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# Chemical and Biochemical Modifications of Parthenin[1]

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**Abstract:** Parthenin, a medicinally important natural sesquiterpenoid and a potent allelochemical underwent different regio- and stereoselective modifications to several interesting analogues by chemical and biochemical means. The compound was treated with various common reducing agents including $NaBH_4$, $NaBH_4/I_2$, Na/EtOH, Mg/MeOH and Zn/HOAc as well as with different oxidizing agents including *m*-CPBA and dilute HCl under different reaction conditions. The retention of the α-methylene-γ-lactone moiety which plays a vital role for bioactivity of the compound was observed in some of the reaction products. The microwave irradiation of the compound afforded anhydroparthenin as the only product. Baker's yeast reduction of parthenin was investigated for the first time and yielded the naturally occurring dihydrocoronopilin. 

*Keywords*: Parthenin, sesquiterpenoid, α-methylene-γ-lactone, chemical modifications, baker's yeast reduction.

## INTRODUCTION

Parthenin **1**[2,3] the major sesquiterpenoid constituent of the obnoxious weed, *Parthenium hysterophorus* L. (Compositae) exhibits significant medicinal and allelopathic activities. Medicinally, the compound has been found to be of interest for its anticancer,[4,5] antibacterial,[6] antiamoebic[7] and antimalerial properties.[8] As an allelochemical the compound acts as an inhibitor of seed germination[9,10] and possesses antifungal activity.[10] However, the compound is toxic and is known to create allergic contact dermatitis in humans and animals.[11] Various modifications of parthenin **1** have recently been carried out[12-14] to obtain more potent analogues with lower toxicity. The compound **1** contains an α -methylene - γ - lactone moiety which plays a vital role for the bioactivity of the compound and related sesquiterpenoids.[4,13,15] It is difficult to reduce parthenin **1** keeping intact its α -methylene - γ - lactone moiety and still there is no report of the reduction of the compound with retention of this active functionality (ring C). In continuation of our recent work[16,17] on chemical and biochemical modifications of bioactive natural products we have prepared several analogues of parthenin **1**. In some of the reaction products the C ring remains intact.

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## RESULTS AND DISCUSSIONS

The reduction of parthenin **1** was carried out with various readily available reducing agents including $NaBH_4$, $NaBH_4/I_2$, Na/EtOH, Mg/MeOH and Zn/HOAc under different reaction conditions (Scheme 1). On treatment of parthenin **1** with $NaBH_4$ in MeOH two isomeric novel dienes, **2** and **3** were obtained. The first diene is somewhat more polar than the latter. The exocyclic methylene group at C - 11 of **1** was saturated to a methyl in both of compounds **2** and **3.** Compound **2** contains a β - methyl group at C-11 while **3** contains an α - methyl group. The $^1H$ NMR signals of H-7 and Me-11 of **2** appeared at δ 2.88 (1H, m) and 1.07 (3H, d, J = 7.5 Hz) respectively while those of **3** at δ 2.48 and 1.24 (3H, d, J = 7.5 Hz) respectively. The stereochemistry of C-11 of **2** and **3** was settled[18] by comparison of the $^1H$ NMR spectral values of H-7 and Me-11 with those of the compounds of similar stereostructures.

