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Synthesis of Vlasouliolides, a Pathway Towards Guaiane-eudesmane C_{17}/C_{15} Dimers by Photochemical and Michael Additions

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vlasouliolides • photochemical addition • sesquiterpene dimers • vladimiria souliei • anti-inflammatory activity

ABSTRACT: *Vladimiria souliei* is a plant located in China applied in traditional medicine. Recent isolation studies have led to the discover of vlasouliolides, natural sesquiterpene dimers. However, the yields obtained from isolation have proven to be really low (<0.01%) greatly hindering the study of these molecules. In this work, we propose a simple synthetic route to obtain different vlasouliolides in good yields from dehydrocostuslactone and costunolide, which will lead further bioactivity studies at higher scale.

Introduction

Vladimiria souliei is a recently studied plant from the Asteraceae family. This plant is distributed in China and it is widely applied in traditional medicine. Sesquiterpene lactones isolated from the roots are characterized by a structurally complex skeleton, with a mixed union of germacranes, eudesmanes and guaianolides[1,2]. The structure of vlasoulamine A has been elucidated by X-ray analysis. This compound is one of the structurally unusual guaianolides isolated from this plant as it is a dimer linked with a pyrrolo[2,1,5-cd]indolizine fragment[3]. Nevertheless, vlasouliolides are members of the sesquiterpene dimer family and these compounds have achieved relevance due to their anti-inflammatory activity and NO suppression.

Vlasouliolides A–K were recently isolated by Wu et al. and they have a C32 skeleton in which two sesquiterpene lactones are linked by a C11–C13' bond and one acetyl group is attached to C13 in one of the units[4]. Extraction of these compounds from plants gives extremely low yields; for example, Chen et al. obtained only ~1.8 mg of vlasouliolide G from 20.0 kg of dried roots. As a consequence, improvements in the yields of vlasouliolide production could facilitate future medicinal applications. Furthermore, other isolated sesquiterpene lactones have also shown relevant biological activities, e.g., against human hepatoblastoma (HepG2)[5] or neuroprotective effects against glutamate-induced PC-12 cells[6].

In the study reported here, vlasouliolides A, C, D, E, G, H and I (Figure 1) were synthesized from dehydrocostuslactone and costunolide by the photochemical addition of a methyl ketone fragment and subsequent carbon-carbon single bond formation with the appropiate enolate.

An efficient synthetic pathway has been developed for seven different vlasouliolides using dehydrocostuslactone **1** and costunolide **2** as starting materials. The synthetic route was split into two stages: the first stage (Scheme 1) involved the preparation of the first monomer according to the procedure partially described in previous works[7]. The second stage corresponds to the union of the monomers and subsequent modifications to obtain the final natural products.

Results and discussions

Firstly, 50 g of *Saussurea lappa* root extract were employed to obtain 2.3 g of **1** as a colorless crystalline solid (5% yield) and 2.8 g of **2** as a colorless crystalline solid (5.6% yield), according to procedures described in the literature[7,8].

Stage one is split into three steps. The first step involved the addition of the C-2 fragment through a photochemical reaction in which acetaldehyde attacks the C-13 position of the lactone. After the methyl ketone derivative had been obtained, the new carbonyl group was protected to guarantee the formation of an enolate at C-11, which is needed in the next reaction. Protection of the aforementioned carbonyl group as a ketal was carried out with 2-ethyl-2-methyl-1,3-dioxolane (MED), catalytic amounts of *p*-toluenesulfonic (*p*-TsOH) acid and ethylene glycol. The ketal derivative was the substrate used for the dimerization reaction in the second stage.

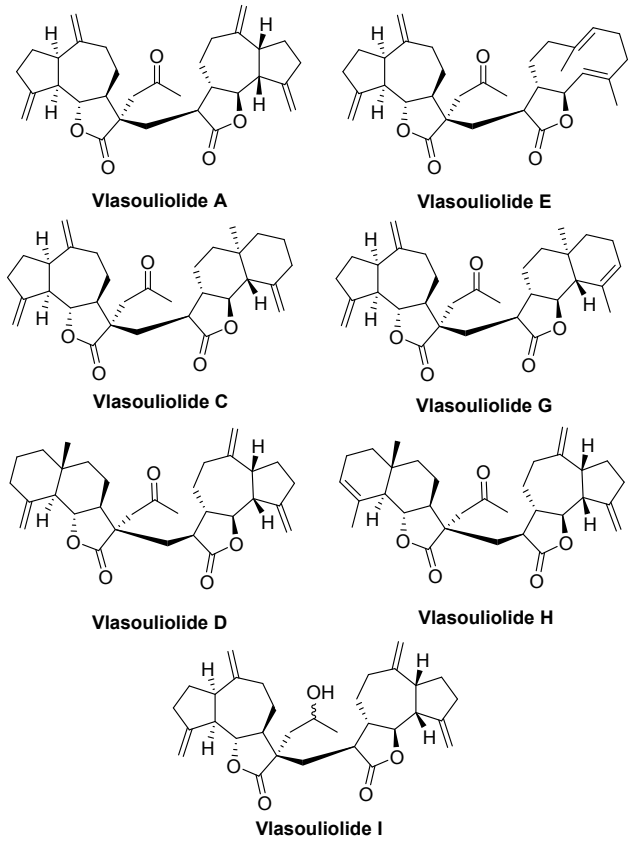


Figure 1. Vlasouliolides synthesized from costunolide and dehydrocostuslactone.

The application of this route to **1** provided methyl ketone derivative **3** in 70% yield and subsequent protection with MED afforded the ketal derivative **4** in 60% yield.

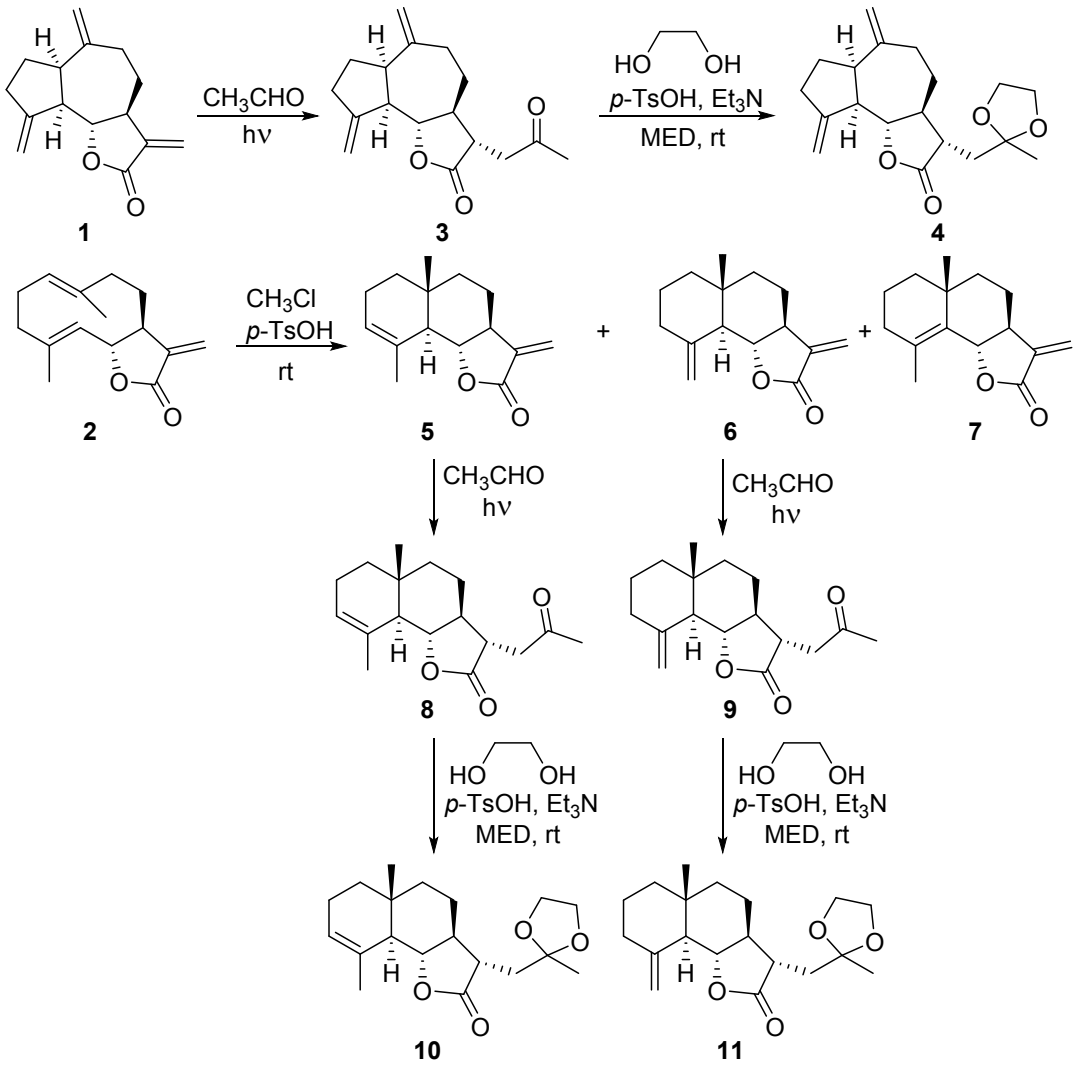
In the case of **2**, a prior cyclization of costunolide was required to obtain *α*-cyclocostunolide **(5)** and *β*-cyclocostunolide **(6)**. A catalytic amount of *p*-TsOH produced the cyclization of **2** into **5** (25% yield), **6** (55 % yield) and *γ*-cyclocostunolide **7** (5% yield).

Treatment of **5** and **6** under the conditions shown in Scheme 1 led to methyl ketone derivatives **8** and **9** in 47% and 65% yields, respectively, and the ketal derivatives **10** and **11** in 51% and 76%, respectively.

