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# In Search of Novel Water Soluble Forskolin Analogues for Positive Inotropic Activity

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**Abstract**—Using the novel lead from hydroxy acetyl substituted forskolin analogues, such as 7β-hydroxyacetyl-7β-deacetyl forskolin or 6β-hydroxyacetyl forskolin, a number of water soluble ω-amino acyl derivatives were synthesized. Two such compounds **6** and **18** showed better in vitro activity but failed to show in vivo activity. 

## Introduction

Forskolin was isolated from *Coleus forskolii*.[1] It showed excellent pharmacological properties such as positive inotropic, antihypertensive, blood pressure lowering, intraoccular pressure lowering, adenylate cyclase activation etc.[2]

One of the major disadvantages for which forskolin as such had not been developed subsequently, was its water insolubility. Subsequent effort was made by others to synthesize water soluble forskolin analogues through introduction of ω-amino acyl chain at 6β- or 7β-positions. Some of these derivatives showed interesting pharmacological activity.[3a,3b] One such compound NKH-477 is now under clinical development.[3b] In our earlier publication[4] we have shown that by introducing a 'spacer' in the form of hydroxy acyl chain in 6β- or 7β-position of deacetyl forskolin or 6β-position of forskolin retains the biological activity to large extent (Fig. 1). Moreover the introduction of acyl chain on primary –OH group of the extended chain could be achieved in a regioselective manner and the resulting derivatives, particularly in 7β-position improved positive inotropic activity (as shown in Figure 1).

Since we were involved in developing forskolin analogues with better positive inotropic activity preferably with water solubility, the above information prompted us to undertake a synthetic project to introduce amino acyl chain to get water soluble forskolin analogues.

In this paper we would like to report the synthesis and biological activities of such an effort on two forskolin derivatives such as **A** and **B**.

## Results and Discussion

### Chemistry

Our initial target molecule involved the replacement of $-COCH_3$ (in **C** or **D**)[4] by $COCH_2NR_2$ group and solubilize by making appropriate salt. An appropriate intermediate was chosen depending upon the type of substituent to be introduced. When R = H (glycine residue) or homologous ω-amino acyl chain to be introduced, the corresponding protected amino acid was used. While the preferred approach for the introduction of secondary amine could be the nucleophilic substitution reaction on $-COCH_2Cl$ intermediate or Michael addition across the conjugated double bond (such as

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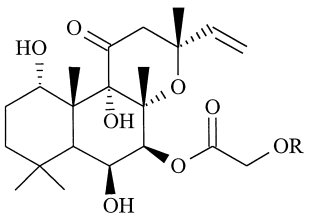
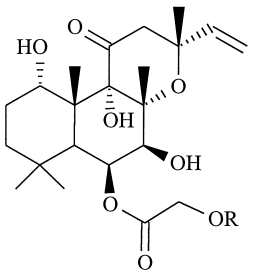


**A**; R = H ; $EC_{50}$= 1.0 μg/ml
**C**; R = $COCH_3$ ; $EC_{50}$= 0.008 μg/ml



**B**; R = H ; $EC_{50}$= 0.72 μg/ml
**D**; R = $COCH_3$; inactive.

**Figure 1.**

–COCH = $CH_2$). Protecting groups that are acid labile (under mild condition) being chosen for amino group protection keeping in mind the presence of olefin double bond for which hydrogenolizable groups are unsuitable. Using this basic approach the synthetic strategy was adopted.

Thus Boc-Gly[5] was reacted with 7β-hydroxyacetoxy-7β-deacetyl forskolin (**A**) in presence of DCC and DMAP to give compound **1** (Scheme 1). All attempt to remove the Boc- group even under mild condition such as formic acid-anisole[6] was unsuccessful leading to a bad mixture. At this stage we decided to use trityl group as N-protection. The required intermediate **2** could be obtained in a similar fashion by reacting **1** with Trit-Gly[7] in presence of DCC-DMAP. In this case also the removal Trit- group by 85% AcOH[8] could not provide clean reaction. However, when the reaction was carried out with TFA under dilution (TFA:ether = 1:50 v/v), a clean reaction occurred. The desired product **3** being isolated from the reaction mixture directly as hydrochloride salt since solvent could not be removed in presence of TFA as it causes complete decomposition of the product. Introduction of disubstituted glycyl residue on primary OH group was quite straightforward. Chloroacetic acid was reacted with **A** in presence of DCC and DMAP to get chloroacetyl derivative **4** in high yield. It was then reacted with the desired secondary amine in dichloromethane at room temperature to yield disubstituted glycyl analogues **6** and **9**–**13**. However the yields were not very good (~ 40–60%), because of partial hydrolysis of chloroacetyl group. In some instances formation of product corresponding to the migration of the complete chain from 7β to 6β position, which can easily be seen by the downfield shift of 6H proton (triplet) and upfield shift of 7H doublet in $^1H$ NMR. Diisopropyl amine and trimethoxy aniline failed to react at room temperature. However when **4** was reacted with diisopropyl amine at 45 °C and trimethoxy aniline at 70–80 °C desired compounds **7** and **8** could be formed in 40% and 20% yields respectively.

Further we decided to introduce higher homologue of amino acyl chain at 7β-$OCOCH_2OH$ residue. This had been done by converting primary OH group of **A** to acrylic acid ester followed by Michael addition across the double bond with different amines. Therefore when **A** had reacted with acrylic acid in presence of DCC-DMAP the reaction had found to be very slow, most of the starting material remained intact in spite of using large excess of acrylic acid, DCC and DMAP. A small amount of product formed in the reaction had found to be a bad mixture. An alternative approach was adopted for the synthesis of disubstituted propanoyl analogue. As a representative example 3,3-diamino propionic acid was reacted with **A** in presence of DCC-DMAP to yield compound **5**.

A similar series of steps could be performed on 6β-hydroxy acetyl-7-deacetyl forskolin **B** to generate compounds **14** to **21** as shown in Scheme 2.

