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First Synthesis of Two Naturally Occurring Oxetane Lactones: Clementein and Clementein B

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Abstract: *Clementein (1) and clementein B (2), sesquiterpene lactones with an 11,13-oxetane ring isolated from Centaurea clementei Boiss, have been synthesized from the α,β-unsaturated γ-lactone cynaropicrin (6). Conjugated photoaddition, stereoselective α-hydroxylation and mild cyclization to form the oxetane ring using THP as leaving group have been employed in this transformation.*

INTRODUCTION

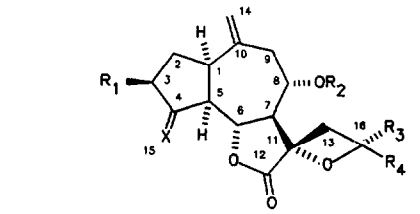
Only a few oxetane ring containing compounds have been isolated from natural sources[1] and it has been reported that the bioactivity of these compounds could be related to the presence of this particular kind of ring in the molecule (plaquets aggregant[1a], anticancer[2], antibiotic[3]).

The interest for natural products containing oxetane rings has increased in recent years. A reason is the high anticancer activity that taxol and some derivatives have shown. Clinical results on taxol have been extremely encouraging and have induced an important effort to obtain more active and available derivatives[4].

We previously reported the isolation of the first natural oxetane lactones clementein (**1**), clementein B (**2**), clementein C (**3**), subexpinnatin B (**4**) and subexpinnatin C (**5**) from *Centaurea clementei* Boiss.[5] and *Centaurea canariensis* Brouss. var. *subexpinnata* Burchd.[6] (Figure 1). Here we report our approach to the first synthesis of clementein and clementein B employing our previously reported[7] methodology for the formation of an oxetane ring at C-11,C-13 position from the correponding α-methylene-γ-lactone, via photochemical addition of an acyl radical to the C_{11}-C_{13} double bond and further cyclization to oxetane ring using THP as the leaving group under mild acid conditions.

RESULTS AND DISCUSSION

The starting material was cynaropicrin (**6**), a relatively abundant metabolite present in several species of the Cynareae Family, as *Cynara scolimus*[8]. The presence of the hydroxymethacrylic moiety introduces serious problems of selectivity, if we take into account that one of the key steps in the



	X	R_1	R_2	R_3	R_4
1	$=CH_2$	OH	Meacr	CH_3	H
2	$=CH_2$	OH	Meacr	H	CH_3
3	H, CH_3	OH	Meacr	H	CH_3
4	$=CH_2$	H	Meacr	H	CH_3
5	$=CH_2$	H	H	H	CH_3

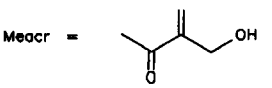
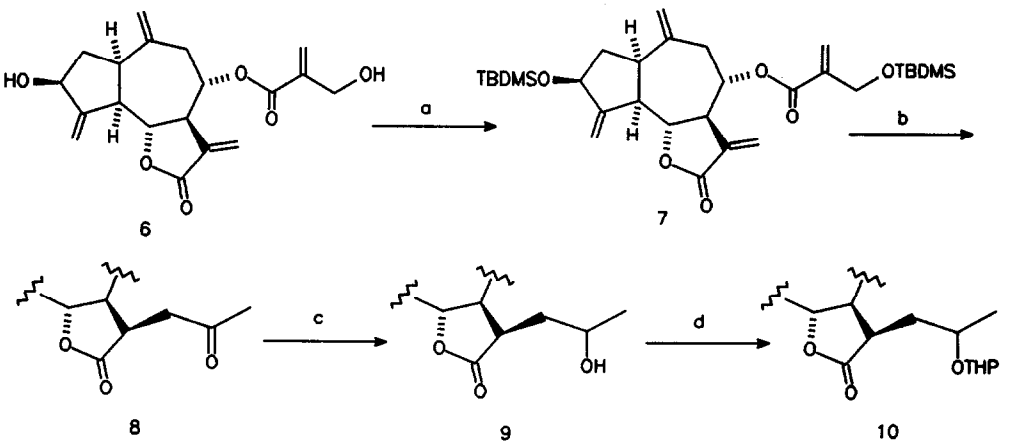


Figure 1

elaboration of the oxetane ring is a conjugated photoaddition to an α,β-unsaturated-γ-lactone. In fact, when **6** was irradiated in the presence of acetaldehyde, a complex mixture of photoadducts was obtained.[9]

We have found[10] that steric hindrance exerts a great influence in the photochemical addition of the acyl radical to electron-deficient olefins. The strategy used in our solution to the selectivity problems, above mentioned, is based in this observation and involves the introduction of a suitable bulky protecting group at the ester chain in order to direct the photoaddition to the unsaturated γ-lactone.

