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Enantiopure cycloheptenones from (*R*)-(−)-carvone: intermediates for perhydroazulene terpenoids

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Abstract—Two routes for the synthesis of enantiopure cycloheptenones, intermediates for perhydroazulene terpenoids, have been developed. They feature totally regioselective Tiffeneau–Demjanov and Nozaki ring expansion reactions of (*R*)-(−)-carvone.

1. Introduction

Enantiopure seven-membered carbocycles are building blocks for the syntheses of biologically active compounds, such as sesquiterpenes,[1a] diterpenes[1b] and sesterterpenes,[1c] which contain a seven-membered ring frequently in fusion with a five-membered ring in a perhydroazulene relationship. Newer synthetic approaches to seven-membered rings involve transition metal mediated reactions, such as ring-closing metathesis[2] and cycloaddition processes.[3] Other methodologies have also been described in a recent review.[4] However, the traditional ring expansion reactions of readily available six-membered ring starting materials are still very important, especially when the processes are enantioselective.

Over the course of our studies on the synthesis of perhydroazulene terpenoids,[5] we have developed methodologies for the ring expansion[6] of chiral enantiopure *para*-menthane monoterpenes **I**, already containing methyl and isopropyl groups in the desired 1,4-relationship (Fig. 1). Our strategy has been to cyclopropanate a single isomer of *para*-menthene-1 **II** followed by cleavage of the central single bond of **III** (route a), a decision based on an expected lack of regioselectivity in the ring expansion rearrangement of **IV** shown in route b. Recently, we chose to examine this question experimentally, and were surprised by the total regioselectivity[7] discovered in two independent ring expansion reactions of **IV** leading to cycloheptanone **V**. Fundamental to these two sequences is the complete transference of the original chirality and enantiomeric purity.

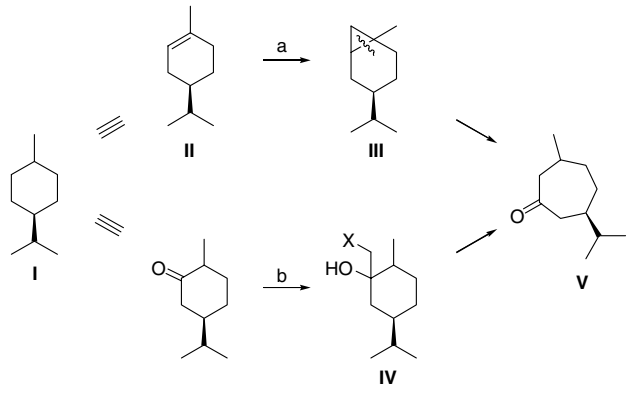

Figure 1. Ring expansion of *para*-menthane monoterpenes.

Herein, we report these two sequences (Scheme 1) for the synthesis of enantiopure cycloheptenones **4** and **5**, based upon the Tiffeneau–Demjanov and Nozaki reactions in totally regioselective ring expansions of (*R*)-(−)-carvone **1**. Although carvone itself has been widely used as a chiral starting material for enantioselective syntheses of natural products,[8–11] we have not found any synthetic methodologies reported for this type of ring expansion.

