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Hydroxyacyl Derivatives of Forskolin—their Positive Inotropic Activity

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Abstract—Using appropriate protection and deprotection sequence novel hydroxyacyl chains of the type $CO(CH_2)_nOH$ are synthesized and are utilized to develop new analogues of forskolin. Several compounds showed good positive inotropic activity. Compound **12** is almost 10 times more active than forskolin ($EC_{50} = 0.002\,\mu g/ml$).].

Introduction

Forskolin, a polyhydroxylated labdane diterpenoid was isolated from *Coleus forskolii*.[1] It exhibited interesting biological properties such as positive inotropic, antihypertensive, lowering of intraoccular pressure and adenylate cyclase activator activities.[2] Our involvement on forskolin was to improve its positive inotropic activity.

Earlier observation on forskolin derivatization indicated following SAR status: (a) importance of free 1α-OH and 9α-OH groups,[3] (b) replacement of 7β-acetyl group by various other amino acyl chains lead to water soluble derivatives without loss of activity,[4] (c) substitution of acyl group at 6β-position which is achieved through the migration of 7β-acyl group to 6β position in both alkaline as well as acidic conditions,[5,6] not only retains but, in several cases, enhances the activity of forskolin molecule.[4]

In order to improve the positive inotropic activity of forskolin molecule we were looking for acyl 'spacer' which are novel and also wanted to exploit the chemical modification at 6β position through 7β to 6β acyl migration step. Direct modification at 6β position was rather difficult due to steric hindrance. It was decided to modify the acetyl group of forskolin to hydroxyacyl functionality of the type $CO(CH_2)_nOH$, in which the hydroxyl group was incorporated in the terminal position with a varying chain length. The main assumption was that when this group was attached at the 7β position it may retain or enhance the activity of forskolin, and further allow subsequent derivatization in a regioselective manner due to the presence of a more reactive primary OH group. Secondly, when migrated to 6β position, it could act as a new 'spacer' for subsequent modification at 6β.

This paper reports the chemistry and SAR on the introduction of a number of novel hydroxyacyl chain in the forskolin molecule.

Results and Discussion

Chemistry

Our initial task was to devise a synthetic route for OH-protected acid chain in such a fashion that when required the deprotection could be achieved under mild condition without disturbing 7β-acetyl group. Thus we chose *p*-methoxybenzyl group for OH protection which could be removed by mild treatment with DDQ without disturbing acyl function as reported in the literature.[7]

Key words: Forskolin; 2-hydroxyacetyl; positive inotropic activity.
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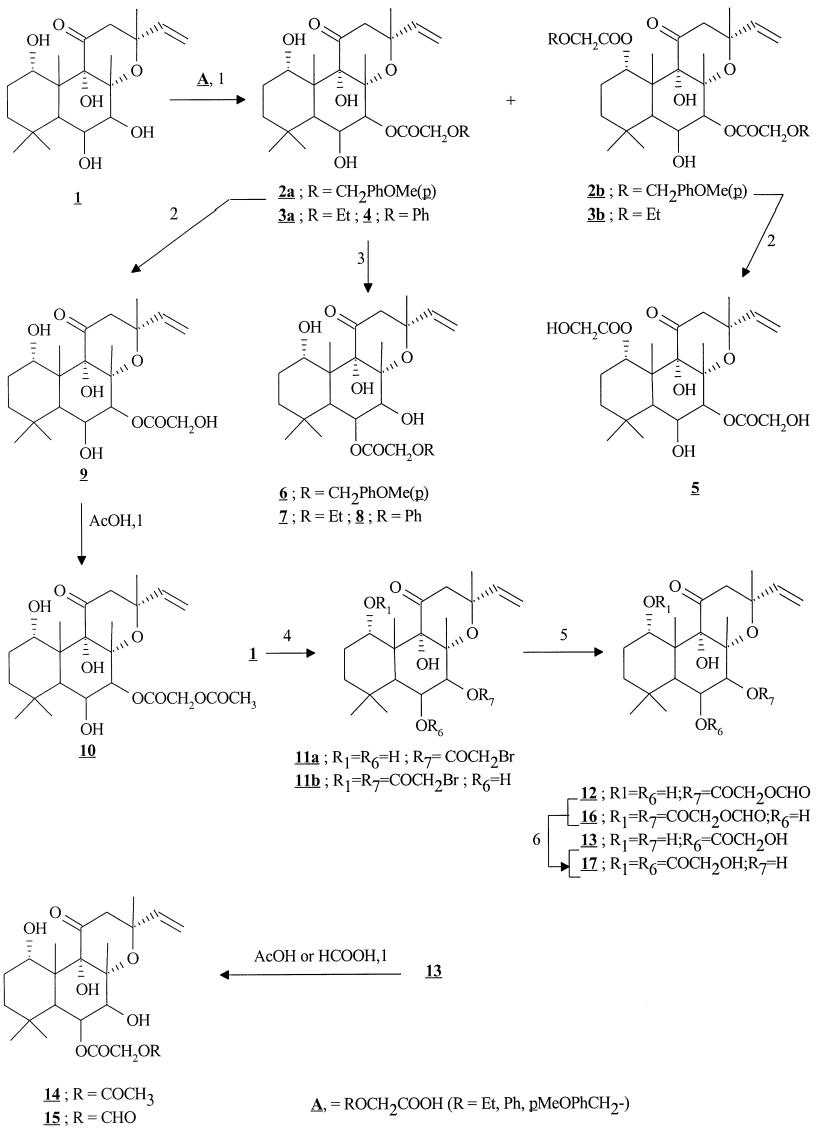
Hence the required *p*-methoxybenzyloxyacetic acid was prepared by reacting ethyl bromoacetate with *p*-methoxybenzyl alcohol in presence of NaH followed by alkaline hydrolysis (see Experimental).

7-Deacetyl forskolin (**1**)[1,5b] was reacted with *p*-methoxybenzyloxy acetic acid in presence of DCC–DMAP to give 7β-acyl substituted product **2a** with a small amount of diacyl substituted product **2b**. When **2a** was treated with diluted NaOH in acetonitrile (pH∼8.5) 6β-acyl derivative **6** was obtained in 42% yield. During the migration reaction, partial hydrolysis of acyl chain also occurred. The *p*-methoxybenzyl group was removed from **2a**, **2b** and **6** by treatment with DDQ in a dichloromethane–water system[7] to obtain compounds **9**, **5** and **13**, respectively. Thus the above method enabled us to introduce hydroxyacetyl chain in the forskolin skeleton at 7β-, 6β-, and 1α,7β-positions corresponding to the compounds **9**, **13** and **5**. In a similar fashion ethoxy and phenoxy acetyl chains were introduced using the required acid as shown in Scheme 1.

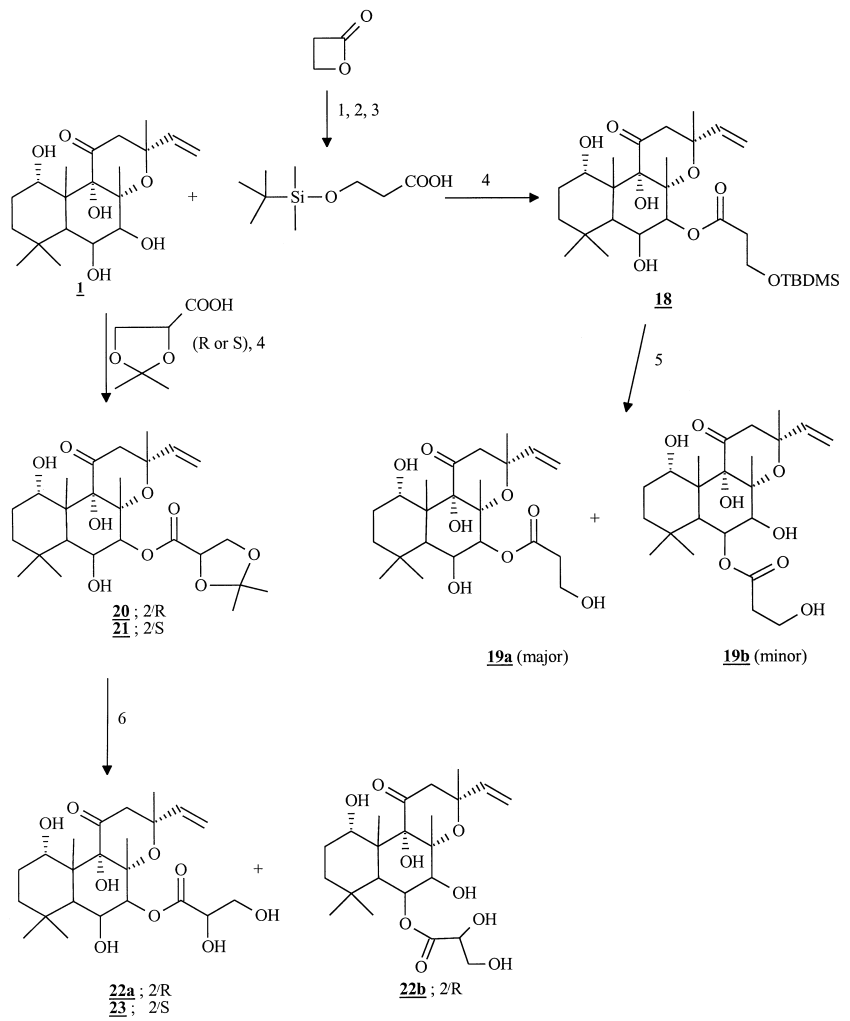
Another alternative approach to introduce hydroxyacetyl at the 7β-position was attempted as shown in Scheme 1. The compound **1** was treated with bromoacetyl bromide and pyridine in dichloromethane at 0 °C



Scheme 1. 1. DCC, DMAP, EtOAc; 2. DDQ, CH_2Cl_2, H_2O; 3. 1N NaOH, CH_3CN, H_2O; 4. $BrCH_2COBr$, pyridine, CH_2Cl_2, 0 °C; 5. Sodium formate, HMPA; 6. Neutral alumina, MeOH, CH_2Cl_2.

to obtain 7β-bromoacetyl **11a** and 1α,7β-dibromoacetyl **11b** derivatives, respectively, as reported earlier.[5b,8] When **11a** and **11b** were treated with sodium formate in HMPA[9] in separate reactions, the corresponding formate derivatives **12** and **16** were formed, which were purified by silica gel flash column chromatography. Subsequently these compounds were passed through neutral alumina[9] in order to generate 7β-hydroxyacetyl and 1α,7β-bis(hydroxyacetyl) derivatives. To our surprise, in both the cases the resultant hydroxyacetyl chain had migrated from 7β- to 6β-position exclusively, leading to the formation of 6β-hydroxyacetyl-7β-deacetyl forskolin (**13**) and 1α,6β-bis(hydroxyacetyl)-7β-deacetyl forskolin (**17**), respectively. This transformation clearly indicated that even neutral alumina was enough to effect the migration of the acyl group. Although it was not an intended result, however, it was found to be an excellent method to introduce hydroxyacetyl chain at 6β-position. Further derivatization of more reactive primary OH group of compounds **9** and **13** were demonstrated by converting them into acetyl and/or formyl derivatives **10**, **14** and **15** after a coupling reaction with acetic acid or formic acid in presence of DCC and DMAP (Scheme 1) in a regioselective manner.

