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Synthesis of Spirovetivane Sesquiterpenes from Santonin. Synthesis of (+)-Anhydro-β-rotunol and All Diastereomers of 6,11-Spirovetivadiene

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The synthesis of the spirovetivane sesquiterpenes (+)-anhydro-β-rotunol and all the diastereomers of 6,11-spirovetivadiene in enantiomerically pure form has been achieved starting from santonin. The key step is the silicon-guided acid-promoted rearrangement of a 1-trimethylsilyl-4,5-epoxy-eudesmane prepared from santonin in several steps involving lactone reductive opening, conjugate addition of TMSLi−CuCN, deoxygenation of a carbonyl group, and epoxidation. Rearrangement of the epoxide gave a spiro[4,5]decanediol which was used as a synthetic intermediate. From this compound, (+)-anhydro-β-rotunol was prepared after elimination of the primary hydroxyl group in the side chain, followed by allylic oxidation at C8 and elimination of the tertiary hydroxyl group in the cyclohexane ring. On the other hand, elimination of the hydroxyl group in the side chain and reduction of the hydroxyl in the cyclohexane ring gave (−)-premnaspirodiene and (−)-hinesene. The synthesis of the rest of the diastereomers for these compounds required formal inversion of the C5 spiro carbon. The synthesis of these compounds showed that the structure of (−)-agarospirene isolated from *Scapania* sp. was erroneously assigned, and it has been corrected to be identical to that of (−)-hinesene.

Spirovetivanes constitute one of the largest groups of spirocyclic sesquiterpenes. Many of these compounds, such as hinesol (**1**)[1] or agarospirol (**2**),[2] are fragrant principles that have been isolated from essential oils from plants. Others, however, are not produced by healthy plants, but they are phytoalexins produced as defense substances after infection by fungi or bacteria. (+)-Anhydro-β-rotunol (**3**) and (−)-solavetivone (**4**) are examples of natural products produced in this way from infected potato tubers and tobacco leaves.[3] Stereochemical elucidation of compounds of this variety is sometimes troublesome, and one can find in the literature examples of structures with undetermined stereochemistry or contradictory stereochemical data. Furthermore, biological activity of 6-spirovetivenes appears to be dependent on the relative stereochemistry of the methyl group at C10 and the C1−C5 bond. Thus, *trans*-spirovetivenes, characterized by a trans configuration between these groups, such as solavetivone (**4**), possess inhibitory activity against bacteria, while *cis*-spirovetivenes such as hinesol (**1**) and agarospirol (**2**) are inactive.[4] Therefore, the synthesis of spirovetivenes with known stereochemistry is important for structural elucidation as well as for evaluating structure−activity relationships in these compounds. These molecules present a synthetic challenge since they contain several stereogenic centers as well as a quaternary spiro center in a sterically congested environment represented by the flanking methyl groups (Figure 1).

In the past decade, our group has carried out intense research on the synthesis of sesquiterpenes using santonin (**6**) as starting material in most of the cases.[5] The availability and functionality of this compound makes it a suitable starting material for the synthesis of other sesquiterpenes, especially eudesmanes, guaianes, and elemanes.[6] We recently became interested in the synthesis of spirovetivanes from santonin, a challenge that has not been achieved so far to the best of our knowledge. In

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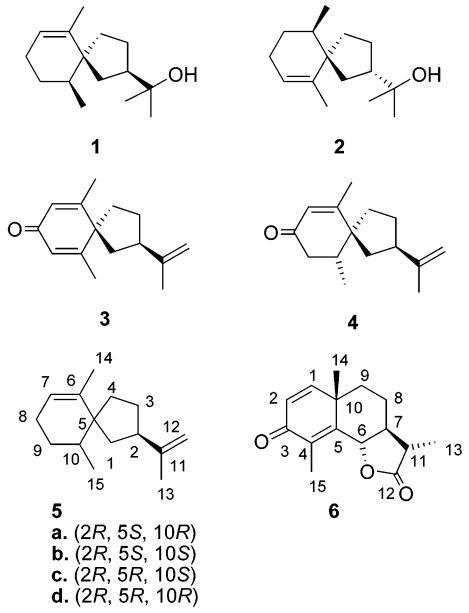

FIGURE 1. Structures of some spirovetivanes and the numbering system followed throughout the text.

this paper, we report the transformation of santonin into the phytoalexin (+)-anhydro-β-rotunol (**3**) and the preparation of all diastereomers of spirovetivadiene **5** in enantiomerically pure form. Structure **5a** has been assigned to (−)-premnaspirodiene, isolated from *Premna latifolia*[7] and *Lepichinia* sp.,[8] and it is an intermediate in a reported synthesis of (−)-solavetivone (**4**).[9] Structure **5b** has been assigned to (−)-hinesene, a natural product isolated from *Lepidozia reptans*,[10] *Rolanda fructifrosa*,[11] and *Frullania* sp.[12] Structure **5c** has not been described yet as a natural product, while structure **5d** has been tentatively assigned to (−)-agarospirene, a natural product isolated from the Taiwanese liverworts *Scapania robusta* and *Scapania maxima*,[13] although the authors did not exclude a structure enantiomeric to **5a** for this natural product. The most difficult challenge in the synthesis of spirovetivanes from santonin is the conversion of the eudesmane carbon skeleton into a spirovetivane framework with stereochemical control of the newly created quaternary spiro carbon. With regard to this challenge, it is worth mentioning the pioneering work by Marshall and Brady[14] on the synthesis of (±)-hinesol where the spiro[4.5]decane system is generated upon a stereocontrolled base-induced fragmentation of a 1,3-diol monosulfonate on a [4.4.0]decane framework.

According to a biomimetic approach,[4,15] this transformation should involve the selective migration of the methylene C9 to C5 (eudesmane numbering) via a cationic rearrangement promoted by an electron-deficient center at C5, i.e., a hydroxyl group or an epoxide under acidic conditions. Although some examples of this transformation have been reported in the literature,[16] most of them were unsuccessful due to one or more of the following reasons: (a) lack of selectivity of the migrating group, (b) 1,2-elimination of the hydroxyl group before rearrangement, and (c) a Grob-type fragmentation of the 1,3-hydroxycarbocations that result after the initial rearrangement in the case of epoxides.[17] These problems can be overcome by introducing a trimethylsiliyl (TMS) group on C1. The TMS group can promote migration of the methyl or methylene groups in β to the TMS group by stabilizing the resulting carbocation at C10 (β-effect), and at the same time it prevents further rearrangements in the resulting carbocation by rapidly eliminating the TMS group to form a double bond between C1 and C10 (super proton behavior).[18] This strategy has been used by Hwu in a total synthesis of solavetivone from carvone.[9] Furthermore, we have shown that it is possible to achieve selective migration of the C9 methylene or C14 methyl groups by properly choosing the disposition between the TMS group and the epoxide, so selective migration of the C9 methylene group is observed when they are both in the same ring.[19]

According to this strategy, the sequence shown in Scheme 1 was carried out. The first transformations were designed to remove the lactone moiety. This was achieved following the procedure by Piers and Cheng[20] in three steps involving epimerization of C6 by treatment of santonin (**6**) with dry DMF containing 5% HCl, followed by reductive cleavage of the C6−O bond with Zn in AcOH/MeOH and esterification of the resulting acid with MeOH−H_2SO_4 to give ester **7** in 68% overall yield. In the next step, the TMS group was introduced at C1 by conjugate addition of a TMS anion to the cross-conjugated dienone system. A first attempt using TMSLi was unsuccessful probably because this reagent was too reactive toward the ester group. However, the reaction worked very well with the mixed cuprate obtained from TMSLi and CuCN[21] to give compound **8** in 85% yield. The reaction took place regio- and stereoselectively, with the TMS group being introduced exclusively from the less hindered α side of the molecule, opposite to the methyl