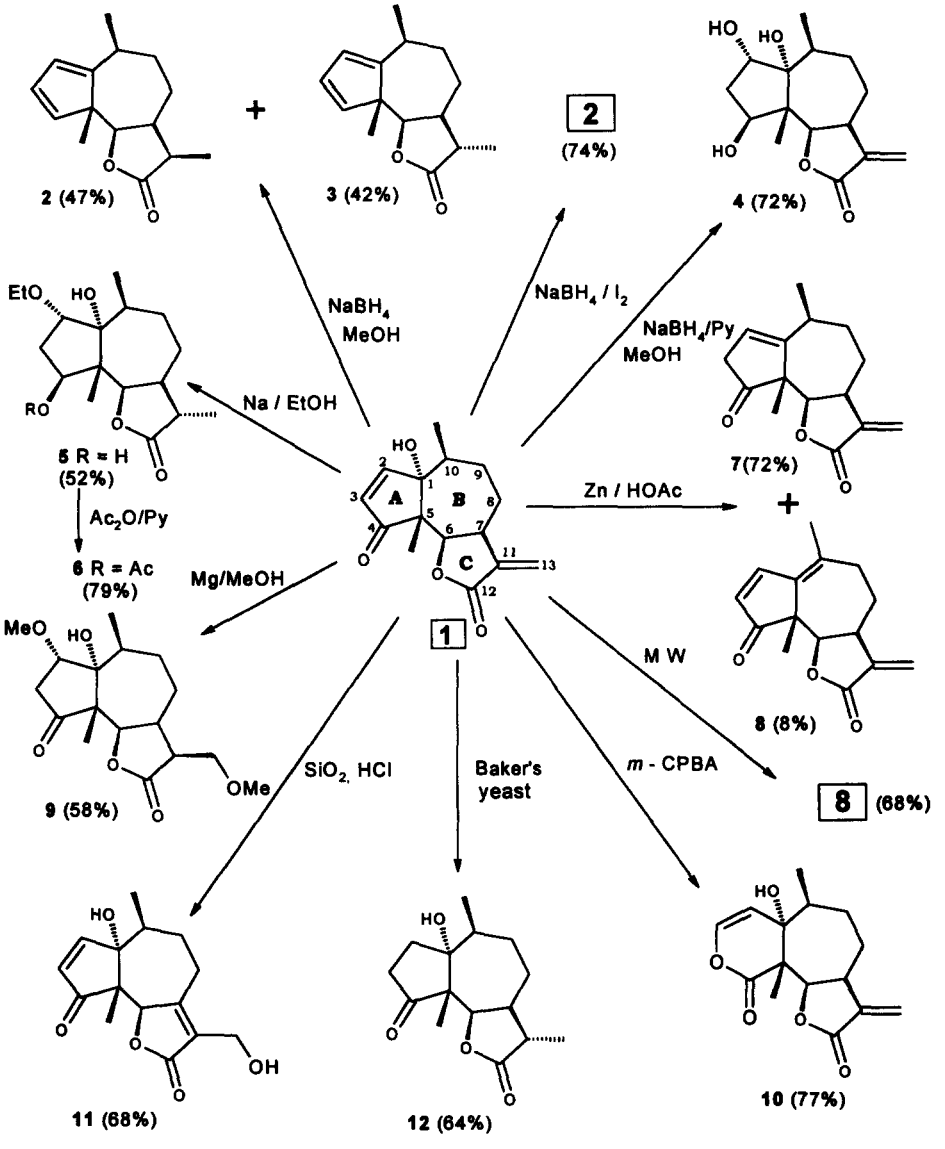
Retention of the α -methylene - γ - lactone moiety of **1** was observed when the compound was treated with $NaBH_4$ in methanolic pyridine. The reduction afforded the product **4** with complete saturation of the A - ring. The product can be utilized for the preparation of various analogues of parthenin with a saturated A-ring and these analogues will be useful for bioevaluation. The stereochemistry at C-2 and C-4 of compound **4** was established by comparison of the $^1H$ NMR values of H-2, H-4, Me-5 and Me-10 of the compound with those reported[19] for the corresponding protons of compounds of a similar system. The formation of **4** can be explained by a Michael type addition of water at the C-2, C-3 double bond of **1** involving attack of a water molecule at C-2 followed by subsequent reduction of the carbonyl group at C-4. Both the addition of a water molecule and the hydride ion occurred from the less hindered α - face of the molecule **1**.

The reduction of parthenin **1** with $NaBH_4/I_2$ in THF afforded only diene **2.** The mixture of $NaBH_4$ and $I_2$ is known[20] to produce borane which transfers hydrogen from the α - face of **1** to saturate its exocyclic double bond forming the β-methyl at C-11.