## Biological activity

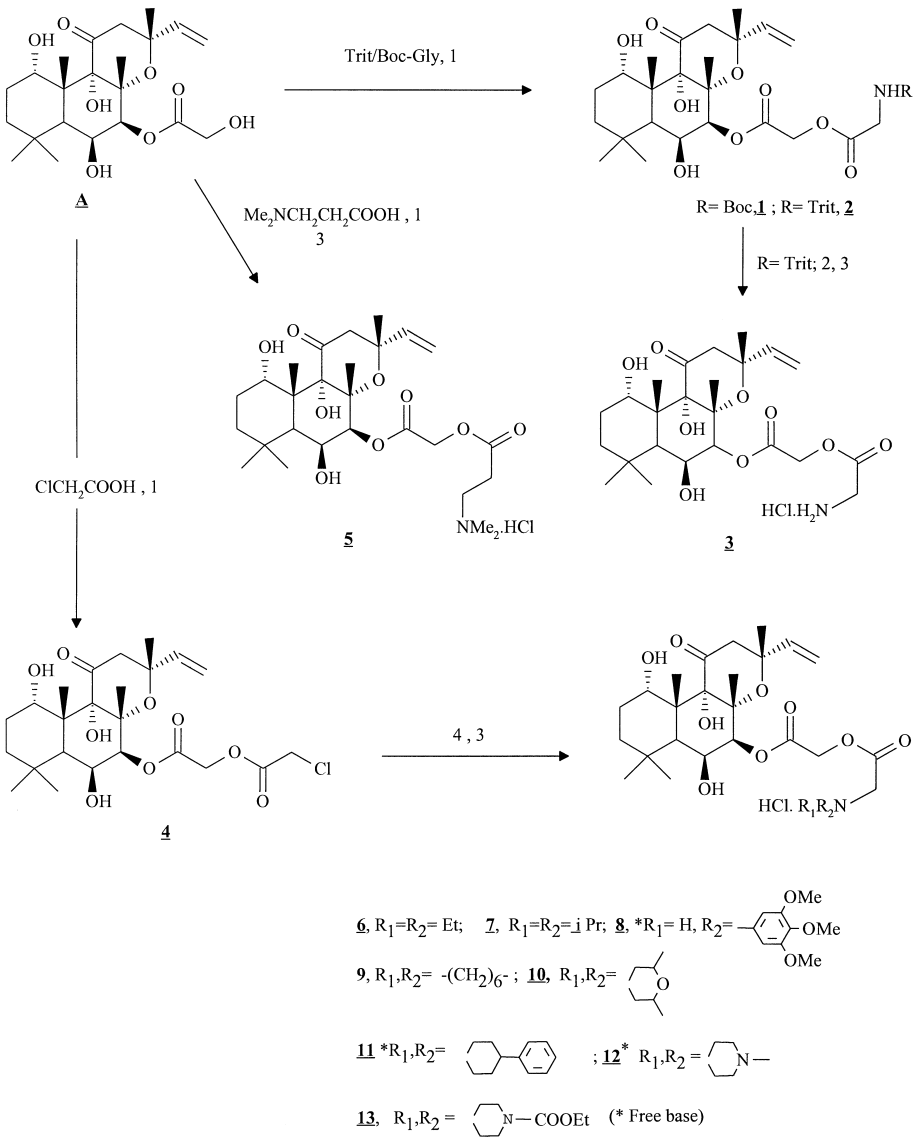
The blood pressure lowering activity of forskolin derivatives was evaluated by intravenous administration to anesthetized normotensive cats. The positive inotropic activity of forskolin analogues was tested in spontaneously beating isolated guinea pig atrial preparation. The minimum concentration of the compound required to obtain 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 earlier publication.[9]

The results of blood pressure lowering activity and positive inotropic activity are summarized in Table 1. From the table it is quite apparent that when 7β-hydroxy acetyl chain was substituted with ω-amino acyl chain the positive inotropic activity increased in most of the cases viz. **3**, **5**, **6**, **8**, **11** and **12** with $EC_{50}$ values of 0.1, 0.3, 0.03, 0.55, 0.18 and 0.1 μg/ml respectively when compared with hydroxy acetyl derivative **A**. All these

compounds were found to be highly water soluble. The most potent compound in the series was found to be **6** which was 1.5 times less active than forskolin which had $EC_{50}$ of 0.02 μg/ml. While the similar substitutions on 6β-hydroxyacetyl group (**B**) were found to be less effective, except in one compound **18** ($EC_{50}$ = 0.04 μg/ml), all the compounds were found to be inactive. Considering some hypotensive effect showed in anesthetized cat, lower doses were tested for positive inotropic activity (without causing significant fall in blood pressure) in anesthetized dog. Compound **6** (in vitro $EC_{50}$ = 0.03 μg/ml) in an iv. infusion of 0.5 μg/kg/min. could increase cardiac force of contraction only by 20%, while compound **18** (in vitro $EC_{50}$ = 0.04 μg/ml) was inactive after 1 μg/kg/min. iv. infusion. All these data suggests a rapid metabolic degradation of these compounds. One such possibility could be the hydrolysis of amino acyl chain from the primary OH group.

## Conclusion

In our attempt to develop water soluble forskolin analogues with positive inotropic activity, the modification under current study resulted two water soluble compounds with good in vitro activity but failed to provide desired result in vivo.