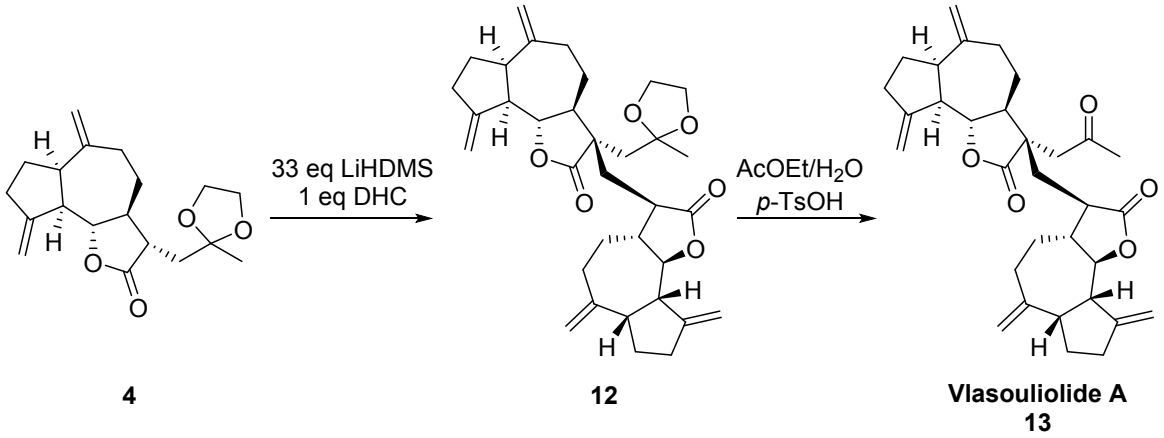
Having obtained ketal derivatives **4**, **10** and **11**, different vlasouliolides could be easily prepared by a combination of these derivatives with dehydrocostuslactone and *α*- or *β*-cyclocostunolide. The procedure is shown in Scheme 2, in which the synthesis of vlasouliolide A **(13)** is outlined as a representative example.

Firstly, the reaction of a strong base such as lithium bis(trimethylsilyl)amide (LiHDMS) would produce an enolate at the C-11 position. In a subsequent Michael reaction the enolate reacts with the α,β-unsaturated bond of the other lactone, thus leading to the formation of a C–C single bond between the C-11 carbon of the ketal derivative and the C-13' carbon of the sesquiterpene lactone. On first consideration, 5% w/w CuI was employed to weaken the C-13 double bond with the aim of facilitating the Michael addition. Nevertheless, it appeared that Cu^+ blocked the C–C bond formation, with unreacted substrates recovered. Trials with sodium bis(trimethylsilyl)amide (NaHDMS) and potassium bis(trimethylsilyl)amide (KHDMS) were carried out. Secondary products appeared on using the sodium and potassium bases and the yields of the vlasouliolides were lower. Several authors have suggested that the counterion of the base plays an important role in the mechanism of the reaction in fixing a given conformation[9]. Authors suggest that the ether oxygens of the protecting group and the carbonyl of the cyclic ester are chelated by the alkaline metal at low temperature, thus controlling the formation of a single epimer at C-11. This could also explain why reaction was not observed when the substrates were treated with CuI as the Cu^+ ionic radius is 135 pm (cf. Li^+ 145 pm, Na^+ 180 pm and K^+ 220 pm) and Cu^+ would thus prevent formation of the chelate complex with the alkaline cation. Following this pathway we can synthetize all the vlasouliolides shown in scheme 3.

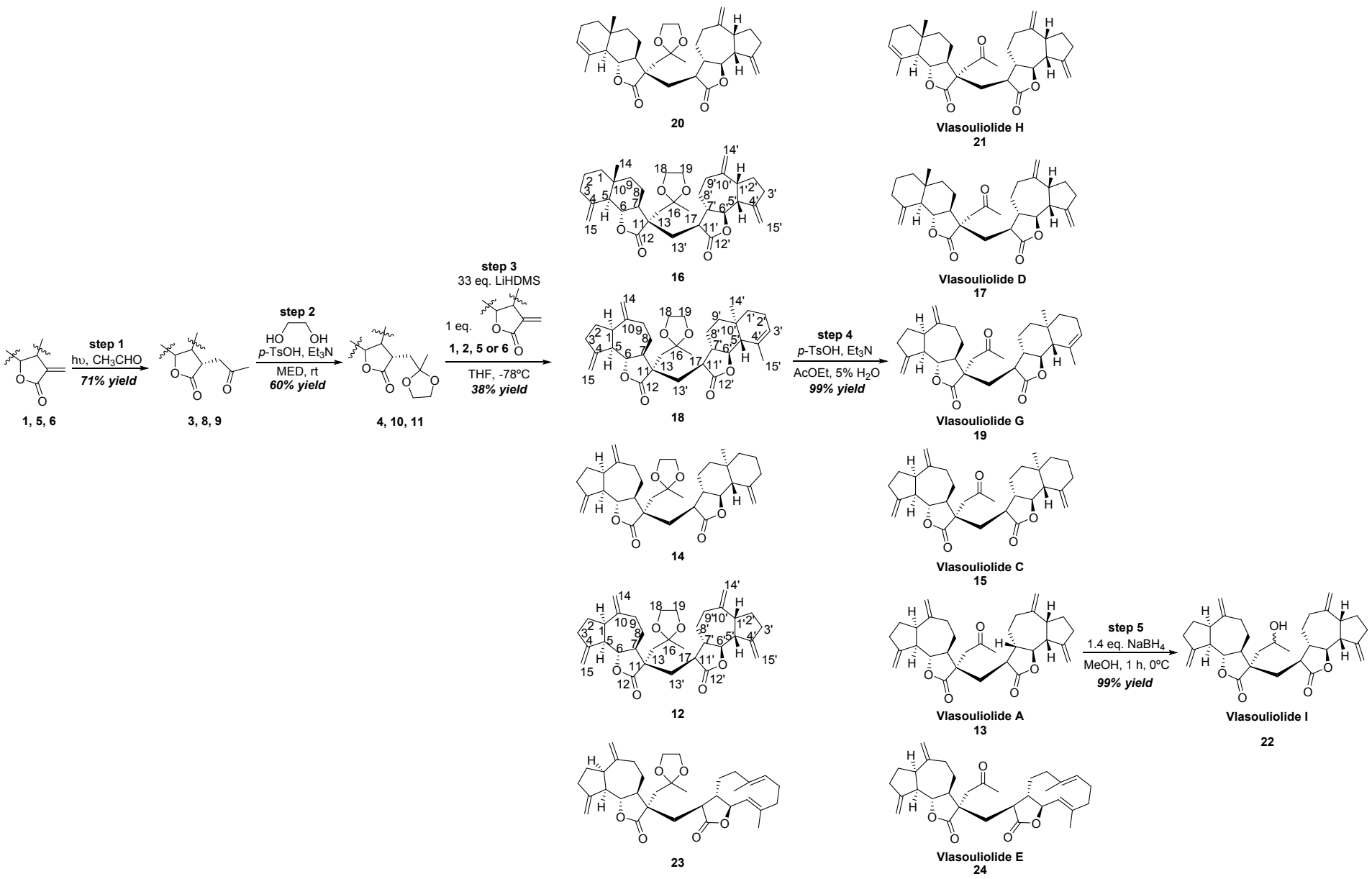
Scheme 1. Synthesis of the methyl ketone and subsequent ketal derivatives of dehydrocostuslactone and costunolide.



Scheme 2. Pathway to vlasouliolide A from the ketal derivative.

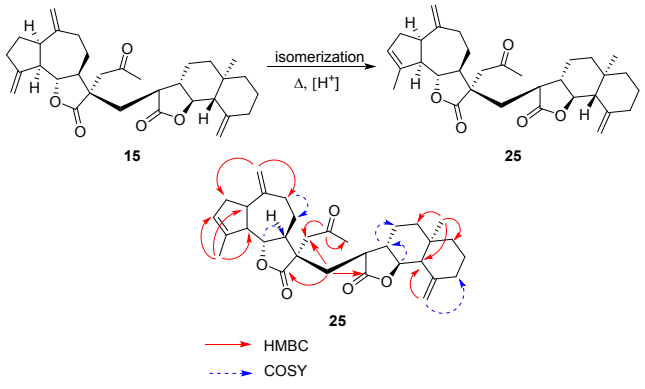


Scheme 3. Synthesis of vlasouliolides.



Protected vlasouliolides show characteristic proton signals in the range 3.84–3.97 ppm with complex multiplicity and these correspond to the dioxolane group attached at C-16. The multiplicity becomes more complex due to the presence of the H-6' signal in the same region of the spectrum. In the $^{13}C\{^1H\}$-NMR spectra the most characteristic signals appear at 63.9 and 64.5 ppm, which are assigned to the protecting group. Deprotection of the carbonyl group to obtain the vlasouliolide led to some significant differences in the $^{13}C\{^1H\}$-NMR spectra: a slight difference of 0.02 ppm was observed in the C6 and C6' signals, the signals of the ketal group disappeared and a new carbonyl carbon signal was observed at 205.1 ppm. Vlasouliolide A shifts are used as a representative example in this discussion but similar observations were made for the other vlasouliolides prepared. In the case of α- and β-cyclocostunolide derivatives, the main differences are the double bond proton signals. H-3 of α-cyclocostunolide **(8)** gave a signal at 5.36 ppm, while H-3 and H-3' of **9** were shifted to 2.32 ppm and 1.99 ppm, respectively, with a geminal coupling constant of 13.1 Hz. Furthermore, in compound **9** the C-3 carbon is shielded (35.9 ppm) in comparison with C-3 of **8** (122.4 ppm). In the case of the protected derivatives, the proton signals of the protecting group overlapped with H-6 for **4** and **11** but not for **10**. Once the dimer had been obtained, removal of the ketal protecting group was carried out in the C-16 position. In a first approach, deprotection was attempted with 1.0 M HCl in methanol overnight at room temperature. However, different side reactions, mostly due to isomerization of double bonds, were observed and the desired vlasouliolide was only obtained in low yield. A clear example of this was observed during the deprotection of vlasouliolide C **(14)**. In this case, when HPLC separation was carried out to isolate **15** a complex chromatogram was obtained. Different peaks were observed and, among them, the two major peaks were due to **15** (15.5% yield) and another compound in which the double bond had isomerized at C-15 **(25)** (12% yield) (Scheme 4).

