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# Enantiodivergent syntheses of cycloheptenone intermediates for guaiane sesquiterpenes

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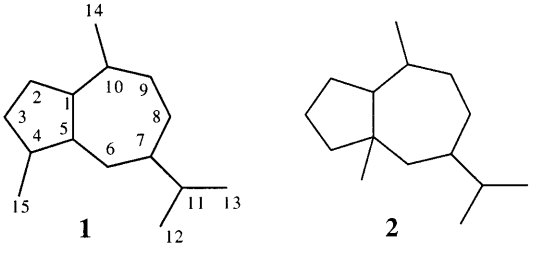
**Abstract**

The syntheses of enantiomeric 6-isopropenyl-3-methyl-2-cycloheptenones **16** and **22** have been effected starting from (*R*)-(−)-carvone. In the synthesis of **16**, (*R*)-(−)-carvone was reduced and the resulting dihydrocarvone transformed regioselectively into silyl enol ethers. Cyclopropanation with dibromocarbene and in situ rearrangement gave an α-bromo-cycloheptenone which was reduced to the (*R*)-(+)-cycloheptenone **16**. In the synthesis of **22**, (*R*)-(−)-carvone was cyclopropanated with a sulfur ylide, followed by reduction with $LiAlH_4$ and acid-catalyzed cyclopropylcarbinyl rearrangement to afford a cycloheptenol. Oxidation and double bond conjugation led to the (*S*)-(−)-cycloheptenone **22** in a partially racemized form. Four cycloheptenones have been obtained and are suitable intermediates for the enantiodivergent syntheses of guaiane sesquiterpenes. 

## 1. Introduction

The guaiane **1** and pseudoguaiane **2** sesquiterpenes are interesting targets for syntheses due to their structural complexity and wide range of biological activities.[1–5]




**1** **2**

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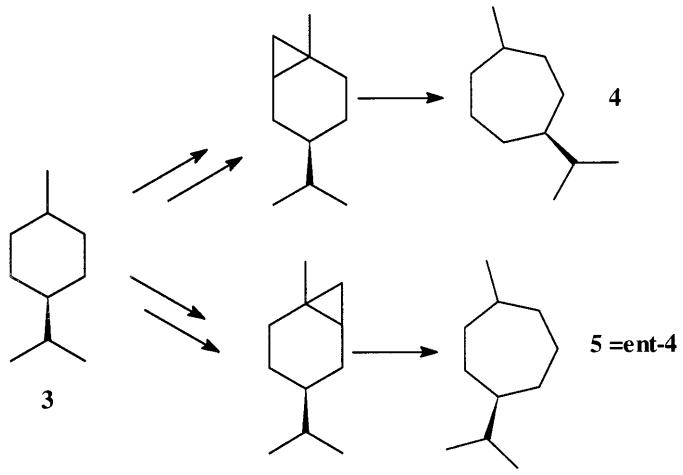
Several strategies for the construction of the perhydroazulene ring system characteristic of the guaiane **1** and pseudoguaiane **2** sesquiterpenes have been developed.[6–12] The pentannulation[13] of cycloheptane derivatives has been successfully applied in only a few cases,[6–8] and depends upon effective methods for the synthesis of suitably functionalized cycloheptane intermediates. Our synthetic strategy involves ring expansion of enantiopure *p*-menthane monoterpenes (symbolized as **3**) by cyclopropanation on both sides of the symmetry plane followed by cleavage or fragmentation of the central bond between the two rings (Scheme 1). This process leads to both enantiomeric series of the required cycloheptane precursors **4** and **5**.

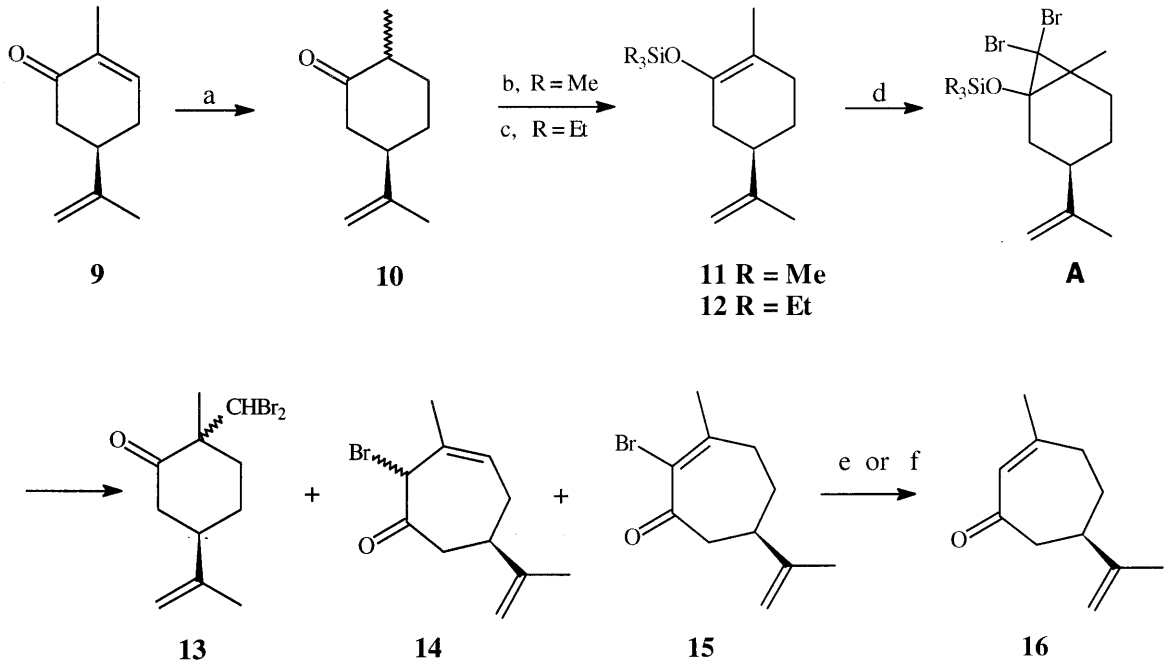



Scheme 1.

