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# Synthesis of (+)-8-Deoxyvernolepin and Its 11,13-Dihydroderivative. A Novel Reaction Initiated by Sulfene Elimination Leads to the 2-Oxa-*cis*-decalin Skeleton

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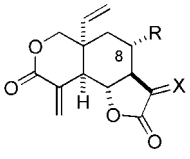
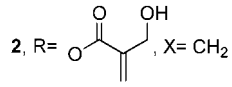
The title compounds are interesting candidates for antifungal screening. This paper describes the enantiospecific synthesis of these compounds starting from (+)-costunolide isolated from a commercially available extract. We used two novel reactions as key synthetic steps in this work: the acid-induced cyclization of an $\delta,\epsilon$-epoxy ester, which stereoselectively gave a hydroxymethyl-substituted $\delta$-lactone, with the hydroxyalkyl group in the desired $\beta$-equatorial disposition, and a reaction cascade, initiated by a base-promoted sulfene elimination, which led to a 10-oxiranyl-2-oxa-*cis*-decalin from the mesylate of a *trans*-fused $\delta$-lactone. We also found that the reaction between selenium dioxide and the 1,5-diene system of elemanolides gave selenadecalins analogous to natural eudesmanolides. Our results prove that the synthetic strategy employed, on the basis of biomimetic concepts, is a useful procedure for the enantiospecific preparation of (+)-vernolepin-related compounds from accessible germacrolides.

## Introduction

(+)-Vernolepin (**1**) and (+)-vernodalin (**2**), from the Ethiopian plants *Vernonia hymenolepis*[1] *and V. amigdalina*,[2] respectively, and the synthetic derivative 8-deoxyvernolepin[3] (**3**) form a small group of sesquiterpene lactones (elemanolides)[4] with a unique 10-vinyl-2-oxa-*cis*-decalin skeleton. These substances have interesting



**1**, R= OH, X= $CH_2$



**2**, R= , X= $CH_2$

**3**, R= H, X= $CH_2$

**4**, R= H, X= $\alpha CH_3$, $\beta H$

biological properties,[5−7] and thus, **1** and **2** showed stronger antibacterial potency than ampicilin and neomycin[8] and an antifungal activity comparable to that of amphotericin B.[9] As far as 8-deoxyvernolepin is concerned, the racemic form exhibits higher cytotoxic potency than vernolepin against human lymphoblastic leukemia cells in culture,[3] and the (+)-enantiomer (**3**) also shows antitumor activity in vivo.[10] Moreover, as it is believed that the antifungal activity of sesquiterpene lactones is inversely related to their polarity,[11] **3** (which is less polar than **1** and **2**) is an interesting candidate for antifungal screening.

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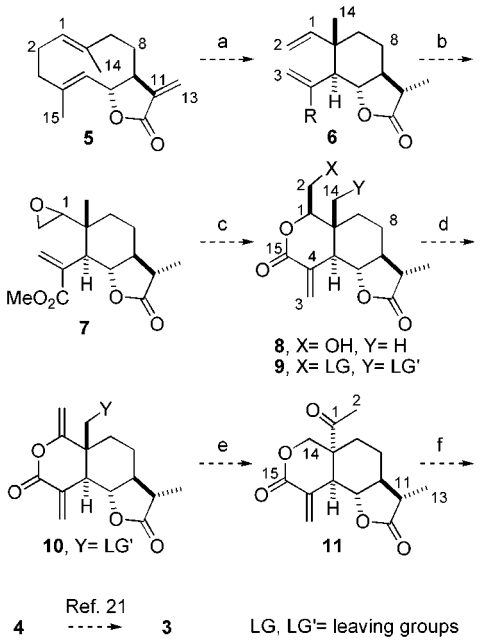
The research groups of Grieco,[3,12] Danishefsky,[13] and others[14] have reported the total synthesis of **1** and/or **3** in racemic form, and more recently, the asymmetric synthesis of one of Danishefsky's intermediates has allowed the enantioselective preparation of (+)-vernolepin.[15] These syntheses require numerous steps, however, and provide low overall yields. Some procedures for the synthesis of (+)-8-deoxyvernolepin (**3**) from (−)-α-santonin (in 15 or more steps) have been reported also.[16] Santonin, however, lacks any functional group at C-8, and this is a serious drawback if one wants to extend this strategy to the synthesis of the C-8 functionalized compounds **1** and **2**. Moreover, the procedures employed to build the $\Delta^3$ exocyclic double bond of **3** always produced isomeric mixtures and a concomitant fall in overall yield.[10,17]

Elemanolides are believed to be synthesized from germacrolides in nature.[4] So, encouraged by this idea, we have developed a new strategy that might facilitate the synthesis of elemanolides **1**−**3**, starting from accessible germacrolides.[18] The aim of the present work has been to prove the value of this strategy for the syntheses of (+)-8-deoxyvernolepin (**3**) and the 11,13-dihydrogenated derivative **4**. Further screening of these compounds might help us find new antifungal drugs and provide information about the potential relationships, if any, between the antifungal activity of sesquiterpene lactones and the α-methylene-γ-lactone group, which is mainly responsible for the toxic activity of these compounds against mammalian cells.[19]

## Results and Discussion

Our synthetic planning (Scheme 1) was based on the following key transformations: first, the Cope rearrangement of the germacrane skeleton of **5** to the elemane skeleton of **6** (step a), previously tested by us under both thermal and catalytic conditions;[18b,20] second (step c), the cyclization of the δ,ϵ-epoxy ester **7** to the δ-lactone **8**, which should leave the hydroxymethyl group of **8** in the most stable equatorial position required to perform the long-range functionalization of C-14, which would allow the attachment of a suitable leaving group (Y) at this carbon atom; and third (step e), the intramolecular displacement of the Y leaving group by the carboxylate ion derived from selective saponification of the enol

**SCHEME 1**




lactone **10** (step d) to afford 2-oxa-*cis*-decalin **11**. The remaining transformations of Scheme 1 can be achieved by conventional methods, especially by using Grieco's procedure to build the $\Delta^{11(13)}$ double bond of **3**.[21]

Costunolide, the raw material proposed in Scheme 1, can be obtained in racemic form by total synthesis.[22] Nevertheless, we chose to start with (+)-costunolide (**5**) isolated from commercially available Costus Resinoid,[20] in order to confer an enantiospecific character to our process. The synthesis began with the selective reduction of the conjugate double bond of **5** to avoid potential complications with a reactive Michael acceptor group. This double bond can easily be restored at the end of the synthetic sequence.[21] Thus, catalytic hydrogenation of **5**, under mild conditions, took place regio- and stereoselectively, giving 11β,13-dihydrocostunolide[23] (**12**) at a yield of 93% (Scheme 2). Similar selectivity degrees were previously observed for related sesquiterpene lactones under the same conditions.[18b]

With the germacrolide **12** in our hands, we envisaged the first key step of our synthesis, which was the rearrangement of the germacrane skeleton to the elemane one. Our previous work showed that 15-oxogermacrolides undergo Cope rearrangement in toluene at reflux, giving elemanolides in medium-to-high yields.[18b] It might, therefore, be thought that, to facilitate the subsequent rearrangement, the transformation of **12** into elemanolides such as **6** (Scheme 1) should start with the allylic oxidation of the C-15 methyl group. In the present case, however, this was not feasible because the allylic oxidation of germacrolides occurs with a concomitant isomerization of the neighboring double bond, generally

