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Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (−)-Valpara-2,15-diene and (+)-Isodaucene

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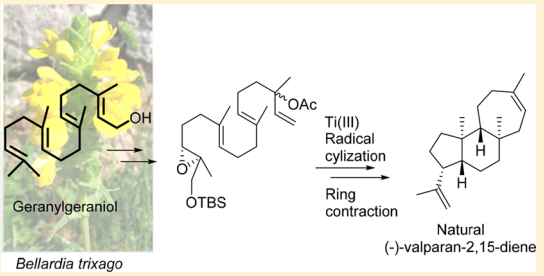
Supporting Information

ABSTRACT: The first total synthesis of a natural diterpene valparane, (−)-valpara-2,15-diene (**1**), has been achieved from all-*trans*-geranylgeraniol (**9**), a natural renewable compound. The key steps involve a Ti(III)-mediated radical cyclization of the chiral monoepoxypolyene (14*R*,15*R*)-14,15-epoxy,16-*tert*-butyldimethylsilyloxygeranyllinalyl acetate (**8**) to give the 6,6,7-tricyclic intermediate **7** with stereocontrolled formation of six stereocenters; a stereo- and regio-directed contraction of the A ring in **7** to produce a cyclopentane ring; and the ready generation of the target isopropenyl group. This research provides access to structurally related natural products such as the sesquiterpene (+)-isodaucene (**3**), the synthesis of which is also reported herein.



Five-, six-, and seven-membered carbocycles co-occur in natural terpenes possessing different molecular backbones. Among them, diterpene valparanes, isolated from the Cistaceae family of plants,[1] contain a cyclohexane fused between five- and seven-membered rings. A large majority of these diterpenes share the stereochemistry seen in valpara-2,15-diene (**1**) as well as the presence of an isopropenyl group at C-14 of the cyclopentane ring. Structurally related to valparanes, sesquiterpenes such as daucanes **3** and **4**[2] and diterpenoids such as sphenolobanes (**5**)[3] and dilospiranes (**6**)[4] contain five- and seven-membered rings.

Although the biological activities of valparanes have not been reported, some related compounds, such as those depicted in Figure 1, show interesting biological activities.[2f,5] Among them, schisanwilsonene A (**4**) is a potent antiviral,[2f] while dilospirane B (**6**) possesses antitumor properties.[5i] These reported activities, together with the difficulty associated with developing synthetic approaches for producing these skeletons, particularly those of valparanes, prompted us to explore the synthesis of natural compounds containing five- and seven-membered rings in their structures. Only a few synthetic efforts toward this goal have been reported to date.[6]

On the basis of a study that demonstrated the radical opening of oxiranes using Nugent's reagent[7a−c] in 2001, we designed a general synthetic methodology for the production of cyclic terpenoids that involves a radical cyclization of monoepoxypolyprenoids triggered by Cp_2TiCl.[7d] Based on the designed strategy, Justicia et al. reported the racemic synthesis of nonnatural racemic valpara-2,14-diene in 2005.[6b] Although their work represents the only reported synthetic approach for the generation of the valparane skeleton, some features of the method prevent or complicate its application for the generation of isomeric natural valpara-2,15-dienes. In fact, the literature does not describe any application of valpara-2,14-diene as an intermediate in the synthesis of natural valparanes.

To address the ultimate goal of accessing natural valparanes, we describe herein an enantioselective route for obtaining natural (−)-valpara-2,15-diene (**1**). This synthesis has two key steps: the Ti(III)-mediated 6-*endo*-6-*endo*-7-*endo*-*trig* cyclization process[7,9] of acyclic silyloxymethyl oxirane **8** to afford the tricyclic intermediate **7** and the generation of target **1** from **7** through A-ring contraction, the most important transformation of this protocol[8] as shown in Scheme 1.

RESULTS AND DISCUSSION

As outlined in Scheme 2, the synthesis of (−)-valpara-2,15-diene (**1**) was started with all-*trans*-geranylgeraniol **9**. As reported earlier,[7d] the geometry of the internal double bonds is fundamental to the success of the approach because only the all-*E* isomer can be utilized in the planned Ti(III) cyclization. Consequently, the ability to reliably obtain multiple grams of naturally occurring *E,E,E*-geranylgeraniol (**9**) from flowers of *Bellardia trixago* (L.) with the GeGeOH chemotype[10] constitutes one of the advantages of this approach. In this sense, considering the cost of *all-trans*-geranylgeraniol (Sigma-Aldrich Spain, 100 mg: €78.5), the availability of this compound from natural sources should not be undervalued.

Epoxidation of geranylgeraniol (**9**) using the Sharpless protocol afforded its 2,3-epoxy derivative (**10**), and geranyllinalyl acetate (**11**) was obtained by subjecting epoxide **10** to Dorta's rearrangement conditions.[11] This reaction proceeds through the corresponding epoxyiodide, which undergoes reductive elimination due to the phosphine hydroxyiodide present in the reaction medium. Acetylation of the intermediate tertiary alcohol produced geranyllinalyl acetate (three steps) in 51% yield. Since there are nine allylic positions