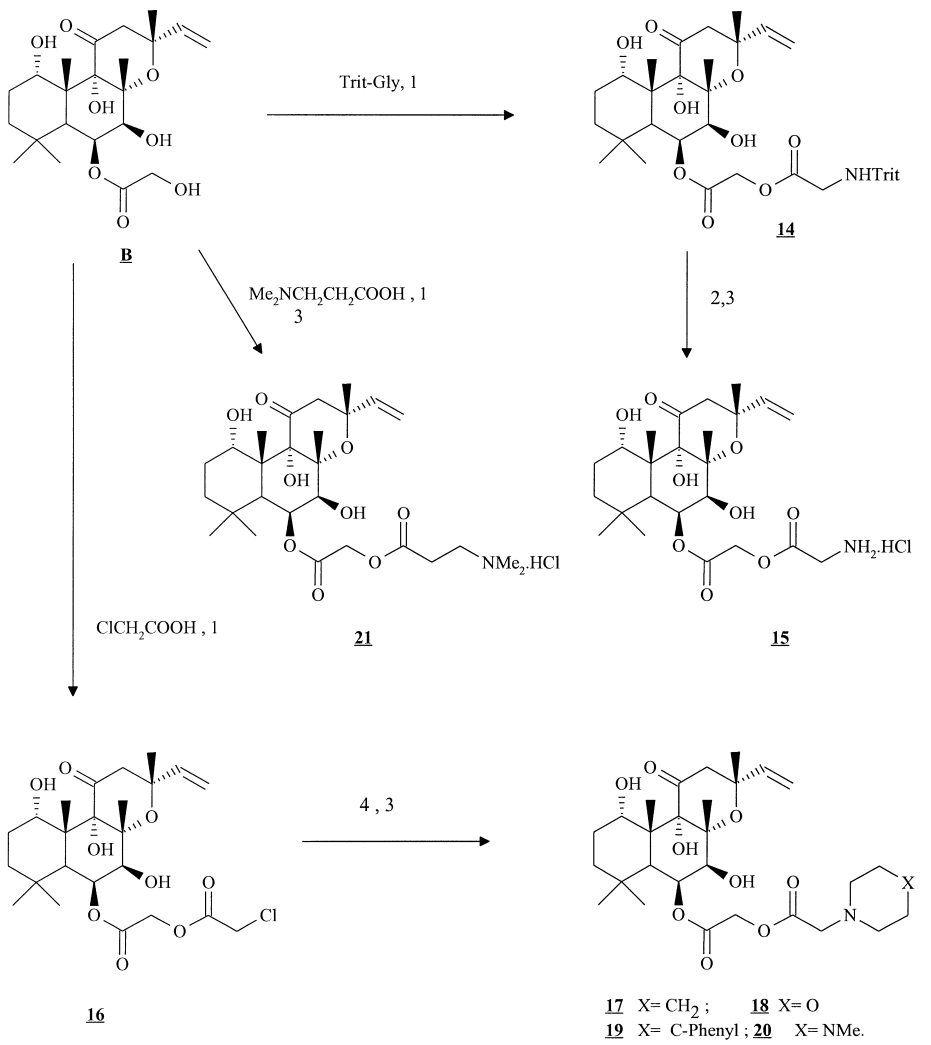

**Scheme 1.** 1. DCC, DMAP, EtOAc or (EtOAc + DMF) 2. TFA, ether. 3. HCl, ether. 4. $R_1R_2NH$, $CH_2Cl_2$, r.t./45 °C (for **7**)/70–80 °C (for **8**).

## 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 and the values were expressed in $cm^{-1}$. $^1H$ NMR spectra were recorded in $CDCl_3$ unless otherwise mentioned on a JEOL FT-90 Spectrometer with TMS as internal standard and coupling constant values are expressed in Hz. (Protons at positions 2 & 3 of ring A in Forskolin are buried under methyl signals, hence have not been mentioned separately). 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 anisaldehyde-$H_2SO_4$ spray reagent were used and heated the plates at 110 °C for visualization. All compounds were homogeneous on TLC and gave proper spectral characteristics.

**8,13-Epoxy-7β-(2-tertiarybutyloxycarbonylaminomethylcarbonyloxy)acetyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (1).** To a solution of compound **A** (0.43 g; 1 mmol) and DCC (0.247 g; 1.2 mmol) in EtOAc (15 mL), a solution of Boc-Gly (0.192 g; 1.1 mmol) in EtOAc (5 mL) was added under stirring at room temperature, followed by DMAP (0.12 g; 1 mmol). The reaction mixture was stirred at room temperature for 3 h. The DCU was filtered off and the filtrate was washed with aqueous $NaHCO_3$ followed by brine. The EtOAc layer was dried over anhydrous $Na_2SO_4$. The




**Scheme 2.** 1. DCC, DMAP, EtOAc (or EtOAc + DMF) 2. TFA, ether. 3. HCl, ether. 4. HN⟨ ⟩X, $CH_2Cl_2$, r.t.

**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.) |
| **1** | NA | 0.3 | 40 | 60 |
| **3** | 0.1 | 1.0 | 120 | > 70 |
| **5** | 0.3 | 0.1 | 40 | 120 |
| **6** | 0.03 | — | — | — |
| **7** | 1.0 | 0.1 | 20 | > 210 |
| **8** | 0.55 | 3.0 | 100 | > 120 |
| **9** | NA | 1.0 | 60 | 60 |
| **10** | NA | — | — | — |
| **11** | 0.5 | 1.0 | 60 | 30 |
| **12** | 0.1 | 0.3 | 80 | 60 |
| **13** | > 1.0 | 3.0 | 80 | 100 |
| **15** | > 10.0 | 5.0 | 80 | > 90 |
| **17** | 0.58 | — | — | — |
| **18** | 0.04 | 1.0 | 40 | 30 |
| **19** | — | NA | | |
| **20** | — | 3.0 | 20 | 30 |
| **21** | 1.0 | — | — | — |
| **Forskolin** | 0.02 | 0.1 | 63.7 ± 5.5 | 55.0 ± 3.9 |

NA = Not active; - = Not done *No significant activity below the dose mentioned.

solvent was evaporated. The residue was purified by flash chromatography with 30% EtOAc–light petroleum. Yield, 0.43 g (73.7%) as amorphous powder; IR: 3460 (br), 3000, 2960, 1765 (br), 1725 (br); $^1$H NMR: 1.02, 1.26, 1.34, 1.71 (4×s, 12H, 4×C$\underline{H}_3$), 1.46 [s, 12H, C$\underline{H}_3$ + C(C$\underline{H}_3$)$_3$], 2.14 (d, 1H, J = 2.53, 5$\underline{H}$), 2.44 (d, 1H, $J_{gem}$ = 16.71, 12β$\underline{H}$), 3.16 (d, 1H, $J_{gem}$ = 16.71, 12α$\underline{H}$), 3.85–4.02 (m, 2H, COC$\underline{H}_2$NH), 4.44 (t, 1H, J = 3.04, 6$\underline{H}$), 4.54 (br, 1H, 1$\underline{H}$), 4.72 (s, 2H, COC$\underline{H}_2$O), 4.93 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 1.6, 15$\underline{H}_{cis}$), 5.21 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.6, 15$\underline{H}_{trans}$), 5.45 (d, 1H, J = 4.05, 7$\underline{H}$), 5.91 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{29}H_{45}O_{11}N$ : C, 59.68; H, 7.77; N, 2.40; found: C, 59.88; H, 7.92; N, 2.31%.

**8,13-Epoxy-1α,6β,9α-trihydroxy-7β-(tritylaminomethylcarbonyloxy)acetyloxylabd-14-en-11-one (2).** The compound **A** was treated with Trit-Gly by the same method. The pure product was amorphous solid. Yield, 82%; IR: 3542 (br), 2975, 2945, 1757, 1725; $^1$H NMR: 1.03, 1.24, 1.31, 1.43, 1.64 (5×s, 15H, 5×C$\underline{H}_3$), 2.16 (br, 1H, 5$\underline{H}$), 2.41 (d, 1H, $J_{gem}$ = 17.2, 12β$\underline{H}$), 3.18 (d, 1H, $J_{gem}$ = 17.2, 12α$\underline{H}$), 3.34 (br, 2H, C$\underline{H}_2$NH), 4.40–4.60 (m, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.60 (br s, 2H, COC$\underline{H}_2$O), 4.90 (dd, 1H, $J_{cis}$ = 10.6, $J_{gem}$ = 2.0, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, $J_{trans}$ = 17.2, $J_{gem}$ = 2.0, 15$\underline{H}_{trans}$), 5.43 (d, 1H, J = 3.04, 7$\underline{H}$), 5.92 (dd, 1H, $J_{trans}$ = 17.2, $J_{cis}$ = 10.6, 14$\underline{H}$), 7.2–7.5 (m, 15H, 15×Ph$\underline{H}$). Anal. calcd for $C_{42}H_{51}O_9N$: C, 71.15; H, 7.08; N, 1.93; found: C, 70.98; H, 7.04; N, 1.89%.