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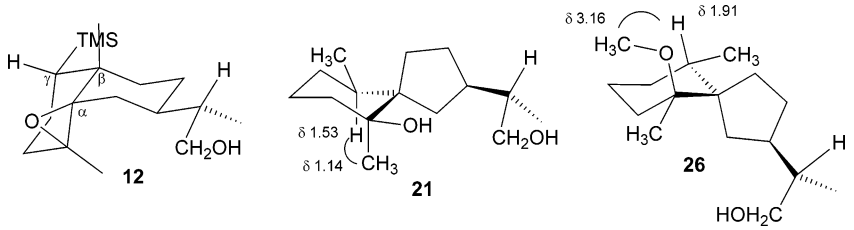
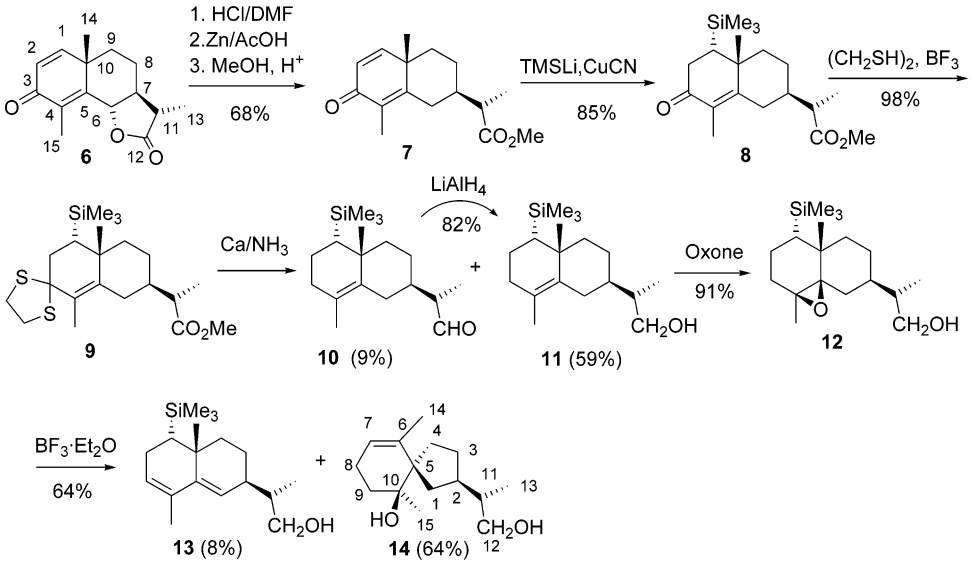


FIGURE 2. γ Effect in compound **12** and most significant NOES in compounds **21** and **26**.

SCHEME 1



group as we will discuss below.[22] No products arising from 1,2- or conjugate addition to C5 were obtained.

Next we undertook the deoxygenation of the carbonyl group at C3. This was carried out in two steps involving formation of a thioketal and reductive desulfurization. Thioketal **9** was obtained in very high yield by treatment of compound **8** with ethanedithiol in acetic acid containing $BF_3 \cdot Et_2O$. Attempts to carry out desulfuration with Raney nickel brought about partial migration of the double bond to the C5−C6 position. To avoid this inconvenience, desulfurization was carried out with Ca in liquid ammonia.[23] During this treatment, the ester group was also reduced to give alcohol **11** as the major product (59%) together with aldehyde **10** (9%). Aldehyde **10** could be conveniently transformed into **11** by reduction with LAH in THF. NOE experiments were carried out with compound **11** in order to determine the stereochemistry of C1 in this and all precedent compounds. Irradiating at the frequency of the H1 double doublet at δ 0.74 produced enhancement of the singlet at δ 1.07 corresponding to the bridgehead methyl H14. The observed NOE is only possible if both H1 and H14 are to the same face of the molecule, i.e., the β face. This would be in good agreement with the preference of the TMS anion to give axial 1,4 addition in cyclohexenones[21b,c] and to approach from the less sterically hindered α face of the molecule in compound **7**. On the other hand, the coupling constants of the double doublet corresponding to H1 at δ 0.74 (J = 10.5, 2.5 Hz) show that H1 is in axial disposition; this indicates a distorted geometry of the ring A as a consequence of the bulky TMS group.

Finally epoxidation of **11** with oxone®/acetone[24] provided only one epoxide diastereoselectively. A complete assignment of the ^{1}H and ^{13}C NMR spectra for compound **12** was carried out with the aid of ^{1}H-^{13}C bidimensional correlation and decoupling experiments. No NOE effect was found between H14 (δ 1.13) and H15 (δ 1.32). NOESY experiments showed some interaction between H15 and the signal corresponding to H7 at δ 1.44, which would be in accordance with the α-disposition of methyl H15. However, because of the partial overlapping of the signal of H15 with the signals of H2 and the proximity between the signals of H7 and H6α (δ 1.41) this result should be considered with caution. Nevertheless, a marked upfield shift for the ^{13}C NMR signal corresponding to C1 (δ 30.7) was observed with respect to the parent olefin (δ 37.5). This was attributed to a γ effect which in polycyclic compounds containing six-membered rings causes an upfield shift on those carbons in γ position with respect to the epoxide having an axial hydrogen syn to the epoxide oxygen (Figure 2).[25] According to this effect, as well as considering the absence of NOEs between H14 and H15 which are normally observed in eudesmanes

(22) Because of the proximity of the signals corresponding to H1 and H14 in the ^{1}H NMR spectrum of **8**, lack of selectivity during irradiation prevented determining the stereochemistry of H1 by NOE experiments. The stereochemistry of H1 was determined by NOEs in compound **11**.

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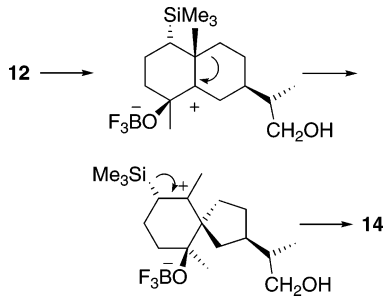
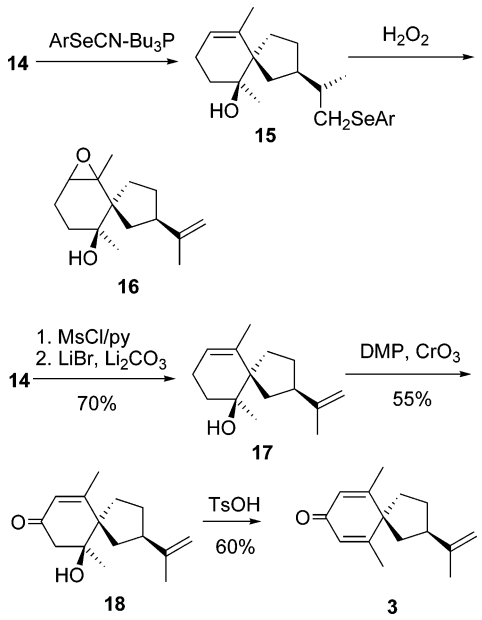
SCHEME 2



when the epoxide and the methyl H14 are *trans*,[26] we assigned the β orientation for the epoxide in compound **12**. This is also in good agreement with the expected approach of the epoxidating reagent from the less sterically congested side of the molecule because of the convexity of the molecule and the presence of the bulky TMS group to the α side.

With this epoxide available we attempted the acid-promoted rearrangement of the carbon skeleton. We expected that a carbocation at C5 should be formed, which would promote selective migration of methylene C9 (guided by the TMS group on C1) to give compound **14** with the spirovetivane skeleton (Scheme 2). Effectively, treatment of compound **12** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −40 °C brought about migration of the C9 methylene to C5 with concomitant contraction of the B ring to give the spiro compound **14** in 64% yield. A diene **13** resulting from opening of the epoxide and dehydration was also obtained as a byproduct (8%), although no additional rearranged products were detected in the reaction mixture. The ^{1}H NMR spectrum of compound **14** did not show any signal corresponding to a TMS group. A signal corresponding to an olefinic proton appeared at δ 5.17 indicating the existence of a trisubstituted double bond that was confirmed in the ^{13}C NMR spectra by the presence of two signals at δ 119.0 (d) and at δ 141.4 (s). A signal corresponding to a singlet methyl group attached to the double bond appeared at δ 1.69 which was assigned to C14. This indicated that, during the rearrangement, the angular methyl group in compound **12** remains bonded to the former bridgehead carbon so the double bond is formed by elimination of the TMS toward a carbocation that is produced upon migration of the C9 methylene. The new spiro carbon C5 appeared at δ 53.7 (s) while a signal at δ 74.7 (s) was assigned to the carbon bearing the tertiary alcohol which results after opening of the epoxide moiety. The results of this reaction are interpreted in terms of stabilization of the incipient carbocation at C10 by the silicon atom at C1 (β effect). Although there is an inductive factor,

SCHEME 3



hyperconjugation accounts for most of the stabilization by the β silicon.[27] Our results are consistent with those reported by Lambert and co-workers which have shown that a *anti* coplanar alignment of the C−Si bond and the migrating C−C bond is not a requirement for hyperconjugative interaction between the silicon atom and the developing positive charge, but there is a cosine-squared dependence on the Si−C−C−C(migrating) dihedral angle.[27,28] Examination of models of *cis*-4,5-epoxi-10-methyldecalines indicates that the Si−C−C−C9(methylene) array is closer to coplanarity than the Si−C−C−C14(methyl) array, which may account, in the absence of more precise calculations out of the scope of this paper, for the preferential migration of C9.

