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Synthesis of Phytuberin. 4-*endo-tet* Acid-Catalyzed Cyclization of α-Hydroxy Epoxides

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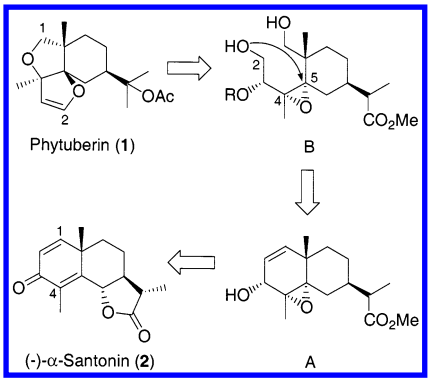
The total synthesis of phytuberin, a phytoalexin of the *Solanum* genus, from (−)-α-santonin is reported. The key steps include (a) reductive cleavage of the C−O bond of the γ-lactone with concomitant protection of the C1 double bond, (b) Sharpless stereocontrolled hydroxy-assisted epoxidation of allylic alcohol **6** and simultaneous deprotection of the C1 double bond, (c) a rare 4-*endo-tet* acid-catalyzed cyclization of an α-hydroxy epoxide, and (d) an unprecedented 4-*exo* selenocyclization of a homoallylic alcohol.

The phytoalexin phytuberin (**1**) is produced by potato tubers and tobacco leaves in response to bacterial and fungal elicitors treatment.[1] Its structure was determined by X-ray crystallographic analysis of its dihydro derivative,[2] and biosynthetic studies directly related this stress metabolite with 2-secoeudesman sesquiterpenes.[3] The antimicrobial activity of phytuberin has been studied in vitro against potato pathogenic and nonpathogenic fungi and bacteria, and only modest antifungal activity was observed.[4] The tetrahydrofuro[3,2-*b*]furan moiety has attracted considerable attention from synthetic chemists, and a number of strategies have been published.[5] All of them started with readily accessible terpenoids such as (−)-carvone,[5a,c,e,f] (−)-2-carone,[5b] and elemol.[5d]

Our own strategy for the synthesis of phytuberin (**1**) from (−)-α-santonine (**2**) is outlined in the retrosynthetic pathway depicted in Scheme 1. The basic approach

SCHEME 1. Retrosynthetic Analysis of Phytuberin



involves reductive cleavage of the C−O of the γ-lactone, selective reduction of the carbonyl group, and stereo- and regiocontrolled hydroxyl-assisted epoxidation of the allylic alcohol to give the intermediate **A**. The intermediate diol **B** may be prepared by ozonolysis of the olefin, after protection of the hydroxyl group at C-3, followed by reductive workup. Intramolecular acid-catalyzed cyclization of the 3,4-hydroxy epoxide (C2−O → C5−O) and subsequent Mitsunobu cyclization of the newly formed C1, C4 diol would be expected to lead to the required hydrofuro[3,2-*b*]furan system. It should be noted that although the intramolecular cyclization of the epoxide implies an, a priori, disfavored 5-*endo-tet* process,[6] many examples of this reaction have been highlighted in the recent literature.[7] No problems are anticipated in the final steps of the sequence, elimination of the 3-hydroxyl group and formation of the hydroxyisopropyl side chain.

Intramolecular opening of an epoxide by an appropriately situated hydroxyl group is one of the most conve-

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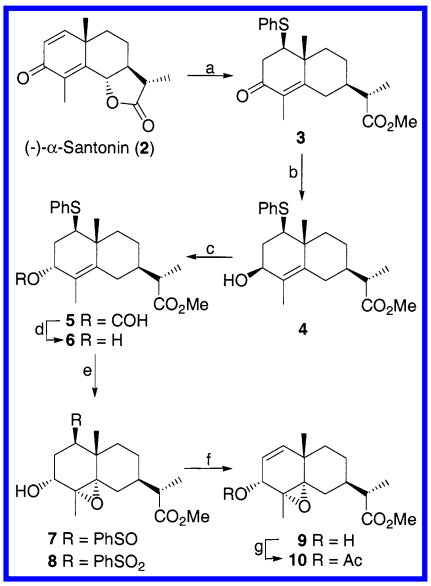
nient methods to build up substituted tetrahydrofuran rings.[8] Nevertheless, this is not an easy process since the reaction may lead to a number of products, depending on the substrate structure and reaction conditions. For example, one of the most studied processes, the opening of γ-hydroxy epoxides, may occur in either an 6-*endo* or 5-*exo-tet* fashion depending on substituents,[9] and the use of an antibody[10] or Co(salen) complex catalysts.[11] The rearrangement of β-hydroxy epoxides may also occur through the two possible 5-*endo*[7] or 4-*exo*[12] cyclization modes. Some examples of cyclization of α-hydroxy epoxides via 3-*exo-tet* (Payne rearrangement) have been described,[13] but the alternative 4-*endo* cyclization mode remains unknown.

Results and Discussion

We chose the commercially available (−)-α-santonin (**2**) as the starting material on the basis of the above-mentioned retrosynthetic analysis. The reaction of **2** with an excess of ethanolic sodium phenoxide afforded, after acid methylation, the phenylsulfanyl derivative **3**, in which apart from the desired cleavage of the lactone ring the protection of the C1 double bond was achieved by Michael addition (Scheme 2).[14] Unfortunately, all attempts to reduce the C3 carbonyl group stereoselectively to the α-alcohol failed, possibly due to the highly sterically hindered β-face of the molecule. Instead, the β-alcohol **4** was obtained by $NaBH_4/CeCl_3$ reduction[15] and subsequently inverted by using a Mitsunobu reaction[16] to give the desired α-alcohol **6** in 82% overall yield.

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) PhSH, Na, EtOH, reflux, 20 h; (ii) CH_2N_2, Et_2O, 68%; (b) $NaBH_4$, $CeCl_3$, MeOH, rt, 15 min, 91%; (c) Ph_3P, HCO_2H, DEAD, THF, 96%; (d) K_2CO_3, MeOH, 0 °C, 15 min, 94%; (e) TBHP, $VO(acac)_3$, PhH, rt, 4 h, 91%; (f) *i*-Pr_2NH, PhH, 120 °C, sealed tube, 20 h, 86%; (g) Ac_2O, Py, rt, 18 h, 94%.

Sharpless stereocontrolled hydroxyl-assisted epoxidation of allylic alcohol **6** with TBHP in the presence of $VO(acac)_3$ as catalyst was achieved concomitantly with sulfide oxidation to furnish the sulfoxide **7**.[17] Under these conditions the yield of overoxidation to the undesired sulfone **8** could be kept to an acceptable level (9%). The required allyl alcohol **9** was produced by pyrolytic *syn*-elimination of the sulfoxide **7** in benzene at 120 °C.[18] It is worth noting that the necessary protection−deprotection of the C1 double bond has been performed in a convenient manner by taking advantage of other reactions of the synthetic protocol.

Acetylation of alcohol **9** followed by ozonolysis under reductive workup afforded diol **11** (Scheme 3). After considerable experimentation, we found that the acid-catalyzed cyclization of the hydroxy epoxide **11** was best performed by treatment with methanesulfonic acid at 0

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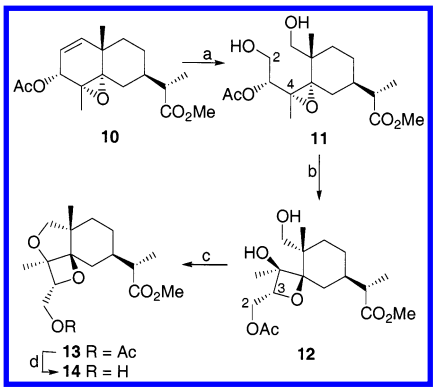
SCHEME 3[a]

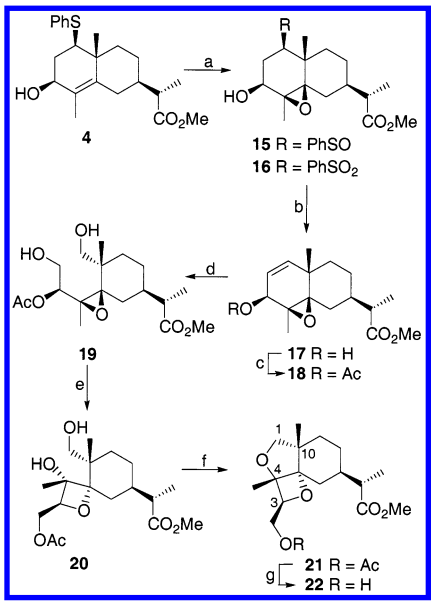


[a] Reagents and conditions: (a) (i) O_3, Me_2S, CH_2Cl_2−MeOH (1:1), −78 °C, 20 min; (ii) $NaBH_4$, −78 °C to rt, 1.5 h, 81%; (b) MsOH, CH_2Cl_2, 0 °C, 1 h, 53%; (c) Ph_3P, DEAD, $CHCl_3$, 1 h, 95%; (d) K_2CO_3, MeOH, rt, 15 min, 87%.

°C. After a preliminary ^{1}H NMR study, it became evident that the obtained diol **12** did not have the required tetrahydofuran structure; instead, a rather unexpected spirooxetane had been formed. Since all our attempts at obtaining crystalline material suitable for X-ray analysis were to no avail, we decided to continue with our synthetic plan. Intramolecular cyclization of the diol **12** under Mitsunobu conditions afforded the tetrahydrofuran derivative **13** in excellent yield. Mild hydrolysis with K_2CO_3 in methanol afforded the crystalline alcohol **14**. The structure and stereochemistry of alcohol **14** was determined unambiguously by single-crystal X-ray crystallographic analysis. The reaction seems to proceed through 4-*endo-tet* type ring closure, a hitherto unknown process. On the other hand, the stereochemistry is inverted at the reactive center, while that of C3 and C4 remains unchanged. Evidently, an intramolecular transesterification of the C3 acetate moiety to the primary adjacent alcohol must take place prior to the cyclization stage. When the C3 protective group was changed (e.g. benzyl), to avoid the transesterification reaction and to favor the 5-*exo* rearrangement, the reaction gave unchanged starting material or led to rather complex mixtures if run under more forcing conditions.