The synthetic strategy for the introduction of β-hydroxypropanoyl chain is outlined in Scheme 2. The OH group of 3-hydroxypropionic acid was protected by *t*-butyldimethylsilyl (TBDMS) group. The required acid was prepared from propionolactone by a ring opening reaction with NaOMe under anhydrous condition followed by silylation in situ with TBDMS-Cl and imidazole.[10] The isolated ester was hydrolyzed with 1N NaOH in methanol to provide the required



Scheme 2. 1. NaOMe; 2. TBDMS-Cl, imidazole; 3. lN NaOH, MeOH; 4. DCC, DMAP, EtOAc; 5. 1M nBu$_4$N$^+$F$^-$, THF; 6. PTSA, MeOH.

TBDMS-protected hydroxypropionic acid chain which was used without further purification. The crude acid was reacted with **1** in presence of DCC and DMAP to yield 7β-(3-tertbutyldimethylsilyloxypropanoyloxy)-7β-deacetyl forskolin (**18**). The TBDMS-group from **18** was removed with the use of nBu$_4$N$^+$F$^-$ in THF [10] with the formation of 7β-(3-hydroxypropanoyloxy)-7β-deacetyl forskolin (**19a**) in ~50% yield, also 6β acyl migration product **19b** in 10% yield and a small amount of hydrolysis product **1** were also isolated.

Another novel chain, 2,3-dihydroxypropionic acid was introduced in its optically pure form. The corresponding optically pure *R*- and *S*-form of acetonide protected acids were prepared from mannitol[11,12] and L-ascorbic acid,[12,13] respectively, according to the reported procedure. These two acids were separately reacted with **1** by DCC-DMAP method as shown in Scheme 2 with the formation of compounds **20** and **21**, respectively. The deprotection of the acetonide was best achieved with the use of *p*-toluene sulfonic acid in methanol[14] leading to the formation of 7β-(*R*)-(2,3-dihydroxypropanoyloxy)-7β-deacetyl forskolin (**22a**), with a small amount of acyl migrated product **22b** from the starting material **20**. Similarly 7β-(*S*)-(2,3-dihydroxypropanoyloxy)-7β-deacetyl forskolin (**23**) was also prepared starting from **21**. While we had completed our synthesis of both *R*- and *S*-isomers, a paper appeared in the literature which described the synthesis and adenylate cyclase stimulating activity of *R*-isomer, however *S*-isomer was not reported in the publication.[15]

In order to introduce the hydroxyacetyl chain at the 1α-position, the *p*-methoxybenzyloxyacetic acid was reacted with forskolin as described earlier (Scheme 3) followed by deprotection of *p*-methoxybenzyl-group with DDQ-water in dichloro-methane. The required compound **25** was obtained in good yield.

We next targeted our attention to keep the 7β-acetyl group of forskolin intact and introduce hydroxyacetyl chain at 6β-position. To achieve our objective, we adopted the synthetic strategy as shown in Scheme 3. 1α-t-Butyldimethylsilyloxy-7β-deacetyl forskolin (**26**)[4] was converted into 1α-t-butyldimethylsilyloxy-7β-*p*-methoxybenzyloxy acetyl derivative **27** in high yield. The protected group was then migrated to 6β- position to obtain compound **28** in 60–70% yield after treating **27** with aqueous NaOH in acetonitrile (pH~8.5) for 30 min. The unreacted starting material and some amount of hydrolyzed product formed during the reaction could be recycled in the first step. The compound **28** was reacted with AcOH in presence of DCC and DMAP to give 1α-t-butyldimethylsilyloxy-6β-*p*-methoxybenzyloxy-acetylforskolin (**29**) in near quantitative yield. The *p*-methoxybenzyl-protecting group was removed by DDQ-water in dichloromethane,[7] to obtain 1α-t-butyldimethylsilyloxy-6β-hydroxy-acetylforskolin (**30**). The TBDMS-group from **30** was removed by nBu$_4$N$^+$F$^-$[10] in THF to obtain the required compound **31** in which the hydroxyacetyl chain was in 6β-position of forskolin. Further derivatization on primary hydroxy group at 6β-position was demonstrated by the reaction of **31** with AcOH and formic acid separately in presence of DCC and DMAP to obtain the corresponding acetyl (**32**) and formyl (**33**) derivatives, respectively, in excellent yield. None of the analogues were found to be soluble in water.

Biological activity

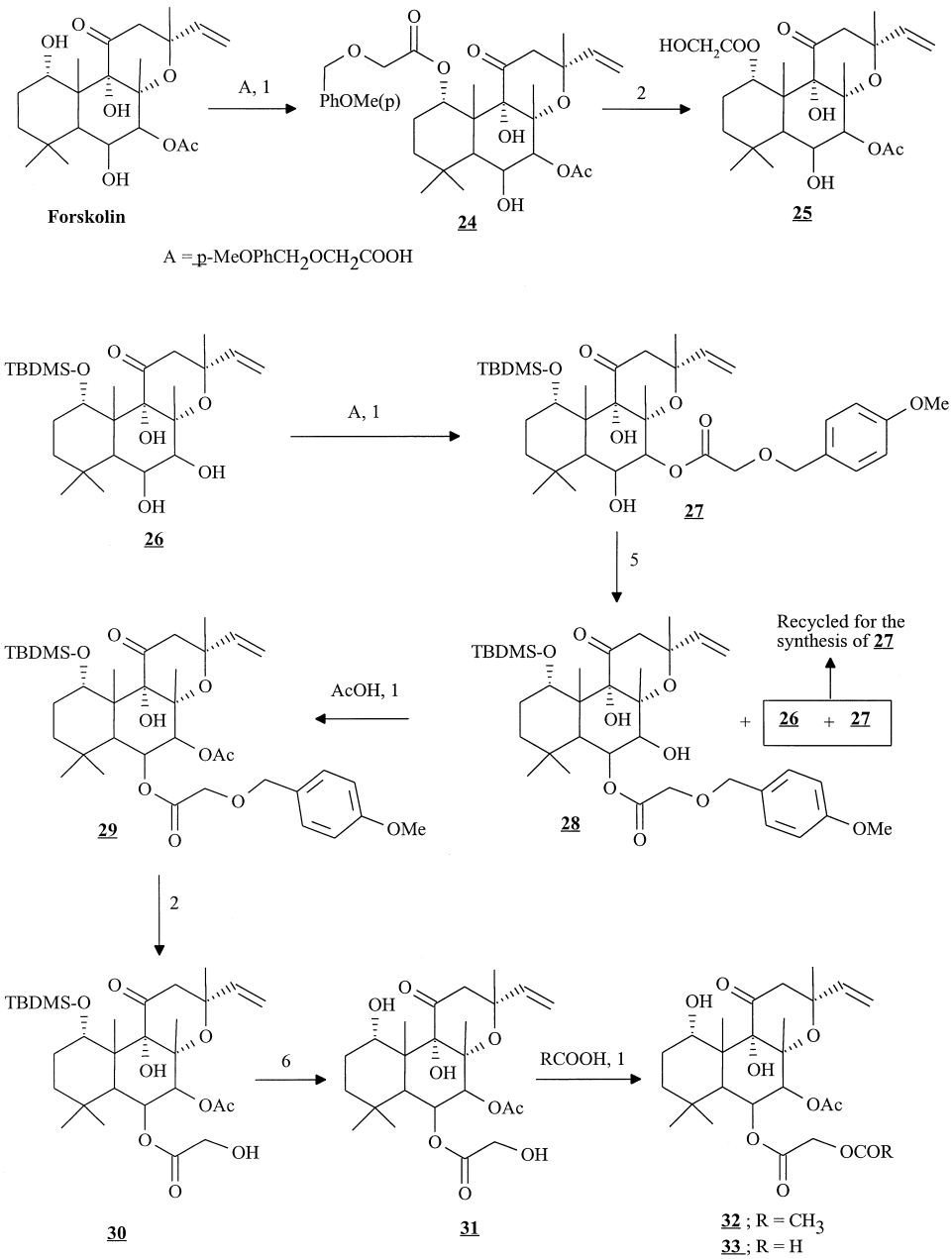
The blood pressure lowering activity of forskolin derivatives was evaluated by intravenous administration to anaesthetized normotensive cats. The positive inotropic activity of forskolin analogues was tested in spontaneously beating isolated guinea pig atrial preparation. The minimum concentration of the compound required to obtain an increase in the force of contraction by 50% (EC_{50}) was determined and compared with forskolin. The experimental details for the evaluation of biological activity could be found in an earlier publication.[16]

The results of blood pressure lowering activity and positive inotropic activity are summarized in Table 1. Some of the intermediates were also tested to obtain some SAR correlation.

All the compounds reported here failed to show better blood pressure lowering activity in comparison to forskolin. Particularly when the 1α-OH group was functionalized, complete loss of activity was observed in conformity with the earlier results by others.[3] Substitution of hydroxy acyl chain at 7β-position (viz. **9**, **19a**, **22a**, **23**) or at 6β-position (**13**, **31**) showed relatively better blood pressure lowering activity. Introduction of alkoxy acyl group at 7β- or 6β-positions (viz. **2a**, **3a**, **4**, **6**–**8**), 3-silyloxypropanoyl (**18**) and acetonide protected (*R*) or (*S*)-2,3-dihydroxypropanoyl (**20**, **21**) failed to show desired level of blood pressure lowering or positive inotropic activity. Incorporation of hydroxyacetyl chain at 7β-position (**9**), 6β-position (**13**) of deacetyl forskolin and substitution of hydroxy acetyl chain at 6β-position of forskolin (**31**) lead to improved positive inotropic activities, viz. $EC_{50} = 1.0\,\mu g/ml$, $0.72\,\mu g/ml$ and $EC_{50} = 0.16\,\mu g/ml$, respectively, However when the terminal OH-group in the chain of these compounds **9**, **13** and **31** were converted into formyl and/or acetyl derivatives such as **10**, **12**, **14**, **15**, **32** and **33** interesting positive inotropic activity resulted. Except two compounds **14** and **15**, the remaining four, showed significant increase in positive inotropic activity. While compound **32** ($EC_{50} = 0.16\,\mu g/ml$) was eight times less

active than forskolin (EC_{50} = 0.02 μg/ml), the remaining three compounds **10**, **12** and **33** were found to be 2.5-fold (EC_{50} = 0.008 μg/ml), 10-fold (EC_{50} = 0.002 μg/ml) and twofold (EC_{50} = 0.01 μg/ml) more active than forskolin, respectively.

