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Synthesis of Bioactive 7-β-Hydroxyeudesmanolides

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Abstract: Several eudesmanolides functionalized at C-7 have been synthesized and tested against the fungus Botrytis cinerea for their potential antifungal activity. The strategy followed support the proposed biogenetic route to 7-hydroxy-eudesmanolides.

INTRODUCTION

Over the last few years we have undertaken a research programme directed towards the synthesis of compounds with fungicidal activity. Several sesquiterpene lactones with the eudesmanolide skeleton have shown this activity [1]. In addition a relatively high number of 7-hydroxysesquiterpene lactones with biocidal activity have been isolated[2] from natural sources.

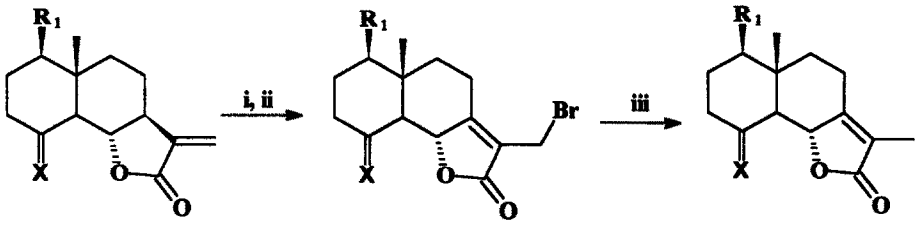
Recently we described the selective addition of bromine to the C11-C13 double bond in the eudesmanolides, using phenyltrimethylammoniun perbromide reagent (TMPAP). This provided a facile route to sesquiterpene lactones functionalized on the lactone ring[3].

In a preliminary communication[4] we described the application of this reaction to the first synthesis of 7β-hydroxy-β-cyclocostunolide. We describe herein the synthesis of several 7-β-hydroxy eudesmanolides, in order to study their fungicidal activity and the structure-activity relationships.

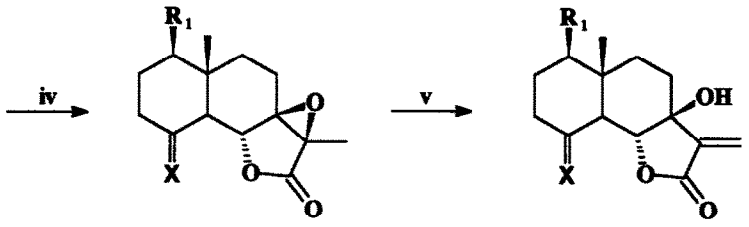
RESULTS AND DISCUSSION

The synthesis of 7-β-hydroxy eudesmanolides **15, 16** and **17** has achieved as shown in scheme 1. The starting materials (**1-4**), prepared from costunolide following the methods previously described[5-6] were subsequently converted to the corresponding 13-bromoderivatives following our methodology[6,7] which involves nucleophilic addition of bromine with TMPAP followed by dehydrobromination with $LiBr/Li_2CO_3$ in DMF (average yield 97%). Satisfactory spectroscopic data were obtained for compounds **5-8**. The ^{1}H-NMR spectra of these lactones showed that the signals corresponding to C11-C13 double bond were absent and a new

signal appeared (br s, 2H) at δ 4.03, 4.07, 4.09 and 4.09 respectively. On the other hand, the signals of H-6, (doublet, 1H) were deshielded (+ 0.61 ppm) with respect to the starting materials.



1	R=H X = CH_2	**5**		**2**	R_1= H X= CH_2
2	R_1=Br X = CH_2	**6**		**10**	R_1=OH X= CH_2
3	R_1 = OH X = CH_2	**7**		**11**	R_1=H X = α OH, βCH_3
4	R_1=H X= α OH, β CH_3	**8**			



12	R_1= H X = CH_2	**15**	R_1= H X= CH_2
13	R_1 = OH X = CH_2	**16**	R_1= OH X = CH_2
14	R_1 = H X= α OH,β CH_3	**17**	R_1 =H X= α OH, β CH_3

Reagents: i)TMPAP/Dioxane; ii)LiBr/Li_2CO_3; iii)nBu_3SnH; iv)H_2O_2/NaOH; v)tBuO$^-K^+$/THF

Scheme 1

Treatment of **5** and **7** with n-Bu_3SnH in toluene afforded the unsaturated methyllactones **9** and **11** in high yield. When dibromolactone **6** was submitted to the same experimental conditions, a mixture of **5** and **9** was obtained, thus indicating that the rate of debromination at C1 is higher than that at C13.