Scheme 4. Double bond isomerization of H-3 produced by protecting group removal with HCl.



Traces of vlasouliolide D **(17)** were also obtained by isomerization of the double bond of the β-cyclocostunolide monomer. It was postulated that the strongly acidic HCl medium had caused the appearance of these side products and, to avoid this, different deprotection approaches were tried. The best results were obtained when the protected vlasouliolide was dissolved in ethyl acetate/water (95:5) containing a catalytic amount of *p*-TsOH. Under these conditions the vlasouliolide compounds were obtained in quantitative yields. The desired deprotection was confirmed by NMR spectroscopy, NMR spectra for all molecules are available in the support information. In case of vlasouliolide A, the disappearance of the signals at 64.5 ppm and 63.9 ppm of the protecting group and the high field shift of C-16 (from 77.2 ppm to 205.7 ppm) due to the formation of the carbonyl group in that position are the most relevant changes. Two major changes were observed in the proton spectra: the first change was the disappearance of the signals from 3.98 to 3.82 ppm, which correspond to –CH_2– of the 1,3-dioxolane ring in the C-16 position. The second change concerned the shift of the methyl group protons from 1.34 ppm to 2.17 ppm due to the influence of the new α-carbonyl group. Similar changes were observed for the other vlasouliolides. The spectra of the synthesized vlasouliolides were identical to those reported for the natural products[4,10].

Vlasouliolide I **(22)** was obtained by reduction of the carbonyl group at C-16. Treatment of **13** with sodium borohydride in MeOH at 0 ºC gave **22** in quantitative yield. The characteristic shift of the singlet due to the methyl fragment in the α-position with respect to the carbonyl group of **13** at 2.17 ppm (Me-17) disappeared and a doublet was observed at 1.25 ppm (J = 6.1 Hz) corresponding to a methyl group α to the hydroxyl unit. In addition, a new signal (*qdd*) was observed at 3.91 ppm, i.e., below H-6. COSY experiments confirmed the correlation of the new proton with Me-17 and this was therefore assigned as H-16. The $^{13}C\{^1H\}$-NMR spectrum confirmed the reduction of the carbonyl group, since the C-16 signal was shifted from 205.7 ppm to 64.3 ppm. Only one epimer at C-16 was obtained in this reaction but identification of the absolute configuration at that position was not achieved. An (electronic circular dichroism) ECD simulation employing B3LYP/6-311G (d,p) DFT studies did not show any relevant differences to elucidate which epimer had been synthesized. Due to the complexity of the molecule and the presence of several chiral centers no significant difference was observed in the ECD simulations and identification of the epimer was not possible. However, the synthesized molecule was confirmed to be vlasouliolide I **(22)** by comparison with the ^1H-NMR spectra found in the literature[10].

Figure 2 shows the most relevant correlations between carbons and protons by HMBC and COSY experiment. Double bond proton signal are the main target in the elucidation, that let the total assignation of the molecules. In all cases, we have found HMBC interaction among H-13' signal (belonging to the carbon bridge between monomers) and both carbonyl carbons of the lactones. This is the main fact that supports the correct structure achieved. Furthermore, correlations between 11 and 11' carbons and H-13', can be observed in most cases and also support the arrangement. The analysis of HMBC signals

between H-13 and C-7, as in case of **18**, confirms the presence of the methyl ketone group in the monomer. In the case of **23**, both correlations were observed in HMBC experiment. COSY correlations between protons H-1 and H-5, and H-6 and H-7 make an essential contribution to discern that the cycle arrangements in costunolide and DHC monomers remain.

Having successfully synthesized vlasouliolides C, E and G, a new synthetic approach was developed in which costunolide (**2**) would be directly linked with **4**. The main idea was to obtain vlasouliolides **15** and **17** in one step, thus avoiding cyclization of **2**. Following this procedure, the protected vlasouliolide **23** would be synthesized and then, during the deprotection reaction in an acidic medium, the costunolide monomer would cyclize into **5** and **6** to yield vlasouliolides C and G in the same reaction, as shown in Scheme 5.

Once **23** had been obtained by the same methodology as the other vlasouliolides, it was subjected to a protecting group removal with catalytic *p*-TsOH and a 5% AcOEt:water mixture. This route, let the first synthetization of vlasouliolide E. Notwithstanding, as shown in Scheme 6, when this synthetic procedure was carried out a complex mixture with vlasouliolides C, Eand G and their protected forms was obtained. Prior cyclization of costunolide led to the best yields when compared to a direct dimerization of dehydrocostuslactone and costunolide.

This finding suggests that the cyclization procedure of **2** and protecting group removal are two competitive pathways.

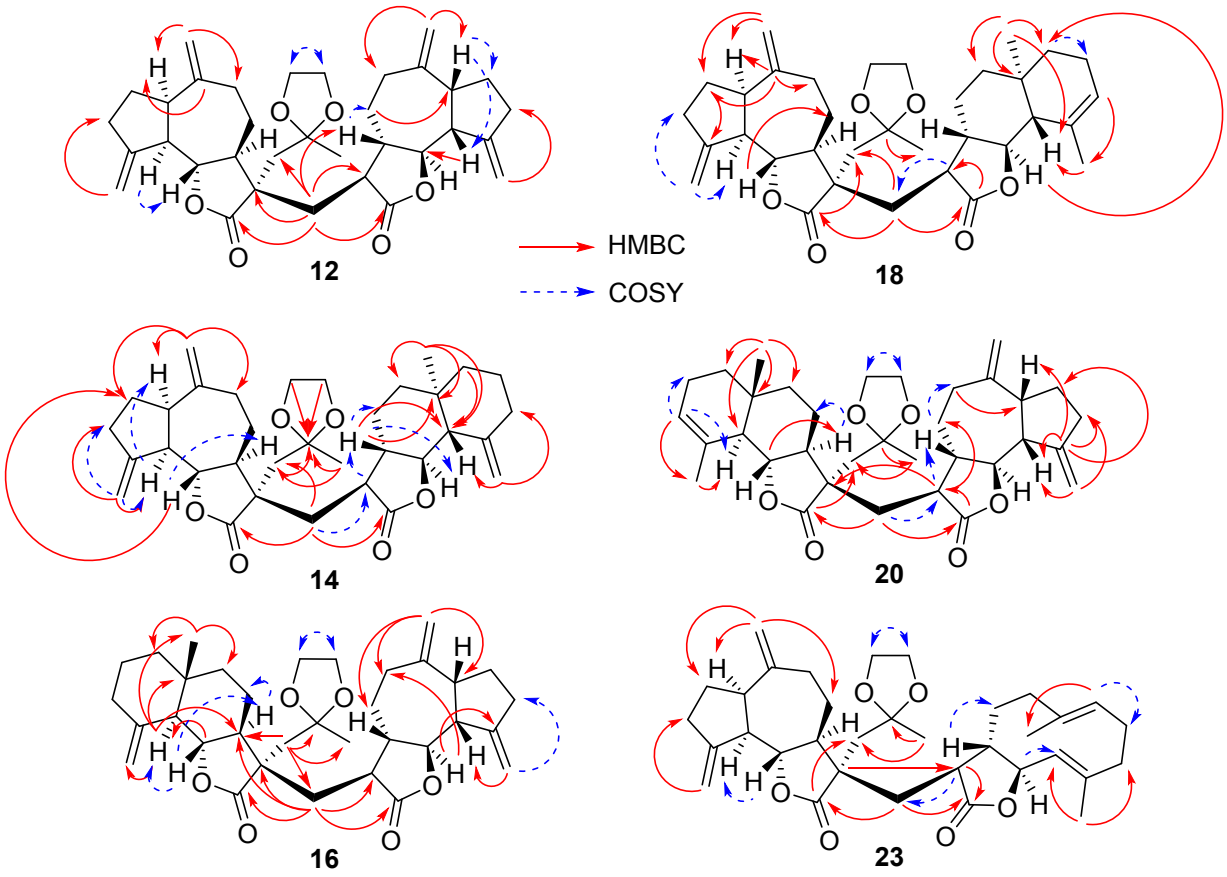
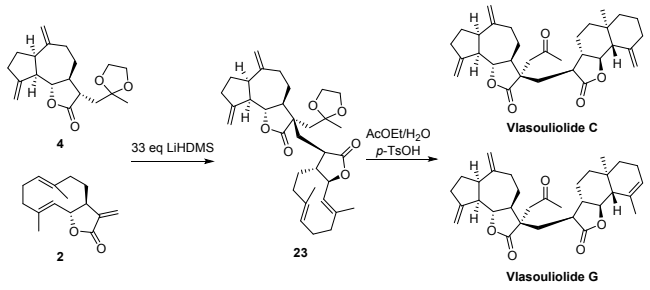


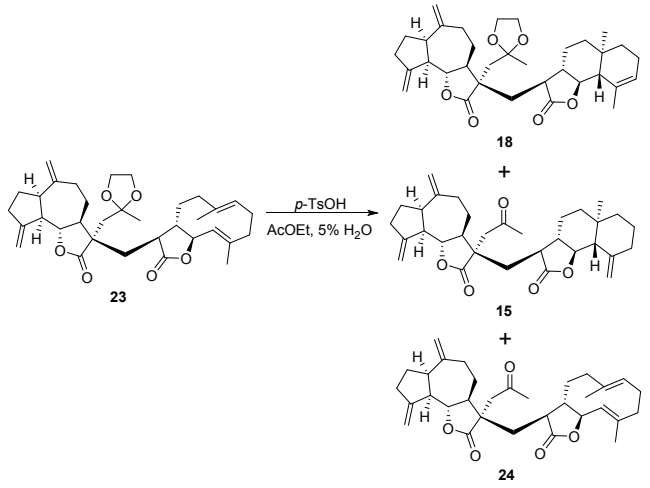
Figure 2. Most representative HMBC and COSY correlations.