**7β - (Aminomethylcarbonyloxy)acetyloxy - 8, 13 - epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one, hydrochloride (3).** Compound **2** (0.1 g; 0.14 mmol) was dissolved in ether (10 mL) and TFA (0.2 mL) was added. The clear solution was kept at room temperature. When most of the starting material disappeared (nearly 1 h), ethereal HCl was added dropwise till no further precipitation occurred. The white solid was filtered off and washed with dry ether several times. The solid was dried in a vacuum pump for 2 h. The white solid was recrystallized from MeOH–dry ether. Yield 0.052 g (68.9%); IR: 3360 (br), 2950 (br), 1765, 1760, 1727; $^1$H NMR ($CD_3OD$): 1.0, 1.25, 1.32, 1.43, 1.70 (5×s, 15H, 5×C$\underline{H}_3$), 2.1 (d, 1H, J = 3.04, 5$\underline{H}$), 2.35 (d, 1H, $J_{gem}$ = 16.2, 12β$\underline{H}$), 3.2 (d, 1H, $J_{gem}$ = 16.2, 12α$\underline{H}$), 3.94 (s, 2H, COC$\underline{H}_2$N), 4.35–4.46 (m, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.85 (dd, 1H, $J_{cis}$ = 10.53, $J_{gem}$ = 1.62, 15$\underline{H}_{cis}$), 4.90 (s, 2H, COC$\underline{H}_2$O), 5.06 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.62, 15$\underline{H}_{trans}$), 5.95 (d, 1H, J = 4.56, 7$\underline{H}$), 6.02 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.53, 14$\underline{H}$). Anal. calcd for $C_{24}H_{38}O_9NCl$, $H_2O$: C, 53.57; H, 7.49; N, 2.60; Cl, 6.59; found: C, 53.63; H, 7.59; N, 2.58; Cl, 6.44%.

**7β-(Chloroacetyloxy)acetyloxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (4).** Compound **A** (4.4 g; 10.33 mmol) was stirred at room temperature with chloroacetic acid (1.04 g; 11 mmol), DCC (2.47 g; 12 mmol) and DMAP (1.34 g; 10.98 mmol) in EtOAc (60 mL) for 16 h. The DCU was filtered off and the filtrate was washed with 1N aq. $NaHCO_3$ followed by brine. The EtOAc layer was dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the crude product was purified by flash chromatography with 10% $CH_3CN$–$CHCl_3$. Yield 4 g. (77.1%); m.p., 168–70 °C (EtOAc–light petroleum); IR: 3450, 2950, 1790, 1775, 1715, 1705; $^1$H NMR: 1.06, 1.30, 1.37, 1.46, 1.71 (5×s, 15H, 5×C$\underline{H}_3$), 2.19 (d, 1H, J = 3.04, 5$\underline{H}$), 2.45 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.19 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 4.06 (s, 2H, C$\underline{H}_2$Cl), 4.56 (m, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.80 (s, 2H, COC$\underline{H}_2$O), 4.94 (dd, 1H, $J_{cis}$ = 11.13, $J_{gem}$ = 2.03, 15$\underline{H}_{cis}$), 5.21 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 2.03, 15$\underline{H}_{trans}$), 5.48 (d, 1H, J = 4.05, 7$\underline{H}$), 5.96 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.13, 14$\underline{H}$). Anal. calcd for $C_{24}H_{35}O_9Cl$ : C, 57.31; H, 7.01; Cl, 7.05; found: C, 57.29; H, 7.23; Cl, 7.20%.

**7β-[3-(Dimethylamino)propanoyloxy]acetyloxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (5).** Compound **A** (0.426 g; 1 mmol) and DCC (0.21 g; 1.02 mmol) were dissolved in EtOAc (5 mL) and DMF (2 mL). To the clear solution 3-dimethylaminopropionic acid hydrochloride (0.153 g; 1 mmol) was added followed by DMAP (0.185 g; 1.5 mmol). The reaction mixture was stirred at room temperature for 16 h. After usual work up (see exptl for **1**). The crude product was purified by flash chromatography with 20% $CH_3CN$–$CHCl_3$

followed by 10% MeOH–$CHCl_3$. The pure material was converted into hydrochloride salt in EtOAc and HCl–dry ether. Yield 56%; m.p., 214–15 °C (MeOH-dry ether); IR: 3400–3300 (br), 2950 (br), 1775, 1750 (br), 1720; $^1$H NMR ($CDCl_3 + CD_3OD$): 1.03, 1.27, 1.36, 1.43, 1.71 (5×s, 15H, 5×C$\underline{H}_3$), 2.14 (d, 1H, J = 3.04, 5$\underline{H}$), 2.39 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.86, 2.89 [2×s, 6H, N(C$\underline{H}_3$)$_2$], 2.93–3.17 (br, 3H, $CH_2C\underline{H}_2N$ & 12α$\underline{H}$), 3.37 (t, 2H, J = 6.08, COC$\underline{H}_2CH_2$), 4.49 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.70, 4.91 (2×d, 2H, $J_{gem}$ = 15.2, COC$\underline{H}_2$O), 4.91 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.5, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.5, 15$\underline{H}_{trans}$), 5.41 (d, 1H, J = 4.05, 7$\underline{H}$), 6.00 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$). Anal. calcd for $C_{27}H_{44}O_9NCl$, $2H_2O$: C, 54.22; H, 8.08; N, 2.34; Cl, 5.93; found: C, 54.03; H, 8.24; N, 2.32; Cl, 5.69%.

**7β-(Diethylaminomethylcarbonyloxy)acetyloxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one, hydrochloride (6).** To a solution of **4** (3.96 g; 7.88 mmol) in $CH_2Cl_2$ (40 mL), diethyl amine (4 mL) was added and the clear solution was kept at room temperature for 14 h. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography with 10% $CH_3CN$–$CHCl_3$ (to remove unreacted **4** and hydrolyzed product **A** followed by 20% $CH_3CN$–$CHCl_3$. The fraction containing the required compound was evaporated and redissolved in EtOAc. To the clear solution HCl in dry ether was added. The mixture was evaporated to small volume and excess dry ether was added. The white precipitate was collected and dried. It was recrystallized from dry MeOH–dry ether. Yield, 2 g (44%); m.p., 140–42 °C; IR: 3380 (br), 2960 (br), 1765 (br), 1728; $^1$H NMR: 1.03, 1.26, 1.34, 1.43, 1.69 (5×s, 15H, 5×C$\underline{H}_3$), 1.47 (t, 6H, J = 6.58, 2×$CH_2C\underline{H}_3$), 2.16 (d, 1H, J = 3.04, 5$\underline{H}$), 2.41 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.19 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.26–3.47 (m, 4H, 2×$CH_3C\underline{H}_2N$.HCl), 3.99 (s, 2H, COC$\underline{H}_2NEt_2$), 4.37–4.60 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.84 (s, 2H, COC$\underline{H}_2$O), 4.87 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 2.03, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 2.03, 15$\underline{H}_{trans}$), 5.50 (d, 1H, J = 4.05, 7$\underline{H}$), 5.90 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{28}H_{46}O_9NCl$, $1.5H_2O$: C, 55.76; H, 8.19; N, 2.32; Cl, 5.88; found: C, 55.98; H, 8.25; N, 2.23; Cl, 6.18%.

