Synthesis of (+)-8-Deoxyvernolepin

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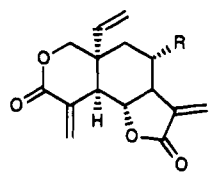
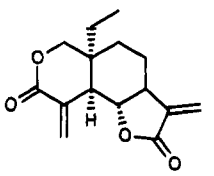
A short and efficient synthesis of (+)-8-deoxyvernolepin (**2**) from (−)-α-santonin (**8**), by functionalization of the angular methyl from a 2β- or 6β-alkoxy radical generated by reaction of the alcohol **6** or **7** with diphenylhydroxyselenium acetate and iodine and 1,4-fragmentation of the γ-hydroxystannane **35** using hypervalent organoiodine reagents as the key steps, is described. The most important structural features of this compound and other vernolepin congeners, the δ-valerolactone *cis*-fused to ring B moiety and the angular vinyl group, are introduced in the same step.

The elemane sesquiterpenoid bis(α-methylene lactone) vernolepin (**1**), isolated from *Veronica hymenolepis*,[1] possesses a synthetically interesting 2-oxa-*cis*-decalin unit having an angular vinyl group and is noteworthy for its cytotoxic and antiumor activity. Although the unique structure and biological properties of this sesquiterpenoid have aroused much attention among organic chemists,[2] synthetic approaches to this compound continue to be devised.[3]

(±)-8-Deoxyvernolepin (**2**) and (±)-dihydro-8-deoxyvernolepin (**3**) present more potent activity against *in vitro* CCRF-CEM tumor cell cultures than does natural (+)-vernolepin (**1**).[4a] To our knowledge, since the first



vernolepin (1, R = OH)
8-deoxyvernolepin (2, R = H)



dihydrodeoxyvernolepin (3)

racemic synthesis of 8-deoxyvernolepin,[4b,c] two asymmetrical routes starting from α-santonin (**8**) have been reported,[5] while a sole racemic synthesis of dihydro-8-deoxyvernolepin has been described.[4a] In all these strategies one of the key steps is the oxidative cleavage of a *trans*-fused decalin precursor possessing a C_2-C_3 double bond and then the 2-oxadecalone unit and angular vinyl group are prepared in multistep sequences.[4,5]

In the present paper we describe in full detail our own approach[6] for preparing (+)-8-deoxyvernolepin (**2**), the retrosynthetic analysis of which is shown in Figure 1, that relied on the use of alkoxy radical chemistry in the key steps. The starting material was (−)-α-santonin (**8**), a commercially available product. (−)-α-Santonin and its hydro derivatives have been frequently employed as useful chiral starting points for the syntheses of a variety of natural and unnatural sesquiterpenoids.[7-9] In the primary step of the synthesis we need the functionalization of the angular methyl group. It is known that for

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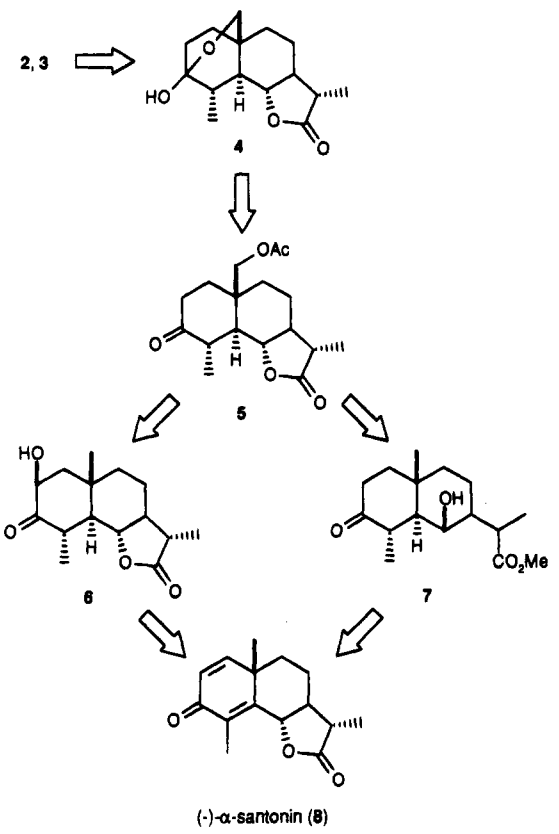
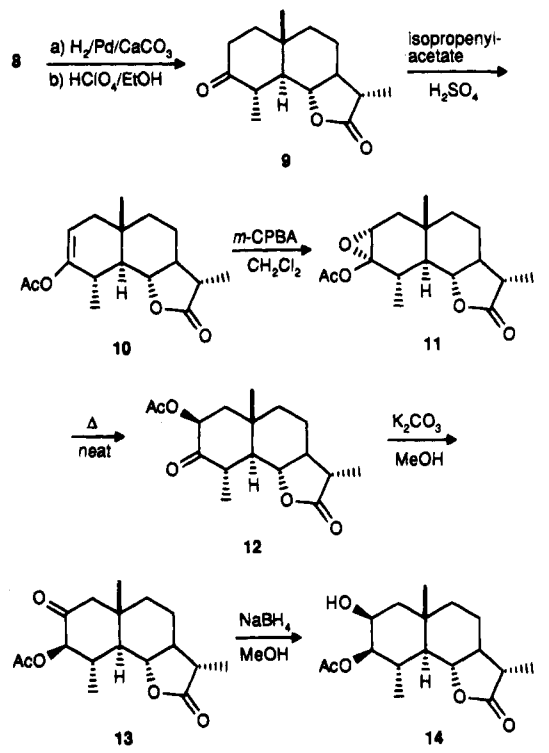


Figure 1. Retrosynthetic plan.

the remote oxidation of inactive carbons atom from alkoxy radicals the stereochemical disposition of the participating groups is of crucial importance.[10] In our case this can be done by alkoxy radicals generated from alcohol at C-2β or C-6β such as compound **6** or **7**. The same keto acetate **5** could be obtained from both compounds. Finally, regioselective carbon–carbon β-fragmentation of the alkoxy radical generated from hemiacetal **4** would give us an immediate precursor of (+)-(8)-deoxyvernolepin (**2**). In this approach the *cis*-fused δ-valerolactone AB-ring and the angular methyl group were prepared, in very high yield, in one step. This methodology is based on that recently developed in our laboratory for intramolecular hydrogen abstraction[11] to functionalize nonactivated angular methyl groups and the regioselective β-fragmentation of hemiacetals,[12] e.g., **4**.

Hydrogenation of (−)-α-santonin (**8**) in neutral medium led to the predominant formation of *trans* A/B ring-junction isomers in the presence of palladium catalysts[8] (Scheme 1). The fused A/B *trans* 4α-tetrahydrosantonin

Scheme 1



(**9**) is separated from the *cis* minor isomer by fractional crystallization after acid or basic isomerization of the mixture reaction, although in low to moderate yields. We explored different commercially available palladium catalysts, in particular Pd/$CaCO_3$, as well as reaction conditions, but the results were not reproducible, and poor to moderate yields were obtained.[13]

We decided to prepare 5% Pd/$CaCO_3$ following a procedure analogous to that previously described for the preparation of Pd/$BaCO_3$.[14] We observed that the catalyst prepared under nonreductive conditions (brown powder) showed a greater selectivity in the A/B *trans* hydrogenation of α-santonin than that obtained by pre-reduction with formaldehyde (black powder). With the first catalyst, pure compound **9** could be obtained after perchloric acid isomerization,[8j] chromatography, and a single crystallization in 75% overall yield from a 92:8 A/B *trans*:*cis* mixture reaction. On the other hand, with the second catalyst the ratio A/B *trans*:*cis* was never higher than 78:22 (^{1}H NMR analysis) and a fractional crystallization was necessary.

With α-tetrahydrosantonin (**9**) at hand, we focused our attention on its conversion to the product **5**. Compound **9** treated under thermodynamically controlled conditions with isopropenyl acetate and H_2SO_4 under argon at reflux for 3.5 h gave the enol acetate **10** in quantitative yield. Epoxidation of **10** in $CHCl_3$ at 0 °C with 2 equiv of *m*-CPBA for 48 h, provided a 93% yield of the 2α,3α-epoxy acetate **11**, which by heating[7,15] at 160 °C under argon for 5 min, rearranged to the product **12**[16] in quantitative yield, while if the heating was performed in benzene at

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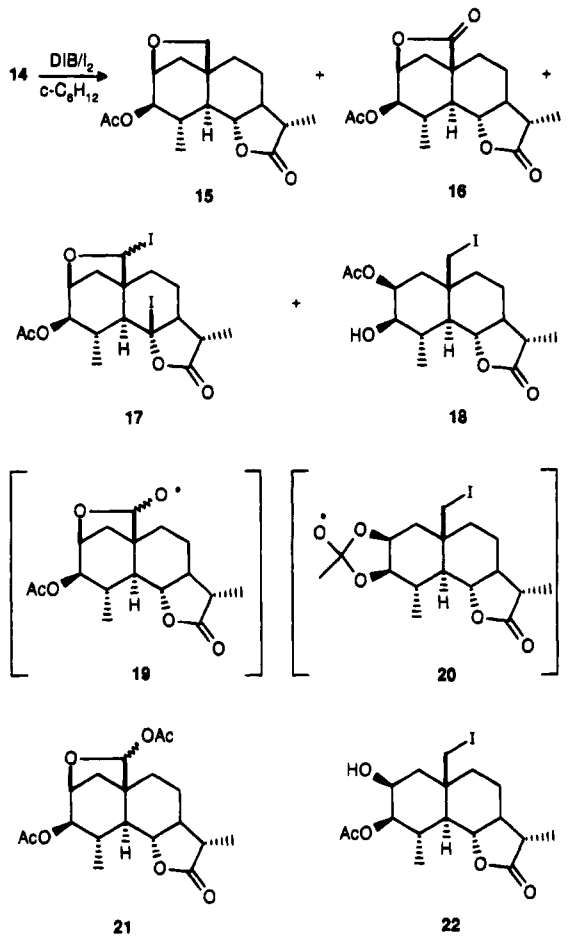
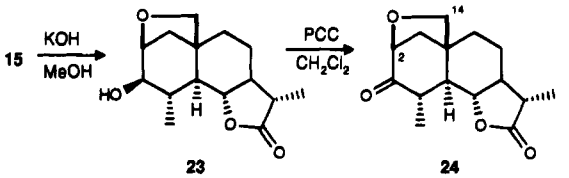
Scheme 2