We now present synthetic methodologies for the preparation of enantiomeric cycloheptenones **16** and **22** using (*R*)-(−)-carvone **9** as starting material, in an enantiodivergent manner, and incorporating the more functionalized isopropenyl group at position 6.[14]

## 2. Results and discussion

The synthesis of cycloheptenone **16** is shown in Scheme 2. Dihydrocarvone **10** was obtained in 84% yield by reduction of (*R*)-(−)-carvone **9** with zinc dust and methanolic potassium hydroxide,[15] and converted regioselectively into its trimethylsilyl enol ether **11** (89%). This compound reacted with bromoform and potassium *tert*-butoxide in hexane,[16] producing α-bromo-cycloheptenones **14** (4%) and **15** (30%), together with the cyclohexanone **13** (2%) and recovered **10** (15%), which were separated by chromatography on silica gel. In order to verify if the obtention of cycloheptenones **14** and **15** in relatively low yields is due to the trimethylsilyl enol ether, the more stable triethylsilyl enol ether **12** was submitted to the same ring expansion conditions. The results were quite similar, leading to **14** (2%), **15** (23%), **13** (1.5%) and **10** (16%). The compounds **13**, **14** and **15** are expected to be formed from the intermediate dibromocarbene cycloaddition product **A** shown in Scheme 2. The α-bromo-cycloheptenone **15** was reduced to cycloheptenone **16** with zinc in acetic acid[17] (47% yield) or with zinc in refluxing methanol in 54% yield (72% based on consumed **15**, and 25% of recovered **15**).

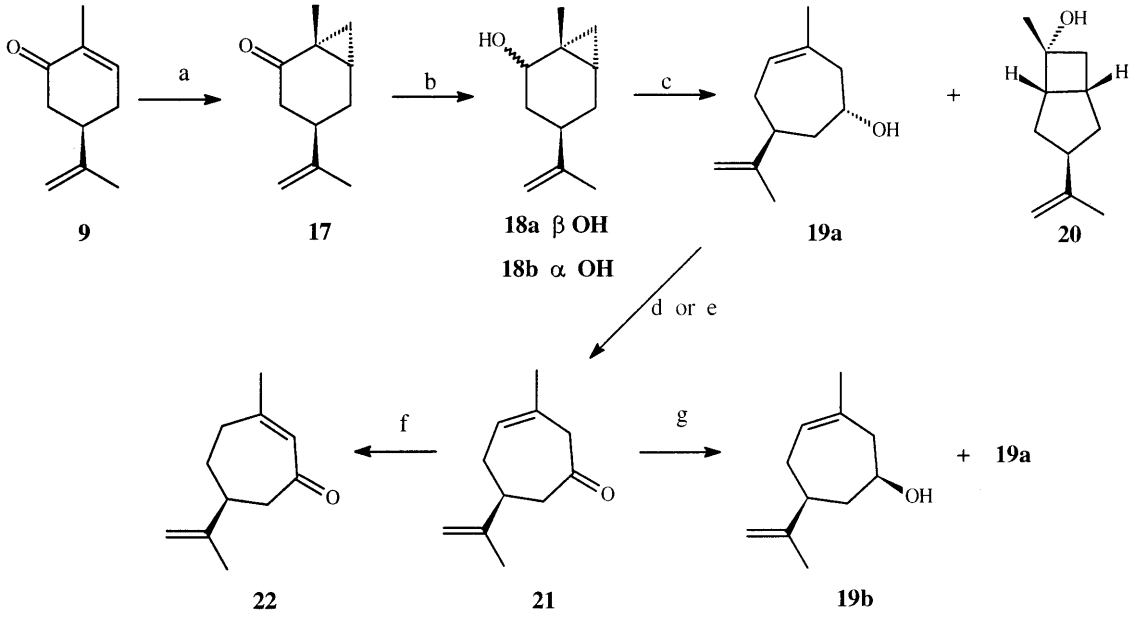



Scheme 2. Reagents and conditions: (**a**) Zn°, KOH, MeOH/$H_2O$, reflux, 9 h, 84%; (**b**) $Me_3SiCl$, NaI, $Et_3N$, $CH_3CN$, rt, 1 h, 89%; (**c**) $Et_3SiCl$, NaI, $Et_3N$, $CH_3CN$, rt, 4 h, 73%; (**d**) *tert*-BuOK, $CHBr_3$, hexane, −30°C, 2 h; (**e**) Zn°, $CH_3CO_2H$, 90°C, 1.5 h, 47%; (**f**) Zn°, MeOH, reflux, 9 h, 54% (72% based on consumed **15**; 25% of recovered **15**)

In the second sequence (Scheme 3), cyclopropylcarvone **17** was prepared in 96% yield from (*R*)-(−)-carvone **9** following the conditions described by Corey and Chaykovsky,[18] and then reduced with $LiAlH_4$[19] to produce a mixture of the pseudo-equatorial alcohol **18a** and pseudo-axial alcohol **18b** in 94% yield in an 84:16 ratio. Cyclopropylcarbinyl–homoallyl rearrangement by solvolysis of the mixture of **18a** and **18b** with dilute $HClO_4$ in acetone/water[20] afforded a mixture of compounds **19a** and **20** (61 and 11% yield, respectively), which were separated by chromatography on silica gel. Oxidation of the alcohol **19a** with PCC (68%) or Collins' reagent (72%) furnished the β,γ-cycloheptenone **21**, which was conjugated to the α,β-isomer **22** using potassium *tert*-butoxide (70%). As an important complement, ketone **21** was reduced with $LiAlH_4$ to a mixture of **19a** and **19b** in 86% yield, which were separated by chromatography on silica gel allowing the identification of both epimers at the carbinolic center.