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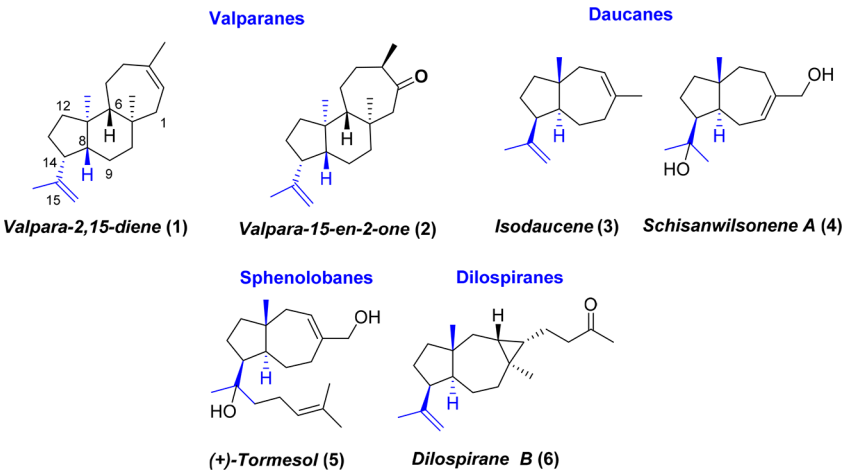
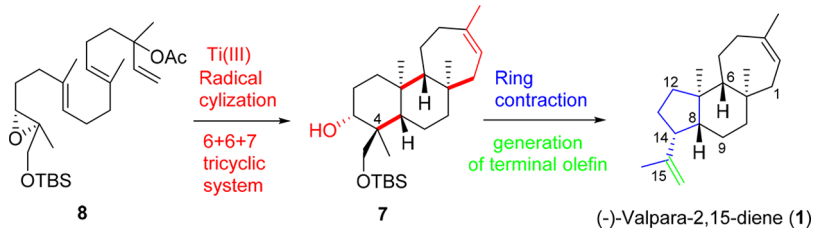
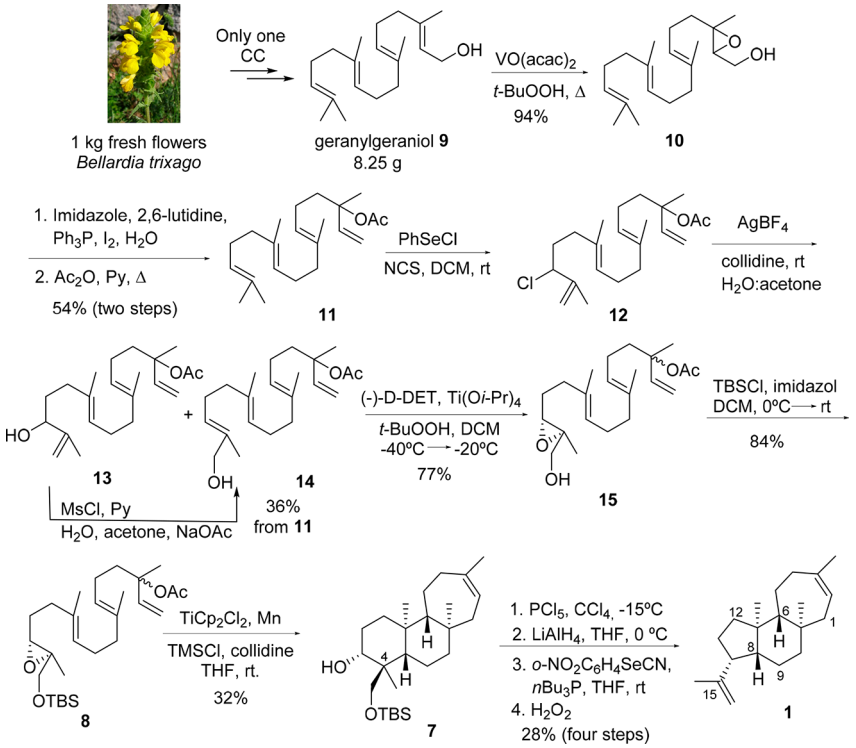


Figure 1. Natural compounds containing five- and seven-membered rings.

Scheme 1. Key Steps in the Synthesis Protocol



Scheme 2. Synthesis of (−)-Valpara-2,15-diene (1)



in **11**, the selective hydroxylation of this molecule at C-16 is not a straightforward transformation. In practice, it could be achieved via a highly chemoselective NCS/PhSeCl-mediated allylic chlorination followed by hydrolysis in the presence of $AgBF_4$.[12] Using this protocol, a quasi-equimolecular mixture of secondary and primary alcohols (**13** and **14**, respectively) was obtained from **11**. The secondary alcohol **13** could be recycled into **14** via mesylation and S_N2' hydrolysis, and considering this recycling, the primary alcohol **14** was obtained from **11** in a 36% overall yield. Since natural valparadiene (**1**) has been reported to be the *ent*-form,[1] chiral (−)-diethyl tartrate was used to perform the key asymmetric Sharpless epoxidation,[13]