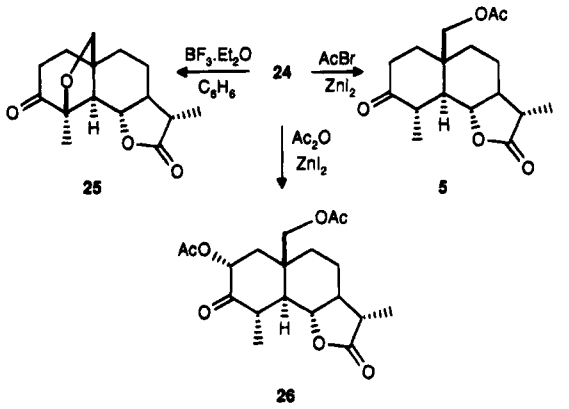
120 °C for 6 h, **12** was obtained only in 80% yield. When 3-oxo 2β-acetate **12** was treated with 5 equiv of K_2CO_3 in 2-propanol at rt for 11 h, the rearranged product 2-oxo 3β-acetate **13** was obtained in 76% yield by 1,2-carbonyl transposition.[17] **13** was reduced with sodium borohydride (1.6 equiv) in methanol[18] at rt for 5 min to give the hydroxy acetate **14** in 87% yield, which bears the axial hydroxyl function at the C-2 position.

Irradiation of the hydroxy acetate **14**, in cyclohexane in the presence of (diacetoxyiodo)benzene (DIB) (1.5 equiv) and iodine (0.5 equiv), with two tungsten-filament lamps[11] at 40 °C for 10.5 h, gave a mixture of compounds **15**–**18** in moderate overall yield (Scheme 2). Since remote oxidation of angular methyl groups from C-2 axial alcohols in analogous steroidal models gave cyclic ethers and hemiacetals,[10,11b] lactone **16** can be formed by β-fragmentation of an alkoxy radical intermediate such as **19**. Diiodo derivative **17** is probably produced by intramolecular hydrogen abstraction of the C-6β hydrogen from the initially formed C-14 radical[11a,19] and two consecutive hydrogen abstractions at C-14 hydrogens from the C-2 alkoxy radical and subsequent cyclization to the iodotetrahydrofuran group. Iodohydrin **18** can be produced

Scheme 3



Scheme 4



by 1,2-alkoxy radical rearrangement via an orthoacetate radical intermediate such as **20** (Scheme 2).

When the reaction was performed in the presence of diphenylhydroxyselenium acetate[20] as oxidant agent in refluxing cyclohexane for 7 h, the products **15**, **16**, **18**, hemiacetal acetate **21**, and iodohydrin **22** were obtained in 50, 9, 4, 9, and 8% yield, respectively. When the crude reaction mixture reaction was treated with 0.8 equiv of silver acetate in acetone, in the dark at rt for 70 h, the ether **15** was obtained in acceptable yield (58%). Gratifyingly, compound **15** was obtained in 84% yield when the reaction was run at reflux with 2.5 equiv of mercuric oxide and 2 equiv of iodine.

Next, our attention was turned to the cleavage of the 2,14-oxolane ring in the ketone derivative **24**, which was obtained from **15** by treatment with 5% methanolic KOH and subsequent oxidation of the resulting alcohol **23** with pyridinium chlorochromate[21] in CH_2Cl_2, in 75% overall yield (Scheme 3). Many attempts were made to bring about cleavage of the tetrahydrofuran ring. When compound **24** in benzene was treated with $BF_3{\cdot}Et_2O$ or triflic anhydride, the rearranged 4β,14-oxolane **25** was obtained in quantitative yield, while treatment with acetic anhydride–ZnI_2[22] gave the diacetate **26** in excellent yield (Scheme 4). When the compound **24** in CH_2Cl_2 was treated with acetyl bromide–ZnI_2, the keto acetate **5** was produced in 63% yield. Many attempts were made to improve this yield, but they were unsuccessful. Compound **25**, is presumably formed by C-2 cation rearrangement to the more stable C-4 position, via enolic ketone isomerization and cyclization, while diacetate **26** is obtained by nucleophilic acetate cleavage of the tetrahydrofuran ring assisted by the ZnI_2-activated oxygen atom.

Concerned with the overall length of this sequence, we devised a more efficient scheme for the conversion of **8** to **5**. This second route involves the use of β-tetrahydrosantonin **27** as starting material, which was also

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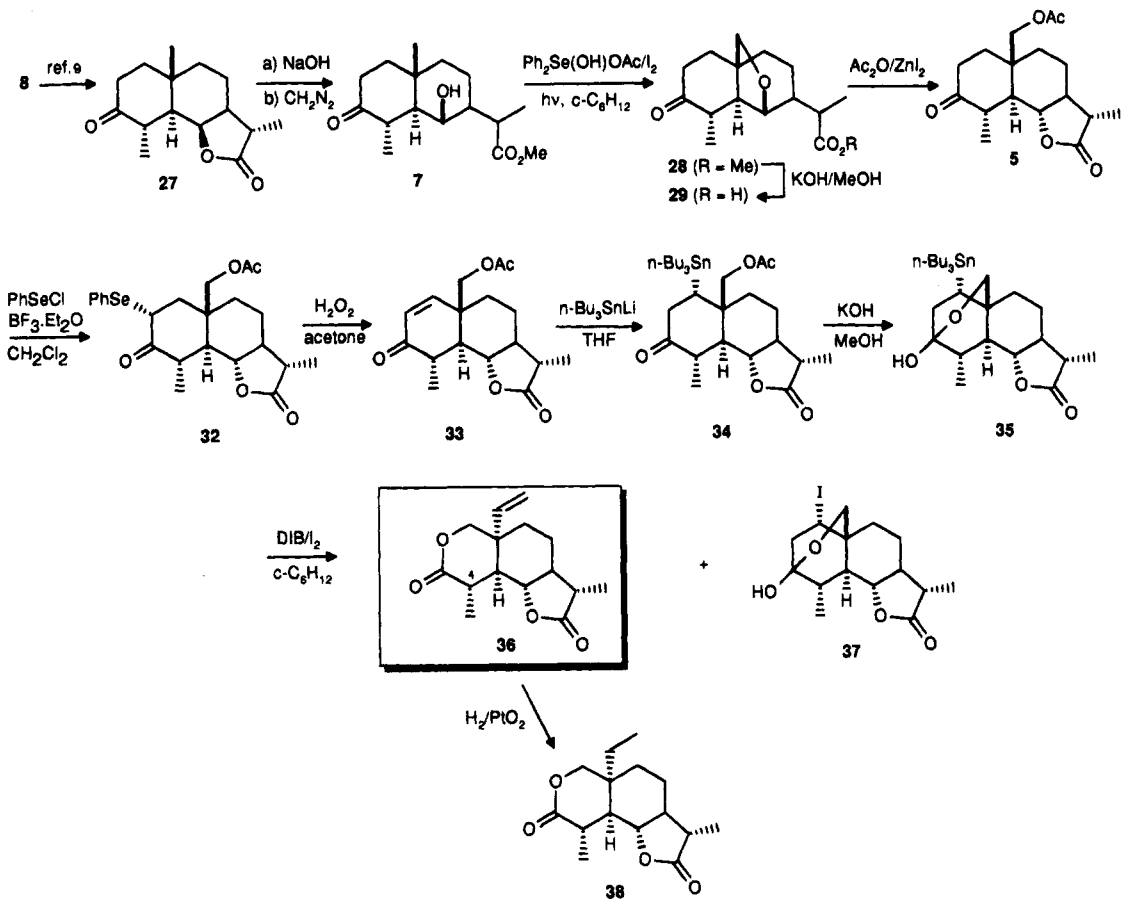
Scheme 5

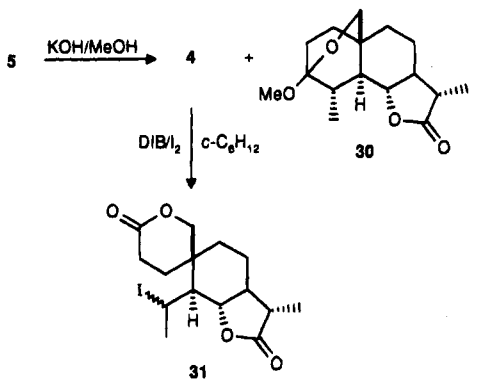


prepared from α-santonin (**8**) by the known two-step procedure,[9] involving C-6 epimerization on α-santonin with HCl–DMF followed by hydrogenation in ethyl acetate using 10% Pd/C and subsequent $HClO_4$–EtOH C-4 isomerization (Scheme 5). Base-catalyzed cleavage of the lactone moiety of compound **27** in refluxing 3% aqueous NaOH for 1 h, followed by CH_2Cl_2 addition and careful neutralization with 5% aqueous HCl of the ice bath precooled reaction mixture and further treatment of the organic phase with etheral diazomethane provided the hydroxy ester **7** in 61% overall yield from **27**. Irradiation of the 6β-hydroxy compound **7** in cyclohexane in the presence of DIB (1.5 equiv) and iodine (1 equiv)[11] with tungsten-filament lamps produced the epoxy ester **28** in 65% yield. If the reaction was performed in refluxing cyclohexane and diphenylhydroxyselenium acetate[20] as oxidant agent, compound **28** was obtained in improved yield (84%). An analogous 6,14-oxolane has been obtained as byproduct in the synthesis of rishitin using the Barton nitrite protocol to generate the alkoxy radical in 5% yield.[7h]

The regioselective cleavage of the tetrahydrofuran ring of product **28** occurred smoothly and cleanly by treatment with acetic anhydride containing 1.6 equiv of ZnI_2, being accompanied by simultaneous C-6 inversion configuration by carboxylic acid-assisted lactonization to give **5** as sole product (Scheme 5). In a similar way, the epoxy acid **29** obtained by hydrolysis of the methyl ester function of compound **28** gave the product **5** in 84% overall yield.