The required protected compound **7** was prepared in quantitative yield by reaction of **6** with *tert*-butyldimethylsilyl chloride in DMF in the presence of collidine (Scheme 1). Subsequently, in a critical step of the process, 12.2 mmol of **7** were irradiated in acetaldehyde using a modified Hannovia reactor to afford a complex mixture from which compound **8** was isolated in 40% yield. Inspection of its ^1H NMR showed the presence of a three protons singlet at δ2.11 which can be attributed to the acetyl group added to C-13 position, with the α,β-unsaturated ester remaining unchanged [δ: 6.16 (1H, d, J = 1.9 Hz, C_4-H), 5.97 (1H, brd, J = 1.9 Hz, C_4-H'), 4.36 (2H, brs, C_3-H_2)]. Reduction of **8** with sodium



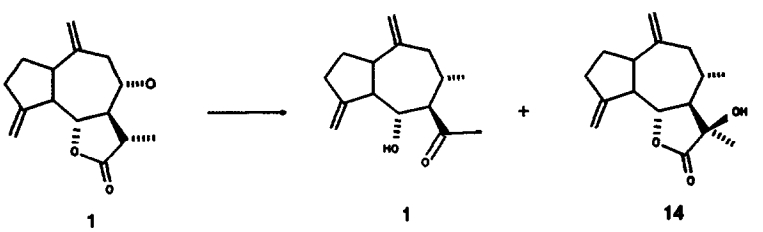
a) TBDMSCl, collidine, DMF, 25°C; b) CH_3CHO, hν, 25°C; c) $NaBH_4$, MeOH, 25°C; d) DHP, p-TsOH

Scheme 1

borohydride at room temperature afforded **9** in 88% yield. Its ^{1}H NMR spectrum showed a double signal for H-6 in a ratio of 9:1 [δ4.23 and 4.21 (1H, dd, $J_{5,6}=J_{6,7}=9.5$ Hz)]. The absorption assigned to H-16 appeared as a complex signal thus indicating that **9** is actually a mixture of epimers at C-16. The hydroxy group was protected with DHP and *p*-toluenesulfonic acid as catalyst, yielding an epimeric mixture of diasteroisomers **10**.

α-Hydroxylation of **10** under the same conditions as described for the synthesis of subexpinnatin C[7] could not be accomplished and resulted in the formation of a mixture of compounds. Also other α-hydroxylation methods did not conduce to the corresponding α-hydroxy-γ-lactone[11]. In order to analyze the different factors that reduce the amount of side products, we employed substrate **12**, which has a bulky group near to the reaction site. This fact could be determinant, since this reaction requires an effective collision between the enolate and the formed peroxide[12]. The enolate of **12** was generated at -70°C in THF by deprotonation with potassium hexamethyldisilazide (KHMDS) under a dry nitrogen atmosphere. Dry oxygen was then bubbled through the solution for a period of 30 minutes at 0°C. The reaction was quenched by addition of a buffer solution (pH=7) and extracted with diethyl ether. After chromatographic purification, the mixture afforded two major compounds, **13** (70%) and **14** (10%). The IR spectrum of **13** showed an absorption at 3400 cm^{-1} attributed to a hydroxyl group and one at 1709 cm^{-1} atributed to the carbonyl stretch of a ketone. The chemical shift of H-6 [δ3.27 (1H, dd, $J_{5,6}=J_{6,7}=9.4$ Hz, C_6-H], suggests that **13** is not a lactone. Based on these data and MS spectrum, we propose structure **13**. The spectroscopic data of the minor compound support the structure of the 11-hydroxylactone **14**. (Scheme 2)

When the reaction was carried out in the presence of triethyl phosphite, and oxygen bubbled at -73°C, **14** was the only product detected in 81% yield. It is worth noticing the stereoselectivity of this reaction, where the orientation of the methyl group at the 11 position is maintened. These results suggest that a reduction agent "in situ" is necessary for these substrates with steric hinderance near the reaction centre.