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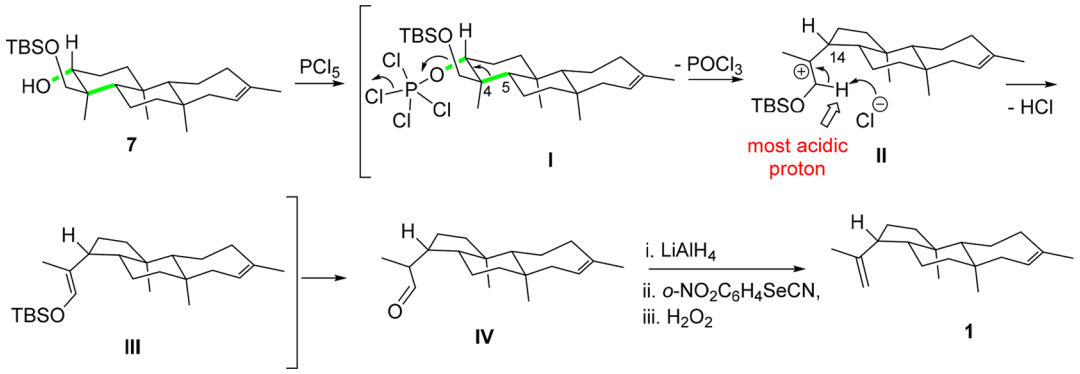
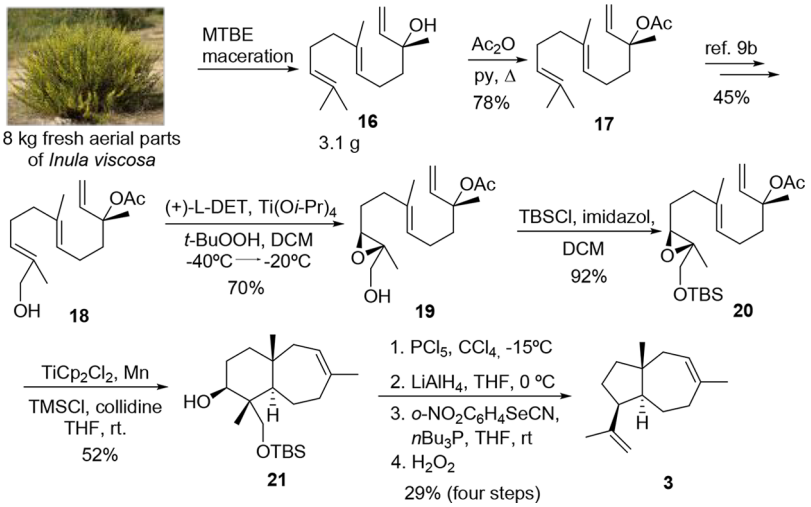
Scheme 3. Mechanistic Proposal for the Ring Contraction of A-Ring Dioxygenated 7



Scheme 4. Synthesis of (+)-Isodaucene (3)



which afforded **15** in 77% yield. The silyl ether protection of the resulting asymmetric epoxy alcohol **15** afforded the key intermediate **8**. The cyclization of epoxide **8** triggered by catalytic Ti(III)[9a] yielded the tricyclic alcohol **7** in an acceptable yield of 32% and an enantiomeric excess of 87%. This result deserves to be highlighted because the domino process led to the closure of a 6,6,7 tricycle and to the stereocontrolled formation of six stereocenters. Coordination between the equatorially positioned titanoxy group at C-3 and the oxygen of the *tert*-butyldimethylsilyl ether in the transition state can be used to rationalize the final stereochemical outcome at C-4.[9d] A number of NMR resonances were key to assign the structure of **7**, namely, the signal at δ 3.60 (dd, J = 11.5, 5.0 Hz, 1H), which allowed us to establish the equatorial position of the hydroxy group at C-3; the three methyl singlets at δ 0.88, 0.83, and 0.82, confirming the cyclization process; and finally, a signal corresponding to an olefinic proton at δ 5.37−5.32 (m, 1H), which appeared as result of the loss of AcOH in the cyclization process. Next, the unprecedented contraction of the γ-dioxygenated A ring in **7** was attempted by treating this compound with PCl_5. Although different experimental conditions were assayed, complex mixtures containing silyl enol ethers and aldehydes were ultimately obtained (Scheme 3).[14] Thus, a process starting from the tricyclic alcohol **7** was developed, and the target product was obtained in a 28% yield through a four-step process that did not involve the isolation of any intermediates. The sequence involved the hydrolysis of the corresponding silyl enol ethers, followed by formyl group reduction and alcohol dehydration.[15] The spectroscopic properties and specific rotation value of +10.1 of the synthetic compound **1** were identical to those of natural (−)-valpara-2,15-diene (**1**).[1c]

Focusing on the key A-ring contraction and the subsequent generation of **1**, the rationale behind this process is shown in Scheme 3. The equatorially disposed primary oxygenated functional group at C-16 in compound **7** plays a key role in the success of the synthetic approach. Thus, the correct alignment of the C-4−C-5 bond and the activated hydroxy group in **I** would justify the migration of this bond to induce displacement of the leaving group and the generation of carbocation **II** with the appropriate configuration at C-14. This tertiary carbocation is converted to the corresponding silyl enol ether (**III**) by regiodirected deprotonation as a result of the higher acidity of the protons of the $-CH_2OTBS$ moiety and the stability of aldehyde **IV**. Finally, the resulting aldehyde (**IV**) is converted into the target isopropenyl derivative **1** in a straightforward manner using standard transformations.

