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Article

Enantioselective Synthesis of (*R*)-Isocarvone from (*S*)-Perillaldehyde

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Este trabalho descreve a preparação enantiosseletiva da (*R*)-(+)-isocarvona, (*S*)-(-)-5-isopropenilcicloex-2-enona e (*S*)-(-)-3-isopropenilcicloexanona, a partir do *(S)*-(-)-perilaldeído. Estes compostos podem ser usados como blocos de construção importantes para a síntese orgânica.

This work describes the enantioselective preparation of (*R*)-(+)-isocarvone, (*S*)-(-)-5-isopropenylcyclohex-2-enone and (*S*)-(-)-3-isopropenylcyclohexanone starting from *(S)*-(-)-perillaldehyde. These compounds hold the prospect of serving as useful chiral building blocks or intermediates in organic synthesis.

Keywords: isocarvone, preparation, perillaldehyde, building block, cyclohex-2-enone

Introduction

Synthesis of enantiopure cyclohex-2-enone derivatives from natural monoterpenes, has been of continuing interest in organic chemistry, since these compounds have been employed as convenient building blocks for the preparation of a variety of biologically important compounds including natural products.[1-5] Often, when such cyclohex-2-enones are needed, they are derived from naturally occurring sources, such as carvone,[6,7] pulegone,[8-10] sugars,[11] pinene,[12] quinic acid,[13,14] or quebrachitol.[15,16]

A critical role in complex molecule construction relies on availability into specific optically pure targets along with reactions to elaborate and couple them.

Chiral cyclohex-2-enones with substituents in the 5-position are particularly difficult to construct stereoselectively.[5,7]

Isocarvone (**1**: 5-isopropenyl-3-methyl-cyclohex-2-enone), a methyl positional isomer of the monoterpene carvone (**2**), 5-isopropenylcyclohex-2-enone (**3**), 3-isopropenylcyclohexanone (**4a**) and 3-isopropylcyclohexanone (**4b**) are examples of building blocks with limited synthetic access in both enantiopure forms (Figure 1).[7] Theodorakis and co-workers have recently reported the first synthesis of isocarvone (in both enantiomerically pure forms) using an enantiodivergent approach, starting from monoterpene carvone.[7] Nakao and co-workers,[17] in their reported results on the enantioselective 1,4-addition of tetraorganosilicon reagents under the rhodium–chiral diene catalysis to α,β-unsaturated carbonyl acceptors, have prepared (*R*)-3-isopropenylcyclohexanone (**4a**) with a high enantiomeric excess (96 %) from cyclohexen-2-one. The higher saturated 3-isopropylcyclohexanone (**4b**) can be prepared more easily with a high yield and enantiomeric excess by catalytic 1,4-addition of organometallic reagents to cyclohexenone,[18] by organocatalytic asymmetric transfer hydrogenation of 3-isopropyl-2-cyclohexenone[19] or by a chemoenzymatic process.[20]

The (*R*)-enantiomer form of isocarvone (**1**) has also been shown to be a valuable building block for the synthesis of the complex target (C_1-C_{24}) carbon framework of Norzoanthamine, which has a broad spectrum of potent biological activities.[21]

(*R*)-5-isopropenylcyclohex-2-enone (**3**) has been used as a building block in the synthetic approach of aglycone Ouabagenin, which is a cardiotonic steroid used in the treatment of congestive heart failure.[22] The same enantiomeric form (*R*)-**3** has been used in the stereoselective synthesis of (-)-Rishitin, which is a defensive agent (phytoalexin) against *Phytophora infestans.*[23]

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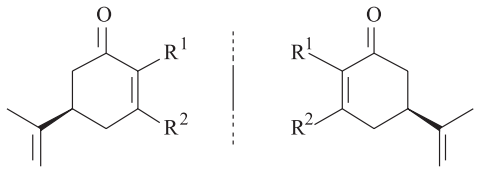
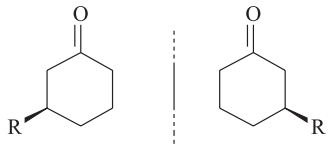


1 $R^1 = H$, $R^2 = CH_3$ isocarvone

2 $R^1 = CH_3$, $R^2 = H$ carvone

3 $R^1 = R^2 = H$ 5-isopropenylcyclohex-2-enone



4a $CH_3C{=}CH_2$ 3-isopropenylcyclohexanone

4b $(CH_3)_2CH$ 3-isopropylcyclohexanone

Figure 1.