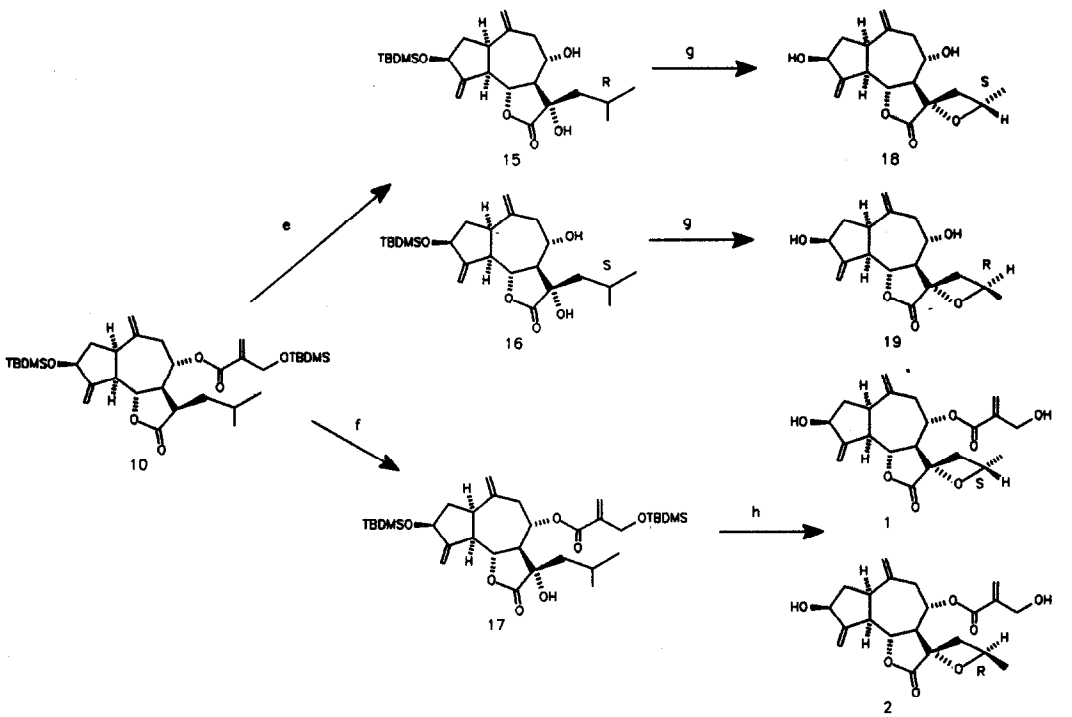


1 1 14

Scheme 2

Another problem was encountered while attempting to prepare the C-11-hydroxylactone by treating a solution of **10** with KHMDS in THF and a current of dry O_2 with triethylphosphite as reducing agent. From the ^1H NMR of the crude reaction mixture no signals of the ester substituent were detected, thus indicating that saponification had taken place. After chromatography, epimeric hydroxylactones **15** and **16** were isolated in very low yield (Scheme 3).

However, better results were obtained by employing bipyridine as acid-base indicator, dry acetic acid as neutralizing agent and controlling the pH with a buffer solution. These modifications prevented the undesired side chain saponification. Under these conditions, the diastereoisomeric mixture **17** could be obtained in 34% yield. Analysis of the ^1H NMR spectrum confirmed the presence of the protected hydroxymethacrylic ester [δ: 6.25 (1H, br d, J=2 Hz, C_4-H), 5.97 (1H, br d, J= 2 Hz, C_4-H'), 4.40 (2H, brs, C_3-H_2)]. The multiplicity of the H-7 signal, double doublet ($J_{8,7}$= 9.4 Hz, $J_{6,7}$= 9.6 Hz) and its chemical shift (δ2.48) are consistent with an α-orientation of the hydroxyl group at C-11 [6].



e) KHMDS, -73°C, $(EtO)_3P$, O_2; f) (a) KHMDS, -73°C, $(EtO)_3P$, O_2, biPy, (b) dry CH_3COOH; g) p-TsOH, MeOH; h) HCl, MeOH

Scheme 3

Mild acid treatment of **15** and **16** gave the corresponding deacylderivatives of clementein (**18**) (60 %) and clementein B (**19**) (65 %) respectively, in a stereospecific cyclization, including simultaneous

deprotection of the silyl group. Similar cyclization of **17** produced, after separation, clementein (**1**) and clementein B (**2**) (75%) in a ratio of 1:10.

In summary, a partial synthesis of clementein and clementein B was achieved in an overall yield of 6% over six steps from the natural sesquiterpene lactone **6**.

EXPERIMENTAL SECTION

Materials and General Procedures: Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer in film. ^1H NMR and ^{13}C NMR spectra were made on Varian Gemini-200 and Bruker AM-400 spectrometers, using $CDCl_3$ as internal standard. Mass spectra were recorded on a VG 12-250 spectrometer using 70 eV. High-resolution mass spectra were obtained on a KRATOS, model MS-80-RFA using EI technique (70 or 20 eV). Chromatographic separations were made on silica gel (Merck), employing hexane, ethyl acetate mixtures as eluent.

