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Enantioselective synthesis of 1-(*R*)-hydroxypolygodial and its 9α epimer, 1-(*R*)-hydroxyisotadeonal☆

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Abstract—The enantioselective synthesis of 1-(*R*)-hydroxypolygodial and its epimer at C-9 is described. α-Ionone was the starting material. Key steps of these syntheses included a Corey–Bakshi–Shibata oxazaborolidine-mediated reduction and a stereoselective Diels–Alder reaction. No vanilloid activity was detected for both compounds in assays on VR1 vanilloid receptor in HEK cells transfected with the human VR1.

1. Introduction

Terpenoid unsaturated 1,4-dialdehydes, such as **1** (Fig. 1), are often involved in the defensive strategies of terrestrial and marine organisms against predators. These compounds are also known for their pungent sensation in the human tongue.[1] Some years ago, it was suggested that biological activities of these compounds are linked to the dialdehyde moiety and to reactivity towards nucleophiles.[2] Recently, a vanilloid activity has been reported for polygodial **1** and other related dialdehydes, but a clear comprehension of their mode of action is still incomplete.[3] In the course of our investigation on the relationship between structure and vanilloid activity of these dialdehydes, we were recently interested on the influence of hydroxy groups in their skeleton. Very recently, we published the stereoselective synthesis of **2**.[4] In the present paper, we describe in full our stereoselective synthesis of **2** and its analogue **3** (Fig. 1), the latter being an epimer of **2** at the carbon C-9. For the enantioselective construction of the drimane skeleton of **2** and **3** we relied upon the same general concept used in our previous synthesis, where a Diels–Alder reaction played the key role in the construction of the bicyclic moiety.

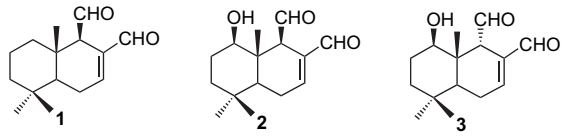
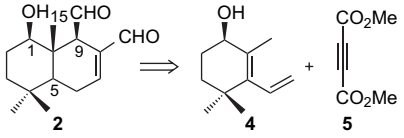


Figure 1.

In fact, even though different synthetic strategies to natural products with this skeleton have been suggested, the use of an intermolecular Diels–Alder reaction of an appropriate 1,3-diene with dimethyl acetylene dicarboxylate (DMAD) to construct the drimane skeleton was particularly attractive (Scheme 1).



Scheme 1. Retrosynthetic analysis for **2**.

2. Results and discussion

The appropriate diene for our synthesis contains a hydroxy group in the ring and we initially decided to investigate the influence of this substituent on the diastereoselectivity of the reaction. In fact, it is well known that dienes containing an allylic heteroatom substituent can control diastereofacial selectivity in intermolecular Diels–Alder reactions.[5]

☆ This work is dedicated to the memory of Professor G. Sodano.
Keywords: Total synthesis; Diels–Alder reaction; Terpenoids; Polygodial; Vanilloid activity.
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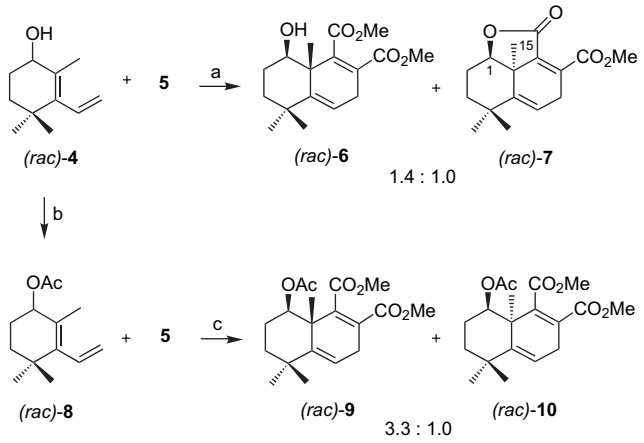
The Diels–Alder reaction of hydroxydiene (*rac*)-**4**, easily prepared from α-ionone following a known procedure,[6] was first studied. When a neat mixture of DMAD and **4** was heated at 110 °C for 24 h, a smooth reaction took place giving a 1.4:1.0 mixture of adducts **6** and **7** (Scheme 2). This result showed that unprotected hydroxy group was not able to give marked diastereofacial selectivity. The relative stereochemistry shown in **6** and **7** was consistent with the results obtained by 1D ^{1}H NMR NOE experiments. In fact, for compound **7** the irradiation of H-1 (δ 4.35) led to the enhancement of the signal due to Me-15 (δ 1.27) establishing a *syn*-relationship between H-1 and Me-15. An NOE experiment conducted on compound **6** did not exhibit any enhancement of Me-15 (δ 1.07) after irradiation of H-1 (δ 3.85).



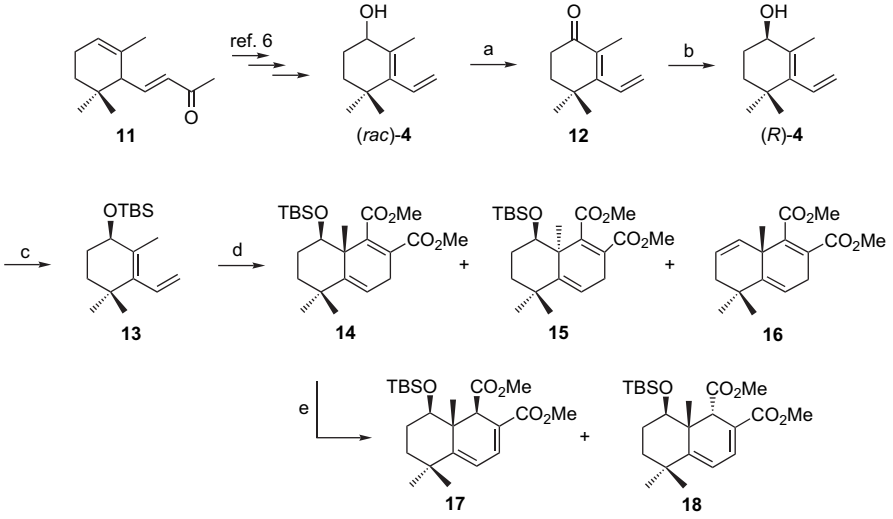
Scheme 2. *Reagents and conditions*: (a) 110 °C, 24 h, (*rac*)-**6**: 44%, (*rac*)-**7**: 31%; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 21 h, 97%; (c) 110 °C, 46 h, (*rac*)-**9**: 53%, (*rac*)-**10**: 16%.