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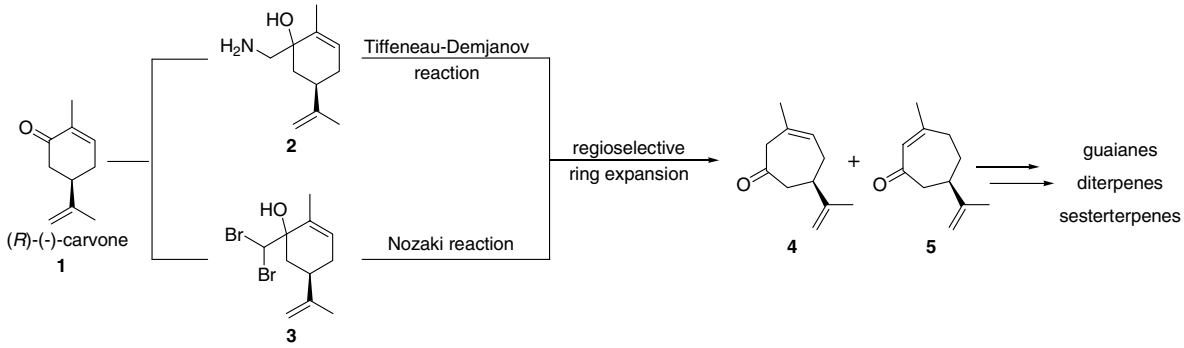
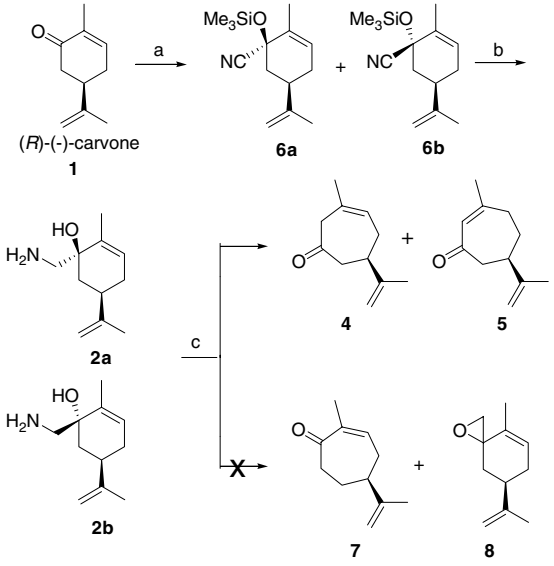


Scheme 1. Synthetic methodologies for the preparation of cycloheptenones **4** and **5** from (*R*)-(−)-carvone **1**.

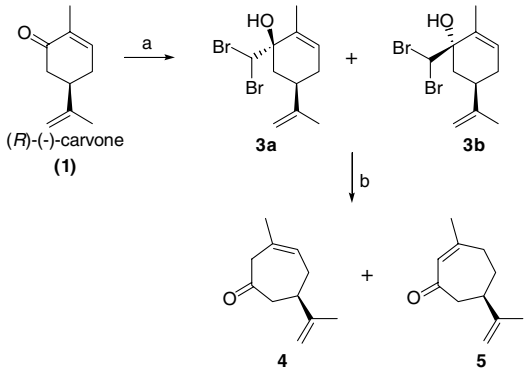
2. Results and discussion

Reaction of (*R*)-(−)-carvone **1** with trimethylsilylcyanide[12] gave a 9:1 mixture of protected cyanohydrins **6a** and **6b** in 98% yield (Scheme 2), which was used directly in the next reaction. Reduction[13] of this **6a/6b** mixture with $LiAlH_4$ produced the amino alcohols **2a/2b** as a white solid in 67% yield. This **2a/2b** mixture was then submitted to the Tiffeneau–Demjanov reaction[14] with HNO_2 at 0 °C for 2 h to give cycloheptenones **4** and **5** in 68% and 10% yield, respectively, easily separable by chromatography on silica gel. The ring expansion reaction proceeded with total regioselectivity to **4** and **5**, without the formation of the alternative cycloheptenone **7** or epoxide **8**.



Scheme 2. Reagents and conditions: (a) KCN, NaI, Me_3SiCl, py, CH_3CN, rt, 62 h; 97%; (b) $LiAlH_4$, diethyl ether, 0 °C, 2 h; 67%; (c) $NaNO_2$, AcOH, 0 °C, rt, 2 h, 78%.