The increase of chain length at 7β-position (**19a**) and at 6β-position (**19b**) lead to loss of activity. Introduction of (*R*)-2,3-dihydroxypropanoyl chain (i.e. additional OH group at 2-position which means additional polarity) further improved the positive inotropic activity (**22a**; EC_{50} = 0.065 μg/ml) when compared with hydroxyacetyl derivative (**9**; EC_{50} = 1.0 μg/ml) and 3-hydroxypropanoyl derivative (**19a**; inactive). On the other hand the incorporation of (*S*)-2,3-dihydroxypropanoyl chain at 7β-position (**23**) had less potency (EC_{50} = 0.22 μg/ml) and at 6β-position (**22b**), the compound did not show any activity.



Scheme 3. 1. DCC, DMAP, EtOAc; 2. DDQ, CH_2Cl_2, H_2O; 3. TBDMS-Cl, imidazole; 4. lN NaOH, MeOH; 5. 1N NaOH, CH_3CN, H_2O; 6. 1M $nBu_4N^+F^-$ in THF, THF.

Table 1. Biological activity of forskolin derivatives

Compound no.	EC_{50} (GP atrium) (μg/mL)	BP lowering activity (cat)*		
		Dose (iv) (mg/kg)	Fall in BP (mm of Hg)	Duration (in min)
2a	NA	10	30	> 90
2b	NA	10	30	10
3a	> 10	—	—	—
3b	NA	—	—	—
4	—	10	60	> 60
5	NA	10	20	60
6	3.7	—	—	—
7	3.7	—	—	—
8	NA	—	—	—
9	1.0	0.5	60	60
10	0.008	1.0	90	> 120
12	0.002	0.3	55	60
13	0.72	3.0	60	20
14	NA	—	—	—
15	1.0	—	—	—
16	Weak activity	—	—	—
17	NA	NA		
18	—	3.0	20	> 120
19a	NA	1.0	110	> 120
19b	> 30	3.0	100	> 120
20	0.14	0.1	40	60
22a	0.065	1.0	70	> 180
22b	> 30	10	90	180
23	0.22	0.3	60	50
25	NA	NA	—	—
30	NA	10	NA	NA
31	0.16	0.3	50	120
32	0.16	—	—	—
33	0.01	—	—	—
Forskolin	0.02	0.1	63.7 ± 5.5	55.0 ± 3.9

NA, not active; — not done.
*No significant effect below the dose mentioned.

Conclusion

We have achieved the target of introducing a 'spacer' hydroxyacetyl/acyl chain at different positions of forskolin skeleton such as 1α-position (**25**), 6β-position (**31**) of forskolin molecule and 6β-position (**13**), 7β-position (**9**), 1α,6β-positions (**17**), 1α,7β-positions (**5**) of deacetyl forskolin. Some of these derivatives, **9**, **13** and **31**, showed excellent regioselectivity towards acetylation/formylation reaction. We have shown that these groups can be used as a novel pharmacophore since their introduction in forskolin molecule selectively enhances the positive inotropic activity without affecting too much the blood pressure lowering activity. When the terminal OH group of these chains was substituted with acetyl/formyl group the positive inotropic activity increased sharply while alkyl substitution did not show desired activity.

In short, we have synthesized novel compounds with superior positive inotropic activity than parent forskolin molecule.

Experimental

General procedures

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were determined with a Perkin–Elmer 157 Spectrophotometer as KBr film unless otherwise mentioned. ^{1}H NMR spectra were recorded in $CDCl_3$ unless otherwise mentioned on a Jeol FT-90 Spectrometer with TMS as internal standard, chemical shift values were expressed in δ and coupling constant values are expressed in Hz. The four protons corresponding to 2α-H, 2β-H, 3α-H and 3β-H positions of forskolin appears at δ 1.43 (doublet of quartets), 2.17 (triplet of dd), 1.77 (triplet of doublets) and 1.10 (doublet of triplets), respectively, in 270 MHz ^{1}H NMR spectrum. However in routine 90 MHz ^{1}H NMR spectrum of forskolin and its derivatives, the signals of 2-H and 3-H are hidden under the strong methyl peaks and are not correctly recognized. Therefore we have not included the assignment of these peaks in the experimental section. Petroleum ether refers to the fraction of b.p. 60–80 °C. For flash column chromatography silica gel (finer than 0.08 mm particle size) was used. Precoated (silica gel 60 F_{254}) TLC plates were used for checking purity of compounds. Vaniline-50% orthophosphoric acid or anisaldehide-H_2SO_4 spray reagent were used and heated the plates at 110 °C for visualization. All compounds were homogeneous on TLC and gave proper spectral characteristics.

***p*-Methoxybenzyloxy acetic acid.** Sodium hydride (55–65% in oil; 20 g; ~0.5 mol) was washed with dry toluene (3×50 mL) and then suspended in dry dioxane (1000 mL). To this suspension *p*-methoxybenzyl alcohol (68 g; 0.5 mol) was slowly added (1 h) under stirring at room temperature. Stirring continued until the evolution of H_2 ceased. Ethyl bromoacetate (55 mL; 0.5 mol) was added dropwise at 0 °C (1 h). After the addition was over the reaction mixture was slowly brought to room temperature and stirring was continued for 16 h. The reaction mixture was diluted with EtOAc (1500 mL) and slowly poured over crushed ice (~2 kg) containing ammonium chloride (50 g). The ethyl acetate layer was separated and washed with brine. It was dried over anhydrous Na_2SO_4. Solvent was removed and the residue was dried in a vacuum pump for 3 h. The crude ester was dissolved in methanol (1500 mL) and 1N NaOH (500 mL; 0.5 mol) was added. The mixture was stirred for 1 h at room temperature. Methanol was removed under reduced pressure. The residue was diluted with water (500 mL) and was extracted with EtOAc (3×50 mL). The aqueous layer was acidified with dilute

HCl. The oily layer separated, was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. Solvent was removed. It was crystallized from light petroleum containing trace amount of EtOAc and kept in a freezer overnight. Yield: 68.6 g (70%); m.p. 54–56 °C; IR (KBr): 3500 (br), 1772, 1750, 1628, 1530 cm^{-1}; ^1H NMR (60 MHz): 3.74 (s, 3H, $OC\underline{H}_3$), 4.32 (s, 2H, $OC\underline{H}_2COOH$), 4.75 (s, 2H, $OC\underline{H}_2Ph$), 6.85 (d, 2H, $J=8.6$, Ar $\underline{H}_{3,5}$), 7.35 (d, 2H, $J=8.6$, Ar$\underline{H}_{2,6}$), 9.75 (br, 1H, $-COO\underline{H}$, exchangeable); Anal. calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.19; H, 6.10%.

8,13-Epoxy-7β-[(4-methoxybenzyloxy)acetoxy]-1α,6β,9α-trihydroxylabd-14-en-11-one (2a) and 1α,7β,-bis[(4-methoxybenzyloxy)acetoxy]-6β,9α-dihydroxy-8,13-epoxy labd-14-en-11-one (2b). Deacetyl forskolin **1** (7.36 g; 20 mmol) and DCC (5.15 g; 25 mmol) were dissolved in EtOAc (90 mL). A solution of *p*-methoxybenzyloxy acetic acid (4.31 g; 22 mmol) in EtOAc (10 mL) was added slowly followed by DMAP (2.4 g; 20 mmol). The mixture was stirred at room temperature for 3 h. DCU was filtered off. The filtrate was transferred into a separating funnel and washed successively with water and brine. The EtOAc layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with 2.5% CH_3CN–$CHCl_3$. Compound **2a** was eluted first, followed by the compound **2b**. **2a**. Yield: 10 g (91.4%); m.p. 96 °C (EtOAC–light petroleum). IR (KBr): 3470, 3310. 1762, 1740, 1715, 1613 cm^{-1}; ^1H NMR: 1.03, 1.24, 1.31, 1.43, 1.70 (5×s, 15H, 5×$C\underline{H}_3$), 2.18 (d, 1H, $J=2.54$, 5$\underline{H}$), 2.42 (d, 1H, $J_{gem}=17.21$, 12β$\underline{H}$), 3.18 (d, 1H, $J_{gem}=17.21$, 12α$\underline{H}$), 3.76 (s, 3H, $OC\underline{H}_3$), 4.11 (s, 2H, $COC\underline{H}_2O$-), 4.37–4.56 (m, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.57 (s, 2H, O-$C\underline{H}_2$-Ar), 4.93 (dd, 1H, $J_{cis}=10.18$, $J_{gem}=1.5$, 15$\underline{H}_{cis}$), 5.24 (dd, 1H, $J_{trans}=17.21$, $J_{gem}=1.5$, 15$\underline{H}_{trans}$), 5.53 (d, 1H, $J=4.05$, 7$\underline{H}$), 5.91 (dd, 1H, $J_{trans}=17.21$, $J_{cis}=10.18$, 14$\underline{H}$), 6.81 (d, 2H, $J=8.6$, Ar $\underline{H}_{3,5}$), 7.23 (d, 2H, $J=8.6$, Ar$\underline{H}_{2,6}$). Anal. calcd for $C_{30}H_{42}O_9$: C, 65.91; H, 7.75. Found: C, 65.71; H, 8.26%.

2b, Yield: 0.46 g (3.1%), oil; IR (neat): 3408, 2941, 1724, 1695, 1600 cm^{-1}. ^1H NMR: 1.03, 1.26, 1.30, 1.53, 1.70 (5×s, 15H, 5×$C\underline{H}_3$), 2.25 (d, $J=3.04$, 5$\underline{H}$), 2.36 (d, 1H, $J_{gem}=17.2$, 12β$\underline{H}$), 3.09 (d, 1H, $J_{gem}=17.2$, 12α$\underline{H}$), 3.79 (s, 6H, 2×$OC\underline{H}_3$), 3.91 (s, 2H, 1α-$OCOC\underline{H}_2$-), 4.14 (s, 2H, 7β-$OCOC\underline{H}_2$), 4.47–4.60 (m, 5H, 2×$C\underline{H}_2$-Ar + 6$\underline{H}$), 4.89 (dd, 1H, $J_{cis}=11.14$, $J_{gem}=1.6$, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, $J_{trans}=17.2$, $J_{gem}=1.6$, 15 $\underline{H}_{trans}$), 5.51 (br, 1H, 1$\underline{H}$), 5.62 (d, 1H, $J=4.0$, 7$\underline{H}$), 5.89 (dd, 1H, $J_{trans}=17.2$, $J_{cis}=11.14$, 14 $\underline{H}$), 6.64 (d, 4H, $J=8.1$, 2×Ar$\underline{H}_{3,5}$), 7.23, 7.25 (2×d, 4H, $J=8.1$, 2×Ar-$\underline{H}_{2,6}$). Anal. calcd for $C_{40}H_{52}O_{12}$: C, 66.28; H, 7.23. Found: C, 66.75; H, 7.42%.

Compounds **3a** and **3b** were prepared from **1** and ethoxy acetic acid by the same method and the products were purified by flash chromatography with 10% CH_3CN–$CHCl_3$.

