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Directed Hydrogenation of Acyclic Homoallylic Alcohols: Enantioselective Syntheses of (+)- and (−)-Laurenditerpenol

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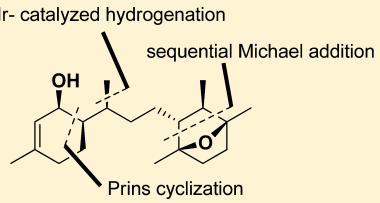
Supporting Information

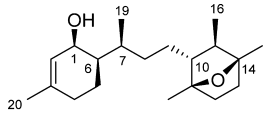
ABSTRACT: Laurenditerpenol is the first marine natural product shown to inhibit hypoxia-inducible factor 1 (HIF-1) activation. Preclinical studies support that the inhibition of HIF-1 is one of the molecular targets for antitumor drug discovery. The synthetically challenging molecular architecture of laurenditerpenol, its absolute stereostructure, and the biological activity of several diastereoisomers were accomplished by our group in 2007 by diastereoselective synthesis. Herein, we report enantioselective syntheses of both enantiomers of laurenditerpenol involving sequential Michael addition and remote homoallylic hydroxyl group-directed asymmetric hydrogenation at ambient temperature and pressure as key reaction steps. The current approach is elegant and overall more efficient than the ones previously reported in the literature.



INTRODUCTION

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that is activated in response to deprived oxygen conditions in solid tumors as a result of genetic adaptations that activate oncogenes and inactivate tumor-suppressing genes.[1,2] It controls the expression of genes influencing angiogenesis, glucose metabolism, cell proliferation, survival, and invasion of solid tumors and is therefore considered to be a central regulator of major adaptive responses to hypoxia in cancer progression.[3−8] Moreover, hypoxia is known to induce tumor radioresistance through the activation of HIF-1.[9−11] Consistent with these findings, there is clinical evidence that both the size of the intratumoral hypoxic fraction and the level of HIF-1α correlate with poor prognosis after radiation therapy. A growing number of anticancer agents including natural products have been shown to inhibit HIF-1 activity from submicromolar to nanomolar concentrations.[12] A recent tumor xenograft model suggests that HIF-1 inhibitors suppress the translocation of cancer cells that survive radiation therapy and decrease the incidence of postirradiation tumor recurrence.[13]

Laurenditerpenol **1** is a marine bicyclic diterpene isolated[14] from red algae *Laurencia intricata* that was found to inhibit hypoxia (1% O_2)-induced HIF-1 activation in a T47D-cell-based luciferase reporter assay with an IC_{50} value of 0.4 μM. Mitochondrial respiration studies suggest that laurenditerpenol is the first member of a structurally novel class of marine natural product-based mitochondrial inhibitors that block mitochondrial oxygen consumption and promote the degradation of HIF-1α protein under hypoxic conditions.[14] Laurenditerpenol ($C_{20}H_{34}O_2$) is unique because a fifth of its carbons are nonfunctional chiral centers. In 2007, our group[15] successfully achieved the installation of nonfunctional chiral centers and total synthesis of laurenditerpenol from eight plausible stereoisomers. Subsequently, convergent racemic synthesis by Jung and Im,[16] formal synthesis using chiral oxazaborolidinium triflimide-catalyzed Diels−Alder reaction by Corey and co-workers,[17] and, more recently, low-yielding convergent total synthesis of (−)-laurenditerpenol have been accomplished through an organolithium to aldehyde nucleophilic addition by Pitsinos et al.[18]



(-)-Laurenditerpenol **1**

RESULTS AND DISCUSSION

In our earlier approach,[15] three bottleneck issues were identified: linear, multistep synthesis; low-yielding epimerization to create the necessary chirality at C-6 position; and recognition of the unstable nature of a ketal allyl bromide. All of these three issues were necessary to make all the possible isomers for determination of the absolute configuration of **1**. Thus, in order to develop an elegant, efficient, and enantioselective synthetic route for (−)-laurenditerpenol, these issues need to be addressed. Herein we report an improved and enantioselective syntheses of both (−)- and (+)-laurenditerpenol starting from the corresponding (+)- or (−)-citronellal (**5**) chirons. Our retrosynthetic strategy is outlined in Scheme 1, wherein the introduction of the required chirality (*S*) at the nonfunctional C-7 position was envisioned by use of the C1 chirality (*S*) of isopulegol as a remote directing group in asymmetric hydrogenation. The envisioned analysis is the result of our previous approach that eliminated

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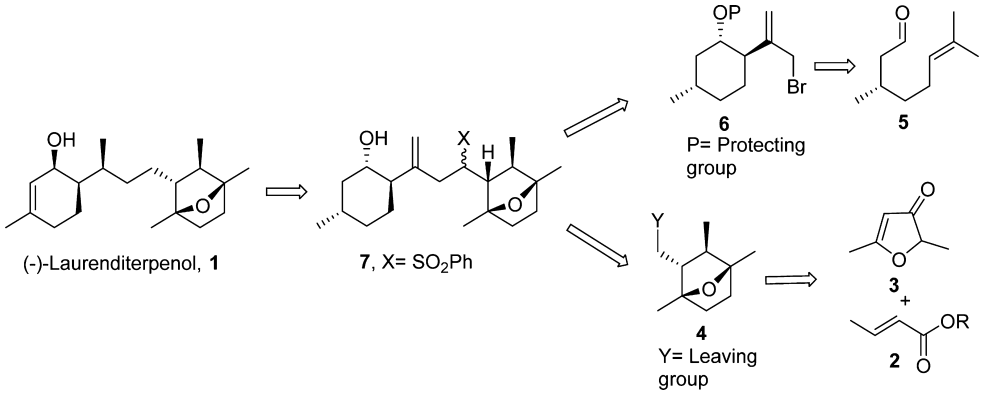
Scheme 1. Retrosynthetic Analysis of (−)-Laurenditerpenol 1



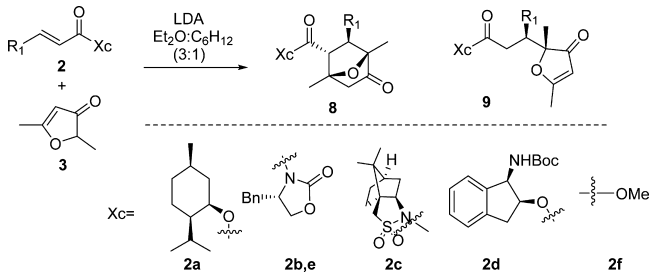
unstable intermediates and obvious construction strategies leading to a rather straightforward sulfone-mediated C−C bond formation between allyl bromide **6** and sulfone **4**. Additionally, isopulegol would serve as a chiral synthon to give the required stereochemistry at C-6 position and would yield stable allyl bromide **6**. The asymmetric double Michael/Diels−Alder addition of crotonates or amides **2** to the furanone **3** enolate can provide the 7-oxabicyclo[2.2.1]heptane scaffold for **4** with appropriately adorned chirality and substituents.

The synthetic endeavor commenced with the excellent diastereoselectivity observed between lithium enolate **3** and methyl crotonate **2f** to yield (±)-6-*exo*-keto ester **8f**.[19,20] The formation of the resulting adduct was due to either an "anion-assisted" Diels−Alder reaction or sequential Michael additions. To gain further insights into the mechanism and to perform chiral synthesis, representative crotonates **2a** and **2d** and amides **2b**, **2c**, and **2e** were prepared by tethering the appropriate chiral auxiliary and subjecting the product to the lithium enolate of furanone **3**. Crotonates **2a** and **2d** yielded the 6-*exo*-keto esters **8a** and **8d** with poor diastereoselectivity ranging between 55% and 69%, whereas the crotonamides **2b** and **2c** furnished only mono-Michael adducts **9b** and **9c** in 80−85% yield with >75% diastereomeric excess (de). On the basis of these results, if product formation were due to a Diels−Alder cycloaddition, all the crotonates or amides **2** would have yielded the bicyclic compound **8**. The exclusive formation of **9** in the case of amides **2b** and **2c** suggests that the formation of adduct was due to mono-Michael addition and not "anion-assisted" Diels−Alder reaction. Chemical discrimination in the formation of bicyclic **8** or monocyclic **9** products can be attributed to the reactivity of the resulting enolates (after initial addition of furanone enolate to α,β-unsaturated double bond) of crotonates and crotonamides in the second Michael addition. Additionally, the product distribution is highly sensitive to temperature, solvent, and solubility of the substrates **2** (see Table 1).

An attempt to perform intramolecular Michael addition on adducts **9** proved to be difficult even with boron and titanium triflates.[21] A chiral lithium enolate of furanone **3** with a chiral ternary complex[22] derived from the dimethyl ether of (*R*,*R*)-(+)-hydrobenzoin proved unsuccessful in achieving chiral induction in the sequential Michael addition. Finally, induction was achieved with fumaric ester amide **2e**,[23] wherein both mono- (**9e**, 65% yield with 58% de) and double-Michael adducts (**8e**, 20% yield with 95% de) were isolated (Table 1).

To achieve substantial amounts of 7-oxabicyclo[2.2.1]-heptane intermediate **12**, the earlier method, which relied on

Table 1. Chiral Auxiliary Induced Double Michael Addition of Lithium Enolate of Furanone 3 to α,β-Unsaturated Crotonates/Amides 2



compd	R_1	adduct **8** yield, de (%)	adduct **9** yield, de (%)
2a	Me	82, 55	
2b[a]	Me		80, 75
2c	Me		84, 90
2d	Me	76, 60	
2e[b]	CO_2Et	20, 95	65, 58
2f	Me	69	

[a]Instead of Et_2O/cyclohexane (3:1), the following were used as solvent at −78 °C: Et_2O gave **9b** (80, 76); THF gave **9b** (78, 80); and toluene gave **9b** (70, 78). [b]Instead of Et_2O/cyclohexane (3:1), the following were used as solvent: Et_2O at −78 °C gave **9e** (75, 60); Et_2O at 0 °C gave **9e** (76, 60); and Et_2O/cyclohexane (3:2) at 0 °C gave no **8e** product.

chemical resolution, was found to be highly practical. Both enantiomers of sulfone **12** were prepared on a multigram scale starting from **8f** via thioketalization, saponification, resolution with (*S*)-(−)-4-benzyl-2-oxazolidinone, desulfurization, reduction, iodination, and sulfonation[15] to yield the corresponding enantiomers (−)-**12** [80%, three steps from (+)-**10**] and (+)-**12** [87%, three steps from (+)-**11**] as crystalline solids (Scheme 2).

Following the synthetic strategy, $ZnCl_2$-catalyzed[24] intramolecular Prins cyclization of (*S*)-citronellal resulted in 70% (+)-isopulegol and 11% (−)-*neo*-isopulegol with the required C6 stereochemistry. The major (+)-isopulegol, (+)-**13**, was separated via purification, silyl protection, and regioselective allylic bromination[25] with N-bromosuccinimide (NBS) employing Yamanaka conditions, which furnished bromide (+)-**14** in 92% yield (two steps) (Scheme 3).