Despite avoiding the need for an additional step in the process, the desired vlasouliolides were obtained in lower yields when compared to those obtained in the original cyclization method. In addition, a complex mixture was obtained that proved difficult to purify and it can therefore be concluded that the original route is preferable.

Scheme 5. Alternative mechanism proposed for the synthesis of vlasouliolides C and G.



Scheme 6. Protecting group removal on protected vlasouliolide 23 results in a complex mixture with vlasouliolides 15, 16 and 24 as the main constituents.



Experimental section

1. General information

The starting materials (dehydrocostuslactone **1** and constunolide **2**) were isolated from a root oil extract from *Saussurea lappa* purchased from Pierre Chauvet S.A. (Seillans, France). The reagents for the reactions were supplied by either Sigma-Aldrich Co. (St. Loius, Missouri) or Merck (Darmstadt, Germany). The isolation and purification of the compounds was performed by column chromatography using silica gel Geduran® Si 60 (0.063-0.200 mm) or HPLC using a Varian PrepStar system equipped with a Varian (Model 350) refractive index detector and a Phenomenex Luna 10u Silica column (21.20 x 250 mm x 10 µm). ^{1}H-NMR and ^{13}C{^{1}H}-NMR were recorded on Agilent spectrometers at 400/100 MHz, 500/125 MHz and 600/150 MHz using $CDCl_3$ provided by MagniSolv™, Merck as internal reference set to δ 7.26 ppm for ^{1}H-NMR and δ 77.0 ppm for ^{13}C{^{1}H}-NMR. FTIR spectra were obtained using a Perkin-Elmer Spectrum TWO IR spectrophotometrer providing major absorptions as wavenumbers $\tilde{\upsilon}$ in cm^{-1}. UV spectra were recorded with a VWR UV-6300PC Double Beam spectrometer from 190 to 400 nm using acetonitrile as solvent. Optical rotation was obtained with a Jasco P-2000 polarimeter. Exact masses were measured on a UPLC-QTOF ESI (Waters Synapt G2, Manchester, UK) high-resolution mass spectrometer (HRTOFESIMS).

2. General procedures to obtain vlasouliolides

2.1. General procedure for the cyclization of costunolide.

100 mg ($4.30 \cdot 10^{-1}$ mmol) of costunolide **(2)** was dissolved in 15 mL of dichloromethane in a 25 mL flask and catalytic amounts of *p*-TsOH was added. The mixture was stirred overnight at room temperature. The crude product was then extracted three times with ethyl acetate, dried with anhydrous $NaSO_4$ and the solvent was evaporated under reduced pressure. The products were purified by column chromatography using hexane/ethyl acetate 95:5 as eluent. α-Cyclocostunolide **(5)** and β-cyclocostunolide **(6)** were obtained in 25% (24.8 mg, $1.07 \cdot 10^{-1}$ mmol) and 55% (52.5 mg, $2.26 \cdot 10^{-1}$ mmol) yield, respectively. Spectra data for **5** and **6** matches the one reported in the bibliography[11].

2.2. General procedure for the synthesis of the methyl ketone derivatives.

100 mg of the sesquiterpene lactone was dissolved in 100 mL of acetaldehyde (previously distilled) and introduced into a modified Hanovia reactor with a Pyrex jacket (Figure 3). The solution was irradiated with a 125 W medium pressure Hg lamp model Radium from Radium (Wipperfürth, Germany) The strongest peaks of emission of these kind of lamps are: 184.4, 253.7, 365.4, 404.7, 435.8 and 546.1 nm[12]. To minimize the formation of undesired products a filter solution of $NiSO_4 \cdot 6H_2O$ (46 g) and $CoSO_4 \cdot 7H2O$ (14 g) in 100 mL of water was used to restrict the wavelengths to a small window at around 300 nm[13]. The lamp is introduced into the Hanovia reactor and its distance to the reaction mixture is approximately 10.0 cm. The reaction was stirred for 1 hour and the solvent was evaporated under reduced pressure adding small quantities of cyclohexane to remove the acetic acid produced as byproduct. The mixture was purified by column chromatography with a gradient of hexane/ethyl acetate 90:10 to 60:40 to give the corresponding methyl ketones.

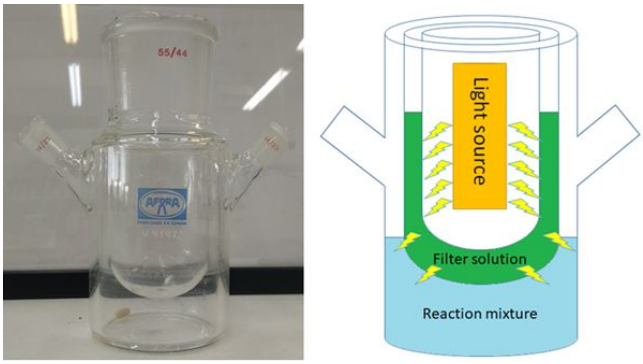


Figure 3. Hanovia reactor for the photochemical addition.

2.3. General procedure for the synthesis of the ketal derivatives.

100 mg of the ketone derivatives was dissolved in 2 mL of 2-ethyl-2-methyl-1,3-dioxolane (MED) in a 25 mL flask and catalytic amounts of *p*-toluenesulfonic acid and ethylene glycol were added. The reaction was stirred at room temperature for 4 hours. Then, the mixture was neutralized with 0.1 mL of triethylamine to eliminate the excess of acid, 20 mL of aqueous Na_2CO_3 was added and then extracted three times with 20 mL of ethyl acetate. The organic layers were combined, dried with anhydrous $NaSO_4$ and the solvent was evaporated under reduced pressure. The products were purified by column chromatography with a gradient of hexane/ethyl acetate 90:10 to 60:40 to give the corresponding ketal derivatives.

2.4. General procedure for the dimerization of the ketal derivatives and the sesquiterpene lactones.

50 mg of the ketal derivative (first monomer) was dissolved in 15 mL of dry THF in a 100 mL flask. The reaction was carried out under nitrogen atmosphere and at −73 °C using an acetone/liquid air bath. After reaching this temperature 33 equivalents of LiHDMS were slowly added to the mixture to form the enolate at C-11 and allowed to react for 30 minutes. After the enolate has been formed, 1 equivalent of the second monomer was added and the mixture was stirred at −73 °C for 2 hours. Then, the mixture was warmed to room temperature and neutralized with 20 mL of Sorensen's buffer (100 mL of an aqueous solution of 133 mM Na_2HPO_4 and 133 mM KH_2PO_4). The crude product was extracted three times with 20 mL of chloroform, the organic layers were dried with anhydrous $NaSO_4$ and evaporated under reduced pressure. The products were purified by HPLC using an eluent of hexane/acetone 20%. This step gave the protected vlasouliolides A **12**, C **14**, D **16**, G **18**, H **20** and E **23**. None of the protected vlasouliolides were obtained as a stereoisomeric mixture, the stereoisomer obtained corresponded to the one of the natural products.

2.5. General procedure for the deprotection of protected vlasouliolides

2.5.1. HCl method.

20 mg of protected vlasouliolides was dissolved in 15 mL of methanol in a 100 mL flask and a catalytic amount of *p*-TsOH was added. 45 mL of 0.1 N HCl was added. The mixture was stirred overnight at room temperature. The crude product was extracted three times with ethyl acetate, dried with anhydrous $NaSO_4$ and evaporated under reduced pressure. The products were purified by HPLC using an eluent of hexane/acetone 15%.

2.5.2. AcOEt/H_2O method.

20 mg protected vlasouliolides were dissolved in 1.9 mL of ethyl acetate in a 25 mL flask and a catalytic amount of *p*-TsOH was added. 0.1 mL of distilled water was added. The mixture was stirred overnight at room temperature. The crude product was extracted three times with ethyl acetate, dried with anhydrous $NaSO_4$ and evaporated under reduced pressure. The products were purified by HPLC using an eluent of hexane/acetone 15%. This method gave vlasouliolides in quantitative yield.

2.6. General procedure for the reduction of vlasuliolide A.

20 mg of vlasouliolide A **(13)** was dissolved in 5 mL of anhydrous methanol in a 25 mL flask at 0 °C using an ice/water bath under a nitrogen atmosphere. 1.4 equivalents of sodium borohydride ($NaBH_4$) were added to the mixture and after one hour 10 mL of distilled water was added to deactivate $NaBH_4$ and end the reaction. The crude product was extracted three times with ethyl acetate, dried with anhydrous $NaSO_4$ and evaporated under reduced pressure. 22 was purified by HPLC using an eluent of hexane/acetone 15%. This method gave vlasouliolide I **(22)** in quantitative yield. During this reaction, only one stereoisomer was obtained, after comparing the NMR data obtained with the reported in the bibliography[10] we determined it to be the desired compound.

Compound characterization

(3S,3aS,6aR,9aR,9bS)-6,9-dimethylene-3-(2-oxopropyl)decahydroazuleno[4,5-b]furan-2(9bH)-one (3). When 100 mg of 1 ($4.34 \cdot 10^{-1}$ mmol) was treated following the procedure described in 2.2. compound 3 (82.4 mg, $3.00 \cdot 10^{-1}$ mmol) was obtained with 70% yield. Spectra data of **3** is presented in previous work[7].

(3S,3aS,5aR,9bS)-5a,9-dimethyl-3-(2-oxopropyl)-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-b]furan-2(3H)-one (8). Treatment of **5** (100 mg, $4.30 \cdot 10^{-1}$ mmol) under the conditions described in 2.2. produced **8** (54.8 mg, $1.98 \cdot 10^{-1}$ mmol) with 47% yield. Purification of the compound was done with CC (hexane/ethyl acetate 90:10 to 60:40). **8** was obtained as a colorless solid (m.p. 83-85 ºC) with 47% yield. $[\alpha]_{Na}^{25}$ +107.1 (c 0.14, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1767.3 (C=O, C-12), 1717.0 (C=O, C-16). UV (CH_3CN) λ_{max} 201 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{24}O_3Na$

299.1618; found 299.1623. See table 1 for detailed NMR data. NMR data available in SI.