Treatment of **9**, **10** and **11** with H_2O_2/NaOH resulted in selective and stereospecific epoxidation, affording the corresponding 7β,11-β-epoxy derivatives (**12-14**). The ^{1}H-NMR for **12-14** showed that the

signals of H-6 were shifted downfield (0.74 ppm) with respect to starting materials (**1**, **3** and **4**), indicating the presence of a β-oriented oxirane ring in the molecules. This fact was confirmed by single crystal X-ray diffraction analysis of compound **12**[4].

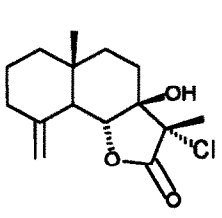
All attempts to obtain the α-epoxide using general or specific epoxidation reagents were unsuccessful.

The rearrangement of epoxides (**12-14**) to allylic alcohols (**15-17**) was undertaken following two different strategies[8].

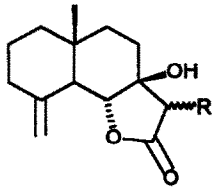
a) treatment with a strong base to abstract a β-proton and epoxide opening to give the desired allylic alcohols.

b) epoxide opening with a nucleophilic agent, ElNU, followed by elimination of HNu to yield allylic alcohol.

Attempts to rearrange **12**, **13** and **14** to the 7-hydroxyeudesmanolides (**15-17**) using LDA, HMPT and $(iProp)_3Al$ were unsuccessful, and the starting material recovered unchanged. The rearrangement was achieved when compounds (**12-14**) were treated with $tBuO^-K^+$/ THF under reflux and very dry conditions.

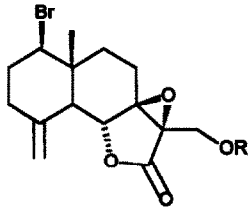


18



19 R= β CH_3

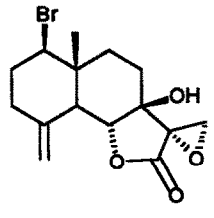
20 R= α CH_3



21 R= H

21a R= Ac

22 R= CH_3



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The structures of compounds (**15-17**) were inferred from their spectral data. Thus, the ^{1}H-NMR spectra for compounds **15**, **16** and **17** revealed the signal characterestic of the α-methylene-γ-lactone as two singlets at δ 6.31, 5.74; 6.29, 5.75 and 6.39, 5.82, respectively . In addition, the β orientation of the hydroxyl group at C7 was confirmed by the study of H-6 signals, which appeared as doublets shifted downfield in **15-17** with respect to those described in the literature[2] for 7-α-hydroxyeudesmanolides. This synthesis supports the biogenetic routes of 7-hydroxy eudesmanolides proposed by Mabry[2b].

On the other hand, compound **17** was obtained in one step from **11** by treatment with SeO_2/ tBuOOH.

No evidence concerning the bioactivity of 7-hydroxydihydroderivatives has been reported. Thus, dihydroderivatives **19** and **20** were synthetized. When **12** was treated with $CaCl_2$/Benzene the oxirane ring was opened yielding chlorocompound **18**. Subsequent dechlorination with tin hydride yielded dihydroderivatives **19** (82%) and **20** (15%).