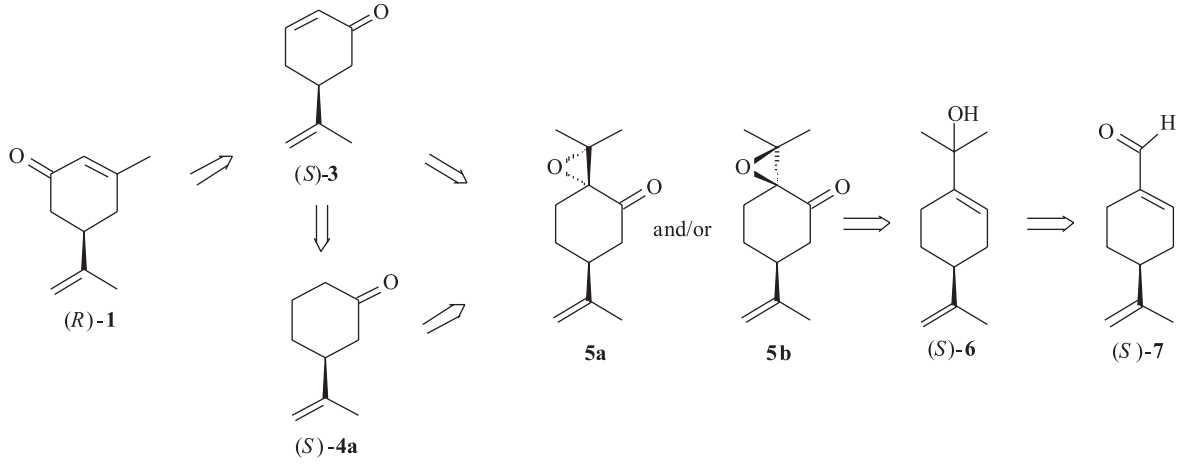
In this paper, we describe the enantiospecific synthesis of (*R*)-(+)-isocarvone. For our starting material we selected *(S)*-(-)-perillaldehyde (**7**). Both enantiomers of this monoterpene are commercially available, but cost considerations led to our choice of the less expensive *(S)*-enantiomer.[24] Another important feature is the fact that the (*S*)-enantiomer of perillaldehyde could be converted to the (*R*)-enantiomer form of (**1**), used by Juhl and co-workers in the synthesis of the target (C_1-C_{24}) carbon framework of Norzoanthamine.[21] From the retrosynthetic perspective (Scheme 1), we anticipated that the methylation of enone (*S*)-**3**, followed by an oxidative carbonyl transposition, would form (*R*)-**1**, while (*S*)-**3** would be accessible by the fragmentation of epoxy ketones **5a** and/or **5b** to afford (*S*)-**3** or (*S*)-**4a** in the presence of sodium thiophenoxide. The oxidative rearrangement of (*S*)-**6** using chromium (VI) reagents could afford **5a** and/or **5b.** Tertiary allylic alcohol (*S*)-**6** could be available from (*S*)-**7** by a two-carbon homologation using methylation and oxidation steps.

Results and Discussion

Reaction of *(S)*-(-)-perillaldehyde (**7**) with methyllithium in tetrahydrofuran at 0 °C gave the corresponding secondary alcohol **8,** which was used directly in the next reaction (Scheme 2). Oxidation of **8** using the Swern protocol[25] afforded the crude ketone (*S*)-**9**. The crude (*S*)-**9** thus obtained was subjected to methyllithium in tetrahydrofuran at 0 °C to afford the crude tertiary allylic alcohol (*S*)-**6** in 85% of overall yield for three steps. The intermediate obtained, was sufficiently clean to be used directly in the next reaction.