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(14) For a review, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, p 93.
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(18) (a) Barrero, A. F.; Oltra, J. E.; Barragán, A. *Tetrahedron Lett.* **1995**, *36*, 311. (b) Barrero, A. F.; Oltra, J. E.; Barragán, A.; Álvarez, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4107. (c) Barrero, A.; Oltra, J. E.; Álvarez, M. *Tetrahedron Lett.* **2000**, *41*, 7639.
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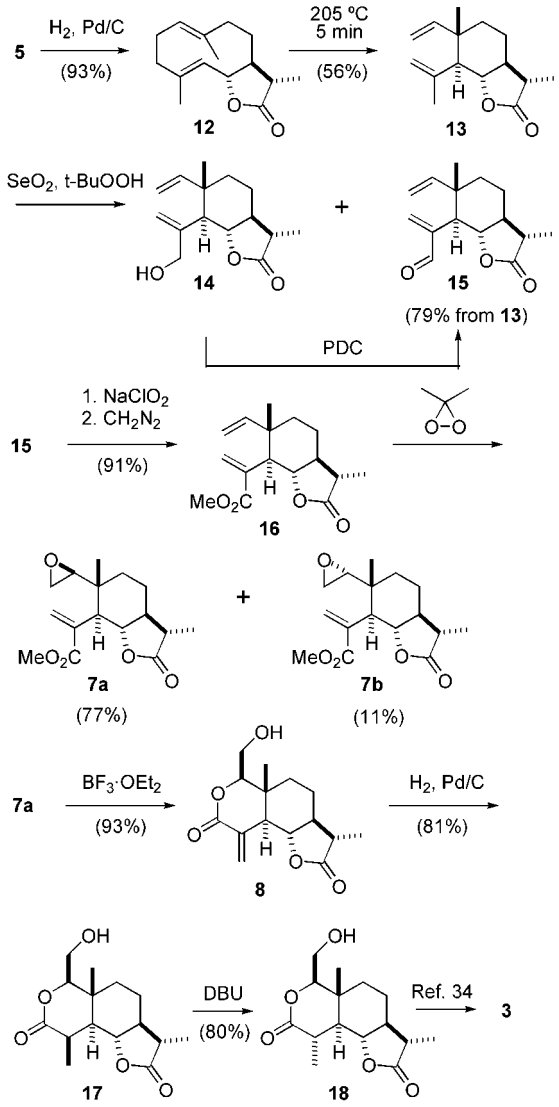
(21) . In contrast with the poor results obtained in the formation of the exocyclic double bond at $\Delta^3$, the $\Delta^{11(13)}$ double bond of **3** has been built in excellent yields using Grieco's procedure via oxidation of the selenide formed from the corresponding enolate.[10,17]
(22) For a review of the synthesis of costunolide and other germacrane sesquiterpenes, see: Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115.
(23) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.

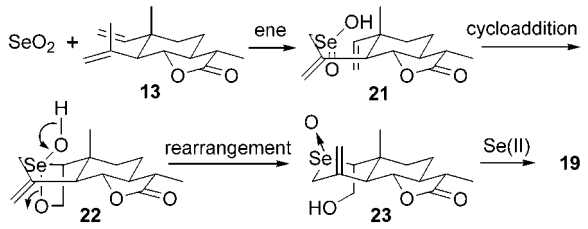
**SCHEME 2**



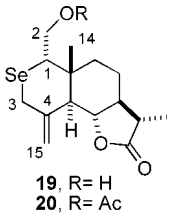

leading to melampolides,[24] and these derivatives are not prone to undergo Cope rearrangements.[25] Therefore, the rearrangement of **12** was attempted directly under thermal conditions. Thus, an equilibrium mixture of the germacrolide **12** and the elemanolide **13** was made at a ratio of 1/1.4 (**12**/**13**). The remaining germacrolide was recovered from the mixture and reused, giving an 88% yield of **13** after three turnovers. The subsequent allylic oxidation of **13** with $SeO_2$/*t*-BuOOH gave a mixture of the alcohol **14** and the aldehyde **15** from which the alcohol could be easily separated and reoxidized to produce **15** at a 79% overall yield (from **13**).

The allylic oxidation of elemanolide **13** was also assayed with $SeO_2$ in boiling anhydrous dioxane[26] to try to reach the aldehyde **15** in only one step and achieve a higher yield. This procedure did not have the desired

**SCHEME 3**




effect, however, but resulted in an inseparable mixture (roughly 1/1 ratio) of alcohol **14** and a tricyclic organoselenium compound **19**, together with a low yield of **15**




(32%). Nevertheless, the chemical and pharmacological interest aroused in recent years by organoselenium compounds[27] prompted us to spend some effort in confirming the chemical structure of the unexpected selenadecalin **19**. After conventional acetylation of the alcohol mixture, the derivative **20** could be isolated and analyzed by spectroscopic techniques. The MS showed several molecular ions in relative proportions in accordance with those of Se isotopes,[28] and exhaustive NMR experiments confirmed the chemical structure of **20**. We could thus infer the structure and stereochemistry of **19**, including the α-axial disposition of the hydroxymethyl group (it is noteworthy that we did not detect the presumably more stable 1$\beta$-hydroxymethyl epimer of **19**). Although $SeO_2$ is a widely used reagent in organic synthesis,[29] reactions of this compound with diene systems to give selenaheterocycles are still scarcely documented.[30] In fact, none of the mechanisms proposed so far can account for the structure and stereochemistry of the selenacyclohexane **19**. A plausible mechanism was suggested to us by the following observations: the ene reaction proposed for the first step of the allylic hydroxylation of alkenes[31] and the reduction of selenoxides to selenides via the exchange of the oxygen atom between selenoxides and species of Se(II).[32] Therefore, selenide **19** might be formed via the mechanism depicted in Scheme 3. Thus, the initial ene

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(27) (a) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* **2001**, *123*, 8408. (b) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, U.K., 1999.

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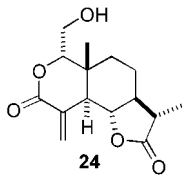
(32) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

reaction between the disubstituted double bond of **13** and $SeO_2$ would lead to the allylseleninic acid **21**. This seleninic acid may undergo an intramolecular [2 + 2] cycloaddition to give the oxaselenetane **22.** (It is known that the relatively poor $\pi$-overlap in C=Se bonds makes them quite reactive in cycloadditions,[27b] and therefore, the possibility that a O=Se bond works in a similar way cannot be ruled out.) The subsequent opening of the strained oxaselenetane **22**, facilitated by the assistance provided by the neighboring OH group, would lead to the selenoxide **23**. Finally, the reduction of **23** by a Se(II) species (derived from the usual allylic oxidation process) would give the cyclic selenide **19**. We could not isolate any of the proposed intermediates **21**−**23**, but whatever the exact mechanism, product **19** provides new evidence to support the formation of a C−Se bond during the allylic hydroxylation mediated by $SeO_2$, as proposed by Sharpless and Lauer.[31a] Our results also indicate that the reaction between $SeO_2$ and the 1,5-diene system of elemanolides can be used for the synthesis of substituted selenacycles, analogous to the case for natural eudesmanolides.