In order to obtain 7-hydroxyeudesmanolides with a bromine atom at C1, compound **6** was directly epoxidized. Three compounds **21** (10%), **22** (15%) and **23** (45%) were isolated from the reaction mixture. The structures were inferred by study of their spectral data and were supported by homo and heteronuclear-2D-correlation experiments. Compounds **23** had a molecular ion m/z 340/342 and a ^{13}C-NMR spectrum consistent with the molecular formula $C_{15}H_{19}O_4Br$. The IR absorption 3390 cm^{-1} and a quaternary carbon signal at δ 70.0 ppm in the ^{13}C-NMR spectrum, revealed the hydroxyl group to be tertiary. No acetylated derivative was obtained with acetic anhydride. Upon treatment with $tBuO^- K^+$/THF, compound **23** was transformed in **21**. Compound **21** gave a monoacetylated derivative **21a** whose ^{1}H-NMR showed that the hydroxyl group was primary, confirming the structured proposed.

The antifungal properties of the synthesized 7-hydroxy derivatives (**15-23**), were determined against the growth of *B. cinerea* using the poisoned food technique[9] . The commercial fungicide ®Euparen, was used as a standard for comparison purpose in this test. Compounds **15-19** displayed weak antifungal activity and the growth of treated mycelium were retarded after four days. Dihydroderivative **20** showed activity at 100 ppm and displayed an 70% of growth inhibition at 200 ppm after seven days. The study of the activity showed by the tested 7-hydroxy derivatives seem to indicate that the α orientation of methyl group in the lactone ring is critical for antifungal activity of this molecules.

EXPERIMENTAL SECTION

Infrared spectra were determinate with a Perkin-Elmer 881 spectrometer. Proton NMR spectra were made on a Varian Gemini XL-200 or a Varian Unity-400 using $SiMe_4$ as internal reference. Mass spectra were recorded on a VG12.250 spectrometer using 70 eV. Thin layer chromatography was done on MN Alugran SIL G/UV 254 plates, 0.25 mm thick. Merck silica gel was used for column chromatography.

General procedure for debromination with nBu_3SnH (TBTH). A solution of 13-bromoderivatives (**5-8**) (150 mg) in toluene were treated with TBTH (1.5 ml) and azoisobutyronitrile (AIBN) (5 mg) under reflux for 2 h.. The solvent was evaporated off, the residue was diluted with acetonitrile, and the solution was washed with light petroleum. The acetonitrile was removed under reduced pressure and the crude chromatographed on silica to afford compounds **9-11**.

7,11-ene-β-cyclodihydrocostunolide (9). According to the procedure above described compound **9** was obtained in 90% yield. **mp** 90-91°; **IR** (cm^{-1}, KBr) 2926, 1736 1673, 1642; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4.95 (br s, 1H, H-14), 4.89 (br s, 1H, H-14´), 4.79 (d, 1H, J=11.1 Hz, H-6), 2.64 (ddd, 1H, J=13.9, 5.0, 2.1 Hz, H-8), 2.40 (td, 1H, J= 13.9, 6.3 Hz H-8), 1.80 (s, 3H, H-13), 0.91(s, 3H, H-15); **EIMS** *m/z* (70 Ev) 232 (91), 217 (17), 189 (12).

7,11-ene-dihydroreinosin (10). Compound **10** (105 mg, 92%) was obtained when **7** (150 mg) was subjected to the treatment described in the general procedure, **mp** 164-5°, **IR** (cm^{-1}, KBr) 3453, 2948, 1734,

1675, 1640; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 5.03 (br s, 1H, H-14), 4.98 (br s, 1H, H-14'), 4,89 (d, 1H, J= 11.5 Hz, H-6), 3.40 (dd, 1H, J= 11.4, 4.7 Hz, H-1), 2.76 (ddd, 1H, J= 12.9, 5.4, 3.1 Hz, H-8), 1.82 (s, 3H, H-13), 0.90 (s, 3H, H-15); **EIMS** m/z (70 Ev) 248 $[M]^+$ (6), 230 $[M-H_2O]^+$ (100), 215 $[M-H_2O-CH_3]^+$ (24).