Next, we examined the oxidative rearrangement of (*S*)-**6** using a variety of conditions, including PCC/NaOAc,[26,27] PCC on alumina,[28] and CrO_3.2py in CH_2Cl_2.[29] Treatment of (*S*)-**6** with PCC/NaOAc in CH_2Cl_2 formed a 2:1 mixture of epoxy alcohol **10** and epoxy ketone **5a,** which were separated by column chromatography. The formation of epoxide mixtures in the oxidative rearrangement of tertiary allylic alcohols was not surprising in view of precedents in the literature, since it is well documented that sterically hindered alcohols seem prone to undergo such reactions.[26]

The use of Ratcliffe's modification of Collins' reagent (CrO_3.2py in CH_2Cl_2) significantly alters the product ratio toward **5a** formation (ratio **10**:**5a**, 1:2), however, lower yield was obtained and large excess of reagent was required. When (*S*)-**6** was treated with PCC on alumina, only starting material was recovered.



Scheme 1. Retrosynthetic analysis for (*R*)-**1** from (*S*)-(**7**).

The stereochemistry assigned to **10** is based on the assumption that the oxochromium(VI) reagent approaches the substrate or a prior allyl cation system from the least hindered α-face opposite to the isopropenyl group.

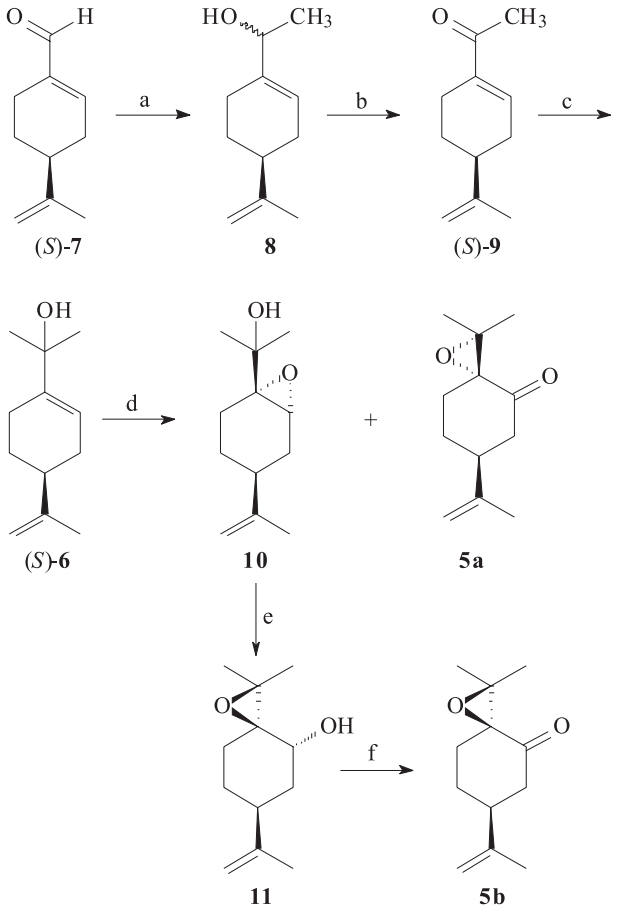
The ^{1}H NMR spectrum of **10** exhibited a singlet at 3.48 ppm, corresponding to a CH-epoxide in a pseudo-equatorial direction. In comparison with a literature result, a doublet with the coupling constant $J > 5$ Hz should be expected to a CH-epoxide in a pseudo-axial direction.[30]

Since the desired keto epoxide **5a** was easily separated from **10**, conversion of the latter to the diastereoisomeric epoxy ketone **5b** was performed in two steps. Treatment of **10**, with *t*-BuOK/*t*-BuOH at 40 °C, favors the epoxy alcohol migration of **10** to **11** as a mixture readily separable by column chromatography in a ratio of 1:2.2 (63% for **11** and 29% for recovered **10**). Attempts with a number of variations in the reaction conditions failed to significantly improve this ratio.[31] It is worth mentioning that the epoxy alcohol migration reaction proceeded in a stereoselective manner and only one stereoisomer was obtained. This stereoselectivity is in agreement with the deprotonation of the epoxy alcohol **10** to form an alkoxide, followed by direct intramolecular displacement at the adjacent epoxide center. The ^{1}H NMR spectrum of **11** showed a singlet at 3.78 ppm, consistent with a carbinolic hydrogen in an equatorial direction.

Oxidation of **11** using the Swern protocol[25] afforded ketone **5b**. No attempt was made to further assign the stereochemistry of keto epoxides **5a** and **5b,** which were used directly in the fragmentation step.