The configurations at the carbinolic center of **19a** and **19b** were assigned by $^1H$ NMR spectra at 200 MHz. The alcohol **19a** has a carbinolic hydrogen signal at $\delta$ 4.0 (triple triplet) with coupling constants of 6.0 and 3.0 Hz, while alcohol **19b** shows a carbinolic hydrogen signal as a triple triplet at $\delta$ 3.48 with coupling constants of 10.0 and 3.0 Hz. Based upon these chemical shifts and multiplicities we can propose that **19a** is the *trans* epimer. The structure of the interesting minor product **20** was proposed based upon the analyses of $^1H$ and $^{13}C$ NMR using 2D-technics, as well as on the accepted mechanism of this rearrangment.[21]

The (*R*)-cycloheptenone **16** obtained in Scheme 2 has an $[\alpha]_D^{25}$ +51 (*c* 1.47, $CHCl_3$), whereas the expected enantiomeric (*S*)-cycloheptenone **22** showed an $[\alpha]_D^{25}$ −3.68 (*c* 1.46, $CHCl_3$). This difference could at first sight be attributed to chemical impurities, so we very thoroughly checked this with GC, $^1H$ and $^{13}C$ NMR, and elemental analyses. Having demonstrated

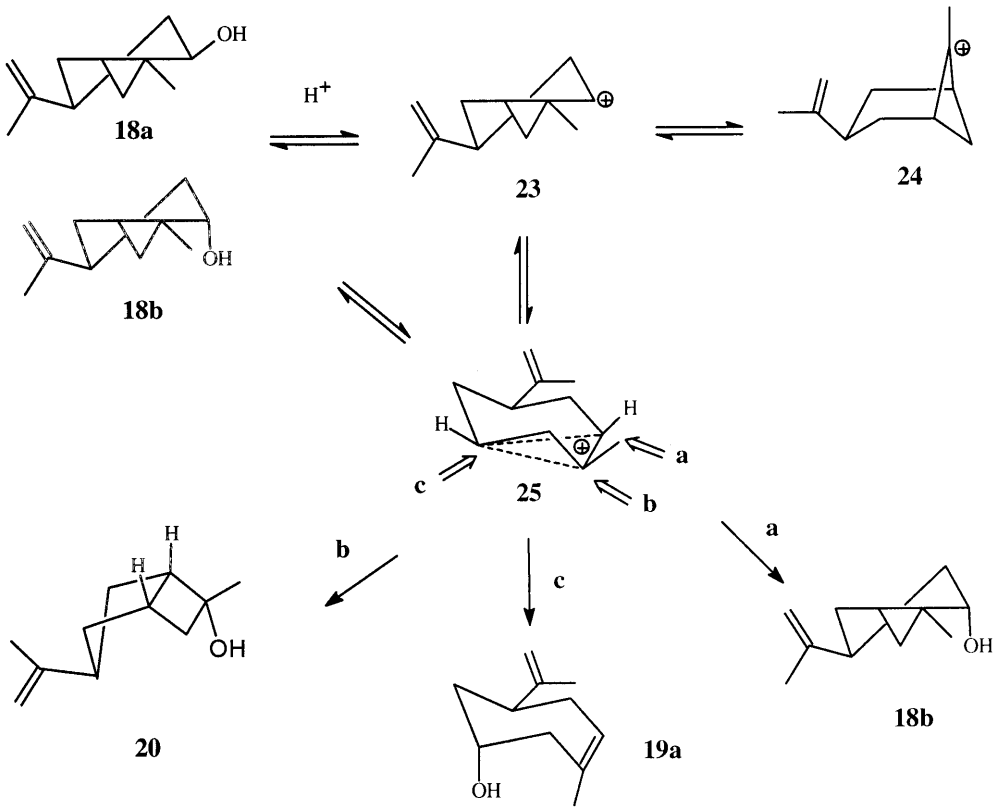



Scheme 3. Reagents and conditions: (**a**) $Me_3SOI$, NaH, DMSO, 50°C, 3 h, 96%; (**b**) $LiAlH_4$, $Et_2O$, rt, 4 h, 94%; (**c**) 7% $HClO_4$, $CH_3COCH_3/H_2O$, rt, 22 h, **19a**, 61%; **20**, 11%; (**d**) PCC, $CH_2Cl_2$, $CH_3CO_2Na$, rt, 2 h, 68%; (**e**) Collins, rt, 1.5 h, 72%; (**f**) *tert*-BuOK, *tert*-BuOH, rt, 1 h 40 min, 70%; (**g**) $LiAlH_4$, $Et_2O$, rt, 1.5 h, 86%

chemical identity and high purity, we were left with enantiomeric purity, and chiral HPLC analyses (cellulose 3,5-dimethylphenylcarbamate 20% g/g APS-Hypersil stationary phase, polarimeter detector) showed that indeed **16** is enantiopure, while product **22** has an enantiomeric excess of about 12%. As the oxidation of cycloheptenol **19a** and the base-catalyzed conjugation to **22** should not lead to partial racemization, we were led back to the acid-catalyzed rearrangement of **18a**,**b** to **19a**. As **18a** and **18b** have much larger numerical optical activities than both **19a** and **20**, we felt that this might be the explanation.

Based upon perchloric acid-catalyzed acetolysis studies described by Friedrich and Jassawalla[22] and upon the studies of the ionization of bicyclo[*n*.1.0]alkan-2-ols in superacids reported by Olah and co-workers,[23,24] we suggest that the observed partial racemization occurs during the rearrangement of the alcohols **18a** and **18b** into the cycloheptenol **19a**.