7,11-ene-colartin (11). Compound **11** (101 mg, 88%) was obtained from **8** (150 mg) following the general procedure; **mp** 152-3 °; **IR** (cm^{-1}, KBr) 3571, 2930, 1758, 1680; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4,84 (d, 1H, J= 11.6 Hz, H-6), 3.40 (dd, 1H, J= 11.5, 4.8 Hz, H-1), 2.76 (ddd, 1H, J= 12.9, 5.4, 3.1 Hz, H-8), 1.81 (s, 3H, H-13), 1.35 (s, 3H, H-14), 0.90 (s, 3H, H-15); **EIMS** m/z (70 Ev): 250 $[M]^+$ (10), 235 $[M-CH_3]^+$ (62), 232 $[M-H_2O]^+$ (100), 217 $[M-H_2O-CH_3]^+$ (36).

General Procedure for the epoxidation. To a stirred solution of compounds **9-11** (50 mg) in 5 ml of CH_3OH, 0.5 ml of 2 M solution of H_2O_2 and 0.5 ml of a solution of NaOH (4%,) were simultaneously added dropwise, then, the mixture was allowed to stand in the dark for 3 days. The reaction mixture was then extracted with EtOAc, washed with a saturated solution of Na_2SO_3 and dried over anhydrous Na_2SO_4 . After the removal of the solvent the crude was purified by column chromatography yielding compounds **12-14.**

7β,11-epoxy-β-cyclodihydrocostunolide (12). Compound **12** (42 mg, 80%) was obtained from **9** as described in the general procedure; **mp** 116-7°; **IR** (cm^{-1}, KBr) 2931, 1763, 1638, 1097, 878; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.97 (br s, 1H, H-14), 4.73 (br s, 1H, H-14'),4.64 (d, 1H, J=10.8 Hz, H-6), 2.37 (br d, 1H, J=10.8 Hz, H-5), 2.34 (td, J=14.5, 5.2 Hz, H-8), 1.93 (td, 1H, J=14.5, 5.6 Hz, H-8'), 1.77 (br d, 1H, J=10.8Hz, H-5), 1.55 (s, 3H, H-13), 0.89 (s, 3H, H-15); **EIMS** M/z (70 Ev) 249 $[M+1]^+$ (0.2), 232 $[M-O]^+$ (0.6), 220 $[M-CO]^+$ (0.5), 43 $[C_2H_3O]^+$. **HRMS** obsd. 248.1415 M^+, requires 248.14124

7β-11-epoxy-11,13-dihydroreinosin (13). Compound **11** (50 mg) was subjected to the treatment described above in the general procedure yielding 45 mg of **13** (85%). **mp** 181-2 °; **IR** (cm^{-1}, KBr) 3430, 2938, 1769, 1639, 1098, 882; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 5.04 (br s, 1H, H-14), 4.71 (br s, 1H, H-14'), 4,71 (d, 1H, J= 10.6 Hz, H-6), 3.44 (dd, 1H, J= 11.2, 4.8 Hz, H-1), 2.28 (d, 1H, J= 10.4 Hz, H-5), 1.57 (s, 3H, H-13), 0.88 (s, 3H, H-15); **EIMS** m/z (70 Ev) 264 $[M]^+$ (40), 247 $[M-OH]^+$ (12), 230 $[M-O-H_2O]^+$ (45). **HRMS** obsd. 264.1380 M^+, requires 264.13616

7β,11-epoxy-colartin (14).Compound **14** (43 mg, 82%) was obtained from **12** (49 mg) as described above in the general procedure; **mp** 148-9°; **IR** (cm^{-1}, KBr) 3532, 2941, 771, 1635, 1100, 889; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4,71 (d, 1H, J= 10.9 Hz, H-6), 2.36 (br d, 1H, J= 9.7 Hz, H-8) 1.56 (s, 3H, H-13), 1.41 (s, 3H, H-14), 0.87 (s, 3H, H-15); **EIMS** m/z (70 Ev) 266 $[M]^+$ (14), 249 $[M-OH]^+$ (31), 230 $[M-O-H_2O]^+$ (41).. **HRMS** obsd. 266.1523 M^+, requires 266.15181

Rearrangement of compounds 12-14. General Procedure. Starting materials **(12-14)** were separately dissolved in dry THF (15 ml) and an excess of *t*-BuOK was added, the reaction mixtures were refluxed for 3 h. After the reaction mixture was neutralized with HCl 2N , extracted with EtOAc and purified by column chromatography, compounds **15-17** were obtained.

