 (C-4, +), 33.51 (C-18, −), 37.79 (C-10, +), 38.97 (C-1, +), 41.84 (C-3, +), 44.31 (C-12, +), 54.43 (C-5, −), 55.05 (C-9, −), 65.42 (C-11, −), 72.20 (C-13, +), 76.41 (C-8, +), 82.12 (C-7, −), 110.32 (C-15, +), 147.53 (C-14, −), 170.90 (CH_3*C*O, +); $C_{22}H_3O_4$ (364.53, 364.2614), ESI MS: *m*/*z* 365.2 $[M+H]^+$, 387.2 $[M+Na]^+$.

4.2.3. (7*S*,8*S*,13*R*)-7-Acetoxy-8,13-epoxy-1-oximino-14-labden-11-ol (16a). Into a solution of **15a** (258 mg, 0.71 mmol) in dry CH_2Cl_2, (50 mL) and dry pyridine (0.5 mL) at −20°C NOCl was bubbled until the starting material was consumed (TLC control, petroleum ether–EtOAc 2:1). After work-up (extraction with CH_2Cl_2) the residue was dissolved in 100 mL of dry degassed benzene (5 mL), placed into a quartz tube, cooled to 0°C and irradiated at 350 nm under argon for 5 h. The solvent was evaporated and the product was purified by FC (petroleum ether–EtOAc, 2:1) to give **16a** (140 mg, 50%). Mp 218–219°C (from petroleum ether); $[\alpha]_D^{28}$=+64 (*c* 2.0, $CHCl_3$); IR (film): 3536, 3262, 3176, 1731, 1243, 1029, 968 cm^{-1}; ^1H NMR (600 MHz, H,H COSY, HMQC, HMBC) δ 0.93 (s, 3H, CH_3-18), 0.96 (s, 3H, CH_3-19), 1.19 (s, 3H, CH_3-16), 1.22 (s, 3H, CH_3-20), 1.39 (s, 3H, CH_3-17), 1.40–1.55 (m, 3H, H_a-3, 5-H, 6-H_b), 1.63 (dt, 1H, $J_{3b,2a,b}$=5.2 Hz, $J_{3a,3b}$=13.8 Hz, 3-H_b), 1.84 (ddd, 1H, $J_{6a,5}$=2.6 Hz, $J_{6a,7}$= 4.8 Hz, $J_{6a,6b}$=12.6 Hz, 6-H_a), 1.88 (dd, 1H, $J_{12a,11}$=3.1 Hz, $J_{12a,12b}$=15.4 Hz, 12-H_a), 2.06 (s, 3H, CH_3CO), 2.16 (d, 1H, $J_{9,11}$=7.3 Hz, 9-H), 2.24 (dd, 1H, $J_{12b,11}$=5.2 Hz, $J_{12b,12a}$=14.6 Hz, 12-H_b), 2.25–2.30 (m, 1H, 2-H_a), 3.11 (dt, 1H, $J_{2b,3a,b}$=5.2 Hz, $J_{2b,2a}$=15.2 Hz, 2-H_b), 4.17 (ddd, 1H, $J_{11,12a}$=3.1 Hz, $J_{11,12b}$=5.2 Hz, $J_{11,9}$=7.3 Hz, 11-H), 4.88 (dd, 1H, $J_{7,6a}$=4.8 Hz, $J_{7,6b}$=11.5 Hz, 7-H), 4.92 (dd, 1H, $J_{15a,15b}$=1.6 Hz, $J_{15a,14}$=10.5 Hz, 15-H_a), 5.27 (d, 1H $J_{15a,15b}$=1.6 Hz, $J_{15b,14}$=17.3 Hz, 15-H_b), 5.94 (dd, 1H, $J_{14,15a}$=10.5 Hz, $J_{14,15b}$=17.3 Hz, 14-H); ^{13}C NMR (50.3 MHz, APT, HMQC, HMBC) δ 16.85 (C-20, −), 18.90 (C-2, +), 21.46 (*C*H_3CO, −), 23.06 (C-17, C-19, −), 25.78 (C-6, +), 31.24 (C-16, −), 32.22 (C-18, −), 34.05 (C-4, +), 39.43 (C-3, +), 42.89 (C-12, +), 47.01 (C-10, +), 53.67 (C-5, −), 54.65 (C-9, −), 63.72 (C-11, −), 73.08 (C-13, +), 76.52 (C-8, +), 80.13 (C-7, −), 110.79 (C-15, +), 147.20 (C-14, −), 167,19 (C-1, +), 170.57 (CH_3*C*O, +); $C_{22}H_{35}NO_5$ (393.52, 393.2515), ESI MS: *m*/*z* 394.2 $[M+H]^+$, 416.2 $[M+Na]^+$.