8,13-Epoxy-7β-ethoxyacetoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (3a). Yield: 76.23%, m.p. 165–166 °C (EtOAc–light petroleum); IR (KBr): 3540, 3440 (br), 2950 (br), 1730 (br), 1710 cm^{-1}; ^1H NMR: 1.03, 1.24 (2×s, 6H, 2×$C\underline{H}_3$), 1.24 (t, 3H, $J=7.5$ $CH_2C\underline{H}_3$), 1.31, 1.43, 1.70 (3×s, 9H, 3×$C\underline{H}_3$), 2.19 (d, 1H, $J=2.54$, 5$\underline{H}$), 2.44 (d, 1H, $J_{gem}=17.2$, 12β$\underline{H}$), 2.87 (br, 1H, exchangeable O$\underline{H}$), 3.16 (d, 1H, $J_{gem}=17.21$, 12α$\underline{H}$), 3.60 (quartet, 2H, $J=7.5$, $C\underline{H}_2CH_3$), 4.13 (s, 2H, $COC\underline{H}_2OEt$), 4.40–4.57 (m, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.91 (dd, 1H, $J_{cis}=10.13$, $J_{gem}=1.6$, 15$\underline{H}_{cis}$), 5.21 (dd, 1H, $J_{trans}=17.2$, $J_{gem}=1.6$, 15$\underline{H}_{trans}$), 5.51 (d, 1H, $J=4.05$, 7$\underline{H}$), 5.90 (dd, 1H, $J_{trans}=17.2$ $J_{cis}=10.13$, 14$\underline{H}$). Anal. calcd for $C_{24}H_{38}O_8$: C, 63.41; H, 8.43. Found: C, 63.43; H, 8.33%.

1α,7β-Bis-ethoxyacetoxy-6β,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one (3b). Yield: 11%, m.p. 138 °C (EtOAc–light petroleum); IR (KBr): 3490, 2970, 2930, 1750 (br), 1720, 1670 (br) cm^{-1}; ^1H NMR: 1.04 (s, 3H, $C\underline{H}_3$), 1.12–1.33 (m, 14H, 2×$C\underline{H}_3$, 2×$CH_2C\underline{H}_3$,$C\underline{H}_2$), 1.52, 1.69 (2×s, 6H, 2×$C\underline{H}_3$), 2.26 (d, 1H, $J=2.6$, 5$\underline{H}$), 2.36 (d, 1H, $J_{gem}=16.2$, 12β$\underline{H}$), 3.08 (d, 1H, $J_{gem}=16.2$, 12α$\underline{H}$), 3.34–3.71 (m, 4H, 2×$C\underline{H}_2CH_3$), 3.93 (s, 2H, 1α-$OCOC\underline{H}_2OEt$), 4.14 (s, 2H, 7β-$OCOC\underline{H}_2OEt$), 4.47 (t, 1H, $J=3.54$, 6$\underline{H}$), 4.84 (dd, 1H, $J_{cis}=10$, $J_{gem}=1.62$. 15$\underline{H}_{cis}$), 5.15 (dd, 1H, $J_{trans}=17.2$, $J_{gem}=1.62$, 15 $\underline{H}_{trans}$), 5.46 (br, 1H, 1$\underline{H}$), 5.58 (d, 1H, $J=4.05$, 7$\underline{H}$), 5.87 (dd, 1H, $J_{trans}=17.2$, $J_{cis}=10$, 14$\underline{H}$). Anal. calcd for $C_{28}H_{45}O_{11}$: C, 62.13; H, 8.38. Found: C, 62.18; H, 8.18%.

8,13-Epoxy-7β-phenoxyacetoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (4). The compound **4** was also prepared by this method after reacting **1** with phenoxy acetic acid. The crude product obtained after workup was purified by flash chromatography with 10% $CH_3CN/CHCl_3$. Yield: 82.2%; m.p. 179 °C (EtOAc–light petroleum). IR (KBr): 3520 (br), 2950 (br), 1760, 1730, 1510, 1220 (br) cm^{-1}; ^1H NMR: 1.0, 1.20, 1.26, 1.39, 1.56 (5×s, 15H, 5×$C\underline{H}_3$), 2.15 (d, 1H, $J=2.54$, 5$\underline{H}$), 2.40 (d, 1H, $J_{gem}=17.2$, 12β$\underline{H}$), 3.16 (d, 1H, $J_{gem}=17.2$, 12 α$\underline{H}$), 4.33 (t, 1H, $J=3.04$, 6$\underline{H}$), 4.49 (br, 1H, 1$\underline{H}$), 4.71 (s, 2H, $OCOC\underline{H}_2O$), 4.91 (dd, 1H, $J_{cis}=10.1$, $J_{gem}=2.0$, 15 $\underline{H}_{cis}$) 5.21 (dd, 1H, $J_{trans}=17.2$, $J_{gem}=2.0$, 15$\underline{H}_{trans}$), 5.53 (d, 1H, $J=4.05$, 7$\underline{H}$), 5.89 (dd, 1H, $J_{trans}=17.2$, $J_{cis}=10.1$ 14$\underline{H}$), 6.80–7.30 (m, 5H, 5×Ph$\underline{H}$). Anal. calcd for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 67.22; H, 7.65%.

1α,7β-Bis-hydroxyacetyloxy-6β,9α-dihydroxy-8,13-epoxy-labd-14-en-11-one (5). Compound **2b** (2.0 g; 2.75 mmol) was dissolved in a heterogenous mixture of dichloromethane (144 mL) and water (8 mL). To this soln,

DDQ (2.27 g; 10 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was transferred into a separating funnel and shaken well with 5% aq sodium dithionate till the colour of organic layer became light pink. The dichloromethane layer was successfully washed with water and brine. It was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by flash chromatography with 20% $CH_3CN/CHCl_3$. Yield: 0.98 g (73.7%); m.p. 102–104 °C. IR (KBr): 3490 (br), 2950 (br), 1755, 1745 (br), 1715 cm^{-1}; ^1H NMR: 1.04, 1.27, 1.33, 1.52, 1.71 (5×s, 15H, 5×C$\underline{H}_3$), 2.21 (d, 1H, J = 2.54, 5$\underline{H}$), 2.45 (d, 1H, J = 17.2, 12β$\underline{H}$), 3.04 (d, 1H, J_{gem} = 17.2, 12α$\underline{H}$), 4.02 (s, 2H, 1α-OCOC$\underline{H}_2$OH), 4.23 (s, 2H, 7β-OCOC$\underline{H}_2$OH), 4.46 (t, 1H, J = 3.54, 6$\underline{H}$), 4.94 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.52, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.52, 15$\underline{H}_{trans}$), 5.45 (d, 1H, J = 4.05, 7$\underline{H}$), 5.60 (br, 1H, 1$\underline{H}$), 5.84 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13; 14$\underline{H}$). Anal. calcd for $C_{24}H_{36}O_{10}$,1/2 H_2O: C, 58.40; H, 7.56. Found: C,58.38; H, 7.95%.

8,13-Epoxy-6β-[(4-methoxybenzyloxy)acetoxy]-1α,7β,9α-trihydroxylabd-14-en-11-one (6). To a solution of compound **2a** (0.17 g; 1.3 mmol) in acetonitrile (26 mL) and water (32 mL), 1N NaOH (2.3 mL; 2.3 mmol) was added. The mixture was stirred for 20 min. Acetonitrile was removed under reduced pressure after neutralizing the reaction mixture with diluted HCl. The oil separated was extracted with ethyl acetate. The EtOAc layer was washed successively with water and brine. The solvent was removed after drying over anhydrous Na_2SO_4. The crude product thus obtained was purified by flash chromatography over silica gel with 5% CH_3CN–$CHCl_3$. Yield: 0.3 g (42.2%), oil; IR (neat): 3420 (br), 2950, 2870, 1710 (br) 1650 cm^{-1}; ^1H NMR: 0.97, 1.09, 1.37, 1.40, 1.56 (5×s, 15H, 5×C$\underline{H}_3$), 2.36 (d, 1H, J = 2.5, 5$\underline{H}$), 2.45 (d, 1H, J = 17.2, 12β$\underline{H}$), 3.19 (d, 1H, J_{gem} = 17.2, 12α$\underline{H}$), 3.79 (s, 3H, OC$\underline{H}_3$), 4.06 (s, 2H, OCOC$\underline{H}_2$-O), 4.29 (d, 1H, J = 4.05, 7$\underline{H}$), 4.56 (br, 1H, 1$\underline{H}$), 4.61 (s, 2H, OC$\underline{H}_2$Ph), 4.96 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.6, 15$\underline{H}_{cis}$), 5.14 (d, 1H, J_{trans} = 17.2, J_{gem} = 1.6, 15$\underline{H}_{trans}$), 5.91 (br, 1H, 6$\underline{H}$), 6.11 (dd, 1H, J_{trans} = 17.2, J_{cis} = 10.13, 14$\underline{H}$), 6.84 (d, 2H, J = 8.1, Ar-$\underline{H}_{3,5}$), 7.26 (d, 2H, J = 8.1 Ar-$\underline{H}_{2,6}$). Anal. calcd for $C_{30}H_{42}O_9$: C, 65.91; H, 7.45. Found: C, 66.02; H, 7.61%.

8,13-Epoxy-6β-ethoxyacetoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (7). This compound was prepared from **3a** according to the method described for the synthesis of **6**. The reaction time was 30 min and the crude product was purified by flash chromatography over silica gel with 10% $CH_3CN/CHCl_3$. Yield: 28.33% (semi solid); IR (KBr): 3470 (br), 3000, 2960, 1770, 1750, 1055 cm^{-1}; ^1H NMR: 0.97, 1.08 (2×s, 6H, 2×C$\underline{H}_3$), 1.22 (t, 3H, J = 7.09, $CH_2C\underline{H}_3$), 1.40, 1.41, 1.60 (3×s, 9H, 3×C$\underline{H}_3$), 2.33 (d, 1H, J = 2.5, 5$\underline{H}$), 2.48 (d, 1H, J_{gem} = 17.2, 12β$\underline{H}$), 3.17 (d, 1H, J_{gem} = 17.2, 12α$\underline{H}$), 3.56 (quartet, 2H, J = 7.09, C$\underline{H}_2$CH$_3$), 4.06 (s, 2H, COC$\underline{H}_2$-OEt), 4.25 (d, 1H, J = 4.56, 7$\underline{H}$), 4.95 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.1, 15$\underline{H}_{cis}$), 5.14 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.1, 15$\underline{H}_{trans}$), 5.89 (t, 1H, J = 2.54, 6$\underline{H}$), 6.80 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13, 14$\underline{H}$). Anal. calcd for $C_{24}H_{38}O_8$: C, 63.41; H, 8.42. Found: C, 63.64; H, 8.55%.