3,3'-Bis-O-(*tert*-butyldimethylsilyl)-cynaropicrin (7). To a solution of **6** (5 g) and *tert*-butyl-dimethylsilyl chloride (10 g) in dry DMF(50 mL) was added collidin (28 mL). The solution was stirred under dry nitrogen atmosphere, until complete dissapearance of the starting material (2 h, TLC monitoring). The mixture was diluted with ethyl ether (200 mL) and water (100 mL). The organic layer was washed with water (100mL), brine (twice) and neutralized with 1N HCl (pH,6-7). All aqueous phases were extracted with ethyl ether and subjeted to the same procedure. The combined organic extracts were dried with Na_2SO_4 and the solvent removed under reduced pressure at 0-5°C. The oily residue was chromatographed (Hexane-AcOEt 19:1) to give **7** (7.4 g, 90%); IR (film) cm^{-1}: 1770 (γ-lactone), 1708 (α,β-unsaturated ester); MS, m/z (relative intensity): 574 $[M]^+$ (2), 199 $[CO\ C(CH_2)\ CH_2O\ Si(CH_3)_2C(CH_3)_3]^+$ (74), 75 $[(CH_3)_2\ SiOH]^+$ (100); ^1H-NMR (400 MHz, $CDCl_3$) δ: 6.30 (d, $J_{4',3'}$= 1.5 Hz, $C_{4'}$-H), 6.19 (d, $J_{13b,7}$= 3.5Hz, C_{13}-Hb), 5.99 (d, $J_{4',3'}$= 1.8 Hz, $C_{4'}$-H'), 5.60 (d, $J_{13b,7}$= 3.0 Hz, C_{13}-Ha), 5.43 (brs, C_{15}-H), 5.24 (brs, C_{15}-H'), 5.12 (brs, C_{14}-H), 5.07 (ddd, $J_{8,9}$= 4.1 Hz, $J_{8,9\alpha}$= 5.1 Hz, $J_{8,7}$= 9.5 Hz), 4.91 (brs, C_{14}-H'), 4.48 (brdd, $J_{2,3}$= $J_{2',3}$= 7.6 Hz, C_3-H), 4.38 (brs, 2H, $C_{3'}$-H_2), 4.23 (dd, $J_{5,6}$= $J_{6,7}$= 9.6 Hz), 3.20 (dddd, $J_{6,7}$= 9.6 Hz, $J_{7,8}$= 9.5 Hz, $J_{13a,7}$= 3.0 Hz, $J_{13b,7}$= 3.5 Hz, C_7-H), 2.95 (brddd, $J_{1,2}$= 9 Hz, $J_{1,2'}$= 7.5 Hz, $J_{1,5}$= 10 Hz, C_1-H), 2.83 (brdd, $J_{1,5}$= 10 Hz, $J_{5,6}$= 9.6 Hz, 1H, C_5-H), 2.66 (dd, $J_{8,9\alpha}$= 5.1 Hz, $J_{9,9'}$= 14.3 Hz, C_9-Hα), 2.34 (dd, $J_{8,9\beta}$= 4,1, $J_{9,9'}$= 14.3, C_9-Hβ), 2.07 (ddd, $J_{1,2\beta}$= 9 Hz, $J_{2,2'}$= 13 Hz, $J_{2,3}$= 7.6 Hz, C_2-H), 1.68 (ddd, $J_{1,2\alpha}$= 7.5 Hz, $J_{2,2'}$= 12 Hz, $J_{2,3}$= 7.6 Hz, C_2-H'), 0.91-0.89 (18 H, Si-C-($C\underline{H}_3$)$_3$), 0.09-0.07 (12H, Si-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.1 (C-12), 164.9 (C-1'), 151.7 (C-4), 142.1 (C-10), 139.6 (C-2'), 137.3 (C-11), 124.9 (C-4'), 122.6 (C-13), 117.6 (C-14), 111.9 (C-15), 79.1 (C-6), 74.1 (C-3)*, 74.0 (C-8)*, 61.42 (C-14), 49.96 (C-5), 47.12 (C-7), 44.71 (C-1), 39.81 (C-2), 37.71 (C-9), 25.8, 25.63 (Si-C-$\underline{C}$), -3.61, -4.73, -5.47 (Si-C). Assignments denoted with asterisks may be interchanged.

3,3'-Bis-O-(tert-butyldimethylsilyl)-11αH,13-acetyldihydrocynaropicrin (8). Photochemical reactions were carried out in a modified Hanovia reactor equipped with a Pyrex jacket as filter and a 125 W Hg/medium pressure lamp. The filter solution contained $NiSO_4 \cdot 6H_2O$ (46 g) and $CoSO_4 \cdot 7H_2O$ (14 g) per 100 mL of water. Compound **7** (1 g) in freshly distilled acetaldehyde (100 mL) was irradiated for three hours under oxygen atmosphere with vigorous stirring. The reaction mixture was concentrated under reduced pressure with addition of small amounts of cyclohexane to remove the acetic acid produced.