The diene **8**, obtained after acetylation of **4**, was then used in the Diels–Alder reaction with DMAD (Scheme 2). In this case a 3.3:1.0 mixture of diastereomers **9** and **10** was obtained. ^{1}H NOE experiments allowed assignment of the relative stereochemistry of products. The major adduct was the stereomer **9** obtained by approach of the dienophile *anti* to the allylic substituent. From these results, we concluded that in order to have good diastereofacial selectivity a bulkier group should be introduced in the allylic position of the diene. Therefore, we decided to protect the alcoholic functionality as dimethyl-*tert*-butyl-silyl ether. In order to obtain an enantioselective process, we planned to use the *R* enantiomer of hydroxydiene **4**.

Preparation of (*R*)-2,4,4-trimethyl-3-vinyl-2-cyclohexene-1-ol (**13**) started with enantioselective reduction of dienone **12** using (*S*)-Me-Corey–Bakshi–Shibata [(*S*)-MeCBS] oxazaborolidine-borane reagent,[7] which afforded dienol (*R*)-**4** in 94% yield and 93% enantiomeric excess (Scheme 3). Dienol (*R*)-**4** was then converted into silyl derivative **13** (98%).

The Diels–Alder reaction of **13** with DMAD (**5**) proceeds quite slowly (neat, 110 °C, 48 h) affording compound **14** as a major product (40%) together with small amounts of its diastereomer **15** (5%) and triene **16** (8.5%).[8] The reaction was stopped after 48 h, although unreacted diene **13** was still present (15%), because longer reaction time favoured the increase of triene **16**. As expected, with a bulky silyl group as the allylic substituent, the facial selectivity of the cycloaddition was enhanced. Compound **14** was then subjected to a base catalyzed isomerization followed by partial hydrogenation, following a known strategy.[9] DBU catalyzed isomerization[10] of **14** afforded mainly the conjugated diene **17** (90% yield). Once again, ^{1}H NMR NOE experiments (Fig. 2) secured the stereochemical assignment of diene **17**.

Hydrogenation of **17** (H_2, Pd/C, MeOH) afforded compound **19** (85% yield) (Scheme 4) whose stereochemistry was established via ^{1}H NMR NOE measurements (Fig. 2). Irradiation of H-1 (δ 3.74 ppm) led to the enhancements of the signals due to H-5 (δ 1.17 ppm) and H-9 (δ 3.21 ppm). Reduction of the ester functionalities produced diol **20**, which was then oxidized using Swern conditions ($C_2O_2Cl_2$, DMSO, NEt_3) to give dialdehyde **21** (87%). The last step of the synthesis, involving the hydroxy group



Scheme 3. *Reagents and conditions*: (a) PDC, CH_2Cl_2, rt, 1 h, 91%; (b) (*S*)-MeCBS reagent, $BH_3 \cdot THF$ (syringe-pump addition: 1.2 mmol/h), THF, 35 °C, 94%, 93% ee; (c) TBSCl, imidazole, CH_2Cl_2, rt, 12 h, 98%; (d) **5**, neat, 110 °C, 48 h, **14**: 40%, **15**: 5%, **16**: 8.5%; (e) DBU, THF, 40 °C, 4 h, **17**: 90%, **18**: 5%.

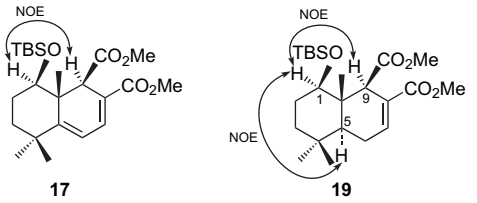
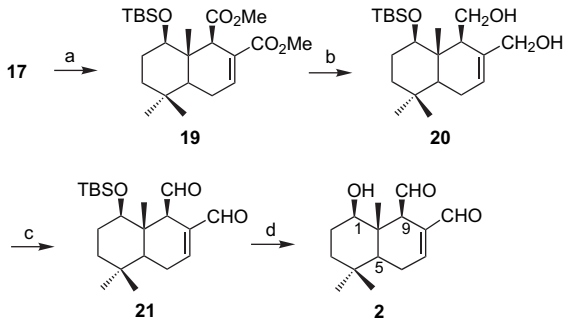


Figure 2.

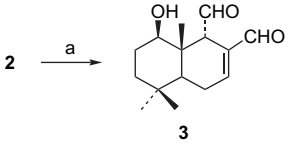
deprotection, proved to be surprisingly complicated. Usual deprotection with TBAF caused epimerization at C-9, probably due to the basicity of F^-. We found that the correct conditions to yield the desired compound, avoiding epimerization, consisted in using HF in the deprotection step (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) H_2, Pd/C, MeOH, 1 h, 85%; (b) DIBAL–H, THF, toluene, −78 °C→rt, 12 h; (c) Swern conditions, 1 h, 87% (two steps); (d) 48% HF (aq), CH_3CN, rt, 12 h, 79%.

^{1}H NMR NOE experiments allowed the correct stereochemistry of the obtained compound **2** to be deduced. In fact, irradiation of H-1 (δ 3.62 ppm) led to the enhancement of the signal due to H-9 (δ 3.20 ppm). Furthermore, irradiation of H-5 (δ 1.25 ppm) caused enhancements of both signals at δ 3.20 ppm (H-9) and at δ 3.62 ppm (H-1). Therefore, H-1, H-9 and H-5 are all in cis-relationship confirming that these deprotection conditions (48% HF (aq), CH_3CN, rt) do not cause epimerization at C-9.

Easy epimerization of hydroxypolygodial **2** was obtained after exposition to basic conditions (basic Al_2O_3, CH_2Cl_2, 20 h), which afforded the 9α epimer **3** in 82% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) basic Al_2O_3, CH_2Cl_2, rt, 20 h, 82%.

3. Vanilloid activity

Vanilloid activity was evaluated in assays on VR1 vanilloid receptor in HEK cells transfected with the human VR1. Preliminary results showed that both hydroxy derivatives **2** and **3** were devoid of any significant vanilloid activity.