Using excess of PhSH/PhSNa (4.5 molar equivalents), opening of **5a** and **5b** (individually or as a mixture) was followed by retro-aldol expulsion of acetone and subsequent desulfenylation of **12** by thiophenoxide to afford (*S*)-**4a** in 90% yield (Scheme 3). However, upon addition of one or two molar equivalents of PhSH/PhSNa, a complex mixture containing **12** was observed. Despite varying the reaction conditions (reaction time, solvent and temperature), the β-keto sulfide **12** was never obtained in appreciable amounts. It should be noted that, for the similar fragmentation of pulegone oxide, using PhSH/PhSNa (2.0 molar equivalents) favors the corresponding β-keto sulfide in a high yield.

The regiospecificity of the sulfenylation of the unsymmetrical ketone (*S*)-**4a** was examined. The sequential treatment of (*S*)-**4a** with lithium diisopropylamide and diphenyldisulfide yielded regioisomerically pure β-keto sulfide **12** as a mixture of stereoisomers. Oxidation of **12** to the sulfoxides **13** with sodium metaperiodate at room temperature and subsequent heating of **13** in refluxing benzene furnished the cyclohexenone (*S*)-**3** in 66% overall yield from **12**. Treatment of (*S*)-**3** with MeLi produced the



a: MeLi, THF, 0 ºC, 1 h; b: ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, –78 ºC, 5 h; **c:** MeLi, THF, 0 ºC, 3 h, 85% (three steps); d: PCC, NaOAc, CH_2Cl_2, rt, 18 h, (yield: 47% for **10** and 23% for **5a**); e: *t*-BuOK, *t*-BuOH, 40 ºC, 20 h, (yield: 63% for **11** and 29% for recovered starting material **10**); f: ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, –78 ºC, 5 h, 85%.

Scheme 2.

corresponding tertiary alcohol, which underwent a PCC-induced oxidative rearrangement to form (*R*)-(-)-isocarvone (**1**) in 64% combined yield.[32, 7]

In summary, this study reports an alternative practical synthesis of enantiopure (*R*)-(-)-isocarvone (**1**), (*S*)-(+)-5-isopropenylcyclohex-2-enone (**3**) and (*S*)-3-(-)-isopropenylcyclohexanone (**4a**), starting from *(S)*-(-)-perillaldehyde. These compounds are versatile key building blocks for the construction of a variety of biologically important compounds, including natural products. The key strategic feature is the thiophenoxide opening of the new α,β-epoxy ketones **5a** and **5b** with concomitant retro-aldol reaction.

Ackowledgments

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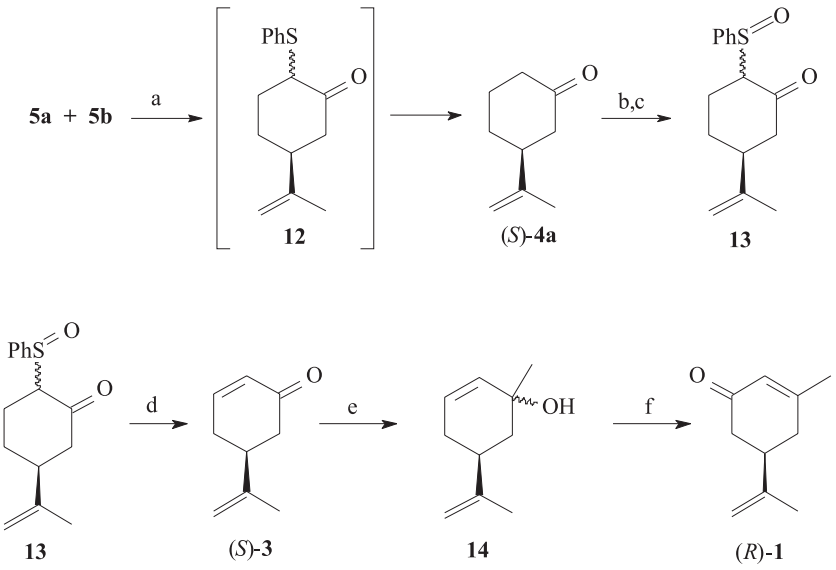

a: PhSH, NaH, THF, 90 °C, 24 h, 90%; b: LDA, PhSSPh, THF, -78 °C, 3 h, 77%; c: $NaIO_4$, $MeOH/H_2O$, rt, 4 days, 66%; d: benzene, $CaCO_3$, 95 °C, 3.5 h, 93% ; e: MeLi, Et_2O, 0 °C, 2 h, 80%; f: PCC, CH_2Cl_2, 25 °C, 3 h, 80%.