To confirm that this strategy can be used to synthesize other natural polycyclic products containing a cyclopentane moiety with an isoprenyl substituent, the synthesis of (+)-isodaucene (**3**) (Scheme 4) was addressed. As the starting material, (+)-(*E*)-nerolidol (**16**), another natural renewable compound, was used. Up to 3.1 g of (+)-(*E*)-nerolidol (**16**) was isolated from the maceration of 8 kg of leaves and flowers of *Inula viscosa*.[16] The synthetic sequence toward (+)-isodaucene paralleled that of the synthesis of valpara-2,15-diene, and it is

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detailed in Scheme 4. The synthesis of (+)-isodaucene (**1**) began with the acetylation of **16** and resulted in the production of nerolidyl acetate (**17**) in a 78% yield. The selective hydroxylation of nerolidyl acetate produced primary alcohol **18** through the same two-step protocol used in the synthesis of isodaucene, i.e., NCS/PhSeCl-mediated allylic halogenation followed by $AgBF_4$-mediated hydrolysis of the corresponding chlorinated derivative.[9b] Enantiocontrol was achieved through the Sharpless asymmetric epoxidation of **18** using L-(+)-diethyl tartrate to furnish the epoxide **19** in a yield of 70%. Protection of the primary hydroxy moiety to produce silyl ether **20** was achieved by treatment with TBSCl in the presence of imidazole (92%). Exposure of the epoxide **20** to catalytic Ti(III), as previously reported,[9b] led to the *trans* bicyclic alcohol **21** in an acceptable 52% yield, and only one out of the 16 possible stereoisomers was generated. At this point, it was shown that contraction of the γ-dioxygenated A ring provided the target stereo- and regiochemistry, albeit in a modest yield. Thus, as described for the synthesis of (−)-valpara-2,15-diene (**1**), a four-step sequence that included A-ring rearrangement, formyl group reduction, and alcohol dehydration allowed the synthesis of the target natural compound from the bicyclic structure **21**. The spectroscopic properties of the synthetic compound correlated well with those published for natural isodaucene (**3**). The specific rotation of synthetic **3** was +11.2, which is similar to that reported by Hashidoko (+13.0) for the same compound isolated from *Rosa rugosa*.[2g] Additionally, a study using *Cupressocyparis leylandii* that was performed by Cool led to the isolation of a compound with the same NMR data as those reported by Hashidoko, but a negative $[\alpha]_D$ value.[2d] In this regard, our synthesis permitted confirmation of the absolute configuration of the two natural enantiomers of isodaucene.

In conclusion, the first access to natural valparanes is described. The key feature of the strategy is the stereo- and regio-directed contraction of the cyclohexane moiety with two hydroxy-derived substituents, which is the transformation that ultimately enabled the enantioselective synthesis of the natural valparane. Other relevant features are the availability of the starting material, which could be obtained on multigram scale from natural sources, the use of Ti(III)-mediated methodology to generate a tricyclic system with six contiguous stereocenters, and the use of a Sharpless asymmetric epoxidation to control the stereochemistry. This research may also provide access to other naturally related structures, as demonstrated by the synthesis of (+)-isodaucene (**3**).

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a PerkinElmer 141 polarimeter. Silica gel SDS 60 (35−70 μm) was used for flash column chromatography. IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were acquired with Varian Direct-Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz), and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. Accurate mass determinations were achieved with a SYNAPT G2-Si mass spectrometer (Waters, Milford, MA, USA) equipped with high-efficiency T-Wave ion mobility, and an orthogonal Z-spray electrospray ionization (ESI) source was used for mass analyses. MassLynx v.4.1 software was used for HRMS instrument control, peak detection, and integration. The reactions were monitored by TLC, which was performed on 0.25 mm E. Merck silica gel plates (60F-254) and involves the use of UV light for visualization and solutions of phosphomolybdic acid in EtOH and heat as the developing agents. HPLC with UV light and RI detection was also used. Semipreparative HPLC separations were conducted on a silica column (5 μm, 10 × 250 mm) at a flow rate of 2.0 mL/min using an Agilent Series 1100 instrument. The reagents were purchased at the highest quality that was commercially available and were used without further purification.

Plant Material. Aerial parts of *Bellardia trixago* of chemotype GeGeOH were collected in June 2014 in the Pantano del Cubillas zone (Granada, Spain) and identified by Prof. F. del Valle (Department of Fisiologia Vegetal, University of Granada). Voucher specimens are available for inspection at the herbarium of the University of Granada. The aerial parts of *Inula viscosa* L. Greuter were collected in October 2014, in the Parque Almunia zone (Granada, Spain), and identified by Prof. F. del Valle (Department of Fisiología Vegetal, the University of Granada). Voucher specimens are available for inspection at the herbarium of the University of Granada.

Isolation of Geranylgeraniol (9) from the Extract of *Bellardia trixago*. Fresh flowers of *Bellardia trixago* (3 kg) were macerated in *tert*-butyl methyl ether (MTBE) at room temperature for 20 min to afford 55 g of extract. KOH (10% in MeOH, 10 mL) was added to a 10 g portion of this extract suspended in MeOH (50 mL). The solution was maintained at room temperature for 6 h. After removing most of the MeOH and diluting with H_2O (50 mL), the solution was extracted with MTBE (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product, and the product was subjected to silica gel column chromatography using hexanes (H)/TBME mixtures of increasing polarity to afford **9**[17] (4.5 g, H/MTBE, 7:3). The spectroscopic data of this compound were consistent with those previously reported.[18]