8,13-Epoxy-6β-phenoxyacetoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (8). The compound **8** was prepared as described for the synthesis of **6**. The reaction time was 20 min. After workup the crude product was purified by flash chromatography with 10% $CH_3CN/CHCl_3$. Yield: 32%; m.p. 180–182 °C (EtOAc-light petroleum); IR (KBr): 3490 (br), 2970, 1750, 1725, 1610, 1505 cm^{-1}; ^1H NMR: 0.96, 1.09, 1.36, 1.39, 1.53 (5×s, 15H, 5×C$\underline{H}_3$), 2.34 (d, 1H, J = 2.54, 5$\underline{H}$), 2.46 (d, 1H, J_{gem} = 17.2, 12β$\underline{H}$), 3.16 (d, 1H, J_{gem} = 17.2, 12α$\underline{H}$), 4.26 (d, 1H, J = 4.56, 7$\underline{H}$), 4.63 (br, 3H, 1$\underline{H}$ and COC$\underline{H}_2$OPh), 4.94 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.02, 15$\underline{H}_{cis}$), 5.12 (dd, 1H, J_{trans} = 17.21, J_{gem} 1.02, 15$\underline{H}_{trans}$), 5.94 (t, 1H, J = 2.54, 6$\underline{H}$), 6.06 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13, 14$\underline{H}$), 6.77–7.29 (m, 5H, 5×Ar$\underline{H}$). Anal. calcd for $C_{28}H_{38}O_8$: C, 67.91; H, 7.62. Found: C, 67.62; H, 7.38%.

8,13-Epoxy-7β-hydroxyacetoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (9). Compound **2a** (12 g; 22 mmol) was dissolved in a heterogenous mixture of dichloromethane (810 mL) and water (45 mL). To the vigorously stirred soln at room temperature, DDQ (6.09 g; 26.4 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The solid was filtered off and the filtrate was washed with 5% aq. soln of sodium dithionate until the organic layer was almost colourless. It was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with 30% EtOAc–light petroleum. The product was finally crystallized from hot EtOAc–light petroleum.

Yield: 6.8 g (72.5%); m.p. 189 °C; IR (KBr): 3535, 3430, 3290, 1730, 1698 cm^{-1}; ^1H NMR: 1.04, 1.25, 1.33, 1.44, 1.69 (5×s, 15H, 5×C$\underline{H}_3$), 2.18 (d, 1H, J = 2.54, 5$\underline{H}$), 2.46 (d, 1H, J_{gem} = 16.7, 12β$\underline{H}$), 3.20 (d, 1H, J_{gem} = 16.7, 12α$\underline{H}$), 4.23 (s, 2H, COC$\underline{H}_2$OH), 4.37–4.63 (m, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.93 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.01, 15$\underline{H}_{cis}$), 5.21 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.01, 15$\underline{H}_{trans}$), 5.56 (d, 1H, J = 4.05, 7$\underline{H}$), 5.93 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13; 14$\underline{H}$). Anal. calcd for $C_{22}H_{34}O_8$,H_2O: C, 59.44; H, 8.09. Found: C, 59.91; H, 8.20%.

7β-Acetoxyacetoxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (10). To a well-stirred soln of compound **9** (0.424 g; 1 mmol) and DCC (0.23 g; 1.1 mmol) in EtOAc (15 mL), AcOH (0.07 mL; 1.22 mmol) in EtOAc (1 mL)

was added followed by DMAP (0.12 g; 1 mmol). The reaction mixture was stirred for 3 h at room temperature. The DCU was filtered off and the filtrate was washed with brine. The EtOAc layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was crystallized from EtOAc–light petroleum. Yield: 0.44 g (94.5%); m.p. 142–143 °C; IR (KBr): 3548, 3470, 2940 (br), 1760, 1730 (br), 1705 cm^{-1}; ^1H NMR: 1.03, 1.25, 1.34, 1.42, 1.69 (5×s, 15H, 5×C$\underline{H}_3$) 2.16 (br, 4H, COC$\underline{H}_3$ + 5$\underline{H}$), 2.44 (d, 1H, J_{gem} = 16.7, 12β$\underline{H}$), 3.19 (d, 1H, J_{gem} = 16.71, 12α$\underline{H}$), 4.44–4.60 (m, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.64 (s, 2H, COC$\underline{H}_2$OAc), 4.93 (dd, 1H, J_{cis} = 10.13, J_{gem} = 2.03, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, J_{trans} = 17.21, J_{gem} = 2.03, 15$\underline{H}J_{trans}$), 5.41 (d, 1H, J = 4.05, 7$\underline{H}$), 5.94 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13; 14$\underline{H}$). Anal. calcd for $C_{24}H_{36}O_9$: C, 61.52; H, 7.75. Found: C, 61.71; H, 7.63%.

8,13-Epoxy-7β-formyloxyacetoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (12). To a soln of compound **11a**[5b] (0.5 g; 1 mmol) in HMPA (6 mL, freshly distilled over CaH_2), dry sodium formate (0.136 g; 2 mmol) was added under dry N_2. The reaction mixture was stirred at room temperature for 16 h. It was diluted with ether (~100 mL) and quickly washed with cold water followed by brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography with 5% CH_3CN–$CHCl_3$. The pure product was finally crystallized from hot EtOAc–light petroleum. Yield: 0.435 g (94.5%); m.p. 199–201 °C; IR (KBr): 3510, 3440, 3280, 2970, 1740, 1730, 1705 cm^{-1}; ^1H NMR: 1.03, 1.26, 1.35, 1.43, 1.69 (5×s,15H, 5×C$\underline{H}_3$), 2.17 (d, 1H, J = 2.54, 5$\underline{H}$), 2.43 (d, 1H, J_{gem} = 17.21, 12β$\underline{H}$), 3.18 (d, 1H, J_{gem} = 17.21, 12α$\underline{H}$), 4.44–4.57 (m, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.75 (s, 2H, C$\underline{H}_2$OCOH), 4.91 (dd, 1H, J_{cis} = 10.63, J_{gem} = 1.62, 15$\underline{H}_{cis}$), 5.18 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.62, 15$\underline{H}_{trans}$), 5.45 (d, 1H, J = 4.05, 7$\underline{H}$), 5.93 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.63, 14$\underline{H}$), 8.11 (s, 1H, –C$\underline{H}$O). Anal. calcd for $C_{23}H_{34}O_9$: C, 60.78; H, 7.54. Found: C, 60.38; H, 7.36%.

1α,7β-Bis-formyloxyacetoxy-6β,9α-dihydroxy-8,13-epoxylabd-14-en-11-one (16). The compound was prepared from **11b** by the above mentioned method. The molar ratio of **11b** to sodium formate was 1:4. After the workup, the crude product was purified by flash chromatography over silica gel with 30% EtOAc–light petroleum. Yield: 94.3%, m.p. 159 °C (EtOAc–light petroleum); IR (KBr): 3530, 3410, 2920, 1770, 1745, 1710, 1415 cm^{-1}; ^1H NMR: 1.03, 1.25, 1.34, 1.42, 1.69 (5×s, 15H, 5×C$\underline{H}_3$), 2.16 (d, 1H, J = 2.54, 5$\underline{H}$), 2.43 (d, 1H, J_{gem} = 17.21, 12β$\underline{H}$), 3.18 (d, 1H, J_{gem} = 17.21, 12α$\underline{H}$), 4.40–4.62 (br, 2H, 1$\underline{H}$ and 6$\underline{H}$), 4.74 (s, 2H, COC$\underline{H}_2$O–), 4.81 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.5, 15$\underline{H}_{cis}$), 5.17 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.5, 15$\underline{H}_{trans}$), 5.45 (d, 1H, J = 4.05, 7$\underline{H}$), 5.92 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.63; 14$\underline{H}$), 8.11 (s, 2H, 2×OC$\underline{H}$). Anal. calcd for $C_{26}H_{36}O_{12}$: C, 57.87; H, 6.71. Found: C, 58.15; H, 6.68%.

8,13-Epoxy-6β-hydroxyacetoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (13). The compound **12** (0.2 g; 0.44 mmol) was dissolved in 1% MeOH–CH_2Cl_2 (20 mL) and was passed through a column of neutral alumina (20 g). The column was eluted with 5% MeOH–CH_2Cl_2. All the fractions containing the product were evaporated to dryness. The crude product thus obtained was purified by flash chromatography over silica gel with 20% CH_3CN–$CHCl_3$. It was finally crystallized from EtOAc–light petroleum. Yield: 0.15 g (80%); m.p. 221–223 °C; IR (KBr): 3500, 3440 (br), 2940, 1755, 1705, 1400 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD): 0.94, 1.06, 1.36, 1.40, 1.53 (5×s, 15H, 5×C$\underline{H}_3$), 2.34 (d, 1H, J = 3.04, 5$\underline{H}$), 2.40 (d, 1H, J_{gem} = 16.2, 12β$\underline{H}$), 3.24 (d, 1H, J_{gem} = 16.2, 12α$\underline{H}$), 4.11 (br, 2H, OCOC$\underline{H}_2$OH), 4.27 (d, 1H, J = 4.56, 7$\underline{H}$), 4.49 (br, 1H, 1$\underline{H}$), 4.93 (dd, 1H, J_{cis} = 10.6, J_{gem} = 1.01, 15$\underline{H}_{cis}$), 5.11 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.01, 15$\underline{H}_{trans}$), 5.87 (dd, 1H, J = 4.56 and 2.54, 6$\underline{H}$), 6.11 (dd, 1H, J_{trans} = 17.2, J_{cis} = 10.6, 14$\underline{H}$). Anal. calcd for $C_{22}H_{34}O_8$: C, 61.95; H, 8.03. Found: C, 62.27; H, 7.92%.

1α,6β-Bis-hydroxyacetoxy-7β,9α-dihydroxy-8,13-epoxylabd-14-en-11-one (17). The above mentioned method was utilized to prepare compound **17**. The crude product was purified by flash chromatography over silica gel with 20% CH_3CN–$CHCl_3$ followed by crystallization from $CHCl_3$–light petroleum. Yield: 67%; m.p. 121–123 °C; IR (KBr): 3450 (br), 2920 (br), 1730 (br), 1705 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD): 0.98, 1.09, 1.41, 1.47, 1.58 (5×15H, 5×C$\underline{H}_3$), 2.42 (d, 1H, J = 2.6, 5$\underline{H}$), 2.43 (d, 1H, J_{gem} = 16.61, 12β$\underline{H}$), 3.13 (d, 1H, J_{gem} = 16.61, 12α$\underline{H}$), 4.03–4.12 (2×s, 4H, COC$\underline{H}_2$OH), 4.23 (d, 1H, J = 4.56, 7$\underline{H}$), 4.96 (dd, 1H, J_{cis} = 10.13, J_{gem} = 2.03, 15$\underline{H}_{cis}$), 5.15 (dd, 1H, J_{trans} = 16.41, J_{gem} = 2.03, 15$\underline{H}_{trans}$), 5.51 (br, 1H, 1$\underline{H}$), 5.87 (t, 1H, J = 3.5, 6$\underline{H}$), 6.04 (dd, 1H, J_{trans} = 16.41, J_{cis} = 10.13, 14$\underline{H}$). Anal. calcd for $C_{24}H_{36}O_{10}$: C, 59.49; H, 7.49. Found: C, 59.01; H, 7.28%.