4. Conclusions

In summary, a total synthesis of 1-(*R*)-hydroxypolygodial and its epimer at C-9 has been achieved in a highly stereoselective way starting from α-ionone, through a synthetic strategy involving a Corey–Bakshi–Shibata oxazaborolidine-mediated reduction and a stereoselective Diels–Alder reaction as key steps. Both compounds were devoid of vanilloid activity in VR1 assays. Further evaluation of biological activity of these compounds is now in progress and results will be given in due course.

5. Experimental

5.1. General

All reactions were carried out under a dry argon atmosphere using freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Dichloromethane was distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over P_2O_5 or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and spraying with phosphomolybdic acid, *p*-anisaldehyde or $Ce(SO_4)_2$ solutions and drying.

Flash chromatography was performed on Merck silica gel 60 (particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure materials. The NMR spectra were recorded at room temperature on a Bruker DRX 400, a Bruker DRX 300 or a Bruker AV 250 spectrometer. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ=7.26, $^{13}CDCl_3$: δ=77.0). Assignments were made on the basis of homonuclear decoupling experiments or 1D correlation spectroscopic experiments (COSY, HSQC). Relative stereochemical assignments were made on the basis of NOE experiments. Assignments in the ^{13}C NMR spectra were confirmed by DEPT spectroscopic experiments. ESIMS spectra were performed on a Micromass Quattro micro API™ mass spectrometer equipped with an electrospray ionization source operating in positive mode. EIMS spectra were obtained with a Thermo Finnigan PolarisQ (70 eV) mass spectrometer operating in positive mode. IR spectra were obtained at a resolution of 2.0 cm^{-1} with a Vector 22 Bruker Spectrometer. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

5.2. (8*RS*,8a*SR*)-8-Hydroxy-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (6) and (8a*RS*,8b*RS*)-6,6,8b-trimethyl-2-oxo-4,6,7,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan-3-carboxylic acid methyl ester (7)

A mixture of diene (*rac*)-**4** (74.0 mg, 0.264 mmol) and freshly distilled DMAD (**5**) (130.0 μL, 1.056 mmol) was heated in a reacti-vial at 110 °C for 24 h, under a nitrogen

atmosphere. After cooling, the reaction mixture was flash-chromatographed (30–80% diethyl ether in petroleum ether) to give 36.0 mg (0.117 mmol, 44%) of the major adduct (*rac*)-**6** and 23.0 mg (0.083 mmol, 31%) of the lactone (*rac*)-**7**, as clear pale yellow oils.

Compound (*rac*)-**6**: R_f=0.50 (100% diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.38 (2H, m, H-3 and H-3′ overlapped), 1.71 (1H, m, H-2), 1.81 (1H, m, H-2′), 2.08 (1H, br s, OH), 2.78 (1H, dd, J=1.4, 22.6 Hz, H-7), 3.06 (1H, dd, J=5.5, 22.6 Hz, H-7′), 3.68 (3H, s, CO_2CH_3), 3.75 (3H, s, CO_2CH_3), 3.85 (1H, dd, J=5.0, 11.4 Hz, H-1), 5.69 (1H, dd, J=1.4, 5.5 Hz, H-6). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.1 (CH_3), 26.5 (CH_2), 28.2 (CH_2), 30.7 (CH_3), 32.1 (CH_3), 35.7 (C), 37.3 (CH_2), 45.7 (C), 52.0 (CH_3), 52.3 (CH_3), 72.8 (CH), 118.9 (CH), 125.6 (C), 147.1 (C), 148.4 (C), 166.2 (C), 171.2 (C). IR ($CHCl_3$): ν=3487 (br), 1725 (br) cm^{-1}. ESIMS: *m*/*z* 309 [M+H]$^+$. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.48; H, 7.79.

Compound (*rac*)-**7**: R_f=0.75 (70% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15 (3H, s, CH_3), 1.18 (1H, m, H-2), 1.21 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.44 (1H, ddd, J=3.7, 13.8, 14.1 Hz, H-3), 1.61 (1H, ddd, J=3.7, 3.7, 14.1 Hz, H-3′), 1.96 (1H, m, H-2′), 3.04 (1H, dd, J=1.2, 21.7 Hz, H-7), 3.18 (1H, dd, J=5.9, 21.7 Hz, H-7′), 3.85 (3H, s, CO_2CH_3), 4.37 (1H, dd, J=4.8, 12.0 Hz, H-1), 5.74 (1H, dd, J=1.2, 5.9 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.6 (CH_3), 27.5 (CH_2), 30.3 (CH_2), 30.9 (CH_3), 33.7 (CH_3), 34.8 (C), 35.5 (CH_2), 44.5 (C), 52.5 (CH_3), 85.1 (CH), 119.1 (CH), 135.1 (C), 139.1 (C), 149.6 (C), 165.4 (C), 167.5 (C). IR ($CHCl_3$): ν=2869, 1766, 1730, 1692, 1435, 1122 cm^{-1}. ESIMS: *m*/*z* 277 [M+H]$^+$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.61; H, 7.26.

5.3. Acetic acid (*RS*)-2,4,4-trimethyl-3-vinyl-cyclohex-2-enyl ester (8)

To a solution of (*rac*)-**4** (152.0 mg, 0.914 mmol) in dry CH_2Cl_2 (20 mL), pyridine (0.222 mL, 2.74 mmol), DMAP (5.62 mg, 0.046 mmol) and Ac_2O (0.173 mL, 1.83 mmol) were sequentially added at room temperature, under a nitrogen atmosphere. The mixture was stirred for 21 h and then concentrated under reduced pressure. The resulting crude was directly purified by flash chromatography (0–10% diethyl ether in petroleum ether) to afford 185.0 mg (0.889 mmol, 97%) of (*rac*)-**8**, as yellow oil.

Compound (*rac*)-**8**: R_f=0.45 (10% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.41 (1H, m, H-3), 1.60 (1H, m, H-3′), 1.67 (3H, s, CH_3), 1.72 (1H, m, H-2), 1.90 (1H, m, H-2′), 2.07 (3H, s, CH_3CO), 5.03 (1H, dd, J=2.4, 17.8 Hz, *H*HC=CH), 5.21 (1H, t-like, J=4.4 Hz, H-1), 5.31 (1H, dd, J=2.4, 11.4 Hz, H*H*C=CH), 6.19 (1H, ddd, J=0.9, 11.4, 17.8 Hz, H_2C=C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.9 (CH_3), 21.3 (CH_3), 25.1 (CH_2), 26.8 (CH_3), 28.5 (CH_3), 34.0 (C), 34.3 (CH_2), 72.2 (CH), 119.2 (CH_2), 125.4 (C), 134.4 (CH), 144.5 (C), 170.9 (C). IR ($CHCl_3$): ν=2965, 2927, 2856, 1720 cm^{-1}. EIMS: *m*/*z* (%)=148 (41), 133 (98), 105 (100), 91 (67). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.81; H, 9.62.