*Compound **10**.* To a solution of 1.00 g of geranylgeraniol (**9**) (3.43 mmol) in 110 mL of toluene was added 45 mg of $VO(acac)_2$. The resulting mixture was refluxed under argon for 10 min, and 1.25 mL of 5−6 M *tert*-butylhydroperoxide in decane (6.87 mmol) was added. After heating for 5 min, the mixture was diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (3 × 100 mL) and brine, and dried over Na_2SO_4. The residue was subjected to column chromatography (H/MTBE, 1:1) on silica gel to give epoxide **10** as a colorless syrup (992 mg, 94%). The spectroscopic data of this compound were consistent with those previously reported.[19]

*Geranyllinalyl Acetate (**11**).* To a solution of **10** (2786 mg, 9.105 mmol) in 370 mL of a 3:1 mixture of benzene/1,2-dichloroethane were added imidazole (546 mg, 9.09 mmol), 2,6-lutidine (3.16 mL, 27.3 mmol), triphenylphosphine (9536 mg, 36.36 mmol), iodine (6921 mg, 27.27 mmol), and water (0.163 mL, 9.09 mmol). After stirring for 20 min under argon at room temperature, the crude reaction mixture was diluted with Et_2O, washed with saturated $Na_2S_2O_3$ (2 × 30 mL), saturated $NaHCO_3$ (2 × 30 mL), and brine, and dried over Na_2SO_4. The crude product was purified by column chromatography over silica gel (H/MTBE, 8:1) to afford all-*trans*-geranyllinalool (1954 mg, 74%).[20] Acetic anhydride (13 mL) and 4-dimethylaminopyridine (10 mg) were added to a solution of all-*trans*-geranyllinalool (1280 mg, 4.414 mmol) in pyridine (7 mL). The mixture was heated at reflux for 8 h and poured into ice (100 g). The mixture was extracted with MTBE (3 × 100 mL). The organic layer was washed with 2 N HCl (3 × 100 mL), saturated Na_2CO_3 (3 × 100 mL), and brine (3 × 100 mL), dried over Na_2SO_4, and concentrated. The resulting crude was chromatographed over silica gel (H/MTBE, 97:3) to obtain acetate **11** as a colorless syrup (1055 mg, 72%). The spectroscopic data of this compound were consistent with those previously reported.[21]

*3-Acetoxy-16-hydroxygeranyllinalool (**14**).* PhSeCl (20 mg, 0.1 mmol) and NCS (154 mg, 1.10 mmol) were added to a solution of **11** (350 mg, 1.05 mmol) in dry CH_2Cl_2 (4.3 mL) under an argon atmosphere at room temperature. The mixture was stirred for 45 min, concentrated under reduced pressure, and diluted with Et_2O (150 mL). The organic layer was washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was dissolved in

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acetone/H_2O (1:2, 30 mL), and 2,4,6-collidine (0.55 mL, 4.1 mmol) and $AgBF_4$ (402 mg, 2.10 mmol) were added. The resulting mixture was heated at 60−70 °C for 1 h. The solvent was removed *in vacuo*, and the residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with 2 N HCl (3 × 25 mL) and brine (3 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was separated by column chromatography (H/MTBE, 3:1) on silica gel to give alcohols **13** (102 mg, 28%) and **14** (88 mg, 24%). Compound **13** was obtained as a colorless syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (ddd, J = 17.6, 11.0, 0.9 Hz, 1H), 5.15 (dd, J = 17.6, 0.8 Hz, 1H), 5.14 (bt, J = 6.9 Hz, 1H), 5.12 (dd, J = 11.0, 0.8 Hz, 1H), 4.94 (bs, 1H), 4.84 (bs, 1H), 4.04 (t, J = 6.4 Hz, 1H), 2.12−1.95 (m, 8H), 2.01 (s, 3H), 1.90−1.74 (m, 2H), 1.73 (s, 3H), 1.69−1.59 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 170.0, 147.5, 141.8, 135.3, 134.7, 124.6, 123.8, 113.1, 110.9, 82.9, 75.6, 39.7, 39.5, 35.6, 33.1, 26.4, 23.6, 22.2, 22.2, 17.6, 16.0, 15.9; HRMS (ESI+) calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2541. Compound **14** was obtained as a colorless syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dd, J = 17.6, 11.0 Hz, 1H), 5.39 (bt, J = 6.4 Hz, 1H), 5.15 (dd, J = 17.6, 0.8 Hz, 1H), 5.14−5.08 (m, 2H), 5.12 (dd, J = 11.0, 0.8 Hz, 1H), 3.98 (s, 2H), 2.16−1.94 (m, 10H), 2.00 (s, 2H), 1.90−1.69 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 170.0, 141.8, 135.3, 134.7, 134.6, 126.0, 124.4, 123.7, 113.1, 82.9, 68.9, 39.7, 39.6, 39.3, 26.5, 26.2, 23.6, 22.2, 22.2, 16.0, 15.9, 13.7; HRMS (ESI+) calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2544.