(3S,3aS,5aR,9bS)-5a-methyl-9-methylene-3-(2-oxopropyl)decahydronaphtho[1,2-b]furan-2(9bH)-one (9). When the procedure described in 2.2. was carried out with 100 mg of **6** ($4.30 \cdot 10^{-1}$ mmol) compound **9** is obtained with 65% yield (77.5 mg, $2.80 \cdot 10^{-1}$ mmol). Purification of the compound was done with CC (hexane/ethyl acetate 90:10 to 60:40). **9** was obtained as a colorless solid (m.p. 117-119 ºC) with 65% yield. $[\alpha]_{Na}^{25}$ +171.1 (c 0.13, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1766.1 (C=O, C-12), 1715.1 (C=O, C-16). UV (CH_3CN) λ_{max} 201 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{24}O_3Na$ 299.1618; found 299.1623. See table 1 for detailed NMR data. NMR data available in SI.

(3S,3aS,6aR,9aR,9bS)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-6,9-dimethylenedecahydroazuleno[4,5-b]furan-2(9bH)-one (4). When 100 mg of **3** (3.64·10-1 mmol), was treated following the procedure described in 2.3. compound **4** (70.1 mg, $2.20 \cdot 10^{-1}$ mmol) was obtained with 60 % yield. Spectra data for **4** is presented in previous work[7].

(3S,3aS,5aR,9bS)-5a,9-dimethyl-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-b]furan-2(3H)-one (10). Treatment of **8** (100 mg, $3.62 \cdot 10^{-1}$ mmol) under the conditions described in 2.3. produced **10** (58.8 mg, $1.83 \cdot 10^{-1}$ mmol) with 51% yield. Purification of the compound was done with CC (hexane/ethyl acetate 90:10 to 60:40). **10** was obtained as a colorless oil with 51% yield. $[\alpha]_{Na}^{25}$ +74.5 (c 0.24, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1774.2 (C=O, C-12). UV (CH_3CN) λ_{max} 200 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{28}O_4Na$ 343.4124; found 343.1885. See table 1 for detailed NMR data. NMR data available in SI.

(3S,3aS,5aR,9bS)-5a-methyl-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-9-methylenedecahydronaphtho[1,2-b]furan-2(9bH)-one (11). When the procedure described in 2.3. was carried out with 100 mg of **9** ($3.62 \cdot 10^{-1}$ mmol) compound **11** is obtained with 76% yield (87.7 mg, $2.74 \cdot 10^{-1}$ mmol). Purification of the compound was done with CC (hexane/ethyl acetate 90:10 to 60:40). **11** was obtained as a colorless solid (m.p. 133-135 ºC) with 76% yield. $[\alpha]_{Na}^{25}$ +126.5 (c 0.14, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1779.3 (C=O, C-12). UV (CH_3CN) λ_{max} 199 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{28}O_4Na$ 343.4124; found 343.1885. See table 1 for detailed NMR data. NMR data available in SI.

(3S,3aS,6aR,9aR)-3-(((3S,3aS,6aR)-6,9-dimethylene-2-oxododecahydroazuleno[4,5-b]furan-3-yl)methyl)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-6,9-dimethylenedecahydroazuleno[4,5-b]furan-2(9bH)-one (12). When 50 mg of **4** ($1.57 \cdot 10^{-1}$ mmol), was treated following the procedure described in 2.4 with 37.0 mg of **1** ($1.60 \cdot 10^{-1}$ mmol) compound **12** (44.2 mg, $8.05 \cdot 10^{-2}$ mmol) was obtained with 48 % yield. Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **12** was obtained as a colorless oil with 48% yield. $[\alpha]_{Na}^{25}$ +18.6 (c 0.15, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1763.9 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 197 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{44}O_6Na$ 571.3036; found 571.3033. See table 2 for detailed NMR data. NMR data available in SI.

((3S,3aS,6aR,9aR)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-3-(((3S,3aS,5aR,9aS)-5a-methyl-9-methylene-2-oxododecahydronaphtho[1,2-b]furan-3-yl)methyl)-6,9-dimethylenedecahydroazuleno[4,5-b]furan-2(9bH)-one (14). Treatment of **4** (50 mg, $1.57 \cdot 10^{-1}$ mmol) under the conditions described in 2.4. with **6** (37.2 mg, $1.60 \cdot 10^{-1}$ mmol) produced **14** with 18 % yield (16.5 mg, $3.00 \cdot 10^{-2}$ mmol). Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **14** was obtained as a colorless oil with 18% yield. $[\alpha]_{Na}^{25}$ +33.7 (c 0.06, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1767.8 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 196 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_6Na$ 573.3187; found 573.3192. See table 3 for detailed NMR data. NMR data available in SI.

(3S,3aS,5aR,9aR)-5a,9-dimethyl-3-(((3S,3aS,6aR,9aR)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-6,9-dimethylene-2-oxododecahydroazuleno[4,5-b]furan-3-yl)methyl)-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-b]furan-2(3H)-one (16). When the procedure described in 2.4. was carried out with 50 mg of **11** ($1.56 \cdot 10^{-1}$ mmol) with **1** (36.9 mg, $1.60 \cdot 10^{-1}$ mmol) compound **16** is obtained with 25 % yield (22.0 mg, $3.99 \cdot 10^{-2}$ mmol). Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **16** was obtained as a colorless oil with 25% yield. $[\alpha]_{Na}^{25}$ +47.0 (c 0.05, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1769.9 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 283, 236 and 195 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_6Na$ 573.3187; found 573.3192. See table 4 for detailed NMR data. NMR data available in SI.

(3S,3aS,5aR,9aS)-3-(((3S,6aR,9bS)-6,9-dimethylene-2-oxododecahydroazuleno[4,5-b]furan-3-yl)methyl)-5a-methyl-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-9-methylenedecahydronaphtho[1,2-b]furan-2(9bH)-one (18). When 50 mg of **4** ($1.57 \cdot 10^{-1}$ mmol), was treated following the procedure described in 2.4 with 37.2 mg of **5** ($1.60 \cdot 10^{-1}$ mmol) compound **18** (16.5 mg, $3.00 \cdot 10^{-2}$ mmol) was obtained with 21 % yield. Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **18** was obtained as a colorless oil with 21% yield. $[\alpha]_{Na}^{25}$ +23.5 (c 0.12, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1769.0 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 267, 228 and 200 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_6Na$ 573.3187; found 573.3192. See table 2 for detailed NMR data. NMR data available in SI.

(3S,3aS,5aR,9aR)-3-(((3S,6aR,9bS)-6,9-dimethylene-2-oxododecahydroazuleno[4,5-b]furan-3-yl)methyl)-5a,9-dimethyl-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-3a,4,5,5a,6,7,9a,9b-octahydronaphtho[1,2-b]furan-

2(3H)-one (20). Treatment of **10** (50 mg, $1.56 \cdot 10^{-1}$ mmol) under the conditions described in 2.4. with **1** (36.9 mg, $1.60 \cdot 10^{-1}$ mmol) produced **20** with 27 % yield (23.8 mg, $4.32 \cdot 10^{-2}$ mmol). Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **20** was obtained as a colorless oil with 27% yield. $[\alpha]Na^{25}$ +9.7 (c 0.19, $CHCl_3$). IR (film) ῦ cm^{-1} 1766.9 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 280, 235 and 196 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_6Na$ 573.3187; found 573.3192. See table 6 for detailed NMR data. NMR data available in SI.

(3S,3aS,6aR,9aR,9bS)-3-(((3S,3aR,6E,10E,11aR)-6,10-dimethyl-2-oxo2,3,3a,4,5,8,9,11a-octahydrocyclodeca[b]furan-3-yl)methyl)-3-((2-methyl-1,3-dioxolan-2-yl)methyl)-6,9-dimethylenedecahydroazuleno[4,5-b]furan-2(9bH)-one (23). When the procedure described in 2.4. was carried out with 50 mg of **4** ($1.57 \cdot 10^{-1}$ mmol) with **2** (37.3 mg, $1.60 \cdot 10^{-1}$ mmol) compound **23** is obtained with 12 % yield (11.0 mg, $2.00 \cdot 10^{-2}$ mmol). Purification of the compound was done with HPLC using an eluent of hexane/acetone 20%. **23** was obtained as a colorless oil with 12% yield. $[\alpha]_{Na}{}^{25}$ +52.1 (c 0.74, $CHCl_3$). IR (film) ῦ cm^{-1} 1765.9 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 198 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_6Na$ 573.3187; found 573.3192. See table 7 for detailed NMR data. NMR data available in SI.

Vlasouliolide A (13). When 20 mg of **12** ($3.64 \cdot 10^{-2}$ mmol), was treated following the procedure described in 2.5.1. compound **13** (3.0 mg, $5.92 \cdot 10^{-3}$ mmol) was obtained with 16 % yield. Vlasouliolide A was purified by HPLC using an eluent of hexane/acetone 15%. Vlasouliolide A **(13)** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +6.8 (c 0.05, $CHCl_3$). IR (film) ῦ cm^{-1} 1764.2 (C=O, C-12 and C-12'), 1715.1 (C=O, C-16). UV (CH_3CN) λ_{max} 235 and 196 nm. HRMS (ESI) m/z: $[M -H]^-$ Calcd for $C_{32}H_{39}O_5$ 505.2959; found 505.2592. NMR data obtained for **13** matches the one reported in the bibliography[4]. NMR data available in SI.

When 20 mg of **12** ($3.64 \cdot 10^{-2}$ mmol), was treated following the procedure described in 2.5.2. compound **13** (19.8 mg, $3.92 \cdot 10^{-2}$ mmol) was obtained with quantitative yield. Vlasouliolide A **(13)** was obtained with 20% global yield.