4.2.4. (1*S*,7*S*,8*S*,11*R*,13*R*)-7-Acetoxy-1-Allyloxycarbonylamino-8,13-epoxy-14-labden-11-ol (16b). To a cooled

(0°C) solution of oxime **16a** (52 mg, 0.132 mmol) in methanol (10 mL) sodium cyanoborohydride (24.9 mg, 0.397 mmol) and ammonium acetate (122.3 mg, 1.587 mmol) were added under stirring. After 15 min, a 30% solution of $TiCl_3$ in 2 mol L^{-1} HCl (155 μL, 0.397 mmol) dissolved in water (155 μL) was dropped within 1 h into the above mixture at 0°C and the resulting mixture was stirred for 15 h allowing the temperature to rise to rt. Then, the mixture was cooled to 0°C and quenched by addition of brine (30 mL). Work-up (extraction with EtOAc (5×20 mL), water (1×20 mL)) gave a crude product which was used without further purification. It was dissolved in a 2:1 mixture of dioxane and water (12 mL). $NaHCO_3$ (133.3 mg, 1.587 mmol) was added. After cooling the mixture to 0°C allyl chloroformate (42.3 μL, 0.397 mmol) was added dropwise with stirring. After 7 h, a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) were added. Work-up (extraction with diethyl ether, 5×20 mL) followed by FC, petroleum ether–EtOAc 3:1) gave **16b** (47.3 mg, 77%). Mp 129–130°C (from toluene); $[\alpha]_D^{24}=+14$ (*c* 2.0, $CHCl_3$); IR (KBr): 3446 (broad), 1699, 1543, 1253, 1037 cm^{-1}; ^1H NMR (600 MHz, H,H COSY, HMQC, HMBC) δ 0.89 (s, 3H, CH_3-19), 0.92 (s, 3H, CH_3-18), 1.17 (s, 3H, CH_3-20), 1.23 (dd, 1H, $J_{5,6a}=2.6$ Hz, $J_{5,6b}=12.5$ Hz, 5-H), 1.26 (s, 3H, CH_3-16), 1.28–1.37 (m, 2H, CH_2-3), 1.40 (s, 3H, CH_3-17), 1.41–1.45 (m, 2H, 2-H_a, 6-H_b), 1.48–1.55 (m, 2H, 9-H, 12-H_a), 1.84 (ddd, 1H, $J_{6a,5}=2.6$ Hz, $J_{6a,7}=4.2$ Hz, $J_{6a,6b}=13.1$ Hz, 6-H_a), 2.05 (s, 3H, CH_3CO), 2.07–2.15 (m, 1H, 2-H_b, 12-H_b), 4.20 (dt, *J*=4.2, 9.9 Hz, 1H, 11-H), 4.40–4.45 (m with $J_{1,NH}=10.2$ Hz, 1H, 1-H), 4.51 (ddt, 1H, $J_{1'a,3'Z,E}=1.6$ Hz, $J_{1'a,2'}=5.7$ Hz, $J_{1'a,1'b}=13.1$ Hz, 1′-H_a), 4.60 (ddt, 1H, $J_{1'b,3'Z,E}=1.6$ Hz, $J_{1'b,2'}=5.7$ Hz, $J_{1'b,1'a}=13.1$ Hz, 1′-H_b), 4.80 (dd, 1H, $J_{7,6a}=4.2$ Hz, $J_{7,6b}=12.0$ Hz, 7-H), 4.83 (dd, 1H, $J_{15a,15b}=1.1$ Hz, $J_{15a,14}=11.0$ Hz, 15-H_a), 5.11 (dd, 1H $J_{15a,15b}=1.1$ Hz, $J_{15b,14}=17.2$ Hz, 15-H_b), 5.21 (m with $J_{NH,1}=10.2$ Hz, 1H, NH), 5.24 (ddt, 1H, $J_{3'E,1'}=1.6$ Hz, $J_{3'E,3'Z}=1.6$ Hz, $J_{3'E,2'}=10.5$ Hz, 3′-H_E), 5.33 (ddt, 1H, *J*=$J_{3'Z,1'}=1.6$ Hz, $J_{3'Z,3'E}=1.6$ Hz, $J_{3'Z,2'}=17.2$ Hz, 3′-H_Z), 5.77 (dd, 1H, $J_{14,15a}=11.0$ Hz, $J_{14,15b}=17.2$ Hz, 14-H), 5.92 (ddt, 1H, $J_{2',1'}=5.7$ Hz, $J_{2',3'E}=10.5$ Hz, $J_{2',3'Z}=17.2$ Hz, 2′-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 16.07 (C-20, −), 20.55 (C-17, −), 21.49 (*C*H_3CO, −), 22.32 (C-19, −), 23.66 (C-2, +), 25.08 (C-6, +), 29.39 (C-16, −), 33.58 (C-4, +), 34.01 (C-18, −), 35.01 (C-3, +), 41.74 (C-10, +), 46.30 (C-5, −), 48.32 (C-12, +), 53.95 (C-1, −), 54.84 (C-9, −), 65.14 (C-11, −), 66.25 (C-1′, +), 75.03 (C-13, +), 78.98 (C-8, +), 80.53 (C-7, −), 110.00 (C-15, +), 118.54 (C-3′, +), 132.56 (C-2′, −), 147.27 (C-14, −), 157.25 (NCO, +), 170.69 (CH_3*C*O, +); $C_{26}H_{41}NO_6$ (463.61, 463.2934), ESI HRMS: found 464.3005, calcd for $[M+H]^+$ 464.3007, found 927.5927, calcd for $[2M+H]^+$ 927.5940. Crystal data for $C_{26}H_{41}NO_6$: space group $P2_12_12_1$, a=14.3787(8) Å, b=17.4107(10) Å, c=20.9292(12) Å. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 196905). Copies may be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@c.ck.cam.ac.uk).