Compound ***15***. A mixture of powdered, activated 4 Å molecular sieves (208 mg) and dry CH_2Cl_2 (4.5 mL) was cooled to 0 °C. L-(+)-Diethyl tartrate (0.08 mL, 0.44 mmol), titanium isopropoxide (0.11 mL, 0.36 mmol), and *tert*-butylhydroperoxide (5−6 M in decane, 0.65 mL, 3.56 mmol) were added sequentially. After 20 min, the mixture was cooled to −20 °C, and **14** (620 mg, 1.78 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise over 15 min. After 3.5 h of stirring at −20 °C, the reaction mixture was warmed to 0 °C, quenched with water (10 mL), and warmed to room temperature. NaOH (5 mL, 40% aqueous solution) was added, and the mixture was stirred for 20 min and filtered through a pad of Celite. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE, 1:1) to afford epoxide **15** as a colorless syrup (500 mg, 77%): $[\alpha]_D$ = −9.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, J = 17.5, 11.0 Hz, 1H), 5.19−5.09 (m, 4H), 3.67 (dd, J = 12.1, 4.5 Hz, 1H), 3.57 (dd, J = 12.1, 8.5 Hz, 1H), 3.02 (t, J = 6.3 Hz, 1H), 2.19−2.04 (m, 4H), 2.02 (s, 3H), 2.01−1.96 (m, 5H), 1.90−1.83 (m, 1H), 1.80−1.65 (m, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 141.8, 135.2, 133.9, 125.0, 123.8, 113.1, 82.9, 65.4, 60.9, 59.9, 39.7, 39.5, 36.2, 26.8, 26.5, 23.6, 22.2 (2C), 16.0, 15.9, 14.3; HRMS (ESI+) calcd for $C_{22}H_{36}O_4Na$ $[M + Na]^+$ 387.2511, found 387.2508.

Compound ***8***. Imidazole (238 mg, 3.50 mmol) was added to a cold (0 °C) solution of **15** (490 g, 1.35 mmol) in dry CH_2Cl_2 (21 mL) under an argon atmosphere and stirred for 15 min, and TBSCl (405 mg, 2.69 mmol) was added. The mixture was kept at room temperature for 45 min, diluted with CH_2Cl_2 (25 mL), and washed with H_2O (3 x15 mL), 2 N HCl (3 × 15 mL), saturated aqueous $NaHCO_3$ solution (3 × 15 mL), and brine (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE, 9:1) to obtain epoxide **8** as a colorless syrup (540 mg, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, J = 17.6, 10.9 Hz, 1H), 5.19−5.09 (m, 4H), 3.59 (d, J = 11.4 Hz, 1H), 3.56 (d, J = 11.4 Hz, 1H), 2.85 (t, J = 6.3 Hz, 1H), 2.20−1.96 (m, 4H), 2.02 (s, 3H), 2.01−1.96 (m, 4H), 1.90−1.82 (m, 1H), 1.80−1.72 (m, 1H), 1.70−1.60 (m, 2H), 1.62 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.28 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 141.8, 135.3, 134.0, 124.8, 123.7, 113.1, 82.9, 67.9, 61.0, 60.7, 39.8, 39.6, 36.3, 27.0, 26.6, 25.8 (3C), 23.6, 22.2, 22.1, 18.3, 16.0, 15.9, 14.1, −5.4 (2C); HRMS (ESI+) calcd for $C_{28}H_{50}O_4NaSi$ $[M + Na]^+$ 501.3376, found 501.3481.

Compound ***7***. A mixture of Cp_2TiCl_2 (112 mg, 0.45 mmol) and Mn dust (532 mg, 9.68 mmol) in rigorously deoxygenated tetrahydrofuran (THF) (25 mL) was stirred at room temperature until the red solution turned green. A solution of oxirane **8** (540 mg, 1.13 mmol), 2,4,6-collidine (0.91 mL, 7.91 mmol), and TMSCl (0.6 mL, 4.52 mmol) in rigorously deoxygenated THF (12 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred for 19 h, diluted with MTBE (25 mL), quenched with 2 N HCl, and extracted with MTBE (3 × 25 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel (H/MTBE, 9:1) to obtain tricycle **7** as a colorless syrup (151 mg, 32%): $[\alpha]_D$ = +13.2 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37−5.32 (m, 1H), 3.70 (d, J = 9.2 Hz, 1H), 3.60 (dd, J = 11.5, 5.0 Hz, 1H), 3.36 (d, J = 9.2 Hz, 1H), 2.12−2.04 (m, 1H), 2.00 (dd, J = 14.6, 6.8, 1.5 Hz, 1H), 1.89−1.82 (m, 1H), 1.83 (dt, J = 13.2, 6.6 Hz, 1H), 1.73 (s, 3H), 1.68−1.58 (m, 4H), 1.52−1.42 (m, 2H), 1.28−1.10 (m, 3H), 0.99−0.89 (m, 3H), 0.92 (s, 9H), 0.88 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 122.5, 76.8, 74.0, 64.5, 50.7, 46.4, 44.2, 41.7, 38.4, 37.9, 35.8, 34.6, 26.3, 25.8 (3C), 25.3, 20.5, 20.4, 19.0, 18.1, 16.2, 11.6, −5.7 (2C); HRMS (ESI+) calcd for $C_{26}H_{48}O_2SiNa$ $[M + Na]^+$ 443.3321, found 443.3317. Enantiomeric excess: 87%. The enantiomeric excess was calculated using chiral-phase liquid chromatography: column, Chiralcel OD; column size, 0.46 cm i.d. × 25 cm; eluent, Hex/IPA, 9.5/0.5; flow rate, 1.0 mL/min; temperature, 25 °C.