Compound **14** was used as the common intermediate for the synthesis of the title spirovetivane sesquiterpenes.

The synthesis of (+)-anhydro-β-rotunol (**3**) was achieved first (Scheme 3).[29] For this purpose, the primary hydroxyl group in the side chain was eliminated in order to construct the isopropenyl moiety. In a first approach to this transformation, the primary alcohol was converted into an *o*-nitrophenylselenide;[30] however, subsequent treatment with H_2O_2 afforded an epoxide **16**. Epoxidation of the double bond may be caused by *o*-nitrophenylselenenic acid which is produced as byproduct in this reaction, although the fact that it could not be avoided even in the presence of pyridine may indicate that it arises via an intramolecular process.[31] For this reason, we changed the strategy for the elimination of this hydroxyl

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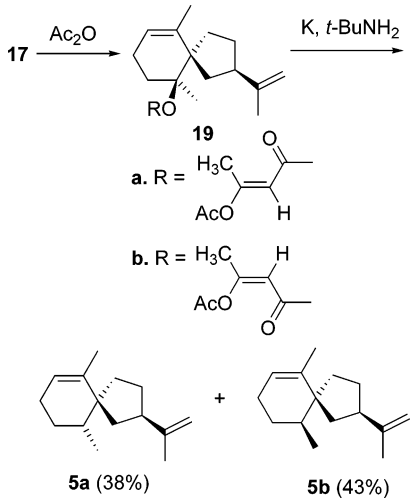
SCHEME 4



group. Alcohol **14** was treated with mesyl chloride, and the resulting mesylate was heated with $LiBr-Li_2CO_3$ in DMF to give compound **17** in 70% yield.[32] During this reaction, the corresponding bromide is formed as an intermediate; it eliminates on prolonged heating in the basic medium. To complete the synthesis, the cyclohexane ring of compound **17** was modified in order to create the cross-conjugated dienone unit characteristic of (+)-anhydro-*β*-rotunol (**3**). Allylic oxidation was carried out with CrO_3/2,5-dimethylpyrazole (2,5-DMP)[33] to give compound **18** in 55% yield. No oxidation of the other allylic positions was observed under these conditions. Finally, elimination of the tertiary hydroxyl group in compound **18** with TsOH at benzene reflux temperature afforded 60% of (+)-anhydro-*β*-rotunol (**3**) whose physical and spectral data were consistent with those described for the natural product.[3]

Next, we undertook the synthesis of all diastereomers of 6,11-spirovetivadiene. The synthesis of compounds **5a** and **5b** could be achieved directly from compound **17** by deoxygenation of the tertiary alcohol (Scheme 4). The procedure chosen was the reduction of its acetate ester by K in *tert*-butylamine.[34] However, treatment of compound **17** with acetic anhydride/pyridine did not yield the expected acetate; instead, two isomeric compounds in a ratio of ca. 2:1 were obtained and separated. HRMS gave a molecular formula $C_{21}H_{30}O_4$, indicating the incorporation of three acetate units; this was corroborated by the ^{13}C NMR spectra. According to these and other spectral data the esters contained the 3-acetoxy-2-butenoyl unit. This moiety presumably resulted from a Claisen acylation of the initial acetate followed by *O*-acetylation of the intermediate dicarbonyl enolate. The stereochemistry about the double bond was assigned in accord with the chemical shifts for the allylic methyl group in the ^1H NMR spectra which appeared at δ 2.15 in the major *E*-isomer **19a** and at δ 1.97 in the minor *Z*-isomer **19b**.[35] Although formation of these compounds could not be prevented even by using equivalent amounts of acetic anhydride, treatment of **19a**, **19b**, or mixtures of both compounds with K in *tert*-butylamine brought about reduction of the ester to the expected epimeric hydrocarbons, which were separated by HPLC. The structure of the minor compound **5a** (38% yield from **17**) was determined by comparison of its NMR data with those reported in the literature[9] for a synthetic product obtained in an independent synthesis of (−)-solavetivone. The identity of that compound had been unambiguously established by chemical synthesis and by its transformation into (−)-solavetivone.[36] Compound **5a** also showed spectral data identical to that of natural (−)-premnaspirodiene.[7,8] The major product (43% yield from **17**) was therefore assigned the epimeric structure at C10 **5b** and showed spectral data identical to that of natural (−)-hinesene.[10−12]

For the synthesis of compounds **5c** and **5d** the inversion of the spiro carbon was required. This could be formally achieved by hydrogenation of the double bond in the cyclohexane ring and elimination of the tertiary hydroxyl group to form a new double bond. To avoid possible selectivity problems during the hydrogenation of the double bond, we started from compound **14** instead of compound **17** (Scheme 5). Thus, compound **14** was hydrogenated over Pd/C to give two epimeric compounds in 52% and 43% yield, respectively. The stereochemistry of these compounds was assigned by NOE and NOESY experiments. The major compound **20** was derivatized by protection of the primary hydroxyl group as a TBS ether and alkylation of the tertiary hydroxyl group with NaH/MeI. Assignment of the key peaks in the ^1H NMR of the resulting compound **26** was carried out by COSY and decoupling experiments. Reciprocal NOEs between the methoxy group at δ 3.16 and a solitary multiplet at δ 1.91 corresponding to the CH in the cyclohexane ring were observed, clearly indicating the *cis* disposition between these groups and, hence, between methyls C14 and C15 in compound **26** as well as in its precursor **20**. On the other hand, irradiation of the singlet methyl signal (δ 1.14) in the minor compound **21** gave NOE with the CH in the cyclohexane ring (δ 1.53), indicating the *trans* disposition between the C14 and C15 methyl groups in this product.

The transformation of compounds **20** and **21** into the target molecules required the elimination of both hydroxyl groups in the molecule. A first attempt to dehydrate the tertiary alcohol by acid in compound **20** resulted

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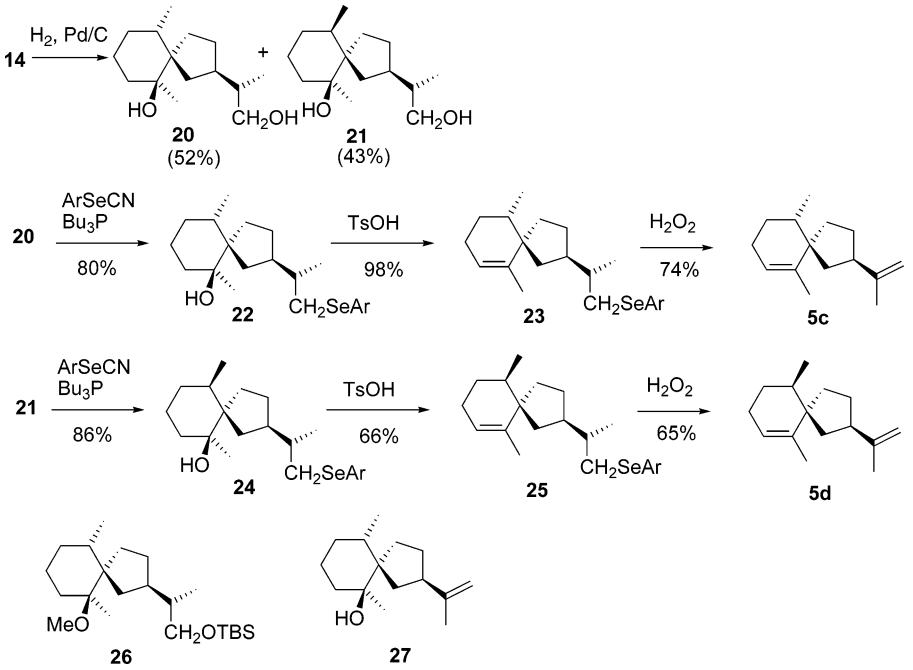
SCHEME 5



in decomposition. Therefore, we decided first to carry out the elimination of the primary alcohol in the side chain by its conversion into an arylselenide: Treatment of compound **20** with *o*-nitrophenyl selenocyanate and *n*-Bu_3P[30] gave 80% yield of *o*-nitrophenylselenide **22** which was transformed into compound **27** after oxidation with H_2O_2. However, acidic treatment of this hydroxyalkene led again to decomposition. We assumed that these results were due to the presence of groups sensitive to acid in the isopropyl side chain. Consequently, elimination of the tertiary hydroxyl group was carried out on hydroxyselenide **22**. Treatment of this compound with TsOH under benzene reflux brought about elimination of the tertiary hydroxyl group to give alkene **23** in almost quantitative yield (98%). In the last step, oxidation of the *o*-nitrophenylselenide with H_2O_2 followed by elimination of the resulting selenoxide brought about the formation of a double bond affording the expected diene **5c** in 74% yield for the last step. No epoxidation of the double bond in the cyclohexane ring was observed in this case. Transformation of diol **21** into diene **5d** was performed in a similar way. In this case, elimination of the tertiary hydroxyl in compound **24** was more troublesome since prolonged acidic treatment gave rise to decomposition. A short treatment gave, besides 13% of unreacted starting material, 66% of alkene **25** containing ca. 10% of the exocyclic double bond isomer which was separated from diene **5d** after oxidative elimination.