Cycloheptenones **4** and **5** were also prepared with total regioselectivity by the Nozaki reaction[15] in only two steps. Treatment of (*R*)-(−)-carvone **1** with 2 equiv of dibromomethyllithium (prepared in situ from dibromomethane and lithium dicyclohexylamide) at −78 °C gave a 1:1 mixture of **3a** and **3b** in 77% yield after 1 h (Scheme 3). This mixture was purified by simple filtration through silica gel, and then treatment with 2.1 equiv



Scheme 3. Reagents and conditions: (a) CH_2Br_2, Cy_2NLi, THF, −78 °C, 1 h; 77%; (b) *n*-BuLi, THF, −78 °C, 1 h; 0 °C, 15 min; 51%.

of *n*-butyllithium at −78 °C produced directly cycloheptenones **4** and **5** in 47% and 4% yield, respectively. We did not observe any formation of compound **7**, establishing once again the totally regioselective nature of this Nozaki ring expansion.

The conjugated cycloheptenone **5** can be converted into **4** by treatment with methylmagnesium bromide and $FeCl_3$ in diethyl ether[16] (79% yield), whereas **5** was obtained from **4** by treatment with *t*-BuOK in *t*-BuOH[5b] (65% yield) or on attempted distillation in a Kugelrohrofen (88% yield).

Chiral gas chromatographic analyses of **1** and the two cycloheptenones **4** and **5**, obtained from both synthetic routes, display greater than 99% enantiomeric purity, indicating that the formation of **4** and **5** occurs with no loss of stereochemical integrity.

3. Conclusion

In conclusion, we have developed two synthetic routes to the appropriately functionalized cycloheptenone **4** and also **5**, both useful enantiopure intermediates for perhydroazulene terpenes.[5] Using these methodologies, compound **4** has been prepared on a multi-gram scale with practically no extended chromatographic separations needed, and with no interference from regioisomer **7**. Starting from 12.0 g of (*R*)-(−)-carvone, we obtained 6.34 g (45% overall yield) of cycloheptenone **4** in a

Tiffeneau–Demjanov reaction. The Nozaki reaction furnished 1.19 g (36% overall yield) of **4** from 5.0 g of (*R*)-(−)-carvone.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra of compounds **4** and **5** were obtained on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively, and on a Bruker ARX-400 spectrometer for compounds **2a**, **3a**, **3b** and **6a**, with $CDCl_3$ as solvent. Chemical shifts are in ppm downfield from a tetramethylsilane internal standard. Infrared spectra were recorded on a Bomen Michelson model 102 FTIR and the most intense or representative bands reported (in cm^{-1}). Mass spectra were determined by electron spray ionization (ESI), using a Micromass Quattro LC/MS and a Shimadzu GC/MS-QP5000 spectrometers. Melting points were determined on a Micro Química model APF 301 apparatus and are uncorrected. Radial chromatography was performed on a Chromatotron® model 8924 with 2 mm plates of silica gel 60, PF 254 with calcium sulfate, E. Merck 7749. Gas liquid chromatographic analyses were performed on a Shimadzu GC-17A, equipped with a DB-1 capillary column (0.25 mm × 30 m) and using nitrogen as carrier gas. Reactions with compounds sensitive to air or moisture were performed under nitrogen. Diethyl ether and tetrahydrofuran were distilled from sodium under nitrogen and used immediately. Acetonitrile was dried by distillation from calcium hydride. Trimethylsilyl chloride was distilled from quinoline. Dibromomethane and *N*,*N*-dicyclohexylamine were freshly distilled before use.

4.2. (1*R*,5*R*)-5-Isopropenyl-2-methyl-1-trimethyl-silanyl-oxy-cyclohex-2-ene-1-carbonitrile 6a and (1*S*,5*R*)-5-isopropenyl-2-methyl-1-trimethyl-silanyloxy-cyclohex-2-ene-1-carbonitrile 6b