*(−)-Valparan-2,15-diene (**1**).* PCl_5 (150 mg, 0.72 mmol) was added to a cold (−15 °C) solution of **7** (100 mg, 0.24 mmol) in dry CCl_4 (8 mL) under an argon atmosphere. The mixture was kept at that temperature with stirring for 25 min. The mixture was diluted with CH_2Cl_2 and quenched via dropwise addition of a saturated aqueous $NaHCO_3$ solution until bubbling stopped. The organic phase was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The product crude was dissolved in dry THF (6 mL) at 0 °C, and $LiAlH_4$ (9 mg) was added under an argon atmosphere and vigorous stirring. After 20 min the reaction was diluted with MTBE and water (1 drop), and a 6 N NaOH solution (1 drop) and water (3 drops) were successively added. The resulting mixture was stirred for 10 min, filtered through a bed of Na_2SO_4 and silica gel, washed with MTBE, and concentrated to afford a crude product, which was chromatographed over silica gel (H/MTBE, 9:1) to obtain a 5:1 mixture of the corresponding epimeric alcohols (21 mg, 31%, two steps). To a solution of this mixture in 1.5 mL of THF were added tri-*n*-butylphosphine (10 mg, 0.048 mmol) and *o*-nitrophenylselenocyanate (11 mg, 0.048 mmol). After stirring under an argon atmosphere for 35 min at room temperature, the reaction crude was diluted with MTBE and quenched with the dropwise addition of 5% NH_4Cl. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product (33 mg), which was redissolved in dry THF (1.5 mL) under argon, and 30% H_2O_2 (0.02 mL) was added. The mixture was stirred for 30 min at 45 °C, diluted with Et_2O (10 mL), washed with brine (3 × 5 mL), and worked up as usual. The crude product was column chromatographed over silica gel (H/MTBE, 97:3) to afford diene **1** as a colorless syrup (17 mg, 89% after two steps): $[\alpha]_D$ = +10.1 (c 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37−5.33 (m, 1H), 4.79 (bs, 1H), 4.78 (bs, 1H), 2.70 (q, J = 8.7 Hz, 1H), 2.22−2.13 (m, 1H), 1.98 (dd, J = 14.4, 6.5 Hz, 1H), 1.91−1.77 (m, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.67−1.42 (m, 7H), 1.37 (q, J = 13.4 Hz, 1H), 1.21 (td, J = 11.6, 4.1 Hz, 1H), 1.13−1.05 (m, 2H), 0.80 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 141.0, 122.9, 110.3, 64.1, 55.4, 47.1, 46.7, 46.4, 45.1, 41.7, 34.9, 36.2, 27.3, 25.8, 25.1, 24.0, 22.2, 20.9, 16.2. The spectroscopic data of this compound were consistent with those previously reported.[1b,c]

Isolation of (+)-Nerolidol (16) from the Extract of *Inula viscosa*. Fresh aerial parts of *Inula viscosa* (8 kg) were macerated two times with MTBE (25 L) for 20 min each time. Evaporation under

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reduced pressure afforded 60 g of crude extract. The extract was dissolved in MTBE (2.5 L) and washed with a 2 N NaOH solution (4 × 300 mL) to yield 17.4 g of neutral fraction and 39 g of an acid fraction after 2 N HCl treatment. The neutral fraction was subjected to silica gel column chromatography using H/MTBE mixtures of increasing polarity to afford (+)-nerolidol (**16**) (4.1 g, H/MTBE, 7:3): colorless oil; $[\alpha]_D$ = +14.2 (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[22]

*(E)-Nerolidyl Acetate (**17**).* Acetic anhydride (31 mL) and 4-dimethylaminopyridine (10 mg) were added to solution of nerolidol (4.10 g, 18.5 mmol) in pyridine (42 mL). The mixture was heated at reflux for 6 h and worked up as usual to give a crude product, which was chromatographed over silica gel (H/MTBE, 4:1) to obtain acetate **17** as a colorless oil (3.8 g, 78%): $[\alpha]_D$ = +2.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 11.0, 17.5 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 5.13−5.09 (m, 2H), 2.09−1.96 (m, 8H), 2.02 (s, 3H), 1.89−1.76 (m, 2H), 1.70 (s, 3H), 1.61 (s, 6H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 142.1, 135.6, 131.5, 124.5, 123.9, 113.2, 83.1, 40.0, 39.9, 26.9, 25.9, 23.8, 22.5, 22.4, 17.9, 16.1; HRMS (ESI+) calcd for $C_{15}H_{25}$ [M − CH_3CO_2H + H]$^+$ 205.1956; found 205.1964.

*3-Acetoxy-12-hydroxynerolidol (**18**).* The synthesis and structural elucidation of this compound was described in ref 9b.

*(R,E)-9-[(2S,3S)-3-(Hydroxymethyl)-3-methyloxiran-2-yl]-3,7-dimethylnona-1,6-dien-3-yl Acetate (**19**).* A mixture of powdered, activated 4 Å molecular sieves (990 mg) and dry CH_2Cl_2 (20 mL) was cooled to 0 °C. L-(+)-Diethyl tartrate (0.36 mL, 2.11 mmol), titanium isopropoxide (0.50 mL, 1.69 mmol), and *tert*-butylhydroperoxide (5−6 M in decane, 4.3 mL) were added sequentially. After 25 min, the mixture was cooled to −20 °C and **19** (2.38 g, 8.50 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 15 min. After stirring at −20 °C for 45 min, the reaction was warmed to 0 °C, quenched with water (22 mL), and warmed to room temperature. NaOH (5 mL, 40% aqueous solution) was added, and the mixture was stirred for 20 min and filtered through a pad of Celite. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE, 1:1) to afford epoxide **19** as a colorless syrup (1.76 g, 70%): $[\alpha]_D$ = −7.0 (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[9b]