Neither compound **5c** nor **5d** showed spectroscopic data coincident with those reported for natural (−)-agarospirene isolated from *S. robusta* and *S. maxima*,[13] indicating that the reported structure for this natural product needed to be revised. As a matter of fact, comparison of the ^1H and ^{13}C NMR spectra of the natural product[37] with those of our synthetic products showed that the natural product was identical to **5b**; coincidence was also extensive to optical rotation signs, indicating that (−)-hinesene and (−)-agarospirene are the same compound.

In summary, we report here the first synthesis of spirovetivane sesquiterpenes from commercially available santonin. The synthetic strategy is based on a regio- and stereoselective silicon-guided rearrangement of a C4−C5 eudesmane epoxide. The synthetic utility of this strategy has been shown by the preparation of (+)-anhydro-*β*-rotunol and by the synthesis of all diastereomers of 6,11-spirovetivadiene, three of them being synthesized in enantiomerically pure form for the first time. As a consequence of this work, the structure of (−)-agarospirene isolated from *Scapania* sp. has been established to be identical, including absolute stereochemistry, to (−)-hinesene isolated from *L. reptans*, *R. fructifrosa*, and *Frullania sp*.

Experimental Section

Methyl (11*S*)-3-Oxo-1α-trimethylsilyl-7α*H*-eudesm-4-en-12-oate (8). A solution of hexamethyldisilane (9.2 mL, 45.8 mmol) in HMPA (20 mL) was frozen at −78 °C under argon. To the frozen solution was added dry THF (50 mL) followed by 1.6 M MeLi in ethyl ether (25.5 mL, 40.8 mmol). The reaction flask was introduced in an ice bath and the frozen solution allowed to melt. After 15 min of stirring at 0 °C, CuCN (1.7 g, 19.0 mmol) was added, and stirring at this temperature was continued for 30 min. After this time, the reaction mixture was cooled at −23 °C, and a solution of compound **7** (5.44 g, 20.7 mmol) in THF (70 mL) was added dropwise over a period of 20 min. When the addition was complete, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated under reduced pressure. Column chromatography eluting with hexanes−EtOAc (8:2) afforded 5.95 g (85%) of compound **8**: oil; $[\alpha]^{25}_D$ −53 (*c* 2.1); IR (NaCl) 1736, 1668 cm^{-1}; MS *m/e* 336 (M^+, 39), 321 (100), 261 (52), 231 (90); HRMS found 336.2117, $C_{19}H_{32}O_3Si$ required 336.2121; ^1H NMR *δ* 3.69 (3H, s, MeO), 2.53 (1H, dt, *J* = 12.0, 3.0 Hz), 2.5−2.3 (3H, m), 2.04 (1H, t, *J* = 12.0 Hz), 1.74 (3H, s), 1.9−1.4 (5H, m), 1.23

(37) We thank professor Chia-Li Wu from Tamkang University for sending us copies of the NMR spectra for natural (−)-agarospirene.

(1H, dd, J = 10.7, 5.6 Hz), 1.21 (3H, s), 1.16 (3H, d, J = 7.2 Hz), 0.05 (9H, s); ^{13}C NMR δ 199.7 (s), 176.0 (s), 161.7 (s), 128.1 (s), 51.6 (q), 45.1 (d), 42.0 (d), 40.1 (s), 35.9 (t), 35.7 (t), 34.0 (d), 32.2 (t), 26.2 (q), 24.9 (t), 14.1 (q), 11.1(q), 0.0 (q).

Methyl (11*S*)-1α-Trimethylsilyl-3,3-(1,2-ethanediyldithio)-7α*H*-eudesm-4-en-12-oate (9). To a solution containing compound **8** (5.69 g, 16.9 mmol) and 1,2-ethanedithiol (10.5 mL, 124 mmol) in AcOH (50 mL) was added $BF_3{\cdot}Et_2O$ (1.4 mL). The solution was stirred at room temperature for 7 h and then diluted with water and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried. Evaporation of the solvent under reduced pressure and column chromatography (hexanes−EtOAc, 9:1) gave 6.83 g (98%) of compound **9**: oil; $[\alpha]^{23}_D$ −89 (*c* 1.8); IR (NaCl) 1736 cm^{-1}; ^{1}H NMR δ 3.66 (3H, s), 3.5−3.1 (4H, m), 2.31 (1H, q, J = 7.0 Hz), 2.28 (1H, dt, J = 12.0, 3.0 Hz), 2.03 (1H, d, J = 2.2 Hz), 2.00 (1H, s), 1.87 (1H, t, J = 11.5 Hz), 1.83 (3H, s), 1.7−1.4 (5H, m), 1.30 (1H, dd, J = 6.9, 8.9 Hz), 1.11 (3H, d, J = 7.0 Hz), 1.04 (3H, s), 0.01 (9H, s); ^{13}C NMR δ 176.5 (s), 143.4 (s), 125.6 (s), 73.6 (s), 51.4 (q), 45.2 (d), 42.2 (d), 39.3 (t), 38.6 (s), 35.8 (d), 35.7 (t), 31.3 (t), 26.5 (q), 25.3 (t), 16.5 (q), 13.9 (q), −0.2 (q).

(11*S*)-1α-Trimethylsilyl-7α*H*-eudesm-4-en-12-al (10) and (11*S*)-1α-Trimethylsilyl-7α*H*-eudesm-4-en-12-ol (11). Calcium metal (430 mg, 10.7 mmol) was dissolved in liquid ammonia (50 mL) at −78 °C under argon in a flask equipped with a dry ice−acetone cooled condenser. To the blue solution was added dry ethyl ether (20 mL) and a solution of compound **9** (880 mg, 2.13 mmol) in dry diethyl ether (2 mL). The cooling bath was removed, and the solution was kept at reflux for 5 h. Solid NH_4Cl was added cautiously, followed by ether (25 mL), and ammonia was allowed to evaporate overnight. Saturated aqueous NH_4Cl was added, and the aqueous phase was extracted with ether. The organic layer was washed with saturated aqueous NH_4Cl, 10% aqueous NaOH, and brine, dried, filtered, and concentrated under reduced pressure. Column chromatography of the residue eluting with hexanes−EtOAc (9:1) gave 59 mg (9%) of compound **10** (containing ca. 20% of its epimer at C_{11}) and 370 mg (59%) of compound **11**. Compound **10** had the following features: oil; $[\alpha]^{25}_D$ −17 (*c* 0.8); IR (NaCl) 2697, 1726 cm^{-1}; MS *m/e* 292 (M$^+$, 10), 277 (63), 234 (10), 187 (28), 160 (23), 145 (45), 73 (100); HRMS found 292.2214, $C_{18}H_{32}OSi$ required 292.2222; ^{1}H NMR δ 9.64 (1H, s), 2.43 (1H, dd, J = 1.5, 12.0 Hz), 2.26 (1H, m), 2.0−1.7 (4H, m), 1.7−1.3 (6H, m), 1.57 (3H, s), 1.37 (3H, s), 1.09 (3H, s), 0.75 (1H, dd, J = 2.8, 10.5 Hz), 0.04 (9H, s); ^{13}C NMR δ 295.5 (d), 135.8 (s), 125.2 (s), 51.7 (d), 39.8 (d), 38.4 (s), 37.6 (t), 37.4 (d), 34.0 (t),30.1 (t), 26.5 (q), 25.2 (t), 21.7 (t), 19.7 (q), 10.1 (q), 0.3 (q). Compound **11** had the following features: oil; $[\alpha]^{25}_D$ −32 (*c* 0.9); IR (NaCl) 3362 cm^{-1}; MS *m/e* 294 (M$^+$, 24), 280 (23), 279 (100), 220 (30), 131 (70), 73 (70); HRMS found 294.2368, $C_{18}H_{34}OSi$ required 294.2378; ^{1}H NMR δ 3.62 (1H, dd, J = 10.5, 5.8 Hz), 3.47 (1H, dd, J = 10.5, 6.8 Hz), 2.40 (1H, dd, J = 13.0, 1.8 Hz), 1.87 (2H, t,), 1.79 (1H, brt, J = 13.0 Hz), 1.58 (3H, s), 1.7−1.1 (7H, m), 1.07 (3H, s, H14), 0.90 (3H, d, J = 7.0 Hz), 0.74 (1H, dd, J = 10.5, 2.5 Hz, H1), 0.02 (9H, s); ^{13}C NMR δ 136.8 (s), 124.3 (s), 66.5 (t), 40.8 (d), 40.7 (d), 38.6 (s), 37.9 (t), 37.5(d), 34.1 (t), 29.9 (t), 26.6 (q), 24.5 (t), 21.8 (t), 19.8 (q), 13.2 (q), 0.3 (q).