Scheme 3.

de Desenvolvimento Científico e Tecnológico), FAPERGS (Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul) and PROPESQ – UFRGS (Pró-Reitoria de Pesquisa da Universidade Federal do Rio Grande do Sul).

Experimental

Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. IR spectra were measured on a Mattson Galaxy Series FT-IR 3000 (model 3020). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. The chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and *J* standard values are given in Hz. Optical rotations were measured in a Perkin-Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20 °C. ESI-HRMS data on the positive mode were collected on a Waters® Micromass® Q-Tof micro mass spectrometer YB320 with Z-spray electrospray source. Samples were infused from a 100 µL gas-tight syringe at 30 µL/min. The instrument settings were the following: capillary voltage 3000 V, cone voltage 40 V, source temperature 100 °C, desolvation gas temperature 100 °C. Nitrogen was used as the desolvation gas. The samples were dissolved in an acetonitrile/milliQ water 1:1 solution (TEDIA) HPLC grade, made lightly acid with five drops of formic acid 0.1% solution.

Purification by column chromatography was carried out on silica gel 60 (70-230 mesh). Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates with 0.2 mm of silica gel 60F-254.

*(4S)-1-(4-Isopropenylcyclohex-1-enyl-1)-ethanone (**9**)*

To a solution containing 33 mmol of (*S*)-perillaldehyde (technical grade, 92%) in 300 mL of dry THF at 0 °C under an argon atmosphere was added MeLi (35 mL of 1 mol L^{-1} solution in Et_2O) dropwise over a period of 20 min. The reaction mixture was stirred for 1h at the same temperature, during which the reaction was complete (TLC). It was then quenched with saturated NH_4Cl (200 mL), poured into water (100 mL), and extracted with Et_2O (3 × 200 mL). The combined organic layer was washed with brine (200 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give allylic alcohol **8** in quantitative yield, which was subjected to Swern oxidation without further purification.

Oxalyl chloride (12 mL, 69 mmol) was dissolved in dry CH_2Cl_2 (100 mL) under argon and cooled to –78 °C, and DMSO (22 mL) was added dropwise and the reaction mixture was stirred for 1 h at the same temperature. Compound **8** (5 g, 30 mmol) in dry CH_2Cl_2 (42 mL) was added and the resulting mixture was stirred over 1 h. Dry triethylamine (38 mL) was added, and solution was stirred for 1h at –78 °C and allowed to reach rt. The reaction was quenched with water (100 mL). The organic phase was separated and washed with aq HCl (5 × 100 mL,

1 mol L^{-1}), water (3 × 100 mL), and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product (4.7 g, 95%) was used without any further purification in the next step. For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel. Elution with hexane:EtOAc (9.2:0.8) gave ketone (*S*)-**9** as a colourless oil. $[\alpha]_D^{20}$ −124 (*c* 2.1, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3080, 2967, 2933, 1668, 1641 1246, 1198, 1069; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (br, 1H), 4.77 (br, 1H), 4.73 (br, 1H), 2.56-2.32 (m, 2H), 2.30 (s, 3H), 2.26-2.05 (m, 3H), 1.95-1.84 (m, 1H), 1.76 (s, 3H), 1.51-1,30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 148.5, 140.1, 139.1, 109.1, 40.1, 31.3, 26.8, 25.1, 23.3, 20.6; ESI-HRMS *m/z* Found: 165.1280; Calc. for $C_{11}H_{16}O$ + H: 165.1279.