**7β-(Diisopropylaminomethylcarbonyloxy)acetyloxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one, hydrochloride (7).** The compound **4** (0.25 g; 0.5 mmol) was heated with diisopropyl amine (2 mL) at 45 °C for 3 h. Diisopropyl amine was removed under reduced pressure and the residue was purified by flash chromatography as described for **6**. Yield, 0.121 g (40%); m.p., 148–50 °C (MeOH-dry ether); IR: 3410 (br), 2990 (br), 1770 (br), 1730; $^1$H NMR: 1.03, 1.30, 1.34, 1.43, (4×s, 12H, 4×C$\underline{H}_3$), 1.49–1.63 [br m, 12H, 2×CH(C$\underline{H}_3$)$_2$], 1.70 (s, 3H, C$\underline{H}_3$), 2.14 (d, 1H, J = 2.53, 5$\underline{H}$), 2.44 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.18 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.99 (m, 4H, 2×C$\underline{H}$Me$_2$ + COC$\underline{H}_2$NPr$^i_2$.HCl), 4.43–4.63 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.83 (s, 2H, COC$\underline{H}_2$O), 4.89 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 1.63, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, $J_{trans}$ = 16.21, $J_{gem}$ = 1.63, 15$\underline{H}_{trans}$), 5.51 (d, 1H, J = 4.05, 7$\underline{H}$), 5.94 (dd, 1H, $J_{trans}$ = 16.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{30}H_{50}O_9NCl$, $1.5H_2O$: C, 57.08; H, 8.46; N, 2.22; Cl, 5.62; found: C, 56.97; H, 8.44; N, 2.01; Cl, 5.53%.

**8,13-Epoxy-1α,6β,9α-trihydroxy-7β-[(3,4,5-trimethoxyanilino)methylcarbonyloxy]acetyloxylabd-14-en-11-one (8).** A solution of **4** (0.25 g; 0.5 mmol) and 3,4,5-trimethoxyaniline (0.18 mL) in toluene (3 mL) was heated at 70–80 °C for 16 h. The solvent was removed and the residue was purified by flash chromatography with 10% $CH_3CN$–$CHCl_3$. Yield, 0.06 g (20%); m.p., 108–09 °C (EtOAc–light petroleum); IR; 3440 (br), 2950 (br), 1765, 1760, 1725; $^1$H NMR: 1.03, 1.24, 1.34, 1.41, 1.67 (5×s, 15H, 5×C$\underline{H}_3$), 2.19 (d, 1H, J = 3.04, 5$\underline{H}$), 2.44 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.19 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.74 (s, 3H, OC$\underline{H}_3$), 3.81 (s, 6H, 2×OC$\underline{H}_3$), 4.03 (s 2H, COC$\underline{H}_2$N), 4.54 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.79 (s, 2H, COC$\underline{H}_2$O), 4.93 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.62, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.62, 15$\underline{H}_{trans}$), 5.47 (d, 1H, J = 4.05, 7$\underline{H}$), 5.86 (s, 2H, Ar$\underline{H}$), 5.96 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$). Anal. calcd for $C_{33}H_{47}O_{12}N$, $H_2O$: C, 59.35; H, 7.39; N, 2.09 ; found: C, 59.54 H, 7.22; N, 2.18%.

Compounds **9**–**13** were prepared from **4** with the use of appropriate amine by the method as described for the synthesis of compound **6**.

**8,13-Epoxy-7β-[(homopiperidino)methylcarbonyloxy]-acetyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (9).** The crude product was purified by flash chromatography with 20% $CH_3CN$–$CHCl_3$. Yield, 30%, as hydrochloride salt; m.p., 146–48 °C; IR; 3400 (br), 2960 (br), 1765 (br), 1728; $^1$H NMR: 1.04, 1.27, 1.34, 1.44, 1.71 (5×s, 15H, 5×C$\underline{H}_3$), 1.74–2.31 [m, 8H, 4×C$\underline{H}_2$ (3′, 4′, 5′ & 6′)], 2.14 (d, 1H, J = 3.04, 5$\underline{H}$), 2.43 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.19 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.43 [br, 4H, 2×C$\underline{H}_2$ (2′ & 7′)], 4.04 (br 2H, COC$\underline{H}_2$N), 4.56 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.86 (br, 2H, COC$\underline{H}_2$O), 4.91 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.82, 15$\underline{H}_{cis}$), 5.21 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.82, 15$\underline{H}_{trans}$), 5.51 (d, 1H, J = 4.05, 7$\underline{H}$), 5.94 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$). Anal. calcd for $C_{30}H_{48}O_9NCl$, 1.5 $H_2O$: C, 58.76; H, 8.39; N, 2.28; Cl, 5.78 ; found: C, 58.56 H, 8.12; N, 2.27; Cl, 5.39%.

**7β-(2,6-Dimethylmorpholinomethylcarbonyloxy)acetyloxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one (10).** Yield, 0.094 g (30.5%), as hydrochloride salt; m.p., 158–60 °C; IR: 3400 (br), 2950 (br), 1762 (br), 1723; $^1$H

NMR: 1.05 (s, 3H, $C\underline{H}_3$), 1.23, 1.30 (2×d, 6H, J = 6.38, 2×CHC$\underline{H}_3$), 1.26 (s, 6H, 2×C$\underline{H}_3$), 1.43, 1.69 (2×s, 6H, 2×C$\underline{H}_3$), 2.27 (d, 1H, J = 2.03, 5$\underline{H}$), 2.41 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.57–2.91 [m, 4H, 2×C$\underline{H}_2$ (3′ & 5′)], 3.18 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.41 (m, 2H, 2×CHC$\underline{H}_3$), 3.84 (m, singlet after $D_2O$ exchange, 2H, COC$\underline{H}_2$N), 4.37–4.58 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.81 (s, 2H, COC$\underline{H}_2$O), 4.87 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 1.6, 15$\underline{H}_{cis}$), 5.17 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.6, 15$\underline{H}_{trans}$), 5.48 (d, 1H, J = 4.05, 7$\underline{H}$), 5.89 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{30}H_{48}O_{10}NCl$: C, 58.29; H, 7.83; N, 2.27; Cl, 5.74; found: C, 58.05; H, 7.92; N, 2.21; Cl, 5.90%.