Vlasouliolide C (15). Treatment of **14** (20 mg, $3.63 \cdot 10^{-2}$ mmol) under the conditions described in 2.5.1. produced **15** (2.1 mg, $4.18 \cdot 10^{-3}$ mmol) with 11 % yield. Vlasouliolide C was purified by HPLC using an eluent of hexane/acetone 15%. **15** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +264.9 (c 0.01, $CHCl_3$). IR (film) ῦ cm^{-1} 1766.2 (C=O, C-12 and C-12'), 1717.8 (C=O, C-16). UV (CH_3CN) λ_{max} 236 and 194 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_5Na$ 529.2924; found 529.2930. NMR data obtained for **15** matches the one reported in the bibliography[4]. NMR data available in SI.

Treatment of **14** (20 mg, $3.63 \cdot 10^{-2}$ mmol) under the conditions described in 2.5.2. produced **15** (19.3 mg, $3.82 \cdot 10^{-2}$ mmol) with quantitative yield. Vlasouliolide C **(15)** was obtained with 7% global yield.

Vlasouliolide D (17). When the procedure described in 2.5.1. was carried out with 20 mg of **16** ($3.63 \cdot 10^{-2}$ mmol) compound **17** is obtained with 12% yield (2.3 mg, $4.54 \cdot 10^{-3}$ mmol). Vlasouliolide D was purified by HPLC using an eluent of hexane/acetone 15%. **17** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +75.3 (c 0.07, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1765.6 (C=O, C-12 and C-12'), 1715.6 (C=O, C-16). UV (CH_3CN) λ_{max} 236 and 196 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_5Na$ 529.2924; found 529.2930. NMR data obtained for **17** matches the one reported in the bibliography[4]. NMR data available in SI.

When the procedure described in 2.5.2. was carried out with 20 mg of **16** ($3.63 \cdot 10^{-2}$ mmol) compound **17** is obtained with quantitative yield (18.9 mg, $3.73 \cdot 10^{-2}$ mmol). Vlasouliolide D **(17)** was obtained with 7% global yield.

Vlasouliolide G (19). When 20 mg of **18** ($3.63 \cdot 10^{-2}$ mmol), was treated following the procedure described in 2.5.1. compound **19** (2.2 mg, $4.34 \cdot 10^{-3}$ mmol) was obtained with 13 % yield. Vlasouliolide G was purified by HPLC using an eluent of hexane/acetone 15%. **19** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +40.6 (c 0.03, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1765.4 (C=O, C-12 and C-12'), 1716.2 (C=O, C-16). UV (CH_3CN) λ_{max} 236 and 197 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_5Na$ 529.2924; found 529.2930. NMR data obtained for **19** matches the one reported in the blibliography[10]. NMR data available in SI.

When 20 mg of **18** ($3.63 \cdot 10^{-2}$ mmol), was treated following the procedure described in 2.5.2. compound **19** (19.5 mg, $3.85 \cdot 10^{-2}$ mmol) was obtained with quantitative yield. Vlasouliolide G **(19)** was obtained with 9% global yield.

Vlasouliolide H (21). Treatment of **20** (20 mg, $3.63 \cdot 10^{-2}$ mmol) under the conditions described in 2.5.1. produced **21** (2.4 mg, $4.73 \cdot 10^{-3}$ mmol) with 13 % yield. Vlasouliolide H was purified by HPLC using an eluent of hexane/acetone 15%. **21** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +62.9 (c 0.40, $CHCl_3$). IR (film) ῦ cm^{-1} 1768.9 (C=O, C-12 and C-12'), 1718.3 (C=O, C-16). UV (CH_3CN) λ_{max} 235 and 200 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_5Na$ 529.2924; found 529.2930. NMR data obtained for **21** matches the one reported in the bibliography[10]. NMR data available in SI.

Treatment of **20** (20 mg, $3.63 \cdot 10^{-2}$ mmol) under the conditions described in 2.5.2. produced **21** (19.0 mg, $3.76 \cdot 10^{-2}$ mmol) with quantitative yield. Vlasouliolide H **(21)** was obtained with 2 % global yield.

Vlasouliolide E (24). When the procedure described in 2.5.1. was carried out with 20 mg of **23** ($3.63 \cdot 10^{-2}$ mmol) compound **24** is obtained with 11% yield (2.0 mg, $3.95 \cdot 10^{-3}$ mmol). Vlasouliolide E was purified by HPLC using an eluent of hexane/acetone 15%. **24** was obtained as a colorless oil. $[\alpha]_{Na}{}^{25}$ +49.0 (c 0.17, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 1764.3 (C=O, C-12 and C-12'), 1716.8 (C=O, C-16). UV (CH_3CN) λ_{max} 269 and 200 nm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{32}H_{42}O_5$ 505.2949; found 505.2946. NMR data obtained for **24**

matches the one reported in the bibliography[10]. NMR data available in SI.

When the procedure described in 2.5.2. was carried out with 20 mg of **23** ($3.63 \cdot 10^{-2}$ mmol) compound **24** is obtained with quantitative yield (18.7 mg, $3.70 \cdot 10^{-2}$ mmol). Vlasouliolide E **(23)** was obtained with 0.5% global yield.

Vlasouliolide I (22). When 20 mg of **13** ($3.96 \cdot 10^{-2}$ mmol), was treated following the procedure described in 2.6. compound **22** (19.2 mg, $3.80 \cdot 10^{-2}$ mmol) was obtained with quantitative yield. Vlasouliolide I was purified by HPLC using an eluent of hexane/acetone 15%. **22** was obtained as a colorless oil with 20% global yield. $[\alpha]_{Na}^{25}$ +11.4 (c 0.33, $CHCl_3$). IR (film) $\tilde{\upsilon}$ cm^{-1} 3480.4 (O-H), 1760.5 (C=O, C-12 and C-12'). UV (CH_3CN) λ_{max} 237 and 197 nm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_5Na$ 529.2924; found 529.2930. NMR data obtained for **22** matches the one reported in the bibliography[10]. NMR data available in SI.

Conclusions

We present a synthetic pathway to the synthesis of vlasouliolides from two natural sesquiterpene lactones (dehydrocostuslactone **(1)** and constunolide **(2)** through a photochemical and a Michael addition. Seven recently isolated vlasouliolides (**13**, **15**, **17**, **19**, **21**, **22** and **24**) have been successfully obtained with this procedure with high yields compared to those reported by isolation. The designed route presented uses as starting material two sesquierpene lactones relatively easy to obtain in high quantities, thus making possible to synthetize vlasouliolides in enough amounts for further studies of their possible biological interest. Furthermore, based on the experiment performed with different bases (LiHDMS, NaHDMS and KHDMS) and the use of the copper ion to catalyze the Michael addition, the counterion of the base seems to play an important role in the dimerization mechanism.

Table 1. ^{1}H-NMR and ^{13}C{^{1}H}-NMR data for 8,9,10 and 11, $CDCl_3$, *J* in Hz.

	8[a]		**9**[b]		**10**[a]		**11**[b]	
№	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	1.45 (1H, m) 1.37 (1H, m)	37.8	2.32 (1H, m) 1.99 (1H, m)	36.0	1.45 (1H, m) 1.38 (1H, m)	37.8	2.30 (1H, m) 1.98 (1H, m)	36.0
2	2.05 (2H, m)	22.9	1.63 (2H, m)	22.9	2.02 (2H, m)	22.9	1.59 (2H, m)	22.9
3	5.36 (1H, brd, *J*=1.5)	122.4	1.56 (1H, m) 1.27 (1H, m)	40.0	5.35 (1H, brd, *J*=1.4)	122.3	1.55 (1H, m) 1.31 (1H, m)	40.2
4	-	133.0	-	144.6	-	133.3	-	144.8
5	2.21 (1H, d, *J*=9.5)	50.6	2.12 (1H, d, *J*=10.6)	54.4	2.20 (1H, dd, *J*=11.4,1.2)	50.6	2.11 (1H, d, *J*=11.0)	54.4
6	3.95 (1H, dd, *J*=9.5,9.5)	82.3	4.05 (1H, dd, *J*=10.6,10.6)	80.1	3.86 (1H, dd, *J*=10.1,10.1)	81.9	3.97 (1H, m)	79.7
7	1.67 (1H, m)	52.8	1.74 (1H, m)	51.4	1.68 (1H, m)	53.5	1.75 (1H, m)	52.1
8	1.54 (1H, ddd, *J*= 13.0,3.2,2.6) 1.25 (1H, m)	39.5	1.61 (2H, m)	23,6	2.01 (2H, m)	23.7	2.01 (1H, m) 1.47 (1H, m)	23.7
9	1.67 (2H, m)	23.63	1.45 (1H, m) 1.35 (1H, m)	41.8	1.53 (1H, m) 1.28 (1H, m)	39.7	1.45 (1H, m) 1.33 (1H, m)	41.8
10	-	35.7	-	38.4	-	35.7	-	38.4
11	2.89 (1H, ddd, *J*= 8.0,7.2,3.1)	41.3	2.91 (1H, ddd, *J*=7.3,4.6,4.3)	41.7	2.38 (1H, m)	42.0	2.42 (1H, m)	42.4
12	-	178.5	-	178.2	-	179.4	-	179.0
13	3.04 (1H, dd, *J*=18.1,4.3) 2.54 (1H, dd, *J*=18.1,7.3)	42.0	3.04 (1H, dd, *J*=18.2,4.3) 2.54 (1H, dd, *J*=18.2,7.3)	42.1	2.41 (1H, dd, *J*=15.0,3.7) 1.75 (1H, dd, *J*=15.0,6.1)	37.4	2.40 (1H, m) 1.74 (1H, m)	37.5
14	0.91 (3H, s)	17.3	0.85 (3H, s);	18.0	0.91 (3H, s)	17.4	0.85 (3H, s)	18.0
15	1.80 (3H, s)	23.57	4.92 (1H, brd, *J*=1.4) 4.74 (1H, brd, *J*=1.4)	108.9	1.80 (3H, s)	23.5	4.91 (1H, brd, *J*=1.4) 4.74 (1H, brd, *J*=1.4)	108.8
16	-	205.6	-	205.5	-	108.9	-	108.9
17	2.22 (3H, s)	30.2	2.22 (3H, s)	30.2	1.36 (3H, s)	24.1	1.36 (3H, s)	24.1
18[c]	-	-	-	-	3.96 (2H, m)	64.6	3.97 (2H, m)	64.6
19[c]	-	-	-	-	3.96 (2H, m)	64.4	3.95 (2H, m)	64.3

[a]500/125 MHz. [b]400/100 MHz. [c]Interchangeable.