*(4S)-4-Isopropenyl-1-cyclohexenyl-propan-2-ol (**6**)*

To an ice-cooled solution of (*S*)-**9** (4.8 g, 29 mmol) in 200 mL of dry THF under an argon atmosphere was added MeLi (35 mL of 1 mol L^{-1} solution in Et_2O) dropwise. The reaction mixture was stirred for 1 h at the same temperature, during which, the reaction was complete (TLC). It was then quenched with saturated NH_4Cl (200 mL), poured into water (100 mL), and extracted with Et_2O (3 × 200 mL). The combined organic layer was washed with brine (200 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the allylic alcohol (*S*)-**6** (4.7 g, 90%) which was used without any further purification in the next step. For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel. Elution with hexane:EtOAc (8:2) gave (*S*)-**6** as a slightly yellow oil. $[\alpha]_D^{20}$ −76 (*c* 1.3, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3376, 2973, 2927, 1644, 1373, 1150, 950, 887; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (br, 1H), 4.71 (br, 2H), 2.29-2.11 (m, 4H), 2.10-1.47 (m, 4H), 1.74 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 143.5, 118.3, 108.4, 72.7, 40.9, 30.5, 28.8 (2C), 27.9, 24.8, 20.7; ESI-HRMS *m/z* Found: 180.1557; Calc. for $C_{12}H_{20}O$: 180.1514

*(3R,6S)-6-Isopropenyl-2,2-dimethyl-1-oxaspiro[2.5] octan-4-one (**5a**) and 2-[(1S,4S,6R)-4-isopropenyl-7-oxabicyclo[4.1.0]hept-1-yl]propan-2-ol (**10**)*

To a stirred solution of PCC (24 g, 111 mmol) in dry CH_2Cl_2 (175 mL) was added (*S*)-**6** (5 g, 28 mmol) in dry CH_2Cl_2 (175 mL). The mixture was stirred at rt overnight, then diluted with Et_2O and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluting with hexane:EtOAc, 7:3) to give epoxy alcohol **10** as a colourless oil (2.6 g, 13 mmol, 47%) and epoxy ketone **5a** as a colourless oil (1.2 g, 6.4 mmol, 23%).

*Data for **10**.* $[\alpha]_D^{20}$ −37 (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3469, 3081, 2973, 2932, 1644, 1370, 1181, 1153, 956; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (s, 1H), 4.69 (s, 1H), 3.48 (s, 1H), 2.30-2.05 (m, 3H), 2.00 (ddd, *J* 15.3, 6.0, 2.8 Hz, 1H), 1.84-1.56 (m, 3H), 1.70 (s, 3H), 1.29-1.08 (m, 1H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 109.1, 69.9, 64.9, 56.4, 36.6, 30.4, 26.6, 25.2, 24.5, 24.3, 20.9.

*Data for **5a**.* $[\alpha]_D^{20}$ −39 (*c* 1.7, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 2967, 2864, 1724, 1646, 1454, 1378, 1118, 909; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (s, 1H), 4.78 (s, 1H), 2.72-2.65 (m, 1H), 2.55-2.47 (m, 1H), 2.25-1.9 (m, 4H), 1.77 (s, 3H), 1.75-1.48 (m, 1H), 1.46 (s, 3H), 1.24(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.1, 146.4, 110.1, 70.1, 63.2, 47.9, 45.1, 29.7, 29.6, 20.4, 19.5, 19.2. ESI-HRMS *m/z* Found: 195.1329; Calc. for $C_{12}H_{18}O_2$ + H: 195.1385.

*(3R,4R,6S)-6-Isopropenyl-2,2-dimethyl-1-oxaspiro[2.5] octan-4-ol (**11**)*

To a stirred solution of **10** (600 mg, 3.1 mmol) in *t*-BuOH (45 mL) was added *t*-BuOK (860 mg, 7.6 mmol). The reaction mixture was stirred overnight while the temperature was maintained at 40 °C. After the mixture was concentrated in vacuo and a saturated solution of NH_4Cl (30 mL) was added. The aqueous solution was extracted with AcOEt (3 × 30 mL). The combined extracts were washed with water, dried over Na_2SO_4, and concentrated in vacuo to give a crude product (590 mg) consisting of compounds **11** and the starting material **10** which were separated by column chromatography. Eluting with hexane:EtOAc (95:5) furnished epoxy alcohol **11** as a white solid (374 mg, 63%) and epoxy alcohol **10** (168 mg 29%).