As shown in Scheme 4, both alcohols **18a** or **18b** can lead after protonation to a classical carbocation **23**, and also to the non-classical carbocation **25**, but now with differing kinetics, since **18a** has the preferred alignment of the central C–C σ bond and the pseudo-equatorial hydroxyl bond. The intermediate **23** can undergo a 1,2 Wagner–Meerwein shift to the achiral carbocation **24**. Non-classical and chiral carbocation **25** offers three susceptible positions and directions for nucleophilic attack leading to **18b** (direction a), **19a** (direction c) and **20** (direction b), respectively. Thus, the observed products can be formed from the achiral carbocation **24** via racemized intermediate **23**, or from the still chiral carbocations **23** and **25**. Perhaps the remaining and surprising result is the partial racemization, which suggests product formation from both chiral and achiral sources at different rates, favoring the original chirality of the alcohols **18**.




Scheme 4.

## 3. Conclusion

The present study shows that the two synthetic routes lead to the appropriately functionalized cycloheptenones **15**, **16**, **21** and **22**, suitable as intermediates for pentannulation to guaiane sesquiterpenes. The methodology utilized for the synthesis of (*S*)-(−)-cycloheptenone **22**, and also **21**, presents a 28% overall yield, but with only 12% ee. The methodology for the synthesis of enantiopure (*R*)-(+)-cycloheptenone **16**, along with **15**, presents an overall 19% yield. The partial racemization in the rearrangement of epimers **18a**,**b** into **19a** is quite interesting and we are investigating this reaction in more detail with a view to reducing the racemization.

## 4. Experimental

### 4.1. General procedures

Melting points were determined on a Micro Química model APF-301 apparatus and are uncorrected. Optical rotations were taken on a Perkin–Elmer polarimeter model 241. GC analyses were obtained on a Shimadzu GC-17A Chromatograph equipped with a DB-1 capillary column (0.25 mm i.d.×30 m), using a 1.5 mL/min $H_2$ carrier gas flow and a temperature program from 70°C (for 1 min) to 250°C (for 10 min) at 8°C/min. HPLC analyses were

performed with a Shimadzu model LCIOAD pump, and UV detector model SPD-6AV or with a IBZ Messtechnik polarimeter (the chiral stationary phase is described in the text). Column chromatography was performed on silica gel 60 (70–230 mesh ASTM Merck). Infrared spectra were recorded either with a Bomen Michelson model 102 FTIR or with a Bomen Hartman & Braun MB-Series. Low resolution mass spectra (70 eV) were measured on a Fisons VG GC/MS8000, a Shimadzu GC/MS-QP5000 or a Hewlett–Packard 5995 GC/MS spectrometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded either on a Brucker AC-200 (200MHz) or a Brucker ARX-400 (400 MHz) spectrometer using $CDCl_3$ with TMS as an internal standard. UV spectra were determined on a Hitachi U-2001 instrument. Microanalyses were performed on a Fisons EA 1108 CHNS-O Analyser, by Mr. Paulo Lambertucci of our Department.

### *4.2. Dihydrocarvone **10***

Dihydrocarvone **10** was prepared by the same procedure as previously described,[15] from (*R*)-(−)-carvone **9** (25.0 g, 166.7 mmol) using 95% methanol–water instead of ethanol as solvent, at reflux for 10 h. The use of methanol at reflux gives a cleaner and higher yielding reaction, leading to **10** (21.20 g; 84%) as a 1:3 mixture of C-1 epimers (*cis*-1,4: *trans*-1,4).

### *4.3. (4*R*)-4-Isopropenyl-1-methyl-2-(trimethylsilyloxy)-1-cyclohexene **11***

A solution of 2.92 g (19.48 mmol) of sodium iodide in 22 mL of dry acetonitrile was added dropwise to a mixture of 1.48 g (9.72 mmol) of dihydrocarvone **10**, 2.12 g (19.51 mmol) of trimethylsilyl chloride and 2.96 g (29.25 mmol) of dry triethylamine, and this solution was stirred at room temperature for 1 h under nitrogen. The mixture was poured into 30 mL of ice and extracted with hexane (3×15 mL). The combined organic layers were washed with saturated ammonium chloride until neutral, and dried over anhydrous $Na_2SO_4$. Removal of the solvent yielded 1.95 g (89%) of enol ether **11** as a colorless oil. $^{1}H$ NMR (200 MHz, $CDCl_3$): 0.16 (s, 9H); 1.25–1.44 (m, 1H); 1.54 (s, 3H); 1.68–1.77 (m, 1H); 1.71 (s, 3H); 1.85–2.31 (m, 5H); 4.69 (s, 2H). $^{13}C$ NMR (50 MHz, $CDCl_3$): 0.7; 16.1; 20.8; 27.9; 30.1; 35.6; 42.4; 108.7; 111.4; 142.2; 149.4.

### *4.4. (6*R*)-2-Bromo-6-isopropenyl-3-methyl-2-cyclohepten-1-one **15** from trimethylsilyl enol ether **11**; compounds **13** and **14***

To a three-necked, round-bottomed flask containing a −30°C cooled solution of the enol ether **11** (1.00 g, 4.45 mmol) in dry hexane (36 mL) were added simultaneously, during 2 h, 5.60 g (22.27 mmol) of dry bromoform and 3.00 g (26.73 mmol) of potassium *tert*-butoxide and the mixture was allowed to warm to room temperature under vigorous stirring. After 24 h the mixture was diluted with hexane and poured into ice (31 mL). The aqueous layer was extracted with hexane (3×40 mL) and the combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was evaporated and the resulting yellow oil (1.95 g) was filtered through silica gel (hexane:AcOEt 80:20 as eluant). The filtrate was evaporated and the residue purified by column chromatography on silica gel (hexane:AcOEt 95:5 as eluant) to give 29 mg (2%) of ketone **13**, 43 mg (4%) of **14**, 332 mg (30%) of **15** and 105 mg (15%) of dihydrocarvone **10**.