A mixture of NaI (2.60 g; 17.4 mmol) in anhydrous CH_3CN (55 mL) was treated successively with anhydrous KCN (16.8 g; 343 mmol), freshly distilled Me_3SiCl (16.5 mL; 129 mmol) and dry pyridine (0.51 mL; 6.4 mmol) at room temperature for 2 h. A solution of (*R*)-(−)-carvone **1** (12.9 g; 86.0 mmol) in anhydrous CH_3CN (10.0 mL) was then added and the resulting mixture stirred for 62 h. Hexane and cold water were added and the phases separated. The organic phase was washed with cold water, saturated $Na_2S_2O_4$ and dried over Na_2SO_4. The solvent was eliminated under vacuum to give compounds **6a** and **6b** in a 9:1 ratio by GLC, (20.9 g; 83.8 mmol) in 97% yield. For analytical purposes, a small sample of the above product was purified by radial chromatography using a mixture of hexane–EtOAc (9:1) as eluent. Analytical and spectral data for **6a**: $[\alpha]_D^{25} = -124$ (*c* 2.9 $CHCl_3$). IR (film) *v* 2957, 2361, 1647, 1127, 904, 847 cm^{-1}. MS *m*/*z* 234 (M-15). ^{1}H NMR: δ 0.27 (9H, s), 1.75 (3H, s), 1.81 (3H, m), 1.94 (2H, m), 2.25 (2H, m), 2.35 (1H, dt, $J_1 = J_2 = 2.0$ Hz, $J_3 = 12.4$ Hz), 2.5 (1H, m), 4.79 (1H, s), 4.75 (1H, s), 5.64 (1H, m). ^{13}C NMR: 147.1, 133.7, 126.9, 121.1, 109.9, 71.3, 42.3, 39.1, 30.6, 20.4, 17.3, 13.3 (3C). Anal. Calcd for $C_{14}H_{23}NOSi$: C, 67.41; H, 9.29. Found: C, 67.17; H, 9.44.

4.3. (1*R*,5*R*)-1-(Aminomethyl)-5-isopropenyl-2-methyl-cyclohex-2-enol-1 2a and (1*S*,5*R*)-1-(aminomethyl)-5-isopropenyl-2-methylcyclohex-2-enol-1 2b

A solution of compounds **6a** and **6b** (21.6 g; 86.8 mmol) in anhydrous Et_2O (15.0 mL) was added to $LiAlH_4$ (6.45 g; 170.0 mmol) in anhydrous Et_2O (75 mL) at 0 °C. The suspension was stirred at this temperature for 2 h. The reaction mixture was then quenched by the successive addition of water (7.8 mL), 15% aqueous NaOH (7.8 mL) and again water (23.0 mL). The solid was removed by filtration and the solvent eliminated under vacuum to give a mixture of compounds **2a** and **2b** (10.0 g; 55.2 mmol) as a white solid in 67% yield. For analytical purposes, a small sample of the above product was purified by radial chromatography using a mixture of hexane–EtOAc (7:3) as eluent. Analytical and spectral data for **2a**: $[\alpha]_D^{25} = -92.2$ (*c* 2.0, $CHCl_3$). Mp = 99.2–99.7 °C. IR (KBr) *v* 3416, 3361, 2913, 1640, 1593, 1171, 1038, 888 cm^{-1}. MS *m*/*z* 182. ^{1}H NMR: δ 1.50 (1H, t, $J = 12.8$ Hz), 1.71 (3H, s), 1.73 (3H, s), 1.94 (2H, m), 2.02 (1H, m), 2.07 (1H, br s), 2.11 (1H, m), 2.82 (1H, d, $J = 13.1$ Hz), 2.76 (1H, d, $J = 13.1$ Hz), 4.75 (2H, m), 5.5 (1H, br s). ^{13}C NMR: 148.9, 137.0, 124.9, 109.0, 72.8, 46.5, 39.3, 38.1, 31.1, 20.4, 17.1. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.62; H, 10.43; N, 7.50.

4.4. (*R*)-6-Isopropenyl-3-methyl-cyclohept-3-enone 4 and (*R*)-6-isopropenyl-3-methyl-cyclohept-2-enone 5

A mixture of compounds **2a** and **2b** (10.05 g; 55.4 mmol) in 10% aqueous AcOH (110 mL) at 0 °C was treated with a 1.29 M aqueous solution of $NaNO_2$ (29 mL). The reaction mixture was stirred for 30 min at 0 °C and 2 h at room temperature. The solution was again cooled to 0 °C and 15% aqueous solution of NaOH added to bring the pH to 10. The aqueous phase was extracted with Et_2O and the combined ethereal extracts were washed with brine and then dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel using *n*-hexane–EtOAc (9.5:0.5) as eluent to first give **4** (6.34 g; 38.6 mmol: 68% yield) and then **5** (0.71 g; 4.33 mmol: 10% yield).