With the keto acetate **5** at hand, we envisaged the last stage of the tetrahydrovernolepin synthesis as arising from β-fragmentation of a hemiacetal intermediate such as **4** (Figure 1), providing that the β-fragmentation regioselectivity could be controled. This is necessary because, when hemiacetal **4**, obtained in 87% yield by hydrolysis of the acetyl group of **5** with 4% KOH in MeOH, together with the methyl acetal **30** (5%) (Scheme 6), was irradiated in the presence of DIB/I_2 as described previously, the iodo spirolactone **31** was obtained in high yield as a C-4 epimeric mixture (1:1, ^1H and ^{13}C NMR analysis). As expected, the cleavage occurs exclusively by the C_3–C_4 bond and no compounds arising from the required C_2–C_3 bond cleavage were detected. We therefore proceeded as follows (Scheme 5): α-phenylselenylation of the ketone **5** with phenylselenium chloride in the

Scheme 6



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presence of boron trifluoride etherate,[23] followed by oxidative deselenylation[24] with 30% H_2O_2 of the intermediate seleno derivative **32**, gave the enone **33** in 80% overall yield. In THF at −78 °C **33** was treated with 4 equiv of freshly prepared lithium *n*-tributyltin,[25] from hexabutylditin and metallic lithium,[26] and afforded the corresponding C-1 stannane derivative **34** in 87% yield. Hydrolysis of the acetyl group and oxidative 1,4-fragmentation[27] by irradiation of the resulting hemiacetal **35** in cyclohexane in the presence of DIB/I_2 under Ar at 40−42 °C for 35 min, as described above, gave the expected δ-valerolactone **36** and the iodine derivative **37** in 70 and 19% yield, respectively. Since the substitution of the tributyltin group by iodine is a radical process that is inhibited by oxygen,[28] when the aforementioned reaction was performed while a stream of oxygen was bubbled through the reaction mixture, compound **36** was obtained in quantitative yield. As observed, complete inversion in the fragmentation regioselectivity was achieved.

Previous authors[5] have assigned a 4β-equatorial stereochemistry for the secondary methyl group on the δ-valerolactone ring of compound **36** on the basis of a hypothetically greater stability than that of its 4α-axial epimer. However, we have found, using molecular mechanics calculations, that the δ-valerolactone ring in compound **36** adopts a half-chair form as a minimum energy conformation, with the alkyl−oxygen bond, the carbonyl group, and the C-4 atom almost in the same plane.[29] Compound **36** is ca. 2 kcal/mol more stable than its 4β-isomer. On this basis and after a careful study of the ^{1}H NMR spectrum we have assigned a 4α-axial stereochemistry to this methyl group. Thus, the observed coupling constant (5.0 Hz) between 4β-H and 5α-H is in good agreement with the calculated one over a minimized structure using the program PCMODEL (4.71 Hz), while the calculated constant for the coupling 4α-H and 5α-H in the epimeric 4β-equatorial methyl group would be 7.85 Hz. The simulated shape of the 4-proton signal using these constants is also in accord with the spectroscopic data obtained.

Conversion of (+)-8-deoxytetrahydrovernolepin (**36**) into (+)-8-deoxyvernolepin (**2**) has been previously reported[5] and therefore the present sequence constitutes the formal synthesis of the title compound. This methodology also permits access to other A/B ring analogues of vernolepin if an additional hydroxyl function is incorporated at the C-8 position, a process that is now in progress.

Hydrogenation of the methylene group on compound **36** in the presence of PtO_2 gave the dihydro derivative **38**, that presumably can be transformed into dihydro-(+)-8-deoxyvernolepin (**3**) in a similar manner to (+)-8-deoxyvernolepin.

In conclusion, the presented methodology permits us to elaborate in one step, smoothly, and in high yield, the 2-oxa-*cis*-decalin unit and the angular vinyl group of vernolepin congeners.

Experimental Section

General. Melting points were determined with a Mettler FP82 hot-stage apparatus and are uncorrected. Optical rotation measurements were recorded at room temperature in $CHCl_3$ on a Perkin-Elmer 141 or 142 polarimeter. IR spectra were recorded on a Perkin-Elmer 1605/FTIR spectrometer in $CHCl_3$ solutions. UV spectra were obtained with a Perkin-Elmer 550SE spectrometer. ^{1}H NMR spectra (δ) were determined with a Bruker WP200SY (200 MHz) or AMX 400 (400 MHz) spectrometer while ^{13}C NMR spectra were recorded with a Bruker WP 200 SY (50.3 MHz) spectrometer with Me_4Si as internal standard. Low-resolution mass spectra were determined with a Hewlett-Packard 5930A or VG Micromass ZAB-2F spectrometer and high-resolution mass spectra on a VG Micromass ZAB-2F spectrometer. Merck silica gel 60 PF_{254} and 60 (0.063−0.2 mm) were used for preparative thin-layer chromatography (TLC) and column chromatography, respectively. Circular layers of 1 mm of Merck silica gel 60 PF_{254} were used as on a Harrison Chromatotron for centrifugally assisted chromatography. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use.[30] All reactions involving air- or moisture-sensitive materials were carried out under an argon atmosphere. The spray reagent for TLC was vanillin (1 g) in H_2SO_4−EtOH (4:1; 200 mL). (Diacetoxyiodo)benzene (DIB) 98% and (−)-α-santonin were purchased from Aldrich. Most selenium and tin compounds are toxic; all operations in this work have been conducted in a well ventilated hood.

3-Oxo-5αH,4,6,11βH-eudesman-12,6-olide (9). To a solution of (−)-α-santonin (**8**) (5 g, 20.3 mmol) in EtOAc (350 mL) was added freshly prepared 5% Pd/$CaCO_3$ catalyst (2.2 g) and the degassed mixture was stirred under hydrogen, at 50 °C and atmospheric pressure, for 3 h. The reaction mixture was cooled to rt and filtered through Celite 454 (Koch-Light) packing in a short column, and the solvent was evaporated under vacuum. The oily residue (5.6 g) in EtOH (350 mL) and 70% perchloric acid (0.35 mL) was heated at 80 °C for 1 h. The reaction mixture was cooled, poured into water, and extracted with CH_2Cl_2. The combined extracts were washed with aqueous $NaHCO_3$, water, and dried (Na_2SO_4). The solvent was evaporated and the residue purified by chromatography (hexane−EtOAc, 65:35) and crystallized once from EtOH to give **9** (3.8 g, 75% from **8**): mp 155−157 °C; $[\alpha]_D$ +31° (c = 0.246) (lit.[8] 152−158 °C; $[\alpha]_D$ +28 to +30°); IR 1765, 1700 cm^{-1}; ^{1}H NMR 1.15 (3H, s), 1.17 (3H, d, J = 7.2 Hz), 1.19 (3H, d, J = 6.7 Hz), 3.87 (1H, t, J = 10.2 Hz); ^{13}C NMR 211.46 (s), 179.06 (s), 83.17 (d), 53.61 (d), 52.96 (d), 45.02 (d), 40.75 (t), 40.67 (d), 40.28 (t), 37.35 (t), 36.66 (s), 23.15 (t), 18.43 (q), 13.96 (q), 12.50 (q); MS m/z (rel intensity) 250 (M^+, 36), 235 (5), 206 (2), 177 (11); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1572.

3β-Acetoxy-5αH,4,6,11βH-eudesm-2-en-12,6-olide (10). To a solution of compound **9** (3.65 g, 14.6 mmol) in isopropenyl acetate (20 mL) was added concd H_2SO_4 (0.03 mL). The mixture was then stirred at reflux under argon for 3.5 h. After cooling at rt, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel column chromatography of the residue (hexane−EtOAc, 3:1) gave the title compound **10** (4.22 g, 99%) as a crystalline solid: mp 119−122 °C (from acetone); $[\alpha]_D$ = +46° (c = 0.202); IR 1750, 1675 cm^{-1}; ^{1}H NMR 1.07 (3H, s), 1.20 (3H, d, J = 6.8 Hz), 1.21 (3H, d, J = 6.9 Hz), 2.14 (3H, s), 3.83 (1H, t, J = 10.3 Hz), 5.28 (1H, m); ^{13}C NMR 179.04 (s), 169.24 (s), 150.50 (s), 111.80 (d), 84.21 (d), 52.65 (d), 51.48 (d), 40.70 (d), 40.16 (t), 39.91 (t),

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35.71 (s), 33.82 (d), 23.43 (t), 20.60 (q), 18.81 (q), 16.59 (q), 12.33 (q); MS *m/z* (rel intensity) 292 (M^+, 3), 250 (100), 235 (11), 232 (3), 217 (2), 177 (15); HRMS calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1642.

