Approaches to the synthesis of 8-*epi*-vernolepin from germacrolides

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As part of our program aimed at the synthesis of bioactive products, the enantiospecific synthesis of 8-*epi*-vernolepin derivatives, starting from accessible germacrolides, was attempted. Synthesis of (+)-8-*O*-acetyl-1,2,11β,13-tetrahydro-8-*epi*-vernolepin (**23**) from (+)-salonitenolide (**6**) was performed in nine steps with an acceptable overall yield. On the other hand, the synthesis from (+)-stenophyllolide (**5**) presented several intrinsic difficulties and was discarded. (+)-Salonitenolide provides one of the most useful raw materials for the synthesis of (+)-vernolepin related compounds preserving its functionalization at C-8.

Introduction

(+)-Vernolepin (Fig. 1), isolated from the Ethiopian plant *Vernonia hymenolepis*,[1] is a sesquiterpene dilactone with spasmolytic, anti-aggregating and de-aggregating activities,[2] as well as antitumor activity *in vitro* and *in vivo*.[3,4] Moreover, its potent antimicrobial effect has been reported recently.[5] The biological activity and the unique structure of vernolepin have attracted the interest of synthetic organic chemists and several total syntheses in racemic form,[6,7] as well as an enantioselective procedure (86% ee),[8] have been described. However, total synthesis requires numerous steps, and provides poor yields. The antitumor power of (+)-vernolepin lies basically in the α-methylene-γ-lactone group and is enhanced by the additional α-methylene-δ-lactone, whereas the hydroxy at C-8 and the angular vinyl groups seem to be irrelevant for the activity.[4] Thereby 8-deoxyvernolepin[9] and 1,2-dihydrovernolepin[4] have an activity analogous to that of vernolepin against the tumor cell lines assayed. Hence, 8-*epi*-vernolepin derivatives, such as **1**, could also display a biological activity analogous to that of vernolepin. These derivatives preserve the OH group at C-8, which could be chemically employed for the introduction of side chains in order to modulate their biological activity. In the present paper, our enantiospecific approach to 8-*epi*-vernolepin derivatives such as **1**,[10] starting from accessible homochiral germacrolides, is described with full details.

Results and discussion

Synthesis of **1** could be performed according to the retrosynthetic Scheme 1. Formation of the δ-lactone **1** could be achieved through intramolecular transesterification of the methoxycarbonyl group of compounds **2a** and **2b** by the hydroxy group at C-14 obtained by cleavage of the corresponding ether. In the case of compound **2a**, ether cleavage would be facilitated

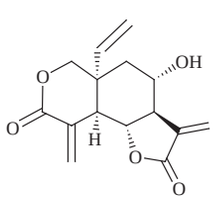
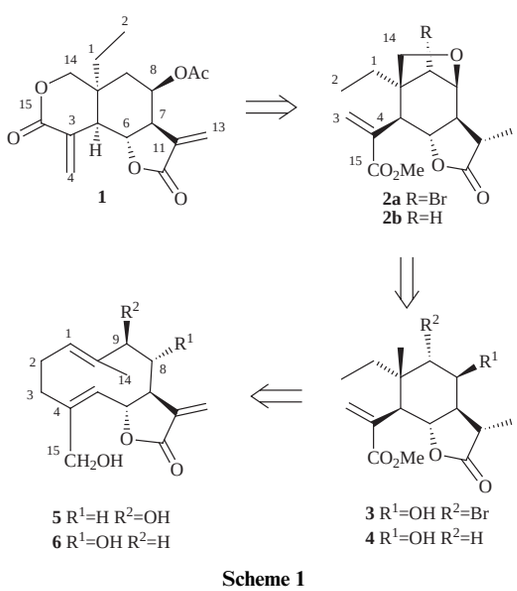


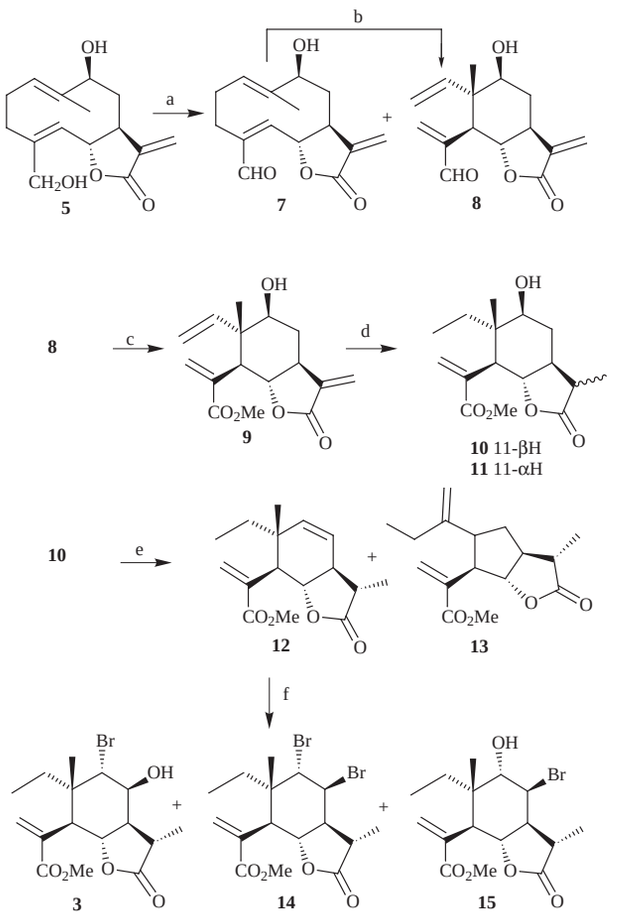
Fig. 1 (+)-Vernolepin.



Scheme 1

by the bromine atom located at C-9. Formation of the cyclic ethers **2a** and **2b** could be performed by long range functionalization, taking advantage of the β-axial hydroxy group of **3** and **4**. Finally, the elemanolide skeleton of **3** and **4**, could be obtained by Cope rearrangement of the germacrolides (+)-stenophyllolide (**5**) and (+)-salonitenolide (**6**), respectively. These two germacrolides are found abundantly in the plant kingdom. Besides other Compositae, they occur in notable quantities in different species of the *Centaurea* genus.[11] Thus, compound **5** is abundant in *Centaurea aspera*[12] and *C. malacitana*[13] and was obtained by immersion of the latter plant in organic solvents.[14] Cope rearrangement of the germacrolide **5** to the elemanolide skeleton is one of the key steps in Scheme 1. Conventional thermal Cope rearrangements of germacrolides, usually carried out in a sealed tube at temperatures of around 210 °C, lead to a germacrolide ⇌ elemanolide equilibrium,[15] and pyrolyse part of the products, offering poor yields. Recently, we have found that palladium(II) catalysis permits Cope rearrangement of germacrolides at lower temperatures, preventing thermal decomposition.[16] However, palladium(II) promoted rearrangements provide mixtures

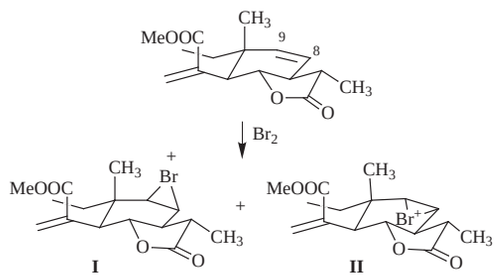
of elemanolides and eudesmanolides, which are probably derived from a non-concerted reaction mechanism *via* a carbocationic intermediate. Fortunately, it is known that conjugation of one of the double bonds with π-substituents makes [3,3]-sigmatropic rearrangements easier.[17] Bearing this idea in mind, we began the synthesis of **1** (Scheme 2) assaying the selective