7β-hydroxy-β-cyclocostunolide (15) .When compound **12** (105 mg) was subjected to the treatment described in the general procedure , 31 mg of **15** (30%) were obtained; **mp** 165-7 °; **IR** (cm^{-1}, KBr) 3382, 2982, 1748, 1642, 1112, 1144, 1176; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.31 (s, 1H, H-13), 5.74 (s, 1H, H-13'), 4.90 (br s, 1H, H-14), 4.72 (br s, 1 H, H-14'), 4.57 (d, 1H, J=10.7 Hz, H-6), 4.32 (s, HOC-7), 1.56 (br d, J=10.7 Hz, H-5), 2.14 (td, J=13.1, 3.4 Hz, H-8), 2.05 (td , J=13.1, 5.0 Hz, H-8'), 0.78 (s, 3H, H-15); **EIMS** m/z (70 Ev) 248 $[M]^+$ (37), 230 $[M-H_2O]^+$ (28), 201 $[M-CHO]^+$ (15), 178 $[M-C_4H_6O]^+$ (14). **HRMS** obsd. 248.1427 M^+, requires 248.14124

7β-hydroxyreinosin (16). Compound **16** (49 mg, 49%) was obtained from **13** (100 mg) following the general procedure; **mp** 196-7 °; **IR** (cm^{-1}, KBr) 3521, 3430, 2978, 1745, 1638; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.29 (s, 1H, H-13), 5.75 (s, 1H, H-13'), 4.94 (br s, 1H, H-14), 4.78 (br s, 1H, H-14'), 4.61 (d, 1H, J= 10.5 Hz, H-6), 3.25 (dd, 1H, J= 11.0, 4.8 Hz, H-1), 0.74 (s, 3H, H-15); **EIMS** m/z (70 Ev):264 $[M]^+$ (21), 246 $[M-H_2O]^+$ (9), 230 $[M-2H_2O]^+$ (24). **HRMS** obsd. 264.1355 M^+, requires 264.13616

7β-hydroxyarbusculin A (17). Compound **14** (81 mg) was subjected to the treatment described in the general procedure yielding 37 mg of **17** (46%); **mp** 162-3°; **IR** (cm^{-1}, KBr) 3560, 3395, 2935, 2857, 1746; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 6.39 (s, 1H, H-13), 5.82 (s, 1H, H-13'), 4.73 (d, 1H, J= 11.5 Hz, H-6), 1.78 (br d , 1H, J= 11.6 Hz, H-5), 1.35 (s, 3H, H-14), 0.96 (s, 3H, H-15); **EIMS** m/z (70 Ev):266 $[M]^+$ (1), 251 $[M-CH_3]^+$ (10), 248 $[M-H_2O]^+$ (5), 233 $[M-H_2O-OH]^+$ (8). **HRMS** obsd. 266.1501 M^+, requires 266.15181

11α-Chloro-7β-hydroxy-β-cyclocostunolide(18). Compound **12** (65 mg) was dissolved in benzene (15 ml) at 50°, then $CaCl_2$ (100 mg) and p-TsOH (50 mg) were added. The reaction mixture was stirred for 2 days, filtered over celite and extracted with EtOAc as described in the general procedure for epoxidation. The crude obtained was purified by column chromatography yielding 60 mg of **18** (70%); **mp** 155-7°; **IR** (cm^{-1}, KBr) 3415, 2953, 1746, 1633; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4.92(s br, 1H, H-14), 4.71 (br s, 1H, H-14'), 4.57(d, 1H, J= 11.4, H-6), 2.44 (m, 2H, H-8, H-8'), 1.85(d, 1H, J= 11.4, H-5), 1.67(s, 3H,H-13), 0.80(s, 3H, H-15); **EIMS** m/z (70 Ev) 285:286 $[M]^+$ (19:7), 269:271 $[M-CH_3]^+$ (25:11), 266:268 $[M-H_2O]^+$ (4:1), 249 $[M-Cl]^+$ (3).