Compound **4**: $[\alpha]_D^{25} = +30$ (*c* 0.26, $CHCl_3$). IR (film) *v* 3077, 2969, 1704, 1439, 859 cm^{-1}. MS *m*/*z* 165 (M+1). ^{1}H NMR: δ 1.73 (3H, s), 1.79 (3H, s), 2.29 (2H, m), 2.56 (2H, m), 2.60 (1H, d, $J_1 = 8.0$ Hz), 2.76 (1H, m), 3.00 (1H, d, $J_1 = 14.7$ Hz), 3.32 (1H, d, $J_1 = 14.7$ Hz), 4.74 (1H, m), 4.76 (1H, m), 5.56 (1H, m). ^{13}C NMR: 208.0, 148.2, 130.3, 124.5, 110.1, 48.9, 48.2, 43.2, 33.1, 26.1, 20.5. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.05; H, 9.99.

Compound **5**: $[\alpha]_D^{25} = +49.0$ (*c* 0.13, $CHCl_3$), lit.[6a] +51.0, (*c* 1.47, $CHCl_3$). IR (film) *v* 1652, 1436, 1375, 1280, 891 cm^{-1}. MS *m*/*z* 165 (M+1). ^{1}H NMR: δ 1.66 (3H,

dd, $J_1 = 0.8$ Hz, $J_2 = 1.5$ Hz), 1.73 (1H, ddt, $J_1 = 3.5$ Hz, $J_2 = J_3 = 8.1$ Hz, $J_4 = 14.3$ Hz), 1.87 (1H, ddddd, $J_1 = 1.0$ Hz, $J_2 = 3.5$ Hz, $J_3 = 5.8$ Hz, $J_4 = 8.3$ Hz, $J_5 = 14.3$ Hz), 1.89 (3H, d, $J = 0.8$ Hz), 2.28 (1H, dddt, $J_1 = 0.8$ Hz, $J_2 = 1.3$ Hz, $J_3 = 3.5$ Hz, $J_4 = 8.3$ Hz, $J_5 = 17.5$ Hz), 2.46 (1H, ddddq, $J_1 = 1.3$ Hz, $J_2 = 3.5$ Hz, $J_3 = 8.1$ Hz, $J_4 = 17.5$ Hz), 2.47 (1H, ddddd, $J_1 = 0.8$ Hz, $J_2 = 5.1$ Hz, $J_3 = 5.8$ Hz, $J_4 = 8.1$ Hz, $J_5 = 9.3$ Hz), 2.59 (1H, ddt, $J_1 = 1.0$ Hz, $J_2 = 1.3$ Hz, $J_3 = 5.1$ Hz, $J_4 = 14.9$ Hz), 2.63 (1H, dd, $J_1 = 9.3$ Hz, $J_2 = 14.9$ Hz), 4.66 (1H, quint, $J = 1.5$ Hz), 4.68 (1H, dquint, $J_1 = 0.8$ Hz, $J_2 = 1.5$ Hz), 5.86 (1H, qq, $J_1 = 0.8$ Hz, $J_2 = 1.3$ Hz, $J_3 = 1.3$ Hz, $J_4 = 1.3$ Hz). ^{13}C NMR: 202.8, 159.2, 148.6, 130.0, 110.3, 48.0, 40.9, 33.9, 31.4, 27.8, 20.9.