Coming back to the synthesis of **3**, we addressed the preparation of the key intermediate **7** foreseen in Scheme 1. The oxidation of **15** with sodium chlorite followed by the addition of $CH_2N_2$ afforded a 91% yield of methyl ester **16** (Scheme 2). This ester proved to be an unusually inert olefin and thus was recovered unchanged after treatment with different oxidative reagents. Finally, the reaction of **16** with dimethyldioxirane furnished us with an isomeric mixture of the epoxides **7a** (77% yield) and **7b** (11% yield). We were pleased to find that both isomers could be easily isolated by flash chromatography and analyzed by spectroscopic techniques. Except for the ABX system corresponding to the hydrogen atoms of the monosubstituted oxirane ring, the $^1$H NMR spectra of **7a** and **7b** showed closely related signals, thus confirming the C-1 epimeric relationship existing between these compounds. The 1*S* configuration of **7a** was assigned by comparing the signals of its ABX system with those of the corresponding protons of (1*S*)-1,2-epoxysaussurea lactone.[33] Consequently, the opposite stereochemistry, 1*R*, was attributed to the epimer **7b**.

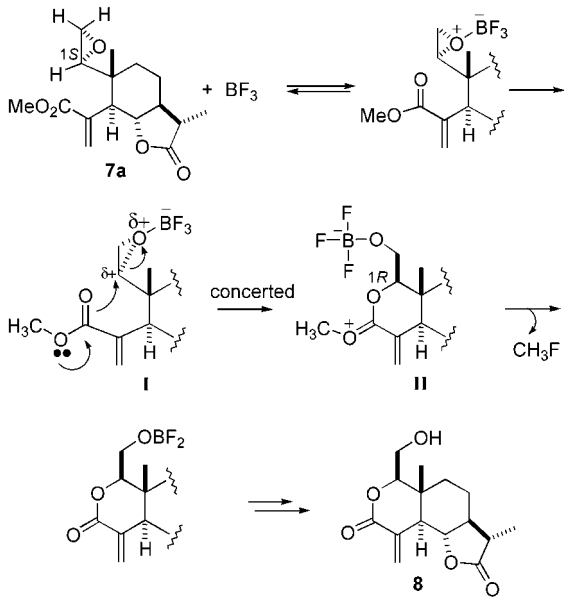
The configurations assigned to the epoxides **7a** and **7b** were confirmed by the stereochemistry of the rearranged products obtained by the acid-promoted opening of their oxirane rings. In this way, the electrophilic opening of the epoxide **7a** stereoselectively gave the $\delta$-lactone **8** (93% yield) foreseen in Scheme 1, with the hydroxymethyl group in the desired $\beta$-equatorial position. The 1*R* configuration of **8** was suggested by the chemical shift of C-14 ($\delta$ 13.9)[18c] (cf. $\delta$ value for C-14 of the 1*S* epimer **24**



**24**

in the Experimental Section) and was confirmed by the NOEs observed between H-1 and H-5, as well as between H-2 and $H_3$-14. The reaction took place with a complete inversion of the C-1 configuration, and thus, no formation of the 1*S* isomer **24** was detected. In contrast, the reaction of epoxide **7b** under the same conditions was considerably slower and gave a mixture of epimers **8** and **24** at a ratio of 1/2, respectively. The stereochemical outcome of these reactions can be rationalized in terms of a concerted mechanism for **7a** (Scheme 4) and a dual one for **7b**, which are consistent with the configurations proposed for these epoxides.

**SCHEME 4**




In the case of **7a**, the incipient secondary carbocation developing at C-1 by the electrophilic opening of the epoxide would be attacked by the nucleophilic methoxycarbonyl group, leading directly to the intermediate **II** with a complete inversion of the C-1 configuration. This intermediate would then evolve toward **8** (Scheme 4). On the other hand, with epoxide **7b** the reaction is slower, presumably because the transition state (TS) leading to **24** by a concerted mechanism is higher in energy than the corresponding TS leading to **II**. Thus, a stepwise mechanism leading to a mixture of **8** and **24**, via a secondary carbocation, may compete with the concerted one. Despite this, the main product obtained was the epimer **24**, with the hydroxymethyl group in the (presumably less stable) α-axial disposition; this fact suggests that the concerted mechanism might work simultaneously with the stepwise one.

When we had dilactone **8** in our possesion, the synthesis of **3** from arsantin (a natural eudesmanolide) via the hydrogenated derivative **18** was reported by Astudillo et al.[34] Therefore, we addressed the preparation of **18** from **8** in order to complete the synthesis of **3** in a formal sense (Scheme 2). In this way, the catalytic hydrogenation of **8** followed by base-promoted isomerization of **17** gave acceptable yields of **18** (65% from **8**). Thus, the formal synthesis of the target molecule (+)-8-deoxyvernolepin (**3**) was achieved, proving the utility of the

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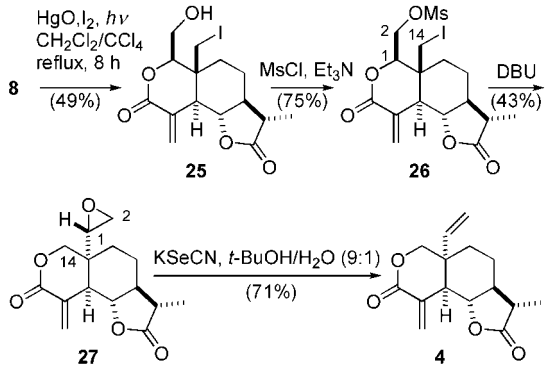
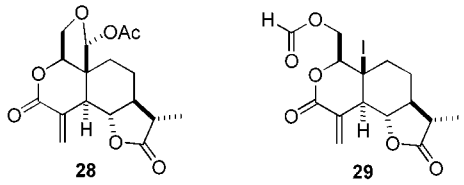
(34) Astudillo, L.; González, A.; Galindo, A.; Mansilla, H. *Tetrahedron Lett.* **1997**, *38*, 6737.

**SCHEME 5**




accessible germacrolide **5** as an alternative raw material for the enantiospecific synthesis of bioactive elemanolides such as **3**.

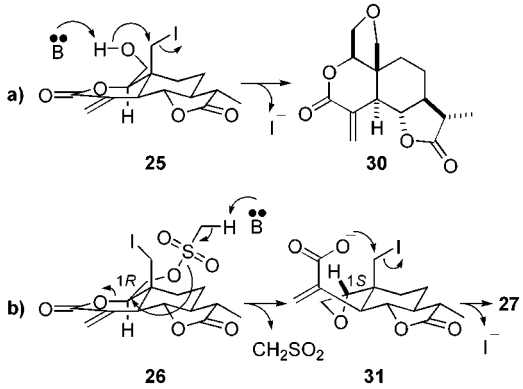
Two reports, however, deal with the difficulties involved in building the $\Delta^3$ exocyclic double bond of vernolepin-related compounds while avoiding mixtures with an endocyclic regioisomer and a concomitant decrease in yield.[10,17] Therefore, we decided to preserve the corresponding exocyclic double bond of **8**, as was foreseen in the original synthetic plan (see Scheme 1), to facilitate the synthesis of our second target molecule **4** (Scheme 5). We tried transforming **8** into **25**, taking advantage of the suitable spatial disposition of the primary alcohol of **8** to perform the remote functionalization of the C-14 methyl group.[35] For this purpose, we assayed several reagents under photochemical conditions, obtaining different results. The irradiation of **8** in the presence of a mixture of iodine and either (diacetoxyiodo)benzene[36] or lead tetraacetate gave tetracyclic derivative **28**,[37] whereas




**8** was recovered unchanged when the irradiation was performed in the presence of diphenylhydroxyselenium acetate[38] and iodine. Finally, under the condition summarized in Scheme 5, a 30% yield of **25** was obtained but 60% of **8** could be recovered and reused, increasing the yield of iodohydrin to 49%. Longer reaction times transformed **25** into the transposed iodoformate **29**,[39] and thus, the yield of iodohydrin was not improved.