6β-Acetoxyacetoxy-8,13-epoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (14). This compound was prepared from **13** by the method similar to the synthesis of compound **10** as described earlier. The crude product was purified by crystallization from EtOAc–light petroleum. Yield: 89.3%; m.p. 173–175 °C; IR (KBr): 3479, 2940 (br), 1785, 1750 (br), 1730 cm^{-1}; ^1H NMR: 1.01, 1.09, 1.40, 1.42, 1.60 (5×s, 15H, 5×C$\underline{H}_3$), 2.14 (s, 3H, –COC$\underline{H}_3$), 2.36 (d, 1H, J = 3.04, 5$\underline{H}$), 2.49 (d, 1H, J_{gem} = 17.2, 12β$\underline{H}$), 3.19 (d, 1H, J_{gem} = 17.2, 12α$\underline{H}$), 4.28 (d, 1H, J = 4.05, 7$\underline{H}$), 4.60 (s, 3H, COC$\underline{H}_2$OAc + 1$\underline{H}$), 4.95 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.5, 15$\underline{H}_{cis}$), 5.14 (dd, 1H,

J_{trans} = 17.21, J_{gem} = 1.5, 15H$_{trans}$), 5.90 (dd, 1H, J = 3.04, 4.05, 6H). 6.08 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13; 14H). Anal. calcd for $C_{24}H_{36}O_9$: C, 61.52; H, 7.75. Found: C, 61.61; H, 7.69%.

6β-Formyloxyacetoxy-8,13-epoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (15). Compound **15** was prepared from compound **13** and formic acid using DCC method as described for the synthesis of compound **10**. Yield: 86.8%, m.p. 160–161 °C; IR (KBr): 3555, 3455, 2990, 1785, 1773, 1750 1710 cm^{-1}; ^{1}H NMR: 1.03, 1.11, 1.41, 1.43, 1.61 (5×s, 15H, 5×CH$_3$), 2.37 (d, 1H, J = 3.04, 5H), 2.51 (d, 1H, J_{gem} = 17.2, 12βH), 3.19 (d, 1H, J_{gem} = 17.2, 12αH), 4.30 (d, 1H, J = 4.05, 7H), 4.66 (br, 1H, 1H), 4.76 (s, 2H, COCH$_2$O), 4.97 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.01, 15H$_{cis}$), 5.16 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.01, 15H$_{trans}$), 5.97 (m, 1H, 6H), 6.11 (dd, 1H, J_{trans} = 17.2, J_{cis} = 10.13, 14H), 8.14 (s, 1H, O–CHO). Anal. calcd for $C_{23}H_{34}O_9$: C, 60.78; H, 7.54. Found: C, 61.07; H, 7.67%.

8,13-Epoxy-7β-(3-tertiarybutyldimethylsilyloxy)propanoyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (18). Propiolactone (12.6 g; 175 mmol) in dry DMF (20 mL) was added to a well-stirred suspension of NaOMe (12.8 g; 237 mmol) in DMF (130 mL) at 0 °C. After the addition was over, the mixture was stirred at room temperature for 1 h. Tertiarybutyldimethylsilyl chloride (30 g; 196 mmol) and imidazole (5 g) were added and the stirring was continued overnight. The solvent (DMF) was distilled and the residue was taken up in ether. The ethereal layer was washed with cold diluted HCl followed by brine. The solvent was removed and the residue was dissolved in MeOH (330 mL). 1N NaOH (110 mL, 110 mmol) was added at room temperature and stirring was continued for 1 h. Methanol was removed under reduced pressure and the residue was extracted with ether (2×50 mL). The aqueous layer was acidified with cold diluted HCl. The oily residue was extracted with ether and washed with brine. The ethereal layer was dried over anhydrous Na_2SO_4. The solvent was removed to give chromatographically pure 3-tertiarybutyl dimethylsilyloxypropionic acid.

The compound **1** was treated with the above acid in the presence of DCC–DMAP in EtOAc as described for the preparation of **2a**. The crude material was purified by flash chromatography over silica gel with 5% CH_3CN–$CHCl_3$. Yield: 45%; m.p. 150–153 °C. (from light petroleum with a trace of EtOAc). IR (KBr), 3460, 2960, 2930, 1715, 1705 cm^{-1}; ^{1}H NMR: 0.08 [s, 6H, Si(CH$_3$)$_2$], 0.89 [(s, 9H, SiC(CH$_3$)$_3$], 1.01, 1.24, 1.37, 1.43, 1.73 (5×s, 15H, 5×CH$_3$), 1.60 (s, 1H, OH exchangable), 2.16 (d, 1H, J = 3.04, 5H), 2.35 (d, 1H, J_{gem} = 16.71, 12βH), 2.51 (t, 2H, J = 5.06, COCH$_2$·CH$_2$–), 3.09 (d, 1H, J_{gem} = 16.71, 12αH), 3.83, (m, 2H, CH$_2$–CH$_2$–OSi), 4.27-4.51 (m, 2H, 1H and 6H), 4.84 (dd, 1H, J_{cis} = 10.63, J_{gem} = 2.03, 15H$_{cis}$), 5.11 (dd, 1H, J_{trans} = 17.21, J_{gem} = 2.03, 15H$_{trans}$), 5.22 (d, 1H, J = 4.05, 7H), 5.86 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.63, 14H). Anal. calcd for $C_{29}H_{49}O_8Si$: C, 62.78; H, 9.09. Found: C, 63.48; H, 9.12%.

8,13-Epoxy-7β-(3-hydroxypropanoyloxy)-1α,6β,9α-trihydroxylabd-14-en-11-one (19a) and 8,13-epoxy-6β-(3-hydroxypropanoyloxy)-1α,7β,9α-trihydroxylabd-14-en-11-one (19b). To a soln of compound **18a** (1.4 g; 2.52 mmol) in freshly distilled THF (over LAH) (60 mL), 1M nBu$_4$N$^+$F$^-$ in THF (3 mL, 3 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 15 min. Solvent was removed under reduced pressure and the residue was quickly purified by flash chromatography over silica gel with 10% CH_3CN–$CHCl_3$. The compound **19a** was eluted first, followed by compound **19b**.

19a. Yield: 0.53 g (47.8%); m.p. 165 °C (EtOAc-light petroleum); IR (KBr): 3440, 3290, 2895, 1735, 1695 cm^{-1}; ^{1}H NMR: 1.04, 1.25, 1.36, 1.44, 1.74 (5×s, 15H, 5×CH$_3$), 2.12 (d, 1H, J = 3.04, 5H), 2.43 (d, 1H, J_{gem} = 16.7, 12βH), 2.64 (t, 2H, J = 6.08, COCH$_2$CH$_2$), 3.21 (d, 1H, J_{gem} = 16.7, 12αH), 3.90 (t, 2H, J = 6.08, OCOCH$_2$CH$_2$–OH), 4.47–4.60 (br, 2H, 1H and 6H), 4.93 (dd, 1H, J_{cis} = 10.13, J_{gem} = 2.03, 15H$_{cis}$), 5.18 (dd, 1H, J_{trans} = 17.2, J_{gem} = 2.03, 15H$_{trans}$), 5.41 (d, 1H, J = 4.05, 7H)), 5.96 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13; 14H). Anal. calcd for $C_{23}H_{36}O_8$: C, 62.71; H, 8.24. Found: C, 62.54; H, 8.03%.

19b. Yield: 0.12 g (10.8%), m.p. 204–206 °C (EtOAc-light petroleum); IR (KBr): 3400 (br), 2950, 1745, 1715 (br) cm^{-1}; ^{1}H NMR: 1.0, 1.11, 1.40, 1.41, 1.62 (5×s, 15H, 5×CH$_3$), 2.36 (d, 1H, J = 5.04, 5H), 2.48 (d, 1H, J_{gem} = 17.2, 12βH), 2.58 (t, 2H, J = 5.60, –COCH$_2$ CH$_2$OH), 3.20 (d, 1H, J_{gem} = 17.2, 12αH), 3.89 (t, 2H, J = 5.60, –COCH$_2$CH$_2$OH), 4.29 (d, 1H, J = 5.06, 7H), 4.63 (br, 1H, 1H), 4.96 (dd, 1H, J_{cis} = 10.1, J_{gem} = 1.6; 15H$_{cis}$), 5.14 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.6, 15H$_{trans}$), 5.91 (t, 1H, J = 2.5, 6H), 6.09 (dd, 1H, J_{trans} = 17.2, J_{cis} = 10.1, 14H). Anal. calcd for $C_{23}H_{36}O_8$: C, 62.71; H, 8.24. Found: C, 62.63; H, 7.98%.

7β-[(*R*)-2,3-O-Isopropylidinopropanoyloxy]-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (20). This compound was prepared from compound **1** and (*R*)-2,3-O-isopropilidino propionic acid by DCC method as described for the synthesis of compound **18**. The crude product was purified by flash chromatography over silica gel with 10% CH_3CN–$CHCl_3$. Yield: 55%, m.p. 173–175 °C (EtOAc–light petroleum); IR (KBr): 3500, 3200, 2990, 1745, 1735, 1720 cm^{-1}; ^{1}H NMR: 1.03, 1.26, 1.31, 1.41, 1.44, 1.52, 1.74 (7×s, 21H, 7×CH$_3$), 2.17 (d,

1H, $J = 3.04$, 5H), 2.41 (d, 1H, $J_{gem} = 16.7$, 12βH), 3.17 (d, 1H, $J_{gem} = 16.7$, 12αH), 4.06–4.38 (m, 2H, 3′-CH_2), 4.43–4.73 (m, 3H, 1H, 6H and 2′-CH), 4.90 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 2.03$, 15H_{cis}), 5.18 (dd, 1H, $J_{trans} = 16.71$, $J_{gem} = 2.03$, 15H_{trans}), 5.51 (d, 1H, $J = 4.05$, 7H), 5.89 (dd, 1H, $J_{trans} = 16.71$, $J_{cis} = 10.13$, 14H). Anal. calcd for $C_{26}H_{40}O_9$: C, 62.88; H, 8.12. Found: C, 63.21; H, 8.42%.

7β-[(*S*)-2,3-O-Isopropylidinopropanoyloxy]-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (21). This compound was prepared from compound **1** and (*S*)-2,3,-O-isopropilidinopropionic acid. The crude product was directly used for deblocking of acetonide ring.

7β-[(*R*)-2,3-dihydroxypropanoyloxy]-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (22a) and 6β-[(*R*)-2,3-dihydroxypropanoyloxy]-8,13-epoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (22b). Compound **20** (0.496 g; 1 mmol) was dissolved in methanol (15 mL) and *p*-toluene sulfonic acid (0.17 g; 1 mmol) was added at room temperature. After stirring the reaction mixture for 2 h, methanol was evaporated under reduced pressure and the residue was taken up in EtOAc. The EtOAc layer was washed with diluted aq $NaHCO_3$, followed by brine. Organic layer was dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography over silica gel with 20% CH_3CN–$CHCl_3$. Compound **22a** was eluted first, followed by **22b**.