**13**: White solid; mp 67.2–71.6°C. $[\alpha]_D^{25}$ +129.6 (*c* 2.25, $CHCl_3$). IR (KBr, $cm^{-1}$): 3028, 2935, 2866, 1702, 1658, 1444, 894, 702, 638. $^{1}H$ NMR (400 MHz, $CDCl_3$): 1.33 (s); 1.35 (s); 1.57–1.74

(m, 2H); 1.76 (s, 3H); 1.79–1.86 (m, 1H); 2.23–2.31 (m, 1H); 2.37–2.55 (m, 2H); 4.74 (s); 4.76 (s); 4.81 (s); 4.83 (s); 6.17 (s); 6.28 (s). $^{13}$C NMR (100 MHz, $CDCl_3$): 20.00; 20.86; 21.07; 23.96; 25.39; 26.42; 32.57; 36.17; 43.66; 43.82; 44.10; 46.13; 51.88; 55.23; 56.72; 111.08; 146.58; 208.23. Anal. calcd for $C_{11}H_{16}OBr_2$: C, 40.77; H, 4.98. Found: C, 40.66, H, 4.99.

**14**: Pale yellow liquid unstable at room temperature. $[\alpha]_D^{23}$ −135.2 (*c* 1.80, $CHCl_3$). IR (neat, $cm^{-1}$): 3082, 2973, 2924, 1706, 1646, 1441, 895. $^1$H NMR (400 MHz, $CDCl_3$): 1.74 (s, 3H); 1.93 (s, 3H); 2.22–2.65 (m, 3H); 3.18–3.28 (m); 3.42 (dd, 1H, $J$=12.0, 8.0 Hz); 4.59 (s); 4.63 (s); 4.76–4.80 (m, 2H); 5.76–5.80 (m); 5.86–5.90 (m). $^{13}$C NMR (100 MHz, $CDCl_3$): 20.05; 20.35; 23.61; 24.02; 32.25; 32.46; 39.32; 44.28; 44.55; 45.27; 56.08; 56.84; 110.51; 130.41; 130.82; 131.88; 132.39; 147.09; 147.85; 201.99; 202.17. Anal. calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 53.91; H, 6.30.

**15**: Pale yellow liquid. $[\alpha]_D^{28}$ +39.08 (*c* 3.10, $CHCl_3$). IR (neat, $cm^{-1}$): 2931, 1675, 1599, 1441, 896. $^1$H NMR (400 MHz, $CDCl_3$): 1.74 (s, 3H); 1.76–1.80 (m, 1H); 1.88–1.97 (m, 1H); 2.23 (s, 3H); 2.50 (ddd, 1H, $J$=16.0, 8.0, 4.0 Hz); 2.55–2.59 (m, 1H); 2.66 (ddd, 1H, $J$=16.0, 12.0, 4.0 Hz); 2.77 (d, 1H, $J$=4.0 Hz); 2.79 (d, 1H, $J$=0.8 Hz); 4.77 (s, 1H); 4.78 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): 20.92; 28.57; 29.70; 33.93; 39.87; 45.33; 110.40; 123.74; 146.90; 156.29; 196.18. MS *m*/*z* (relative intensity): 200 (2), 187 (7), 163 (5), 121 (16), 107 (16), 105 (13), 93 (28), 91 (22), 79 (28), 77 (22), 67 (41), 65 (24), 55 (24), 53 (71), 51 (26), 44 (91), 41 (100). Anal. calcd for $C_{11}H_{15}OBr$: C, 54.34; H 6.22. Found: C, 54.29; H, 6.23.

### *4.5. (4R)-4-Isopropenyl-1-methyl-2-(triethylsilyloxy)-1-cyclohexene* ***12***

A solution of 2.95 g (19.68 mmol) of sodium iodide in 20 mL of dry acetonitrile was added dropwise at room temperature to a mixture of 1.50 g (9.85 mmol) of dihydrocarvone **10**, 2.97 g (19.70 mmol) of triethylsilyl chloride and 2.69 g (26.58 mmol) of dry triethylamine, and the mixture was stirred at room temperature for 4 h under nitrogen. Then the mixture was poured into 44 mL of ice and extracted with hexane (3×30 mL). The combined organic layers were washed with saturated ammonium chloride until neutral and dried over anhydrous $Na_2SO_4$. Removal of the solvent and purification of the residue (4.20 g) by column chromatography on silica gel impregnated with 2% of triethylamine, using hexane as eluant, gave 1.92 g (73%) of a 28:1 mixture of **12** and its regioisomer, respectively, as determined by GC. Further purification by column chromatography on silica gel impregnated with 2% of triethylamine using hexane as eluant gave 1.84 g (70%) of **12** as a colorless oil. $[\alpha]_D^{29}$ +65.5 (*c* 5.90, $CHCl_3$). IR (neat, $cm^{-1}$): 3077, 2914, 1690, 1645, 1450, 1183, 890. $^1$H NMR (200 MHz, $CDCl_3$): 0.60–0.69 (m, 6H); 0.90–1.01 (m, 9H); 1.25–1.46 (m, 1H); 1.57 (s, 3H); 1.70–1.72 (m, 1H); 1.71 (s, 3H); 2.03–2.30 (m, 5H); 4.69 (s, 2H). $^{13}$C NMR (J-Modi-50 MHz, $CDCl_3$): 5.7; 6.7; 16.0; 20.8; 28.0; 30.0; 35.5; 42.5; 108.6; 110.9; 142.4; 149.4. Anal. calcd for $C_{16}H_{30}SiO$: C, 72.11; H, 11.35. Found: C, 72.06; H, 11.56.