3β-Acetoxy-2α,3α-epoxy-5αH,4,6,11βH-eudesman-12,6-olide (11). To a solution of compound **10** (0.58 g, 1.98 mmol) in dry $CHCl_3$ (58 mL), over 3–4 Å molecular sieves, was added *m*-CPBA (0.68 g, 3.97 mmol) at 0 °C. The mixture was kept at this temperature for 48 h, poured into water and extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. Chromatrotron chromatography of the residue (hexane–EtOAc, 85:15) gave the title compound **11** (0.57 g, 93%) as a crystalline solid: mp 123–124 °C (from acetone–*n*-hexane); $[\alpha]_D$ = +20° (*c* = 0.208); IR 1760, 1735 cm^{-1}; ^1H NMR 1.19 (3H, d, *J* = 7.2 Hz), 1.21 (3H, s), 1.34 (3H, d, *J* = 6.6 Hz), 2.09 (3H, s), 3.44 (1H, d, *J* = 5.6 Hz), 3.80 (1H, t, *J* = 10.4 Hz); ^{13}C NMR 178.80 (s), 169.20 (s), 85.34 (s), 83.44 (d), 59.45 (d), 52.78 (d), 48.00 (d), 41.16 (t), 40.66 (d), 40.54 (t), 35.14 (s), 32.97 (d), 23.05 (t), 20.92 (q), 20.25 (q), 13.58 (q), 12.30 (q); MS *m/z* (rel intensity) 308 (M^+, 1), 266 (100), 251 (2), 248 (1), 233 (3), 207 (1), 189 (1), 175 (7), 160 (1); HRMS calcd for $C_{17}H_{24}O_5$ 308.1623, found 308.1632.

3-Oxo-2β-acetoxy-5αH,4,6,11βH-eudesman-12,6-olide (12). Neat compound **11** (3.18 g, 10.3 mmol) was heated at 160 °C under argon for 5 min. Silica gel column chromatography of the residue (hexane–EtOAc, 6:4) gave the title compound **12** (3.18 g, 100%): mp 171–173 °C (from acetone–*n*-hexane) (lit.[16] mp 188–190 °C); $[\alpha]_D$ = +133° (*c* = 0.208); IR 1765, 1735, 1720 cm^{-1}; ^1H NMR 0.97 (3H, s), 1.23 (3H, d, *J* = 6.9 Hz), 1.36 (3H, d, *J* = 7.19 Hz), 2.15 (3H, s), 3.81 (1H, t, *J* = 10.3 Hz), 5.49 (1H, dd, *J* = 6.9, 11.3 Hz); ^{13}C NMR 208.81 (s), 178.51 (s), 169.65 (s), 83.44 (d), 70.56 (d), 52.03 (d), 50.12 (d), 45.35 (t), 45.14 (d), 41.05 (t), 40.56 (d), 35.80 (s), 23.13 (t), 20.95 (q), 20.50 (q), 17.92 (q), 12.36 (q); MS *m/z* (rel intensity) 308 (M^+, <1), 266 (68), 248 (2), 233 (2), 220 (2), 193 (6), 175 (2); HRMS calcd for $C_{17}H_{24}O_5$ 308.1623, found 308.1627.

2-Oxo-3β-acetoxy-5αH,4,6,11βH-eudesman-12,6-olide (13). To a solution of compound **12** (110 mg, 0.35 mmol) in 2-propanol (15 mL) was added a solution of potassium carbonate (226 mg, 1.85 mmol) in water (1.25 mL). The mixture was stirred at rt for 11 h, poured into water and extracted with CH_2Cl_2. The extract was washed with dilute hydrochloric acid (5%) and water, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatrotron chromatography of the residue (hexane–EtOAc, 60:40) gave the title compound **13** (84 mg, 76%) as a crystalline solid: mp 200–202 °C (from acetone–*n*-hexane) (lit.[5a] mp 214–216 °C); $[\alpha]_D$ = +139° (*c* = 0.208); IR 1765, 1735, 1720 cm^{-1}; ^1H NMR 0.93 (3H, s), 1.24 (3H, d, *J* = 6.9 Hz), 1.27 (3H, d, *J* = 6.4 Hz), 2.20 (3H, s), 3.89 (1H, t, *J* = 10.3 Hz), 4.82 (1H, d, *J* = 11.3 Hz); ^{13}C NMR 201.35 (s), 178.62 (s), 170.19 (s), 82.18 (d), 81.01 (d), 54.45 (t), 53.18 (d), 52.09 (d), 40.47 (d), 40.42 (t), 40.36 (s), 38.53 (d), 22.75 (t), 20.47 (q), 19.18 (q), 17.76 (q), 12.36 (q); MS *m/z* (rel intensity) 308 (M^+, 1), 266 (100), 251 (4), 248 (23), 233 (5), 220 (10), 175 (16); HRMS calcd for $C_{17}H_{24}O_5$ 308.1623, found 308.1615.

3β-Acetoxy-2β-hydroxy-5αH,4,6,11βH-eudesman-12,6-olide (14). To a solution of compound **13** (65 mg, 0.21 mmol) in methanol (13 mL) was added sodium borohydride (13 mg, 0.34 mmol). The mixture was then stirred at rt for 5 min, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with hydrochloric acid (5%) and water, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane–EtOAc, 6:4) gave the compound **14** (57 mg, 87%): mp 137–140 °C (from acetone–*n*-hexane) (lit.[5a] mp 158–169 °C); $[\alpha]_D$ = +69° (*c* = 0.220); IR 3595, 1760 cm^{-1}; ^1H NMR 1.04 (3H, d, *J* = 6.6 Hz), 1.17 (3H, d, *J* = 5.7 Hz), 1.18 (3H, s), 2.11 (3H, s), 3.94 (1H, t, *J* = 10.1 Hz), 4.08 (1H, m), 4.53 (1H, dd, *J* = 3.4, 10.9 Hz); ^{13}C NMR 179.32 (s), 170.32 (s), 82.29 (d), 79.41 (d), 67.80 (d), 53.53 (d), 53.12 (d), 45.18 (t), 40.67 (t), 40.47 (d), 36.47 (s), 30.70 (d), 22.39 (t), 20.92 (q), 20.70 (q), 15.59 (q), 12.29 (q); MS *m/z* (rel intensity) 310 (M^+, 1), 268 (1), 250 (44), 235 (100), 232 (2), 222 (2), 217 (4), 207 (4); HRMS calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1793.