*Data for **11**.* $[\alpha]_D^{20}$ −49 (*c* 1.8, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3439, 3082, 3007, 2933, 2860, 1643, 1451, 1433, 1216, 1154, 1092, 984; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (s, 2H), 3.78 (s, 1H), 2.45-2.37 (m, 1H), 2.17-2.08 (m, 1H), 2.00–1.84 (m, 2H), 1.83-1.64 (m, 2H), 1.74 (s, 3H), 1.57-1.44 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 109.0, 69.3, 65.6, 63.3, 37.4, 36.4, 28.3, 24.8, 20.7 (2C), 19.8. mp= 49.5-52.5 °C

*(3R,6S)-6-Isopropenyl-2,2-dimethyl-1-oxaspiro[2.5]octan-4-one (**5b**)*

This compound was prepared in the same way as ketone (*S*)-**9**, from epoxy alcohol **11** (4 g, 20 mmol). The crude **5b** (3.4 g, 17 mmol) was obtained in 85% yield and sufficiently clean to be used directly in the next reaction.

For analytical purposes, a small sample of the above product was purified by column chromatography on silica gel, hexane:EtOAc (95:5) to give **5b** as a white solid.

*Data for ketone **5b***. $[\alpha]_D^{20}$ +28 (*c* 1.7, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 2962, 2886, 1710, 1642, 1375, 1175, 1113, 899; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.79 (s, 1H), 2.86-2.77 (m, 2H), 2.45-2.38 (m, 1H), 2.14-1.94, (m, 3H), 1.83-1.73 (m 1H), 1.77 (s, 3H), 1.44 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 145.7, 113.2, 70.1, 63.8, 46.8, 42.0, 26.9, 26.4, 22.1, 20.0 (for two CH_3), mp = 67.3–69.6 ºC.

*(S)-3-Isopropenylcyclohexanone (**4a**)*

A 60% oil dispersion of NaH (370 mg, 9.3 mmol) under argon was washed with dry hexane (3 × 5 mL) in order to remove the oil. Dry THF (10 mL) was added followed by a solution of thiophenol (1.5 g, 14 mmol) in dry THF (15 mL). The mixture was stirred at room temperature for 40 min, and then the mixture of epoxides **5a** and **5b** (600 mg, 3.1 mmol) in dry THF (4.5 mL) was added. The resulting mixture was heated at reflux for 24 h and allowed to cool. Ice (5 g) was added and, after stirring for 15 min, the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using hexane:Et_2O (95:5) as an eluent to afford (*S*)-**4a** as a highly volatile colourless oil in 90% (386 mg, 2.8 mmol) yield. $[\alpha]_D^{20}$ −17 (*c* 1.7 , $CHCl_3$); IR, ^1H NMR and ^{13}C NMR spectra gave the same absorptions as reported earlier.[17]

*(5S)-5-Isopropenyl-2-(phenylthio)cyclohexanone (**12**)*

A solution of LDA was prepared by adding 2.8 mL of 1 mol L^{-1} *n*-BuLi in 0.5 mL (3.5 mmol) of *i*-Pr_2NH dissolved in 5 mL of dry THF at –78 ºC under argon atmosphere. To this solution was added 190 mg (1.4 mmol) of (*S*)-**4a** in 1 mL of dry THF. The reaction mixture was stirred at the same temperature for 0.5 h and allowed to reach 0 °C. Subsequently, a solution of PhSSPh (630 mg, 2.9 mmol) in 3 mL of dry THF was added to this mixture. The resultant mixture was stirred at rt for 1.5 h and poured into a saturated NH_4Cl solution (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with 10% aq. HCl-solution, and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane:Et OAc (96:4) as eluent to afford **12** as a slightly yellow oil (262 mg, 1.1 mmol, 77%). IR (KBr) ν_{max}/cm^{-1}: 2940, 1714, 1646, 1583, 1440, 896, 748, 691; ^1H NMR ($CDCl_3$, 300 MHz, *mixture of diastereomers 2:1*): δ 7.50-7.27 (m, 5H), 4.80-4.73 (m, 2H), 3.89 (dd, *J* 10.2, 5.70 Hz, 1H, *minor isomer*) and 3.76 (br, 1H, *major isomer*), 3.09 (t, *J* 13.0 Hz, 1H, *major isomer*) and 2.72 (dt, *J* 11.1, 2.0 Hz, 1H *minor isomer*), 2.58-1.60 (m, 6 H), 1.76 (s, CH_3, *major isomer*) and 1.73 (s, CH_3, *minor isomer*); δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7 and 206.0 (C=O), 147.0 and 146.5 (C), 133.7, 133.6, 132.4, 131.5, 129.0, 128.9, 127.5, 127.4, 110.6 and 110.3 (CH_2), 57.4, 54.4, 46.2, 45.8, 42.0, 32.9, 31.3, 29.5, 26.0, 20.7, 20.3.