This procedure was repeated seven times. The reactions mixtures were purified by chromatography (Hexane-EtOAc 9:1) to give **8** (3.1 g, 40%); IR, (film) cm^{-1}: 1774 (γ-lactone), 1712 (α,β-unsaturated ester), 1720 (ketone); HRMS EI (20 eV): calcd for $C_{33}H_{54}O_7Si_2$ 618.3407, found 618.3419; $[M - t\text{-But}]^+$ calcd 561.2704, found 561.2708; MS, m/z (relative intensity): 618 $[M]^+$ (0.1), 575 $[M\text{-}COCH_3]^+$ (0.03), 561 $[M\text{- }C(CH_3)_3]^+$ (4), 199 $[CO\ C(CH_2)\ CH_2O\ Si(CH_3)_2\ C(CH_3)_3]^+$, (21), 75 $[(CH_3)_2\ Si\ OH]^+$ (100); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.16 (d, J= 1,9 Hz, $C_{4'}$-H), 5.97 (d, J= 1.9 Hz, $C_{4'}$-H'), 5.36 (brs, C_{15}-H), 5.23 (brs, C_{15}-H'), 5.11 (brs, C_{14}-H), 4.97 (brs, C_{14}-H'), 4.98 (m overlapped to C_{14}-H', C_8-H), 4.48 (brdd, $J_{2,3}= J_{2',3}= 7.5$ Hz, C_3-H), 4.36 (brs, 2H, $C_{3'}$-H_2), 4.19 (dd, $J_{5,6}= J_{6,7}= 9.5$ Hz), 2.16 (m, C_2-Hβ), 2.11 (s, 3H, C_{16}-CH_3), 1.69 (m, C_2-Hα), 0.93, 0.91 (18H, Si-C $(CH_3)_3$), 0.10, 0.097, 0.089 (12H, Si- CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 206.2 (C-16), 176.8 (C-12), 164.9 (C-1'), 152.1 (C-4), 142.2 (C-10), 140.0 (C-10), 123.9 (C-4'), 117.0 (C-14), 110.6 (C-15), 79.8 (C-6), 76.3 (C-8), 73.7 (C-3), 61.4 (C-3'), 49.4 (C-5)*, 48.8 (C-1)*, 43.8 (C-7)*, 42.1 (C-13)*, 41.5 (C-9)*, 40.7 (C-11)*, 39.5 (C-2)*, 29.8 (C-17), 25.84 (Si - C-C), -4.73, -4.77, -5.44 (Si-C). Assignments denoted with asterisks may be interchanged.

3,3'-Bis-O-(tert-butyl dimethylsilyl)-11αH-13(1'-Hydroxyethyl)cynaropicrin (9). To a solution of **8** (3 g) in methanol (200 mL) was added in portions $NaBH_4$ (0.3 g) at 25°C with continuous stirring over a period of 10 min until complete disapperance of the starting material (0.5h, TLC monitoring, EtOAc-Hexane 2:8). The mixture was diluted with water (100 mL), extracted with Et_2O and purified by chromatography (Hexane-EtOAc 9:1) to give **9** (2.65 g); IR (film) cm^{-1}: 3500 (hydroxyl group), 1777 (γ-lactone), 1715 (α,β-unsaturated ester); MS m/z (relative intensity): 620 $[M]^+$ (0.2), 605 $[M\text{- }CH_3]^+$ (0.1), 3477 $[C_{19}O_6\ H_{23}]^+$ (18), 199 $[COC(CH_2)\ CH_2\ O\ Si(CH_3)_2C(CH_3)_3]^+$ (7), 75 $[(CH_3)_2\ Si\ OH]^+$ (100); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.21 (d, J= 1.7 Hz, $C_{4'}$-H), 5.98 (d, J= 1.7 Hz, $C_{4'}$-H'), 5.32 (brs, C_{15}-H), 5.22 (brs, C_{15}-H'), 5.12 (brs, C_{14}-H), 5.04 (ddd, $J_{8,9'}= 7.2$ Hz, $J_{8,7}= 9.3$ Hz, C_8-H), 4.99 (brs, C_{14}-H'), 4.48 (brdd, $J_{2,3}= J_{2',3}= 7.5$ Hz, C_3-H), 4.36 (brs, 2H, $C_{3'}$-H_2), 4.23, 4.21 (dd, $J_{5,6}= J_{6,7}= 9.5$ Hz, C_6-H), 4.08, 3.88 (m, C_{16}-H), 2.90 (ddd, $J_{1,2}= J_{1,2'}= J_{1,5}= 8.5$ Hz, C_1-H), 2.83 (dd, $J_{1,5}= 8.5$ Hz, $J_{5,6}= 9.5$ Hz), 2.72 (dd, $J_{9,9'}= 13.4$ Hz, $J_{8,9}= 5.2$ Hz, C_9-H), 2.21 (dd, $J_{9,9'}= 13.4$, $J_{8,9'}= 7.2$ Hz, C_9-H'), 1.17 (d, $J_{16,17}= 6.3$ Hz, C_{17}-H_3), 0.92, 0.91, 0.90 (m, Si-C $(CH_3)_3$), 0.098, 0.089 (m, Si CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.6 (C-12), 164.8 (C-1'), 152.2 (C-4), 142.3 (C-10), 139.8 (C-2'), 124.4 (C-4'), 116.9 (C-14), 110.5 (C-15), 79.9 (C-6),

76.2 (C-8), 73.7(C-3), 64.8 (C-16), 61.4 (C-3'), 49.5 (C-5)*, 48.4 (C-1)*, 43.7 (C-7)*, 42.8 (C-13)*, 41.0 (C-9), 39.4 (C-2)*, 37.5 (C-11), 25.8 (Si- C-C), 24.0 (C-17), -4.7, -4.8, -5.4 (Si-C).