Stereoselective alkylation of bromide (+)-**14** with sulfone (−)-**12** was successfully achieved to furnish (+)-**15a** and (+)-**15b** in 80% yield with good diastereoselectivity (diastereomeric ratio, dr, 85:12) (Scheme 3). The presence of additive

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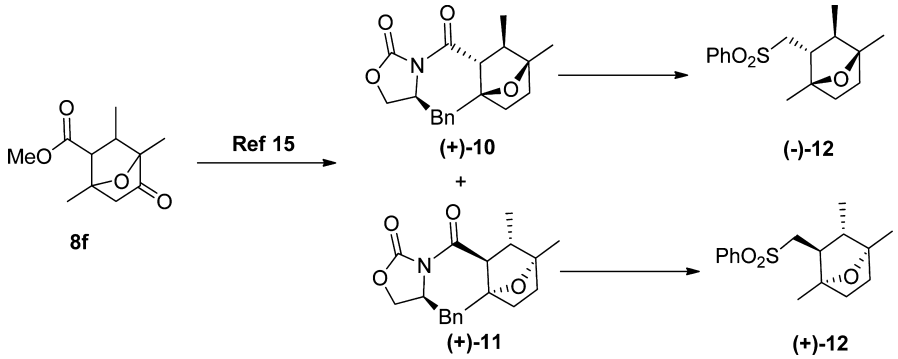
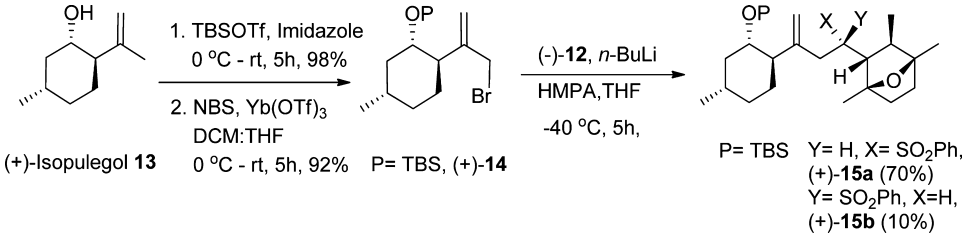
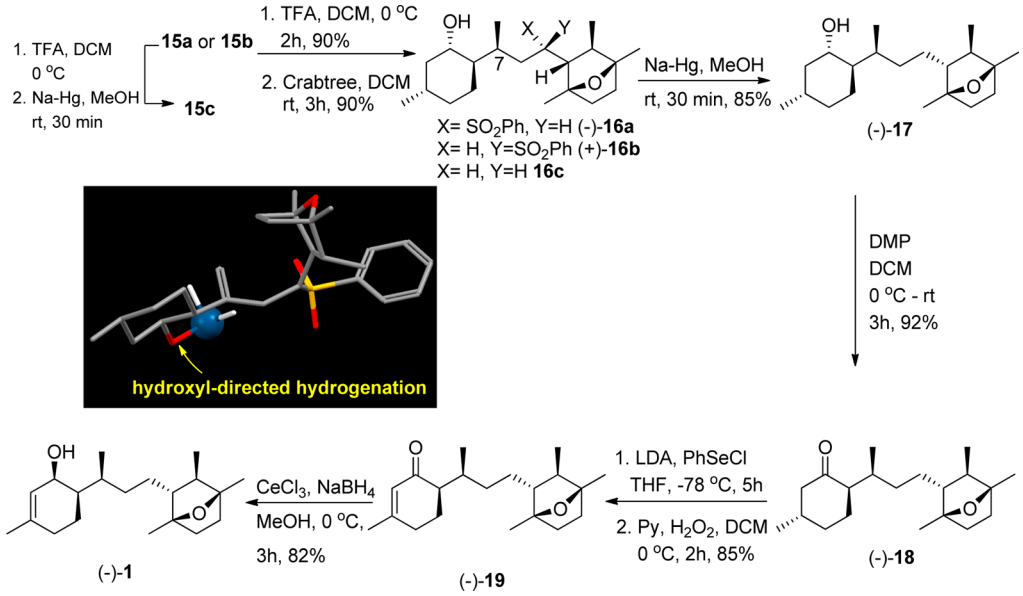
Scheme 2. Synthesis and Chemical Resolution of 7-Oxabicyclo[2.2.1]heptane Fragment



Scheme 3. Synthesis of Allyl Bromide and Alkylation with Sulfone, (+)-12



Scheme 4. Substrate-Induced Asymmetric Hydrogenation with Crabtree's Catalyst to Create a Remote Asymmetric Center at C7: Synthesis of (−)-Laurenditerpenol 1[a]



[a]In the inset, hydrogen atoms are shown only on iridium metal, and all other H atoms and ligands are omitted for clarity.

hexamethylphosphoramide (HMPA) proved to be critical for the successful transformation. The absolute stereochemistry of newly created center at C9 in the major isomer (+)-**15a** was confirmed with coupling constants and 2D NMR data. The resulting olefinic 1,1-disubstituted homoallylic hydroxy compound (+)-**15a** was subjected to TBS deprotection followed by hydrogenation with Crabtree's cationic iridium catalyst[26] $[Ir(COD)(py)(PCy_3)]PF_6$ at atmospheric pressure and room temperature. Directed hydrogenations at ambient conditions are scarce, and the majority of the reported methods involve elevated temperature and pressure.[27] As anticipated, due to simultaneous coordination of iridium to the hydroxyl group of C1 and alkene between C7−C19, a rigid, chairlike intermediate results to furnish the 7*S* isomer with extremely high diastereoselectivity, >98% (see inset in Scheme 4).

Directed hydrogenation of the free alcohol derived from **15b** also yielded *S*-configuration at C7, suggesting that the stereochemical outcome of the reaction was dictated solely by the hydroxyl group and was independent of the stereochemistry at the C9 position. However, the reduction in this case was found to be sluggish (24 h with 15 mol % catalyst) and resulted in 85% **16b** and 10% 1,1,2-trisubstituted allylic alcohol. This may be due to steric factors and higher pyridine concentration. The free hydroxyl group was found, as expected, to be

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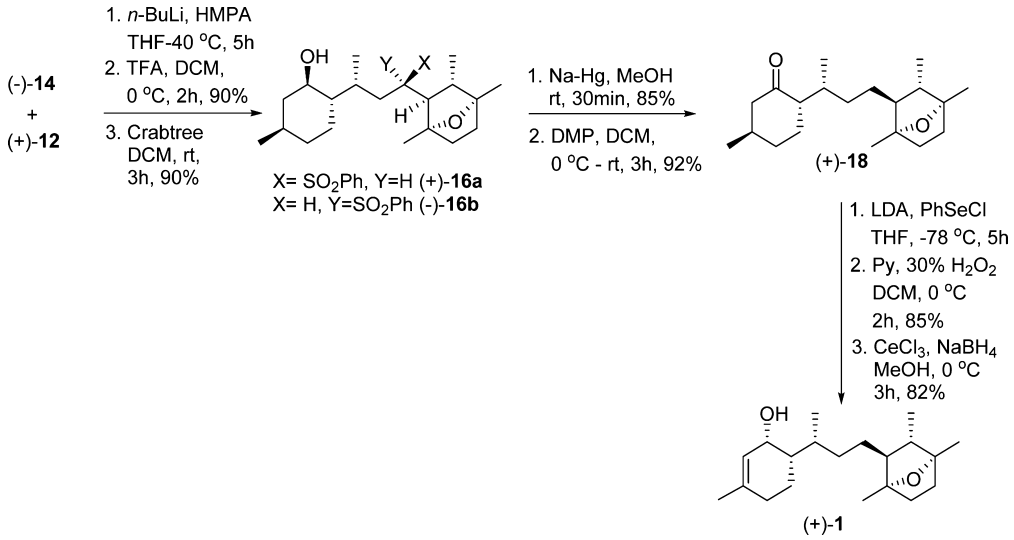
Scheme 5. Enantioselective Synthesis of Unnatural (+)-Laurenditerpenol 1



necessary for the reduction of the 1,1-acyclic homoallylic alcohols, and the isomerized trisubstituted 1,1,2-trialkyl olefin did not react under these conditions. Interestingly, diastereoselectivity of the directed hydrogenation was found to be influenced by the presence of a bulky phenylsulfonyl group at the C9 position. Thus, in the absence of the phenylsulfonyl group, hydrogenation gave the desired product with 86% diastereoselectivity at the newly created C7 center. In view of the superior stereoselectivity observed with phenylsulfonyl-substituted homoallylic alcohols, desulfonylation was performed after the hydrogenation step, using sodium−mercury in MeOH at room temperature to produce the secondary alcohol (−)-**17** in 85% yield. Dess−Martin periodinane oxidation and regioselective enolization with lithium diisopropylamide (LDA), followed by addition of PhSeCl, produced the corresponding selenoethers (3:2 ratio of diastereomers), which were further subjected to oxidative elimination to yield α,β-unsaturated ketone (−)-**19**, whose NMR and other analytical data were in agreement with previously reported data.[15]

Finally, chemoselective reduction of the unsaturated ketone under Luche conditions at −20 °C produced separable laurenditerpenol (−)-**1** and its C1 epimer in 82% yield with 7:3 ratio.

Following the same synthetic sequence, starting from sulfone (+)-**12** and bromide (−)-**14** prepared from commercially available isopulegol, resulted in (+)-laurenditerpenol **1** in seven steps with 29% overall yield (Scheme 5).

CONCLUSIONS

In summary, efficient and enantioselective syntheses of natural (−)-laurenditerpenol and its (+)-enantiomer were successfully achieved starting from citronellal chirons. Crabtree's iridium catalyst at atmospheric pressure and ambient temperature proved to be an efficient cationic metal catalyst for the reduction of acyclic 1,1-disubstituted olefins with excellent stereocontrol. The scope, generality, substrate tolerance, and stereochemical factors associated with chiral induction in hydrogenation of acyclic homoallylic alcohols are under investigation. Overall, the current approach is elegant and more efficient than the ones previously reported in the literature by other synthetic sequences. The naturally occurring (−)-laurenditerpenol was achieved in 14 steps with 8% overall yield from commercially available 2,5-dimethylfuran-3(2*H*)-one.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an atmosphere of argon with oven-dried glassware and standard syringe/septa techniques. All reactions were magnetically stirred with Teflon stir bars, and temperatures were measured externally. Solvents were distilled under an argon atmosphere prior to use. The solvents tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone, while CH_2Cl_2 and cyclohexane were dried over P_2O_5. Triethylamine and hexamethylphosphoramide (HMPA) were distilled from CaH_2. Ethanol and methanol used were bottle-grade solvents. All reagents obtained commercially were used without further purification. The reaction progress was monitored on precoated silica gel thin-layer chromatography (TLC) plates. Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of 2 mL of anisaldehyde, 10 mL of glacial acetic acid, and 5 mL of H_2SO_4 in 340 mL of EtOH, followed by heating with a heat gun. Column chromatography was performed with silica gel (230−400 mesh). All the solvents (hexanes, ethyl acetate, CH_2Cl_2, Et_2O) were distilled prior to use for column chromatography. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ or C_6D_6 on 400 MHz (100 MHz) or 500 MHz (125 MHz) machines. Chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (δ) as the internal standard, and coupling constants are in hertz (Hz). Assignment of proton resonances were confirmed by correlated spectroscopy. IR spectra were recorded by use of a universal attenuated total reflection sampling accessory (diamond ATR) on an Agilent Cary 630 FT-IR spectrometer. High-resolution mass spectra were recorded on an Agilent electrospray ionization quadrupole time-of-flight (ESI-QTOF) instrument.