Treatment of parthenin **1** with sodium in ethanol produced compound **5** with saturation of both the A and C rings. The stereochemistry at C-2 and C-4 of **5** was found to be similar to that of **4** while the methyl group at C-11 was as the α - form which is thermodynamically more stable.[18] No product with a β - methyl at C-11 could be detected. Acetylation of compound **5** with acetic anhydride and pyridine afforded monoacetate **6.**

The retention of the C-ring of parthenin **1** was also observed when the compound was treated with Zn and HOAc. The major product was characterized as neoambrosin **7**,[21] a sesquiterpenoid previously isolated from *Hymenoclea salsola.* The minor product was anhydroparthenin **8**,[3] a constituent of *parthenium hysterophorus*. The formation of **7** can be rationalized (Scheme 2) by an electron transfer from the metal to

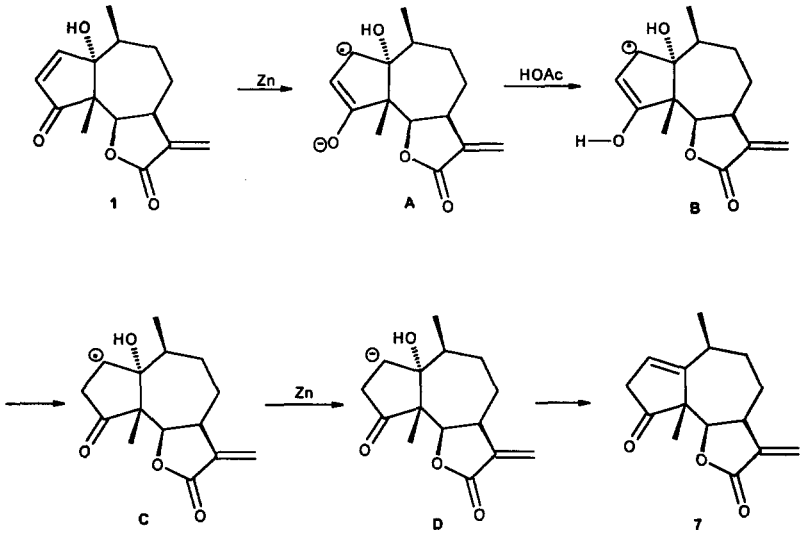
the reacting molecule 1 to form a radical anion A which is trapped by a proton from the solvent to produce the radical C. The latter was converted to the anion D by another electron transfer from the metal. The anion D was subsequently converted to 7. Previously the reduction of parthenin 1 with Zn/HOAc was also carried out by other workers.[2] However, the reduction resulted in deoxygenation of parthenin 1 accompanied by the reduction of exocyclic methylene group.




**Scheme 1:** Reactions of Parthenin 1

Treatment of parthenin **1** with Mg in MeOH saturated both the double bonds present in the compound keeping both the carbonyl groups intact. The structure of the product **9** was clearly established from its spectroscopic data. The compound has been characterized as 2α-13-dimethoxydihydrocoronopilin.[22]

The oxidation of parthenin **1** with *meta*-chloroperbenzoic acid afforded an interesting product **10** where rings B and C were intact while ring A was converted to an unsaturated six-membered lactone. Another interesting compound **11** was formed when parthenin **1** adsorbed on silica gel was treated with dilute HCl. The ring A in the product was unchanged while the double bond in ring C was isomerized and subsequently the C-11 methyl group was oxidized. The ring C generated in **11** has been found in the natural sesquiterpenoid, parthoxetine,[23] a constituent of *Parthenium fruticosum*.




**Scheme 2:** Formation of **7** from **1** by treatment with Zn/HOAc

Microwave irradiation[24] of parthenin **1** for 8 minutes afforded as the only product, anhydroparthenin **8**,[3] an important intermediate for the synthesis of analogues of the parent compound **1**. Previously different methods have been reported [2,3,13,25,26] for the preparation of **8**. However, the present method is most convenient for its preparation.

Parthenin **1** was also treated with baker's yeast which has the capacity of regioselective reduction of the double bond and stereoselective reduction of the carbonyl group. The product was identified here as the naturally occurring dihydrocoronopilin **12**[18,21] which was formed by reduction of both the double bonds of parthenin **1** without affecting its carbonyl groups. Such a biotransformation of parthenin **1** by baker's yeast has not previously been investigated.

In summary, the important bioactive natural sesquiterpenoid, parthenin **1** underwent several regio- and stereoselective modifications to different and interesting analogues by various readily available and inexpensive reducing and oxidizing agents. These analogues will be useful for bioevaluation. The retention of the C-ring which plays a vital role for the bioactivity of parthenin has been observed in some of the reaction products.