**8,13-Epoxy-7β-[(4-phenylpiperidino)methylcarbonyloxy]-acetyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (11).** The crude product was purified by flash chromatography with 10% $CH_3CN$–$CHCl_3$. Yield, 33%; m.p., 99–101 °C (EtOAc–light petroleum); IR: 3445 (br), 3150 (br), 2970 (br), 1775 (br), 1725; $^1$H NMR: 1.03, 1.27, 1.36, 1.43, 1.70 (5×s, 15H, 5×C$\underline{H}_3$), 1.86, 2.20 (2×m, 5H, 3′-C$\underline{H}_2$, 5′-C$\underline{H}_2$ + 5$\underline{H}$), 2.44 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.79 (m, 1H, 4′-C$\underline{H}$), 3.07, 3.17 (2×m, 5H, 2′-C$\underline{H}_2$, 6′-C$\underline{H}_2$ & 12α$\underline{H}$), 3.39 (s, 2H, COC$\underline{H}_2$N), 4.43–4.60 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.74 (s, 2H, COC$\underline{H}_2$O), 4.93 (dd, 1H, $J_{cis}$ = 10.63, $J_{gem}$ = 2.03, 15$\underline{H}_{cis}$), 5.20 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 2.03, 15$\underline{H}_{trans}$), 5.48 (d, 1H, J = 4.56, 7$\underline{H}$), 5.94 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.63, 14$\underline{H}$), 7.21 (br 5H, 5×Ph-$\underline{H}$). Anal. calcd for $C_{35}H_{49}O_9N$: C, 66.96; H, 7.86; N, 2.23; found: C, 67.23; H, 8.10; N, 2.39%.

**8,13-Epoxy-7β-[(4-methylpiperazino)methylcarbonyloxy]-acetyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (12).** The crude product was purified by flash chromatography with 20% $CH_3CN$–$CHCl_3$ followed by 10% MeOH–$CHCl_3$. Yield, 51% as free base; m.p., 95–97 °C (EtOAc–light petroleum); IR: 3550 (br), 3220 (br), 2970 (br), 1775 (br), 1725; $^1$H NMR: 1.04, 1.26, 1.34, 1.43, 1.70 (5×s, 15H, 5×C$\underline{H}_3$), 2.17 (d, 1H, J = 3.04, 5$\underline{H}$), 2.29 (s, 3H, NC$\underline{H}_3$), 2.44 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.56, 2.63 (2×m, 8H, 2′-C$\underline{H}_2$, 3′-C$\underline{H}_2$, 5′-C$\underline{H}_2$ & 6′-C$\underline{H}_2$), 3.19 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.33 (s, 2H, COC$\underline{H}_2$N), 4.40–4.57 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.74 (s, 2H, COC$\underline{H}_2$O), 4.91 (dd, 1H, $J_{cis}$ = 11.13, $J_{gem}$ = 1.82, 15$\underline{H}_{cis}$), 5.19 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.82, 15$\underline{H}_{trans}$), 5.48 (d, 1H, J = 4.05, 7$\underline{H}$), 5.95 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.13, 14$\underline{H}$). Anal. calcd for $C_{29}H_{46}O_9N_2$: C, 61.46; H, 8.18; N, 4.94; found: C, 61.28; H, 8.39; N, 4.99%.

**8,13-Epoxy-7β-[(4-carbethoxypiperazino)methylcarbonyloxy]acetyloxy-1α,6β,9α-trihydroxylabd-14-en-11-one (13).** The crude product was purified by flash chromatography with 18% $CH_3CN$–$CHCl_3$. Hydrochloride salt was prepared from EtOAc–HCl in dry ether. Yield, 28.4%; m.p., 157–58 °C (MeOH–dry ether); IR: 3420 (br), 2950 (br), 1765 (br), 1725; $^1$H NMR: 1.04 (s, 3H, C$\underline{H}_3$), 1.20 (t, 3H, J = 7.08, OCH$_2$C$\underline{H}_3$), 1.30, 1.37, 1.46, 1.71 (4×s, 12H, 4×C$\underline{H}_3$), 2.14 (d, 1H, J = 3.04, 5$\underline{H}$), 2.42 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.80 (br, triplet after $D_2O$ exchange, 4H, J = 6.08, 2′-C$\underline{H}_2$, 6′-C$\underline{H}_2$), 3.20 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.30 (br, t after $D_2O$ exchange, 4H, J = 6.08, 3′-C$\underline{H}_2$ & 5′-C$\underline{H}_2$), 3.91 (br, triplet after $D_2O$ exchange, 2H, COC$\underline{H}_2$N), 4.14 (quartet, 2H, J = 7.08, C$\underline{H}_2$CH$_3$), 4.57 (br, 2H, 1$\underline{H}$ & 6$\underline{H}$), 4.86 (s, 2H, COC$\underline{H}_2$O), 4.91 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.62, 15$\underline{H}_{cis}$), 5.18 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.62, 15$\underline{H}_{trans}$), 5.50 (d, 1H, J = 4.05, 7$\underline{H}$), 5.95 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$). Anal. calcd for $C_{31}H_{49}O_{11}N_2Cl$: C, 54.82; H, 7.57; N, 4.12; Cl, 5.21; found: C, 55.01; H, 7.65; N, 4.12; Cl, 5.92%.

**8,13-Epoxy-1α,7β,9α-trihydroxy-6β-(tritylaminomethylcarbonyloxy)acetyloxylabd-14-en-11-one (14).** Compound **B** was treated with Trit-Gly by DCC-DMAP method (see experimental for compound **1**) The crude product was purified by flash chromatography with 15% EtOAc–light petroleum. Yield, 75%; white amorphous powder; IR: 3450 (br), 2940 (br), 1755 (br), 1720; $^1$H NMR: 0.92, 1.04, 1.24, 1.38, 1.45 (5×s, 15H, 5×C$\underline{H}_3$), 2.31(d, 1H, J = 3.04, 5$\underline{H}$), 2.46 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.16 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.18 (s, 2H, COC$\underline{H}_2$N), 4.23 (br, doublet after $D_2O$, 1H, J = 4.23, 7$\underline{H}$), 4.56 (br, 3H, COC$\underline{H}_2$O & 1$\underline{H}$), 4.93 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 1.52, 15$\underline{H}_{cis}$), 5.11 (dd, 1H, $J_{trans}$ = 16.7, $J_{gem}$ = 1.52, 15$\underline{H}_{trans}$), 5.86 (t, 1H, J = 2.33, 6$\underline{H}$), 6.05 (dd, 1H, $J_{trans}$ = 16.7, $J_{cis}$ = 10.13, 14$\underline{H}$), 7.07–7.53 (m, 15H, 15×Ph$\underline{H}$). Anal. calcd for $C_{43}H_{51}O_9N$: C, 71.15; H, 7.08; N, 1.93; found: C, 71.32; H, 7.19; N, 1.87%.