Syntheses. *1. (±)-Methyl 1,3,4-Trimethyl-5-oxo-7-oxabicyclo-[2.2.1]heptane-2-carboxylate, (±)-8f.* To a freshly prepared solution of lithium diisopropylamine (31.2 mL, 220 mmol) in cyclohexane/diethyl ether at 1:3 ratio (400 mL) was added furanone **3** (22.4 g, 200 mmol) at −78 °C. The mixture was stirred for 1 h at −78 °C. Then a solution of methyl crotonate **2f** (20 g, 200 mmol) in 1:3 cyclohexane/ether (100 mL) was added slowly to the enolate solution at −78 °C, and the resulting yellow colored mixture was stirred at the same temperature. After 5 h, the reaction mixture was quenched with saturated NH_4Cl solution (100 mL) and extracted with ether (3 × 100 mL). The combined layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting product (±)-**8f** was distilled under high vacuum to yield a yellow viscous liquid[20] (29.25 g, 69%; 95−100 °C at 1 mmHg). IR

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(cm^{-1}) 2975, 2932, 1762, 1729, 1436, 1380, 1163, 1017, and 867. ^1H NMR (400 MHz, chloroform-*d*) δ 3.66 (s, 3H), 2.49 (d, *J* = 17.8 Hz, 1H), 2.39 (dd, *J* = 5.5, 2.1 Hz, 1H), 2.26 (qd, *J* = 6.9, 5.4 Hz, 1H), 2.14 (dd, *J* = 17.9, 2.2 Hz, 1H), 1.59 (s, 3H), 1.24 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 172.0, 88.6, 82.9, 61.4, 52.2, 45.3, 40.1, 21.5, 16.2, 11.1. ESI-HRMS calcd for $C_{11}H_{17}O_4$, 213.1127 $[M + H]^+$; found, 213.1127.

2. (±)-1,4,6-Trimethyl-7-oxaspiro(bicyclo[2.2.1]heptane-2,2′-[1,3]dithiolane)-5-carboxylic Acid, (±)-20. To a solution of bicyclic keto methyl ester **8f** (25.0 g, 118 mmol) in anhydrous benzene (300 mL) were added *p*-toluenesulfonic acid (*p*-TSA; 2.0 g, 11.8 mmol) and ethanedithiol (19.8 mL, 235 mmol). The resulting mixture was stirred for 12 h under reflux temperature and water was removed by use of a Dean−Stark apparatus. After 6 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give crude residue, which was subjected to saponification without further purification. The crude product was dissolved in methanol (300 mL), 2 N LiOH in water (145 mL) was added at room temperature, and the mixture was stirred for 2 h at 40 °C. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with EtOAc (3 × 100 mL). The resulting aqueous layer was cooled to 0 °C, and the pH was carefully adjusted to 2 with 2 N HCl. The resulting pale cream-colored solid was filtered and dried under vacuum to furnish (±)-**20** as a pale white solid (29.7 g, 92%). IR (cm^{-1}) 2922, 1698, 1422, 1375, 1273, 1220, 1121, 892, and 778. ^1H NMR (400 MHz, chloroform-*d*) δ 3.28 (ddt, *J* = 7.1, 5.0, 2.0 Hz, 3H), 3.06−2.97 (m, 1H), 2.88−2.79 (m, 2H), 2.31 (dd, *J* = 6.4, 2.2 Hz, 1H), 2.21 (dd, *J* = 14.4, 2.3 Hz, 1H), 1.52 (s, 3H), 1.46 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 91.9, 83.9, 76.8, 62.4, 53.4, 41.9, 40.7, 40.5, 21.1, 19.0, 13.1. ESI-HRMS calcd for $C_{12}H_{19}O_3S_2$, 275.0776 $[M + H]^+$; found, 275.0777.

3. Chemical Resolution of 7-Oxabicyclo[2.2.1]heptane. The acid (±)-**20** (17.0 g, 62 mmol) was dissolved in anhydrous dichloromethane (DCM; 300 mL). Triethylamine (36 mL, 257 mmol) was added, and the solution was cooled to 0 °C. To the resulting cold solution was added pivaloyl chloride (7.62 mL, 62 mmol), and the mixture was stirred for an additional 1 h at 0 °C. Then solid LiCl (2.19 g, 51.6 mmol) and (*S*)-4-benzyloxazolidin-2-one (9.14 g, 51.6 mmol) were added in one portion, and stirring was continued. After 12 h, TLC indicated formation of two new spots along with a small amount of starting material oxazolidinone. The whole reaction mixture was concentrated, diluted with water (300 mL), and extracted with DCM (3 × 100 mL). The combined organic layers were washed with 1 N HCl (125 mL), 1 N NaOH (125 mL), and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting viscous crude product was subjected to partial crystallization with hot ether as a solvent. The compound (+)-**21a**[28] was partially soluble in ether, and (+)-**21b** was freely soluble in hot ether. After repeated crystallization, (+)-**21a** (11.3 g) and (+)-**21b** (11.2 g) were obtained in 42% and 41.6% yield, respectively.

(+)-(S)-4-Benzyl-3-[(1R,4R,5R,6R)-1,4,6-Trimethyl-7-oxaspiro(bicyclo[2.2.1]heptane-2,2′-[1,3]dithiolan)-5-ylcarbonyl]oxazolidin-2-one, (+)-21a. White solid; $[\alpha]_D$ = +40.9 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) 2991, 2935, 1774, 1682, 1384, 1188, 1054, and 697. ^1H NMR (400 MHz, chloroform-*d*) δ 7.36−7.27 (m, 3H), 7.23−7.20 (m, 2H), 4.80 (ddt, *J* = 9.8, 7.5, 3.5 Hz, 1H), 4.24−4.14 (m, 2H), 4.03 (dd, *J* = 6.3, 1.6 Hz, 1H), 3.35−3.26 (m, 4H), 3.11 (d, *J* = 14.2 Hz, 1H), 3.08−3.01 (m, 1H), 3.01−2.94 (m, 1H), 2.71 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.10 (dd, *J* = 14.1, 1.7 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 153.1, 135.0, 129.4 (2C), 129.0 (2C), 127.4, 92.8, 85.3, 77.0, 65.9, 59.3, 55.4, 52.1, 43.2, 40.4, 40.0, 38.3, 20.7, 18.7, 12.9. ESI-HRMS calcd for $C_{22}H_{28}NO_4S_2$, 434.1460 $[M + H]^+$; found, 434.1465.

(+)-(S)-4-Benzyl-3-[(1S,4S,5S,6S)-1,4,6-trimethyl-7-oxaspiro(bicyclo[2.2.1]heptane-2,2′-[1,3]dithiolan)-5-ylcarbonyl]oxazolidin-2-one, (+)-21b. White solid; $[\alpha]_D$ = +27.7 (*c* = 2.0, $CHCl_3$). IR (cm^{-1}) 2969, 2925, 1775, 1685, 1374, 1188, 1107, and 703. ^1H NMR (400 MHz, chloroform-*d*) δ 7.31 (dt, *J* = 14.7, 6.9 Hz, 3H), 7.23−7.20 (m, 2H), 4.74−4.66 (m, 1H), 4.17 (d, *J* = 4.8 Hz, 2H), 4.07 (dd, *J* = 6.5, 1.6 Hz, 1H), 3.33−3.26 (m, 4H), 3.09 (d, *J* = 14.2 Hz, 1H), 3.01 (q, *J* = 6.6 Hz, 2H), 2.86 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.08 (dd, *J* = 14.3, 1.8 Hz,1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 153.0, 135.0, 129.5 (2C), 128.9 (2C), 127.4, 92.7, 85.1, 76.9, 65.7, 59.2, 55.9, 52.2, 43.5, 40.4, 40.1, 37.4, 20.8, 18.7, 12.9. ESI-HRMS calcd for $C_{22}H_{28}NO_4S_2$, 434.1460 $[M + H]^+$; found, 434.1461.

4. (+)-(S)-4-Benzyl-3-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo-[2.2.1]heptane-2-carbonyl]oxazolidin-2-one, (+)-10. To a suspension of Raney-2800 Ni (80 mL) in ethanol (40 mL) was added a solution of (+)-**21a** (6.0 g, 13.85 mmol) in 60 mL of ethanol/THF (8:2 v/v; THF is necessary to solubilize the starting material). The reaction mixture was refluxed for 3 h, cooled to room temperature and allowed to settle to two layers. The supernatant layer was carefully decanted, then another 60 mL of EtOH/THF (8:2) was added, and the mixture was stirred and decanted; the washings were repeated three more times. The combined cloudy white organic layer was filtered over Celite and concentrated under reduced pressure to give a crude solid. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 9:1) to give (+)-**10** in 98% (4.6 g) yield as a white solid. $[\alpha]_D$ = +71.6 (*c* = 0.9, $CHCl_3$). IR (cm^{-1}) 2966, 2917, 2849, 1773, 1686, 1376, 1205, and 699, ^1H NMR (400 MHz, chloroform-*d*) δ 7.37−7.32 (m, 2H), 7.29 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.25−7.22 (m, 2H), 4.79 (ddt, *J* = 9.8, 7.6, 3.6 Hz, 1H), 4.24−4.13 (m, 2H), 4.00 (dd, *J* = 4.9, 1.8 Hz, 1H), 3.30 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.70 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.37 (qd, *J* = 7.1, 4.8 Hz, 1H), 1.93 (dddd, *J* = 29.8, 11.1, 9.0, 4.2 Hz, 2H), 1.71 (td, *J* = 11.5, 3.5 Hz, 1H), 1.53 (s, 3H), 1.50−1.44 (m, 1H), 1.36 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 153.3, 135.2, 129.4 (2C), 129.1 (2C), 127.5, 86.5, 86.3, 66.0, 60.2, 55.5, 46.1, 38.8, 38.7, 34.0, 21.2, 18.4, 17.9. ESI-HRMS calcd for $C_{20}H_{26}NO_4$, 344.1862 $[M + H]^+$; found, 344.1860.