Scheme 2 *Reagents and conditions:* a) PDC. b) Toluene, reflux. c) (i) $NaClO_2$, (ii) CH_2N_2. d) H_2, Pd/C. e) $POCl_3$, pyridine, reflux. f) NBS–H_2O, THF.

oxidation of the primary alcohol of **5** with different reagents. An acceptable result was obtained with pyridinium dichromate (PDC), which gave a mixture of 15-oxogermacrolide **7** (77% yield) and the unexpected elemanolide **8** (8% yield). In the ^1H NMR of **8**, signals of the ABX system (H-1, H-2a and H-2b), confirmed the elemanolide skeleton. Formation of **8**, during a reaction taking place at room temperature, indicated the facility with which the Cope rearrangement occurs once the formyl group at C-15 has been formed. Therefore, **7** was heated in toluene under reflux yielding **8** (63% yield). Treatment of **8** with sodium chlorite was found to be the best method for the oxidation of the conjugated aldehyde, then the acid was esterified with diazomethane yielding **9** (78% yield from **8**). Catalytic hydrogenation of **9** gave a mixture of the epimers **10** (73% yield) and **11** (25% yield). The α-disposition of the new C-13 methyl group in **10** was inferred from the coupling constant between H-11 and H-7 (J = 12.0 Hz).

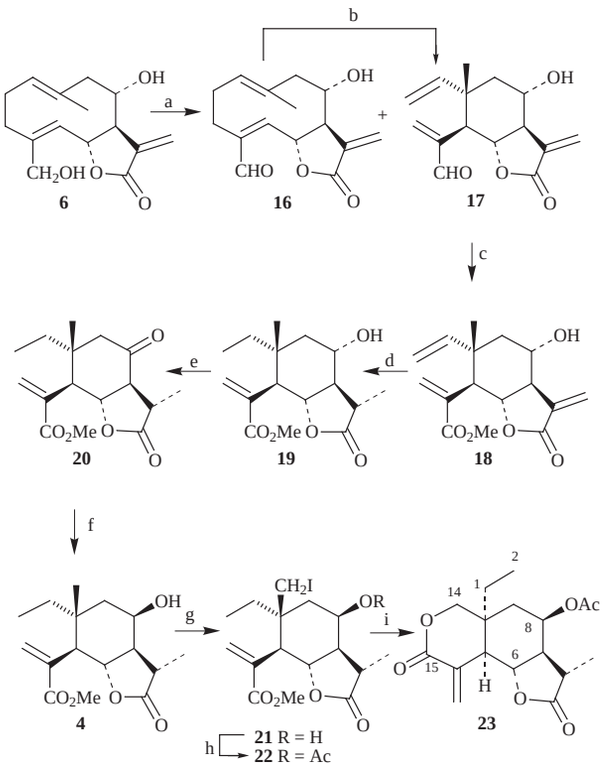
The second key step of the retrosynthetic Scheme 1 is the long range functionalization at C-14 of **3**. In order to achieve this transformation, a β-oriented hydroxy group at C-8 was needed. For this purpose, dehydration of the alcohol **10** and hydrobromination of the alkene **12** were planned. Nevertheless, several attempts to eliminate the hydroxy group of **10** were unsuccessful. Finally, treatment with $POCl_3$ in pyridine at reflux gave a mixture of the desired alkene **12** (64% yield) and a by-product which was tentatively identified as **13**. Trying to improve the yield of the dehydration process, Mitsunobu inversion of the secondary alcohol **10** was attempted. However, several assays under different conditions were unsuccessful. Treatment of **10** with NBS in aqueous THF, again led to a mixture of the desired 8β-hydroxy derivative **3** (44% yield) and the by-products, **14** and **15**. The positions of the bromine atom and the hydroxy group in each compound were deduced from the chemical shifts and coupling constant values of H-8 and H-9. Formation of these compounds can be justified through the intermediate bromonium ions **I** and **II** (Scheme 3).



Scheme 3

Nucleophilic attack by the α-face of ion **I** takes place only at C-9, whereas nucleophilic attack by the β-face of bromonium ion **II** takes place only at C-8. Different modifications in the experimental conditions of the hydrobromination were not able to enhance the yield of the desired 8β-hydroxy derivative **3**. At this point, the relatively low overall yield of bromohydrin **3** (8% yield from **5**), an intermediate which occupies a mid-point in the retrosynthetic scheme, cast serious doubts on the utility of **5** as a raw material for an effective synthesis of **1**. Therefore, we decided to check this synthesis starting out from (+)-salonitenolide (**6**), the second raw material foreseen in Scheme 1, taking advantage of the knowledge obtained during the experiments performed from **5**.

Lactone **6** can be easily obtained from *C. malacitana,* and by selective saponification of (+)-cnicin isolated from the same plant.[14] However, the best source for **6** was found to be *C. calcitrapa*. This plant is a common weed, widespread in the South and East of Spain. It has been reported that *C. calcitrapa* (collected in summer) yielded (+)-cnicin, (+)-cnicin acetate and small amounts of (+)-salonitenolide.[18] Nevertheless, when the plant was collected in spring, (+)-salonitenolide was the main component of the organic extract. Treatment of **6** with tetra-*n*-propylammonium perruthenate (TPAP) (in this case TPAP was better than PDC) gave a mixture of 15-oxogermacrolide **16** (30% yield) and elemanolide **17** (38% yield) (Scheme 4). When compound **16** was heated in toluene under reflux, **17** was obtained quantitatively, confirming the easy Cope rearrangement of 15-oxogermacrolides. As in **8**, sodium chlorite was the best reagent for the oxidation of the conjugated aldehyde **17** (83% yield for **18**). Catalytic hydrogenation of **18** stereoselectively led to the tetrahydro derivative **19** (95% yield) in five hours. A shorter reaction time (30 min) gave the corresponding 11β,13-dihydro derivative, revealing the high reactivity of the α-methylene-γ-lactone group. The stereochemistry of **19** was confirmed by the NOE observed between H-11 and H-6. In order to perform the C-14 long range functionalization foreseen in Scheme 1, a β-oriented hydroxy group at C-8 was needed. However, as happened with **10**, Mitsunobu methodology was unsuccessful for achieving the C-8 configuration inversion of **19**. Therefore, we dealt with this inversion in two steps: oxidation of **19** with pyridinium chlorochromate (PCC) and stereoselective reduction of the ketone **20**. Thus, the 8β-hydroxy derivative **4** was obtained in a 24% overall yield from **6**. Comparison of the overall yield for **4** with that of **3**, encouraged us to continue the synthesis from **6**, and that from **5** was finally discarded. Nevertheless, we had some doubt about the subsequent steps foreseen in the



Scheme 4 *Reagents and conditions:* a) TPAP, NMO. b) Toluene, reflux. c) (i) $NaClO_2$. (ii) CH_2N_2. d) H_2, Pd/C. e) PCC. f) L-Selectride®. g) IBDA, I_2, *hv*. h) Ac_2O, pyridine. i) NaOAc.