*(5S)-5-Isopropenyl-2-(phenylsulfinyl)cyclohexanone (**13**)*

To a stirred solution of **12** (215 mg, 0.9 mmol) in 15 mL of MeOH was added a solution of $NaIO_4$ (205 mg, 1.0 mmol) in 1.5 mL of H_2O. After being stirred at rt for 4 days, the reaction mixture was diluted with 40 mL of MeOH and filtered through a short pad of Celite. The filtrate was concentrated in vacuo, and the remaining residue was taken up in 40 mL of Et_2O. The solution was washed with H_2O (2 × 40 mL), brine (1 × 40 mL) and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using hexane:EtOAc (4:1) to give **13** (157 mg, 0.6 mmol, 66%) as a pale yellow foam (mixture of four diastereomers); IR (KBr) ν_{max}/cm^{-1}: 2935, 1712, 1638, 1442, 1086, 1040, 749, 689; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76-7.49 (m, 5H), 4.87-4.68 (m, 2H), 3.72 (dd, *J* 11.4, 5.7 Hz, 1H), 3.45-3.38 (m, 2H), 2.62-1.40 (m, 5H), 1.77, 1.72 and 1.69 (s, corresponding to three CH_3).

*(5S)-5-Isopropenylcyclohex-2-en-1-one (**3**)*

A solution of ketosulfoxides **13** (143 mg, 0.5 mmol) in 3 mL of benzene was heated in the presence of $CaCO_3$ (20 mg, 0.2 mmol) at 95 ºC for 3.5h. After cooling to rt, the solvent was evaporated under reduced pressure and the residue thus obtained, was purified by column chromatography using pentane:Et_2O (9:1) to give (*S*)-**3** as a highly volatile colourless oil in 93% (69 mg, 0.5 mmol) yield. $[\alpha]_D^{20}$ +40 (*c* 1.6, $CHCl_3$); IR (KBr) ν_{max}/cm^{-1}: 3084, 2969, 2937, 1682, 1646, 1616, 1246, 894; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (ddd, *J* 10.1, 5.8, 2.5 Hz, 1H), 6.05 (d of m, *J* 10.1 Hz, 1H), 4.83 (br, 1H), 4.78 (br, 1H), 2.78-2.67 (m, 1H), 2.62-2.25 (m, 4H), 1.77 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 199.7, 149.7, 146.4, 129.6, 110.7, 43.0, 42.0, 30.9, 20.4.

*(5S)-5-Isopropenyl-1-methylcyclohex-2-en-1-ol (**14**)*

To an ice-cooled solution of (*S*)-**3** (60 mg, 0.4 mmol) in 2 mL of dry Et_2O under an argon atmosphere was added

MeLi (0.7 mL of 1 mol L^{-1} solution in Et_2O) dropwise. The reaction mixture was stirred for 2.5 h at the same temperature, during which, the reaction was complete (TLC). It was then quenched with saturated NH_4Cl (5 mL), poured into water (10 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography using hexane:EtOAc (9:1) to give **14** (52 mg, 0.34 mmol, 78%) as a colourless oil (mixture of two diastereomers). IR, and ^{1}H NMR spectra gave the same absorptions as reported earlier.[33]

*(5R)-Isopropenyl-3-methyl-cyclohex-2-enone (isocarvone **1**)*

To a stirred suspension of PCC (91 mg, 0.42 mmol) and silica (91 mg) in 3 mL of dry CH_2Cl_2 was added a solution of the alcohol **14** (43 mg, 0.28 mmol) in 2 mL of dry CH_2Cl_2. The reaction mixture was vigorously stirred at rt under argon atmosphere for 3 h. The resulting dark brown slurry was filtered though a short column of silica gel and eluted with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluting with hexane:EtOAc, 9:1) to afford (*R*)-**1** (34 mg, 0.22 mmol) in 80% yield as a colourless oil. $[\alpha]_D^{20}$ −60 (*c* 0.40, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ −60.9 (*c* 0.41, $CHCl_3$)]; IR, ^{1}H NMR and ^{13}C NMR spectra gave the same absorptions as reported earlier.[7]

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