### *4.6. (R)-(+)-6-Isopropenyl-3-methyl-2-cyclohepten-1-one* ***16***

(a) Reduction with Zn° in AcOH: 235 mg (0.96 mmol) of **15** was stirred with 229 mg (3.51 mmol) of zinc powder and 1.5 mL of glacial acetic acid at 90°C for 1.5 h. The reaction mixture was neutralized with saturated $NaHCO_3$, extracted with ethyl acetate and dried over anhydrous $Na_2SO_4$. Removal of the solvent provided 156 mg of a residual oil which was purified by column chromatography on silica gel (hexane:AcOEt 95:5 as eluant) to give 74 mg (47%) of **16** as a pale

yellow liquid. $[\alpha]_D^{25}$ +51 (*c* 1.47, $CHCl_3$). IR (neat, $cm^{-1}$): 3075, 2920, 1694, 1440, 893. UV (hexane): $\lambda_{max}$ 229 nm ($\varepsilon$ 26,100). $^1H$ NMR (400 MHz, $CDCl_3$): 1.73 (s, 3H); 1.75–1.84 (m, 1H); 1.91–1.99 (m, 1H); 1.96 (s, 3H); 2.34 (ddd, 1H, $J=16.0$, 8.0, 4.0 Hz); 2.48–2.57 (m, 2H); 2.66–2.69 (m, 2H); 4.73–4.75 (m, 2H); 5.93 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 20.59; 27.45; 31.18; 33.72; 40.65; 47.78; 110.00; 129.79; 148.34; 158.54; 202.35. MS *m*/*z* (relative intensity): 164 ($M^+$, 9), 149 (11), 121 (48), 109 (33), 107 (100), 106 (45), 95 (51), 94 (50), 93 (78), 91 (23), 82 (75), 81 (34), 79 (41), 68 (39), 67 (64), 53 (37), 41 (57). Anal. calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.45; H, 10.10.

(b) Reduction with $Zn^o$ in methanol: 55 mg (0.23 mmol) of **15** was stirred with 59 mg (0.90 mmol) of zinc powder and 0.6 mL of 95% methanol at 70°C. After 5 h, additional 34 mg (0.52 mmol) of zinc powder and 0.5 mL of 95% methanol were added and the mixture was stirred at 70°C for 3.5 h. The cooled reaction mixture was filtered through a short pad of Celite and the filtrate extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. Removal of the solvent provided 48 mg of a residual oil, which was purified by column chromatography on silica gel (hexane:AcOEt 95:5 as eluant) to give 14 mg (25%) of recovered **15** and 20 mg (54%; 72% based on consumed **15**) of **16**.

### *4.7. (1*R,*4*R,*6*S*)-4-Isopropenyl-1-methyl-bicyclo[4.1.0]heptan-2-one* **17**

Compound **17** was prepared[18] from (*R*)-(−)-carvone **9** (6.00 g, 40 mmol). Yield 6.28 g (96%) of cyclopropyl ketone **17**. $^1H$ NMR and IR spectral data of **17** correspond with the published data.[18] GC analyses showed the presence of compound **17** and its diastereomer in a 97:3 ratio. **17**: $[\alpha]_D^{22}$ −9.8 (*c* 7.84, $CHCl_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$): 17.51; 19.58; 20.37; 25.09; 26.80; 29.08; 36.54; 41.66; 109.98; 146.89; 210.02. MS *m*/*z* (relative intensity): 164 ($M^+$, 13), 149 (11), 121 (23), 107 (25), 96 (37), 95 (29), 93 (28), 91 (23), 79 (38), 68 (100), 67 (93), 53 (51).

### *4.8. (1*R,*2*R,*4*R,*6*S*)-4-Isopropenyl-1-methyl-bicyclo[4.1.0]heptan-2-ol* **18a** *and (1*R,*2*S,*4*R,*6*S*)-4-isopropenyl-1-methyl-bicyclo[4.1.0]heptan-2-ol* **18b**

A solution of **17** (1.00 g, 6.09 mmol) in anhydrous ethyl ether (4 mL) was added dropwise to a magnetically stirred slurry of lithium aluminum hydride (120 mg, 3.21 mmol) in ethyl ether (15 mL). The reaction mixture was stirred at room temperature for 2 h, saturated ammonium chloride was added dropwise at 0°C and the mixture was filtered through a short pad of Celite. The filtrate was extracted with ethyl acetate (50 mL) and the organic layer was washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. After removal of the solvent, the residue (1.05g) was eluted through a short silica gel column (hexane:AcOEt 80:20 as eluant) to give 955 mg (94%) of **18a**,**b** as a colorless oil. IR (neat, $cm^{-1}$): 3379, 3063, 2924, 2864, 1643, 1447, 1049, 888. Anal. calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.41; H, 11.29.

The mixture of **18a**,**b** was separated by column chromatography on silica gel (hexane:AcOEt 85:15 as eluant), giving **18a** (687 mg, 68%), **18b** (152 mg, 15%) and **18a**,**b** (100 mg, 10%).

**18a**: $[\alpha]_D^{22}$ −42.3 (*c* 19.36, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): 0.22 (t, 1H, $J=4.0$ Hz); 0.39 (dd, 1H, $J=8.0$, 4.0 Hz); 0.92–0.96 (m, 1H); 1.12 (s, 3H); 1.26–1.34 (m, 1H); 1.73 (s, 3H); 1.75–1.84 (m, 4H); 2.07 (s, 1H); 3.87 (dd, 1H, $J=8.0$, 4.0 Hz); 4.72–4.73 (m, 1H); 4.75 (s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 16.95; 19.59; 20.71; 20.87; 21.74; 28.69; 36.40; 36.59; 71.79; 109.06; 150.15.