To gain insight into the mechanism of the reaction, the 3β-acetoxy β-epoxide **18** was prepared starting from the 3β-hydroxy derivative **4** by following an identical reaction sequence as described for **10** (Scheme 4). Molecular mechanics calculations showed that the steric energy of compound **20** is approximately 2 kcal mol^{-1} more stable than that of the corresponding diastereomer **12**, and no special steric interactions were expected to hinder the reaction.[19] Indeed, under the same acidity conditions, diol **19** rearranged to the isomeric spirooxetane **20**. No other isomers due to different modes of competing cyclization reactions were detected by careful ^{1}H NMR analysis of the reaction mixture. The moderate yield obtained may be due to adventitious intermolecular hydrolysis of the epoxide or other undetermined reactions. Analogously, the diol **20** under intramolecular Mitsunobu cyclization conditions afforded the dioxa-bicyclo[3.2.0]heptane derivative **21**, which was hydrolyzed to alcohol **22**. Structural confirmation of alcohol **22** was accomplished by a combination of the double resonance and NOESY spectra. Notable features of the NOESY spectra are the cross-peaks between the C-3 proton and the C-4 methyl protons and C-1α proton, and between the C-4 methyl protons and the C-10 methyl protons (1,3-pseudodiaxial disposition). An important diagnostic feature emerged when a small yet significant ^4J (W)-coupling of 0.8 Hz between H-1α and the methyl group at C-10 (established by decoupling and COSY correlation) was observed in the ^{1}H NMR spectrum of **22**. A quasiperfect coplanarity among the implicated atoms is observed in a minimized structure of **22**. This long-range coupling was not found in the spectrum of the diastereoisomeric alcohol **14**. These facts strongly support the stereo- and regiochemical arrangement of structure **21**, and since no appreciable amount of other stereoisomers was detected, the rearrangement can be regarded as essentially stereospecific.

SCHEME 4[a]



[a] Reagents and conditions: (a) TBHP, $VO(acac)_3$, PhH, rt, 3 h, 85%; (b) PhH, reflux, 5 h, 93%; (c) Ac_2O, Py, rt, 18 h, 94%; (d) (i) O_3, Me_2S, CH_2Cl_2−MeOH (1:1), −78 °C, 15 min; (ii) $NaBH_4$, −78 °C to rt, 1.5 h, 82%; (e) MsOH, CH_2Cl_2, 0 °C, 30 min, 46%; (f) Ph_3P, DEAD, $CHCl_3$, rt, 15 min, 91%; (g) K_2CO_3, MeOH, rt, 15 min, 85%.

Although we have been unsuccessful in obtaining the hydrofuro[3,2-*b*]furan system of phytuberin by the methodology outlined in the introductory section, we believed that oxetane **14** can be transformed into the required system by the three-step ring-expansion reaction described in Scheme 5. This methodology was first tested on the model **14** being aware that the 2,3-dihydrofuran moiety is too reactive to be compatible with the modification of the side chain. For the reductive opening of the hydroxy-oxetane **14** we have used our previously reported methodology for the rearrangement of 2,3-epoxy alcohols.[20] Thus, treatment with imidazole, triphenylphosphine, and iodine afforded the homoallyl alcohol **24** in good yield. As expected, the iodine derivative **23** could be isolated as an intermediate formed in the early stage of the reaction,[21] that it is transformed into compound

(19) Molecular mechanics calculation was carried out with CS Chem3D Ultra, version 6.0.

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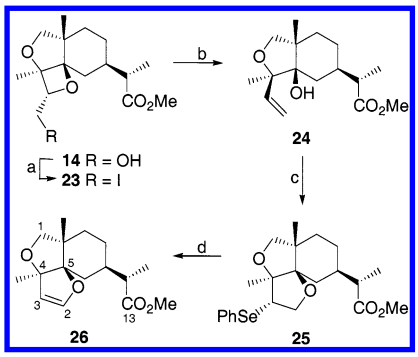
SCHEME 5[a]

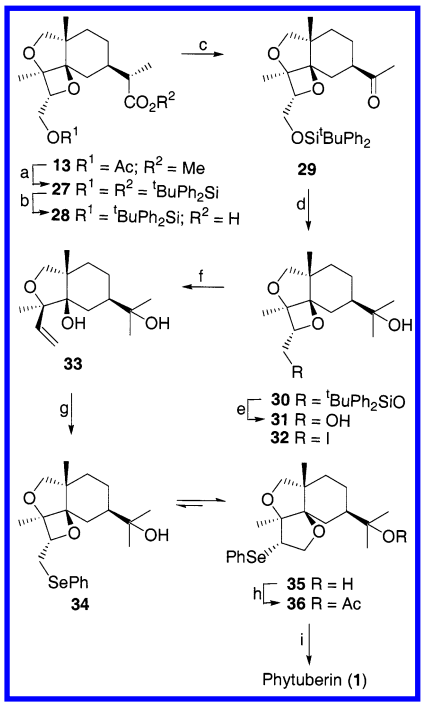


[a] Reagents and conditions: (a) Ph_3P, imidazole, I_2, $PhCH_3$, reflux, 2 h, 97%; (b) Ph_3P, imidazole, I_2, $PhCH_3$, reflux, 4 h, 70%; (c) *N*-(phenylseleno)phthalimide, *p*-TsOH, CH_2Cl_2, rt, 7 h, 75%; (d) (i) O_3, CH_2Cl_2, −78 °C; (ii) Et_3N, cyclohexane, reflux, 30 min, 60%.

24 after a prolonged reaction time. The acid-catalyzed reaction of compound **24** with *N*-(phenylseleno)phthalimide gave the 5-*endo* cyclized compound **25**.[22] Finally, by using organoselenium methodology the aryl selenide afforded the desired olefin **26** by an oxidation−selenoxide elimination sequence. The structure of **26** was confirmed by spectroscopic data, the chemical shift and shape of the signals of the protons at C1, C2, and C3 being identical with those found in the downfield portion of the ^{1}H NMR spectrum of phytuberin.[1a]

Taking into account the impossibility of modifying the side chain when the 2,3-dihydrofuran is present, it was decided to return to oxetane **13**. Hydrolysis to the hydroxy acid and protection of the primary alcohol with TBDPSCl as described in Scheme 6 afforded acid **28**, which was submitted to Barton's oxidative radical decarboxylation.[23] The isomeric mixture of alcohols obtained was oxidized with PCC to give ketone **29**, and subsequent treatment with methylmagnesium bromide afforded alcohol **30**. Desilylation, and reductive opening of the α-hydroxyoxetane as described for compound **14**, gave homoallylic alcohol **33**. As in the case of compound **14**, the iodine **32** is an isolable intermediate of the reaction. The following phenylselenylation reaction deserves a brief comment: when the reaction was stopped immediately after the starting material was consumed (monitored by TLC), the oxetane **34** (51%) was the principal product obtained apart from the expected tetrahydrofuran derivative **35** (22%). Upon prolonged reaction time all oxetane was transformed into the tetrahydrofuran (75%). This also happened when pure oxetane was submitted to the standard reaction conditions. Furthermore, when oxetane **34** was submitted to

SCHEME 6[a]



[a] Reagents and conditions: (a) (i) KOH, MeOH, 40 °C, 23 h; (ii) *t*-$BuPh_2SiCl$, TEA, DMAP, CH_2Cl_2, rt, 2 h 45 min, 95%; (b) KOH, MeOH, rt, 1 h, 82%; (c) (i) $(COCl)_2$, DMF, PhH, rt, 1 h; (ii) *N*-hydroxypyridine-2-thione sodium salt, CH_2Cl_2, rt, 2 h; (iii) $(PhS)_3Sb$, Et_2O, rt, 1.5 h, 72%; (iv) PCC, NaOAc; CH_2Cl_2, rt, 2 h, 79%; (d) MeMgBr, Et_2O, −78 °C, 45 min, 96%; (e) tetrabutylammonium fluoride, THF, rt, 2.5 h, 100%; (f) I_2, Ph_3P, imidazole, 2,6-lutidine, H_2O, PhH, 1,2-dichloroethane, 80 °C, 15 min, 98%; (g) *N*-(phenylseleno)phthalimide, *p*-TsOH, CH_2Cl_2, rt, 6.5 h, 75%; (h) Ac_2O, Py, DMAP, 40 °C, 24 h, 60%; (i) O_3, CH_2Cl_2, −78 °C, then Py, CCl_4, reflux, 1.5 h, 62%.

acidic conditions an equilibrium was reached after 6.5 h and a mixture was obtained containing **34** and **35** in a 3:7 ratio, as established by ^{1}H NMR. The structures and stereochemistries of **34** and **35** were elucidated by extensive NMR studies including COSY, DEPT, HMQC, HMBC, and NOESY experiments. For example, NOESY correlations between H-1β and H-3 and the C-10 methyl group, and between 2H-2 and the C-4 methyl group for compound **34**, and between H-1β and H-2β and the C-10 methyl group for compound **35** were clearly observable. These facts seem to indicate that the kinetic oxetane, formed by a 4-*exo* pathway, rearranges to the thermodynamic 5-*endo* tetrahydrofurane ring through regioselective nucleophilic *anti*-opening of the same seleniranium cation intermediate originated by attack at the *Si* face of the double bond. As far as we know, no examples of 4-*exo* processes in the selenocyclization reaction of homoallylic alcohols have been reported until now. An analogous equilibrium between 5-*exo* and 6-*endo*-*tet* cyclizations in 3-hydroxy seleniranium ions shifted toward the formations of tetrahydropyrans has been observed.[24]

At this stage, acetylation of the tertiary hydroxyl group to give **36** and oxidation to the selenoxide followed by thermal *syn*-elimination afforded phytuberin (**1**), identical with an authentic sample obtained by infection of potato tubers with *Erwinia carotovora* var. *carotovora*.

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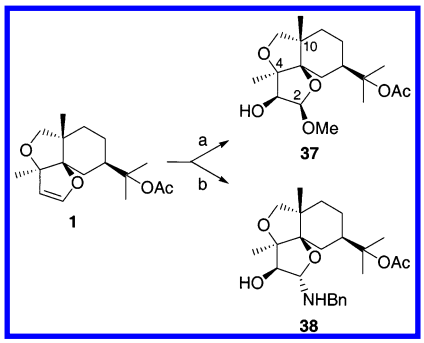
(22) For reviews see: (a)*Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: NewYork, 1987. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, UK, 1986. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, PA, 1984. For 5-*endo* cyclization of homoallylic alcohols with organoselenium reagents see: (d) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084−1086. (e) Fragale, G.; Wirth, T. *Eur. J. Org. Chem.* **1998**, 1361−1369.