Treatment of 18 with TBTH. To a solution of **18** (90 mg) in 15 ml of dry toluene, 130 μl of TBTH and a catalytic amount of AIBN were added. The reaction mixture was refluxed for 2 h, and then it was filtered over silica gel eluting with hexane (3x25 ml) and EtOAc (3x25 ml). The solvent was removed under reduced pressure and the crude product purified by column chromatography yielding compounds **19** (65 mg, 85%) and **20** (12 mg, 15%). **7β-hydroxy-11β-methyldihydrocostunolide (19) mp** 149-151°; **IR** (cm^{-1}, KBr) 3426, 2973, 1750, 1644, 1185; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4.92 (br s, 1H, H-14), 4.72 (br s, 1H, H-14'), 4.52(d, 1H, J=11.1, H-6), 2.1(m,2H, H-8, H-8'), 2.52 (q, 1H, J=8.0 Hz, H-11), 2.31 (br d, 1H, J=11.1 Hz, H-5), 1.33(d, 3H, J=8.0 Hz, H-13), 0.80(s, 3H, H-15); **EIMS** m/z 251 $[M]^+$ (2), 232 $[M-H_2O]^+$ (13), 222 $[M-CO]^+$ (5). **7β-hydroxy-11α-methyldihydrocostunolide (20) mp** 160-162º; **IR** (cm^{-1}, KBr) 3404, 2936, 1756, 1737, 1644; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 4.94(br s, 1H, H-14), 4.76 (br s, 1H, H-14'); 4.51(d, 1H, J=11.0

Hz, H-6), 2.74 (q, 1H, J=7.1 Hz, H-11), 2.36 (br d, 1H, J=11.0 Hz, H-5), 1.91 (m, 1H, H-8), 1.18 (d, 3H, J= 7.1 Hz, H-13), 0.83(s, 3H, H-15); **EIMS** m/z (70Ev) 251 $[M]^+$ (4), 232 $[M-H_2O]^+$ (9), 222 $[M-CO]^+$ (6).