**18b**: $[\alpha]_D^{25}$ −73.0 (*c* 0.95, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): 0.27 (dd, 1H, $J=8.0$, 4.0 Hz); 0.52 (t, 1H, $J=4.0$ Hz); 0.99–1.05 (m, 1H); 1.15 (s, 3H); 1.34–1.40 (m, 2H); 1.50 (ddd, 1H, $J=16.0$, 8.0, 4.0 Hz); 1.70 (s, 3H); 1.72–1.77 (m, 2H); 1.94–2.00 (m, 1H); 4.04 (t, 1H, $J=4.0$ Hz); 4.70–4.72 (m, 1H); 4.74–4.75 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): 13.15; 21.29; 21.79; 22.08; 25.53; 28.61; 34.54; 35.54; 70.47; 109.07; 148.74. MS *m*/*z* (relative intensity): 166 ($M^+$, 7), 133 (15), 109 (33), 107 (43), 105 (35), 98 (39), 97 (42), 95 (35), 93 (42), 91 (67), 83 (52), 81 (54), 79 (79), 77 (44), 69 (100), 67 (76), 55 (78), 53 (60).

### *4.9. (1*R,*6*S*)-6-Isopropenyl-3-methyl-3-cyclohepten-1-ol **19a** and (1*S,*3*R,*5*S,*6*R*)-3-isopropenyl-6-methyl-bicyclo[3.2.0]heptan-6-ol **20***

To a solution of **18a**,**b** (1.00 g, 6.02 mmol) in acetone (14 mL) was added dropwise 7% aqueous $HClO_4$ (8 mL) at room temperature. After stirring for 22 h, the solution was neutralized with 10% aqueous $NaHCO_3$ and extracted with ethyl ether (3×20 mL). The organic layer was washed with brine (25 mL) and dried over anhydrous $Na_2SO_4$. Removal of the solvent, followed by purification by column chromatography on silica gel (hexane:AcOEt:acetone 100:15:5 as eluant) gave **19a** (611 mg, 61%) and **20** (110 mg, 11%). The published procedure[20] uses 70% aqueous $HClO_4$, which we find to cause side-reactions with the isopropenyl group, thus the modification to the dilute 7% $HClO_4$ solution.

**19a**: Colorless oil. $[\alpha]_D^{22}$ −4.1 (*c* 11.40, $CHCl_3$). IR (neat, $cm^{-1}$): 3361, 3074, 2913, 1643, 1441, 1074, 1021, 884. $^1H$ NMR (200 MHz, $CDCl_3$): 1.63 (s, 3H); 1.66 (s, 3H); 1.65–1.79 (m, 2H); 1.86–2.03 (m, 3H); 2.17–2.34 (m, 3H); 4.00 (tt, 1H, $J=6.0$, 3.0 Hz); 4.58–4.61 (m, 2H); 5.59 (t, 1H, $J=6.0$ Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$): 20.4; 27.0; 33.0; 39.0; 40.4; 43.9; 66.5; 108.8; 125.7; 134.7; 150.3. MS *m*/*z* (relative intensity): 166 ($M^+$, 0.4), 151 (8), 133 (16), 108 (46), 107 (34), 93 (28), 91 (28), 83 (29) 79 (36), 69 (100), 67 (39), 55 (39), 53 (28), 43 (32), 41 (82). Anal. calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.41, H, 11.36.

**20**: Colorless oil. $[\alpha]_D^{20}$ +4.9 (*c* 4.98, $CHCl_3$). IR (neat, $cm^{-1}$): 3365, 3077, 2925, 1643, 1442, 1138, 889. $^1H$ NMR (400 MHz, $CDCl_3$): 1.36 (s, 3H); 1.39–1.48 (m, 3H); 1.60 (dd, 1H, $J=12.0$, 8.0 Hz); 1.64 (dd, 1H, $J=12.0$, 4.0 Hz); 1.77 (s, 3H); 2.00 (dd, 1H, $J=12.0$, 8.0 Hz); 2.17 (ddd, 1H, $J=12.0$, 8.0, 4.0 Hz); 2.41–2.48 (m, 1H); 2.56–2.60 (m, 1H); 2.84 (tt, 1H, $J=12.0$, 6.0 Hz); 4.70–4.72 (m, 1H); 4.75–4.77 (m, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$): 21.5; 29.7; 30.4; 30.8; 37.1; 40.8; 45.4; 50.0; 69.2; 108.2; 147.9. MS *m*/*z* (relative intensity): 166 ($M^+$, 2), 148 (6), 135 (14), 133 (14), 107 (35), 105 (23), 93 (100), 91 (40), 79 (32), 77 (32), 69 (32), 55 (33), 43 (26), 41 (45). Anal. calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.38; H, 11.05.

### *4.10. (6*S*)-6-Isopropenyl-3-methyl-3-cyclohepten-1-one **21***

(a) Oxidation with pyridinium chlorochromate: pyridinium chlorochromate (1.60 g, 7.42 mmol) and sodium acetate (125 mg, 1.52 mmol) were suspended in 6 mL of anhydrous $CH_2Cl_2$, and **19a** (617 mg, 3.71 mmol) in 5 mL of anhydrous $CH_2Cl_2$ was added dropwise to the magnetically stirred solution. The reaction mixture was stirred at room temperature for 2 h, diluted with ethyl ether (15 mL) and filtered through a silica gel column with a plug of active carbon. The filtrate was evaporated and the residue (600 mg) purified by column chromatography on silica gel (hexane:AcOEt 95:5 as eluant) to give **21** (415 mg, 68%) as a colorless oil. $[\alpha]_D^{27}$ −3.9 (*c* 8.20, $CHCl_3$). IR (neat, $cm^{-1}$): 2929, 1706, 1441, 893. $^1H$ NMR (400 MHz, $CDCl_3$): 1.73 (s, 3H); 1.79 (s, 3H); 2.19–2.36 (m, 2H); 2.60 (d, 2H, $J=8.0$ Hz); 2.73–2.80 (m, 1H); 3.00 (d, 1H,

$J=16.0$ Hz); 3.31 (d, 1H, $J=16.0$ Hz); 4.73–4.75 (m, 1H); 4.76–4.77 (m, 1H); 5.55–5.59 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): 20.37; 25.97; 32.97; 43.12; 48.14; 48.85; 110.04; 124.39; 130.22; 148.14; 207.93. MS $m/z$ (relative intensity): 164 ($M^+$, 8), 122 (39), 107 (36), 93 (44), 91 (29), 80 (51), 79 (55), 77 (25), 69 (26), 68 (100), 67 (87), 53 (59), 41 (74). Anal. calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.05; H, 9.99.