A solution of aldehyde **10** (121 mg, 0.41 mmol) in THF (7 mL) was treated with $LiAlH_4$ (16 mg, 0.41 mmol) at 0 °C for 10 min. The excess $LiAlH_4$ was destroyed by careful addition of water. The solution was diluted with diethyl ether, stirred, and dried over $MgSO_4$. Solvent removal followed by chromatography eluting with 9:1 hexanes−EtOAc gave 99 mg (82%) of compound **11**.

(11*S*)-4*β*,5*β*-Epoxy-1α-trimethylsilyl-7α*H*-eudesm-12-ol (12). A solution containing compound **10** (460 mg, 1.58 mmol), $NaHCO_3$ (2.1 g, 25.3 mmol), 18-crown-6 (35 mg), H_2O (20 mL), acetone (20 mL), and CH_2Cl_2 (20 mL) was cooled at 0 °C. To this solution was added Oxone (2.6 g, 4.2 mmol) carefully in several portions. The mixture was vigorously stirred for 1.5 h and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, 10% $Na_2S_2O_3$, and aqueous $NaHCO_3$ and dried and the solvent evaporated. Column chromatography eluting with hexanes−EtOAc (9:1) gave 445 mg (91%) of compound **12**: oil; $[\alpha]^{24}_D$ −126 (*c* 0.9); IR (NaCl) 3436 cm^{-1}; MS *m/e* 310 (M$^+$, 7), 295 (30), 237 (100), 121 (64), 73 (91); HRMS found 310.2315, $C_{18}H_{34}O_2Si$ required 310.2328; ^{1}H NMR δ 3.61 (1H, dd, J = 10.5, 5.9 Hz, H12), 3.48 (1H, dd, J = 10.5, 6.6 Hz, H12′), 1.79 (2H, m, H8, H8′), 1.74 (1H, t, J = 12.5 Hz, H6*β*), 1.70 (1H, td, J = 13.0, 4.3 Hz, H9α), 1.65−1.55 (2H, m, H8α, H11), 1.51 (1H, dt, J = 13.0, 3.5 Hz, H9*β*), 1.47 (1H, m, H7), 1.42−1.28 (3H, m, H8*β*, 2H2), 1.41 (1H, br d, J = 12.5 Hz, H6α), 1.32 (3H, s, H15), 1.13 (3H, s, H14), 0.92 (3H, d, J = 6.8 Hz, H13), 0.82 (1H, dd, J = 13.0, 2.6 Hz, H1), 0.01 (9H, s, TMS); ^{13}C NMR δ 69.3 (s), 66.0 (t), 64.5 (s), 40.2 (d), 38.8 (d), 37.5 (s), 33.3 (t), 32.0 (t), 30.8 (d), 30.8 (t), 24.0 (t), 19.3 (t), 22.8 (q), 22.2 (q), 13,4 (q), 0.13 (q).

(2*R*,5*R*,10*S*,11*S*)-6-Spirovetivene-10,12-diol (14). A solution of $BF_3{\cdot}Et_2O$ (195 *μ*L, 0.72 mmol) in CH_2Cl_2 (11 mL) was added dropwise to a solution of epoxide **12** (225 mg, 0.72 mmol) in CH_2Cl_2 (11 mL) at −40 °C. The reaction mixture was stirred at this temperature for 2 h. Saturated aqueous $NaHCO_3$ was added, and the temperature was allowed to reach room temperature until the frozen mixture melted. The mixture was extracted with EtOAc, washed with brine, and dried. Column chromatography (9:1 to 5:5 hexanes−EtOAc) eluted in this order 17 mg of compound **13** (8%) and 112 mg (64%) of compound **14**.

Compound **13**: oil; MS *m/e* 292 (M$^+$, 3), 277 (1), 233 (5), 159 (34), 73 (100); HRMS found 292.2238, $C_{18}H_{32}OSi$ required 292.2222; ^{1}H NMR δ 5.52 (1H, br d, J = 6.0 Hz), 5.33 (1H, s), 3.66 (1H, dd, J = 10.5, 6.8 Hz), 3.59 (1H, dd, J = 10.5, 6.7 Hz), 2.54 (2H, m), 2.16 (1H, dd, J = 18.6, 6.0 Hz), 1.85 (2H, m), 1.76 (3H, br s), 1.7−1.5 (3H, m), 1.46 (1H, dt, J = 12.0, 3.4 Hz), 1.10 (3H, s), 0.90 (3H, d, J = 7.0 Hz), 0.84 (1H, d, J = 6.2 Hz), −0.03 (9H, s).

Compound **14**: mp 90−93 °C; $[\alpha]^{24}_D$ −86 (*c* 1.0); IR (NaCl) 3350 cm^{-1}; MS *m/e* 238 (M$^+$, 18), 220 (13), 180 (49), 161 (40), 121 (100); HRMS found 238.1934, $C_{15}H_{26}O_2$ required 238.1933; ^{1}H NMR δ 5.17 (1H, s), 3.61 (1H, dd, J = 10.5, 4.0 Hz), 3.52 (1H, dd, J = 10.5, 6.0 Hz), 2.09 (1H, ddd, J = 12.5, 7.5, 1.2 Hz), 2.05 (2H, m), 2.04−1.4 (8H, m), 1.64 (1H, dd, J = 12.5, 6.6 Hz), 1.4−1.1 (2H, m), 1.69 (3H, d, J = 1.3 Hz), 1.14 (3H, s), 0.99 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 141.4 (s), 119.0 (d), 74.7 (s), 67.0 (t), 53.7 (s), 43.6 (d), 41.5 (d), 41.3 (t), 34.3 (t), 33.6 (t), 30.8 (t), 24.2 (t), 22.6 (q), 19.6 (q), 15.8 (q).

(2*R*,5*R*,10*S*)-6,11-Spirovetivadien-10-ol (17). To a solution of compound **14** (400 mg, 1.68 mmol) in pyridine (8 mL) at 0 °C was added MsCl (325 *μ*L, 4.2 mmol). The reaction mixture was stirred for 0.5 h, and then it was diluted with EtOAc (150 mL), washed twice with 2 M HCl, saturated aqueous $NaHCO_3$, and brine until neutrality, and dried. Evaporation of the solvent under reduced pressure afforded 525 mg (99%) of an oil which mainly consisted of the mesylate of **14**: ^{1}H NMR δ 5.13 (1H, br s), 4.15 (1H, dd, J = 3.8, 9.6 Hz), 4.03 (1H, dd, J = 6.6, 9.6 Hz), 2.98 (3H, s), 2.05 (1H, dd, J = 12.0, 6.0 Hz), 2.01 (2H, m), 2.0−1.6 (7H, m), 1.64 (3H, d, J = 1.5), 1.49 (1H, dt, J = 12.0, 4.5 Hz), 1.4−1.1 (2H, m), 1.07 (3H, s), 0.99 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 140.8 (s), 119.6 (d), 74.3 (s), 74.2 (t), 53.7 (s), 43.6 (d), 40.8 (t, broad), 38.8 (d), 37.3 (q), 34.5 (t), 33.2 (t), 30.9 (t, broad), 24.1 (t), 22.9 (q), 19.8 (q), 15.6 (q).