retrosynthetic analysis, due to the anticipated difficulty of cleaving the ether **2b** (Scheme 1) in acceptable yield. Surprisingly, photochemical treatment of **4**, in the presence of iodobenzene diacetate (IBDA), gave the iodohydrin **21** (67% yield), and only a low proportion of the ether **2b**. Possible conformational effects leading to this result have previously been discussed.[10] In any case, from a synthetic point of view, **21** was a more favorable intermediate than **2b**. Consequently, we performed alkaline treatment of **21**, in order to form the δ-lactone ring of **1**, but this reaction led to ether **2b** quantitatively. Therefore, acetylation of **21** was carried out to prevent ether formation. Once the 8-OH was suitably protected in **22**, treatment with NaOAc led to **23** (87% yield). The ^{1}H NMR spectrum of **23**[10] showed both the doublet (J = 12.2 Hz) and the double doublet (J = 12.2, J = 2.0 Hz) characteristic of the diastereotopic hydrogens in C-14 of vernolepin.[19] On the other hand, after treatment with aqueous Ag_2O under reflux, **22** was recovered unchanged. Oxidation of selenide formed *via* enolate is a well established method for restoring the $\Delta^{11,13}$ double bond of (+)-vernolepin related compounds.[20] Therefore, from a formal point of view, Scheme 4 is a useful procedure for the enantiospecific synthesis of 1,2-dihydro-8-*epi*-vernolepin derivatives such as **1**.

In conclusion, the present work proved that the accessible germacrolide **6** provides one of the most convenient raw materials for the synthesis of (+)-vernolepin related compounds whilst preserving the hydroxy group at C-8.

Experimental

General details

Melting points were obtained on a Reichert apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. UV spectra were obtained on UV–VIS Baush-Lamb Spectronic 2000 and Beckman DU-8B spectrophotometers. IR spectra were recorded, in liquid film between NaCl plates or in $CHCl_3$ solution, on a Perkin-Elmer 983G apparatus. LRMS were determined on a Hewlett-Packard 5988A instrument. HRMS were registered on an Autospec-Q VG-Analytical (FISONS) mass spectrometer. NMR spectra were recorded on Bruker WP 80 SY, Bruker AM 300 and Bruker ARX 400 spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS, and coupling constants (J) are in Hz. Carbon substitution degrees were established by DEPT multipulse sequence. Thin-layer chromatography (TLC) was performed on precoated 0.25 mm thick Merck plates of Si gel 60 F_{254}, using a 7% phosphomolybdic acid solution (EtOH) to visualize the spots. Gravity column chromatography was carried out on silica gel and flash chromatography was performed as described previously.[21] All solvents were purified and dried following standard procedures.[22]

(+)-Stenophyllolide 5

This compound was obtained from *Centaura malacitana* as previously described.[14]

(+)-Salonitenolide 6

Centaurea calcitrapa L. (25 kg) was collected at Suspiro del Moro (Granada, Spain) in May, 1996. The plant was taxonomically identified by Professor G. Blanca (Departamento de Biología Vegetal, Universidad de Granada, Spain). A voucher specimen (no. 40136) is deposited at the Herbarium of the Faculty of Sciences of the University of Granada. The freshly cut plant was submerged in $CHCl_3$ (8 hours) at room temperature. The solvent was removed and 120 g of a residue was obtained. 18 g of the extract were chromatographed on a silica gel column eluting with a $CHCl_3$–acetone gradient. (+)-Salonitenolide (6 g, $CHCl_3$: Me_2CO 75 : 25) was obtained. Its physical properties, including optical rotation were in agreement with those previously described.[14]

Oxidation of (+)-stenophyllolide 5

Pyridinium dichromate (PDC) (8.978 g, 23.86 mmol) was added to a solution of **5** (4.201 g, 15.91 mmol) in anhydrous THF (50 mL) under inert atmosphere. After stirring the reaction at room temperature for 19 h, it was diluted with *t*-BuOMe and filtered through Florisil®. The residue was purified by flash chromatography ($CHCl_3$: acetone 7 : 3) to give **7** (3.212 g, 12.26 mmol) and **8** (318 mg, 1.21 mmol). Compound **7**: colourless needles, mp 135 °C; $[a]_D^{25}$ +70.2 (*c* 1.02, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.11), 228 (4.04) nm; ν_{max} ($CHCl_3$)/cm^{-1} 3600 (OH), 3008, 2938, 2870, 1767 (CO, α-methylene-γ-lactone), 1677 (CO, aldehyde), 1633 (C=C), 1249, 1137, 982; δ_H(300 MHz; Me_2CO-d_6) 10.07 (1H, s, H-15), 6.19 (1H, d, J 3.6, H_a-13), 6.05 (1H, d, J 10.7, H-5), 5.72 (1H, d, J 3.3, H_b-13), 5.41 (1H, dd, J 8.6 and 10.7, H-6), 5.28 (1H, ddd, J 1.2, 5.4 and 11.6, H-1), 4.19 (1H, ddd, dd in D_2O–$CDCl_3$, J 2.7, 3.1 and 10.8, H-9), 3.95 (1H, br d, J 2.7, C-9-OH, exchanges with D_2O), 2.97 (1H, ddd, J 2.2, 5.2 and 11.6, H_b-3), 2.91 (1H, dddt, J 1.4, 3.3, 3.6 and 8.6, H-7), 2.25–1.88 (3H, m, $H_{a,\beta}$-2, H_b-8), 2.24 (1H, ddd, J 6.3, 11.6 and 12.0, H_a-3), 1.20 (3H, d, J 1.2, H-14); δ_C(75 MHz; Me_2CO-d_6) (from C-1 to C-15): 127.6 (d), 26.7 (t), 31.0 (t), 141.5 (s), 146.0 (d), 79.0 (d), 47.6 (d), 36.2 (t), 77.8 (d), 139.8 (s), 142.8 (s), 169.6 (s), 120.4 (t), 11.5 (q), 190.1 (d); *m*/*z* (CI) 263.1288 ([M + H]$^+$. $C_{15}H_{19}O_4$ requires 263.1283), 245 [263 − H_2O]$^+$ (31%), 229 (12), 211 (5), 155 (6), 119 (9), 79 (100).

(5*R*,6*S*,7*S*,9*S*,10*S*)-9-Hydroxy-15-oxoelema-1,3,11(13)-trien-12,6-olide 8†

Compound **7** (3.480 g, 13.28 mmol) was refluxed in toluene (40 mL) under an inert atmosphere for 10 h. The solvent was

† IUPAC name: 2-[(3a*S*,5*S*,6*S*,7*R*,7a*S*)-5-hydroxy-6-methyl-3-methylene-2-oxo-6-vinyloctahydro-1-benzofuran-7-yl]acrylaldehyde. The numbering used in the NMR assignments corresponds to the elemane system and not the IUPAC name.