(23) (a) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1989**, *45*, 2615−2626. (b) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1066−1068. For the preparation of $(PhS)_3Sb$ see: (c) Bielig, H.-J.; Lützel, G.; Reidies, A. *Chem. Ber.* **1956**, *89*, 775−790.

SCHEME 7[a]



[a] Reagents and conditions: (a) dimethyldioxirane, CH_2Cl_2, −17 °C, 30 min, then MeOH, 1 h, 46%; (b) dimethyldioxirane, CH_2Cl_2, −17 °C, 30 min, then $BnNH_2$, 23 h, 53%.

Due to its low antifungal activity it seems unlikely that phytuberin itself has any relevance to the resistance of solanum plants to fungal infection.[4] We considered the possibility that the hitherto unknown 2,3-epoxy-phytuberin could be the active principle in a manner similar to that described in the aflatoxin family.[25]

With the small amount of phytuberin available we decided to study the formation of this epoxide and its reactivity under mild hydrolysis conditions. The reactions are outlined in Scheme 7; phytuberin was epoxidized with dimethyldioxirane[26] in acetone and in situ hydrolyzed with an excess of anhydrous methanol or benzylamine to afford compound **37** or **38**, respectively. The apparent lability of the epoxide discouraged us from attempting its isolation.[27] The stereochemistry of compounds **37** and **38** was tentatively assigned exclusively on the basis of NOESY experiments;[28] strong NOEs between the C-3α proton and the C-4 methyl protons are observed in both compounds, while cross-peaks between the C-2β proton and C-1β and the C-10 methyl protons are only observable in the spectrum of **38**. On the other hand, a strong interaction between the C-1β and the methyl protons of the O-Me can be detected in the NOESY spectrum of **37**.

Although the relatively low yields obtained (approximately 40−50%) preclude a stereochemical analysis of the hydrolysis reactions, both compounds **37** and **38** could be formed from the same β-epoxide, through a stabilized oxycarbenium ion intermediate in the first case and by an S_N2 mechanism in the latter.[29]

In conclusion, during the transformation of (−)-α-santonin into phytuberin, following in essence a biomimetic methodology, we have discovered examples of a number of apparently unprecedented processes: The 4-*endo-tet* acid-catalyzed cyclization of α-hydroxy epoxides, the 4-*exo* selenocyclization of a homoallylic alcohol, and the equilibrium between 4-*exo* and 5-*endo* cyclizations that, through a 3-hydroxyseleniranium ion, is observed in the aforementioned seleniocyclization of homoallylic alcohols.

Experimental Section

Methyl (11*S*)-1β-Phenylthio-3-oxo-eudesm-4-en-13-oate (3). To a solution of sodium thiophenoxide (200 mL, 15.9 mmol) prepared from sodium (366 mg, 15.9 mmol) and benzenethiol (15.7 gr, 143.1 mmol) in ethanol (185 mL) was added (−)-α-santonin (**2**) (1 g, 4.07 mmol) and the mixture was stirred under argon at reflux temperature for 20 h. The reaction mixture was then poured into 5% aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in ether (20 mL) and treated at 0 °C with an ethereal solution of diazomethane. After 1 h the solution was evaporated and the residue purified by silica gel column chromatography (hexanes−EtOAc, 9:1) to give compound **3** (1.03 g, 2.77 mmol, 68%) and methyl (11*S*)-3-oxo-eudesma-1,4-dien-13-oate (140 mg, 0.53 mmol, 13%). Compound **3**: R_f 0.28 (hexanes−EtOAc, 8:2); mp 114.5−115.5 °C (from *n*-pentane−acetone); $[\alpha]_D$ −70 (*c* 0.222); IR 1650, 1740 cm^{-1}; UV (EtOH) 249 nm (ϵ 17 224); ^1H NMR (200 MHz) δ 1.19 (3H, d, J = 7.0 Hz), 1.26 (3H, s), 1.74 (3H, s), 3.32 (1H, br t, J = 9.6 Hz), 3.70 (3H, s), 7.26 (3H, m), 7.42 (2H, m); ^{13}C NMR (50.3 MHz) δ 11.0 (CH_3), 14.2 (CH_3), 18.0 (CH_3), 24.7 (CH_2), 32.4 (CH_2), 39.4 (CH_2), 40.9 (CH), 40.9 (C), 41.8 (CH_2), 45.0 (CH), 51.7 (CH_3), 56.7 (CH), 127.6 (CH), 129.3 (2 × CH), 129.6 (C), 132.9 (2 × CH), 134.8 (C), 161.8 (C), 176.1 (C), 197.0 (C); MS *m*/*z* (rel intensity) 372 (M^+, 23), 344 (2), 263 (93), 236 (12), 231 (13), 203 (34), 175 (100); HRMS calcd for $C_{22}H_{28}O_3S$ 372.1759, found 372.1730. Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58; S, 8.61. Found: C, 70.84; H, 7.38; S, 8.49. Methyl (11*S*)-3-oxo-eudesma-1,4-dien-13-oate: oil; IR (CCl_4) 1738, 1664 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (3H, s), 1.22 (3H, d, J = 6.8 Hz), 1.89 (3H, d, J = 0.8 Hz), 2.47 (1H, dddd, J = 7.2, 7.2, 7.2, 7.2 Hz), 2.74 (1H, ddd, J = 13.2, 3.2, 2.0 Hz), 3.72 (3H, s), 6.23 (1H d, J = 9.8 Hz), 6.74 (1H, d, J = 9.6 Hz); ^{13}C NMR (50.3 MHz) δ 10.4 (CH_3), 14.3 (CH_3), 23.4 (CH_3), 24.2 (CH_2), 31.9 (CH_2), 37.8 (CH_2), 40.3 (C), 42.2 (CH), 44.9 (CH), 51.6 (CH_3), 126.3 (CH), 129.3 (C), 156.4 (CH), 159.0 (C), 175.9 (C), 186.2 (C); MS *m*/*z* (rel intensity) 262 (M^+, 45), 247 (5), 230 (19), 215 (6), 175 (100); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1590. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.29.

Methyl (11*S*)-3β-Hydroxy-1β-phenylthio-eudesm-4-en-13-oate (4). To a solution of ester **3** (100 mg, 0.27 mmol) in methanol (6 mL) were added cerium trichloride (100.7 mg, 0.27 mmol) and sodium borohydride (10.3 mg, 0.27 mmol). The mixture was stirred at room temperature for 10 min, diluted with water, and extracted with CH_2Cl_2. The combined organic

(24) For the formation of tetrahydrofurans and tetrahydropyrans by acid-catalyzed cyclization of 3-hydroxy selenides see: (a) Gruttadauria, M.; Noto, R. *Tetrahedron Lett.* **1999**, *40*, 8477−8482. (b) Clive, D. L. J.; Russel, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399−1408. (c) Rouessac, A.; Rouessac, F. *Tetrahedron* **1981**, *37*, 4165−4170. (d) Murata, S.; Suzuki, T. *Tetrahedron Lett.* **1987**, *28*, 4415−4416. (e) Toshimitsu, A.; Aoai, T.; Uemura, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 3021−3026.

(25) (a) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929−7931. (b) For a review on epoxides as DNA-alkylating agents see: Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723−2795.

(26) (a) Murray, R. W.; Jeyaramen, R. *J. Org. Chem.* **1985**, *50*, 2847−2853. (b) Adam, W.; Chen, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800−2830. (c) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(27) When the crude epoxidation residue, obtained by careful elimination of the excess of dimethyldioxirane (DMD) and solvent with dry nitrogen following the standard protocol (ref 25a), was treated with dry methanol, a complex mixture resulted in which we were unable to detect any compound **37**. For previous reports on the intrinsic lability of the 2,6-dioxabicyclo[3.1.0]hexane system prepared by DMD oxidation of 2,3-dihydrofurans see: (a) Timmers, C. M.; Verheijen, J. C.; Marel, A.; Boom, J. H. *Synlett* **1997**, 851−853. (b) Johnson, W. W.; Harris, T. M.; Guengerich, F. P. *J. Am. Chem. Soc.* **1996**, *118*, 8213−8220.

(28) Although the NOESY experimental results support the proposed structures we are aware of their inherent limitations in this type of system when only one stereoisomer is available. Both hydrolysis compounds **37** and **38** should be formed from the theoretically more hindered, but also probably more stable, *endo*-epoxide. A similar situation is observed for the *exo*- and *endo*-epoxides of aflatoxin B_1 (ref 29).

(29) Iyer, R. S.; Coles, B. F.; Raney, K. D.; Thier, R.; Guengerich, F. P.; Harris, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 1603−1609.

extracts were washed with brine, dried, and evaporated. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 8:2) to give ester **4** (92 mg, 0.24 mmol, 91%): R_f 0.20 (hexanes−EtOAc, 8:2); mp 83.5−85 °C (from *n*-pentane); $[\alpha]_D$ −28 (*c* 0.222); IR 3580, 3500−3340, 1720 cm^{-1}; UV (EtOH) 257 nm (ϵ 10 846); ^1H NMR (200 MHz) δ 1.16 (3H, d, J = 6.7 Hz), 1.17 (3H, s), 1.66 (3H, s), 2.98 (1H, dd, J = 13.4, 2.7 Hz), 3.70 (3H, s), 4.03 (1H, m), 7.26 (3H, m), 7.41 (2H, m); ^{13}C NMR (50.3 MHz) δ 14.3 (CH_3), 14.4 (CH_3), 19.4 (CH_3), 25.3 (CH_2), 30.9 (CH_2), 36.8 (CH_2), 39.9 (C), 40.2 (CH_2), 41.6 (CH), 45.3 (CH), 51.6 (CH_3), 56.7 (CH), 71.5 (CH), 126.9 (CH), 128.0 (C), 129.1 (2 × CH), 132.1 (2 × CH), 136.2 (C), 138.2 (C), 176.7 (C); MS *m*/*z* (rel intensity) 374 (M^+, 17), 357 (0.3), 264 (13), 247 (48), 233 (16), 215 (20), 187 (32), 159 (100); HRMS calcd for $C_{22}H_{30}O_3S$ 374.1949, found 374.1932. Anal. Calcd for $C_{22}H_{30}O_3S$: C, 70.55; H, 8.07; S, 8.56. Found: C, 70.64; H, 8.04; S, 8.47.