3,3'-Bis-O-(tert-butyldimetylsilyl)-13-(1'-hydroxyethyl)-16-(2"-tetrahydropyranyl)-11α-H-dihydrocynaropicrin (10): To a solution of **9** (2.5 g) in dry THF (50 mL), fresh distilled DHP (5mL) and a few crystals of *p*-toluenesulfonic acid were added. After 6 h, anhydrous potassium carbonate was added and the mixture allowed to stand overnight. The salts were separated by filtration and excess of dihydropyran was removed by distillation under reduced pressure. The mixture was chromatographed (Hexane-EtOAc, 9:1) to give **10** (2.33 g, 82%) as a yellowish gum; IR, (film) cm^{-1}: 1760 (γ-lactone), 1706 (α,β-unsaturated ester); MS, m/z (relative intensity): 704 $[M]^+$ (0.01), 620 $[M-84]^+$ (0.2), 199 [CO C (CH_2) CH_2 O Si $(CH_3)_2$ C $(CH_3)_3)]^+$ (5), 75 $[(CH_3)_2$ Si OH$]^+$ (100); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.21 (d, J= 1.9 Hz, C_4-H), 5.94 (d, J= 2.0 Hz, C_4-H'), 5.31 (brs, C_{15}-H), 5.01 (m overlapped to C_{14}-H', C_8-H), 4.98 (brs, C_{14}-H'), 4.36 (brs, $C_{3'}$-H_2), 4.14 (m, C_{16}-H), 4.11 and 4,10 (dd, $J_{5,6}$= $J_{6,7}$= 9.4 Hz), 3.82, 3.47 (m, $C_{6'}$-H_2), 1.5-1.3 (THP), 1.15 (d, 3H, $J_{16,17}$= 6.5 Hz, C_{17}-H_3), 0.9 (18 H, Si-C-$(CH_3)_3$), 0.1 (12H, Si-$(CH_3)_2$).

8α-((*tert*-butyldimethylsisyl)oxy)-11β,13H-dehydrocostus lactone (12): 12 was obtained from 8α-hydroxy-11β,13H-dehydrocostus lactone (**11**) as described for the preparation of **7** in a 85% yield.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.19 (d, J=1.8, C_{15}-H), 5.02 (d, J= 1.8, C_{15}-H'), 4.90 (brs, C_{14}-H), 4.83 (br s, C_{14}-H'), 3.87 (dd, $J_{5,6}$= $J_{6,7}$=9.5 Hz, C_6-H), 2.82 (br dd, $J_{1,5}$= $J_{5,6}$= 9.5, C_5-H), 2.61 (dd, $J_{9,9'}$= 12.6, $J_{9,8}$= 5.3 Hz, C_9-H), 2.41 (dd, $J_{9,9'}$= 12.6, $J_{9',8}$= 9.0, C_9-H'), 1.36 (d, 3H, $J_{11,13}$= 7.1 Hz, C_{13}-H_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 179.1 (C-12), 151.4 (C-4), 145.0 (C-10), 114.0 (C-15), 109.5 (C-14), 80.60 (C-6), 76.60 (C-8), 55.48 (C-5), 52.57 (C-1), 48.21 (C-7), 46.75 (C-9), 41.09 (C-11), 32.47 (C-2), 30.00 (C-3), 25.90, 25.61, (Si-C-$\underline{C}H_3$), 16.73 (C-13).

Ketone 13 and 8α-((*tert*-butyldimethylsilyl)oxy)-11β-hydroxy-13H-dehydrocostus lactone (14): To a solution of **12** (100 mg) in dry THF (25 mL) at -73°C a 0.4M solution of KHMDS (8 mL) in dry THF was added under N_2. After 30 min of stirring at -73°C the mixture was warmed to 0°C and a current of dry oxygen was bubbled for 1 h, then, a buffer solution (pH=7) was added. Extractive workup with Et_2O (5x25 mL) and chromatographic separation (Hexane:AcOEt 8:2) gave **13** (68 mg, 70%) and **14** (10 mg, 10%).

13: IR (film) cm^{-1}: 3540 (hydroxyl group), 1709 (ketone). HRMS EI (70 eV): calcd for $C_{20}H_{34}O_3Si$ 350.2277, found 350.2298; $[M - t\text{-But}]^+$ calcd 293.1573, found 293.1567; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.17 (brs, C_{15}-H), 5.05 (brs, C_{15}-H'), 4.91 (s, 2H, C_{14}-H_2), 4.14 (ddd, $J_{7,8}$= 9.5, $J_{8,9}$= 5 Hz, $J_{8,9'}$= 7.8, C_8-H), 4.05 (dd, $J_{5,6}$= $J_{6,7}$= 9.8, C_6-H), 2.87 (m, C_1-H), 2.73 (brdd, $J_{5,6}$= 9.8, $J_{1,5}$= 8.4, C_5-H), 2.57 (dd, $J_{6,7}$= 9.8, $J_{7,8}$= 9.5, C_7-H), 1.55 (s, 3H, C_{13}-H_3), 0.91 (s, 9H, Si-C $(CH_3)_3$), 0.15, 0.12 (s, 6H, Si CH_3).