## EXPERIMENTAL

M.p.s were measured in a Buchi - 510 apparatus and are uncorrected. Spectra were recorded with the following instruments: UV, Shimadzu 240 spectrophotometer; IR, Nicolet 740 FTIR spectrophotometer; $^1$H NMR, Varian Gemini 200 MHz and MS, VG Micromass 7070 H (70eV) and VG-Autospec M. Column chromatography was performed on silica gel (BDH, 100 - 200 mesh) and TLC with silica gel G. The spots were detected under UV light and in an iodine chamber.

### *Reduction of Parthenin* (1) *with $NaBH_4$ in MeOH*

Parthenin **1** (100 mg, 0.382 mmol) was dissolved in MeOH (10 ml) and cooled in ice. The solution was treated with $NaBH_4$ (100 mg, 2.632 mmol) in small portions. The mixture was kept overnight. MeOH was removed under reduced pressure and water (20 ml) was added to the reaction mixture. The mixture was extracted with $CHCl_3$ (3 x 20 ml). The extract was concentrated and purified by column chromatography over silica gel with hexane and EtOAc (3:2) as eluents. Two new dienes **2** (42 mg, 47%) and **3** (37 mg, 42%) were isolated.

***Diene* 2:** Viscous oil, $[\alpha]_D^{25}$ -45.60 (c 0.5122, $CHCl_3$), IR: $\nu_{max}$ (neat) 2970, 1760, 1630, 1460 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 5.95 (1H, d, J = 6.0 Hz, H-2), 5.86 (1H, dd, J = 6.0 and 2.0 Hz, H-3), 5.13 (1H, d, J = 2.0 Hz, H-4), 4.92 (1H, d, J = 8.0 Hz, H-6), 2.88 (1H, m, H-7), 2.31-1.40 (6H, m, $H_2$-8, $H_2$-9, H-10, H-11), 1.07 (3H, d, J = 7.0 Hz, Me-11), 1.03 (3H, s, Me-5), 0.98 (3H, d, J = 7.0 Hz, Me-10); MS: m/z (%) 232 ($M^{+\cdot}$, 45), 204(15), 176 (32), 150 (50), 124 (100), 110 (85); Found, C: 77.87; H: 8.51. $C_{15}H_{20}O_2$ requires C: 77.58; H: 8.62%.

***Diene* 3:** Viscous oil, $[\alpha]_D^{25}$ -100.81 (c 0.2531, $CHCl_3$), IR: $\nu_{max}$ (neat) 2958, 1763, 1626, 1455 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 5.94 (2H, m, H-2, H-3), 5.10 (1H, d, J = 2.0 Hz, H-4), 5.26 (1H, d, J = 8.0 Hz, H-6), 2.48 (1H, m, H-7), 2.40-1.50 (6H, m, $H_2$-8, $H_2$-9, H-10, H-11), 1.24 (3H, d, J = 7.5 Hz, Me-11), 1.02 (3H, s, Me-5), 1.00 (3H, d, J = 7.0 Hz, Me-10); MS: m/z (%) 232 ($M^{+\cdot}$, 13), 204 (4), 175 (35), 135 (62), 109 (58); Found, C: 77.76; H: 8.53. $C_{15}H_{20}O_2$ requires C: 77.58; H: 8.62 %.

***Reduction of parthenin* (1) *with sodium borohydride and iodine in THF.***

A slurry of $NaBH_4$ (100 mg, 2.632 mmol) and parthenin **1** (350 mg, 1.336 mmol) in THF (10 ml) was stirred at 0°C. To this mixture, $I_2$ (250 mg, 0.984 mmol) in THF (10 ml) was added dropwise over a period of 10 min under $N_2$ atmosphere. After 20 min the reaction mixture was quenched with MeOH till the effervescence was ceased. Evaporation of the solvent followed by purification of the crude product over silica gel afforded the diene **2** (228 mg, 74%) as viscous oil. The spectral (IR, $^1H$ NMR and MS) properties of the compound were identical to those reported above.