5.4. (8*RS*,8a*SR*)-8-Acetoxy-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (9) and (8*RS*,8a*RS*)-8-acetoxy-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (10)

A mixture of diene (*rac*)-**8** (387.0 mg, 1.86 mmol) and freshly distilled DMAD (**5**) (915.0 μL, 7.44 mmol) was heated in a reacti-vial at 110 °C for 46 h, under a nitrogen atmosphere. After cooling, the reaction mixture was flash-chromatographed (5–50% diethyl ether in petroleum ether) to give 51.0 mg (0.250 mmol, 13%) of the unreacted diene (*rac*)-**8**, 340.0 mg (0.970 mmol, 53%) of the major adduct (*rac*)-**9** and 105.0 mg (0.300 mmol, 16%) of the minor adduct (*rac*)-**10**.

Compound (*rac*)-**9**: R_f=0.25 (40% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.43 (2H, m, H-3 and H-3′ overlapped), 1.47 (3H, s, CH_3), 1.73 (1H, m, H-2), 1.96 (1H, m, H-2′), 2.01 (3H, s, CH_3CO), 2.80 (1H, dd, J=2.2, 22.6 Hz, H-7), 3.07 (1H, dd, J=5.6, 22.6 Hz, H-7′), 3.69 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 4.86 (1H, dd, J=4.7, 11.1 Hz, H-1), 5.75 (1H, dd, J=2.2, 5.6 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5 (CH_3), 22.0 (CH_3), 23.7 (CH_2), 26.5 (CH_2), 30.7 (CH_3), 32.1 (CH_3), 35.8 (C), 36.6 (CH_2), 43.4 (C), 52.0 (CH_3), 52.1 (CH_3), 75.6 (CH), 119.5 (CH), 126.0 (C), 146.3 (C), 147.4 (C), 166.0 (C), 169.2 (C), 170.0 (C). IR ($CHCl_3$): ν=2952, 1730 (br) cm^{-1}. EIMS: *m*/*z* (%)=350 (2), 275 (20), 243 (64), 215 (26), 258 (100), 199 (28), 177 (40). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.35; H, 7.39.

Compound (*rac*)-**10**: R_f=0.30 (40% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.26 (1H, m, H-3), 1.52 (3H, s, CH_3), 1.62 (1H, ddd, J=4.0, 4.0, 13.8 Hz, H-3′), 1.81 (1H, m, H-2), 1.98 (3H, s, CH_3CO), 2.03 (1H, m, H-2′), 2.81 (1H, dd, J=2.4, 23.0 Hz, H-7), 3.22 (1H, dd, J=5.3, 23.0 Hz, H-7′), 3.68 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 4.86 (1H, m, H-1), 5.79 (1H, m, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2 (CH_3), 22.1 (CH_2), 26.0 (CH_3), 27.1 (CH_2), 31.5 (CH_3), 32.3 (CH_3), 33.4 (CH_2), 35.3 (C), 43.2 (C), 52.2 (×2) (CH_3), 74.2 (CH), 117.9 (CH), 128.6 (C), 144.5 (C), 145.5 (C), 166.9 (C), 168.6 (C), 170.6 (C). IR ($CHCl_3$): ν=2952, 1722 (br) cm^{-1}. ESIMS: *m*/*z* 373 [M+Na]$^+$.

5.5. 2,4,4-Trimethyl-3-vinyl-cyclohex-2-enone (12)

To a solution of the alcohol (*rac*)-**4** (0.543 g, 3.26 mmol) in dry CH_2Cl_2 (17 mL), 4 Å molecular sieves (1.09 g) and PDC (2.45 g, 6.52 mmol) were added at room temperature under a nitrogen atmosphere. The mixture was stirred for 1 h, then diluted with diethyl ether (100 mL) and allowed to stir for additional 1 h. Filtration through a short pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash-chromatographed (10–40% diethyl ether

in petroleum ether) to afford pure enone **12** (0.488 g, 2.97 mmol, 91%) as a colourless oil.

Compound **12**: R_f=0.56 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (6H, s, $(CH_3)_2C$), 1.81 (3H, s, CH_3C═), 1.84 (2H, t, J=6.7 Hz, H-3 and H-3′ overlapped), 2.50 (2H, t, J=6.7 Hz, H-2 and H-2′ overlapped), 5.17 (1H, dd, J=1.9, 17.8 Hz, *H*HC═CH), 5.49 (1H, dd, J=1.9, 11.8 Hz, H*H*C═CH), 6.33 (1H, dd, J=11.8, 17.8 Hz, H_2C═C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.3 (CH_3), 27.2 (×2) (CH_3), 34.3 (CH_2), 35.2 (C), 37.2 (CH_2), 120.7 (CH_2), 129.8 (C), 133.9 (CH), 161.5 (C), 199.6 (C). IR ($CHCl_3$): ν=2964, 2929, 1660 cm^{-1}. EIMS: *m*/*z* (%)=164 (100), 149 (4), 107 (15). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.32; H, 9.87.

5.6. (*R*)-2,4,4-Trimethyl-3-vinyl-cyclohex-2-enol (4)

A solution of $BH_3\cdot$THF (1 M in THF, 1.87 mL, 1.87 mmol) was slowly added (1.2 mmol/h by syringe pump) to a warm solution (35 °C) of dienone **12** (342.0 mg, 2.08 mmol) and (*S*)-methyl-oxazaborolidine (1 M in toluene, 2.29 mL, 2.29 mmol) in 2.1 mL of dry THF, under a nitrogen atmosphere. After the completion of the addition, TLC analysis showed the disappearance of the starting material. The reaction mixture was then cooled and quenched with water at 0 °C. Then THF was removed in vacuo and (*R*)-**4** was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. Flash chromatography of the crude (20–60% diethyl ether in petroleum ether) afforded pure (*R*)-**4** (324.0 g, 1.95 mmol, 94%) as a white amorphous solid.