The resulting oil, Li_2CO_3 (330 mg, 4.45 mmol), and LiBr (450 mg, 5.2 mmol) in DMF (7.5 mL) were heated at 140 °C. Li_2CO_3 (330 mg) was added after 5 h, and the reaction mixture was heated for an additional 5 h. After this time, water was added and the mixture extracted with pentane. The usual procedure followed by chromatography (9:1 hexanes−EtOAc) gave 259 mg (70%) of compound **17**: mp 41−42 °C; $[\alpha]^{24}_D$ −92 (*c* 0.8); IR (KBr) 3350, 1643 cm^{-1}; MS *m/e* 220 (M$^+$, 47), 202 (14), 162 (76), 119 (100); HRMS found 220.1823, $C_{15}H_{24}O$ required 220.1827; ^{1}H NMR δ 5.15 (1H, s), 4.68 (1H, d, J =

0.8 Hz), 4.65 (1H, d, J = 0.8 Hz), 2.44 (1H, m), 2.03 (3H, m), 1.95−1.55 (4H, m), 1.5−1.1 (3H, m), 1.72 (3H, s), 1.68 (3H, q, J = 1.5 Hz), 1.39 (1H, dd, J = 13.5, 12.0 Hz), 1.12 (3H, s); ^{13}C NMR δ 148.2 (s), 141.2 (s), 119.3 (d), 108.2 (t), 74.5 (s), 53.4 (s), 48.3 (d), 40.4 (t), 34.5 (t), 33.5 (t), 31.5 (t), 24.1 (t), 23.0 (q), 21.4 (q), 19.9 (q).

(2*R*,5*R*,10*S*)-10-Hydroxy-6,11-spirovetivadien-8-one (18). Dimethylpyrazole (245 mg, 2.5 mmol) was added to a suspension of anhydrous CrO_3 (256 mg, 2.5 mmol) in CH_2Cl_2 (1.3 mL) at −25 °C under argon and stirred for 30 min. Then the temperature was raised to 0 °C, and compound **17** (28 mg, 0.13 mmol) dissolved in CH_2Cl_2 (1.3 mL) was added. After 30 min, the reaction was filtered through a short pad of Celite and the chromium salts extensively washed with EtOAc. After solvent removal, column chromatography eluting with hexanes−EtOAc (7:3) allowed us to obtain 16.5 mg (55%) of compound **18**: oil; $[\alpha]^{24}_D$ −130 (*c* 1.7); IR (NaCl) 3350, 1696, 1643 cm^{-1}; MS *m*/*e* 234 (M^+, 4), 216 (36), 176 (100); HRMS found 234.1625, $C_{15}H_{22}O_2$ required 234.1620; ^{1}H NMR δ 5.71 (1H, s), 4.71 (2H, s), 2.74 (1H, br d, J = 16.4 Hz), 2.57 (1H, m), 2.5−2.4 (2H, m), 2.1−1.3 (5H, m), 1.99 (3H, d, J = 1.3 Hz), 1.73 (3H, s), 1.22 (3H, s); ^{13}C NMR δ 198.3 (s), 168.4 (s), 147.2 (s), 124.8 (d), 108.9 (t), 75.6 (s), 55.2 (s), 47.4 (d), 40.7 (t), 33.4 (t), 24.5 (q), 21.4 (q).

(+)-Anhydro-*β*-rotunol (3). A solution containing compound **18** (18.2 mg, 0.077 mmol) and a catalytic amount of TsOH in benzene (1.5 mL) was heated at reflux temperature for 1 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. Column chromatography over silica gel eluting with hexanes−EtOAc (8:2) gave 10.0 mg (60%) of compound **3** and 1.8 mg (10%) of unreacted starting material. Compound **3**: mp 43−44 °C (lit.[3] mp 44−44.5 °C); $[\alpha]^{24}_D$ +52 (*c* 0.7) (lit.[3] $[\alpha]^{24}_D$ +57); IR (KBr) 1667, 1625, 1609 cm^{-1}; MS *m*/*e* 216 (M^+, 47), 201 8349, 173 (57), 160 (72), 135 (100); HRMS found 216.1515, $C_{15}H_{20}O$ required 216.1514; ^{1}H NMR δ 6.01 (2H, s), 4.76 (2H, dd, J = 1.0 Hz), 2.82 (1H, m), 2.1−1.9 (2H, m), 2.07 (3H, d, J = 0.8 Hz), 2.03 (3H, d, J = 0.8 Hz), 1.9−1.6 (4H, m), 1.77 (3H, s); ^{13}C NMR δ 186.5 (s), 164.6 (s), 164.4 (s), 146.2 (s), 126.0 (d), 125.9 (d), 109.7 (t), 52.8 (s), 49.3 (d), 41.3 (t), 36.4 (t), 33.5 (5), 21.4 (q), 20.8 (two signals, q).

(−)-Premnaspirodiene (5a) and (−)-Hinesene (5b). To a solution of compound **17** (60 mg, 0.26 mmol) in pyridine (0.7 mL) were added acetic anhydride (0.68 mL, 7.3 mmol) and 4-DMAP (30 mg, 0.25 mmol) at room temperature. After 2 h, additional Ac_2O (0.68 mL) and 4-DMAP (30 mg) were added, and stirring was continued at room temperature for 3 h. The reaction mixture was diluted with EtOAc, washed with 2 M HCl, saturated aqueous $NaHCO_3$, and brine, and dried. Filtration and solvent evaporation under reduced pressure afforded 93 mg (99%) of an oil which was composed of a ca. 2:1 mixture of two compounds. Analytical samples of both compounds were obtained after chromatography over silica gel (99:1 hexanes−EtOAc) in an independent run.

Compound **19a** (major compound): oil; $[\alpha]^{24}_D$ −78 (*c* 0.5); IR (NaCl) 3440, 1767, 1720, 1665 cm^{-1}; MS *m*/*e* 346 (M^+, 7), 303 (21), 287 (33), 219 (61), 202 (100); HRMS found 346.2144, $C_{21}H_{30}O_4$ required 346.2144; ^{1}H NMR δ 5.55 (1H, d, J = 0.9 Hz), 5.17 (1H, br s), 4.68 (1H, d, J = 0.6 Hz), 4.66 (1H, d, J = 0.6 Hz), 2.7−2−4 (2H, m), 2.30 (3H, d, J = 0.9 Hz), 2.15 (3H, s), 2.1−1.9 (3H, m), 1.9−1.7 (3H, m), 1.72 (3H, s), 1.7−1.4 (2H), 1.67 (3H, br d, J = 1.5 Hz), 1.50 (3H, s), 1.38 (1H, t, J = 12.0 Hz); ^{13}C NMR δ 168.3 (s), 165.3 (s), 163.1 (s), 148.3 (s), 139.9 (s), 119.7 (d), 111.5 (d), 108.2 (t), 87.5 (s), 53.9 (s), 48.0 (d), 33.3 (t), 29.0 (t), 23.8 (t), 21.5 (q), 21.1 (q), 19.7 (q), 19.4 (q), 17.8 (q).

Compound **19b** (minor compound): oil; $[\alpha]^{24}_D$ −71 (*c* 0.8); IR (NaCl) 3423, 1770, 1720, 1669 cm^{-1}; MS *m*/*e* 346 (M^+, 2), 303 (4), 287 (6), 219 (20), 202 (75); HRMS found 346.2145, $C_{21}H_{30}O_4$ required 346.2144; ^{1}H NMR δ 5.49 (1H, dd, J = 1.0 Hz), 5.16 (1H, br s), 4.70 (1H, d, J = 0.7 Hz), 4.68 (1H, d, J = 0.7 Hz), 2.7−2.4 (2H, m), 2.22 (3H, s), 2.08 (1H, dddd, J = 13.0, 6.5, 1.1 Hz), 2.05−1.92 (2H, m), 1.97 (3H, d, J = 1.0 Hz), 1.9−1.7 (3H, m), 1.7−1.4 (2H, m), 1.74 (3H, s), 1.67 (3H, br d, J = 1.5 Hz), 1.46 (3H, s), 1.37 (1H, dd, J = 13.1, 12.1 Hz); ^{13}C NMR δ 168.1 (s), 163.0 (s), 159.1 (s), 139.9 (s), 119.8 (d), 109.5 (d), 108.3 (t), 87.2 (s), 53.9 (s), 48.1 (d), 33.4 (t), 28.9 (t), 23.8 (t), 21.6 (q), 21.6 (q), 21.5 (q), 21.0 (q), 19.7 (q), 19.3 (q).