5. (−)-[(1R,2S,3R,4S)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]methanol, (−)-22. To a suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in anhydrous ether (20 mL) at 0 °C was added dropwise (+)-**10** (3.6 g, 10.5 mmol) in ether (20 mL). The reaction mixture was stirred for 5 h at 0 °C, carefully quenched with saturated NH_4Cl (5 mL) solution, and stirred for an additional 1 h at room temperature. The resulting white suspension was filtered over anhydrous $MgSO_4$, washed thoroughly with ether (2 × 20 mL), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexanes/Et_2O, 7:3) to produce (−)-**22** as a white solid in 95% yield. $[\alpha]_D$ = −7.23 (*c* = 0.7, $CHCl_3$). IR (cm^{-1}) 3434, 2961, 2923, 2879, 1455, 1374, 1016, and 853. ^1H NMR (400 MHz, chloroform-*d*) δ 3.73 (dd, *J* = 10.8, 7.1 Hz, 1H), 3.63 (dd, *J* = 10.7, 7.8 Hz, 1H), 1.87−1.77 (m, 2H), 1.64 (td, *J* = 13.2, 12.6, 3.9 Hz, 1H), 1.57−1.48 (m, 3H), 1.45 (s, 3H), 1.43−1.36 (m, 1H), 1.30 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.8, 84.7, 64.2, 60.1, 46.0, 39.0, 32.1, 21.5, 18.6, 17.8. ESI-HRMS calcd for $C_{10}H_{19}O_2$, 171.1385 $[M + H]^+$; found, 171.1383.

6. (−)-(1R,2R,3R,4S)-2-(Iodomethyl)-1,3,4-trimethyl-7-oxabicyclo-[2.2.1]heptane, (−)-23. To a solution of alcohol (−)-**22** (1.5 g, 8.82 mmol) in anhydrous DCM (60 mL) were added imidazole (1.8 g, 26.4 mmol) and triphenylphosphine (3.46 g, 13.2 mmol) at room temperature. The reaction mixture was stirred for 30 min and then cooled to 0 °C. Iodine (2.24 g, 17.63 mmol) was added to the resulting cold solution, and the mixture was allowed to stir for 12 h at room temperatureand then diluted with water (30 mL) and extracted with DCM (2 × 25 mL). The combined organic layer was washed with 1 N $Na_2S_2O_3$ (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude residue, which was purified by silica gel column chromatography (hexanes/Et_2O, 9:1) to yield (−)-**23** (2.3 g) as a white solid in 94% yield. $[\alpha]_D$ = −40.6 (*c* = 1.03, $CHCl_3$). IR (cm^{-1}) 2964, 2871, 1449, 1377, 1189, and 863. ^1H NMR (400 MHz, chloroform-*d*) δ 3.12 (dd, *J* = 7.9, 3.9 Hz, 2H), 1.78 (dtt, *J* = 13.7, 6.3, 3.0 Hz, 2H), 1.66−1.51 (m, 2H), 1.48−1.40 (m, 2H), 1.39 (s, 3H), 1.25 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.7, 84.9, 60.1, 50.5, 38.6, 31.7, 20.8, 18.6, 18.2, 6.0. ESI-HRMS calcd for $C_{10}H_{18}IO$, 281.0402 $[M + H]^+$; found, 281.0405.

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7. (−)-(1S,2R,3R,4R)-1,2,4-Trimethyl-3-[(phenylsulfonyl)methyl]-7-oxabicyclo[2.2.1]heptane, (−)-12. To a suspension of anhydrous sodium benzene sulfinate (2.05 g, 12.5 mmol) in hydrous *N*,*N*-dimethylformamide (DMF) (40 mL) was added iodo compound (−)-**23** (2.0 g, 7.14 mmol). The mixture was stirred for 12 h at 60 °C and then cooled, diluted with water (100 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure, and purified by silica gel column chromatography (hexanes/EtOAc, 8:2) to furnish (−)-**12** (1.95 g) as a white solid in 95% yield. $[\alpha]_D = -15.07$ (*c* = 0.96, $CHCl_3$). IR (cm^{-1}) 3059, 2969, 2935, 1446, 1304, 1141, and 865. ^1H NMR (400 MHz, chloroform-*d*) δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.67−7.62 (m, 1H), 7.56 (dd, *J* = 8.4, 7.0 Hz, 2H), 3.07−3.03 (m, 2H), 1.79−1.66 (m, 2H), 1.63−1.57 (m, 2H), 1.56−1.39 (m, 2H), 1.28 (s, 3H), 1.26 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 133.8, 129.4 (2C), 128.0 (2C), 85.6, 85.1, 58.9, 50.5, 48.6, 38.5, 32.6, 19.8, 18.1, 18.0. ESI-HRMS calcd for $C_{16}H_{23}O_3S$, 295.1368 $[M + H]^+$; found, 295.1369.

8. (+)-(1S,2R,5S)-5-Methyl-2-(prop-1-en-2-yl)cyclohexanol, (+)-13. An oven-dried 250 mL round-bottom flask was charged with freshly prepared anhydrous $ZnCl_2$ (0.35 g, 2.6 mmol) and anhydrous diethyl ether (10 mL). The solution was further diluted with anhydrous DCM (40 mL) and cooled to −78 °C. To the resulting cold solution was added (*S*)-citronellal **5** (4.0 g, 25.93 mmol) in 80 mL of DCM at −78 °C; the mixture was stirred for 2 h at the same temperature and then allowed to warm to room temperature for an additional 12 h. TLC indicated two new spots in the ratio of 3:1. The reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexanes/Et_2O, 7:3) to yield (+)-isopulegol **13** (2.8 g, 70%) as a major compound, along with 0.44 g (11%) of (−)-neoisopulegol.[24] $[\alpha]_D$ = +11.9 (*c* = 2.0, $CHCl_3$). IR (cm^{-1}) 3369, 3072, 2920, 2968, 1644, 1447, 1374, 1094, 1026, and 883. ^1H NMR (400 MHz, chloroform-*d*) δ 4.85−4.79 (m, 2H), 3.41 (td, *J* = 10.4, 4.3 Hz, 1H), 2.03 (s, 1H), 1.98 (ddt, *J* = 9.6, 4.2, 1.8 Hz, 1H), 1.83 (ddd, *J* = 13.0, 9.9, 3.4 Hz, 1H), 1.67−1.66 (m, 3H), 1.64−1.59 (m, 2H), 1.45 (tdt, *J* = 11.9, 6.5, 3.3 Hz, 1H), 1.33−1.21 (m, 1H), 0.98−0.91 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 112.7, 70.4, 54.1, 42.8, 34.4, 31.5, 29.7, 22.2, 19.2. ESI-HRMS calcd for $C_{10}H_{19}O$, 155.1436 $[M + H]^+$; found, 155.1430.

9. (+)-{[(1S,2R,5S)-2-(3-Bromoprop-1-en-2-yl)-5-methylcyclohexyl]oxy}(tert-butyl)dimethylsilane, (+)-14. To a solution of (+)-**13** (2.0 g, 12 mmol) in anhydrous DCM (40 mL) was added *N*,*N*-diisopropylethylamine (DIPEA; 4.4 mL, 25.7 mmol), and the mixture was stirred for 30 min at 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf; 3.4 g, 15.4 mmol) in DCM (20 mL) was added dropwise to the reaction mixture at 0 °C, and stirring was continued for 5 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were evaporated under reduced pressure to give crude TBS-protected (+)-isopulegol, which was subjected to allylic bromination without further purification. The crude residue (3.2 g, 11.9 mmol) was dissolved in 30 mL of DCM/THF (4:1, v/v), *N*-bromosuccinimide (2.5 g, 14.1 mmol) was added, and the mixture was cooled to 0 °C. After 5 min, trimethylsilyl chloride (TMSCl; 64.3 mg, 5 mol %) and $Yb(OTf)_3$ (369 mg, 5 mol %) were added at 0 °C, and stirring was continued for 5 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl, diluted with DCM (30 mL), washed with $NaHCO_3$, Na_2SO_3, and H_2O, and dried over $MgSO_4$. The organic layer was concentrated and purified by silica gel column chromatography with hexanes to yield compound (+)-**14** (3.8 g) in 92% yield as a colorless liquid. $[\alpha]_D$ = +81.03 (*c* = 2.0, $CHCl_3$). IR (cm^{-1}) 2951, 2926, 2855, 1458, 1361, 1100, 1060, and 830. ^1H NMR (400 MHz, chloroform-*d*) δ 5.24 (s, 1H), 4.99 (s, 1H), 4.07 (dd, *J* = 9.8, 1.1 Hz, 1H), 4.00 (d, *J* = 9.7 Hz, 1H), 3.46 (td, *J* = 10.2, 4.2 Hz, 1H), 2.04 (ddd, *J* = 13.0, 9.7, 3.8 Hz, 1H), 1.86 (dtd, *J* = 12.9, 3.9, 2.0 Hz, 1H), 1.78 (dq, *J* = 10.2, 3.3 Hz, 1H), 1.71−1.60 (m, 1H), 1.51−1.44 (m, 1H), 1.36 (dd, *J* = 13.1, 3.5 Hz, 1H), 1.10−1.00 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 114.0, 77.0, 49.3, 45.5, 39.7, 34.6, 32.0, 31.7, 26.0 (3C), 22.4, 18.1, −4.0, −4.5. ESI-HRMS calcd for $C_{16}H_{32}BrOSi$, 347.1406 $[M + H]^+$; found, 347.1403.

10. Alkylation with Allyl Bromide (+)-14. In a 100 mL oven-dried two-neck round-bottom flask, (−)-**12** (1.2 g, 4.08 mmol) was dissolved in anhydrous THF (20 mL) and cooled to −40 °C. To the resulting cold solution were added freshly distilled HMPA (0.2 mL) and *n*-BuLi (2.37 mL of 2.5 M in hexanes, 6.1 mmol), and the mixture was stirred for 2 h at −40 °C. After 2 h, bromide (+)-**14** (2.83 g, 8.15 mmol) in anhydrous THF (20 mL) was added and stirring was continued. After 5 h at −40 °C, TLC indicated formation of two new nonpolar spots along with some amount of starting material (−)-**12**. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and then extracted with EtOAc (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexanes/EtOAc, 8.5:1.5) to yield (+)-**15a** (1.53 g, 70%) and (+)-**15b** (0.23 g, 10%) as viscous liquids.