Photolysis of 3β-Acetoxy-2β-hydroxy-5αH,4,6,11βH-eudesman-12,6-olide (14). Method A. A solution of compound **14** (81 mg, 0.26 mmol) in cyclohexane (20 mL) containing DIB (125 mg, 0.39 mmol) and iodine (32.5 mg, 0.13 mmol) under argon was irradiated with two 80 W tungsten-filament lamps at 40 °C for 10.5 h. The reaction mixture was then poured into aqueous saturated sodium thiosulfate and extracted with CH_2Cl_2, dried, and concentrated. Chromatotron chromatography of the residue (hexane–EtOAc, 3:1) gave 3β-acetoxy-2β,14-epoxy-5αH,4,6,11βH-eudesman-12,6-olide (**15**) (12 mg, 15%), 3β-acetoxy-5αH,4,6,11βH-eudesmane-12,6:14,2β-diolide (**16**) (13 mg, 15.5%), 6,14–diiodo-3β-acetoxy-2β,14-epoxy-5αH,4,11βH-eudesman-12,6-olide (**17**) (7 mg, 5%), and 14–iodo-2β-acetoxy-3β-hydroxy-5αH-4,6,11βH-eudesman-12,6-olide (**18**) (5 mg, 4%). Compound **15**: mp 175–176 °C (from acetone–*n*-hexane) (lit.[5a] mp 189–191 °C); $[\alpha]_D$ +12° (*c* = 0.30); IR 1760, 1720 cm^{-1}; ^1H NMR 1.17 (3H, d, *J* = 6.4 Hz), 1.22 (3H, d, *J* = 6.9 Hz), 2.10 (3H, s), 3.47 (1H, d, *J* = 8.7 Hz), 4.07 (1H, *J* = 8.7 Hz), 3.76 (1H, t, *J* = 10.5 Hz), 4.25 (1H, d, *J* = 6.5 Hz), 4.38 (1H, dd, *J* = 1.3, 9.7 Hz); ^{13}C NMR 178.82 (s), 171.00 (s), 85.07 (d), 80.20 (d), 76.77 (d), 75.01 (t), 51.97 (d), 51.05 (d), 46.11 (s), 42.55 (t), 40.58 (d), 35.60 (d), 34.55 (t), 25.42 (t), 21.14 (q), 17.22 (q), 12.44 (q); MS *m/z* (rel intensity) 308 (M^+, 4), 266 (63), 248 (85), 235 (59), 233 (33), 230 (31), 218 (32), 203 (14), 175 (40), 154 (100); HRMS calcd for $C_{17}H_{24}O_5$ 308.1623, found 308.1627. Compound **16**, crystalline solid: mp 171.5–173.5 °C (from acetone–*n*-hexane); $[\alpha]_D$ = +109° (*c* = 0.20); IR 1775, 1765, 1730 cm^{-1}; ^1H NMR 1.24 (3H, d, *J* = 6.9 Hz), 1.26 (3H, d, *J* = 6.4 Hz), 2.14 (3H, s), 3.89 (1H, t, *J* = 10.6 Hz), 4.56 (1H, dd, *J* = 1.2, 9.6 Hz), 4.70 (1H, dd, *J* = 1.2, 6.7 Hz); ^{13}C NMR 178.60 (s), 177.62 (s), 170.95 (s), 82.70 (d), 76.36 (2 × d), 51.20 (d), 49.09 (d), 45.77 (s), 41.31 (t), 40.35 (d), 36.43 (d), 31.35 (t), 22.90 (t), 20.95 (q), 17.30 (q), 12.47 (q); MS *m/z* (rel intensity) 322 (M^+, 1), 294 (4), 280 (3), 278 (1), 262 (56), 247 (1), 244 (19), 238 (1), 234 (17), 220 (3), 218 (36), 216 (96), 144 (100); HRMS calcd for $C_{17}H_{22}O_6$ 322.1416, found 322.1389. Compound **17**: amorphous; IR 1790, 1730 cm^{-1}; ^1H NMR 1.14 (3H, d, *J* = 6.9 Hz), 1.21 (3H, d, *J* = 7.1 Hz), 2.10 (3H, s), 4.44 (1H, d, *J* = 6.7 Hz), 4.50 (1H, dd, *J* = 10.1, J_w = 0.8 Hz), 5.18 (1H, s); ^{13}C NMR 177.41 (s), 171.23 (s), 114.73 (s), 107.02 (d), 80.44 (d), 79.20 (d), 54.09 (s), 53.98 (d), 50.84 (d), 38.27 (d), 36.48 (t), 31.96 (d), 29.59 (t), 24.19 (t), 21.17 (q), 19.80 (q), 12.59 (q); MS *m/z* (rel intensity) 560 (M^+, <1), 246 (1), 233 (4), 216 (68), 204 (2), 201 (6), 144 (100), 141 (2); HRMS calcd for $C_{17}H_{22}O_5I_2$ 559.9551, found 559.9495. Compound **18**: amorphous; IR 3590, 1765, 1725 cm^{-1}; ^1H NMR 1.18 (3H, d, *J* = 6.9 Hz), 1.23 (3H, d, *J* = 6.2 Hz), 2.08 (3H, s), 3.24 (1H, dd, *J* = 3.9, 10.3 Hz), 3.4 (1H, dd, *J* = 10.1, J_w = 2.0 Hz), 3.96 (1H, dd, *J* = 10.1, J_w = 2.0 Hz), 3.91 (1H, t, *J* = 10.4 Hz), 5.15 (1H, m); ^{13}C NMR 178.65 (s), 170.98 (s), 81.82 (d), 75.69 (d), 71.45 (d), 53.83 (d), 51.13, (d), 40.43 (d), 40.10 (t), 39.06 (s), 38.15 (t), 34.97 (d), 21.61 (q), 21.48 (t), 16.02 (q), 15.48 (t), 12.35 (q); MS *m/z* (rel intensity) 437 (M^+ + 1, 2), 419 (1), 376 (28), 362 (1), 309 (9), 291 (11), 267 (5), 249 (100), 231 (59), 271 (4), 175 (43), 157 (26), 142 (2); HRMS calcd for $C_{17}H_{26}O_5I$ 437.0826, found 437.0861.

Method B. A solution of compound **14** (340 mg, 1.10 mmol) in cyclohexane (68 mL) containing diphenylhydroxyselenium acetate [$Ph_2Se(OH)OAc$] (644 mg, 2.1 mmol) and iodine (136 mg, 0.54 mmol) under argon was irradiated with two 80 W tungsten-filament lamps at reflux for 7 h. Workup as previously described and chromatotron chromatography of the residue (hexane–EtOAc, 6:4) gave compound **15** (170 mg, 50%), compound **16** (32 mg, 9%), compound **18** (19 mg, 4%), 3β,14-diacetoxy-2β,14-epoxy-5αH,4,6,11βH-eudesman-12,6-olide (**21**) (40 mg, 10%) and 14-iodo-2β-hydroxy-3β-acetoxy-5αH,4,6,11βH-eudesman-12,6-olide (**22**) (43 mg, 9%). Compound **21**: amorphous; IR 1772, 1737, 1725 cm^{-1}; ^1H NMR 1.19 (3H, d, *J* = 6.4 Hz), 1.22 (3H, d, *J* = 6.9 Hz), 2.09 (3H, s), 2.09 (3H, s), 3.87 (1H, t, *J* = 10.6 Hz), 4.33 (1H, dd, *J* = 9.2, J_w = 0.7 Hz), 4.45 (1H, d, *J* = 8.0 Hz), 6.23 (1H, s); ^{13}C NMR 178.53 (s), 171.01 (s), 169.89 (s), 96.48 (d), 84.17 (d), 78.91 (d), 77.93 (d), 52.06 (d), 50.60 (d), 49.41 (s), 40.56 (d), 39.09 (t), 35.27 (d), 30.77 (t), 24.34 (t), 21.14 (q), 21.05 (q), 17.34 (q), 12.37 (q); MS *m/z* (rel intensity) 324 ($M^+ - CH_2CO$, 17), 307 (36), 306 (25), 278 (2), 264 (47), 246 (31), 219 (40), 218 (100),

144 (76); HRMS calcd for $C_{17}H_{24}O_6$ 324.1573, found 324.1582. Compound **22**: amorphous; IR 3600, 1772, 1235 cm^{-1}; ^1H NMR 1.08 (3H, d, J = 6.4 Hz), 1.22 (3H, d, J = 6.9 Hz), 2.14 (3H, s), 3.42 (1H, d, J = 9.5 Hz), 3.98 (1H, t, J = 10.6 Hz), 4.12 (1H, m), 4.41 (1H, d, J = 9.5 Hz), 4.57 (1H, dd, J = 3.2, 10.8 Hz); ^{13}C NMR 178.67 (s), 170.12 (s), 81.81 (d), 79.33 (d), 67.60 (d), 53.83 (d), 51.50 (d), 41.41 (t), 40.48 (d), 39.04 (s), 38.75 (t), 31.21 (d), 21.42 (t), 20.94 (q), 16.63 (t), 15.70 (q), 12.34 (q); MS *m/z* (rel intensity) 419 (M^+ − OH, 6), 377 (3), 376 (19), 362 (1), 359 (8), 331 (3), 309 (14), 249 (50), 231 (28), 216 (3), 189 (6), 174 (3), 157 (23), 142 (3); HRMS calcd for $C_{17}H_{24}O_4I$ 419.0721, found 419.0697. The reaction performed with **14** (500 mg, 1.6 mmol), $Ph_2Se(OH)OAc$ (950 mg, 3.07 mmol), and iodine (200 mg, 0.78 mmol) in cyclohexane (100 mL) as above and the residue in acetone (50 mL) was treated with silver acetate (125 mg, 0.75 mmol) at rt for 70 h in the dark. The mixture was filtered through a short Celite packed column and the organic solution evaporated under reduced pressure. Chromatography of the residue gave **15** (287 mg, 58%), **16** (80 mg, 15%), **18** (42 mg, 6%), and **21** (75 mg, 14%).

Method C. Compound **14** (186 mg, 0.6 mmol) in cyclohexane (30 mL) was treated with mercury oxide (263 mg, 1.2 mmol) and iodine (152 mg, 0.6 mmol) and was irradiated at reflux for 8 h. Workup as described previously and chromatotron chromatography (hexane−EtOAc, 1:1) gave compound **15** (152 mg, 84%).

3β-Hydroxy-2β,14-epoxy-5αH,4,6,11βH-eudesman-12,6-olide (23). Compound **15** (1 g, 3.24 mmol) was treated with 5% methanolic KOH (150 mL) and the solution was then stirred at rt for 6 h, poured into water, and extracted with CH_2Cl_2. The extract was washed with dilute hydrochloric acid (5%) and water, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane−EtOAc, 1:1) gave the compound **23** (860 mg, quantitative) as a crystalline solid: mp 133.5−136 °C (from acetone−*n*-hexane); $[\alpha]_D$ = +93° (c = 0.214); IR 3683, 1770 cm^{-1}; ^1H NMR 1.21 (3H, d, J = 6.9 Hz), 1.31 (3H, d, J = 5.9 Hz), 3.05 (1H, dd, J = 8.2, J_w = 1.2 Hz), 3.47, (1H, d, J = 8.6 Hz), 3.73 (1H, t, J = 10.2 Hz), 4.01 (1H, d, J = 8.6 Hz), 4.20 (1H, dd, J = 7.5, J_w = 0.7 Hz); ^{13}C NMR 178.94 (s), 85.39 (d), 79.49 (d), 78.36 (d), 74.81 (t), 51.90 (d), 51.22 (d), 46.14 (s), 42.40 (t), 40.55 (d), 40.01 (d), 34.73 (t), 25.42 (t), 17.69 (q), 12.38 (q); MS *m/z* (rel intensity) 266 (M^+, 34), 248 (16), 238 (6), 233 (2), 222 (9), 218 (18), 193 (23), 165 (20); HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1544.