4.2.5. (1*S*,7*S*,8*S*,13*R*)-7-Acetoxy-1-allyloxycarbonylamino-8,13-epoxy-14-labden-11-one (17). A solution of **16b** (106 mg, 0.229 mmol) in DMSO (6 mL) was added to a stirred solution of IBX (192 mg, 0.686 mmol) in DMSO (6 mL). After 10 h, the reaction mixture was cooled to 0°C and water (20 mL) was added. Extraction with diethyl ether, solvent evaporation and purification by FC (petroleum ether–EtOAc, 3:1) furnished 11-ketone **17** (104.7 mg, 99%). Mp 158–159°C (from petroleum ether); $[\alpha]_D^{23}=-64$ (*c* 2.0, $CHCl_3$); IR (KBr): 1724, 1240, 1041 cm^{-1}; ^1H NMR (300 MHz, H,H COSY, HMQC, HMBC) δ 0.83 (s, 3H, CH_3-19), 0.89 (s, 3H, CH_3-18), 1.05 (dd, 1H, $J_{5,6a}=2.3$ Hz, $J_{5,6b}=12.5$ Hz, 5-H), 1.19 (s, 6H, CH_3-16, CH_3-20), 1.22–1.28 (m, 2H, CH_2-3), 1.30 (s, 3H, CH_3-17), 1.35–1.48 (m, 2H, 2-H_a, 6-H_b), 1.84 (ddd, 1H, $J_{6a,5}=2.3$ Hz, $J_{6a,7}=4.7$ Hz, $J_{6a,6b}=12.9$ Hz, 6-H_a), 2.01–2.08 (m, 1H, 2-H_b), 2.10 (s, 3H, CH_3CO), 2.46 and 2.67 (AB system, 2H, *J*=18.1 Hz, CH_2-12), 3.20 (br s, 1H, 9-H), 4.41 (dt, 1H, $J_{1,2}=3.0$ Hz, $J_{1,NH}=10.4$ Hz, 1-H), 4.48 (m, 2H, CH_2-1′), 4.87 (d, 1H, $J_{NH,1}=10.4$ Hz, NH), 4.99 (dd, 1H, $J_{7,6a}=4.7$ Hz, $J_{7,6b}=11.8$ Hz, 7-H), 5.01 (br d, 1H, $J_{15a,14}=11.0$ Hz, 15-H_a), 5.18 (br d, 1H, $J_{15b,14}=17.6$ Hz, 15-H_b), 5.17–5.23 (m, 1H, 3′-H_E), 5.25–5.33 (m, 1H, 3′-H_Z), 5.82–5.92 (m, 1H, 2′-H), 5.95 (dd, 1H, $J_{14,15a}=11.0$ Hz, $J_{14,15b}=17.6$ Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 16.85 (C-20, −), 21.47 (*C*H_3CO, −), 21.84 (C-19, −), 22.97 (C-17, −), 23.26 (C-2, +), 25.48 (C-6, +), 31.48 (C-16, −), 33.16 (C-4, +), 33.44 (C-18, −), 35.13 (C-3, +), 39.96 (C-10, +), 46.59 (C-5, −), 49.62 (C-12, +), 51.98 (C-1, −), 58.20 (C-9, −), 65.67 (C-1′, +), 75.38 (C-13, +), 78.87 (C-8, +), 80.46 (C-7, −), 112.25 (C-15, +), 118.10 (C-3′, +), 132.94 (C-2′, −), 146.47 (C-14, −), 155.50 (NCO, +), 170.63 (CH_3*C*O, +), 205.34 (C-11, +); $C_{26}H_{39}NO_6$ (461.60, 461.2778), ESI HRMS: found 462.2851, calcd for $[M+H]^+$ 462.2850, found 923.5622, calcd for $[2M+H]^+$ 923.5627.