(+)-tert-Butyldimethyl{[(1S,2R,5S)-5-methyl-2-[(S)-4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl]cyclohexyl]oxy}silane, (+)-15a. $[\alpha]_D$ = +8.7 (*c* = 0.99, $CHCl_3$). IR (cm^{-1}) 2951, 2926, 2855, 1446, 1305, 1144, 1060, and 831. ^1H NMR (400 MHz, chloroform-*d*) δ 7.85 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.64−7.59 (m, 1H), 7.56−7.51 (m, 2H), 5.00 (s, 1H), 4.89 (s, 1H), 3.48 (td, *J* = 10.1, 4.2 Hz, 1H), 3.20 (dt, *J* = 9.6, 2.2 Hz, 1H), 2.92 (dd, *J* = 16.2, 9.4 Hz, 1H), 2.38 (d, *J* = 16.2 Hz, 1H), 1.84 (dddt, *J* = 19.7, 12.3, 7.7, 3.9 Hz, 4H), 1.74 (td, *J* = 6.7, 3.3 Hz, 2H), 1.68−1.57 (m, 4H), 1.55−1.40 (m, 4H), 1.28 (s, 3H), 1.02 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.7, 133.6, 129.3 (2C), 129.1 (2C), 111.8, 85.6, 85.5, 76.8, 61.3, 55.4, 50.9, 45.8, 41.9, 39.3, 35.1, 34.8, 33.1, 31.7, 31.7, 26.1 (3C), 22.3, 19.8, 18.4, 18.3, 18.2, −4.0, −4.2. ESI-HRMS calcd for $C_{32}H_{53}O_4SSi$, 561.3434 $[M + H]^+$; found, 561.3434.

(+)-tert-Butyldimethyl{[(1S,2R,5S)-5-methyl-2-[(R)-4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl]cyclohexyl]oxy}silane, (+)-15b). $[\alpha]_D$ = +37.5 (*c* = 0.93, $CHCl_3$). IR (cm^{-1}) 2952, 2926, 2856, 1446, 1304, 1146, 1060, and 832. ^1H NMR (400 MHz, chloroform-*d*) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.74 (d, *J* = 8.3 Hz, 2H), 3.19 (td, *J* = 10.2, 4.1 Hz, 1H), 3.03 (dt, *J* = 8.3, 3.1 Hz, 1H), 2.63 (p, *J* = 6.7 Hz, 1H), 2.57−2.51 (m, 1H), 2.34 (ddd, *J* = 12.8, 9.2, 4.2 Hz, 1H), 2.27 (dd, *J* = 15.2, 8.3 Hz, 1H), 1.93 (ddd, *J* = 11.3, 9.1, 4.6 Hz, 1H), 1.83−1.79 (m, 1H), 1.65 (ddt, *J* = 11.7, 7.8, 4.1 Hz, 2H), 1.54−1.46 (m, 4H), 1.32 (d, *J* = 2.7 Hz, 7H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.00 (dd, *J* = 13.1, 3.4 Hz, 1H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.79 (s, 9H), 0.64−0.46 (m, 2H), −0.08 (s, 3H), −0.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 139.9, 133.4, 129.3 (2C), 128.7 (2C), 111.3, 85.7, 85.7, 76.8, 61.8, 58.7, 50.4, 45.4, 43.0, 41.3, 39.4, 34.6, 33.9, 31.4, 31.4, 26.0 (3C), 22.3, 21.9, 19.2, 18.2, 18.1, −4.0, −4.2. ESI-HRMS calcd for $C_{32}H_{53}O_4SSi$, 561.3434 $[M + H]^+$; found, 561.3431.

11. (−)-(1S,2R,5S)-5-Methyl-2-{4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexanol, (−)-24a. To a solution of (+)-**15a** (1.0 g, 1.78 mmol) in anhydrous DCM (10 mL) at 0 °C was added dropwise a 2 M solution TFA in DCM (10 mL), and stirring was continued for 2 h at 0 °C. The reaction mixture was carefully quenched with saturated $NaHCO_3$ solution and extracted with DCM (2 × 10 mL). The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography (hexanes/EtOAc, 8:2) to give (−)-**24a** (0.715 g, 90%) as a white solid. $[\alpha]_D$ = −7.06 (*c* = 0.81, $CHCl_3$). IR (cm^{-1}) 3503, 2950, 2924, 2871, 1446, 1379, 1303, 1143, 1083, and 867. ^1H NMR (500 MHz, chloroform-*d*) δ 7.90 (dt, *J* = 7.2, 1.3 Hz, 2H), 7.69−7.65 (m, 1H), 7.58 (t, *J* = 7.7 Hz, 2H), 5.05 (s, 1H), 4.95 (s, 1H), 3.58 (td, *J* = 10.4, 4.2 Hz, 1H), 3.37 (dt, *J* = 9.0, 2.0 Hz, 1H), 2.79 (dd, *J* = 18.0, 8.9 Hz, 2H), 2.46 (dq, *J* = 18.4, 2.1 Hz, 1H), 2.04 (dtd, *J* = 12.7, 3.9, 1.9 Hz, 1H), 1.89 (dqd, *J* = 9.3, 4.0, 2.7, 2.2 Hz, 2H), 1.81−1.75 (m, 1H), 1.68 (dtd, *J* = 13.3, 7.2, 6.6, 3.4 Hz, 4H), 1.52 (ddt, *J* = 12.6, 6.2, 3.8 Hz, 2H), 1.48−1.40 (m, 2H), 1.32 (s, 3H), 1.27 (d, *J* = 2.4 Hz, 1H), 1.23 (dd, *J* = 13.1, 3.2 Hz, 1H), 1.07 (d,

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J = 6.7 Hz, 3H), 1.01 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 137.8, 133.9, 129.3 (2C), 129.3 (2C), 110.1, 85.7, 85.6, 72.6, 61.2, 55.0, 53.4, 43.4, 42.3, 39.0, 34.6, 32.9, 31.6 (2C), 31.5, 22.3, 19.6, 18.4, 18.3. ESI-HRMS calcd for $C_{26}H_{39}O_4S$, 447.2569 $[M + H]^+$; found, 447.2569.

12. (+)-(1S,2R,5S)-5-methyl-2-{(R)-4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexanol, (+)-24b. By the same procedure as for (−)-**24a** (section 11), (+)-**24b** (0.178 g, 90%) was prepared from (+)-**15b** (0.250 g, 0.45 mmol) as a white solid. $[\alpha]_D$ = +13.9 (c = 2.5, $CHCl_3$). IR (cm^{-1}) 3511, 2955, 2922, 2869, 1446, 1378, 1301, 1142, 1083, and 866. ^{1}H NMR (400 MHz, chloroform-d) δ 7.92−7.89 (m, 2H), 7.63 (dd, J = 8.3, 6.3 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 4.90 (s, 1H), 4.82 (s, 1H), 3.49 (td, J = 7.3, 4.0 Hz, 1H), 3.27 (td, J = 10.3, 4.2 Hz, 1H), 2.59 (dd, J = 17.9, 6.8 Hz, 1H), 2.45−2.38 (m, 1H), 2.06 (dd, J = 5.3, 2.0 Hz, 1H), 1.94 (ddq, J = 13.5, 9.1, 4.7 Hz, 2H), 1.85 (ddd, J = 7.7, 4.9, 2.1 Hz, 1H), 1.66−1.58 (m, 4H), 1.50 (ddd, J = 13.2, 6.1, 2.6 Hz, 3H), 1.45 (s, 3H), 1.27 (s, 3H), 1.13 (td, J = 12.9, 3.5 Hz, 2H), 1.06 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.82 (dd, J = 13.3, 10.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 139.7, 133.8, 129.2 (2C), 128.8 (2C), 111.9, 86.0, 84.9, 71.7, 63.2, 57.1, 53.1, 46.1, 43.2, 38.8, 34.5, 33.9, 33.5, 31.5, 30.6, 22.9, 22.2, 18.6, 18.2. ESI-HRMS calcd for $C_{26}H_{39}O_4S$, 447.2569 $[M + H]^+$; found, 447.2575.

13. (+)-(1S,2R,5S)-5-Methyl-2-{4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexanol, (+)-15c. Both (−)-**24a** and (+)-**24b** were subjected to desulfonylation with sodium−mercury. For example, (−)-**24a** (0.035 g, 0.078 mmol) was dissolved in methanol (2 mL), and sodium−mercury granules (0.021g, 0.094 mmol) were added. The mixture was stirred for 30 min at room temperature and then concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexanes/EtOAc, 8.5:1.5) to yield (+)-**15c** (0.030 g, 85%) as a colorless viscous liquid. $[\alpha]_D$ = +3.48 (c = 0.9, $CHCl_3$). IR (cm^{-1}) 3451, 2951, 2920, 2870, 1639, 1449, 1376, 1221, 1048, and 866. ^{1}H NMR (400 MHz, chloroform-d) δ 4.92−4.90 (m, 2H), 4.87 (s, 1H), 3.51 (td, J = 10.4, 4.3 Hz, 1H), 2.15−1.93 (m, 4H), 1.89−1.80 (m, 3H), 1.69 (td, J = 5.5, 4.6, 2.8 Hz, 1H), 1.66−1.62 (m, 1H), 1.58 (dd, J = 12.3, 4.2 Hz, 2H), 1.51 (ddd, J = 11.7, 7.7, 4.4 Hz, 2H), 1.36 (s, 5H), 1.27 (s, 3H), 1.24−1.18 (m, 2H), 1.00−0.96 (m, 1H), 0.94 (d, J = 3.3 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 110.3, 85.7, 84.8, 71.6, 58.1, 53.6, 48.8, 42.9, 39.2, 34. 7, 33.6, 32.3, 31.6, 31.0, 30.7, 22.3, 20. 8, 19.4, 18.2. ESI-HRMS calcd for $C_{20}H_{34}O_2$, 324.2659 $[M + H_2O]^+$; found, 324.2658.

14. (−)-(1S,2R,5S)-5-Methyl-2-{(2S,4S)-4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]-butan-2-yl}cyclohexanol, (−)-16a. To a solution of (−)-**24a** (0.5 g, 1.12 mmol) in anhydrous DCM (10 mL) was added [Ir(COD)(py)-(PCy_3)]PF_6 (Crabtree's catalyst; 45 mg, 0.05 mmol). The reaction mixture was stirred for 2 h under H_2 gas at atmospheric pressure and room temperature and then concentrated under reduced pressure and purified by silica gel column chromatography (hexanes/EtOAc, 8.5:1.5) to yield (−)-**16a** (450 mg, 90%) as a white solid. $[\alpha]_D$ = −6.68 (c = 0.8, $CHCl_3$). IR (cm^{-1}) 3495, 2951, 2922, 2870, 1446, 1379, 1302, 1142, 1083, and 865. ^{1}H NMR (400 MHz, chloroform-d) δ 7.90 (d, J = 7.7 Hz, 2H), 7.64 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 3.33 (td, J = 10.4, 4.2 Hz, 1H), 3.00 (dt, J = 8.6, 3.1 Hz, 1H), 2.39 (q, J = 7.9, 7.1 Hz, 1H), 2.07−1.93 (m, 3H), 1.86 (dt, J = 5.0, 2.5 Hz, 1H), 1.73 (dddd, J = 22.2, 13.4, 7.9, 4.0 Hz, 3H), 1.61 (td, J = 13.7, 13.0, 3.6 Hz, 2H), 1.54−1.48 (m, 2H), 1.45 (t, J = 4.8 Hz, 1H), 1.43−1.40 (m, 1H), 1.36 (t, J = 3.3 Hz, 1H), 1.33 (d, J = 3.2 Hz, 1H), 1.29 (s, 3H), 1.17−1.07 (m, 2H), 1.03 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 133.7, 129.3 (2C), 129.3 (2C), 85.7, 85.4, 71.2, 61.3, 55.4, 49.3, 45.2, 42.1, 39.1, 34.6, 32.9, 32.8, 31.7, 29.5, 23.6, 22.3, 19.9, 18.5, 18.3, 14.1. ESI-HRMS calcd for $C_{26}H_{41}O_4S$, 449.2726 $[M + H]^+$; found, 449.2731.