22a. Yield: 0.35 g (75.2%); m.p. 166–168 °C (EtOAc–light petroleum); IR (KBr): 3440 (br), 2940 (br), 1735, 1725, 1695 cm^{-1}; ^1H NMR: 0.99, 1.10, 1.40, 1.41, 1.57 (5×s, 15H, 5×CH_3), 2.38 (d, 1H, $J = 3.04$, 5H), 2.41(d, 1H, $J_{gem} = 16.71$, 12βH), 3.24 (d, 1H, $J_{gem} = 16.71$, 12αH), 3.82 (d, 2H, $J = 4.05$, –CH_2OH), 4.23 (t, 1H, $J = 4.05$, CH(OH)–CH_2), 4.25 (d, 1H, $J = 4.6$, 7H), 4.51 (br, 1H, 1H), 4.94 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 1.6$, 15H_{cis}), 5.13 (dd, 1H, $J_{trans} = 17.7$, $J_{gem} = 1.6$, 15H_{trans}), 5.89 (t, 1H, $J = 2.5$, 6H), 6.09 (dd, 1H, $J_{trans} = 17.7$, $J_{cis} = 10.13$, 14H). Anal. calcd for $C_{23}H_{36}O_9$,0.5 H_2O: C, 59.33; H, 8.01. Found: C, 59.25; H, 8.21%.

22b. Yield: 0.025 g (5.4%), m.p. 217–219 °C (EtOAc–light petroleum). IR (KBr): 3450–3300, 2950, 1735, 1720 cm^{-1}; ^1H NMR: 0.99, 1.1, 1.40, 1.41, 1.57 (5×s, 15H, 5×CH_3), 2.38 (d, 1H, $J = 3.04$, 5H), 2.41 (dd, 1H, $J_{gem} = 16.71$, 12βH), 3.24 (d, 1H, $J_{gem} = 16.71$, 12αH), 3.82 (d, 2H, $J = 4.05$, –CH_2OH), 4.23 (t, 1H, $J = 4.05$, CH(OH)–), 4.25 (d, 1H, $J = 4.6$, 7H), 4.51 (br, 1H, 1H), 4.94 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 1.62$, 15H_{cis}), 5.13, (dd, 1H, $J_{trans} = 17.7$, $J_{gem} = 1.62$, 15H_{trans}), 5.89 (t, 1H, $J = 2.5$, 6H), 6.09 (dd, 1H, $J_{trans} = 17.72$, $J_{cis} = 10.13$, 14H). Anal. calcd for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.31; H, 8.12%.

7β-[(*S*)-2,3-dihydroxypropanoyloxy]-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (23). The compound was prepared from crude **21** using the method described above. Yield: 79.5%, m.p. 191–193 °C (EtOAc–light petroleum); IR (KBr): 3425 (br), 3300, 2920 (br), 1748, 1700, 1655 cm^{-1}; ^1H NMR: 1.03, 1.24, 1.37, 1.43, 1.74 (5×s, 15H, 5×CH_3), 2.18 (d, 1H, $J = 3.04$, 5H), 2.40 (d, 1H, $J_{gem} = 16.2$, 12βH), 3.23 (dd, 1H, $J_{gem} = 16.2$, 12αH), 3.78, 3.96 (2×dd, 2H, $J_{gem} = 14.11$, $J_{2-3} = 3.04$, –CH_2OH), 4.31 (t, 1H, $J = 3.04$, –CHOH), 4.47–4.60 (m, 2H, 1H and 6H), 4.93 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 1.6$, 15H_{cis}), 5.14 (dd, 1H, $J_{trans} = 17.21$, $J_{gem} = 1.6$, 15H_{trans}), 5.45 (d, 1H, $J = 4.05$, 7H), 5.99 (dd, 1H, $J_{trans} = 17.21$, $J_{cis} = 10.13$, 14H). Anal. calcd for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.64; H, 8.13%.

7β-Acetoxy-6β,9α-dihydroxy-8,13-epoxy-1α-[(4-methoxybenzyloxy)acetoxy]labd-14-en-11-one (24). The procedure of getting this compound was the same as described for the synthesis of **2a**. The crude product was purified by flash chromatography over silica gel with 10%, CH_3CN–$CHCl_3$. Yield: 92% (oil); IR (neat): 3490, 2935, 1740 (br), 1712, 1615 cm^{-1}; ^1H NMR: 1.04, 1.25, 1.31, 1.53, 1.68 (5×s, 15H, 5×CH_3), 2.15 (s, 3H, $COCH_3$), 2.25 (d, 1H, $J = 2.54$, 5H), 2.36 (d, 1H, $J_{gem} = 17.2$, 12βH), 3.08 (d, 1H, $J_{gem} = 17.2$, 12βH), 3.76 (s, 3H, OCH_3), 3.89 (s, 2H, –$COCH_2$–O–), 4.45 (br, 3H, PhCH_2O, 6H), 4.85 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 1.5$, 15H_{cis}), 5.18 (dd, 1H, $J_{trans} = 17.21$, $J_{gem} = 1.5$, 15H_{trans}), 5.47–5.51 (m, 2H, 1H and 7H), 5.85 (dd, 1H, $J_{trans} = 17.2$, $J_{cis} = 10.13$, 14H), 6.82 (d, 2H, $J = 9.1$, Ar$H_{3,5}$), 7.20 (d, 2H, $J = 9.1$, Ar$H_{2,6}$). Anal. calcd for $C_{32}H_{44}O_{10}$: C, 65.29; H, 7.53. Found: C, 65.59; H, 7.66%.

7β-Acetoxy-6β,9α-dihydroxy-8,13-epoxy-1α-hydroxyacetoxylabd-14-en-11-one (25). The compound **24** (4.4 g; 6.4 mmol) was dissolved in a heterogenous mixture of CH_2Cl_2 (180 mL) and water (10 mL) and DDQ (2.18 g; 9.6 mmol) was added under vigorous stirring conditions. The reaction mixture was stirred at room temperature for 5 h. The reaction was worked up in a manner similar to the synthesis of compound **5**. The crude product was purified by flash chromatography over silica gel with 20% CH_3CN–$CHCl_3$. Yield: 2.41 g (83%); m.p. 196 °C (EtOAc-light petroleum). IR (KBr): 3571, 2899, 1754, 1709 cm^{-1}; ^1H NMR: 1.05, 1.29, 1.34, 1.54, 1.73 (5×s, 15H, 5×CH_3), 2.16 (s, 3H, –$COCH_3$), 2.19 (d, 1H, $J = 2.54$, 5H), 2.45 (d, 1H, $J_{gem} = 17.2$, 12βH), 2.57 (t, 1H, $J = 5.06$, exchangable –CH_2OH), 3.04 (d, 1H, $J_{gem} = 17.2$, 12αH), 4.03 (d, 2H, $J = 5.06$, singlet in D_2O exchange, $COCH_2$–OH), 4.39 (t, 1H, $J = 3.04$, 6H), 4.95 (dd, 1H, $J_{cis} = 10.13$, $J_{gem} = 1.01$, 15H_{cis}), 5.23 (dd, 1H, $J_{trans} = 17.21$, $J_{gem} = 1.5$, 15H_{trans}), 5.35 (d, 1H, $J = 4.05$, 7H), 5.61 (br, 1H, 1H), 5.83 (dd, 1H, $J_{trans} = 17.21$, $J_{cis} = 10.13$, 14H). Anal. calcd for $C_{24}H_{36}O_9$: 61.52; H, 7.75. Found: C, 61.76; H, 7.69%.

6β,9α-Dihydroxy-8,13-epoxy-7β-[(4-methoxybenzyloxy)-acetoxy]-1α-tertbutyldimethylsilyloxylabd-14-en-11-one (27). Compound **26** (24.8 g; 51.4 mmol) and 4-methoxybenzyloxyacetic acid (11.1 g, 56.6 mmol) were coupled together with DCC (13.03 g; 63.3 mmol) and DMAP (6.27 g; 51.4 mmol) in a manner similar to the synthesis of **2a**. The crude material was purified by flash chromatography over silica gel with 3% CH_3CN–$CHCl_3$. Yield: 33 g (97.3%), oil; IR (neat): 3510 (br), 3310 (br), 2942 (br), 1750 (br), 1718, 1615 cm^{-1}; ^1H NMR: 0.01, 0.13 [2×s, 6H, $Si(C\underline{H}_3)_2$], 0.86 [s, 9H, $SiC(C\underline{H}_3)_3$], 1.02, 1.23, 1.29, 1.44, 1.63 (5×s, 15H, 5×$C\underline{H}_3$), 2.2 (d, 1H, J = 2.5, 5$\underline{H}$), 2.31 (d, 1H, J_{gem} = 16.7, 12β$\underline{H}$), 3.22 (d, 1H, J_{gem} = 16.7, 12(α$\underline{H}$), 3.77 (s, 3H, $OC\underline{H}_3$), 4.11 (s, 2H, –$C\underline{H}_2$–Ar(OMe)], 4.57 (br, 3H, $COC\underline{H}_2O$, 1$\underline{H}$), 4.46 (t, 1H, J = 3.5, 6$\underline{H}$), 4.81 (dd, 1H, J_{cis} = 10.13, J_{gem} = 1.6, 15$\underline{H}_{cis}$), 5.10 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.6, 15$\underline{H}_{trans}$), 5.59 (d, 1H, J = 4.05, 7$\underline{H}$), 5.98 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.13, 14$\underline{H}$), 6.82 (d, 2H, J = 8.1, Ar$\underline{H}_{3,5}$), 7.24 (d, 2H, J = 8.1, Ar$\underline{H}_{2,6}$). Anal. calcd for $C_{36}H_{56}O_9Si$: C, 65.42; H, 8.54. Found: C, 65.12; H, 8.82%.