3-Oxo-2β,14-epoxy-5αH,4,6,11βH-eudesman-12,6-olide (24). To a solution of compound **23** (35 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added pyridinium chlorochromate (42.5 mg, 0.2 mmol). The mixture was stirred at rt for 6 h, poured into water, and extracted with CH_2Cl_2. The organic layer was washed with dilute hydrochloric acid (5%) and water, and concentrated under reduced pressure. Chromatroton chromatography of the residue (hexane−EtOAc, 6:4), gave the title compound **24** (30 mg, 75%) as a crystalline solid: mp 184−185 °C (acetone−*n*-hexane); $[\alpha]_D$ = +139° (c = 0.20) (lit.[7c] mp 184−185.5 °C; $[\alpha]_D$ +131°); IR 1778, 1725 cm^{-1}; ^1H NMR 1.24 (3H, d, J = 6.7 Hz), 1.27 (3H, d, J = 6.4 Hz), 3.66 (1H, d, J = 8.9 Hz), 3.97 (1H, t, J = 10.4 Hz), 4.30 (1H, d, J = 8.9 Hz), 4.31 (1H, d, J = 6.6 Hz); ^{13}C NMR 209.46 (s), 178.41 (s), 84.58 (d), 81.40 (d), 74.68 (t), 53.34 (d), 51.71 (d), 46.45 (s), 44.86 (t), 42.78 (d), 40.61 (d), 33.88 (t), 25.28 (t), 13.03 (q), 12.44 (q); MS *m/z* (rel intensity) 264 (M^+, 54), 236 (24), 222 (1), 218 (3), 205 (1), 192 (19), 162 (14); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1305.

3-Oxo-4β,14-epoxy-5αH,6,11βH-eudesman-12,6-olide (25). To a solution of compound **24** (15 mg, 0.057 mmol) in dry benzene (1.5 mL) was added boron trifluoride etherate (15 μL). The mixture was stirred at reflux for 6.5 h and then was washed with aqueous saturated $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by crystallization from acetone−*n*-hexane to give compound **25** (15 mg, 100%): mp 176−178 °C; $[\alpha]_D$ = −31° (c = 0.20); IR 1780, 1727, 1226 cm^{-1}; ^1H NMR 1.25 (3H, d, J = 6.9 Hz), 1.40 (3H, s), 3.93 (1H, t, J = 10.2 Hz), 3.87, (1H, d, J = 8.7 Hz), 4.06 (1H, dd, J = 8.7 J_w = 2.3 Hz); ^{13}C NMR 208.39 (s), 178.62 (s), 88.16 (s), 78.43 (d), 73.11 (t), 55.30 (d), 50.23 (d), 46.26 (s), 40.44 (d), 38.40 (t), 35.14 (t), 23.20 (t), 30.01 (t), 12.48 (q), 15.84 (q); MS *m/z* (rel intensity) 264 (M^+, 10), 236 (11), 222 (1), 221 (2), 207 (100), 194 (1); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1349. Analogous yield for **25** was obtained when compound **24** in benzene was treated with triflic anhydride (4 equiv) at rt for 24 h.

3-Oxo-2α,14-diacetoxy-5αH,4,6,11βH-eudesman-12,6-olide (26). To a solution of compound **24** (15 mg, 0.057 mmol) in acetic anhydride (2.5 mL) was added ZnI_2 (30 mg, 0.09 mmol). The reaction mixture was stirred at 40 °C for 22 h and then cooled to rt, poured into water, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was concentrated under reduced pressure and the residue purified by crystallization (acetone−*n*-hexane) to give compound **26** (20.8 mg, 100%) as a crystalline solid: mp 200−202 °C (from acetone−*n*-hexane); $[\alpha]_D$ = +43° (c = 0.204); IR 1774, 1738, 1732 cm^{-1}; ^1H NMR 1.19 (3H, d, J = 6.9 Hz), 1.26 (3H, d, J = 6.2 Hz), 2.12 (3H, s), 2.13 (3H, s), 3.95 (1H, t, J = 10.3 Hz), 4.41 (1H, d, J = 12.0 Hz), 4.49 (1H, d, J = 12.0 Hz), 5.33 (1H, dd, J = 6.3, 13.2 Hz); ^{13}C NMR 203.10 (s), 178.07 (s), 170.60 (s), 169.72 (s), 80.76 (d), 72.89 (d), 61.38 (t), 54.15 (d), 52.74 (d), 43.74 (d), 40.45 (t), 40.33 (s), 40.17 (d), 34.29 (t), 22.11 (t), 20.62 (q), 20.47 (q), 12.81 (q), 12.20 (q); MS *m/z* (rel intensity) 367 (M^+ + 1, <1), 324 (100), 306 (7), 282 (54), 264 (15), 251 (12), 246 (4), 233 (9), 209 (40), 173 (8); HRMS calcd for $C_{19}H_{27}O_7$ 367.1771, found 367.1764.

3-Oxo-14-acetoxy-5αH,4,6,11βH-eudesman-12,6-olide (5). To a solution of compound **24** (15 mg, 0.057 mmol) in CH_2Cl_2 (0.3 mL) containing ZnI_2 (17 mg, 0.05 mmol) was added acetyl bromide (0.15 mL) and stirred at rt under argon for 24 h. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane−EtOAc, 6:4) gave the title compound **5** (11 mg, 63%) as a crystalline solid: mp 129.5−130.5 (from acetone−*n*-hexane) (lit.[5a] mp 131−133 °C); $[\alpha]_D$ +16° (c = 0.27); IR 1772, 1731, 1707 cm^{-1}; ^1H NMR 1.22 (3H, d, J = 6.8 Hz), 1.27 (3H, d, J = 6.5 Hz), 2.11 (3H, s), 3.88 (1H, t, J = 10.7 Hz), 4.39 (2H, s); ^{13}C NMR 210.23 (s), 178.48 (s), 170.85 (s), 81.89 (d), 61.43 (t), 53.70 (d), 52.93 (d), 44.76 (d), 40.59 (d), 39.78 (s), 36.90 (t), 34.74 (t), 34.62 (t), 22.83 (t), 20.62 (q), 14.57 (q), 12.43 (q); MS *m/z* (rel intensity) 308 (M^+, 12), 266 (10), 262 (9), 249 (6), 248 (10), 235 (2), 233 (4), 230 (3), 216 (2), 175 (15), 143 (6); HRMS calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1620.

Methyl 3-Oxo-6β-hydroxy-5,6αH,4,11βH-eudesman-12-oate (7). A suspension of lactone **27** (163 mg, 0.65 mmol) in 0.75 N aqueous NaOH (9 mL) was heated at reflux for 1 h. The mixture was cooled at rt, carefully acidified with 10% HCl, and extracted with CH_2Cl_2. The combined extracts were washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue in Et_2O (20 mL) was cooled at 0 °C and treated with an excess of ethereal solution of diazomethane. The excess of diazomethane was destroyed with acetic acid and the mixture concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane−EtOAc, 7:3) furnished the title compound **7** (112.4 mg, 61%) as an amorphous solid; IR 3635, 1710, 1705 cm^{-1}; ^1H NMR 1.01 (3H, d, J = 6.4 Hz), 1.21 (3H, d, J = 6.9 Hz), 1.29 (3H, s), 3.69 (3H, s), 3.73 (1H, m); ^{13}C NMR 213.74 (s), 177.35 (s), 67.71 (d), 53.15 (d), 51.72 (q), 46.23 (d), 42.65 (d), 42.57 (t), 42.08 (d), 40.62 (t), 37.99 (t), 33.26 (s), 20.45 (t), 19.31 (q), 14.97 (q), 10.54 (q); MS *m/z* (rel intensity 282 (M^+, 1), 264 (14), 250 (35), 232 (13), 195 (100), 177 (53); HRMS calcd for $C_{16}H_{26}O_4$ 282.18306, found 282.18260.

Methyl 3-Oxo-6β,14-epoxy-5,6αH,4,11βH-eudesman-12-oate (28). Method A. A solution of compound **7** (28.2 mg, 0.1 mmol) in cyclohexane (8 mL) containing DIB (48.3 mg, 0.15 mmol) and iodine (25.4 mg, 0.1 mmol) was irradiated with two 100 W tungsten-filament lamps at 42−43 °C for 5 h. Workup as previously described and chromatotron chromatography of the residue (hexane−EtOAc, 3:1) gave the title compound **28** (19.4 mg, 69%) as a crystalline solid: mp 57−59 °C (from *n*-hexane); $[\alpha]_D$ = +55° (c = 0.112); IR 1735, 1715 cm^{-1}; ^1H

NMR 0.98 (3H, d, J = 6.4 Hz); 1.11 (3H, d, J = 7.1 Hz), 3.65 (3H, s), 3.68 (1H, dd, J = 9.6, J_w = 1.0 Hz), 3.92 (1H, s), 4.11 (1H, d, J = 9.6 Hz); ^{13}C NMR 212.40 (s), 176.72 (s), 82.30 (d), 72.16 (t), 59.81 (d), 51.48 (q), 44.69 (d), 42.82 (d), 42.55 (d), 42.48 (s), 37.71 (t), 37.27 (t), 31.30 (t), 22.89 (t), 14.85 (q), 11.89 (q); MS *m/z* (rel intensity) 280 (M^+, 69), 262 (5), 248 (15), 220 (12), 193 (12), 151 (100); HRMS calcd for $C_{16}H_{24}O_4$ 280.16715, found 280.16438.

Method B. A solution of compound **7** (113 mg, 0.4 mmol) in cyclohexane (32 mL) containing diphenylhydroxyselenium acetate (254 mg, 0.8 mmol) and iodine (104 mg, 0.8 mmol) was irradiated as above at reflux for 3 h. Workup as previously described and chromatotron chromatography of the residue gave the compound **28** (94 mg, 84%).