A blue solution of potassium was generated by stirring potassium (ca. 50 mg) and 18-crown-6 (10 mg) in dry *tert*-butylamine under argon. To this solution was added the mixture of compounds **19a** and **19b** dissolved in *tert*-butylamine (2.2 mL), and the reaction mixture was stirred at room temperature for 30 min. The excess of potassium was destroyed by careful addition of *tert*-butyl alcohol. Water was added and the mixture extracted with pentane and washed with brine. After careful evaporation of the solvent, the resulting mixture was separated by HPLC (normal phase, hexanes) to afford in order of elution 21.2 mg (38%) of compound **5a** and 23.6 mg (43%) of compound **5b**.

(−)-Premnaspirodiene (5a): oil; $[\alpha]^{24}_D$ −85 (*c* 0.6) (lit.[8b] $[\alpha]_D$ −88); IR (NaCl) 3085, 3040, 1645 cm^{-1}; MS *m*/*e* 204 (M^+, 28), 189 (28), 175 (20), 161 (61), 147 (62), 107 (100); HRMS found 204.1873, $C_{15}H_{24}$ required 204.1878; ^{1}H NMR δ 5.25 (1H, br s), 4.69 (1H, s), 4.65 (1H, s), 2.40 (1H, m), 1.97 (2H, m), 1.9−1.2 (9H, m), 1.72 (3H, s), 1.64 (3H, s), 0.87 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 148.7 (s), 139.3 (s), 120.9 (d), 108.1 (t), 48.4 (s), 46.7 (d), 43.7 (t), 37.7 (d), 34.0 (t), 32.8 (t), 27.0 (t), 21.9 (t), 21.2 (q), 20.1 (q), 14.8 (q).

(−)-Hinesene (5b): oil; $[\alpha]^{24}_D$ −40 (*c* 0.2) (lit.[11] $[\alpha]^{24}_D$ −44); IR (NaCl) 3080, 3042, 1645 cm^{-1}; MS *m*/*e* 204 (M^+, 27), 189 (40), 175 (26), 161 (64), 147 (62), 133 (68), 107 (100); HRMS found 204.1876, $C_{15}H_{24}$ required 204.1878; ^{1}H NMR δ 5.29 (1H, br s), 4.69 (1H, s), 4.65 (1H, s), 2.42 (1H, m), 1.93 (2H, m), 1.9−1.2 (8H, m), 1.72 (3H, s), 1.66 (3H, d, J = 1.5 Hz), 1.36 (1H, t, J = 12.5 Hz), 0.92 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 148.7 (s), 140.3 (s), 121.6 (d), 108.0 (t), 48.7 (s), 47.6 (d), 37.5 (d), 37.1 (t), 35.8 (t), 32.2 (t), 28.2 (t), 24.5 (t), 21.3 (q), 19.8 (q), 16.4 (q).

(2*R*,5*R*,6*S*,10*S*,11*S*)-6,12-Spirovetivanediol (20) and (2*R*,5*R*,6*S*,10*R*,11*S*)-6,12-Spirovetivanediol (21). Compound **14** (274 mg, 1.15 mmol) dissolved in absolute EtOH (12 mL) was hydrogenated over 5% palladium adsorbed onto carbon (120 mg) for 2 h. After this time, the mixture was filtered through a short pad of silica gel and concentrated. Chromatography of the residue (7:3 hexanes−EtOAc) successively eluted 143 mg (52%) of compound **20** and 115 mg (43%) of compound **21**.

Compound **20**: mp 123−125 °C; $[\alpha]^{22}_D$ +63 (*c* 1.4); IR (KBr) 3374 cm^{-1}; MS *m*/*e* 240 (M^+, 1.1), 222 (51), 163 (100); HRMS found 240.2080, $C_{15}H_{28}O_2$ required 240.2089; ^{1}H NMR δ 3.63 (1H, dd, J = 10.5, 4.0 Hz), 3.37 (1H, dd, J = 10.5, 7.1 Hz), 1.96 (1H, br dd, J = 13.7, 5.8 Hz), 1.84−1.70 (2H, m, H10), 1.68−1.56 (3H, m), 1.52−1.38 (6H, m), 1.26−1.04 (4H, m), 1.10 (3H, s), 0.92 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz); ^{13}C NMR δ 75.1 (s), 67.5 (t), 52.9 (s), 43.8 (d), 41.6 (d), 36.7 (t), 36.1 (t), 35.1 (d), 33.0 (t), 31.3 (t), 28.4 (t), 26.4 (q), 20.8 (t), 17.7 (q), 15.6 (q).

Compound **21**: oil; $[\alpha]^{22}_D$ −3 (*c* 1.3); IR (NaCl) 3350 cm^{-1}; MS *m*/*e* 240 (M^+, 1), 222 (50), 163 (100); HRMS found 240.2094, $C_{15}H_{28}O_2$ required 240.2089; ^{1}H NMR δ 3.58 (1H, dd, J = 10.9, 4.9 Hz), 3.51 (1H, dd, J = 10.9, 3.8 Hz), 3.21 (2H, br s, 2 OH), 1.85 (1H, dd, J = 7.0, 1.7 Hz), 1.8−1.6 (4H, m), 1.6−1.4 (3H, m), 1.4−1.2 (4H, m), 1.14 (3H, s), 1.1−0.9 (3H, m), 0.91 (3H, d, J = 6.8 Hz), 0.76 (3H, d, J = 6.6 Hz); ^{13}C NMR δ 76.2 (s), 67.1 (t), 53.6 (s), 43.5 (d), 41.5 (d), 38.9 (d), 38.0 (t), 32.9 (t), 32.5 (t), 32.4 (t), 31.0 (t), 23.3 (t), 22.3 (q), 17.3 (q), 15.8 (q).

(2*R*,5*R*,6*S*,10*S*,11*S*)-12-(*tert*-Butyldimethylsilyloxy)-6-methoxyspirovetivane (26). A solution of compound **20** (32.0 mg, 0.14 mmol), imidazole (35.4 mg, 0.52 mmol), and TBSCl (44.9 mg, 0.29 mmol) in DMF (1 mL) was stirred at room temperature for 2 h. After this time, the reaction mixture was diluted with EtOAc, washed with water and brine, and dried with anhydrous Na_2SO_4. After filtration, the solvent was

removed under reduced pressure and chromatographed with hexanes−EtOAc (8:2). The resulting oil (30 mg) was dissolved under argon in THF (1 mL) containing HMPA (0.1 mL) and treated with a 60% dispersion of NaH in mineral oil (14 mg, 0.35 mmol) and MeI (55 μL, 8.9 mmol). The reaction mixture was stirred for 48 h and, after this time, quenched with aqueous NH_4Cl and extracted with EtOAc. After the usual procedure column chromatography eluting with hexane−diethyl ether (9:1) afforded 29.1 mg (89%) of compound **26**: oil; $[\alpha]^{24}_D$ +53 (*c* 1.3); MS *m/e* 368 (M^+, 0.1), 311 (5), 279 (12), 236 (40), 205 (52), 81 (100); HRMS found 368.3180, $C_{22}H_{44}SiO_2$ required 368.3110; ^{1}H NMR δ 3.64 (1H, dd, J = 9.6, 3.9 Hz), 3.34 (1H, dd, J = 9.6, 7.3 Hz), 3.16 (3H, s), 2.05 (1H, br dd, J = 13.5, 7.9 Hz), 1.91 (1H, ddq, J = 11.5, 3.5, 6.9 Hz, H10), 1.77 (1H, dt, J = 11.5, 5.9 Hz), 1.73−1.51 (3H, m), 1.50−1.22 (4H, m), 1.21−1.04 (5H, m), 1.02 (3H, s), 0.92 (3H, d, J = 6.7 Hz), 0.90 (9H, s), 0.78 (3H, d, J = 6.9 Hz), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR δ 79.2 (s), 67.5 (t), 53.6 (s), 48.2 (q), 43.7 (d), 41.9 (d), 36.4 (t), 34.4 (t), 32.8 (t), 31.8 (t), 29.8 (t), 28.6 (t), 25.9 (q), 20.9 (t), 18.9 (q), 18.3 (s), 17.7 (q), 15.9 (q), −5.35 (q).