15. (+)-(1S,2R,5S)-5-Methyl-2-{(2S,4R)-4-(phenylsulfonyl)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]-butan-2-yl)cyclohexanol, (+)-16b. By the same procedure as for (−)-**16a** (section 14), the diastereomer (+)-**16b** (0.127 g, 85%) was prepared from (+)-**24b** (0.15 g, 0.34 mmol) as a white solid, along with 5% trisubstituted olefin. $[\alpha]_D$ = +12.1 (c = 1.8, $CHCl_3$). IR (cm^{-1}) 3491, 2958, 2921, 2871, 1447, 1379, 1303, 1143, 1082, and 866. ^{1}H NMR (400 MHz, chloroform-d) δ 7.90 (d, J = 7.4 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 3.21 (td, J = 10.4, 4.2 Hz, 1H), 2.98 (ddd, J = 9.0, 5.8, 3.4 Hz, 1H), 2.47 (p, J = 6.6 Hz, 1H), 2.11 (td, J = 11.8, 10.4, 4.0 Hz, 1H), 1.97 (dp, J = 6.9, 4.0, 3.6 Hz, 1H), 1.93−1.87 (m, 1H), 1.85−1.79 (m, 1H), 1.76 (td, J = 5.7, 2.3 Hz, 1H), 1.70−1.57 (m, 4H), 1.54−1.49 (m, 2H), 1.45 (s, 3H), 1.32 (s, 3H), 1.18 (d, J = 6.7 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.9 Hz, 6H), 0.79−0.72 (m, 2H), 0.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 133.6, 129.1 (2C), 128.9 (2C), 85.9, 85.2, 70.8, 62.9, 58.8, 49.5, 45.2, 44.5, 39.2, 36.6, 34.3, 33.5, 31.6, 27.9, 23.4, 22.2, 21.9, 19.0, 18.2, 12.4. ESI-HRMS calcd for $C_{26}H_{42}O_5S$, 466.2744 $[M + H_2O]^+$; found, 466.2741.

16. (−)-(1S,2R,5S)-5-Methyl-2-{(S)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohexanol, (−)-17. Both (−)-**16a** and (+)-**16b** were subjected to desulfonylation by use of sodium−mercury. For example, (−)-**16a** (0.4 g, 0.89 mmol) was dissolved in methanol (10 mL), and Na−Hg granules (0.24g, 1.07 mmol) were added. The reaction mixture was stirred for 30 min at room temperature and then concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexanes/EtOAc, 8.5:1.5) to yield (−)-**17** (0.233 g, 85%) as a colorless viscous liquid. $[\alpha]_D$ = −4.86 (c = 0.4, $CHCl_3$). IR (cm^{-1}) 3416, 2955, 2920, 2866, 1455, 1378, 1215, 1038, and 864. ^{1}H NMR (400 MHz, chloroform-d) δ 3.43 (td, J = 10.4, 4.3 Hz, 1H), 2.01−1.94 (m, 2H), 1.84 (ddd, J = 12.5, 8.9, 4.0 Hz, 1H), 1.70−1.49 (m, 6H), 1.41 (ddd, J = 12.3, 5.4, 2.1 Hz, 2H), 1.34 (s, 3H), 1.30 (d, J = 1.8 Hz, 2H), 1.27 (s, 3H), 1.25 (d, J = 1.5 Hz, 2H), 1.17 (dq, J = 9.5, 2.7 Hz, 2H), 1.03−0.97 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 3.6 Hz, 1H), 0.80 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.9, 84.8, 71.3, 58.5, 48.9, 48.9, 45.2, 39.2, 35.0, 34.7, 32.2, 31.8, 31.5, 30.6, 23.3, 22.3, 20.8, 19.4, 18.2, 14.0. ESI-HRMS calcd for $C_{20}H_{37}O_2$, 309.2794 $[M + H]^+$; found, 309.2790.

17. (−)-(2R,5S)-5-Methyl-2-{(S)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohexanone, (−)-18. To a solution of (−)-**17** (0.2 g, 0.64 mmol) in anhydrous DCM (10 mL) was added Dess−Martin periodinane (0.302 g, 0.71 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (as indicated by TLC), the reaction mixture was concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (hexanes/EtOAc, 9:1) to yield (−)-**18** (0.180 g, 95%) as a colorless liquid. $[\alpha]_D$ = −4.73 (c = 0.6, $CHCl_3$). IR (cm^{-1}) 3464, 2955, 2920, 2871, 1455, 1378, 1215, 1038, and 864. ^{1}H NMR (400 MHz, benzene-d_6) δ 2.34−2.27 (m, 1H), 2.21 (p, J = 6.1 Hz, 1H), 1.86 (dt, J = 13.0, 5.1 Hz, 1H), 1.79 (ddd, J = 14.1, 10.0, 3.9 Hz, 1H), 1.69 (ddt, J = 13.0, 6.0, 3.5 Hz, 1H), 1.65−1.53 (m, 2H), 1.52−1.34 (m, 5H), 1.40 (s, 3H), 1.29 (s, 3H), 1.24 (t, J = 4.7 Hz, 5H), 1.20−1.14 (m, 2H), 0.98 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, C_6D6) δ 209.5, 85.5, 84.4, 58.9, 54.2, 50.7, 49.3, 39.6, 35.0, 35.0, 34.1, 32.7, 31.5, 30.8, 27.2, 22.4, 21.1, 19.7, 18.4, 16.3. ESI-HRMS calcd for $C_{20}H_{35}O_2$, 307.2637 $[M + H]^+$; found, 307.2635.

18. (−)-(R)-3-Methyl-6-{(S)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohex-2-enone, (−)-19. In a 25-mL two-neck round-bottom flask, (−)-**18** (0.12 g, 0.3 mmol) was dissolved in anhydrous THF (6 mL) and cooled to −78 °C. A 2.0 M solution of lithium diisopropylamide (LDA; 0.25 mL, 0.47 mmol) was added and the mixture was stirred at the same temperature. After 1 h, phenylselenyl chloride (0.104 g, 0.54 mmol) in anhydrous THF (2 mL) was added, and stirring was continued for an additional 4 h at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O (2 × 15 mL). The ether layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue (0.18 g) was dissolved in DCM (5 mL) and cooled to 0 °C, and pyridine (0.37 mL, 0.47 mmol) and 30% H_2O_2 (0.66 mL, 0.58 mmol) were added. The reaction mixture was was stirred for 2 h at 0 °C and then concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography

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(hexanes/EtOAc, 9:1) to yield (−)-**19** (0.1 g, 85%) as a pale yellow liquid. $[\alpha]_D$ = −35.9 (*c* = 0.3, $CHCl_3$). IR (cm^{-1}) 2963, 2923, 2870, 1664, 1450, 1376, 1207, and 866. ^1H NMR (400 MHz, chloroform-*d*) δ 5.88−5.83 (m, 1H), 2.33−2.28 (m, 2H), 2.14 (dt, *J* = 12.0, 4.3 Hz, 1H), 1.93 (s, 3H), 1.90 (q, *J* = 4.3 Hz, 1H), 1.81 (dddd, *J* = 16.6, 12.8, 8.2, 4.7 Hz, 3H), 1.63−1.49 (m, 3H), 1.41 (ddd, *J* = 12.4, 5.6, 2.3 Hz, 2H), 1.34 (s, 3H), 1.32−1.28 (m, 3H), 1.27 (s, 3H), 1.19−1.13 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 161.3, 127.2, 85.8, 84.8, 58.3, 50.0, 48.9, 39.2, 34.2, 32.2, 31.2, 30.9, 30.2, 24.3, 22.7, 20.8, 19.4, 18.2, 15.9. ESI-HRMS calcd for $C_{20}H_{33}O_2$, 305.2481 $[M + H]^+$; found, 305.2486.

*19. (−)-(1S,6R)-3-Methyl-6-{(S)-4-[(1R,2R,3R,4S)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohex-2-enol, (−)-**1**.* To a solution of (−)-**19** (0.08 g, 0.26 mmol) in methanol (5 mL) were added $CeCl_3$ (0.07 g, 1.1 mmol) and $NaBH_4$ (0.005 g, 0.5 mmol) at −20 °C, and stirring was continued for an additional 3 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (hexanes/EtOAc, 8:2) to give the final compound (−)-laurenditerpenol, (−)-**1**, as a viscous colorless liquid (46.7 mg, 58%). All the spectral data are matched with reported data.[1]

*20. (+)-(S)-4-Benzyl-3-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptane-2-carbonyl]oxazolidin-2-one, (+)-**11**.* By following the same procedure for the preparation of (+)-**10** (section 4), (+)-**11** (6.0 g, 96%) was prepared from (+)-**21b** (8.0 g, 18.47 mmol) as a white solid. $[\alpha]_D$ = +31.5 (*c* = 0.9, $CHCl_3$). IR (cm^{-1}) 2966, 2923, 2872, 1776, 1697, 1375, 1195, and 702. ^1H NMR (400 MHz, chloroform-*d*) δ 7.33 (t, *J* = 7.2 Hz, 2H), 7.30−7.27 (m, 1H), 7.21 (d, *J* = 7.3 Hz, 2H), 4.66 (dq, *J* = 8.7, 4.4 Hz, 1H), 4.17 (d, *J* = 4.8 Hz, 2H), 4.02 (dd, *J* = 5.1, 1.7 Hz, 1H), 3.29 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.83 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.43−2.34 (m, 1H), 1.99 (ddd, *J* = 12.2, 9.2, 3.9 Hz, 1H), 1.88 (ddd, *J* = 14.2, 9.1, 4.9 Hz, 1H), 1.70 (td, *J* = 12.0, 3.9 Hz, 1H), 1.49 (d, *J* = 7.3 Hz, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.00 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 153.1, 135.3, 129.5 (2C), 129.1 (2C), 127.5, 86.5, 86.2, 65.8, 60.1, 56.3, 46.6, 38.8, 37.7, 34.0, 21.2, 18.4, 17.9. ESI-HRMS calcd for $C_{20}H_{26}NO_4$, 344.1862 $[M + H]^+$; found, 344.1861.