In any case, iodohydrin **25** showed suitable enough functionalization to be transformed easily into an adequate precursor (like **9**, with different leaving groups at C-2 and C-14) of the enol lactone **10** foreseen in Scheme 1. Therefore, mesylate **26** was prepared (75% yield) by a reaction between **25** and methanesulfonyl chloride. Unexpectedly, basic treatment of **26** resulted in a mixture of *cis*-fused $\delta$-lactone **27** and tetrahydrofuran derivative **30** instead of a *trans*-fused enol lactone such as **10**. The reaction was carried out under different experimental conditions (temperatures ranging from −10 to 100 °C, reaction times from 1 to 24 h, and different solvents), but the expected enol lactone was never detected. In contrast, the interesting product **27** could be isolated at a moderate 43% yield by working in THF at 25 °C. In the $^1$H NMR spectrum of **27**,[18c] the signals corresponding to the exocyclic methylene ($\delta$ 6.76, t, $J$ = 1.0 Hz, 1H; $\delta$ 5.98, t, $J$ = 1.0 Hz, 1H) as well as the diastereotopic protons H-14a ($\delta$ 4.55, d, $J$ = 12.3 Hz, 1H) and H-14b ($\delta$ 4.14, dd, $J$ = 12.3, 1.6 Hz, 1H) showed chemical shifts, multiplicities, and coupling constant values characteristic of the 2-oxa-*cis*-decalin skeleton of vernolepin-related compounds.[41] Additionally, in the $^{13}$C NMR spectrum of **27**,[18c] the chemical shift and multiplicity of C-14 ($\delta$ 70.0, t) supported the *cis*-fused $\delta$-lactone unit.[8,36] We did not have direct evidence for the stereochemistry of the oxirane ring of **27**, but we tentatively proposed a 1*S* configuration because this was consistent with a plausible mechanism to explain the formation of **27** from **26** (see Scheme 6b and discussion below). We did not detect the formation of the potential 1*R* epimer of **27** in any of our experiments.

**SCHEME 6**




The methanesulfonyl group of **26** plays a critical role in the reaction leading to **27**, and thus, when iodohydrin **25** was treated under the same conditions, only the tetrahydrofuran derivative **30** was obtained (Scheme 6a). A simple inspection of structures **26** ($C_{16}H_{21}IO_7S$) and **27** ($C_{15}H_{18}O_5$) suggests sulfene ($CH_2SO_2$) and HI eliminations instead of the expected elimination of methanesulfonic acid, which would have led to an enol lactone such as **10**. Sulfene elimination from organic mesylates is an unusual reaction, although evidence of sulfene formation from methanesulfonyl chloride in the presence of pyridine has been reported.[42] With this idea in mind,

(35) For an update on remote intramolecular functionalizations, see: Majetich, G.; Wheles, K. *Tetrahedron* **1995**, *51*, 7095.

(36) Hernández, R.; Velázquez, S. M.; Suárez, E.; Rodríguez, M. S. *J. Org. Chem*. **1994**, *59*, 6395.

(37) Experimental details and spectroscopic data of **28** are described in the Supporting Information available.

(38) Dorta, R. L.; Francisco, C. G.; Freire, R.; Suárez, E. *Tetrahedron Lett*. **1988**, *29*, 5429.

(39) Regioselective $\beta$-scission of alkoxy radicals (obtained from alcohols by a multistep sequence) to iodoformates has already been used for the syntheses of 18- and 19-norsteroids,[40] but to the best of our knowledge, reactions directly leading to transposed iodoformates from alcohols (presumably via 1,4-halohydrins) have not been reported before. For experimental details and the spectroscopic properties of **29**, see the Supporting Information available.

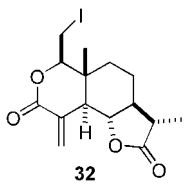
(40) (a) Suginome, H.; Senboku, H.; Yamada, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2199. (b) Suginome, H.; Nakayama, Y.; Senboku, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1837.

(41) Abegaz, B. M.; Keige, A. W.; Díaz, J. D.; Herz, W. *Phytochemistry* **1994**, *37*, 191.

(42) Crossland, R. K.; Servis, K. L. *J. Org. Chem*. **1970**, *35*, 3195.

we propose the mechanism depicted in Scheme 6b to rationalize the formation of **27** from **26**. Thus, the selective abstraction of a relatively acidic hydrogen from the methanesulfonyl group would promote sulfene elimination and the resultant oxirane formation process leading to intermediate **31**. (The preference for the hydrogen of the methanesulfonyl group might derive from the steric hindrance around H-1, which would obstruct the approach of the bulky base employed.) The iodine atom of **31** would subsequently be displaced by the nucleophilic carboxylate group in a second intramolecular substitution to give the *cis*-fused *δ*-lactone **27**. Despite the moderate yield obtained (43%), transformation of a *trans*-fused *δ*-lactone into a *cis*-fused one bearing an oxirane ring attached to a quaternary carbon atom is an interesting reaction from a synthetic point of view. The chemical building of quaternary centers is generally a difficult task,[43] whereas oxiranes are present in many natural products and are one of the most versatile intermediates in organic synthesis.[44]

Having obtained the epoxide **27**, we only needed to deoxygenate the oxirane ring to reach the target molecule **4** (Scheme 5). There are several reagents described for performing oxirane deoxygenations,[45] and therefore, we decided to assay some of them, using a less elaborate model compound than **27**, to determine the optimum experimental conditions for the deoxygenation reaction. We eventually chose epoxide **7a** because of the close relationship between its functional groups and those of **27**. The deoxygenation of epoxide **7a**, however, turned out to be no trivial task. After conventional treatment with lithium diphenylphosphide and methyl iodide,[46] **7a** was recovered unchanged, whereas more recently described reagents, such as $Cp_2TiCl_2$/Mn,[47] $Me_3SiCl$/NaI,[48] and Amberlyst/NaI,[49] afforded cyclization products **8** or **32**[50] instead of the expected vinyl derivative **16**.



**32**

Finally, the treatment of **7a** with KSeCN in aqueous MeOH, as described by Behan et al.,[51] gave a promising mixture of **16** and some byproducts derived from the Michael addition of MeOH to the conjugated double bond. Therefore, the reaction was assayed in other solvents to avoid the formation of byproducts. The combination of *t*-BuOH and water at a ratio of 9:1 provided the best results, giving a virtually quantitative yield of **16**. Once the optimum experimental conditions were established for the model compound, they were applied to the deoxygenation of epoxide **27** (Scheme 5). Thus, the 10-vinyl-2-oxa-*cis*-decalin **4** was obtained at an acceptable yield of 71%. In this way, the synthesis of (+)-11*β*,13-dihydro-8-deoxyvernolepin (**4**) from (+)-costunolide (**5**) was completed in 10 steps with an overall yield of almost 5%.