4.5. (1*R*,5*R*)-1-(Dibromomethyl)-5-isopropenyl-2-methylcyclohex-2-enol-1 3a and (1*S*,5*R*)-1-(dibromomethyl)-5-isopropenyl-2-methylcyclohex-2-enol-1 3b

A solution of *N*,*N*-Cy_2NLi, prepared by the addition of *n*-BuLi (6.0 mL; 7.0 M in *n*-hexane; 42.0 mmol) to *N*,*N*-Cy_2NH (7.48 g; 41.3 mmol) in anhydrous THF (30 mL) at 0 °C, was cooled to −78 °C and treated with a solution of (*R*)-(−)-carvone **1** (5.00 g; 33.3 mmol) and CH_2Br_2 (11.5 g; 66.8 mmol) in anhydrous THF (50 mL). The mixture was then stirred for 1 h at −78 °C, quenched by the addition of water and the product was extracted with Et_2O. The organic extract was dried over Na_2SO_4 and the solvent removed under vacuum. The solid residue was removed by filtration through a pad of silica gel, using a mixture of *n*-hexane and EtOAc (9:1) as eluent. The solvent was removed under vacuum to give a mixture of compounds **3a** and **3b** in a 1:1 ratio, as a pale yellow oil (8.23 g; 25.6 mmol) in 77% yield. Isomers **3a** and **3b** were isolated by column chromatography on silica gel, by using a mixture of hexane–EtOAc (9.5:0.5) as eluent.

Compound **3a**: $[\alpha]_D^{25} = -65.8$ (*c* 1.5, $CHCl_3$). IR (film) *v* 3473, 1643, 1042, 893, 672 cm^{-1}. MS *m*/*z* 227 (M-97). ^{1}H NMR: δ 1.79 (3H, s), 1.80 (3H, s), 2.12 (1H, m), 2.16 (2H, m), 2.57 (1H, dd, $J_1 = 4.0$, $J_2 = 12.3$ Hz), 2.74 (1H, m), 4.80 (2H, d, $J = 6.0$ Hz), 5.75 (1H, m), 5.88 (1H, s). ^{13}C NMR: 148.3, 132.3, 129.01, 109.9, 75.7; 55.1, 38.3, 37.7, 30.1, 21.1, 17.0. Anal. Calcd for $C_{11}H_{16}Br_2O$: C, 40.77; H, 4.98. Found: C, 40.81; H, 4.92.

Compound **3b**: $[\alpha]_D^{25} = -20.4$ (*c* 1.2, $CHCl_3$). IR (film) *v* 3475, 1644, 1041, 892, 670 cm^{-1}. MS *m*/*z* 227 (M-97). ^{1}H NMR: δ 1.76 (3H, s), 1.78 (3H, s), 1.89 (1H, m), 2.02 (2H, m), 2.12 (1H, dd, $J_1 = 1.80$, $J_2 = 4.0$ Hz), 2.17 (1H, s), 2.33 (1H, m), 2.40 (1H, m), 4.79 (2H, s), 5.78 (1H, dt, $J_1 = J_2 = 1.8$, $J_3 = 6.2$ Hz), 5.94 (1H, s). ^{13}C NMR: 148.3, 131.1, 130.9, 109.7, 76.3; 55.4, 37.1, 36.7, 31.2, 20.7, 16.7. Anal. Calcd for $C_{11}H_{16}Br_2O$: C, 40.77; H, 4.98. Found: C, 40.67; H, 5.05.

4.6. (*R*)-6-Isopropenyl-3-methyl-cyclohept-3-enone 4 and (*R*)-6-isopropenyl-3-methyl-cyclohept-2-enone 5

A solution of compounds **3a** and **3b** (5.00 g; 15.5 mmol) in anhydrous THF (50 mL) maintained at −78 °C was treated with *n*-BuLi (4.6 mL; 7.0 M in *n*-hexane; 32.2 mmol) and stirred at this temperature for 1 h and then at 0 °C for 15 min. Et_2O and 1.0 M HCl were then added to bring the pH to 3 and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with saturated brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel using *n*-hexane–EtOAc (9.5:0.5) as eluent to give **4** (1.19 g; 7.25 mmol: 47% yield) and **5** (0.10 g; 0.61 mmol: 4% yield). The spectroscopic and physical data for both **4** and **5** are practically identical to those described above.