(b) Collins' oxidation: chromium trioxide (1.74 g, 17.40 mmol), was added at 0°C to a magnetically stirred solution of 2.9 mL (35.39 mmol) of dry pyridine in 35 mL of anhydrous $CH_2Cl_2$. The reaction mixture was stirred at room temperature for 15 min, and 489 mg (2.94 mmol) of alcohol **19a** in 50 mL of anhydrous $CH_2Cl_2$ was added dropwise. After stirring for an additional 1.5 h at room temperature, the solution was filtered through a silica gel column with a plug of active carbon. The filtrate was washed with 0.5 M aqueous HCl (3×29 mL), 29 mL of 10% aqueous $NaHCO_3$, 29 mL of saturated aqueous NaCl, and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent, followed by purification by column chromatography on silica gel (hexane:AcOEt 95:5 as eluant) gave 350 mg (72%) of **21** as a colorless oil.

### *4.11. (1*R*,6*S*)-6-Isopropenyl-3-methyl-3-cyclohepten-1-ol **19a** and (1*S*,6*S*)-6-isopropenyl-3-methyl-3-cyclohepten-1-ol **19b***

A solution of **21** (345 mg, 2.1 mmol) in anhydrous ethyl ether (2 mL) was added dropwise to a magnetically stirred slurry of lithium aluminum hydride (40 mg, 1.05 mmol) in ethyl ether (5 mL). The reaction mixture was stirred at room temperature for 1.5 h, saturated ammonium chloride was added dropwise at 0°C and the mixture was filtered through a short pad of Celite. The filtrate was extracted with ethyl ether (3×15 mL), washed with brine (10 mL) and dried over anhydrous $Na_2SO_4$. After removal of the solvent, the residue (315 mg) was eluted through a short silica gel column (hexane:AcOEt 80:20 as eluant) to give 302 mg (86%) of **19a**,**b**. Separation of **19a** and **19b** by column chromatography on silica gel (hexane:dichloromethane:acetone = 70:25:5 as eluant) gave **19a** (144 mg, 41%), **19b** (62 mg, 18%) and **19a**,**b** (85 mg, 24%).

**19a**: Identical IR, $^1$H and $^{13}$C NMR spectral data to those previously obtained from **18a**,**b**, in Section 4.9.

**19b**: IR (neat, $cm^{-1}$): 3361, 3074, 2913, 1643, 1441, 1074, 1021, 884. $^1$H NMR (200 MHz, $CDCl_3$): 1.52–1.70 (m, 1H); 1.61 (s, 3H); 1.65 (s, 3H); 1.87–2.09 (m, 5H); 2.36–2.51 (m, 2H); 3.48 (tt, 1H, $J=10.0$, 3.0 Hz); 4.53–4.58 (m, 2H); 5.52–5.55 (m, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): 20.2; 26.0; 32.9; 43.0; 44.0; 47.5; 68.6; 108.5; 126.0; 134.8; 150.7.

### *4.12. (6*S*)-6-Isopropenyl-3-methyl-2-cyclohepten-1-one **22***

To a solution of **21** (446 mg, 2.72 mmol) in 5 mL of dry *tert*-BuOH was added dropwise, during 10 min, 2 mL of a *tert*-BuOK/*tert*-BuOH solution (100 mg *tert*-BuOK in 5 mL of *tert*-BuOH). The reaction mixture was stirred at room temperature for 100 minutes. Saturated ammonium chloride (10 mL) was added dropwise at 0°C, and the mixture was extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine (20 mL), dried over anhydrous $Na_2SO_4$ and evaporated. Purification of the residue (414 mg) by column chromatography on silica gel (hexane:AcOEt 90:10 as eluant) gave 314 mg (70%) of **22** as a pale yellow liquid. $[\alpha]_D^{25}$ −3.7 ($c$ 1.46, $CHCl_3$). IR (neat, $cm^{-1}$): 3082, 2934, 1660, 1444, 891. UV (hexane): $\lambda_{max}$ 229 nm ($\varepsilon$ 26,100). $^1$H NMR (400 MHz, $CDCl_3$): 1.73 (s, 3H); 1.75–1.84 (m, 1H); 1.91–1.98

(m, 1H); 1.96 (s, 3H); 2.34 (ddd, 1H, $J=16.0$, 8.0, 4.0 Hz); 2.48–2.57 (m, 2H); 2.66–2.69 (m, 2H); 4.73–4.75 (m, 2H); 5.93 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): 20.58; 27.46; 31.13; 33.68; 40.60; 47.74; 109.98; 129.75; 148.29; 158.64; 202.39. MS $m/z$ (relative intensity): 164 ($M^+$, 2), 149 (5), 121 (29), 109 (24), 107 (80), 106 (34), 95 (43), 94 (42), 93 (68), 91 (27), 82 (61), 81 (33), 79 (45), 68 (37), 67 (91), 53 (53), 41 (76). Anal. calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.53; H, 9.97.

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