Compound (*R*)-**4**: R_f=0.35 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.41 (1H, m, H-3), 1.43 (1H, br s, OH), 1.63 (1H, m, H-3′), 1.71 (1H, m, H-2), 1.81 (3H, s, CH_3C═), 1.90 (1H, m, H-2′), 3.98 (1H, m, H-1), 5.01 (1H, dd, J=2.5, 17.7 Hz, *H*HC═CH), 5.29 (1H, dd, J=2.5, 11.4 Hz, H*H*C═CH), 6.19 (1H, dd, J=11.4, 17.7 Hz, H_2C═C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.2 (CH_3), 27.1 (CH_3), 28.4 (CH_2), 28.7 (CH_3), 34.2 (C), 34.4 (CH_2), 70.0 (CH), 118.8 (CH_2), 129.2 (C), 134.8 (CH), 142.1 (C). $[\alpha]_D^{25}$ +43.1 (*c* 1.0, $CHCl_3$). EIMS: *m*/*z* (%)=166 (8), 149 (100), 148 (50), 133 (9), 90 (20). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.32; H, 10.60.

HPLC conditions for ee determination: column: Chiralcel OD; solvent: 1% propan-2-ol in hexane; flow rate: 1 mL/min; detector: UV detector (254 nm); retention time: (*R*), 10.37 min; (*S*), 9.21 min.

5.7. (*R*)-*tert*-Butyl-dimethyl-(2,4,4-trimethyl-3-vinyl-cyclohex-2-enyloxy)-silane (13)

To a solution of (*R*)-**4** (1.45 g, 8.72 mmol) in dry CH_2Cl_2 (18 mL) were sequentially added, at room temperature, imidazole (1.78 g, 26.1 mmol) and TBSCl (3.93 g, 26.1 mmol). The resulting mixture was left stirring overnight and then diluted with H_2O. The separated aqueous layer was extracted with CH_2Cl_2 (3×40 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was flash-chromatographed (0–30% ethyl ether in petroleum ether) to afford 2.39 g (8.52 mmol, 98%) of pure colourless oil **13**.

Compound **13**: R_f=0.62 (0.5% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.08 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si), 0.91 (9H, s, $(CH_3)_3CSi$), 0.96 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.37 (1H, ddd, J=3.1, 9.8, 13.0 Hz, H-3), 1.59–1.68 (2H, m, H-3′ and H-2 overlapped), 1.72 (3H, s, CH_3), 1.80 (1H, m, H-2′), 4.01 (1H, t-like, J=5.6 Hz, H-1), 5.00 (1H, dd, J=2.6, 17.7 Hz, *H*HC═CH), 5.26 (1H, dd, J=2.6, 11.3 Hz, H*H*C═CH), 6.18 (1H, dd, J=11.3, 17.7 Hz, H_2C═C*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.6 (CH_3), −4.2 (CH_3), 18.1 (CH_3), 18.2 (C), 26.0 (×3) (CH_3), 28.1 (CH_3), 28.2 (CH_3), 29.3 (CH_2), 34.2 (C), 35.3 (CH_2), 71.2 (CH), 118.5 (CH_2), 130.7 (C), 135.3 (CH), 140.7 (C). $[\alpha]_D^{25}$ +2.4 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{32}OSi$: C, 72.79; H, 11.50. Found: C, 72.46; H, 11.36.

5.8. (8*R*,8a*S*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (14)

A mixture of the diene **13** (187.0 mg, 0.667 mmol) and freshly distilled DMAD (**5**) (369.0 μL, 3.00 mmol) was heated in a reacti-vial at 110 °C for 48 h, under a nitrogen atmosphere. After cooling, a first flash chromatography of the reaction mixture (2–40% ethyl acetate in petroleum ether) furnished 28.0 mg (0.100 mmol, 15%) of the starting material **13**, 13.0 mg (0.031 mmol, 5%) of the minor adduct **15** as an oil, a mixture of the major adduct **14** and DMAD (**5**) and 16.4 mg (0.057 mmol, 8.5%) of the pure triene **16**. The fraction containing the major adduct **14** was re-purified (5–40% diethyl ether in petroleum ether). Pure **14** (114.0 mg, 40%) was obtained as pale yellow oil.

Compound **14**: R_f=0.40 (20% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si), 0.89 (9H, s, $(CH_3)_3CSi$), 1.08 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.34 (1H, m, H-3), 1.47 (1H, ddd, J=4.5, 4.5, 13.6 Hz, H-3′), 1.73–1.79 (2H, m, H-2 and H-2′ overlapped), 2.78 (1H, dd, J=2.1, 22.4 Hz, H-7), 3.04 (1H, dd, J=5.8, 22.4 Hz, H-7′), 3.69 (3H, s, CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 4.17 (1H, dd, J=5.8, 8.4 Hz, H-1), 5.70 (1H, dd, J=2.1, 5.8 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.0 (CH_3), −2.6 (CH_3), 18.9 (C), 21.7 (CH_3), 26.4 (×3) (CH_3), 26.8 (CH_2), 28.5 (CH_2), 31.3 (CH_3), 32.2 (CH_3), 35.4 (C), 36.1 (CH_2), 46.3 (C), 51.9 (CH_3), 52.5 (CH_3), 74.1 (CH), 119.0 (CH), 126.6 (C), 148.0 (C), 148.8 (C), 166.4 (C), 169.2 (C). $[\alpha]_D^{25}$ −50.7 (*c* 0.95, $CHCl_3$). IR ($CHCl_3$): ν=2954, 2930, 1729 (br) cm^{-1}. ESIMS: *m*/*z* 423 $[M+H]^+$. Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.36; H, 9.06. Found: C, 65.84; H, 9.04.

Compound **15**: R_f=0.80 (20% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.80 (9H, s, $(CH_3)_3CSi$), 1.14 (3H, s, CH_3), 1.16 (1H, m, H_3), 1.19 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.58 (1H, m, H-2), 1.82 (1H, ddd, J=3.8, 13.1, 13.1 Hz, H-3′), 2.01 (1H, dddd, J=1.6, 3.8, 14.0, 14.0 Hz, H-2′), 2.89 (1H, dd, J=2.8, 23.3 Hz, H-7), 3.03 (1H, dd, J=4.6, 23.3 Hz, H-7′), 3.70 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 4.14 (1H, br s, H-1), 5.68 (1H, dd,

J=2.8, 4.6 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.5 (CH_3), −3.4 (CH_3), 18.2 (C), 25.1 (CH_2), 25.2 (CH_3), 25.8 (×3) (CH_3), 27.9 (CH_2), 31.4 (CH_3), 33.2 (CH_3), 33.9 (CH_2), 35.5 (C), 45.6 (C), 51.7 (CH_3), 51.9 (CH_3), 72.3 (CH), 116.7 (CH), 131.4 (C), 142.9 (C), 144.6 (C), 168.3 (C), 168.5 (C). $[\alpha]_D^{30}$ −29.4 (c 1.0, $CHCl_3$). IR ($CHCl_3$): ν=2950, 2929, 1717 (br), 1095 cm^{-1}. ESIMS: m/z 445 [M+Na]$^+$.