***Reduction of parthenin* (1) *with $NaBH_4$ in methanolic pyridine.***

To a mixture of pyridine (6 ml) and MeOH (2 ml) at 0°C parthenin **1** (262 mg, 1 mmol) was added. The mixture was stirred. $NaBH_4$ (38 mg, 1 mmol) was added in portions. The reaction mixture was kept at room temperature for 3 h. This was poured onto cold 10% HCl (20 ml) and extracted with EtOAc (3x20 ml). The extract was washed with water (3x20 ml), concentrated and purified by column chromatography to afford **4** (204 mg, 72%) as a white solid, m.p. 91-92°C (MeOH), $[\alpha]_D^{25}$ +28.18 (c 0.5016, $CHCl_3$), IR: $\nu_{max}$ (KBr) 3490, 2940, 1760, 1622 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.35 (1H, dd, J = 2.0 and 1.5 Hz, H-13), 5.82 (1H, dd, J = 2.0 and 1.5 Hz, H-13), 4.75 (1H, d, J = 9.0 Hz, H-6), 4.29 (1H, m, H-2), 4.10 (1H, d, J = 7.0 Hz, H-4), 3.6 (1H, m, H-7), 2.50-2.35 (2H, m, $H_2$-3), 2.12-1.48 (5H, m, $H_2$-8, $H_2$-9, H-10), 1.27 (3H, s, Me-5), 1.04 (3H, d, J = 7.0 Hz, Me-10); MS: m/z (%) 282 ($M^+$, 3), 254 (3), 200 (22); Found, C: 63.62; H: 7.65. $C_{15}H_{22}O_5$ requires C: 63.83; H: 7.80%.

***Reduction of parthenin* (1) *with sodium in ethanol.***

To a solution of parthenin **1** (100 mg, 0.382 mmol) in dry EtOH (50 ml) Na (1 g, 43.478 mmol) was added at room temperature. The mixture was kept for 6 h, acidified with dilute HCl (1N) and extracted with EtOAc (3 x 50 ml). The organic layer was washed with aqueous $NaHCO_3$ solution (3 x 50 ml) followed by water (3 x 50 ml) and concentrated. The residue was purified by column chromatography to yield **5** (62 mg, 52%) as a white solid, m.p. 135-136°C (MeOH), $[\alpha]_D^{25}$ +10.50 (c 0.411, $CHCl_3$), IR: $\nu_{max}$ (KBr): 3515, 2970, 1765,1460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.13 (1H, d, J = 8.0 Hz, H-6), 4.68 (1H, dd, J = 8.0 and 6.0 Hz, H-4), 4.15 (1H, dd, J = 6.0 and 4.0 Hz, H-2), 3.70-3.42 (2H, m, -OC<u>$H_2$</u>Me), 2.32 (1H, m, H-7), 2.20-1.45 (7H, m, $H_2$-3, $H_2$-8, $H_2$-9, H-10), 1.21 (3H, d, J = 7.0 Hz, Me-11), 1.13 (3H, t, J = 7.0 Hz, -OC$H_2$<u>Me</u>), 0.96 (3H, s, Me-5). MS: m/z (%) 294 ($M^+$ -$H_2O$, 9), 248 (13), 211 (25), 193 (72), 165 (35); Found, C: 65.12; H: 8.65. $C_{17}H_{28}O_5$ requires C: 65.38; H: 8.97%.

***Acetylation of* 5.**

To the compound **5** (20 mg) acetic anhydride (2 ml) and pyridine (0.1 ml) were added. The mixture was kept overnight. After usual work-up the product was purified by column chromatography over silica gel to obtain the acetylated product **6** as a viscous oil (18 mg, 79%), IR: $\nu_{max}$ (neat): 3500, 2964, 1765, 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 5.58 (1H, dd, J = 8.0 and 6.0 Hz, H-4), 5.08 (1H, d, J = 8.0 Hz, H-6), 4.17 (1H, dd, J = 8.0 Hz and 6.0 Hz, H-2), 3.70-3.42 (2H, m, -OC$\underline{H_2}$Me), 2.40 (1H, m, H-7), 2.28-1.48 (7H, m, $H_2$-3, $H_2$-8, $H_2$-9, H-10), 2.03 (3H, s, -OCO$\underline{Me}$), 1.34-1.12 (9H, Me-10, Me-11 and -OC$H_2\underline{Me}$), 1.04 (3H, s, Me-5); MS: m/z (%) 294 ($M^{+\cdot}$ -HOAc, 10).