Methyl (11*S*)-3α-Formyloxy-1*β*-phenylthio-eudesm-4-en-13-oate (5). To a solution of ester **4** (2 g, 5.35 mmol), triphenylphosphine (2.803 g, 10.7 mmol), and formic acid (0.4 mL, 10.7 mmol) in THF (50 mL) was added dropwise a solution of DEAD (1.68 mL, 10.7 mmol) in dry THF (8 mL) at room temperature under argon. After 1 h the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo to give a crude product that was purified by silica gel column chromatography (hexanes−EtOAc, 9:1) to yield ester **5** (2.07 g, 5.15 mmol, 96%): oil; R_f 0.45 (hexanes−EtOAc, 8:2); IR 1715 cm^{-1}; ^1H NMR (200 MHz) δ 1.11 (3H, s), 1.17 (3H, d, J = 7.1 Hz), 1.62 (3H, s), 3.27 (1H, dd, J = 11.1, 5.5 Hz), 3.70 (3H, s), 5.28 (1H, m), 7.31 (5H, m), 8.05 (1H, s); ^{13}C NMR (50.3 MHz) δ 14.1 (CH_3), 16.6 (CH_3), 18.0 (CH_3), 25.1 (CH_2), 30.4 (CH_2), 32.8 (CH_2), 39.5 (C), 39.6 (CH_2), 41.3 (CH), 45.1 (CH), 51.3 (CH_3), 53.9 (CH), 72.2 (CH), 126.5 (CH), 128.9 (2 × CH), 131.0 (2 × CH), 131.8 (C), 136.0 (C), 143.3 (C), 160.5 (C), 176.1 (C); MS *m*/*z* (rel intensity) 402 (M^+, 12), 356 (5), 325 (1), 309 (1), 247 (68), 215 (28), 159 (100); HRMS calcd for $C_{23}H_{30}O_4S$ 402.1927, found 402.1896. Anal. Calcd for $C_{23}H_{30}O_4S$: C, 68.63; H, 7.51; S, 7.96. Found: C, 68.50; H, 7.32; S, 8.09.

Methyl (11*S*)-3α-Hydroxy-1*β*-phenylthio-eudesm-4-en-13-oate (6). To a solution of potassium carbonate (1 g, 7.23 mmol) in methanol (50 mL) was added ester **5** (2 g, 4.98 mmol) and the solution was stirred at 0 °C for 15 min. The reaction mixture was then poured into 10% aqueous HCl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give a crude product that was purified by silica gel column chromatography (hexanes−EtOAc, 8:2), to give ester **6** (1.751 g, 4.68 mmol, 94%): oil; R_f 0.18 (hexanes−EtOAc, 8:2); IR 3590, 3520−3340, 1725 cm^{-1}; ^1H NMR (200 MHz) δ 1.05 (3H, s), 1.12 (3H, d, J = 6.9 Hz), 1.69 (3H, s), 3.35 (1H, dd, J = 9.7, 6.8 Hz), 3.64 (3H, s), 3.85 (1H, m), 7.27 (5H, m); ^{13}C NMR (50.3 MHz) δ 14.1 (CH_3), 17.2 (CH_3), 18.0 (CH_3), 25.2 (CH_2), 30.3 (CH_2), 36.0 (CH_2), 39.6 (C), 39.6 (CH_2), 41.4 (CH), 45.2 (CH), 51.4 (CH_3), 53.3 (CH), 69.9 (CH), 126.1 (CH), 128.9 (2 × CH), 130.5 (2 × CH), 131.9 (C), 136.6 (C), 139.6 (C), 176.5 (C); MS *m*/*z* (rel intensity) 374 (M^+, 28), 357 (1), 264 (94), 249 (34), 177 (100), 159 (75); HRMS calcd for $C_{22}H_{30}O_3S$ 374.1939, found 374.1927. Anal. Calcd for $C_{22}H_{30}O_3S$: C, 70.55; H, 8.07; S, 8.56. Found: C, 70.44; H, 8.08; S, 8.37.

Methyl (11*S*)-4α,5α-Epoxy-3α-hydroxy-1*β*-phenylsulfinyl-eudesman-13-oate (7). To a solution of ester **6** (3.1 g, 8.3 mmol) and vanadyl acetylacetonate (44 mg, 0.166 mmol) in benzene (64 mL) was added dropwise over 30 min *tert*-butyl hydroperoxide (2.55 M in toluene, 19.5 mL, 49.7 mmol). The mixture was stirred at room temperature for 2 h, poured into a 2% aqueous solution of sodium bisulfite, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give a crude product that was purified by column chromatography (hexanes−EtOAc, 1:1 → 3:7) to give sulfoxide **7** (3.07 g, 7.56 mmol, 91%) and sulfone **8** (306 mg, 0.72 mmol, 9%). Compound **7**: R_f 0.10 (hexanes−EtOAc, 4:6); ^1H NMR (200 MHz) δ 1.18 (3H, d, J = 7.1 Hz), 1.32 (3H, s), 1.38 (3H, s), 3.68 (3H, s), 3.89 (1H, m), 7.48 (5H, m); MS *m*/*z* (rel intensity) 280 (M^+ − PhSOH, 15), 263 (6), 247 (8), 234 (14), 186 (26), 147 (38). Anal. Calcd for $C_{22}H_{30}O_5S$: C, 65.00; H, 7.44; S, 7.89. Found: C, 64.93; H, 7.49; S, 7.91. Compound **8**: R_f 0.22 (hexanes−EtOAc, 4:6); IR (CCl_4) 1736 cm^{-1}; ^1H NMR (500 MHz) δ 1.16 (3H, d, J = 7.1 Hz), 1.33 (3H, s), 1.35 (3H, s), 2.38 (1H, dddd, J = 7.0, 7.0, 7.0, 7.0 Hz), 2.69 (1H, ddd, J = 13.5, 2.5, 2.5 Hz), 2.92 (1H, dd, J = 13.7, 3.3 Hz), 3.67 (3H, s), 3.71 (1H, br d, J = 4.9 Hz), 7.47 (3H, m), 7.65 (2H, m); ^{13}C NMR (125.7 MHz) δ 13.9 (CH_3), 16.4 (CH_3), 17.6 (CH_3), 24.3 (CH_2), 24.3 (CH_2), 29.0 (CH_2), 34.9 (CH_2), 37.6 (CH), 38.0 (C), 44.5 (CH), 51.4 (CH_3), 65.5 (C), 65.8 (CH), 67.5 (CH), 72.9 (C), 126.1 (2 × CH), 129.1 (2 × CH), 131.7 (CH), 142.5 (C), 175.8 (C); MS *m*/*z* (rel intensity) 407 (M^+ − Me, <1), 375 (4), 347 (5), 281 (69), 263 (28), 237 (46); HRMS calcd for $C_{21}H_{27}O_6S$ 407.1428, found 407.11613. Anal. Calcd for $C_{22}H_{30}O_6S$: C, 62.54; H, 7.16; S, 7.59. Found: C, 62.67; H, 7.32; S, 7.58.

Methyl (11*S*)-4α,5α-Epoxy-3α-hydroxy-eudesm-1-en-13-oate (9). To a solution of ester **7** (4 g, 9.85 mmol) in benzene (100 mL) was added diisopropylamine (1.7 mL, 12.3 mmol) in a heavy wall hydrolysis tube with a high vacuum Teflon valve. The tube was immersed in a preheated silicon oil bath at 120 °C for 20 h. After this time the reaction mixture was poured into water and the organic layer was successively washed with 10% aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated in vacuo to give a crude product that was purified by column chromatography (hexanes−EtOAc, 6:4) to give ester **9** (2.37 g, 8.46 mmol, 86%): oil; R_f 0.40 (hexanes−EtOAc, 1:1); IR 3560, 3520−3200, 1720 cm^{-1}; ^1H NMR (500 MHz) δ 1.00 (3H, s), 1.15 (3H, d, J = 7.1 Hz), 1.50 (3H, s), 2.42 (1H, dddd, J = 6.4, 6.4, 6.4, 6.4 Hz), 3.67 (3H, s), 4.13 (1H, br s), 5.26 (1H, dd, J = 10.3, 1.7 Hz), 5.35 (1H, dd, J = 10.3, 1.6 Hz); ^{13}C NMR (100.6 MHz) δ 13.8 (CH_3), 14.7 (CH_3), 23.1 (CH_3), 24.0 (CH_2), 28.7 (CH_2), 34.0 (CH_2), 36.0 (C), 38.2 (CH), 44.5 (CH), 51.4 (CH_3), 66.4 (C), 68.8 (C), 69.5 (CH), 123.8 (CH), 135.9 (CH), 176.0 (C); MS *m*/*z* (rel intensity) 280 (M^+, 2), 265 (13), 237 (13), 219 (11), 205 (41); HRMS calcd for $C_{16}H_{24}O_4$ 280.1674, found 280.1650. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.65. Found: C, 68.34; H, 8.48.

Methyl (11*S*)-3α-Acetoxy-4α,5α-epoxy-eudesm-1-en-13-oate (10). To a solution of ester **9** (200 mg, 0.714 mmol) in pyridine (3 mL) was added acetic anhydride (1 mL, 10.61 mmol) and the reaction mixture was stirred at room temperature overnight. The solution was then poured into 10% aqueous HCl solution and extracted with EtOAc. The organic extracts were washed with $NaCO_3H$ and brine, dried over Na_2SO_4, and evaporated in vacuo. The reaction crude was purified by Chromatotron chromatography (hexanes−EtOAc, 8:2) to give ester **10** (216 mg, 0.67 mmol, 94%): R_f 0.33 (hexanes−EtOAc, 8:2); mp 76.5−77.8 °C (from *n*-pentane); $[\alpha]_D$ +8 (*c* 0.238); IR 1725 cm^{-1}; ^1H NMR (200 MHz) δ 1.02 (3H, s), 1.14 (3H, d, J = 7.0 Hz), 1.34 (3H, s), 2.13 (3H, s), 3.66 (3H, s), 5.20 (1H, dd, J = 10.2, 1.8 Hz), 5.35 (1H, dd, J = 10.2, 2.2 Hz), 5.52 (1H, dd, J = 2.0, 2.0 Hz); ^{13}C NMR (50.3 MHz) δ 13.8 (CH_3), 14.6 (CH_3), 20.9 (CH_3), 22.6 (CH_3), 24.1 (CH_2), 28.5 (CH_2), 34.1 (CH_2), 36.4 (C), 38.2 (CH), 44.5 (CH), 51.2 (CH_3), 63.7 (C), 67.0 (C), 71.7 (CH), 120.3 (CH), 137.1 (CH), 170.6 (C), 175.7 (C); MS *m*/*z* (rel intensity) 322 (M^+, 1), 307 (3), 291 (10), 280 (100), 263 (48), 205 (59); HRMS calcd for $C_{18}H_{26}O_5$ 322.1802, found 322.1791. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.93; H, 8.22.