7β,9α-Dihydroxy-8,13-epoxy-6β-[(4-methoxybenzyloxy)-acetoxy]-1α-tertbutyldimethylsilyloxylabd-14-en-11-one (28). To a soln of **27** (7.5 g; 11.36 mmol) in CH_3CN (190 mL) and water (300 mL), 1N NaOH (20 mL; 20 mmol) was added. The reaction mixture was stirred at room temperature for 45 min. It was neutralized with 1N HCl and acetonitrile was removed under reduced pressure. The oil separated was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography over silica gel with 15% EtOAc–light petrolium. Yield: 6.5 g (87%)*, oil (* with varying batch sizes the yield varies from 60–87%). IR (neat): 3465 (br), 3290 (br), 2940 (br), 1758, 1713, 1612 cm^{-1}; ^1H NMR: 0.03, 0.14 [2×s, 6H, $Si(C\underline{H}_3)_2$], 0.87 [s, 9H, $SiC(C\underline{H}_3)_3$], 0.94, 1.07, 1.38, 1.39, 1.51 (5×s, 15H, 5×CH_3), 2.36 (d, 1H, J = 3.04, 5$\underline{H}$), 2.41 (d, 1H, J_{gem} = 17.21, 12β$\underline{H}$), 3.21 (d, 1H, J_{gem} = 17.21, 12α$\underline{H}$), 3.79 (s, 3H, $OC\underline{H}_3$), 4.04 (s, 2H, $OC\underline{H}_2$–Ar), 4.33 (d, 1H, J = 4.56, 7$\underline{H}$), 4.57 (s, 2H, $COC\underline{H}_2$–O–), 4.64 (br, 1H, 1$\underline{H}$), 4.93 (dd, 1H, J_{cis} = 11.14, J_{gem} = 1.62, 15$\underline{H}_{cis}$), 5.07 (dd, 1H, J_{trans} = 16.71, J_{gem} = 1.62, 15$\underline{H}_{trans}$), 5.93 (br, 1H, 6$\underline{H}$), 6.17 (dd, 1H, J_{trans} = 16.71, J_{cis} = 11.14, 14$\underline{H}$), 6.80 (d, 2H, J = 8.6, Ar–$\underline{H}_{3,5}$) 7.21 (d, 2H, J = 8.6, Ar$\underline{H}_{2,6}$). Anal. calcd for $C_{36}H_{59}O_9Si$: C, 65.42; H, 8.54. Found: C, 65.84; H, 8.55%.

7β-Acetoxy-8,13-epoxy-9α-hydroxy-6β-[(4-methoxybenzyloxy)acetoxy]-1α-tertbutyldimethylsilyloxylabd-14-en-11-one (29). This compound was prepared according to the method discribed for the synthesis of compound **14** (Scheme 1). The crude product was purified by flash chromatography over silica gel with 15% EtOAc–light-petroleum. Yield: 98%, semi solid; IR (neat): 3300 (br), 2940, 1760, 1755, 1718, 1615, 1515 cm^{-1}; ^1H NMR: 0.06, 0.13 [2×s, 6H, $Si(C\underline{H}_3)_2$], 0.86 [s, 9H, Si $C(C\underline{H}_3)_3$], 0.93, 1.03, 1.30, 1.39, 1.54 (5×s, 15H, 5×$C\underline{H}_3$), 2.0 (s, 3H, –$(COC\underline{H}_3)$), 2.33 (d, 1H, J_{gem} = 16.2, 12β$\underline{H}$), 2.41 (br, 1H, 5$\underline{H}$), 3.21 (d, 1H, J_{gem} = 16.2, 12α$\underline{H}$), 3.77 (s, 3H, $OC\underline{H}_3$), 4.03 (s, 2H, $OC\underline{H}_2$–Ar), 4.51 (s, 2H, $COC\underline{H}_2$–), 4.58 (br, 1H, 1$\underline{H}$), 4.84 (dd, 1H, J_{cis} = 10.6; J_{gem} = 1.6, 15$\underline{H}_{cis}$), 5.07 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.6, 15$\underline{H}_{trans}$), 5.57 (d, 1H, J = 4.56, 7$\underline{H}$), 5.87 (br, 1H, 6$\underline{H}$), 5.98 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.6, 14$\underline{H}$), 6.82 (d, 2H, J = 8.6, Ar–$\underline{H}_{3,5}$), 7.22 (d, 2H, J = 8.6, Ar$\underline{H}_{2,6}$). Anal. calcd for $C_{38}H_{61}O_{10}Si$: C, 64.65; H, 8.71. Found: C, 65.06; H, 8.50%.

7β-Acetoxy-8,13-epoxy-9α-hydroxy-6β-[(hydroxyacetoxy)]-1α-tertbutyldimethylsilyloxylabd-14-en-11-one (30). Compound **29** (16.5 g; 22.79 mmol) was dissolved in a heterogeneous mixture of CH_2Cl_2, 55 mL) and water (36.5 mL), DDQ (9.2 g; 40.6 mmol) was added to the soln with vigorous stirring at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction was worked up in a manner similar to **9** (Scheme 1). The crude product was purified by flash chromatography over silica gel with 10% CH_3CN–$CHCl_3$. Yield: 12.3 g (92.8%), m.p. 162 °C (EtOAc–light petroleum); IR (KBr): 3450, 3320, 2940, 1760, 1715, 1705 cm^{-1}; ^1H NMR: 0.03, 0.14 [2×s, 6H, $Si(C\underline{H}_3)_2$], 0.86 [s, 9H, $SiC(C\underline{H}_3)_3$], 0.92, 1.02, 1.31, 1.39, 1.52 (5×s, 15H, 5×$C\underline{H}_3$), 2.0 (s, 3H, –$COC\underline{H}_3$), 2.34 (d, 1H, J_{gem} = 16.2, 12β$\underline{H}$), 2.44 (d, 1H, J = 2.03, 5$\underline{H}$), 3.22 (d, 1H, J_{gem} = 16.2, 12α$\underline{H}$), 4.11 (d, 2H, J = 4.05, $COC\underline{H}_2OH$, singlet after D_2O exchange)*, 4.58 (br, 1H, 1H), 4.84 (dd, 1H, J_{cis} = 10.6; J_{gem} = 1.6, 15$\underline{H}_{cis}$), 5.06 (dd, 1H, J_{trans} = 17.21, J_{gem} = 1.6, 15$\underline{H}_{trans}$), 5.56 (d, 1H, J = 5.06, 7$\underline{H}$), 5.89 (t, 1H, J = 2.5, 6$\underline{H}$), 5.98 (dd, 1H, J_{trans} = 17.21, J_{cis} = 10.6, 14$\underline{H}$). Anal. calcd for $C_{24}H_{36}O_9$: C, 61.54; H, 7.75. Found: C, 61.41; H, 7.68%.

7β-Acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-(hydroxyacetoxy)-labd-14-en-11-one (31). To a solution of compound **30** (5.82 g; 10 mmol) in THF (freshly distilled over LAH) (300 mL), 1M $n$$Bu_4N^+F^-$ in THF (kept over molecular seive 4A type for 3 h before use) (10 mL; 10 mmol) was added. The soln was stirred for 5 min at room temperature. Solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with 15% CH_3CN–$CHCl_3$ as eluent. The product was finally crystallized from hot EtOAc. Yield: 4.47 g (95.5%), m.p. 258–260 °C; IR (KBr) 3495, 3210, 1745, 1724, 1400 cm^{-1}; ^1H NMR: ($CDCl_3$ + CD_3OD): 0.94, 1.03, 1.34, 1.39, 1.57 (5×s, 15H, 5×$C\underline{H}_3$), 2.01 (s, 3H, –$COC\underline{H}_3$), 2.37 (d, 1H, J_{gem} = 16.2, 12β$\underline{H}$), 2.41 (d, 1H, J = 2.54, 5$\underline{H}$), 3.25 (d, 1H, J_{gem} = 16.2, 12α$\underline{H}$), 4.11 (s, 2H, $COC\underline{H}_2OH$), 4.47 (br, 1H, 1$\underline{H}$), 4.89 (dd, 1H, J_{cis} = 10.1, J_{gem} = 1.62, 15$\underline{H}_{cis}$), 5.14 (dd, 1H, J_{trans} = 17.2, J_{gem} = 1.62 15$\underline{H}_{trans}$),

5.51 (d, 1H, $J=4.56$, 7H), 5.85 (t, 1H, $J=3.04$, 6H), 5.95 (dd, 1H, $J_{trans}=17.2$, $J_{cis}=10.1$, 14H). Anal. calcd for $C_{24}H_{36}O_9Si$: C, 61.54; H, 7.75. Found: C, 61.41; H, 7.68%.

7β-Acetoxy-6β-acetoxyacetoxy-1α,9α-dihydroxy-8,13-epoxylabd-14-en-11-one (32) and 7β-acetoxy-1α,9α-dihydroxy-8,13-epoxy-6β-(formyloxy)acetoxylabd-14-en-11-one (33). These two compounds were prepared from **31** by using the same method as described for the synthesis of compound **14** (Scheme 1) with appropriate acid EtOAc:DMF (5:1) as reaction solvent. The crude products were purified by flash chromatography over silica gel with 8% CH_3CN–$CHCl_3$ as eluent.

32. Yield: 98%, m.p. 190–191 °C (EtOAc–light petroleum). IR (KBr): 3400, 3340, 3270, 2940 (br), 1755, 1720, 1630 cm^{-1}; ^1H NMR: 0.99, 1.04, 1.35, 1.41, 1.63 (5×s, 15H, 5×CH$_3$), 2.03, 2.14 (2×s, 6H, 2×COCH$_3$), 2.42 (d, 1H, $J=2.54$, 5H), 2.45 (d, 1H, $J_{gem}=17.21$, 12βH), 3.21 (d, 1H, J = 17.21, 12αH), 4.48, 4.70 (2×d, 2H, $J_{gem}=16.1$, COCH$_2$O), 4.6 (br, 1H, 1H), 4.91 (dd, 1H, $J_{cis}=10.13$; $J_{gem}=1.68$, 15H$_{cis}$), 5.19 (dd, 1H, $J_{trans}=17.21$, $J_{gem}=1.68$ 15H$_{trans}$), 5.48 (d, 1H, $J=4.05$, 7H), 5.82 (t, 1H, $J=3.04$, 6H), 5.83 (dd, 1H, $J_{trans}=17.21$, $J_{cis}=10.13$, 14H). Anal. calcd for $C_{26}H_{38}O_{10}$: C, 61.16; H, 7.50. Found: C, 61.32; H, 7.60%.

33. Yield: 92.5%, m.p. 197–200 °C (EtOAc–light petroleum); IR (KBr) 3360 (br), 2982, 2955, 1775, 1755, 1745, 1707 cm^{-1}; ^1H NMR: 0.99, 1.04, 1.35, 1.41, 1.62 (5×s, 15H, 5×CH$_3$), 2.03 (s, 3H, COCH$_3$), 2.44 (d, 1H, $J=2.54$, 5H), 2.45 (d, 1H, $J_{gem}=16.7$, 12βH), 3.21 (d, 1H, $J=16.7$, 12αH), 4.56, 4.79 (2×d, 2H, $J_{gem}=15.2$, COCH$_2$O), 4.93 (dd, 1H, $J_{cis}=10.13$; $J_{gem}=2.03$, 15H$_{cis}$), 5.19 (dd, 1H, $J_{trans}=17.21$, $J_{gem}=2.03$, 15H$_{trans}$), 5.50 (d, 1H, $J=4.56$, 7H), 5.84 (t, 1H, $J=3.04$, 6H), 5.93 (dd, 1H, $J_{trans}=17.21$, $J_{cis}=10.13$, 14H), 8.07 (s, 1H, CHO). Anal. calcd for $C_{25}H_{36}O_{10}$: C, 60.47; H, 7.31. Found: C, 60.63; H, 7.29%.

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