Compound **16**: R_f=0.69 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.82 (1H, dd, J=6.3, 16.9 Hz, H-3), 1.98 (1H, br d, J=16.9 Hz, H-3′), 2.78 (1H, dd, J=1.0, 21.9 Hz, H-7), 3.23 (1H, dd, J=6.0, 21.9 Hz, H-7′), 3.73 (3H, s, CO_2CH_3), 3.81 (3H, s, CO_2CH_3), 5.48 (1H, dd, J=2.7, 10.0 Hz, H-1), 5.72 (1H, br d, J=6.0 Hz, H-6), 5.77 (1H, br dd, J=6.3, 10.0 Hz, H-2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.6 (CH_2), 26.8 (CH_3), 28.8 (CH_3), 29.5 (CH_3), 35.5 (C), 39.4 (CH_2), 41.2 (C), 51.9 (CH_3), 52.1 (CH_3), 116.8 (CH), 126.7 (CH), 126.8 (C), 129.5 (CH), 147.1 (C), 150.3 (C), 166.1 (C), 169.2 (C). EIMS: m/z (%)=290 (7.5), 275 (12), 243 (100), 231 (24), 199 (23), 171 (20), 157 (17), 142 (14).

5.9. (1*R*,8*R*,8a*S*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-5,5,8a-trimethyl-1,5,6,7,8,8a-hexahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (17)

To a solution of **14** (110.0 mg, 0.260 mmol) in dry THF (2.6 mL) was added DBU (35.0 μL, 0.234 mmol) under a nitrogen atmosphere. The mixture was heated at 40 °C for 4 h and then cooled at room temperature. The resulting orange solution was diluted with Et_2O and filtered through a pad of silica gel (particle size 0.063–0.200 mm); the filter cake was washed thoroughly with Et_2O. The combined filtrate and washings were concentrated in vacuo. The residue was purified by flash chromatography (15–30% diethyl ether in petroleum ether) affording **17** (99.0 mg, 0.234 mmol, 90%) and its epimer **18** (5.5 mg, 0.013 mmol, 5%) as colourless oils.

Compound **17**: R_f=0.23 (20% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (3H, s, CH_3Si), 0.07 (3H, s, CH_3Si), 0.90 (9H, s, $(CH_3)_3CSi$), 1.13 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.36 (1H, ddd, J=5.6, 10.6, 12.5 Hz, H-3), 1.58 (1H, ddd, J=4.7, 4.7, 12.5 Hz, H-3′), 1.68–1.80 (2H, m, H-2 and H-2′ overlapped), 3.48 (1H, br d, J=2.4 Hz, H-9), 3.68 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 3.90 (1H, dd, J=5.2, 8.7 Hz, H-1), 5.98 (1H, d, J=6.2 Hz, H-6), 6.94 (1H, dd, J=2.4, 6.2 Hz, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.4 (CH_3), −3.2 (CH_3), 14.6 (CH_3), 18.7 (C), 26.3 (×3) (CH_3), 28.3 (CH_2), 31.3 (CH_3), 31.8 (CH_3), 36.0 (C), 36.5 (CH_2), 46.5 (C), 51.6 (CH_3), 51.8 (CH_3), 53.1 (CH), 77.7 (CH), 118.2 (CH), 125.1 (C), 133.7 (CH), 160.0 (C), 167.3 (C), 173.0 (C). $[\alpha]_D^{25}$ −87.7 (c 1.0, $CHCl_3$). IR ($CHCl_3$): ν=2954, 2929, 2858, 1733, 1710, 1279, 1253 cm^{-1}. ESIMS: m/z 445 [M+Na]$^+$. Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.36; H, 9.06. Found: C, 65.24; H, 9.03.

Compound **18**: R_f=0.28 (20% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (6H, s, $(CH_3)_2Si$), 0.91 (9H, s, $(CH_3)_3CSi$), 1.13 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.41–1.52 (2H, m, H-3 and H-3′ overlapped), 1.65 (1H, m, H-2), 1.76 (1H, m, H-2′), 3.58 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.78 (1H, s, H-9), 3.93 (1H, dd, J=4.8, 11.2 Hz, H-1), 5.96 (1H, d, J=6.0 Hz, H-6), 7.06 (1H, d, J=6.0 Hz, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3 (CH_3), −3.6 (CH_3), 18.1 (C), 18.4 (CH_3), 25.8 (×3) (CH_3), 27.8 (CH_2), 30.7 (CH_3), 32.0 (CH_3), 35.4 (C), 36.7 (CH_2), 44.4 (C), 47.5 (CH), 51.3 (CH_3), 51.7 (CH_3), 74.0 (CH), 117.2 (CH), 122.5 (C), 135.4 (CH), 162.0 (C), 167.0 (C), 172.0 (C). $[\alpha]_D^{28}$ −325.2 (c 0.7, $CHCl_3$). IR ($CHCl_3$): ν=2954, 2927, 1735, 1716 cm^{-1}. ESIMS: m/z 445 [M+Na]$^+$.

5.10. (1*R*,4a*S*,8*R*,8a*S*)-8-(*tert*-Butyl-dimethyl-silanyl-oxy)-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-1,2-dicarboxylic acid dimethyl ester (19)

To a vigorously stirred suspension of **17** (794.0 mg, 1.88 mmol) and a catalytic amount of 10% Pd/C in MeOH (21 mL), in a conical flask, was introduced H_2 gas at room temperature. After the disappearance of the starting material (1 h), the reaction mixture was filtered through a Celite® bed and the filtrate was concentrated in vacuo. The residue was flash-chromatographed (10–40% diethyl ether in petroleum ether) affording pure **19** (679.0 mg, 1.60 mmol, 85%) as colourless oil.