Methyl (3*R*,4*R*,5*S*,11*S*)-3-Acetoxy-1,2-dihydroxy-4,5-epoxy-1,2-secoeudesman-13-oate (11). A solution of compound **10** (221 mg, 0.69 mmol) in CH_2Cl_2/MeOH (46 mL, 1:1) was cooled to −78 °C, and a slow stream of ozone was introduced into the solution until it became blue. Excess ozone was removed by flushing the solution with argon. Me_2S (0.61 mL, 8.28 mmol) was then added and the resulting mixture was stirred for 20 min at this temperature before being treated

with sodium borohydride (79 mg, 2.07 mmol). The reaction mixture was allowed to rise to room temperature and stirring was continued for 1.5 h. The reaction was quenched by the addition of 5% aqueous HCl solution and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 6:4) to give ester **11** (199 mg, 0.556 mmol, 81%): oil; R_f 0.16 (hexanes−EtOAc, 1:1); ^{1}H NMR (500 MHz) δ 1.04 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.34 (3H, s), 2.12 (3H, s), 3.67 (3H, s), 3.22 (1H, br d, J = 8.2 Hz), 3.81 (1H, br d, J = 9.3 Hz), 4.24 (1H, dd, J = 11.2, 2.7 Hz), 4.28 (1H, m), 4.38 (1H, dd, J = 11.2, 7.7 Hz); ^{13}C NMR (50.3 MHz) δ 13.5 (CH_3), 14.4 (CH_3), 20.0 (CH_3), 20.8 (CH_3), 24.0 (CH_2), 33.7 (CH_2), 36.3 (CH_2), 37.8 (CH), 38.3 (C), 44.5 (CH), 51.4 (CH_3), 66.8 (C), 67.0 (CH_2), 71.3 (CH), 71.8 (C), 72.0 (CH_2), 171.7 (C), 176.0 (C); MS m/z (rel intensity) 340 ($M^+ - H_2O$, 1), 322 (1), 279 (11), 223 (48), 149 (100); HRMS calcd for $C_{18}H_{28}O_7$ 340.1886, found 340.1914. Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44. Found: C, 60.43; H, 8.47.

Methyl (3*R*,4*R*,5*R*,11*S*)-2-Acetoxy-3,5-epoxy-1,4-dihydroxy-1,2-secoeudesman-13-oate (12). To a solution of ester **11** (75 mg, 0.209 mmol) in CH_2Cl_2 (5 mL) was added methanesulfonic acid (7 μL, 0.104 mmol) and the solution was stirred at 0 °C for 20 min. The reaction mixture was then poured into aqueous saturated $NaCO_3H$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (benzene−EtOAc, 6:4) to give ester **12** (40 mg, 0.11 mmol, 53%): oil; R_f 0.21 (hexanes−EtOAc, 6:4); IR (CCl_4) 3230, 1739 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.91 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.45 (3H, s), 2.08 (3H, s), 3.68 (3H, s), 3.50 (1H, d, J = 11.7 Hz), 4.09 (1H, dd, J = 12.1, 7.7 Hz), 4.19 (1H, d, J = 11.7 Hz), 4.29 (1H, dd, J = 12.1, 3.5 Hz), 4.64 (1H, dd, J = 7.7, 3.5 Hz); ^{13}C NMR (100.6 MHz) δ 14.5 (CH_3), 19.1 (CH_3), 19.3 (CH_3), 20.9 (CH_3), 23.4 (CH_2), 30.7 (CH_2), 36.2 (CH_2), 37.9 (CH), 43.8 (C), 44.8 (CH), 51.5 (CH_3), 64.8 (CH_2), 68.0 (CH_2), 77.1 (C), 86.1 (CH), 94.9 (C), 171.0 (C), 176.3 (C); MS m/z (rel intensity) 327 (M^+ − OMe, 1), 309 (1), 297 (2), 281 (4), 265 (4), 255 (7), 237 (12), 225 (24); HRMS calcd for $C_{17}H_{25}O_5$ 309.1702, found 309.1680. Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44. Found: C, 60.54; H, 8.39.

Methyl (3*R*,4*R*,5*R*,11*S*)-2-Acetoxy-1,4:3,5-diepoxy-1,2-secoeudesman-13-oate (13). To a solution of ester **12** (42 mg, 0.117 mmol) and triphenylphosphine (77 mg, 0.29 mmol) in dry $CHCl_3$ was added dropwise a solution of DEAD (46 μL, 0.29 mmol) at room temperature under argon. After 30 min the reaction mixture was poured into a 1% aqueous solution of sodium hydroxide and extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous HCl solution and dried (Na_2SO_4), and the solvent was evaporated in vacuo to give a crude product that was purified by Chromatotron chromatography (benzene−EtOAc, 8:2) to yield ester **13** (38 mg, 0.112 mmol, 95%): oil; R_f 0.42 (hexanes−EtOAc, 8:2); ^{1}H NMR (200 MHz) δ 0.95 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.39 (3H, s), 2.10 (3H, s), 3.68 (3H, s), 3.66 (1H, d, J = 8.8 Hz), 3.95 (1H, d, J = 8.8 Hz), 4.10 (1H, dd, J = 6.7, 12.1 Hz), 4.25 (1H, dd, J = 4.0, 12.3 Hz), 4.40 (1H, dd, J = 4.0, 6.6 Hz); ^{13}C NMR (50.3 MHz) δ 13.3 (CH_3), 14.7 (CH_3), 15.5 (CH_3), 21.0 (CH_3), 24.0 (CH_2), 33.7 (CH_2), 34.1 (CH_2), 38.5 (CH), 43.6 (C), 45.2 (CH), 51.6 (CH_3), 64.7 (CH_2), 77.0 (CH_2), 82.1 (CH), 86.2 (C), 96.1 (C), 176.3 (C), 177.7 (C); MS m/z (rel intensity) 322 ($M^+ - H_2O$, 1), 309 (5), 297 (2), 280 (2), 267 (1), 256 (1), 249 (4), 238 (59), 223 (100); HRMS calcd for $C_{18}H_{28}O_6$ 340.1886, found 340.1874. Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.72; H, 8.13.

Methyl (3*R*,4*R*,5*R*,11*S*)-1,4:3,5-Diepoxy-2-hydroxy-1,2-secoeudesman-13-oate (14). Acetate **13** (34.4 mg, 0.1 mmol) in 2% of K_2CO_3 in MeOH (3.3 mL) was stirred at room temperature for 15 min, poured into a saturated aqueous solution of $NaHSO_4$, and extracted with $CHCl_3$. The organic layer was washed twice with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 1:1) to give alcohol **14** (26.1 mg, 0.087 mmol, 87%): R_f 0.14 (hexanes−EtOAc, 6:4); mp 95−95.7 °C (*n*-hexane); IR 3528, 1731 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.96 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.41 (3H, s), 2.05 (1H, ddd, J = 13.4, 3.2, 2.2 Hz), 2.29 (1H, dddd, J = 7.1, 7.1, 7.1, 7.1 Hz), 3.64 (1H, d, J = 8.7 Hz), 3.69 (3H, s), [3.74 (2H, m) after D_2O: 3.68 (1H, dd, J = 12.4, 4.3 Hz) and 3.73 (1H, dd, J = 12.4, 4.3 Hz)], 3.95 (1H, d, J = 8.7 Hz), 4.27 (1H, dd, J = 4.7, 4.7 Hz); ^{13}C NMR (50.3 MHz) δ 13.3 (CH_3), 14.2 (CH_3), 15.2 (CH_3), 23.8 (CH_2), 33.1 (CH_2), 34.1 (CH_2), 38.5 (CH), 43.6 (C), 45.0 (CH), 51.5 (CH_3), 62.3 (CH_2), 76.7 (CH_2), 84.6 (CH), 86.2 (C), 95.8 (C), 176.1 (C); MS (CI) m/z (rel intensity) 299 (M^+ + H, 50), 280 (2), 267 (4), 238 (99), 223 (100), 211 (13); HRMS calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1656. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.63; H, 8.90. Crystal data for **14**: a crystal of 0.1 × 0.3 × 0.5 mm^3 was grown from methanol, $C_{16}H_{26}O_5$, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 25.656(4) Å, b = 6.288(2) Å, c = 9.913(3) Å. The data were measured on a Philips PW-1100 four-circle automatic diffractometer operating with Cu Kα radiation (λ = 1.5418 Å) monochromated by graphite, at room temperature, up to 2θ = 126°. Two equivalent portions of the reciprocal space were recorded (2528 intensities). The structure was solved by direct methods and refined with anisotropic thermal factors for non-hydrogen atoms to R = 6.5% (unitary weights) and R_w = 5.8% [weights = $5.3/\sigma(F)^2$]. All the hydrogens were located on Fourier-difference syntheses. Data merging and processing led to a unique set of 1285 structure factors (R_{symm} = 2.8%) of which 1025 were observed [$I \geq 2\sigma(I)$]. No decomposition corrections were applied but empirical absorption corrections were made at the end of the isotropic refinements, using the unmerged data set.