Table 2. ^{1}H-NMR (500 MHz) and ^{13}C{^{1}H}-NMR (125 MHz) data for 12, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	2.89 (1H, brddd, *J*=7.9, 7.9, 7.9)	47.3	1'	2.80 (1H, m)	47.1
2	1.95 (2H, m)	30.1	2'	1.83 (2H, m)	30.0
3	2.50 (2H, m)	32.3[a]	3'	2.50 (2H, m)	32.3[a]
4	-	151.2	4'	-	151.3
5	2.80b (1H, m)	52.6	5'	2.71 (1H, dd, *J*=8.7, 8.7)	51.9
6	4.15 (1H, dd, *J*=9.4)	82.4	6'	3.90 (1H, dd, *J*=9.3, 9.3)	84.4
7	2.84b (1H, m)	46.8	7'	1.92 (1H, m)	49.6
8	1.84 (1H, m) 1.44 (1H, ddd, *J*=12.3, 12.3, 4.5)	27.1	8'	2.11 (1H, dddd, *J*=12.8, 4.6, 4.6, 4.6) 1.34 (1H, m)	32.3
9	2.51 (1H, m) 1.98 (1H, ddd, *J*=12.0, 4.7, 4.7)	37.4	9'	2.47 (1H, m) 1.98b (1H, ddd, *J*=12.0, 4.7, 4.7)	37.2
10	-	150.4	10'	-	149.6
11	-	46.5	11'	2.55(1H, ddd, *J*=12.2, 6.2, 2.3)	41.8
12	-	178.6	12'	-	177.9
13	2.31 (1H, d, *J*=14.3) 1.70 (1H, d, *J*=14.3)	42.6	13'	2.26 (1H, dd, *J*=14.7, 6.3) 1.23 (1H, dd, *J*=14.7, 2.3)	32.9
14	4.85 (1H, s) 4.77 (1H, s)	111.7	14'	4.87 (1H, s) 4.78 (1H, s)	112.0
15	5.06 (1H, d, *J*=2.0) 5.26 (1H, d, *J*=2.0)	109.9	15'	5.02 (1H, d, *J*=1.6) 5.14 (1H, d, *J*=1.6)	109.4
16	-	108.5	-	-	-
17	1.34 (3H, s)	26.2	-	-	-
18[b]	3.98 (2H, m)	64.5	-	-	-
19[b]	3.84 (2H, m)	63.9	-	-	-

[a]Carbon signal overlapped. [b]Interchangeable

Table 3. ^{1}H-NMR (600 MHz) and ^{13}C{^{1}H}-NMR (150 MHz) data for 14, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	2.89 (1H, dd, *J*=8.0, 6.6)	47.3	1'	1.44 (1H, m) 1.34 (1H, m)	41.7
2	1.83 (1H, m) 1.41 (1H, m)	27.1	2'	1.60 (2H, m)	22.9
3	2.51 (2H, m)	32.4	3'	2.30 (1H, m) 1.97 (1H, m)	36.0
4	-	151.3	4'	-	144.5
5	2.81 (1H, m)	52.7	5'	2.05 (1H, d, *J*=10.8)	54.3
6	4.14 (1H, dd, *J*=9.5, 9.5)	82.8	6'	4.01 (1H, dd, *J*=9.8,9.8)	79.1
7	2.80 (1H, m)	46.5[a]	7'	1.60 (1H, m)	52.5
8	1.83 (1H, m) 1.61 (1H, m)	23.7	8'	1.98 (1H, m) 1.84 (1H, m)	30.0
9	2.50 (1H, m) 1.94 (1H, m)	37.4	9'	1.58 (1H, m) 1.27 (1H, m)	40.0
10	-	150.1	10'	-	38.4
11	-	46.5[a]	11'	2.66 (1H, dt, *J*=12.3,4.2)	41.3
12	-	179.0	12'	-	178.6
13	2.28 (1H, d, *J*=15.0) 1.71 (1H, d, *J*=15.0)	42.7	13'	2.31 (1H, m) 1.27 (1H, m)	32.1
14	4.86 (1H, brs); 4.79 (1H, brs)	111.9	14'	0.85 (3H, s)	18.0
15	5.25 (1H, brd, *J*=1.6) 5.06 (1H, brd, *J*=1.6)	109.8	15'	4.90 (1H, brs) 4.70 (1H, brs)	108.9
16	-	108.5	-	-	-
17	1.34 (3H, s)	26.2	-	-	-
18[b]	3.98 (2H, m)	64.5	-	-	-
19[b]	3.86 (2H, m)	63.9	-	-	-

[a]Carbon signal overlapped. [b]Interchangeable.

Table 4. ^{1}H-NMR (600 MHz) and ^{13}C{^{1}H}-NMR (150 MHz) data for 16, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	1.43 (2H, m)	41.8	1'	2.83 (1H, m)	47.1
2	1.60 (2H, m)	22.9	2'	1.93 (2H, m)	30.1
3	2.32 (1H, m) 1.99 (1H, m)	35.9	3'	2.49 (2H, m)	32.4
4	-	144.4	4'	-	151.4
5	2.14 (1H, d, *J*=10.7)	54.9	5'	2.74 (1H, dd, *J*=9.1,9.1)	51.9
6	4.43 (1H, dd, *J*=10.8,10.8)	76.4	6'	3.92 (1H, dd, *J*=9.4)	84.7
7	2.46 (1H, m)	49.8	7'	1.94 (1H, m)	49.2
8	1.60 (2H, m)	19.2	8'	2.08 (1H, dddd, *J*=12.8, 4.3, 4.3, 4.3) 1.36 (1H, brddd, *J*=12.8, 5.9, 5.9)	32.3
9	1.58 (1H, m) 1.33 (1H, m)	40.1	9'	2.50 (1H, m) 2.00 (1H, m)	37.4
10	-	38.4	10'	-	149.6
11	-	45.9	11'	2.59 (1H, ddd, *J*=6.2,3.0,1.2)	41.6
12	-	179.1	12'	-	178.2
13	2.37 (1H, d, *J*=14.8) 1.70 (1H, d, *J*=14.8)	42.9	13'	2.35 (1H, dd, *J*=14.6, 7.6) 1.27 (1H, *J*=14.6, 1.2)	31.4
14	0.84 (3H, s)	18.1	14'	4.88 (1H, brs) 4.78 (1H, brs)	112.0
15	4.94 (1H, brd, *J*=1.2) 4.92 (1H, brd, *J*=1.2)	109.5	15'	5.15 (1H, brd, *J*=2.0) 5.03 (1H, brd, *J*=2.0)	109.4
16	-	108.6	-	-	-
17	1.33 (3H, s)	26.1	-	-	-
18[a]	3.97 (2H, m)	64.4	-	-	-
19[a]	3.84 (2H, m)	64.1	-	-	-

[a]Interchangeable.

Table 5. ^{1}H-NMR (600 MHz) and ^{13}C{^{1}H}-NMR (150 MHz) data for 18, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	2.89 (1H, brdd, *J*=8.6, 5.6)	47.3	1'	1.43 (1H, brd, *J*=5.0) 1.38 (1H,brd, *J*=6.9)	37.7
2	1.96 (1H, brddd, *J*=12.0,6.3,3.0) 1.84 (1H, brddd, *J*=12.0,6.3,3.0)	30.0	2'	1.95 (1H, m) 1.83 (1H, m)	22.9
3	2.53 (1H, brddd, *J*=11.6,3.8,3.8) 2.49 (1H, brddd, *J*=11.6,3.8,3.8)	32.4	3'	5.35 (1H, brs)	122.3
4	-	151.3	4'	-	133.2
5	2.80 (1H, brdd, *J*=8.3, 3.0)	52.7	5'	2.14 (1H, brd, *J*=10.6)	50.4
6	4.15 (1H, dd, *J*=9.4,9.4)	82.7	6'	3.89 (1H, m)	81.2
7	1.57 (1H, m)	53.7	7'	2.84 (1H, ddd, *J*=12.3, 2.4,2.4)	46.5[a]
8	1.81 (1H, brdd, *J*=6.9,6.9) 1.40 (1H, m,)	27.1	8'	1.82 (1H, m); 1.64 (1H, brdd, *J*=13.1, 3.8)	23.6
9	2.50 (1H, m) 1.97 (1H, brdd, *J*=4.7,4.7)	37.4	9'	1.56 (1H, m) 1.25 (1H, m)	39.6
10	-	150.2	10'	-	35.7
11	-	46.5[a]	11'	2.62 (1H, ddd, *J*=12.9, 4.0,4.0)	40.8
12	-	178.9	12'	-	179.0
13	2.30 (1H, d, *J*=14.7) 1.72 (1H, d, *J*=14.7)	42.7	13'	2.29 (1H, m) 1.27 (1H,dd, *J*=8.8, 3.4)	32.0
14	4.86 (1H, brs) 4.79 (1H, brs)	111.8	14'	0.90 (3H, s)	17.3
15	5.26 (1H, d, *J*=2.0) 5.07(1H, d, *J*=2.0)	109.8	15'	1.77 (3H, brs)	23.7
16	-	108.5	-	-	-
17	1.35 (3H, s)	26.2	-	-	-
18[b]	3.87 (2H, m)	63.9	-	-	-
19[b]	3.98 (2H, m)	64.5	-	-	-

[a]Carbon signal overlapped. [b]Interchangeable.