*21. (+)-[(1S,2R,3S,4R)-1,3,4-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]methanol, (+)-**22**.* By following the same procedure for the preparation of (−)-**22** (section 5), the enantiomeric compound (+)-**22** (2.37 g, 96%) was prepared from (+)-**11** (5.0 g, 14.6 mmol) as a white solid. $[\alpha]_D$ = +6.66 (*c* = 0.6, $CHCl_3$). IR (cm^{-1}) 3436, 2962, 2924, 2877, 1455, 1374, 1016, and 852. ^1H NMR (400 MHz, chloroform-*d*) δ 3.67 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.57 (dd, *J* = 10.8, 7.7 Hz, 1H), 2.21 (s, 1H), 1.79 (ddd, *J* = 12.1, 9.3, 4.0 Hz, 1H), 1.59 (td, *J* = 13.1, 12.6, 5.8 Hz, 1H), 1.52−1.43 (m, 3H), 1.41 (s, 3H), 1.36 (dd, *J* = 7.2, 5.0 Hz, 1H), 1.25 (s, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.0, 84.8, 64.1, 60.1, 46.1, 39.0, 32.2, 21.6, 18.7, 17.9. ESI-HRMS calcd for $C_{10}H_{19}O_2$, 171.1385 $[M + H]^+$; found, 171.1384.

*22. (+)-(1S,2S,3S,4R)-2-(Iodomethyl)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptane, (+)-**23**.* By following the same procedure for the preparation of (−)-**23** (section 6), the enantiomer (+)-**23** (3.1 g, 95%) was prepared from (+)-**22** (2.0 g, 11.76 mmol). $[\alpha]_D$ = +37.79 (*c* = 0.6, $CHCl_3$). IR (cm^{-1}) 2967, 2899, 1459, 1374, 1188, and 872. ^1H NMR (500 MHz, chloroform-*d*) δ 3.18 (m, 2H), 1.84 (m, 2H), 1.68 (td, *J* = 12.24, 3.95 Hz, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.46 (m, 4H), 1.31 (s, 3H), 1.07 (d, *J* = 6.84 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.8, 84.9, 60.2, 50.6, 38.8, 31.9, 21.1, 18.8, 18.4, 6.3. ESI-HRMS calcd for $C_{10}H_{18}IO$, 281.0402 $[M + H]^+$; found, 281.0405.

*23. (+)-(1R,2S,3S,4S)-1,2,4-Trimethyl-3-[(phenylsulfonyl)methyl]-7-oxabicyclo[2.2.1]heptane, (+)-**12**.* By following the same procedure for the preparation of (−)-**12** (section 7), the enantiomer (+)-**12** (2.46 g, 95%) was prepared from (+)-**23** (2.5 g, 8.9 mmol). $[\alpha]_D$ = +15.41 (*c* = 0.3, $CHCl_3$). IR (cm^{-1}) 2964, 2926, 2875, 1446, 1298, 1131, and 866. ^1H NMR (400 MHz, chloroform-*d*) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.68−7.61 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 3.05 (d, *J* = 7.2 Hz, 2H), 1.73 (d, *J* = 16.6 Hz, 2H), 1.58 (dd, *J* = 17.3, 9.8 Hz, 2H), 1.53−1.38 (m, 2H), 1.27 (d, *J* = 7.8 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 133.7, 129.3 (2C), 127.8 (2C), 85.4, 84.9, 58.7, 50.4, 48.3, 38.4, 32.5, 19.6, 17.9, 17.8. ESI-HRMS calcd for $C_{16}H_{23}O_3S$, 295.1368 $[M + H]^+$; found, 295.1368.

*24. (−)-{[(1R,2S,5R)-2-(3-Bromoprop-1-en-2-yl)-5-methylcyclohexyl]oxy}(tert-butyl)dimethylsilane, (−)-**14**.* By following the same procedure for the preparation of (+)-**14** (section 9), (−)-**14** (4.49 g, 86%) was prepared from commercially available (−)-isopulegol (2.5 g, 16.1 mmol) as a colorless low-melting solid. $[\alpha]_D$ = −86.31 (*c* = 2.0, $CHCl_3$). IR (cm^{-1}) 2955, 2926, 2855, 1461, 1361, 1099, 1060, and 830. ^1H NMR (500 MHz, chloroform-*d*) δ 5.24 (s, 1H), 4.99 (s, 1H), 4.08−3.98 (m, 2H), 3.48−3.42 (m, 1H), 2.06−2.00 (m, 1H), 1.85 (ddt, *J* = 12.7, 4.1, 1.9 Hz, 1H), 1.80−1.75 (m, 1H), 1.67−1.62 (m, 1H), 1.50−1.44 (m, 1H), 1.36 (ddd, *J* = 13.2, 3.9, 1.3 Hz, 1H), 1.04 (tdd, *J* = 12.2, 10.7, 1.4 Hz, 2H), 0.92 (dd, *J* = 6.7, 1.4 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), −0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 114.0, 77.0, 49.2, 45.4, 40.0, 34.6, 31.9, 31.7, 26.0 (3C), 22.4, 18.1, −4.0, −4.6. ESI-HRMS calcd for $C_{16}H_{32}BrOSi$, 347.1406 $[M + H]^+$; found, 347.1406.

*25. Alkylation with Allyl Bromide (−)-**14**.* By following the same procedure for the preparation of (+)-**15a** and (+)-**15b** (section 10), (−)-**15a** (1.94 g, 68%) and (−)-**15b** (0.2 g, 7%) were prepared from (+)-**12** (1.5 g, 5.1 mmol) as viscous liquids.

*(−)-tert-Butyldimethyl{[(1R,2S,5R)-5-methyl-2-{(R)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexyl]oxy}silane, (−)-**15a**.* $[\alpha]_D$ = −9.1 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) 2958, 2926, 2855, 1446, 1305, 1145, 1060, and 832. ^1H NMR (500 MHz, chloroform-*d*) δ 7.85 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.63−7.58 (m, 1H), 7.52 (dd, *J* = 8.3, 6.9 Hz, 2H), 4.99 (s, 1H), 4.88 (s, 1H), 3.48 (td, *J* = 10.2, 4.2 Hz, 1H), 3.20 (dt, *J* = 9.3, 2.2 Hz, 1H), 2.91 (dd, *J* = 16.2, 9.3 Hz, 1H), 2.40 − 2.36 (m, 1H), 1.85 (dddd, *J* = 17.7, 12.7, 6.7, 3.2 Hz, 3H), 1.78−1.70 (m, 3H), 1.66−1.58 (m, 4H), 1.54−1.40 (m, 4H), 1.28 (s, 3H), 1.02 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.97, 138.90, 133.60, 129.38 (2C), 129.14 (2C), 111.78, 85.64, 85.47, 76.79, 61.42, 55.46, 50.99, 45.83, 42.00, 39.32, 35.16, 34.88, 33.16, 31.76, 31.72, 26.14 (3C), 22.35, 19.85, 18.43, 18.29, 18.24, −4.00, −4.19. ESI-HRMS calcd for $C_{32}H_{53}O_4SSi$, 561.3435 $[M + H]^+$; found, 561.3430.

*(−)-tert-Butyldimethyl{[(1R,2S,5R)-5-methyl-2-{(S)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexyl]oxy}silane, (−)-**15b**.* $[\alpha]_D$ = −39.2 (*c* = 1.0, $CHCl_3$). IR (cm^{-1}) 2955, 2925, 2870, 1447, 1304, 1144, 1083, and 734. ^1H NMR (500 MHz, chloroform-*d*) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.64 (dd, *J* = 8.5, 6.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 4.77 (s, 1H), 4.75 (s, 1H), 3.22 (td, *J* = 10.1, 4.0 Hz, 1H), 3.06 (dt, *J* = 8.4, 3.2 Hz, 1H), 2.64 (p, *J* = 6.8 Hz, 1H), 2.56 (d, *J* = 14.6 Hz, 1H), 2.35 (ddd, *J* = 12.7, 9.0, 4.1 Hz, 1H), 2.29 (dd, *J* = 15.1, 8.3 Hz, 1H), 1.94 (ddd, *J* = 11.5, 9.1, 4.6 Hz, 1H), 1.83 (dt, *J* = 6.1, 2.9 Hz, 1H), 1.66 (td, *J* = 11.9, 3.9 Hz, 2H), 1.53 (ddd, *J* = 16.7, 8.1, 4.5 Hz, 4H), 1.34 (s, 7H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.02 (dd, *J* = 13.1, 3.4 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.81 (s, 9H), 0.62 − 0.52 (m, 2H), −0.06 (s, 3H), −0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.34, 140.12, 133.42, 129.31, 128.83, 111.30, 85.74, 76.82, 61.95, 58.76, 50.54, 45.50, 43.15, 41.24, 39.52, 34.68, 34.01, 31.49, 26.09, 22.33, 21.97, 19.25, 18.28, 18.15, −4.14, −4.33. ESI-HRMS calcd for $C_{32}H_{52}O_4SSi$, 561.3435 $[M + H]^+$; found, 561.3438.

*26. (+)-(1R,2S,5R)-5-Methyl-2-{(S)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxa bicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexanol, (+)-**24a**.* By following the same procedure for the preparation of (−)-**24a** (section 11), the enantiomeric compound (+)-**24a** (0.86 g, 90%) was prepared from (−)-**15a** (1.2 g, 2.1 mmol) as a white solid. $[\alpha]_D$ = +6.9 (*c* = 0.8, $CHCl_3$). IR (cm^{-1}) 3531, 2916, 1445, 1379, 1304, 1144, 1084, and 734. ^1H NMR (500 MHz, chloroform-*d*) δ 7.87 (dd, *J* = 7.3, 1.7 Hz, 2H), 7.63 (dd, *J* = 8.4, 6.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 5.01 (d, *J* = 1.6 Hz, 1H), 4.91 (s, 1H), 3.52 (td, *J* = 10.4, 4.2 Hz, 1H), 3.35 (dt, *J* = 8.6, 2.3 Hz, 1H), 2.76 (dd, *J* = 18.1, 8.7 Hz, 1H), 2.45−2.40 (m, 1H), 2.01−1.93 (m, 2H), 1.89−1.81 (m, 2H), 1.75 (p, *J* = 6.6 Hz, 1H), 1.67−1.59 (m, 4H), 1.53−1.45 (m, 2H), 1.44−1.34 (m, 2H), 1.29 (s, 3H), 1.26−1.23 (m, 1H), 1.20 (dd, *J* = 12.8, 3.4 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.01 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

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148.5, 138.0, 133.9, 129.3 (2C), 129.3 (2C), 110.1, 85.7, 85.6, 72.6, 61.0, 55.1, 53.4, 43.4, 42.4, 39.0, 34.7, 32.9, 31.7 (2C), 31.6, 22.3, 19.7, 18.4, 18.3. ESI-HRMS calcd for $C_{26}H_{39}O_4S$, 447.2569 $[M + H]^+$; found, 447.2565.