4.7. (*R*)-6-Isopropenyl-3-methylcyclohept-3-enone 4

To a solution of MeMgBr (3.9 mmol) and $FeCl_3$ (0.014 g; 0.087 mmol) in dry Et_2O (5 mL) maintained at 10 °C, was added a solution of **5** (0.500 g; 3.04 mmol) in dry Et_2O (3 mL). The reaction mixture was heated at reflux for 1 h and then cooled to 0 °C. Crushed ice and cold AcOH (0.22 mL) were added and the phases separated. The organic phase was washed with saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel using *n*-hexane–EtOAc (9.5:0.5) as eluent to give **4** (0.395 g; 2.40 mmol; 79% yield).

4.8. (*R*)-6-Isopropenyl-3-methylcyclohept-2-enone 5

To a solution of *t*-BuOK (0.347 g; 3.10 mmol) in dry *t*-BuOH (20 mL) was added a solution of compound **4** (0.500 g; 3.04 mmol) in dry *t*-BuOH (1 mL) and stirred for 30 min at room temperature. Saturated NH_4Cl was added dropwise at 0 °C, and the mixture extracted with EtOAc. The organic phase was washed with water, brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel using *n*-hexane–EtOAc (9.5:0.5) as eluent to give **5** (0.325 g; 1.98 mmol; 65% yield).

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References

1. (a) Fraga, B. M. *Nat. Prod. Rep.* **2004**, *21*, 669–693; (b) Hanson, J. R. *Nat. Prod. Rep.* **2004**, *21*, 785–793; (c) Hanson, J. R. *Nat. Prod. Rep.* **1996**, *13*, 529–535.
2. Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.
3. (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3307; For a [5+2] process see: (b) Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154–9155; For a [4+3] process see: (c) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058–2959.

4. Kantorowski, E.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317–4353; See also: Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH: Weinheim, 1988, Chapters 5, 8, 11 and 12.
5. (a) Brocksom, T. J.; Brocksom, U.; Frederico, D. *Tetrahedron Lett.* **2004**, *45*, 9289–9291; (b) Zukerman-Schpector, J.; Caracelli, I.; Carvalho, C. C.; de Faria, M. L.; Silva, F. C.; Matias, L. G. de O.; Brocksom, T. J. *J. Braz. Chem. Soc.* **2001**, *12*, 154–158.
6. (a) De Faria, M. L.; Magalhães, R. A.; Silva, F. C.; Matias, L. G. O.; Ceschi, M. A.; Brocksom, U.; Brocksom, T. J. *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103; (b) Brocksom, T. J.; Pesquero, E. T. C.; Lopes, F. T. *Synth. Commun.* **1990**, *20*, 1181–1191.
7. (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 1058–1061 and 1075; (b) Krief, A.; Laboureur, J. L. *Chem. Commun.* **1996**, 702–704. The total regioselectivity observed in both ring expansion reactions is unexpected and difficult to attribute to the expected migratory aptitudes and/or antiperiplanar stereoelectronic controls, especially as we use epimeric mixtures of both **2** and **3** directly.
8. Ho, T.-L. *Enantioselective Synthesis, Natural Products from Chiral Terpenes*; Wiley and Sons: New York, 1992, Chapter 6.
9. Olkohvik, V.; Masalov, N.; Jansen, B. J. M.; de Groot, A. *Tetrahedron Lett.* **2001**, *42*, 4903–4905.
10. Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B.; Giménez-Saiz, C. *Tetrahedron* **2003**, *59*, 9523–9536.
11. Srikrishna, A.; Satyanarayana, G. *Org. Lett.* **2004**, *6*, 2337–2339.
12. Duboudin, F.; Cazeau, F. M.; Laporte, O. A. *Synthesis* **1982**, 212–214.
13. Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914–917.
14. McKinney, M. A.; Patel, P. P. *J. Org. Chem.* **1973**, *38*, 4059–4064.
15. Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 1592–1595.
16. Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308–2316.