***tert*-Butyl(diphenyl)silyl (3*R*,4*R*,5*R*,11*S*)-2-*tert*-Butyl(diphenyl)silyloxy-1,4:3,5-diepoxy-1,2-secoeudesm-13-oate (27).** To a solution of ester **13** (82 mg, 0.24 mmol) in methanol (0.5 mL) was added 5.7 N aqueous KOH (0.2 mL) under stirring. The mixture was kept at 40 °C for 23 h then cooled to room temperature and acid resin Dowex 50× (195 mg) was added and stirring continued at room temperature until pH 5. The reaction was diluted with CH_2Cl_2, filtered, and concentrated under reduced pressure and the residue was directly used for the next step without further purification. To a solution of the above acid in CH_2Cl_2 (1 mL) were added sequentially triethylamine (69.6 mg, 0.69 mmol), 4-(dimethylamino)pyridine (9.8 mg, 0.08 mmol), and *tert*-butyldiphenylsilyl chloride (132 mg, 0.48 mmol) at room temperature. The reaction mixture was stirred under argon for 2 h and 45 min, then poured into a saturated aqueous solution of $NaHSO_4$ and extracted with EtOAc. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 95:5) to give compound **27** (173 mg, 0.227 mmol, 95%) as a syrup: R_f 0.27 (hexanes−EtOAc, 9:1); IR 2933, 1717, 1472, 1114 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.93 (3H, s), 1.07 (9H, s), 1.11 (9H, s), 1.15 (3H, d, J = 7.0 Hz), 1.42 (3H, s), 1.85 (1H, m), 2.05 (1H, br d, J = 13.6 Hz), 2.43 (1H, dddd, J = 6.9, 6.9, 6.9, 6.9 Hz), 3.64 (1H, d, J = 8.7 Hz), 3.73 (2H, d, J = 5.9 Hz), 3.96 (1H, d, J = 8.7 Hz), 4.26 (1H, dd, J = 5.9, 5.9 Hz), 7.36 (10H, m), 7.66 (10H, m); ^{13}C NMR (50.3 MHz) δ 12.8 (CH_3), 13.2 (CH_3), 15.5 (CH_3), 19.2 (2 × C), 22.9 (CH_2), 26.8 (3 × CH_3), 27.0 (3 × CH_2), 33.8 (CH_2), 33.9 (CH_2), 37.9 (CH), 43.4 (C), 46.1 (CH), 64.4 (CH_2), 76.7 (CH_2), 84.3 (CH), 86.5 (C), 95.2 (C), 127.7 (8 × CH), 129.7 (CH), 129.7 (CH), 130.1 (2 × CH), 131.8 (2 × C), 133.5 (2 × C), 135.3 (4 × CH), 135.6 (2 × CH), 135.7 (2 × CH), 174.6 (C); MS−FAB m/z (rel intensity) 783 (M^+ + Na, 3), 761(3), 703 (4), 684 (2), 527 (1), 463(18), 405 (9), 385(48), 241 (62), 199 (67), 135 (100); HRMS-FAB calcd for $C_{47}H_{60}NaO_5Si_2$ 783.3877, found 783.3888. Anal. Calcd for $C_{47}H_{60}O_5Si_2$: C, 74.17; H, 7.95. Found: C, 74.03; H, 7.91.

(3*R*,4*R*,5*R*,11*S*)-2-*tert*-Butyl(diphenyl)silyloxy-1,4:3,5-diepoxy-1,2-secoeudesm-13-oic Acid (28). To a solution of compound **27** (105 mg, 0.138 mmol) in methanol (0.28 mL) was added 2.9 N aqueous KOH (0.14 mL) under stirring. The mixture was kept at room temperature for 1 h. Acid resin Dowex 50× (82 mg) was added and the mixture was stirred until it reached pH 6. The reaction was diluted with CH_2Cl_2, filtered, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 7:3 → 2:8 then $CHCl_3$–MeOH, 5:5) to give compound **28** (59 mg, 0.113 mmol, 82%) and a small amount of the hydroxy acid (4 mg, 0.014 mmol, 10%). Compound **28**: R_f 0.53 (hexanes−EtOAc, 1:1); IR 3514, 2931, 1706, 1464, 1112 cm^{-1}; ^1H NMR (200 MHz) δ 0.95 (3H, s), 1.07 (9H, s), 1.14 (3H, d, J = 7.2 Hz), 1.47 (3H, s,), 3.65 (1H, d, J = 8.6 Hz), 3.75 (2H, d, J = 5.5 Hz), 3.96 (1H, d, J = 8.7 Hz), 4.27 (1H, dd, J = 5.7, 5.7 Hz), 7.39 (5H, m), 7.68 (5H, m); ^{13}C NMR (50.3 MHz) δ 13.2 (CH_3), 13.3 (CH_3), 15.5 (CH_3), 19.1 (C), 23.2 (CH_2), 26.8 (3 × CH_3), 33.2 (CH_2), 33.9 (CH_2), 37.8 (CH), 43.4 (CH), 44.3 (C), 64.3 (CH_2), 76.6 (CH_2), 84.3 (CH), 86.5 (C), 95.2 (C), 127.7 (4 × CH), 129.7 (2 × CH), 133.1 (C), 133.2 (C), 135.61 (2 × CH), 135.63 (2 × CH), 181.1 (C); MS-FAB *m*/*z* (rel intensity) 545 (M^+ + Na, 13), 241 (24), 221 (17), 199 (14), 135 (24); HRMS-FAB calcd for $C_{31}H_{42}NaO_5Si$ 545.2699, found 545.2675. Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 71.09; H, 7.91.

(3*R*,4*R*,5*R*)-2-*tert*-Butyl(diphenyl)silyloxy-1,4:3,5-diepoxy-1,2-seco-12-nor-eudesman-11-one (29). The acid chloride was prepared immediately prior to use by treatment of the acid **28** (167 mg, 0.32 mmol) in benzene (1.6 mL) with oxalyl chloride (229 mg, 1.8 mmol) and DMF (0.09 mL) at room temperature under argon and stirring for 1 h. The reaction mixture was evaporated to dryness, redissolved in benzene (1.6 mL), and evaporated to dryness again yielding the crude acid chloride that was used in the following reaction without purification. To a solution of the acid chloride (0.32 mmol) in dry degassed CH_2Cl_2 (1.6 mL) was added the sodium salt of *N*-hydroxypyridine-2-thione (50 mg, 0.33 mmol). After being stirred for 2 h at room temperature under an inert atmosphere, the reaction mixture was rapidly filtered through a short pad of Celite, and the solvent was evaporated under vacuum without heating. The light-sensitive yellow residue was used as such in the next reaction. The crude thiohydroxamate ester (0.32 mmol) and antimony trisphenylsulfide (359 mg, 0.8 mmol) in ether (16 mL) were stirred for 1.5 h at room temperature under aerial oxidation. The white solid was filtered through a short pad of Celite, and the solution was evaporated to dryness. Purification of the residue by column chromatography (hexanes → hexanes−EtOAc, 9:1) afforded the mixture of nor-alcohols (115 mg, 0.23 mmol, 72%). To a solution of the alcohols (115 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (0.33 mL) were added pyridinium chlorochromate (109 mg, 0.506 mmol) and sodium acetate (8.2 mg, 0.1 mmol) and the mixture was stirred at room temperature for 2 h. Then dry ether (1 mL) was added and the supernatant solution was decanted from the black gum. The insoluble residue was washed thoroughly with anhydrous ether whereupon it became a black granular solid. The combined organic extracts were passed through a short pad of Celite and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 9:1) to afford ketone **29** (89.3 mg, 0.18 mmol, 79%): R_f 0.53 (hexanes−EtOAc, 7:3); IR 2932, 1708, 1464, 1113 cm^{-1}; ^1H NMR (500 MHz) δ 0.98 (3H, s), 1.06 (9H, s), 1.48 (3H, s), 2.11 (3H, s), 3.65 (1H, d, J = 8.7 Hz), 3.74 (1H, dd, J = 11.6, 4.5 Hz), 3.78 (1H, dd, J = 11.6, 6.1 Hz), 3.97 (1H, d, J = 8.7 Hz), 4.27 (1H, dd, J = 5.8, 4.9 Hz), 7.40 (6H, m), 7.68 (4H, m); ^{13}C NMR (50.3 MHz) δ 13.2 (CH_3), 15.7 (CH_3), 19.2 (C), 23.1 (CH_2), 26.7 (3 × CH_3), 28.0 (CH_3), 29.7 (CH_2), 33.7 (CH_2), 43.5 (C), 49.2 (CH), 64.1 (CH_2), 76.7 (CH_2), 84.5 (CH), 86.5 (C), 94.7 (C), 127.7 (4 × CH), 129.8 (2 × CH), 133.0 (C), 135.1 (C), 135.7 (4 × CH), 210.9 (C); MS-FAB *m*/*z* (rel intensity) 515 (M^+ + Na, 1), 401 (2), 355 (2), 341 (1), 327 (2), 281 (8), 241 (13); HRMS-FAB calcd for $C_{30}H_{40}NaO_4Si$ 515.2593, found 515.2563. Anal. Calcd for $C_{30}H_{40}O_4Si$: C, 73.13; H, 8.18. Found: C, 73.19; H, 8.25.

(3*R*,4*R*,5*R*)-2-*tert*-Butyl(diphenyl)silyloxy-1,4:3,5-diepoxy-1,2-secoeudesman-11-ol (30). To a solution of ketone **29** (21.8 mg, 0.044 mmol) in ether (0.9 mL) at −78 °C was added dropwise methylmagnesium bromide (0.32 mL, 0.95 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 45 min, then quenched at this temperature with cold saturated aqueous sodium bisulfate solution and allowed to warm to room temperature for 30 min. Then it was poured into a saturated aqueous sodium bisulfate solution and extracted with EtOAc. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and twice with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 8:2) to give alcohol **30** (23.3 mg, 0.046 mmol, 96%): R_f 0.31 (hexanes−EtOAc, 7:3); IR 3609, 2934, 1472, 1383, 1242, 1113 cm^{-1}; ^1H NMR (200 MHz) δ 0.97 (3H, s), 1.07 (9H, s), 1.16 (6H, s), 1.46 (3H, s), 3.65 (1H, d, J = 8.6 Hz), 3.76 (1H, d, J = 5.2 Hz), 3.77 (1H, d, J = 6.6 Hz), 3.97 (1H, d, J = 8.7 Hz), 4.29 (1H, dd, J = 5.6, 5.6 Hz), 7.40 (6H, m), 7.69 (4H, m); ^{13}C NMR (50.3 MHz) δ 13.4 (CH_3), 15.6 (CH_3), 19.2 (C), 21.6 (CH_2), 26.7 (CH_3), 26.8 (3 × CH_3), 27.2 (CH_3), 30.2 (CH_2), 34.2 (CH_2), 43.4 (C), 46.7 (CH), 64.3 (CH_2), 72.2 (C), 76.7 (CH_2), 84.2 (CH), 86.5 (C), 95.6 (C), 127.7 (4 × CH), 129.7 (2 × CH), 133.1 (2 × C), 135.7 (4 × CH); MS *m*/*z* (rel intensity) 451 ($M^+ - C_4H_9$, 12), 433 (13), 403 (3), 373 (5), 355 (3), 307 (7), 241 (100). Anal. Calcd for $C_{31}H_{44}O_4Si$: C, 73.18; H, 8.72. Found: C, 73.09; H, 8.90.