removed under vacuum and the crude was purified by flash chromatography ($CHCl_3$:acetone, 7:3) yielding the elemanonolide **8** (2.19 g, 8.37 mmol) and **7** (0.730 g, 2.79 mmol). Compound **8**: colorless needles, mp 110 °C; $[\alpha]_D^{25}$ +3.6 (*c* 1.01, MeOH); UV (MeOH) λ_{max} (log ε) 211 (4.14) nm; ν_{max} (film)/cm^{-1} 3478 (OH), 2986, 2950, 2870, 1767 (CO, α-methylene-γ-lactone), 1686 (CO, aldehyde), 1638 (C=C), 1244, 1137, 994, 973, 755; δ_H(300 MHz; Me_2CO-d_6) 9.47 (1H, s, H-15), 6.47 (1H, s, H_a-3), 6.40 (1H, s, H_b-3), 5.94 (1H, d, *J* 3.3, H_a-13), 5.65 (1H, dd, *J* 10.7 and 17.4, H-1), 5.50 (1H, d, *J* 3.1, H_b-13), 4.94 (1H, dd, *J* 1.2 and 10.7, H_a-2), 4.84 (1H, dd, *J* 1.2 and 17.4, H_b-2), 4.41 (1H, dd, *J* 11.0 and 12.0, H-6), 3.86 (1H, ddd, dd in D_2O–Me_2CO-d_6, *J* 4.3, 4.8 and 11.1, H-9), 3.75 (1H, d, *J* 4.8, C-9-OH, exchanges with D_2O), 3.18 (1H, d, *J* 12.0, H-5), 2.81 (1H, dddt, *J* 3.1, 3.3, 11.0 and 12.0, H-7), 2.33 (1H, ddd, *J* 3.3, 4.3 and 12.6, H_a-8), 1.71 (1H, ddd, *J* 11.1, 12.0 and 12.6, H_b-8), 1.01 (3H, s, H-14); δ_C(75 MHz; Me_2CO-d_6) (from C-1 to C-15): 146.1 (d), 114.8 (t), 138.0 (t), 146.4 (s), 45.3 (d), 80.1 (d), 47.1 (d), 30.4 (t), 75.5 (d), 49.0 (s), 140.7 (s), 170.3 (s), 116.7 (t), 10.2 (q), 194.5 (d); NMR data were assigned with the aid of 2D NMR experiments: ^1H–^1H homonuclear correlation (COSY) and direct heteronuclear ^1H–^{13}C correlation; *m*/*z* (CI) 263.1284 ($[M + H]^+$. $C_{15}H_{19}O_4$ requires 263.1283), 245 $[263 - H_2O]^+$ (100%), 227 $[245 - H_2O]^+$ (46), 199 $[227 - CO]^+$ (15), 173 (4).

(5*R*,6*S*,7*S*,9*S*,10*S*)-15-Methoxy-15-oxo-9-hydroxyelema-1,3,11(13)-trien-12,6-olide 9

The aldehyde **8** (2.720 g, 10.38 mmol) was dissolved in 214 mL of *t*-BuOH and 55 mL of 2-methylbut-2-ene. A solution of sodium chlorite (8.608 g, 95.18 mmol) and sodium dihydrogenphosphate (8.608 g, 71.73 mmol) in 88 mL of water was added dropwise for 30 minutes. The reaction mixture was stirred at room temperature for 1 h 15 min more. Volatile components were then removed under vacuum. The residue was dissolved in 25 mL of water and it was extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and chilled to −20 °C. Then, a solution of diazomethane in Et_2O was added. The mixture was stirred at this temperature for 10 min, and then evaporated to dryness. Purification by flash chromatography ($CHCl_3$:acetone 97:3) gave **9** (2.364 g, 8.10 mmol): oil, $[\alpha]_D^{25}$ +57.3 (*c* 1.00, MeOH); ν_{max} (film)/cm^{-1} 3506 (OH), 2951, 1771 (CO, α-methylene-γ-lactone), 1715 (CO, ester), 1628 (C=C), 1412, 1290, 1247, 1197, 1077, 1061, 992, 756; δ_H(400 MHz; $CDCl_3$) 6.38 (1H, s, H_a-3), 6.06 (1H, d, *J* 3.2, H_a-13), 5.71 (1H, dd, *J* 10.8 and 17.4, H-1), 5.52 (1H, s, H_b-3), 5.42 (1H, d, *J* 3.0, H_b-13), 5.12 (1H, d, *J* 10.8, H_a-2), 4.98 (1H, d, *J* 17.4, H_b-2), 4.12 (1H, dd, *J* 10.9 and 11.8, H-6), 3.71 (1H, br dd, *J* 4.2 and 11.1, H-9), 3.66 (3H, s, OMe), 3.22 (1H, d, *J* 11.8, H-5), 2.68 (1H, ddddd, *J* 3.0, 3.2, 3.4, 10.9 and 12.1, H-7), 2.32 (1H, ddd, *J* 3.4, 4.2 and 12.1, H_a-8), 1.98 (1H, br s, C-9-OH, exchanges with D_2O), 1.64 (1H, ddd, *J* 11.1, 12.1 and 12.7, H_β-8), 0.92 (3H, s, H-14); δ_C(100 MHz; $CDCl_3$) (from C-1 to C-15): 143.6 (d), 116.6 (t), 127.8 (t), 135.3 (s), 46.2 (s), 79.2 (d), 47.4 (d), 28.5 (t), 74.9 (d), 48.5 (s), 138.5 (s), 169.9 (s), 117.8 (t), 9.4 (q), 167.6 (s), 52.1 ($COOCH_3$); *m*/*z* (CI) 293.1382 ($[M + H]^+$. $C_{16}H_{21}O_5$ requires 293.1389), 275 $[293 - H_2O]^+$ (100%), 261 $[293 - CH_3OH]^+$ (30), 257 $[275 - H_2O]^+$ (37), 243 $[275 - CH_3OH]^+$ (68), 215 $[243 - CO]^+$ (20), 51 (84).

Catalytic hydrogenation of 9

Compound **9** (291 mg, 1.00 mmol) in MeOH (13 mL) was hydrogenated using 10% palladium-on-charcoal (17 mg) and H_2 at atmospheric pressure. The mixture was vigorously stirred for 4 h. Then, the catalyst was filtered off. Removal of the MeOH yielded a crude, which purification by flash chromatography ($CHCl_3$:acetone 93:7) yielded **10** (216 mg, 0.73 mmol) and **11** (74 mg, 0.25 mmol). Compound **10**: oil, $[\alpha]_D^{25}$ +16.1 (*c* 0.99, $CHCl_3$); ν_{max} (film)/cm^{-1} 3500 (OH), 2946, 1772 (CO, α-methylene-γ-lactone), 1717 (CO; ester), 1625 (C=C), 1259, 1171, 1121, 1017, 757; δ_H(300 MHz; $CDCl_3$) 6.48 (1H, s, H_a-3), 5.60 (1H, s, H_b-3), 4.19 (1H, dd, *J* 9.6 and 11.7, H-6), 3.80–3.70 (1H, m, H-9), 3.72 (3H, s, OMe), 3.02 (1H, br d, *J* 11.7, H-5), 2.36 (1H, dq, *J* 6.9 and 12.0, H-11), 2.04 (1H, ddd, *J* 2.6, 4.4 and 11.5, H_a-8), 1.65 (1H, dddd, *J* 2.6, 9.6, 12.0 and 12.2, H-7), 1.55 (1H, dt, 11.5 and 12.2, H_b-8), 1.41 (1H, dq, *J* 7.5 and 14.6, H_a-1), 1.19 (3H, d, *J* 6.9, H-13), 1.05 (1H, dq, *J* 7.5 and 14.6, H_b-1), 0.86 (3H, t, *J* 7.5, H-2), 0.84 (3H, br s, H-14); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 31.4 (t), 7.4 (q), 128.5 (t), 136.3 (s), 44.5 (d), 80.8 (d), 48.7 (d), 29.5 (t), 72.3 (d), 44.1 (s), 41.6 (d), 178.8 (s), 12.5 (q), 15.1 (q), 167.8 (s), 52.1 ($COOCH_3$); *m*/*z* (CI) 297.1705 ($[M + H]^+$. $C_{16}H_{25}O_5$ requires 297.1702), 279 $[297 - H_2O]^+$ (100%), 261 $[279 - H_2O]^+$ (47), 247 $[279 - CH_3OH]^+$ (71), 233 (29), 219 (22), 205 (45), 51 (93). Compound **11**: δ_H(80 MHz; $CDCl_3$) 6.42 (1H, br s, H_a-3), 5.59 (1H, br s, H_b-3), 3.70 (3H, s, OMe), 3.01 (1H, br d, *J* 11.0, H-5), 1.15 (3H, d, *J* 7.0, H-13), 0.81 (3H, t, *J* 7.0, H-2), 0.81 (3H, br s, H-14).