**8,13-Epoxy-6β-(aminomethylcarbonyloxy)acetyloxy-1α,7β,9α-trihydroxylabd-14-en-11-one, hydrochloride (15).** This compound was obtained by deprotecting trityl group from **14** (for details see experimental for **3**). Yield, 55%; m.p., 165–67 °C (MeOH–dry ether); IR: 3425 (br), 2925 (br), 1758 (br), 1715; $^1$H NMR ($CD_3OD$):1.01, 1.03, 1.37, 1.41, 1.53 (5×s, 15H, 5×C$\underline{H}_3$), 2.36 (d, 1H, J = 3.04, 5$\underline{H}$), 2.35, 3.23 (2×d, 2H, $J_{gem}$ = 16.2, 12β$\underline{H}$ & 12α$\underline{H}$), 3.91 (s, 2H, COC$\underline{H}_2$N), 4.22 (d, 1H, J = 5.06, 7$\underline{H}$), 4.46 (br, 1H, 1$\underline{H}$), 4.81 (s, 2H, COC$\underline{H}_2$O), 4.84 (dd, 1H, $J_{cis}$ = 10.33, $J_{gem}$ = 1.5, 15$\underline{H}_{cis}$), 5.09 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.5, 15$\underline{H}_{trans}$), 5.80 (dd, 1H, J = 3.04, 5.06, 6$\underline{H}$), 6.11 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.33, 14$\underline{H}$). Anal. calcd for $C_{24}H_{38}O_9NCl$, $H_2O$: C, 53.57; H, 7.49; N, 2.60; Cl, 6.59; found: C, 53.85; H, 7.49; N, 2.25; Cl, 6.58%.

**6β-(Chloroacetyloxy)acetyloxy-8,13-epoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (16).** This compound was prepared by the same method as described for the preparation of **4** (Scheme 1). The crude product was purified by flash chromatography with 8% $CH_3CN$–$CHCl_3$. Yield, 40%; $^1$H NMR: 1.0, 1.09, 1.39, 1.41, 1.59 (5×s,

15H, 5×C$\underline{H}_3$), 2.37 (d, 1H, J = 3.04, 5$\underline{H}$), 2.49 (d, 2H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.20 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 4.16 (s, 2H, COC$\underline{H}_2$Cl), 4.30 (d, 1H, J = 4.56, 7$\underline{H}$), 4.64 (br, 1H, 1$\underline{H}$), 4.74 (s, 2H, COC$\underline{H}_2$O), 4.97 (dd, 1H, $J_{cis}$ = 10.53, $J_{gem}$ = 1.82, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.82, 15$\underline{H}_{trans}$), 5.94 (dd, 1H, J = 4.05, 3.04, 6$\underline{H}$), 6.11 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.53, 14$\underline{H}$). Anal. calcd for $C_{24}H_{35}O_9Cl$: C, 57.31; H, 7.01; Cl, 7.05; found: C, 57.25; H, 7.08; Cl, 7.25%.

The compound **16** was treated with the required amine in dichloromethane for 16 h as described for the synthesis of compound **6** to generate **17** to **20**.

**8,13-Epoxy-6β-(piperidinomethylcarbonyloxy)acetyloxy-1α,7β,9α-trihydroxylabd-14-en-11-one, hydrochloride (17).** The crude product was purified by flash chromatography with 15% $CH_3CN$–$CHCl_3$ followed by 5% MeOH–$CHCl_3$. Yield, 41%; m.p., 149–50 °C (MeOH–dry ether); IR: 3450–3280 (br), 2970 (br), 1765 (br), 1705; $^1$H NMR: 1.0, 1.09, 1.37, 1.40, 1.56 (5×s, 15H, 5×C$\underline{H}_3$), 1.60–2.57 (m, 6H, 3′-C$\underline{H}_2$, 4′-C$\underline{H}_2$ & 5′-C$\underline{H}_2$), 2.36 (d, 1H, J = 3.04, 5$\underline{H}$), 2.49 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.20 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$), 3.57–3.97 (2×m, 4H, 2′-C$\underline{H}_2$ & 6′C$\underline{H}_2$), 4.17 (br, 2H, COC$\underline{H}_2$N), 4.31 (d, 1H, J = 5.06, 7$\underline{H}$), 4.64 (br, 1H, 1$\underline{H}$), 4.74 (s, 2H, COC$\underline{H}_2$O), 4.96 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.82, 15$\underline{H}_{cis}$), 5.15 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.82, 15$\underline{H}_{trans}$), 5.91 (br, 1H, 6$\underline{H}$), 6.12 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$). Anal. calcd for $C_{29}H_{46}O_9NCl$: C, 59.22; H, 7.88; N, 2.38; Cl, 6.03 ; found: C, 59.42; H, 8.14; N, 2.29; Cl, 5.88%.

**8,13-Epoxy-6β-(morpholinomethylcarbonyloxy)acetyloxy-1α,7β,9α-trihydroxylabd-14-en-11-one (18).** The crude product was purified by flash chromatography with 5% MeOH–$CHCl_3$ and was converted into hydrochloride salt in EtOAc and HCl–ether. Yield, 40%; m.p., 168–70 °C (MeOH–dry ether); IR: 3450 (br), 2960 (br), 1765 (br), 1722; $^1$H NMR: 1.0, 1.1, 1.39, 1.41, 1.57 (5×s, 15H, 5×C$\underline{H}_3$), 2.39 (d, 1H, J = 3.04, 5$\underline{H}$), 2.49 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 3.21 (d, 1H, $J_{gem}$ = 17.21, 12α$\underline{H}$); 3.39–3.53 (m, 4H, 3′-C$\underline{H}_2$ & 5′-C$\underline{H}_2$), 4.0 (br, 2H, COC$\underline{H}_2$N), 4.03–4.20 (m, 4H, 2′-C$\underline{H}_2$ & 6′-C$\underline{H}_2$), 4.31 (d, 1H, J = 4.05, 7$\underline{H}$), 4.67 (br, 1H, 1$\underline{H}$), 4.77 (br, 2H, COC$\underline{H}_2$O), 4.97 (dd, 1H, $J_{cis}$ = 10.13, $J_{gem}$ = 2.03, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 2.03, 15$\underline{H}_{trans}$), 5.91 (dd, 1H, J = 3.04, 4.05, 6$\underline{H}$), 6.05 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{28}H_{44}O_{10}NCl$, 2.5 $H_2O$ : C, 53.11; H, 7.48; N, 2.21; Cl, 5.59 ; found: C, 53.15; H, 7.91; N, 2.13; Cl, 5.60%.