Table 6. ^{1}H-NMR (500 MHz) and ^{13}C{^{1}H}-NMR (125 MHz) data for 20, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	1.48 (1H, ddd, *J*=11.0,11.0, 7.3) 1.40 (1H, m)	37.8	1'	2.83 (1H, ddd, *J*=8.9,8.9,5.3)	47.1
2	1.82 (1H, m) 2.05 (1H, m)	22.9	2'	1.84 (1H, m) 1.92 (1H, m)	30.1
3	5.34 (1H, brs)	121.8	3'	2.47 (1H, brdd, *J*=6.5,3.0)	32.4
4	-	133.8	4'	-	149.6
5	2.23 (1H, brd, *J*=10.9)	51.2	5'	2.74 (1H, dd, *J*=8.9,8.9)	51.9
6	4.30 (1H, dd, *J*=10.9,10.9)	78.7	6'	3.92 (1H, dd, *J*=9.5,8.9)	84.6
7	2.41 (1H, m)	51.3	7'	1.94 (1H, m)	49.3
8	1.63 (2H, m)	19.2	8'	2.09 (1H, dddd, *J*=12.7, 4.3, 4.3, 4.3) 1.37 (1H, m)	32.2
9	1.30 (1H, brd, *J*=4.6) 1.56 (1H, brd, *J*=3.0)	39.8	9'	2.49 (1H, m) 2.00 (1H, m)	37.3
10	-	35.8	10'	-	151.3
11	-	45.3	11'	2.59 (1H, brdd, *J*=12.1,6.8)	41.6
12	-	179.5	12'	-	178.1
13	2.38 (1H, d, *J*=14.5) 1.70 (1H, d, *J*=14.5)	42.6	13'	2.31 (1H, dd, *J*=14.6,7.29) 1.27 (1H, m)	31.6
14	0.89 (3H, s)	17.4	14'	4.88 (1H, s) 4.78 (1H,s)	112.0
15	1.85 (3H, s)	23.7	15'	5.13 (1H, d, *J*=1.7) 5.02 (1H, d, *J*=1.7)	109.4
16	-	108.7	-	-	-
17	1.32 (3H, s)	25.7	-	-	-
18[a]	3.86 (2H, m)	63.9	-	-	-
19[a]	3.95 (2H, m)	64.5	-	-	-

[a]Interchangeable.

Table 7. ^{1}H-NMR (500 MHz) and ^{13}C{^{1}H}-NMR (125 MHz) data for 23, $CDCl_3$, *J* in Hz.

Nº	^{1}H	^{13}C	Nº	^{1}H	^{13}C
1	2.89 (1H, bddd, *J*=15.2,7.3,1.4)	47.3	1'	4.77[a] (1H, bdd, *J*=1.2,0.5)	127.2
2	1.95 (1H, m) 1.83 (1H, m)	30.0	2'	2.24 (1H, m) 2.15 (1H, m)	26.1
3	2.52 (1H, m) 2.45 (1H, m)	32.2	3'	2.27 (1H, m) 1.96 (1H, m)	39.5
4	-	151.0	4'	-	140.4
5	2.82 (1H, m)	52.5	5'	4.55[b] (1H, m)	127.0
6	4.19 (1H, dd, *J*=9.2,9.2)	82.1	6'	4.56[b] (1H, dd, *J*=9.6,9.6)	80.8
7	2.82 (1H, m)	47.1	7'	1.64 (1H, m)	53.7
8	1.85 (1H, m) 1.44 (1H,dddd, *J*=10.0,7.9,6.1,4.4)	27.1	8'	1.82 (1H, m) 1.63 (1H, m)	27.9
9	2.51 (1H, m) 1.98 (1H, m)	37.3	9'	2.39 (1H, m) 1.97 (1H, m)	40.9
10	-	150.4	10'	-	136.9
11	-	46.5	11'	2.63 (1H, ddd, *J*=5.9,3.5,1.1)	41.9
12	-	178.5	12'	-	177.8
13	2.36 (1H, d, *J*=14.7) 1.70 (1H, d, *J*=14.7)	42.6	13'	2.23 (1H, m) 1.20 (1H, dd, *J*=14.5,1.3)	32.1
14	4.85 (1H, bd, *J*=0.6) 4.78[a] (1H, bs)	111.7	14'	1.40 (3H, s)	16.1
15	5.27 (1H, bd, *J*=1.9) 5.06 (1H, dd, *J*=2.2, 0.5)	110.0	15'	1.66 (3H, s)	17.2
16	-	108.5	-	-	-
17	1.36 (3H, s)	26.3	-	-	-
18[c]	3.98 (2H, m)	64.5	-	-	-
19[c]	3.87 (2H, m)	63.9	-	-	-

[a,b]Proton signals overlapped. [c]Interchangeable.

ASSOCIATED CONTENT

Supplementary information containing: Copies of ^{1}H-NMR and ^{13}C{^{1}H}-NMR, FTIR and UV spectra.
This material is available free of charge via the Internet at http://pubs.acs.org."

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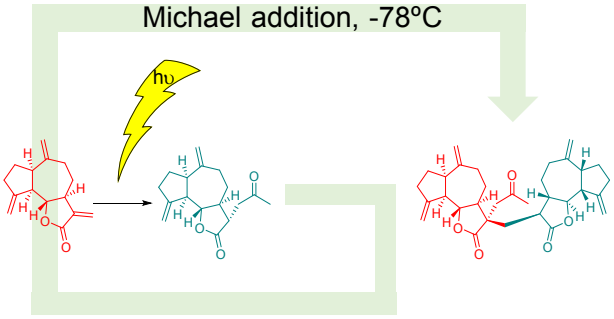
REFERENCES

(1) Jakupovic, J.; Bohlmann, F.; Jia, Z. J. Sesquiterpene Lactones from Vladimiria Souliei. *Phytochemistry* **1990**, *29*, 1209–1212.
(2) Hill, R. A.; Sutherland, A. Hot off the Press. *Nat. Prod. Rep.* **2019**, *36* (2), 258–262. https://doi.org/10.1039/c9np90001b.
(3) Wu, Z. L.; Wang, Q.; Wang, J. X.; Dong, H. Y.; Xu, X. K.; Shen, Y. H.; Li, H. L.; Zhang, W. D. Vlasoulamine A, a Neuroprotective [3.2.2]Cyclazine Sesquiterpene Lactone Dimer from the Roots of Vladimiria Souliei. *Org. Lett.* **2018**, *20* (23), 7567–7570. https://doi.org/10.1021/acs.orglett.8b03306.
(4) Chen, L.; Wu, G.; Zhang, J.; Ye, J.; Liu, Q.; Shen, Y. Vlasouliolides A-D, Four Rare C17/C15 Sesquiterpene Lactone Dimers with Potential Anti-Inflammatory Activity from Vladimiria Souliei. *Sci. Rep.* **2017**, *7* (March), 43837. https://doi.org/10.1038/srep43837.
(5) Mao, J.; Yi, M.; Tao, Y.; Huang, Y.; Chen, M. Costunolide Isolated from Vladimiria Souliei Inhibits the Proliferation and Induces the Apoptosis of HepG2 Cells. *Mol. Med. Rep.* **2019**, *19* (2), 1372–1379. https://doi.org/10.3892/mmr.2018.9736.
(6) Wu, Z. li; Wang, Q.; Dong, H. yuan; Hui-liang Li; Wang, S. mei; Zhang, W. dong. Five Rare Dimeric Sesquiterpenes Exhibiting Potential Neuroprotection Activity from Vladimiria Souliei. *Fitoterapia* **2018**, *128* (May), 192–197. https://doi.org/10.1016/j.fitote.2018.05.022.
(7) Cárdenas, D. M.; Cala, A.; Molinillo, J. M. G.; Macías, F. A. Preparation and Phytotoxicity Study of Lappalone from Dehydrocostuslactone. *Phytochem. Lett.* **2017**, *20* (February), 66–72. https://doi.org/10.1016/j.phytol.2017.04.017.
(8) Zorrilla, J. G.; Rial, C.; Varela, R. M.; Molinillo, J. M. G.; Macías, F. A. Facile Synthesis of Anhydrojudaicin and 11,13-Dehydroanhydrojudaicin, Two Eudesmanolide-Skeleton Lactones with Potential Allelopathic Activity. *Phytochem. Lett.* **2019**, *31* (February), 229–236. https://doi.org/10.1016/j.phytol.2019.04.014.
(9) Cox, M. T.; Heaton, W. D.; Horbury, J. Preparation of Protected Trans -olefinic Dipeptide Isosteres. *J. Chem. Soc. Chem. Commun.* **1980**, 799–800.
(10) Wu, Z.; Wang, J.; Chen, L.; Dong, H.; Li, H. Five Rare C32 Sesquiterpene Lactone Dimers with Anti-Inflammation Activity from Vladimiria Souliei. *Fitoterapia* **2018**, *125* (January), 117–122. https://doi.org/10.1016/j.fitote.2018.01.002.
(11) Jain, T. C.; McCloskey, J. E. Carbocyclization in Natural Products-I. Amberlite IR-120 Cation Exchange Resin Catalyzed Cyclization of Costunolide. Structure of β-Cyclocostunolide. *Tetrahedron* **1975**, *31* (18), 2211–2214. https://doi.org/10.1016/0040-4020(75)80217-1.
(12) Physics.nist.gov. Persistent Lines of Neutral Mercury (Hg I). https://physics.nist.gov/PhysRefData/Handbook/Tables/mercurytable3.htm.
(13) Macías, F. A.; Molinillo, J. M. G.; Massanet, G. M.; Rodríguez-Luis, F. Study of Photochemical Addition of Acyl Radical to Electron-Deficient Olefins. *Tetrahedron* **1992**, *48* (16), 3345–3352. https://doi.org/10.1016/0040-4020(92)85010-C.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