***Treatment of parthenin* (1) *with Zn/HOAc.***

Parthenin **1** (100 mg, 0.382 mmol) was taken in HOAc (20 ml). Activated Zn (1.5 g, 23.077 mmol) was added. The mixture was refluxed at 80°C for 6 h and cooled. Unreacted Zn was removed by filtration. The filtrate was extracted with $CHCl_3$ (3 x 20 ml). The $CHCl_3$ extract was washed with aqueous $NaHCO_3$ solution (3x20 ml) and then with water (3x50 ml). The extract was concentrated and the residue was purified by column chromatography to yield two white solids, neoambrosin (**7**, 68 mg, 72%) and anhydroparthenin (**8**, 7 mg, 8%).

***Neoambrosin* (7)**: m.p.126-127°C (MeOH), $[\alpha]_D^{25}$ -66.03 (c 0.2376, $CHCl_3$). IR, $^1H$ NMR and MS data were found to be similar to those reported for the naturally occurring compound.[18,21] Found, C: 64.52; H: 6.52. $C_{15}H_{18}O_5$ requires C: 64.75; H: 6.47%.

***Anhydroparthenin* (8)**: m.p. 125-126°C ($C_6H_6$), $[\alpha]_D^{25}$ -120.38 (c 0.5762, $CHCl_3$); IR, $^1H$ NMR and MS data were identical to those reported for the naturally occurring compound.[3,24] Found, C: 73.86; H: 6.43. $C_{15}H_{16}O_3$ requires C: 73.77; H: 6.56%. The compound was directly compared with an authentic sample.

***Treatment of parthenin* (1) *with Mg in MeOH***

To a solution of parthenin **1** (100 mg, 0.382 mmol) in MeOH (15 ml) Mg (500 mg, 20.83 mmol) was added. The mixture was kept at room temperature with stirring for 2 h. MeOH was removed under reduced pressure and the unreacted Mg was quenched with $NH_4Cl$ solution. The mixture was extracted with $CHCl_3$ (3x20 ml) and washed with water (3x50 ml). The concentrated extract was purified by column chromatography to yield **9** as a colourless gum (72 mg, 58%), IR: $\nu_{max}$ (neat) 3300, 1767, 1720 $cm^{-1}$, $^1H$ NMR ($CDCl_3$): δ 4.92 (1H, d, J = 8.0 Hz, H-6), 4.30 (1H, t, J = 7.0 Hz, H-2), 3.63 (2H, d, J = 5.0 Hz, $H_2$-13), 3.49 (3H, s, OMe-2), 3.38 (3H, s, OMe-13), 2.90 -2.70 (2H, m, H-7 and H-3), 2.50-2.23 (2H, m, H-11 and H-3), 2.15-1.50 (5H, m, $H_2$-8, $H_2$-9, H-10), 1.18 (3H, d, J = 7.0 Hz, Me-10), 1.17 (3H, s, Me-5); MS m/z

(%): 326 ($M^{+\cdot}$, 4), 294 ($M^{+\cdot}$ -MeOH, 6), 249 (34), 223 (30), 191 (24), 171 (15), 163 (30), 149 (34). Found, C: 62.41; H: 7.86. $C_{17}H_{26}O_6$ requires C: 62.58; H: 7.97%.

***Oxidation of parthenin* (1) *with meta-chloroperbenzoic acid.***

Parthenin **1** (100 mg, 0.382 mmol) was dissolved in $CH_2Cl_2$ (20 ml) and cooled at 0°C. The solution was treated with *m*-CPBA (170 mg, 0.494 mmol, 50%) and kept for 3 h. $CH_2Cl_2$ (20 ml) was further added. The mixture was washed with saturated $NaHCO_3$ solution (3x30 ml) and then with water (3x50 ml). The organic extract was dried, concentrated and purified by column chromatography to yield **10** (82 mg, 77%) as a white solid, m.p. 244-245°C ($CHCl_3$), $[\alpha]_D^{25}$ -34.00 (c 0.5403, MeOH), IR: $\nu_{max}$ (KBr) 3420, 2920, 1760, 1710, 1615, 1445 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 6.70 (1H, d, J = 9.0 Hz, H-2), 6.07 (1H, d, J = 9.0 Hz, H-3), 6.29 (1H, d, J = 2.5 Hz, H-13), 5.65 (1H, d, J = 2.5 Hz, H-13), 5.30 (1H, d, J = 9.0 Hz, H-6), 3.47 (1H, m, H-7), 2.32-1.60 (5H, m, $H_2$-8, $H_2$-9, H-10), 1.41 (3H, s, Me-5), 1.10 (3H, d, J = 7.0 Hz, Me-10), LSIMS m/z (%): 279 ($M^{+\cdot}$+1, 100), 262 (46), 243 (40), 215 (20). Found, C: 64.52, H: 6.62. $C_{15}H_{18}O_5$ requires C: 64.75; H: 6.47%.