(3*R*,4*R*,5*R*)-1,4:3,5-Diepoxy-1,2-secoeudesmane-2,11-diol (31). To a solution of silyl ether **30** (12.1 mg, 0.024 mmol) in THF (0.9 mL) was added a solution of tetrabutylammonium fluoride (15.7 mg, 0.06 mmol) in THF (0.2 mL). The reaction mixture was stirred at room temperature for 2.5 h, poured into a saturated aqueous solution of $NaHCO_3$, and extracted with chloroform. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 1:9) to afford the diol **31** (6.5 mg, 0.024 mmol, 100%): R_f 0.15 (hexanes−EtOAc, 4:6); ^1H NMR (200 MHz) δ 0.99 (3H, s), 1.22 (6H, s), 1.43 (3H, s), 3.66 (1H, d, J = 8.7 Hz), 3.74 (2H, m), 3.67 (1H, d, J = 8.7 Hz), 4.31 (1H, dd, J = 4.6, 4.6 Hz); ^{13}C NMR (50.3 MHz) δ 13.4 (CH_3), 15.3 (CH_3), 21.6 (CH_2), 27.0 (2 × CH_3), 29.6 (CH_2), 34.3 (CH_2), 43.5 (C), 46.8 (CH), 62.3 (CH_2), 72.2 (C), 76.7 (CH_2), 84.6 (CH), 86.2 (C), 96.4 (C); MS *m*/*z* (rel intensity) 270 (M^+, <1), 269 (1), 210 (100); HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1746. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.72; H, 9.91.

(3*S*,4*R*,5*R*)-1,4:3,5-Diepoxy-2-iodo-1,2-secoeudesman-11-ol (32) and (4*R*,5*R*)-1,4-Epoxy-1,2-secoeudesm-2-ene-5,11-diol (33). To a solution of the diol **31** (2.4 mg, 0.0089 mmol) in benzene (0.29 mmol) were added sequentially 1,2-dichloroethane (0.09 mL), water (1.6 μL), imidazole (0.5 mg, 0.0074 mmol), 2,6-lutidine (2.0 mg, 0.019 mmol), triphenylphosphine (9.3 mg, 0.0356 mmol), and iodine (6.8 mg, 0.0267 mmol). More benzene (0.19 mL) was added to the reaction mixture and it was stirred at room temperature until the reagents were completely dissolved. Then the reaction mixture was stirred at 80 °C for 15 min, poured into an ice-cooled aqueous solution of sodium thiosulfate, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (benzene−EtOAc, 7:3) to give the olefin **33** (1.2 mg, 0.0047 mmol, 54%) and iodine **32** (1.6 mg, 0.0042 mmol, 44%). Olefin **33**: crystalline solid, R_f 0.18 (hexanes−EtOAc, 7:3); mp 84.3−86.2 °C (from *n*-pentane); $[\alpha]_D$ +47 (*c* 0.94); IR (film) 3418, 3086, 2970, 1639, 1470, 1368, 1274, 1041, 919 cm^{-1}; ^1H NMR (500 MHz) δ 0.97 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.35 (3H, s), 3.57 (1H, d, J = 8.6 Hz), 3.68 (1H, d, J = 8.6 Hz), 5.09 (1H, ddd, J = 10.8, 1.7, 1.2 Hz), 5.30 (1H, ddd, J = 17.4, 1.6, 1.3 Hz), 5.99 (1H, dd, J = 17.4, 10.8 Hz); ^{13}C NMR (50.3 MHz) δ 19.2 (CH_3), 20.4 (CH_2), 25.3

(CH_3), 27.6 (CH_3), 27.7 (CH_3), 31.6 (CH_2), 35.1 (CH_2), 44.2 (C), 44.3 (CH), 72.4 (C), 77.6 (CH_2), 81.1 (C), 88.4 (C), 112.3 (CH_2), 140.8 (CH); MS *m*/*z* (rel intensity) 254 (M^+, 8), 236 (3), 218 (11), 203 (15), 165 (30), 151 (26), 137 (15), 123 (100); HRMS calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1971. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.95; H, 10.23. Iodine **32**: R_f 0.30 (hexanes−EtOAc, 7:3); IR (film) 3443, 2929, 1470, 1026, 956 cm^{-1}; ^1H NMR (500 MHz) δ 0.98 (3H, s), 1.20 (6H, s), 1.43 (3H, s), 2.06 (1H, ddd, J = 13.4, 3.4, 1.9 Hz), 3.23 (1H, dd, J = 10.0, 8.6 Hz), 3.27 (1H, dd, J = 10.3, 6.4 Hz), 3.66 (1H, d, J = 8.6 Hz), 3.94 (1H, d, J = 9.0 Hz), 4.46 (1H, dd, J = 8.6, 6.2 Hz); ^{13}C NMR (100.6 MHz) δ 5.4 (CH_2), 13.4 (CH_3), 15.2 (CH_3), 21.6 (CH_2), 26.8 (CH_3), 27.1 (CH_3), 31.2 (CH_2), 34.3 (CH_2), 43.3 (C), 46.9 (CH), 72.3 (C), 76.9 (CH_2), 84.4 (CH), 86.3 (C), 95.0 (C); MS-FAB *m*/*z* (rel intensity) 382 (M^+ + 2, 8), 369 (3), 313 (11), 154 (15), 136 (30), 109 (26); HRMS-FAB calcd for $C_{15}H_{27}IO_3$ 382.1005, found 382.0993. Anal. Calcd for $C_{15}H_{25}IO_3$: C, 47.38; H, 6.63. Found: C, 47.51; H. 6.47.

(3*R*,4*R*,5*R*)-1,4:3,5-Diepoxy-2-phenylselanyl-1,2-secoeudesman-11-ol (34) and (3*S*,4*S*,5*R*)-1,4:2,5-Diepoxy-3-phenylselanyl-1,2-secoeudesman-11-ol (35). Method A: To a solution of compound **33** (10 mg, 0.04 mmol) and *p*-TsOH (3.8 mg, 0.02 mmol) in CH_2Cl_2 (0.74 mL) was added dropwise a solution of *N*-(phenylseleno)phthalimide (18.1 mg, 0.06 mmol) in CH_2Cl_2 (0.36 mL) for 15 min. The reaction mixture was stirred at room temperature for 2 h and 20 min under inert atmosphere, poured into a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a short chromatography column (hexanes) for elimination of the $(PhSe)_2$ and then by Chromatotron chromatography (benzene−EtOAc, 85:15) to give compound **34** (8.3 mg, 0.02 mmol, 51%) and compound **35** (3.6 mg, 0.0088 mmol, 22%). Compound **34**: R_f 0.20 (benzene−EtOAc, 8:2); $[\alpha]_D$ +78 (*c* 1.5); IR (film) 3444, 3057, 2929, 1732, 1580, 1479, 1384, 1260, 1022, 957 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (3H, s), 1.17 (3H, s), 1.18 (3H, s), 1.38 (3H, s), 3.06 (1H, d, J = 7.3 Hz), 3.60 (1H, d, J = 8.6 Hz), 3.89 (1H, d, J = 8.6 Hz), 4.31 (1H, dd, J = 7.3, 7.3 Hz), 7.23 (3H, m), 7.51 (2H, m); ^{13}C NMR (50.3 MHz) δ 13.3 (CH_3), 15.4 (CH_3), 21.6 (CH_2), 26.9 (2 × CH_3), 30.8 (CH_2), 31.2 (CH_2), 34.2 (CH_2), 43.3 (C), 46.8 (CH), 72.2 (C), 76.7 (CH_2), 82.9 (CH), 86.8 (C), 95.0 (C), 127.2 (CH), 129.1 (2 × CH), 132.4 (C), 133.2 (2 × CH); MS *m*/*z* (rel intensity) 410 (M^+, 1), 392 (2), 235 (4), 210 (83), 192 (89), 177 (100); HRMS calcd for $C_{21}H_{30}O_3{}^{80}Se$ 410.1360, found 410.1335. Anal. Calcd for $C_{21}H_{30}O_3Se$: C, 61.61; H, 7.39. Found: C, 61.79; H, 7.54. Compound **35**: R_f 0.25 (benzene−EtOAc, 8:2); $[\alpha]_D$ +33.4 (*c* 0.38); IR (film) 3452, 3060, 2928, 1732, 1580, 1470, 1379, 1263, 1047 cm^{-1}; ^1H NMR (500 MHz) δ 1.02 (3H, s), 1.15 (3H, s), 1.16 (3H, s), 1.63 (3H, s), 3.41 (1H, dd, J = 11.4, 8.0 Hz), 3.56 (1H, d, J = 8.5 Hz), 3.59 (1H, d, J = 8.4 Hz), 3.78 (1H, dd, J = 11.4, 8.9 Hz), 4.18 (1H, dd, J = 8.7, 8.4 Hz), 7.23 (3H, m), 7.51 (2H, m); ^{13}C NMR (50.3 MHz) δ 16.5 (CH_3), 21.2 (CH_2), 22.9 (CH_3), 26.8 (CH_3), 27.1 (CH_3), 31.6 (CH_2), 35.2 (CH_2), 44.9 (CH), 46.5 (C), 56.1 (CH), 72.4 (C), 73.5 (CH_2), 80.4 (CH_2), 91.9 (C), 92.4 (C), 127.2 (CH), 129.1 (2 × CH), 129.9 (C), 133.7 (2 × CH); MS *m*/*z* (rel intensity) 410 (M^+, 9), 392 (18), 235 (9), 184 (100); HRMS calcd for $C_{21}H_{30}O_3{}^{80}Se$ 410.1360, found 410.1354. Anal. Calcd for $C_{21}H_{30}O_3Se$: C, 61.61; H, 7.39. Found: C, 61.75; H, 7.13. **Method B:** To a solution of compound **34** (2 mg, 0.005 mmol) and *p*-TsOH (1 mg, 0.005 mmol) in CH_2Cl_2 (0.16 mL) was added dropwise a solution of *N*-(phenylseleno)phthalimide (4.5 mg, 0.015 mmol) in CH_2Cl_2 (0.09 mL) for 5 min. The reaction mixture was stirred at room temperature for 6.5 h under inert atmosphere, poured into a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by a short chromatography column (hexanes) for elimination of $(PhSe)_2$ and this was followed by Chromatotron chromatography (benzene−EtOAc, 8:2) to afford compound **35** (1.5 mg, 0.0037 mmol, 75%).