(5*R*,6*S*,7*S*,10*R*,11*S*)-15-Methoxy-15-oxoelema-3,8-dien-12,6-olide 12

$POCl_3$ (1.1 mL, 11.8 mmol) was added dropwise to a solution of **10** (693 mg, 2.34 mmol) in anhydrous pyridine (17 mL). The reaction mixture was refluxed under argon for 10 min, and then it was cooled and extracted with *t*-BuOMe. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography on silica gel with $AgNO_3$ (20%), using a hexane:ether gradient, to give **12** (416 mg, 1.50 mmol, hexane:ether 80:20) and **13** (136 mg, hexane:ether 75:25). Compound **12**: colorless needles, mp 48–50 °C; $[\alpha]_D^{25}$ +31.6 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 2965, 1780 (CO, α-methylene-γ-lactone), 1717 (CO; ester), 1625 (C=C), 1455, 1268, 1166, 1007; δ_H(300 MHz; $CDCl_3$) 6.43 (1H, d, *J* 0.8, H_a-3), 5.74 (1H, dd, *J* 1.2 and 9.8, H-9), 5.62 (1H, t, *J* 0.8, H_b-3), 5.30 (1H, dd, *J* 2.5 and 9.8, H-8), 4.34 (1H, br dd, *J* 9.6 and 12.1, H-6), 3.73 (3H, s, OMe), 3.30 (1H, br d, *J* 12.1, H-5), 2.40 (1H, dq, *J* 6.6 and 13.0, H-11), 2.37 (1H, dddd, *J* 1.2, 2.5, 9.6 and 13.0, H-7), 1.35 (1H, dq, *J* 7.3 and 14.3, H_a-1), 1.27 (3H, d, *J* 6.6, H-13), 1.25 (1H, dq, *J* 7.3 and 14.3, H_b-1), 0.88 (3H, t, *J* 7.3, H-2), 0.88 (3H, br s, H-14); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 32.9 (t), 8.6 (q), 129.0 (t), 136.0 (s), 50.0 (d), 79.2 (d), 50.4 (d), 121.3 (d), 138.8 (d), 44.1 (s), 41.3 (d), 178.9 (s), 12.7 (q), 25.8 (q), 167.6 (s), 51.9 ($COOCH_3$); *m*/*z* (CI) 279.1595 ($[M + H]^+$. $C_{16}H_{23}O_4$ requires 279.1596), 261 $[279 - H_2O]^+$ (47%), 247 $[279 - CH_3OH]^+$ (22), 233 $[261 - CO]^+$ (35), 205 (18), 51 (37). Compound **13**: δ_H(80 MHz; $CDCl_3$) 6.51 (1H, br s, H_a-3), 5.20 (1H, br s, H_b-3), 4.90 (1H, br s, H_a-14), 4.64 (1H, br s, H_b-14), 3.71 (3H, br s, OMe).

Hydrobromination of 12

NBS (78 mg, 0.44 mmol) was added to a solution of **12** (60 mg, 0.22 mmol) in THF (0.8 mL) and water (0.4 mL). The mixture was stirred at room temperature under argon for 18 h. Then, it was diluted with water (50 mL) and extracted with *t*-BuOMe. The combined *t*-BuOMe extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was chromatographed on silica gel using a hexane:*t*-BuOMe gradient, yielding **3** (36 mg, 0.096 mmol, hexane:ether 65:35), **14** (15 mg, 0.034 mmol, hexane:ether 80:20), and **15** (30 mg, 0.080 mmol, hexane:ether 65:35). Compound **3**: oil, $[\alpha]_D^{25}$ −6.4 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 3481 (OH), 2971, 1778 (CO, α-methylene-γ-lactone), 1717 (CO, ester), 1625 (C=C), 1455, 1268, 1166, 1007; δ_H(300 MHz; $CDCl_3$) 6.50 (1H, s, H_a-3), 5.68 (1H, s, H_b-3), 4.68 (1H, br dd, *J* 9.5 and 11.6, H-6), 4.49 (1H, m, H-8), 4.18 (1H, d, *J* 2.8, H-9), 3.75 (3H, s, OMe), 3.35 (1H, br d, *J* 11.6, H-5), 2.80–2.65 (1H, m, H-7), 2.66 (1H, dq, *J* 6.6 and 13.8, H-11), 1.70 (1H, dq, *J* 7.2 and 14.3, H_a-1), 1.63 (1H, dq, *J* 7.2 and 14.3, H_b-1), 1.22 (3H, br s, H-14), 1.21 (3H, d, *J* 6.6,

H-13), 0.82 (3H, t, *J* 7.2, H-2); δ_C(100 MHz; $CDCl_3$) (from C-1 to C-15): 35.3 (t), 6.7 (q), 129.0 (t), 136.1 (s), 45.9 (d), 75.8 (d), 49.9 (d), 62.6 (d), 71.4 (d), 43.9 (s), 36.3 (d), 178.8 (s), 12.2 (q), 21.2 (q), 167.9 (s), 52.3 ($COOCH_3$); *m/z* (CI) 377 $[M + 2 + H]^+$ (19%), 375 $[M + H]^+$ (19), 359 $[377 - H_2O]^+$ (4), 357 $[375 - H_2O]^+$ (4), 345 $[377 - CH_3OH]^+$ (3), 343 $[375 - CH_3OH]^+$ (3), 295 [377 and 375 − Br]$^+$ (15), 277 $[295 - H_2O]^+$ (11), 99 (42), 51 (100). Compound **14**: oil, $[\alpha]_D^{25}$ −22.6 (*c* 0.99, $CHCl_3$); ν_{max} (film)/cm^{-1} 2973, 1788 (CO, α-methylene-γ-lactone), 1718 (CO, ester), 1626 (C=C), 1457, 1202, 1164, 1113, 1019, 958; δ_H(80 MHz; $CDCl_3$) 6.51 (1H, br s, H_a-3), 5.69 (1H, br s, H_b-3), 4.89 (1H, br t, *J* 2.5, H-8), 4.80–4.50 (1H, m, H-6), 4.60 (1H, d, *J* 2.5, H-9), 3.73 (3H, s, OMe), 3.39 (1H, br d, *J* 12.0, H-5), 2.91–2.63 (1H, m, H-7), 1.34 (3H, br s, H-14), 1.19 (3H, d, *J* 7.0, H-13), 1.78 (3H, t, *J* 7.0, H-2); *m/z* (CI) 441 $[M + 4 + H]^+$ (10%), 439 $[M + 2 + H]^+$ (13), 437 $[M + H]^+$ (5), 409 (3), 407 (3), 231 (6), 113 (2), 51 (100). Compound **15**: oil, $[\alpha]_D^{25}$ −16.9 (*c* 0.98, $CHCl_3$); ν_{max} (film)/cm^{-1} 3487 (OH), 2972, 1773 (CO, α-methylene-γ-lactone), 1717 (CO, ester), 1625 (C=C), 1455, 1118, 1006; δ_H(80 MHz; $CDCl_3$) 6.47 (1H, br s, H_a-3), 5.67 (1H, br s, H_b-3), 4.63 (1H, br dd, *J* 10.0 and 11.0, H-6), 4.37 (1H, br t, *J* 3.0, H-8), 4.09 (1H, br dd, d in D_2O–$CDCl_3$, *J* 4.0 and 3.0, H-9), 3.71 (3H, s, OMe), 3.27 (1H, br d, *J* 11.0, H-5), 2.90–2.30 (2H, m, H-7, H-11), 2.35 (1H, br d, *J* 4.0, C-9-OH, exchanges with D_2O), 1.52 (3H, d, *J* 7.0, H-13), 1.13 (3H, br s, H-14), 0.79 (3H, t, *J* 7.0, H-2); *m/z* (CI) 377 $[M + 2 + H]^+$ (7%), 375 $[M + H]^+$ (7), 345 $[377 - CH_3OH]^+$ (2), 299 (7), 249 (3), 85 (11), 51 (100).