3-Oxo-6β,14-epoxy-5,6αH,4,11βH-eudesman-12-oic Acid (29). A solution of methyl ester **28** (19 mg, 0.06 mmol) in MeOH–H_2O (9:1, 5 mL) containing sodium hydroxide (200 mg, 5 mmol) was stirred at rt for 24 h. The mixture was then poured into water, neutralized with 5% HCl, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane–EtOAc, 1:1) furnished the acid **29** (16.4 mg, 91%) as a crystalline solid: mp 128–129 °C (from acetone–*n*-hexane); $[\alpha]_D$ = +53° (c = 0.132); IR 1715, 1710 cm^{-1}; ^{1}H NMR (1.02 (3H, d, J = 6.4 Hz), 1.18 (3H, d, J = 7.1 Hz), 3.94 (1H, dd, J = 8.3, J_w = 1.0 Hz), 4.17 (1H, d, J = 8.3 Hz), 4.10 (1H, s); ^{13}C NMR 212.53 (s), 181.18 (s), 82.38 (d), 72.15 (t), 59.82 (d), 44.16 (d), 42.81 (d), 42.49 (d), 42.49 (s), 37.66 (t), 37.24 (t), 31.25 (t), 22.73 (t), 14.74 (q), 11.90 (q); MS *m/z* (rel intensity) 266 (M^+, 86), 248 (14), 151 (100), 123 (99); HRMS calcd for $C_{15}H_{22}O_4$ 266.15714, found 266.15107.

3-Oxo-14-acetoxy-5αH,4,6,11βH-eudesman-12,6-olide (5). Method A. A solution of compound **28** (40 mg, 0.14 mmol) and ZnI_2 (74 mg, 0.24 mmol) in acetic anhydride (4 mL) was stirred at rt for 96 h. The mixture was then poured into water and extracted with CH_2Cl_2, and the organic layer was washed with aqueous solution of sodium bicarbonate and water, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography (hexane–EtOAc, 65:35) of the residue gave the title compound **5** (44 mg, 100%).

Method B. A solution of compound **29** (16 mg, 0.06 mmol) and ZnI_2 in Ac_2O (2 mL) was treated as above for 48 h to give **5** after chromatotron chromatography (15.5 mg, 84%).

3-Oxo-14-hydroxy-5αH,4,6,11βH-eudesman-12,6-olide (4). A solution of compound **5** (70 mg, 0.22 mmol) in MeOH (10 mL) containing KOH (50 mg, 1.25 mmol) was stirred at rt for 30 min. Workup and chromatotron chromatography (hexane–EtOAc, 6:4) gave compound **4** (53 mg, 88%) and a small amount of methyl acetal **30** (3.3 mg, 5%). Compound **4**: mp 179.8–180.6 °C (from acetone–*n*-hexane) (lit.[5a] mp 183–184 °C); $[\alpha]_D$ = +67° (c = 0.18); IR 3550, 1765 cm^{-1}; ^{1}H NMR 1.13 (3H, d, J = 7.0 Hz), 1.21 (3H, d, J = 6.9 Hz), 2.29 (1H, m), 3.66 (1H, dd, J = 9.2 J_w = 1.3 Hz), 4.19 (1H, dd, J = 9.2, J_w = 3.3 Hz), 3.95 (1H, t, J = 10.7 Hz); ^{13}C NMR 179.35 (s), 97.74 (s), 84.82 (d), 71.09 (t), 51.24 (d), 50.73 (d), 42.04 (d), 40.88 (d), 34.81 (t), 34.08 (s), 32.81 (t), 27.25 (t), 23.47 (t), 17.56 (q), 12.47 (q); MS *m/z* (rel intensity) 266 (M^+, 74), 248 (3), 193 (50), 107 (31); HRMS calcd for $C_{15}H_{22}O_4$ 266.15198, found 266.15355. Compound **30**: mp 119–121 °C (from acetone–*n*-hexane); $[\alpha]_D$ = +48° (c = 0.062); IR 1770 cm^{-1}; ^{1}H NMR 1.05 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 7.0 Hz), 2.35 (1H, m), 3.28 (3H, s), 3.64 (1H, dd, J = 9.2, J_w = 1.2 Hz), 4.17 (1H, dd, J = 9.2, J_w = 3.3 Hz), 3.95 (1H, t, J = 10.6 Hz); ^{13}C NMR 179.37 (s), 99.88 (s), 85.05 (d), 71.08 (t), 51.25 (d), 50.65 (d), 49.04 (q), 41.12 (d), 37.89 (d), 34.73 (t), 34.06 (s), 32.89 (t), 25.52 (t), 23.57 (t), 17.36 (q), 12.57 (q); MS *m/z* (rel intenisty) 280 (M^+, 77), 265 (1), 218 (1), 131 (7); HRMS calcd for $C_{16}H_{24}O_4$ 280.16738, found 280.16668.

Reaction of 3-Oxo-14-hydroxy-5αH,4,6,11βH-eudesman-12,6-olide (4) with DIB–I_2. A solution of hemiacetal **4** (15 mg, 0.056 mmol) in cyclohexane (10 mL) containing DIB (27 mg, 0.084 mmol) and iodine (11.3 mg, 0.044 mmol) under argon was irradiated with two 100 W tungsten-filament lamps at 40–42 °C for 35 min. Workup as previously described and chromatotron chromatography (hexane–EtOAc, 4:6) gave the mixture of the iodide derivatives **31** (22 mg, 99%) (1:1, ^{1}H NMR analysis) as an amorphous solid: IR 1770, 1735 cm^{-1}; ^{1}H NMR 1.26, 1.27 (3H, d, J = 6.8 Hz), 2.12, 1.99 (3H, d, J = 7.3 Hz), 4.01, 3.90 (1H, t, J = 10.7 Hz), 4.16, 4.10 (1H, dd, J = 12.0, J_w = 1.5 Hz), 4.78, 4.29 (1H, d, J = 11.9 Hz), 4.45, 4.58 (1H, q, J = 7.2 Hz); MS *m/z* (rel intensity) 265 (M^+ – I, 100), 247 (15), 219 (35), 163 (9), 111 (9); HRMS calcd for $C_{15}H_{21}O_4$ 265.14407, found 265.14487.

3-Oxo-14-acetoxy-2α-(phenylseleneyl)-5αH,4,6,11βH-eudesman-12,6-olide (32). To a solution of compound **5** (150 mg, 0.48 mmol) in dry THF (45 mL) containing boron trifluoride etherate (1.19 mL) was added dropwise a solution of benzeneselenenyl chloride (170.2 mg, 0.9 mmol) in dry CH_2Cl_2 (2.14 mL) at rt under argon for 20 min. The mixture was then stirred for 20 h, poured into aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography (hexane–EtOAc, 8:2) gave the title compound **32** (215 mg, 96%) as an amorphous solid; IR 1780, 1745, 1715 cm^{-1}; ^{1}H NMR 1.21 (3H, d, J 6.6 Hz), 1.34 (3H, d, J = 6.5 Hz), 2.04 (3H, s), 3.88 (1H, t, J = 10.5 Hz), 4.25 (1H, d, J = 12.2 Hz), 4.26 (1H, dd, J = 12.2, 5.2 Hz), 4.41 (1H, d, J = 12.2 Hz), 7.30 (3H, m), 7.56 (2H, m); ^{13}C NMR 206.45 (s), 178.23 (s), 170.27 (s), 136.19 (s), 134.92 (2 × d), 128.82 (2 × d), 127.68 (d), 81.05 (d), 60.65 (t), 53.64 (d), 52.29 (d), 48.11 (d), 44.72 (d), 43.11 (t), 41.00 (s), 39.99 (d), 33.76 (t), 22.12 (t), 20.18 (q), 14.58 (q), 12.07 (q); MS *m/z* (rel intensity) 464 (M^+, 30), 247 (21), 219 (17), 145 (17); HRMS calcd for $C_{23}H_{28}O_5{}^{80}Se$ 464.11012, found 464.10945.

3-Oxo-14-acetoxy-5αH,4,6,11βH-eudesm-1-en-12,6-olide (33). To a solution of compound **32** (193 mg, 0.41 mmol) in acetone (12 mL) at 0 °C was added dropwise during 15 min a solution of 30% H_2O_2 (0.34 mL) in acetone (2.7 mL). After 5 h, at rt, the reaction mixture was poured into water and extracted with CH_2Cl_2, and the extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane–EtOAc, 7:3) gave the enone **33** (86.2 mg, 68%) as a crystalline solid: mp 110–112 °C (from acetone–*n*-hexane); $[\alpha]_D$ = −76° (c = 0.246); IR 1778, 1737, 1672 cm^{-1}; UV (EtOH, 0.1 cm) λ_{max} 202 nm (ϵ = 8252); ^{1}H NMR 1.21 (3H, d, J = 6.8 Hz), 1.34 (3H, d, J = 6.9 Hz), 2.00 (3H, s), 4.03 (1H, t, J = 10.9 Hz), 4.19 (1H, d, J = 11.4 Hz), 4.36 (1H, d, J = 11.4 Hz), 6.03 (1H, d, J = 10.0 Hz), 6.35 (1H, d, J = 10.0 Hz); ^{13}C NMR 200.05 (s), 178.36 (s), 170.46 (s), 152.99 (d), 129.34 (d), 80.92 (d), 64.87 (t), 52.75 (d), 51.87 (d), 42.20 (d), 41.32 (s), 40.47 (d), 33.27 (t), 22.75 (t), 20.69 (q), 16.06 (q), 12.36 (q); MS *m/z* (rel intensity) 306 (M^+, 10), 246 (13), 234 (100), 159 (34): HRMS calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1506.