Compound **19**: R_f=0.33 (30% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.04 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si), 0.85 (3H, s, CH_3), 0.90 (9H, s, $(CH_3)_3CSi$), 0.91 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.17 (1H, dd, J=6.0, 10.7 Hz, H-5), 1.26 (1H, m, H-3), 1.43 (1H, ddd, J=3.3, 3.3, 13.6 Hz, H-3′), 1.58 (1H, dddd, J=3.3, 11.2, 13.4, 13.6 Hz, H-2), 1.71 (1H, dddd, J=3.3, 4.2, 4.2, 13.4 Hz, H-2′), 2.15–2.28 (2H, m, H-6 and H-6′ overlapped), 3.21 (1H, m, H-9), 3.61 (3H, s, CO_2CH_3), 3.66 (3H, s, CO_2CH_3), 3.74 (1H, dd, J=4.2, 11.2 Hz, H-1), 7.02 (1H, m, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −2.9 (CH_3), −2.3 (CH_3), 9.2 (CH_3), 18.9 (C), 21.8 (CH_3), 24.5 (CH_2), 26.6 (×3) (CH_3), 28.5 (CH_2), 32.5 (C), 32.6 (CH_3), 39.4 (CH_2), 43.4 (C), 48.1 (CH), 51.6 (CH_3), 51.7 (CH_3), 56.6 (CH), 80.6 (CH), 129.6 (C), 140.3 (CH), 167.3 (C), 173.3 (C). $[\alpha]_D^{25}$ −39.6 (c 1.0, $CHCl_3$). IR ($CHCl_3$): ν=2952, 1721 (br), 1256 cm^{-1}. ESIMS: m/z 425 [M+H]$^+$. Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.13; H, 9.39.

5.11. (1*R*,4a*S*,8*R*,8a*S*)-[8-(*tert*-Butyl-dimethyl-silanyl-oxy)-1-hydroxymethyl-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-2-yl]-methanol (20)

To a stirring solution of **19** (193.0 mg, 0.454 mmol) in 2 mL of dry THF, cooled to −78 °C, was added dropwise a solution of diisobutylaluminium hydride (DIBAL–H) (1.5 M in toluene, 6.0 mL, 9.0 mmol) under a nitrogen atmosphere. The solution was allowed to warm to room temperature and stir overnight. Then, it was cooled to −78 °C and 5 mL of MeOH/H_2O (1/1) solution was carefully added. The resulting mixture was concentrated and dried under high vacuum. The residue was suspended in MeOH, filtered through a Celite® bed and the pad was thoroughly washed with MeOH. The filtrate was concentrated in vacuo to afford the crude

diol **20** as a white amorphous solid, which was used without any further purification. For a complete characterization, flash chromatography (50–90% diethyl ether in petroleum ether) of a small aliquot of crude gave pure **20**.

Compound **20**: R_f=0.20 (40% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.11 (6H, s, $(CH_3)_2Si$), 0.84 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.92 (9H, s, $(CH_3)_3CSi$), 1.15 (1H, dd, J=4.8, 11.2 Hz, H-5), 1.28 (1H, ddd, J=3.6, 13.6, 13.6 Hz, H-3), 1.39 (1H, ddd, J=3.2, 3.2, 13.6 Hz, H-3′), 1.51 (1H, dddd, J=3.2, 3.6, 4.0, 13.6 Hz, H-2), 1.65 (1H, dddd, J=3.2, 11.2, 13.6, 13.6 Hz, H-2′), 1.91–2.04 (2H, m, H-6 and H-6′ overlapped), 2.26 (1H, m, H-9), 2.89 (2H, br s, 2×OH), 3.55 (1H, dd, J=4.0, 11.2 Hz, H-1), 3.72 (1H, dd, J=7.2, 10.4 Hz, H-11), 3.92 (1H, d, J=12 Hz, H-12), 4.30 (1H, d, J=12 Hz, H-12′), 4.55 (1H, dd, J=2.4, 10.4 Hz, H-11′), 5.80 (1H, m, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.1 (CH_3), −3.6 (CH_3), 9.1 (CH_3), 18.2 (C), 22.3 (CH_3), 23.2 (CH_2), 26.1 (×3) (CH_3), 29.1 (CH_2), 32.8 (C), 33.1 (CH_3), 40.0 (CH_2), 41.7 (C), 49.4 (CH), 53.3 (CH), 62.9 (CH_2), 67.1 (CH_2), 82.9 (CH), 127.0 (CH), 137.9 (C). $[\alpha]_D^{25}$ −20.4 (c 1.0, $CHCl_3$). IR ($CHC1_3$): ν=3474 (br) cm^{-1}. ESIMS: m/z 369 [M+H]$^+$. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94. Found: C, 68.54; H, 10.89.

5.12. (1*R*,4a*S*,8*R*,8a*S*)-8-(*tert*-Butyl-dimethyl-silanyl-oxy)-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-1,2-dicarbaldehyde (21)

To a stirring solution of oxalyl chloride (377.7 mg, 2.98 mmol, 0.260 mL) in 7 mL of dry CH_2C1_2 cooled to −78 °C was added dropwise 464.9 mg (5.95 mmol, 0.549 mL) of DMSO under a nitrogen atmosphere. After 5 min, a solution of 137.0 mg (0.372 mmol) of **20** in 2.5 mL of CH_2C1_2/DMSO (3/1) was added via cannula. After 1 h, 1.40 g (13.8 mmol, 1.93 mL) of freshly distilled triethylamine was added and the resulting mixture was allowed to stir at −78 °C for 5 min and then warmed to room temperature. Then it was passed through a short pad of silica gel (particle size 0.040–0.263 mm) eluting with ethyl acetate, under N_2, and the eluent was concentrated to give a yellow oil. The oil was purified by flash chromatography (40–60% diethyl ether in petroleum ether) under N_2 to give 118.0 mg (0.324 mmol, 87% for two steps) of **21** as a white amorphous solid.