14: IR (film) cm^{-1}: 3438 (hydroxyl group), 1755 (γ-lactone). HRMS EI (70 eV): [M - *t*-But]$^+$ calcd 321.1522, found 321.1519; ^{1}H-NMR (200MHz, $CDCl_3$) δ: 5.17 (brs, C_{15}-H), 5.10 (brs, C_{15}-H'), 4.94 (brs, C_{14}-H), 4.89 (brs, C_{14}-H'), 3.86 (ddd, $J_{7,8}= J_{8,9'}= 8.4$, $J_{8,9}= 4.2$ Hz, C_8-H), 3.27 (dd, $J_{5,6}= J_{6,7}= 9.4$, C_6-H), 2.82 (dd, $J_{1,5}= J_{5,6}= 9.4$, C_5-H), 2.79 (m, C_1-H), 2.50 (dd, $J_{8,9}= 4.5$, $J_{9,9'}= 14$ Hz, C_9-H), 2.25 (s, 3H, $C_{13}H_3$), 0.88 (s, 9H, Si-C-CH_3), 0.12 (s, 6H, Si CH_3).

To a solution of **12** (100 mg) in dry THF (25 mL) at -73°C a 0.4M solution of KHMDS (8 mL) in dry THF and triethyl phosphite (120 µL) were added under N_2. After 1 h of stirring at -73°C, a current of dry oxygen was bubbled for 1 h, then, the reaction mixture was warmed to -20°C and a buffer solution (pH=7) was added. The reaction mixture was extracted affording **14** (82 mg 81%), and no amount of **13** was detected.

(16S)-3-O-(tert-Butyldimethylsilyl)-13-(1'-hydroxymethyl)-16-(2"-(tetrahydropyranyl)oxy)-11α-hydroxy-dihydrodeacylcynaropicrin (15) and (16R)-3-O-(tert-bytyldimethylsilyl)-13-(1'-hydroxymethyl)-16-(2"-(tetrahydropyranyl)oxy)-11α-hydroxy-dihydrodeacylcynaropicrin (16). To a solution of **10** (0.2 g) in dry THF (25 mL) at -73°C a 0.4M solution of KHMDS (8 mL) in dry THF and triethyl phosphite (120 µL) were added under N_2. After 1 h of stirring at -73°C, a current of dry oxygen was bubbled for 1 h, then, the reaction mixture was warmed to -20°C and a buffer solution (pH=7) was added. Extractive workup with Et_2O (5x25 mL) and chromatographic separation (column and prep. TLC) gave **15** (5 mg, 4%) and **16** (25 mg, 17%) as oily products.

15:IR (film) cm^{-1}: 3412 (hydroxyl groups), 1740 (γ-lactone).MS m/z (relative intensity): 440 [M-DHP]$^+$ (0.2), 85 [DHP]$^+$ (100), 43 [CO-CH_3]$^+$ (89): ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.35 (brs, C_{15}-H), 5.23 (brs, C_{15}-H'), 5.11 (brs, C_{14}-H), 5.00 (brs, C_{14}-H'), 4.92 (m, $C_{2"}$-H), 4.46 (m, C_3-H), 4.26 (dd, $J_{5,6}= J_{6,7}= 10$Hz, C_6-H), 4.15 (m, C_{16}-H), 3.78 (m, C_8-H), 3.64 (m, $C_{6"}$-H_2), 1.65, 1.4 (THP), 1.29 (d, $J_{16,17}= 7.5$ Hz, 3H, C_{17}-H_3), 0.93 (s, 9H, Si-C-CH_3), 0.1 (s, 6H, Si-CH_3).

16:IR (film) cm^{-1}: 3440 (hydroxyl groups), 1760 (γ-lactone). MS m/z (relative intensity): 440 [M-DHP]$^+$ (0.2), 85 [DHP]$^+$ (100): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.33 (brs, C_{15}-H), 5.22 (brs C_{15}-H'), 5.07 (brs, C_{14}-H), 4.98 (brs, C_{14}-H'), 4.89 (m, $C_{2"}$-H), 4.47 (m, C_3-H), 4.28 (dd, $J_{5,6}= J_{6,7}= 10$ Hz, C_6-H), 4.18 (m, C_{16}-H), 3.64 (m, C_8-H), 3.59 (m, $C_{6"}$-H_3), 1.65, 1.4 (THP), 1.24 (d, $J_{16,17}= 6.5$ Hz, 3H, C_{17}-H_3), 0.92 (s, 9H, Si-C-$(CH_3)_3$), 0.09 (s, 6H, Si-$(CH_3)_2$).