*(R,E)-9-[(2S,3S)-3-(tert-Butyldimethylsilyloxymethyl)-3-methyloxiran-2-yl)]-3,7-dimethylnona-1,6-dien-3-yl Acetate (**20**).* Imidazole (1.050 g, 15.44 mmol) was added to a cold (0 °C) solution of **19** (1.76 g, 5.94 mmol) in dry CH_2Cl_2 (94 mL) under an argon atmosphere. The mixture was stirred for 15 min, and TBSCl (1.790 g, 11.91 mmol) was added. The mixture was kept to room temperature for 30 min, diluted with CH_2Cl_2 (100 mL), and washed with H_2O (3 × 50 mL), 2 N HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (H/MTBE, 9:1) to obtain epoxide **20** as a colorless syrup (2.24 g, 92%): $[\alpha]_D$ = −3.1 (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[9b]

*(1R,2S,4aR,9aR)-1-(tert-Butyldimethylsilyloxymethyl)-1,4a,7-trimethyl-2,3,4,4a,5,8,9,9a-octahydro-1H-benzo[7]annulen-2-ol (**21**).* A mixture of Cp_2TiCl_2 (544 mg, 2.18 mmol) and Mn dust (2.400 g, 43.68 mmol) in rigorously deoxygenated THF (114 mL) was stirred at room temperature until the red solution turned green. A solution of **20** (2.24 g, 5.46 mmol), 2,4,6-collidine (4.15 g, 4.8 mL, 34.3 mmol), and TMSCl (2.65 g, 2.9 mL, 24.5 mmol) in rigorously deoxygenated THF (55 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred for 8 h, diluted with MTBE (100 mL), and washed with 2 N HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ solution (3 × 50 mL), and brine (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (H/MTBE, 9:1) to obtain bicycle **21** as a colorless syrup (1.0 g, 52%): $[\alpha]_D$ = +15.9 (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[19]

*(+)-Isodaucene (**3**).* PCl_5 (1.54 g) was added to a cold (−15 °C) solution of **21** (846 mg, 2.40 mmol) in dry CCl_4 (69 mL) under an argon atmosphere. The mixture was kept at that temperature for 20 min, diluted with MTBE, and quenched with the dropwise addition of saturated aqueous $NaHCO_3$ solution until bubbling stopped. The organic layer was washed with brine (3 × 20 mL), dried with anhydrous Na_2SO_4, and evaporated *in vacuo*. The crude product was dissolved in dry THF (94 mL) at 0 °C, and $LiAlH_4$ (146 mg) was added under an argon atmosphere and vigorous stirring. After 15 min the reaction was quenched by successive addition of water (4 drops), 6 N NaOH solution (4 drops), and water (12 drops). The resulting mixture was stirred for 10 min, filtered through a bed of Na_2SO_4 and silica gel, washed with MTBE, and concentrated *in vacuo* to afford a crude product, which was chromatographed over silica gel (H/MTBE, 3:1) to obtain a 5:1 mixture of epimeric alcohols (175 mg, 33%, two steps). To a solution of these alcohols in THF (6 mL) were added tri-*n*-butylphosphine (350 mg, 1.75 mmol) and *o*-nitrophenylselenocyanate (400 mg, 1.75 mmol) under an argon atmosphere at room temperature. The mixture was stirred for 7 h, diluted with MTBE, and quenched with the dropwise addition of 5% NH_4Cl. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product (355 mg), which was redissolved in dry THF (12 mL) under argon, and 30% H_2O_2 (0.2 mL) was added. The mixture was stirred for 30 min at room temperature, diluted with Et_2O (20 mL), washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product obtained was purified by column chromatography over silica gel (H/MTBE, 97:3) to afford diene **3** as a colorless oil (144 mg, 89% after two steps): $[\alpha]_D$ = +11.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42−5.37 (m, 1H), 4.79 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.72 (dt, *J* = 2.5, 0.8 Hz, 1H), 2.96 (dt, *J* = 11.6, 9.1 Hz, 1H), 2.10 (dd, *J* = 14.6, 8.7 Hz, 1H), 2.10−1.97 (m, 2H), 1.86 (bd, *J* = 14.0 Hz, 1H), 1.83−1.69 (m, 3H), 1.75 (bs, 3H), 1.72 (bs, 3H), 1.57−1.48 (m, 2H), 1.39 (td, *J* = 12.2, 8.0 Hz, 1H), 1.26 (dtd, *J* = 13.5, 12.2, 2.9 Hz, 1H), 0.83 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 138.8, 122.7, 112.6, 56.8, 50.4, 42.6, 42.4, 42.0, 35.4, 28.3, 27.6, 23.1 (2C), 19.3; HRMS (ESI+) calcd for $C_{15}H_{25}$ [M + H]$^+$ 205.1956, found 205.1950. The spectroscopic data of this compound were consistent with reported data.[1g]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00129.

^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **8**, **9**, **11**, **12**, **14**−**16**, **18**−**22** (PDF)

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Notes

The authors declare no competing financial interest.

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carrying out the chiral chromatography necessary to calculate the enantiomeric excess.

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