In conclusion, we describe here the syntheses of (+)-8-deoxyvernolepin (**3**) and (+)-11*β*,13-dihydro-8-deoxyvernolepin (**4**) from (+)-costunolide (**5**) isolated from a commercially available extract. During these syntheses, the following novel reactions were used as key steps: the stereoselective cyclization of a *δ*,*ϵ*-epoxy ester to a hydroxymethyl-substituted *δ*-lactone and a cascade reaction, initiated by sulfene elimination, which led to a 10-oxiranyl-2-oxa-*cis*-decalin from the mesylate of a *trans*-fused *δ*-lactone. We also found that the reaction of selenium dioxide with the 1,5-diene system of elemanolides gave selenacycles analogous to natural eudesmanolides. Our results indicate that the strategy employed, on the basis of biomimetic concepts, should provide a useful alternative for the enantiospecific preparation of (+)-vernolepin-related compounds from accessible germacrolides. At the moment, we are using this strategy to synthesize (+)-vernolepin (**1**), (+)-vernodalin (**2**), and their corresponding 11,13-dihydroderivatives from (+)-salonitenolide, an 8-hydroxygermacrolide easily isolated in (multi)gram quantities from *Centaurea calcitrapa* and other plants widespread in the Mediterranean area.[11b,18b] We trust that this work will facilitate further studies about the structure−activity relationships and the physiological mechanisms involved in the antifungal activity of vernolepin-related compounds.

## Experimental Section

**General Details.** The NOE-difference (NOE-dif) technique was employed to observe nuclear Overhauser effects. $^{13}C$ NMR peak assignments were made with the aid of DEPT and 2D NMR (COSY, HMQC, and HMBC) experiments. The numbering used in the NMR assignments corresponds to the germacrane system and not the IUPAC nomenclature. Other general experimental details have been reported elsewhere.[18b]

**Costunolide (5).** This compound was obtained in (multi)gram quantities from the commercially available extract Costus Resinoid (Pierre Chauvet S. A., Seillans, France) as described elsewhere.[20]

**11*β*,13-Dihydrocostunolide (12).** 10% Pd/C (34 mg) was added to **5** (1.3 g, 5.5 mmol) in MeOH (40 mL), and the suspension was slowly stirred for 30 min under $H_2$ at atmospheric pressure. The mixture was then filtered and the solvent removed in vacuo from the filtrate, affording **12** (1.2 g, 93% yield). White solid: mp 70−71 °C; $[\alpha]^{25}_D$ +107° (*c* 1.08,

(43) For recent reviews of the enantioselective construction of quaternary stereocenters, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(44) For a recent overview of the syntheses of selected natural products containing elegant examples concerning the usefulness of oxiranes in organic synthesis, see: Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

(45) For a review on stereospecific deoxygenations of epoxides, see: Wong, H. N. C.; Fok, C. C. M.; Wong, T. *Heterocycles* **1987**, *26*, 1345.

(46) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178.

(47) (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849.

(48) Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* **1981**, *22*, 3551.

(49) Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* **2000**, *56*, 1733.

(50) Reaction of **7a** with $Cp_2TiCl_2$/Mn gave **8**, whereas reactions with either $Me_3SiCl$/NaI or Amberlyst 15/NaI gave iodo-derivative **32**. These results confirm that the stereoselective cyclization of *δ*,*ϵ*-epoxy esters is a versatile reaction useful for the synthesis of *δ*-alkyl-substituted *δ*-lactones with different functional groups attached to the *ϵ*-position. For experimental details and the spectroscopic properties of **32**, see Supporting Information available.

(51) Behan, J. M.; Johnstone, R. A. W.; Wright, M. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216.

$CHCl_3$) (lit.[23] mp 74−75 °C, $[\alpha]^{24}_D$ +108°); IR and $^1$H NMR spectra in ref 23; $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 178.6 (s), 140.3 (s), 136.9 (s), 127.4 (d), 127.1 (d), 81.5 (d), 54.7 (d), 42.3 (d), 41.2 (t), 39.6 (t), 28.6 (t), 26.2 (t), 17.2 (q), 16.2 (q), 13.3 (q). HRCIMS *m*/*z* calcd for $C_{15}H_{23}O_2$: 235.1698. Found 235.1705. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.59; H, 9.85.

**Sasussurea Lactone (13).** Compound **12** (95 mg) was heated to 205−210 °C for 5 min under an Ar atmosphere in a sealed flask. Subsequent flash chromatography (hexane/*t*-BuOMe 9:1) of the mixture obtained gave **12** (39 mg, 41%) and **13** (53 mg, 56% yield). Compound **13**, colorless needles: mp 147−148 °C; $[\alpha]^{25}_D$ +76.5° (*c* 0.69, $CHCl_3$) (lit.[52] mp 146−147 °C, $[\alpha]^{22}_D$ +65.4°); IR and $^1$H NMR spectra in ref 52; $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 179.3 (s), 147.8 (d), 141.0 (s), 115.2 (t), 111.5 (t), 81.3 (d), 55.7 (d), 52.2 (d), 42.7 (s), 41.6 (d), 39.4 (t), 24.0 (q), 23.6 (t), 18.3 (q), 12.6 (q). HRFABMS *m*/*z* calcd for $C_{15}H_{22}O_2Na$: 257.1518. Found: 257.1517.

**8-Deoxymelitensin (14) and Aldehyde 15.** Compound **13** (550 mg, 2.35 mmol) in $CH_2Cl_2$ (10 mL) was added to a solution of $SeO_2$ (130 mg, 1.17 mmol) and *t*-BuOOH (1.8 mL of a 5−6 M solution in decane) in $CH_2Cl_2$ (10 mL) at 0 °C. The mixture was allowed to reach rt and stirred under an Ar atmosphere for 60 h. The mixture was then diluted with $CH_2Cl_2$ and washed with brine. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. The residue was submitted to flash chromatography (hexane/*t*-BuOMe 1:1), affording **14** (235 mg, 40% yield) and **15** (250 mg, 43% yield). 8-Deoxymelitensin (**14**), oil: $[\alpha]^{25}_D$ +50.1° (*c* 1.28, $CHCl_3$) (lit.[52] $[\alpha]^{22}_D$ +52.4°); IR and $^1$H NMR spectra in ref 52; $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 179.0 (s), 147.3 (d), 145.1 (s), 114.2 (t), 112.1 (t), 81.4 (d), 67.4 (t), 52.5 (d), 51.1 (d), 42.4 (s), 41.8 (d), 39.4 (t), 23.5 (t), 17.7 (q), 12.6 (q). HRFABMS *m*/*z* calcd for $C_{15}H_{22}O_3Na$: 273.1467. Found: 273.1470. Aldehyde **15**, white solid: mp 149−150 °C; $[\alpha]^{25}_D$ +13.9° (*c* 0.91, $CHCl_3$); IR (film) 1770, 1689 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.42 (s, 1H), 6.24 (s, 1H), 6.22 (s, 1H), 5.66 (dd, *J* = 17.4, 10.7 Hz, 1H), 4.87 (d, *J* = 10.7 Hz, 1H), 4.79 (d, *J* = 17.4 Hz, 1H), 4.31 (dd, *J* = 11.8, 10.4 Hz, 1H), 2.99 (d, *J* = 11.8 Hz, 1H), 2.37 (dq, *J* = 12.4, 6.9 Hz, 1H), 1.90 (dq, *J* = 12.4, 3.2 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 194.0 (d), 178.9 (s), 146.7 (d), 145.7 (s), 137.3 (t), 112.0 (t), 80.0 (d), 52.3 (d), 46.2 (d), 42.5 (s), 41.6 (d), 39.0 (t), 23.5 (t), 16.8 (q), 13.6 (q); EIMS *m*/*z* 248 (3) $[M]^+$, 219 (6), 179 (11), 175 (21), 123 (18), 107 (31), 81 (77), 55 (82), 41 (100). HRFABMS *m*/*z* calcd for $C_{15}H_{20}O_3Na$: 271.1310. Found: 271.1309. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.11; H, 8.44.