Compound **21**: R_f=0.50 (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.12 (3H, s, CH_3Si), 0.14 (3H, s, CH_3Si), 0.83 (3H, s, CH_3), 0.90 (9H, s, $(CH_3)_3CSi$), 0.91 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.26 (1H, dd, J=4.9, 11.1 Hz, H-5), 1.33 (1H, ddd, J=4.2, 13.2, 13.2 Hz, H-3), 1.50 (1H, ddd, J=3.2, 3.2, 13.2 Hz, H-3′), 1.56–1.71 (2H, m, H-2 and H-2′ overlapped), 2.26–2.42 (2H, m, H-6 and H-6′ overlapped), 3.30 (1H, br s, H-9), 3.65 (1H, dd, J=4.5, 10.8 Hz, H-1), 7.03 (1H, m, H-7), 9.32 (1H, s, OHCC-8), 10.0 (1H, d, J=3.6 Hz, OHCC-9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.7 (CH_3), −3.1 (CH_3), 9.9 (CH_3), 18.3 (C), 22.4 (CH_3), 24.6 (CH_2), 26.1 (×3) (CH_3), 28.0 (CH_2), 32.6 (C), 32.8 (CH_3), 39.8 (CH_2), 44.8 (C), 49.0 (CH), 59.4 (CH), 81.7 (CH), 141.2 (C), 152.0 (CH), 192.7 (CH), 201.0 (CH). $[\alpha]_D^{25}$ +45.3 (c 1.0, $CHCl_3$). IR ($CHC1_3$): ν=2929, 2856, 1715, 1682, 1255 cm^{-1}. ESIMS: m/z 387 [M+Na]$^+$. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.29; H, 9.81.

5.13. (1*R*,4a*S*,8*R*,8a*S*)-8-Hydroxy-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-1,2-dicarbaldehyde [1-(*R*)-hydroxypolygodial] (2)

To a solution of **21** (60.0 mg, 0.165 mmol) in acetonitrile (5.60 mL), in a silicon vessel, 48% aqueous hydrofluoric acid (1.7 mL) was added at room temperature. The mixture was stirred at room temperature overnight and then $NaHCO_3$ was carefully added until the mixture was neutralized. The organic solvent was removed in vacuo and the residual aqueous layer was extracted with ethyl acetate (3×4 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the crude (30–60% ethyl acetate in petroleum ether) under N_2 afforded pure **2** (32.6 mg, 0.130 mmol, 79%) as a white amorphous solid.

Compound **2**: R_f=0.50 (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.25 (1H, dd, J=4.9, 11.4 Hz, H-5), 1.36 (1H, m, H-3), 1.51 (1H, ddd, J=3.2, 3.2, 13.5 Hz, H-3′), 1.56–1.66 (2H, m, H-2 and H-2′), 2.37 (1H, dddd, J=2.4, 3.8, 11.4, 20.0 Hz, H-6), 2.45 (1H, m, H-6′), 3.20 (1H, br s, H-9), 3.62 (1H, dd, J=7.6, 8.2 Hz, H-1), 7.09 (1H, m, H-7), 9.37 (1H, s, OHCC-8), 9.82 (1H, d, J=3.2 Hz, OHCC-9). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 9.3 (CH_3), 22.0 (CH_3), 24.8 (CH_2), 27.8 (CH_2), 32.7 (CH_3), 32.8 (C), 39.6 (CH_2), 43.5 (C), 48.5 (CH), 59.8 (CH), 79.8 (CH), 139.5 (C), 153.1 (CH), 192.9 (CH), 203.9 (CH). $[\alpha]_D^{25}$ −8.2 (c 1.0, $CHCl_3$). IR ($CC1_4$): ν=3513 (br), 2960, 2928, 2873, 2855, 2739, 1722, 1690 cm^{-1}. ESIMS: m/z 273 [M+Na]$^+$. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.77; H, 8.91.

5.14. (1*S*,4a*S*,8*R*,8a*S*)-8-Hydroxy-5,5,8a-trimethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-1,2-dicarbaldehyde [1-(*R*)-hydroxyisotadeonal] (3)

To a solution of **2** (5.5 mg, 0.022 mmol) in CH_2Cl_2 (2.5 mL) basic Al_2O_3 (10.0 mg) was added at room temperature. The mixture was stirred for 20 h and then filtered on a short pad of silica gel. The pad was thoroughly washed with ethyl acetate, under N_2, and the filtrate was concentrated in vacuo to afford a crude mixture containing **3** and **2** in a ratio of 4.4:1 (determined by ^{1}H NMR). The crude was purified by flash chromatography (30–70% ethyl acetate in petroleum ether) under N_2 to give 4.5 mg (0.018 mmol, 82%) of **3**, as white amorphous solid, and 1.0 mg (0.004 mmol, 18%) of **2**.

Compound **3**: R_f=0.57 (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.95 (3H, s, CH_3), 1.20–1.33 (2H, m, H-3 and H-3′ overlapped), 1.49 (1H, dd, J=5.0, 11.7 Hz, H-5), 1.62 (1H, dddd, J=4.0, 4.0, 4.0, 13.0 Hz, H-2), 1.73 (1H, dddd, J=3.3, 11.2, 11.2, 13.0 Hz, H-2′), 2.28 (1H, dddd, J=2.4, 2.4, 11.7, 20.5 Hz, H-6), 2.56 (1H, ddd, J=5.0, 5.0, 20.5 Hz, H-6′), 3.53 (1H, dd, J=4.0, 11.2 Hz, H-1), 3.66 (1H, br s, H-9), 7.11 (1H, dd, J=2.4, 5.0 Hz, H-7), 9.44 (1H, s, OHCC-8), 9.89 (1H, d, J=2.5 Hz, OHCC-9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.8 (CH_3), 22.1 (CH_3), 25.3 (CH_2), 27.5 (CH_2), 32.3 (CH_3), 32.7 (C), 39.6

(CH_2), 43.1 (C), 43.6 (CH), 54.9 (CH), 74.7 (CH), 137.5 (C), 152.7 (CH), 192.9 (CH), 203.1 (CH). $[\alpha]_D^{25}$ −98.1 (*c* 0.15, $CHCl_3$). IR ($CHCl_3$): ν=3467 (br), 2976, 2929, 2896, 1717, 1682 cm^{-1}. ESIMS: *m*/*z* 273 $[M+Na]^+$.

5.15. Vanilloid activity assays

All prepared compounds have been assayed for TRPV1 sensitivity using fluorometric measurements of changes in intracellular calcium concentration. HEK293 (human embryonic kidney) cells were plated on poly-(D)-lysine and transfected transiently by using TRPV1 plasmids. After transfection, cells have been loaded with a cytoplasmic calcium indicator. $[Ca^{2+}]_i$ was determined before and after the addition of various concentrations of test compounds.

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