***Treatment of parthenin* (1) *adsorbed on silica gel with dilute HCl***

To a solution of parthenin **1** (100 mg, 0.382 mmol) in $CH_2Cl_2$ (10 ml) silica gel (100-200 mesh, 3 g) was added and $CH_2Cl_2$ was removed under reduced pressure to adsorbed the compound on silica gel. Dilute HCl (5%, 0.1 ml) was added and was thoroughly mixed to make a homogeneous mass. The mixture was kept overnight at room temperature. This was shaken with $CH_2Cl_2$ (20 ml) and filtered. The residue was again shaken with $CH_2Cl_2$-MeOH (1:1, 20 ml). The filtrate after filtration was concentrated and dissolved in EtOAc (20 ml). The solution was washed with saturated aqueous $NaHCO_3$ solution (3x20 ml) followed by water (3x20 ml), concentrated and purified by column chromatography to produce **11** as viscous oil (72 mg, 68%), IR: $\nu_{max}$ (neat) 3526, 1754, 1705, 1672 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.53 (1H, d, J = 6.0 Hz, H-2), 6.10 (1H, d, J = 6.0 Hz, H-3), 5.44 (1H, s, H-6), 4.30 (2H,s, $H_2$-13), 2.98 (2H, t, J=6 Hz, $H_2$-8), 2.35-2.10 (3H, m, $H_2$-9, H-10), 1.07 (3H, d, J = 7.0 Hz, Me-10), 0.91 (3H, s, Me-5); MS m/z (%): 260 ($M^+$ -$H_2O$, 20), 245 (16), 161 (16), 145 (17), 113 (30), 117 (33). Found C: 64.52; H: 6.54. $C_{15}H_{18}O_5$ requires C: 64.75; H: 6.47%.

***Microwave irradiation of parthenin* (1)**

In an Erlenmeyer flask parthenin **1** (100 mg, 0.382 mmol) was taken and placed in an alumina both in a commercial microwave oven (BPL BMO 700T). The compound was irradiated at 233 watt for 8 min. The reaction mixture was taken out from the oven and cooled to room temperature. The mixture was shaken with

$CH_2Cl_2$ (10 ml) and filtered. The filtrate was concentrated and purified by column chromatography to yield anhydroparthenin **8** (63 mg, 68%) as a white solid, m.p. 124-125°C ($C_6H_6$), $[\alpha]_D^{25}$ -120.5 (c 0.8632, $CHCl_3$). A direct comparison of the compound with the naturally occurring authentic sample[3] showed that both the compounds are identical in all respects [$R_f$, m.p., IR, $^1H$ NMR and MS].

***Baker's yeast reduction of parthenin* (1)**

Baker's yeast (*Saccharomyces cerevisiae*) (2 g) was added to a vigorously stirred solution of sucrose (1.5 g) in tap water (200 ml). The mixture was stirred for 1 h at room temperature. Parthenin **1** (100 mg, 0.382 mmol) was added and stirring was continued. Three portions of fermenting baker's yeast [1.5 g in a solution of sucrose (750 g) in tap water (50 ml)] was added during 72 h and the suspension was stirred for another 120 h at room temperature. The mixture was extracted with EtOAc (3x100 ml). The extract was concentrated and purified by column chromatography to afford dihydrocoronopilin **12** (65 mg, 64%) as a white solid, m.p. 174-176°C (MeOH), $[\alpha]_D^{25}$ +24.52 (c 0.7815, $CHCl_3$). The IR, $^1H$ NMR and MS data were found to be identical to those reported for the naturally occurring compound.[2,18,21] Found, C: 67.42; H: 8.35. $C_{15}H_{22}O_4$ requires C: 67.63; H: 8.27%.

## ACKNOWLEDGEMENT

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