Epoxidation of compound 6. When compound **6** was subjected to the treatment described above in the general procedure for epoxidation, three compounds were isolated from the reaction mixture: 1β-bromo-7β,11β-epoxy-13-hydroxy-β-cyclodihydrocostunolide (**21**, 10%), 1β-bromo-7β,11β-epoxy-13-methoxy-β-cyclo dihydrocostunolide (**22**, 15%) and 1β-bromo-7β-hydroxy-11α,13-epoxy-β-cyclodihydrocostunolide (**23**, 45%). **1β-bromo-7β,11β-epoxy-13-hydroxy-β-cyclodihydrocostunolide (21) mp** 142-3ºC **IR** (cm^{-1}, KBr) 3450, 2924, 1777, 999; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.06 (br s, 1H, H-14), 4.83 (br s, 1H, H-14'), 4.72 (d, 1H, J=10.5 Hz, H-6), 4.28 (d, 1H, J= 12.8 Hz, H-13), 4.02 (dd, 1H, J= 4.9, 11.8 Hz, H-1), 3.82 (d, 1H, J=12.8 Hz, H-13'), 2.38 (m, 1H, H-3), 2.30 (m, 2H, H-8), 2.09 (m, 2H, H-2, H-3'), 1.92 (d, 1H, J= 10.5 Hz, H-5), 1.73 (m, 1H, H-9), 1.45 (m, 1H, H-9'), 1.00 (s, 3H, H-15); **EIMS** m/z (70 Ev) 344:342 (5:4), 283:585 (22:17), 258:256 (77:76), 243:241, 263(4). **1β-bromo-7β,11β-epoxy-13-methoxy-β-cyclodihydrocostunolide (22)** oil; **IR** (cm^{-1}, film) 2925, 1783, 1091, 1000; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.04 (br s, 1H, H-14), 4.81 (br s, 1H, H-14'), 4.67 (d, 1H, J=10.7 Hz, H-6), 4.11 (d, 1H, J= 11.1 Hz, H-13), 4.03 (dd, 1H, J= 4.3, 12.0 Hz, H-1), 3.53 (d, 1H, J=11.1 Hz, H-13'), 3.43 (s, 3H, O-$\underline{C}H_3$), 2.38 (dd, 1H, J=2.3, 8.0 Hz, H-3), 1.92 (d, 1H, J= 10.7 Hz, H-5), 1.80 (m, 1H, H-9), 1.42 (m, 1H, H-9'), 0.98 (s, 3H, H-15); **EIMS** m/z (70 Ev) 358:356 $[M]^+$ (6:6), 312:310 (8:8), 270:268 (16:17), 257:255 (14:27), 189 (100). **1β-bromo-7β-Hydroxy-11α,13-epoxy-β-cyclodihydrocostunolide (23) mp** 49-51ºC; **IR** (cm^{-1}, KBr) 3304, 2941, 2848, 1776, 1433, 1100; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.04 (br s, 1H, H-14), 4.81 (br s, 1H, H-14'), 4.77 (d, 1H, J=13.9 Hz, H-13), 4.71 (d, 1H, J= 10.6 Hz, H-6), 4.15 (d, 1H, J= 13.9 Hz, H-13'), 4.02 (dd, 1H, J= 4.3, 11.9 Hz, H-1), 2.39 (m, 1H, H-3), 2.31-2.09 (m, 3H, H-2, H-8, H-8'), 2.10 (m, 2H, H-2', H-3'), 2.02 (d, 1H, J= 10.6 Hz, H-5), 1.85 (m, 1H, H-9), 1.57 (m, 1H, H-9'), 1.00 (s, 3H, H-15); **EIMS** m/z (70 Ev) 344:342 $[M]^+$ (1:1), 285:283 (9:10), 258:256 (44:45), 177 (37), 159 (37), 149 (58).

1β-bromo-7β,11β-epoxy-13-acetoxy-β-cyclodihydrocostunolide (21a). To compound **21** (18 mg) dissolved in acetic anhydride (2 ml), a catalytic amount of *p*-toluenesulphonic acid was added. The reaction mixture was stirred at room temperature overnight, then it was quenched with water, neutralized with Na_2CO_3 and extracted with brine and dried over Na_2SO_4 anhydrous. The solvent was removed under reduced pressure and the crude purified by hplc (He:EtOAc, 95:5) yielding starting material (6 mg) and the acetyl derivative **21a** (8 mg, 40%) **mp** 40-41ºC; **IR** (cm^{-1}, KBr) 2933, 1771, 1461, 1378, 1240, 1110; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.05 (br s, 1H, H-14), 4.82 (br s, 1H, H-14'), 4.69 (d, 1H, J=10.5 Hz, H-6), 4.67 (d, 1H, J= 12.6 Hz, H-13), 4.27 (d, 1H, J=12.6 Hz, H-13'), 3.99 (dd, 1H, J= 4.3, 12.0 Hz, H-1), 2.41-2.24 (m, 4H, H-3, H-8, H-8', H-2), 2.12 (s, 3H, $COC\underline{H}_3$), 2.11-2.02 (m, 2H, H-3', H-2'), 1.88 (d, 1H, J= 10.5 Hz, H-5), 1.80 (m, 1H, H-9), 1.00 (s, 3H, H-15); **EIMS** m/z (70 Ev) 326:324 $[M-AcOH]^+$ (1.5:1), 298:296 (0.6:0.6), 270:268 (2:2), 258:256 (10:8).

Treatment of 23 with t-BuOK/THF. Compound **23** (11 mg) in dry THF (2 ml), 1 M solution of *t*-BuOOK (0.5 ml) in THF was added, the reaction mixture was neutralized and extracted as described above for compound **21a**. After purification by hplc (He:EtOAc, 90:10), 7 mg of **21** (64%) were obtained.

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