Acid-Catalyzed Isomerization of (3*R*,4*R*,5*R*)-1,4:3,5-Diepoxy-2-phenylselanyl-1,2-secoeudesman-11-ol (34). To a solution of pure **34** (1.6 mg, 0.004 mmol) in CH_2Cl_2 (0.15 mL) was added *p*-TsOH (2 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 7.5 h, poured into a saturated aqueous solution of $NaHCO_3$, and extracted with CH_2Cl_2. After this time the equilibrium ratio of **35**/**34** in the crude reaction mixture was determined to be 70/30 by ^1H NMR.

(3*S*,4*S*,5*R*)-1,4:2,5-Diepoxy-3-phenylselanyl-1,2-secoeudesman-11-yl Acetate (36). To a solution of compound **35** (6.6 mg, 0.016 mmol) in pyridine (0.07 mL) were added 4-(dimethylamino)pyridine (1 mg, 0.008 mmol) and acetic anhydride (24.5 mg, 0.24 mmol). The reaction mixture was stirred at 40 °C for 24 h, poured into a saturated aqueous solution of $NaHSO_4$, and extracted with EtOAc. The organic extract was washed with a saturated aqueous solution of $NaHCO_3$ and brine and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 8:2) to give compound **36** (4.3 mg, 0.0095 mmol, 60%): R_f 0.70 (hexanes−EtOAc, 7:3); $[\alpha]_D$ +40 (*c* 0.77); IR (film) 2927, 1728, 1580, 1470, 1368, 1258, 1130 cm^{-1}; ^1H NMR (500 MHz) δ 1.02 (3H, s), 1.39 (3H, s), 1.42 (3H, s), 1.63 (3H, s), 1.94 (3H, s), 3.41 (1H, dd, J = 11.4, 8.1 Hz), 3.56 (1H, d, J = 8.5 Hz), 3.59 (1H, d, J = 8.5 Hz), 3.80 (1H, dd, J = 11.4, 9.0 Hz), 4.18 (1H, dd, J = 8.6, 8.5 Hz), 7.24 (3H, m), 7.53 (2H, m); ^{13}C NMR (50.3 MHz) δ 16.4 (CH_3), 21.1 (CH_2), 22.4 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 23.4 (C), 31.1 (CH_2), 35.0 (CH_2), 42.5 (CH), 46.6 (C), 56.1 (CH), 73.6 (CH_2), 80.3 (CH_2), 84.1 (C), 91.8 (C), 92.4 (C), 127.3 (CH), 129.8 (C), 129.1 (2 × CH), 133.8 (2 × CH), 170.4 (C); MS *m*/*z* (rel intensity) 452 (M^+, 57), 392 (7), 295 (5), 235 (14), 184 (100); HRMS calcd for $C_{23}H_{32}O_4{}^{80}Se$ 452.1466, found 452.1458. Anal. Calcd for $C_{23}H_{32}O_4Se$: C, 61.19; H, 7.14. Found: C, 61.01; H, 7.52.

Phytuberin [(4*R*,5*R*)-1,4:2,5-Diepoxy-1,2-secoeudesm-2-en-11-yl Acetate] (1). A solution of compound **36** (4 mg, 0.009 mmol) in CH_2Cl_2 (1.3 mL) was cooled to −78 °C, and ozone was bubbled through it until the solution turned light blue. Then nitrogen was bubbled through the solution to expel excess ozone, the mixture was allowed to warm to room temperature, and pyridine (7.1 mg, 0.09 mmol) was added. This mixture was then added dropwise to preheated (60 °C) carbon tetrachloride, and the solution was refluxed for 1.5 h. The solution was washed consecutively with saturated aqueous solutions of $NaHSO_4$, $NaHCO_3$, and brine. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a short chromatography column (benzene−EtOAc, 95:5) to afford phytuberin (**1**) (1.6 mg, 0.0054 mmol, 62%): R_f 0.35 (benzene−EtOAc, 9:1); $[\alpha]_D$ −38.8 (EtOH, *c* 0.92) {lit.[1a] $[\alpha]_D$ −35.9 (EtOH)}; IR 3080, 2918, 2841, 1731, 1622, 1470, 1369, 1257, 1150, 1037 cm^{-1}; ^1H NMR (500 MHz) δ 1.01 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 1.55 (3H, s), 1.98 (3H, s), 3.27 (1H, d, J = 8.5 Hz), 3.38 (1H, d, J = 8.5 Hz), 4.67 (1H, d, J = 2.7 Hz), 6.43 (1H, d, J = 2.7 Hz); ^{13}C NMR (50.3 MHz) δ 16.6 (CH_3), 21.5 (CH_2), 21.6 (CH_3), 22.4 (CH_3), 23.1 (CH_3), 23.5 (CH_3), 28.9 (CH_2), 34.5 (CH_2), 43.8 (CH), 45.1 (C), 73.7 (CH_2), 84.1 (C), 93.3 (C), 94.8 (C), 104.7 (CH), 146.7 (CH), 170.3 (C); MS *m*/*z* (rel intensity) 294 (M^+, 25), 249 (6), 235 (16), 219 (7), 205 (100); HRMS calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1785. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.42; H, 9.03.

(2*R*,3*S*,4*R*,5*R*)-1,4:2,5-Diepoxy-3-hydroxy-2-methoxy-1,2-secoeudesman-11-yl Acetate (37). To a solution of phytuberin (**1**) (10 mg, 0.034 mmol) in CH_2Cl_2 (0.34 mL) cooled to −17 °C was added, under a nitrogen atmosphere, a solution of dimethyldioxirane (0.5 mL, 0.04 mmol, 0.08 M) in acetone and the mixture was stirred for 30 min. Then an excess of anhydrous MeOH (0.34 mL) was added and stirring was continued for 1 h at this temperature. The concentration under reduced pressure gave a residue that was purified by Chro-

matotron chromatography (hexanes−EtOAc, 6:4) to give methoxy alcohol **37** (5.3 mg, 0.015 mmol, 46%): R_f 0.30 (hexanes−EtOAc, 1:1); IR (film) 3443, 2848, 1732, 1471, 1372, 1258 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (3H, s), 1.41 (3H, s), 1.45 (3H, s), 1.51 (3H, s), 1.97 (3H, s), 2.28 (1H, dddd, J = 3.8, 3.8, 13.1, 13.1 Hz), 3.41 (3H, s), 3.50 (1H, d, J = 7.7 Hz), 3.86 (1H, d, J = 7.7 Hz), 3.94 (1H, s), 4.83 (1H, s); ^{13}C NMR (125.7 MHz) δ 14.1 (CH_3), 16.9 (CH_3), 20.8 (CH_3), 22.7 (CH_3), 23.5 (CH_3), 24.7 (CH_2), 31.2 (CH_2), 34.5 (CH_2), 42.5 (CH), 44.7 (C), 55.8 (CH_3), 78.2 (CH_2), 84.4 (C), 85.6 (CH), 91.9 (C), 95.6 (C), 109.0 (CH), 170.3 (C); MS *m*/*z* (rel intensity) 311 (M^+ − OMe, 6), 284 (16), 269 (11), 252 (18), 221 (32), 192 (39); HRMS calcd for $C_{17}H_{27}O_5$ 311.1858, found 311.1906. Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 63.27; H, 8.93.

(2*S*,3*S*,4*R*,5*R*)-1,4:2,5-Diepoxy-3-hydroxy-2-benzylamino-1,2-secoeudesman-11-yl Acetate (38). A solution of phytuberin (**1**) (11 mg, 0.038 mmol) in CH_2Cl_2 (0.38 mL) cooled to −17 °C was treated with dimethyldioxirane (0.5 mL, 0.04 mmol, 0.08 M) analogously to the case of **37**. Then anhydrous benzylamine (0.4 mL) was added and the mixture was allowed to warm to room temperature over the course of 6 h and stirring was continued at this temperature for a further 17 h. The reaction mixture was then poured into a saturated aqueous solution of $NaHSO_4$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (hexanes−EtOAc, 4:6) to give amine alcohol **38** (8.4 mg, 0.02 mmol, 53%) as an inseparable mixture (86:14) of two stereoisomers: R_f 0.28 (hexanes−EtOAc, 1:1); IR (film) 3418, 2930, 1732, 1471, 1456, 1372, 1258 cm^{-1}; major product ^1H NMR (500 MHz) δ 1.03 (3H, s), 1.42 (3H, s), 1.45 (3H, s), 1.54 (3H, s), 1.98 (3H, s), 2.28 (1H, dddd, J = 12.9, 12.9, 3.8, 3.8 Hz), 3.41 (1H, d, J = 8.3 Hz), 3.56 (1H, d, J = 8.3 Hz), 3.62 (1H, d, J = 3.0 Hz), 3.86 (1H, d, J = 13.0 Hz), 4.06 (1H, d, J = 13.0 Hz), 4.52 (1H, d, J = 3.0 Hz), 7.3 (5H, m); major product ^{13}C NMR (125.7 MHz) δ 16.6 (CH_3), 21.1 (CH_2), 21.2 (CH_3), 22.5 (CH_3), 23.3 (CH_3), 23.4 (CH_3), 30.9 (CH_2), 34.8 (CH_2), 42.6 (CH), 46.0 (C), 50.4 (CH_2), 79.1 (CH_2), 81.1 (CH), 84.4 (C), 89.6 (CH), 90.8 (C), 92.4 (C), 127.2 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 139.4 (C), 170.5 (C); MS *m*/*z* (rel intensity) 417 (M^+, 3), 400 (23), 252 (15), 222 (22), 205 (100); HRMS calcd for $C_{24}H_{35}NO_5$ 417.2515, found 417.2570. Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.04; H, 8.45; N, 3.35. Found: C, 69.23; H, 8.37; N, 3.41.

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Supporting Information Available: Detailed experimental procedures and spectral and analytical data for compounds **15**−**26**; isolation of phytuberin from potato tubers inoculated with *E. carotovora* var. *carotovora*; tables of X-ray crystallographic data for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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