3-Oxo-14-acetoxy-5αH,4,6,11βH-1α-(tributylstannyl)-eudesman-12,6-olide (34). To a solution of enone **33** (102 mg, 0.33 mmol) in dry THF (9.5 mL) cooled at −78 °C, under argon, was added dropwise freshly prepared lithium tri-*n*-butyltin (1.32 mmol) in THF (6.1 mL). The mixture was stirred for 6 h, poured into an aqueous solution of sodium bisulfate, and extracted with CH_2Cl_2. The combined extracts were treated with KF in order to eliminate the excess of tin compounds and stirred for 4 h.[31] The mixture was then filtered and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane–EtOAc, 6:4) gave the title compound **34** (172.4 mg, 87%) as an amorphous solid: IR 1775, 1730, 1708 cm^{-1}; ^{1}H NMR 0.89 (9H, t, J = 7.0 Hz), 1.23 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 6.5 Hz), 2.11 (3H, s), 2.87 (1H, dd, J = 7.9, 15.1 Hz), 3.95 (1H, t, J = 10.5 Hz), 4.51 (1H, d, J = 11.9 Hz), 4.39 (1H, d, J = 11.9 Hz; ^{13}C NMR 210.41 (s), 178.42 (s), 170.80 (s), 81.99 (d), 61.61 (t), 53.19 (d), 52.81 (d), 44.88 (d), 43.45 (s), 41.11 (t), 40.45 (d), 36.13 (t), 32.03 (d), 28.88 (3 × t), 27.29 (3 × t), 22.95 (t), 22.77 (q), 14.33 (q), 13.51 (3 × q), 12.34 (q), 10.66 (3 × t); MS *m/z* (rel intensity) 541 (M^+ – Bu, 3), 263 (2), 234 (100) 177 (73), 146 (5); HRMS calcd for $C_{25}H_{41}O_5{}^{120}Sn$ 541.19793, found 541.20093.

3-Oxo-14-hydroxy-5αH,4,6,11βH-1α-(tributylstannyl)-eudesman-12,6-olide (35). A solution of compound **34** (95 mg, 0.16 mmol) in MeOH (10 mL) containing KOH (50 mg,

(31) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

1.25 mmol) was stirred at rt for 30 min. Workup and chromatotron chromatography (hexane–EtOAc, 6:4) furnished the hemiacetal **35** (60.2 mg, 68%) as a crystalline solid: mp 164–166 °C (from acetone–*n*-hexane); $[\alpha]_D = +93°$ ($c = 0.134$); IR 3300, 1765 cm^{-1}; ^1H NMR 0.91 (9H, t, $J = 7$ Hz), 1.15 (3H, d, $J = 6.9$ Hz), 1.24 (3H, d, $J = 6.8$ Hz), 2.30 (1H, dd, $J = 6.9$, 12.0 Hz), 3.65 (1H, dd, $J = 8.9$, $J_w = 1.3$ Hz), 4.33 (1H, d, $J = 8.9$ Hz), 3.94 (1H, t, $J = 10.5$ Hz); ^{13}C NMR 179.19 (s), 97.77 (s), 85.72 (d), 74.60 (t), 50.94 (d), 49.02 (d), 42.86 (d), 40.85 (d), 37.47 (s), 34.94 (t), 34.20 (d), 32.75 (t), 29.19 (3 × t), 27.41 (3 × t), 23.61 (t), 16.91 (q), 13.55 (3 × q), 12.50 (q), 10.08 (3 × t); MS *m/z* (rel intensity) 557 ($M^+ + 1$, 3), 499 (41), 385 (26), 234 (34), 179 (79), 149 (16); HRMS calcd for $C_{27}H_{49}O_4{}^{120}Sn$ 557.26524, found 557.26491.

8-Deoxytetrahydrovernolepin (36). Method A. A solution of hemiacetal **35** (30 mg, 0.05 mmol) in cyclohexane (10 mL) containing DIB (24.1 mg, 0.075 mmol) and iodine (10.2 mg, 0.04 mmol) under argon was irradiated with two 100 W tungsten-filament lamps at 40–42 °C for 35 min. Workup as previously described and chromatotron chromatography of the residue (hexane–EtOAc, 3:1) gave the title compound **36** (10 mg, 70%) and the iodide derivative **37** (4.1 mg, 19%). Compound **36**: mp 127.5–129.4 °C (from acetone–*n*-hexane); $[\alpha]_D = +37°$ ($c = 0.068$) (lit.[5] mp 127–133 °C; lit.[5c] $[\alpha]_D = +47.7°$); IR 1775, 1730, 1635 cm^{-1}; ^1H NMR 1.25 (3H, d, $J = 6.9$ Hz), 1.40 (3H, d, $J = 7.1$ Hz), 2.33 (1H, dq, $J = 12.2$, 6.8 Hz), 2.70 (1H, dq, $J = 7.0$, 5.0 Hz), 4.00 (1H, t, $J = 10.6$ Hz), 4.14 (1H, dd, $J = 11.7$, $J_w = 1.4$ Hz), 4.39 (1H, d, $J = 11.7$ Hz), 5.25 (1H, d, $J = 17.5$ Hz), 5.27 (1H, d, $J = 10.9$ Hz), 5.78 (1H, dd, $J = 10.9$, 17.5 Hz); ^{13}C NMR 178.28 (s), 173.74 (s), 142.25 (d), 115.67 (t), 83.86 (d), 71.65 (t), 48.53 (d), 46.70 (d), 41.88 (s), 41.46 (d), 37.41 (d), 31.83 (t), 23.00 (t), 17.26 (q), 12.58(q); MS *m/z* (rel intensity) 264 (M^+, 2), 235 (7), 107 (37), 93 (77); HRMS calcd for $C_{15}H_{20}O_4$ 264.13609, found 264.13547. Compound **37**: amorphous; IR 3600, 1765 cm^{-1}; ^1H NMR (400 MHz) 1.11 (3H, d, $J = 7.0$ Hz), 1.22 (3H, d, $J = 7.0$ Hz), 2.31 (1H, m), 2.58 (1H, ddd, $J = 5.3$, 15.0, $J_w = 2.4$ Hz), 2.99 (1H, dd, $J = 10.6$, 15.1 Hz), 3.97 (1H, t, $J = 10.6$ Hz), 4.08 (1H, dd, $J = 8.6$ $J_w = 2.4$ Hz), 4.11 (1H, dd, $J = 8.6$, $J_w = 1.2$ Hz), 4.28 (1H, ddd, $J = 10.6$, 5.4, $J_w = 2.6$ Hz); ^{13}C NMR 178.96 (s), 96.6 (s), 84.67 (d), 67.61 (t), 51.10 (d), 49.06 (d), 44.20 (t), 41.66 (d), 40.99 (d), 37.95 (s), 36.06 (d), 35.55 (t), 23.34 (t), 17.50 (q), 12.48 (q); MS *m/z* (rel intensity) 265 (M^+ – I, 100), 244 (32), 234 (12), 191 (14); HRMS calcd for $C_{15}H_{21}O_4$ 265.14382, found 265.14243.

Method B. A solution of hemiacetal **35** (13 mg, 0.023 mmol) in cyclohexane (5 mL) containing DIB (11 mg, 0.034 mmol) and iodine (4.7 mg, 0.018 mmol) was irradiated at 40–42 °C for 35 min as above while a stream of oxygen was bubbled through the reaction mixture. Workup and chromatotron chromatography of the residue gave the title compound **36** as the sole product (6.1 mg, 100%).

Dihydro-8-deoxytetrahydrovernolepin (38). To a solution of compound **36** (8 mg, 0.03 mmol) in EtOH (2 mL) was added PtO_2 (4 mg), and the resulting mixture was stirred under atmospheric hydrogen pressure at rt for 16 h. The catalyst was removed by filtration and the organic phase was concentrated under reduced pressure. Chromatotron chromatography of the residue (hexane–EtOAc, 7:3) gave the title compound **38** (4 mg, 50%) as an amorphous solid; IR 1775, 1732 cm^{-1}; ^1H NMR 0.93 (3H, d, $J = 7.4$ Hz), 1.26 (3H, d, $J = 6.9$ Hz), 1.41 (3H, d, $J = 7.0$ Hz), 2.31 (1H, dq, $J = 12.2$, 6.8 Hz), 2.64 (1H, dq, $J = 7.0$, 5.0 Hz), 3.95 (1H, t, $J = 10.7$ Hz), 4.02 (1H, dd, $J = 11.6$, $J_w = 1.5$ Hz), 4.24 (1H, d, $J = 11.6$ Hz); ^{13}C NMR 170.55 (s), 169.67 (s), 84.79 (d), 70.45 (t), 53.40 (t), 48.85 (d), 48.68 (d), 41.50 (d), 38.59 (s), 37.62 (d), 31.33 (t), 29.69 (q), 23.09 (t), 18.33 (q), 12.60 (q); MS *m/z* (rel intensity) 266 (M^+, 8), 236 (7), 209 (3), 193 (38), 150 (100); HRMS calcd for $C_{15}H_{22}O_4$ 266.1519, found 266.1533.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of compounds **7**, **10**, **11**, **16–18**, **21–23**, **25**, **26**, **28–30**, and **32–37**, and ^1H NMR spectrum of compounds **38** (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.