**8,13-Epoxy-6β-[(4-phenylpiperidino)methylcarbonyloxy]-acetyloxy-1α,7β,9α-trihydroxylabd-14-en-11-one (19).** The crude material was purified by flash chromatography with 15% $CH_3CN$–$CHCl_3$. The pure product was converted into hydrochloride salt from dry EtOAc–dry HCl and crystallized from MeOH–dry ether. Yield, 31%; m.p., 155–56 °C ; IR: 3420–3250 (br), 2970 (br), 1760 (br), 1720; $^1$H NMR: 1.0, 1.07, 1.39, 1.40, 1.57 (5×s, 15H, 5×C$\underline{H}_3$), 1.91–2.14 (m, 4H, 3′-C$\underline{H}_2$, & 5′-C$\underline{H}_2$), 2.37 (br, 1H, 5$\underline{H}$), 2.47 (d, 1H, $J_{gem}$ = 16.2, 12β$\underline{H}$), 2.61 (m, 1H, 4′-C$\underline{H}$), 2.71–3.64 (2×m, 4H, 2′-C$\underline{H}_2$ & 6′-C$\underline{H}_2$), 3.21 (d, 1H, $J_{gem}$ = 16.2, 12α$\underline{H}$); 4.06 (m, 2H, COC$\underline{H}_2$N), 4.32 (d, 1H, J = 5.06, 7$\underline{H}$), 4.66 (br, 1H, 1$\underline{H}$), 4.73 (br, s after $D_2O$ exchange, 2H, COC$\underline{H}_2$O), 4.96 (dd, 1H, $J_{cis}$ = 11.14, $J_{gem}$ = 1.52, 15$\underline{H}_{cis}$), 5.15 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.52, 15$\underline{H}_{trans}$), 5.91 (dd, 1H, J = 3.04, 5.06, 6$\underline{H}$), 6.12 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 11.14, 14$\underline{H}$), 7.29 (br s, 5H, 5×Ph$\underline{H}$). Anal. calcd for $C_{35}H_{50}O_9NCl$, 0.5 $H_2O$: C, 62.44; H, 7.64; N, 2.08; Cl, 5.27; found: C, 62.51; H, 7.65; N, 2.36; Cl, 5.31%.

**8,13-Epoxy-6β-[(4-methylpiperazino)methylcarbonyloxy]-acetyloxy-1α,7β,9α-trihydroxylabd-14-en-11-one (20).** The crude product was partitioned between cold dil. HCl and EtOAc. The EtOAc layer containing unreacted **16** and hydrolyzed product **B**. The aqueous layer was basified and extracted with EtOAc. The EtOAc layer was washed with brine, dried over anhydrous $Na_2SO_4$. The pure product was converted into hydrochloride salt from EtOAc–dry ether. The product was finally crystallized from dry MeOH–ether. Yield, 34%; m.p., 161–62 °C; IR: 3440 (br), 2970 (br), 1765 (br), 1725; $^1$H NMR ($CDCl_3$ + $CD_3OD$): 1.0, 1.06, 1.40, 1.43, 1.54 (5×s, 15H, 5×C$\underline{H}_3$), 2.39 (d, 1H, J = 3.04, 5$\underline{H}$), 2.40 (d, 1H, $J_{gem}$ = 16.71, 12β$\underline{H}$), 2.96 (s, 3H, NC$\underline{H}_3$), 3.20 (d, 1H, $J_{gem}$ = 16.71, 12α$\underline{H}$); 3.70, 3.97–4.11 (2×m, 10H, 2′-C$\underline{H}_2$, 3′-C$\underline{H}_2$, 5′-C$\underline{H}_2$, 6′-C$\underline{H}_2$ & COC$\underline{H}_2$N), 4.29 (d, 1H, J = 5.06, 7$\underline{H}$), 4.51 (br, 1H, 1$\underline{H}$), 4.80 (br, 2H, COC$\underline{H}_2$O), 4.97 (dd, 1H, $J_{cis}$ = 10.63, $J_{gem}$ = 1.62, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.62, 15$\underline{H}_{trans}$), 5.89 (dd, 1H, J = 3.04, 5.06, 6$\underline{H}$), 6.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.63, 14$\underline{H}$). Anal. calcd for $C_{29}H_{47}O_9N_2Cl$, 1.5 $H_2O$: C, 55.27; H, 8.00; N, 4.45; Cl, 5.63; found: C, 55.38; H, 8.25; N, 4.15; Cl, 5.95%.

**6β-(3-Dimethylaminopropanoyloxy)acetyloxy-8,13-epoxy-1α,7β,9α-trihydroxylabd-14-en-11-one (21).** This was prepared by the treatment of **B** with 3-dimethylamino propionic acid in a manner similar to the synthesis of compound **5**. The crude product was purified by flash chromatography with 5% MeOH–EtOAc followed by 10% MeOH–EtOAc. The pure product was converted into hydrochloride salt from EtOAc and HCl–dry ether. Yield, 50%; m.p., 132–33 °C (MeOH–dry ether); IR: 3450 (br), 2975 (br), 1760 (br), 1728; $^1$H NMR: 1.0, 1.06, 1.37, 1.41, 1.57 (5×s, 15H, 5×C$\underline{H}_3$), 2.37 (d, 1H, J = 3.04, 5$\underline{H}$), 2.48 (d, 1H, $J_{gem}$ = 17.21, 12β$\underline{H}$), 2.82, 2.86 (2×s, 6H, N(C$\underline{H}_3$)$_2$], 2.99–3.43 (m, 5H, COC$\underline{H}_2$C$\underline{H}_2$N & 12α$\underline{H}$); 4.30 (d, 1H, J = 5.06, 7$\underline{H}$), 4.63 (br, 1H, 1$\underline{H}$), 4.69 (s, 2H, COC$\underline{H}_2$O), 4.95 (dd, 1H,

$J_{cis}$ = 10.13, $J_{gem}$ = 1.82, 15$\underline{H}_{cis}$), 5.16 (dd, 1H, $J_{trans}$ = 17.21, $J_{gem}$ = 1.82, 15$\underline{H}_{trans}$), 5.89 (dd, 1H, J = 3.04, 5.06, 6$\underline{H}$), 6.12 (dd, 1H, $J_{trans}$ = 17.21, $J_{cis}$ = 10.13, 14$\underline{H}$). Anal. calcd for $C_{27}H_{44}O_9NCl$, 0.5 $H_2O$: C, 56.78; H, 7.94; N, 2.45; Cl, 6.21; found: C, 56,76; H, 8.24; N, 2.10; Cl, 6.16%.

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