A sample of PDC (530 mg, 1.4 mmol) was added to **14** (235 mg, 0.94 mmol) in anhyd THF (10 mL) at 0 °C. The mixture was allowed to reach rt and stirred under an Ar atmosphere for 48 h. The mixture was then diluted with *t*-BuOMe and filtered through a pad of Florisil. The solvent was removed, and **15** (208 mg) was obtained.

**Reaction of 13 with $SeO_2$ in Boiling Dioxane.** We added $SeO_2$ (398 mg, 3.58 mmol) to a solution of **13** (600 mg, 2.56 mmol) in anhyd dioxane (80 mL) under an Ar atmosphere and heated the mixture to reflux for 40 min. The mixture was then filtered and the solvent removed, leaving a residue that was submitted to flash chromatography (hexane/*t*-BuOMe 6:4), giving **13** (60 mg, 0.256 mmol, 10%), **15** (200 mg, 0.81 mmol, 32%), and an inseparable mixture (190 mg) of two alcohols. Acetic anhydride (0.07 mL, 5 mmol) and DMAP (660 mg, 5.4 mmol) were added to this mixture dissolved in $CH_2Cl_2$, and the solution was stirred at rt for 30 min. The solution was then washed with 2 N HCl, 2 N NaOH, and brine. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography (*t*-BuOMe/AcOEt 6:4) of the residue gave **20** (43 mg) and the acetylated derivative of **14** (53 mg, 0.18 mmol). Compound **20**, colorless oil: $[\alpha]^{25}_D$ +227.9° (*c* 0.61, $CHCl_3$); IR (film) 1775, 1738 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.21 (s, 1H), 4.84 (d, *J* = 1.4 Hz, 1H), 4.80 (dd, *J* = 11.7, 7.2 Hz, 1H), 4.64 (dd, *J* = 11.7, 4.6 Hz, 1H), 4.07 (t, *J* = 10.6 Hz, 1H), 3.62 (d, *J* = 11.8 Hz, 1H), 3.04 (d, *J* = 11.8 Hz, 1H), 2.64 (dd, *J* = 7.2, 4.6 Hz, 1H), 2.43 (d, *J* = 10.7 Hz, 1H), 2.34 (dq, *J* = 12.3, 6.9 Hz, 1H), 2.11 (s, 3H), 1.30 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H); NOE-dif experiments, $\delta$ proton irradiated ($\delta$ NOEs observed) 2.64 (4.80, 4.64, 1.30), 2.43 (4.80, 4.64, 3.62), 1.30 (4.07, 2.64); $^{13}$C NMR in Table 1; CIMS *m*/*z* 375 (2) [M + H, $^{82}$Se]$^+$, 373 (8), 371 (4), 313 (25), 161 (26), 81 (42), 61 (100). HRFABMS *m*/*z* calcd for $C_{17}H_{24}O_4Na^{80}Se$: 395.0737. Found: 395.0737.

**TABLE 1. $^{13}$C NMR Data ($CDCl_3$, 100 MHz) of *trans*-Fused Heterodecalins 17, 18, 20, and 24−26 and *cis*-Fused Heterodecalin 4**

| C | 17 | 18 | 20[a] | 24 | 25 | 26[b] | 4 |
|---|---|---|---|---|---|---|---|
| 1 | 90.2 | 89.0 | 45.5 | 88.3 | 90.9 | 87.0 | 141.0 |
| 2 | 61.1 | 61.1 | 65.1 | 61.9 | 61.6 | 67.4 | 116.3 |
| 3 | 14.9 | 18.3 | 24.8 | 130.2 | 130.9 | 131.9 | 134.9 |
| 4 | 35.1 | 38.0 | 140.8 | 134.0 | 132.3 | 131.7 | 130.9 |
| 5 | 46.9 | 51.2 | 49.2 | 44.3 | 49.9 | 50.1 | 47.1 |
| 6 | 78.5 | 81.7 | 79.2 | 80.5 | 78.9 | 78.7 | 80.8 |
| 7 | 52.4 | 52.2 | 51.9 | 51.7 | 51.5 | 51.6 | 50.6 |
| 8 | 22.9 | 22.9 | 24.0 | 22.6 | 22.4 | 22.2 | 23.2 |
| 9 | 35.8 | 34.4 | 36.7 | 33.1 | 35.6 | 35.0 | 33.2 |
| 10 | 37.3 | 37.7 | 43.4 | 38.1 | 40.1 | 40.5 | 40.7 |
| 11 | 41.0 | 40.7 | 41.4 | 40.4 | 40.5 | 40.4 | 41.5 |
| 12 | 178.7 | 178.5 | 178.9 | 178.6 | 178.0 | 177.6 | 178.1 |
| 13 | 12.5 | 12.5 | 12.5 | 12.5 | 12.4 | 12.5 | 12.6 |
| 14 | 14.9 | 13.6 | 23.2 | 20.2 | 2.6 | 1.6 | 70.6 |
| 15 | 173.3 | 172.9 | 111.3 | 165.1 | 163.2 | 162.2 | 163.6 |

[a] Chemical shifts for $CH_3CO_2$: $\delta$ 21.3 (q), 170.9 (s). [b] Chemical shift for $CH_3SO_3$: $\delta$ 38.2 (q).

**Methyl Ester 16.** A solution of $NaClO_2$ (3.191 g, 35.28 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (3.761 g, 24.11 mmol) in $H_2O$ (31 mL) was dripped into a mixture of **15** (1.050 g, 4.23 mmol) and 2-methyl-2-butene (18 mL) in *t*-BuOH (90 mL) for 30 min. The mixture was then stirred for 4 h, and the volatile compounds were removed in vacuo. $H_2O$ was added, the organic compounds were extracted with *t*-BuOMe, and the ethereal solution was dried over anhyd $Na_2SO_4$ and filtered. A saturated solution of $CH_2N_2$/*t*-BuOMe (14 mL) was then added to the filtrate at 0 °C and stirred until the yellow color disappeared. The solvent was removed and the residue submitted to flash chromatography (hexane/*t*-BuOMe 8:2), giving **16** (1073 mg, 3.86 mmol, 91% yield). White solid: mp 105−106 °C; $[\alpha]^{25}_D$ +61.2° (*c* 1.33, $CHCl_3$); IR (film) 1767, 1723 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.34 (s, 1H), 5.70 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.49 (s, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.82 (d, *J* = 17.4 Hz, 1H), 4.18 (dd, *J* = 11.4, 10.9 Hz, 1H), 3.66 (s, 3H), 3.04 (d, *J* = 11.4 Hz, 1H), 2.36 (dq, *J* = 12.6, 6.9 Hz, 1H), 1.87 (dq, *J* = 12.5, 3.1 Hz, 1H), 1.72 (dq, *J* = 12.0, 3.0 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.98 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.9 (s), 167.9 (s), 146.5 (d), 136.7 (s), 126.9 (t), 111.9 (t), 80.0 (d), 52.2 (d), 51.9 (q), 48.8 (d), 42.5 (s), 41.7 (d), 39.0 (t), 23.5 (t), 16.4 (q), 12.6 (q); EIMS *m*/*z* 278 (1) $[M]^+$, 246 (11), 218 (10), 145 (17), 105 (23), 81 (51), 55 (65), 41 (100). HRFABMS *m*/*z* calcd for $C_{16}H_{22}O_4Na$: 301.1416. Found: 301.1418. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.74; H, 7.87.