Oxidation of (+)-salonitenolide 6

TPAP (39 mg, 0.11 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (344 mg, 2.94 mmol), were added under argon to a pre-stirred (1 h) suspension of powdered 4 Å activated molecular sieves (3 g) in a solution of **6** (490 mg, 1.86 mmol) in anhydrous THF at room temperature. After stirring (48 h), the suspension was filtered, washed with acetone and the filtrate was evaporated to dryness *in vacuo.* Purification by chromatography on silica gel ($CHCl_3$:$MeCO_2$ gradient) gave **17** (185 mg, 0.71 mmol, $CHCl_3$:$MeCO_2$ 85:15), **16** (146 mg, 0.56 mmol, $CHCl_3$:$MeCO_2$ 85:15) and **6** (69 mg, 0.26 mmol, $CHCl_3$:$MeCO_2$ 65:35). Compound **16**: oil, ν_{max} (film)/cm^{-1} 3395 (OH), 2917, 2849, 1764 (CO, α-methylene-γ-lactone), 1685 (CO, aldehyde), 1460, 1260, 1103, 801; δ_H(300 MHz; $CDCl_3$) 9.94 (1H, s, H-15), 6.44 (2H, m, $H_{a,b}$-13), 5.80 (1H, br d, *J* 10.1, H-5), 5.14–5.05 (1H, m, H-1), 5.07 (1H, dd, *J* 8.4 and 10.1, H-6), 4.11 (1H, ddd, *J* 3.1, 9.1 and 10.7, H-8), 3.06 (1H, ddd, *J* 2.2, 5.1 and 11.9, H_b-3), 2.87 (1H, ddt, *J* 3.2, 8.4 and 9.1, H-7), 2.68 (1H, br dd, *J* 3.1 and 12.8, H_β-9), 2.40 (1H, dd, *J* 10.7 and 12.8, H_a-9), 2.30–1.90 (2H, m, $H_{a,b}$-2), 1.72 (1H, dt, *J* 5.1 and 11.9, H_a-3), 1.16 (3H, s, H-14); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 129.7 (d), 26.6 (t), 30.7 (t), 140.6 (s), 144.2 (d), 73.6 (d), 54.4 (d), 71.1 (d), 52.4 (t), 135.1 (s), 135.5 (s), 169.8 (s), 128.0 (t), 17.6 (q), 189.3 (d); *m/z* (CI) 263 $[M + H]^+$ (4%), 245 $[263 - H_2O]^+$ (3), 227 $[245 - H_2O]^+$ (2), 85 (31), 51 (100).

(5*R*,6*R*,7*R*,8*S*,10*S*)-8-Hydroxy-15-oxoelema-1,3,11(13)-trien-12,6-olide 17

Compound **16** (7.680 g, 29.31 mmol) was heated in toluene (113 mL) at reflux for 10 min under an inert atmosphere. The solvent was removed and the residue was flash chromatographed ($CHCl_3$:acetone 85:15) giving the elemanolide **17** (7.369 g, 28.13 mmol) as colourless needles: mp 137–8 °C; $[\alpha]_D^{25}$ +57.6 (*c* 1.02, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 210 (4.20) nm; ν_{max} ($CHCl_3$)/cm^{-1} 3453 (OH), 2928, 1744 (CO, α-methylene-γ-lactone), 1686 (CO, aldehyde), 1640 (C=C), 1282, 1158, 1064, 972; δ_H(300 MHz; $CDCl_3$) 9.44 (1H, s, H-15), 6.26 (1H, s, H_a-3), 6.24 (1H, s, H_b-3), 6.16 (1H, d, *J* 3.1, H_a-13), 5.99 (1H, d, *J* 2.9, H_b-13), 5.66 (1H, dd, *J* 10.7 and 17.5, H-1), 4.93 (1H, d, *J* 10.7, H_a-2), 4.82 (1H, d, *J* 17.5, H_b-2), 4.32 (1H, dd, *J* 11.0 and 12.0, H-6), 4.11 (1H, ddd, *J* 4.3, 10.4 and 10.8, H-8), 3.10 (1H, d, *J* 12.0, H-5), 2.66 (1H, dddd, *J* 2.9, 3.1, 10.4 and 11.0, H-7), 1.88 (1H, dd, *J* 4.5 and 13.1, H_β-9), 1.68 (1H, dd, *J* 10.8 and 13.1, H_a-9), 1.00 (3H, s, H-14); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 145.6 (d), 112.7 (t), 137.9 (t), 144.9 (s), 46.3 (d), 77.6 (d), 55.1 (d), 67.6 (d), 49.5 (t), 42.1 (s), 137.3 (s), 169.9 (s), 120.8 (t), 18.3 (q), 193.8 (d); *m/z* (FAB) 285.1094 $([M + Na]^+$. $C_{15}H_{18}O_4Na$ requires 285.1103); *m/z* (CI) 263 $[M + H]^+$ (45%), 245 $[263 - H_2O]^+$ (100), 227 $[245 - H_2O]^+$ (44), 195 (94), 177 (67), 85 (44).

(5*R*,6*R*,7*R*,8*S*,10*S*)-15-Methoxy-15-oxo-8-hydroxyelema-1,3,11(13)-trien-12,6-olide 18

The aldehyde **17** (443 mg, 1.69 mmol) was dissolved in 36 mL of *t*-BuOH and 9 mL of 2-methylbut-2-ene. A solution of sodium chlorite (1.402 g, 15.5 mmol) and sodium dihydrogenphosphate (1.403 g, 11.69 mmol) in 14 mL of water was added dropwise for 30 min. The reaction mixture was stirred at room temperature for 1 h 15 min more. Then, volatile components were removed under vacuum. The residue was dissolved in 10 mL of water and it was extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and chilled to −78 °C. Then, a solution of diazomethane in Et_2O was added. The mixture was stirred at this temperature for 15 min, and then, evaporated to dryness. Purification by chromatography on silica gel ($CHCl_3$:acetone, gradient) gave **18**[10] (413 mg, 1.41 mmol, $CHCl_3$:acetone 97:3). *m/z* (FAB) 315.1209 $([M + Na]^+$. $C_{16}H_{20}O_5Na$ requires 315.1208).