4.2.6. (1*S*,7*S*,8*S*,13*R*)-7-Acetoxy-1-amino-8,13-epoxy-14-labden-11-one (1α-amino-1,6,9-trideoxy-forskolin) (1c). Morpholine (95 μL, 1.084 mmol) was added to a solution of **17** (100 mg, 0.217 mmol) in THF (5 mL). The reaction flask was several times evacuated and flushed with argon. Then a catalytic amount of $Pd(PPh_3)_4$ was added under a stream of argon. After 30 min, TLC showed the complete consumption of the starting material. The solvent and traces of morpholine were carefully evaporated. The residue was dissolved in diethyl ether (20 mL), the solution washed with sat. aq. $NaHCO_3$ (5 mL), dried, filtered and concentrated. Purification by FC (LiChroprep® RP-18, Merck, methanol–water, 5:1) gave amino compound **1c** (amorphous solid, 76 mg, 93%). $[\alpha]_D^{22}=-83$ (*c* 1.5, CH_2Cl_2); IR (film): 3500–3100, 1735, 1637, 1386, 1240, 1035 cm^{-1}; ^1H NMR (400 MHz, H,H COSY, HMQC, HMBC) δ 0.73 (s, 3H, CH_3-19), 0.81 (s, 3H, CH_3-18), 0.97 (s, 3H, CH_3-20), 1.04–1.10 (m, 1H, 3-H_a), 1.15 (s, 3H, CH_3-16), 1.23–1.35 (m, 6H, 2-H_a, 5-H, 6-H_a, with CH_3-17 at 1.26), 1.37–1.49 (m, 1H, 3-H_b), 1.71–1.77 (m, 1H, 6-H_b), 1.98 (s, 3H, CH_3CO), 2.00–2.08 (m, 1H, 2-H_b), 2.44 and 2.58 (AB system, 1H, *J*=17.7 Hz, CH_2-12), 3.27 (br s, 1H, 9-H), 3.44 (m, 1H, 1-H), 4.92 (dd, 1H, $J_{7,6a}=4.6$ Hz, $J_{7,6b}=11.3$ Hz, 7-H), 4.96 (dd, 1H, $J_{15a,15b}=1.1$ Hz, $J_{15a,14}=10.7$ Hz, 15-H_a), 5.18 (dd, 1H, $J_{15b,15a}=1.1$ Hz, $J_{15b,14}=17.3$ Hz, 15-H_b), 5.89 (dd, 1H, $J_{14,15a}=10.7$ Hz, $J_{14,15b}=17.3$ Hz, 14-H); ^{13}C NMR (75.4 MHz, APT, HMQC, HMBC) δ 16.51 (C-20, −), 20.25 (*C*H_3CO, −), 20.32 (C-19, −), 22.35 (C-17, −), 24.53 (C-6, +), 25.14 (C-2, +), 30.15 (C-16, −), 32.10 (C-18, −), 32.31 (C-4, +), 33.47 (C-3, +), 40.45 (C-10, +), 43.74 (C-5, −), 49.15 (C-12, +), 50.34 (C-1, −), 58.57 (C-9, −), 74.18

(C-13, +), 78.11 (C-8, +), 79.79 (C-7, −), 111.29 (C-15, +), 145.53 (C-14, −), 169.35 (CH_3CO, +), 206.45 (C-11, +); $C_{22}H_{35}NO_4$ (377.52, 377.2566) ESI HRMS: found 378.2643, calcd for $[M+H]^+$ 378.2639, found 755.5161, calcd for $[2M+H]^+$ 755.5198.

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