**Epoxidation of 16 with Dimethyldioxirane (DMDO).** A solution of DMDO in acetone, previously prepared from 120 g of caroate,[53] was added to **16** (800 mg, 2.88 mmol) in acetone (15 mL). The mixture was stirred for 2 h at rt, and the solvent was then removed. Flash chromatography (hexane/*t*-BuOMe 1:1) of the residue gave **7a** (657 mg, 77% yield) and **7b** (90 mg, 11% yield). Epoxide **7a**, white solid: mp 135−136 °C; $[\alpha]^{25}_D$ +59.7° (*c* 1.33, $CHCl_3$); IR (film) 1769, 1724 cm$^{-1}$; $^1$H NMR ($CDCl_3$ 400 MHz) $\delta$ 6.45 (s, 1H), 5.58 (s, 1H), 4.18 (t, *J* = 11.1 Hz, 1H), 3.73 (s, 3H), 3.16 (d, *J* = 11.7 Hz, 1H), 2.77 (t, *J* =

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3.4 Hz, 1H), 2.45 (d, $J$ = 3.4 Hz, 2H), 2.36 (dq, $J$ = 12.6, 6.9 Hz, 1H), 1.92 (dq, $J$ = 12.6, 3.2 Hz, 1H), 1.23 (d, $J$ = 6.9 Hz, 3H), 0.70 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.7 (s), 167.6 (s), 136.2 (s), 128.4 (t), 79.7 (d), 58.8 (d), 52.2 (d), 52.1 (q), 47.5 (d), 43.8 (t), 41.7 (d), 39.9 (s), 35.6 (t), 23.1 (t), 12.6 (q), 12.1 (q); EIMS $m/z$ 294 (0.3) $[M]^+$, 262 (2), 244 (2), 189 (6), 161 (8), 121 (14), 91 (30), 67 (28), 55 (88), 41 (100); HRFABMS $m/z$ calcd for $C_{16}H_{22}O_5Na$: 317.1365. Found: 317.1368. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.96; H, 7.96. Epoxide **7b**, white solid: mp 95−96 °C; $[\alpha]^{25}_D$ +61.3° ($c$ 1.69, $CHCl_3$); IR (film) 1776, 1719 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.45 (s, 1H), 5.58 (s, 1H), 4.14 (dd, $J$ = 11.6, 10.5 Hz, 1H), 3.76 (s, 3H), 3.26 (d, $J$ = 11.6 Hz, 1H), 2.82 (dd, $J$ = 3.8, 3.1 Hz, 1H), 2.53 (dd, $J$ = 4.4, 3.8 Hz, 1H), 2.50 (dd, $J$ = 4.4, 3.1 Hz, 1H), 2.37 (dq, $J$ = 12.5, 6.9 Hz, 1H), 1.23 (d, $J$ = 6.9 Hz, 3H), 0.72 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.7 (s), 167.6 (s), 136.5 (s), 126.9 (t), 80.1 (d), 59.2 (d), 52.3 (q), 52.2 (d), 48.8 (d), 42.2 (t), 41.7 (d), 39.9 (s), 35.3 (t), 23.0 (t), 13.0 (q), 12.6 (q). HRFABMS $m/z$ calcd for $C_{16}H_{22}O_5Na$: 317.1365. Found: 317.1369.

***δ*-Lactone 8.** $BF_3{\cdot}OEt_2$ (0.11 mL, 0.9 mmol) was added to a solution of **7a** (430 mg, 1.46 mmol) in anhyd $CH_2Cl_2$ (25 mL) under an Ar atmosphere. The mixture was stirred at rt for 30 min, $CH_2Cl_2$ was added, and the organic solution was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography (*t*-BuOMe/AcOEt 6:4) of the residue gave **8**[18c] (380 mg, 93% yield).

**Acid-Promoted Cyclization of Epoxide 7b.** $BF_3{\cdot}OEt_2$ (10 $\mu$L, 0.09 mmol) was added to a solution of **7b** (50 mg, 0.17 mmol) in anhyd $CH_2Cl_2$ (4 mL) under an Ar atmosphere. The mixture was stirred at rt for 3.5 h, $CH_2Cl_2$ was added, and the organic solution was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography (*t*-BuOMe/AcOEt 7:3) of the residue gave **8** (8 mg, 17% yield), **24** (16 mg, 34% yield), and **7b** (4 mg, 8%). Compound **24**, colorless oil: $^1$H NMR ($CDCl_3$ 300 MHz) $\delta$ 6.59 (d, $J$ = 2.6 Hz, 1H), 6.09 (d, $J$ = 2.6 Hz, 1H), 4.05−3.95 (m, 4H), 3.33 (dt, $J$ = 10.3, 2.6 Hz, 1H), 2.33 (dq, $J$ = 12.6, 6.9 Hz, 1H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.11 (s, 3H); $^{13}$C NMR in Table 1.

**Hydrogenated Derivative 17.** 10% Pd/C was added to **8** (60 mg, 0.21 mmol) in MeOH (40 mL), and the suspension was bubbled with $H_2$ and vigorously stirred for 1.5 h. The mixture was then filtered and the solvent removed in vacuo from the filtrate, affording **17** (50 mg, 85% yield). Oil: $^1$H NMR ($CDCl_3$ 400 MHz) $\delta$ 4.17 (dd, $J$ = 6.2, 4.4 Hz, 1H), 3.92 (dd, $J$ = 11.3, 10.3 Hz, 1H), 3.77−3.73 (m, 2H), 3.05 (dq, $J$ = 8.1, 7.8 Hz, 1H), 2.35 (dq, $J$ = 12.4, 6.9 Hz, 1H), 2.15 (dd, $J$ = 11.3, 8.1 Hz, 1H), 1.94 (dq, $J$ = 13.0, 3.0 Hz, 1H), 1.71 (ddd, $J$ = 13.2, 4.0, 3.0 Hz, 1H), 1.43 (d, $J$ = 7.8 Hz, 3H), 1.38 (dt, $J$ = 13.0, 4.0 Hz, 1H), 1.22 (d, $J$ = 6.9 Hz, 3H), 1.06 (s, 3H). NOE-dif experiments, $\delta$ proton irradiated ($\delta$ NOEs observed): 3.92 (2.35, 1.43, 1.06), 3.05 (2.15, 1.43), 2.15 (4.17, 3.05), 1.43 (3.92, 3.05). $^{13}$C NMR in Table 1.

**Base-Promoted Isomerization of 17.** Diazabicycloundecane (DBU) (15 $\mu$L, 0.04 mmol) was added to a solution of **17** (50 mg, 0.18 mmol) in toluene (2 mL) under an Ar atmosphere. The mixture was heated to 60 °C and stirred for 2 h. Then $CHCl_3$ was added, and the solution was washed with 1 N HCl and $H_2O$. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography of the residue (*t*-BuOMe/AcOEt 85:15) afforded **18**[34] (40 mg, 80% yield). Oil: $[\alpha]^{25}_D$ +28.0 ($c$ 0.4, $Cl_3CH$); IR (film) 3454, 1779, 1725 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.19 (t, $J$ = 5.3 Hz, 1H), 3.80 (t, $J$ = 10.5 Hz, 1H), 3.74 (d, $J$ = 5.3 Hz, 2H), 2.62 (dq, $J$ = 10.8, 7.1 Hz, 1H), 2.28 (dq, $J$ = 12.3, 6.9 Hz, 1H), 1.51 (d, $J$ = 7.1 Hz, 3H), 1.22 (d, $J$ = 6.9 Hz, 3H), 1.02 (s, 3H); $^{13}$C NMR in Table 1. HRFABMS $m/z$ calcd for $C_{15}H_{22}O_5Na$: 305.1364. Found: 305.1365.