3,3'-Bis-O-(tert-butyldimethylsilyl)-13-(1'-hydroxymethyl)-16-(2"-(tetrahydropyranyl)oxy)-11α-hydroxy-dihydrocynaropicrin (17): **10** (0.2 g) and bipyridyne (a few crystals) were disolved in dry THF (50 mL). A 0.4M solution of KHMDS (10 mL) in THF was added at -73°C with continuous stirring. The solution

immediately turned dark orange. Triethyl phosphite (15 mL) was added and the mixture was stirred for 1 hour. Then, a current of dry oxygen was bubled for 1h and the system was warmed to -20°C. Neutralization was carefully accomplished by addition of 30% solution of dry acetic acid in THF (until desappearance of the orange colour). A buffer solution (pH=7) was added in advance of being extracted with Et_2O (5x25 mL). The crude product was chromatographed (Hexane-EtOAc 85:15) to give **17** as a yellowish gum (68 mg, 34%); IR (film) cm^{-1}: 3410 (hydroxyl group), 1755 (γ-lactone), 1730 (α,β-unsaturated ester); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.25 (brd, J= 2Hz, $C_{4'}$-H), 5,97 (brd, J= 2Hz, $C_{4'}$-H'), 5.43 (ddd, $J_{8,9}$= 4.8 Hz, $J_{8,9'}$= 6.2 Hz, $J_{7,8}$= 9.4 Hz, C_8-H), 5.41 (brs, C_{15}-H), 5.24 (brs, C_{15}-H'), 5.07 (brs, C_{14}-H), 4.91 (brs, C_{14}-H), 4.61 (m, $C_{2'}$-H), 4.47 (brdd, $J_{2,3}$= $J_{2',3}$= 7.5 Hz, C_3-H), 4.40 (brs, 2H, $C_{3'}$-H_2), 4.37 (dd, $J_{5,6}$= $J_{6,7}$= 9.6 Hz, C_6-H), 3.90, 3.50 (m, $C_{6'}$-H_2), 2.48 (dd, $J_{6,7}$= 9.6 Hz, $J_{7,8}$= 9.4 Hz, C_7-H), 1.7, 1.4 (m, THP), 1.12 (d, $J_{16,17}$= 6 Hz, C_{17}-H_3), 0.93, 0.92 (18H, Si-C$(CH_3)_3$), 0.10, 0.09 (12H, Si-$(CH_3)_2$).

Deacylclementein (18): To a solution of **15** (5 mg) in 20 mL of methanol (98%), a few crystals of *p*-toluenesulfonic acid were added. After 24 h potassium carbonate was added and the mixture stirred for some minutes. The salts were removed by filtration and the solvent by distillation under reduced pressure. The mixture was chromatographed (prep TLC, Hexane:EtOAc 1:1) to give **18** (2 mg, 60%); IR (film) cm^{-1}: 3400 (hydroxyl groups), 1730 (γ-lactone); HRMS EI (70 eV): calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1466; MS m/z (relative intensity): 306 $[M]^+$ (1), 266 $[M-C_3H_4]^+$ (13); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 5.35 (brs, C_{15}-H), 5.31 (brs, C_{15}-H'), 5.06 (brs, C_{14}-H), 5.02 (brs, C_{14}-H'), 4.47 (brdd, $J_{2,3}$= $J_{2',3}$= 7.6 Hz, C_3-H), 4.15 (dd, $J_{5,6}$= $J_{6,7}$= 9.4 Hz, C_{16}-H), 4.3 (m, 2H, C_8-H, C_6-H), 2.93 (m, C_1-H), 2.74 (brdd, $J_{5,6}$= 9.4 Hz, $J_{1,5}$= 6.4 Hz, C_5-H), 2.66 (dd, $J_{8,9}$= 5.5 Hz, $J_{9,9'}$= 11 Hz, C_9-H), 2.39 (m, 2H, C_{13}-H_2), 2.30 (dd, $J_{8,9'}$= 7.5 Hz, $J_{9,9'}$= 11 Hz, C_9-H'), 2.22 (dd, $J_{6,7}$= 9.4 Hz, $J_{7,8}$= 9 Hz, C_7-H), 2.17 (m, C_2-H), 1.66 (m, C_2-H).

Deacylclementein B: **16** (20 mg) was treated as described for the preparation of **18**, and after purification gave **19** (9 mg, 65%). The spectroscopic data of **19** are identical to those of desacylclementein B. ^{13}C-NMR (125 MHz, $CDCl_3$-Methanol-d_4 1:1) δ: 179.0 (C-12), 153.4 (C-4), 144.1(C-10), 116.1(C-14), 112.2(C-15), 79.6(C-6), 76.3(C-11), 73.6(C-3), 67.5(C-8), 64.5(C-16), 55.8(C-5), 51.0(C-7), 44.8(C-1), 44.2(C-13), 39.(3C-2), 30.3(C-9), 24.4(C-17).

Clementein (1) and clementein B (2): **17** (55 mg) was dissolved in HCl_{aq}(2N):MeOH (1:19) and allowed to stand for 24 hours. The solvent was removed under reduced pressure and the mixture chromatographed (prep TLC, 3x Hexane-AcOEt, 2:8) to give **1** (2 mg) and **2** (18 mg). The spectroscopic data of compounds **1** and **2** are identicals to those of clementein and clementein B.

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