(5*R*,6*R*,7*R*,8*S*,10*R*,11*S*)-15-Methoxy-15-oxo-8-hydroxyelema-3-en-12,6-olide 19

Compound **18** (6.258 g, 21.43 mmol) in MeOH (272 mL) was hydrogenated using 10% palladium-on-charcoal (0.712 g) and H_2 at atmospheric pressure. The mixture was vigorously stirred for 5 h. Then, the catalyst was filtered off. Removal of the MeOH yielded **19** (6.010 g, 20.30 mmol): oil, $[\alpha]_D^{25}$ +130.0 (*c* 0.50, $CHCl_3$); ν_{max} (film)/cm^{-1} 3462 (OH), 2947, 1753 (CO, α-methylene-γ-lactone), 1716 (CO, ester), 1620 (C=C), 1448, 1271, 1123, 997; δ_H(300 MHz; $CDCl_3$) 6.42 (1H, s, H_a-3), 5.55 (1H, s, H_b-3), 4.24 (1H, dd, *J* 10.7 and 11.9, H-6), 3.87 (1H, m, H-8), 3.72 (3H, s, OMe), 2.92 (1H, br d, *J* 11.9, H-5), 2.56 (1H, dq, *J* 6.9 and 12.1, H-11), 2.03 (1H, br d, *J* 3.0, C-8-OH, exchanges with D_2O), 1.86 (1H, dd, *J* 4.2 and 13.0, H_β-9), 1.71 (1H, ddd, *J* 10.5, 10.7 and 12.1, H-7), 1.39 (1H, dd, 11.0 and 13.0, H_a-9), 1.33 (3H, d, *J* 6.9, H-13), 1.26 (1H, dq, *J* 7.4 and 14.3, H_a-1), 1.14 (1H, dq, *J* 7.4 and 14.3, H_b-1), 0.85 (3H, s, H-14), 0.80 (3H, t, *J* 7.4, H-2); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 34.7 (t), 7.6 (q), 128.3 (t), 136.5 (s), 48.9 (d), 78.7 (d), 58.6 (d), 69.0 (d), 47.2 (t), 39.1 (s), 41.7 (d), 179.0 (s), 14.4 (q), 20.2 (q), 167.9 (s), 52.2 ($COOCH_3$); *m/z* (CI) 297.1709 $([M + H]^+$. $C_{16}H_{25}O_5$ requires 297.1702), 279 $[297 - H_2O]^+$ (82%), 261 (56), 247 (41), 245 (43), 209 (56).

(5*R*,6*R*,7*R*,10*R*,11*S*)-15-Methoxy-8,15-dioxoelem-3-en-12,6-olide 20

PCC (4.276 g, 19.93 mmol) and anhydrous NaOAc (0.409 g, 4.99 mmol) were added to a stirred solution of **19** (2.950 g, 9.97 mmol) in anhydrous CH_2Cl_2 (89 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 18 h. Then, it was diluted with *t*-BuOMe, and filtered through Florisil®. The residue was removed and purified by flash chromatography ($CHCl_3$) to give **20** (2.555 g, 8,69 mmol): oil, $[\alpha]_D^{25}$ −29.1 (*c* 0.97, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2970, 1782 (CO, α-methylene-γ-lactone), 1723 (CO, ester), 1625 (C=C), 1117, 970; δ_H(400 MHz; $CDCl_3$) 6.50 (1H, s, H_a-3), 5.62 (1H, s, H_b-3), 4.35 (1H, br dd, *J* 11.4 and 11.8, H-6), 3.75 (3H, s, OMe), 3.42 (1H, br d, *J* 11.8, H-5), 2.87 (1H, t, *J* 11.4, H-7), 2.83 (1H,

dq, *J* 6.5 and 11.4, H-11), 2.51 (1H, br d, *J* 13.6, H_a-9), 2.23 (1H, d, *J* 13.6, H_b-9), 1.42 (1H, dq, *J* 7.5 and 14.5, H_a-1), 1.24 (1H, d, *J* 6.5, H-13), 1.23 (1H, dq, *J* 7.5 and 14.5, H_b-1), 0.84 (3H, br s, H-14); δ_C(100 MHz; $CDCl_3$) (from C-1 to C-15): 34.2 (t), 7.8 (q), 129.1 (t), 135.8 (s), 49.1 (d), 79.0 (d), 62.0 (d), 203.1 (s), 52.1 (t), 41.9 (s), 36.7 (d), 167.5 (s), 13.4 (q), 20.1 (q), 177.1 (s), 52.3 ($COOCH_3$); *m/z* (CI) 295.1553 ($[M + H]^+$. $C_{16}H_{23}O_5$ requires 295.1545), 277 $[295 - H_2O]^+$ (100%), 263 (12), 245 (7), 197 (5).

(5*R*,6*R*,7*R*,8*R*,10*R*,11*S*)-15-Methoxy-15-oxo-8-hydroxyelem-3-en-12,6-olide 4

L-Selectride® 1.0 M in THF (2.1 mL, 2.1 mmol) was added dropwise to a cooled (−78 °C) solution of **20** (615 mg, 2.09 mmol) in anhydrous THF (6 mL). The mixture was stirred at −78 °C under argon until the reaction was complete (23 min). EtOH (1.4 mL), H_2O (0.4 mL), NaOH 3 M (0.8 mL) and H_2O_2 30% (1.4 mL) were added. After dilution with brine, the mixture was extracted with *t*-BuOMe, dried (anhydrous Na_2SO_4) and the solvent was removed. Compound **4** (607 mg, 2.05 mmol) was obtained: oil, $[\alpha]_D^{25}$ +14.8 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3457 (OH), 2968, 1779 (CO, α-methylene-γ-lactone), 1716 (CO, ester), 1625 (C=C), 1118, 1007. δ_H(300 MHz; $CDCl_3$) 6.40 (1H, s, H_a-3), 5.61 (1H, s, H_b-3), 4.68 (1H, dd, *J* 10.7 and 11.9, H-6), 4.23 (1H, ddd, *J* 2.2, 2.6 and 3.0, H-8), 3.69 (3H, s, OMe), 2.95 (1H, br d, *J* 11.9, H-5), 2.70 (1H, dq, *J* 7.0 and 12.7, H-11), 1.81 (1H, dd, *J* 2.6 and 14.8, H_β-9), 1.74 (1H, ddd, *J* 2.2, 10.7 and 12.7, H-7), 1.49 (1H, dd, *J* 3.0 and 14.8, H_a-9), 1.27 (1H, dq, *J* 7.4 and 14.7, H_a-1), 1.20–1.10 (1H, m, H_b-1), 1.14 (3H, d, *J* 7.0, H-13), 0.98 (3H, br s, H-14), 0.75 (3H, t, *J* 7.4, H-2); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 35.6 (t), 7.6 (q), 127.9 (t), 136.6 (s), 49.7 (d), 76.4 (d), 56.0 (d), 64.8 (d), 43.3 (t), 39.5 (s), 37.0 (d), 178.4 (s), 12.1 (q), 21.5 (q), 168.0 (s), 51.9 ($COOCH_3$); *m/z* (CI) 297.1710 ($[M + H]^+$. $C_{16}H_{25}O_5$ requires 297.1702), 279 $[297 - H_2O]^+$ (25%), 261 $[279 - H_2O]^+$ (11), 233 (6), 227 (7), 209 (10), 51 (100).