**Iodohydrin 25.** HgO (201 mg, 0.93 mmol) and $I_2$ (118 mg, o.46 mmol) were added to a solution of **8** (130 mg, 0.46 mmol) in anhyd 1:1 $CH_2Cl_2/CCl_4$ (50 mL) under an Ar atmosphere. The mixture was heated to reflux and irradiated with two 100 W tungsten filament lamps for 8 h. The mixture was then diluted with $CH_2Cl_2$ and washed with a $Na_2S_2O_3$ saturated solution. The organic layer was dried over anhyd $Na_2SO_4$ and filtered, and the solvent was removed. Flash chromatography (*t*-BuOMe) of the residue gave **25** (45 mg, 24% yield) and **8** (78 mg). Compound **25**, pale yellow solid: mp 114−115 °C (decompose); $[\alpha]^{25}_D$ +3.3 ($c$ 0.9, $Cl_3CH$); IR (film) 3470, 1780, 1725 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.68 (d, $J$ = 2.6 Hz, 1H), 6.14 (d, $J$ = 2.6 Hz, 1H), 4.46 (br d, $J$ = 8.7 Hz, 1H), 4.22 (dd, $J$ = 12.2, 8.7 Hz, 1H), 4.15 (br d, $J$ = 12.2 Hz, 1H), 3.97 (t, $J$ = 10.5 Hz, 1H), 3.81 (br s, 1H), 3.34 (d, $J$ = 12.0 Hz, 1H), 3.09 (dd, $J$ = 12.0, 1.1 Hz, 1H), 2.89 (dt, $J$ = 10.5, 2.6 Hz, 1H), 1.28 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR in Table 1. HRCIMS $m/z$ calcd for $C_{15}H_{20}O_5I$: 407.0355. Found: 407.0356.

**Mesylate 26.** Methanesulfonyl chloride (20 $\mu$L, 0.25 mmol) and $Et_3N$ (80 $\mu$L, 0.55 mmol) were added to iodohydrin **25** (45 mg, 0.11 mmol) in anhyd $CH_2Cl_2$ (2 mL) at 0 °C. The mixture was stirred at this temperature for 11 h and at 25 °C for a further 6 h. The mixture was then diluted with $CH_2Cl_2$ and washed with saturated solutions of $KHSO_4$ and $NaHCO_3$. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography (*t*-BuOMe) of the residue gave mesylate **26** (40 mg, 75% yield). White solid: mp 103−104 °C; $[\alpha]^{25}_D$ +20.5° ($c$ 1.27, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.69 (d, $J$ = 2.5 Hz, 1H), 6.17 (d, $J$ = 2.5 Hz, 1H), 4.66−4.58 (m, 3H), 3.95 (t, $J$ = 10.6 Hz, 1H), 3.35 (dd, $J$ = 12.2, 1.4 Hz, 1H), 3.13 (s, 3H), 3.12 (d, $J$ = 12.2 Hz, 1H), 2.92 (dt, $J$ = 10.6, 2.5 Hz, 1H), 2.43 (dt, $J$ = 13.3, 3.0 Hz, 1H), 2.38 (dq, $J$ = 12.6, 6.9 Hz, 1H), 2.01 (dq, $J$ = 13.3, 3.1 Hz, 1H), 1.45 (dt, $J$ = 13.3, 3.0 Hz, 1H), 1.28 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR in Table 1. HRCIMS $m/z$ calcd for $C_{16}H_{22}O_7IS$: 485.0131. Found: 485.0132.

**Reaction between 26 and DBU at 25 °C.** DBU (0.2 mL, 1.34 mmol) was added to mesylate **26** (40 mg, 0.083 mmol) in THF (2 mL) under an Ar atmosphere, and the mixture was stirred at 25 °C for 24 h. The mixture was then diluted with $CH_2Cl_2$ and washed with 1 N HCl and $H_2O$. The organic layer was dried over anhyd $Na_2SO_4$, and the solvent was removed. Flash chromatography (*t*-BuOMe) of the residue gave 2-oxa-*cis*-decalin **27**[18c] (10 mg, 43%) and tetracyclic ether **30** (11 mg, 47%). Compound **30**, oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.57 (d, $J$ = 2.2 Hz, 1H), 6.01 (d, $J$ = 2.2 Hz, 1H), 4.70 (d, $J$ = 3.1 Hz, 1H), 4.01 (d, $J$ = 10.8 Hz, 1H), 3.89 (dd, $J$ = 10.8, 3.1 Hz, 1H), 3.83 (dd, $J$ = 9.2, 1.5 Hz, 1H), 3.71 (t, $J$ = 10.6 Hz, 1H), 3.61 (d, $J$ = 9.2 Hz, 1H), 2.99 (dt, $J$ = 10.6, 2.2 Hz, 1H), 2.35 (dq, $J$ = 12.4, 6.9 Hz, 1H), 1.96 (dt, $J$ = 13.2, 3.2 Hz, 1H), 1.28 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.9 (s), 132.3 (s), 128.9 (t), 88.2 (d), 80.4 (d), 73.2 (t), 72.0 (t), 51.1 (d), 47.7 (s), 45.2 (d), 40.5 (d), 34.3 (t), 23.5 (t), 12.6 (q). HRFABMS $m/z$ calcd for $C_{15}H_{18}O_5Na$: 301.1052. Found: 301.1055.

**11*β*,13-Dihydro-8-deoxyvernolepin (4).** KSeCN (12 mg, 0.083 mmol) was added to a solution of **27** (18 mg, 0.063 mmol) in 9:1 *t*-BuOH/$H_2O$ (3 mL), and the mixture was stirred at 65 °C for 6 h. Then, *t*-BuOMe was added, the solution was filtered, and the solvent was removed from the filtrate. Flash chromatography (*t*-BuOMe/AcOEt, 85:15) of the residue afforded **4** (12 mg, 71%). Oil: $[\alpha]^{25}_D$ +28.0° ($c$ 0.25, $CHCl_3$); IR (film) 1779, 1720 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.67 (dd, $J$ = 1.1, 0.7 Hz, 1H), 5.86 (t, $J$ = 1.1 Hz, 1H), 5.69 (dd, $J$ = 17.2, 11.2 Hz, 1H), 5.24 (d, $J$ = 11.2 Hz, 1H), 5.22 (d, $J$ = 17.2 Hz, 1H), 4.55 (d, $J$ = 12.1 Hz, 1H), 4.20 (dd, $J$ = 12.1, 1.8 Hz, 1H), 3.94 (t, $J$ = 10.8 Hz, 1H), 2.81 (br d, $J$ = 11.0, 1H), 2.37 (dq, $J$ = 12.4, 6.8 Hz, 1H), 1.25 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR in Table 1; CIMS $m/z$ 263 $[M + H]^+$ (13), 217 (10), 141 (41), 123 (100). HRCIMS $m/z$ calcd for $C_{15}H_{19}O_4$: 263.1283. Found: 263.1284.

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**Supporting Information Available:** Experimental details and spectroscopic data for compounds **28**, **29**, and **32**. Copies of the $^{13}C$ NMR spectra of compounds **4**, **7b**, **17**, **20**, **24**−**26**, **29**, **30**, and **32**. A copy of the $^{1}H$ NMR spectrum of **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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