(2*R*,5*R*,6*S*,10*S*,11*S*)-12-(*o*-Nitrophenylselenenyl)-6-spirovetivanol (22). To a solution of diol **20** (50 mg, 0.21 mmol) and *o*-nitrophenylseleno cyanate (80 mg, 0.35 mmol) in 3:1 THF−pyridine (2 mL) was added via syringe *n*-Bu_3P (0.124 mL, 0.49 mmol) under argon. After 18 h, the reaction mixture was diluted with EtOAc, washed with 2 M HCl and brine, and dried with $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed (8:2 hexanes−EtOAc) to give 70 mg (80%) of compound **22**: yellow oil; IR (NaCl) 3578, 3480, 1513, 1332, 730 cm^{-1}; ^{1}H NMR δ 8.24 (1H, dd, J = 8.2, 1.3 Hz), 7.50 (2H, m), 7.27 (1H, td, J = 8.2, 1.3 Hz), 3.14 (1H, dd, J = 10.9, 3.5 Hz), 2.73 (1H, dd, J = 10.9, 8.7 Hz), 2.14 (1H, ddq, J = 13.3, 6.8, 1.1 Hz), 1.9−1.0 (15H, m), 1.15 (3H, s), 1.08 (3H, d, J = 6.2 Hz), 0.81 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 146.9 (s), 134.0 (s), 133.4 (d), 129.3 (d), 126.3 (d), 125.1 (d), 75.0 (s), 52.3 (s), 47.6 (d), 38.5 (d), 36.9 (t), 36.1 (t), 35.1 (d), 33.7 (t), 33.2 (t), 31.3 (t), 28.6 (t), 26.4 (q), 20.8 (t), 19.2 (q), 17.7 (q).

(2*R*,5*R*,10*S*,11*S*)-12-(*o*-Nitrophenylselenenyl)-6-spirovetivene (23). A solution containing compound **22** (35 mg, 0.080 mmol) and TsOH (4 mg) in benzene (2.5 mL) was heated at reflux temperature for 45 min under argon. After this time, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvents gave 32.7 mg (98%) of compound **23**: yellow oil; IR (NaCl) 1515, 1337, 730 cm^{-1}; ^{1}H NMR δ 8.25 (1H, dd, J = 8.3, 1.2 Hz), 7.50 (2H, m), 7.26 (1H, td, J = 8.3, 1.2 Hz), 5.28 (1H, br s), 3.11 (1H, dd, J = 10.9, 3.4 Hz), 2.73 (1H, dd, J = 10.9, 8.9 Hz), 2.0−0.8 (13 H, m), 1.68 (3H, q, J = 1.5 Hz), 1.10 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 147.1 (s), 140.5 (s), 134.0 (s), 133.3 (d), 129.3 (d), 126.4 (d), 125.2 (d), 121.5 (d), 48.8 (s), 47.9 (d), 41.9 (t), 38.8 (d), 38.5 (d), 33.8 (t), 32.5 (t), 32.0 (t), 28.1 (t), 24.8 (t), 20.0 (q), 19.2 (q), 16.6 (q).

(2*R*,5*R*,10*S*)-6,11-Spirovetivadiene (5c). To a solution of compound **23** (30 mg, 0.073 mmol) in THF (0.6 mL) cooled to 0 °C was added 30% H_2O_2 (15 μL, 0.15 mmol). The mixture was stirred at room temperature for 3.5 h, diluted with pentane, and washed with 8% aqueous $Na_2S_2O_3$ and brine. The usual procedure and chromatography (hexane) gave 11.2 mg (74%) of compound **5c**: oil; $[\alpha]^{22}_D$ −3 (*c* 0.6); IR (NaCl) 3080, 3040, 1645 cm^{-1}; MS *m/e* 204 (M^+, 71), 189 (61), 175 (21), 161 (86), 147 (45), 107 (100); HRMS found 204.1870, $C_{15}H_{24}$ required 204.1878; ^{1}H NMR δ 5.28 (1H, br s), 4.70 (1H, s), 4.66 (1H, s), 2.53 (1H, m), 1.92 (2H, m), 1.9−1.2 (9H), 1.73 (3H, s), 1.69 (3H, d, J = 1.3 Hz), 0.91 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 148.9 (s), 141.1 (s), 121.6 (d), 108.3 (t), 48.8 (s), 48.7 (d), 41.6 (t), 39.1 (d), 33.0 (t), 32.4 (t), 28.6 (t), 25.3 (t), 21.6 (q), 20.2 (q), 17.0 (q).

(2*R*,5*R*,6*S*,10*R*,11*S*)-12-(*o*-Nitrophenylselenenyl)-6-spirovetivanol (24). By the same procedure used in the synthesis of compound **22**, from compound **21** (38 mg, 0.342 mmol) was obtained 58.9 mg (86%) of compound **24**: yellow oil; IR (NaCl) 3578, 3480, 1513, 1332, 730 cm^{-1}; ^{1}H NMR δ 8.22 (1H, d, J = 8.1 Hz), 7.50 (2H, m), 7.25 (1H, td, J = 8.1, 1.5 Hz), 3.14 (1H, dd, J = 10.9, 3.2 Hz), 2.68 (1H, dd, J = 10.9, 9.4 Hz), 1.9−0.9 (15H, m), 1.17 (3H, s), 1.06 (3H, d, J = 6.6 Hz), 0.80 (1H, m), 0.78 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 146.9 (s), 133.3 (s), 129.3 (d), 126.3 (d), 125.1 (d), 75.7 (s), 53.5 (s), 47.9 (d), 38.9 (d), 38.3 (t), 38.1 (d), 33.7 (t), 33.0 (t), 32.5 (t), 32.0 (t), 31.0 (t), 23.2 (t), 22.6 (q), 18.9 (q), 17.4 (q).

(2*R*,5*R*,10*R*,11*S*)-12-(*o*-Nitrophenylselenenyl)-6-spirovetivene (25). By the same procedure used in the synthesis of compound **23**, from compound **24** (29.3 mg, 0.069 mmol) was obtained 18.6 mg (66%) of compound **25** containing ca. 9% of the exomethylene isomer and 4.2 mg (13%) of starting material. Compound **25**: yellow oil; IR (NaCl) 1515, 1335, 730 cm^{-1}; ^{1}H NMR (major peaks) δ 8.25 (1H, d, J = 8.3 Hz), 7.50 (2H, m), 7.25 (1H, td, J = 8.3, 1.2 Hz), 5.23 (1H, br s), 3.11 (1H, dd, J = 10.9, 3.4 Hz), 2.73 (1H, dd, J = 10.9, 8.9 Hz), 2.2−1.0 (13H), 1.66 (3H, q, J = 1.3 Hz), 1.10 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 147.1 (s), 139.8 (s), 134.1 (s), 133.4 (d), 129.3 (d), 126.4 (d), 125.2 (d), 120.6 (d), 48.6 (d), 48.5 (s), 40.3 (t), 39.1 (d), 38.5 (d), 38.5 (t, overlapped), 33.7 (t), 31.5 (t), 27.2 (t), 22.4 (t), 20.5 (q), 19.2 (q), 15.3 (q);^{1}H NMR (minor peaks) 4.78 (s), 4.64 (s), 3.04 (dd, J = 10.5, 3.5 Hz), 2.66 (dd, J = 11.0, 8.5 Hz), 0.83 (d, J = 6.6 Hz).

(2*R*,5*R*,10*R*)-6,11-Spirovetivadiene (5d), Proposed Structure for (−)-Agarospirene. By the same procedure used in the synthesis of compound **5c**, from compound **25** (17.9 mg, 0.044 mmol) was obtained 5.3 mg (59%, 65% based on consumed starting material) of compound **5d**: oil; $[\alpha]^{22}_D$ −11 (*c* 0.3); IR (NaCl) 3080, 3040, 1645 cm^{-1}; MS *m/e* 204 (M^+, 97), 189 (72), 175 (32), 161 (98), 119 (100), 107 (89); HRMS found 204.1868, $C_{15}H_{24}$ required 204.1878; ^{1}H NMR δ 5.78 (1H, br s), 5.24 (1H, s), 5.18 (1H, s), 2.51 (1H, m), 1.75 (3H, s), 2.1−1.5 (6H, m), 1.69 (3H, d, J = 1.3 Hz), 1.5−1.0 (4H, m), 0.92 (3H, d, J = 6.8 Hz), 0.85 (1H, m); ^{13}C NMR δ 148.8 (s), 139.8 (s), 120.5 (d), 107.9 (t), 49.0 (d), 48.1 (s), 40.1 (t), 39.1 (d), 38.7 (t), 31.6 (t), 27.2 (t), 22.2 (t), 21.5 (q), 20.3 (q), 15.0 (q).

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Supporting Information Available: General experimental methods. Preparation of compounds **7**, **15**, and **16**. ^{1}H NMR spectra of compounds **3**, **5a**−**d**, **7**−**14**, and **17**−**2**6. This material is available free of charge via the Internet at http://pubs.acs.org.

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