Photochemical reaction of 4 with IBDA and I_2

IBDA (1.463 g, 4.54 mmol) and I_2 (455 mg, 1.79 mmol) were added in two portions to a solution of compound **4** (708 mg, 2.39 mmol) in anhydrous benzene (20 mL) and cyclohexane (200 mL). The reaction mixture was irradiated with a tungsten-filament lamp (200 W) at 40 °C under argon for 8 h. After dilution with brine, the organic layer was decanted and the aqueous layer was extracted with *t*-BuOMe. The organic phase was washed with aqueous $Na_2S_2O_3$ 5% and with brine, was dried (Na_2SO_4 anh.) and the solvent was removed. The residue was purified by column chromatography on silica gel (hexane:ether gradient), yielding **21**[10] (681 mg, 1.61 mmol, hexane: ether 6:4), **2b** (94 mg, 0.22 mmol, hexane: ether 1:1) and **4** (64 mg, 0.22 mmol, hexane: ether 1:1). Compound **2b**: colourless needles, mp 107–108 °C; $[\alpha]_D^{25}$ −11.1 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 2930, 1781 (CO, α-methylene-γ-lactone), 1718 (CO, ester), 1625 (C=C), 1107, 999; δ_H(300 MHz; $CDCl_3$) 6.42 (1H, s, H_a-3), 5.85 (1H, s, H_b-3), 4.39 (1H, br d, *J* 5.9, H-8), 4.35 (1H, dd, *J* 10.5 and 11.8, H-6), 4.04 (1H, br d, *J* 9.5, H_a-14), 3.78 (3H, s, OCH_3), 3.44 (1H, br d, *J* 9.5, H_b-14), 3.31 (1H, br d, *J* 11.8, H-5), 2.64 (1H, dq, *J* 6.9 and 12.6, H-11), 2.07 (1H, dd, *J* 5.9 and 11.9, H_β-9), 1.81 (1H, br d, *J* 11.9, H_a-9), 1.74 (1H, dd, *J* 10.5 and 12.6, H-7), 1.55 (1H, dq, *J* 7.5 and 14.6, H_a-1), 1.23 (3H, d, *J* 6.9, H-13), 0.89 (3H, t, *J* 7.5, H-2); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 25.8 (t), 9.2 (q), 126.6 (t), 137.8 (s), 46.1 (d), 79.7 (d), 57.9 (d), 73.0 (d), 43.6 (t), 50.6 (s), 39.1 (d), 178.4 (s), 12.5 (q), 73.7 (t), 167.7 (s), 52.3 ($COOCH_3$); *m/z* (CI) 295.1539 ($[M + H]^+$. $C_{16}H_{23}O_5$ requires 295.1545), 277 $[295 - H_2O]^+$ (54%), 261 (25), 247 (17), 233 (17), 209 (24), 205 (49), 106 (11). Compound **21**[10]: *m/z* (CI) 423.0672 ($[M + H]^+$. $C_{16}H_{24}O_5I$ requires 423.0668).

(5*S*,6*R*,7*R*,8*R*,10*S*,11*S*)-15-Methoxy-15-oxo-8-acetoxy-14-iodoelem-3-en-12,6-olide 22

Ac_2O (1.5 mL) was added to a solution of **21** (150 mg, 0.36 mmol) in anhydrous pyridine (1.5 mL). The solution was stirred at room temperature for 3 h. The reaction was quenched with ice and the resulting mixture was extracted with *t*-BuOMe. The organic layers were washed with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and water; then, dried (anhydrous Na_2SO_4) and concentrated. Compound **22** (160 mg, 0.34 mmol) was obtained: oil, $[\alpha]_D^{25}$ +20.1 (*c* 0.99, $CHCl_3$); ν_{max} (film)/cm^{-1} 2927, 1781 (CO, α-methylene-γ-lactone), 1742 (CO, acetate), 1718 (CO, ester), 1625 (C=C), 1233, 1176, 1114, 1017; δ_H(300 MHz; $CDCl_3$) 6.50 (1H, s, H_a-3), 5.69 (1H, s, H_b-3), 5.31 (1H, td, *J* 2.4 and 2.9, H-8), 4.73 (1H, dd, *J* 10.9 and 12.0, H-6), 3.79 (1H, d, *J* 10.0, H_a-14), 3.74 (3H, s, OMe), 3.31 (1H, br d, *J* 12.0, H-5), 3.15 (1H, br dd, *J* 2.0 and 10.0, H_b-14), 2.42 (1H, dq, *J* 6.9 and 12.8, H-11), 2.30 (1H, dd, *J* 2.9 and 15.6, H_β-9), 2.14 (3H, s, $COCH_3$), 1.84 (1H, ddd, *J* 2.4, 10.9 and 12.8, H-7), 1.64 (1H, ddd, *J* 2.0, 2.9 and 15.6, H_a-9), 1.59 (1H, dq, *J* 7.4 and 14.7, H_a-1), 1.20 (3H, d, *J* 6.9, H-13), 1.06 (1H, dq, *J* 7.4 and 14.7, H_b-1), 0.84 (3H, t, *J* 7.4, H-2); δ_C(75 MHz; $CDCl_3$) (from C-1 to C-15): 31.9 (t), 8.0 (q), 129.9 (t), 135.6 (s), 52.3 (d), 75.8 (d), 54.4 (d), 66.8 (d), 37.1 (t), 41.8 (s), 37.5 (d), 177.6 (s), 12.4 (q), 20.1 (t), 167.2 (s), 52.3 ($COOCH_3$), 170.2 ($OCOCH_3$), 21.4 ($OCOCH_3$); *m/z* (CI) 465.0752 ($[M + H]^+$. $C_{18}H_{26}O_6I$ requires 465.0774), 423 $[465 - COCH_3]^+$ (12%), 405 $[465 - AcOH]^+$ (53), 387 $[405 - H_2O]^+$ (9), 337 $[465 - HI]^+$ (14), 295 $[337 - COCH_3]^+$ (8), 277 $[337 - AcOH]^+$ (10), 57 (100).

(5*R*,6*R*,7*R*,8*R*,10*S*,11*S*)-8-Acetoxyelem-3-en-15,14:12,6-diolide 23

A mixture of **22** (142 mg, 0.31 mmol), anhydrous NaOAc (25 mg, 0.31 mmol) and anhydrous DMF (25 mL) was refluxed under argon for 1 h 30 min. Then, it was diluted with water (50 mL), extracted with *t*-BuOMe, dried (anhydrous Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (hexane:ether gradient) to give **22** (9 mg, 0.02 mmol, hexane:ether 6:4) and **23**[10] (86 mg, 0.27 mmol, hexane:ether 3:7). Compound **23**: *m/z* (CI) 323.1497 ($[M + H]^+$. $C_{17}H_{23}O_6$ requires 323.1497).

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