27. (−)-(1R,2S,5R)-5-Methyl-2-{(R)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]but-1-en-2-yl}cyclohexanol, (−)-24b. By following the same procedure for the preparation of (+)-**24b** (section 12), its enantiomer (−)-**24b** (214 mg, 90%) was prepared from (−)-**15b** (300 mg, 0.53 mmol) as a white solid. $[\alpha]_D$ = −14.2 (*c* = 2.2, $CHCl_3$). IR (cm^{-1}) 3467, 2912, 2868, 1447, 1289, 1143, and 726. ^1H NMR (500 MHz, chloroform-*d*) δ 7.90 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.65−7.60 (m, 1H), 7.57−7.51 (m, 2H), 4.90 (s, 1H), 4.81 (d, *J* = 1.8 Hz, 1H), 3.48 (ddd, *J* = 8.2, 6.8, 4.0 Hz, 1H), 3.26 (td, *J* = 10.3, 4.2 Hz, 1H), 2.58 (dd, *J* = 17.8, 6.8 Hz, 1H), 2.44−2.37 (m, 1H), 2.05 (td, *J* = 6.8, 4.8 Hz, 1H), 1.93 (dddd, *J* = 14.1, 9.5, 6.9, 3.9 Hz, 2H), 1.84 (td, *J* = 5.1, 2.4 Hz, 1H), 1.82 (s, 1H), 1.66−1.56 (m, 4H), 1.49 (dtd, *J* = 12.7, 6.1, 2.7 Hz, 2H), 1.44 (s, 3H), 1.27 (s, 3H), 1.12 (td, *J* = 12.9, 3.5 Hz, 2H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86−0.79 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 139.7, 133.7, 129.2, 128.7, 111.9, 86.0, 84.8, 71.7, 63.2, 57.1, 53.1, 46.0, 43.2, 38.8, 34.5, 33.9, 33.5, 31.5, 30.6, 22.9, 22.2, 18.5, 18.2. ESI-HRMS calcd for $C_{26}H_{39}O_4S$, 447.2569 $[M + H]^+$; found, 447.2547.

28. (+)-(1R,2S,5R)-5-Methyl-2-{(2R,4R)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]-butan-2-yl}cyclohexanol, (+)-16a. By following the same procedure for the preparation of (−)-**16a** (section 14), the enantiomer (+)-**16a** (450 mg, 90%) was prepared from (+)-**24a** (0.5 g, 1.12 mmol) as a white solid. $[\alpha]_D$ = +6.5 (*c* = 0.8, $CHCl_3$). IR (cm^{-1}) 3482, 2952, 2921, 2870, 1446, 1302, 1142, 1082, and 731. ^1H NMR (500 MHz, chloroform-*d*) δ 7.94−7.91 (m, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 3.36 (td, *J* = 10.4, 4.3 Hz, 1H), 3.03 (dt, *J* = 8.6, 3.0 Hz, 1H), 2.42 (tdd, *J* = 13.6, 6.7, 4.3 Hz, 1H), 2.09−1.97 (m, 3H), 1.89 (dt, *J* = 5.2, 2.3 Hz, 1H), 1.82−1.71 (m, 3H), 1.64 (ddd, *J* = 16.3, 9.2, 3.5 Hz, 2H), 1.52 (ddt, *J* = 10.5, 6.8, 3.8 Hz, 2H), 1.45 (dd, *J* = 5.1, 2.4 Hz, 1H), 1.42 (dd, *J* = 6.6, 3.2 Hz, 1H), 1.41−1.38 (m, 1H), 1.38−1.35 (m, 1H), 1.32 (s, 3H), 1.16 (ddt, *J* = 12.9, 9.9, 4.9 Hz, 2H), 1.07 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.67, 133.73, 129.34, 129.29, 85.75, 85.44, 71.23, 61.38, 55.44, 49.35, 45.29, 42.13, 39.16, 34.60, 32.98, 32.88, 31.74, 29.84, 29.55, 23.66, 22.28, 19.91, 18.55, 18.33, 14.13. ESI-HRMS calcd for $C_{26}H_{42}O_5S$, 466.2742 $[M + H_2O]^+$; found, 446.2747.

29. (−)-(1R,2S,5R)-5-Methyl-2-{(2R,4S)-4-(phenylsulfonyl)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]-butan-2-yl}cyclohexanol, (−)-16b. By following the same procedure for the preparation of (+)-**16b** (section 15), the enantiomer (−)-**16b** (127 mg, 85%) was prepared from (−)-**24b** (150 mg, 0.34 mmol) as a white solid. $[\alpha]_D$ = −12.5 (*c* = 2.0, $CHCl_3$). IR (cm^{-1}) 3482, 2952, 2921, 2870, 1446, 1379, 1302, 1142, 1082, and 736. ^1H NMR (400 MHz, chloroform-*d*) δ 7.91 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.67−7.62 (m, 1H), 7.58 (dt, *J* = 8.8, 6.3 Hz, 2H), 3.22 (td, *J* = 10.4, 4.3 Hz, 1H), 3.04−2.95 (m, 1H), 2.48 (p, *J* = 6.5 Hz, 1H), 2.12 (ddd, *J* = 12.3, 9.1, 4.1 Hz, 1H), 2.02−1.87 (m, 3H), 1.84−1.80 (m, 1H), 1.80−1.73 (m, 1H), 1.69−1.58 (m, 5H), 1.55−1.49 (m, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.19 (d, *J* = 6.7 Hz, 1H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.80−0.72 (m, 2H), 0.26 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 133.6, 129.1, 128.8, 85.9, 85.1, 70.7, 62.9, 58.8, 49.5, 45.2, 44.5, 39.2, 36.5, 34.3, 33.4, 31.6, 27.8, 23.3, 22.2, 21.9, 19.0, 18.2, 12.3. ESI-HRMS calcd for $C_{26}H_{42}O_5S$, 466.2742 $[M + H_2O]^+$; found, 446.2742.

30. (+)-(2S,5R)-5-Methyl-2-{(R)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohexanone, (+)-18. By following the same procedure for the preparation of (−)-**18** (section 17), the corresponding enantiomer (+)-**18** was prepared from **16a** or **16b** by desulfonylation with sodium−mercury and oxidation with Dess−Martin periodinane. $[\alpha]_D$ = +5.86 (*c* = 0.15, $CHCl_3$). IR (cm^{-1}) 2955, 2925, 2870, 1707, 1454, 1376, and 864. ^1H NMR (500 MHz, benzene-d_6) δ 2.31 (ddd, *J* = 13.3, 4.0, 2.3 Hz, 1H), 2.23 (ddd, *J* = 13.3, 8.9, 5.4 Hz, 1H), 1.86 (dt, *J* = 13.1, 5.0 Hz, 1H), 1.79 (ddd, *J* = 14.5, 10.1, 4.0 Hz, 1H), 1.68 (ddt, *J* = 12.7, 6.1, 3.4 Hz, 1H), 1.64−1.53 (m, 2H), 1.51−1.34 (m, 5H), 1.40 (s, 3H), 1.29 (s, 3H), 1.28−1.20 (m, 5H), 1.20−1.14 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ 209.5, 85.5, 84.4, 58.9, 54.2, 50.7, 49.3, 39.6, 35.0, 34.9, 34.0, 32.7, 31.5, 30.8, 27.1, 22.4, 21.1, 19.7, 18.4, 16.3. ESI-HRMS calcd for $C_{20}H_{35}O_2$, 307.2637 $[M + H]^+$; found, 307.2638.

31. (+)-(S)-3-Methyl-6-{(R)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohex-2-enone, (+)-19. By following the same procedure for the preparation of (−)-**19** (section 18), the enantiomeric compound (+)-**19** (0.047 g, 85%) was prepared from (+)-**18** (0.06g, 0.15 mmol) as a pale yellow liquid. $[\alpha]_D$ = +34.83 (*c* = 1.47, $CHCl_3$). IR (cm^{-1}) 2969, 2926, 2865, 1661, 1457, 1377, 1209, and 874. ^1H NMR (400 MHz, chloroform-*d*) δ 5.83 (dd, *J* = 2.6, 1.3 Hz, 1H), 2.28 (dt, *J* = 14.4, 6.7 Hz, 3H), 2.11 (dt, *J* = 12.0, 4.3 Hz, 1H), 1.94−1.86 (m, 4H), 1.79 (dtd, *J* = 15.3, 8.1, 7.3, 3.2 Hz, 2H), 1.61−1.44 (m, 2H), 1.38 (ddd, *J* = 12.2, 5.5, 2.0 Hz, 1H), 1.31 (s, 3H), 1.30−1.26 (m, 3H), 1.25−1.22 (m, 5H), 1.13 (td, *J* = 6.7, 3.6 Hz, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 161.1, 127.2, 85.7, 84.8, 58.3, 50.0, 48.9, 39.2, 34.1, 32.2, 31.2, 30.8, 30.1, 24.2, 22.7, 20.7, 19.3, 18.1, 15.9. ESI-HRMS calcd for $C_{20}H_{36}NO_2$, 322.2740 $[M + NH_4]^+$; found, 322.2741.

32. (+)-(1R,6S)-3-Methyl-6-{(R)-4-[(1S,2S,3S,4R)-1,3,4-trimethyl-7-oxabicyclo[2.2.1]heptan-2-yl]butan-2-yl}cyclohex-2-enol, (+)-1. By following the same procedure for the preparation of (−)-**1** (section 19), the unnatural isomer (+)-laurenditerpenol (+)-**1** (5.6 mg, 56%) was prepared from (+)-**19** (10 mg, 0.026 mmol). $[\alpha]_D$ = +86.0 (*c* = 0.15, $CHCl_3$). IR (cm^{-1}) 3431, 2962, 2925, 2871, 1449, 1376, 1130, and 864. ^1H NMR (300 MHz, chloroform-*d*) δ 5.64 (dd, *J* = 4.5, 2.2 Hz, 1H), 4.12 (s, 1H), 2.08−1.93 (m, 2H), 1.90−1.80 (m, 1H), 1.70 (s, 3H), 1.68 (s, 1H), 1.64−1.59 (m, 2H), 1.56 (d, *J* = 3.9 Hz, 1H), 1.54−1.40 (m, 2H), 1.35 (s, 3H), 1.34−1.28 (m, 5H), 1.27 (s, 3H), 1.22−1.12 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 1H), 0.95 (d, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 123.9, 85.9, 84.8, 65.5, 58.5, 49.0, 44.4, 39.3, 33.6, 33.5, 32.3, 31.7, 29.2, 23.5, 20.8, 20.6, 19.4, 18.2, 17.3. ESI-HRMS calcd for $C_{20}H_{35}O_2$, 307.2637 $[M + H]^+$; found, 307.2636.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR, ^{13}C NMR, HRMS, and IR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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